



Swansea University
Prifysgol Abertawe

**Screening for metabolic dysfunction-associated steatotic liver
disease and advanced liver fibrosis in people with type 2 diabetes
or obesity in secondary care**

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Summary

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognised as a complication of type 2 diabetes (T2D) and obesity, observed in around two-thirds of these patients. In people with MASLD and liver fibrosis there is major excess cardiovascular and malignancy-related morbidity and mortality. However, liver disease screening is not recommended in the United Kingdom as part of these patients' routine care, despite growing international consensus. This is because of concerns around test accuracy, the need to re-design hepatology services, and the absence of approved pharmacological treatments. In this thesis, four studies are presented to address concerns around MASLD screening.

Study 1 explores the accuracy of blood biomarkers and fibroscan for hepatic steatosis and fibrosis in a cohort of 153 patients with biopsy-confirmed MASLD. Further analysis describes the bidirectional relationship between MASLD and T2D in this cohort.

Study 2 is a pilot study examining the role of additional blood tests and fibroscan to screen for MASLD in 200 people with T2D attending hospital diabetes clinics. The estimated prevalence of MASLD and advanced fibrosis were determined. The consistency between different tests was investigated, and biomarkers were correlated with cardiovascular risk.

Study 3 is a pilot study examining the use of a range of screening tests for MASLD in 22 people with severe obesity undergoing bariatric surgery. The prevalence of MASLD and advanced fibrosis were determined, and test consistency was assessed.

Study 4 is a questionnaire-based study to evaluate the understanding MASLD and views of screening for MASLD in 403 people with diabetes attending hospital-based diabetes clinics, and 70 clinicians practising in diabetes & endocrinology or primary care.

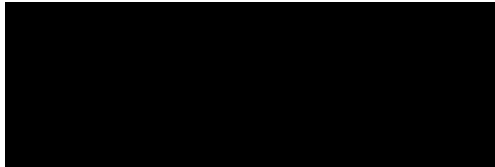
The results from these studies support MASLD screening in the routine care of people with T2D or obesity and highlight further work and the next steps needed to support developing this process into local practice.

Declaration and statements

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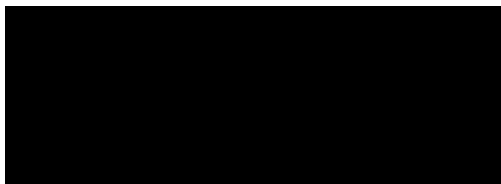
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Statement 1

This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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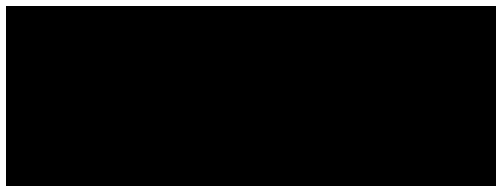
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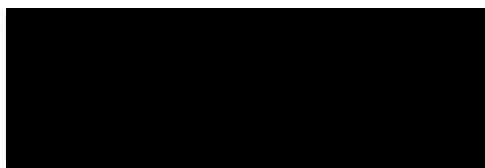
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Finally, I would like to extend my gratitude to the participants in the studies presented in this thesis. Their willingness to contribute to this research made this work possible, and I am grateful for their time, trust, and commitment.

Summary of my role in the studies presented in this thesis

Throughout this project, I contributed to every stage of each study presented in this thesis. My involvement included the conceptualisation of each of the research aims and study design with my supervisors, obtaining the necessary approvals as required, leading data collection, managing each database, and the statistical analysis. I was responsible for presenting the findings throughout this thesis, the poster and oral presentations, and peer-reviewed publications which were generated by the results of each study as presented in Appendix I.

In study 1, I was supported by my supervisors Dr Thinzar Min and Professor Jeffrey Stephens, with guidance from Dr Chin Lye Ch'ng, a consultant hepatologist in Swansea when the study commenced. I was supported with the statistical analysis by Dr Ivy Cheung.

In study 2, I was supported by my supervisors Dr Thinzar Min and Professor Jeffrey Stephens, with guidance from Dr Jagadish Nagaraj, a consultant hepatologist in Swansea. I attended all meetings with the Research Ethics Committee and personnel in Swansea to develop the study. I consented the participants, collected the study data, and performed the Fibroscan in all participants. I referred those meeting pre-agreed criteria to hepatology, and both requested and managed the results of investigations taken whilst waiting review. I was supported with the statistical analysis by Dr Ivy Cheung.

In study 3, I developed the idea for the pilot study, with support from my supervisors Professor Jeffrey Stephens and Dr Thinzar Min, with guidance from Mr Andrew Beamish (lead for the Welsh Institute of Metabolic and Obesity Surgery service). I led the application for approval as a service evaluation project and the revision process. I consented the participants, collected the study data and performed the Fibroscan in all participants.

In study 4, I suggested the idea to survey patients and clinicians involved in the care of people with diabetes, supported by my supervisors Professor Jeffrey Stephens and Dr Thinzar Min. The surveys were drafted by me and developed with Dr Laura Wilkinson, an associate professor working in the school of psychology at Swansea University. I attended all clinics in which patient data were collected, and the meetings in which clinician data were collected.

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List of abbreviations

Abbreviation	Definition
3P-MACE	3-Point Major Adverse Cardiovascular Events
AACE	American Association of Clinical Endocrinology
ADAPT	Age, Presence of Diabetes, PRO-C3, and Platelet count
APASL	Asia-Pacific Association for the study of the Liver
AASLD	American Association for the Study of Liver Diseases
ACE	Angiotensin-Converting Enzyme
ADA	American Diabetes Association
ALD	Alcohol-Related Liver Disease
ALT	Alanine Transaminase
ANA	Anti-Nuclear Antibodies
ANOVA	Analysis of Variance
APRI	Aspartate Aminotransferase to Platelet Ratio Index
AST	Aspartate Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
ARB	Angiotensin-Receptor Blocker
AUC	Area Under the Curve
BARD	Body Mass Index- Aspartate Aminotransferase/Alanine Transaminase Ratio-Diabetes Mellitus
BP	Blood Pressure
BPD	Biliopancreatic Diversion
BMI	Body Mass Index
CAP	Controlled Attenuation Parameter
CCI	Charlson Comorbidity Index
CFS	Clinical Frailty Score
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLD	Chronic Liver Disease
CT	Computerized Tomography
CVD	Cardiovascular Disease
DESMOND	Diabetes Education and Self-Management for Ongoing and Newly Diagnosed
DPP-4	Dipeptidyl Peptidase-4
DNHL	De Novo Hepatic Lipogenesis
EASD	European Association for the Study of Diabetes
EASL	European Association for the Study of the Liver
EASO	European Association for the Study of Obesity
ELF	Enhanced Liver Fibrosis
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FAST	Fibroscan-AST

FASN	Fatty Acid Synthase
FBG	Fasting Blood Glucose
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
FIB-4	Fibrosis-4
FLI	Fatty Liver Index
FXR	Farnesoid X receptor
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP-1RA	Glucagon-Like Peptide-1 Receptor Analogues
GP	General Practitioner
HA	Hyaluronic Acid
HbA1c	Glycated haemoglobin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCRW	Health and Care Research Wales
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HF	Hepatic fibrosis
HIV	Human Immunodeficiency Virus
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HRA	Health Research Authority
HS	Hepatic Steatosis
HSI	Hepatic Steatosis Index
ICER	Incremental Cost-Effectiveness Ratio
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IgA	Immunoglobulin A
IQR	Interquartile Range
IR	Insulin Resistance
LAP	Lipid Accumulation Product
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LSG	Laparoscopic Sleeve Gastrectomy
LSM	Liver Stiffness Measurement
MALO	Major Adverse Liver Outcomes
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MELD	Model for End-Stage Liver Disease
MetALD	Metabolic Dysfunction-Associated Steatotic Liver Disease with Increased Alcohol Intake

MEFIB	Magnetic Resonance Elastography combined with FIB-4 score
MetS	Metabolic Syndrome
MI	Myocardial Infarction
MR	Magnetic Resonance
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging Proton Density Fat Fraction
NAFLD	Non-Alcoholic Fatty Liver Disease
NAFLD-LFS	Non-Alcoholic Fatty Liver Disease Liver Fat Score
NAS	Non-Alcoholic Fatty Liver Disease Activity Score
NASH	Non-Alcoholic Steatohepatitis
NFS	Non-Alcoholic Fatty Liver Disease Fibrosis Score
NICE	National Institute of Health and Care Excellence
NPV	Negative Predictive Value
NHS	National Health Service
NS	Not Significant
PAD	Peripheral Arterial Disease
PCSK9	Proprotein Convertase Subtilisin/Kexin type 9
PDR	Proliferative Diabetes-related Retinopathy
PIIINP	Procollagen III Amino-Terminal Peptide
PIS	Participant Information Sheet
PIVENS	Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Nondiabetic Patients with Non-Alcoholic Steatohepatitis
PPAR- γ	Peroxisome proliferator-activated receptor-gamma
PPV	Positive Predictive Value
PVD	Peripheral Vascular Disease
QALY	Quality-Adjusted Life Year
QR	Quick Response
QRISK3	QRESEARCH cardiovascular risk score-3
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic
RYGB	Roux-en-Y gastric bypass
SGLT-2	Sodium-Glucose Co-Transporter-2
SLD	Steatotic Liver Disease
SBUHB	Swansea Bay University Health Board
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TE	Transient Elastography
TIMP-1	Tissue Inhibitor of Matrix Metalloproteinase-1
TR- α	Thyroid Hormone- α Receptors
TR- β	Thyroid Hormone- β Receptors

TyG	Triglycerides and Glucose Index
UACR	Urine Albumin-to-Creatinine Ratio
UKPDS	UK Prospective Diabetes Study
VAI	Visceral Adiposity Index
WC	Waist Circumference
WHO	World Health Organisation
WIMD	Welsh Index of Multiple Deprivation
WIMOS	Welsh Institute for Metabolic and Obesity Surgery
X-PERT	Expert Education versus Routine Treatment

Chapter One:
Introduction and review of the literature

1.1 Diabetes mellitus

Diabetes mellitus is a group of metabolic disorders characterised by high glucose levels. In practice, there are two main types of diabetes though some classifications describe at least 12 types. Type 1 diabetes (T1D) is characterised by lack of endogenous insulin secretion due to autoimmune-mediated pancreatic β -cell failure to secrete insulin. Type 2 diabetes (T2D) is a disorder of peripheral insulin resistance (IR) and impaired hepatic glucose metabolism, which associates with progressive pancreatic β -cell dysfunction resulting in insulin deficiency during later stages (Zaccardi et al., 2016). Both T1D and T2D are characterised by hyperglycaemia and share similarities in their presentation and risk of complications.

1.1.1 Clinical presentation and diagnosis of diabetes

People with T1D classically present at an earlier age with a relatively rapid onset of symptoms compared to people with T2D, who often have a more varied presentation. Typical symptoms include polyuria, polydipsia, excess fatigue, blurred vision, and unexplained weight loss. Though, many with T2D may be asymptomatic and are diagnosed on opportunistic testing following complications such as stroke or myocardial infarction (MI). People with T2D frequently have other cardiovascular disease (CVD) risk factors such as hypertension, dyslipidaemia, obesity, steatotic liver disease (SLD) or microalbuminuria (Chatterjee et al., 2017). Therefore, people at risk of T2D should be screened for earlier diagnosis.

A diagnosis of diabetes is made in symptomatic individuals with one of the following criteria, or two criteria on different days in the absence of symptoms (American Diabetes Association, 2024a; International Diabetes Federation, 2025; World Health Organisation, 2019);

1. Fasting plasma glucose >7.0 mmol/L
2. Random glucose >11.1 mmol/L
3. Random plasma glucose >11.1 mmol/L two hours post 75g oral glucose tolerance test
4. Glycated haemoglobin (HbA1c) ≥ 48 mmol/mol (6.5%).

1.1.2 Epidemiology and economic burden of type 2 diabetes

The international diabetes federation (IDF) estimated 11.1% of the global population (588.7 million people) were living with diabetes in 2024, and this will increase to 13.0% (852.5 million people) by 2050 (International Diabetes Federation, 2025). Over 90% of people with diabetes have T2D. The growing prevalence is driven by low and middle-income countries in which population growth and ageing populations are greatest. Differences in the prevalence of diagnosed and undiagnosed diabetes in different IDF regions are presented in Table 1.1.

In the UK 4.4 million people lived with diabetes in 2022-2023, and 90% of this population were diagnosed with T2D, 8% with T1D and 2% with rarer forms of diabetes. A further 1.2 million people were estimated to live with undiagnosed T2D in this period (Diabetes UK, 2024). Should the prevalence of diabetes continue to rise at its current rate, 5.5 million people will have diabetes by 2030. The prevalence of diabetes in 2019 differed across the UK regions, and was greatest in Wales (6.3%), and least in Northern Ireland (5.3%) (Diabetes UK, 2020).

Table 1.1: Global prevalence of diabetes by International Diabetes Federation region

IDF Region	Number of people with diabetes (millions)	Diabetes prevalence (%)	Number of people with undiagnosed diabetes (millions)	Proportion undiagnosed (%)
Africa	24.6	4.2	17.9	72.6
Europe	65.6	9.8	22.0	33.6
Middle East and North Africa	84.7	17.6	31.5	37.2
North America and Caribbean	56.2	15.1	16.3	29.1
South and Central America	35.4	10.0	10.7	30.4
South-East Asia	106.9	9.7	45.6	42.7
Western Pacific	215.4	12.4	107.6	50.0
Total	588.7	11.1	251.7	42.8

The global prevalence of diabetes and undiagnosed diabetes by IDF region (International Diabetes Federation, 2025). Abbreviation: *IDF* international diabetes federation.

One study observed that for every decade of life with diabetes, there is a 3–4-year lower life expectancy (Emerging Risk Factors Collaboration, 2023). The economic burden associated with diabetes is staggering, estimated in 2015 at US \$1.3 trillion, and projected to increase to US \$2.5 trillion by 2030 (Bommer et al., 2018). In the UK, the direct cost of diabetes in 2021/22 was £10.7 billion, with a further £3.3 billion in indirect costs associated with productivity losses and premature mortality (Hex et al., 2024). This will rise given its growing prevalence and does not include the cost of managing diabetes complications, which is greater than the direct costs of the disease (Hex et al., 2024). Therefore, there is growing focus on earlier identification and prevention of complications, and preventing T2D in people at risk. Further action nationally, and internationally, is needed.

1.2 Clinical management of people with type 2 diabetes

The treatment of people with T2D has evolved over the last 20 years from a focus on glycaemic control to managing modifiable risk factors for complication development to improve quality and duration of life. The treatment approach should be tailored to the individual by the clinician and patient in consort (American Diabetes Association, 2024b, 2024c, 2024e, 2024f; NICE, 2026; Williams, Jones, et al., 2022).

1.2.1 Non-pharmacological treatments for people with type 2 diabetes

Despite international guidelines promoting structured education to permit self-management (American Diabetes Association, 2024c; NICE, 2026), many with T2D are not able to undertake this given a perceived lack of benefit, or practical difficulties attending (Horigan et al., 2017). Nevertheless, evidence supports non-pharmacological interventions in people with T2D, particularly patient education and the dietary and lifestyle measures.

1.2.1.1 Structured education programmes for people with type 2 diabetes

Educational courses for people with T2D in the UK include the Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND), and Expert Education versus Routine Treatment (X-PERT) programmes. The DESMOND programme is a one day group course, designed for people with newly-diagnosed T2D to discuss the impact of diet and lifestyle on CVD risk. People attending DESMOND had greater weight loss, changes in illness belief scores and lower depression scores after 12 months, but no HbA1c change (Davies et al., 2008). This may have been confounded by the low baseline HbA1c in this group resulting in a lack of statistical change. Nonetheless, only changes in illness belief scores persisted at 3 years follow-up with no persisting differences in body mass index (BMI), BP, depression scores, HbA1c, or lipid profiles (Khunti et al., 2012). The X-PERT programme runs as six weekly sessions for people with T1D or T2D to discuss lifestyle choices or those treated with insulin. People with T2D attending X-PERT had improved diabetes knowledge, self-management skills, and fruit and vegetable consumption with improved BMI, HbA1c and lipid profiles after 14 months (Deakin et al., 2006). Subsequent audits show improvements in CVD risk factors and knowledge (X-PERT Health, 2020), though there is limited data on longer term outcomes. Around 90% of people with T2D invited to these diabetes self-management courses are unable to attend, and non-attenders are typically those at greatest risk, with sub-optimal glucose control and adherence to self-management strategies (Coningsby et al., 2022).

1.2.1.2 Diet and lifestyle measures for people with type 2 diabetes

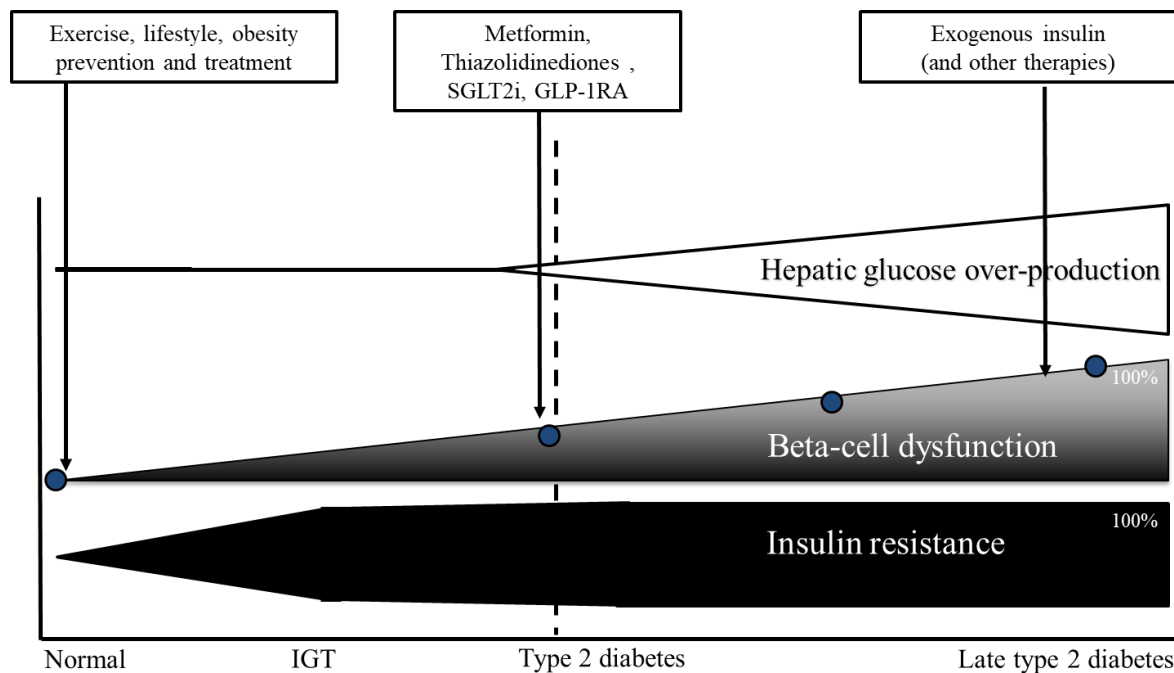
People with T2D should be given individualised dietary advice, preferably from a dietician with an interest in diabetes. This is associated with HbA1c reductions ranging 0.3-2.0% (Franz et al., 2017). The goal is to promote healthy eating to support that person's treatment goals, such as weight loss, or glycaemic control (American Diabetes Association, 2024c; NICE, 2026). The impact of diet on T2D was emphasised by the DiRECT study which included people with T2D diagnosed in the previous six years and BMI 27-45 kg/m². Participants' usual treatments were stopped with a total diet replacement of 850 kcal daily. Remission of T2D was observed in 50% of participants with mean weight loss 10.0 kg at one year (Lean et al., 2018). Routine use of very-low-calorie diets are discouraged given the lack of longer-term safety data.

Promoting physical activity and exercise in people with T2D is important; it improves glycaemia and derives other health benefits (American Diabetes Association, 2024c). When advising people with T2D to undertake activity, clinicians should be mindful of pre-existing complications such as foot disease, or neuropathy may affect exercise ability. Any activity is associated with health benefits and should be encouraged. Though, the Look-AHEAD study observed that intensive lifestyle intervention did not reduce CVD occurrence in people with T2D. Here, over 5,000 people with T2D who were overweight or obese participated in an intensive lifestyle intervention with increased activity and calorie restriction. Those in the intervention arm had improvements in HbA1c, BP, bodyweight, and lipid profiles. However, this did not translate into a reduced 3-point major adverse cardiovascular events (3P-MACE), a composite measure of death from CVD, nonfatal MI, and nonfatal stroke over a median 9.6 years follow-up and the trial was discontinued early on futility basis (Look et al., 2013). The apparent lack of impact of an intensive lifestyle intervention on 3P-MACE was confounded by several factors. Firstly, the control group in this study achieved improved cardiometabolic risk factors minimising the between group difference associated with the intervention. Secondly, modern medicines used in people with T2D including those used for glycaemic control, dyslipidaemia or hypertension would confound the cardiovascular impact of the lifestyle intervention trialled. These factors resulted in a lower number of cardiovascular events across both groups in the study than expected, which inevitably impacted the statistical analysis.

1.2.2 Pharmacological treatments for people with type 2 diabetes

Most people with T2D require pharmacological treatment despite diet and lifestyle measures. As described, T2D is a disorder of both peripheral and hepatic IR, which requires greater endogenous circulating insulin to maintain glucose homeostasis than in people without T2D. With greater T2D duration, pancreatic β -cell function declines requiring therapy escalation. The pharmacological treatment of T2D should reflect the stage of disease and is summarised in Figure 1.1. Drug classes used to treat T2D include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor analogues (GLP-1RA), sodium-glucose co-transporter-2 (SGLT-2) inhibitors, thiazolidinediones, sulphonylureas, and insulin. Several factors influence the choice of pharmacotherapy, including their relative efficacy, patient preference, other associated metabolic benefits, route of administration, dosing frequency, side-effect profile and cost. Frequently, patients require multiple agents to achieve target glycaemia.

Figure 1.1: The treatment approach in people with type 2 diabetes



The treatment approach in people with T2D based on the duration of T2D and relative beta-cell dysfunction with IR. Figure used with permission from Williams et al. (Williams, Jones, et al., 2022).

The National Institute for Health and Care Excellence (NICE) offers guidance for the treatment of T2D (NICE, 2026). The recent guidance highlights the need to commence therapies such as SGLT-2 inhibitors early to prevent cardiovascular disease and to treat comorbidities such as obesity or chronic kidney disease aggressively to prevent complication progression (NICE, 2026). The expected improvements in HbA1c and co-morbidities considered for treatment with each drug class for the treatment of T2D are presented in Table 1.2 (Chaudhury et al., 2017).

Table 1.2: Treatment considerations for people with type 2 diabetes

Drug class (examples)	Mechanism of action	Expected HbA1c reduction	Other considerations	Adverse effects
Biguanides (Metformin)	Reduced peripheral IR and hepatic gluconeogenesis	11-22 mmol/mol [1.0-2.0%]	Some CVD benefits, and mild weight loss	GI: Diarrhoea, abdominal cramps, lactic acidosis, vitamin B12 deficiency.
Sulphonylureas (Gliclazide, glyburide)	Induces insulin secretion	11-22 mmol/mol [1.0-2.0%]	Useful for people with T2D & marked hyperglycaemia	Hypoglycaemia, weight gain.
Thiazolidinediones (Pioglitazone)	PPAR- γ receptor agonist	5-15 mmol/mol [0.5-1.4%]	May be useful in SLD	Weight gain, heart failure, bladder cancer, bone fracture
SGLT-2 inhibitors (Dapagliflozin, empagliflozin)	Increased urinary glucose excretion	6-10 mmol/mol [0.6-0.9%]	Useful in people with CKD, heart failure or high risk of CVD	Urogenital infections, diabetic ketoacidosis
DPP-4 inhibitors (Linagliptin, saxagliptin, sitagliptin)	Inhibits GLP-1 degradation to stimulate insulin	5-9 mmol/mol 0.5-0.8%	Generally well-tolerated and safe in ESRD	GI: nausea, diarrhoea
GLP-1RA (Dulaglutide, liraglutide, semaglutide)	Stimulates insulin secretion	5-16 mmol/mol 0.5-1.5%	Useful in people with obesity, SLD, CKD, or high risk of CVD	GI: Nausea, vomiting, abdominal cramps

The mechanism of action and considerations for the drug classes used to treat T2D (Chaudhury et al., 2017). Abbreviations: *CKD* chronic kidney disease; *CVD* cardiovascular disease; *DPP-4* dipeptidyl peptidase-4; *ESRD* end-stage renal disease; *GI* gastrointestinal; *GLP-1* glucagon-like peptide-1; *GLP-1RA* glucagon-like peptide-1 receptor analogues; *HbA1c* glycated haemoglobin; *IR* insulin resistance; *PPAR- γ* Peroxisome proliferator-activated receptor-gamma; *SGLT-2* sodium-glucose co-transporter-2; *SLD* steatotic liver disease; *T2D* type 2 diabetes.

1.3 Complications associated with type 2 diabetes

People with T2D have a greater risk of vascular complications, described as macrovascular (e.g., stroke, MI, and peripheral vascular disease) or microvascular (e.g., retinopathy, nephropathy, and neuropathy). Identification of complications often precedes T2D diagnosis. One study observed 50% of people with newly-diagnosed T2D had at least one diabetes complication. Microvascular disease was evident in 30.8%, previous macrovascular disease in 9.3% or evidence of both in a further 9.1% (Bonora et al., 2020). With growing focus on complication prevention in the management of people with T2D over last 20-30 years, there has been a significant reduction in the frequency of atherosclerotic CVD, stroke, lower extremity amputation and proliferative diabetes-related retinopathy in people with T2D (Harding et al., 2019). Associated with this and the greater life expectancy observed, there is better recognition of other co-morbidities associated with T2D. The emerging complications associated with T2D include dementia, cancer, and liver disease, amongst others (Tomic et al., 2022). Nevertheless, the vascular complications associated with T2D are responsible for most T2D-related morbidity and mortality, and socioeconomic burden (Young et al., 2019).

1.3.1 Macrovascular complications

Poor glycaemic control, especially hypoglycaemia, results in oxidative stress causing damage to the vascular endothelium leading to atherosclerosis, vascular remodelling, inflammation and fibrosis in the vascular system. This causes stroke, CVD, and peripheral arterial disease (PAD) (Sena et al., 2018; Stephens et al., 2006). People with diabetes have two-fold greater incidence of MI, and the risk of MI increases alongside poorer glycaemic control (de Jong et al., 2020). Likewise, people with T2D have greater risk of stroke; 3.0-6.5 times greater in women, and 2.0–3.0 times greater in men (Bejot & Giroud, 2010), with poorer rehabilitation outcomes and greater mortality (Piernik-Yoder & Ketchum, 2013). Moreover, people with T2D have 2-7 times greater risk of PAD, with a prevalence of 20-50% (Stoberock et al., 2021), associated with a greater risk of lower limb amputation and all-cause mortality.

Together with maturing screening and prevention strategies (see Section 1.4), the incidence of macrovascular disease in people with T2D declined between 1990 and 2010. For example, the frequency of MI in people with T2D declined from 150 events/10,000 people to 50 events/10,000 people, stroke declined from 110 events/10,000 people to 60 events/10,000 people, and limb amputation rates reduced from 60 events/10,000 people to 40 events/10,000 people in this timeframe (Beckman & Creager, 2016).

1.3.2 Microvascular complications

The main forms of microvascular disease in people with T2D are retinopathy, nephropathy, and neuropathy. Development of these complications is more closely associated with poor glycaemic control than in macrovascular disease, which is multifactorial and influenced by dyslipidaemia and hypertension (Gaede et al., 2008; UKPDS, 1998). Signs of these are often evident for years before symptoms, and patients typically present with irreversible disease. Therefore, screening and prevention for microvascular disease is essential.

Diabetes-related retinopathy is the most prevalent microvascular disease in people with T2D, affecting one-third of people, and is the leading cause of blindness in this population. The rate of retinopathy progressing to proliferative disease has declined over 30-40 years, due to improved interventions to prevent progressive disease at earlier stages (Harding et al., 2019; Liew et al., 2017). One study found 4.9% of people with newly-diagnosed T2D had retinopathy (4.2% background, 0.7% proliferative) (Bonora et al., 2020), implying important implications on the screening programme for people with T2D.

Diabetes-related nephropathy manifests with albuminuria and declining renal function over years, occurring in 25% of people with T2D. It is the commonest cause of end-stage renal disease (ESRD), diagnosed in 50% of people requiring renal replacement therapy (Tuttle et al., 2014). Screening and use of preventative pharmacotherapies for nephropathy is important. However, their impact to reduce ESRD varies geographically with mixed temporal trends, and the incidence of ESRD has remained steady at 25 events/10,000 people with T2D between 1990 and 2010 (Beckman & Creager, 2016).

The burden of such complications in people with T2D is unquestionable, though through the implementation of increasingly robust screening strategies and the targeted use of therapies to improve glycaemia and modify other risk factors, their prevalence is decreasing. Therefore, considering such an approach to address other increasingly recognised complications such as liver disease or others is of topical interest. This is expanded upon in section 1.4 and 1.5.

1.4 Screening and preventing complications in type 2 diabetes

Over the last 20-30 years, there has been expansion of national programmes to screen for risk factors and disease-related complications earlier to allow timely intervention to prevent disease progression (American Diabetes Association, 2024f, 2024g, 2024h; NICE, 2019, 2026). This has been associated with a reduction in the rates of most macrovascular and microvascular diseases in people with T2D both in the UK and internationally (Beckman & Creager, 2016).

1.4.1 Screening for vascular complications in type 2 diabetes

The American Diabetes Association (ADA) and NICE advocate an ‘annual review’ for people with T2D (American Diabetes Association, 2024b; NICE, 2026). This includes CVD risk assessment (e.g., QRISK3), review of glycaemic control, diabetes treatments, screening for neuropathy, PAD and retinal disease. Current screening guidelines in people with T2D are summarised in Table 1.3 (American Diabetes Association, 2024f, 2024g, 2024h; NICE, 2019, 2026). Screening should be commenced at diagnosis, as complications are frequently seen early in people with T2D (Bonora et al., 2020). There is good rationale to screening for cardiovascular risk factors and signs of microvascular and macrovascular disease in people with T2D. This is because the screening for these conditions satisfies the principles of screening proposed by Wilson and Junger (Wilson & Junger, 1968), presented in Table 1.4.

Table 1.3: Complication and risk factor screening in people with type 2 diabetes

Condition	Screening method
Diabetes-related retinopathy	Digital retinal imaging
Diabetes-related nephropathy	Urinary ACR and eGFR
Diabetes-related neuropathy	10g monofilament testing
PAD	Foot examination
Hypertension	BP monitoring
Dyslipidaemia	Lipid profile
Glycaemic control	HbA1c, CGM

Methods for risk factor and disease screening in people with T2D. Abbreviations: *ACR* albumin-creatinine ratio; *BP* blood pressure; *CGM* continuous glucose monitoring; *eGFR* estimated glomerular filtration rate; *PAD* peripheral arterial disease; *T2D* type 2 diabetes.

Table 1.4: Wilson and Junger principles of screening

Suggested requirements for the basis of any screening programme:	
(i)	the condition(s) represent an important health problem,
(ii)	the natural history of the condition(s) is well understood,
(iii)	there are recognisable latent and early stages of these conditions,
(iv)	there are appropriate tests with acceptable accuracy, sensitivity, and specificity,
(v)	the test is acceptable to the screening population,
(vi)	it should be clear on whom to treat as patients,
(vii)	there should be acceptable treatment available for those identified with the disease,
(viii)	any facilities required to provide further diagnostic tests and treatment should be available to the screening population,
(ix)	the cost of screening, further investigations, and treatment of patients with the identified conditions(s) should be economically balanced,
(x)	finding people with the condition(s) should be a continuing process.

The original principles of a screening programme proposed in 1968 (Wilson & Junger, 1968).

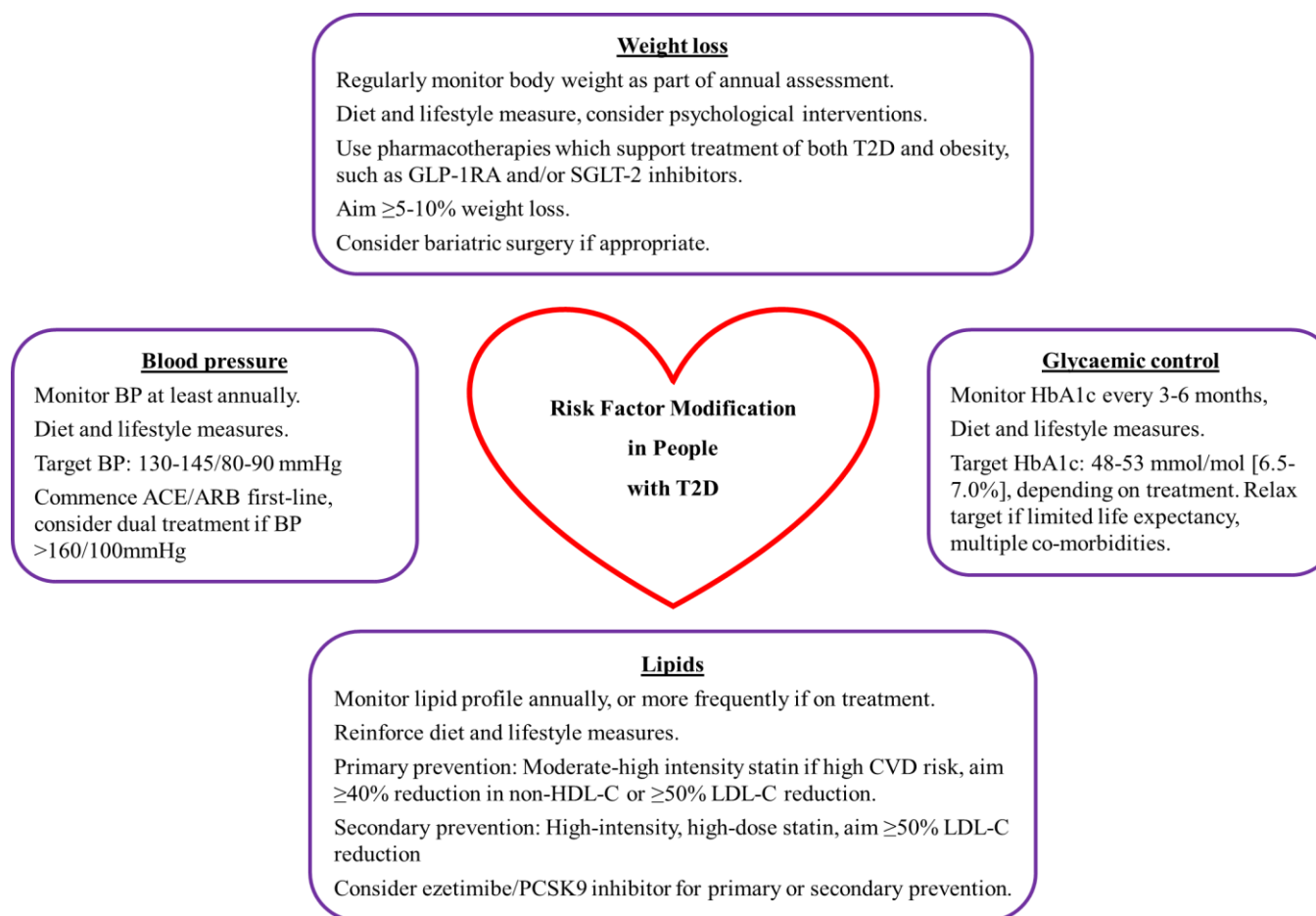
1.4.2 Prevention of vascular complications in type 2 diabetes

1.4.2.1 Risk factor modification

In the UK Prospective Diabetes Study (UKPDS), the greatest predictor of coronary artery disease in over 3,000 people with T2D was low-density lipoprotein (LDL) cholesterol. In descending order of impact on the occurrence of coronary artery disease, the UKPDS found that LDL cholesterol, systolic BP, HbA1c and smoking status were further modifiable risk factors (Turner et al., 1998). These findings in the late 1990s illustrated the need for holistic risk factor modification beyond glycaemic control, now a focus of care in modern practice (American Diabetes Association, 2024f; NICE, 2023a, 2026).

Current strategies to improve CVD risk in people with T2D are presented in Figure 1.2. These strategies include targeting a range of risk factors beyond glycaemic control, including dyslipidaemia, hypertension and obesity. The breadth of such an approach to management highlights the focus on complication prevention within contemporary clinical practice guidelines in managing people with T2D.

Figure 1.2: Cardiovascular risk factor modification for people with type 2 diabetes



ADA and NICE guidance for CVD risk management in people with T2D (American Diabetes Association, 2024d, 2024f; NICE, 2023a, 2023c, 2026). Abbreviations: *ACE* angiotensin-converting enzyme; *ARB* angiotensin receptor blocker; *BP* blood pressure; *CVD* cardiovascular disease; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *HbA1c* glycated haemoglobin; *HDL-C* high-density lipoprotein cholesterol; *LDL-C* low-density lipoprotein cholesterol; *SGLT-2* sodium glucose co-transporter-2; *T2D* type 2 diabetes; *PCSK9* proprotein convertase subtilisin/kexin type 9.

1.4.2.2 Cardiovascular risk modification and diabetes medications

Over the last 20 years, dedicated cardiovascular outcome trials (CVOTs) have been instigated to determine the cardiovascular safety of newer drug therapies in people with T2D. All drugs in the newer classes have been proven safe with respect to 3P-MACE (nonfatal stroke, nonfatal MI, and cardiovascular death) (Patoulas et al., 2021; Williams & Evans, 2020; Williams et al., 2021). Sub-analyses also demonstrate cardiovascular and other benefits, frequently resulting in further trials and label expansion for their use in other diseases.

The use of GLP-1RAs or SGLT-2 inhibitors in people with T2D in CVOTs reduce 3P-MACE, hospitalisation for heart failure, and all-cause mortality (Giugliano et al., 2021; Sattar et al., 2021). As such, NICE suggest their early use in people with a high-risk or history of CVD (NICE, 2026), and SGLT-2 inhibitors have been granted licence extensions to treat heart failure irrespective of underlying T2D (Hao & Zhang, 2022). Moreover, GLP-1RAs are associated with major weight loss, and both liraglutide and semaglutide have been granted licence extensions to treat obesity, irrespective of underlying T2D (Shi et al., 2022; Williams et al., 2020a). Conversely, pioglitazone and sulphonylureas associate with weight gain, so their use in people with heart failure or high CVD risk is limited (Bain et al., 2017; Liao et al., 2017).

People with diabetes-related nephropathy are treated with ACE inhibitors or ARBs to prevent nephropathy progression, alongside lipid-modifying therapies and other CVD risk management (Kidney Disease: Improving Global Outcomes Group, 2020). There is less high-level evidence such as primary outcome data from CVOTs to support diabetes interventions for microvascular complications of T2D, and associations are usually derived as secondary endpoints. Nonetheless, GLP-1RA use in CVOTs associates with reduced albuminuria progression and SGLT-2 inhibitor use reduces both albuminuria progression and the decline in estimated glomerular filtration rate (eGFR) (Williams et al., 2020b). Since the original CVOTs, dedicated renal outcome trials have observed reductions in progressive renal disease with the SGLT-2 inhibitors dapagliflozin (Heerspink et al., 2020), and empagliflozin (The EMPA-KIDNEY Collaborative Group, 2023), which have been granted licence extensions for chronic kidney disease (CKD). Therapeutic implications of diabetes complications are shown in Figure 1.3.

Given the success of the screening and preventative measures for CVD complications, there is growing demand for a similar approach for other complications, including SLD in people with T2D. Evidence supporting screening and prevention of SLD in people with T2D has developed over the last few decades and is discussed in section 1.5 and section 1.6.

Figure 1.3: The impact of diabetes-related complications on the choice of treatment



The diabetes related drug-class or drugs of choice for the prevention of complications in people with T2D including stroke, cardiovascular disease, obesity, diabetes-related nephropathy, and SLD. Abbreviations: *GIP* gastric inhibitory polypeptide; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *SGLT-2* sodium glucose co-transporter-2.

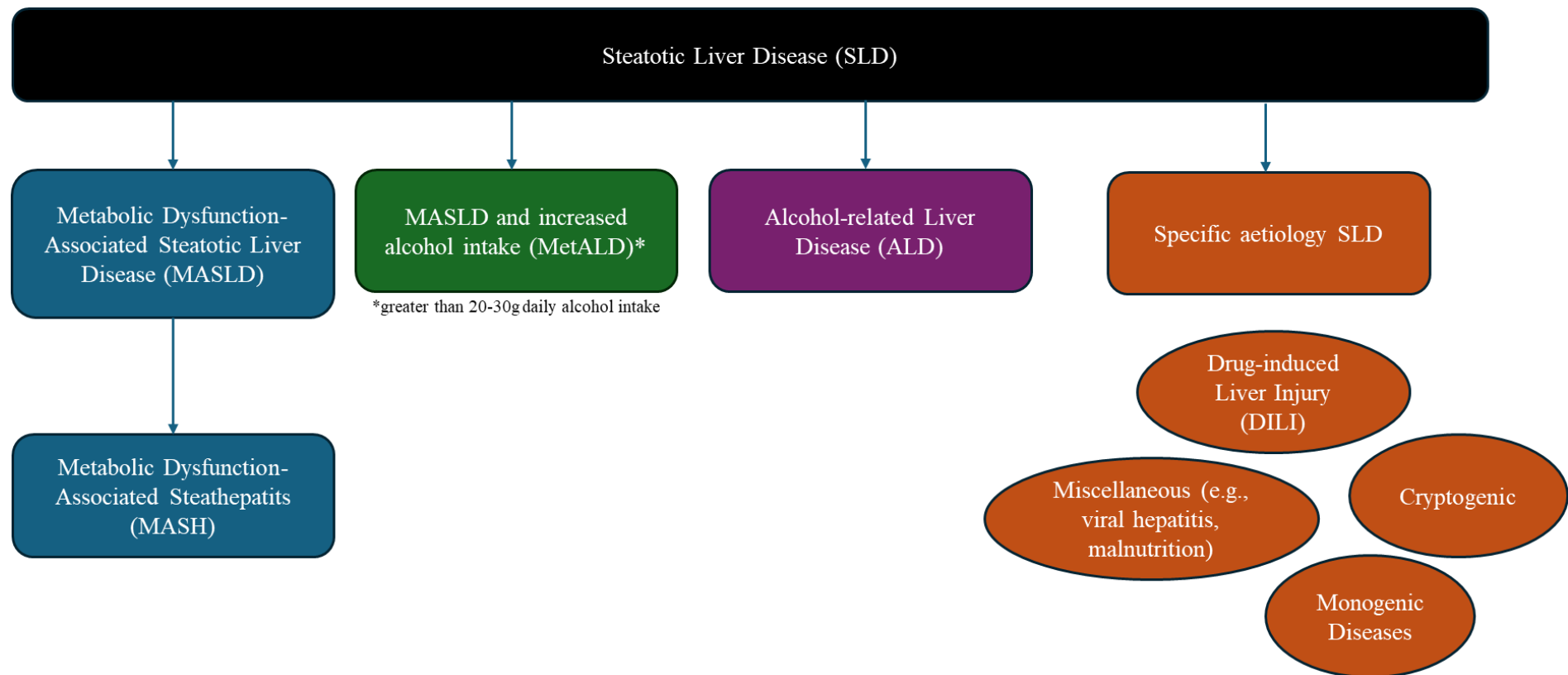
1.5 Steatotic liver disease in people with type 2 diabetes

There is growing recognition that people with T2D are at risk for non-vascular complications. Treating these complications may minimise excess CVD risk in people with T2D and improve other health outcomes (Tomic et al., 2022). There is significance attributed to the development of SLD because of its association with CVD, malignancy and liver-related morbidity and mortality (Lindenmeyer & McCullough, 2018), and partly because therapies for T2D reverse SLD and liver fibrosis, which may reverse the excess risk (Isaacs et al., 2025). Identifying people with SLD remains a problem given the lack of symptoms, and limitations of available non-invasive tests (Duell et al., 2022). Recent international consensus around changes in disease definition and classification have fuelled current interest (Rinella, Lazarus, et al., 2023).

1.5.1 The spectrum and definition of steatotic liver disease

The term SLD reflects a spectrum of conditions which result in the accumulation of liver fat. These include metabolic dysfunction-associated steatotic liver disease (MASLD), MASLD with increased alcohol intake (MetALD), alcohol-related liver disease (ALD), and others including drug-induced liver injury, and monogenic diseases, presented in Figure 1.4. Previously, MASLD was termed non-alcoholic fatty liver disease (NAFLD), until a change in international nomenclature was agreed in 2023 (Rinella, Lazarus, et al., 2023), now adopted extensively by various international groups (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023). Therefore, the term MASLD is used preferentially throughout the thesis in keeping with recent international consensus and for consistency, unless comparison between definitions is made. The change in nomenclature was taken for several reasons. Firstly, there were frustrations that NAFLD had no positive definition, as it was diagnosed after exclusion of other causes of excess liver fat, despite being the most common cause. Secondly, NAFLD was defined as $\geq 5\%$ hepatic fat accumulation, implicating the need for liver biopsy, despite improving imaging techniques using magnetic resonance imaging (MRI) and ultrasound, which is often inappropriate given the risk of injury and discomfort. Thirdly, the term “fatty liver disease” was felt to be stigmatising given most people with the disease live with excess bodyweight. Finally, in practice it is often assumed that the presence of excess liver fat is a benign feature related to excess total body fat. This resulted in clinicians often overlooking other causes of hepatic steatosis or not considering the presence of advanced liver fibrosis and these patients’ risk of CVD (Rinella, Lazarus, et al., 2023).

Figure 1.4: The sub-classification of steatotic liver disease



The sub-classification of SLD proposed in the recent Delphi consensus statement by Rinella and colleagues (Rinella, Lazarus, et al., 2023).

Within the recent updated disease definition and sub-classification consensus (Rinella, Lazarus, et al., 2023), there is now a positive definition of MASLD, making diagnosis easier. Patients with hepatic steatosis on imaging or biopsy who meet one or more cardiometabolic criteria shown in Table 1.6, without excess alcohol intake are diagnosed with MASLD. Those with presence of both one or more cardiometabolic criteria and alcohol excess, are diagnosed with MetALD. If the patient does not meet the cardiometabolic criteria or have excess alcohol intake, further investigation for alternative aetiologies such as drug-induced liver injury, monogenic forms of SLD or cryptogenic SLD may be warranted, including liver biopsy.

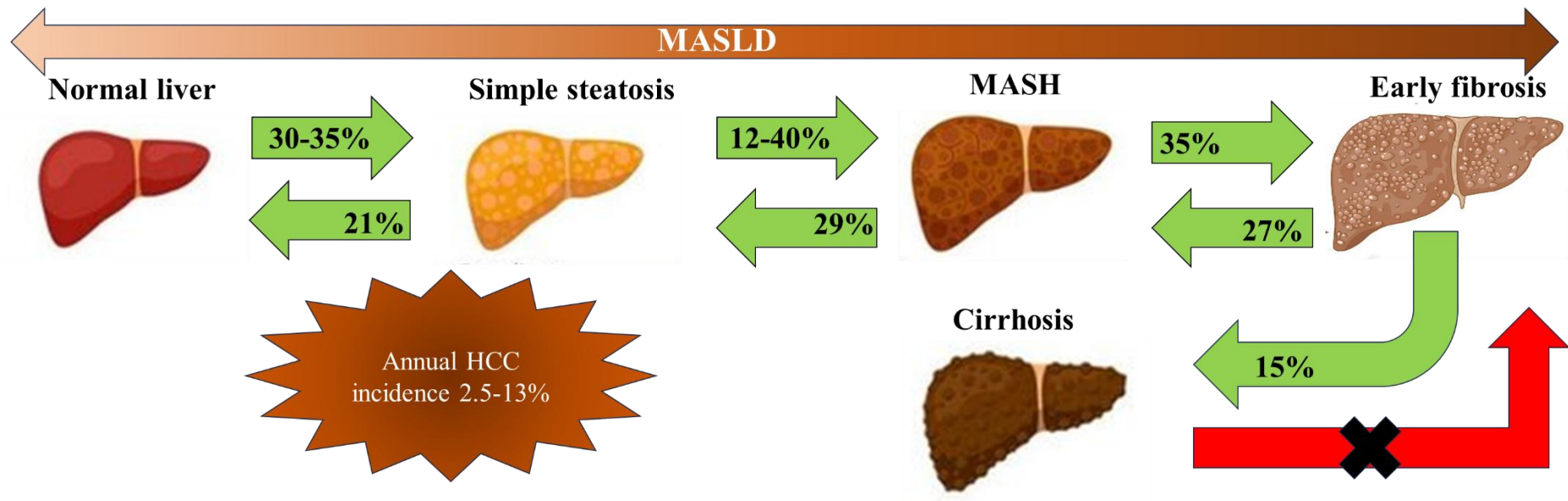
Table 1.5: Cardiometabolic criteria to diagnose MASLD or MetALD

At least 1 of the 5 criteria must be met:	
1.	BMI ≥ 25.0 kg/m ² (≥ 23.0 kg/m ² in Asian people), or waist circumference >94 cm in men or >80 cm in women.
2.	Presence of pre-diabetes or T2D.
3.	Blood pressure $\geq 130/85$ mmHg or prescribed hypertension treatment.
4.	Plasma triglycerides ≥ 1.7 mmol/L, or prescribed lipid-lowering treatment.
5.	Plasma HDL-cholesterol ≤ 1.0 mmol/L, or prescribed lipid-lowering treatment.

The cardiometabolic criteria used to diagnose MASLD or MetALD. Abbreviations: *BMI* body mass index; *HDL* high-density lipoprotein.

There are different stages of MASLD, ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and advanced fibrosis or cirrhosis which associate with the risk of decompensated liver disease, hepatocellular carcinoma (HCC), and cardiovascular mortality. Importantly, whilst HCC risk is greatest in those with cirrhosis, it can occur at any stage of MASH and should be considered in all patients with MASLD. Simple hepatic steatosis is defined as excess liver fat in the absence of liver injury (i.e., hepatocyte inflammation, cell death or fibrosis), whilst MASH is characterised by excess liver fat with signs of hepatocellular inflammation, severe cellular injury (e.g., ballooning) and often hepatic fibrosis. Finally, liver cirrhosis is defined as stage 4 hepatic fibrosis, discussed in section 1.5.2. Often, MASLD progresses from simple steatosis to MASH and may reverse to simple steatosis with treatment. However, regression from cirrhosis to MASH or simple steatosis is less likely, though increasingly novel pharmacotherapies demonstrate promise in this area. The spectrum of disease in MASLD is shown in Figure 1.5.

Figure 1.5: The spectrum of MASLD



The stages of MASLD ranging from simple hepatic steatosis to MASH, early fibrosis and cirrhosis. The green arrows indicate that progression or regression from each of the various stages of MASLD is possible with progression or regression rates inside the arrow (Le et al., 2023; Singh et al., 2015). The red arrow indicates that regression from cirrhosis to MASH is not possible. Abbreviations: *HCC* hepatocellular carcinoma; *MASLD* metabolic dysfunction-associated steatotic liver disease; *MASH* metabolic dysfunction-associated steatohepatitis.

Identifying risk factors for MASLD may identify those who warrant further investigation or changes in therapy to minimise disease progression. These include metabolic, drug-related, and genetic risk factors (Duell et al., 2022; Kolaric et al., 2021; Vincent et al., 2020), summarised in Table 1.6.

Table 1.6: Risk factors for developing MASLD

Metabolic	Drugs	Genetic
Obesity	Alcohol	
Visceral adiposity	Amiodarone	Family history
Prediabetes & diabetes	Corticosteroids	<i>GCKR</i>
Dyslipidaemia (high triglycerides, low HDL-C)	Methotrexate	<i>HSD16B13</i>
Chronic kidney disease	Tamoxifen	<i>MBOAT7</i>
Hypertension	Tetracyclines	<i>PNPLA3</i>
Lipodystrophy	NSAIDs	<i>TM6SF2</i>
	Omeprazole	

Metabolic, drug-related, and genetic factors for MASLD (Duell et al., 2022; Kolaric et al., 2021; Vincent et al., 2020). Abbreviations: *GCKR* glucokinase regulator; *HDL-C* high-density lipoprotein cholesterol; *HSD16B13* hydroxysteroid 17-beta dehydrogenase 13; *MBOAT7* Membrane Bound O-Acyltransferase 7; *NSAIDs* non-steroidal anti-inflammatory drugs; *PNPLA3* patatin-like phospholipase domain-containing 3; *TM6SF2* transmembrane 6 superfamily member 2.

1.5.2 Diagnosis and clinical presentation of MASLD

The diagnosis of MASLD is often incidental on ultrasound, computerized tomography (CT) scan, or MRI scan undertaken for another reason. Most people with MASLD are asymptomatic and only present when MASLD has progressed to advanced fibrosis with decompensated liver disease. Decompensated liver disease presents as abdominal distension, bruising, confusion, fatigue, jaundice, leg swelling, or weight loss (Sharma & Arora, 2020). Nevertheless, most with MASLD, including those with MASLD cirrhosis may never present clinically, meaning interventions to minimise progressive liver disease or surveillance for complications such as CVD, decompensated liver disease or HCC are too late to have an impact on disease outcomes (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

Once hepatic steatosis is identified, it is important to assess that person for risk of advanced fibrosis (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; NICE, 2016, 2023b; Rinella, Neuschwander-Tetri, et al., 2023). Guidelines advocate blood tests for risk-scoring systems such as the NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) score, or the aspartate aminotransferase (AST) to platelet ratio index (APRI) to identify people with MASLD at risk

of advanced liver fibrosis. In the UK, NICE advocate the enhanced liver fibrosis (ELF) test to identify advanced hepatic fibrosis. The ELF test measures three markers of fibrosis (hyaluronic acid, procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)) to generate a fibrosis risk score. NICE suggest a score over 10.51 indicates high-risk of advanced fibrosis warranting hepatology referral, consideration of a HCC surveillance programme and preventative measures for progressive liver disease. People with MASLD and an ELF test score less than 10.51 are unlikely to have advanced fibrosis and should have a repeat test every three years (NICE, 2016, 2023b). However, ELF test availability varies around the UK, despite this guideline being published in 2016. This variability is likely a consequence of how different healthcare systems implement changes in practice. For example, the ELF test requires a specialised assay and the analyser is not routinely available, thereby requiring the test to be commissioned externally in some areas which may have be too expensive. Moreover, clinicians may prefer fibroscan as a second-line test based on their experience, which has been supported in subsequent international guidance as an alternative to the ELF test since the NICE recommendation. Should the ELF test be unavailable, alternative scoring tools such as the NFS, FIB-4 score, or APRI should be used. Additionally, NICE suggest that further tests to exclude alternative causes of liver disease should be undertaken in those identified with MASLD. The tests which NICE suggest undertaking are summarised in Table 1.7.

Table 1.7: Evaluation of MASLD

Variable	Tests recommended
Degree of MASLD fibrosis	Albumin
	ALT
	AST
	ELF test
	Platelet count
	Clotting profile
Metabolic causes	Alpha-1-antitrypsin deficiency
	Caeruloplasmin (if younger than 40 years)
	Ferritin
	HbA1c
	Immunoglobulin screen and IgA
	Lipid profile
	Thyroid function tests
Viral causes	Urea & electrolytes
	Hepatitis B and C serology
Autoimmune causes	ANA
	ASMA

NICE recommendations in the evaluation of people identified with MASLD (NICE, 2016). Abbreviations: *ALT* alanine aminotransferase; *ANA* Anti-nuclear antibodies; *ASMA* Anti-smooth muscle antibodies; *AST* aspartate aminotransferase; *ELF* enhanced liver fibrosis; *HbA1c* glycated haemoglobin; *IgA* immunoglobulin A; *MASLD* metabolic dysfunction-associated steatotic liver disease.

Whilst blood biomarkers for advanced fibrosis predict patients likely to benefit from hepatology review, these are not diagnostic, and further imaging is typically needed. The American Association of Clinical Endocrinology (AACE), American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and European Association for the Study of Diabetes (EASD) recommend transient elastography (TE) (Fibroscan) or possibly MRI-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) to quantify hepatic steatosis and fibrosis (Cusi et al., 2022; EASL-EASD-EASO, 2024; EASL., 2021; Rinella, Neuschwander-Tetri, et al., 2023). The clinical picture generated by the clinical history, examination, biochemical findings, and imaging is typically enough to arrive at a diagnosis. However, liver biopsy may be needed in patients in whom there are competing aetiologies (Table 1.7), patients with unclear risk of

advanced fibrosis or HCC, and to select patients for clinical trials (Rinella, Neuschwander-Tetri, et al., 2023). The advantage of biopsy is that it permits definitive diagnosis. The grade and stage of MASLD are reported by the Brunt classification. Here, the NAFLD activity score (NAS) and fibrosis stage (0-4) are determined, with the NAS comprising scores related to steatosis (0-3), lobular inflammation (0-3), and ballooning (0-2) to generate a total score ranging 0-8 (Brunt et al., 1999; Kleiner et al., 2005). This is presented in Table 1.8.

Table 1.8: Brunt classification in the histopathology of MASLD

Component	Definition	Score
NAFLD activity score	<5%	0
	5-33%	1
	33-66%	2
	>66%	3
	No foci	0
	<2 foci/field	1
	2-4 foci/field	2
	>4 foci/field	3
	None	0
	Few balloon cells	1
	Prominent ballooning	2
Fibrosis	Perisinusoidal fibrosis	1
	+ Portal fibrosis	2
	+ Bridging fibrosis	3
	Cirrhosis	4

The Brunt classification in MASLD. The NAFLD activity score is generated by the sum of steatosis, lobular inflammation and ballooning scores, and fibrosis stage described separately (Brunt et al., 1999; Kleiner et al., 2005). Abbreviation: *NAFLD* non-alcoholic fatty liver disease.

Unfortunately, many identified with hepatic steatosis do not have further assessment to determine their risk of fibrosis (Mari et al., 2019; Williams, Krishnamoorthy, et al., 2022). This is frequently a result of a lack of clinician knowledge, as hepatic steatosis is common and may be misidentified as a benign feature (Mari et al., 2019). Investigations to determine the extent of fibrosis and cardiovascular risk are needed to inform prevention strategies (EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023).

Despite advances in blood biomarkers to predict advanced fibrosis and the improving accuracy of imaging techniques for hepatic steatosis and fibrosis, tests remain imperfect (Cusi et al., 2022; Duell et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Their validation is frequently in populations without MASLD or risk factors for MASLD. Consequently, the gold standard investigation for diagnosis of MASLD remains liver biopsy, though usually reserved for cases of diagnostic doubt. However, liver biopsy itself is limited by sampling error, cost, inter and intra-observer variability, and complications of the procedure (Sumida et al., 2014). Therefore, reliable non-invasive measures to assess hepatic steatosis and fibrosis in MASLD remain highly sought, discussed in Section 1.6.

1.5.3 Epidemiology of MASLD

1.5.3.1 Epidemiology of MASLD in global populations

Rigorous epidemiological studies investigating the prevalence of MASLD since changes in disease definitions are lacking, though one study found that within datasets including around 19,000 individuals with NAFLD, 99.8% met the MASLD criteria (Younossi, Paik, et al., 2024). Therefore, previous epidemiological studies exploring NAFLD remain useful when discussing MASLD, and many consider the terms interchangeable. However, changes in disease definition and nomenclature highlight the variability of epidemiological studies prior to 2023, given the varied approaches used to previously define MASLD. Some studies used liver biopsy, whilst others relied upon imaging studies, and some used biochemistry alone. Non-invasive tests are not as reliable to establish the degree of inflammation or fibrosis needed to stage MASLD (Golabi et al., 2016). However, as biopsy is not always appropriate, its inclusion to define MASLD limits studies when drawing comparisons with real populations (Sumida et al., 2014). This results in some variation in the prevalence of MASLD, based on the methodologies used (Araujo et al., 2018). Moreover, MASLD prevalence is affected by the relative prevalence of risk factors, resulting in variable geographical prevalence (Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024; Younossi et al., 2025). These factors, amongst others, result in uncertainty when resource planning for services in the UK and internationally.

Globally, the prevalence of MASLD was estimated at 30.1% in one meta-analysis of 92 studies, which included 9.4 million people (Younossi, Golabi, et al., 2023). Here, the prevalence of MASLD was greatest in Latin America region, and least in Europe. The global prevalence of MASLD by global region is summarised in Table 1.9. In the same meta-analysis, prevalence of MASH was estimated at 5.3% worldwide, ranging from 4.0% in Europe to 7.1% in Latin America (Younossi, Golabi, et al., 2023).

Meta-analyses have observed several risk factors for MASLD. Firstly, risk increases with age, observed in around 22.4% of people aged 30-39 years and 34.0% of people aged 70-79 years. Features of the metabolic syndrome increase the risk of developing MASLD and MASH. In people with NAFLD or non-alcoholic steatohepatitis (NASH), the prevalence of obesity was 51.3% and 81.8%, T2D was 22.5% and 43.6%, dyslipidaemia was 69.2% and 72.1%, and hypertension was 39.3% and 68.0% (Younossi, Koenig, et al., 2016). Metabolic syndrome was diagnosed in 42.5% and 70.7% of people with NAFLD and NASH highlighting the association between these diseases. In European studies, 75.3% of people with the metabolic syndrome had NAFLD, versus 17.9% of people who did not have metabolic syndrome (Cholongitas et al., 2021). Of course, given the use of metabolic syndrome variables to now diagnose MASLD, prevalence rates of these features may differ. Worryingly, global prevalence of MASLD is increasing in tandem with T2D and obesity and will likely emerge as the leading cause of end-stage liver disease in the next 10-30 years (Younossi et al., 2018).

Table 1.9: Global prevalence of MASLD in the general population

Region	MASLD prevalence (%)
Asia Pacific	28.0 [24.7-31.6]
Australasia	31.2 [25.9-37.1]
East Asia	29.7 [26.0-33.8]
Latin America	44.4 [30.7-59.0]
Middle East and North Africa	36.5 [28.6-45.2]
North America	31.2 [25.9-37.1]
South Asia	33.8 [22.9-46.8]
Western Europe	25.1 [20.6-30.3]
Overall	30.1 [27.8-32.3]

Global prevalence of MASLD in unselected populations presented by region (Younossi, Golabi, et al., 2023). Data presented as prevalence (%) [95% confidence interval]. Abbreviations: *MASLD* metabolic dysfunction-associated steatotic liver disease.

In Wales, there is a similar rising burden of liver disease. Over the last 20 years, there has been a 3.6-fold increase in liver disease incidence, driven by a 10-fold greater incidence of MASLD, whilst ALD incidence is stable (Pembroke et al., 2023). Around 21.6% of people in Wales have MASLD and with greater MASLD incidence compared with ALD since 2014 (Pembroke et al., 2023). The most likely reasons for the increased prevalence including rising prevalence of risk factors such as T2D and obesity, and improved detection, awareness and clinical coding. However, since the new entity of MetALD was described, it would be interesting to observe the prevalence of MASLD, MetALD and ALD in this population. In Wales, there has been a three-fold increase in cirrhosis, decompensated liver disease, HCC, and all-cause mortality over 20 years, and liver-related mortality has doubled (Pembroke et al., 2023).

1.5.3.2 Epidemiology of MASLD in populations with type 2 diabetes

One meta-analysis of 80 studies reported that in people with T2D, the mean global prevalence of MASH was 66.4%, significant fibrosis 40.8% and advanced fibrosis 15.5% (Younossi, Golabi, et al., 2024), double that of the general population. Like the differing trends in global MASLD epidemiology, there is geographical variation in MASLD prevalence in T2D. In people with T2D, European populations report the greatest and African populations describe the least MASLD prevalence. The risk of MASLD in people with T2D in African studies was less than half than in people with T2D in European studies. This may reflect differing risk factors such as dyslipidaemia, hypertension and obesity, or differing tests used to diagnose MASLD. Regional prevalence of MASLD in people with T2D is presented in Table 1.10.

Table 1.10: Global prevalence of MASLD in people with type 2 diabetes

Region	MASLD prevalence (%)
Africa	53.1 [26.1–78.4]
Asia Pacific	53.2 [41.1–64.9]
Australasia	68.4 [59.6–76.1]
East Asia	60.0 [55.3–64.4]
Eastern Europe	80.6 [75.7–84.7]
Latin America	51.4 [35.2–67.2]
Middle East	71.2 [62.2–78.8]
North America	68.4 [59.6–76.1]
South Asia	61.0 [55.2–66.5]
Western Europe	68.6 [64.1–72.8]
Overall	55.5 [47.3–63.7]

Global prevalence of MASLD in people with T2D (Younossi, Golabi, et al., 2024). Data presented as prevalence (%) [95% confidence interval]. Abbreviations: *MASLD* metabolic dysfunction-associated steatotic liver disease.

Most studies associating MASLD and T2D are retrospective and use inconsistent definitions of MASLD, limiting generalisability. However, there are prospective studies exploring MASLD prevalence in people with T2D using non-invasive tests. One pilot study in the USA using MRI-PDFF and MRE observed that of 100 people with T2D in primary care without previous liver disease, 65% had MASLD and 7% had advanced fibrosis, of which one had undiagnosed HCC (Doycheva et al., 2016). People with MASLD were younger (57.9 vs 63.1 years), had greater BMI (32.5 vs 27.6 kg/m²), and more likely to be diagnosed with metabolic syndrome (84.6 vs 40.0%) (Doycheva et al., 2016). A Croatian study of 679 adults with T2D used TE to screen for MASLD. The study reported 83.6% had elevated TE-controlled attenuation parameter (CAP) indicative of moderate-severe liver steatosis, and 39.5% had elevated TE-liver stiffness measurement (LSM) indicative of moderate-to-advanced fibrosis (Mikolasevic et al., 2020). A Spanish study of 104 people with T2D without known liver disease observed the TE-LSM demonstrated advanced fibrosis in 20%, and severe steatosis in over 50% (Martinez-Ortega et al., 2022). A prospective study in the USA used MRI-PDFF, MRE, and TE to assess for MASLD in 501 people with T2D aged greater than 50 years in primary or secondary care (Ajmera, Cepin, et al., 2022). The study observed 65.3% had MASLD, 14.0% had advanced fibrosis and 5.9% had cirrhosis, of which in the latter group two participants had HCC and one had gallbladder adenocarcinoma. People with more advanced fibrosis had greater BMI, frequency of insulin use, liver enzymes, and lower serum albumin, and HDL-C (Ajmera, Cepin, et al., 2022).

Studies investigating MASLD in primary care cohorts have also been described in the UK. The earliest was taken in 2012, in over 1,100 patients in Birmingham. Participants were patients with incidental abnormal liver tests, and of these 26.3% were diagnosed with MASLD, and 7.6% of these subjects had a raised FIB-4 indicative of advanced fibrosis (Armstrong et al., 2012). Later, Mansour and colleagues screened 467 participants with T2D in primary care using the FIB-4 test, and 18.5% had a score indicative of advanced fibrosis. Of those who subsequently had TE to evaluate for fibrosis, 43.1% had a TE-LSM score supporting advanced fibrosis, and 22.4% had a score supporting cirrhosis (Mansour et al., 2021). Most recently, Forlano and colleagues observed that in 300 participants with T2D in primary care, 17%, 11% and 3% had clinically significant fibrosis, advanced fibrosis, and cirrhosis due to MASLD (Forlano et al., 2024). There are no prospective data for MASLD prevalence in people with T2D in Wales, or secondary care in the UK. In Swansea, one study using biochemistry data

observed 60% of people with T2D in secondary care had moderate risk of advanced hepatic fibrosis defined by the NFS or FIB-4 score (Williams, Krishnamoorthy, et al., 2022).

Most studies exploring the relationship between T2D and MASLD imply MASLD is increased by T2D, but this relationship is bidirectional (Targher et al., 2021; Tomah et al., 2020). Whilst T2D does increase MASLD prevalence and acceleration to advanced fibrosis (Younossi et al., 2018; Younossi, Golabi, et al., 2024), the reverse is also true as MASLD increases T2D risk two-fold, independent of other metabolic associations (Targher et al., 2021; Tomah et al., 2020). People with MASLD have a 2.2 greater risk of developing T2D, and people with increasing degrees of steatosis and fibrosis have greater T2D risk, independent of age, sex, and BMI (Mantovani et al., 2018; Mantovani, Petracca, et al., 2021).

The economic burden of MASLD is growing. One study estimated that 21.9% and 4.1% of the UK population had a diagnosis of MASLD and MASH in 2016, which are projected to increase to 24.7% and 5.5% by 2030. Associated with this is the increasing burden of end-stage liver disease, including cirrhosis, decompensated liver disease and HCC (Estes et al., 2018). Longer-term studies are needed to better understand the excess CVD and liver-related morbidity and mortality associated with MASLD. One study estimated the total economic cost of MASLD in the UK at £2.3–£4.2 billion in 2018 (Morgan et al., 2021). The cost of MASLD is estimated at €35 billion across Germany, France, Italy, and the UK, whilst in the USA the estimated cost is over \$100 billion (Younossi, Blissett, et al., 2016). A more recent analysis concluded the cost of managing people with MASLD was two-fold compared with age-matched controls without MASLD and increased linearly with hepatic fibrosis. MASLD was observed to cause the greatest impact on disability-adjusted life years compared with other liver diseases globally (A. M. Allen et al., 2023). Naturally, people with MASLD and CVD generate greater economic burden than those without cirrhosis or CVD (Sayiner et al., 2017). Strategies to prevent, delay or reverse MASLD to diminish fibrosis risk may mitigate excess CVD and have major economic implications.

1.5.3.3 The impact of deprivation on MASLD prevalence

It is well-established that socioeconomic factors associate with health outcomes, and measures of deprivation correlate with the risk of all-cause or cardiovascular mortality, and cancer-related outcomes. These adverse health outcomes are associated with unhealthy lifestyle factors which are more frequently seen in those with greater deprivation (Foster et al., 2023). Likewise, risk of developing MASLD is significantly greater in individuals from lower socioeconomic

backgrounds, and in migrant populations. This is attributed to several social factors including systemic barriers limiting access to healthcare, poor diet quality and less physical activity compared with individuals in higher-income populations (Lorek et al., 2025).

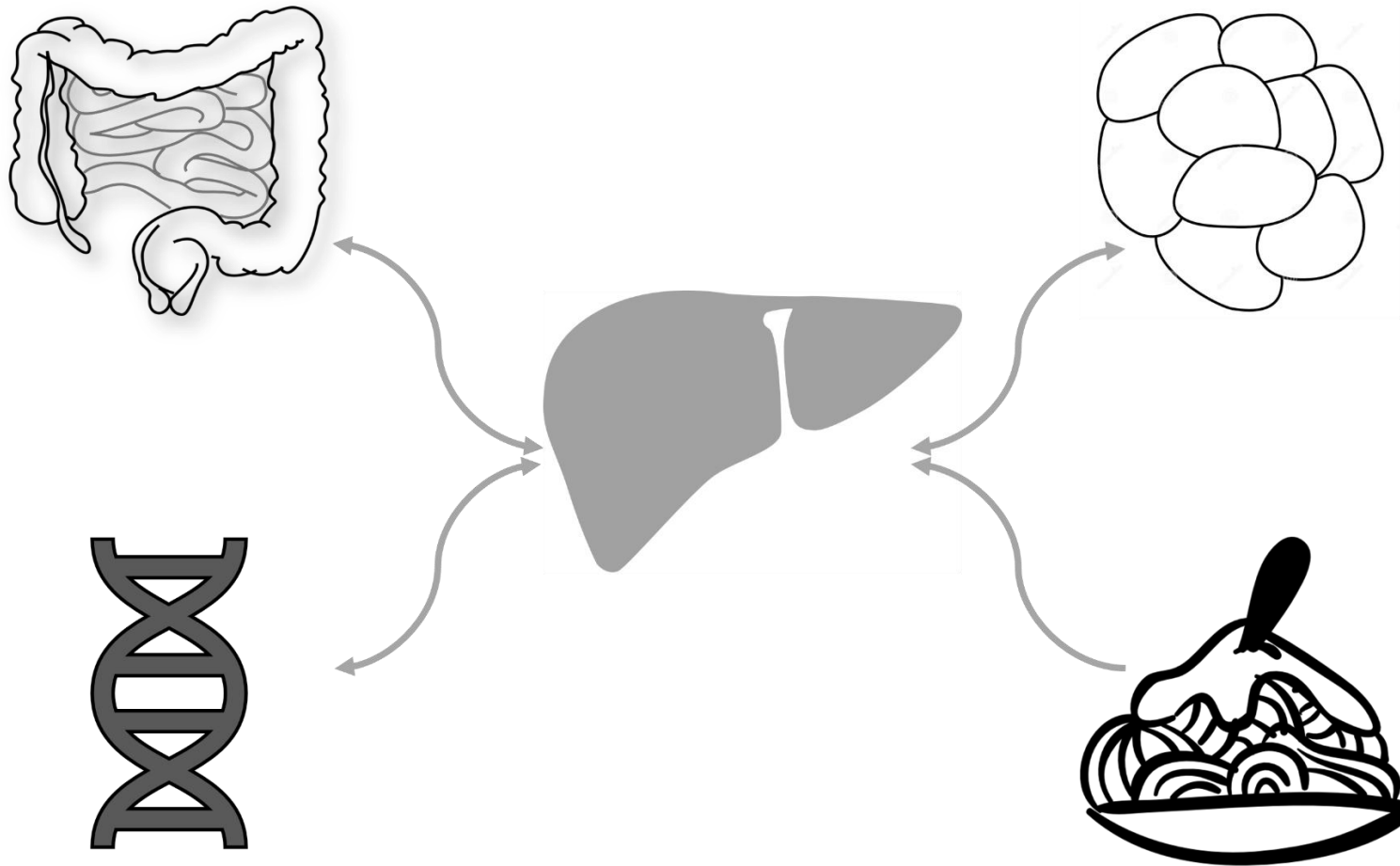
A prospective study included 304 patient with MASLD in the USA, and observed that those with liver cirrhosis were significantly more likely to live in a deprived area, and to have lower self-reported vegetable intake and exercise. Poorer health-related quality of life was seen in those with greater deprivation, history of CVD and a TE-LSM over 8 kPa (Czapla et al., 2025). Likewise, a retrospective study of around 70,000 patients with MASLD observed that those living in the most disadvantaged areas had greater risk of cirrhosis, several cardiovascular comorbidities, T2D, hypertension, mortality and liver-related events (Faulkner et al., 2025).

Addressing such inequalities in practice is essential to support patients to reduce their own risk. Further work is needed through changes in national policy to address this, improving equitable healthcare access, supporting lifestyle modifications, and innovative approaches to diminish risk factors attributed to MASLD and poor outcomes (Lorek et al., 2025).

1.5.4 Pathophysiology of MASLD

The pathophysiological processes underpinning MASLD are complicated, with numerous mechanisms at play (Tilg et al., 2021; Vincent et al., 2020; Yu et al., 2016). There are several distinct MASLD phenotypes based on differing risk factors and risk of CVD and liver-related complications. One study described five MASLD subtypes based on varying pre-existing risk factors and CVD and liver-related morbidity or mortality (Vandromme et al., 2020). Originally, MASLD was considered to develop in a ‘two-hit’ process of firstly intrahepatic triglyceride accumulation increasing hepatic susceptibility to a ‘second hit’ of proinflammatory cytokines, oxidative stress or gut-derived endotoxins leading to inflammation, fibrosis and hepatocellular death (Day & James, 1998). However, this approach is challenged by the more recent ‘multiple-parallel’ hits theory in which multiple stressors act synergistically (e.g., genetic, environmental, dietary factors) to induce liver fat accumulation, and subsequent hepatic inflammation develops progressively (Tilg & Moschen, 2010). Accumulation of hepatic triglycerides may be a protective mechanism (Tilg et al., 2021; Yu et al., 2016). This theory has continued to mature over the last decade with better understanding of adipose tissue dysfunction, gut microbiome, dietary factors, and genetic pathways (Tilg et al., 2021). Most recently, associations between intrahepatic hypothyroidism and MASLD progression have raised further mechanisms underpinning the disease and opened novel therapeutic targets (Kuchay et al., 2024). The multiple-parallel hits theory is presented in Figure 1.6 and expanded upon below.

Figure 1.6: The multiple-parallel hits aetiology of MASLD



The multiple parallel hits theory in MASLD development involves several synergistic ‘hits’ which accelerate the MASLD progression (Tilg et al., 2021; Tilg & Moschen, 2010). The major factors involved include adipose tissue inflammation, the gut microbiome, dietary factors, and genetic influences which interact synergistically.

A major player in the development of MASLD is adipose tissue, comprising visceral and subcutaneous components which interact with the liver for lipid and glucose homeostasis, and become dysfunctional in obesity or T2D (Siklova et al., 2024). Here, adipose tissue is characterised by increased expression of inflammatory cells, cytokines, and chemokines, which impair its ability to mobilise lipids (E. Lee et al., 2023; Tilg et al., 2021). Expression of genes which regulate adipose tissue inflammation correlate with liver inflammation in MASLD (du Plessis et al., 2015). The situation is driven by systemic and hepatic IR. Systemic IR causes hyperinsulinaemia, and the associated hepatic lipogenesis generates a systemic inflammatory response, exacerbating adipose tissue inflammation. This manifests through adipose tissue inflammation hastening lipolysis and therefore the influx of hepatic free fatty acids to promote hepatic steatosis and inflammation (Bell et al., 2012; E. Lee et al., 2023; Tilg et al., 2021). Hepatic pathways for lipid metabolism and storage become overwhelmed, resulting in accumulation of hepatotoxic lipids and a pro-inflammatory and pro-fibrotic state (Azzu et al., 2020). Measures of IR correlate with hepatic steatosis, inflammation and fibrosis with insulin-sensitising medicines such as pioglitazone improving hepatic inflammation and steatosis (Bell et al., 2012). There is uncertainty whether such pharmacotherapies act in adipose tissue, the liver, or both, to improve IR. Pharmacotherapies for MASLD are discussed below.

There is an emerging role for the gut microbiome in MASLD (Tilg et al., 2021). Bacteria-derived endotoxins from *Escherichia coli* demonstrated in MASH livers and the general circulation associate with measures of inflammation (Carpino et al., 2020; Tilg et al., 2021). Studies identify differing patterns of gut microbial changes in people with MASLD (Boursier, Mueller, et al., 2016; Loomba et al., 2017; Zhu et al., 2013). The causative nature of the endotoxin-producing *Enterobacter cloacae*, *Escherichia coli*, and *Klebsiella pneumoniae* were supported when they were observed to promote MASLD in mice (Fei et al., 2020). Similarly, bacterial-derived faecal metabolites which associate with hepatic steatosis in women with obesity induce hepatic steatosis in mice following faecal transfer (Hoyles et al., 2018). Treatments such as probiotics, prebiotics, faecal microbiota transfer, or specific diets which affect the gut microbiome modulate MASLD risk or improve resolution in those with earlier disease, warranting investigation (Aron-Wisniewsky et al., 2020).

The impact of dietary factors on the MASLD progression may be multifactorial, in that diet affects the gut microbiome, hepatic glucose and lipid metabolism. Additionally, given the varying diet of people around the world, dietary factors may explain regional differences in MASLD epidemiology even in people with similar comorbidities. Some foods such as red or

processed meats, fructose, saturated fatty acids, and alcohol seen in Western diets are pro-inflammatory and increase MASLD progression (Berna & Romero-Gomez, 2020; Tilg et al., 2021). Foods such as low-carbohydrate or Mediterranean diets reduce hepatic steatosis (Berna & Romero-Gomez, 2020; Mardinoglu et al., 2018; Meslier et al., 2020). Therefore, this forms part of the lifestyle measures which remain the basis of current MASLD management strategies (Duell et al., 2022; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023).

Genetic factors, including polymorphisms and epigenetic changes associate with MASLD risk (Martin et al., 2021; Yu et al., 2016). The most significant polymorphism is in the Patatin-Like Phospholipase Domain Containing 3 (*PNPLA3*) gene expressed in the liver, adipose tissue, and retina, functioning to catalyse the hydrolysis of triglycerides. Homozygous carriers of the *PNPLA3*-I148M variant are at risk of MASLD, including younger diagnosis, disease severity, and HCC (Martin et al., 2021). Moreover, people with this genetic variant do not typically present with metabolic syndrome. Other genetic polymorphisms have been since identified to associate with MASLD, including the transmembrane 6 superfamily member 2 (*TM6SF2*), membrane bound O-acyltransferase domain containing 7 (*MBOAT7*), glucokinase regulatory protein (*GKRP*), and hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), amongst others (Martin et al., 2021; Yu et al., 2016). The impact of epigenetic changes in the presentation and risk of MASLD are emerging, though several factors including DNA methylation, histone modification, and activity of microRNAs are implicated in altered hepatocellular metabolism. The clinical relevance of these changes remains to be elucidated (Buzzetti et al., 2016).

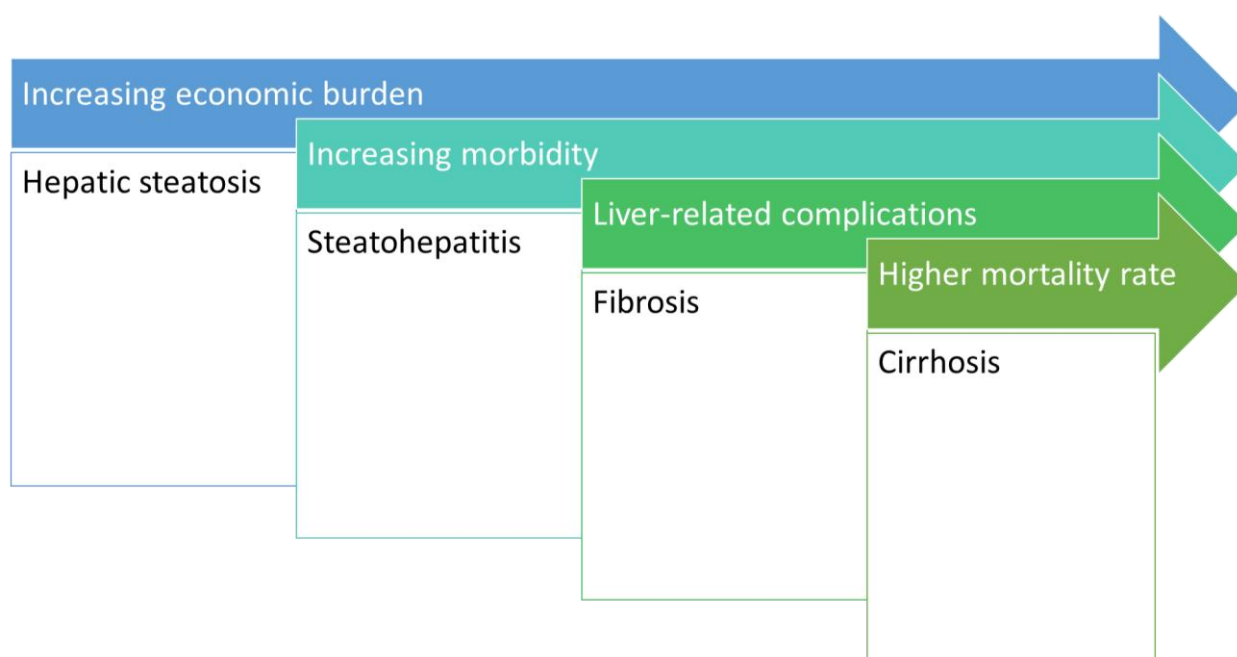
Given recent developments in the pharmacotherapeutic options for MASLD with GLP-1RAs, and associations between T2D and its treatments with MASLD, there is developing interest in how GLP-1 and other incretin hormones are implicated in MASLD (Vincent et al., 2020). There are GLP-1 receptors in the liver, and exogenous administration of GLP-1 or its analogues is associated with improved hepatic and adipose tissue insulin sensitivity, enhancing insulin-driven suppression of lipolysis and *de novo* hepatic lipogenesis (DNHL). Administration of GLP-1RAs increase serum adiponectin and decrease serum leptin which reduces DNHL (Armstrong, Hull, et al., 2016). The mechanism by which GLP-1RAs reduce inflammation and DNHL may be indirect through a combination of reduced systemic inflammation and improved control of risk factors such as glycaemic control, hypertension and obesity (Vincent et al., 2020). Though, given that the expression of the GLP-1 receptor is decreased in people with MASH (Svegliati-Baroni et al., 2011), direct mechanisms probably exist and GLP-1RAs represent a novel option for MASLD (Newsome et al., 2021; Vincent et al., 2020).

People with MASLD have intrahepatic hypothyroidism, and people with systemic hypothyroidism have greater MASLD risk (Kuchay et al., 2024). The liver expresses thyroid hormone- β receptors (TR- β), whilst thyroid hormone- α receptors (TR- α) are expressed more systemically (Nappi et al., 2022). Activation of TR- β , results in mitochondrial fatty acid uptake, DNHL, and β -oxidation, which reduces production of toxic lipid substrates and hepatic steatosis (Kuchay et al., 2024). Systemic thyroid hormone administration improves peripheral lipid profiles and reduces total cholesterol by increasing LDL cholesterol receptor expression through a reduction in hepatocellular PCSK9 levels (Bonde et al., 2014). Therefore, hypothyroidism (both systemic and intrahepatic) cause steatohepatitis. However, the reverse is also true because liver injury from any cause, including MASLD-related fibrosis, induces a switch in hepatic metabolism of thyroid hormone from activation via the deiodinase-1 pathway to deactivation via the deiodinase-3 pathway (Bohinc et al., 2014). This therefore produces the inactive reverse T3 hormone instead of active T3 hormone, rendering the liver relatively hypothyroid to peripheral thyroid hormone. The association between reverse T3 and cirrhosis has been recognised for over 40 years (Kabadi & Premachandra, 1983), and led some to consider reverse T3 as a novel biomarker for advanced fibrosis (Kuchay et al., 2024). Naturally, this led to production of TR- β agonists to treat MASLD. These observations led to advances in the therapeutic options available to people with MASLD, presented in section 1.5.6.

1.5.5 Natural history of MASLD

People with MASLD are at greater risk for poorer health outcomes, including CVD and liver-related morbidity and mortality, increased hepatic and extra-hepatic malignancies, and CKD (Adams, Lymp, et al., 2005; Lindenmeyer & McCullough, 2018; Xiao, 2023; Younossi & Henry, 2016). The commonest cause of death in people with MASLD is CVD, affecting two-thirds, but is greater with advancing hepatic fibrosis (e.g., stage 3-4), older age, and presence of T2D (Adams, Lymp, et al., 2005). One study reported the risk of incident CVD and mortality increases incrementally with presence of additional metabolic syndrome features. Mortality was five times greater in those with all five metabolic syndrome features compared with one feature over five-years (Guzder et al., 2006). However, the single greatest risk factor for cardiovascular and all-cause mortality in people with MASLD is advancing liver fibrosis (Angulo et al., 2015). One meta-analysis observed a 1-, 5-, and 10-year all-cause mortality of 0.1%, 3.3% and 7.7% in people with stage 0-2 MASLD-related fibrosis, compared with a 1-, 5-, and 10-year all-cause mortality of 0.3%, 20.6%, and 41.5% in people with stage 4 MASLD-related fibrosis (Ng et al., 2022). Similar observations are reported by others, with greater all-cause mortality, cardiovascular mortality, cancer-related mortality, and liver-related mortality with increasing liver fibrosis (Fu et al., 2023; Mantovani, Csermely, et al., 2021; Ng et al., 2022; Xiao, 2023). Compared to people with ALD, people with MASLD have a lesser risk of death from liver disease, but greater risk of CVD-related death (Younossi & Henry, 2016). This was noted in the Welsh population, in which a liver-related death was 10 times less likely in people with MASLD than ALD (Pembroke et al., 2023). However, those with decompensated liver disease with MASLD cirrhosis have a worse prognosis than people with decompensated liver disease resulting from other causes (Lekakis & Papatheodoridis, 2024). This is likely a consequence of differing characteristics in people with MASLD, who are often older, with a more chronic liver disease (compared with acute liver injury), and greater metabolic risk. The impact of the spectrum of MASLD on the individual and society is presented in Figure 1.7.

Figure 1.7: The impact of progressive MASLD on the individual and society



The personal and societal burden associated with progressive MASLD in people with or without T2D. Figure used with permission from Vincent *et al.* (Vincent *et al.*, 2020).

People with T2D and MASLD have over two-fold greater risk for both all-cause mortality and liver-related mortality (Stepanova *et al.*, 2013). This may be a result of an accelerated disease process, associated with metabolic risk (Younossi, Golabi, *et al.*, 2024; Younossi *et al.*, 2025). For example, one study found that people with T2D had a 76% greater risk of MASLD, 81% greater risk of liver cirrhosis, and 49% greater risk of HCC. People without known T2D also had an increasing risk of MASLD, liver cirrhosis and HCC with increasing random plasma glucose levels (Pang *et al.*, 2018). Nonetheless, it is the associated excess CVD which remains the unmet need in people with MASLD (Duell *et al.*, 2022).

Progression and regression of hepatic steatosis, steatohepatitis and fibrosis is difficult to predict, with marked heterogeneity in the observations of such cohorts to date. Meta-analyses suggest a third of people will progress from normal liver to simple steatosis, to MASH and to early fibrosis, with 15% of those developing early fibrosis progressing to cirrhosis. Likewise, regression over time is possible from early fibrosis to MASH to simple steatosis and resolution of hepatic steatosis, though regression from cirrhosis is less likely (Le *et al.*, 2023; Lekakis & Papatheodoridis, 2024; Singh *et al.*, 2015), presented in Figure 1.5. This illustrates that development of fibrosis is not inevitable consequence of MASH. Nonetheless, fibrosis may develop over time, with one study reporting progression of fibrosis by one stage over a mean 14 years in people with simple steatosis and 7 years in people with MASH (Singh *et al.*, 2015).

In those with progressive fibrosis, signs of steatohepatitis such as steatosis, inflammation, and ballooning, tend to regress along with liver enzymes. This makes use of routine liver enzymes in isolation practically meaningless in the diagnosis and follow-up of people with MASLD.

Associated with MASLD and necro-inflammatory fibrosis is an increased risk of various cancers. One meta-analysis reported that people with MASLD are 1.5-2.0 times more likely to develop gastrointestinal malignancy, and 1.2-1.5 times more likely to develop cancer of the lung, breast, gynaecological or urinary systems (Mantovani et al., 2022). This risk remained significant, though attenuated, following multivariable adjustment for important confounders such as age, sex, smoking, BMI or diabetes status. This suggests that MASLD is an independent risk factor for cancer development. This additional risk may be explained by the associations of chronic inflammation in people with MASLD, or hepatic and systemic lipotoxicity and IR. The commonest hepatic cancer is HCC, accounting for 85% of cases. One study observed an annual HCC cumulative incidence of 2.6% in people with MASLD cirrhosis (Ascha et al., 2010), representing a potentially huge burden of disease given the prevalence of advanced fibrosis in people with T2D is about 15% (Younossi, Golabi, et al., 2024). One meta-analysis observed 15.1% of 95,000 patients with HCC had MASLD-related HCC and these were more likely to be older, have higher BMI, suffer with metabolic comorbidities and be non-cirrhotic at HCC diagnosis than people with HCC from other causes (Tan et al., 2022). Patients with MASLD-related HCC had larger tumours, which were more likely uninodular, and these people were less likely to be enrolled within an HCC surveillance program than those diagnosed with HCC from other causes. Another study found 13% of 1,500 US veterans with HCC did not have liver cirrhosis, and in this group the major risk factors for HCC were MASLD with early fibrosis and metabolic syndrome features (Mittal et al., 2016).

There is naturally a pressure to target HCC screening to those at greatest risk, such as people with hepatitis C virus (HCV), which is associated with greater individual HCC risk than MASLD (Ascha et al., 2010; White et al., 2012). However, these studies highlight a missed opportunity for HCC surveillance in people without advanced fibrosis but with other risk factors such as T2D or metabolic syndrome, possibly resulting in more aggressive HCC. Previous pilot studies exploring MASLD screening in people with T2D have exposed unknown cases of HCC or biliary tract cancers (Ajmera, Cepin, et al., 2022; Doycheva et al., 2016).

1.5.6 Clinical management of MASLD

1.5.6.1 Diet and lifestyle measures

Encouraging people with MASLD to follow a healthy diet and undertake regular exercise is often the basis of their management, encouraged by the AACE, AASLD, EASL, EASD, and NICE (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023). High-calorie diets especially those with high saturated fat, refined carbohydrate, and sugars (particularly fructose), associate with MASLD progression (Vilar-Gomez et al., 2022). Diets with a 500-1000 kcal deficit and little refined carbohydrates or saturated fats support 5-10% weight loss, which is associated with improved signs of steatohepatitis in people with MASLD (Haigh et al., 2022; Properzi et al., 2018; Pugliese et al., 2022). Typically, this is presented as a ‘Mediterranean diet’ which gives a balance of lean proteins (e.g., fish) with vegetables. Reiterating alcohol limits to a maximum 20g daily with 2-3 alcohol-free days weekly minimises alcohol-driven hepatosteatosis (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023). This is because even moderate alcohol consumption (e.g., 5-6 alcoholic drinks/week) increases MASLD-related fibrosis, termed MetALD (Blomdahl et al., 2023; Rinella, Lazarus, et al., 2023). The importance of liver fat on metabolic control, and the impact of dietary intervention for MASLD is emphasised by the DiRECT study, in which a hypocaloric diet was given to people with newly-diagnosed T2D to determine whether this could achieve remission. The study found almost half of patients with newly-diagnosed T2D went into T2D remission and a quarter of participants lost over 15% bodyweight (Lean et al., 2018). In this study, participants who did or did not achieve diabetes remission had similar initial reductions in liver fat content during the weight loss phase of the study (-13.4% vs -11.9%, $p=0.60$). However, the reduction in liver fat content was only sustained in those who achieved remission at 12 months, and liver fat content increased again in those who did not achieve remission, in association with greater weight regain in this group (Taylor et al., 2018).

In the UK, people are encouraged to undertake at least 30 minutes of moderate exercise five times per week. Such exercise improves cardiometabolic outcomes including occurrence and progression of MASLD, independent of weight loss (Bae et al., 2012; Sung et al., 2016). The nature and duration of the exercise should be individualised to encourage as much physical activity as possible considering their limitations. Whilst suggesting lifestyle measures is useful, it is often overlooked in practice, in favour of drug intervention. Therefore, it is important that patients have multidisciplinary input, as people with MASLD (and other health disorders)

frequently benefit from dietetic, nursing and psychological services to help them attain the lifestyle intervention required to lose 5-10% total bodyweight (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023).

1.5.6.2 Pharmacological measures

In 2024 the first drug for MASLD was approved by the Food and Drug Administration (FDA). Though, several drug classes have shown benefit for its treatment, particularly in people with MASH. Pharmacological interventions suggested include vitamin E (NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023), thiazolidinediones (NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023), SGLT-2 inhibitors (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), GLP-1RAs (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), and the TR- β agonist resmetirom (EASL-EASD-EASO, 2024). Most of these options were originally derived for the treatment of T2D, highlighting shared disease processes.

Vitamin E is a fat-soluble vitamin, found in corn, peanut and soybean, which has benefit in MASLD. Vitamin E may exert a benefit by binding to and stabilising the hepatocyte membrane to limit injury from reactive oxygen species generated by lipid peroxidation. Therefore, vitamin E acts as an antioxidant to protect from oxidation-associated inflammation (El Hadi et al., 2018). Trial evidence supports vitamin E use in MASLD. The pioglitazone versus vitamin E versus placebo for the treatment of nondiabetic patients with non-alcoholic steatohepatitis (PIVENS) trial reported vitamin E therapy significantly improved histological signs of MASH versus placebo (43% vs 19%), including steatosis, and lobular inflammation but not hepatic fibrosis (Sanyal et al., 2010). Similarly, a meta-analysis observed improved biochemical and histological measures of MASLD including liver enzymes, hepatic steatosis, inflammation, and ballooning, but not fibrosis (Xu et al., 2015). Its use reduced decompensated liver disease in people with advanced MASH in another study (Vilar-Gomez, Vuppalanchi, et al., 2020). However, there are concerns regarding vitamin E use given reports of greater mortality, risk of haemorrhagic stroke and prostate cancer which limit its use (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

Thiazolidinediones such as pioglitazone are peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonists, which enhance lipid uptake into fat cells to reduce lipotoxicity and enhance adiponectin release from adipocytes to improve insulin sensitivity (Ahmadian et al., 2013). Pioglitazone improves hepatic steatosis, inflammation, and ballooning, but not hepatic fibrosis (Sanyal et al., 2010). Subsequent meta-analyses show improved biochemical and histological

measures independent of T2D status (Majzoub et al., 2021). Nevertheless, pioglitazone use is limited in practice given its association with worsening heart failure, weight gain, risk of bony fractures, and bladder cancer (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Some authors argue that whilst there are important risks associated with pioglitazone, the absolute risk of these adverse outcomes is small, and as pioglitazone is associated with improved overall CVD outcomes (Dormandy et al., 2005), their use in a cohort with high atherosclerotic CVD risk may be well-placed (Dawson, 2018). Given the success of other drug classes for CVD prevention in T2D, pioglitazone use for people with T2D and MASLD has waned, even in people with both disease states (Le et al., 2020).

The AACE, AASLD, EASD, and EASL suggest consideration of GLP-1RAs and SGLT-2 inhibitors in people with T2D and MASLD given their association with improved CVD and liver-related outcomes (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Indeed, GLP-1RAs probably ameliorate MASLD outcomes through both direct and indirect mechanisms. Indirectly, these drugs improve glycaemic control, lipid profiles, and weight loss. Direct mechanisms include anti-inflammatory effects and regulation of DNHL, whilst improving measures of IR (Vincent et al., 2020). One meta-analysis observed GLP-1RA use in people with T2D resulted in significant reductions in liver enzymes (alanine aminotransferase (ALT), AST, gamma glutamyl transferase (GGT)), liver fat content, and MASH resolution on histology (Ghosal et al., 2021). Another meta-analysis observed use of the GLP-1RAs liraglutide or semaglutide were the most effective interventions for MASLD (Majzoub et al., 2021). Subsequently, the SEMA-NASH study used daily subcutaneous semaglutide in people with MASH and stage 2-3 hepatic fibrosis, and observed greater MASH resolution versus placebo (59 vs 17%) irrespective of underlying T2D (Newsome et al., 2021). Recently, the ESSENCE study reported participants with MASH and stage 2-3 fibrosis receiving semaglutide 2.4 mg once weekly had greater MASH resolution versus placebo (62.9% vs 34.3%) and greater fibrosis regression (32.7% vs 16.1%) (Sanyal et al., 2025). A recent meta-analysis concluded semaglutide was more effective than placebo in achieving MASH resolution and fibrosis regression in people with biopsy-proven MASH (Souza et al., 2025). However, semaglutide does not associate with MASH resolution or improved fibrosis in people with T2D and MASLD cirrhosis (Loomba, Abdelmalek, et al., 2023).

There is growing interest in dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists for the treatment of T2D and MASLD. Tirzepatide associated with a reduction in liver fat content of 8.1%, compared to 3.4% in people with T2D treated with insulin degludec

(Gastaldelli et al., 2022), greater than the liver fat content reduction observed with semaglutide. A more recent phase 2 study trialled tirzepatide for MASLD in people with liver fibrosis (F1-3) and reported a greater number of participants with MASH resolution versus placebo (62 vs 10%) and in the number of people improving by ≥ 1 fibrosis stage (51 vs 30%) (Loomba et al., 2024). Here, the high proportion of participants in the placebo arm with improved fibrosis by at least 1 stage may be surprising, though a few factors may explain this. Firstly, this group did receive additional support by participating in the trial, and behavioural changes may support fibrosis regression. However, confounders such as liver biopsy sampling error, or interobserver variability between pathologists may play a role. Nonetheless, the number achieving this endpoint was significantly greater in the tirzepatide group. A recent meta-analysis concluded tirzepatide was more effective than placebo for MASH resolution and fibrosis regression in people with MASH and appeared more effective than semaglutide (Souza et al., 2025). Drugs in the GLP-1RA class reduced 10-year major adverse liver outcomes (MALO) (decompensated cirrhosis, HCC, liver transplant or liver-related death), in a large observational study using Swedish healthcare register (Wester et al., 2024), though prospective trials are lacking.

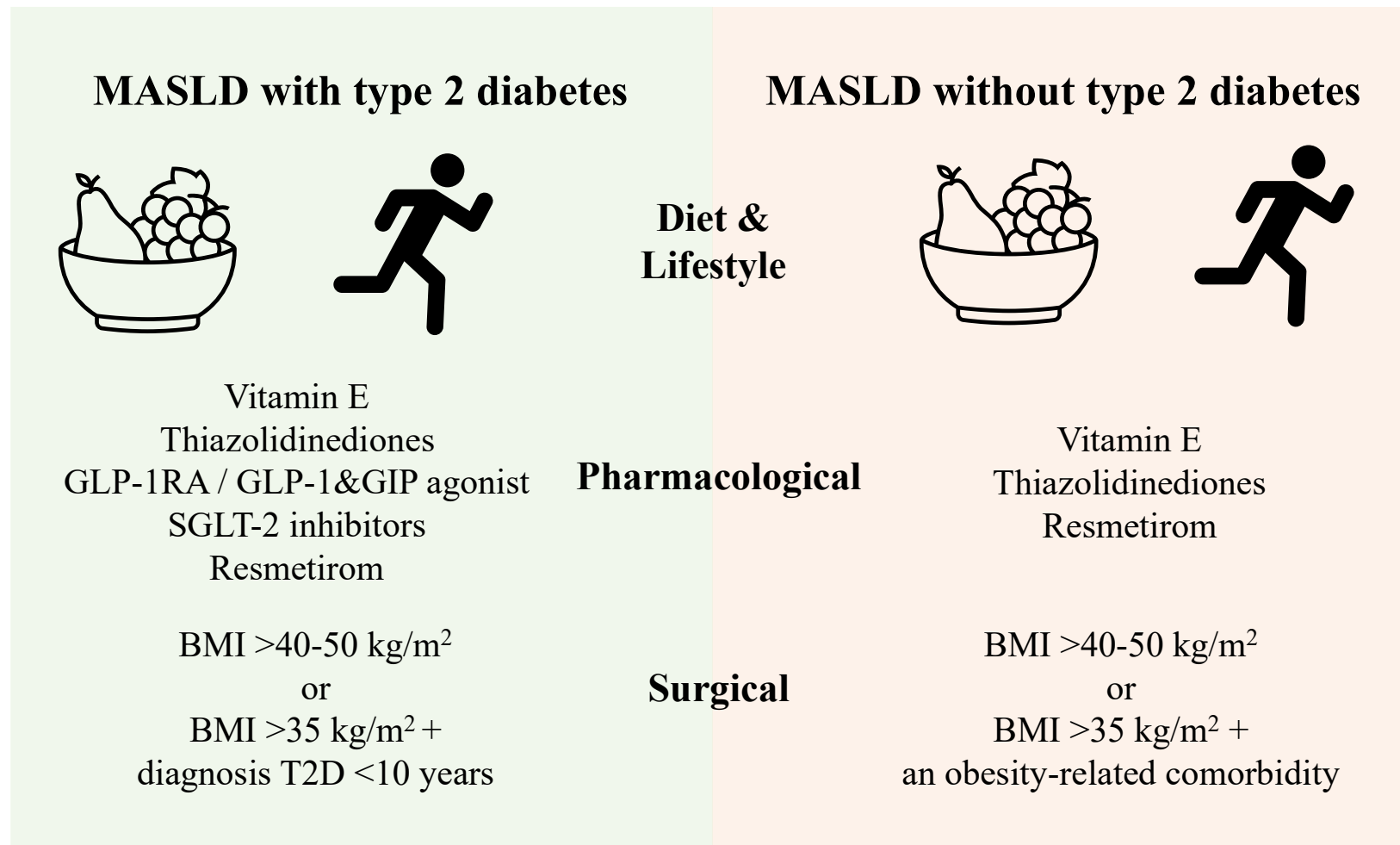
The other drug class useful for people with T2D and MASLD is SGLT-2 inhibitors (Rinella, Neuschwander-Tetri, et al., 2023). These have important metabolic effects which improve outcomes in T2D, including heart failure, and CKD (Williams et al., 2021). These drugs inhibit sodium and glucose reabsorption in kidney, resulting in greater natriuresis and glycosuria. By improving glycaemia via glucose excretion in people with T2D there is a shift in lipid metabolism given changing serum insulin and glucagon levels, reducing oxidative stress and low-grade inflammation, supporting MASLD treatment (Androutsakos et al., 2022a; Vincent et al., 2020). In trials, SGLT-2 inhibitors reduce liver enzymes, liver fat content, and body fat. Little evidence investigates histological outcomes, and no evidence indicates improved fibrosis (Song et al., 2021; Wei et al., 2021). Given their improvements on cardiometabolic outcomes and impact on liver fat content, these are a useful adjunctive therapy in people with T2D (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

The TR- β agonist resmetirom has proven to be useful in people with MASLD. In a phase 3 trial including paired biopsies with almost 1,000 participants, resmetirom achieved MASH resolution in 29.9% of participants (versus 9.7% receiving placebo), and improvement in fibrosis in 24.2% of participants (versus 14.2% receiving placebo). The drug appeared to be safe, with main adverse effects of diarrhoea and nausea noted, and no significant impact on the thyroid axis (Harrison et al., 2024). These observations led to the FDA approving resmetirom

to treat MASLD with stage F2-3 fibrosis (Food and Drug Administration, 2024), the first drug ever approved for this disease. The European Medicines Agency are expected to follow with further regulatory approval. The EASL guidelines in 2024 already advocates its use where available (EASL-EASD-EASO, 2024). The treatment of MASLD is summarised in Figure 1.8.

Other medicines have been studied for a beneficial effect in people with MASLD, without much success. Examples include metformin (Pinyopornpanish et al., 2021), ursodeoxycholic acid (Lin et al., 2022), DPP-4 inhibitors (Vincent et al., 2020), n-3 polyunsaturated fatty acids (Lee et al., 2020), and ezetimibe (H. Y. Lee et al., 2019). Whilst statin treatment is associated with some improvements in people with MASLD (Fatima et al., 2022), their impact on MASH-related outcomes is not meaningful. Given the relative inefficacy of these drugs to meaningfully improve histological measures of hepatic steatosis or fibrosis, these drugs are not recommended for the treatment of MASLD (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023). However, they are safe in this group and should be considered for the treatment of other conditions if needed.

Figure 1.8: The treatment of MASLD



Therapies used to treat people with MASLD, including dietary & lifestyle, pharmacological and surgical. Abbreviations: *BMI* body mass index; *GLP-1RA* glucagon-like peptide-1 receptor analogues; *MASLD* metabolic dysfunction-associated steatotic liver disease; *SGLT-2* sodium-glucose co-transporter-2; *T2D* type 2 diabetes.

1.5.6.3 Emerging treatment approaches for MASLD

The approach to the management of MASLD has developed considerably, with developments in pharmacological agents and a shift to focus on modifiable risk factors for CVD. This shift in approach requires multidisciplinary input. Moreover, there is emerging evidence that bariatric surgery is safe in people with MASLD and improves outcomes.

There are numerous pharmacological approaches in development or with an increasing evidence base for the treatment of MASLD beyond the agents above. Others in development programmes with alternative mechanisms of action work as antioxidants, regulate lipotoxicity, modulate nuclear transcription factors, or diminish the pro-inflammatory cytokine toxicity involved in progression of hepatic steatosis to MASH and fibrosis (Nguyen et al., 2024). Generally, these have a good evidence base in early trials of people with MASLD, but a relatively limited evidence base in larger trials. Nonetheless, there is promise of newer drug therapies for MASLD, summarised in Table 1.11.

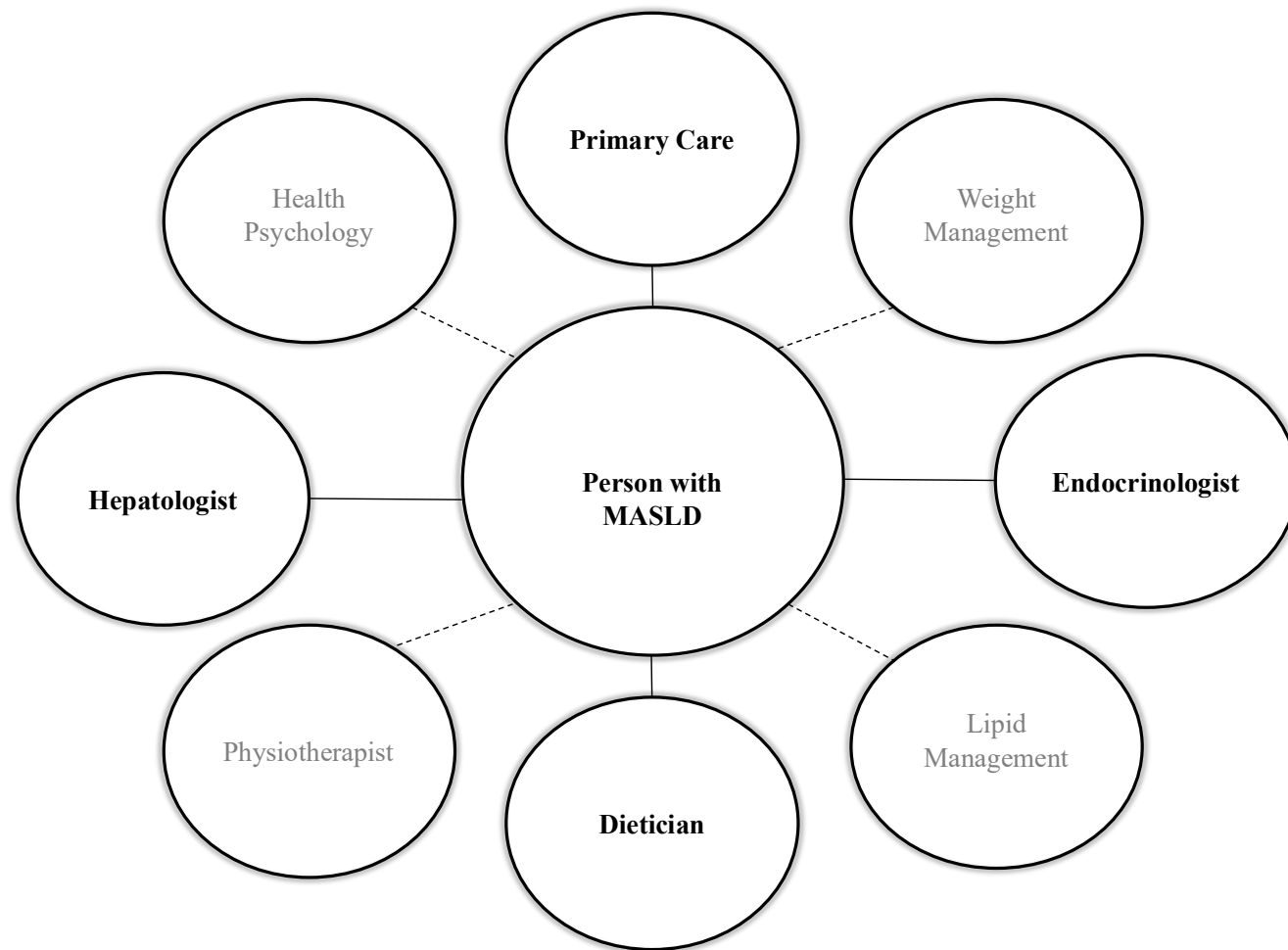
The AACE, AASLD, EASD, and EASL make clear that a multidisciplinary approach is needed (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Various models of care have been proposed and typically include primary care-led screening using blood biomarkers and imaging. These support referral of those at risk of advanced fibrosis to secondary care teams including hepatologists, endocrinologists, specialist nurses, specialist dietetic, physiotherapist, and health psychologist services with additional lipid or weight management services (Zoncape et al., 2022), presented in Figure 1.9. Interestingly, UK-based models show outcome benefits, including improved liver enzymes, HbA1c, reductions in total cholesterol, bodyweight and non-invasive measures of hepatic fibrosis with reduced predicted CV risk (Moolla et al., 2019). Yet, such teams infrequently exist. Whilst improving cardiometabolic risk will likely translate into improved outcomes, there remain a lack of prospective evidence to support this.

Table 1.11: Prospective pharmacological treatments for MASLD

Example	Mechanism	Benefits shown	Evidence
Aldafermin	FGF-19 analogue	Reduction in liver fat content vs placebo (7.8% vs 2.6%). No difference in MASH resolution or improvement in fibrosis vs placebo.	Phase II, 78 participants with biopsy-confirmed MASH (Harrison et al., 2021)
Denifanstat	FASN inhibitor	MASH resolution vs placebo (36% vs 13%), improvement in fibrosis by ≥ 1 stage vs placebo (41% vs 18%)	Phase IIb, included 126 participants and paired biopsy data (Sagimet Biosciences, 2024)
Obeticholic acid	FXR agonist	MASH resolution vs placebo (12% vs 8%), improvement in fibrosis by ≥ 1 stage vs placebo (23% vs 12%)	Phase III, with 1,968 participants and paired biopsy data (Younossi et al., 2019)
Pegozafermin	FGF-21 analogue	MASH resolution vs placebo (26% vs 2%), improvement in fibrosis by ≥ 1 stage vs placebo (27% vs 7%)	Phase IIb, with 219 participants and paired biopsy data (Loomba, Sanyal, et al., 2023)
Survodutide	Glucagon and GLP-1 agonist	MASH resolution vs placebo (62% vs 14%), improvement in fibrosis by ≥ 1 stage vs placebo (36% vs 22%)	Phase II trial, with 293 participants and paired biopsy data (Sanyal, Bedossa, et al., 2024)
Tropifexor	FXR agonist	Reduction in liver fat content vs placebo (15% vs 6%), reduced liver enzymes	Phase II, 198 participants with biopsy data (Sanyal et al., 2023)

Emerging MASLD therapies in phase II/III trials. Abbreviations: *FASN* fatty acid synthase; *FGF* fibroblast growth factor; *FXR* Farnesoid X receptor; *MASH* metabolic dysfunction-associated steatohepatitis.

Figure 1.9: The multidisciplinary model for the management of MASLD



The multidisciplinary model of care for MASLD.

1.5.6.4 Bariatric surgery for MASLD

There is growing evidence that bariatric surgery is safe and improves MASLD outcomes in people with obesity (Gluszynska et al., 2021; Hwang et al., 2024). In the UK, NICE recommend consideration of bariatric surgery in anyone with a BMI over 40 kg/m², or people with BMI over 35 kg/m² and a reversible obesity-related diagnosis (NICE, 2025b), similar to international guidelines (Mechanick et al., 2019). Increasingly, MASLD is recognised as an obesity-related comorbidity which benefits from bariatric surgical intervention, and is listed as a reversible weight-related comorbidity (NICE, 2025b). Though, longer-term studies are needed to confirm its benefit and safety as a frontline treatment (Mazzini et al., 2022). As such MASLD is not often considered an obesity-related comorbidity to trigger referral for bariatric surgery, despite the association between the disease states and CVD risk. This may reflect MASLD historically being considered benign and required work-up for diagnosis.

Given the lack of previously diagnosed liver disease, incidental diagnosis of MASLD cirrhosis is often made intraoperatively. A macroscopic cirrhotic liver is observed in 1-4% of cases undergoing bariatric surgery without known cirrhosis (Jan et al., 2015; Younus et al., 2020). There are concerns around bariatric surgery in people with MASLD cirrhosis, given potential anaesthetic, surgical, and postoperative complication risk (Younus et al., 2020). However, greater perioperative mortality in MASLD cirrhosis is associated with malabsorptive procedures, such as biliopancreatic diversion (BPD) and Roux-en-Y-gastric bypass (RYGB), but not restrictive interventions such as laparoscopic sleeve gastrectomy (LSG) or adjustable gastric banding (Geerts & Lefere, 2023; Jan et al., 2015). Recent evidence demonstrates bariatric surgery in people with MASLD lowers 3P-MACE and all-cause mortality (Krishnan et al., 2023). Contemporary guidelines advocate for bariatric surgery in people with MASLD cirrhosis following work-up for individuals with compensated cirrhosis (EASL-EASD-EASO, 2024; Geerts & Lefere, 2023; Patton et al., 2021; Rinella, Neuschwander-Tetri, et al., 2023).

Numerous studies report improvements in liver-related outcomes associated with bariatric surgery in MASLD, including biochemical, radiological, and histopathological measures (Bower et al., 2015; de Brito et al., 2021; Fakhry et al., 2019; Y. Lee et al., 2019). Histopathological measures of steatosis, steatohepatitis and hepatic fibrosis improve in 66-88%, 50-60%, and 30-40% of patients following bariatric surgery (Fakhry et al., 2019; Y. Lee et al., 2019). Interestingly, these studies also report that patients undergoing RYGB have greater improvements than those who have LSG or adjustable gastric band (de Brito et al., 2021; Fakhry et al., 2019). One study found MASH resolution associated with bariatric surgery

occurred in 85% of patients within 1 year (Lassailly et al., 2015), sustained at 5 years (Lassailly et al., 2020). A recent well-designed randomised trial including 288 participants reported 70% of participants demonstrated MASH resolution following RYGB or LSG, versus 19% receiving lifestyle interventions (Verrastro et al., 2023). Following surgery, the degree of MASH resolution correlated with the degree of weight loss (Lassailly et al., 2015; Lassailly et al., 2020). Around 12% of people undergoing bariatric surgery have worsening MASLD fibrosis, which is more likely in people undergoing malabsorptive procedures such as BPD (Y. Lee et al., 2019). There remain relatively limited studies in this area, especially in those with cirrhosis. Further trials are needed to support early bariatric surgery in this group (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023).

1.5.6.5 Hepatocellular carcinoma surveillance programme

An essential component of care for people with cirrhosis from any cause is to undertake regular HCC screening. This is achieved using 6-monthly ultrasound surveillance with or without measurement of serum alpha-fetoprotein (NICE, 2017; Rinella, Neuschwander-Tetri, et al., 2023). Traditionally, HCC was considered a greater risk in people with viral- or ALD-related liver cirrhosis, but MASLD-associated HCC is increasingly recognised (Cholankeril et al., 2017). The risk of HCC increases by stage of fibrosis in MASLD, and the greatest individual risk is observed in people with cirrhosis. Still, there is a major burden of HCC in people with non-cirrhotic MASLD (Tan et al., 2022). Moreover, people with MASLD-associated HCC are typically diagnosed with larger tumours, frequently not enrolled in a HCC surveillance programme, and have worse prognosis than HCC from other causes (Tan et al., 2022).

There remains significant risk of HCC in some people with MASLD and earlier stages of fibrosis, particularly people with a family history, the *PNPLA3* polymorphism, T2D and obesity (Dyson et al., 2014; Liu et al., 2014). However, there is currently insufficient data to support extending HCC surveillance to such groups (NICE, 2017; Rinella, Neuschwander-Tetri, et al., 2023). The risk of HCC in routine T2D populations is highlighted by previous screening studies which have identified several new cases (Ajmera, Cepin, et al., 2022; Doycheva et al., 2016). This area of MASLD care is likely to become increasingly important given the increasing prevalence of liver disease generally and the associated risk of HCC in these patients. Further cost and epidemiological studies are needed to better understand the role and appropriateness of HCC screening, particularly in earlier stages of MASLD.

1.6 Screening for MASLD in people with type 2 diabetes

Systematic routine screening for MASLD is recommended in high-risk patients, such as people with T2D or obesity, by international groups including the AASLD (Rinella, Neuschwander-Tetri, et al., 2023), AACE (Cusi et al., 2022), EASL-EASD joint guidance (EASL-EASD-EASO, 2024), and in India (Misra et al., 2025). The Asia-Pacific Association for the study of the Liver (APASL) currently recommend to consider screening at-risk populations (Eslam et al., 2020), and NICE do not recommend MASLD screening (NICE, 2016). This difference is most likely because these NICE guidelines are older than the recently published international guidelines, but may also reflect variations in important factors such as infrastructure for developing such services in the UK, differences in healthcare funding, and lower prevalence of MASLD compared with other global regions (Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024; Younossi et al., 2025). Despite these guidelines, most remain identified with MASLD incidentally, and often with advanced fibrosis. There is considerable variation as to whether people identified are worked up to determine their risk of advanced fibrosis or have intervention to support MASLD treatment and reverse excess CVD risk. Given the higher prevalence of MASLD in T2D, obesity, metabolic syndrome and those aged over 50 years, some argue such people should be screened regularly (Dietrich et al., 2021). Despite these guidelines, there are important concerns around screening for MASLD, detailed below.

1.6.1 Debate around MASLD screening in type 2 diabetes

The Wilson and Junger principles provide a judicious methodology to consider whether screening for disease is worthwhile and achievable (Wilson & Junger, 1968), using the 10 principles presented in Table 1.4. When considering MASLD, most principles are met. The burden of MASLD and its consequences including cardiovascular and liver-related morbidity and mortality are difficult to refute (Adams, Lymp, et al., 2005; Xiao, 2023; Younossi & Henry, 2016). Our understanding of the natural history of MASLD has matured over the last 20-30 years (Adams, Lymp, et al., 2005; Lindenmeyer & McCullough, 2018; Tilg et al., 2021; Yu et al., 2016). Significantly, developments in lifestyle, pharmacological, and surgical options to treat steatohepatitis and moderate hepatic fibrosis cannot be ignored (Cusi et al., 2022; EASL-EASD-EASO, 2024; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023). Many of these are commercially available for other disorders, such as T2D, and there are now disease-specific treatments available with promising ongoing trials. However, whilst identification of earlier stages of MASLD such as hepatic steatosis are reasonably accurate with non-invasive tests, they are frequently limited at identifying the stage of fibrosis (Golabi et al., 2016). This means

that liver biopsy remains the gold standard investigation for diagnosis, though recent updates in nomenclature have made this easier (Rinella, Lazarus, et al., 2023). Identifying the stage of fibrosis is important because this best predicts liver- and cardiovascular-related outcomes (Angulo et al., 2015; Ng et al., 2022), and negatively correlates with likelihood of response to available treatment options (Rinella, Neuschwander-Tetri, et al., 2023).

There are additional concerns about effective healthcare resource management, as the number of people identified at risk of advanced fibrosis may overwhelm services (Macpherson et al., 2022). Many patients would require bi-annual ultrasound HCC surveillance, and there is the cost of the screening program itself, which would vary by the technique used, and population in which screening is taken (Choo et al., 2022; Congly et al., 2021; Phisalprapa et al., 2017; Zhang et al., 2015). There are limited studies exploring acceptability of MASLD screening. This is important as additional appointments and tests would be in addition to the extensive screening protocols people with T2D are already subjected to, discussed in section 1.4.

Over the last 20-30 years, there has been interest in developing non-invasive tests to predict hepatic steatosis and fibrosis to prevent invasive testing for MASLD. These tests are often recommended to support risk stratification in people with MASLD, discussed below.

1.6.2 Screening for MASLD in type 2 diabetes: blood tests

1.6.2.1 Hepatic steatosis

Numerous biochemical tests and risk predictive algorithms have been developed to predict the presence of hepatic steatosis. Such tests include the fatty liver index (FLI) (Bedogni et al., 2006), hepatic steatosis index (HSI) (J. H. Lee et al., 2010), lipid accumulation product (LAP) (Kahn, 2005), NAFLD-liver fat score (NAFLD-LFS) (Kotronen et al., 2009), steatotest (Poynard et al., 2005), triglycerides and glucose index (TyG) (Simental-Mendia et al., 2008), and visceral adiposity index (VAI) (Vural Keskinler et al., 2021). Each score is determined by an algorithm incorporating numerous biochemical variables and were validated in a range of populations using different ‘gold standard’ tests to confirm hepatic steatosis including ultrasound, magnetic resonance (MR) spectroscopy and liver histology. These differences are presented in Table 1.12. Differences in the populations in which these tests were validated make their comparison challenging. The FLI, HSI, NAFLD-LFS, and steatotest were originally developed in mixed chronic liver disease (CLD) populations, whilst other tests were developed for other purposes and later validated for hepatic steatosis. The VAI was developed to estimate visceral adiposity dysfunction (Amato et al., 2010), the TyG was developed as a measure of IR

in healthy people (Simental-Mendia et al., 2008), and the LAP was developed to identify CVD risk in the general population (Kahn, 2005).

The utility of these scores extends beyond predicting hepatic steatosis. The FLI associates with CVD, hepatic, and all-cause mortality (Chung, Jeong, Cho, Yoo, et al., 2022), and the NAFLD-LFS associates with liver-related and cardiovascular death (Cheung et al., 2014; Lee et al., 2021). The VAI associates with cardiovascular and all-cause mortality (Wang & Yi, 2022), the TyG associates with risk of CVD (Lopez-Jaramillo et al., 2023) and the LAP associates with all-cause mortality in people without T2D (Ioachimescu et al., 2010). Though, neither the HSI (Oh et al., 2021; Unalp-Arida & Ruhl, 2018), nor steatotest (Munteanu et al., 2018) predict all-cause, liver-related or cardiovascular mortality. Moreover, the FLI (Cuthbertson et al., 2021), HSI (Cai et al., 2022), TyG (Lopez-Jaramillo et al., 2023), and LAP (Yu et al., 2021) can each predict the risk of developing T2D. So, these scores appear to be a measure of general metabolic health beyond screening for hepatic steatosis.

Nonetheless, there are concerns around using these algorithms in people with T2D. Firstly, neither the FLI, HSI nor steatotest could reliably predict hepatic steatosis in one study of 220 consecutive patients with T2D compared with MR spectroscopy (Guiu et al., 2012). When compared with histological findings, the HSI had poor sensitivity of 73.2% and specificity of 58.1% to predict moderate steatosis in people with T2D, though the HSI was more reliable than the FLI (Eletreby et al., 2021). Whilst the steatotest demonstrated a moderate association with the degree of steatosis on MR spectroscopy or liver biopsy in two studies in people with T2D, the test was less reliable in people with T2D compared to the original validation study population (Bril et al., 2019; Poynard et al., 2021). Other limitations to the use of these scores in practice include their availability and cost. For example, whilst the NAFLD-LFS is probably the best predictor of hepatic steatosis compared to other non-invasive scores (Cheung et al., 2014; Jung et al., 2020), the need for a fasting insulin level is unhelpful compared to the others which utilise routinely collected biochemical data. Finally, there is debate around the need to even use such a tool to predict hepatic steatosis, given its relatively benign nature compared to hepatic fibrosis, and presence in most people with T2D or obesity. Therefore many suggest the need is to screen for hepatic fibrosis to improve clinical outcomes in this population.

Table 1.12: Risk predictive scores for hepatic steatosis

Risk score	Variables included in algorithm	Original study population	Accuracy for hepatic steatosis	Evidence in people with T2D
FLI	BMI, WC, serum TG, and GGT	n=496 General population (Italy). HS diagnosis compared to ultrasound (Bedogni et al., 2006).	FLI <30 rules out HS: sensitivity 87%; specificity 64%. FLI ≥60 rules in HS: sensitivity 61%; specificity 86%.	Mixed associations with MR spectroscopy (Cuthbertson et al., 2014; Guiu et al., 2012)
HSI	BMI, sex, presence of T2D, ALT and AST	n=10,724 People attending for hospital for a health check-up (Korea). HS diagnosis compared to ultrasound (J. H. Lee et al., 2010)	HSI <30 rules out HS: sensitivity 92.5%, specificity 40.0% HSI >36 rules in HS: sensitivity 46.0%, specificity 92.4%	Moderate association with ultrasound (Mori et al., 2021)
LAP	Gender, WC, fasting TG	n=9,180 General population in the National Health and Nutrition Examination Survey (USA) (Kahn, 2005). Validated using MR spectroscopy data (Cuthbertson et al., 2014).	Using cut-off LAP ≤20: sensitivity 99%, specificity 16% Using cut-off LAP ≥80: sensitivity 43%, specificity 91%	The utility of LAP did not differ significantly in 54 people with T2D (Cuthbertson et al., 2014)
NAFLD-LFS	Presence of T2D and MetS, fasting AST, AST/ALT ratio and fasting insulin	n=470 People recruited for metabolic studies or deranged LFTs (Finland). HS compared to MR spectroscopy (Kotronen et al., 2009)	Score >-0.640 rules in HS: sensitivity 86%, specificity 71%	Original validation included 111 (23.6%) people with T2D
Steatotest	Age, gender, BMI, alpha-2-microglobulin, ALT, apolipoprotein A1, bilirubin, GGT,	n=884 Patients with chronic hepatitis C or B virus, ALD, MASLD & controls. HS diagnosis	Score <0.30 rules out HS: sensitivity 91%, specificity 45% Score >0.70 rules in HS: sensitivity 45%, specificity 89%	Moderate association with HS versus MR spectroscopy or biopsy. Poorer versus original

	haptoglobin, TC, TG, and glucose	compared to biopsy (Poynard et al., 2005)		validation (Bril et al., 2019; Poynard et al., 2021)
TyG	TG, fasting glucose	n=748 Healthy participants with prediabetes (Mexico) (Simental-Mendia et al., 2008). Validated in a cohort using ultrasound (Guo et al., 2020). n=1,813	Using a cut-off 8.70: Sensitivity 70.6% Specificity 69.1%	In people with T2D, TyG strongly associated with MASLD risk (Li et al., 2022)
VAI	WC, BMI, TGs, and HDL	Modelled on healthy subjects, validated in primary care patients (Italy) (Amato et al., 2010). Later validated in a cohort using biopsy data (Vural Keskinler et al., 2021).	Sensitivity 72% Specificity 68%	People with T2D had significantly lower VAI versus people without T2D (Ismaiel et al., 2021)

Variables used, original study population and reported accuracy of various algorithms to predict hepatic steatosis. Abbreviations: *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *BMI* body mass index; *FLI* fatty liver index; *GGT* gamma glutamyl transferase; *HDL* high-density lipoprotein; *HS* hepatic steatosis; *HSI* hepatic steatosis index; *LAP* lipid accumulation product; *LFTs* liver function tests; *MetS* metabolic syndrome; MR magnetic resonance; *NAFLD-LFS* non-alcoholic fatty liver disease liver fat score; *T2D* type 2 diabetes; *TC* total cholesterol; *TG* triglyceride; *TyG* triglycerides and glucose index; *VAI* visceral adiposity index; *WC* waist circumference.

1.6.2.2 Hepatic fibrosis

Some authors argue that predicting hepatic steatosis is less important than hepatic fibrosis, given poor health outcomes associated with MASLD correlate with the degree of fibrosis. Risk scores for advanced fibrosis are available to identify those at risk. These include the age, presence of diabetes, PRO-C3, and platelet count (ADAPT) score (Daniels et al., 2019), APRI (Wai et al., 2003), the AST:ALT ratio (De Ritis et al., 1957), the BMI-AST/ALT ratio-diabetes mellitus (BARD) score (Harrison et al., 2008), ELF test (Rosenberg et al., 2004), FIB-4 score (Sterling et al., 2006), Fibrotest (Imbert-Bismut et al., 2001), Fibrometer score (Cales et al., 2009), Hepascore (Adams, Bulsara, et al., 2005), and NFS (Angulo et al., 2007). Variables included in these scores and their validation cohorts are compared in Table 1.13.

Non-patented fibrosis scores

The AST:ALT ratio and BARD score

The AST:ALT ratio is the oldest algorithm used, described in 1957 by de Ritis to indicate the aetiology of hepatitis (De Ritis et al., 1957). Viral hepatitis resulted in a greater relative ALT level, and subsequent work observed alcohol-related hepatitis associated with the inverse, in which the AST is relatively high. Therefore, elevated AST:ALT ratio (>2.0) suggests an ALD aetiology, and reduced AST:ALT ratio indicates viral hepatitis (Botros & Sikaris, 2013). More recent observations demonstrate that whilst both AST and ALT rise with increasing BMI and IR, there is a greater relative rise in ALT. Therefore, in patients with MASLD the AST:ALT ratio is typically reduced (Sattar et al., 2014). Though, with increasing steatohepatitis and fibrosis in MASLD, the AST:ALT ratio increases and a score >0.8 suggests advanced fibrosis (McPherson et al., 2010). The AST:ALT ratio reliably excludes advanced fibrosis in MASLD, with a negative predictive value (NPV) of 93%, though poor positive predictive value (PPV) meaning further investigation is often needed (McPherson et al., 2010). The AST:ALT ratio also associates with risk of CVD and CKD (Ciardullo et al., 2020), and associates with the risk of developing T2D (Niu & Zhou, 2021). The AST:ALT ratio is limited in screening for fibrosis in people with MASLD in practice given most have an intermediate score requiring further evaluation, highlighting its poor PPV (Ciardullo et al., 2020).

Given the simplicity of the AST:ALT ratio, others have sought to include this within algorithms to improve its prediction value for advanced fibrosis. One example is the BARD score. A BMI ≥ 28.0 kg/m² or history of T2D are given one point each, and two points are given if the AST:ALT ratio is >0.8 . If the BARD score is 0-1 points, there is a NPV of 96% for advanced fibrosis (Harrison et al., 2008), validated in other MASLD populations (Cichoz-Lach et al.,

2012; Raszeja-Wyszomirska et al., 2010; Ruffillo et al., 2011). The BARD score associates with all-cause mortality and risk of liver decompensation, though is less accurate than the NFS and FIB-4 score (Cianci et al., 2022; Wu et al., 2021). When used in sequence with the FLI, the BARD score reliably predicted all-cause, liver-specific, and cancer-related mortality in one cohort (Chung, Jeong, Cho, Yoon, et al., 2022). However, there are concerns about applying the BARD score to some ethnic groups, given varying metabolic risk associated with different BMI cut-offs. Moreover, in the context of screening high-risk groups, such as those with T2D or obesity, all would have a score of at least 1, limiting its exclusion value.

The AST-to-platelet ratio index

The APRI is an attractive scoring algorithm because it uses routinely collected AST and platelet count. The APRI was initially developed in patients with chronic HCV infection, with good sensitivity and specificity for advanced fibrosis (Wai et al., 2003) and in subsequent meta-analyses (Lin et al., 2011). In people with MASLD, the APRI may better predict advanced fibrosis and liver cirrhosis than other predictive algorithms, but there are mixed observations (Amernia et al., 2021; Kolhe et al., 2019; Siddiqui et al., 2019; Wu et al., 2021). Whilst the APRI is useful in the prediction of hepatic decompensation (Ahmed et al., 2020), it had the poorest utility of several biomarkers to predict all-cause mortality in one meta-analysis (Cianci et al., 2022). Moreover, there is some concern given only two variables are required to generate the APRI score, and other factors which affect the AST or platelets can have major influence on the score leading to false results and limiting its recommended use.

The fibrosis-4 score

The FIB-4 score was developed in a retrospective, multicentre cohort study of 733 patients with coexistent human immunodeficiency virus (HIV) and HCV infection (Sterling et al., 2006). The algorithm developed had good sensitivity and specificity to identify or exclude advanced fibrosis and was later validated in a European population with MASLD, observing declining specificity with greater age, at just 35% in people aged over 65 years. This led to suggested age-adjusted thresholds in MASLD, in which a higher screening cut-off score ≥ 2.0 was proposed in people aged ≥ 65 years to improve test specificity (McPherson et al., 2017). More recent studies do not report greater test utility using higher cut-off scores in people aged ≥ 65 years and recommend a threshold of 1.3 irrespective of age (Sung et al., 2025). Nonetheless, most current guidelines advocate a FIB-4 cut-off ≥ 2.0 in this age group (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), but some do not (Misra et al., 2025). Nonetheless, the FIB-4 score is the recommended screening test for

use in routine practice for advanced fibrosis, advocated first-line by all of these international groups. This is because the test is easily achieved in clinical practice given its use of routinely collected clinical data and relatively low cost (Williams, Nagaraj, et al., 2025). However, whilst the FIB-4 score is highly sensitive, it is less specific, and those with positive screening require further investigation (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023). Reassuringly, studies report the number of referrals generated using the FIB-4 score are manageable compared with other scores in people with T2D, as 6.7% had predicted advanced fibrosis and 40.4% had an intermediate score (Ciardullo et al., 2020). The FIB-4 score had similar utility as the NFS in predicting all-cause mortality in people with MASLD, and liver-related complications such as decompensated disease and HCC (Cianci et al., 2022; Johnson et al., 2022). A recent meta-analysis reported the FIB-4 score had similar utility to predict 5-year all-cause mortality and liver outcomes as histological measures of MASLD fibrosis (Mozes et al., 2023).

The NAFLD fibrosis score

The NFS was originally developed in people with MASLD on liver biopsy to predict the risk of liver fibrosis, and 30% of participants had T2D. Using a low cut-off score of -1.455, the NFS had reasonable sensitivity and specificity to exclude advanced fibrosis, and the high cut-off score of 0.676 had 98% specificity for significant liver fibrosis (Angulo et al., 2007). One meta-analysis found that compared with other algorithms, it was the best predictor of all-cause mortality in people with MASLD (Cianci et al., 2022), and other studies observe strong associations with decompensated liver disease risk (Johnson et al., 2022; Treeprasertsuk et al., 2013). The accuracy of the NFS to predict all-cause mortality and liver-related outcomes is comparable to histological measures of hepatic fibrosis (Mozes et al., 2023). Nonetheless, its use in practice leads to excess referrals in people with T2D, and has poorer accuracy to detect advanced fibrosis in people with T2D, obesity or in those aged ≤ 35 years or ≥ 65 years (McPherson et al., 2017; Qadri et al., 2022). One study of 2,770 people with T2D in Italy observed a third of patients had a high-risk NFS and another 53.8% had an intermediate NFS, resulting in an unsustainable number of hepatology referrals (Ciardullo et al., 2020). Therefore, the NFS is not recommended to screen for advanced fibrosis in people with T2D or obesity in contemporary international guidelines (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023).

Patented fibrosis scores

The ADAPT score

The ADAPT score uses age, platelet count, presence of T2D, and PRO-C3 level to determine the risk of advanced fibrosis and was originally determined in a cohort of people with MASLD (Daniels et al., 2019). Studies exploring the use of this algorithm are relatively limited in number compared with other tests, yet the ADAPT score has outperformed other scores including the ELF test, FIB-4 score, and APRI previously (Daniels et al., 2019; Nielsen et al., 2021; Tang et al., 2022), and maintains accuracy in people with obesity, unlike others except for the FIB-4 score (Qadri et al., 2022). Nonetheless, use the ADAPT score is limited by its cost and availability, so is not recommended in current practice guidelines.

The enhanced liver fibrosis test

The ELF test is the primary NICE recommended blood test to evaluate for liver fibrosis in MASLD (NICE, 2016, 2023b), with a score generated from an algorithm using hyaluronic acid, TIMP-1, and PIIINP. The ELF test was validated to diagnose moderate-to-severe hepatic fibrosis in people with CLD due to HCV, MASLD or ALD (Rosenberg et al., 2004). Subsequently, further algorithms have been validated in subpopulations, including people with hepatitis B virus (HBV), HCV, MASLD and ALD (Guha et al., 2008; Lichtinghagen et al., 2013; Xie et al., 2014), with similar reliability in people with or without T2D (Younossi, Felix, et al., 2021). Various screening cut-offs have been proposed, and the NICE suggest a very high-risk cut-off score 10.51, whilst the AASLD, AACE, EASL-EASD guidelines recommend a high-risk score of 9.8 and intermediate risk score of 7.7 when used a second-line screening test after the FIB-4 score (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). In people with MASLD, one meta-analysis concluded the ELF test is highly sensitive but has limited specificity which may result in excess referrals, especially if used in the general population (Vali et al., 2020). The ELF test is a useful predictor of liver-related events in people with MASLD (Johnson et al., 2022; Parkes et al., 2010), but does not associate with the risk of developing T2D (Y. Wang et al., 2020). Despite NICE guidance, the availability of the ELF test in practice varies across the UK as described previously, and is frequently limited for use in routine practice in South Wales.

FibroMeter

The FibroMeter tests are a series of assays to detect advanced fibrosis in numerous CLD states. The Fibrometer-NAFLD algorithm includes age, ALT, AST, bodyweight, ferritin, glucose, and platelet count to determine risk of advanced fibrosis (Cales et al., 2010). Accuracy of this test was similar to non-patented tests (Aykut et al., 2014; Subasi et al., 2015), but it was later observed the accuracy of the FibroMeter Virus second generation (FibroMeterV2G) test developed for people with HCV infection was more useful (Van Dijk et al., 2021). The FibroMeterV2G test closely associated with all-cause and extra-hepatic mortality than other non-invasive tests in one study (Boursier, Vergniol, et al., 2016). However, the cost and limited international availability of this test limits its use in routine clinical practice.

Fibrotest

The fibrotest was originally developed to identify advanced fibrosis and necrosis in people with HCV infection (Imbert-Bismut et al., 2001). The algorithm includes several α 2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, and bilirubin, adjusted for age and sex. Subsequent studies validated the use of the fibrotest to identify MASLD fibrosis (Ratzu et al., 2006), and observed it predicted fibrosis progression (Poynard et al., 2012). Studies highlight an association between the Fibrotest and liver outcomes in MASLD, irrespective of T2D or obesity (Munteanu et al., 2018). However, use of the test is limited by a lack of routinely collected data, with excess cost and limited availability compared with non-patented fibrosis scores and other patented fibrosis scores.

Hepascore

The Hepascore is a patented test which includes the α 2 macroglobulin, patient age, bilirubin, gender, GGT, and hyaluronic acid to determine advanced fibrosis risk. This was originally validated in people with HCV (Adams, Bulsara, et al., 2005). Subsequently, it was validated in people with MASLD and reported to be one of the most accurate tests to predict advanced fibrosis compared with APRI, FIB-4 score, FibroMeter-NAFLD, and FibroMeterV2G scores. Moreover, the test predicts all-cause, liver-related and extra-hepatic mortality in this group (Boursier, Vergniol, et al., 2016). Like other patented tests, this test is limited by its cost and general availability internationally.

Each of these scoring systems have been validated to screen for advanced fibrosis in people with MASLD, either in a primary study or in a subsequent validation cohort with MASLD. However, factors can affect the accuracy of these tests to predict advanced fibrosis. Firstly, the presence of obesity can reduce the utility of these scores to predict fibrosis, as several studies

observe that the NFS loses accuracy with increasing BMI by over-predicting fibrosis, with poor specificity (Drolz et al., 2021; Qadri et al., 2022). However, the FIB-4 score appears to be less affected by increasing BMI and numerous studies observe that the FIB-4 score, ADAPT score and APRI generally have better accuracy for advanced fibrosis in people with obesity (de Carli et al., 2020; Drolz et al., 2021; Qadri et al., 2022; Schmitz et al., 2020). However, a study exploring the use of non-invasive tests for MASLD-related advanced fibrosis in people undergoing bariatric surgery concluded that the NFS, FIB-4 score and APRI were all poor predictors to diagnose advanced fibrosis, but useful for its exclusion (Alqahtani et al., 2021). Additionally, one meta-analysis concluded that whilst biomarker panels such as the ELF test were more accurate to detect advanced fibrosis than simple the NFS, FIB-4 score, and BARD, these were poorly validated in people living with obesity (Ooi et al., 2018).

Presence of T2D and increasing age may affect test accuracy. The importance of T2D in predicting advanced fibrosis is highlighted by its inclusion in the NFS and BARD algorithms. However, the FIB-4 score, which does not include presence of T2D in its algorithm, may be less accurate at predicting cirrhosis and liver-related morbidity and mortality in T2D (Bertot et al., 2018; Ito et al., 2023). Moreover, TE is more sensitive than the FIB-4 in detecting advanced fibrosis in people with T2D and some suggest that screening using the FIB-4 index may miss some people with T2D and advanced fibrosis (Chung et al., 2023). One study including 1,051 patients with biopsy-proven MASLD observed a reduced accuracy for several non-invasive measures of advanced fibrosis in people with T2D, including the NFS, FIB-4 score, fibrotest and fibrometer (Boursier et al., 2023). Similarly, age is an important variable, included in the NFS, FIB-4 score, and Fibrometer. Age may affect the accuracy of these tests in people aged ≤ 60 years (Ito et al., 2023), and in those aged < 35 years or ≥ 65 years (McPherson et al., 2017).

Current NICE guidance (NICE, 2016, 2023b) favours the ELF test, NFS or FIB-4 score to identify advanced fibrosis or to predict prognosis in people with MASLD, but this is under review (NICE, 2025a). More recently published international guidelines advocate the FIB-4 score first-line and the ELF test second-line given costs and global availability. Indeed, the potential utility of using these sequential blood biomarkers in practice was demonstrated by the Camden & Islington NAFLD pathway, which observed improved detection of advanced fibrosis and reduced inappropriate referrals associated with using the FIB-4 score and ELF test in sequence (Srivastava, Gailer, et al., 2019).

Table 1.13: Risk predictive scores for hepatic fibrosis

Risk score	Variables included in algorithm	Original study population	Accuracy in MASLD	Evidence in people with T2D
<u>Non-patented scores</u>				
APRI	AST, platelet count	n=579 Patients with HCV in the USA, using biopsy data (Wai et al., 2003)	A score ≥ 0.56 predicts advanced fibrosis (Boursier, Vergniol, et al., 2016); - Sensitivity 61.0% - Specificity 76.4%	The study in MASLD included 48.0% with T2D (Boursier, Vergniol, et al., 2016).
AST:ALT ratio	AST, ALT	n=147 Patients with viral hepatitis, cholangitis, obstructive icterus, or heart failure (De Ritis et al., 1957).	A score >0.8 predicts advanced fibrosis (McPherson et al., 2010): - Sensitivity 74% - Specificity 78%	The subsequent study in MASLD included 73 (50.3%) people with T2D (McPherson et al., 2010).
BARD	BMI, AST, ALT, T2D	n=827 Patients with MASLD across 2 sites (USA), using biopsy data (Harrison et al., 2008).	A score ≥ 2 predicts advanced fibrosis (Harrison et al., 2008): - PPV 43% - NPV 96%	The original study included 35% living with T2D (Harrison et al., 2008)
FIB-4 score	Age, AST, ALT, platelet count	n=832 Patients with HIV and HCV coinfection, using biopsy data (Sterling et al., 2006).	A score ≥ 1.3 predicts advanced fibrosis (McPherson et al., 2010): - Sensitivity 85% - Specificity 65%	The subsequent study in MASLD included 73 (50.3%) people with T2D (McPherson et al., 2010).
NFS	Age, BMI, IFG/T2D, AST, ALT, platelet count, albumin	n=733 Patients with biopsy proven MASLD in Australia, UK, USA (Angulo et al., 2007).	A score >-1.455 predicts advanced fibrosis (Angulo et al., 2007) - Sensitivity 82% - Specificity 77%	The original study population included 219 (29.9%) people with T2D (Angulo et al., 2007)

Patented scores				
ADAPT score	Age, platelet count, presence of T2D, PRO-C3 level,	n=431 Patients with MASLD on biopsy (Daniels et al., 2019)	AUC 0.87 in original cohort study	The study included 37.4% with T2D (Daniels et al., 2019)
ELF test	HA, TIMP-1, PIIINP	n=1,021 Patients with biopsy data with HCV, MASLD or ALD (Rosenberg et al., 2004).	A score ≥ 9.8 predicts advanced fibrosis (Younossi, Felix, et al., 2021): • Sensitivity 57.5% • Specificity 88.9%	Accuracy not affected by T2D status (Younossi, Felix, et al., 2021).
Fibrometer-NAFLD	Age, ALT, AST, bodyweight, ferritin, glucose, platelet count	n=226 Patients with MASLD on biopsy (Cales et al., 2010)	To detect advanced fibrosis (Subasi et al., 2015) • Sensitivity: 66.7% • Specificity: 74.5%	The subsequent study in MASLD included 20.3% with T2D
Fibrotest	$\alpha 2$ -macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin, age, sex	n=339 Patients with HCV using liver biopsy data (Imbert-Bismut et al., 2001)	A score ≥ 0.30 predicts advanced fibrosis (Ratziu et al., 2006): • Sensitivity 77% • Specificity 77%	The subsequent study in MASLD included 34.5% with T2D (Ratziu et al., 2006)
Hepascore	$\alpha 2$ macroglobulin, age, bilirubin, gender, GGT, HA	n=221 Patients with HCV using liver biopsy data (Adams, Bulsara, et al., 2005)	A score ≥ 0.322 predicts advanced fibrosis (Boursier, Vergniol, et al., 2016): • Sensitivity 67.4% • Specificity 76.1%	A study in MASLD included 48.0% with T2D (Boursier, Vergniol, et al., 2016)

Variables used, original study population, and accuracy of algorithms to predict advanced fibrosis in MASLD. Abbreviations: *ADAPT* age, presence of diabetes, PRO-C3, and platelet count; *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *AUC* area under the curve; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *ELF* Enhanced liver fibrosis; *FIB-4* fibrosis-4; *GGT* gamma glutamyl transferase; *HA* hyaluronic acid; *HCV* hepatitis C virus; *HIV* human immunodeficiency virus; *IFG* impaired fasting glucose; *MASLD* metabolic dysfunction associated steatotic liver disease; *NAFLD* non-alcoholic fatty liver disease; *NFS* non-alcoholic fatty liver disease fibrosis score; *PIIINP* Procollagen 3 N-terminal peptide; *PPV* positive predictive value; *NPV* negative predictive value; *T2D* type 2 diabetes; *TIMP-1* Tissue inhibitor matrix metalloproteinase 1.

1.6.3 Screening for MASLD in type 2 diabetes: imaging

Frequently, MASLD is identified incidentally when abdominal imaging is taken for another reason. Therefore, imaging may represent a useful means to screen for MASLD. Given use of CT is more limited in detecting mild hepatic steatosis, and associated with radiation exposure, there is no place for CT to screen for MASLD (Lee, 2017). Therefore, there may be a place for ultrasound and/or MRI to screen and stage MASLD, discussed below.

1.6.3.1 Ultrasonography

For MASLD screening, there are two main forms of ultrasound imaging with proven utility: conventional B-mode ultrasonography, and TE (Fibroscan). Use of transabdominal B-mode ultrasonography is attractive; it is widely available, with low cost, and good accuracy for moderate-severe steatosis (Tamaki, Ajmera, et al., 2022). Hepatic steatosis appears as an area of increased echogenicity within the liver parenchyma and graded on a 4-point scale: grade 0 (normal), grade 1 (slight echogenicity), grade 2 (moderate echogenicity), and grade 3 (marked echogenicity) (Saadeh et al., 2002). Though, B-mode ultrasonography has poor sensitivity for mild steatosis (Bohte et al., 2011; Hernaez et al., 2011), and given the subjectivity in grading, some report poor interobserver and intra-observer reproducibility, and poor accuracy in people with obesity (Tamaki, Ajmera, et al., 2022). Addition of the ultrasound-measured attenuation coefficient improves the accuracy of identifying and grading any steatosis to 76% and 84%, and severe steatosis to 87% and 79%, respectively (Jang et al., 2022). Nonetheless, conventional ultrasound is unreliable to identify fibrosis (D'Onofrio et al., 2005; Li et al., 2019), and its accuracy to detect steatosis is further impaired when accompanied by hepatic fibrosis (Lee & Park, 2014), as fibrosis also increases the echogenicity of liver parenchyma.

To address the lack of reliability associated with conventional ultrasound for milder steatosis or fibrosis, further ultrasound parameters have been developed including the CAP and LSM. These can be determined using the Fibroscan tool developed by Echosens (Echosens, 2020). The Fibroscan is a portable TE device (using ultrasound) which quantifies the velocity of a mechanically induced shear wave and ultrasonic attenuation of an echo wave within the liver in real-time to derive the LSM and CAP, respectively. At least 10 scan results are needed, which produce a median CAP and LSM score, and interquartile range (IQR). Generation of an IQR/median ratio <30% represents an acceptably accurate scan. In some people, the accuracy of the result is improved using the XL probe, and the device itself suggests using the “XL” probe during the examination if it detects error associated with obesity (Echosens, 2023). The portable nature and ease of use make it attractive for diagnosis, and monitoring.

The CAP algorithm calculates the attenuation of ultrasound signal and scores between 100-400 dB/m. The result correlates with hepatic steatosis on biopsy, and is therefore a surrogate measure of liver fat. The original validation of the CAP to predict hepatic steatosis and fibrosis was in people with CLD secondary to HCV, giving an area under the curve (AUC) 0.80-0.88 to differentiate between grades of hepatic steatosis (Sasso et al., 2012). It has been validated to assess for hepatic steatosis and fibrosis in MASLD (Cao et al., 2022; Eddowes et al., 2019). However, caution is needed when interpreting in people with comorbidities. For example, one meta-analysis reported that presence of MASLD or T2D shifted the optimal CAP threshold by 10 dB/m and 4.4 dB/m for each additional BMI 1.0 kg/m² score (Karlas et al., 2017). Whilst the manufacturer suggests a CAP score ≥ 302 dB/m to identify significant hepatic steatosis in MASLD, a cut-off CAP score ≥ 222 dB/m is recommended in CLD secondary to HCV (Echosens, 2020; Eddowes et al., 2019; Sasso et al., 2012). The CAP thresholds suggested for grading hepatic steatosis in MASLD are summarised in Table 1.14 (Eddowes et al., 2019).

The LSM score is determined by the speed of a mechanically-induced shear wave in liver tissue, quantified by ultrasound. The score correlates with liver fibrosis on biopsy, allowing it to be used as a non-invasive measure of liver fibrosis. This score was validated in the same cohort of people with HCV as the CAP score, with AUC of 0.84-0.96 to predict the fibrosis grade (Sasso et al., 2012). The LSM was validated in people with MASLD, and a score of 8.2 kPa identified people with MASLD-related fibrosis with a sensitivity and specificity of 71% and 70%, respectively (Eddowes et al., 2019). This is different to cut-offs for hepatic fibrosis from other causes, such as 7.4 kPa in HCV (Sasso et al., 2012), and 9.0 kPa for ALD (Nguyen-Khac et al., 2018). Obesity may impact the assessment of hepatic steatosis using the CAP, but the LSM is less affected by increasing BMI when the XL probe is used appropriately (Cao et al., 2022). The TE-LSM is more reliable to exclude MASLD-related cirrhosis in people with obesity than tests such as the FIB-4 score (Damjanovska et al., 2022). Confounders can affect the LSM score derived by TE, including acute hepatic inflammation, ascites, liver congestion (e.g., right ventricular failure) and cholestasis (Mueller & Sandrin, 2010). However, baseline LSM and change in LSM over time associate with risk of liver-related mortality and hepatic decompensation, highlighting its utility in practice (Petta et al., 2021). This was corroborated in a meta-analysis of 2500 patients with biopsy-proven MASLD, which observed the TE-LSM score associated with all-cause mortality, HCC, liver transplantation, and cirrhosis comparable to histological measures over five years (Mozes et al., 2023). The recommended LSM score thresholds for MASLD are in Table 1.14.

The TE-CAP and TE-LSM scores used in this thesis are shown in Table 1.14 and chapter 2, based on manufacturer recommendations. However, there is variability in test thresholds from previous studies and used in various guidelines that complicate comparisons between studies. One meta-analysis of 1277 patients reported TE-CAP scores of 294 dB/m, 310 dB/m and 331 dB/m to identify S1, S2, and S3 steatosis, respectively (Petroff et al., 2021). For liver fibrosis, American and European guidelines suggest TE-LSM scores of <8, 8-12, and >12 kPa to define low, intermediate and high-risk of advanced fibrosis in MASLD (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), whilst in Asian Indians current guidelines suggest scores of <8, 8-15, and >15 kPa respectively (Misra et al., 2025).

Table 1.14: Thresholds to predict hepatic steatosis and fibrosis using transient elastography in MASLD

Hepatic steatosis		
CAP score (dB/m)	Steatosis grade	Hepatocytes with fatty changes
<302	S0	0-10%
302-331	S1	11-33%
331-337	S2	34-66%
>337	S3	≥67%
Hepatic fibrosis		
LSM score (kPa)	Fibrosis grade	
<8.2	F0-1	
8.2-9.6	F2	
9.7-13.6	F3	
>13.6	F4	

The CAP and LSM thresholds recommended for MASLD to estimate hepatic steatosis and fibrosis, respectively (Eddowes et al., 2019). Abbreviations: *CAP* controlled attenuation parameter; *LSM* liver stiffness measure.

1.6.3.2 Magnetic resonance imaging

The use of MR-based imaging to screen for MASLD may be more valuable than ultrasound. Firstly, MRI-PDFF can quantify liver fat content with a high degree of accuracy, determined by the ratio derived from the signal strength from triglycerides to the signal from both triglycerides and water (Tamaki, Ajmera, et al., 2022). One meta-analysis reported a sensitivity and specificity of 92% and 93% to identify clinically significant hepatic steatosis, and MRI-PDFF was more accurate than the TE-CAP (Gu et al., 2021). Indeed, MRI-PDFF is considered the most accurate non-invasive method to quantify liver fat content and is often used to recruit to trials (Tamaki, Ajmera, et al., 2022). Changes in MRI-PDFF independently predict changes in liver fibrosis, as $\geq 30\%$ reduction in liver fat content assessed by MRI-PDFF independently associates with improved fibrosis (Tamaki, Munaganuru, et al., 2022).

In the evaluation of MASLD, MRE reliably predicts liver fibrosis. During MRE, the stiffness of liver tissue is assessed following application of shear wave to generate a score. One meta-analysis observed MRE had sensitivity and specificity of 78% and 89% for clinically significant hepatic fibrosis and was more accurate than TE at higher fibrosis grades (Selvaraj et al., 2021). The impact of confounders such as obesity, or ascites are less important in MRE, though steatohepatitis, hepatic congestion or cholestasis may confound fibrosis assessment in MRE (Akkaya et al., 2018). Compared with other modalities and non-invasive algorithms, MRE is the most accurate (Akkaya et al., 2018; Selvaraj et al., 2021). Additionally, MRE-derived LSM can predict the risk liver-related death or hepatic decompensation in MASLD (Gidener et al., 2021; Gidener et al., 2022).

Despite the greater accuracy of MR-based imaging to assess hepatic steatosis or fibrosis in MASLD, concerns around limited access, excess cost and the additional impact of MRI on treatment decision making is debated. NICE advise against MRE use in MASLD, even in those with indeterminate results from other fibrosis tests (NICE, 2023d). Moreover, patients who are unable to lie still, repeatedly hold their breath or have claustrophobia are unsuitable for this assessment (Akkaya et al., 2018). The benefits, limitations, and accuracy of these modalities to screen for hepatic steatosis and fibrosis is summarised in Table 1.15.

Table 1.15: Benefits and limitations of ultrasound and magnetic resonance imaging to screen for MASLD

Modality	Benefits	Limitations	Accuracy for HS (sensitivity/specificity)	Accuracy for HF (sensitivity/specificity)
B-mode ultrasound	High availability, low cost, identifies HCC	Operator dependant, poor accuracy for mild HS and HF	<u>>0-5% HS:</u> 73.3%/84.4%	≥1 US feature of HF: 68%/68% (D'Onofrio et al., 2005)
			<u>>10-20% HS:</u> 90.5%/69.6%	
			<u>>50-66% HS:</u> 91.1%/91.9% (Bohte et al., 2011)	
TE	Simultaneo us measure of HS and HF, quick (~5 minutes), portable	Limited by BMI, liver congestion & ascites. Unable to see focal lesions	<u>S ≥1</u> 84%/86%	<u>F ≥F1</u> 73%/80%
			<u>S ≥2</u> 79%/64%	<u>F ≥F2</u> 76%/73%
			<u>S =3</u> 75%/62% (Cao et al., 2022)	<u>F ≥F3</u> 83%/79%
				<u>F =F4</u> 83%/85% (Cao et al., 2022)
MRI- PDFF (HS), or MRE (HF)	High degree of accuracy	High cost, limited availability and use in claustrophobi a	<u>S ≥1</u> 92%/93%	<u>F ≥F1</u> 71%/85%
			<u>S ≥2</u> 79%/88%	<u>F ≥F2</u> 78%/89%
			<u>S =3</u> 71%/89% (Gu et al., 2021)	<u>F ≥F3</u> 83%/89%
				<u>F =F4</u> 81%/90% (Selvaraj et al., 2021)

Benefits, limitations, and accuracy of B-mode ultrasonography, TE, and MRI-PDFF for hepatic steatosis and hepatic fibrosis. Abbreviations: *HF* hepatic fibrosis; *HS* hepatic steatosis; *MRE* magnetic resonance elastography; *MRI-PDFF* magnetic resonance imaging-proton density fat fraction; *TE* transient elastography.

1.6.4 Combination screening: blood tests & imaging

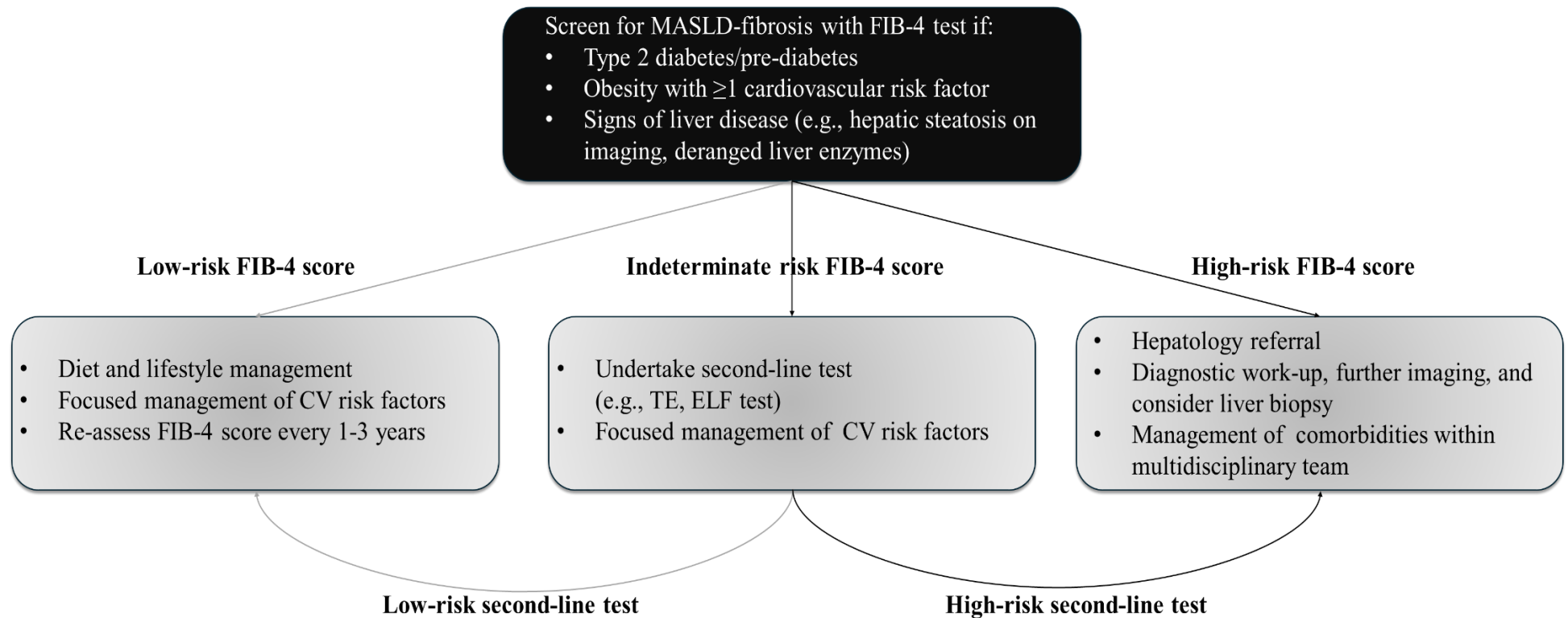
Given any test has limitations, some suggest a two-tiered screening approach for MASLD, targeted in people with specific risk factors. The APASL (Eslam et al., 2020) support screening in people with risk factors such as T2D, obesity, or metabolic syndrome using ultrasonography since 2020, with subsequent evaluation for fibrosis if steatosis is identified. More recently, the AACE (Cusi et al., 2022), AASLD (Rinella, Neuschwander-Tetri, et al., 2023), joint EASL-EASD (EASL-EASD-EASO, 2024), and Indian guidelines (Misra et al., 2025) support routine screening for hepatic fibrosis in people with risk factors such as T2D or obesity. These groups each advocate a similar approach, using the FIB-4 index initially, followed by the ELF test or TE to assess for advanced fibrosis if the FIB-4 index 1.30-2.66. If the FIB-4 score is ≥ 2.67 , patients should be referred to hepatology services, and if < 1.30 patients have the FIB-4 score repeated every 1-3 years. Guidelines highlight the need to treat modifiable CVD risk factors in, though in those with advanced fibrosis, should include multidisciplinary management. The approach suggested by international groups is summarised in Figure 1.10.

Prospective studies exploring use of sequential non-invasive tests have been taken previously. A Nottingham-based group identified patients at risk of CLD, including those with harmful alcohol use, asymptomatic raised AST:ALT ratio (≥ 0.8), or metabolic risk factors such as obesity or T2D (with FLI ≥ 60) and undertook TE. Those with a TE-LSM ≥ 8.0 kPa were referred to hepatology. Over 12 months, 968 patients in a population of ~700,000 people required TE, of whom 222 (22.9%) had elevated TE-LSM (≥ 8.0 kPa) and 57 (5.9%) had a TE-LSM indicating advanced CLD (≥ 15.0 kPa) (Chalmers et al., 2020). This approach identified many with liver cirrhosis and normal liver enzymes who would be missed using a conventional approach (Harman et al., 2015). Another group reported a model based on Fibroscan (LSM and CAP) and AST to generate the Fibroscan-AST (FAST). This had good accuracy to discriminate patients at risk of MASH in a cohort of 350 people planned to undergo liver biopsy with suspected MASLD, and later validated in international cohorts to avoid biopsy (Newsome et al., 2020). These tests represent credible methods to screen for MASLD in people at risk, and the cost-effectiveness and patient acceptability of these are discussed below. However, some studies observe that sequential non-invasive tests may be less accurate in people with T2D. For example, one study reported FIB-4 score followed by TE-LSM was had 90.3% accuracy in people without T2D, but only 79.0% accuracy in people with T2D (Boursier et al., 2023).

Further investigation has been taken combining non-invasive blood tests with MRI. A group based in the US observed that the accuracy of MRE for the detection of fibrosis in 238 patients with biopsy-proven MASLD improved when combined with the FIB-4 score to generate the MEFIB index (Jung et al., 2021). Subsequently, the group reported that the MEFIB index was more accurate than the FAST algorithm (Tamaki, Imajo, et al., 2022). The group reported the MEFIB score correlated with liver outcomes including varices, ascites, encephalopathy, and liver-related death (Ajmera, Kim, et al., 2022; Ajmera, Nguyen, et al., 2022). However, use of costly and time-consuming techniques to risk assess people for MASLD is impractical. Such assessments may have a place to avoid biopsy in those with incongruous results, but this would be discouraged in UK-based practice (NICE, 2023d; Tamaki, Imajo, et al., 2022). The use of a two-step approach using blood tests alone can reduce inappropriate referrals, with one group observing that the FIB-4 score followed by the ELF test in primary care reduced unnecessary referrals (Srivastava, Gailer, et al., 2019) and was better than any screening test in isolation.

Nevertheless, NICE do not recommend MASLD screening in neither the general population nor in those with risk factors. However, NICE do advise fibrosis risk assessment in those who are identified with fatty liver on imaging taken for another indication (NICE, 2016). Similarly, the British Association for the Study of the Liver, and British Society of Gastroenterology NAFLD special interest group suggest services should have agreed local pathways to investigate liver disease, and to consider the possibility of fibrosis secondary to MASLD in people with features of the metabolic syndrome (McPherson et al., 2022). Therefore, further work is needed locally to develop services given the lack of a nationalised process.

Figure 1.10: Clinical practice guidelines on non-invasive tests for MASLD



A flowchart adapted from recent AACE, AASLD, and EASL-EASD clinical practice guidelines for the use of non-invasive tests to screen for MASLD (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Abbreviations: *CV* cardiovascular; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; MASLD metabolic dysfunction-associated steatotic liver disease; *TE* transient elastography.

1.6.5 Cost-effectiveness of screening for MASLD

A crucial feature of a screening programme is that it should be cost-effective. This is frequently a challenge when planning to implement a strategy nationally. Numerous international studies have been performed to determine the cost-utility of various approaches. The difficulty in comparing these approaches lies in the proposed screening strategies, and varying thresholds used to determine a cost-effective approach. The key difference in these analyses is some explore MASLD screening in a general population, others investigate targeted screening in high-risk groups, such as those with greater age, T2D or obesity.

One multicentre study with 6,295 participants from six general population cohorts in Europe (France, Spain, Denmark, UK, and Germany) and Asia (Hong Kong) found that screening for MASLD or ALD in primary care using TE is cost-effective. The study used a TE-LSM ≥ 9.1 kPa to screen for significant fibrosis in MASLD and ALD, and reported an incremental cost-effectiveness ratio (ICER) €2,570 for ALD screening and €6,217 for population-based CLD screening, meaning there was 12% probability that CLD screening using TE would be cost-saving (Serra-Burriel et al., 2019).

A community-based study based in Nottingham used a serial test algorithm of the AST:ALT ratio or BARD score followed by TE to screen for CLD in people with risk factors (metabolic, alcohol, deranged liver enzymes). This identified numerous people with compensated liver cirrhosis and normal liver enzymes, who would be missed using conventional tests (Harman et al., 2015). Cost analysis reported the pathway was more effective than current practice, and cost £2138 per quality-adjusted life year (QALY) at an ICER between -£1895 to £7035/QALY. There was 85% probability of cost-effectiveness using the UK threshold of £20,000 per QALY (Tanajewski et al., 2017). Another UK-based group used a simulated cohort of 1000 people with MASLD to estimate the cost of population screening using the FIB-4 score, ELF test and TE (Srivastava, Jong, et al., 2019). The approach compared the reduction in unnecessary referrals and cost using (i) FIB-4 index followed by ELF test in those with indeterminate results, (ii) FIB-4 index followed by TE in those with indeterminate results, (iii) ELF test alone, or (iv) TE alone compared with the standard of care. The authors reported that scenario (i), (ii), (iii), or (iv) reduced unnecessary referrals by 85%, 78%, 71% and 42%, with cost-savings of 25.2%, 22.7%, 15.1% and 4.0%, respectively (Srivastava, Jong, et al., 2019).

Most recently, Forlano and colleagues screened for MASLD in primary care including 300 people living with T2D in London using the ELF test, FIB-4 index, and TE. They reported 11% and 3% had advanced fibrosis or compensated cirrhosis, respectively (Forlano et al., 2024).

Each of the approaches trialled were associated with QALY gains, and TE and FIB-4 tests had greatest benefit. Per QALY, the observed ICER was £2480 for TE, £2541 for ELF and £2060 for FIB-4 (Forlano et al., 2024), cost-effective based on NICE thresholds.

Similar observations have been reported elsewhere. One American-based study explored the cost effectiveness of MASLD screening in people with T2D. The authors reported screening with ultrasound plus ALT or AST measurements followed by TE with lifestyle intervention in those with predicted MASLD fibrosis stage 2 or greater was cost-effective. In people with T2D aged greater than 55 years, annual screening using this approach cost \$36,000/QALY, and in people aged over 40 years cost \$18,000/QALY. The study suggested in areas with limited TE, the FIB-4 score would represent a cost-effective alternative (Noureddin et al., 2020). Another US-based study observed a combination of FIB-4 index and TE resulted in greatest diagnostic accuracy in people with cirrhosis and lowest cost of several non-invasive tests. The estimated cost was \$401-\$1024/person, depending on MASLD cirrhosis prevalence. The study reported the FIB-4 index followed by MRE was next most costly, followed by TE plus liver biopsy and each of these were cost-effective based on US thresholds (Vilar-Gomez, Lou, et al., 2020).

A Canadian-based study used an algorithm including the NFS, TE, acoustic radiation force impulse imaging, and plasma cytokeratin-18 with confirmation testing using MRE or liver biopsy. Compared with no screening, the proposed approach was associated with an ICER of CAN \$9,051 and CAN \$7,991 in people with obesity or T2D, compared to the ICER in the general population of CAN \$26,143 (Zhang et al., 2015). Another Canadian cost-effectiveness study reported the most cost-effective strategy to diagnose MASLD was combining FIB-4 score and ultrasound with shear-wave elastography (Congly et al., 2021). Likewise, a MASLD screening programme undertaken in patients with metabolic syndrome in Thailand using ultrasonography and the NFS was cost-effective with ICER of \$958 per QALY (Phisalprapa et al., 2017). A Singapore-based study offered ultrasound-based screening to all patients aged ≥ 50 years old with T2D and were subsequently diagnosed with advanced fibrosis if the FIB-4 score ≥ 3.25 or TE-LSM ≥ 15 kPa. Those identified with advanced fibrosis were enrolled on an lifestyle intervention course. The study estimated the cost of TE at \$25,000/QALY, compared with the FIB-4 score at \$36,800/QALY and any treatment for MASLD costing less than \$750 annually would be cost effective (Choo et al., 2022).

Nevertheless, some studies report that MASLD screening is not cost-effective using other approaches. One study observed use of the NFS to screen for MASLD fibrosis in a simulated cohort of 10,000 Americans with MASLD was most cost-effective at a willingness-to-pay

threshold of \$100,000 (Tapper et al., 2016), unlikely acceptable in European practice (EASL-EASD-EASO, 2024). A different approach, inconsistent with usual practice, modelled a screening algorithm of abdominal ultrasound followed by liver biopsy in people identified to have significant hepatic steatosis using a hypothetical cohort of people with T2D in America. The model assumed those with confirmed MASH were treated with therapies available in 2016. However, as this associated with a decreased QALY of 0.02 years, the process was neither cost-effective nor appropriate (Corey et al., 2016).

The studies discussed in this section demonstrate a two-tiered approach to MASLD screening using routinely available and non-patented blood tests followed by TE or patented tests such as the ELF test is likely cost-effective when used with a meaningful intervention, in high-risk cohorts. However, most evidence is from North American studies and should be interpreted cautiously when generalising to other populations, and further UK-based studies are needed.

1.6.6 Understanding and acceptability of MASLD screening

Despite MASLD becoming the leading cause of CLD, there remains a lack of awareness and understanding amongst the public, people at risk, and even practising physicians (Eskridge et al., 2023). Naturally, improved MASLD awareness amongst patients may provide additional motivation to improve their health and progressive disease (Kjaergaard et al., 2024). Improved clinician awareness may support earlier identification of MASLD to permit intervention (Allen et al., 2024), and counselling. As proposed by Wilson and Junger (Wilson & Junger, 1968), an integral part of any screening programme is the proposed investigations must be acceptable to the proposed population. This may be an even greater consideration in people with T2D, who already undergo extensive regular screening for complications in the UK (NICE, 2019, 2026). Therefore, it is important to establish barriers and enablers in people with T2D or other risk factors which may support the development of a MASLD screening programme. Before this can be introduced, studies exploring patient and clinician understanding of MASLD and the acceptability of additional MASLD screening methods are needed. Joined up efforts between people living with MASLD or risk factors for MASLD and liver experts are needed to develop guidelines and protocols for screening (Lazarus et al., 2022).

1.6.6.1 Patient awareness

There is a lack of awareness in the general population about MASLD. An American study surveyed 5,000 individuals, and only 2% reported hearing about MASLD from their doctors, and 20% had heard of liver cirrhosis. Importantly, 84% were unaware of conditions which cause MASLD or cirrhosis, and 96% were unaware of its reversibility at earlier stages (Ghevariya et al., 2014). A telephone survey of 521 people in the general population in Hong Kong revealed 42% did not know how common MASLD was, 47% did not know symptoms of MASLD, and 78% believed blood tests were accurate to provide definite diagnosis. The commonest risk factors were thought to be smoking, HBV and hepatitis A infection (Leung et al., 2009). Likewise, in a study of 500 adults in the general Singaporean population, 91.2% agreed regular screening was important. However, 25% were unaware of MASLD, and 12.3% were aware MASLD can progress to cirrhosis. Around 25% correctly identified risk factors for MASLD such as T2D, dyslipidaemia and hypertension, and 45% reported that fibrosis in MASLD was associated with a lack of exercise, obesity, and alcohol excess (Tan et al., 2021).

There is a similar lack of awareness in people with risk factors or diagnosis of MASLD. In a population-based cross-sectional study of 825 patients with MASLD, 8.1% of people with diagnosed hepatic steatosis on imaging knew they had MASLD. Whilst MASLD awareness increased with progressive fibrosis on TE, only 17.9% of people with stage 3-4 fibrosis reported knowing they had MASLD, compared with 11.8% with stage 2 fibrosis and 4.9% with stage 0-1 fibrosis (Ciardullo et al., 2021). A Singaporean study taken at a gastroenterology public forum included 227 participants with a 40% prevalence of MASLD and 7% had T2D. Of these, 71% had heard of MASLD previously, and 25% felt they were at risk of MASLD with no significant difference in perceived risk between those with or without metabolic syndrome features. Of participants with ≥ 1 metabolic risk factor of MASLD, 76% did not feel at risk of MASLD (Goh et al., 2016). Only 18% were aware of MASLD in a questionnaire-based study of 302 adults with high metabolic risk attending endocrinology outpatients in the US. Moreover, there was no greater awareness of MASLD in people living with T2D or obesity. However, 75% of respondents reported interest in learning more about MASLD, suggesting opportunity for public health intervention (Wieland et al., 2015). Qualitative studies exploring the understanding of people with T2D about MASLD and its relationship with IR highlight the need for further education and integration of MASLD content into routine T2D educational programmes (Alemany-Pages et al., 2020).

1.6.6.2 Physician awareness

There are also concerns about the working knowledge of practising doctors and other health professionals about MASLD. The recent change in nomenclature for people diagnosed with SLD was partly driven to improve clinician understanding of its metabolic causes and consequences (Rinella, Lazarus, et al., 2023). An Australian study including 100 hospital specialists and specialists-in-training found 75% believed the population prevalence of MASLD was $\leq 10\%$. Despite over 90% of respondents knowing that obesity, dyslipidaemia and T2D are risk factors for MASLD, 90% felt that MASLD was uncommon in their practice. Interestingly, 75% agreed that liver enzymes alone are not useful to diagnose MASLD or MASH, but two-thirds indicated bi-annual monitoring of liver function tests was an effective method to monitor for MASLD progression (Bergqvist et al., 2013). Such contradictions may stem from clinicians' perception of their practice as they reflect on what feels practical and familiar. Here, measuring liver function tests may feel both practical and familiar and as many with previously identified MASLD will not have this documented, its prevalence in practice may feel low. Clinicians may also be unfamiliar with recent guideline updates, as shown in a recent study of 584 physicians in the Middle East and North Africa. This highlighted issues around understanding symptoms of MASLD, and unawareness of international guidelines, appropriate tests, and use of pharmacotherapies which benefit MASLD (Alqahtani et al., 2025). Indeed, a Canadian survey of 214 general practitioners (GPs), hospital specialists and hepatology nurses, 58%, 28% and 39% reported they were unfamiliar or somewhat familiar with MASLD, and 53%, 20% and 35% thought prevalence of MASLD was $\leq 15\%$, respectively. Only 17% and 8% of GPs reported they would consider using vitamin E or pioglitazone to treat MASLD (the drug treatment standard at the time), but 22% would use metformin, and 38% would use a statin to treat MASLD (Sebastiani et al., 2021). Other surveys undertaken in primary care observed that GPs significantly underestimate the prevalence of MASLD in their practice, and many report that they do not have the confidence or knowledge to undertake further assessment in patients with MASLD (Patel et al., 2018; Said et al., 2013).

These studies highlight a lack of awareness and understanding of MASLD amongst doctors and hepatology nurses internationally, but there is little evidence amongst UK-based clinicians. This is important as greater awareness may support earlier disease recognition and its risk factors to permit intervention and minimise progressive fibrosis and associated morbidity.

1.6.6.3 Acceptability of MASLD screening

It is essential that screening for an important health problem is undertaken using acceptable methods to both patients and clinicians. Studies support the acceptability of additional blood tests or TE to screen for liver fibrosis in people who inject drugs and/or have HCV (Crowley et al., 2017; Marshall et al., 2015), HBV (Xia et al., 2019), and excess alcohol intake (Eyles et al., 2013; Matthews et al., 2019), amongst other CLD risk factors (Malekzadeh & Poustchi, 2011). Though it is important to establish similar acceptability in people with suspected MASLD. Reasons that the acceptability of TE to screen for MASLD in people with metabolic risk may be different is related to their understanding of the relative risks of developing CLD complications compared to those with other risk factors, such as alcohol excess or viral hepatitis. Differences may relate to what changes, if any, would be made to their therapies compared to other causes of CLD, if diagnosed.

A qualitative study explored patient acceptability of CLD screening in 20 adults with risk factors for CLD (e.g., excess alcohol, T2D, or persistently elevated liver enzymes), and explored their views on the use of TE to screen for CLD in primary care (Knight et al., 2020). Participants had previously experienced screening for CLD using TE in the previous 6-24 months, as part of another study. All-but-one participant identified alcohol excess as a risk factor, but none were aware that T2D increased CLD risk, and only one knew the association between CLD and obesity. The authors reported that for most participants, additional screening for CLD in primary care was welcomed, and motivation was driven by desire to detect liver disease earlier to support treatment. Most reported TE was acceptable, and all were able to understand the results related to “liver stiffness”. The study highlighted the way the TE scores (i.e., CAP and LSM) were communicated was central to their perception of their risk of developing CLD. Importantly, the TE results improved participants’ understanding of their risk, prompted contemplation of lifestyle changes for CLD prevention, and was an acceptable screening method (Knight et al., 2020). However, dedicated studies exploring patient acceptability of TE to screen for MASLD are lacking. Acceptability of TE to screen for MASLD in people with metabolic disturbance was inferred by one study, which observed greater than 90% compliance over 4 years of annual TE scans following bariatric surgery (Liu et al., 2021), but no qualitative measures were reported.

Qualitative studies report patients and healthcare providers agree that there are five key themes to any CLD screening process, including (M. J. Allen et al., 2023):

- i. Convenience and ease of access, such as travel distance, cost, ease of appointments.
- ii. Worker and consumer interaction, e.g., personal interactions, trust in professionals.
- iii. Consumer motivation, e.g., test discomfort, likelihood of further tests or treatment.
- iv. Screening test and process, such as waiting times, and accuracy of tests taken.
- v. System level issues, including staff training about the condition, and service provision.

Amongst both healthcare professionals and service users, the targeted screening of individuals with high-risk of CLD using non-invasive tests, including those with T2D or obesity, was acceptable in a qualitative study in the UK. A community-based liver health check in Bristol was seen as a novel opportunity, convenient, and had potential for impact by service users and providers (Archer et al., 2024). Another UK-based study including health practitioners across multidisciplinary diabetes clinics in primary and secondary care reported additional MASLD assessment would improve patient care and could be incorporated into routine review. However, many participants reported a lack of knowledge on the consequences of MASLD, issues related to access of required resources and investigations to deliver the additional assessment, and the potential to overburden patients with information (Gracen et al., 2022).

There are ongoing studies exploring the acceptability of additional blood tests and TE in the primary care setting amongst healthcare providers and patients to screen for MASLD (Brain et al., 2020; Brindley et al., 2023). However, there are limited published data to determine the acceptability of additional CLD screening using additional blood tests with or without TE or other imaging to support its use, and further evidence is needed before its routine use.

1.7 Study rationale, aims and objectives

1.7.1 Study rationale

There have been substantial advances in the last 20-30 years in the management of people with T2D, given a shift in approach to identifying and treating modifiable risk factors for microvascular and macrovascular complications. Together with the introduction of newer pharmacotherapies which reduce the risk of cardiovascular complications, the burden of such complications has improved. Alongside this, MASLD has emerged as a significant contributor to adverse long-term outcomes, and studies highlight its growing prevalence in high-risk groups and a growing number of therapies which halt or reverse MASLD progression.

Despite growing understanding and appreciation of MASLD, this often remains unrecognised in clinical practice through a lack of screening process, competing clinical priorities and often limited awareness from both patients and clinicians. Therefore, better identification of liver-related complications represent a critical unmet need in contemporary diabetes care. This is particularly topical in the UK, as national guidance is currently being updated and may soon reflect the need to screen for liver disease in high risk groups.

The study is motivated by the need to further integrate liver health care into routine diabetes practice. Piloting screening approaches for new care models are needed to identify patients with MASLD. This would permit appropriate management strategies and healthcare utilisation to prevent disease progression and support holistic CVD prevention in this group.

1.7.2 Aims and objectives

This thesis aimed to explore the relationship between MASLD with T2D and/or obesity, and to pilot MASLD screening strategies in these patient groups in Swansea Bay University Health Board (SBUHB). The specific objectives of this thesis are:

- i. To determine whether TE or blood biomarkers can reliably predict hepatic steatosis or fibrosis in patients with MASLD and T2D or obesity in Swansea.
- ii. To determine the associations between T2D and glycaemic control on the development of hepatic steatosis and fibrosis, and vice-versa, in people with MASLD.
- iii. To determine the prevalence of MASLD and advanced hepatic fibrosis using non-invasive tests in people with T2D.
- iv. To determine whether clinical or blood biomarkers can predict hepatic steatosis or advanced hepatic fibrosis in people with T2D.
- v. To determine whether clinical or biochemical predictors of hepatic steatosis or fibrosis associate with predicted CVD risk in people with T2D.
- vi. To determine the feasibility of using blood biomarkers or TE to screen perioperatively for advanced hepatic fibrosis prior to bariatric surgery in patients with obesity.
- vii. To evaluate the understanding of MASLD in people with diabetes and their views around need for and appropriate methods of MASLD screening.
- viii. To evaluate the understanding of MASLD in clinicians working in Wales, and their views around the need for and appropriate methods of MASLD screening.

Chapter Two:

Methods

2.1 Introduction and aims

This was a mixed-methods clinical research study, investigating the utility, application and acceptability of non-invasive investigations for MASLD in people with T2D or obesity.

The investigation was accomplished using four main studies, to address the aims and objectives presented in chapter 1. This is summarised in Figure 2.1, and each study is discussed in detail throughout the chapter.

Figure 2.1: Overall study design



The design and participants, aims and relevant chapters for each of the studies in this investigation. Abbreviations: CV cardiovascular; HS hepatic steatosis; HF hepatic fibrosis; MASLD metabolic dysfunction-associated steatotic liver disease; NIT non-invasive test; SBUHB Swansea Bay University Health Board; T2D type 2 diabetes; TE transient elastography.

2.2 Study 1: Patients with MASLD following liver biopsy in Swansea Bay

2.2.1 Study design

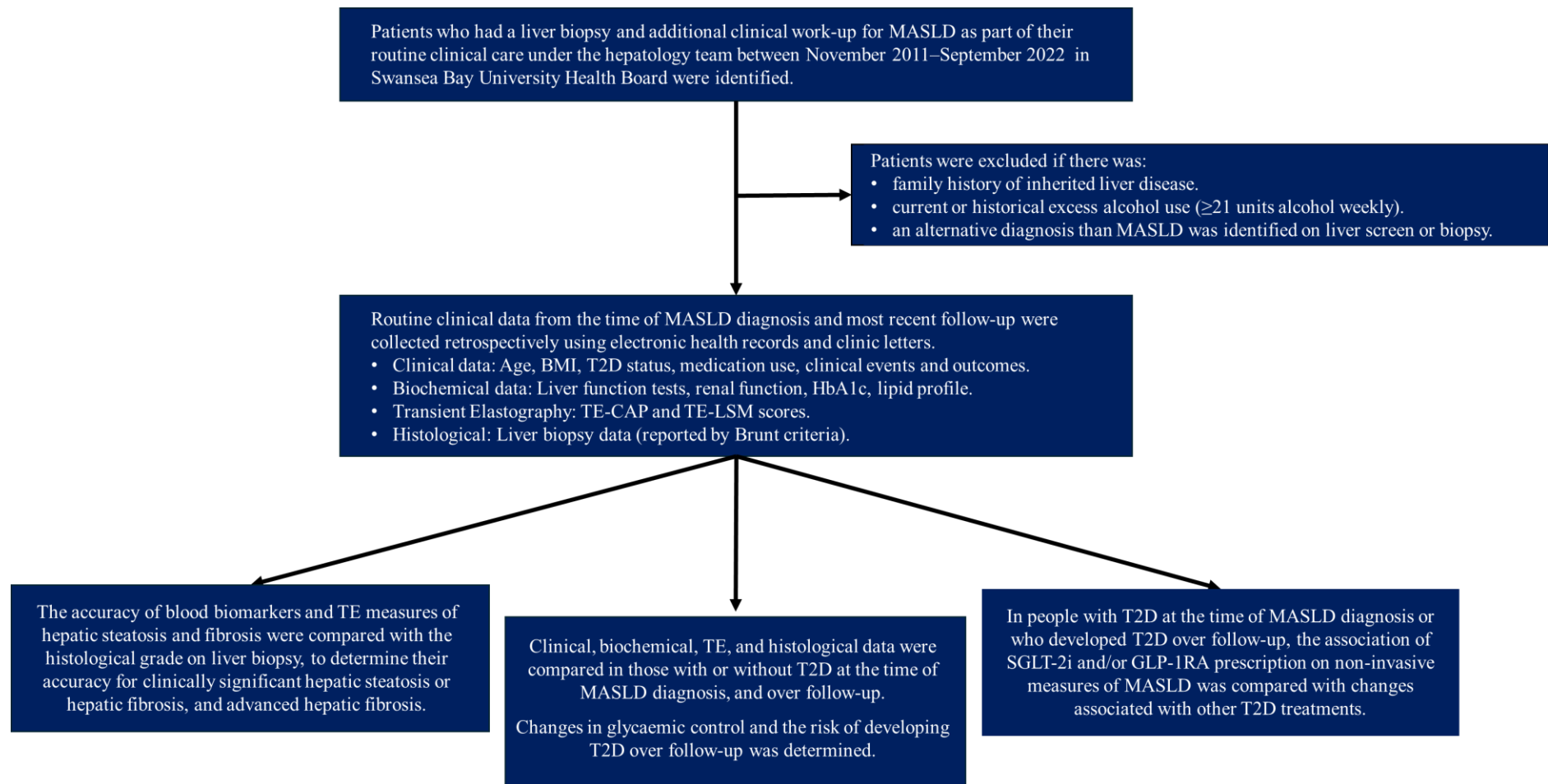
This was a retrospective cohort study of patients diagnosed with MASLD using liver biopsy between November 2011-September 2022. Diagnosis was confirmed under the care of the hepatology team at hospitals based in SBUHB (Morriston Hospital, Neath Port Talbot Hospital, or Singleton Hospital). The study design is presented in Figure 2.2.

2.2.2 Participants

Participants were patients in SBUHB who had MASLD confirmed on liver biopsy, and each sample was reported using the Brunt criteria (Brunt et al., 1999; Kleiner et al., 2005). These patients had been initially referred by primary or secondary care teams with deranged liver function tests, or the incidental finding of a fatty or fibrotic liver on imaging such as ultrasound, CT or MRI. Other causes of hepatic steatosis were excluded through clinical history and further investigations as part of their routine care. Patients included did not drink more than 21 units of alcohol per week at the time of MASLD diagnosis or have a history of alcohol excess, in keeping with national guidance at the time. Routine investigations were taken to exclude other causes such as viral hepatitis (HBV and HCV serology), autoimmune hepatitis (ANA, anti-smooth muscle antibodies, anti-mitochondrial antibodies), and other metabolic causes (ferritin, and if relevant, alpha-1-antitrypsin or caeruloplasmin levels). Most patients were followed up locally to monitor for progressive liver disease, decompensation, HCC, and for treatment.

Patients were deemed to have a diagnosis of T2D if the HbA1c was 48 mmol/mol [6.5%] or greater, and to have a diagnosis of prediabetes if the HbA1c was 42-47 mmol/mol [6.0-6.5%], as per current international guidelines.

Figure 2.2: Design of study 1



The design of study 1. Abbreviations: *BMI* body mass index; *CAP* controlled attenuation parameter; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *HbA1c* glycosylated haemoglobin; *LSM* liver stiffness measure; *MASLD* metabolic dysfunction-associated steatotic liver disease; *SGLT2i* sodium-glucose co-transporter-2 inhibitor; *T2D* type 2 diabetes; *TE* transient elastography. Figure adapted with permission from (Williams et al., 2024)

2.2.3 Data collection

Data which were routinely collected by the clinical hepatology team were used. Electronic health records were accessed through clinical databanks such as Welsh Clinical Portal and an older local databank used at the time of these participants' clinical care called Abertawe Bro Morgannwg University Clinical Portal. Clinic letters, GP letters and biochemical, radiological, or histopathological tests undertaken for routine clinical purposes were used to collect data. Routinely collected data including patient demographics (e.g., age, gender, BMI, postcode), biochemical data (e.g., LFTs, renal function, HbA1c), radiological data (TE), and histopathological data from liver biopsy were collected. Histopathology data which had been incompletely reported were reviewed by Dr Namor Williams, a consultant histopathologist working in SBUHB, to clarify the diagnosis and confirm various scores required by the Brunt criteria. The Welsh Index of Multiple Deprivation (WIMD) was used to measure deprivation, which uses postcode data to classify participants into deciles by deprivation score. Lower WIMD scores indicate greater deprivation, and higher scores indicate lesser deprivation.

Data collected within 12 months of the liver biopsy were taken as baseline, and data from the most recent clinical follow-up were collected. Using these routine data, non-invasive measures of hepatic steatosis and fibrosis were calculated. Biomarkers which could be determined from these routine data included the AST:ALT ratio, APRI, BARD score, FIB-4 score, HSI, NFS, TE-CAP and TE-LSM scores. These were calculated by me using freely-available algorithms. Transient elastography was undertaken by various members of the hepatology team, including consultant hepatologists, specialist nurses and trained support workers during their routine clinic appointments. The thresholds used to define stages of hepatic steatosis and fibrosis are presented in Table 2.1. Thresholds used were determined by previously published cut-offs, or from the manufacturer. Clinically significant hepatic steatosis was hepatic steatosis stage 2 or 3, clinically significant hepatic fibrosis was hepatic fibrosis stage 2, 3 or 4, and advanced fibrosis was hepatic fibrosis stage 3 or 4 using the Brunt criteria.

2.2.4 Funding and ethical approval

No additional funding was received to undertake this study. This study was completed as part of a local service evaluation and quality improvement project taken in collaboration between the hepatology and diabetes teams in SBUHB. All data used were routinely collected as part of that patients' clinical care, gathered retrospectively, and analysed anonymously. The work was approved as a service improvement project by the hepatology clinical lead and therefore, ethical approval was not required.

Table 2.1: Non-invasive test thresholds used in this analysis

Condition	TE- CAP (dB/m)	TE- HSI LSM (kPa)	APRI	AST:ALT ratio	BARD score	FIB-4 score	NFS
Clinically significant steatosis [stage 2-3]	≥331.0	≥36.0	-	-	-	-	-
Clinically significant fibrosis [stage 2-4]	-	-	≥8.2	≥0.7	≥0.8	≥2.0	≥1.3
Advanced fibrosis [stage 3-4]	-	-	≥9.7	≥0.7	≥0.8	≥2.0	≥1.3

Non-invasive tests and thresholds used to screen for hepatic steatosis and hepatic fibrosis (Angulo et al., 2007; Eddowes et al., 2019; Harrison et al., 2008; J. H. Lee et al., 2010; Lin et al., 2011; McPherson et al., 2010). Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter; *FIB-4* fibrosis-4; *HSI* hepatic steatosis index; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *TE* transient elastography.

2.2.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US) throughout. Figures were produced using Microsoft Excel for Microsoft 365 (version 2503), Microsoft PowerPoint for Microsoft 365 (version 2503), or SPSS (version 29). Categorical data were presented as the number (%), and statistical significance of differences in categorical data were determined using a Chi-squared test. Continuous data were checked for normality using the Kolmogorov-Smirnov test and visualised using Q-Q plots. Normally-distributed continuous data were presented using the mean±standard deviation (SD), and continuous data which did not display a normal distribution are presented by the median [IQR]. The statistical significance of differences in normally distributed data were determined by student's t-test or one-way analysis of variance (ANOVA), and the statistical significance of differences in continuous data not following a normal distribution determined using the Kruskal-Wallis test, Mann-Whitney U test or Wilcoxon signed-rank test. The statistical significance of differences in data were determined using paired data and considered at $p < 0.05$.

In chapter three, the sensitivity, specificity, PPV, and NPV for non-invasive tests to diagnose stages of hepatic steatosis and fibrosis were determined. The formulas used to calculate these values are presented in Table 2.2. A receiver operating characteristic (ROC) analysis was performed for each non-invasive test to predict different stages of hepatic steatosis or fibrosis on biopsy, presented by the AUC (95% confidence interval (CI)). The statistical significance of differences between the observed AUC and that expected by chance (i.e., AUC=0.5) was determined by t-test. A further t-test compared the statistical significance of differences between the AUC for the same test in people with or without T2D, or by BMI status. The optimal screening cut-off for each test to identify hepatic steatosis or fibrosis was determined by the corresponding test score using Youden's index derived from the ROC analysis, and the sensitivity and specificity of that test at the optimal cut-off is presented. The ROC analysis was supported by Dr Ivy Cheung, a statistician working in the diabetes research group at Swansea University Medical School. In chapter four, a logistic regression analysis was performed to determine the statistical significance of associations between baseline variables and risk of developing T2D over follow-up.

Table 2.2: Calculating the accuracy of non-invasive tests

Test	Formula
Sensitivity	$\frac{\text{True positives}}{\text{True positives} + \text{false negatives}}$
Specificity	$\frac{\text{True negatives}}{\text{True negatives} + \text{false positives}}$
PPV	$\frac{\text{True positives}}{\text{True positives} + \text{false positives}}$
NPV	$\frac{\text{True negatives}}{\text{True negatives} + \text{false negatives}}$

Formulae used to calculate measures used to define non-invasive test accuracy in the study. Abbreviations: *NPV* negative predictive value; *PPV* positive predictive value.

2.3 Study 2: Screening for MASLD in people with type 2 diabetes attending secondary care

2.3.1 Study design

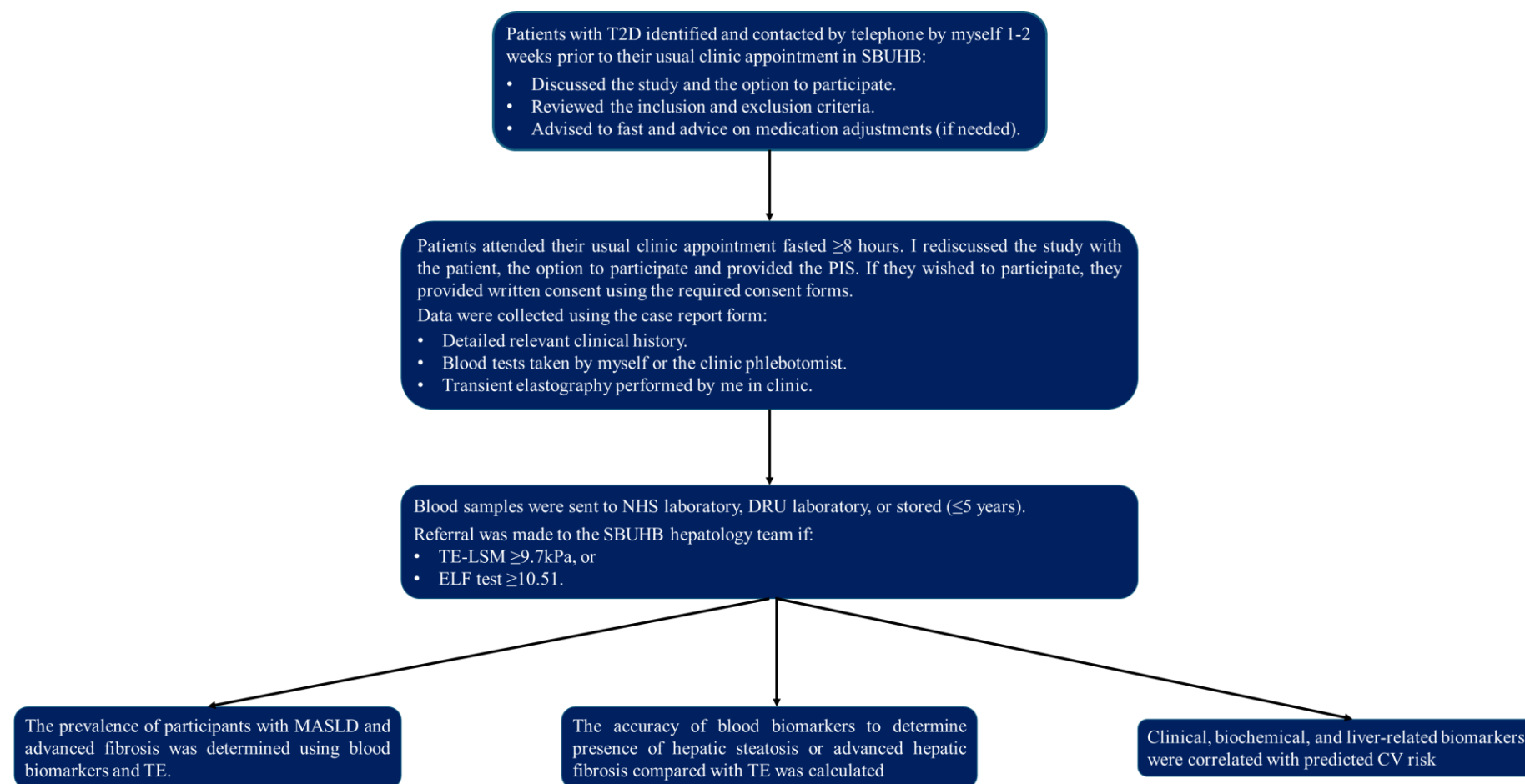
This was a prospective, cross-sectional pilot study to determine the prevalence of MASLD and advanced fibrosis using non-invasive tests in patients treated for T2D within secondary care services in SBUHB (Morrison Hospital, Neath Port Talbot Hospital, or Singleton Hospital). Data were collected October 2023–July 2024. The study design is shown in Figure 2.3.

2.3.2 Participants

All participants were adults treated for T2D under secondary care services in SBUHB. Participants did not have previously diagnosed liver disease and were not currently under investigation for liver disease. The inclusion and exclusion criteria are presented in Table 2.3.

Participants were contacted 1-2 weeks in advance of their planned diabetes appointment by me to discuss the study and review the inclusion and exclusion criteria. In their diabetes clinic, they re-discussed the study with me and were provided with a participant information sheet (PIS). The PIS used is presented in Appendix II, Figure 12.1. Participants provided written and informed consent to take part in the study. Participants were asked to provide written consent to join a MASLD in T2D registry to permit follow-up studies, including storage of an additional plasma sample for future analysis in the next 5 years. The consent forms used to take part in the study, and for participation in future research are presented in Appendix II, in Figure 12.2 and Figure 12.3, respectively. Their participation was communicated to their GP following the clinic appointment, using the standardised letter presented in Appendix II, Figure 12.4, and their results and any actions taken (such as referral to hepatology team) were communicated to their GP, when available.

Figure 2.3: Design of study 2



The design of study 2. Abbreviations: *CV* cardiovascular; *DRU* diabetes research unit; *ELF* enhanced liver fibrosis; *LSM* liver stiffness measure; *MASLD* metabolic dysfunction-associated steatotic liver disease; *NHS* national health service; *SBUHB* Swansea Bay University Health Board; *PIS* participant information sheet; *T2D* type 2 diabetes; *TE* transient elastography.

Table 2.3: Inclusion and exclusion criteria used for study 2

Inclusion		Exclusion	
i.	Aged ≥ 18 years.	i.	Known or suspected excess alcohol intake defined as regular ingestion of >14 units of alcohol per week.
ii.	Clinical diagnosis of T2D managed within secondary care in SBUHB.	ii.	Previously diagnosed or currently suspected CLD of any cause.
iii.	Able and willing to provide written informed consent.	iii.	Family history of inheritable liver disease.
		iv.	Previous surgical treatment for the treatment of obesity.
		v.	Diagnosis of diabetes other than T2D.
		vi.	Current pregnancy.
		vii.	Unable or unwilling to provide written informed consent.

Inclusion and exclusion criteria used for study 2. Abbreviations: *CLD* chronic liver disease; *SBUHB* Swansea Bay University Health Board; *T2D* type 2 diabetes.

2.3.3 Data collection

Data were collected during the clinic appointment by me, using a standardised case report form, presented in Appendix II, Figure 12.5. The participants' past medical and surgical history, medication use, and risk factors for liver disease such as family history, alcohol-related history, and recreational drug use were collected. Postcode data were used to calculate the WIMD. Their clinical frailty score (CFS) was documented, a measure of frailty, scoring between 1 (very fit) and 9 (terminally ill) (Rockwood & Theou, 2020). Their Charlson Comorbidity Index (CCI) was calculated, originally developed to predict 10-year all-cause mortality (Charlson et al., 1987). The presence or absence of each feature of the metabolic syndrome was determined using the criteria described by the multi-society consensus statement from the IDF, American heart association, and others (Alberti et al., 2009). However, BMI was used instead of waist circumference as this was not collected in the study. The criteria used are presented in Table 2.4. A metabolic syndrome diagnosis was made if a participant had three or more features.

Table 2.4: Definitions of the features used to diagnose the metabolic syndrome

Variable	Criteria
1. Body mass index	$\geq 30.0 \text{ kg/m}^2$
2. High triglycerides	$\geq 1.7 \text{ mmol/L}$
3. Hypertension	$\geq 130/85 \text{ mmHg}$, or antihypertensive drug treatment
4. Low HDL cholesterol	$< 1.0 \text{ mmol/L}$ (males) or $< 1.3 \text{ mmol/L}$ (females)
5. Hyperglycaemia	$\text{FBG} \geq 5.6 \text{ mmol/L}$, or diagnosis of T2D

Criteria used to diagnose features of the metabolic syndrome. Abbreviations: *FBG* fasting blood glucose; *HDL* high density lipoprotein; *T2D* type 2 diabetes.

The patient attended their usual diabetes clinic following at least 8 hours fasting. Their weight, BMI and BP were recorded, and blood and urine samples were collected. Tests included their diabetes annual review, and research tests, presented in Table 2.5. Diabetes annual review tests were processed as usual through SBUHB NHS laboratories. Additional research tests were initially processed in SBUHB NHS laboratories before analysis. In SBUHB laboratories, the full blood count and coagulation screen were analysed using the Sysmex XN9000 and Sysmex CS5100 automated analysers, respectively. Liver function tests (including AST and GGT), and fasting blood glucose were measured using standardised Roche Cobas assays. Tests in SBUHB NHS laboratories were analysed in real-time alongside routine workload. Separate aliquots were made on the automated sample sorter in SBUHB NHS laboratories 3-6 hours following arrival in the laboratory, and frozen at -80°C . These samples were sent weekly (ambient) to the University Hospital of Wales (Cardiff) on routine pathology transport to process the ELF test using the Siemens ADVIA Centaur automated immunoassay. A further sample was spun, separated and frozen at -80°C on arrival at the SBUHB NHS laboratory. These samples were packaged in an insulated box with dry ice and transported to the diabetes research unit at Swansea University. Here, fasting insulin was measured by an enzyme-linked immunosorbent assay (ELISA) kit, and the fasting c-peptide was measured using a chemiluminescent immunoassay kit, supplied by Invitron Ltd, and processed in batch analysis at study completion. All measurements followed standardised manufacturer protocols and additional internal quality control procedures.

Table 2.5: Blood and urine tests undertaken as part of study 2

Routine diabetes-related tests	Research-related tests
• HbA1c • Urea & electrolytes • Lipid profile (fasting) • Urinary ACR	• Full blood count • Liver enzymes (including AST and GGT) • ELF test • Coagulation screen • Fasting blood glucose, C-peptide and insulin

Diabetes and research-related tests taken in the diabetes clinic appointment. Abbreviations: *ACR* albumin-to-creatinine ratio; *AST* aspartate transaminase; *ELF* enhanced liver fibrosis; *GGT* gamma-glutamyl transferase.

From these tests, measures of hepatic steatosis (HSI, NAFLD-LFS, TyG), hepatic fibrosis (APRI, AST:ALT ratio, BARD score, FIB-4 score, NFS), and IR (Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)) were calculated by me. All participants underwent TE in the diabetes clinic, performed by me, using one of two fibroscan 430 Mini devices (Echosens; serial numbers F92263 and F92540). A valid TE-LSM score required at least 10 valid scans, with an IQR/median ratio <30% using the appropriate “M” or “XL” probe. Following TE, participants provided feedback using the questionnaire presented in Appendix II, Figure 12.6. Thresholds used to define stages of hepatic steatosis and fibrosis using TE are presented in Table 2.6, and using blood biomarkers in Table 2.7.

Table 2.6: Thresholds used to define stages of hepatic steatosis and fibrosis on transient elastography in study 2

Hepatic steatosis was defined by the TE-CAP:
• Normal [stage 0]: <302 dB/m • Moderate [stage 1-2]: 302-336 dB/m • Severe [stage 3]: ≥337 dB/m
Hepatic fibrosis was defined by the TE-LSM:
• Normal [stage 0-1]: <8.2 kPa • Moderate [stage 2]: 8.2-9.6 kPa • Advanced [stage 3-4]: ≥9.7 kPa

Thresholds to define the risk of hepatic steatosis and fibrosis in study 2 (Eddowes et al., 2019). Abbreviations: *CAP* controlled attenuation parameter; *LSM* liver stiffness measure; *TE* transient elastography.

Table 2.7: Thresholds used for blood biomarkers to determine the risk of hepatic steatosis or advanced hepatic fibrosis

Measures of hepatic steatosis	
HSI	Low risk: <30.0
	Moderate risk: 30.0-36.0
	High risk: ≥36.0
NAFLD-LFS	Low risk: ≤-0.64
	Moderate risk: -0.63-0.15
	High risk: ≥0.16
TyG	Low risk: <4.5
	High risk: ≥4.5
Measures of hepatic fibrosis	
FIB-4 score	Low risk: <1.30
	Moderate risk: 1.30-2.66
	High risk: ≥2.67
ELF test	Low risk: <7.8
	Moderate risk: 7.8-9.7
	High risk: ≥9.8
	Very high risk: ≥10.51
APRI	Low risk: <0.70
	Moderate risk: 0.70-0.99
	High risk: ≥1.00
AST:ALT ratio	Low risk: <0.80
	High risk: ≥0.80
BARD score	Low risk: <2
	High risk: ≥2
NFS	Low risk: <-1.455
	Moderate risk: -1.454 – 0.67
	High risk: ≥0.675

Blood biomarker thresholds to define severe hepatic steatosis or advanced hepatic fibrosis in study 2 (Angulo et al., 2007; Harrison et al., 2008; Kotronen et al., 2009; J. H. Lee et al., 2010; Lin et al., 2011; McPherson et al., 2010; Salazar et al., 2017; Younossi, Felix, et al., 2021). Abbreviations: *ALT* alanine aminotransferase; *APRI* AST-to-platelet ratio index; *AST* aspartate transferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *HSI* hepatic steatosis index; *NFS* non-alcoholic fatty liver disease score; *NAFLD-LFS* non-alcoholic fatty liver disease liver fat score; *TyG* triglyceride and glucose index.

2.3.4 Funding and ethical approval

No additional funding was received to undertake the study. The costs of the additional tests described in Table 2.5 were sponsored by the research and development department in SBUHB. The study received a favourable opinion from the Research Ethics Committee (REC) in Wales in May 2023; the confirmation letter is presented in Appendix II, Figure 12.7. The Health Research Authority (HRA), and Health and Care Research Wales (HCRW) confirmed approval in May 2023; the confirmation letter is shown in Appendix II, Figure 12.8. Approval to commence the study from SBUHB was received in October 2023, presented in Appendix II, Figure 12.9. A minor amendment was approved in October 2024 to permit ongoing analysis of samples which had been collected, presented in Appendix II, Figure 12.10 and Figure 12.11.

2.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503), Microsoft PowerPoint for Microsoft 365 (version 2503), or SPSS (version 29). Categorical data are presented by the number (%), and statistical significance of differences in categorical data determined by Chi-squared test. Continuous data were checked for normality using the Kolmogorov-Smirnov test and visualised using Q-Q plots. Normally distributed continuous data were presented using the mean $\pm$ SD, and continuous data which did not display a normal distribution presented by the median [IQR]. The significance of differences between data which did not follow a normal distribution were determined by Mann-Whitney U test or Kruskal-Wallis test. Correlations using non-normally distributed data were determined using Spearman's rank correlation and linear regression analysis was used to further evaluate associations between continuous data. Statistical significance was defined at $p < 0.05$ throughout.

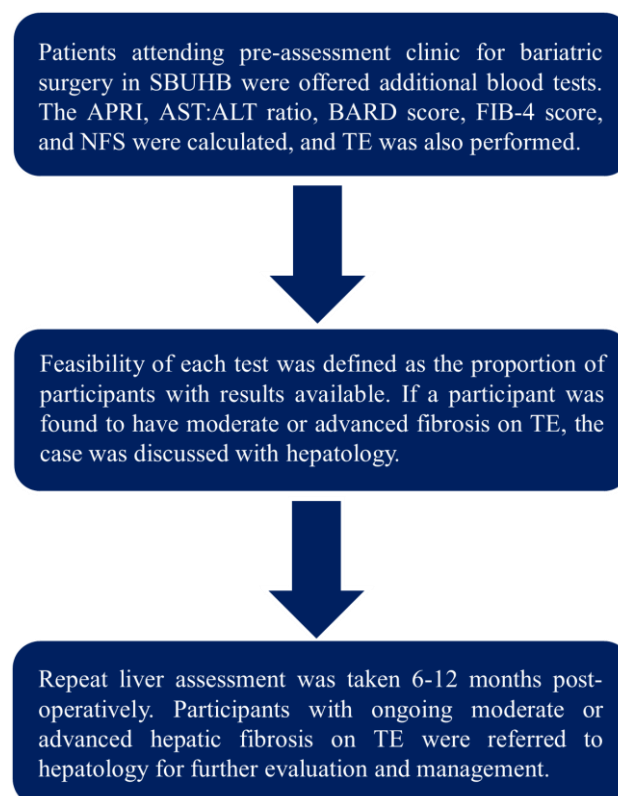
The utility of blood biomarkers to predict moderate-severe hepatic steatosis or advanced fibrosis using the TE-CAP or TE-LSM was determined. The sensitivity, specificity, PPV, and NPV were calculated. A ROC analysis was undertaken to investigate the use of blood biomarkers to predict the TE-CAP or TE-LSM. Data are presented by the AUC (95% CI), and Youden's index. Differences between the AUC for each test and that expected by chance or differences in the AUC between participants with a BMI below or above the cohort mean were determined by t-test. The corresponding test score with the greatest Youden's index was presented as the optimal screening cut-off, and its sensitivity and specificity presented. The ROC analysis was supported by Dr Ivy Cheung, a statistician working with the diabetes research group at Swansea University Medical School.

2.4 Study 3: Perioperative MASLD assessment for bariatric surgery

2.4.1 Study design

This was a pilot study to investigate the feasibility of MASLD screening during perioperative assessment for bariatric surgery in people with obesity in SBUHB. Patients attending preoperative assessment for bariatric surgery in SBUHB (usually within 1 month of surgery) were invited to undergo additional tests for MASLD. This involved additionally testing AST and GGT using blood samples collected as part of their care, and TE. Participants identified with a TE-LSM ≥ 8.2 kPa were discussed with their local hepatologist prior to surgery. This was repeated at a routine clinic visit 6-12 months postoperatively, to determine need for referral to hepatology. Participants with a TE-LSM ≥ 8.2 kPa at the 6–12-month postoperative visit were referred to their local hepatologist. Participants were recruited July-November 2023, and follow-up visits were March-August 2024. The study design is presented in Figure 2.4.

Figure 2.4: Design of study 3



The design of study 3. Abbreviations: *APRI* aspartate transaminase-to-platelet ratio index; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease fibrosis score *SBUHB* Swansea Bay University Health Board; *TE* transient elastography. Figure adapted with permission (Williams, Min, et al., 2025).

2.4.2 Participants

Study participants were patients planning to undergo bariatric surgery under the Welsh Institute for Metabolic and Obesity Surgery (WIMOS) team. Patients had been referred to the WIMOS from South Wales and Mid Powys and discussed within a multidisciplinary team meeting prior to preoperative assessment. All participants were aged 18 years or greater, had a BMI greater than 40.0 kg/m² or greater than 35.0 kg/m² with obesity-related comorbidities. All participants gave verbal consent to take part.

2.4.3 Data collection

Data were collected at preoperative and 6–12-month postoperative clinic visits. At each visit, additional blood tests were undertaken including AST and GGT, to calculate biomarkers for advanced fibrosis (APRI, AST:ALT ratio, BARD score, FIB-4 score and NFS). All blood tests were processed in real-time in SBUHB NHS laboratories as part of their care. Additionally, TE was undertaken by me at both visits to generate the TE-CAP and TE-LSM, using one of two fibroscan 430 Mini devices (Echosens; serial numbers F92263 and F92540). A valid TE-LSM score was defined by at least 10 valid individual scans, with an IQR/median ratio under 30%. The “M” or “XL” probe was used as recommended by the device. Thresholds used to define stages of hepatic steatosis and fibrosis using TE, and risk of advanced fibrosis using blood biomarkers are presented in Table 2.8. The feasibility of non-invasive tests is evaluated as the proportion of participants with valid blood test or TE scores. Patients were asked to provide feedback using a structured questionnaire. This is included in Appendix III, Figure 13.1.

2.4.4 Funding and ethical approval

No additional funding was received to undertake this study. The work was supported by the clinical director for general surgery and the bariatric lead for the WIMOS, the letter of support is in Appendix III, Figure 13.2. The work was approved as a service evaluation project by the Joint Study Review Committee (JSRC) at SBUHB in June 2023. The confirmation received from the research and development team at SBUHB is in Appendix III, Figure 13.3. Therefore, ethical approval was not required.

Table 2.8: Thresholds used to define hepatic steatosis and fibrosis in study 3

Hepatic steatosis was defined by the TE-CAP:	
• Normal: <302 dB/m • Moderate: 302-336 dB/m • Severe: ≥337 dB/m	
Hepatic fibrosis was defined by the TE-LSM:	
• Normal: <8.2 kPa • Moderate: 8.2-9.7 kPa • Advanced: ≥9.7 kPa	
A clinically significant risk of advanced hepatic fibrosis was defined by the following:	
• APRI ≥0.70 • AST:ALT ratio ≥0.80 • BARD score ≥2	• FIB-4 score ≥1.30 • NFS ≥-1.455

Thresholds defining the risk of hepatic steatosis and fibrosis used in study 3 (Angulo et al., 2007; Eddowes et al., 2019; Harrison et al., 2008; Lin et al., 2011; McPherson et al., 2010). Abbreviations: *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *TE* transient elastography.

2.4.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503). Categorical data were presented as number (%). Continuous data were checked for normality using the Kolmogorov-Smirnov test and visualised using Q-Q plots. Data following a normal distribution were presented as the mean±SD, and data not following a normal distribution were presented by the median [IQR]. The statistical significance of changes in data following a normal distribution were determined by paired t test. Statistical significance was considered at p<0.05.

2.5 Study 4: Understanding of MASLD and views on MASLD screening in patients with diabetes and clinicians

2.5.1 Study design

This study used two questionnaires to investigate the understanding of MASLD in patients with diabetes and clinicians in Wales, and their opinions on screening. Patients with T1D or T2D were invited by the clinic receptionist to complete an anonymised survey in the waiting room prior to their diabetes clinic in SBUHB (Morriston hospital, Neath Port Talbot hospital, or Singleton hospital). Surveys were completed using a paper-based form, or electronically using the Qualtrics platform, accessed using a quick response (QR) code. The paper version of this questionnaire with the QR code provided to participants is presented in Appendix IV, Figure 14.1. Patient surveys were completed September 2023-February 2024.

Clinician surveys were completed by GPs, and consultants or other doctors practising diabetes and endocrinology. Surveys were paper-based or electronically completed on the Qualtrics platform. The paper version of the survey and QR code provided to clinician participants is presented in Appendix IV, Figure 14.2. The surveys were advertised at primary care (primary care diabetes update, Swansea) and secondary care meetings (Welsh Endocrine and Diabetes Society, and Young Diabetologists and Endocrinologist Forum), and circulated by email to these groups. The clinician surveys were completed August 2023-April 2025.

2.5.2 Participants

Patients were people with T1D or T2D managed within secondary care in SBUHB. People reporting a diagnosis of other forms of diabetes were excluded. Clinicians included GPs working in Swansea, and consultants or other doctors in diabetes and endocrinology in Wales.

2.5.3 Data collection

Electronically collected data were downloaded into a Microsoft Excel document and paper-based data were subsequently entered by me into the appropriate database. Incomplete questionnaire responses were excluded from the analysis.

2.5.4 Funding and ethical approval

There was no additional funding received for the study. Surveys were completed anonymously, voluntarily, and did not require access to confidential patient data or other medical information beyond that which was self-reported. Therefore, ethical approval was not required.

2.5.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503) or SPSS (version 29). Categorical data are presented by the number (%) and the statistical significance of differences in these data were determined by Chi-squared test. Continuous data were checked for normality using the Kolmogorov-Smirnov test and visualised using Q-Q plots. Data following a normal distribution are presented by the mean $\pm$ SD. Data not following a normal distribution are presented as the median [IQR], and differences in data not following a normal distribution were determined by the Mann-Whitney U test. Statistical significance was defined as $p < 0.05$.

Chapter Three:

**The accuracy of non-invasive tests for
hepatic steatosis and fibrosis in people with
MASLD**

3.1 Introduction

In view of the growing global prevalence of MASLD in people with T2D or obesity, there is increasing recognition that early disease identification would permit better treatment and monitoring (Cusi et al., 2022; Dietrich et al., 2021; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023). This is because advanced fibrosis in MASLD associates with major morbidity and mortality, from excess CVD, malignancy and liver-related disease (Lindenmeyer & McCullough, 2018; Xiao, 2023; Younossi & Henry, 2016). Meaningful intervention with robust lifestyle changes (Haigh et al., 2022; Lean et al., 2018; Properzi et al., 2018; Pugliese et al., 2022) and pharmacotherapies (Ghosal et al., 2021; Loomba et al., 2024; Majzoub et al., 2021; Nguyen et al., 2024; Souza et al., 2025; Wei et al., 2021) is increasingly proven to reverse steatohepatitis and moderate fibrosis. Nonetheless, reservations around MASLD screening remain, such as the intended population, which tests should be used (e.g., blood tests, imaging), and their cost-effectiveness (Dietrich et al., 2021). The consensus is additional assessment for MASLD should be taken in those at risk, but population screening is not appropriate (Cusi et al., 2022; EASL-EASD-EASO, 2024; Eslam et al., 2020; Misra et al., 2025; NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023).

Various approaches have been suggested to screen for hepatic steatosis or fibrosis. Blood biomarkers to screen for hepatic steatosis include the FLI, HSI, LAP, NAFLD-LFS, steatotest, TyG, and VAI. To screen for liver fibrosis, the ADAPT score, APRI, AST:ALT ratio, BARD score, ELF test, FIB-4 score, Fibrotest, Fibrometer score, Hepascore, and NFS are useful. Imaging using B-mode ultrasonography can detect moderate-severe hepatic steatosis (Tamaki, Ajmera, et al., 2022), but its use in practice is surpassed by TE which better predicts the degree of hepatic steatosis and fibrosis (Cao et al., 2022; Eddowes et al., 2019). Whilst MRI has greatest accuracy (Akkaya et al., 2018; Selvaraj et al., 2021), its time-consuming processes and costs make it impractical (NICE, 2023d).

Most blood biomarkers and imaging modalities were validated in cohorts with hepatic fibrosis from alternative causes, such as HBV, HCV or ALD, meaning further validation in people with MASLD or risk factors such as T2D or obesity is important. This is because the aetiology of CLD may affect the interpretation of non-invasive markers of liver disease, highlighted by the variability of the TE-CAP and TE-LSM used to predict the stage of hepatic steatosis or fibrosis. The manufacturer suggests a TE-CAP ≥ 302 dB/m indicates stage 1 steatosis in MASLD compared with a score of ≥ 222 dB/m to indicate stage 1 hepatic steatosis in people with HCV (Echosens, 2020; Eddowes et al., 2019). Similarly, a TE-LSM cut-off ≥ 9.7 kPa indicates

advanced fibrosis in MASLD, compared with a TE-LSM ≥ 12.0 kPa in ALD (Echosens, 2020; Eddowes et al., 2019). Some comorbidities impact the interpretation of non-invasive tests for MASLD fibrosis. For example, the NFS overestimates liver fibrosis in people with obesity, whilst the FIB-4 score is relatively unaffected by BMI (Drolz et al., 2021; Qadri et al., 2022). Blood biomarkers were generally unreliable in one study to detect advanced fibrosis in people undergoing bariatric surgery, but were useful to exclude disease (Alqahtani et al., 2021). Conversely, simple non-invasive tests for advanced fibrosis in MASLD may be less accurate in lean people (Eren et al., 2022), and the FIB-4 score may have lesser accuracy in people with T2D (Bertot et al., 2018; Boursier et al., 2023; Chung et al., 2023; Ito et al., 2023).

There may be need to adjust the diagnostic thresholds for TE-CAP scores in people with obesity or T2D, though the accuracy of TE-LSM is unaffected by BMI (Karlas et al., 2017). The TE-LSM was superior to exclude liver cirrhosis in people with T2D (Damjanovska et al., 2022), and other studies observe the TE-LSM is more sensitive than the FIB-4 score in people with T2D (Chung et al., 2023). Sequential use of the FIB-4 score and TE-LSM had 90.3% accuracy in people without T2D, and 79.0% in people with T2D (Boursier et al., 2023). Further study into the impact of comorbidities such as obesity and T2D on the accuracy of these tests is needed to support their use in practice for MASLD screening.

3.2 Aims of this chapter

The specific aims of this chapter are to determine:

- i. accuracy of non-invasive tests to predict clinically significant hepatic steatosis in people with or without T2D and by BMI status.
- ii. accuracy of non-invasive tests to predict clinically significant hepatic fibrosis in people with or without T2D and by BMI status.
- iii. accuracy of non-invasive biomarkers to predict advanced hepatic fibrosis in people with or without T2D and by BMI status.
- iv. accuracy of blood biomarkers followed by TE in sequence to predict advanced hepatic fibrosis in people with or without T2D and by BMI status.

3.3 Methods

3.3.1 Study design

This was a retrospective, cross-sectional, real-world analysis of patients with biopsy-confirmed MASLD between November 2011-September 2022, who were managed by hepatology in SBUHB. This analysis was undertaken as part of a local service evaluation project using routinely collected data in collaboration between diabetes and hepatology teams in SBUHB.

3.3.2 Study participants

Patients were diagnosed with MASLD based on clinical and histological observations, and the exclusion of other causes of CLD. Patients were typically referred to hepatology following deranged LFTs or incidental findings on imaging. Patients were followed up locally to monitor for progressive fibrosis, HCC, and treatment. Patients were deemed to have T2D if they had a documented diagnosis of T2D or if the HbA1c was ≥ 48 mmol/mol [6.5%].

3.3.3 Data collection

Data were collected retrospectively using electronic records. Routinely collected demographic, biochemical, and radiological data from participants care were collected from within 12 months of liver biopsy. Non-invasive measures of hepatic steatosis (HSI, TE-CAP), and fibrosis (APRI, AST:ALT ratio, BARD score, FIB-4 score, NFS, and TE-LSM) were calculated using freely-available algorithms. The hepatology team (consultant hepatologists, specialist nurses and support workers) performed TE in clinic as part of their routine care. Diagnostic thresholds used as to predict the degree of hepatic steatosis or fibrosis were presented in Table 2.1.

Histopathological data were collected from electronic health records and incomplete data were reviewed by a local histopathologist. Clinically significant hepatic steatosis was defined steatosis stage 2 or 3, clinically significant hepatic fibrosis was defined as fibrosis stage 2-4, and advanced fibrosis was defined as fibrosis stage 3-4 using the Brunt criteria and the comparable TE thresholds were presented in Table 2.1.

3.3.4 Funding and ethical approval

No additional funding was received for this study. This study was approved by the clinical lead for hepatology as a service evaluation project in collaboration between hepatology and diabetes teams in SBUHB. Data used in this study were collected as part of the patients' routine clinical care, and were analysed anonymously. Therefore, ethical approval was not required.

3.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using SPSS (version 29). Categorical data were presented as the number (%), and significance of differences between categorical variables determined by Chi-squared test. Continuous data following a normal distribution were presented by the mean $\pm$ SD, and non-parametric data by the median [IQR]. The sensitivity, specificity, PPV, and NPV and 95% CI of each test were determined using the thresholds shown in Table 2.1. These were compared by T2D status, and by BMI in which the cohort was split into two groups by the median BMI.

A ROC analysis was performed for each non-invasive test to predict hepatic steatosis or fibrosis against liver biopsy, presented by the AUC (95% CI). The significance of differences between the AUC for each test and that expected by chance, or for the same test in people with or without T2D, or by BMI status was determined by t-test. Statistical significance was defined at $p < 0.05$. The optimal screening cut-off for each test to identify hepatic steatosis or fibrosis was determined by Youden's index. The sensitivity, specificity, PPV, NPV and ROC analysis for sequential testing with a blood biomarker followed by TE-LSM was presented for the detection of advanced fibrosis and compared by T2D and BMI status. Here, the ROC analysis was taken for the TE-LSM investigation in the subgroup who had tested positive for the initial blood biomarker screening test at the thresholds presented in Table 2.1.

3.4 Results

3.4.1 Participant characteristics

A total of 153 patients with complete histopathological data were included. At liver biopsy, patients had a mean age 54.0 ± 11.5 years, 80 (52.3%) patients were male, and 73 (47.7%) had pre-existing T2D. Patients had a mean NAS 3.9 ± 1.5 (steatosis 2.0 ± 0.8 , inflammation 1.0 ± 0.6 , and ballooning 0.9 ± 0.7). A total of 30 (19.6%), 33 (21.6%), 13 (8.5%), 43 (28.1%), and 34 (22.2%) patients had a fibrosis stage 0, 1, 2, 3 or 4 respectively, with a mean fibrosis score of 2.1 ± 1.5 . Data are presented with other observations in Table 3.1, and histopathological findings at liver biopsy are summarised in Table 3.2.

3.4.2 Accuracy of non-invasive tests to predict clinically significant hepatic steatosis in people with or without type 2 diabetes and by body mass index status

The sensitivity, specificity, PPV, and NPV for the TE-CAP and HSI to identify clinically significant hepatic steatosis are presented in Table 3.3. The TE-CAP was less sensitive compared with the HSI (73.2 vs 98.6, $p < 0.001$), but more specific (42.9 vs 3.4, $p < 0.001$). Differences in PPV and NPV between the tests for the overall cohort were not statistically significant. Whilst there was greater sensitivity and lesser specificity for TE-CAP and HSI in people with T2D, this did not reach statistical significance.

The ROC analysis is summarised in Table 3.4 and Figure 3.1. In people with T2D, the TE-CAP associated with clinically significant steatosis [AUC 0.72 (0.58–0.85), $p < 0.01$], but not in people without T2D. The optimal screening cut-off in people with T2D was 364.5 dB/m versus 338.5 dB/m in people without T2D, with greater accuracy in T2D. Similarly, in people with a BMI ≤ 36.3 kg/m², the TE-CAP score associated with severe hepatic steatosis [AUC 0.69 (0.56–0.82), $p < 0.01$], but not in people with BMI > 36.3 kg/m². In people with BMI ≤ 36.3 kg/m² the optimal cut-off was 347.5 dB/m, versus 382.0 dB/m in people with BMI > 36.3 kg/m², with greater sensitivity and specificity in the leaner cohort. The HSI associated poorly with the steatosis stage and was similarly poor in people with or without T2D and in both BMI groups.

Table 3.1: Cohort characteristics at the time of liver biopsy

Characteristic	Total cohort (n=153)
Age (years)	54.0±11.5
Male sex	80 (52.3%)
Pre-existing T2D	73 (47.7%)
WIMD decile	4.7±2.9
BMI (kg/m ²)	36.9±7.0
TE–CAP (dB/m)	346.4±52.5
TE–LSM (kPa)	16.2±11.2
<8.2 kPa (F0-1)	28 (18.3%)
8.2-9.7 kPa (F2)	17 (11.1%)
9.7-13.6 kPa (F3)	29 (19.0%)
>13.6 kPa (F4)	62 (40.5%)
Missing data	17 (11.1%)
ALT (U/L)	58.1±43.5
ALP (U/L)	95.1±44.5
AST (U/L)	49.1±53.9
GGT (U/L)	152.2±211.4
Platelets (x10 ⁹ /L)	226.5±72.2
TC (mmol/L)	4.8±1.3
LDL (mmol/L)	2.8±1.2
HDL (mmol/L)	1.2±0.3
TG (mmol/L)	2.4±1.8
HbA1c (mmol/mol)	51.6±18.6
Creatinine (μmol/L)	76.8±19.0
eGFR (mL/min/1.73m ²)	85.3±21.6
HSI	49.2±8.1
AST:ALT ratio	1.0±0.7
BARD score	2.3±1.2
FIB-4 score	2.0±2.1
NFS	-0.9±2.1
APRI	0.8±1.0

Patient characteristics at the time of liver biopsy. Categorical data presented as the number (%), and continuous data presented by mean±SD. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *HbA1c* glycated haemoglobin; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride; *WIMD* Welsh index of multiple deprivation.

Table 3.2: Histopathological characteristics at the time of liver biopsy

Histopathological feature	Total cohort (n=153)
NAS	3.9±1.5
Steatosis	2.0±0.8
S0	4 (2.6%)
S1	41 (26.8%)
S2	66 (43.1%)
S3	42 (27.5%)
Inflammation	1.0±0.6
Ballooning	0.9±0.7
Fibrosis	2.1±1.5
F0	30 (19.6%)
F1	33 (21.6%)
F2	13 (8.5%)
F3	43 (28.1%)
F4	34 (22.2%)

Histopathological characteristics of the cohort. Categorical data are presented as the number (%), and continuous data are presented by the mean±SD. Abbreviations: *NAS* non-alcoholic fatty liver disease activity score.

Table 3.3: Accuracy of non-invasive tests for clinically significant hepatic steatosis

Group	Test	Subgroup	Sensitivity (%) (95% CI)	P	Specificity (%) (95% CI)	P	PPV (%)	P	NPV (%)	P
Overall	TE–CAP		73.2 [63.9-81.3]		42.9 [27.4-59.3]		78.0 [68.8-85.7]		36.6 [23.0-51.8]	
		HSI	98.6 [94.0-99.9]		3.4 [0.2-14.3]		71.7 [62.4-80.0]		50.0 [3.8-96.2]	
T2D status	TE- CAP	T2D	78.0 [65.3-87.9]	NS	30.8 [10.7-57.7]	NS	81.3 [68.7-90.5]	NS	26.7 [9.2-51.5]	NS
		No T2D	68.1 [54.0-80.2]		50.0 [30.0-70.0]		74.4 [60.2-85.8]		42.3 [24.7-61.3]	
	HSI	T2D	100.0	NS	0.0	NS	76.2 [62.0-87.3]	NS	-	-
		No T2D	97.5 [89.5-99.9]		5.3 [0.3-21.2]		68.4 [55.7-79.5]		50.0 [3.8-96.2]	
	TE- CAP	BMI ≤36.3	66.7 [51.7-79.6]	NS	52.6 [30.9-73.7]	NS	75.7 [60.4-87.5]	NS	41.7 [23.5-61.5]	NS
		BMI >36.3	82.0 [69.9-90.9]		28.6 [9.9-54.5]		80.4 [68.2-89.7]		30.8 [10.7-57.7]	
BMI status	HSI	BMI ≤36.3	97.0 [87.3-99.8]	NS	5.9 [0.3-23.4]	NS	66.7 [52.7-78.9]	NS	50.0 [3.8-96.2]	-
		BMI >36.3	100.0		0.0		76.5 [63.7-86.6]		-	

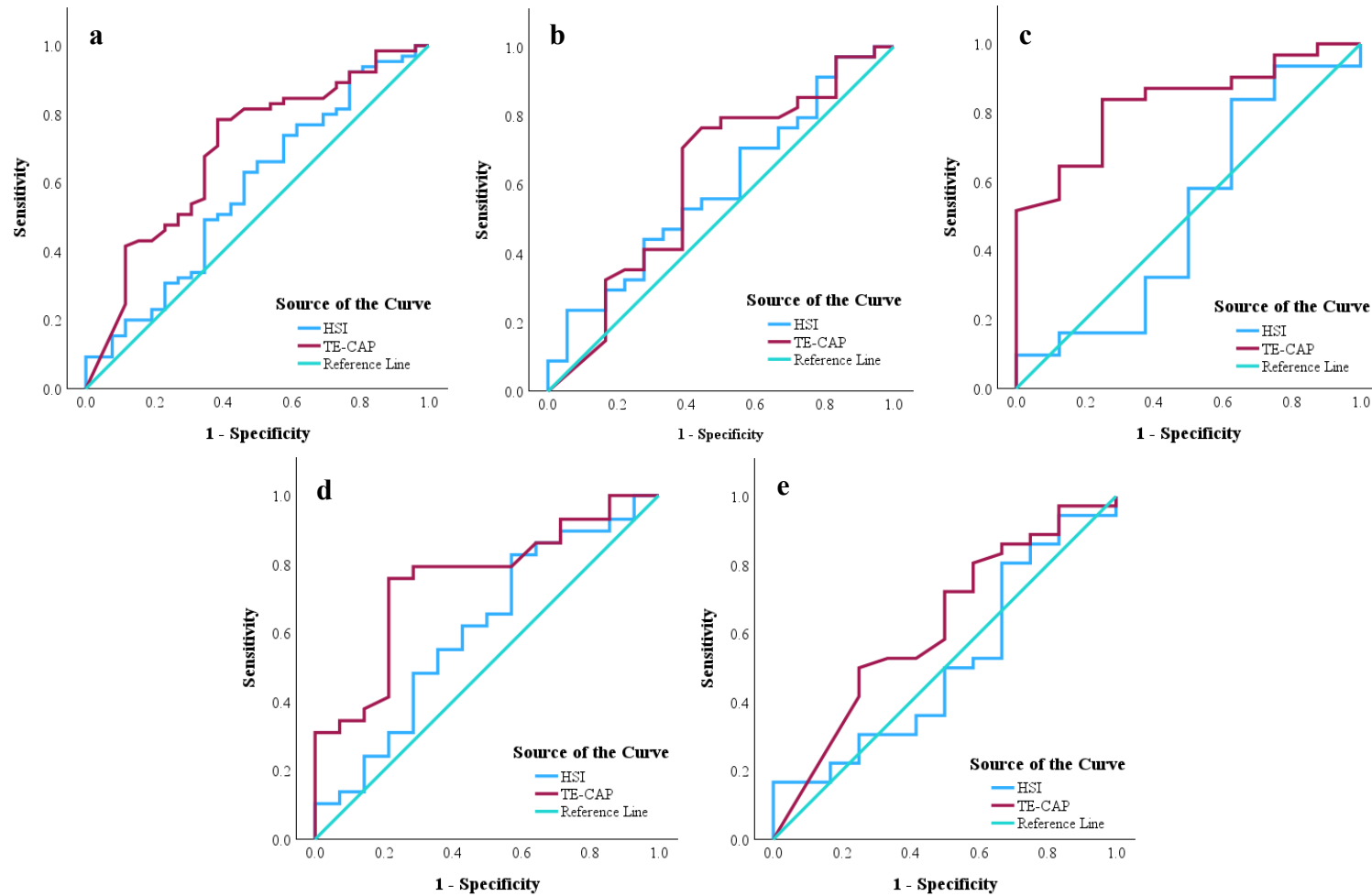
Accuracy of non-invasive tests for hepatic steatosis in MASLD, with or without T2D and by BMI. P values correspond to the statistical significance of the difference in statistical measure between people with or without T2D or by BMI. Abbreviations: *BMI* body mass index; *CAP* controlled attenuation parameter *HSI* hepatic steatosis index; *NPV* negative predictive value; *NS* non-significant; *PPV* positive predictive value; *T2D* type 2 diabetes; *TE* transient elastography.

Table 3.4: Receiver operating characteristic analysis for clinically significant hepatic steatosis

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall		TE-CAP	0.66	0.55–0.76	<0.01	-	0.29	347.0 dB/m	66.0	62.9
		HSI	0.60	0.48–0.73	NS		0.19	39.9	91.7	28.0
T2D status	TE-CAP	T2D	0.72	0.58–0.85	<0.01	NS	0.41	364.5 dB/m	56.0	84.6
		No T2D	0.61	0.46–0.75	NS		0.25	338.5 dB/m	61.7	63.6
	HSI	T2D	0.56	0.33–0.78	NS	NS	0.24	44.5	84.4	40.0
		No T2D	0.61	0.46–0.76	NS		0.20	43.6	72.5	47.4
	TE-CAP	BMI ≤ 36.3 kg/m ²	0.69	0.56–0.82	<0.01	NS	0.38	347.5 dB/m	57.4	81.0
		BMI > 36.3 kg/m ²	0.58	0.41–0.75	NS		0.23	382.0 dB/m	44.0	78.6
BMI status	HSI	BMI ≤ 36.3 kg/m ²	0.62	0.45–0.78	NS	NS	0.29	39.9	81.8	47.1
		BMI > 36.3 kg/m ²	0.51	0.32–0.70	NS		0.18	61.5	17.9	100

The ROC analysis to predict clinically significant hepatic steatosis. P value (null) describes statistical significance compared to the AUC expected by chance, and P value (compare groups) describes the significance of differences in AUC between people with or without T2D, or by BMI status. Abbreviations: *BMI* body mass index; *CAP* controlled attenuation parameter; *CI* confidence interval; *HSI* hepatic steatosis index; *NS* non-significant; *TE* transient elastography; *T2D* type 2 diabetes.

Figure 3.1: Receiver operating characteristic curves for clinically significant hepatic steatosis



The ROC analysis exploring use of the HSI and TE-CAP score. (a) overall cohort, (b) people without T2D, (c) people with T2D, (d) people with BMI ≤ 36.3 kg/m², (e) people with BMI > 36.3 kg/m². Abbreviations: *CAP* controlled attenuation parameter; *HSI* hepatic steatosis index.

3.4.3 Accuracy of non-invasive tests to predict clinically significant hepatic fibrosis in people with or without type 2 diabetes and by body mass index status

The sensitivity, specificity, PPV, and NPV for the TE-LSM, AST:ALT ratio, BARD score, FIB-4 score, NFS and APRI to identify clinically significant hepatic fibrosis ($\geq$ stage 2) are presented in Table 3.5. The TE-LSM was the most sensitive, but with poorer specificity. The FIB-4 score demonstrated the best combination sensitivity and specificity. In people with T2D, there was a trend toward greater sensitivity using the TE-LSM, AST:ALT ratio, BARD, and FIB-4 score, and significantly greater sensitivity and lesser specificity in T2D using the NFS. There were no statistically significant differences in the sensitivity of the tests in different BMI groups, though the BARD score and NFS demonstrated greater specificity for clinically significant hepatic fibrosis in the leaner cohort.

The ROC analysis is presented in Table 3.6 and Figure 3.2. In the overall cohort, the FIB-4 score had greatest AUC, though all the observed tests associated significantly. The Youden index was greatest for the FIB-4 score. The AUC for each test for was not significantly different in people with or without T2D. However, neither the AST:ALT ratio nor BARD score associated in people without T2D. Youden's index for the FIB-4 score was greater in people with T2D (0.74 vs 0.54), suggesting greater test utility. In people with T2D, the Youden index was >0.5 for the AST:ALT ratio, BARD score, FIB-4 score and TE-LSM. In people without T2D the Youden index was >0.5 for the APRI and FIB-4 score only.

In people with a BMI $>36.3\text{kg/m}^2$ or $\leq 36.3\text{kg/m}^2$, the AUC did not significantly differ. Each curve associated with clinically significant hepatic fibrosis in both BMI groups, except the AST:ALT ratio in people with BMI $>36.3\text{ kg/m}^2$. Youden's index was greater in people with a BMI $\leq 36.3\text{ kg/m}^2$ compared to those with BMI $>36.3\text{ kg/m}^2$ for most tests, but was greater for the TE-LSM and APRI in people with BMI $>36.3\text{ kg/m}^2$. In people with BMI $\leq 36.3\text{ kg/m}^2$, the Youden index was >0.5 for the FIB-4 score and NFS, and in people with $>36.3\text{ kg/m}^2$ for the TE-LSM, FIB-4 score and APRI. Therefore, the FIB-4 score seemed the best screening test irrespective of BMI. Data are presented in Table 3.6 and Figure 3.2.

Table 3.5: Accuracy of non-invasive tests for clinically significant hepatic fibrosis

Group	Test	Subgroup	Sensitivity (%) [95% CI]	P	Specificity (%) [95% CI]	PPV (%) [95% CI]	NPV (%) [95% CI]			
Overall		TE-LSM	91.0 [83.4-96.0]		36.2 [24.6-49.0]	65.7 [56.5-74.2]	75.0 [57.2-88.4]			
		AST:ALT	67.2 [54.9-78.1]		64.6 [50.5-77.1]	70.7 [58.3-81.3]	60.8 [47.1-73.4]			
		BARD	80.3 [69.2-88.9]		43.8 [30.3-57.8]	64.5 [53.4-74.6]	63.6 [46.7-78.6]			
		FIB-4	80.3 [69.2-88.9]		70.8 [57.1-82.4]	77.8 [66.5-86.8]	73.9 [60.2-85.1]			
		NFS	80.3 [69.2-88.9]		56.3 [42.2-69.7]	70.0 [58.7-79.9]	69.2 [53.8-82.2]			
		APRI	54.1 [41.6-66.2]		87.5 [76.3-94.8]	84.6 [71.3-93.6]	60.0 [48.3-71.0]			
T2D status	TE-LSM	T2D	93.5 [84.0-98.3]	NS	47.4 [26.3-69.1]	NS	81.1 [69.3-90.1]	<0.001	75.0 [47.2-93.1]	NS
		No T2D	87.5 [73.3-95.9]		30.8 [17.8-46.2]		50.9 [37.9-63.9]	75.0 [51.1-91.5]		
	AST:ALT	T2D	71.9 [55.0-85.4]	NS	84.6 [59.6-97.3]	NS	92.0 [77.3-98.6]	<0.01	55.0 [33.6-75.2]	NS
		No T2D	62.1 [43.9-78.2]		57.1 [40.7-72.6]		54.5 [37.7-70.7]		64.5 [47.0-79.7]	
	BARD	T2D	96.9 [87.0-99.8]	NS	7.7 [0.5-29.7]	<0.01	72.1 [57.7-84.0]	NS	50.0 [3.8-96.2]	NS
		No T2D	62.1 [43.9-78.2]		57.1 [40.7-72.6]		54.5 [37.7-70.7]		64.5 [47.0-79.7]	
	FIB-4	T2D	84.4 [69.4-94.1]	NS	69.2 [42.3-89.3]	NS	87.1 [72.5-95.8]	NS	64.3 [38.3-85.4]	NS
		No T2D	75.9 [58.5-88.8]		71.4 [55.3-84.5]		68.8 [51.7-82.9]		78.1 [62.0-89.9]	
	NFS	T2D	93.8 [81.9-98.9]	<0.01	23.1 [6.3-49.5]	<0.01	75.0 [60.3-86.6]	NS	60.0 [19.9-91.9]	NS
		No T2D	65.5 [47.4-81.0]		68.6 [52.3-82.3]		63.3 [45.5-79.0]		70.6 [54.2-84.0]	
	APRI	T2D	53.1 [36.1-69.7]	NS	92.3 [70.3-99.5]	NS	94.4 [77.7-99.7]	NS	44.4 [26.9-63.0]	<0.05
		No T2D	55.2 [37.2-72.3]		85.7 [71.8-94.6]		76.2 [55.6-90.7]		69.8 [55.2-82.1]	

BMI status	TE- LSM	BMI ≤36.3	87.2 [74.4-95.2]	NS	43.5 [24.7-63.6]	NS	72.3 [58.6-83.7]	NS	66.7 [41.5-86.5]	NS
		BMI >36.3	97.4 [88.9-99.8]		27.6 [13.7-45.3]		63.8 [51.0-75.4]		88.9 [59.5-99.3]	
	AST: ALT	BMI ≤36.3	70.0 [52.4-84.3]	NS	75.0 [53.8-90.2]	NS	80.8 [63.1-92.6]	NS	62.5 [42.6-79.9]	NS
		BMI >36.3	63.0 [44.2-79.4]		58.3 [38.5-76.5]		63.0 [44.2-79.4]		58.3 [38.5-76.5]	
	BARD	BMI ≤36.3	83.3 [67.5-93.7]	NS	60.0 [38.3-79.3]	<0.05	75.8 [59.6-88.1]	NS	70.6 [47.1-88.3]	NS
		BMI >36.3	77.8 [60.0-90.5]		29.2 [13.7-48.8]		55.3 [39.5-70.3]		53.8 [27.9-78.4]	
	FIB-4	BMI ≤36.3	83.3 [67.5-93.7]	NS	85.0 [65.6-96.0]	NS	89.3 [74.5-97.2]	NS	77.3 [57.4-91.2]	NS
		BMI >36.3	81.5 [64.3-92.9]		62.5 [42.6-79.9]		71.0 [53.8-84.8]		75.0 [53.8-90.2]	
	NFS	BMI ≤36.3	76.7 [59.7-89.2]	NS	80.0 [59.5-93.3]	<0.001	85.2 [68.9-95.1]	<0.05	69.6 [49.4-85.6]	NS
		BMI >36.3	92.6 [78.8-98.7]		29.2 [13.7-48.8]		59.5 [44.4-73.5]		77.8 [45.8-95.9]	
	APRI	BMI ≤36.3	50.0 [32.7-67.3]	NS	90.0 [72.2-98.3]	NS	88.2 [67.9-97.9]	NS	54.5 [37.7-70.7]	NS
		BMI >36.3	55.6 [37.0-73.1]		87.5 [70.7-96.7]		83.3 [62.3-95.6]		63.6 [37.0-73.1]	

Accuracy of non-invasive tests for clinically significant hepatic fibrosis, with or without T2D and by BMI. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NPV* negative predictive value; *NS* non-significant; *PPV* positive predictive value; *T2D* type 2 diabetes; *TE* transient elastography.

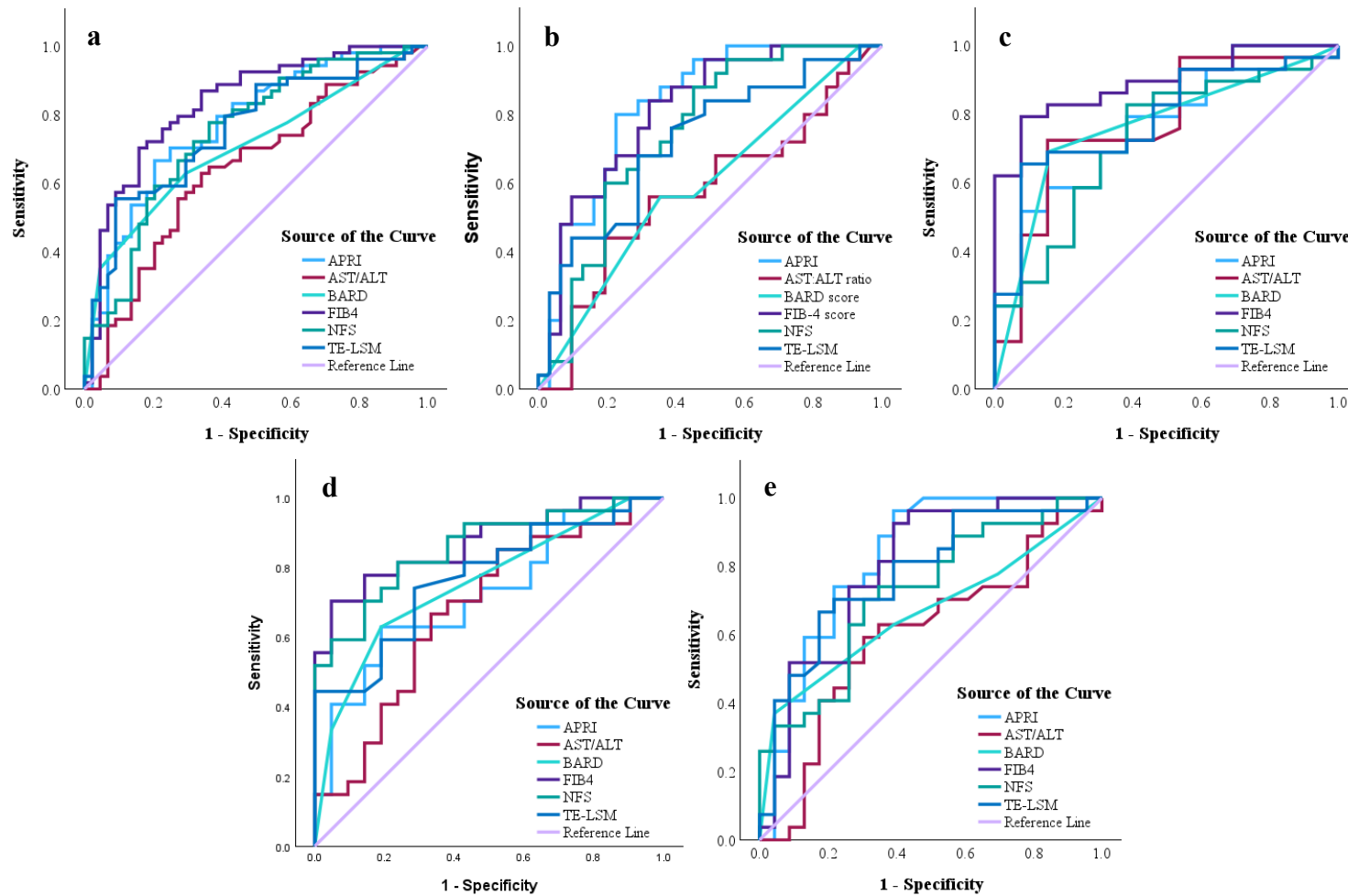
Table 3.6: Receiver operating characteristic analysis for clinically significant hepatic fibrosis

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall		TE-LSM	0.77	0.70–0.85	<0.001	-	0.45	16.7 kPa	55.1	89.7
		AST:ALT	0.68	0.58–0.78	<0.001	-	0.33	0.85	63.9	68.7
		BARD	0.73	0.64–0.82	<0.001	-	0.34	2.5	62.9	71.4
		FIB-4	0.85	0.78–0.93	<0.001	-	0.58	1.45	72.1	85.4
		NFS	0.76	0.67–0.85	<0.001	-	0.44	-1.0	77.0	66.7
		APRI	0.79	0.70–0.88	<0.001	-	0.50	0.58	68.9	81.2
T2D status	TE-LSM	T2D	0.82	0.72–0.93	<0.001	NS	0.61	14.8 kPa	71.7	89.5
		No T2D	0.73	0.61–0.85	<0.001		0.44	11.1 kPa	71.9	71.8
	AST:ALT	T2D	0.79	0.64–0.94	<0.001	NS	0.60	0.79	75.0	84.6
		No T2D	0.63	0.49–0.77	NS		0.28	1.2	44.8	82.9
	BARD	T2D	0.77	0.61–0.92	<0.01	NS	0.54	2.5	69.7	84.6
		No T2D	0.64	0.50–0.77	NS		0.22	2.5	55.2	66.7
	FIB-4	T2D	0.90	0.81–0.99	<0.001	NS	0.74	1.36	81.3	92.3
		No T2D	0.84	0.74–0.93	<0.001		0.54	1.05	82.8	71.4
	NFS	T2D	0.74	0.58–0.90	<0.01	NS	0.41	-0.45	87.5	53.8
		No T2D	0.75	0.62–0.87	<0.001		0.42	-1.00	58.6	82.9
	APRI	T2D	0.78	0.64–0.93	<0.001	NS	0.49	0.68	56.3	92.3
		No T2D	0.84	0.74–0.94	<0.001		0.59	0.58	79.3	80.0

BMI status	TE- LSM	BMI ≤ 36.3 kg/m ²	0.78	0.68–0.89	<0.001	NS	0.45	10.1 kPa	72.5	71.4
		BMI >36.3 kg/m ²	0.80	0.69–0.91	<0.001		0.53	14.8 kPa	73.7	79.3
	AST: ALT	BMI ≤ 36.3 kg/m ²	0.75	0.62–0.88	<0.001	NS	0.43	0.76	76.5	66.7
		BMI >36.3 kg/m ²	0.60	0.44–0.76	NS		0.27	0.96	51.9	75.0
	BARD	BMI ≤ 36.3 kg/m ²	0.80	0.68–0.91	<0.001	NS	0.48	2.5	64.7	83.3
		BMI >36.3 kg/m ²	0.66	0.51–0.81	<0.05		0.32	3.5	35.7	96.0
	FIB-4	BMI ≤ 36.3 kg/m ²	0.89	0.81–0.97	<0.001	NS	0.69	1.50	73.5	95.8
		BMI >36.3 kg/m ²	0.80	0.68–0.93	<0.001		0.55	1.05	92.6	62.5
	NFS	BMI ≤ 36.3 kg/m ²	0.85	0.76–0.95	<0.001	NS	0.59	-2.13	79.4	79.2
		BMI >36.3 kg/m ²	0.73	0.60–0.87	=0.001		0.41	0.20	70.4	69.8
	APRI	BMI ≤ 36.3 kg/m ²	0.75	0.63–0.88	<0.001	NS	0.48	0.58	64.7	83.3
		BMI >36.3 kg/m ²	0.83	0.71–0.95	<0.001		0.59	0.39	96.3	62.5

The ROC analysis to predict clinically significant hepatic fibrosis. P value (null) describes statistical significance comparing the AUC expected by chance, and P value (compare groups) describes the significance of differences in AUC between people with or without T2D, or BMI status, Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* non-significant; *T2D* type 2 diabetes; *TE* transient elastography.

Figure 3.2: Receiver operating characteristic curves for clinically significant hepatic fibrosis



The ROC analysis exploring use of non-invasive tests to diagnose clinically significant hepatic fibrosis. (a) overall cohort, (b) people without T2D, (c) people with T2D, (d) people with BMI ≤ 36.3 kg/m², (e) people with BMI > 36.3 kg/m². Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *TE* transient elastography.

3.4.4 Accuracy of non-invasive biomarkers to predict advanced hepatic fibrosis in people with or without type 2 diabetes and by body mass index status

The sensitivity, specificity, PPV, and NPV for each test to identify advanced fibrosis ($\geq$ stage 3) are presented in Table 3.7. The TE-LSM was the most sensitive test, whilst the APRI the most specific. The APRI and FIB-4 score exhibited the best combination sensitivity and specificity. In people with T2D, the BARD score and NFS were significantly more sensitive and less specific, whilst the APRI was significantly less sensitive in those with T2D. In people with a BMI ≤ 36.3 kg/m², there was a trend to lesser sensitivity with the TE-LSM ($p=0.07$), and greater specificity with the NFS in people with BMI ≤ 36.3 kg/m². There was no difference in the sensitivity of the FIB-4 score to identify advanced fibrosis irrespective of BMI.

The ROC analysis is presented in Table 3.8 and Figure 3.3. The FIB-4 score had the greatest AUC to detect advanced fibrosis, though all tests statistically associated with advanced fibrosis. Youden's index was greatest with the FIB-4 score at 0.56, suggesting the best overall utility. There was no statistically significant difference between the AUC for the tests between people with or without T2D. All tests associated significantly with advanced fibrosis in people with T2D. However, in people without T2D the association was not significant for the AST:ALT ratio, and the BARD score. In people with T2D, the Youden index was >0.5 for the TE-LSM, AST:ALT ratio, FIB-4 score, NFS, and APRI. In people without T2D the Youden index was >0.5 for FIB-4 score and APRI only.

There was no significant difference in the AUC between different BMI groups for these tests. In people with a BMI ≤ 36.3 kg/m², the ROC analysis demonstrated a significant association between each test and presence of advanced fibrosis, but there was no significant association with the AST:ALT ratio in people with BMI >36.3 kg/m². In people with BMI ≤ 36.3 kg/m² the Youden index was >0.5 for the TE-LSM, FIB-4 score and NFS, whilst in people with BMI >36.3 kg/m² the Youden index was >0.5 for the TE-LSM, FIB-4 score and APRI. Neither the AST:ALT ratio nor the BARD score had a Youden index >0.5 in any group. The accuracy and optimal cut-offs for each test are shown in Table 3.8 and Figure 3.3.

Table 3.7: Accuracy of non-invasive tests for advanced hepatic fibrosis

Group	Test	Group	Sensitivity (%) [95% CI]	P	Specificity (%) [95% CI]	P	PPV (%) [95% CI]	P	NPV (%) [95% CI]	P
Overall	TE-LSM		90.1 [82.4-96.3]		50.0 [38.4-61.6]		63.2 [53.2-72.4]		85.4 [72.5-93.9]	
	AST:ALT		68.8 [54.9-80.6]		59.0 [46.5-70.8]		56.9 [44.1-69.1]		70.6 [57.3-81.9]	
	BARD		81.3 [68.7-90.5]		39.3 [27.7-51.9]		51.3 [40.2-62.4]		72.7 [56.2-85.8]	
	FIB-4		83.3 [71.2-92.0]		62.3 [49.8-73.8]		63.5 [51.2-74.7]		82.6 [70.0-91.6]	
	NFS		83.3 [71.2-92.0]		50.8 [38.4-63.1]		57.1 [45.4-68.3]		79.5 [65.2-90.1]	
	APRI		64.6 [50.5-77.1]		86.9 [77.0-93.8]		79.5 [65.2-90.1]		75.7 [64.9-84.7]	
T2D status	TE-LSM	T2D	90.0 [78.3-96.8]	NS	44.0 [25.8-63.3]	NS	72.0 [58.7-83.1]	NS	73.3 [48.5-90.8]	<0.01
		No T2D	100.0		54.3 [40.0-68.2]		53.3 [38.9-67.4]		100.0	
	AST:ALT	T2D	76.9 [58.7-90.1]	NS	73.7 [51.7-89.7]	NS	80.0 [61.8-92.3]	<0.01	70.0 [48.3-86.8]	NS
		No T2D	59.1 [38.4-77.8]		52.4 [37.5-67.0]		39.4 [24.0-56.4]		71.0 [53.8-84.8]	
	BARD	T2D	100.0	<0.001	10.5 [1.8-29.1]	<0.01	60.5 [45.6-74.2]	NS	100.0	NS
		No T2D	59.1 [38.4-77.8]		52.4 [37.5-67.0]		39.4 [24.0-56.4]		71.0 [53.8-84.8]	
	FIB-4	T2D	88.5 [72.7-97.0]	NS	57.9 [35.8-78.0]	NS	74.2 [57.3-87.3]	NS	78.6 [53.4-94.2]	NS
		No T2D	77.3 [57.4-91.2]		64.3 [49.3-77.6]		53.1 [36.1-69.7]		84.4 [69.4-94.1]	
	NFS	T2D	96.2 [84.1-99.8]	<0.01	21.1 [7.1-42.4]	<0.01	62.5 [47.1-76.4]	NS	80.0 [37.2-98.7]	NS
		No T2D	68.2 [47.5-84.9]		64.3 [49.3-77.6]		50.0 [32.7-67.3]		79.4 [64.0-90.6]	
	APRI	T2D	26.9 [12.6-45.6]	<0.01	89.5 [70.9-98.2]	NS	89.5 [70.9-98.2]	NS	47.2 [31.5-63.3]	<0.001
		No T2D	68.2 [47.5-84.9]		85.7 [73.1-94.1]		71.4 [50.4-87.5]		83.7 [70.9-92.7]	

BMI status	TE-LSM	BMI ≤36.3	84.4 [69.4-94.1]	NS	53.3 [35.8-70.4]	NS	65.9 [50.7-79.1]	NS	76.2 [55.6-90.7]	NS
		BMI >36.3	97.1 [87.7-99.8]		42.4 [26.6-59.4]		63.5 [50.0-75.7]		93.3 [73.8-99.6]	
	AST:ALT	BMI ≤36.3	69.6 [49.4-85.6]	NS	63.0 [44.2-79.4]	NS	61.5 [42.4-78.5]	NS	70.8 [51.2-86.3]	NS
		BMI >36.3	65.2 [44.9-82.3]		57.1 [38.8-74.2]		55.6 [37.0-73.1]		66.7 [46.8-83.1]	
	BARD	BMI ≤36.3	82.6 [64.1-94.2]	NS	48.1 [30.1-66.5]	NS	57.6 [40.6-73.4]	NS	76.5 [53.5-92.0]	NS
		BMI >36.3	78.3 [59.0-91.6]		28.6 [14.2-46.7]		47.4 [32.1-63.0]		61.5 [34.8-84.1]	
	FIB-4	BMI ≤36.3	82.6 [64.1-94.2]	NS	66.7 [48.0-82.4]	NS	67.9 [49.5-83.1]	NS	81.8 [62.7-94.0]	NS
		BMI >36.3	82.6 [64.1-94.2]		57.1 [38.8-74.2]		61.3 [43.8-77.0]		80.0 [59.5-93.3]	
	NFS	BMI ≤36.3	78.3 [59.0-91.6]	NS	66.7 [48.0-82.4]	<0.01	66.7 [48.0-82.4]	NS	78.3 [59.0-91.6]	NS
		BMI >36.3	91.3 [75.5-98.5]		25.0 [11.6-42.8]		50.0 [35.2-64.8]		77.8 [45.8-95.9]	
	APRI	BMI ≤36.3	60.9 [40.6-78.9]	NS	88.9 [73.7-97.1]	NS	82.4 [60.4-95.3]	NS	72.7 [56.2-85.8]	NS
		BMI >36.3	65.2 [44.9-82.3]		89.3 [74.5-97.2]		83.3 [62.3-95.6]		75.8 [59.6-88.1]	

Accuracy of non-invasive tests for advanced hepatic fibrosis, comparing accuracy in those with or without T2D and by BMI status. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NPV* negative predictive value; *NS* non-significant; *PPV* positive predictive value; *T2D* type 2 diabetes; *TE* transient elastography.

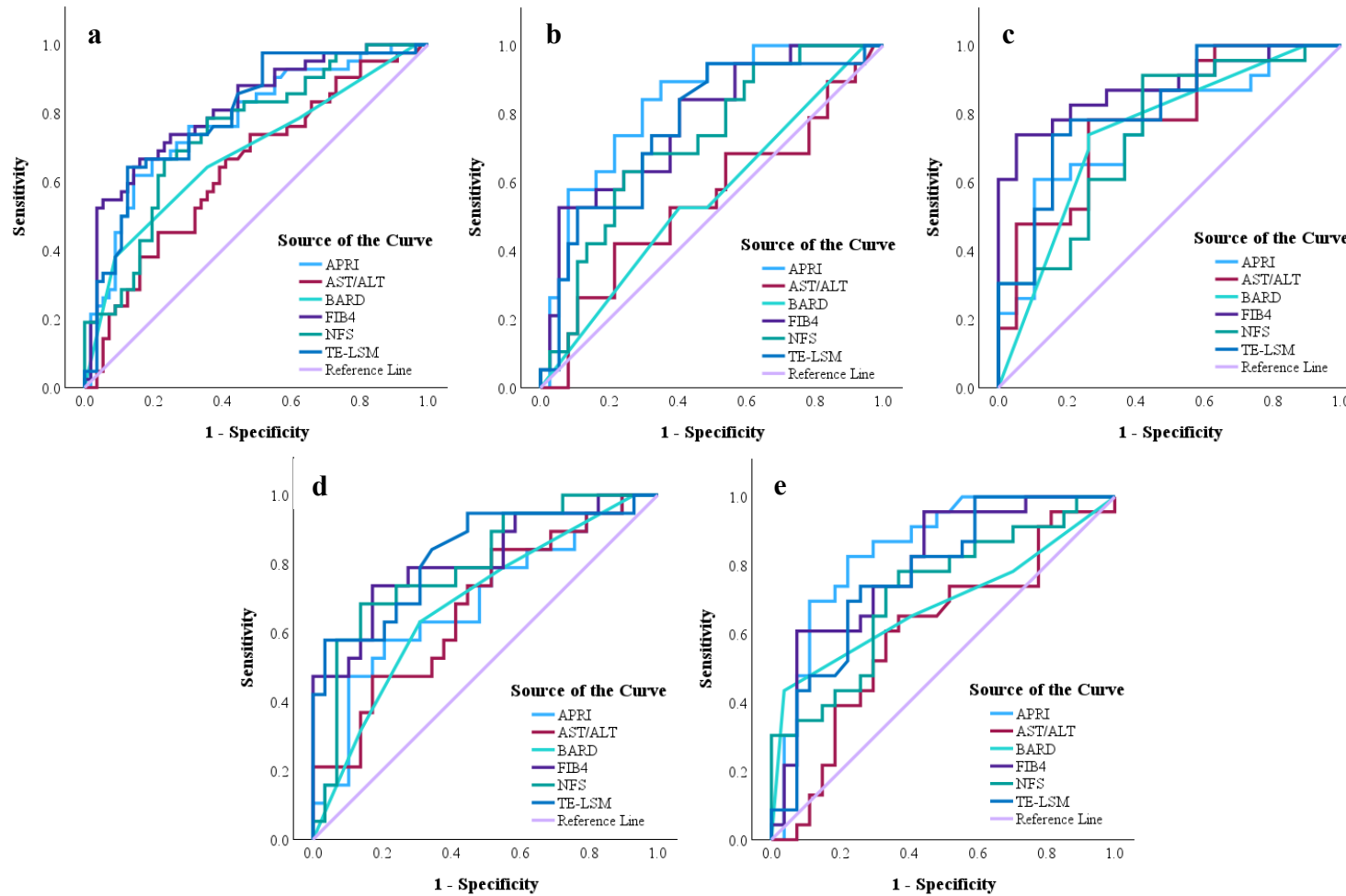
Table 3.8: Receiver operating characteristic analysis for advanced hepatic fibrosis using non-invasive tests

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall		TE-LSM	0.80	0.72–0.87	<0.001	-	0.50	14.8 kPa	66.7	82.9
		AST: ALT	0.68	0.58–0.78	<0.001	-	0.30	0.79	70.8	59.0
		BARD	0.71	0.61–0.81	<0.001	-	0.31	2.5	65.3	66.1
		FIB-4	0.85	0.77–0.92	<0.001	-	0.56	1.7	70.8	85.2
		NFS	0.77	0.69–0.86	<0.001	-	0.47	-0.21	68.8	78.7
		APRI	0.81	0.72–0.89	<0.001	-	0.53	0.63	70.8	82.0
T2D status	TE-LSM	T2D	0.84	0.74–0.93	<0.001	NS	0.62	14.8 kPa	77.5	84.0
		No T2D	0.76	0.64–0.87	<0.001		0.46	11.1 kPa	76.9	68.9
	AST:ALT	T2D	0.80	0.66–0.93	<0.001	NS	0.55	0.79	80.8	73.7
		No T2D	0.61	0.46–0.76	NS		0.26	1.24	45.5	81.0
	BARD	T2D	0.74	0.59–0.89	<0.01	NS	0.48	2.5	74.1	73.7
		No T2D	0.60	0.46–0.74	NS		0.17	2.5	54.5	62.8
	FIB-4	T2D	0.89	0.80–0.99	<0.001	NS	0.72	1.70	76.9	94.7
		No T2D	0.82	0.71–0.93	<0.001		0.54	1.98	59.1	95.2
	NFS	T2D	0.76	0.61–0.90	<0.01	NS	0.50	-0.31	92.3	57.9
		No T2D	0.75	0.63–0.87	<0.001		0.42	-1.00	63.6	78.6
	APRI	T2D	0.78	0.65–0.92	<0.001	NS	0.50	0.68	60.9	89.5
		No T2D	0.86	0.77–0.95	<0.001		0.60	0.58	86.4	73.8

BMI status	TE-LSM	BMI $\leq$ 36.3 kg/m ²	0.81	0.71–0.92	<0.001	NS	0.51	16.3 kPa	56.3	94.6
		BMI >36.3 kg/m ²	0.79	0.68–0.90	<0.001		0.52	14.8 kPa	76.5	75.8
	AST:ALT	BMI $\leq$ 36.3 kg/m ²	0.74	0.61–0.87	<0.001	NS	0.40	0.67	88.0	51.5
		BMI >36.3 kg/m ²	0.60	0.44–0.76	NS		0.26	0.82	65.2	60.7
	BARD	BMI $\leq$ 36.3 kg/m ²	0.74	0.61–0.87	<0.001	NS	0.41	2.5	68.0	72.7
		BMI >36.3 kg/m ²	0.68	0.53–0.83	<0.05		0.38	3.5	41.7	96.6
	FIB-4	BMI $\leq$ 36.3 kg/m ²	0.87	0.77–0.96	<0.001	NS	0.65	1.65	80.0	84.8
		BMI >36.3 kg/m ²	0.81	0.69–0.93	<0.001		0.53	1.05	95.7	57.1
	NFS	BMI $\leq$ 36.3 kg/m ²	0.84	0.74–0.94	<0.001	NS	0.60	-0.76	72.0	87.9
		BMI >36.3 kg/m ²	0.73	0.59–0.87	<0.01		0.43	-0.01	78.3	64.3
	APRI	BMI $\leq$ 36.3 kg/m ²	0.76	0.63–0.89	<0.001	NS	0.50	0.63	68.0	81.8
		BMI >36.3 kg/m ²	0.86	0.75–0.96	<0.001		0.61	0.58	82.6	78.6

The ROC analysis investigating use of non-invasive tests to predict advanced hepatic fibrosis. P value (null) describes statistical significance compared to the AUC expected by chance, and P value (compare groups) describes the significance of differences in AUC between people with or without T2D, or BMI status. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* non-significant; *T2D* type 2 diabetes; *TE* transient elastography.

Figure 3.3: Receiver operating characteristic curves for advanced hepatic fibrosis using non-invasive tests



The ROC analysis exploring use of non-invasive tests to diagnose advanced hepatic fibrosis. (a) overall cohort, (b) people without T2D, (c) people with T2D, (d) people with BMI ≤ 36.3 kg/m², (e) people with BMI > 36.3 kg/m². Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *TE* transient elastography.

3.4.5 Accuracy of blood biomarkers followed by transient elastography in sequence to predict advanced hepatic fibrosis in people with or without type 2 diabetes and by body mass index status.

The accuracy of sequential testing using blood biomarkers first, and followed by TE are shown in Table 3.9. The NFS+TE-LSM was the most sensitive [83.3%], and APRI+TE-LSM most specific [98.2%]. In sequence, the FIB-4+TE-LSM and APRI+TE-LSM gave a combination sensitivity plus specificity >1.5 , whilst the other tests did not. In people with T2D, the BARD+TE-LSM or NFS+TE-LSM sequences were more sensitive and less specific. There was a trend to greater sensitivity for all algorithms in people with T2D. Only FIB-4+TE-LSM and APRI+TE-LSM sequences gave a combined sensitivity plus specificity >1.5 in people with or without T2D. Comparing different BMI groups, the only significant difference was greater specificity with NFS+TE-LSM tests in people with BMI ≤ 36.3 kg/m². Only FIB-4+TE-LSM had combined sensitivity and specificity >1.5 in people with or without T2D, or in both BMI groups. The APRI had a sensitivity and specificity >1.5 in the BMI >36.3 kg/m² group only.

The ROC analysis is shown in Table 3.10 and Figure 3.4. The APRI+TE-LSM sequence demonstrated greatest AUC, followed the AST:ALT+TE-LSM. The Youden index was >0.5 for each test sequence, except for FIB-4+TE-LSM, and the APRI+TE-LSM had the greatest Youden index. In people without T2D, the FIB-4+TE-LSM did not have a greater AUC than by chance, but all other sequences did, irrespective of T2D. There was no significant difference in the AUC observed for test sequences between people with or without T2D. In people with T2D, the Youden index was >0.5 with the AST:ALT+TE-LSM, BARD+TE-LSM, NFS+TE-LSM, and APRI+TE-LSM. In people without T2D, the Youden index was >0.5 for the BARD+TE-LSM, FIB-4+TE-LSM, and APRI+TE-LSM.

When comparing BMI groups, there were no differences in the AUC between groups, and all test sequences associated with advanced fibrosis irrespective of BMI. In people with a BMI ≤ 36.3 kg/m², the Youden index was >0.5 for all five test sequences, but in people with BMI >36.3 kg/m², only the BARD+TE-LSM and APRI+TE-LSM had a Youden index >0.5 , suggesting only these would suffice as a screening algorithm considering the impact of BMI.

Table 3.9: Accuracy of sequential non-invasive tests for advanced hepatic fibrosis

Group	Test	Subgroup	Sensitivity (%) [95% CI]	P	Specificity (%) [95% CI]	P	PPV (%) [95% CI]	P	NPV (%) [95% CI]	P
Overall	AST:ALT+TE-LSM		61.9 [46.8-75.6]		73.2 [60.7-83.6]		63.4 [48.2-77.0]		71.9 [59.5-82.5]	
	BARD+TE-LSM		76.2 [62.0-87.3]		62.5 [49.5-74.4]		60.4 [46.9-72.8]		77.8 [64.3-88.2]	
	FIB-4+TE-LSM		76.8 [64.7-86.5]		78.6 [64.7-89.1]		71.7 [57.8-83.3]		82.7 [71.0-91.3]	
	NFS+TE-LSM		83.3 [70.3-92.5]		62.5 [49.5-74.4]		62.5 [49.5-74.4]		83.3 [70.3-92.5]	
	APRI+TE-LSM		59.5 [4.4-73.5]		98.2 [92.4-99.9]		96.2 [84.1-99.8]		76.4 [65.8-85.2]	
T2D status	AST:ALT+ TE-LSM	T2D	73.9 [54.1-88.7]	NS	73.7 [51.7-89.7]	NS	77.3 [57.4-91.2]	<0.05	70.0 [48.3-86.8]	NS
		No T2D	47.4 [26.3-69.1]		73.0 [57.4-85.4]		47.4 [26.3-69.1]		73.0 [57.4-85.4]	
	BARD+ TE-LSM	T2D	100.0	<0.001	42.1 [22.0-64.2]	<0.05	67.6 [51.0-81.7]	NS	100.0	NS
		No T2D	47.4 [26.3-69.1]		73.0 [57.4-85.4]		47.4 [26.3-69.1]		73.0 [57.4-85.4]	
	FIB-4+ TE-LSM	T2D	87.0 [69.6-96.6]	NS	63.2 [40.8-82.2]	NS	74.1 [55.9-87.9]	NS	80.0 [56.0-94.6]	NS
		No T2D	68.4 [46.1-86.0]		83.8 [69.8-93.2]		68.4 [46.1-86.0]		83.8 [69.8-93.2]	
	NFS+ TE-LSM	T2D	95.7 [82.2-99.7]	<0.05	42.1 [22.0-64.2]	<0.05	66.7 [49.8-81.1]	NS	88.9 [59.5-99.3]	NS
		No T2D	68.4 [46.1-86.0]		73.0 [57.4-85.4]		56.5 [36.4-75.3]		81.8 [66.5-92.3]	
	APRI+ TE-LSM	T2D	60.9 [40.6-78.9]	NS	94.7 [78.8-99.7]	NS	93.3 [73.8-99.6]	NS	66.7 [48.0-82.4]	NS
		No T2D	57.9 [35.8-78.0]		100.0		100.0		82.2 [69.4-91.5]	

BMI status	AST:ALT+ TE-LSM	BMI ≤36.3	55.6 [33.0-76.6]	NS	68.0 [48.6-83.9]	NS	55.6 [33.0-76.6]	NS	68.0 [48.6-83.9]	NS
		BMI >36.3	66.7 [46.8-83.1]		77.8 [60.0-90.5]		72.7 [52.3-88.1]		72.4 [54.7-86.3]	
	BARD+ TE-LSM	BMI ≤36.3	73.7 [51.7-89.7]	NS	62.5 [42.6-79.9]	NS	60.9 [40.6-78.9]	NS	75.0 [53.8-90.2]	NS
		BMI >36.3	78.3 [59.0-91.6]		59.3 [40.5-76.3]		62.1 [43.9-78.2]		76.2 [55.6-90.7]	
	FIB-4+ TE-LSM	BMI ≤36.3	73.7 [51.7-89.7]	NS	80.0 [61.8-92.3]	NS	73.7 [51.7-89.7]	NS	80.0 [61.8-92.3]	NS
		BMI >36.3	82.6 [64.1-94.2]		74.1 [55.9-87.9]		73.1 [54.4-87.4]		83.3 [65.4-94.5]	
	NFS+ TE-LSM	BMI ≤36.3	73.7 [51.7-89.7]	NS	76.0 [57.2-89.7]	<0.05	70.0 [48.3-86.8]	NS	79.2 [60.4-92.0]	NS
		BMI >36.3	91.3 [75.5-98.5]		44.4 [26.9-63.0]		58.3 [42.1-73.4]		85.7 [62.1-97.5]	
	APRI+ TE-LSM	BMI ≤36.3	47.4 [26.3-69.1]	NS	96.0 [83.5-99.8]	NS	90.0 [62.8-99.4]	NS	70.6 [54.2-84.0]	NS
		BMI >36.3	69.6 [49.4-85.6]		100.0		100.0		79.4 [49.4-85.6]	

Accuracy of sequential non-invasive tests for advanced hepatic fibrosis, compared by T2D and BMI status. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NPV* negative predictive value; *NS* non-significant; *PPV* positive predictive value; *T2D* type 2 diabetes; *TE* transient elastography.

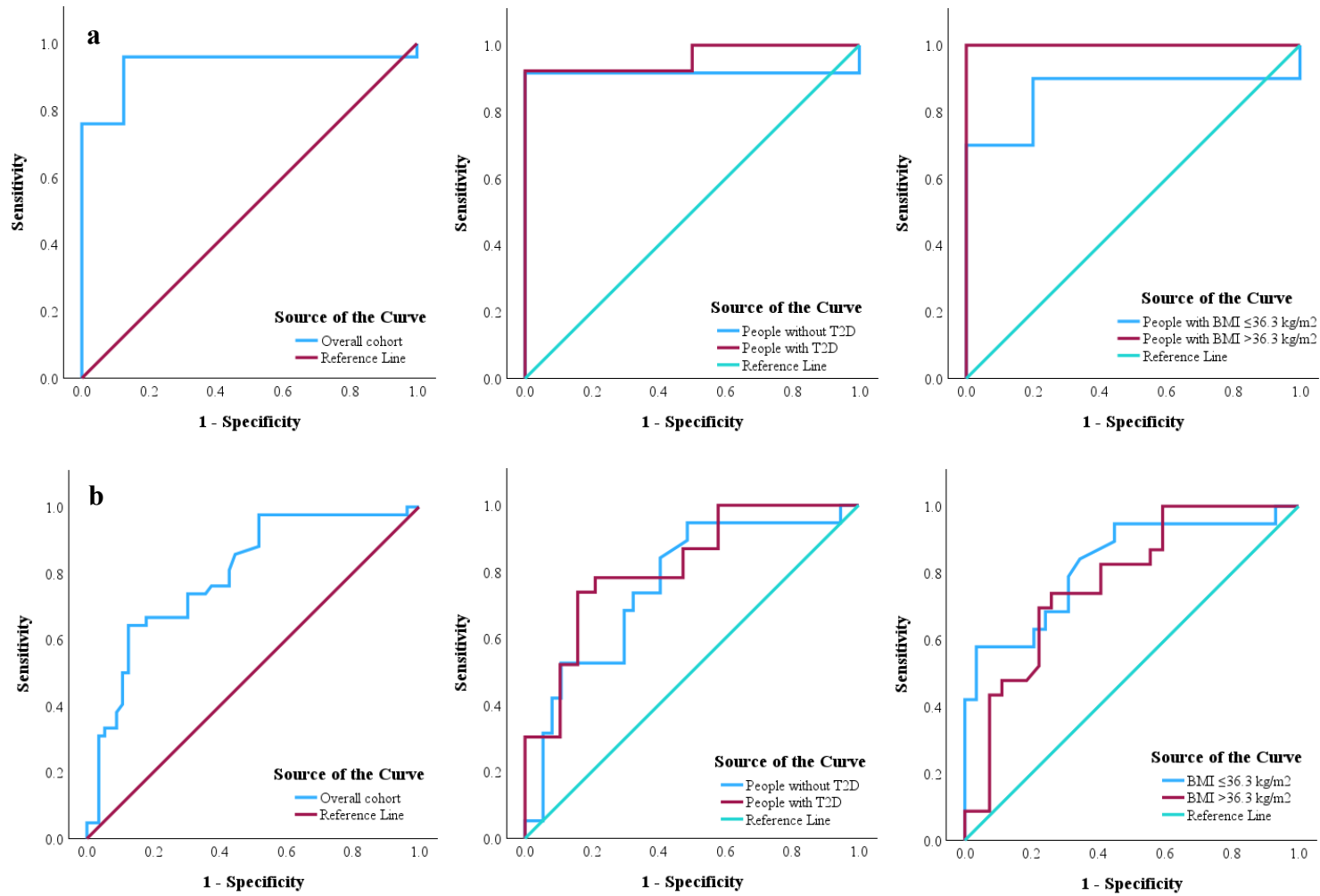
Table 3.10: Receiver operating characteristic analysis for advanced hepatic fibrosis using sequential tests

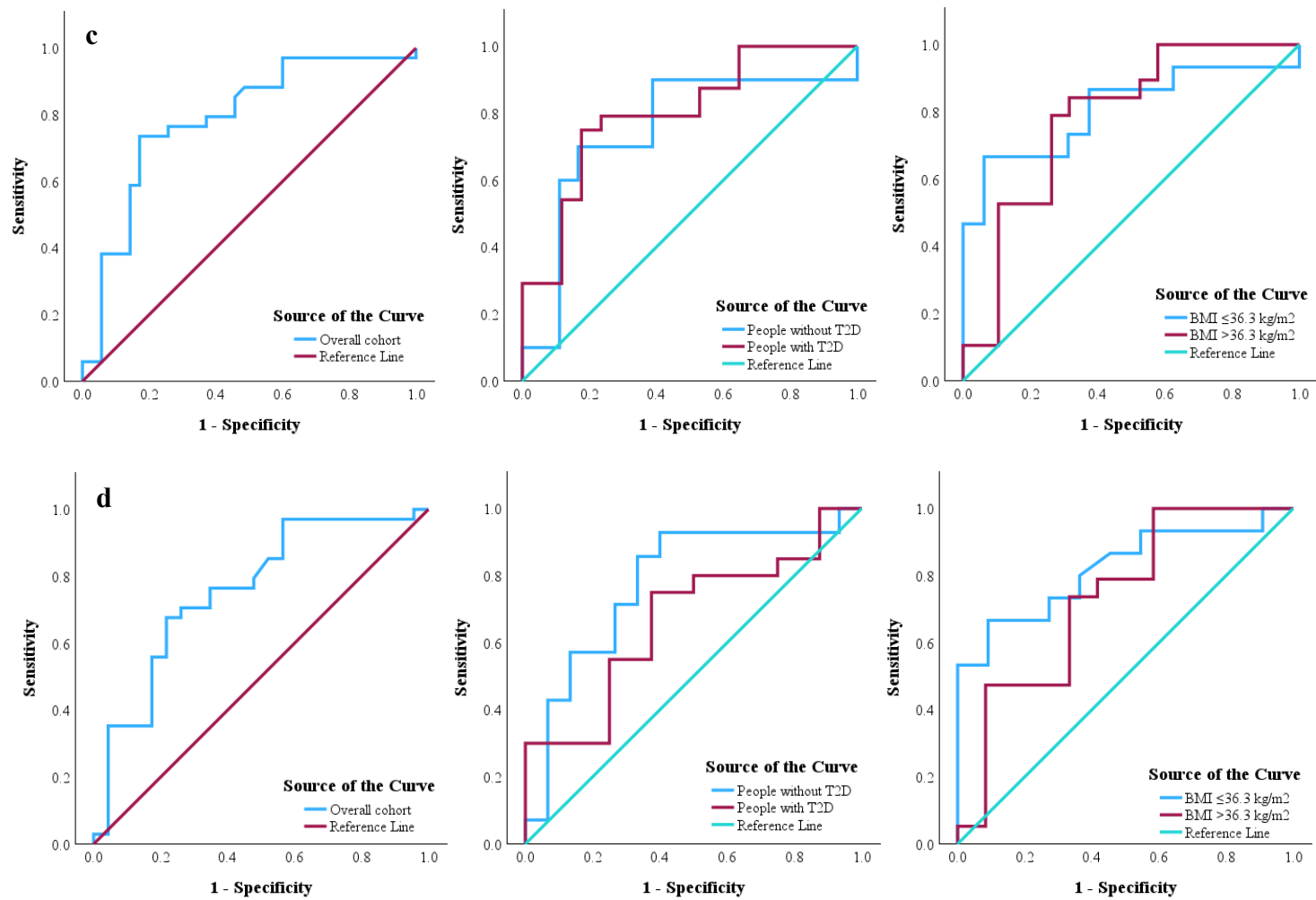
Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off (kPa)	Sensitivity (%)	Specificity (%)
Overall	AST: ALT+TE-LSM (n=98)		0.80	0.71-0.88	<0.001	-	0.52	16.25	64.3	87.5
	BARD+TE-LSM (n=69)		0.79	0.67-0.90	<0.001	-	0.56	16.25	73.5	82.9
	FIB-4+TE-LSM (n=57)		0.76	0.63-0.89	<0.001	-	0.46	16.10	67.6	78.3
	NFS+TE-LSM (n=65)		0.76	0.64-0.88	<0.001	-	0.54	16.10	74.3	80.0
	APRI+TE-LSM (n=33)		0.94	0.84-1.0	<0.001	-	0.84	9.6	96.0	87.5
T2D status	AST:ALT+TE-LSM	T2D (n=42)	0.82	0.69-0.95	<0.001	NS	0.58	16.10	73.9	84.2
		No T2D (n=56)	0.76	0.63-0.89	<0.001		0.46	9.65	94.7	51.4
	BARD+TE-LSM	T2D (n=41)	0.80	0.66-0.94	<0.001	NS	0.57	16.1	75.0	82.4
		No T2D (n=28)	0.75	0.54-0.96	<0.05		0.53	18.6	70.0	83.3
	FIB-4+TE-LSM	T2D (n=28)	0.78	0.60-0.96	<0.01	NS	0.38	16.1	75.0	62.5
		No T2D (n=29)	0.67	0.45-0.89	NS		0.53	9.65	92.9	60.0
	NFS+TE-LSM	T2D (n=37)	0.79	0.63-0.94	<0.001	NS	0.57	16.10	77.3	80.0
		No T2D (n=28)	0.72	0.52-0.91	<0.05		0.49	17.75	69.2	80.0
	APRI+TE-LSM	T2D (n=15)	0.96	0.86-1.0	<0.001	NS	0.92	14.95	92.3	100.0
		No T2D (n=18)	0.92	0.76-1.0	<0.001		0.92	9.85	91.7	100.0

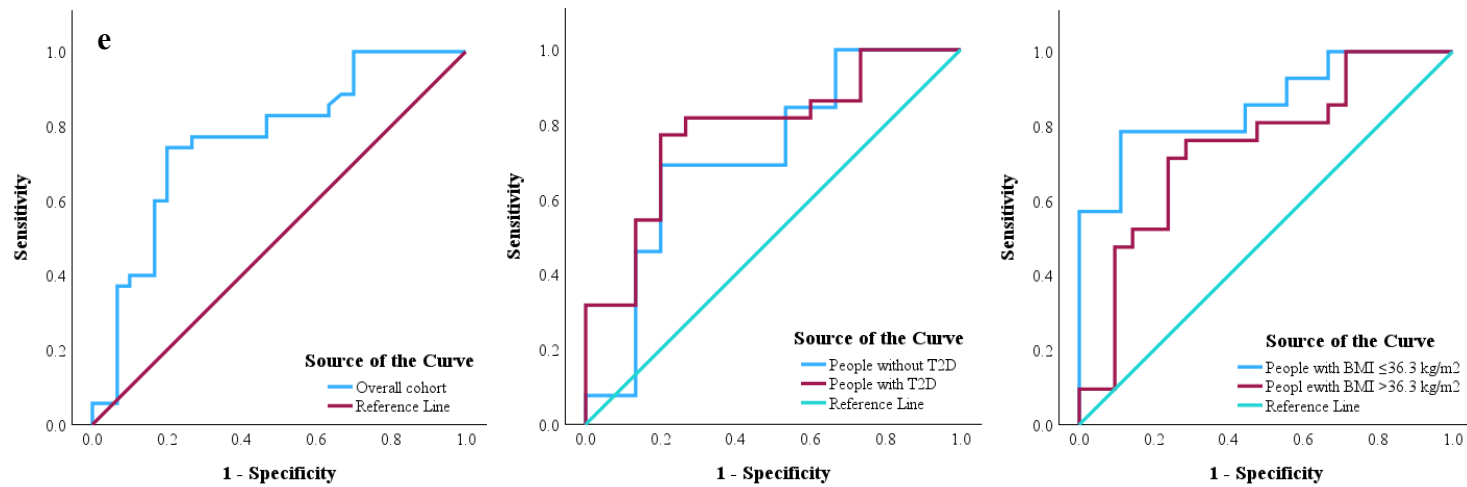
BMI status	AST:ALT+ TE-LSM	BMI ≤ 36.3 kg/m ² (n=48)	0.83	0.70-0.95	<0.001	NS	0.54	16.25	57.9	96.6
		BMI > 36.3 kg/m ² (n=50)	0.77	0.64-0.90	<0.001		0.48	14.95	73.9	74.1
	BARD+ TE-LSM	BMI ≤ 36.3 kg/m ² (n=31)	0.81	0.65-0.97	<0.001	NS	0.60	16.25	66.7	93.7
		BMI > 36.3 kg/m ² (n=38)	0.78	0.63-0.93	<0.001		0.53	16.35	78.9	73.7
	FIB-4+ TE-LSM	BMI ≤ 36.3 kg/m ² (n=26)	0.82	0.66-0.98	<0.001	NS	0.58	16.10	66.7	90.9
		BMI > 36.3 kg/m ² (n=31)	0.73	0.54-0.93	<0.05		0.42	9.6	100.0	41.7
	NFS+ TE-LSM	BMI ≤ 36.3 kg/m ² (n=23)	0.86	0.71-1.0	<0.001	NS	0.68	16.10	78.6	88.9
		BMI > 36.3 kg/m ² (n=42)	0.74	0.59-0.90	<0.01		0.48	16.35	71.4	76.2
	APRI+ TE-LSM	BMI ≤ 36.3 kg/m ² (n=15)	0.86	0.66-1.0	<0.001	NS	0.70	15.5	70.0	100.0
		BMI > 36.3 kg/m ² (n=18)	1.00	1.0-1.0	<0.001		1.00	9.6	100.0	100.0

The ROC analysis investigating sequential non-invasive tests to predict advanced hepatic fibrosis. N indicates the number of participants with paired blood biomarker and TE-LSM data from those with a positive blood biomarker test result. P value (null) describes statistical significance compared to the AUC expected by chance, and the P value (compare groups) describes the significance of differences in AUC between people with or without T2D, or BMI status. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* non-significant; *T2D* type 2 diabetes; *TE* transient elastography.

Figure 3.4: Receiver operating characteristic curves for advanced hepatic fibrosis using sequential tests







The ROC analysis exploring the use of sequential non-invasive tests to diagnose advanced hepatic fibrosis in the overall cohort, by T2D status and BMI status. (a) APRI+TE-LSM, (b) AST:ALT+TE-LSM, (c) BARD+TE-LSM, (d) FIB-4+TE-LSM, (e) NFS+TE-LSM. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TE* transient elastography.

3.5 Discussion

In this chapter, the relative accuracy of several non-invasive tests for MASLD to screen for hepatic steatosis or fibrosis in people with biopsy-confirmed MASLD was explored. The comparative accuracy of these tests in people with or without T2D and by BMI status was assessed. Finally, the accuracy of sequential testing to screen for advanced fibrosis in MASLD was investigated and compared again by T2D or BMI status.

There are several accuracy statistics presented in this chapter which can support the conclusion of whether a test is useful. Firstly, the sum of the sensitivity and specificity should be at least ≥ 1.5 , as this is the mid-point between a useless test (sum=1) and a perfect test (sum=2) (Power et al., 2013). However, to determine whether a test is appropriate in practice further judgement is needed. For example, in the context of diagnosing life-threatening disease it would be essential to have a combined sensitivity and specificity greater than 1.5. Secondly, the greater the AUC, the more reliable it is to predict that disease state. The AUC is the likelihood that someone with the disease is ranked more likely to have the disease than someone who does not (Hajian-Tilaki, 2013). An AUC of 1 reflects perfect distinction of subjects with or without the disease, an AUC of 0 reflects incorrect disease classification in all subjects, and an AUC of 0.5 reflects the degree of discrimination expected by chance. Finally, the Youden index was derived from the ROC curve, calculated as $\text{Youden index} = \text{sensitivity} + \text{specificity} - 1$ (Youden, 1950). Assuming the sensitivity and specificity are of equal diagnostic relevance, the Youden index determines the best test threshold to identify the disease state. The index gives a value ranging from 0 (no value) to 1 (perfect test), with the highest index matching the most appropriate test threshold. A Youden index >0.5 reflects moderate accuracy, though this should be interpreted cautiously given the equal weighting of sensitivity and specificity to derive the statistic. It may be more appropriate to have a test with greater sensitivity or specificity if used as a screening or diagnostic test (Dhamnetiya et al., 2022).

3.5.1 Non-invasive tests for clinically significant hepatic steatosis

The HSI performed poorly to screen for clinically significant hepatic steatosis. The HSI had a very poor specificity of 3.4%, and AUC similar to chance [AUC 0.60, $p=0.10$], irrespective of T2D or BMI status. Whilst the TE-CAP was more useful, this remained insufficient. A cut-off TE-CAP ≥ 331.0 dB/m, had a sensitivity and specificity of 73.2% and 42.9% respectively, falling short of the accepted 1.5 total. Whilst the TE-CAP predicted clinically significant hepatic steatosis better [AUC 0.66] in the overall cohort, it was unreliable in people without T2D, or in people with BMI ≥ 36.3 kg/m². In people with T2D the TE-CAP was better, as it

associated with clinically significant hepatic steatosis with an AUC of 0.72, but with a Youden index of 0.41 giving a screening cut-off of 364.5 dB/m, the test appeared insufficient for use in practice. Therefore, whilst the ROC analysis indicates the TE-CAP was statistically associated with clinically significant hepatic steatosis, it would not be an appropriate screening test.

For the TE-CAP, these findings are similar to a recent meta-analysis reporting an AUC 0.80 to identify steatosis grade 2-3, and poorer diagnostic accuracy in people with BMI ≥ 30.0 kg/m², requiring different thresholds in obesity (Cao et al., 2022). Others report a greater Youden index-derived diagnostic threshold associated with T2D. In people with T2D, one study observed a greater mean TE-CAP of 13.0 dB/m and greater diagnostic threshold 15.5 dB/m than in those without T2D (Karlas et al., 2017). However, these observations were different from previously published evidence for the HSI. The HSI had a reported AUC of 0.82 to detect hepatic steatosis diagnosed by ultrasound. Given their reference was ultrasound, there is limited comparison with our histology-based study (Bohte et al., 2011). We found no association between the HSI and histological scores. Though, the population in this study was different to the original validation study as this cohort all had MASLD, whilst the other studies included around 50% without MASLD, and more participants. Given the retrospective nature of this study, there were insufficient data to generate other non-invasive measures such as the FLI, NAFLD-LFS, or TyG. Nevertheless, as most with T2D have hepatic steatosis and there is little direct association between hepatic steatosis and clinical outcomes, there may be little to gain by screening for hepatic steatosis, and efforts better focussed on screening for hepatic fibrosis.

3.5.2 Non-invasive tests for hepatic fibrosis

The accuracy of non-invasive tests was investigated for hepatic fibrosis. Clinically significant fibrosis was defined as $\geq$ stage 2 fibrosis, as this is frequently the degree of fibrosis required for clinical trial participation (Loomba et al., 2024; Newsome et al., 2021). Advanced fibrosis was defined $\geq$ stage 3 fibrosis given its association with CVD and liver outcomes (Stal, 2015).

The FIB-4 score demonstrated the best combined sensitivity and specificity for clinically significant fibrosis, whilst the TE-LSM was most sensitive and APRI most specific. These observations were broadly similar for advanced fibrosis also, with the FIB-4 test, APRI and TE-LSM demonstrating the best combined sensitivity and specificity, and APRI exhibited high specificity. Only the FIB-4 score for clinically significant fibrosis and APRI for advanced fibrosis demonstrated sufficient accuracy of sensitivity and specificity ≥ 1.5 . For clinically significant or advanced fibrosis the FIB-4 score showed the greatest AUC, both 0.85. The TE-

LSM, NFS and APRI had good accuracy (AUC 0.76-0.81) to detect clinically significant or advanced fibrosis, and the AST:ALT ratio had poorest accuracy. For clinically significant fibrosis, a FIB-4 score ≥ 1.45 gave sensitivity and specificity of 72.1% and 85.4%, whilst for advanced fibrosis, a threshold of 1.7 gave sensitivity 70.8% and specificity of 85.2%. The APRI demonstrated a sensitivity 70.8% and specificity 82.0% at a threshold of 0.63; and sensitivity 68.9% and specificity 81.2% at a threshold of 0.58 for clinically significant and advanced fibrosis, respectively. All other tests failed to demonstrate a Youden index ≥ 0.5 or a sensitivity and specificity ≥ 1.5 . Therefore, the FIB-4 index had the greatest utility as a single test to screen for hepatic fibrosis $\geq$ stage 2 or $\geq$ stage 3 in this cohort, followed by the APRI.

A recent meta-analysis compared the accuracy of the TE-LSM, FIB-4 score, NFS, APRI and AST:ALT ratio to identify advanced fibrosis in 37 studies with 5735 participants, of whom a third had T2D and a third had advanced fibrosis. The study observed the AUC associated with the TE-LSM, FIB-4 score, NFS, APRI and AST:ALT ratio for advanced fibrosis was 0.85, 0.76, 0.73, 0.70, and 0.64 respectively (Mozes et al., 2022). The AUC for these tests in this study was 0.80, 0.85, 0.77, 0.81, and 0.68 respectively, which are broadly similar. However, whilst the previous meta-analysis observed the TE-LSM most closely associated with advanced fibrosis, we observed the FIB-4 score was most accurate. This may be a result of using cohorts with differing characteristics in the studies. In this cohort, there was a selection bias given all patients had a biopsy and clinical work-up for a definite MASLD diagnosis, and there was a high proportion with advanced fibrosis at 50.3% with a high median BMI 36.3 kg/m² and almost half had T2D. Comparatively, this meta-analysis described a cohort with lower BMI, lower proportion with T2D and lower prevalence of advanced fibrosis at 30%, affecting these statistics (Mozes et al., 2023). Another analysis observed the APRI, BARD score, AST:ALT ratio, NFS and FIB-4 score had AUC of 0.83, 0.74, 0.78, 0.82, and 0.81, to diagnose MASH in 45 studies (Contreras et al., 2023). The AST:ALT ratio (AUC 0.68) and BARD score (AUC 0.71) in the cohort presented in this chapter had poorest accuracy, like these meta-analyses. However, comparison is limited by variable populations and methods in the meta-analysis, including MASLD diagnosed by ultrasound. Nonetheless, the SBUHB data are comparable, giving confidence in their local application.

In comparison to previous investigations, the NPV of the AST:ALT ratio, BARD score, FIB-4 and NFS were lower in this analysis, a particular concern for screening tests. For clinically significant hepatic fibrosis, the NPV was 60.8-73.9%, and for advanced fibrosis 70.6-82.6%, compared with a NPV 92-95% in a previous investigation (McPherson et al., 2010). Whilst

these cohorts had similar prevalence of T2D and obesity, the difference may be explained by a greater prevalence of advanced fibrosis in the cohort presented in this chapter (50 vs 19%) inferring a spectrum bias between studies. Moreover, there was a moderate sample size in both cohorts (n=145-153), with some missing data in our sample which may limit analysis.

Overall, the utility of these tests was generally poor compared with the gold standard of liver biopsy. However, biopsy itself is limited given the degree of parenchymal heterogeneity within the liver, meaning that a single biopsy may misclassify the severity of fibrosis, termed sampling error. This is established in other fields, for example in the diagnosis of idiopathic pulmonary fibrosis in which high-resolution CT is often preferred for diagnosis over lung biopsy given risk of sampling error and interobserver reporting variability alongside the additional clinical risk associated with biopsy (Raghu et al., 2011). Therefore, these results need to be interpreted cautiously when considering liver biopsy as a gold standard test given such limitations.

3.5.3 Effect of type 2 diabetes on test accuracy for MASLD fibrosis

In people with T2D, there was a trend to greater sensitivity for most tests. There was greater sensitivity for the NFS to identify clinically significant or advanced fibrosis, and BARD score to identify advanced fibrosis. This is unsurprising given these scores include T2D in their algorithms. The FIB-4 score demonstrated the greatest AUC in people with T2D, and APRI demonstrated the greatest AUC in people without T2D, whilst the TE-LSM and NFS had similar accuracy irrespective of T2D. For clinically significant fibrosis, a FIB-4 ≥ 1.36 had a sensitivity and specificity of 81.3% and 92.3% in people with T2D, and for advanced fibrosis a FIB-4 score ≥ 1.70 had sensitivity 76.9% and specificity 94.7%. In both ROC analyses, the FIB-4 score was sufficiently accurate in people without T2D, with no difference between groups. This conflicts with previous studies which observed poorer FIB-4 accuracy in people with T2D for advanced fibrosis (Bertot et al., 2018; Chung et al., 2023; Ito et al., 2023). This difference is difficult to explain, though one study used the TE-LSM as the gold standard (Chung et al., 2023) limiting comparison. Nonetheless other studies used histology as the gold standard test and included 284 (Bertot et al., 2018) and 1489 (Ito et al., 2023) participants. These were in Australian and Japanese populations which may be an important factor with little published evidence to compare these tests in different populations.

The APRI had a similar AUC in people with or without T2D. For advanced fibrosis the Youden index was >0.5 in people with or without T2D, with good accuracy in both groups. This is like previous studies. In an Australian study with 284 participants and biopsy-proven MASLD, the

AUC was similar in people with T2D compared to people without T2D for advanced fibrosis (Bertot et al., 2018). The AST:ALT ratio and BARD score trended to greater accuracy for fibrosis in people with T2D in the cohort in this chapter. Whilst the accuracy of the BARD score is both confounded and explained by the inclusion of T2D in the algorithm, the trend to greater accuracy of the AST:ALT ratio in T2D is more difficult to explain. There is limited evidence assessing AST:ALT ratio accuracy in T2D to draw comparisons. Overall, the FIB-4 score and APRI showed good accuracy in this cohort as a single test in people with T2D.

3.5.4 Effect of body mass index on test accuracy for MASLD fibrosis

In people with a BMI ≤ 36.3 kg/m², the FIB-4 score demonstrated the greatest AUC for hepatic fibrosis. Accuracy of the TE-LSM and FIB-4 score was similar in those with a BMI above or below the cohort median, making them useful screening tests. The TE-LSM demonstrated a similar accuracy irrespective of BMI group, with AUC 0.78-0.81 and 0.79-0.80 for those with BMI ≤ 36.3 kg/m² and >36.3 kg/m² to identify clinically significant or advanced fibrosis, respectively. Though, the APRI demonstrated a greater AUC for clinically significant and advanced fibrosis in people with a BMI >36.3 kg/m² than in people with BMI ≤ 36.3 kg/m². There was a trend poorer NFS accuracy in people with a BMI >36.3 kg/m² for clinically significant and advanced fibrosis. Whilst the AST:ALT ratio associated significantly with the degree of fibrosis in people with BMI ≤ 36.3 kg/m², the AUC was lower compared with other tests, and the statistical association was not seen in people with a BMI >36.3 kg/m². Similarly, the BARD score had a poor AUC compared to other tests in this cohort.

These data are consistent with previously published observations with the FIB-4 score. Drolz and colleagues observed that the FIB-4 score and APRI were the most accurate tests for advanced fibrosis in their study of 368 patients, irrespective of BMI (Drolz et al., 2021). Similar findings of consistent accuracy of the FIB-4 score to detect advanced fibrosis were reported elsewhere (de Carli et al., 2020; Qadri et al., 2022). Likewise, other groups report excellent accuracy of the APRI in people with obesity, two groups observed that the APRI was the most accurate test in people undergoing bariatric surgery (de Carli et al., 2020; Schmitz et al., 2020), though in neither study was there a control group with a lower BMI to compare. Like the results in this chapter, other studies observed the NFS was less accurate with increasing BMI (Drolz et al., 2021; Qadri et al., 2022). However, there are conflicting observations that these tests may have poorer accuracy in people with obesity, though even in these studies the FIB-4 score and APRI remain most accurate (Alqahtani et al., 2021; Eren et al., 2022; Ito et al., 2023). In this cohort, there was a similar AUC for the TE-LSM test to identify clinically significant or

advanced fibrosis in people with a BMI above or below the median. Likewise, a meta-analysis of 10,537 patients by Cao et al (Cao et al., 2022) reported that the TE-LSM could be used with similar accuracy to identify advanced fibrosis in people with or without obesity, assuming that the appropriate probe was used.

Variability of the observed impact of obesity on test accuracy likely results from biological and methodological differences. Obesity heterogeneously influences liver steatosis and fibrosis distribution and progression which may complicate the use of blood biomarkers and imaging techniques, and increase sampling error related to liver biopsy (Chan et al., 2024). Confounding factors such as smoking status, coexistent infections, additional metabolic comorbidities (e.g. hypothyroidism), or genetic variants may also be implicated. International variability such as differences in laboratory assays, operator-dependent imaging, and varying population-specific reference ranges globally may also play a role (J. K. Lee et al., 2010; Tanaka et al., 2014).

3.5.5 Accuracy of a sequential testing algorithm

A blood biomarker was chosen as the initial screening test as this can be included easily in practice (Williams, Nagaraj, et al., 2025). The TE-LSM test was chosen second-line as this has established diagnostic accuracy and is recommended as a second-line test for advanced fibrosis (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023). The ELF test is an appropriate alternative, but this was not available in this cohort at the time of their clinical care in SBUHB so could not be investigated.

The use of the FIB-4 score or APRI followed by the TE-LSM gave a combined sensitivity and specificity >1.5 , suggesting good utility. However, in the ROC analysis, only the APRI+TE-LSM had a Youden index >0.5 , and this sequence had greatest AUC. These findings contrast with a meta-analysis exploring the accuracy of sequential test algorithms. The FIB-4 score followed by TE-LSM was the most accurate for advanced fibrosis, then the NFS followed by TE-LSM. Moreover, as the APRI had an AUC 0.70 in their analysis, no further investigation using this was undertaken given its limited accuracy (Mozes et al., 2022). In this chapter, the APRI+TE-LSM gave the greatest AUC, but concluding this is the best test sequence is limited given only 33 cases of paired APRI and TE-LSM data (15 with T2D, 18 without T2D) were available. This is because only 39 cases were identified to have a positive APRI score ≥ 0.7 , and 6 had missing TE-LSM data. In comparison, other sequences presented in this analysis had greater patient numbers with a positive screening test allowing greater numbers with paired data as shown in Table 3.10.

There was a trend to each test sequence being more sensitive (and less specific) in T2D, reaching significance with the BARD score or NFS followed by the TE-LSM. Both the FIB-4+TE-LSM and APRI+TE-LSM sequences had sensitivity plus specificity ≥ 1.5 , but in the ROC analysis the FIB-4+TE-LSM did not associate with advanced fibrosis in people without T2D. This may be a consequence of the broad CI associated with the low number of cases with paired data without T2D ($n=29$) in this sub-analysis, limited generalisability in this group. Previous studies report the FIB-4 score is more accurate in people without T2D. A study including 1,051 participants found the AUC for the FIB-4 test was greater in people without T2D (AUC 0.81 vs. 0.72). In sequence with TE-LSM, the accuracy of FIB-4 score was 90.3% in people without T2D, and 79.0% in people with T2D (Boursier et al., 2023). Other studies report similar findings (Bertot et al., 2018; Chung et al., 2023; Ito et al., 2023). It was surprising this sequence was more accurate in people with T2D in this study. However, this may be due to differences in the characteristics of the cohort, as it exclusively included secondary care patients requiring liver biopsy, which is not typically required in routine practice. Given the limited number of patients with paired data in each subgroup and the consistency of previous published observations in this area, these data should be interpreted cautiously. The APRI+TE-LSM showed greatest accuracy across BMI groups, but analysis was limited by the patient numbers, again limiting generalisability of the data presented. One study reported the APRI was the test with greatest AUC in people with MASLD undergoing bariatric surgery (Alqahtani et al., 2021). The cohort in the previous study had greater obesity as the median BMI in this cohort was 36.3 kg/m² and mean BMI in their study was 47.6 kg/m². Due to the limited numbers in the sub-analyses in this chapter, exploring different BMI thresholds was too limited.

Only the FIB-4+TE-LSM test sequence had combined sensitivity plus specificity >1.5 in both BMI subgroups. The AUC was similar in both BMI groups for the FIB-4+TE-LSM. This is similar to previous studies exploring the FIB-4 score and TE-LSM at varying BMI thresholds (Drolz et al., 2021; Karlas et al., 2017; Qadri et al., 2022), and are considered the tests least affected by BMI for MASLD fibrosis. The AUC was >0.74 for test sequences across both BMI groups, suggesting reasonable accuracy irrespective of BMI group. Whilst not reaching significance, there was a trend to greater AUC with sequential testing in the leaner group, except for the APRI+TE-LSM. Similarly, one study reported that in people with a BMI ≥ 25.0 kg/m² there was poorer accuracy for several non-invasive tests for advanced fibrosis. In people with T2D, the impact of a BMI ≥ 25.0 kg/m² was especially marked for the FIB-4 score and NFS (Ito et al., 2023). A meta-analysis reported the TE-LSM, FIB-4 score and NFS, were more

reliable with greater AUC in leaner people in a cohort in which 15.2% had BMI <25.0 kg/m², 37.3% had BMI 25.0-30.0 kg/m², and the remainder had BMI >30.0 kg/m² (Mozes et al., 2022). The major difference in the cohort in this chapter is that people with a BMI greater or lesser than the cohort median were compared. This difference in methodology is because in this cohort only five patients had a BMI <30.0 kg/m², and there no patients with a BMI <25.0 kg/m². Indeed, such differences between cohorts in the accuracy of TE may be related to greater number of false positives seen in people with greater central obesity confounding the LSM as reported in previous investigations (Chan et al., 2024).

3.6 Summary and limitations

In this cohort of MASLD patients, the TE-CAP was the best predictor of clinically significant hepatic steatosis, and the FIB-4 score the best predictor of clinically significant or advanced fibrosis. However, the TE-CAP was unreliable in people with BMI >36.3 kg/m² and in people without T2D, and insufficiently robust for hepatic steatosis. The TE-LSM and APRI also demonstrated good utility to screen for hepatic fibrosis. The FIB-4 score, APRI and TE-LSM appeared similarly accurate irrespective of T2D or BMI status. There was a trend to greater accuracy in people with T2D or leaner BMI, which may have clinical implications. These data support the application of the internationally recommended strategy using the FIB-4 score followed by the TE-LSM to screen for advanced fibrosis. However, different subgroups such as those in the leaner cohort or without diabetes may benefit from using different tests. This supports the possibility of applying personalised screening algorithms to particular subgroups based on their comorbidities. Whilst this requires validation, it could give further confidence in a novel screening approach.

3.6.1 Clinical significance

There are several clinically significant findings. Firstly, whilst the TE-CAP score was the more reliable test for hepatic steatosis it was unreliable in people without T2D or greater BMI, limiting its use. Secondly, whilst each non-invasive test associated with clinically significant or advanced hepatic fibrosis, their accuracy in people with T2D or greater BMI differed. This means that in practice, it may be appropriate to undertake different tests to screen for MASLD fibrosis, depending on the population in question, supporting a personalised medicine approach in this area. This would need to be corroborated in larger studies using similar histological reference standards. For example, the FIB-4 score may be the most accurate test in a person with T2D and BMI ≤36.3 kg/m², whilst the APRI may be best in a person with a BMI >36.3

kg/m² without T2D. Sequential testing will be needed to capture people at greatest risk of advanced fibrosis, as any single test would not prove diagnostic, and the approach recommended internationally seems reasonable based on these data. Further evaluation should be taken to confirm accuracy in patient subgroups. Moving forward, external validation of these data generated within this training set in an independent cohort, such as those within hepatology services in a different NHS health board, would be valuable. Furthermore, longitudinal studies to explore testing frequency would be useful, as this may not be required annually.

3.6.2 Limitations

There are several limitations to this study:

1. This was a retrospective cross-sectional study, which relied upon already collected data. Missing data limited the analysis, and data needed to generate other non-invasive scores of hepatic steatosis or fibrosis were too limited to include (e.g., the FLI).
2. There were limited and unreliably documented data related to smoking status, physical activity and other medical comorbidities. These were too limited for presentation and analysis, but may have contributed to the degree of steatohepatitis and fibrosis.
3. Only four (2.6%) patients had hepatic steatosis stage 0 on biopsy, meaning an analysis to evaluate the use of these tests to rule out any hepatic steatosis was limited.
4. Given that all patients included had diagnosis of MASLD, statistics such as the PPV or NPV may have a degree of bias. A control group without MASLD may support the accuracy of tests to exclude disease.
5. The analysis exploring the impact of BMI on test accuracy was limited by a lack of patients with a BMI in the normal range. Five patients had a BMI <30.0 kg/m², and none with a BMI <25.0 kg/m².
6. Validation of the adjusted screening thresholds proposed in this chapter is needed to support the generalisability of these data, particularly in the subgroup analysis. This could be applied to a cohort of patients with MASLD under hepatology services in another NHS Wales health board or NHS trust.

Chapter Four:

The bidirectional relationship between metabolic dysfunction-associated steatotic liver disease and type 2 diabetes

4.1 Introduction

There is a growing body of evidence to substantiate the bidirectional associations between MASLD and T2D (Targher et al., 2021; Tomah et al., 2020). The importance of these associations on national services grows. In Wales, the prevalence of diabetes is 6.3% with the greatest prevalence amongst the UK regions (Diabetes UK, 2020), and the national burden of MASLD has grown 10-fold (Pembroke et al., 2023). Though many with MASLD will not have this diagnosed, monitored, or treated (Pembroke et al., 2023).

There is a bidirectional relationship between MASLD and T2D. People with T2D have two-fold greater risk of developing MASLD. The estimated global prevalence of MASH, significant hepatic fibrosis, and advanced fibrosis is 66.4%, 40.8% and 15.5%, respectively (Younossi, Golabi, et al., 2024). However, these estimates range considerably by global region, probably due to inconsistent study definitions of NAFLD before the updated international classification (Rinella, Lazarus, et al., 2023). Presence of T2D accelerates progression from hepatic steatosis to advanced fibrosis (Targher et al., 2021), associates with greater all-cause and liver-specific mortality (Stepanova et al., 2013), and HCC amongst other cancers (Pang et al., 2018). The reverse is true, as MASLD associates with two-fold greater risk of developing T2D. The risk of T2D increases by fibrosis stage, with greatest T2D risk in those with advanced fibrosis (Mantovani et al., 2018; Mantovani, Petracca, et al., 2021). However, studies reporting on incident T2D risk in MASLD are limited by relatively small cohorts and inclusion of studies employing non-invasive investigations to diagnose MASLD such as LFTs. Relatively few studies use histological data to investigate this relationship (Ballestri et al., 2016; Mantovani et al., 2018; Mantovani, Petracca, et al., 2021; Musso et al., 2011).

The importance of the association between these disease states is highlighted by their shared treatment potential. Most recommended treatments for MASLD are treatments for T2D, albeit unlicensed. These treatments include thiazolidinediones, GLP-1RAs and SGLT-2 inhibitors, each of which have a growing evidence base in MASLD. These therapies improve the degree of steatohepatitis and hepatic fibrosis in MASLD on both non-invasive tests and histological outcomes (Souza et al., 2025), and CVD risk. Pioglitazone associated with significantly improved measures of steatohepatitis over 96 weeks (Sanyal et al., 2010). Meta-analysis reveals GLP-1RAs, dual GLP-1/GIP agonists improve steatohepatitis and fibrosis in phase II-III studies (Souza et al., 2025). However, these treatments do not improve fibrosis or steatohepatitis in people with MASLD cirrhosis (Loomba, Abdelmalek, et al., 2023). Nonetheless, given these observations, semaglutide is now licensed by the FDA for use in

people with MASLD and stage 2-3 hepatic fibrosis (Food and Drug Administration, 2025). Newer multi-agonists including GLP-1RAs are currently in clinical trials, such as survodutide (Sanyal, Bedossa, et al., 2024), and efinopegdutide (Romero-Gomez et al., 2023). Treating with SGLT-2 inhibitors improves non-invasive measures of MASLD, such as liver enzymes and liver fat content, but histopathological evidence is lacking (Song et al., 2021; Wei et al., 2021). Still, these drugs reduce CVD risk and improve CVD risk factors including T2D incidence, suggesting their clinical utility in this group.

Further real-world investigation into the bidirectional relationship between these disorders may shed further light on shared aetiological processes or missed treatment opportunities for these often difficult-to-treat patient groups with a major risk of poor health outcomes.

4.2 Aims of this chapter

The specific aims of this chapter are to examine:

- i. differences in characteristics and measures of hepatic steatosis or fibrosis in people with MASLD, with or without T2D.
- ii. changes in clinical and biochemical variables in people with MASLD, with or without T2D during follow-up.
- iii. changes in glycaemic control and risk of developing pre-diabetes or T2D in people with MASLD during follow-up.
- iv. real-world use of therapies for MASLD and lipid management in people with MASLD, with or without T2D.
- v. real-world impact of diabetes therapies on measures of MASLD over follow-up in people with type 2 diabetes.

4.3 Methods

4.3.1 Study design

This was a retrospective analysis of patients under the care of the hepatology team in SBUHB with biopsy-confirmed MASLD between November 2011-September 2022. This was explored as part of a local service evaluation project. The study design is detailed in chapter two.

4.3.2 Study participants

All patients were diagnosed with MASLD based on clinical characteristics and liver biopsy. Most were followed up locally for treatment and to monitor for progressive fibrosis and HCC. Further detail about these participants was described in chapter two.

4.3.3 Data collection

Data were collected retrospectively using available electronic health records. Demographic, biochemical, and radiological data were collected from the time of liver biopsy and compared to results at the patient's most recent follow-up. Clinical and biochemical data permitted the calculation of several non-invasive measures of hepatic steatosis and fibrosis. The hepatology team (consultant hepatologists, specialist nurses and support workers) performed TE routinely during these patients' care. Histopathological data were reported using the Brunt criteria. The collection of clinical, biochemical and TE data were described further in chapter two.

4.3.4 Funding and ethical approval

No additional funding was received to undertake this study. As discussed in chapter two, the study was completed in collaboration between the hepatology and diabetes teams in SBUHB. The study used routinely collected clinical data, collected retrospectively and were presented anonymously. Therefore, ethical approval was not required.

4.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503), or Microsoft PowerPoint for Microsoft 365 (version 2503). All categorical data are presented as the number (%). The statistical significance of differences between categorical variables was determined using Chi-squared test. Continuous data following a normal distribution are presented as the mean $\pm$ SD, and statistical significance determined using a student's t-test or one-way ANOVA. The association between baseline variables and risk of developing T2D was examined using logistic regression analysis. Statistical significance was defined as $p < 0.05$ throughout.

4.4 Results

4.4.1 Participant characteristics

A total of 153 patients were included in the analysis, with a mean age 54.0 ± 11.5 years, 80 (52.3%) patients were male, and 73 (47.7%) patients had pre-existing T2D. Detailed patient characteristics at the time of liver biopsy were presented in Table 3.1 in chapter three.

4.4.2 Differences in characteristics and measures of hepatic steatosis or fibrosis in people with MASLD, with or without type 2 diabetes

In comparison with people without T2D at the time of liver biopsy, people with T2D were older, had greater TE-CAP, and greater hepatic fibrosis score on histological assessment. People with T2D had significantly lower total cholesterol, LDL-cholesterol, HDL-cholesterol, and platelet count than people without T2D. The BARD score and NFS were significantly higher in people with T2D, but there were no other significant differences in liver enzymes or risk predictive algorithms between the groups. Table 4.1 summarises these data, and compares further clinical, biochemical, radiological, and histopathological observations from the time of liver biopsy between these groups.

Table 4.1: Differences in baseline characteristics by type 2 diabetes status

Characteristic	People with T2D (n=73)	People without T2D (n=80)	P value
Age (years)	56.3±10.2	51.9±12.3	<0.05
Male sex	41 (56.2%)	39 (48.8%)	NS
WIMD decile	4.6±2.7	4.9±3.1	NS
BMI (kg/m ²)	37.8±6.8	36.0±7.2	NS
NAS	3.9±1.5	3.9±1.5	NS
Steatosis	2.0±0.8	1.9±0.9	NS
Inflammation	1.1±0.6	1.0±0.6	NS
Ballooning	0.9±0.8	1.0±0.7	NS
Fibrosis	2.6±1.4	1.7±1.4	<0.001
F0	7 (9.6%)	23 (28.8%)	<0.001
F1	13 (17.8%)	20 (25.0%)	
F2	6 (8.2%)	7 (8.7%)	
F3	21 (28.8%)	22 (27.5%)	
F4	26 (35.6%)	8 (10.0%)	
TE-CAP (dB/m)	358.3±35.0	335.6±62.7	<0.05
TE-LSM (kPa)	17.7±11.5	14.8±10.9	NS
ALT (U/L)	55.3±38.1	60.7±48.0	NS
ALP (U/L)	96.3±43.6	94.0±45.6	NS
AST (U/L)	41.6±24.0	54.3±67.2	NS
GGT (U/L)	112.1±82.2	188.2±277.5	NS
Platelets (x10 ⁹ /L)	214.6±72.2	237.4±71.0	<0.05
TC (mmol/L)	4.6±1.3	5.1±1.4	<0.05
LDL (mmol/L)	2.4±0.9	3.1±1.3	<0.001
HDL (mmol/L)	1.1±0.3	1.2±0.4	<0.05
TG (mmol/L)	2.7±2.1	2.2±1.3	NS
HbA1c (mmol/mol)	64.4±17.3	37.6±4.9	<0.001
Creatinine (μmol/L)	78.5±21.8	75.1±16.0	NS
eGFR (mL/min/1.73m ²)	84.1±21.9	86.5±21.3	NS
HSI	50.3±7.8	48.4±8.3	NS
AST:ALT ratio	1.0±0.6	1.1±0.7	NS
BARD score	3.0±1.1	1.9±1.1	<0.001
FIB-4 score	2.0±1.5	2.0±2.4	NS
NFS	0.2±1.5	-1.7±2.2	<0.001
APRI	0.7±0.6	0.9±1.2	NS

Comparing characteristics of people with or without T2D. Abbreviations: *ALP* alkaline phosphatase *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NAS* non-alcoholic fatty liver disease activity score; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride; *WIMD* Welsh index of multiple deprivation.

4.4.3 Changes in clinical and biochemical variables in people with MASLD, with or without type 2 diabetes during follow-up

Patients were followed up for a mean 48.0 ± 22.1 months, and duration of follow-up was not significantly different between people with pre-existing T2D compared to people without T2D (45.0 ± 20.6 vs 50.8 ± 23.3 months, $p=0.12$). Over follow-up, 13 (8.5%) patients died, and there was no statistically significant difference in mortality between people with [9 (12.3%)] or without [4 (5.0%)] T2D ($p=0.10$). The cause of death was liver disease ($n=5$), heart failure ($n=2$), MI ($n=1$), bowel cancer ($n=1$), endometrial cancer ($n=1$), renal cell cancer ($n=1$), and sepsis ($n=2$). All four deaths in people without T2D were a consequence of liver disease, whilst the remaining causes of death [(liver disease ($n=1$), CVD ($n=3$), malignancy ($n=3$), sepsis ($n=2$)] were seen in people with T2D. Sixteen patients developed decompensated liver disease, of whom 7 died. Of these, all 16 (10.5%) developed jaundice, 6 (3.9%) developed hepatic encephalopathy, 9 (5.9%) developed ascites, 8 (5.2%) developed a coagulopathy, and none developed HCC. People with pre-existing T2D trended to a reduced risk of decompensated liver disease compared to people without T2D for; incident jaundice (5 (6.9%) vs 11 (13.8%), $p=0.16$), hepatic encephalopathy (1 (1.4%) vs 5 (6.3%), $p=0.12$), ascites (2 (2.7%) vs 7 (8.8%), $p=0.11$), and coagulopathy (2 (2.7%) vs 6 (7.5%), $p=0.19$).

In people with T2D, there were significant reductions in BMI, TE-CAP, ALT, AST, total cholesterol, and LDL-cholesterol. There was a significant increase in ALP, and creatinine over follow-up. In people without T2D there was a significant reduction in BMI, TE-CAP, ALT, platelet count, total cholesterol, and LDL-cholesterol, with a significant increase in the ALP and HbA1c. People with T2D trended to a lower TE-LSM score (17.2 vs 13.6 kPa, $p=0.06$) over follow-up, and people without T2D had a no significant change in the TE-LSM score. The change in TE-LSM in people with T2D compared to people without T2D was not statistically significant (-3.6 vs $+0.9$ kPa, $p=0.11$). These data are presented in Table 4.2.

Table 4.2: Differences in clinical characteristics observed during follow-up in people with or without type 2 diabetes

Characteristic	People with T2D (n=73)		Paired data	P value	People without T2D (n=80)		Paired data	P value
	Baseline	Follow-up			Baseline	Follow-up		
BMI (kg/m ²)	37.4±6.6	35.8±6.7	n=62	<0.001	35.8±7.2	34.7±6.2	n=52	<0.05
TE-CAP (dB/m)	363.7±25.1	333.7±43.4	n=38	<0.001	334.5±57.7	313.0±50.3	n=42	<0.05
TE-LSM (kPa)	17.2±13.1	13.6±6.9	n=38	NS	13.0±9.6	13.9±13.5	n=44	NS
ALT (U/L)	55.1±38.3	37.1±22.6	n=68	<0.001	61.3±50.4	46.5±39.2	n=70	<0.05
ALP (U/L)	95.8±44.0	106.3±39.2	n=68	<0.05	94.3±45.8	105.4±79.3	n=70	<0.05
AST (U/L)	44.2±23.0	33.5±15.0	n=17	<0.05	61.9±99.0	40.3±20.5	n=27	NS
GGT (U/L)	144.8±54.2	134.3±106.5	n=4	NS	180.3±143.0	71.5±30.8	n=4	NS
Platelets (×10 ⁹ /L)	216.1±67.7	221.1±93.0	n=66	NS	237.4±70.8	220.8±73.6	n=70	<0.01
TC (mmol/L)	4.6±1.3	4.2±1.0	n=65	<0.05	5.2±1.5	4.8±1.5	n=51	<0.05
LDL (mmol/L)	2.4±0.8	2.2±1.0	n=65	<0.05	3.2±1.3	2.7±1.3	n=51	<0.01
HDL (mmol/L)	1.1±0.3	1.1±0.3	n=65	NS	1.2±0.4	1.4±0.5	n=51	NS
TG (mmol/L)	2.8±2.2	2.5±1.4	n=65	NS	2.2±1.3	2.1±1.1	n=51	NS
HbA1c (mmol/mol)	64.6±17.0	62.5±19.1	n=67	NS	37.6±4.9	40.6±8.5	n=53	<0.01
Creatinine (μmol/L)	78.4±22.0	91.1±58.8	n=68	<0.05	74.4±15.6	75.2±14.2	n=71	NS
eGFR (mL/min/1.73m ²)	84.0±21.5	79.7±30.2	n=68	NS	86.9±21.5	83.4±17.9	n=71	NS
HSI	51.7±7.8	52.5±15.1	n=16	NS	48.2±11.3	43.3±8.8	n=8	NS
AST:ALT ratio	1.0±0.4	1.2±1.0	n=17	NS	0.9±0.7	1.0±0.7	n=27	NS
BARD score	3.2±1.0	3.4±0.9	n=18	NS	1.5±1.0	1.9±1.1	n=28	NS
FIB-4 score	1.9±0.8	2.6±2.6	n=16	NS	1.7±2.3	2.1±3.2	n=26	NS
NFS	0.5±1.4	0.8±2.2	n=17	NS	-2.5±2.3	-1.8±2.3	n=27	<0.05
APRI	0.7±0.5	0.6±0.4	n=16	NS	1.0±1.7	0.7±0.8	n=26	NS

Comparing differences in characteristics over follow-up in people with or without T2D. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4. *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

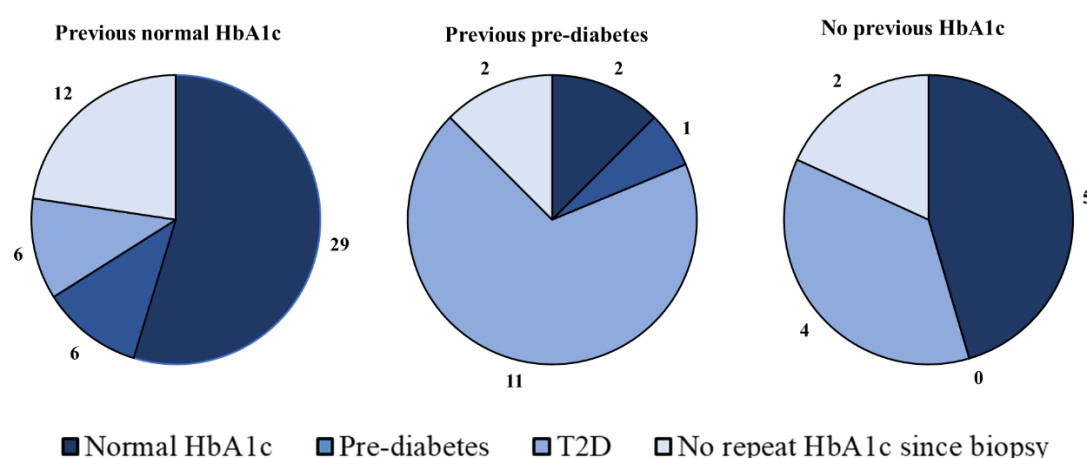
4.4.4 Changes in glycaemic control and risk of developing pre-diabetes or type 2 diabetes in people with MASLD during follow-up

Of the 80 patients without T2D at the time of liver biopsy, 53 (66.3%) had previously normal HbA1c, 16 (20.0%) had pre-diabetes, and 11 (13.7%) had no previous HbA1c. At the most recent follow-up, 21 (26.3%) of these patients developed T2D, an additional 7 (8.7%) patients had pre-diabetes, 36 (45.0%) patients had a normal HbA1c, and 16 (20.0%) had no repeat HbA1c. The mean HbA1c in people without T2D at baseline increased by 3.0 mmol/mol over follow-up ($p<0.01$), shown in Table 4.2. Figure 4.1 presents the glycaemic status of people without T2D at baseline at their follow-up visit.

People who developed T2D over follow-up had a significantly greater HbA1c at the time of biopsy than people who did not develop T2D. On logistic regression, baseline HbA1c was the only statistically significant risk factor identified, with an odds ratio 2.27 [1.32-3.91, $p<0.01$]. Whilst not reaching statistical significance, people who developed T2D trended to greater age, BMI, WIMD, ALT, AST, and ALP at the time of liver biopsy compared to people who did not develop T2D. Differences in baseline variables between those who did and did not develop T2D are presented in Table 4.3, and logistic regression is presented in Table 4.4.

There was no significant association between hepatic fibrosis stage and risk of developing T2D. In people without pre-existing T2D, 21.1%, 53.9%, 16.7%, 57.1% and 14.3% with stage 0, 1, 2, 3, or 4 hepatic fibrosis respectively developed T2D at follow-up ($p=0.38$). Non-significant observations from the logistic regression analysis are shown in Table 4.4 and risk of T2D by stage of fibrosis is presented in Figure 4.2.

Figure 4.1: Type 2 diabetes status at follow-up based on glycaemic status at biopsy



Pie charts presenting the occurrence of prediabetes and T2D at the most recent clinical visit based on HbA1c values observed at the time of the liver biopsy in people without T2D. Abbreviation: T2D type 2 diabetes.

Table 4.3: Characteristics of people who did or did not develop type 2 diabetes

Characteristic	People who developed T2D (n=21)	People who did not develop T2D (n=59)	P value
Age (years)	54.7±12.0	51.0±12.3	NS
Male sex	10 (47.6%)	29 (49.2%)	NS
WIMD decile	3.8±2.8	5.2±3.1	NS
BMI (kg/m ²)	37.1±8.3	35.5±6.8	NS
NAS	4.2±1.2	3.8±1.6	NS
Steatosis	2.1±0.8	1.9±0.9	NS
Inflammation	1.1±0.5	1.0±0.6	NS
Ballooning	1.1±0.6	1.0±0.7	NS
Fibrosis	1.8±1.3	1.6±1.5	NS
TE-CAP (dB/m)	342.5±77.0	333.3±58.0	NS
TE-LSM (kPa)	14.9±8.9	14.8±11.6	NS
ALT (U/L)	76.5±61.4	55.1±41.5	NS
ALP (U/L)	108.2±66.0	89.0±35.2	NS
AST (U/L)	80.6±129.6	46.3±27.3	NS
GGT (U/L)	323.8±427.7	128.0±151.3	NS
Platelets (x10 ⁹ /L)	240.9±56.5	236.2±75.8	NS
TC (mmol/L)	5.3±1.8	5.1±1.2	NS
LDL (mmol/L)	3.3±1.6	3.0±1.1	NS
HDL (mmol/L)	1.2±0.4	1.2±0.3	NS
TG (mmol/L)	2.4±1.6	2.1±1.2	NS
HbA1c (mmol/mol)	42.2±3.8	36.1±4.2	<0.001
Creatinine (μmol/L)	71.4±14.6	76.5±16.4	NS
eGFR (mL/min/1.73m ²)	90.3±23.0	85.2±20.8	NS
HSI	48.2±7.6	48.4±8.6	NS
AST:ALT ratio	1.1±0.7	1.0±0.8	NS
BARD score	2.0±1.1	1.8±1.0	
FIB-4 score	2.2±1.9	1.9±2.6	NS
NFS	-1.3±1.9	-1.8±2.2	NS
APRI	1.2±2.0	0.8±0.8	NS

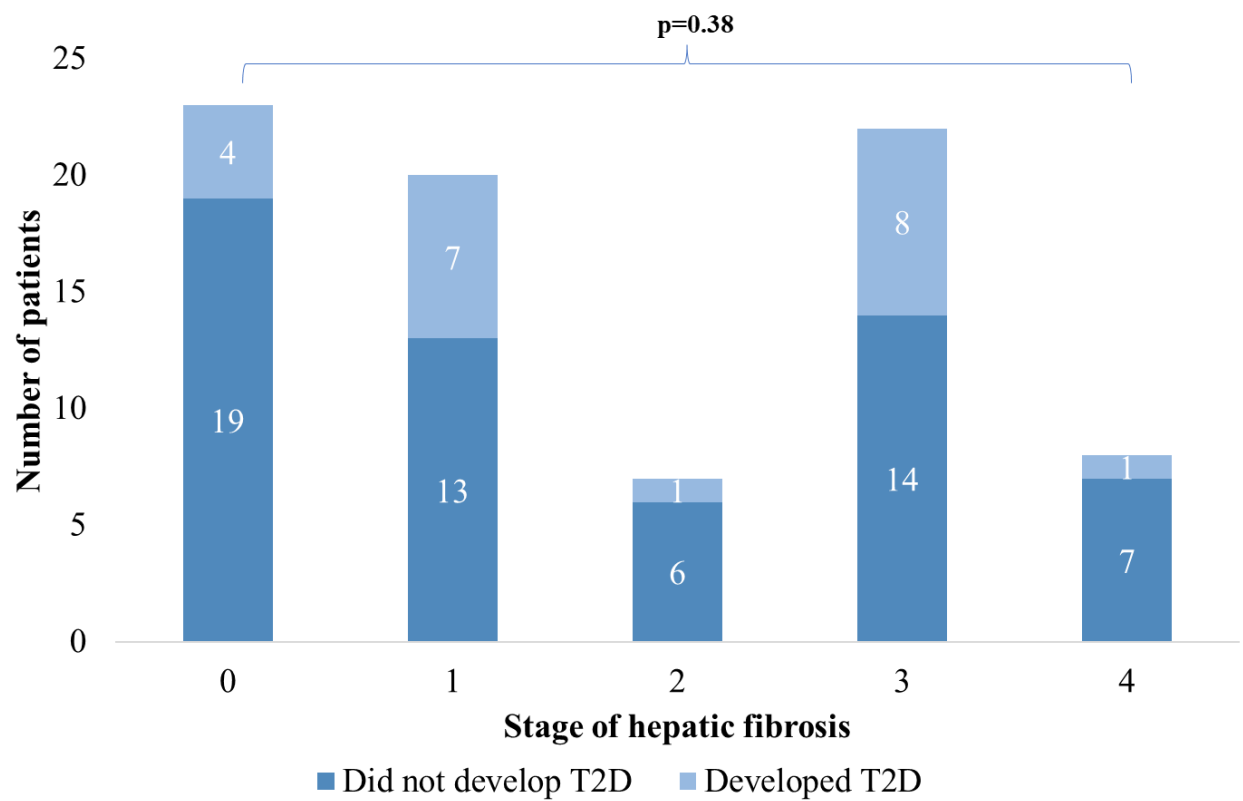
Comparing the characteristics of people without T2D at the time of liver biopsy who did or did not develop T2D over follow-up. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NAS* NAFLD activity score; *NFS* NAFLD fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride; *WIMD* Welsh index of multiple deprivation.

Table 4.4: Logistic regression analysis of baseline characteristics with the risk of developing type 2 diabetes over follow-up

Variable	Odds ratio	95% CI	Significance
Clinical characteristics			
Gender	0.20	0.03–1.52	NS
Age at biopsy	1.03	0.98–1.09	NS
Bodyweight	0.96	0.90–1.03	NS
BMI	1.17	0.93–1.47	NS
WIMD decile	1.06	0.32–3.56	NS
Biochemical variables			
HbA1c	1.97	1.31–2.96	<0.01
ALT	1.01	0.99–1.03	NS
TC	1.93	0.88–4.26	NS
TG	0.67	0.33–1.37	NS
APRI	1.84	0.69–4.86	NS
FIB-4 score	0.72	0.39–1.32	NS
NFS	1.23	0.79–1.90	NS
Other variables			
TE-CAP	1.00	0.99–1.01	NS
TE-LSM	0.99	0.93–1.05	NS
Hepatic steatosis stage	1.35	0.61–2.96	NS
Hepatic fibrosis stage	1.27	0.78–2.08	NS

Logistic regression of baseline characteristics with risk of developing T2D in people without diabetes at baseline. Abbreviations *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *BMI* body mass index; *CAP* controlled attenuation parameter; *CI* confidence interval; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* NAFLD fibrosis score; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride; *WIMD* Welsh index of multiple deprivation.

Figure 4.2: Risk of developing type 2 diabetes over follow-up by fibrosis stage



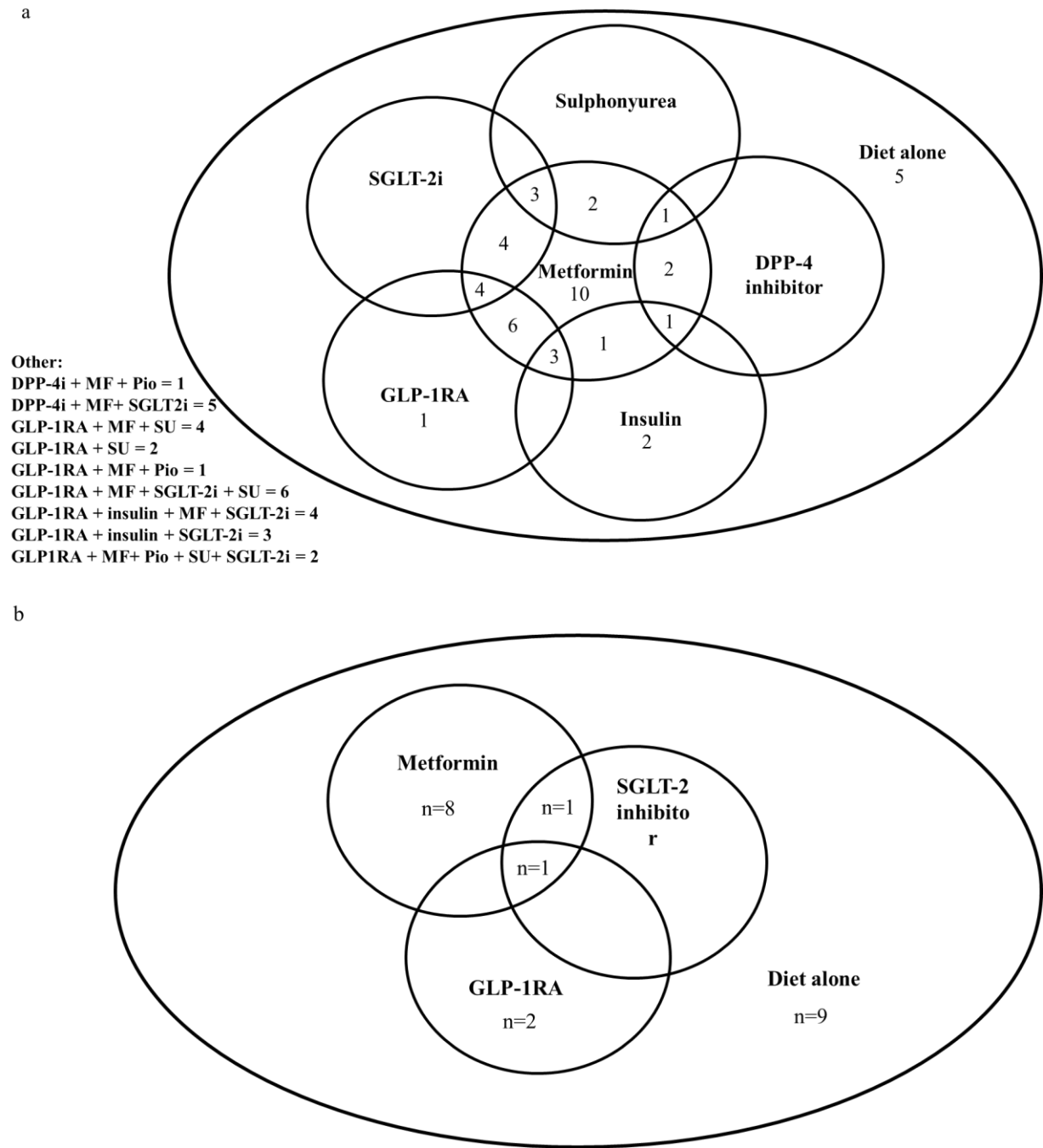
Stacked bar chart demonstrating the risk of developing T2D over follow-up by the stage of hepatic fibrosis in people without T2D. Abbreviation: *T2D* type 2 diabetes.

4.4.5 Real-world use of therapies for MASLD and lipid management in people with MASLD, with or without type 2 diabetes

Of the 153 patients, none were treated with vitamin E, and 4 (2.6%) treated with pioglitazone, of whom all 4 had T2D. In the 73 patients with pre-existing T2D, 31 (42.5%) were prescribed a SGLT-2 inhibitor (2 canagliflozin, 18 dapagliflozin, 11 empagliflozin), and 36 (49.3%) were prescribed a GLP-1RA (12 dulaglutide, 11 liraglutide, 13 semaglutide) at follow-up. In the 21 people who developed T2D during follow-up, none were treated with pioglitazone, 2 (9.5%) were treated with a SGLT-2 inhibitor (1 dapagliflozin, 1 empagliflozin) and 3 (14.3%) treated with a GLP-1RA (3 semaglutide) following T2D diagnosis. The T2D treatments used in people with pre-existing T2D and in those who developed T2D are presented in Figure 4.3.

At the time of liver biopsy, 60 (39.2%) patients were treated with a statin, and 93 (60.8%) were not. Patients with T2D were twice as likely to be prescribed a statin at the time of liver biopsy (39 (53.4%) vs 21 (26.3%), $p<0.001$). Over follow-up, 8 (11.0%) patients with T2D, and 14 (17.5%) without T2D were initiated on a statin ($p=0.25$). At the most recent follow-up, patients with T2D remained more likely to be prescribed a statin (47 (64.4%) vs 35 (43.8%), $p=0.01$).

Figure 4.3: Diabetes treatments used in people with MASLD and type 2 diabetes



T2D treatments used in people with MASLD and T2D at follow-up. Figure 4.3(a) presents treatments in people with pre-existing T2D, Figure 4.3(b) presents treatments in people who developed T2D over follow-up. Abbreviations: *DPP-4i* dipeptidyl peptidase-4 inhibitor; *GLP-1RA* glucagon like peptide-1 receptor agonists; *MF* metformin; *Pio* pioglitazone; *SGLT-2i* sodium-glucose co-transporter-2 inhibitor; *SU* sulphonylurea.

4.4.6 Real-world impact of diabetes therapies on measures of MASLD over follow-up in people with type 2 diabetes

In the 94 patients with T2D (73 pre-existing, 21 diagnosed over follow-up), 51 (54.3%) were male, with a mean pre-treatment age 56.5 ± 10.5 years. At biopsy, these patients had a NAS 4.0 ± 1.5 (steatosis 2.0 ± 0.8 , ballooning 0.9 ± 0.7 , inflammation 1.1 ± 0.6) and fibrosis stage 2.4 ± 1.4 . Medications used by the group were presented in Figure 4.3.

In the T2D cohort, SGLT-2 inhibitors were prescribed in 33 (35.9%) patients (2 canagliflozin, 19 dapagliflozin, 12 empagliflozin), and 39 (42.4%) prescribed a GLP-1RA (12 dulaglutide, 11 liraglutide, 16 semaglutide). Of these, 20 (21.3%) were prescribed both. Over 4.5 ± 1.8 years follow-up, there were reductions in BMI, TE-CAP, ALT, total cholesterol, LDL-cholesterol and HbA1c, and increases in both ALP and creatinine. Data are presented in Table 4.5.

Patients with T2D who were prescribed a SGLT-2 inhibitor and/or GLP-1RA had significantly greater pre-treatment bodyweight, stage of hepatic fibrosis and HbA1c compared to people with T2D receiving other treatments. Similarly, there were differences between groups of people with T2D prescribed a SGLT-2 inhibitor, GLP-1RA, both a SGLT-2 inhibitor and GLP-1RA compared to those prescribed other treatments for T2D, presented in Table 4.6.

During follow-up, people with T2D prescribed a SGLT-2 inhibitor, GLP-1RA, or both had reductions in bodyweight, TE-CAP, ALT, LDL-cholesterol (all $p < 0.001$), total cholesterol, and HbA1c (both $p < 0.01$). Those prescribed other treatments for T2D had less clinically significant reductions in ALT and bodyweight, and no significant reduction in TE-CAP. There were trending reductions in TE-LSM and steatosis or fibrosis biomarker scores in both groups. Data are presented in Table 4.7. In those prescribed either a SGLT-2 inhibitor, GLP-1RA, or both, 4/52 (7.7%) died, versus 5/42 (11.9%) deaths in those prescribed other treatments ($p = 0.48$).

Further subgroup analysis explored changes in non-invasive measures in those taking SGLT-2 inhibitors only ($n = 13$), GLP-1RA only ($n = 19$), both SGLT-2 inhibitors and GLP-1RA ($n = 20$), or other T2D treatments ($n = 42$). In people with T2D prescribed SGLT-2 inhibitors only, there were reductions in bodyweight and BMI, but not measures of MASLD. Those prescribed GLP-1RAs, or both GLP-1RA and SGLT-2 inhibitors had significant reductions in TE-CAP, ALT, total cholesterol, LDL-cholesterol, and HbA1c. There was a trending reduction in the TE-LSM in all three groups. In those receiving other T2D treatments there was reduction in bodyweight, BMI, and ALT though the reductions in TE-CAP and TE-LSM score did not reach significance. The mean HbA1c in this group remained unchanged. Data are presented in Table 4.8.

At the most recent follow-up visit, 39/52 (75.0%) patients prescribed either a SGLT-2 inhibitor, GLP-1RA, or both were prescribed a statin, compared with 21/42 (50.0%) of those prescribed other T2D treatments ($p<0.05$). Over follow-up, those prescribed a SGLT-2 inhibitor, GLP-1RA, or both trended to being less likely to have changes made to their statin prescription (new statin, dose escalation or statin switch) than those prescribed other T2D treatments (14/39 [35.9%] vs 12/21 [57.1%], $p=0.11$).

Table 4.5: Changes in characteristics of people with type 2 diabetes over follow-up

Characteristic	Baseline (n=94)	Follow-up (n=94)	P value
Weight (kg)	109.0±24.8	104.1±25.1	<0.001
BMI (kg/m ²)	37.5±7.3	35.2±9.0	<0.05
TE–CAP (dB/m)	361.6±30.2	339.1±41.5	<0.01
TE–LSM (kPa)	15.5±12.0	13.6±8.4	NS
ALT (U/L)	61.7±48.3	39.5±27.7	<0.001
ALP (U/L)	97.9±47.3	111.2±73.0	<0.01
AST (U/L)	63.0±111.7	30.7±14.7	NS
GGT (U/L)	112.8±57.6	141.3±106.3	NS
Platelets (×10 ⁹ /L)	228.4±62.3	228.4±86.0	NS
TC (mmol/L)	4.6±1.1	4.3±1.3	<0.05
LDL (mmol/L)	2.6±1.1	2.2±1.0	<0.001
HDL (mmol/L)	1.1±0.3	1.2±0.4	NS
TG (mmol/L)	2.4±1.6	2.4±1.6	NS
HbA1c (mmol/mol)	63.6±21.6	58.0±15.6	<0.05
Creatinine (μmol/L)	75.4±19.4	86.6±52.0	<0.05
eGFR (mL/min/1.73m ²)	86.0±20.4	81.1±27.2	NS
HSI	52.9±8.5	50.9±14.2	NS
AST:ALT ratio	1.0±0.6	1.2±0.3	NS
FIB-4 score	1.8±1.7	1.9±2.0	NS
NFS	0.1±1.7	0.3±2.0	NS
APRI	0.9±1.8	0.5±0.3	NS

Changes in clinical characteristics over follow-up in people with T2D. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4. *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

Table 4.6: Differences in patient characteristics by diabetes treatment at baseline

Variable	SGLT2i± GLP-1RA (n=52)	SGLT-2i (n=13)	GLP-1RA n=19)	SGLT-2i & GLP-1RA (n=20)	Other (n=42)
Age at biopsy (years)	57.0±8.9	58.9±10.1	55.7±10.2	57.0±6.7	55.4±12.3
Weight (kg)	114.1±24.6	112.7±27.9	108.1±22.8	120.7±23.7	103.6±23.2*
BMI (kg/m ²)	38.7±7.4	36.8±6.2	36.9±7.0	41.7±7.8	36.1±7.0 ^a
NAS	4.0±1.6	4.3±1.5	4.3±1.5	3.5±1.6	4.0±1.3
Steatosis	2.1±0.7	2.2±0.6	2.2±0.8	2.0±0.8	1.9±0.8
Ballooning	0.9±0.7	1.0±0.8	1.0±0.7	0.7±0.7	1.0±0.7
Inflammation	1.1±0.6	1.2±0.6	1.2±0.7	0.9±0.6	1.1±0.5
Fibrosis	2.8±1.3	3.1±1.1	2.5±1.5	2.9±1.3	2.0±1.4 ^{**, a}
TE-CAP (dB/m)	363.4±29.8	350.9±30.6	372.3±23.4	360.9±35.6	346.3±59.5
TE-LSM (kPa)	18.5±8.4	17.2±8.2	17.3±8.3	21.3±8.6	15.6±13.0
ALT (U/L)	63.5±44.8	60.9±58.7	57.0±37.3	71.8±42.0	60.8±51.7
ALP (U/L)	110.2±41.4	107.7±48.3	100.1±40.7	95.2±36.7	95.8±52.7
AST (U/L)	46.3±26.9	36.7±24.5	50.1±26.1	47.9±33.1	60.6±102.8
GGT (U/L)	153.3±162.8	126.0±75.9	171.6±220.4	150.2±128.6	183.3±323.1
Platelets (×10 ⁹ /L)	221.6±69.3	205.9±82.6	222.8±71.6	230.3±59.3	230.9±57.8
TC (mmol/L)	4.5±1.1	4.3±1.0	4.8±1.5	4.4±0.7	4.8±1.3
LDL (mmol/L)	2.4±1.1	2.2±1.1	2.8±1.4	2.3±0.6	2.8±1.2
HDL (mmol/L)	1.1±0.3	1.1±0.2	1.0±0.1	1.0±0.4	1.2±0.4
TG (mmol/L)	2.7±1.8	2.2±0.9	2.8±1.8	3.0±2.2	2.1±1.2
HbA1c (mmol/mol)	70.7±22.1	68.5±33.6	66.0±20.2	76.4±20.2	52.9±15.0 ^{***, c}
Creatinine (μmol/L)	76.2±21.6	76.1±20.5	76.7±17.9	75.7±26.1	76.2±17.6
eGFR (mL/min/1.73m ²)	86.1±22.1	88.4±19.5	83.9±19.5	86.7±26.6	85.6±21.1
HSI	52.1±7.8	46.9±4.4	51.6±7.5	58.6±7.5	48.8±7.4 ^a
AST:ALT ratio	0.9±0.4	0.9±0.4	1.0±0.4	0.9±0.5	1.1±0.8
FIB-4 score	2.1±1.5	2.8±2.5	2.0±0.9	1.6±1.4	2.1±1.9
NFS	0.5±1.3	0.5±1.8	0.7±0.8	0.2±1.7	0.3±1.8
APRI	0.9±0.7	1.0±1.1	0.8±0.5	0.8±0.7	1.0±1.6

Differences in clinical characteristics at baseline in people with T2D prescribed different treatments. Statistical significance between patients prescribed SGLT-2 inhibitors±GLP-1RAs compared to other treatment is determined by t test, denoted *p<0.05, **p<0.01, ***p<0.001. Statistical significance between patients prescribed either SGLT-2 inhibitors, GLP-1RAs, both SGLT-2 inhibitors and GLP-1RAs, or other T2D treatments is determined by one-way ANOVA, denoted ^ap<0.05, ^bp<0.01, ^cp<0.001. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NAS* non-alcoholic fatty liver disease activity score; *NFS* non-alcoholic fatty liver disease fibrosis score; *SGLT-2i* sodium-glucose co-transporter-2 inhibitor; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

Table 4.7: Changes in characteristics over follow-up by treatment

Variable	SGLT2i± GLP-1RA [pre] (n=52)	SGLT2i± GLP-1RA [post] (n=52)	Other [pre] (n=42)	Other [post] (n=42)
Weight (kg)	113.5±24.8	108.0±26.0***	103.0±23.9	99.0±23.2*
BMI (kg/m ²)	38.5±7.3	37.1±8.0	36.1±7.2	32.7±9.7*
TE-CAP (dB/m)	365.2±26.5	331.5±33.0***	360±32.5	343.6±45.9
TE-LSM (kPa)	15.0±6.8	13.3±7.5	15.7±14.4	13.8±9.0
ALT (U/L)	63.4±45.2	40.0±28.6***	59.6±52.2	39.0±26.8**
ALP (U/L)	99.8±41.4	107.7±42.0	95.5±53.9	115.6±98.7*
AST (U/L)	41.0±27.2	28.3±13.5	87.2±160.2	33.4±16.2
GGT (U/L)	161.0±25.5	190.5±132.2	64.5±0.7	92.0±82.0
Platelets (×10 ⁹ /L)	223.1±66.8	230.4±99.7	234.4±56.9	68.1±10.8
TC (mmol/L)	4.4±0.9	3.9±0.9**	4.8±1.4	4.8±1.6
LDL (mmol/L)	2.4±0.9	1.9±0.8***	2.8±1.2	2.8±1.1
HDL (mmol/L)	1.1±0.3	1.1±0.3	1.2±0.4	1.3±0.4
TG (mmol/L)	2.7±1.9	2.4±1.5	2.1±1.1	2.4±1.7
HbA1c (mmol/mol)	71.6±22.7	60.5±14.5**	53.1±14.8	54.6±16.5
Creatinine (μmol/L)	75.3±21.0	90.3±64.5*	75.6±17.5	82.0±30.0
eGFR (mL/min/1.73m ²)	85.9±20.6	80.4±26.0	86.1±20.5	81.9±28.9
HSI	56.0±7.6	53.6±18.1	49.5±8.5	47.9±8.1
AST:ALT ratio	0.8±0.4	1.1±0.7	1.2±0.8	1.2±1.1
FIB-4 score	1.5±1.0	1.9±2.1	2.0±2.3	1.8±2.1
NFS	0.4±1.3	0.6±1.3	-0.3±2.2	0.0±2.6
APRI	0.6±0.5	0.5±0.4	1.3±2.5	0.5±0.3

Changes in clinical characteristics over follow-up in people with T2D prescribed SGLT-2i and/or GLP-1RA versus other T2D treatments. Statistical significance of differences over follow-up is determined by paired t test, denoted *p<0.05, **p<0.01, ***p<0.001. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *SGLT-2i* sodium-glucose co-transporter-2 inhibitor; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

Table 4.8: Subgroup analysis of changes in characteristics by treatment

Variable	SGLT2i only [pre] (n=13)	SGLT2i only [post] (n=13)	GLP-1RA only [pre] (n=19)	GLP-1RA only [post] (n=19)	SGLT-2i & GLP-1RA [pre] (n=20)	SGLT-2i & GLP-1RA [post] (n=20)	Other [pre] (n=40)	Other [post] (n=40)
Weight (kg)	112.2±29.1	104.8±27.1*	106.4±22.1	104.7±27.6	120.7±23.7	112.8±24.5**	103.0±23.9	99.0±23.2*
BMI (kg/m ²)	36.8±6.5	34.3±5.0*	36.1±6.1	34.8±6.8	41.7±7.8	40.8±9.1	36.1±7.2	32.7±9.7*
TE-CAP (dB/m)	341.7±30.6	323.3±12.1	371.1±21.0	336.1±43.4*	369.0±29.1	329.5±26.6*	360±32.5	343.6±45.9
TE-LSM (kPa)	12.0±6.0	10.5±5.9	15.0±7.0	13.4±8.4	16.7±7.5	14.6±3.2	15.7±14.4	13.8±9.0
ALT (U/L)	64.6±62.8	49.1±41.7	53.8±35.6	32.3±19.5*	71.8±42.0	42.0±26.4**	59.6±52.2	39.0±26.8**
ALP (U/L)	111.8±49.2	107.6±36.8	97.4±40.1	111.0±47.8*	95.2±38.7	104.5±40.8	95.5±53.9	115.6±98.7*
Platelets (×10 ⁹ /L)	219.4±71.6	202.8±75.0	220.1±73.7	222.2±89.3	228.3±60.3	255±119.6	234.4±56.9	68.1±10.8
TC (mmol/L)	4.2±0.9	4.4±1.0	4.6±1.1	4.0±0.8*	4.3±0.6	3.6±0.9**	4.8±1.4	4.8±1.6
LDL (mmol/L)	2.2±1.0	1.9±1.0	2.6±1.1	2.0±0.7*	2.3±0.6	1.7±0.9*	2.8±1.2	2.8±1.1
HDL (mmol/L)	1.1±0.2	1.2±0.2	1.0±0.2	1.1±0.2	1.0±0.4	1.1±0.3	1.2±0.4	1.3±0.4
TG (mmol/L)	2.3±1.0	3.2±1.8*	2.7±1.9	2.0±1.0*	2.9±2.2	2.4±1.7	2.1±1.1	2.4±1.7
HbA1c (mmol/mol)	69.4±35.2	57.9±11.6	67.6±20.0	57.0±12.7*	76.4±17.5	65.1±16.6*	53.1±14.8	54.6±16.5
Creatinine (μmol/L)	72.2±15.5	73.2±15.3	76.8±18.4	84.4±26.9	75.7±26.1	105.8±97.4	75.6±17.5	82.0±30.0
eGFR (mL/min/1.73m ²)	91.9±17.7	90.6±21.0	84.6±19.8	77.2±20.4	83.6±23.1	77.4±32.3	86.1±20.5	81.9±28.9

Changes in characteristics over follow-up in people with T2D prescribed different treatments. Statistical significance of differences over follow-up denoted *p<0.05, **p<0.01. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BMI* body mass index; *CAP* controlled attenuation parameter; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *GLP-1RA* glucagon-like peptide-1 receptor analogue; *HDL* high-density lipoprotein; *HSI* hepatic steatosis index; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *SGLT-2i* sodium-glucose co-transporter-2 inhibitor; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

4.5 Discussion

In this chapter, the relationship between MASLD and T2D in patients with biopsy-confirmed MASLD in SBUHB was explored. Participant characteristics and measures of hepatic steatosis or fibrosis were compared by T2D status in people with MASLD, and over follow-up. Changes in glycaemic control and the risk of developing T2D were examined in people with MASLD during follow-up. Finally, the real-world use of therapies for MASLD and lipid management by T2D status in this population were investigated, and the impact of SGLT-2 inhibitors and GLP-1RAs on measures of MASLD outcomes were explored in people with T2D.

4.5.1 Impact of type 2 diabetes on risk of MASLD and outcomes

There was a high proportion of people diagnosed with T2D in this cohort, which at 48% is around eight times the national prevalence of diagnosed T2D in Wales (Diabetes UK, 2020). Whilst the risk of T2D in MASLD is two-fold (Targher et al., 2021), some studies observe that the presence of SLD with additional risk factors such as IR and obesity increases T2D risk 14-fold (Sung et al., 2012), making the finding of an 8-fold increase in T2D prevalence less surprising considering their additional risk factors such as mean BMI 36.9 kg/m². Such differences in population characteristics are important confounders in observational studies and are important to consider in the interpretation of the work presented in this chapter.

Previous meta-analyses report a two-fold increase in T2D prevalence in people with MASLD (Targher et al., 2021), though real-world studies such as this may bias towards identifying T2D more frequently given these patients' frequent contact with health services. Nevertheless, in those with pre-existing T2D there was greater fibrosis on histology compared to people without T2D, despite similar steatosis, inflammation, and ballooning. Patients with T2D had greater NFS and BARD scores, though given presence of T2D scores points in these algorithms, this was expected. There was high variability associated with the GGT in people without T2D, likely a consequence of several outliers, as seven patients in this group had a GGT >300 U/L. There are several explanations for the observation of greater fibrosis. Firstly, it is well-established that T2D is a major risk factor for accelerating MASLD fibrosis (Targher et al., 2021; Younossi, Golabi, et al., 2024), independent of steatohepatitis. This may be mediated by T2D-specific mechanisms, such as dysfunctional adipose tissue, genetic factors and glucotoxicity (Gastaldelli & Cusi, 2019). A unifying pathological process may instigate the development of both MASLD and T2D, such as IR, rather than these disease states interacting *per se*. Secondly, given the greater age of those with T2D, it may be that people with T2D had a greater duration of unrecognised MASLD resulting in a prolonged hepatic insult and therefore

greater fibrosis. Given the frequency of hepatic steatosis on abdominal imaging in people with T2D, there may be a mistaken perception that MASLD is benign. Thirdly, there was a trend to greater deprivation in those who developed T2D, which may reach statistical significance with greater patient numbers, and is an area of topical interest given the associations between MASLD, T2D and measures of social deprivation (Czapla et al., 2025; Faulkner et al., 2025; Foster et al., 2023). Finally, there may be other, unrecognised differences between the groups, such as the prevalence of other comorbidities or smoking status.

People with T2D had more favourable lipid profiles compared to those without T2D, with lower total and LDL-cholesterol. This was associated with a two-fold greater likelihood of statin prescription in people with T2D. This explains the difference in lipid profiles between the groups. The greater frequency of statin prescription was expected, as people with T2D have greater predicted CVD risk (van den Berg et al., 2019), which guides the need for statin therapy. Though, only 53.4% of people with T2D were prescribed a statin, lower than in previous studies observing statin prescription in 68% (Jones et al., 2014). The difference may relate to physician concerns about hepatotoxicity associated with statin use in CLD, though data were limited to support this in this group. Nonetheless, these observations highlight the greater prospect of risk factor intervention in T2D compared, including those with MASLD. With better control of CVD risk factors, CVD outcomes in people with MASLD without pre-existing T2D may improve (Ayada et al., 2023). There is no liver measure input to the QRISK3 calculator to highlight excess CVD risk (Endeavour Predict, 2024), meaning intervention may be missed, despite the relationship between liver fibrosis and CVD (Angulo et al., 2015). Statin use is unlikely the cause of greater fibrosis in the T2D group, as there is no causal relationship between statin use and MASLD (Ayada et al., 2023; Rinella, Neuschwander-Tetri, et al., 2023). Statins are advocated in people with MASLD to manage dyslipidaemia and CVD risk (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

There was a trend to greater mortality in people with T2D, and those with T2D were twice as likely to die over 4.5 years follow-up. This may reach statistical significance in a larger cohort, or greater duration of follow-up, which would increase the number of events. A high proportion of the group died directly as a result of liver disease, which may be related to how these patients had presented to clinical services initially and diagnosed with MASLD in this real-world study. However, given the small number of events, conclusions are limited. Interestingly, all deaths in people who did not have T2D were related to liver disease, whilst only 1 (11.1%) of those with T2D died of CLD, and deaths related to CVD, or malignancy were evident in this group.

People with T2D trended to lower risk of decompensated liver disease over follow-up. Whilst it is difficult to draw conclusions given the small number of observed events, these findings raise interesting comparisons with previous reports. In keeping with previous observations, this study observed people with T2D trended to greater mortality, and the cause is multifactorial but largely attributable to excess CVD and malignancy (Fu et al., 2023; Mantovani, Csermely, et al., 2021; Mantovani et al., 2022; Pang et al., 2018; Targher et al., 2021). However, the trend to reduced hepatic decompensation risk in people with T2D was unexpected as people with T2D in this cohort had greater hepatic fibrosis, the major risk factor for decompensated liver disease (Huang et al., 2023). Secondly, T2D is associated with a greater risk of decompensation and its presence is included in risk predicting algorithms for hepatic decompensation in MASLD (Ahmed et al., 2020). These observations may be confounded by the use of T2D pharmacotherapies in this group which improve liver-related outcomes, discussed in section 4.5.3. Given the small number of events, limited follow-up, and lack of significance related to differences in mortality and decompensation, longer follow-up in larger cohorts is needed.

There were significant reductions in BMI, TE-CAP, total cholesterol, and LDL-cholesterol in both groups over follow-up. One explanation is the diet and lifestyle interventions promoted in the hepatology clinic. None were prescribed vitamin E and four were prescribed pioglitazone, which were recommended at the time. Though, there was additional statin therapy initiated in some patients, and use of GLP-1RAs and SGLT-2 inhibitors are discussed below. Diet and lifestyle interventions are frequently the cornerstone of treatment, though data were limited with respect to dietetic input and adherence to lifestyle changes to confirm this.

Notable biochemical changes include reduced ALT and increased ALP over follow-up. Reductions in ALT may indicate reduced steatohepatitis over time associated with improved BMI and lipid profiles. Indeed, there was a reduction in TE-CAP score and a trending reduction in TE-LSM to support this. However, comparing changes in the TE-LSM over follow-up between groups may be confounded by the significantly greater baseline TE-CAP score in people with T2D. The rise in ALP is more difficult to explain, due to its non-specific nature. It may be there is a greater prevalence of biliary disease such as gallstones, though there is no evidence to support this. Alternatively, vitamin D deficiency may explain this finding, a frequent observation in people with MASLD. Vitamin D deficiency may cause MASLD by associating with IR and dysregulated insulin secretion, and vitamin D deficiency may be caused by MASLD as a crucial step in vitamin D activation occurs in the liver (Borges-Canha et al., 2021). Some studies have observed around 50% of people with MASLD have vitamin D

deficiency, greater than in those without MASLD (Liu et al., 2019). In this cohort, only 19 (12.4%) patients had a vitamin D level tested within 12 months of biopsy, and 16 (84.2%) were vitamin D deficient. These data were not presented in the results given the frequency of missing data. Vitamin D deficiency causes secondary hyperparathyroidism, increasing bone turnover and ALP. The apparent high prevalence of vitamin D deficiency may be through a selection bias as those who were tested likely had clinical features suggestive of vitamin D deficiency, thereby warranting the test. Despite the critical role of the liver in endogenous vitamin D production, screening for vitamin D deficiency is not recommended (NICE, 2016; Rinella, Neuschwander-Tetri, et al., 2023). Though, vitamin D supplementation may have several benefits on MASLD progression and bone health in this group (Sindhughosa et al., 2022), and some argue routine vitamin D screening or replacement is appropriate.

The other interesting observation was a significant rise in creatinine level in people with T2D, but not those without T2D. There was a trend to reduced eGFR in both groups associated with rising age, and the decline was numerically greater in those with T2D. Limited patient numbers in these groups may explain the lack of statistical significance. Nonetheless, there is always a concern of deteriorating renal function in people with T2D. Previous studies report progressive stages of both hepatic steatosis and fibrosis independently associate with incident CKD, and that T2D increases this risk further (Cai et al., 2021; Sun et al., 2022).

4.5.2 Impact of MASLD on glycaemic control and type 2 diabetes risk

There was no significant change in glycaemic control in people with pre-existing T2D. Though, in those without T2D there was a significant increase in mean HbA1c of 3.0 mmol/mol and 21 (26.3%) patients developed T2D over four years. One meta-analysis reported 5.6% of 501,022 people with or without MASLD developed T2D over 5-years, and people with MASLD had a 2.2-fold greater risk (Mantovani, Petracca, et al., 2021). The results presented in this chapter demonstrate a mean annual incidence of 6.5%, which is far greater than the usual annual population risk locally of developing T2D. The greater incidence of T2D in our study may be related to the study design. The comparative meta-analysis included participants with MASLD based on imaging or histology criteria and may have also included participants with different risk factors to our population such as dissimilar BMI or ethnicities, which were not reported. Generally, patients under secondary care services such as this cohort have greater risk factors for complication development. Whilst there was no apparent statistical relationship between the degree of hepatic fibrosis and risk of developing T2D, the number of participants and those developing T2D were small and so conclusions are limited.

Given the development of T2D and MASLD are linked, we were disappointed that 11 (13.7%) patients did not have a HbA1c prior to liver biopsy, and 16 (20.0%) did not have repeat HbA1c over follow-up including two patients who never had an HbA1c test. This represents a missed treatment opportunity, considering many therapies which benefit MASLD are licensed to treat T2D. The only identified risk factor for developing T2D in this relatively short follow-up was greater HbA1c. Other factors including BMI, and measures of hepatic steatosis and fibrosis did not associate with greater T2D risk in the logistic regression. This may be a consequence of the small sample size, or confounders such as collinearity between biomarkers, overadjustment of the impact of HbA1c attenuating the impact of biomarker associations, or other contributors to T2D risk not measured such as physical activity, diet, or measures of systemic inflammation. Nevertheless, this finding supports earlier introduction of drugs to treat MASLD to reduce the risk of developing T2D. Though, MASLD is unrecognised in national GLP-1RA guidance for the treatment of obesity, limiting clinical management in practice.

4.5.3 Real-world use and impact of drug therapies for MASLD

Current NICE recommendations support pioglitazone use in MASLD (NICE, 2016), though this is associated with worsening heart failure and fractures. International guidance from the AASLD, AACE, EASD and EASL support use of GLP-1RAs and/or SGLT-2 inhibitors in people with MASLD and T2D, (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). In this study, 2.6% of patients were prescribed pioglitazone, and in those with T2D, 42.5% were prescribed a SGLT-2 inhibitor, and 49.3% prescribed a GLP-1RA. In those who developed T2D, 14.3% were treated with a GLP-1RA, 9.5% with a SGLT-2 inhibitor, and none with pioglitazone. Whilst there appears to be a missed therapeutic opportunity for many patients in this group, these prescription rates were much higher than national averages for T2D around this time, with 9.8-13.8% and 4.3-4.9% prescribed SGLT-2 inhibitor or GLP-1RA therapy in the UK between 2017-2018 (Farmer et al., 2021). This discrepancy may relate to the proportion of these patients also under secondary care diabetes services and local practice and interest in these newer T2D therapies. Supporting primary and secondary care clinicians to prescribe such medicines when appropriate supports their MASLD treatment and addresses excess CV risk. Clinical inertia is often described in the treatment of T2D, and given MASLD is a frequent observation in this group, clinical inertia may reflect on MASLD treatment too (Almigbal et al., 2023; Cusi et al., 2024). A multidisciplinary team of specialist doctors (e.g., hepatologists, endocrinologists), nurses, dieticians, physiotherapists, and psychologists may support management of this often under-treated patient group.

In the T2D cohort, there were greater improvements in measures of MASLD, and other variables associated with SGLT-2 inhibitor and GLP-1RA use compared to other treatments. In patients prescribed SGLT-2 inhibitors and/or GLP-1RAs there were significant reductions in bodyweight, TE-CAP, ALT, total cholesterol, and HbA1c. In those given other treatments, there were statistically significant reductions in bodyweight and ALT. This represented about 4% weight loss in this group over follow-up. This may be related to dietetic input, and changes in lifestyle such as reduced calorie or alcohol intake, increased physical activity, or unmeasured concomitant medications in this group. However, there was limited information about such input in their clinical letters to discuss further. The reduction in bodyweight was greater in people taking a SGLT-2 inhibitor, GLP-1RA or both, which is expected given the consistent impact of these drugs on bodyweight (Cheong et al., 2022; Ma et al., 2023; Williams, Staff, et al., 2022), and licensing of some GLP-1RAs for obesity. However, in the subgroup analysis, GLP-1RA therapy did not reduce bodyweight significantly. This may reflect the predominant use of older GLP-1RAs (dulaglutide and liraglutide) which confer less weight loss than newer agents such as semaglutide, which were becoming available at the end of the study. Given the considerable and consistent impact of GLP-1RAs on bodyweight in trials (Ma et al., 2023; Williams, Staff, et al., 2022), further real-world evaluation of the impact of newer GLP-1RAs on bodyweight in people with MASLD is needed. Indeed, the SEMA-NASH study observed a mean 13% total weight reduction in people with MASLD and T2D associated with semaglutide (Newsome et al., 2021), similar to previous studies, indicating the impact of GLP-1RAs on weight outcomes in people with MASLD is likely similar as in those without MASLD.

The use of SGLT-2 inhibitors and/or GLP-1RAs was associated with a significantly improved TE-CAP, and reduction in ALT. The subgroup analysis observed a significant reduction in the TE-CAP with use of GLP-1RAs or combined use of GLP-1RA and SGLT-2 inhibitor, but not in those taking SGLT-2 inhibitors only. Both SGLT-2 inhibitors and GLP-1RAs associate with improved measures of hepatic steatosis, and histopathological improvements in liver fat have been observed with GLP-1RAs (Androutsakos et al., 2022b; Cusi et al., 2022; EASL-EASD-EASO, 2024; Newsome et al., 2021; Rinella, Neuschwander-Tetri, et al., 2023). Likewise, there was a reduction in ALT in those taking SGLT-2 inhibitor and/or GLP-1RA and in the other treatment group, but the reduction was greater in the earlier group. We observed a similar non-significant reduction in the TE-LSM associated with use of SGLT-2 inhibitors and/or GLP-1RA. This is consistent with previous studies exploring the use of these drugs on MASLD-related outcomes, in which little impact on non-invasive or histopathological

measures of fibrosis have been observed on single studies (Armstrong, Gaunt, et al., 2016; Loomba, Abdelmalek, et al., 2023; Newsome et al., 2021; Rinella, Neuschwander-Tetri, et al., 2023), though meta-analyses suggest these drugs benefit fibrosis outcomes (Souza et al., 2025).

Patients prescribed a SGLT-2 inhibitor and/or GLP-1RA had significant improvements in both HbA1c and lipid profile. However, the impact on HbA1c may be confounded by the higher pre-treatment HbA1c in people prescribed a SGLT-2 inhibitor and/or GLP-1RA, and the near-target mean HbA1c 53.1 mmol/mol in those prescribed other treatments. Given the varying treatments used in the other treatment group (diet-only, insulin, tablets) comparison is limited. This was a general limitation of this observational real-world study, given the lack of control group. Some of the apparent treatment effect may be attributable to confounders such as unmeasured changes in dietary or lifestyle behaviours, health-seeking behaviours, or smoking status, amongst others. Moreover, we used prescribing data to infer that participants were taking a medicine, but have no data related to their medicines adherence which may also be an important confounder in the interpretation of these data.

Regarding the use of these medicines to improve lipid profiles, GLP-1RAs have a modest but statistical impact on total cholesterol and LDL-cholesterol (Piccirillo et al., 2023). Whilst, SGLT-2 inhibitors may increase total and LDL-cholesterol, the changes associated with these drugs is modest (Bechmann et al., 2023). Still, given the greater frequency of statin prescription in those prescribed a SGLT-2 inhibitor and/or GLP-1RA (75.0 vs 50.0%), limited conclusions can be drawn about the direct impact of these drugs on lipid profiles from these data.

4.6 Summary and limitations

In this chapter, people with T2D and MASLD had significantly greater hepatic fibrosis on histopathological assessment than people without T2D, despite similar stages of steatohepatitis. In this group, people with T2D were older and had better lipid profiles. People without T2D trended to greater decompensated liver disease or death from liver disease, whilst people with T2D had greater CVD or cancer-related death. Over a mean follow-up of 4 years, 25% of people without T2D at MASLD diagnosis had developed T2D. There was good use of recommended pharmacotherapies compared with contemporary prescribing practice. The use of these medicines in people with T2D associated with improved non-invasive measures of hepatic steatosis, but not non-invasive measures of fibrosis.

4.6.1 Clinical significance

There are several clinically important observations described in this chapter. The first is that the observation of MASLD in people with T2D is not benign. People with T2D had a greater degree of hepatic fibrosis. The presence of T2D suggested a more generalised metabolic dysfunction with greater risk of CVD- and malignancy-related death. The fact that people with T2D and MASLD were diagnosed at an older age may indicate they had a longer duration of unrecognised MASLD. Screening for MASLD in people with T2D may identify those at risk of advanced fibrosis or poorer outcomes to prevent an untreated burden of liver and CV disease.

Another significant finding was the very high risk of developing T2D in people with MASLD, around 1 in 4 over four years. Many of those without T2D at MASLD diagnosis were not treated with pharmacotherapies to modify disease and reduce T2D risk. Concerns around use of vitamin E or pioglitazone may have led to the very low rate of drug treatment, but use of pioglitazone may prevent T2D and CVD in this group. Collaborative working and accessible support and networking across primary and secondary care is needed to develop confidence in this area of prescribing practice and is challenging. With increasing acceptance of using newer T2D therapies to treat MASLD, there may be a place for these drugs in people with MASLD and pre-diabetes to prevent progression to T2D. In this group, the use of SGLT-2 inhibitors and/or GLP-1RAs significantly improved non-invasive measures of steatosis, but not fibrosis.

4.6.2 Limitations

There are some limitations to this study:

1. This study utilised a retrospective cross-sectional cohort design, which relied upon already collected and documented routine clinical data which may be prone to bias, and missing data may undermine the statistical analysis.
2. Greater patient numbers and longer follow-up would enhance statistical analysis to compare those with or without T2D.
3. Some clinical variables such as past medical history, social history, BP and vitamin D status were too poorly documented or unreliable to be included.
4. There was limited information on available secondary care medical records to confirm the dietetic or other support employed, or changes in other health-related behaviours.
5. There was a lack of control group without MASLD which may have given further insight into difference in clinical characteristics and outcomes.

Chapter Five:

Screening for MASLD and advanced fibrosis in people with type 2 diabetes attending secondary care: a pilot study

5.1 Introduction

In this thesis, chapter four described the bidirectional associations between MASLD and T2D in people with biopsy-confirmed MASLD in Swansea. However, in practice it is neither feasible nor appropriate to undertake liver biopsy to screen for MASLD, or to confirm the diagnosis in people with suspected disease. Therefore, we must rely upon non-invasive tests in the work up for MASLD and advanced fibrosis in most cases (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023).

People with high MASLD risk, such those living with T2D, should undergo screening for advanced fibrosis using the FIB-4 score (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Those with a score >2.67 should be referred to hepatology given their very high risk of advanced fibrosis, whilst those with a score 1.30-2.67 should undergo further investigation. The suggested screening algorithm is shown in Figure 1.11. Recommended second-line tests include the ELF test or TE-LSM, depending on local preference. Despite these guidelines, few studies have piloted the process in a prospective real-life cohort.

There remain concerns around screening. Cost-effectiveness is debated, though several UK studies suggest this is cost-effective (Forlano et al., 2024; Serra-Burriel et al., 2019; Srivastava, Jong, et al., 2019), and similar international observations were discussed in section 1.6.5. Given variable study populations, differing screening strategies and cost thresholds, there remains dispute. There is also concern around the service provision of managing patients who screen positive for advanced fibrosis, such that existing services may become overwhelmed.

The FIB-4 test is recommended first-line because its cheap, internationally available and its accuracy is not significantly affected by T2D or obesity (de Carli et al., 2020; Drolz et al., 2021; Qadri et al., 2022; Schmitz et al., 2020). Though, its accuracy is insufficient to diagnose advanced fibrosis alone given its poor specificity, and sequential tests are needed. On the other hand, biomarkers such as the NFS or APRI are less reliable in people with T2D or obesity and may lead to excess referrals (McPherson et al., 2017; Qadri et al., 2022). The ELF test or TE-LSM maintain accuracy in these groups, and are supported as second-line tests (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). If these results are consistent with moderate or advanced fibrosis, the patient should be referred to hepatology for assessment.

Before implementing a strategy locally, or nationally, pilot studies to evaluate the proposed algorithm are essential. In this chapter, I present the results of a pilot study undertaken in Swansea to screen for MASLD and advanced hepatic fibrosis in people living with T2D.

5.2 Aims of this chapter

The specific aims of this chapter are to evaluate:

- i. prevalence of MASLD and advanced hepatic fibrosis using blood biomarkers in people with T2D.
- ii. prevalence of MASLD and advanced hepatic fibrosis using TE in people with T2D.
- iii. impact of BMI on the prevalence of hepatic steatosis and hepatic fibrosis in people with T2D.
- iv. practical application of sequential screening tests for advanced hepatic fibrosis in people treated for T2D.
- v. participant acceptability of using TE to screen for MASLD and advanced hepatic fibrosis in people treated for T2D.

5.3 Methods

5.3.1 Study design

The study design was presented in chapter two. Patients treated for T2D under secondary care services in SBUHB (Morrison Hospital, Singleton Hospital, or Neath Port Talbot Hospital) were invited to undergo additional tests to screen for MASLD and advanced fibrosis. Potential participants were contacted in advance of their routine T2D follow-up appointment. If they agreed to take part, they fasted from midnight before a morning appointment. In clinic, participants signed a consent form to participate. Data were collected October 2023-July 2024.

Additional blood tests were taken, and TE was performed in clinic by me. The additional blood tests are discussed in section 5.3.3. Participants with a TE-LSM ≥ 9.7 kPa or ELF test ≥ 10.51 were referred for ultrasound abdomen and hepatology review, given high-risk of advanced fibrosis. Participants with normal TE-LSM or ELF test results were advised to repeat this investigation in 2-3 years. There was written correspondence of results and plan with their GP.

5.3.2 Participants

Participants were aged ≥ 18 years with a clinical diagnosis of T2D treated under secondary care services in SBUHB. Participants did not have previous alcohol excess, defined as consumption of ≥ 14 units of alcohol per week, in keeping with UK guidance. Participants did not have family history of liver disease, and were not diagnosed or under investigation for another cause of liver disease. Participant inclusion criteria were detailed in Table 2.3 of chapter two.

5.3.3 Data collection

Fasted blood samples were collected in clinic. Tests included diabetes annual review (HbA1c, urea & electrolytes, lipid profile, urinary albumin-to-creatinine ratio), and research tests (AST, coagulation screen, ELF test, fasting glucose, fasting insulin, full blood count, GGT, and LFTs), detailed in chapter two. These data were used to generate measures of hepatic steatosis (HSI, NAFLD-LFS, TyG), and hepatic fibrosis (APRI, AST/ALT, BARD score, ELF test, FIB-4, NFS). During the appointment, the participant was deemed to have valid TE-LSM if ≥ 10 valid scans were achieved, with IQR/median ratio $< 30\%$. Further detail about TE was described in chapter two. Participants with a TE-CAP < 302 dB/m, $302-336$ dB/m, or ≥ 337 dB/m were deemed to have no significant hepatic steatosis (stage 0), moderate steatosis (stage 1-2) or severe steatosis (stage 3), respectively. Participants with a TE-LSM < 8.2 kPa, $8.2-9.6$ kPa, or ≥ 9.7 kPa were deemed to have no significant fibrosis (stage 0-1), moderate fibrosis (stage 2), or advanced fibrosis (stage 3-4). These criteria were presented in Table 2.7.

5.3.4 Funding and ethical approval

No additional funding was received to undertake this study. This pilot study was prospectively reviewed by the REC in Wales and approved by the HRA and HCRW in May 2023 [IRAS ID: 326341]. Approval to commence recruitment was issued by SBUHB in October 2023. Supporting documentation received from the REC Wales and SBUHB to confirm study approval are presented in Appendix II.

5.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503), or Microsoft PowerPoint for Microsoft 365 (version 2503). Categorical data are presented by the number (%). Data following a normal distribution are presented as the mean $\pm$ SD, and data not following a normal distribution are presented by the median [IQR]. The statistical significance of differences in groups of categorical data were determined by Chi-squared test, and the significance of differences in groups of continuous data not following a normal distribution were determined by the Kruskal-Wallis test.

5.4 Results

5.4.1 Participant characteristics

Two-hundred participants were included. They had a mean age 59.4 years, and mean duration of diabetes of 14.8 years. Eighty-seven (43.5%) participants were included from Morriston hospital, 21 (10.5%) from Neath Port Talbot hospital, and 92 (46.0%) from Singleton hospital. Other cohort characteristics are presented in Table 5.1. A total of 143 (71.5%) participants were insulin-treated, and their medications prescribed to treat T2D are presented in Table 5.2. Figure 5.1 presents the distribution of participants across deprivation deciles according to the WIMD.

Table 5.1: Participant characteristics

Characteristic	Result (n=200)
Age (years)	59.4±11.0
Sex (Female/Male)	84 (42.0%)/116 (58.0%)
Duration of T2D (years)	14.8±9.0
WIMD decile	4.5±3.0
Weight (kg)	96.8±20.0
BMI (kg/m ²)	33.3±6.3
Systolic BP (mmHg)	139.1±20.6
Diastolic BP (mmHg)	80.4±11.1
Diabetes-related complications	
PDR	44 (22.0%)
CKD	97 (48.5%)
Neuropathy	61 (30.5%)
Heart failure	23 (11.5%)
ASCVD	41 (20.5%)
Stroke	11 (5.5%)
PVD	16 (8.0%)
Diabetes-related monitoring	
HbA1c (mmol/mol)	73.5±20.0
Fasting insulin (uIU/mL)	30.9±37.0
Fasting C-peptide (pmol/L)	856.3±658.1
FBG (mmol/L)	10.6±4.5
Creatinine (µmol/L)	85.0±30.1
eGFR (mL/min/1.73m ²)	79.5±25.2
TC (mmol/L)	4.2±1.1
TG (mmol/L)	2.3±1.4
LDL (mmol/L)	2.1±0.9
HDL (mmol/L)	1.1±0.3

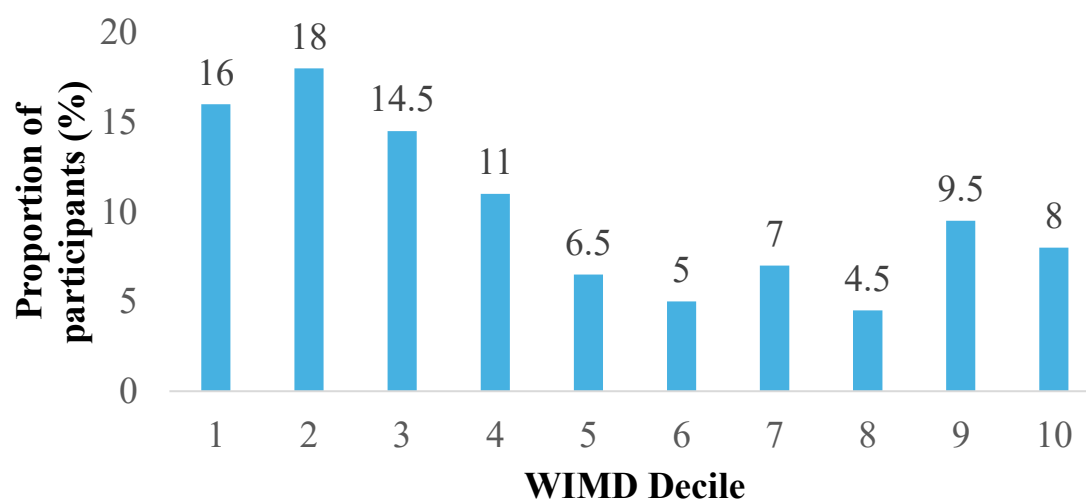
Characteristics of people included in the study. Abbreviations: *ASCVD* atherosclerotic cardiovascular disease; *BMI* body mass index; *BP* diastolic blood pressure; *CKD* chronic kidney disease; *eGFR* estimated glomerular filtration rate; *FBG* fasting blood glucose; *LDL* low density lipoprotein; *HDL* high-density lipoprotein; *PDR* proliferative diabetes-related retinopathy; *PVD* peripheral vascular disease; *T2D* type 2 diabetes; *TC* total cholesterol; *TG* triglyceride; *WIMD* Welsh Index of Multiple Deprivation.

Table 5.2: Participants type 2 diabetes prescriptions

Drug class	Number of participants (n=200)
Biguanide (Metformin)	145 (72.5%)
Sulphonylurea	47 (23.5%)
Thiazolidinedione (Pioglitazone)	11 (5.5%)
DPP-4 inhibitor	30 (15.0%)
• Alogliptin	3 (1.5%)
• Linagliptin	17 (8.5%)
• Saxagliptin	1 (0.5%)
• Sitagliptin	9 (4.5%)
SGLT-2 inhibitor	102 (51.0%)
• Canagliflozin	4 (2.0%)
• Dapagliflozin	59 (29.5%)
• Empagliflozin	39 (19.5%)
GLP-1 receptor analogue	82 (41.0%)
• Dulaglutide	24 (12.0%)
• Exenatide	2 (1.0%)
• Liraglutide	21 (10.5%)
• Semaglutide	34 (17.0%)
• Tirzepatide	1 (0.5%)
Insulin	143 (71.5%)
• Basal only	43 (21.5%)
• Premixed insulin	45 (22.5%)
• Basal-bolus insulin	55 (27.5%)

Medications prescribed for the treatment of T2D in study participants. Abbreviations: *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1; *SGLT-2* sodium-glucose cotransporter-2.

Figure 5.1: Participant deprivation by WIMD



The distribution of participants across deprivation deciles using the WIMD. Abbreviation: *WIMD* welsh index of multiple deprivation

5.4.2 Prevalence of MASLD and advanced hepatic fibrosis using blood biomarkers in people with type 2 diabetes

Of the 200 participants, 2 (1.0%) did not have a valid AST sample due to haemolysis, 2 (1.0%) did not have a valid fasting blood glucose due to lab error, 4 (2.0%) did not have a valid fasting insulin level due to haemolysis, and 1 (0.5%) did not have a valid BMI due to previous bilateral lower limb amputation. This resulted in 197 (98.5%) participants with a valid HSI score, 195 (97.5%) participants with valid NAFLD-LFS, and 198 (99.0%) participants with valid TyG score. Applying the HSI, NAFLD-LFS and TyG, 197 (100%), 170 (87.2%), and 192 (97.0%) people were identified at moderate or high risk of severe hepatic steatosis, respectively. These data are presented in Table 5.3 and Figure 5.2.

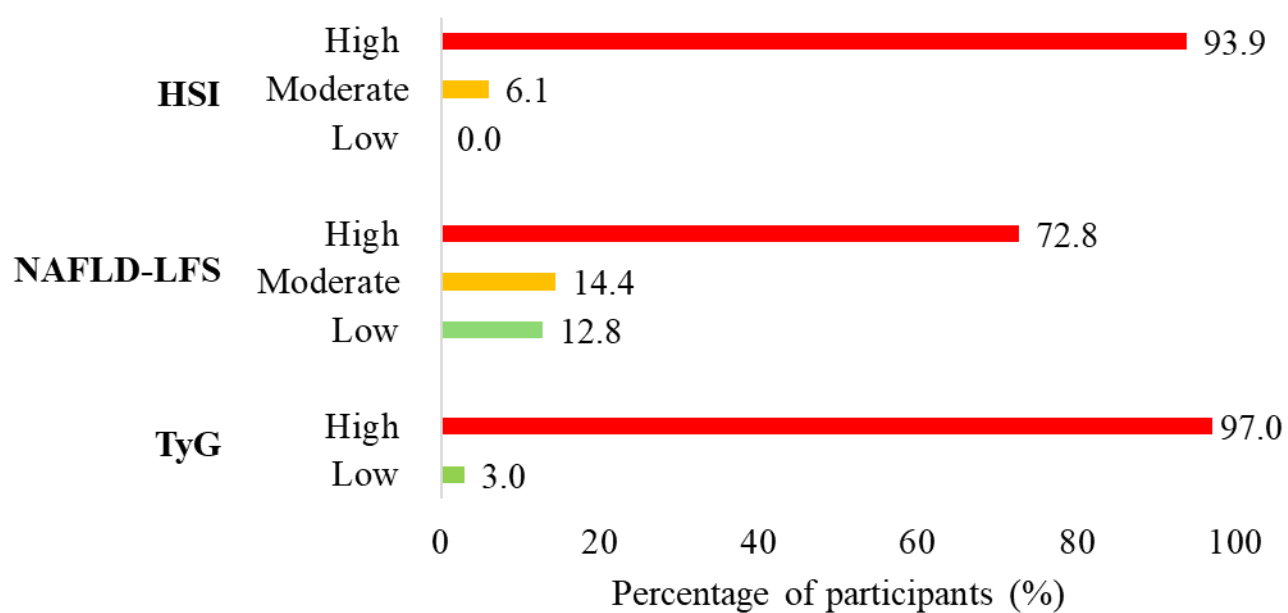
The risk of advanced fibrosis was determined. Of the 200 participants, 2 (1.0%) did not have a valid AST and 1 (0.5%) had an invalid ELF test sample due to haemolysis, and 1 (0.5%) did not have a valid BMI due to previous lower limb amputation. This resulted in 199 (99.5%) participants with a valid ELF test score, 198 (99.0%) participants with a valid APRI, AST:ALT ratio, FIB-4 score, and NFS, and 197 (98.5%) participants with a valid BARD score. There was variation in the proportion identified at risk of advanced fibrosis based on the test applied. The APRI identified only 6 (3.0%) participants at moderate or high risk of advanced fibrosis, whilst with the BARD score identified 186 (94.4%) participants at moderate or high risk of advanced fibrosis. The proportion of participants identified at risk for advanced fibrosis using blood biomarkers are presented in Table 5.3, and Figure 5.3.

Table 5.3: Risk of MASLD and advanced hepatic fibrosis using blood biomarkers

Blood biomarker	Result (n=200)
Hepatic steatosis	
HSI	45.0 [41.1-49.5]
• Low risk (<30.0)	0 (0.0%)
• Moderate risk (30.0-36.0)	12 (6.1%)
• High risk (≥ 36.0)	185 (93.9%)
NAFLD-LFS	1.44 [-0.1-4.9]
• Low risk (≤ -0.64)	25 (12.8%)
• Moderate risk (-0.63-0.15)	28 (14.4%)
• High risk (≥ 0.16)	142 (72.8%)
TyG	5.1 [4.9-5.5]
• Low risk (<4.5)	6 (3.0%)
• High risk (≥ 4.5)	192 (97.0%)
Hepatic fibrosis	
APRI	0.2 [0.2-0.3]
• Low risk (<0.70)	192 (97.0%)
• Moderate risk (0.70-0.99)	2 (1.0%)
• High risk (≥ 1.00)	4 (2.0%)
AST:ALT ratio	0.9 [0.7-1.1]
• Low risk (<0.80)	75 (37.9%)
• High risk (≥ 0.80)	123 (62.1%)
BARD score	3.0 [2.0-4.0]
• Low risk (<2)	11 (5.6%)
• High risk (≥ 2)	186 (94.4%)
ELF test	9.4 [9.0-10.1]
• Low risk (<7.8)	2 (1.0%)
• Moderate risk (7.8-9.7)	124 (62.3%)
• High risk (≥ 9.8)	73 (36.7%)
• Very high risk (≥ 10.51)	20 (10.1%)
FIB-4 score	0.9 [0.7-1.2]
• Low risk (<1.30)	153 (77.3%)
• Moderate risk (1.30-2.66)	40 (20.2%)
• High risk (≥ 2.67)	5 (2.5%)
NFS	-0.8 [-1.6-0.0]
• Low risk (<-1.455)	51 (25.8%)
• Moderate risk (-1.454 – 0.67)	121 (61.1%)
• High risk (≥ 0.675)	26 (13.1%)

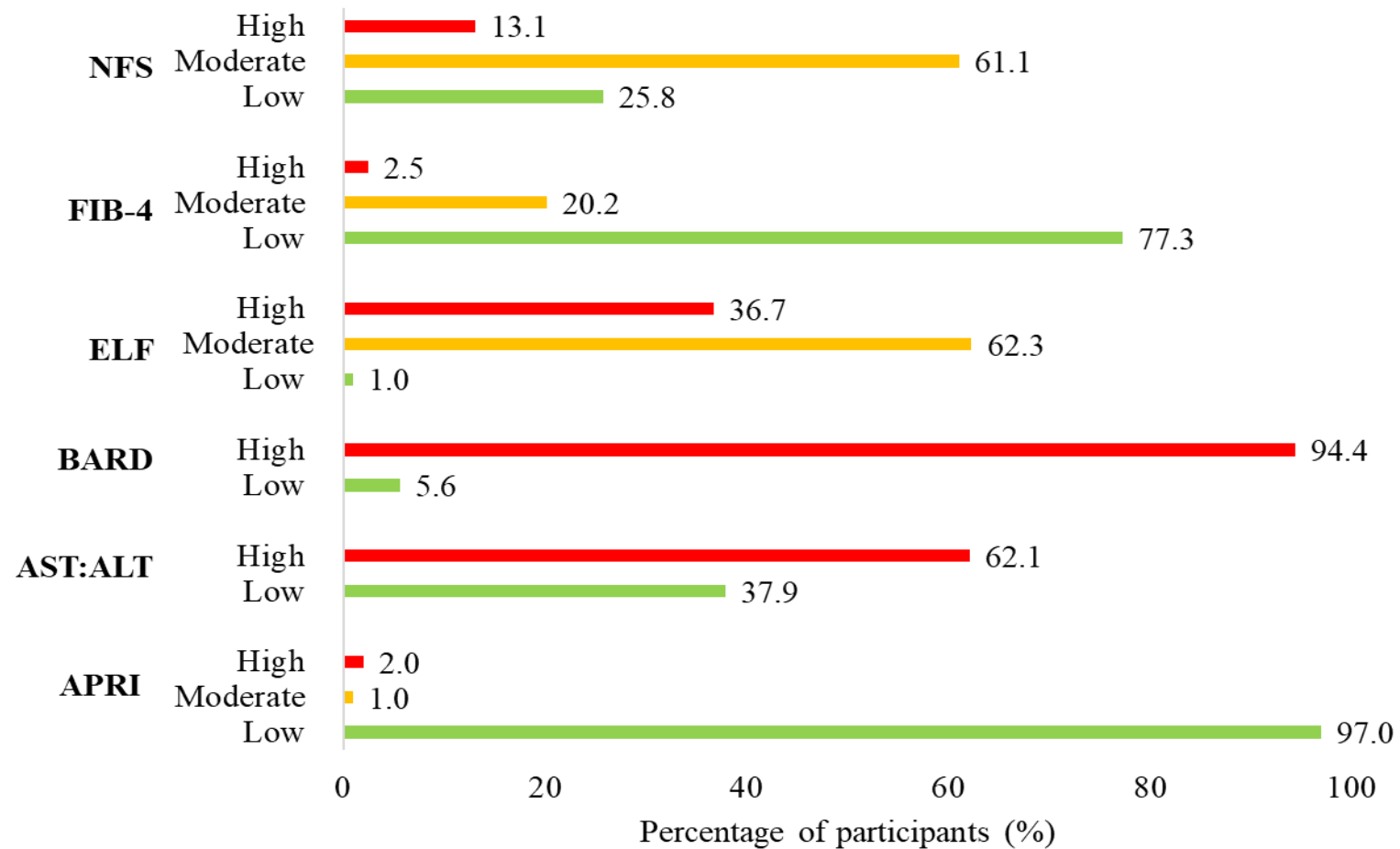
Prevalence of severe hepatic steatosis or advanced fibrosis using different blood biomarkers. Abbreviations: *ALT* alanine aminotransferase; *APRI* AST-to-platelet ratio index; *AST* aspartate transferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *HSI* hepatic steatosis index; *NFS* non-alcoholic fatty liver disease score; *NAFLD-LFS* non-alcoholic fatty liver disease liver fat score; *TyG* triglyceride and glucose index.

Figure 5.2: Risk of severe hepatic steatosis using blood biomarkers



Participants with low, moderate, or high risk of severe hepatic steatosis using blood biomarkers for hepatic steatosis. Abbreviations: *HSI* hepatic steatosis index; *NAFLD-LFS* non-alcoholic liver fat score; *TyG* triglyceride and glucose index

Figure 5.3: Risk of advanced hepatic fibrosis using blood biomarkers



Participants with low, moderate, or high risk of advanced hepatic fibrosis using blood biomarkers for hepatic fibrosis. Abbreviations: *ALT* alanine aminotransferase; *APRI* AST-to-platelet ratio index; *AST* aspartate transferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease score.

5.4.3 Prevalence of MASLD and advanced hepatic fibrosis using transient elastography in people with type 2 diabetes

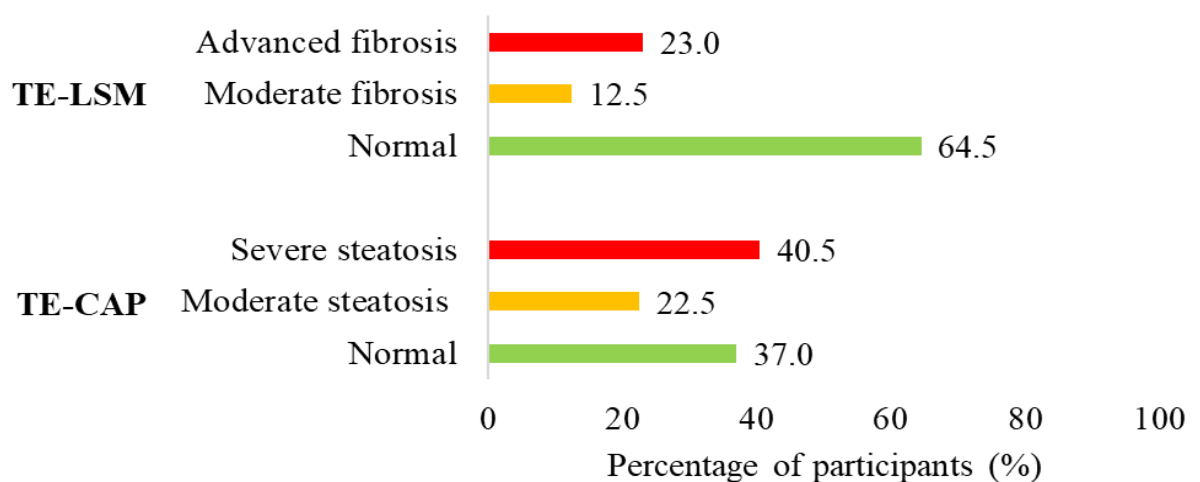
The TE-CAP and TE-LSM were determined to predict risk of severe hepatic steatosis and advanced fibrosis, respectively. All 200 (100%) participants had valid TE-CAP and TE-LSM scores. The median TE-CAP score was consistent with moderate steatosis, and 126 (63.0%) participants had a TE-CAP result consistent with moderate or severe steatosis. The median TE-LSM was in the normal range, though 71 (35.5%) participants had a result consistent with moderate or high-risk for advanced fibrosis. These are presented in Table 5.4 and Figure 5.4.

Table 5.4: Prevalence of MASLD and advanced fibrosis using transient elastography

Hepatic steatosis	
TE-CAP (dB/m)	324.5 [266.5-357.8]
• Normal (<302 dB/m)	74 (37.0%)
• Moderate (302-336 dB/m)	45 (22.5%)
• Severe (≥ 337 dB/m)	81 (40.5%)
Hepatic fibrosis	
TE-LSM (kPa)	6.8 [5.2-9.2]
• Normal (<8.2 kPa)	129 (64.5%)
• Moderate (8.2-9.6 kPa)	25 (12.5%)
• Advanced (≥ 9.7 kPa)	46 (23.0%)

Prevalence of risk for hepatic steatosis and advanced fibrosis. Abbreviations: *CAP* controlled attenuation parameter; *LSM* liver stiffness measure; *TE* transient elastography.

Figure 5.4: Prevalence of MASLD and advanced fibrosis using transient elastography



Proportion of participants with normal, moderate, severe/advanced hepatic steatosis or hepatic fibrosis using TE. Abbreviations: *CAP* controlled attenuation parameter; *LSM* liver stiffness measure; *TE* transient elastography.

5.4.4 Impact of body mass index and duration of diabetes on prevalence of hepatic steatosis and fibrosis in people with type 2 diabetes

There were statistically significant increases in all non-invasive measures of hepatic steatosis (HSI, NAFLD-LFS, TyG and TE-CAP) with increasing BMI in these participants. There were also statistically significant increases in some measures of liver fibrosis (BARD score, NFS, and TE-LSM) with increasing BMI, but not others (APRI, AST:ALT ratio, ELF test, and the FIB-4 score). These data are presented in Table 5.5.

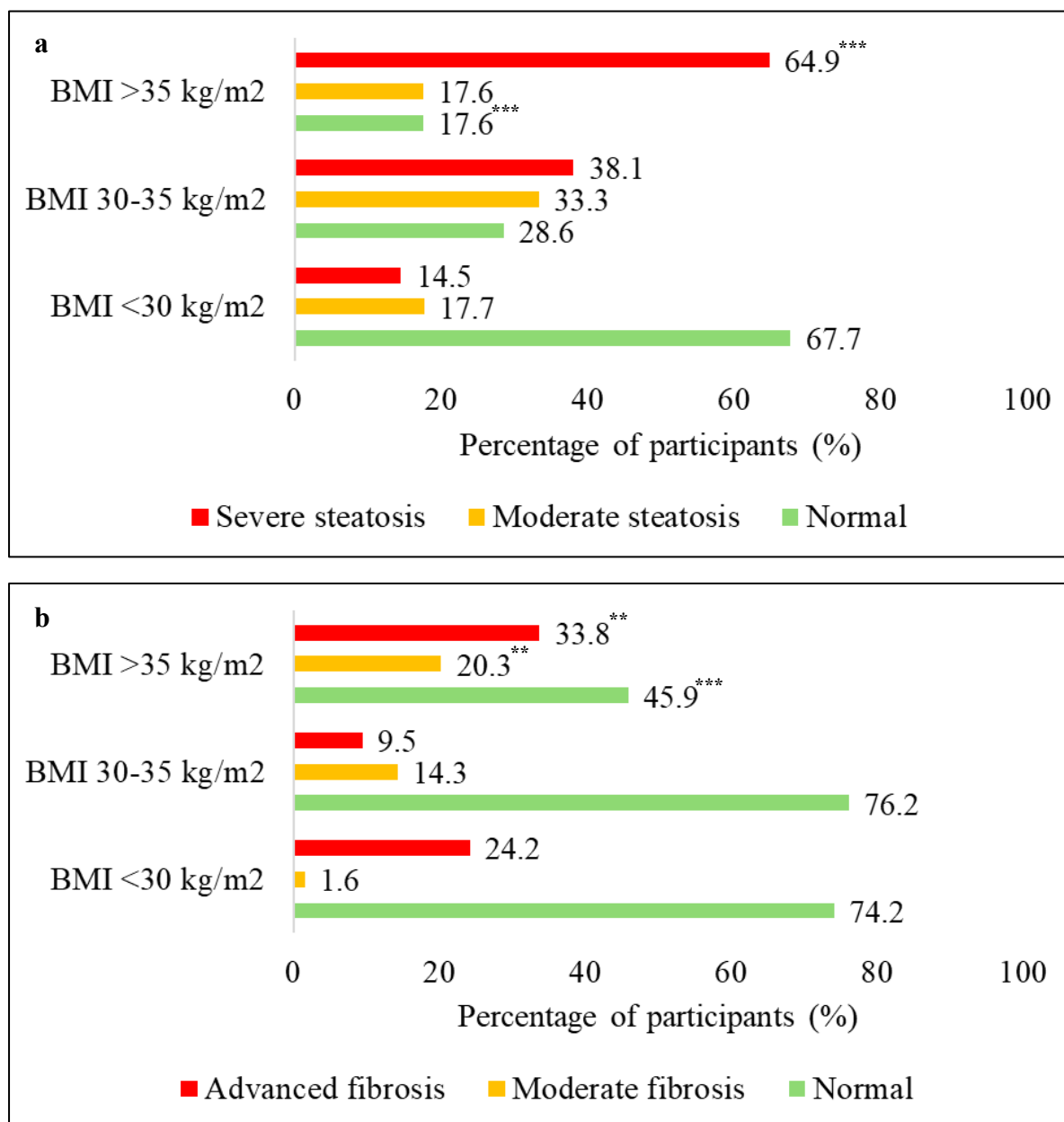
With increasing BMI, there was an increasing prevalence of participants with severe hepatic steatosis on TE, and inversely a decreasing proportion of participants with a normal TE-CAP (both $p<0.001$). There was decreasing prevalence of a normal TE-LSM with increasing BMI ($p<0.001$) and increasing prevalence of moderate or advanced fibrosis with increasing BMI (both $p<0.01$). This is presented in Figure 5.5.

Table 5.5: Differences in measures of hepatic steatosis and fibrosis by body mass index

Variable	BMI <30 kg/m ² (n=62)	BMI 30-35 kg/m ² (n=63)	BMI >35 kg/m ² (n=74)	Significance
HSI	38.0 [36.2-41.3]	44.9 [43.0-47.1]	51.5 [47.7-55.1]	$p<0.001$
NAFLD-LFS	-0.4 [-1.0-1.6]	2.1 [0.7-8.7]	2.1 [0.9-6.3]	$p<0.001$
TyG	5.0 [4.8-5.3]	5.1 [5.0-5.5]	5.2 [5.0-5.5]	$p<0.05$
APRI	0.2 [0.2-0.3]	0.2 [0.2-0.3]	0.2 [0.2-0.3]	NS
AST:ALT	0.9 [0.7-1.1]	0.8 [0.7-1.0]	0.9 [0.7-1.2]	NS
BARD	3.0 [2.0-3.0]	4.0 [2.0-4.0]	4.0 [2.0-4.0]	$p<0.001$
ELF	9.4 [8.8-10.0]	9.4 [9.0-10.0]	9.6 [9.0-10.2]	NS
FIB-4 score	0.9 [0.7-1.3]	0.9 [0.8-1.2]	0.9 [0.7-1.3]	NS
NFS	-1.3 [-2.1- -0.7]	-0.8 [-1.3 - -0.2]	-0.2 [-1.0-1.0]	$p<0.001$
TE-CAP (dB/m)	267.0 [222.5-320.0]	327.0 [287.0-354.0]	352.0 [322.3-375.3]	$p<0.001$
TE-LSM (kPa)	6.2 [4.6-8.8]	6.2 [5.0-7.7]	8.5 [6.3-12.3]	$p<0.001$

Differences in measures of hepatic steatosis and hepatic fibrosis by BMI, presented by the median [IQR]. The statistical significance of the trend in median score for each biomarker across different BMI groups is presented. Abbreviations: *ALT* alanine aminotransferase; *APRI* AST-to-platelet ratio index; *AST* aspartate transferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *HSI* hepatic steatosis index; *LSM* liver stiffness measure; *NAFLD-LFS* non-alcoholic liver fat score; *NFS* non-alcoholic fatty liver disease score; *TE* transient elastography; *TyG* triglyceride and glucose index

Figure 5.5: Prevalence of hepatic steatosis and advanced fibrosis by body mass index status



Prevalence of different stages of (a) hepatic steatosis and (b) hepatic fibrosis on TE, compared by BMI. The statistical significance of the trend in prevalence of each stage of hepatic steatosis or hepatic fibrosis between different BMI groups is noted by ^{**}p<0.01 ^{***}p<0.001. Abbreviation: *BMI* body mass index.

People with T2D diagnosed for more than 10 years had statistically greater age, but similar measures of deprivation, and risk factors such as obesity, glycaemic control, and BP. Those with more recently-diagnosed T2D had a lower NAFLD-LFS, and significantly lower blood biomarker measures for hepatic fibrosis. The groups had similar TE-CAP and TE-LSM scores. These data are presented in Table 5.6

Table 5.6: Impact of T2D duration on measures of hepatic steatosis and fibrosis

Variable	Duration T2D <10 years (n=58)	Duration T2D ≥10 years (n=142)	Significance
Age (years)	57.5 [47.0-64.5]	63.0 [55.0-68.0]	<0.01
WIMD decile	3.0 [2.0-6.3]	4.0 [2.0-7.3]	NS
Weight (kg)	93.2 [80.2-112.6]	93.4 [85.2-108.8]	NS
BMI (kg/m ²)	32.1 [28.1-36.5]	32.7 [29.1-37.2]	NS
Systolic BP (mmHg)	134.5 [121.8-150.0]	139.5 [124.0-154.0]	NS
HbA1c (mmol/mol)	73.5 [57.8-85.0]	72.0 [58.0-88.0]	NS
eGFR (mL/min/1.73m ²)	84.8 [72.8-93.6]	77.1 [58.5-95.0]	NS
HSI	44.4 [41.3-52.1]	45.2-40.7-49.1]	NS
NAFLD-LFS	0.9 [-0.4-3.6]	1.6 [0.3-7.0]	<0.05
TyG	5.2 [4.9-5.5]	5.1 [4.9-5.4]	NS
APRI	0.2 [0.2-0.3]	0.2 [0.2-0.3]	NS
AST:ALT	0.8 [0.7-1.0]	0.9 [0.7-1.2]	<0.05
BARD	2.5 [2.0-4.0]	4.0 [2.0-4.0]	<0.05
ELF	9.1 [8.5-9.8]	9.6 [9.1-10.1]	<0.001
FIB-4 score	0.8 [0.6-1.1]	0.9 [0.7-1.3]	<0.01
NFS	-1.1 [-1.8 - -0.5]	-0.6 [-1.4-0.2]	<0.05
TE-CAP (dB/m)	324.5 [265.5-356.5]	324.5 [269.5-358.0]	NS
TE-LSM (kPa)	6.9 [5.1-9.0]	6.6 [5.3-10.0]	NS

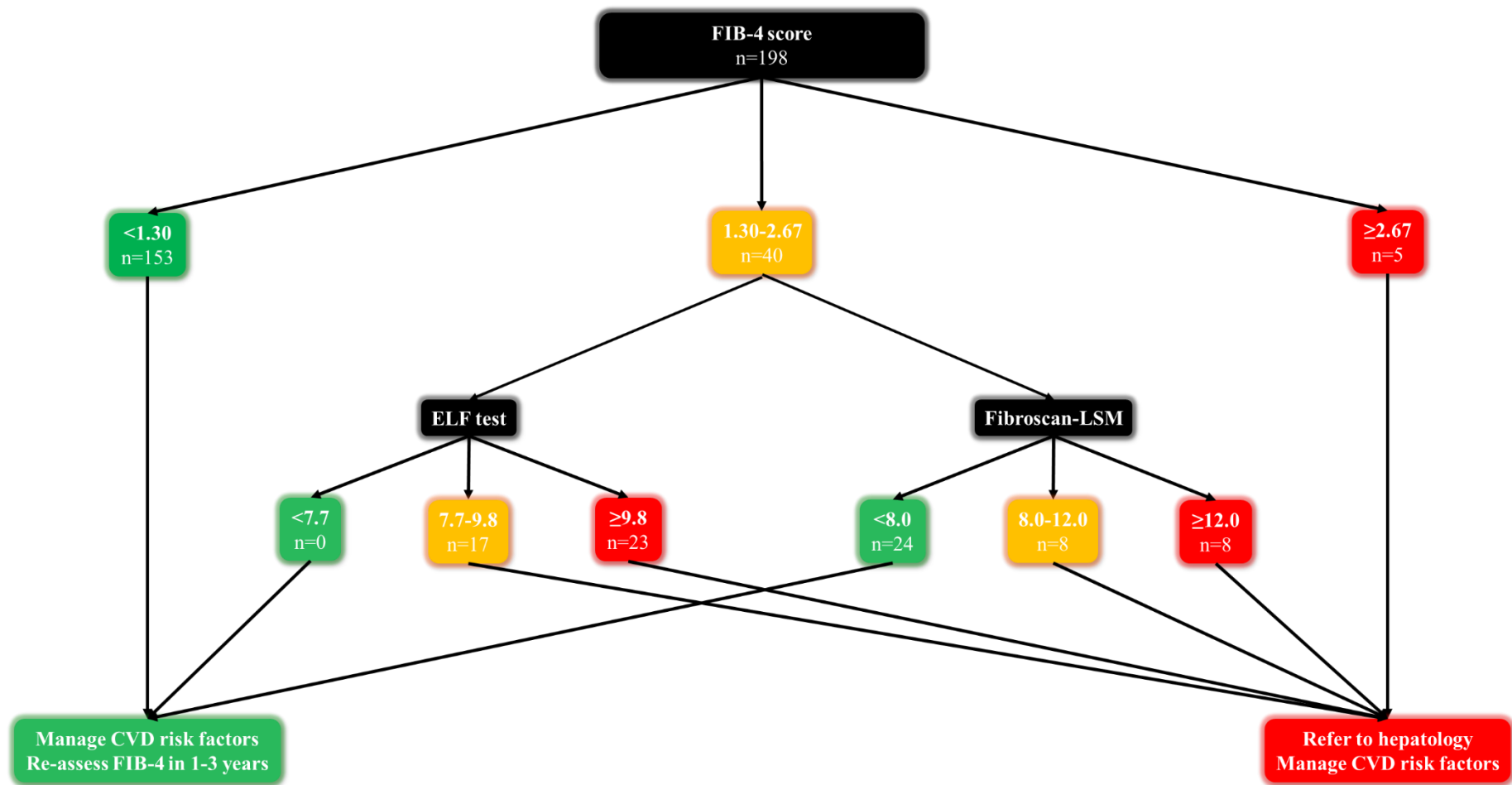
Differences in non-invasive measures of hepatic steatosis and fibrosis between people with T2D diagnosed for less or more than 10 years duration. Abbreviations: *ALT* alanine aminotransferase; *APRI* AST-to-platelet ratio index; *AST* aspartate transferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *BP* blood pressure; *CAP* controlled attenuation parameter; *ELF* enhanced liver fibrosis; *eGFR* estimated glomerular filtration rate; *FIB-4* fibrosis-4; *HSI* hepatic steatosis index; *LSM* liver stiffness measure; *NAFLD-LFS* non-alcoholic liver fat score; *NFS* non-alcoholic fatty liver disease score; *TE* transient elastography; *TyG* triglyceride and glucose index; *WIMD* Welsh index of multiple deprivation

5.4.5 Practical application of sequential screening tests for advanced hepatic fibrosis in people treated for type 2 diabetes

These data were applied to the testing algorithm proposed in recent guidelines. A valid FIB-4 score was reported in 198 (99.0%) participants, of whom 153 (77.3%) had a low-risk score, 5 (2.5%) had a high-risk score, and 40 (20.2%) had an indeterminate score. Of the 40 with indeterminate FIB-4 score, all 40 (100%) had moderate or high risk of advanced fibrosis using the ELF test, and 16 (40.0%) had moderate or high risk of advanced fibrosis using the TE-LSM. The data produced from applying the screening algorithm are shown in Figure 5.6. Using a high-risk ELF score suggested by international guidelines (≥ 9.8) or by NICE (≥ 10.51), 28/40 (70%) and 13/40 (32.5%) participants with an indeterminate FIB-4 score would be referred.

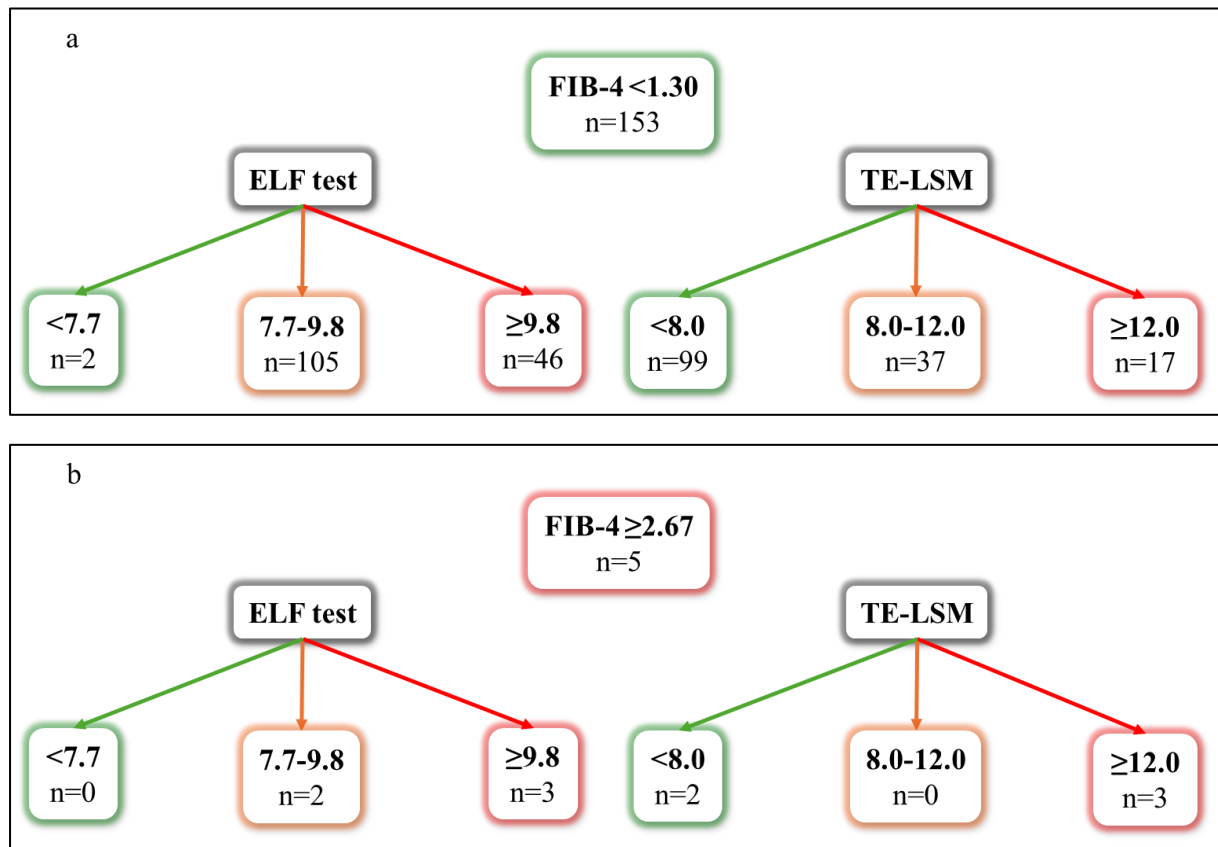
There was some inconsistency between tests in this cohort. In the 153 participants with a low-risk FIB-4 score, only 2 (1.3%) had low-risk ELF score and 99 (64.7%) had low-risk TE-LSM. A moderate or high risk of advanced fibrosis was observed in 151 (98.7%) participants using the ELF test, and 54 (35.3%) participants using the TE-LSM. In the 5 participants with high risk of advanced fibrosis based on the FIB-4 score, all 5 (100%) had moderate or high risk of advanced fibrosis on the ELF test, and 3 (60.0%) had a moderate or high risk on the TE-LSM. These data are presented in Figure 5.7.

Figure 5.6: The application of sequential non-invasive tests to the study cohort



Application of the proposed MASLD screening algorithm. Abbreviations: *CV* cardiovascular; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *TE* transient elastography.

Figure 5.7: Risk of advanced hepatic fibrosis on the enhanced liver fibrosis test or transient elastography in those with low or high-risk fibrosis-4 score

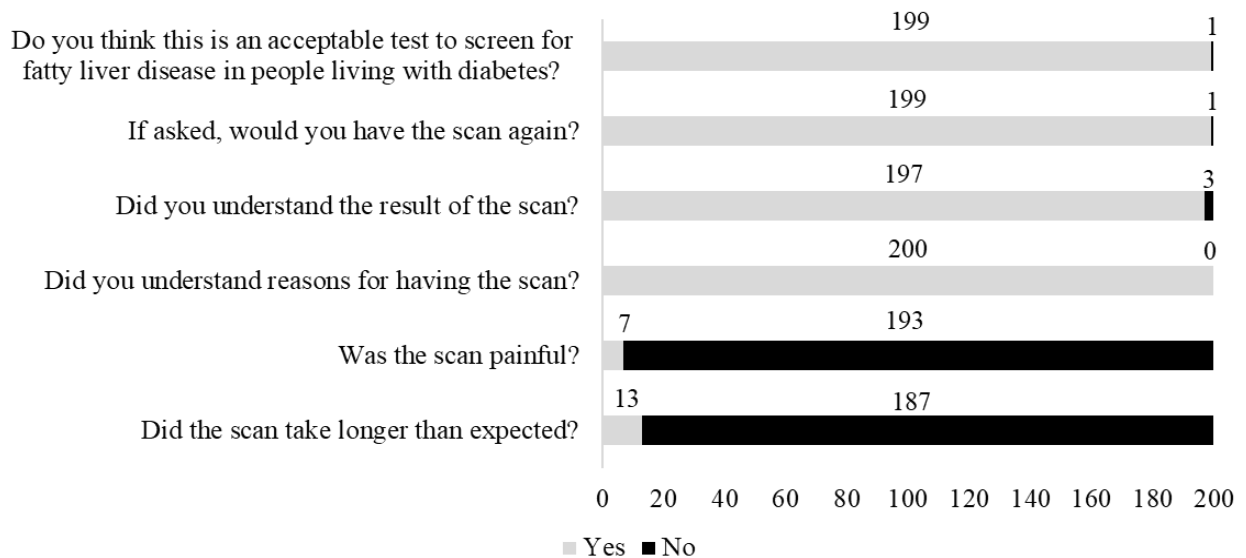


Risk of advanced fibrosis using the ELF test and TE-LSM in people with T2D and (a) low-risk (<1.30) or (b) high-risk (≥2.67) FIB-4 score on screening. Abbreviations: *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *TE* transient elastography.

5.4.6 Participant acceptability of using transient elastography to screen for MASLD and advanced hepatic fibrosis in people treated for type 2 diabetes

Following TE, participants were given a general feedback form to complete. Feedback was provided by all 200 (100%) participants. All 200 (100%) participants reported they understood the reasons for having the scan, and 199 (99.5%) participants reported they would have the scan again if needed and that this is an acceptable test to screen for MASLD in people with T2D. The result was understood by 197 (98.5%) participants. However, 7 (3.5%) reported that the scan was painful, and 13 (6.5%) reported the scan took longer than expected. These results are presented in Figure 5.8.

Figure 5.8: Participant feedback following MASLD screening



A stacked bar chart presenting participant feedback about using TE. Black colour indicates a response of “No”, and the grey colour indicates a response of “Yes”.

5.5 Discussion

In this chapter, I presented the results of a pilot study undertaken in Swansea to screen for MASLD and advanced fibrosis in people with T2D managed under secondary care diabetes services. The prevalence of MASLD and advanced fibrosis based on non-invasive tests was presented, and these data were applied to a screening algorithm proposed by international consensus guidelines for MASLD in people with T2D. Finally, I reported on participant acceptability of TE in this pilot study.

5.5.1 Risk of clinically significant hepatic steatosis

Using the HSI, NAFLD-LFS, and TyG, at least 87.2% of the cohort had moderate or high risk for severe hepatic steatosis. Using the TE-CAP, 40.5% and 22.5% had severe or moderate hepatic steatosis, respectively. Given the criteria used to diagnose MASLD, and the inclusion criteria for this study, 63.0% of this cohort were diagnosed with MASLD given these findings. The risk of severe steatosis was greater in those with a higher BMI; observed in 64.9% of participants with a BMI >35.0 kg/m² and 14.5% of participants with BMI <30.0 kg/m².

The global prevalence of MASLD in people with T2D is 65.3%, and in Western Europe the estimated prevalence is 68.6% (Younossi, Golabi, et al., 2024). In other pilot studies exploring the proportion of people with T2D with MASLD using non-invasive tests, 67.0-83.6% had hepatic steatosis using TE (Forlano et al., 2024; Martinez-Ortega et al., 2022; Mikolasevic et al., 2020), and 65% have MASLD on MRI-PDFF (Ajmera, Cepin, et al., 2022; Doycheva et al., 2016). Only one of these studies used blood biomarkers for steatosis, observing 93.2% of people with T2D were identified at high-risk using the HSI (Martinez-Ortega et al., 2022). Therefore, the results in this chapter are consistent with previous, given 63.0% had a TE-CAP consistent with moderate-severe hepatic steatosis, and 93.9% were at high-risk of steatosis using the HSI. Though, in these previous studies using the TE-CAP, different test thresholds were used to define hepatic steatosis (TE-CAP score ≥ 238 dB/m, and ≥ 266 dB/m), whilst in this cohort, a threshold ≥ 302 dB/m was used in keeping with the manufacturer suggestion.

There are similar observations about the impact of obesity on MASLD prevalence. Obesity is a major risk factor for hepatic steatosis, and previous meta-analysis estimate around 75% of people with obesity have MASLD (Quek et al., 2023). In this cohort, prevalence of moderate-severe steatosis on TE in those with a BMI >35.0 kg/m² was 82.5%, in those with BMI 30.0-35.0 kg/m² was 71.4%, and in participants with BMI <30.0 kg/m² it was 32.2%. This highlights the impact of obesity. Nonetheless, the TE-CAP may over-predict the risk of hepatic steatosis

in those with obesity, leading to false positives (Cao et al., 2022). However, blood biomarkers did increase concurrently with BMI and the previous literature support these findings. Discussion on accuracy is limited in the absence of liver biopsy data.

People with more recently diagnosed T2D had a lower median NAFLD-LFS, but similar TyG, HSI, and TE-CAP. The likeliest explanation for the difference in NAFLD-LFS is that people with more recent T2D will likely have lesser insulin resistance than those with longer duration, and therefore they will have a lower fasting insulin concentration reducing the NAFLD-LFS score given its inclusion in the algorithm. It seems hepatic fat is similar in these groups given the other results, including similar TE-CAP. A previous study observed a lesser duration of T2D was an independent predictor of hepatic steatosis (Williamson et al., 2011) which conflict with the results presented here. However, this study used B-mode ultrasound to define the stage of hepatic steatosis, which differed from the use of TE-CAP in this study. In any case, the high prevalence of hepatic steatosis means that in practice its presence can be assumed and efforts are best focussed on the identification of hepatic fibrosis.

5.5.2 Risk of clinically significant hepatic fibrosis

The APRI, AST:ALT ratio, BARD score, ELF test, FIB-4 score, and NFS were calculated in the cohort, achieving valid results in at least 197 (98.5%) participants. Some tests better discriminated the risk of advanced fibrosis. The AST:ALT ratio, BARD score, ELF test and NFS identified 62.1%, 94.4%, 99.0%, and 74.2% at moderate or high-risk of advanced fibrosis, requiring most to undergo further evaluation. Conversely, the APRI and FIB-4 score identified 3.0% and 22.7% of participants at moderate or high-risk of advanced fibrosis, respectively. The median BARD and NFS scores both increased in association with increasing stages of BMI as expected given the inclusion of BMI in their calculation, but not any other blood biomarker for fibrosis. Similarly, the TE-LSM increased significantly with increasing BMI in this cohort.

Previously, the NFS overestimated the proportion of people with T2D or obesity at risk of advanced fibrosis (McPherson et al., 2017; Qadri et al., 2022), leading to excess referrals. The increase in the NFS in this study cohort may relate to the inclusion of T2D in NFS calculation. Similar to the NFS, isolated use of the ELF test may lead to excess referrals given its low PPV in other studies (Vali et al., 2020). This reflects in our population, given 74.2% and 99.0% had at least moderate risk of advanced fibrosis using the cut-offs proposed in recent guidelines with the NFS and ELF test, respectively. This is surprising as the ELF test is often considered a measure of fibrosis, compared to the other blood biomarkers, given it measures biomarkers

associate with fibrogenesis and tissue remodelling. Likewise, the increasing trend in the ELF test score with increasing BMI seemed consistent with the TE-LSM, though the statistical trend for the ELF test score with increasing BMI failed to reach significance. Neither test is recommended first-line, and the ELF test is suggested second-line in those with indeterminate FIB-4 score (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Similar observations were observed in previous prospective studies screening for advanced fibrosis using non-invasive tests in people with T2D. One study in people with T2D found the NFS led to 67.8% and 20.3% with moderate or high-risk of advanced fibrosis, so the majority required further evaluation. On the other hand, the FIB-4 score better discriminated risk as 20.2% and 1.9% had moderate or high-risk of advanced fibrosis (Martinez-Ortega et al., 2022). The results presented in this chapter observed 20.2% and 2.5% had moderate and high-risk of advanced fibrosis using the FIB-4 score, consistent with the previous study. However, the FIB-4 score seemed to perform relatively poorly compared with the results presented from study 1 in chapter three and chapter four. Though previous studies and this study demonstrate a lesser proportion of patients with T2D required further evaluation using the FIB-4 score than with other blood biomarkers, suggesting it is more feasible to implement into practice.

The BARD score inevitably leads to referring most patients in this cohort because all patients have T2D and their mean BMI was 33.3 kg/m^2 , meaning most scored at least two points. This also explains the trend in increasing BARD score (and NFS) in those with a BMI $>30.0 \text{ kg/m}^2$. Moreover, the other variable of AST:ALT ratio, which if >0.8 gives two additional points, meant 123 (62.1%) participants would be referred using this test alone. The BARD score was designed to screen for MASLD fibrosis in the general population, so application in this group is limited. Previous studies highlight the AST:ALT ratio is not reliable alone to predict advanced fibrosis, given the test has poor PPV (Ciardullo et al., 2020; McPherson et al., 2010). In contrast, the APRI probably underestimated advanced fibrosis in this group given six (3.0%) participants would be identified using this approach. Previous studies trialling screening tests for advanced fibrosis in people with T2D did not report the APRI, but earlier publications highlight mixed findings around its accuracy (Siddiqui et al., 2019; Wu et al., 2021), and this test is not recommended. In practice, it would be essential to have a first test with good NPV to minimise the risk of a high number of false negative results that would be lost to evaluation.

Using the TE-LSM, 12.5% and 23.0% of this cohort had moderate ($\geq F2$, 8.2 kPa) or advanced ($\geq F3$, 9.7 kPa) fibrosis. Previous studies in T2D reported 39.5% with TE-LSM $\geq 7.0 \text{ kPa}$ (Mikolasevic et al., 2020), 35.3% with TE-LSM $\geq 8.0 \text{ kPa}$ (Martinez-Ortega et al., 2022), and

17.8% with TE-LSM ≥ 8.2 kPa (Forlano et al., 2024). The proportion in this cohort is similar at 35.5%, using a threshold ≥ 8.2 kPa. The study reporting least prevalence of fibrosis at 17.8% was in primary care, which used similar methods to evaluate MASLD as in this study, but included participants at an earlier stage of T2D, lower BMI, and better glycaemic control than this cohort. In this study, there was a significantly greater median TE-LSM in participants with a BMI >35.0 kg/m² (8.5 kPa) compared to participants with BMI 30.0-35.0 kg/m² (6.2 kPa) or <30.0 kg/m² (6.2 kPa), and greater prevalence of moderate-advanced fibrosis in participants with greater obesity. The lack of linear relationship between advanced fibrosis on TE-LSM with BMI is difficult to explain, and may related to the need for greater participant numbers, or differences in other risk factors such as other metabolic comorbidities, degree of glycaemic control, age or other confounders. There was greater prevalence of moderate-advanced fibrosis in this study compared to a previous meta-analysis (Quek et al., 2023), but the study presented in this chapter included only people with T2D, whilst the meta-analysis included studies with variable populations and limited information on the proportion living with T2D.

A greater duration of T2D diagnosis associated with greater scores for all the observed blood biomarkers for hepatic fibrosis, except the APRI, with no significant difference between the median TE-LSM scores between groups. As there was a greater median age in the group with longer T2D duration, the greater FIB-4 score and NFS are unsurprising given they include age in their calculation. Whilst, the greater AST:ALT ratio in those with greater T2D duration explains the greater BARD score also between groups, a difference of 0.1 between groups is of questionable clinical significance in practice. Nonetheless, the median ELF test score was greater in those with longer T2D duration indicating there may be greater hepatic fibrosis in this group. Previous studies consistently demonstrate longer T2D duration associates with the risk of advanced hepatic fibrosis (Martinez-Sanchez et al., 2025; Naskar et al., 2024)

5.5.3 Application of a sequential testing algorithm in this cohort

Data were applied to the screening algorithm proposed in recent guidelines to determine the proportion of participants who require hepatology referral. This is because use of the FIB-4 score alone is insufficient to diagnose MASLD and intermediary tests are needed. Using the FIB-4 score followed by an ELF test result ≥ 7.7 as recommended internationally, all 45 (100%) participants identified at moderate or high-risk by the FIB-4 score would require referral, though its utility to discriminate risk was improved through use of higher thresholds. This suggests the ELF test is not a useful intermediary investigation as recommended. On the other hand, using the FIB-4 score followed by TE-LSM >8.0 kPa resulted in 21 (10.6%) participants

in the total cohort requiring referral. This is reassuring, and demonstrates the benefits of using TE as the intermediary test, and is consistent with the findings presented in chapter three in which TE had good specificity for advanced fibrosis. Using different ELF test and TE-LSM scores as recommended by various agencies is confusing when considering factors such as cost, workforce planning and test accuracy. We decided *a priori* to refer participants with an ELF test ≥ 10.51 because this is the NICE recommendation (NICE, 2016), or a TE-LSM of ≥ 9.7 kPa because this is consistent with advanced ($\geq F3$) fibrosis according to the manufacturer. When developing the protocol, guidelines on MASLD were not published. Using the referral thresholds in the original protocol, 20 (10.1%) and 46 (23.0%) participants required referral using the ELF test and TE-LSM, respectively, shown in Table 5.3. Considering some met both criteria, 51 (25.5%) participants were referred to the hepatology team.

The ELF test poorly discriminated risk in this cohort, and most participants had a “moderate risk” score. However, if screening process utilised the higher cut-off scores in international guidelines or as suggested by NICE, the numbers requiring referral would be more manageable. When used as suggested, the ELF test was limited as a second-line investigation as it did not discriminate risk in those with intermediate FIB-4 scores as only 2 (1.0%) participants had a low-risk score in the whole cohort. A previous study reported that using an ELF test threshold of ≥ 9.5 in people with SLD identified at intermediate risk of advanced fibrosis using the FIB-4 score reduced unnecessary referrals by 80% (Srivastava, Gailer, et al., 2019). We had considered utilising a similar approach as by Srivastava and colleagues, but took a broader approach to testing to further determine test consistency as described in chapter six. Given the lack of biopsy data in our study, comment on accuracy is limited. The concerning observation is of those with a normal FIB-4 score, 151 (98.7%) and 54 (35.3%) participants had moderate or high-risk of advanced fibrosis using the ELF test and TE-LSM, respectively, raising concern about possible false negative results with the FIB-4 score. Further analysis to determine the consistency between blood biomarkers and the TE-LSM is presented in chapter six.

5.5.4 Acceptability of TE to screen for MASLD and advanced fibrosis

Following the screening tests we sought participant feedback to determine whether TE was an acceptable test to screen for MASLD and advanced fibrosis. The test was acceptable to most, given 99.5% reported it was an acceptable test to screen for MASLD and would have it again. The scan did take longer than anticipated in 6.5% of participants. Indeed, TE can be technically challenging, especially in those with central obesity. However, there was no significant difference in the BMI of those reporting it took longer than expected compared to those who

did not (34.1 vs 33.2 kg/m², $p=0.64$). Likewise, 7 (3.5%) participants reported the scan was painful, but only 1 (0.5%) participant reported they would not have the scan again. These are reassuring outcomes, given that people with T2D already undergo extensive annual screening tests as part of their routine care, and those with T2D managed in secondary care services often require more frequent hospital appointments.

A previous qualitative study reported most participants felt that targeted screening using TE is appropriate. Feedback from semi-structured interviews of 14 users of a screening programme in Bristol highlighted the key features include motivation for engagement, experience of the screening service, and potential impact for tests to support lifestyle changes (Archer et al., 2024). Another study interviewed 20 adults who underwent TE as part of a study to screen for CLD in people with risk factors, including T2D, to determine their experience. Participants reported TE improved their understanding of their risk for CLD and supported contemplation of lifestyle changes to minimise risk (Knight et al., 2020). The use of TE to screen for and monitor CLD is generally acceptable across different causes of CLD (Marshall et al., 2015; Matthews et al., 2019), though I am unaware of previous studies reporting similar quantitative measures as presented in this cohort. Interestingly, no previous study has explored the acceptability of the ELF test compared to TE, which may be of interest given the relative ease of taking a blood test compared with the immediate feedback from TE.

The feedback presented in this chapter are limited to a binary “Yes” or “No” response to indicate general acceptability. Further evaluation using a qualitative study in people with T2D or other metabolic risk factors would be of interest. This would likely gain further information on the participants’ experiences and may identify additional themes of interest.

5.6 Summary and limitations

This pilot study demonstrated that undertaking targeted testing for MASLD and advanced fibrosis in people with T2D attending secondary care is feasible, as 97.5% of participants had valid blood biomarker results, and 100% had valid TE. Through application of these data into recommended protocols, 21-45 (10.6-22.7%) participants would require hepatology referral. The proportion of people with T2D referred from secondary care may be greater than in primary care, given this cohorts characteristics. The tests used were acceptable to most participants. Further work to implement a strategy to identify people with T2D and earlier stages of liver disease, and pathways to manage those with signs of liver disease such as deranged LFTs would be of major interest locally, at least.

5.6.1 Clinical significance

As clinicians practising in diabetes, it is important to be aware that almost two-thirds of this secondary care T2D cohort have at least moderate hepatic steatosis, because it highlights the proportion who may benefit from specific pharmacotherapies. Only 5.5% were prescribed pioglitazone, 41.0% prescribed a GLP-1RA, and 51.0% prescribed a SGLT-2 inhibitor, which suggests missed treatment potential in those who have significant hepatic steatosis. Over a third of the cohort had a TE-LSM consistent with at least F2 fibrosis, and a quarter consistent with advanced fibrosis. This latter group may benefit from multidisciplinary input to minimise CVD risk and liver-related morbidity and mortality. Whilst the prevalence of biopsy-confirmed MASLD and advanced fibrosis is established; the workability of a targeted testing process is less known. This study demonstrates this is feasible, and acceptable to people with T2D under secondary care in Swansea, at least. Following this, discussions with hepatologists locally and nationally may support targeted testing strategies to support clinicians in diabetes and primary care to best manage patients with T2D and liver disease in Wales.

5.6.2 Limitations

There are some limitations to this study:

- There may be case ascertainment bias in those who agreed to participate:
 - No data were collected about participants who declined to take part, so analysis to compare characteristics of those who did or did not participate is impossible.
 - There was unequal representation of participants included from different hospital sites, and practice may vary between hospital sites.
- There is no liver biopsy data to support discussion on the accuracy of the non-invasive tests used in this study cohort.
- Participant feedback was limited to the binary responses presented, and a further qualitative study to explore participant experience would be useful.
- The study only included people with T2D under secondary care services, and so these data cannot be generalised to patients with T2D managed in primary care. Though there are previous studies in primary care referenced in the discussion.
- Waist circumference was not measured, so the FLI could not be calculated.

Chapter Six:

**Predictors of MASLD and advanced
fibrosis in people with T2D attending
secondary care**

6.1 Introduction

The most accurate non-invasive investigation for MASLD and advanced fibrosis is TE (Mozes et al., 2022), though this is impractical given the need for additional appointments, staffing and time to perform the test. Targeted testing is best taken using blood biomarkers given their ease to introduce in pre-existing programmes (Williams, Nagaraj, et al., 2025). Guidelines advocate the FIB-4 test first-line, given it is cheap and accessible (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). There are numerous blood biomarkers available to screen for hepatic steatosis, or advanced fibrosis as discussed in chapter one. There are some concerns around the reliability of these biomarkers to predict liver disease, and the impact of T2D (Bertot et al., 2018; Boursier et al., 2023; Chung et al., 2023), obesity (Alqahtani et al., 2021; de Carli et al., 2020; Drolz et al., 2021) or advancing age (McPherson et al., 2017) on their accuracy.

Clinical features which indicate IR may also signal those at greater risk of advanced fibrosis, and the risk of advanced fibrosis increases with the number of metabolic syndrome features (Jinjuvadia et al., 2017; Younossi, Koenig, et al., 2016). The impact of IR on the development of MASLD is reflected in the NAFLD-LFS, which uses the fasting insulin level to predict hepatic steatosis (Cheung et al., 2014; Jung et al., 2020). Given the difficulty of obtaining a fasting insulin level, the score is rarely used in practice, but it is of clinical interest to further investigate whether IR predicts hepatic steatosis or fibrosis. Given declining serum C-peptide is observed in patients with advancing T2D (Lin et al., 2025), and greater C-peptide associates with the glycaemic response to GLP-1RA (Jones et al., 2016), it is of interest to determine whether serum C-peptide levels can predict liver disease in people with T2D.

In this chapter, I explore the consistency of clinical and biochemical predictors of hepatic steatosis and advanced hepatic fibrosis compared with TE in people with T2D.

6.2 Aims of this chapter

The specific aims of this chapter are to explore the:

- i. usefulness of simple liver enzymes to predict hepatic steatosis or advanced fibrosis in people with T2D.
- ii. accuracy of blood biomarkers to predict hepatic steatosis in people with T2D.
- iii. accuracy of blood biomarkers to predict advanced fibrosis in people with T2D.
- iv. use of the number of metabolic syndrome features to predict hepatic steatosis or advanced fibrosis in people with T2D.
- v. use of IR measures to predict hepatic steatosis or advanced fibrosis in people with T2D.

6.3 Methods

6.3.1 Study design

The design of this pilot study was detailed in chapter two. The study aimed to pilot the use of non-invasive tests for MASLD and advanced fibrosis in people with T2D under secondary care diabetes services in SBUHB attending their routine diabetes clinic. The additional tests taken were summarised in chapter two. Those identified with a TE-LSM ≥ 9.7 kPa or ELF test ≥ 10.51 were referred to hepatology. Data were collected from October 2023-July 2024.

6.3.2 Participants

Participants were adults with a clinical diagnosis of T2D managed in hospital-based diabetes services in SBUHB. Those with other forms of diabetes, or risk factors for other forms of liver disease were excluded. The inclusion and exclusion criteria were detailed in Table 2.3.

6.3.3 Data collection

All data were collected during the participants' appointment. Blood biomarkers for hepatic steatosis (HSI, NAFLD-LFS, TyG), hepatic fibrosis (APRI, AST/ALT, BARD score, ELF test, FIB4, NFS), and IR (HOMA-IR) were calculated. Presence of each metabolic syndrome feature was determined using criteria in Table 2.4, and the metabolic syndrome was diagnosed if a participant had ≥ 3 features. During the appointment, TE was performed by myself using the manufacturer protocol, and information about this was described in chapter two. Moderate-to-severe hepatic steatosis was defined as TE-CAP ≥ 302 dB/m ($\geq$ stage 1), and advanced fibrosis (stage 3-4) was defined as TE-LSM ≥ 9.7 kPa. Thresholds for TE were shown in Table 2.7.

6.3.4 Funding and ethical approval

No additional funding was received to undertake the study. The study protocol was approved by the HRA and HCRW [IRAS ID: 326341] and participant recruitment in SBUHB was approved in October 2023. This was detailed in chapter two.

6.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were prepared using Microsoft Excel for Microsoft 365 (version 2503), or SPSS (version 29). Data presentation was described in chapter two. The sensitivity, specificity, PPV, and NPV of each test were calculated using the formulas in Table 2.2 and thresholds in Table 2.6. To investigate the use of liver enzymes, an abnormal enzyme titre was deemed greater than or equal to the upper limit of normal using the local reference standard, for ALT (≥ 33 U/L), AST

(≥ 32 U/L), and GGT (≥ 40 U/L in females, ≥ 60 U/L in males). Spearman's rank correlation was used to correlate parametric or non-parametric data with non-parametric data. Linear regression was performed to evaluate associations between the presence of metabolic syndrome features and presence of hepatic steatosis or advanced fibrosis.

A ROC analysis was performed to determine the utility of liver enzymes, blood biomarkers or measures of IR to identify hepatic steatosis, or advanced fibrosis. The statistical significance of differences between the AUC for the same biomarker in people with a BMI greater or lesser than the cohort mean was determined by t-test. The optimal screening cut-off to identify hepatic steatosis or advanced fibrosis was determined by Youden's index. The ROC analysis was described in detail in chapter two.

6.4 Results

6.4.1 Participant characteristics

Two-hundred participants are included in the analysis. Their characteristics were presented in Table 5.1 and Table 5.2. Overall, 126 (63.0%) participants had a TE-CAP score indicating moderate-severe hepatic steatosis, and 46 (23.0%) participants had a TE-LSM indicating advanced fibrosis. These TE data were presented in Table 5.4.

6.4.2 Usefulness of simple liver enzymes to predict hepatic steatosis or advanced fibrosis in people with type 2 diabetes

The utility of liver enzymes to identify hepatic steatosis or advanced fibrosis is shown in Table 6.1. Of the 126 (63.0%) participants with moderate-severe steatosis on TE, 88 (69.4%), 105 (83.3%), and 92 (73.0%) had a normal ALT, AST and GGT, respectively. Of the 46 (23.0%) participants with advanced fibrosis on TE, 32 (69.6%), 36 (78.2%), and 26 (56.5%) had a normal ALT, AST, and GGT, respectively.

There was statistical correlation between the TE-CAP and ALT ($r=0.25$, $p<0.001$) and AST ($r=0.17$, $p<0.05$), but not GGT ($r=0.09$, $p=0.20$). There was statistical correlation between the TE-LSM and ALT ($r=0.24$, $p<0.001$), AST ($r=0.28$, $p<0.001$), and GGT ($r=0.43$, $p<0.001$). These data are shown in Figure 6.1.

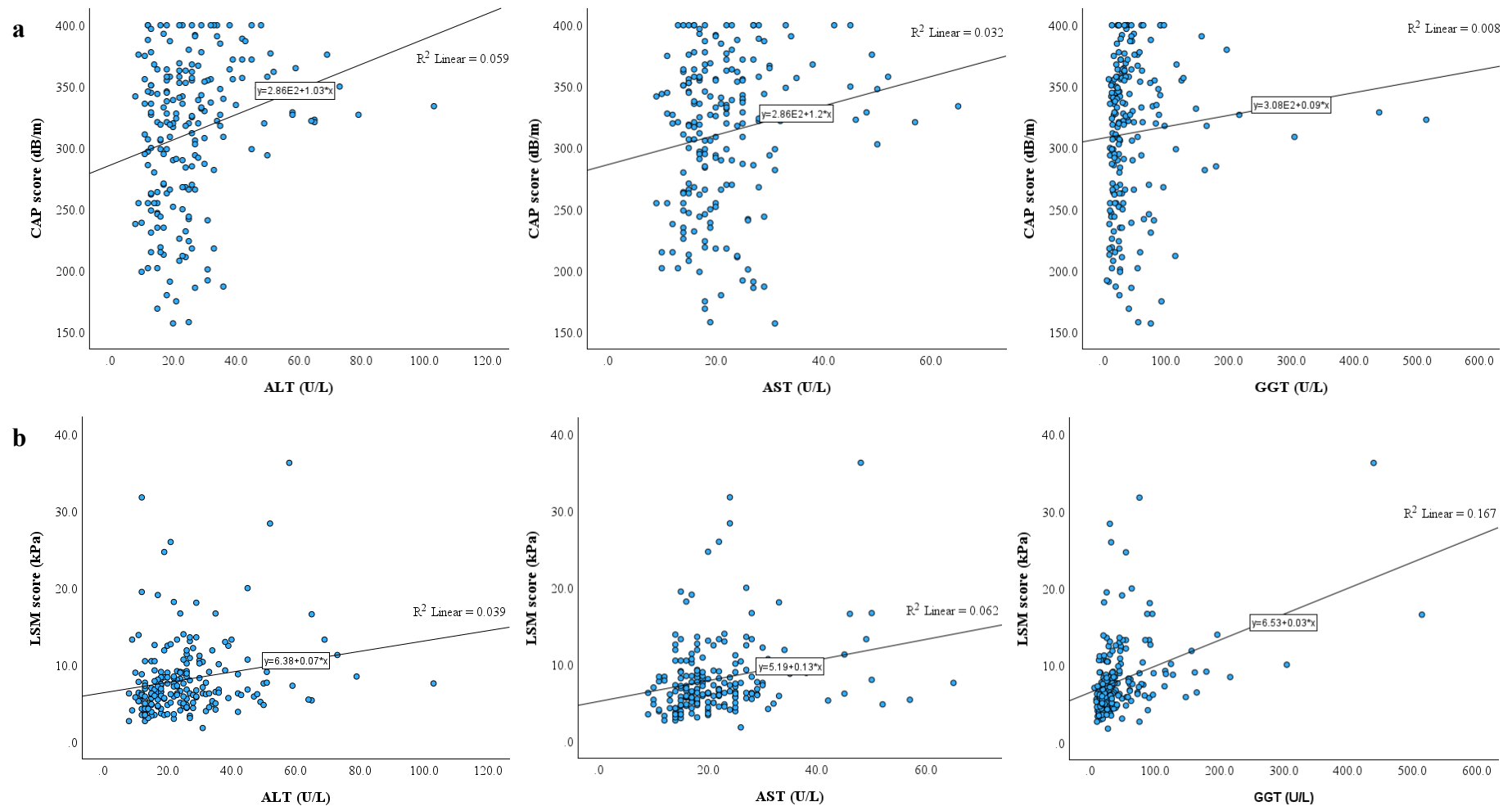
On the ROC analysis, each liver enzyme had significantly greater AUC to predict moderate-severe hepatic steatosis or advanced fibrosis. These data are shown in Table 6.2 and Figure 6.2.

Table 6.1: Accuracy of liver enzymes to identify hepatic steatosis or advanced fibrosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hepatic steatosis				
ALT	30.2 [22.6-38.5]	93.2 [86.0-97.5]	88.4 [76.7-95.7]	43.9 [36.3-51.8]
AST	15.3 [9.7-22.3]	100.0	100.0	41.3 [34.3-48.6]
GGT	27.0 [19.7-35.1]	77.0 [66.6-85.6]	66.7 [53.1-78.6]	38.3 [30.7-46.2]
Advanced hepatic fibrosis				
ALT	30.4 [18.5-44.5]	81.2 [74.5-86.8]	32.6 [19.9-47.3]	79.6 [72.9-85.4]
AST	20.0 [10.2-33.2]	93.5 [88.8-96.7]	47.4 [26.3-69.1]	79.9 [73.6-85.3]
GGT	43.5 [29.8-57.9]	79.9 [73.1-85.7]	39.2 [26.6-52.9]	82.6 [75.9-88.1]

The accuracy of the ALT, AST and GGT to identify moderate-severe hepatic steatosis or advanced fibrosis, presented by the percentage [95% CI]. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *GGT* gamma-glutamyl transferase; *PPV* positive predictive value; *NPV* negative predictive value.

Figure 6.1: Correlations between simple liver enzymes and transient elastography measures of hepatic steatosis or hepatic fibrosis



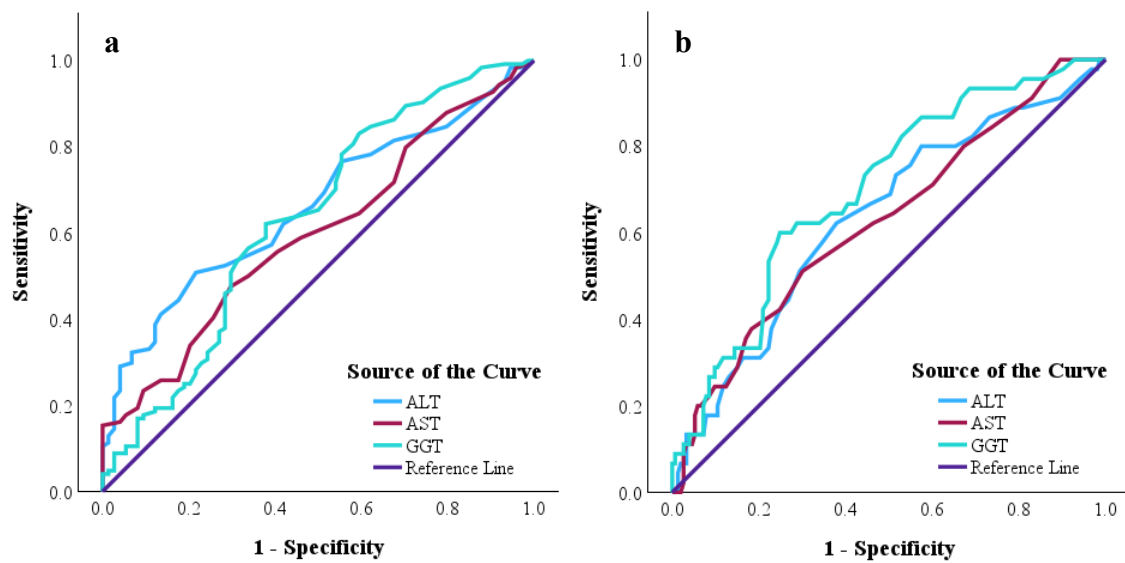
Scatter plots with line of best fit for the ALT, AST, and GGT with (a) TE-CAP and (b) TE-LSM. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *CAP* controlled attenuation parameter; *GGT* gamma-glutamyl transferase; *LSM* liver stiffness measure

Table 6.2: Receiver operating characteristic analysis to identify moderate-severe hepatic steatosis or advanced fibrosis using simple liver enzymes

Group	Test	AUC	95% CI	P (null)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Hepatic steatosis	ALT	0.66	0.59-0.74	<0.001	0.29	25.5 U/L	50.8	78.4
	AST	0.60	0.52-0.68	<0.05	0.18	21.5 U/L	47.6	70.3
	GGT	0.63	0.55-0.72	<0.01	0.24	19.5 U/L	83.1	40.5
Advanced hepatic fibrosis	ALT	0.63	0.54-0.73	<0.01	0.24	24.5 U/L	62.2	62.1
	AST	0.63	0.53-0.72	<0.01	0.21	22.5 U/L	51.1	59.9
	GGT	0.70	0.62-0.78	<0.01	0.35	42.5 U/L	60.0	75.2

The ROC analysis for liver enzymes to predict moderate-severe hepatic steatosis or advanced fibrosis. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *AUC* area under the curve; *CI* confidence interval; *GGT* gamma-glutamyl transferase.

Figure 6.2: Receiver operating characteristic curves for moderate-severe hepatic steatosis or advanced fibrosis using liver enzymes



The ROC curves for liver enzymes to predict (a) moderate-severe hepatic steatosis or (b) advanced fibrosis. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *GGT* gamma-glutamyl transferase

6.4.3 Accuracy of blood biomarkers to predict hepatic steatosis in people with type 2 diabetes

The utility of blood biomarkers to identify hepatic steatosis is presented in Table 6.3. Each biomarker correlated with the TE-CAP; HSI ($r=0.51$, $p<0.001$), NAFLD-LFS ($r=0.42$, $p<0.001$), and TyG ($r=0.27$, $p<0.001$). These data are presented in Figure 6.3.

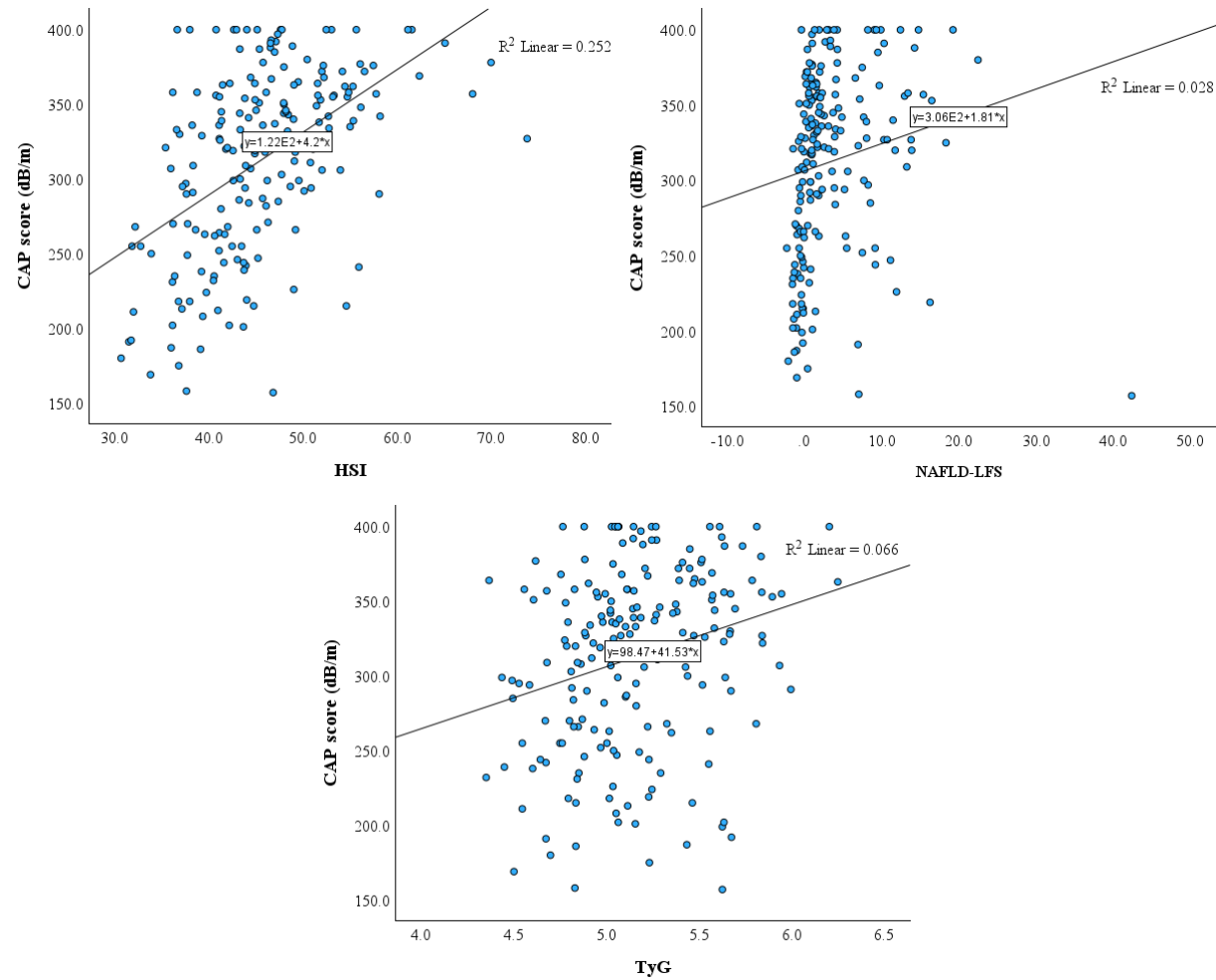
In the ROC analysis, each biomarker had a significant AUC to predict moderate-severe hepatic steatosis. There was no significant difference in the AUC to predict hepatic steatosis in those with a BMI above or below the cohort mean using the HSI or NAFLD-LFS. The AUC for the TyG to predict hepatic steatosis in those with BMI >33.3 kg/m² was like the null hypothesis, and lower than participants with leaner BMI. Data are presented in Table 6.4 and Figure 6.4.

Table 6.3: Accuracy of blood biomarkers to identify hepatic steatosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
HSI	100.0	0.0	37.1 [30.5-43.9]	0.0
NAFLD-LFS	96.7 [92.6-99.0]	30.6 [20.7-41.7]	70.4 [63.3-77.0]	84.6 [67.8-94.9]
TyG	99.2 [96.5-100]	1.4 [0.1-5.9]	63.3 [56.4-69.8]	50.0 [3.8-96.2]

Accuracy of biomarkers to identify hepatic steatosis, presented by the percentage [95% CI]. Abbreviations: *HSI* hepatic steatosis index; *NAFLD-LFS* non-alcoholic fatty liver disease-liver fat score; *NPV* negative predictive value; *PPV* positive predictive value; *TyG* triglyceride glucose index.

Figure 6.3: Correlations between blood biomarkers and transient elastography measures of hepatic steatosis



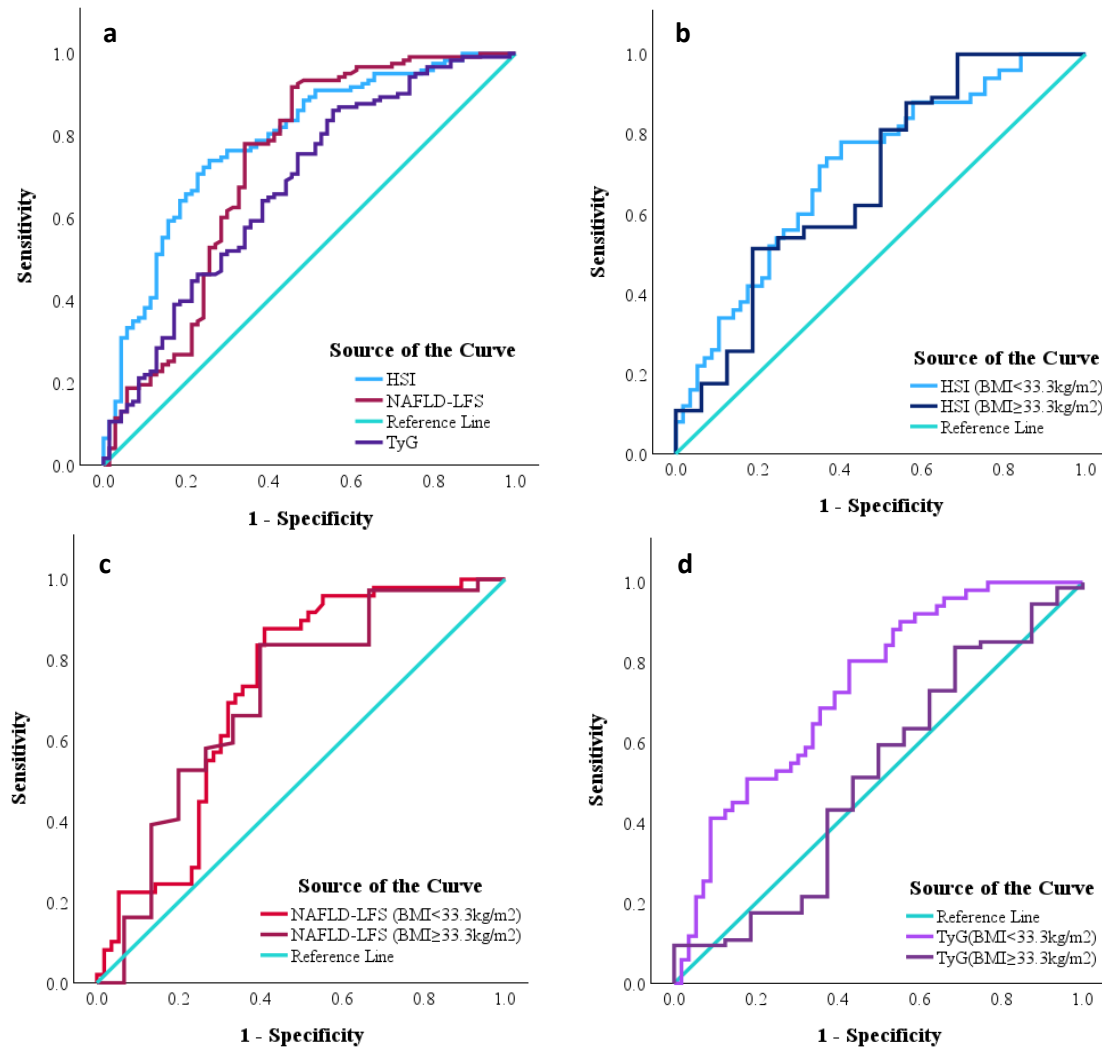
Scatter plots with the line of best fit reflecting the correlation of the HSI, NAFLD-LFS, and TyG with the TE-CAP. Abbreviations: *CAP* controlled attenuation parameter; *HSI* hepatic steatosis index; *NAFLD-LFS* non-alcoholic fatty liver disease-liver fat score; *TyG* triglyceride glucose index.

Table 6.4: Receiver operating characteristic analysis for moderate-severe hepatic steatosis using blood biomarkers

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall	HSI		0.79	0.72-0.86	<0.001		0.48	44.0	74.0	74.3
	NAFLD-LFS		0.73	0.65-0.81	<0.001	-	0.46	0.0	91.9	54.3
	TyG		0.68	0.60-0.76	<0.001		0.24	5.2	46.3	77.1
BMI status	HSI	BMI <33.3	0.71	0.61-0.81	<0.001	NS	0.38	40.7	78.0	59.6
		BMI ≥33.3	0.68	0.53-0.84	<0.05		0.31	46.9	81.1	50.0
	NAFLD-LFS	BMI <33.3	0.72	0.62-0.82	<0.001	NS	0.47	-0.08	87.8	58.9
		BMI ≥33.3	0.71	0.54-0.87	<0.05		0.44	0.86	83.8	60.0
	TyG	BMI <33.3	0.74	0.64-0.83	<0.001	<0.05	0.33	5.06	68.6	64.3
		BMI ≥33.3	0.52	0.35-0.68	NS		0.15	4.88	83.8	31.2

The ROC analysis for biomarkers to identify moderate-severe hepatic steatosis in the overall group and by BMI status. Abbreviations: *AUC* area under the curve; *BMI* body mass index; *CI* confidence interval; *HSI* hepatic steatosis index; *NAFLD-LFS* non-alcoholic fatty liver disease-liver fat score; *TyG* triglyceride glucose index.

Figure 6.4: Receiver operating characteristic curves for moderate-severe hepatic steatosis using blood biomarkers



The ROC curves for moderate-severe hepatic steatosis using blood biomarkers in (a) overall cohort and compared by BMI status using the (b) HSI, (c) NAFLD-LFS, and (d) TyG. Abbreviations: *BMI* body mass index; *HSI* hepatic steatosis index; *NAFLD-LFS* non-alcoholic fatty liver disease-liver fat score; *TyG* triglyceride glucose index.

6.4.4 Accuracy of blood biomarkers to predict advanced fibrosis in people with type 2 diabetes

The utility of the blood biomarkers to identify advanced fibrosis is presented in Table 6.5. The APRI ($r=0.29$, $p<0.001$), ELF test ($r=0.24$, $p<0.001$), FIB-4 score ($r=0.15$, $p<0.05$), and NFS ($r=0.21$, $p<0.01$) each correlated with the TE-LSM. However, there was no correlation with the AST:ALT ratio ($r=-0.07$, $p=0.30$), and BARD score ($r=0.01$, $p=0.95$) with the TE-LSM. These data are presented in Figure 6.5.

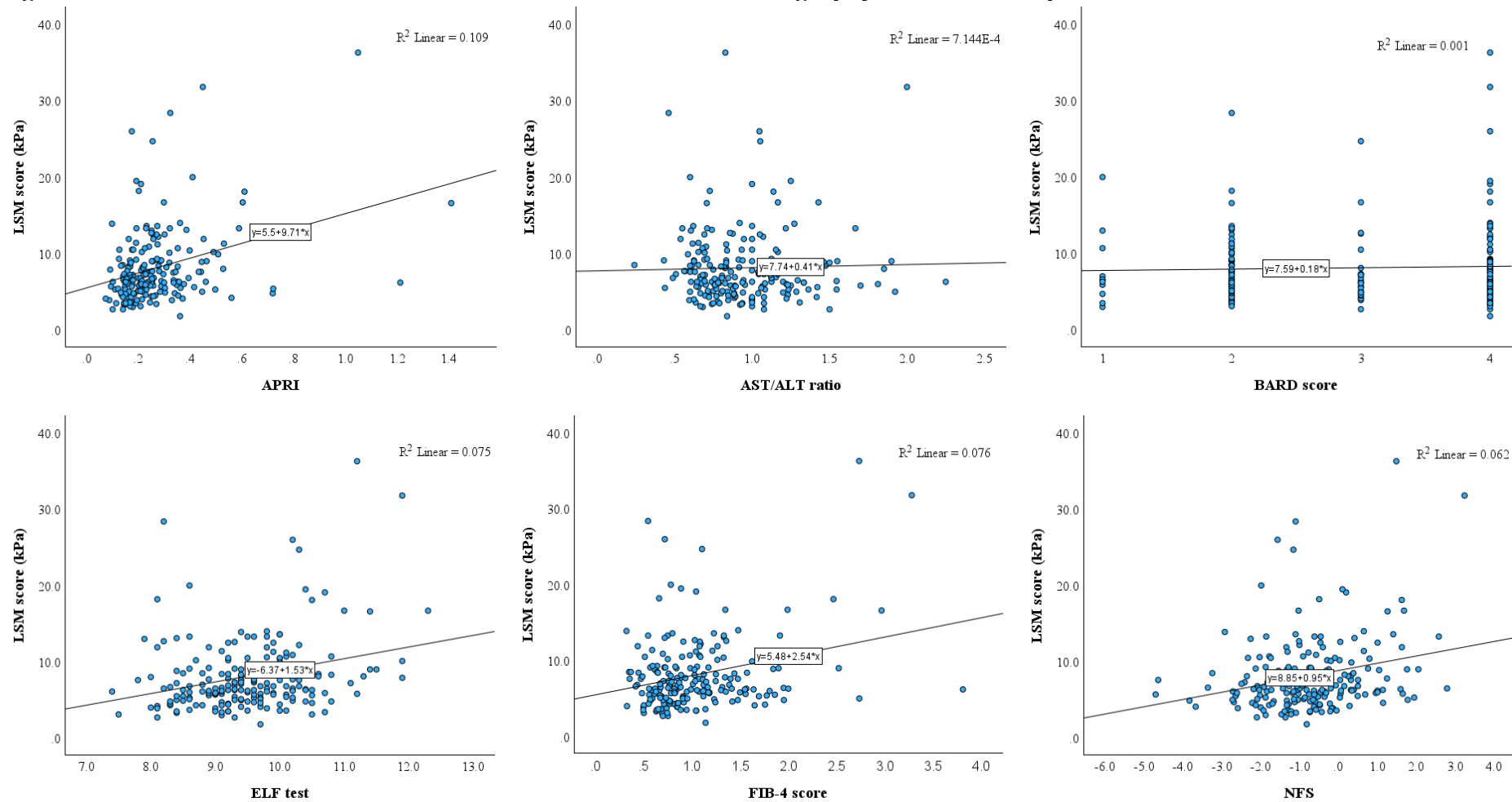
In the ROC analysis, the APRI, ELF test, FIB-4 score, and NFS each had a significant AUC to predict advanced fibrosis. Neither the AST:ALT ratio nor BARD score had a significant AUC. In the sub-analysis exploring the impact of BMI, only the APRI had significantly greater AUC compared to the null hypothesis irrespective of BMI status, whilst leaner participants had an AUC greater by chance using the FIB-4 score. Data are presented in Table 6.6 and Figure 6.6.

Table 6.5: Accuracy of blood biomarkers to identify hepatic fibrosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
APRI	4.4 [0.8-13.1]	97.4 [94.0-99.2]	33.3 [6.5-71.9]	77.6 [71.4-83.1]
AST:ALT	57.8 [43.2-71.5]	36.6 [29.2-44.4]	21.1 [14.6-28.9]	74.7 [64.1-83.6]
BARD	93.3 [83.6-98.3]	5.9 [2.9-10.4]	22.6 [17.0-28.9]	75.0 [47.2-93.1]
ELF	58.7 [44.3-72.2]	69.9 [62.4-76.8]	37.0 [26.5-48.4]	84.9 [78.0-90.4]
FIB-4	31.1 [18.9-45.4]	79.7 [72.9-85.6]	31.1 [18.9-45.4]	79.7 [72.9-85.6]
NFS	80.4 [67.5-90.1]	27.6 [20.9-35.1]	25.2 [18.6-32.6]	82.4 [70.4-91.1]

Accuracy of blood biomarkers to identify advanced fibrosis, presented by the percentage [95% CI]. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease fibrosis score; *NPV* negative predictive value; *PPV* positive predictive value.

Figure 6.5: Correlations between blood biomarkers and transient elastography measures of hepatic fibrosis



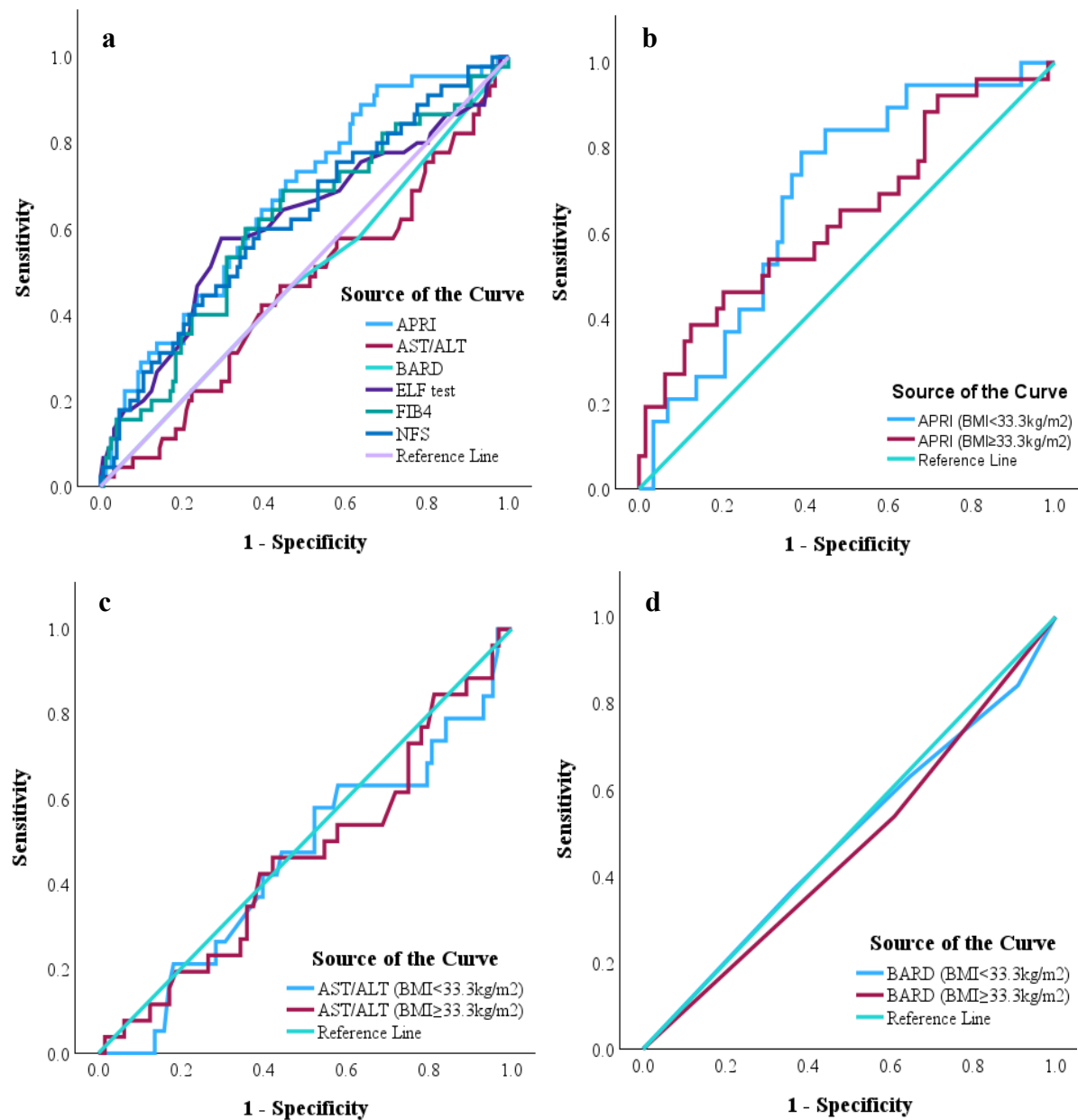
Scatter plots with line of best fit reflecting the correlation of blood biomarkers with the TE-LSM. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score.

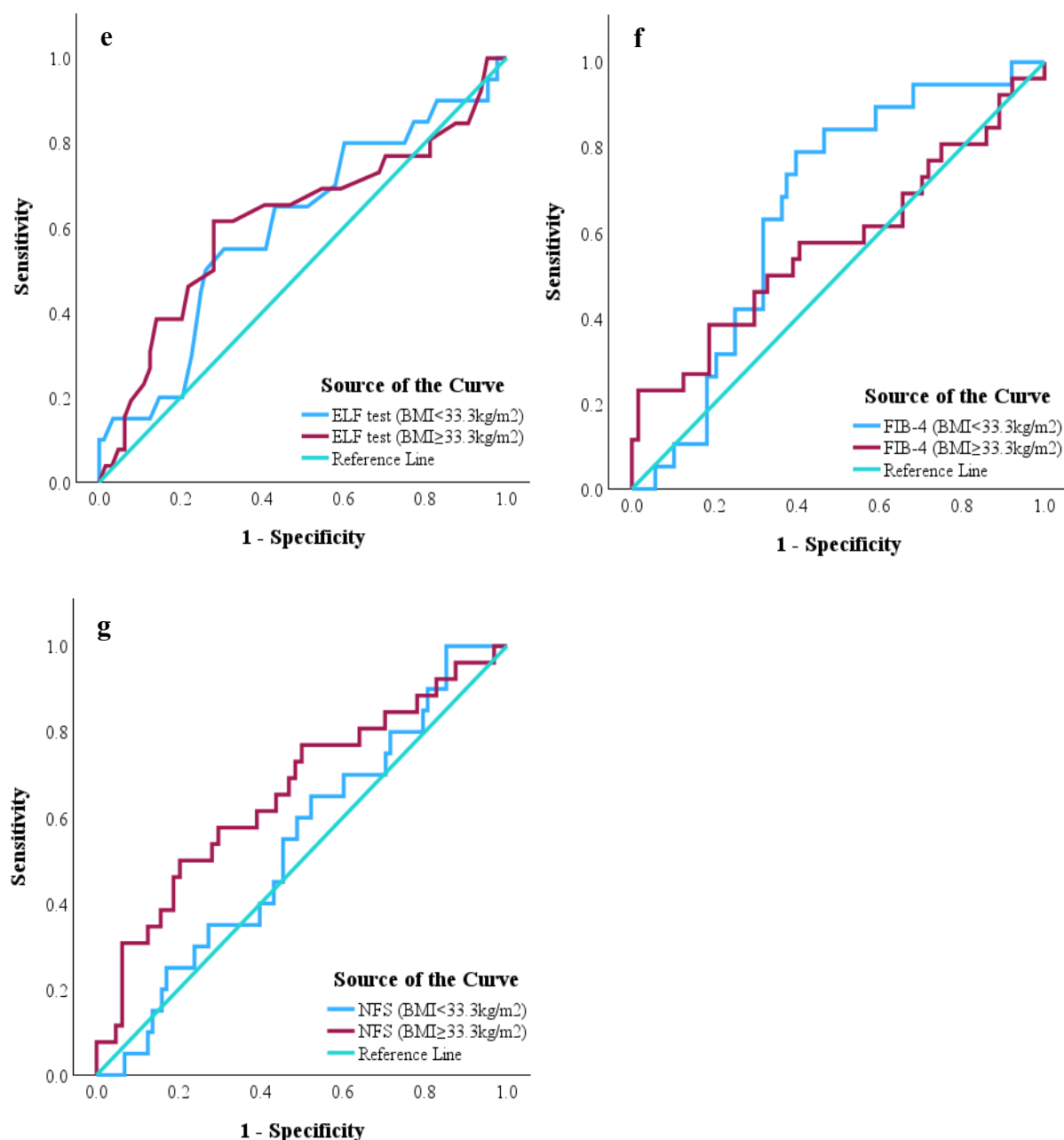
Table 6.6: Receiver operating characteristic analysis for advanced fibrosis using blood biomarkers

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall	APRI		0.67	0.58-0.76	<0.001		0.26	0.17	93.3	32.2
	AST:ALT		0.46	0.36-0.56	NS		0.03	0.92	46.7	55.9
	BARD		0.48	0.39-0.58	NS		-0.01	1.50	93.3	5.3
	ELF		0.61	0.51-0.71	<0.05	-	0.28	9.8	57.8	70.1
	FIB-4		0.61	0.51-0.70	<0.05		0.25	1.03	60.0	64.5
	NFS		0.62	0.53-0.72	<0.05		0.21	-0.62	60.0	61.2
BMI status	APRI	BMI <33.3	0.69	0.57-0.81	<0.01	NS	0.40	0.25	78.9	60.9
		BMI ≥33.3	0.64	0.51-0.77	<0.05		0.26	0.30	46.2	79.7
	AST:ALT	BMI <33.3	0.46	0.31-0.60	NS	NS	0.06	0.85	57.9	47.7
		BMI ≥33.3	0.46	0.33-0.59	NS		0.04	0.91	46.2	57.8
	BARD	BMI <33.3	0.49	0.34-0.63	NS	NS	0.01	3.5	36.8	63.6
		BMI ≥33.3	0.47	0.33-0.60	NS		-0.07	3.0	53.8	39.1
	ELF	BMI <33.3	0.60	0.46-0.75	NS	NS	0.24	9.8	55.0	69.3
		BMI ≥33.3	0.62	0.48-0.76	NS		0.33	9.8	61.5	71.9
	FIB-4	BMI <33.3	0.66	0.54-0.77	<0.01	NS	0.39	0.97	78.9	60.2
		BMI ≥33.3	0.58	0.43-0.72	NS		0.22	1.90	23.1	98.4
	NFS	BMI <33.3	0.54	0.41-0.67	NS	NS	0.15	-2.34	100	14.8
		BMI ≥33.3	0.66	0.53-0.79	<0.05		0.30	0.40	50.0	79.7

The ROC analysis for advanced fibrosis using biomarkers in the overall group and compared by BMI status using the mean BMI 33.3 kg/m². Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *AUC* area under the curve; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *BMI* body mass index; *CI* confidence interval; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease fibrosis score.

Figure 6.6: Receiver operating characteristic curves for advanced hepatic fibrosis using blood biomarkers





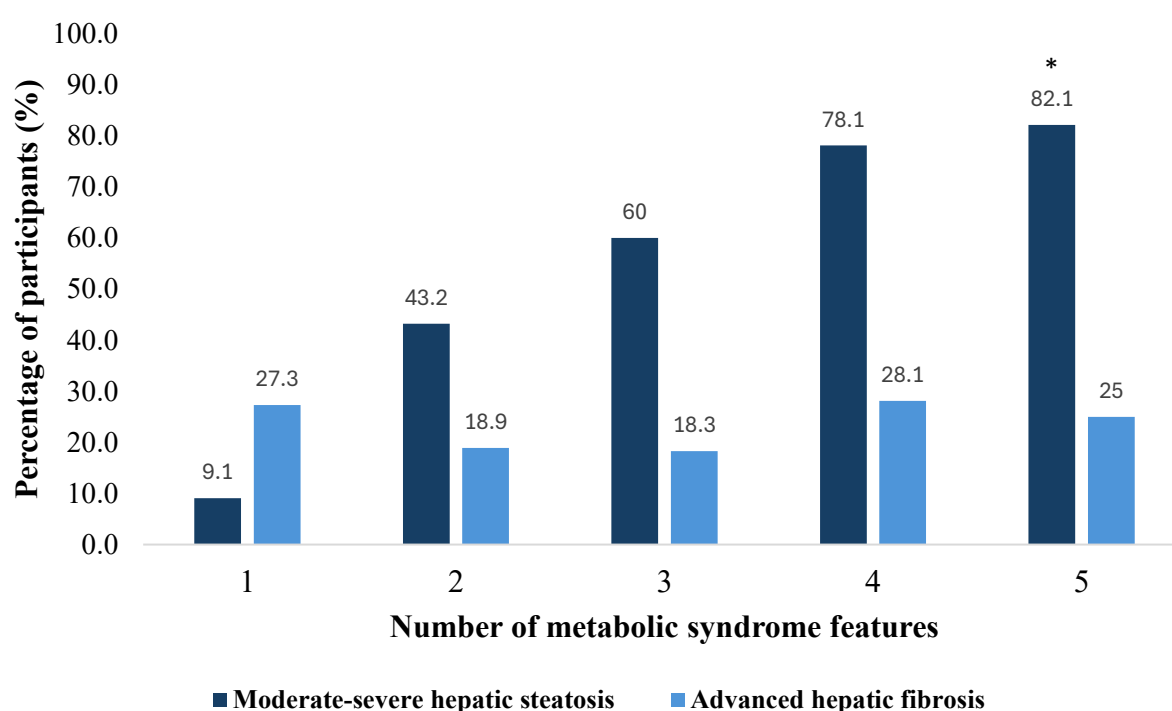
The ROC curves for advanced fibrosis using biomarkers in the (a) overall cohort and compared by BMI status using (b) APRI, (c) AST:ALT ratio, (d) BARD score, (e) ELF test, (f) FIB-4 score, and (g) NFS. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *ELF* enhanced liver fibrosis; *BMI* body mass index; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease fibrosis score.

6.4.5 Use of the number of metabolic syndrome features to predict hepatic steatosis or advanced fibrosis in people with type 2 diabetes

The prevalence of moderate-severe steatosis increased with the number of features from the metabolic syndrome ($p<0.001$). There was no association between the prevalence of advanced fibrosis and number of metabolic syndrome features ($p=0.38$). Data are shown in Figure 6.7.

The utility of the metabolic syndrome diagnosis to identify moderate-severe hepatic steatosis or advanced fibrosis is presented in Table 6.7.

Figure 6.7: Prevalence of moderate-severe hepatic steatosis and advanced fibrosis based on the number of metabolic syndrome features



Prevalence of moderate-severe hepatic steatosis and advanced fibrosis presented by the number of metabolic syndrome features present. * $p<0.001$ for the trend in prevalence of moderate-severe hepatic steatosis.

Table 6.7: Accuracy of metabolic syndrome diagnosis to identify moderate-severe hepatic steatosis or advanced hepatic fibrosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Moderate-severe hepatic steatosis	86.5 [79.8-91.7]	41.9 [31.1-53.3]	71.7 [64.2-78.5]	64.6 [50.5-77.1]
Advanced hepatic fibrosis	78.3 [65.0-88.5]	24.7 [18.3-31.9]	23.7 [17.4-30.8]	79.2 [66.3-89.0]

Sensitivity, specificity, PPV and NPV [95% CI] of the metabolic syndrome diagnosis to identify moderate-severe steatosis or advanced fibrosis. Abbreviations: *PPV* positive predictive value; *NPV* negative predictive value.

To determine whether each metabolic syndrome feature associated with moderate-severe hepatic steatosis or advanced fibrosis, a linear regression analysis was undertaken. Use of BP as a continuous measure of hypertension was excluded, due to the confounding impact of antihypertensive medicine use and limitation of a single clinic BP reading.

For hepatic steatosis, the model demonstrated a R^2 value 0.32, and adjusted R^2 value 0.31 with standard error of 50.8 dB/m, with a statistical correlation to predict moderate-severe steatosis ($p < 0.001$). The BMI, HDL and TG significantly predicted hepatic steatosis, but HbA1c did not. For advanced fibrosis, the model demonstrated a R^2 value 0.10, and adjusted R^2 value 0.08 with standard error of 4.7 kPa, with significant correlation for advanced fibrosis ($p < 0.001$). Only BMI associated with occurrence of advanced fibrosis ($p < 0.001$), and no other variable displayed a significant relationship. Data are presented in Table 6.8.

Table 6.8: Linear regression analysis of features of the metabolic syndrome to predict moderate-severe hepatic steatosis or advanced hepatic fibrosis

Variable	Unstandardised B coefficient	Standard error	Standardised B coefficient	T-value	Significance
Moderate-severe hepatic steatosis					
Constant	175.9	28.3	-	6.2	<0.001
BMI	4.7	0.6	0.5	8.1	<0.001
HbA1c	0.0	0.2	0.1	0.2	NS
HDL	-32.9	12.0	-0.2	-2.7	<0.01
TG	6.8	2.7	0.2	2.5	<0.05
Advanced hepatic fibrosis					
Constant	1.1	2.6	-	0.4	NS
BMI	0.2	0.1	0.2	3.3	<0.001
HbA1c	0.0	0.0	0.1	1.8	NS
HDL	-1.3	1.1	-0.1	-1.2	NS
TG	0.2	0.3	0.1	0.8	NS

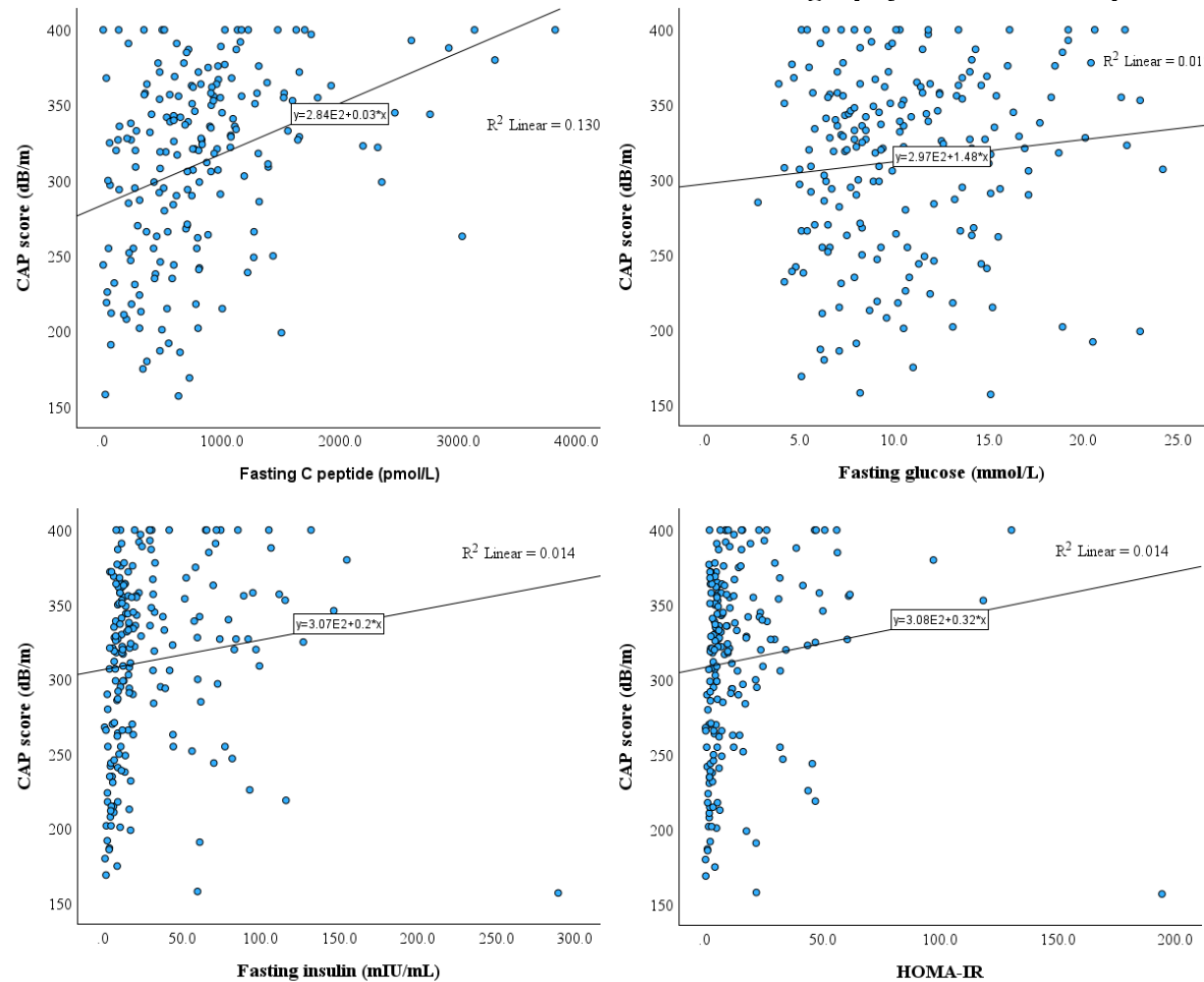
Linear regression investigating the impact of metabolic syndrome features on the occurrence of hepatic steatosis or advanced fibrosis. Abbreviations: *BMI* body mass index; *HDL* high density lipoprotein; *TG* triglyceride.

6.4.6 Use of insulin resistance measures to predict hepatic steatosis or advanced fibrosis in people with type 2 diabetes

There were missing data for the fasting C-peptide (n=4), fasting insulin (n=4), and fasting glucose (n=2), limiting calculation of the HOMA-IR in four participants. The fasting C-peptide ($r=0.39$, $p<0.001$), fasting insulin ($r=0.36$, $p<0.001$), and HOMA-IR ($r=0.36$, $p<0.001$) each correlated with the degree of hepatic steatosis defined by the TE-CAP, but the fasting glucose ($r=0.12$, $p=0.09$) did not. These data are presented in Figure 6.8. The fasting C-peptide ($r=0.25$, $p<0.001$), fasting insulin ($r=0.14$, $p<0.05$), and HOMA-IR ($r=0.19$, $p<0.01$) each correlated with the degree of liver fibrosis defined by the TE-LSM, but the fasting glucose ($r=0.13$, $p=0.06$) did not. These data are presented in Figure 6.9.

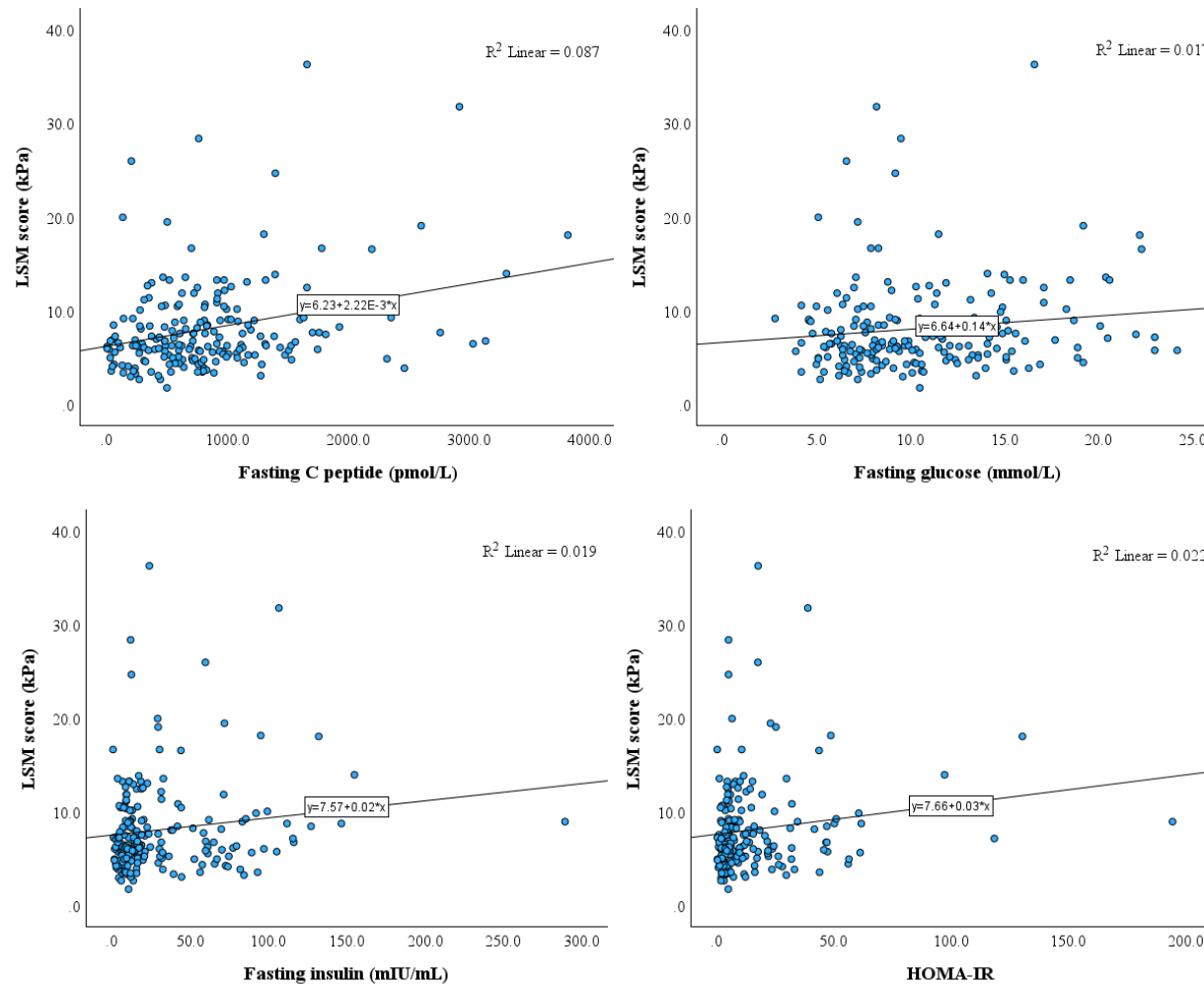
In the ROC analysis, the fasting C-peptide, fasting insulin and HOMA-IR, but not fasting glucose, had an AUC greater than that expected by chance to predict moderate-severe steatosis. There was no significant difference in the AUC between participants with BMI above or below the cohort mean, though the fasting glucose demonstrated an AUC greater than expected by chance in leaner participants. Data are presented in Table 6.9 and Figure 6.10. For advanced fibrosis, only the fasting C-peptide had an AUC greater than expected by chance in the overall cohort, and the AUC was numerically greater for all measures of IR in those with BMI ≥ 33.3 kg/m², reaching significance for the fasting glucose and HOMA-IR. Data are shown in Table 6.10 and Figure 6.11.

Figure 6.8: Correlations between measures of insulin resistance and transient elastography measures of hepatic steatosis



Scatter plots with line of best fit reflecting the correlation of fasting C-peptide, fasting glucose, fasting insulin and HOMA-IR with TE-CAP. Abbreviations: *CAP* Controlled Attenuation Parameter; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.

Figure 6.9: Correlations between measures of insulin resistance and transient elastography measures of hepatic fibrosis



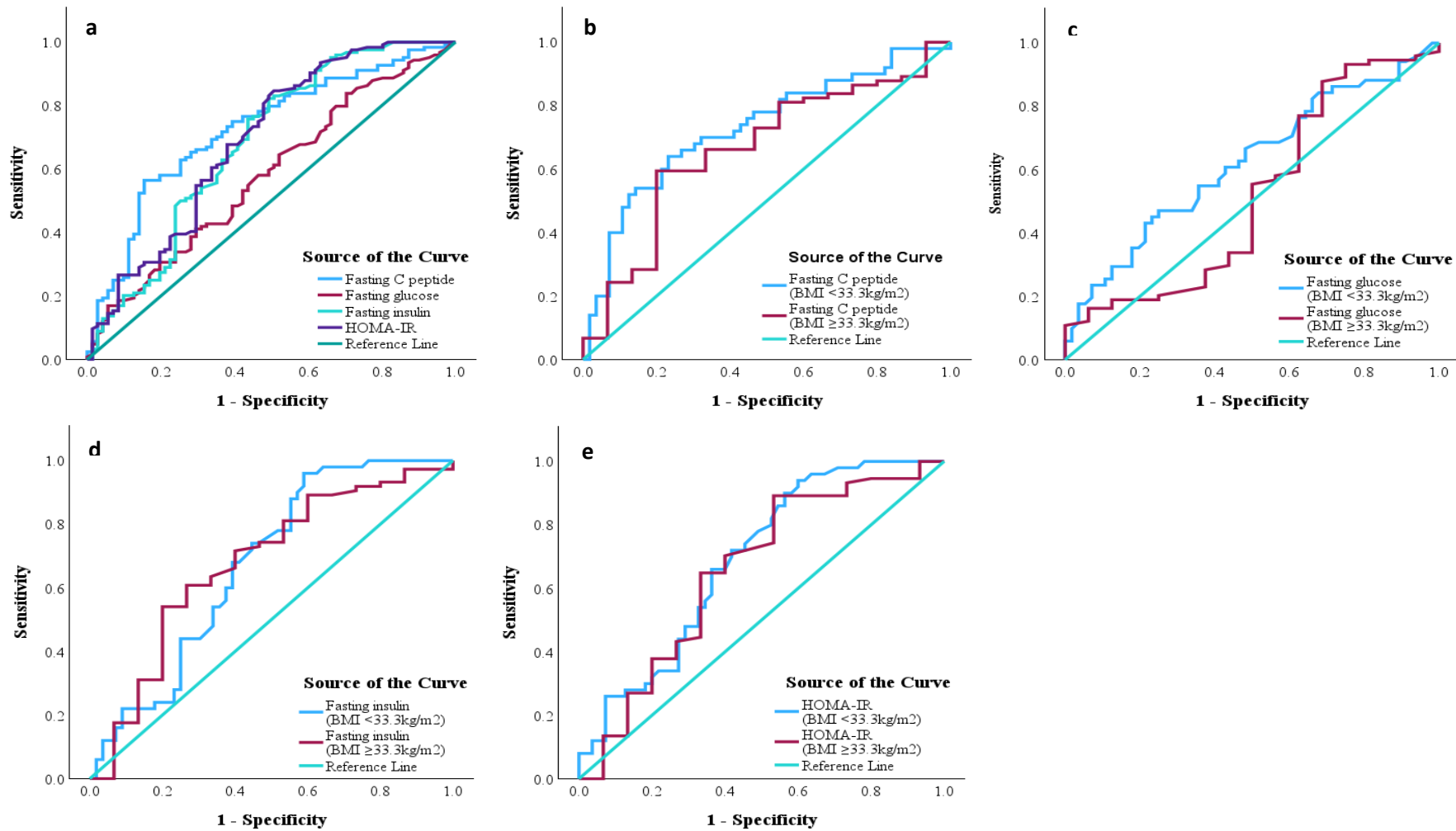
Scatter plots with line of best fit reflecting the correlation of fasting C-peptide, fasting glucose, fasting insulin and HOMA-IR with TE-LSM. Abbreviations: *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance; *LSM* liver stiffness measure.

Table 6.9: Receiver operating characteristic analysis for measures of insulin resistance to predict moderate-severe hepatic steatosis

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall	Fasting C-peptide		0.73	0.65-0.80	<0.001	-	0.41	823.0 pmol/L	56.5	84.5
	Fasting glucose		0.58	0.50-0.66	NS	-	0.13	6.8 mmol/L	83.9	29.6
	Fasting insulin		0.68	0.60-0.76	<0.001	-	0.33	10.0 uIU/mL	82.3	50.7
	HOMA-IR		0.69	0.61-0.77	<0.001	-	0.34	4.0	84.7	49.3
BMI status	Fasting C-peptide	BMI <33.3	0.73	0.63-0.83	<0.001	NS	0.41	717.7 pmol/L	64.0	76.8
		BMI ≥33.3	0.66	0.52-0.81	<0.05		0.40	823.0 pmol/L	59.5	80.0
	Fasting glucose	BMI <33.3	0.62	0.52-0.73	<0.05	NS	0.22	11.4 mmol/L	45.1	76.8
		BMI ≥33.3	0.52	0.35-0.69	NS		0.19	6.4 mmol/L	87.8	32.2
	Fasting insulin	BMI <33.3	0.67	0.57-0.78	<0.01	NS	0.37	6.8 uIU/mL	96.0	41.1
		BMI ≥33.3	0.68	0.52-0.84	<0.05		0.34	16.6 uIU/mL	60.8	73.3
	HOMA- IR	BMI <33.3	0.69	0.59-0.79	<0.001	NS	0.34	2.5	94.0	40.0
		BMI ≥33.3	0.66	0.49-0.83	NS		0.36	4.0	89.2	46.7

The ROC analysis exploring use of measures of IR to predict moderate-severe hepatic steatosis in the overall group and compared by BMI status. Abbreviations: *AUC* area under the curve; *BMI* body mass index; *CI* confidence interval; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.

Figure 6.10: Receiver operating characteristic curves for moderate-severe hepatic steatosis using insulin resistance measures



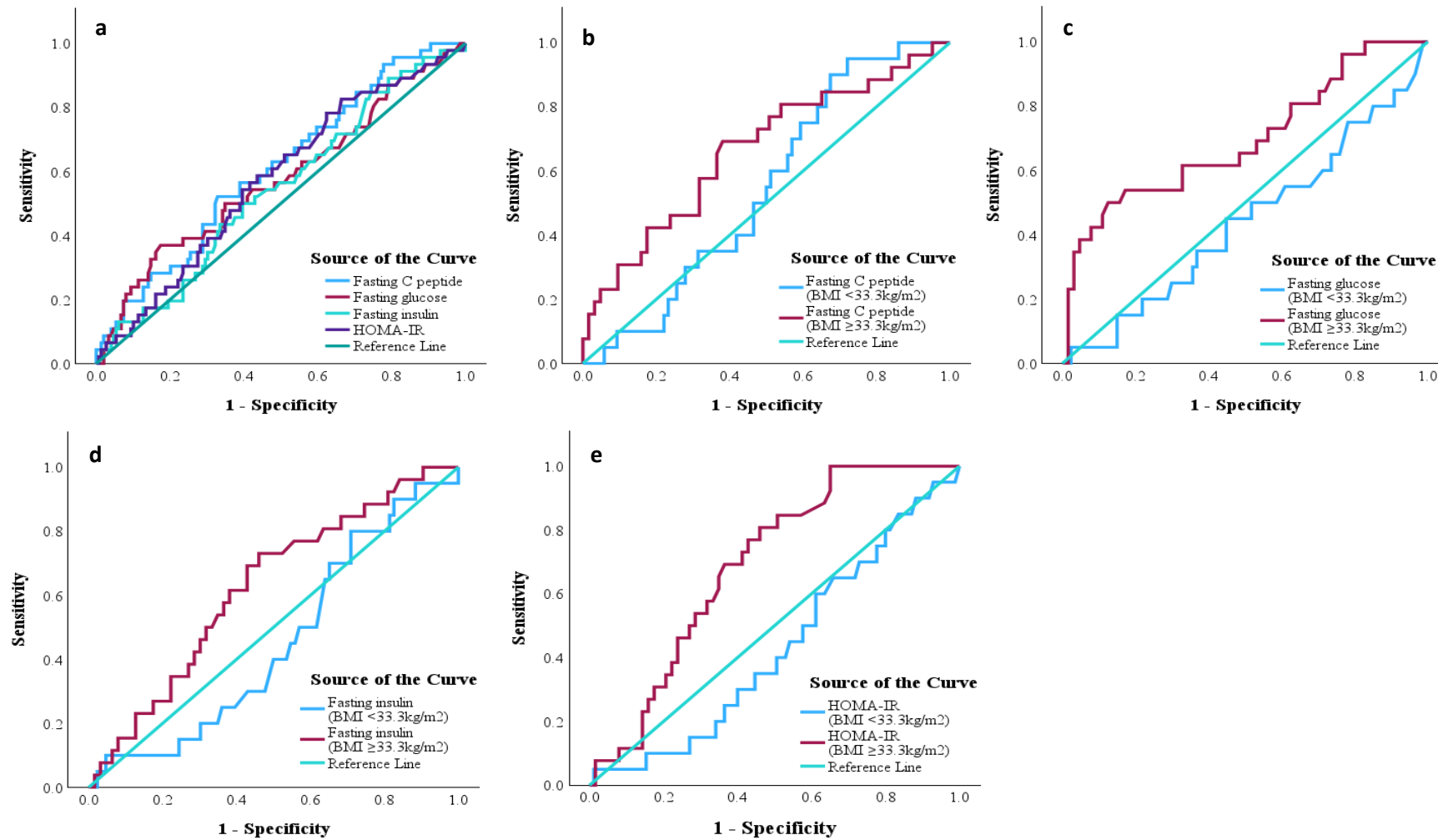
The ROC curves for moderate-severe hepatic steatosis in (a) overall cohort and compared by BMI status using the (b) fasting C-peptide, (c) fasting glucose, (d) fasting insulin, and (e) HOMA-IR. Abbreviations: *BMI* body mass index; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.

Table 6.10: Receiver operating characteristic analysis for measures of insulin resistance to predict advanced hepatic fibrosis

Group	Test	Subgroup	AUC	95% CI	P (null)	P (compare groups)	Youden index	Optimal cut-off	Sensitivity (%)	Specificity (%)
Overall	Fasting C-peptide		0.61	0.52-0.70	<0.05	-	0.19	910.0 pmol/L	52.2	67.8
	Fasting glucose		0.58	0.48-0.67	NS	-	0.20	14.1 mmol/L	37.0	82.6
	Fasting insulin		0.54	0.45-0.64	NS	-	0.10	18.5 uIU/mL	50.0	60.4
	HOMA-IR		0.57	0.48-0.67	NS	-	0.15	7.3	58.7	56.4
BMI status	Fasting C-peptide	BMI <33.3	0.55	0.43-0.67	NS	NS	0.23	274.8 pmol/L	95.0	27.9
		BMI ≥33.3	0.66	0.54-0.79	<0.05		0.31	910.0 pmol/L	69.2	61.9
	Fasting glucose	BMI <33.3	0.44	0.30-0.58	NS	<0.05	0.03	20.6 mmol/L	5.0	97.7
		BMI ≥33.3	0.69	0.57-0.82	<0.01		0.38	14.8 mmol/L	50.0	87.5
	Fasting insulin	BMI <33.3	0.15	0.32-0.58	NS	NS	0.09	7.3 uIU/mL	80.0	29.1
		BMI ≥33.3	0.62	0.50-0.75	<0.05		0.27	17.0 uIU/mL	73.1	54.0
	HOMA- IR	BMI <33.3	0.43	0.30-0.56	NS	<0.01	0.04	58.5	5.0	98.8
		BMI ≥33.3	0.69	0.58-0.80	<0.001		0.35	4.6	100	34.9

The ROC analysis exploring use of measures of IR to predict advanced fibrosis in the overall group and compared by BMI status. Abbreviations: *AUC* area under the curve *BMI* body mass index; *CI* confidence interval; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.

Figure 6.11: Receiver operating characteristic curves for advanced hepatic fibrosis using insulin resistance measures



The ROC curves for advanced fibrosis in (a) overall cohort and compared by BMI status using the (b) fasting C-peptide, (c) fasting glucose, (d) fasting insulin, and (e) HOMA-IR. Abbreviations: *BMI* body mass index; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance.

6.5 Discussion

In this chapter, I aimed to determine the accuracy of various biomarkers to identify moderate-severe hepatic steatosis and advanced fibrosis people with T2D attending secondary care. I presented the clinical utility of various biomarkers for hepatic steatosis, hepatic fibrosis and IR to identify hepatic steatosis or fibrosis on TE. I discuss these observations below.

6.5.1 Use of liver enzymes to predict hepatic steatosis or advanced fibrosis in people with type 2 diabetes

Liver enzymes did demonstrate some statistical utility to identify moderate-severe steatosis or advanced fibrosis. Both the ALT and AST correlated with the TE-CAP, whilst the ALT, AST and GGT correlated with the TE-LSM. Each liver enzyme had an AUC greater than predicted by chance for moderate-severe hepatic steatosis and advanced fibrosis. Nonetheless, using a low threshold of the upper limit of the normal range, enzymes in isolation had a sensitivity less than 30.2% and 43.5% to detect moderate-severe steatosis or advanced fibrosis. Whilst the AUC was greater than 0.50 for each enzyme, an AUC 0.60-0.70 is modest. Moreover, a normal ALT, AST and GGT was observed in most participants with moderate-severe hepatic steatosis (69.4-83.3%) or advanced fibrosis (56.5-78.2%). These observations are consistent with previous, in which use of liver enzymes in isolation can miss liver disease. One study included 2,679 participants with MASLD, and 83.1% had a normal ALT (J. Chen et al., 2024). Here, a lower cut-off of 18.5 IU/L was required to identify MASLD. In this chapter, a lower threshold of 25.5 IU/L was identified to predict moderate-severe steatosis. Similar observations were reported by others in which the ALT performs poorly to identify MASLD or hepatic fibrosis (Lominadze & Kallwitz, 2018; Zheng et al., 2020). Liver enzymes also perform poorly in patients with decompensated ALD or MASLD, and one study reported only a third patients had an elevated ALT or AST (Shrestha et al., 2023). Another study reported people with MASLD and different stages of steatohepatitis and hepatic fibrosis had similar ALT and AST levels, and adipose tissue-related IR and liver triglyceride content were the major determinants of liver enzyme changes (Maximos et al., 2015). This is a useful clinical reminder, as clinicians are often falsely reassured by normal liver enzymes, despite this being a feature in 20% of people with cirrhosis. Secondly, clinicians often fail to act upon or monitor abnormal LFTs, given up to 20% of LFT results contain at least one abnormality and these abnormalities infrequently result in a diagnosis of significant liver disease (Yeoman, 2021). These observations indicate that if screening was implemented in practice, then integration of specific testing beyond simple liver enzymes would be important.

6.5.2 Use of blood biomarkers to predict hepatic steatosis in people with type 2 diabetes

In this analysis, I explored the accuracy of the HSI, NAFLD-LFS and TyG to predict the TE-CAP because these are validated for hepatic steatosis. Each significantly correlated with the TE-CAP, and all had a greater AUC than expected by chance. However, using previously published thresholds these tests had limited clinical utility, which makes their use unattractive, especially considering the relative futility of screening for hepatic steatosis in this group.

The HSI had a sensitivity of 100% and specificity of 0% using a score of 30.0 to exclude hepatic steatosis. Using a HSI score 44.0, there was reduced sensitivity of 74.0% and improved specificity of 74.3%, with an AUC 0.79. This highlights the challenge in determining an appropriate test threshold balancing the need for either improved sensitivity or specificity depending on the test or disease in question. The original validation study for the HSI in over 10,000 participants using ultrasound reference standard, had a sensitivity and specificity of 93.1% and 92.4% respectively, with an AUC 0.81 (J. H. Lee et al., 2010). Subsequent studies offer mixed results for HSI accuracy in MASLD. Some support its accuracy with AUC >0.80 (Fedchuk et al., 2014; Lind et al., 2020; Zou et al., 2025), though others observe poorer AUC 0.58-0.64 (Eletreby et al., 2021; Forouzesh et al., 2025). The AUC for the HSI in this chapter indicates reasonable association with the TE-CAP score but limited utility in practice. This is because the sum of the sensitivity and specificity is less than 1.5 which typically indicates a useful test in practice (Power et al., 2013), and the Youden index was 0.48 which is below the threshold of 0.50 accepted for moderate test accuracy in practice (Dhamnetiya et al., 2022).

A NAFLD-LFS cut-off score of -0.64 had a sensitivity of 96.7% and specificity of 30.6% to identify hepatic steatosis. However, a NAFLD-LFS of 0.0 had lower sensitivity and improved specificity of 91.9% and 54.3% respectively to detect hepatic steatosis, and the ROC analysis observed an AUC 0.73. Like the HSI, the sum of the sensitivity and specificity for the NAFLD-LFS was less than 1.5 and the Youden index was less than 0.50, suggesting limited clinical utility. The original validation study for the NAFLD-LFS was in 470 subjects using MR spectroscopy as the reference standard. Using a cut-off score -0.640 there was sensitivity and specificity of 86% and 71% with AUC 0.86 (Kotronen et al., 2009). Others support its accuracy to predict hepatic steatosis in MASLD given an AUC >0.78 (Fedchuk et al., 2014; Lind et al., 2020). Reassuringly, the AUC for the HSI and NAFLD-LFS were similar irrespective of BMI status. Nonetheless, the lesser AUC and difficulty to undertake the NAFLD-LFS compared with the HSI given the need for a fasting insulin level justifies its limited use.

The TyG was the least consistent blood biomarker for hepatic steatosis. This was evidenced by a lower correlation coefficient, and AUC 0.68 to predict the TE-CAP. At the previous threshold of 4.4, the test had sensitivity and specificity 99.2% and 1.4%, changing to 46.3% and 77.1% respectively using a higher cut-off of 5.2. However, a Youden index 0.24 derived to determine this cut-off was significantly below the target of 0.50 (Dhamnetiya et al., 2022). The TyG was developed to predict IR but was subsequently associated with predicting hepatic steatosis. Previous studies observe a wide-ranging AUC of 0.61-0.90 highlighting the test is not a consistently reliable biomarker for steatosis (Fedchuk et al., 2014; Forouzesht et al., 2025; Zou et al., 2025). The AUC of 0.68 in this cohort is consistent with previous reports and indicates a reasonable association with the TE-CAP, but further studies are needed to understand a role of TyG in this setting. Though, the association between the TyG and TE-CAP on the ROC analysis was lost in those with BMI >33.3 kg/m². This may seem surprising given the test was developed to predict IR, which would likely be higher in those with greater BMI. However, previous studies observe the TyG is useful to discriminate MASLD risk in people with lean MASLD (Zhu et al., 2025), and the addition of BMI into the TyG algorithm improves accuracy in those with higher BMI (Chang et al., 2023; M. Wang et al., 2023). Therefore, given this is a measure of IR, it may be less useful to discriminate risk of hepatic steatosis in people with signs of IR such as T2D and obesity observed in this cohort.

6.5.3 Use of blood biomarkers to predict advanced fibrosis in people with type 2 diabetes

The associations between biomarkers for hepatic fibrosis (APRI, AST:ALT ratio, BARD score, ELF test, FIB-4 score, and NFS) and TE-LSM were explored. There were significant correlations and AUC for the APRI, ELF test, FIB-4 score, and NFS to predict the TE-LSM. However, correlations between biomarkers of fibrosis ($r=0.15-0.29$) were weaker compared to correlations between biomarkers for steatosis ($r=0.27-0.51$). The Youden index from the ROC curves for blood biomarkers of hepatic fibrosis were <0.28, indicating broadly poor clinical utility as a screening test. There was little evidence on correlation or ROC analysis to indicate an association between the AST:ALT ratio or BARD score with TE.

Using a score of 0.7 to identify advanced fibrosis, the APRI demonstrated excellent specificity of 97.4%, but poor sensitivity at 4.4%. Using a lower cut-off score of 0.17 with a Youden index of 0.26, there was a sensitivity 93.3% and specificity 32.2%, but this still falls short of the 1.5 sum considered useful in practice (Power et al., 2013). The APRI had the greatest AUC of the observed biomarkers at 0.67 and was the only biomarker with similar AUC to predict fibrosis in those with a BMI above or below the cohort mean. Previous meta-analyses report the AUC

of the APRI to predict advanced fibrosis using a histological reference standard is 0.70-0.78 (Lopez Torrez et al., 2024; Mozes et al., 2022; Xiao et al., 2017), though there are mixed observations on the impact of obesity on APRI accuracy (Alqahtani et al., 2021; de Carli et al., 2020; Drolz et al., 2021; Ito et al., 2023; Qadri et al., 2022; Schmitz et al., 2020).

The ELF test had a sensitivity 58.7% and specificity 69.9% to identify advanced fibrosis using the cut-off score ≥ 9.8 . Through the ROC analysis, the use of a slightly adjusted score of >9.8 gave a sensitivity and specificity of 57.8% and 70.1%. The AUC of 0.61 was greater than expected by chance, but less than the AUC 0.83-0.87 in previous meta-analyses (Lopez Torrez et al., 2024; Vali et al., 2020). This may be related to using the TE-LSM as the reference standard in this study, though speculation on test accuracy is limited by lack of histological data. The significance of the AUC compared to that expected by chance was lost in both BMI groups above and below the cohort mean, though the AUC remained similar (0.60 vs 0.62). The loss of significance is likely related to the wide 95% CI associated with lower participant numbers in each subgroup, and previous analyses indicate no statistical impact of obesity on ELF test accuracy (Kjaergaard et al., 2023).

Using a cut-off of 1.30, the FIB-4 test had a sensitivity 31.1% and specificity 79.7% to predict advanced fibrosis, which changed to 60.0% and 64.5%, using a lower cut-off of 1.03. In the overall cohort, the AUC was 0.61, and Youden index was poor at 0.25. The AUC was similar to chance in those with a BMI $>33.3 \text{ kg/m}^2$, but greater than expected in the leaner group. Previous meta-analyses report the AUC for the FIB-4 test to predict advanced fibrosis is 0.75-0.84 (Han et al., 2024; Lopez Torrez et al., 2024; Mozes et al., 2022; Xiao et al., 2017), and other studies report FIB-4 score accuracy is consistent irrespective of BMI (de Carli et al., 2020; Drolz et al., 2021; Kjaergaard et al., 2023; Qadri et al., 2022) and it is therefore recommended in people with obesity (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). This is difficult to explain, though given the low AUC, and lack of statistical significance between BMI groups, speculation is limited. This observation may reflect limitations including low numbers in each subgroup, and use of TE as the reference standard.

The NFS had a sensitivity of 80.4% and specificity of 27.6% using the validated score -1.455, which changed to 60.0% and 61.2% using a cut-off score of -0.62. Nevertheless, the improved overall sensitivity and specificity was still below 1.5, indicating poor clinical utility. Whilst the AUC of 0.62 for the NFS to predict advanced fibrosis was greater than chance, it appeared to be useful only in those with a BMI $>33.3 \text{ kg/m}^2$. Previous meta-analyses indicate the AUC for the NFS to predict advanced fibrosis is 0.73-0.84 (Lopez Torrez et al., 2024; Mozes et al.,

2022; Xiao et al., 2017), greater than in this cohort. This may differ as these meta-analyses included far greater participants (n=5,735–46,514) and each used liver histology as a reference standard, whilst TE was used as a reference in this study. Previous studies using histological data as the reference standard show a greater BMI diminishes the accuracy of the NFS (Drolz et al., 2021; Kjaergaard et al., 2023; Qadri et al., 2022). However, those with a greater BMI trended to greater AUC compared to the leaner group and was greater than expected by chance. Given the low AUC in both BMI groups, the relative limitation of using TE as the reference standard, and smaller participant numbers in each subgroup speculation is limited.

Neither the BARD score nor the AST:ALT ratio demonstrated a significant correlation with the TE-LSM, and the AUC for each of these biomarkers was similar to that expected by chance to predict advanced fibrosis. The BARD score is less useful in people with T2D given they all score 1 point for T2D, most will score a further point for their BMI, and a score of ≥ 2 cannot exclude advanced fibrosis (Harrison et al., 2008). The mean BMI in this population was 33.3 kg/m², so most scored for their BMI in addition to T2D. The BARD score is more appropriate in the general population. Previous meta-analyses indicate the AUC for the BARD score to predict advanced fibrosis in MASLD is 0.73-0.76, the lowest AUC of the observed biomarkers in these meta-analyses (Lopez Torrez et al., 2024; Xiao et al., 2017), and the AUC for the AST:ALT ratio to predict advanced fibrosis in another meta-analysis was 0.64, again the lowest of the tests investigated (Mozes et al., 2022). Our results corroborate lesser reliability of the BARD score and AST:ALT ratio for the diagnosis of advanced fibrosis in MASLD.

6.5.4 Use of predictors of insulin resistance to predict hepatic steatosis and advanced fibrosis in people with type 2 diabetes

There was an increasing prevalence of moderate-to-severe steatosis observed with increasing number of metabolic syndrome features. This was expected because MASLD and the metabolic syndrome share common pathophysiology, with IR resulting in lipotoxicity and systemic inflammation with hepatic triglyceride accumulation. Around 40% of people with MASLD have the metabolic syndrome and the individual features of the metabolic syndrome associate with hepatic steatosis (Younossi, Koenig, et al., 2016). Another study reported a similar observation, in which the severity of hepatic steatosis increased with the number of metabolic syndrome features (Jinjuvadia et al., 2017). The HDL, triglyceride, and BMI each significantly associated with hepatic steatosis on linear regression, but the HbA1c did not. In the regression analysis, BP was not included because of the confounding antihypertensive treatment and limitation of a single clinic BP measurement. Likewise, a single HbA1c may be limited because

of treatment confounders and lack of recognition of previous glycaemic control. Moreover, given all participants had T2D the HbA1c itself may be less useful to distinguish glycaemic risk between participants than if controls without T2D were included. Previous studies highlight the major impact of HbA1c on the development of hepatic steatosis and steatohepatitis, and that this association is independent of other factors such as age and BMI (Colosimo et al., 2024; Miyake et al., 2024). In the study presented in this chapter the association was not evident, though may be related to the limitation of using a single HbA1c reading, lack of participants with a normal HbA1c or without T2D, variation in the T2D therapies between participants and use of TE-LSM as the reference measure instead of histological data as used in these previous studies. Whilst a diagnosis of metabolic syndrome was sensitive to identify hepatic steatosis, it was poorly specific. This is in keeping with what is known, and in practice as most people with T2D live with MASLD screening should be focussed on identifying those with significant fibrosis.

There was no statistical relationship between the number of metabolic syndrome features and prevalence of advanced fibrosis. However, in a previous study, participants with five metabolic features did have significantly greater prevalence of advanced fibrosis (Jinjuvadia et al., 2017), which was not observed in this cohort. The limitation in comparison with the study presented in this chapter is the study by Jinjuvadia *et al.* used the NFS to define liver fibrosis, which is less accurate than the TE-LSM used in this study (Loomba & Adams, 2020; Mozes et al., 2022). Nevertheless, it was surprising to see the lack of association between the number of metabolic syndrome features and prevalence of advanced fibrosis, given these features associate with progressive fibrosis (Gangireddy et al., 2022; Mehal, 2023; Seo, 2022). A limitation of the approach in this study is it did not account for the severity of each metabolic syndrome feature, such as those with more severe obesity, dyslipidaemia or dysglycaemia. Those with more severe risk factors may be expected to have greater fibrosis.

On linear regression, BMI associated with advanced fibrosis but no other metabolic syndrome feature did. However, the R² value generated from this model was low, indicating that whilst there was a statistically important relationship between these variables including BMI with advanced fibrosis, there is little clinical use associated with this relationship. In keeping with the results in this chapter, previous studies indicate a major role for BMI on the development of hepatic fibrosis (Askeland et al., 2025; Gopalakrishna et al., 2023), and in people with T2D the BMI is the strongest predictor of hepatic fibrosis (Barb et al., 2021). Though, each of the metabolic syndrome features including dyslipidaemia, glycaemic control and hypertension

have previously impacted on the risk of hepatic fibrosis (Colosimo et al., 2024; Z. Gao et al., 2025; Jinjuvadia et al., 2017; Li et al., 2025; Liu et al., 2023; Miyake et al., 2024). A potential explanation for the lack of association between these features and the TE-LSM includes possible error with TE-LSM. Though, the TE data in this chapter meet the criteria of at least 10 measurements using the appropriate probe and a median/IQR <30%. Previous evidence would indicate that the presence of obesity would not impact the TE-LSM when undertaken correctly (Cao et al., 2022), and it is the TE-CAP which is more prone to inaccuracy in obesity. Given the lack of histological data in the study, speculation on the test accuracy is limited.

The fasting C-peptide, fasting insulin, and HOMA-IR each correlated significantly with the degree of hepatic steatosis and fibrosis, but the fasting glucose did not. The AUC was greater than expected by chance for the fasting C-peptide (AUC 0.73), fasting insulin (AUC 0.68) and HOMA-IR (AUC 0.69) to predict hepatic steatosis. Nevertheless, the Youden index was <0.41 for these tests, the most useful being the fasting C-peptide, which at 823.0 pmol/L had a sensitivity and specificity of 56.5% and 84.5%, inadequate in practice. In the sub-analysis exploring the impact of BMI, there was a trend to greater AUC for all four measures of IR in the leaner group compared with those with a BMI >33.3 kg/m². To identify advanced fibrosis, only the C-peptide demonstrated an AUC (0.61) greater than expected by chance. Though, this only had a sensitivity and specificity of 52.2% and 67.8% with a Youden index of 0.19. In the subgroup analysis, all four markers of IR had a significantly greater AUC in participants with BMI >33.3 kg/m² than expected by chance and compared to those with a leaner BMI, indicating their utility may be greatest in people showing additional clinical signs of IR.

Previous studies show the C-peptide (Cernea et al., 2024; N. Wang et al., 2020), fasting insulin (Bril et al., 2021; Huneault et al., 2024), HOMA-IR (Abenavoli et al., 2025; Cernea et al., 2024; H. Chen et al., 2024; Tian et al., 2024; Zeng et al., 2023), and fasting glucose (Martinez-Sanchez et al., 2025; Teng et al., 2024, 2025) each associate with the degree of hepatic steatosis, and fibrosis. The more consistent association between the fasting C-peptide and development of hepatic steatosis or fibrosis is also biologically sensible, because the C-peptide indicates the degree of insulin production and therefore the stage of T2D. Those with more advanced or longstanding T2D have greatest risk of developing hepatic steatosis and advanced fibrosis. Though, in this study the lack of statistical association with the fasting glucose reading is unsurprising given the variability of this measure, the use of confounding T2D medicines such as insulin and sulphonylureas, and the fasting glucose may be less discriminative in this cohort given all participants have T2D.

6.6 Summary and limitations

In this chapter, I presented the accuracy of liver enzymes and blood biomarkers to predict the degree of hepatic steatosis or fibrosis observed on TE, using data collected in a study piloting target testing in people with T2D. The biomarkers for hepatic steatosis were more consistent than for liver fibrosis, but isolated liver enzymes had little utility. Simple clinical measures of the metabolic syndrome were useful in predicting the prevalence of moderate-severe hepatic steatosis, but not hepatic fibrosis. Biochemical measures of IR had closer association with the degree of hepatic steatosis on TE than with fibrosis, and the fasting C-peptide was the most consistent of these measures to predict either hepatic steatosis or fibrosis.

6.6.1 Clinical significance

This study highlights that validated biomarkers for hepatic steatosis and fibrosis do correlate with TE. However, the inconsistency of these tests draws attention to the limitation of using non-invasive tests for MASLD in practice. Different screening thresholds may have been more useful than previously validated cut-offs and requires further consideration. The study highlights the potential utility of undertaking targeted testing in subsets of people with T2D with additional features of the metabolic syndrome, such as those who also live with obesity, given their higher likelihood of disease, which may improve screening test utility.

6.6.2 Limitations

There are some limitations to the study:

- The use of TE as the reference standard limits discussion around test accuracy and was chosen as the most accurate non-invasive test used in routine practice.
- Greater participant numbers to include people without T2D may have supported further subgroup analysis, investigating the impact of T2D and BMI on test accuracy.
- Subgroup analysis using clinically-relevant BMI thresholds may benefit the discussion of biomarker accuracy in obesity, but this was limited by the numbers in each subgroup (BMI <30 kg/m²=62, BMI 30-35 kg/m²=63, BMI>35 kg/m²=74).
- Waist circumference was not measured, so the FLI could not be calculated and required use of BMI to determine presence of obesity as a metabolic syndrome feature.
- Participants are all under secondary care diabetes services, so the generalisability of these data to people with T2D in primary care may be limited.

Chapter Seven:

**Cardiovascular disease risk in people with
type 2 diabetes and MASLD attending
secondary care**

7.1 Introduction

Predicting CVD risk is commonplace with the development of reliable algorithms, such as the QRESEARCH risk estimator version-3 (QRISK3), which supports the need for treatments such as statin therapy (NICE, 2026). Such algorithms use routine clinical information, such as age, postcode, ethnicity, smoking status, and data related to the metabolic syndrome to determine the 10-year risk of MI or stroke through a publicly accessible, free-to-use website (Endeavour Predict, 2024). People with T2D and higher CVD risk predicted by QRISK3 are more likely to benefit from drugs with proven CVD benefit, such as SGLT-2 inhibitors and GLP-1RAs (American Diabetes Association, 2024e; NICE, 2026). Given the CVD benefit of these medicines in populations without T2D, (R. Patel et al., 2024; S. Patel et al., 2024), people with MASLD and high CVD risk would likely benefit too, especially given their impact on steatohepatitis and fibrosis (Xu et al., 2024). Recent treatment guidelines advocate a CVD risk assessment in people with MASLD, and to consider using such therapies in people with MASLD and T2D, (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

There is well-established excess CVD risk in people with MASLD, 3-4 fold greater than in people without MASLD (Sanyal, Husain, et al., 2024), and is the cause of death in two-thirds of people with MASLD (Duell et al., 2022). Consequently, the nomenclature used to define and classify MASLD was updated to highlight the often-unrecognised burden of CVD in this population (Rinella, Lazarus, et al., 2023). The growing discussion on CVD risk reduction in contemporary treatment guidelines underlines this frequently unmet need. The degree of fibrosis on liver biopsy correlates with CVD risk in people with MASLD, such that those with stage 3-4 hepatic fibrosis have the greatest risk (Hagstrom et al., 2017; Simon et al., 2022), and presence of T2D increases risk further (Michalopoulou et al., 2025). However, in people with MASLD, the most significant CVD risk factor is the degree of fibrosis (Angulo et al., 2015). One study reported that people with MASLD, and stage 3-4 liver fibrosis had 6-fold greater predicted 5- and 10-year CVD risk than people with MASLD and stage 0-2 liver fibrosis (Ng et al., 2022). Additionally, people with MASLD are typically at lower risk than people with other causes of CLD for major adverse liver outcomes (e.g. decompensated liver disease) (Pembroke et al., 2023; Younossi & Henry, 2016).

Despite the observations between the degree of fibrosis and CVD risk, there remain no liver-related measures input to QRISK3. Previous studies report significant correlations between the FIB-4 score, TE-LSM, or NFS, amongst other predictors of liver fibrosis, with CVD risk in people with MASLD (Anstee et al., 2024; Boeckmans et al., 2024; Yan et al., 2022). However,

there is little published evidence exploring the prognostic utility of the ELF test for CVD (Young et al., 2024). Work to establish a relationship between non-invasive measures of MASLD and MASLD-related fibrosis may support the development of future CVD predicting algorithms and is therefore of clinical interest in this group.

7.2 Aims of this chapter

The specific aims of this chapter are to explore:

- i. associations between clinical and biochemical variables and predicted CVD risk in people with T2D.
- ii. associations between measures of hepatic steatosis or fibrosis and predicted CVD risk in people with T2D.
- iii. associations between metabolic syndrome features and MASLD, with predicted CVD risk in people with T2D.

7.3 Methods

7.3.1 Study design

The design of this pilot study was detailed in chapter two. Participants provided written consent to undergo additional tests for MASLD, including fasted blood tests and TE in clinic. Participants with high-risk for advanced fibrosis, defined by a TE-LSM ≥ 9.7 kPa or ELF result ≥ 10.51 were referred to hepatology. Data were collected from October 2023-July 2024.

7.3.2 Participants

Participants were aged ≥ 18 years with a clinical diagnosis of T2D. Patients with known or suspected liver disease, or other risk factors for liver disease were excluded. The inclusion and exclusion criteria were detailed in chapter two.

7.3.3 Data collection

Data were collected during the participants' usual diabetes clinic. From these data, measures of hepatic steatosis, hepatic fibrosis and IR were calculated. Each participants' predicted 10-year CVD risk was calculated using the online QRISK3 calculator (Endeavour Predict, 2024). Their CFS, CCI and WIMD was calculated. The presence or absence of each feature of the metabolic syndrome was determined. In clinic, TE was performed by me and described further in chapter two. Moderate steatosis (stage 1-2) was defined by a TE-CAP 302-336 dB/m and severe steatosis (stage 3) by a TE-CAP ≥ 337 dB/m. Moderate fibrosis and advanced fibrosis were defined by a TE-LSM 8.2-9.6 kPa and ≥ 9.7 kPa, respectively, presented in Table 2.7.

7.3.4 Funding and ethical approval

No additional funding was received to undertake this study. The study was approved by the HRA and HCRW [IRAS ID: 326341], and approval for participant recruitment was issued by SBUHB in October 2023. Supporting documentation are presented in [Appendix II](#).

7.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using SPSS (version 29). Data presentation was described in chapter two. The Mann-Whitney U and Kruskal-Wallis tests were used to compare the statistical significance of differences between non-parametric data. Spearman's rank correlation was used to correlate parametric or non-parametric data with non-parametric data. Multiple linear regression was used to evaluate associations between predicted CVD risk and variables with a statistically significant correlation with QRISK3. Statistical significance was defined at $p < 0.05$.

7.4 Results

7.4.1 Participant characteristics

Two hundred people with T2D are included, their characteristics are presented in Table 5.1. The median QRISK3 score was 23.2 [13.8-35.7] %, with a median relative CVD risk 3.2 [2.1-4.7] times greater than healthy age-matched controls. Of these, 28 (14.0%) had low CVD risk (QRISK3 <10%), 55 (27.5%) had moderate CVD risk (QRISK3 10-20%), and 117 (58.5%) had high CVD risk (QRISK3 >20%). The mean age was 59.4±11.0 years, the oldest participant was 81 years. The healthy heart age from the QRISK3 calculator represents the age of a person with optimal cardiovascular risk factors with the same predicted CVD risk as the individual being assessed. Forty (20.0%) participants had an incalculable healthy heart age, as it was greater than 84 years. Among the remaining 160 (80.0%) participants, the median was 75.0 [69.0-80.0] years substantially greater than their mean biological age.

7.4.2 Associations between clinical and biochemical variables and predicted cardiovascular risk in people with type 2 diabetes

Correlation analysis was undertaken between clinical and biochemical variables with predicted CVD risk in the total cohort, presented in Table 7.1. This analysis was repeated in the 126 (63.0%) participants with moderate-severe hepatic steatosis on TE, shown in Table 7.2. There were no significant correlations between measures of glycaemic control, measures of insulin production or resistance, isolated liver enzymes, measures of deprivation or BMI with predicted CVD risk. In people with MASLD, there were similar results, except the association between albumin and predicted CVD risk was not significant.

Linear regression analysis was undertaken to explore the relationship between these variables. This analysis included ten variables, presented in Table 7.3. The model generated demonstrated a R^2 value 0.62, and adjusted R^2 value 0.60 with standard error of 9.51, and a significant correlation between the model and QRISK3 ($p<0.001$). In this model, age, CCI, systolic BP, albumin, creatinine, eGFR and HDL remained statistically associated with QRISK3.

Table 7.1: Correlations between routine clinical and biochemical variables and predicted cardiovascular risk in people with type 2 diabetes

Variable (n=200)	QRISK3 correlation	Statistical significance
General characteristics		
Age (years)	r=0.64	p<0.001
BMI (kg/m ²)	r=0.02	NS
Clinical Frailty Score	r=0.31	p<0.001
Charlson Comorbidity Index	r=0.56	p<0.001
Diastolic BP (mmHg)	r=0.06	NS
Systolic BP (mmHg)	r=0.43	p<0.001
Weight (kg)	r=0.02	NS
WIMD decile	r=0.05	NS
Diabetes-related measures		
Duration of T2D (years)	r=0.28	p<0.001
Fasting insulin (uIU/mL)	r=0.12	NS
Fasting C-peptide (pmol/L)	r=0.05	NS
FBG (mmol/L)	r=0.01	NS
HbA1c (mmol/mol)	r=-0.02	NS
HOMA-IR	r=0.11	NS
Liver-related measures		
Albumin (g/L)	r=-0.25	p<0.001
ALT (U/L)	r=-0.13	NS
AST (U/L)	r=0.05	NS
GGT (U/L)	r=0.10	NS
Total protein (g/L)	r=-0.20	p<0.01
Kidney-related measures		
Creatinine (μmol/L)	r=0.43	p<0.001
eGFR (mL/min/1.73m ²)	r=-0.36	p<0.001
UACR (mg/mmol)	r=0.39	p<0.001
Lipids		
HDL (mmol/L)	r=-0.25	p<0.001
LDL (mmol/L)	r=-0.16	NS
TC (mmol/L)	r=-0.17	NS
TG (mmol/L)	r=0.14	NS

Correlating clinical and biochemical variables with predicted CVD risk in people with T2D. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *BMI* body mass index; *BP* blood pressure; *eGFR* estimated glomerular filtration rate; *FBG* fasting blood glucose; *GGT* Gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance; *LDL* low-density lipoprotein; *NS* not significant; *QRISK3* QRESEARCH risk estimator version-3. *TC* total cholesterol; *TG* triglyceride; *T2D* type 2 diabetes; *UACR* urine albumin-to-creatinine ratio; *WIMD* Welsh index of multiple deprivation.

Table 7.2: Correlations between routine clinical and biochemical variables and predicted cardiovascular risk in people with type 2 diabetes and MASLD

Variable (n=126)	QRISK3 correlation	Statistical significance
General characteristics		
Age (years)	r=0.60	p<0.001
BMI (kg/m ²)	r=0.01	NS
Clinical Frailty Score	r=0.30	p<0.001
Charlson Comorbidity Index	r=0.59	p<0.001
Diastolic BP (mmHg)	r=0.06	NS
Systolic BP (mmHg)	r=0.45	p<0.001
Weight (kg)	r=-0.01	NS
WIMD decile	r=0.04	NS
Diabetes-related measures		
Duration of T2D (years)	r=0.36	p<0.001
Fasting insulin (uIU/mL)	r=0.16	NS
Fasting C-peptide (pmol/L)	r=0.09	NS
FBG (mmol/L)	r=0.07	NS
HbA1c (mmol/mol)	r=0.04	NS
HOMA-IR	r=0.17	NS
Liver-related measures		
Albumin (g/L)	r=-0.19	NS
ALT (U/L)	r=-0.17	NS
AST (U/L)	r=-0.06	NS
GGT (U/L)	r=0.10	NS
Total protein (g/L)	r=-0.25	p<0.01
Kidney-related measures		
Creatinine (μmol/L)	r=0.47	p<0.001
eGFR (mL/min/1.73m ²)	r=-0.39	p<0.001
UACR (mg/mmol)	r=0.42	p<0.001
Lipids		
HDL (mmol/L)	r=-0.41	p<0.001
LDL (mmol/L)	r=-0.17	NS
TC (mmol/L)	r=-0.20	NS
TG (mmol/L)	r=0.18	NS

Correlating clinical and biochemical variables with predicted CVD risk in people with T2D and MASLD. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *BMI* body mass index; *BP* blood pressure; *eGFR* estimated glomerular filtration rate; *FBG* fasting blood glucose; *GGT* Gamma-glutamyl transferase; *HDL* high-density lipoprotein; *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance; *LDL* low-density lipoprotein; *NS* not significant; *QRISK3* QRESEARCH risk estimator version-3; *TC* total cholesterol; *TG* triglyceride; *T2D* type 2 diabetes; *UACR* urine albumin-to-creatinine ratio; *WIMD* Welsh index of multiple deprivation.

Table 7.3: Multiple linear regression between routine clinical and biochemical variables and predicted cardiovascular risk in people with type 2 diabetes

Variable	Unstandardised B coefficient	Standard error	Standardised B coefficient	T-value	Significance
Constant	-28.06	16.49	-	-1.70	NS
Clinical characteristics					
Age (years)	0.58	0.10	0.42	5.84	<0.001
Duration of T2D (years)	-0.07	0.09	-0.04	-0.85	NS
Clinical Frailty Score	0.08	0.81	0.01	0.10	NS
CCI	1.38	0.64	0.16	2.2	<0.05
Systolic BP (mmHg)	0.27	0.04	0.36	7.32	<0.001
Biochemical variables					
Albumin (g/L)	-0.57	0.28	-0.12	2.05	<0.05
Total protein (g/L)	-0.07	0.17	-0.02	-0.40	NS
Creatinine (µmol/L)	0.15	0.04	0.30	3.40	<0.001
eGFR (mL/min/1.73m ²)	0.14	0.05	0.24	2.69	<0.01
UACR (mg/mol)	0.00	0.01	0.01	0.11	NS
HDL (mmol/L)	-14.129	2.23	-0.30	-6.34	<0.001

Linear regression analysis between selected clinical and biochemical variables with predicted CVD. Abbreviations: *BP* blood pressure; *CCI* Charlson comorbidity index; *eGFR* estimated glomerular filtration rate; *HDL* high-density lipoprotein; *NS* not significant; *T2D* type 2 diabetes; *UACR* urine albumin-to-creatinine ratio.

7.4.3 Associations between measures of hepatic steatosis or fibrosis and predicted cardiovascular risk in people with type 2 diabetes

Correlation analysis was undertaken between the non-invasive measures of hepatic steatosis and fibrosis and correlated with predicted CVD risk in people with T2D, presented in Table 7.4. Scatter plots presenting the statistically significant correlations are presented in Figure 7.1. This was repeated in those with moderate-severe hepatic steatosis, presented in Table 7.5.

There were no statistically significant correlations between any measure of hepatic steatosis with predicted CVD risk in the total cohort, or the subgroup with moderate-severe hepatic steatosis. However, there were significant correlations between four validated measures of hepatic fibrosis, the AST:ALT ratio, ELF test, FIB-4 score, and NFS, with predicted CVD risk. There were significant correlations between predicted CVD risk and each of the three variables used to determine the ELF test score (HA, PIIINP, TIMP1). There were similar results in the subgroup with moderate-severe hepatic steatosis, except the significance associated with the correlation between AST:ALT ratio and predicted CVD risk was lost in this subgroup. There was no significant correlation between predicted CVD risk and the APRI, BARD score, or TE-LSM, irrespective of hepatic steatosis status. Data are presented in Table 7.4 and Table 7.5.

Linear regression was taken to explore the relationship between these variables. Analysis included four variables, presented in Table 7.6. The model generated demonstrated a R^2 value 0.23, and an adjusted R^2 value 0.21 with standard error of 13.40, and a statistically significant correlation between the model and QRISK3 ($p < 0.001$). In this model, only the ELF test and NFS remained statistically associated with CVD risk.

Predicted CVD risk was compared by the score derived from the non-invasive tests used (AST:ALT ratio, ELF test, FIB-4 score and NFS) to predict the risk of advanced fibrosis. With increasing scores from each of these non-invasive measures, there was a statistically significant greater predicted CVD risk. This is presented in Table 7.7 and Figure 7.2.

Table 7.4: Correlations between non-invasive measures of MASLD and predicted cardiovascular risk in people with type 2 diabetes

Variable (n=200)	QRISK3 correlation	Statistical significance
Steatosis-related investigations		
HSI	r=-0.13	NS
NAFLD-LFS	r=0.11	NS
TE-CAP	r=0.01	NS
TyG	r=0.08	NS
Fibrosis-related investigations		
APRI	r=0.09	NS
AST:ALT ratio	r=0.23	p<0.01
BARD score	r=0.17	NS
ELF test	r=0.38	p<0.001
- HA	r=0.33	p<0.001
- PIIINP	r=0.23	p<0.001
- TIMP1	r=0.34	p<0.001
FIB-4 score	r=0.45	p<0.001
NFS	r=0.38	p<0.001
TE-LSM	r=0.12	NS

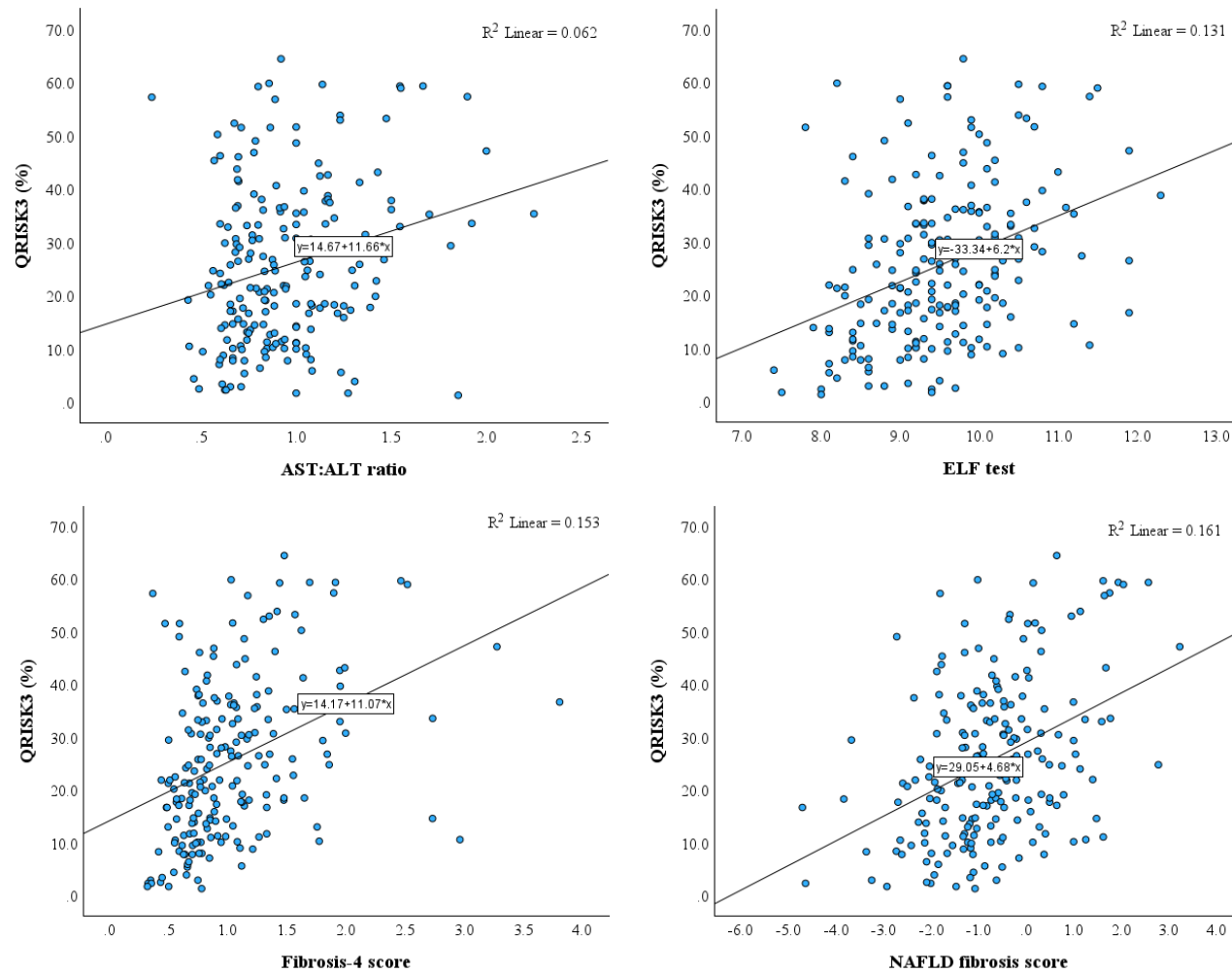
Correlating non-invasive measures of hepatic steatosis or fibrosis with predicted CVD risk. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* body mass index-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter; *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *HA* hyaluronic acid; *HSI* hepatic steatosis index; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NAFLD LFS* non-alcoholic fatty liver disease liver fat score; *NS* not significant; *PIIINP* Procollagen 3 N-terminal peptide; *QRISK3* QRESEARCH risk estimator version-3; *TE* transient elastography; *TIMP-1* Tissue inhibitor matrix metalloproteinase-1; *TyG* triglycerides and glucose index.

Table 7.5: Correlations between non-invasive measures of MASLD and predicted cardiovascular risk in people with type 2 diabetes and MASLD

Variable (n=126)	QRISK3 correlation	Statistical significance
Steatosis-related scores		
HSI	r=-0.16	NS
NAFLD-LFS	r=0.16	NS
TE-CAP	r=0.16	NS
TyG	r=0.15	NS
Fibrosis-related investigations		
APRI	r=0.03	NS
AST:ALT ratio	r=0.21	NS
BARD score	r=0.21	NS
ELF test	r=0.40	p<0.001
- HA	r=0.37	p<0.001
- PIIINP	r=0.26	p<0.01
- TIMP1	r=0.32	p<0.001
FIB-4 score	r=0.41	p<0.001
NFS	r=0.38	p<0.001
TE-LSM	r=-0.02	NS

Correlating non-invasive measures of hepatic steatosis or fibrosis with predicted CVD risk in people with T2D and moderate-to-severe hepatic steatosis. Abbreviations: *ALT* alanine aminotransferase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate aminotransferase; *BARD* body mass index-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter *ELF* enhanced liver fibrosis; *FIB-4* fibrosis-4; *HA* hyaluronic acid; *HSI* hepatic steatosis index; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NAFLD LFS* non-alcoholic fatty liver disease liver fat score; *NS* not significant; *QRISK3* QRESEARCH risk estimator version-3; *PIIINP* Procollagen 3 N-terminal peptide; *TE* transient elastography; *TIMP-1* Tissue inhibitor matrix metalloproteinase-1; *TyG* triglycerides and glucose index.

Figure 7.1: Correlations between non-invasive measures of MASLD and predicted cardiovascular risk in people with type 2 diabetes



Scatter plots with line of best fit reflecting the correlation of measures of MASLD with predicted CVD risk in the cohort. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *ELF* enhanced liver fibrosis; *NAFLD* non-alcoholic fatty liver disease; *QRISK3* QRESEARCH risk estimator version-3.

Table 7.6: Linear regression analysis for non-invasive measures of MASLD and predicted cardiovascular in people with type 2 diabetes

Variable	Unstandardised B coefficient	Standard error	Standardised B coefficient	T-value	Significance
Constant	-14.76	11.42	-	-1.29	NS
AST:ALT ratio	2.32	3.43	0.05	0.68	NS
ELF test	3.88	1.21	0.23	3.21	<0.01
Fibrosis-4 score	3.16	2.72	0.11	1.16	NS
NFS	2.69	1.05	0.23	2.57	<0.05

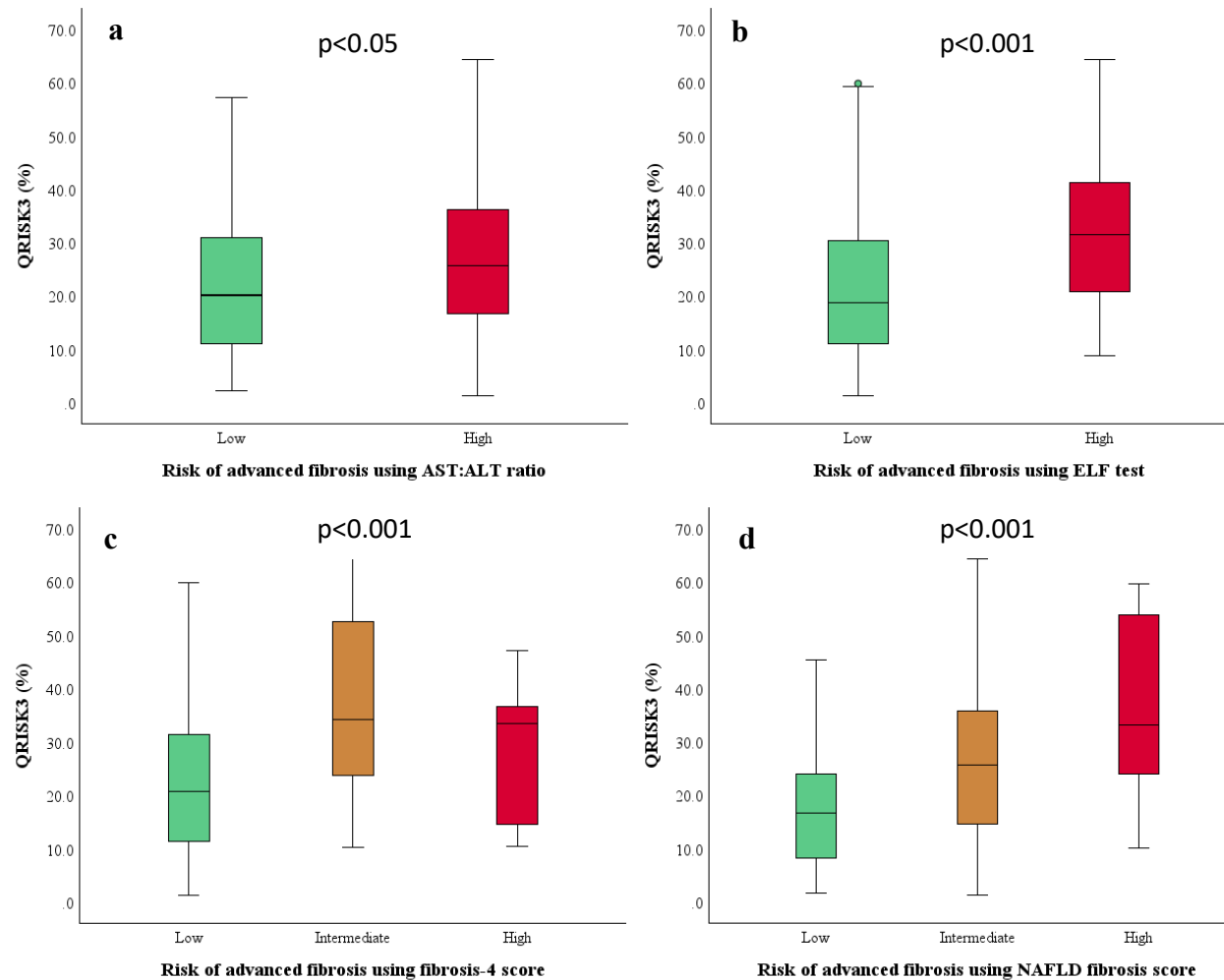
Linear regression analysis between selected non-invasive measures of MASLD with predicted CVD in the cohort of people with T2D. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *ELF* enhanced liver fibrosis; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* not significant.

Table 7.7: Predicted cardiovascular risk by the risk of advanced fibrosis using blood biomarkers

Biomarker	QRISK3 (%)	Interquartile range	Significance
AST:ALT ratio			
• Low risk (<0.80)	20.2	10.6-31.4	<0.05
• High risk (≥0.80)	25.8	16.7-36.5	
ELF test			
• Low risk (<9.80)	18.9	11.2-30.5	<0.001
• High risk (≥9.80)	31.5	20.5-42.3	
Fibrosis-4 score			
• Low risk (<1.30)	20.8	11.4-32.1	<0.001
• Intermediate risk (1.30-2.66)	34.4	23.3-52.9	
• High risk (≥2.67)	33.6	12.6-42.0	
NFS			
• Low risk (<-1.455)	16.7	8.3-24.5	<0.001
• Intermediate risk (-1.455-0.67)	25.8	14.7-36.0	
• High risk (≥0.675)	33.2	23.5-54.7	

Comparing predicted CVD by the risk of advanced fibrosis using blood biomarkers. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *ELF* enhanced liver fibrosis; *NFS* non-alcoholic fatty liver disease fibrosis score; *QRISK3* QRESEARCH risk estimator version-3.

Figure 7.2: Comparing predicted cardiovascular risk by risk of advanced fibrosis using blood biomarkers



Box plots comparing CVD risk by the risk of advanced fibrosis using (a) AST:ALT ratio, (b) ELF test, (c) fibrosis-4 score, and (d) NAFLD fibrosis score. Abbreviations: *ALT* alanine transaminase; *AST* aspartate aminotransferase; *ELF* enhanced liver fibrosis; *NAFLD* non-alcoholic fatty liver disease; *QRISK3* QRESEARCH risk estimator version-3.

7.4.4 Associations between metabolic syndrome features and MASLD with predicted cardiovascular risk in people with type 2 diabetes

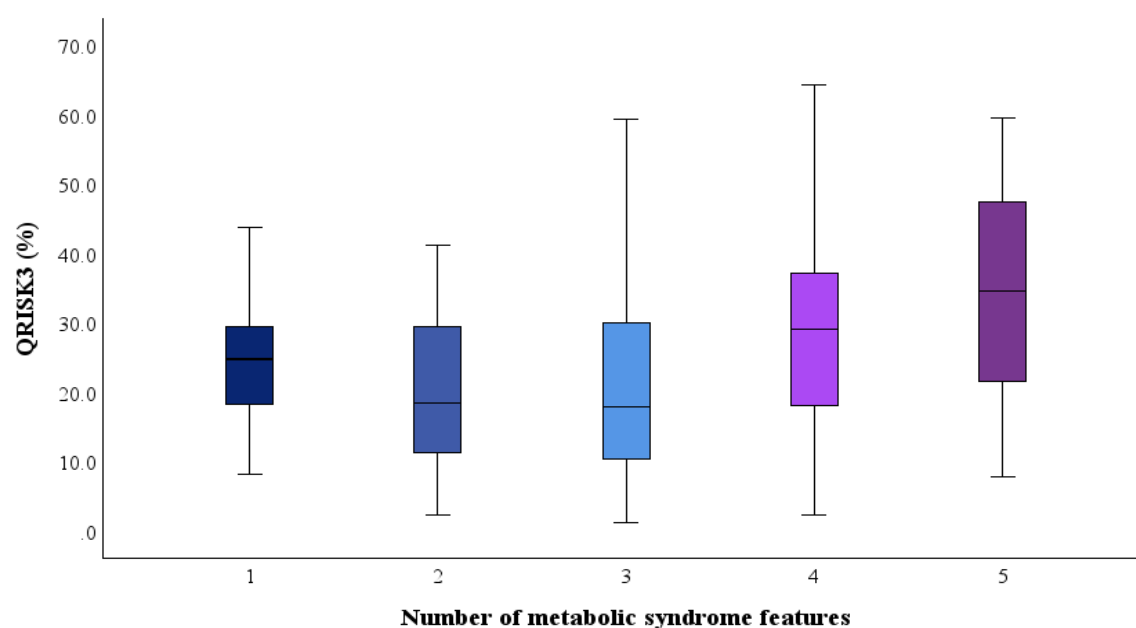
Participants had increasing CVD risk with increasing number of metabolic syndrome features ($p < 0.001$). These data are presented in Table 7.8 and Figure 7.3. There was no significant impact of the presence of moderate-to-severe steatosis on TE on predicted CVD risk, irrespective of the number of metabolic syndrome features, except for those with 2 features, in which those without hepatic steatosis had greater predicted risk. This is presented in Figure 7.4. There was no impact of advanced fibrosis on TE on predicted CVD risk, irrespective of the number of metabolic syndrome features. This is presented in Figure 7.5.

Table 7.8: Predicted cardiovascular risk by number of metabolic syndrome features

Number of metabolic syndrome features	Number of participants	Median QRISK3 (%)
1	11 (5.5%)	24.8 [18.1-30.7]
2	37 (18.5%)	18.5 [10.4-30.0]
3	60 (30.0%)	18.0 [10.4-30.3]
4	64 (32.0%)	29.3 [29.3-34.7]
5	28 (14.0%)	34.7 [20.5-48.1]

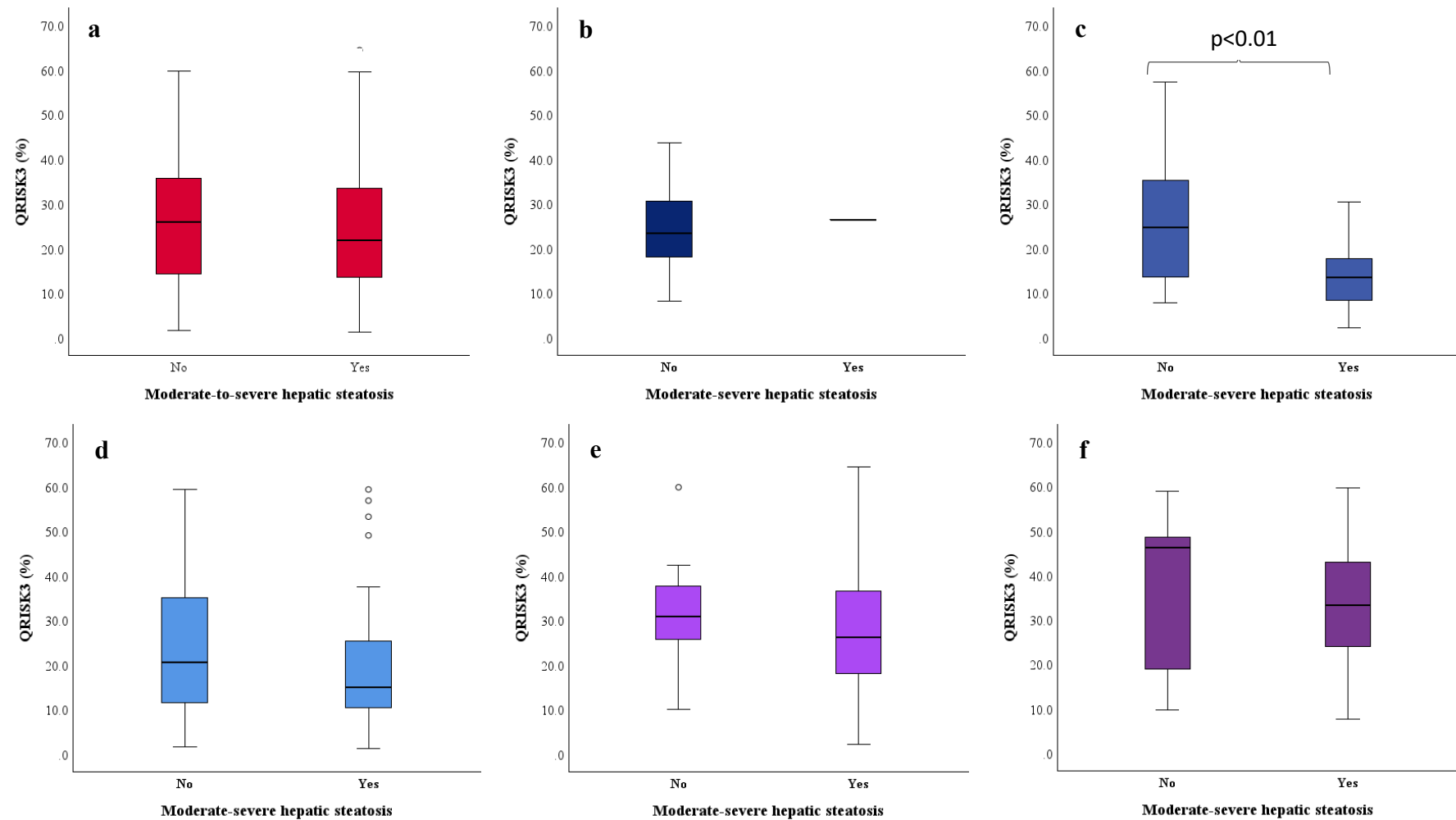
Predicted CVD risk compared between participants with different number of metabolic syndrome features. Abbreviation: *QRISK3* QRESEARCH risk estimator version-3.

Figure 7.3: Predicted cardiovascular risk by number of metabolic syndrome features



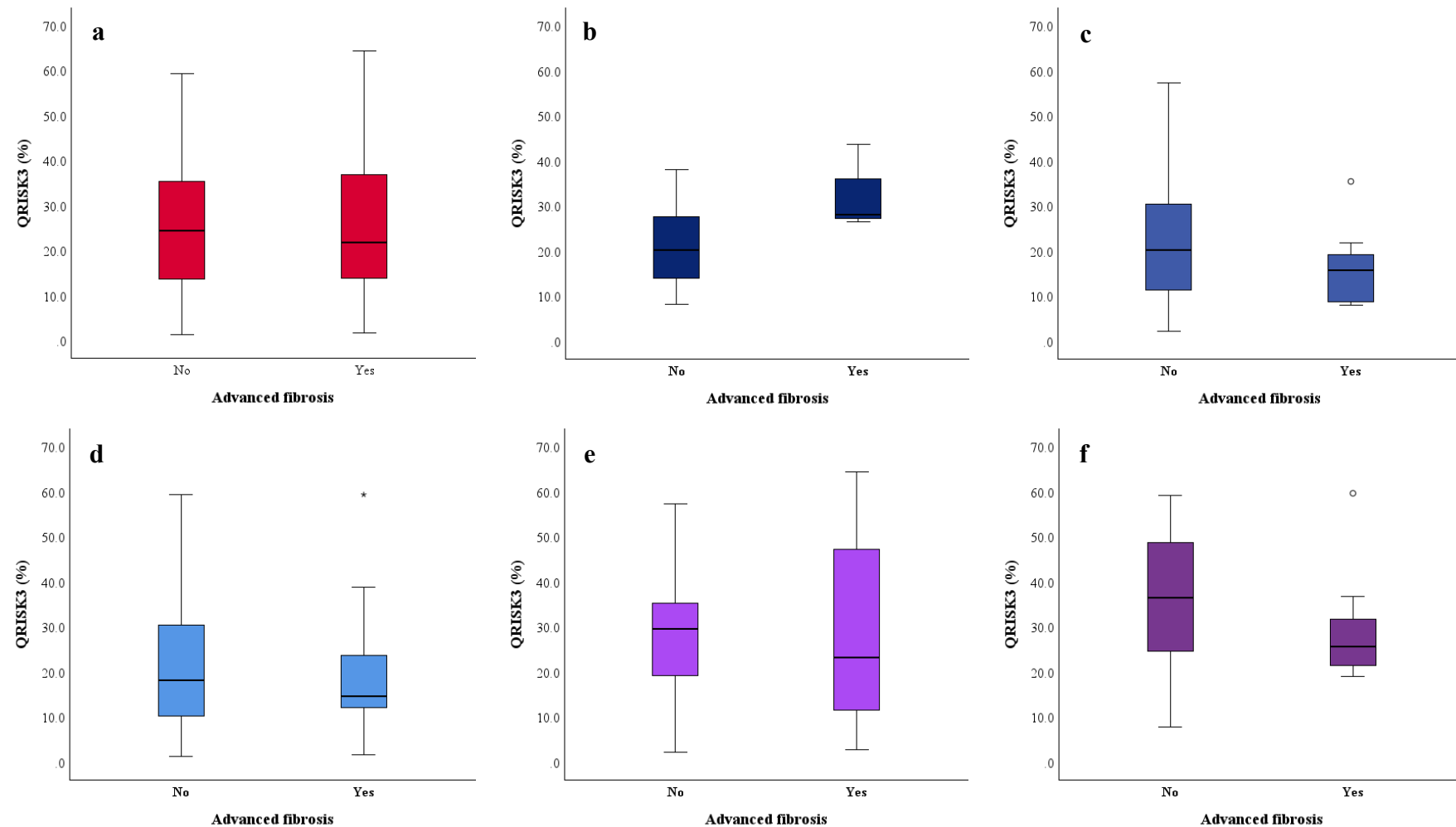
A boxplot presenting predicted CV risk in participants with differing number of metabolic syndrome features. Abbreviation: *QRISK3* QRESEARCH risk estimator version-3.

Figure 7.4: Impact of moderate-severe hepatic steatosis and number of metabolic syndrome features on predicted cardiovascular risk



Impact of moderate-severe hepatic steatosis on predicted CVD risk based on the number of features present from the metabolic syndrome. The graphs represent (a) total cohort and participants with (b) 1, (c) 2, (d) 3, (e) 4, and (f) 5 features of the metabolic syndrome respectively. Abbreviation: *QRISK3* QRESEARCH risk estimator version-3.

Figure 7.5: Impact of advanced hepatic fibrosis and number of metabolic syndrome features on predicted cardiovascular risk



Impact of advanced fibrosis on predicted CVD risk based on the number of features present from the metabolic syndrome. The graphs represent (a) total cohort and participants with (b) 1, (c) 2, (d) 3, (e) 4, and (f) 5 features of the metabolic syndrome respectively. Abbreviation: *QRISK3* QRESEARCH risk estimator version-3.

7.5 Discussion

In this chapter, I presented the associations between routinely collected clinical data, non-invasive measures of hepatic steatosis and fibrosis, and features of the metabolic syndrome with predicted CVD risk. This was explored in a cohort with high predicted CVD risk, evidenced by a median QRISK3 score of 23.2%, and 58.5% of participants had greater than 20% 10-year CVD risk. This is not a surprising observation, given the major impact of T2D on CVD risk for all 200 participants in the study.

7.5.1 Clinical and biochemical measures to predict cardiovascular risk

There were numerous statistically significant correlations between routinely clinical data with QRISK3, though many of these are included in the calculator, such as participant age, systolic BP, and HDL-cholesterol (Endeavour Predict, 2024), making their correlation unsurprising. Though, it was unexpected that body weight and BMI did not correlate with QRISK3 as they are included in the calculator. This is difficult to explain, and possible reasons include multicollinearity between body weight and BMI with other variables (e.g. systolic BP, HDL-cholesterol), the high BMI in the group limiting the analysis, or the relative influence of other features in the calculator (Hippisley-Cox et al., 2017). There was no statistically significant correlation between the WIMD score and predicted CVD risk. However, the analysis exploring the impact of deprivation is limited by the skew of participants living in more deprived areas, as half the cohort lived in the 3 most deprived deciles, previously presented in Figure 5.1.

Recognition of frailty is important, and previous studies observed that frailty scores such as the CFS (Ko et al., 2023), and CCI (Chuang et al., 2017) predict CVD risk. In this analysis, both scores correlated with QRISK3, though on linear regression the impact of the CFS was not significant. Measures of frailty are not input to the QRISK3 calculator, though both frailty and comorbidity associate with age, which is input, and the CCI does score for the presence of diabetes and CKD which are also input. So, these observations are also unsurprising. However, these data do highlight that people living with frailty and T2D do have greater CVD risk and may benefit from therapies to improve risk. Previous studies observed both SGLT-2 inhibitors and GLP-1RAs do improve CVD outcomes in this group (Mone et al., 2024).

Of the liver-related measures only total protein and albumin correlated with QRISK3, and the statistical significance of the association with total protein was lost on linear regression. Whilst the liver does synthesise protein and albumin, and these are reported in the “LFT”, numerous disorders affect circulating total protein and albumin. The most relevant is CKD, because those

with nephropathy have elevated UACR, excreting protein. There were significant correlations between the UACR, creatinine and eGFR with the QRISK3 score. However, the association with the UACR was not statistically significant on linear regression. The QRISK3 calculator does include presence or absence of CKD (Endeavour Predict, 2024), so the association with kidney outcomes is expected, and the associations between these variables with CVD risk is established (Matsushita et al., 2015). None of the liver enzymes correlated with the QRISK3 in this analysis, though previous studies have reported statistical associations between ALT, AST and GGT with CVD risk factors, and CVD outcomes over follow-up including MI, CVD mortality, and heart failure-related outcomes (Choi et al., 2018; Ferrannini et al., 2022; Hasan et al., 2024; Park et al., 2020). This difference may relate to changes observed in ALT in certain populations relevant to this cohort. The ALT falls with increasing age and in those progressive hepatic fibrosis (Dong et al., 2010; Moyana, 2024), which are relevant considerations in this group given their older age and the high proportion with advanced fibrosis. Moreover, the use of predicted CVD risk is different to the previous studies, and we included less participants. It would be interesting to observe whether liver enzymes correlate with observed CVD outcomes in the next 5-10 years', and this is a planned analysis we will undertake in future.

In this study, neither the fasting blood glucose nor HbA1c correlated with QRISK3. It is well-established that measures of glycaemic control associate with microvascular complications, though there is less impact on CVD outcomes (Kunutsor et al., 2024). Therefore, the lack of association in this study is consistent with previous observations. There was lack of association between measures of insulin production and IR (C-peptide, fasting insulin, HOMA-IR) with predicted CVD risk. This was surprising, as previous studies indicate an association between increasing C-peptide levels and HOMA-IR with greater predicted or actual CVD risk (J. H. Lee et al., 2023; Patel et al., 2012; Vladu et al., 2022; Yan et al., 2022). Given these previous studies had larger participant numbers and used actual CVD risk and not predicted risk, it would be interesting to repeat this analysis using the observed CVD risk. This is a part of a planned future study in 5-10 years. The clinical significance of the duration of T2D on predicted CVD risk is questionable given the association with increasing age. Moreover, this statistical association was not observed on linear regression. The only statistically significant lipid parameter associated with QRISK3 was HDL-cholesterol, but this is in the QRISK3 algorithm.

7.5.2 Measures of hepatic steatosis and fibrosis to predict cardiovascular risk

The AST:ALT ratio, ELF test, FIB-4 score and NFS each correlated with the QRISK3, and on linear regression the ELF test and NFS maintained statistical significance to predict the QRISK3. The association between these measures of hepatic fibrosis with the QRISK3 was shown in Table 7.7 and Figure 7.3, in which increasing scores on these tests associated with the increasing CVD risk. The biological processes underpinning the complicated relationship between hepatic fibrosis and CVD risk are multifactorial, with direct (systemic inflammation, endothelial dysfunction) and indirect (greater IR, lifestyle factors and other CVD risk factors) mechanisms implicated (Kasper et al., 2021).

The associations between predicted CVD risk and the ELF test are particularly interesting. This had the most significant statistical correlation and relationship of the fibrosis tests investigated and was consistent in the linear regression model. However, given that the regression model demonstrated only modest explanatory power ($R^2=0.23$), the clinical importance of these associations should be interpreted with caution. Nonetheless, there were statistical correlations observed for each of the ELF test components (hyaluronic acid, PIIINP, TIMP1) highlighting its potential role. Previous studies observed the ELF test correlates closely with occurrence of major adverse liver outcomes in people with MASLD and in the general population (Pearson et al., 2024; Saarinen et al., 2023; Younossi, Anstee, et al., 2021). However, there is little published evidence associating the ELF test with CVD risk (T. Lee et al., 2023; Young et al., 2024), though other studies observe the ELF test associated with vascular inflammation (Stojanovic et al., 2021). Given the ELF test is comprised of individual tests which measure extracellular matrix turnover, fibrogenesis and systemic inflammation (Younossi, Felix, et al., 2021), it stands to reason that it should better predict CVD risk than the other blood biomarkers for liver fibrosis which use indirect risk factors to predict CVD. This may also explain the high false positive rate observed with the ELF test to detect advanced fibrosis in MASLD.

There is a greater evidence base supporting the association between the non-patented tests for hepatic fibrosis with CVD risk (Boeckmans et al., 2024; Yan et al., 2022). The FIB-4 score (Anstee et al., 2024; Higashiura et al., 2022), NFS (Shibata et al., 2024; Takahashi et al., 2018), and AST:ALT ratio (Weng et al., 2015) have each been shown to associate with CVD risk. The results presented in this chapter are consistent with these observations. The FIB-4 score and NFS include age, and the NFS includes diabetes status and albumin in the calculation. Moreover, the statistical association with the FIB-4 score was lost on linear regression. Hence, the association between QRISK3 and the ELF test has greater novelty and significance, given

the ELF test includes unique biochemical variables. Of interest, no measures of inflammation are included in current QRISK3 model, despite the well-established associations between systemic inflammation and CVD outcomes. Further investigation with larger cohorts, and observation of CVD outcomes over follow-up would be of interest.

Neither the BARD score nor the APRI statistically associated with CVD risk. The lack of association with the BARD score may be surprising given the inclusion of BMI and presence of diabetes, also included in the QRISK3 score, and the AST:ALT ratio which independently associated with QRISK3. However, BMI did not correlate with QRISK3, and as all participants had T2D with a mean BMI 33.3 kg/m², most had a score of 2 even before the inclusion of AST:ALT ratio. Therefore the score poorly discriminated the risk of advanced fibrosis, limiting the analysis. Previous studies report some association between the BARD score and CVD mortality (Chung, Jeong, Cho, Yoon, et al., 2022; Park et al., 2022), but the clinical significance is limited given the known associations between the components of the BARD score and CVD. The APRI associates with CVD outcomes in previous studies (L. Z. Chen et al., 2024), though this was not evident in this cohort. It would be useful to determine whether the APRI associates with actual CVD in a future analysis.

We observed no statistical relationship between any measure of hepatic steatosis and predicted CVD. This is consistent with previous observations. Using histological data, there was no association between hepatic steatosis and CVD outcomes, and hepatic fibrosis is the dominant risk factor for CVD outcomes in MASLD (Angulo et al., 2015). Other studies observed little statistical relationship between hepatic steatosis risk as measured by the HSI (Corbin et al., 2023), TE-CAP (Cardoso et al., 2021; Liu et al., 2017), CT (Ahmed et al., 2023), or MRI-PDFF (Roca-Fernandez et al., 2023) with CVD. However, other studies reported associations between CVD risk and the NAFLD-LFS (T. Lee et al., 2023), and TyG (Haring et al., 2024; Lopez-Jaramillo et al., 2023). The latter test was developed as a measure of IR and found to associate with hepatic steatosis, whilst the NAFLD-LFS includes a fasting serum insulin level, also a measure of IR. The association between IR and T2D with CVD risk is well-known (Wang et al., 2022), so the association of these measures with CVD is expected. In this analysis, neither the TyG nor NAFLD-LFS correlated with QRISK3. The poor correlation between the NAFLD-LFS and QRISK3 is less surprising in our cohort given the individual variables included in this algorithm (e.g., fasting insulin, AST and ALT), also did not correlate with the QRISK3 score. However, given previous associations between the NAFLD-LFS and TyG with predicted CVD, future analysis with observed CVD may be of interest.

7.5.3 Features of the metabolic syndrome to predict cardiovascular risk

In this analysis, there was greater QRISK3 score with additional features of the metabolic syndrome. Though, there was no statistically significant impact of the presence of moderate-to-severe hepatic steatosis or advanced hepatic fibrosis observed on TE on the median QRISK3 score, irrespective of the number of metabolic syndrome features present.

The association between the number of metabolic syndrome features and predicted CVD is longstanding, evidenced 20 years ago (Guzder et al., 2006), and these features are input into the QRISK3 calculator. In this cohort, participants with one feature had numerically greater QRISK3 score, though the most likely explanation for this observation is only 11 (5.5%) participants were in this subgroup. However, it was unexpected that the participants with advanced fibrosis on TE-LSM did not have greater CVD risk. Previous studies observe statistical associations between the TE-LSM and all-cause mortality and CVD outcomes in people with T2D, MASLD or pre-existing CVD (Braude et al., 2023; Cardoso et al., 2021; Khan et al., 2020; Shili-Masmoudi et al., 2020), and histological studies demonstrate an association between the degree of liver fibrosis and CVD (Angulo et al., 2015). Some previous studies demonstrated the TE-LSM does not predict CVD or liver outcomes in people with T2D (Grgurevic et al., 2021). It may be that in this study and previous, the lack of association between the TE-LSM and CVD risk is confounded by the impact of high liver fat on the TE-LSM which therefore makes the TE-LSM less reliable. This would explain the disparity between the association of the TE-LSM with CVD risk compared to most of the blood biomarkers investigated in this study. The lack of association between the TE-CAP score and CVD risk was expected and has been shown in several previous studies (Cardoso et al., 2021; Grgurevic et al., 2021; Liu et al., 2017). In the cohort presented in this chapter, the lack of statistical association between the TE-CAP or TE-LSM with CVD risk was consistent in participants with 1, 2, 3, 4, or 5 features of the metabolic syndrome. Nonetheless, it may be of interest to explore this analysis again when 5–10-year outcomes are available in this cohort. This could be explored by inputting the data from this study into national databases to explore hard clinical outcomes (e.g. 3P-MACE or MALO) compared to people without MASLD or T2D. Given the limitation of non-invasive methods in this study, other studies could explore the observed cardiovascular or liver outcomes in people with biopsy proven MASLD such as with the cohort described in chapter 3 and 4.

7.6 Summary and limitations

In this chapter, I presented data exploring the associations between non-invasive measures of hepatic steatosis and fibrosis with predicted CVD risk, and the associations between these variables and metabolic syndrome. The observation that numerous biomarkers for liver fibrosis associated with predicted CVD risk is of clinical interest in this group with a significant burden of CVD. These associations highlight the potential importance of identifying underlying liver fibrosis in the management of people with T2D, and that these biochemical tests function beyond identifying liver fibrosis and may act to guide prognosis and management. We did not find an association between biomarkers of hepatic steatosis or TE measures of steatosis with predicted CVD risk, highlighting that hepatic steatosis is unlikely a risk factors for CVD in the absence of significant fibrosis.

7.6.1 Clinical significance

The correlation between the ELF test and each of its component parts with the QRISK3 score is important. Current NICE guidance suggests using the ELF test to screen for advanced fibrosis in people with hepatic steatosis, whilst international guidance advocates for its use in the identification of liver fibrosis in those with risk factors such as T2D or obesity. However, these results indicate that those with greater ELF test scores may have greater CVD risk and therefore warrant additional review and aggressive treatment of their risk factors. Further investigation would be needed to confirm this association is independent of other factors, and replicable in a larger dataset using actual CVD events and could be extended to investigate this association in cohorts with or without MASLD. In this study, the ELF test associated more closely with QRISK3 than non-patented fibrosis scores, such as the FIB-4 and NFS, but is frequently less available given its cost. Observations such as these may support growing use of the ELF test in people with T2D. It is also interesting to note that an increasing number of metabolic syndrome features associates with predicted CVD risk. Whilst this is previously known, it is of major clinical importance to recognise reversible risk factors and communicate risk with patients. It will be interesting to repeat this analysis with observed 5–10-year CVD outcomes, to mitigate some of the limitations in this analysis.

7.6.2 Limitations

There are some limitations to this study:

- Predicted CVD risk was used because follow-up data are currently unavailable for observed CVD risk. I intend to repeat this analysis with 5–10-year outcome data.
- There was no control group without T2D or without any features of the metabolic syndrome. This may have supported the statistical analysis further.
- There is some statistical bias given some variables investigated in the chapter are included in the QRISK3 algorithm. This was highlighted throughout the discussion.
- Since undertaking the analysis the QRISK4 calculator is available for clinical use. The QRISK3 was retained because QRISK4 is an incremental update highly unlikely to change the study conclusions.
- The FLI could not be calculated and BMI was used to determine the presence of obesity as a metabolic syndrome feature, because waist circumference was not measured.
- There are no liver biopsy data available from the participants, limiting comment on the accuracy of each non-invasive test compared with the gold standard reference.

Chapter Eight:

**Perioperative assessment for MASLD and
advanced fibrosis in people undergoing
bariatric surgery**

8.1 Introduction

The prevalence of MASLD in people with obesity is 75%, approximately 2-3 times greater than in lean individuals, and obesity accelerates steatohepatitis and fibrosis (Quek et al., 2023; van Son et al., 2024; Younossi et al., 2025). Given these associations it is unsurprising that most people undergoing bariatric surgery have MASLD. However, only recent guidance suggests to consider screening for advanced fibrosis in such cohorts. People with obesity who undergo bariatric surgery should be tested using the FIB-4 score, followed by the ELF test or TE in those with a FIB-4 score ≥ 1.30 . Those with cirrhosis should be evaluated with ultrasound for portal hypertension and consideration for upper gastrointestinal endoscopy for oesophageal varices (EASL-EASD-EASO, 2024; Patton et al., 2021; Rinella, Neuschwander-Tetri, et al., 2023). This supports treatment measures to minimise perioperative risk.

In Swansea, there have been several recent cases of liver cirrhosis identified intraoperatively, which is troubling given the potential perioperative morbidity and mortality, particularly in people undergoing BPD or RYGB (Geerts & Lefere, 2023; Jan et al., 2015; Patton et al., 2021; Younus et al., 2020). Though, meaningful pre-operative investigation to assess for hepatic fibrosis was not taken in any of the 100 patients in one cohort receiving bariatric surgery in Swansea between 2007-2014, but surgery did significantly improve liver enzymes (Roberts et al., 2023). This is not a problem unique to Swansea, and there is longstanding recognition of liver cirrhosis identified macroscopically during bariatric surgery in around 4% of patients (Brolin et al., 1998; Jan et al., 2015; Younus et al., 2020). Nonetheless, bariatric surgery is probably the best treatment for MASLD fibrosis, given consistent improvements reported on several measures of steatohepatitis and fibrosis (Bower et al., 2015; de Brito et al., 2021; Fakhry et al., 2019; Y. Lee et al., 2019), and the reduction in adverse liver outcomes in those undergoing bariatric surgery (G. Wang et al., 2023). Though, 1 in 8 people undergoing bariatric surgery will develop new or progressive MASLD fibrosis, particularly in those undergoing malabsorptive procedures such as BPD or RYGB (Y. Lee et al., 2019). Additionally, there are well-established reductions in CVD events, all-cause morbidity and mortality, and frequently remission of various obesity-related comorbidities such as T2D, obstructive sleep apnoea, and hypertension, amongst others (Rajabi et al., 2024; Syn et al., 2021). As such, bariatric surgery should be undertaken in those living with obesity and MASLD, including those with MASLD cirrhosis, if there are no signs of hepatic decompensation and complications such as portal hypertension and oesophageal varices are recognised, and managed appropriately.

Whilst bariatric surgery supports resolution of hepatic fibrosis, and may reduce referrals to hepatology, patients with advanced fibrosis prior to surgery may benefit from hepatology care postoperatively. This permits monitoring strategies for decompensated disease and HCC, and consideration of pharmacological or non-pharmacological measures to improve hepatic and CVD outcomes. Many patients may be eligible for, and benefit from, participation in clinical trials. Ultimately, these patients should be assessed and managed by a multidisciplinary team. Locally, there is currently no agreed process for perioperative liver disease screening, or management of those identified with liver fibrosis.

In this chapter, I aim to pilot the use of non-invasive tests in the perioperative screening pathway for bariatric surgery patients in SBUHB.

8.2 Aims of this chapter

The specific aims of this chapter are to explore the:

- i. feasibility of non-invasive tests for liver fibrosis in the perioperative assessment for bariatric surgery.
- ii. frequency of patients with MASLD and clinically significant liver fibrosis in people undergoing bariatric surgery.
- iii. frequency of patients requiring referral to hepatology services at 6-12 months following bariatric surgery.
- iv. correlation between blood biomarkers and TE in patients prior to, and 6-12 months following bariatric surgery.
- v. patient views and acceptability of the additional tests as part of the perioperative work-up for bariatric surgery.

8.3 Methods

8.3.1 Study design

This was a pilot study to implement a screening pathway for advanced hepatic fibrosis in people undergoing bariatric surgery for obesity in SBUHB. The study design was presented in detail in chapter two. In brief, patients attending the preoperative assessment clinic for bariatric surgery in SBUHB were invited to undergo additional liver assessment including a blood test and TE to assess their risk of MASLD and hepatic fibrosis. The feasibility of using these tests was evaluated as the proportion of participants who agreed to have the additional tests and the proportion of participants with valid blood test-based fibrosis and TE scores, both before and after surgery. The liver assessment was repeated at a clinic visit 6-12 months postoperatively, to inform the need for referral to the hepatology team. Participants were recruited July-November 2023, and follow-up visits were undertaken March-August 2024.

Participants with a TE-LSM ≥ 8.2 kPa ($\geq$ F2 fibrosis) were discussed with their local hepatologist by the surgical consultant prior to surgery in case of need for further investigation or management. Participants with a TE-LSM ≥ 8.2 kPa at the 6–12-month postoperative visit were referred to their local hepatology team for ongoing follow-up.

8.3.2 Participants

Study participants were patients planning to undergo bariatric surgery under the WIMOS team, based in SBUHB. These patients were referred from across South Wales and Mid Powys. All participants were aged ≥ 18 years, had a BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-related comorbidities, and had attempted weight loss strategies with specialist support under hospital weight management services. All patients gave verbal consent to participate.

8.3.3 Data collection

Data were collected prospectively at the preoperative assessment clinic (usually within one month of surgery), and a follow-up clinic visit at 6-12 months postoperatively. At both visits, additional blood tests (AST, GGT) were collected at the same time as their usual preoperative tests, to calculate the FIB-4 score, NFS and APRI. The collection and analysis of biochemical tests were detailed in chapter two. Participants underwent TE at both clinic visits performed by me. Further detail about the validation of TE undertaken in clinic was described in chapter two. Patients provided feedback using a standardised questionnaire, presented in Appendix III.

The degree of hepatic steatosis was defined by the TE-CAP. A TE-CAP < 302 dB/m was normal, a TE-CAP 302-336 dB/m (equivalent S1-S2 steatosis) was consistent with moderate

steatosis, and a score ≥ 337 dB/m was consistent with severe hepatic steatosis. The degree of hepatic fibrosis was defined by the TE-LSM, APRI, FIB-4 score, and NFS. A TE-LSM < 8.2 kPa was normal, 8.2-9.7 kPa was consistent with moderate fibrosis ($\geq F2$ fibrosis), and a TE-LSM ≥ 9.7 kPa was consistent with advanced ($\geq F3$) fibrosis. An APRI ≥ 0.7 , AST:ALT ratio ≥ 0.8 , BARD score ≥ 2 , FIB-4 score ≥ 1.30 , and NFS ≥ -1.455 represented significant risk of advanced ($\geq F3$) fibrosis.

8.3.4 Funding and ethical approval

No additional funding was received to undertake this study. The work was an approved service evaluation project by the JSRC and Information Governance at SBUHB in June 2023. The study design was presented in detail in chapter two.

8.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503). Data presentation was detailed in chapter two. The statistical significance of changes in data following a normal distribution were calculated using paired t test. Statistical significance was usually considered at $p < 0.05$. The statistical significance of correlations of normally distributed data were determined by Pearsons's correlation coefficient and was considered at $p < 0.01$.

8.4 Results

8.4.1 Participant characteristics

Twenty-two patients agreed to have the preoperative liver assessment and are included in the analysis. Their characteristics are shown in Table 8.1.

Table 8.1: Patient characteristics

Characteristic	Total cohort (n=22)
Age (years)	44.8±11.6
Female/Male	18 (81.8%)/4 (18.2%)
Diagnosis of T2D	15 (68.2%)
Weight (kg)	129.8±24.7
BMI (kg/m ²)	45.0±6.5
TE-CAP (dB/m)	321.2±61.3
TE-LSM (kPa)	11.2±7.2
ALT (U/L)	37.7±27.8
ALP (U/L)	81.2±26.8
AST (U/L)	26.9±12.0
GGT (U/L)	45.4±22.7
Platelets (x10 ⁹ /L)	307.5±86.1
TC (mmol/L)	4.9±1.0
LDL (mmol/L)	2.6±0.9
HDL (mmol/L)	1.2±0.3
TG (mmol/L)	1.9±1.0
HbA1c (mmol/mol)	50.0±17.9
AST:ALT ratio	0.9±0.3
APRI	0.3±0.1
BARD score	2.9±0.9
FIB-4 score	0.7±0.3
NFS	-1.5±1.8

The characteristics of patients included in this study. Abbreviations: *ALP* alkaline phosphatase *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

8.4.2 Feasibility of non-invasive tests for liver fibrosis in the perioperative assessment for bariatric surgery

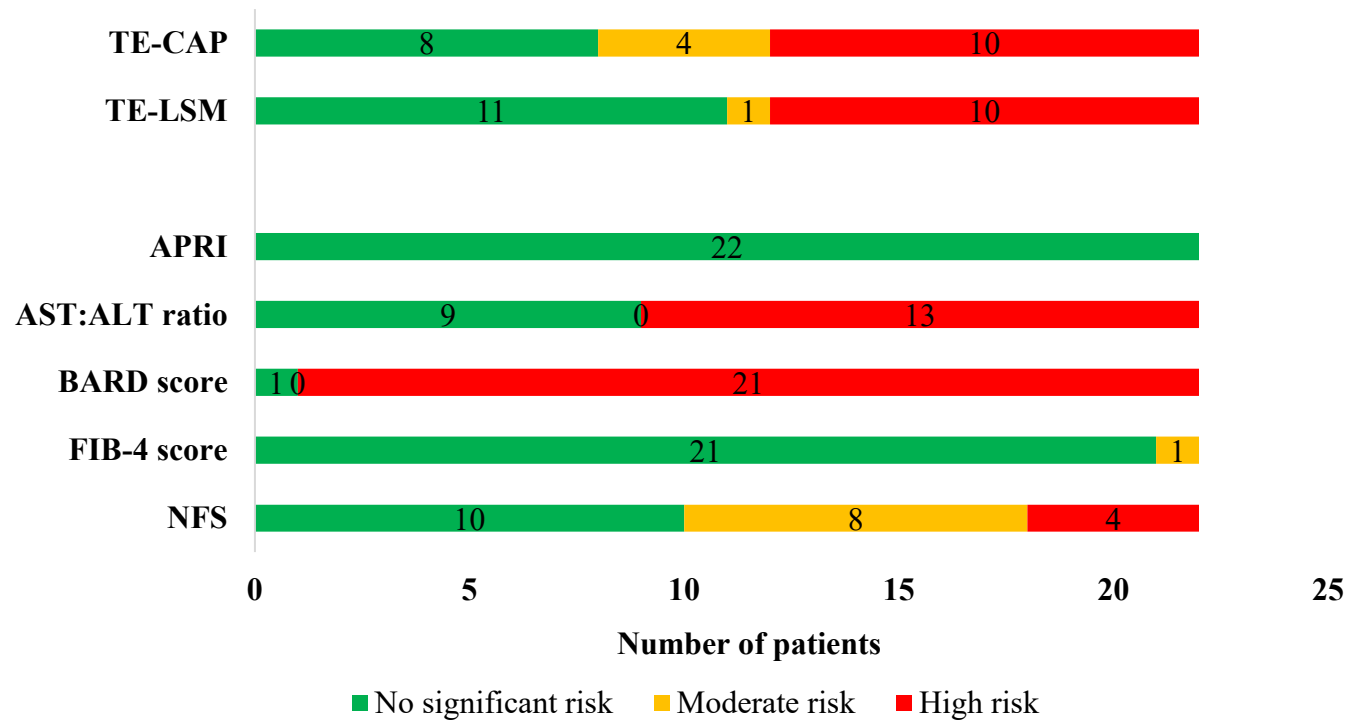
All 22 (100%) patients approached to take part in this pilot study agreed, and none declined. Similarly, all 22 (100%) patients who agreed to take part in the pre-operative phase had valid TE scores, and all 22 (100%) participants had valid blood biomarker test results.

At the postoperative visit, 18 (81.8%) patients had repeat TE, and of these 17/18 (94.4%) had valid blood test scores. Of the 4 patients without follow-up TE, 1 declined due to moving out of area, 1 declined due to recent diagnosis of endometrial cancer, 1 had several missed follow-up appointments, and 1 did not undergo surgery. The 1 participant with repeat TE but missing blood test results did not have a repeat AST alongside the other postoperative blood tests.

8.4.3 Frequency of patients with MASLD and clinically significant liver fibrosis in people undergoing bariatric surgery

At preoperative assessment, 4 (18.2%), and 10 (45.4%) patients had moderate or severe hepatic steatosis, respectively, and the remaining 8 (36.4%) had a normal TE-CAP. Ten (45.4%) and 1 (4.6%) had a TE-LSM consistent with advanced or moderate fibrosis, and the remaining 11 (50.0%) had a normal TE-LSM. Of those with moderate or advanced fibrosis on TE prior to surgery, none required further investigation and proceeded to surgery. Using the APRI, AST:ALT ratio, BARD score, FIB-4 score and NFS, 0 (0.0%), 13 (59.1%), 21 (95.4%), 1 (4.6%), and 12 (54.6%) patients had significant risk for advanced fibrosis, respectively. These data are presented in Figure 8.1.

Figure 8.1: Risk of MASLD and advanced fibrosis at the preoperative visit



Risk of severe hepatic steatosis (TE-CAP) or advanced fibrosis (TE-LSM, AST:ALT ratio, APRI, BARD score, FIB-4 score, and NFS). Abbreviations: *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *CAP* controlled attenuation parameter; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *TE* transient elastography.

8.4.4 Frequency of patients requiring referral to hepatology services at 6-12 months following bariatric surgery

Patients were reviewed after a median 6.9 [5.8-8.6] months. Of the 18 patients with follow-up TE, 9 (50.0%) had LSG and 9 (50.0%) had RYGB. All three patients who had bariatric surgery, but no follow-up TE, had LSG with normal TE-CAP and TE-LSM scores preoperatively. The patient who did not undergo surgery had severe hepatic steatosis, and a normal TE-LSM.

At follow-up, 15/18 (83.3%) had a lower TE-CAP compared to their preoperative score, and 16/18 (88.9%) had lower TE-LSM. Prior to surgery, 11/18 (61.1%) required discussion with hepatology, and at follow-up 7/18 (38.8%) required referral ($p=0.18$). Of the 7 participants requiring referral, 6 had improved TE-LSM scores, though 1 participant had a greater TE-LSM at follow-up following RYGB. Changes in the number of participants requiring hepatology referral are shown in Table 8.2, and changes in the proportion of participants with varying stages of hepatic steatosis and fibrosis on TE are in Figure 8.2.

There were statistically significant reductions in several measures over follow-up, but not in blood biomarkers for hepatic fibrosis. Data are presented in Table 8.3.

Table 8.2: Changes in number of patients requiring referral over follow-up

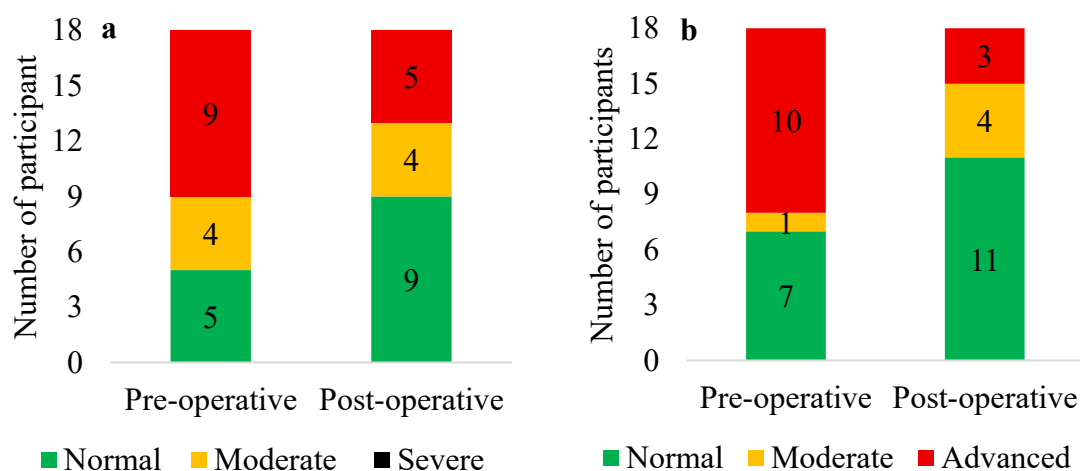
Characteristic	Preoperative (n=18)	Postoperative (n=18)*	Significance
TE-LSM (kPa)	11 (61.1%)	7 (38.9%)	NS
APRI	0 (0.0%)	0 (0.0%)	NS
AST:ALT ratio	11 (61.1%)	14 (77.8%)	NS
BARD score	18 (100.0%)	18 (100.0%)	NS
FIB-4 score	1 (5.6%)	1 (5.6%)	NS
NFS	10 (55.6%)	6 (33.3%)	NS

Patients requiring hepatology referral at the preoperative and postoperative visits. *Indicates missing 1 patient data for APRI, AST:ALT ratio, BARD score, FIB-4 score and NFS at the postoperative visit. Abbreviations: *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *FIB-4* fibrosis-4; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* not significant *TE* transient elastography.

Table 8.3: Changes in non-invasive measures of MASLD over follow-up

Characteristic	Preoperative (n=18)	Postoperative (n=18)*	Significance
Weight (kg)	134.7±23.9	104.7±21.7	<0.001
BMI (kg/m ²)	46.1±5.6	35.9±6.3	<0.001
TE–CAP (dB/m)	329.8±59.7	289.7±61.7	<0.01
TE–LSM (kPa)	12.0±7.6	7.8±4.0	<0.01
ALT (U/L)	35.9±22.2	21.3±9.7	<0.05
ALP (U/L)	80.6±24.6	89.1±19.8	NS
AST (U/L)	29.5±12.5	20.7±12.1	<0.05
GGT (U/L)	43.5±21.9	26.9±15.7	<0.001
Platelets (x10 ⁹ /L)	299.4±78.1	265.0±66.7	<0.01
TC (mmol/L)	4.9±1.0	4.6±0.8	NS
LDL (mmol/L)	2.6±0.9	2.5±0.9	NS
HDL (mmol/L)	1.2±0.3	1.2±0.2	NS
TG (mmol/L)	1.9±1.0	1.5±0.6	<0.05
HbA1c (mmol/mol)	48.4±18.7	38.8±10.7	<0.01
APRI	0.3±0.1	0.3±0.1	NS
AST:ALT ratio	1.0±0.3	1.1±0.4	NS
BARD score	3.0±0.9	3.2±0.7	NS
FIB-4 score	0.8±0.3	0.8±0.4	NS
NFS	-1.4±1.8	-1.9±1.4	NS

Changes over follow-up. *missing 1 patient for AST, APRI, AST:ALT, BARD, FIB-4 and NFS. Abbreviations: *ALP* alkaline phosphatase; *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *BMI* body mass index; *CAP* controlled attenuation parameter; *FIB-4* fibrosis-4; *GGT* gamma-glutamyl transferase; *HDL* high-density lipoprotein; *LDL* low-density lipoprotein; *LSM* liver stiffness measure; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* not significant; *T2D* type 2 diabetes; *TC* total cholesterol; *TE* transient elastography; *TG* triglyceride.

Figure 8.2: Changes in participants stage of hepatic steatosis and fibrosis

A stacked bar chart presenting changes in the proportion of participants with varying stages of (a) hepatic steatosis, and (b) hepatic fibrosis over follow-up on TE. Figure adapted with permission (Williams, Min, et al., 2025)

8.4.5 Correlation between blood biomarkers and transient elastography in patients prior to, and 6-12 months following bariatric surgery

To investigate whether the non-invasive tests could predict advanced fibrosis, blood test results were correlated with the TE-LSM. This was undertaken using both the data prior to bariatric surgery, and at 6–12-months follow-up. None of the observed blood biomarkers correlated with the TE-LSM. These data are presented in Table 8.4.

Table 8.4: Correlation analysis between blood biomarkers and transient elastography

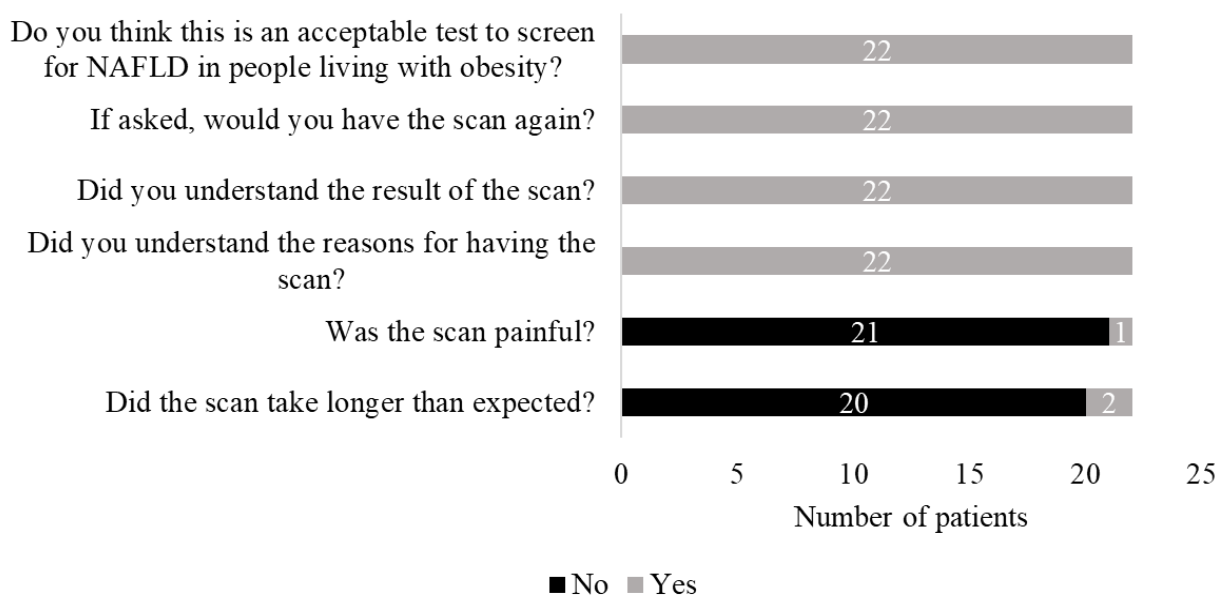
Preoperative (n=22)		
	Pearson correlation	Significance
ALT (U/L)	r=0.21	NS
AST (U/L)	r=0.12	NS
APRI	r=0.29	NS
AST:ALT ratio	r=-0.30	NS
BARD score	r=-0.34	NS
FIB-4 score	r=0.17	NS
NFS	r=0.30	NS
Postoperative (n=17)		
	Pearson correlation	Significance
ALT (U/L)	r=0.13	NS
AST (U/L)	r=0.11	NS
APRI	r=0.12	NS
AST:ALT ratio	r=-0.10	NS
BARD score	r=0.19	NS
FIB-4 score	r=0.23	NS
NFS	r=0.08	NS

Correlations between blood biomarkers used to predict hepatic fibrosis and the TE-LSM in people prior to and 6-12 months following bariatric surgery. Abbreviations: *ALT* alanine transaminase; *APRI* aspartate transaminase-to-platelet ratio index; *AST* aspartate transaminase; *BARD* BMI-AST/ALT ratio-diabetes mellitus; *FIB-4* fibrosis-4; *NFS* non-alcoholic fatty liver disease fibrosis score; *NS* not significant.

8.4.6 Patient views and acceptability of the additional tests as part of the perioperative work-up for bariatric surgery

Participants were given a feedback form to complete following TE taken in the preoperative assessment clinic. All participants felt that TE was an acceptable test to screen for liver disease in people with obesity, and all would have the scan again if needed. Similarly, all participants reported that they understood the scan result and reasons for the scan. However, 1 (4.6%) patient felt the scan was painful, and 2 (9.1%) patients felt the scan took longer than anticipated. These results are presented in Figure 8.3.

Figure 8.3: Patients feedback in preoperative assessment clinic



A stacked bar chart presenting feedback from patients in the preoperative bariatric surgery clinic about the use of TE. Black colour indicates a response of “No”, and grey colour indicates a response of “Yes”. Abbreviation: *NAFLD* non-alcoholic fatty liver disease.

8.5 Discussion

In this chapter, I aimed to determine the feasibility of implementing preoperative assessment for MASLD fibrosis in people undergoing bariatric surgery. I also aimed to determine the proportion of participants with MASLD, and clinically significant fibrosis based on non-invasive tests in both preoperative and postoperative care. Finally, I aimed to determine whether preoperative TE was acceptable to patients undergoing bariatric surgery.

Pre-operatively, all participants agreed to have the additional assessment and all participants had valid blood tests and TE. At follow-up, three declined assessment for reasons unrelated to the tests used, and one did not have bariatric surgery. Of those with postoperative TE follow-up, one participant did not repeat AST due to confusion about blood tests needed alongside her usual dialysis. These data support the feasibility of the proposed intervention. Feasibility of blood biomarkers may seem unsurprising in this setting, the feasibility of TE in people with obesity may be less expected. This is because TE is often considered inappropriate in those with high BMI given concerns over accuracy and difficulty to obtain a valid result (Puthenpura et al., 2020). However, a valid TE-LSM was achieved in all participants. In other studies using TE preoperatively for bariatric surgery, 87.9-99.4% of participants were observed to have a valid TE-LSM (Ali et al., 2022; Avcu et al., 2021; Eilenberg et al., 2021; Garg et al., 2018; Yang et al., 2021), demonstrating the process is feasible elsewhere. The process was often challenging and some patients required prolonged scanning time to achieve a valid score, which would need to be considered when planning for TE in a perioperative pathway in this group. The feasibility of the process in clinical practice was further supported by the lack of adverse safety outcomes during the intervention, most participants adhered to the follow up review, and the reported participant acceptability of the additional TE described below.

There are doubts surrounding TE accuracy in this group, and therefore the validity of this process (Puthenpura et al., 2020). This is particularly concerning for the TE-CAP, which poorly predicts hepatic steatosis in people with obesity (Karlsson et al., 2017). These observations support the findings in chapter three investigating test accuracy in a cohort with a median BMI 36.3 kg/m², in which there was poor association between the TE-CAP and histological steatosis stage. However, severe steatosis is not as clinically relevant as hepatic fibrosis, given it is the latter which associates with CVD and perioperative outcomes (Geerts & Lefere, 2023; Jan et al., 2015; Patton et al., 2021; Younus et al., 2020). When using the appropriate probe, the TE-LSM retains accuracy to identify fibrosis when BMI is >30 kg/m² (Cao et al., 2022), though in those with severe obesity such as this cohort, the very high TE-CAP scores may result in

overestimation of fibrosis using the TE-LSM. Similarly, the TE-LSM may not be as accurate in patients with hepatic congestion, a potential issue for some patients undergoing bariatric surgery such as the participant who required dialysis in this real-world pilot study. Nonetheless, the TE-LSM is more accurate in people with advancing obesity than most blood biomarkers to predict advanced fibrosis. There are concerns around the accuracy of the AST:ALT ratio, BARD score, and NFS, with mixed observations for the APRI in people with obesity (de Carli et al., 2020; Drolz et al., 2021; Qadri et al., 2022; Schmitz et al., 2020). However, there is good evidence that the FIB-4 score retains accuracy to predict advanced fibrosis in people with obesity, like the TE-LSM (de Carli et al., 2020; Drolz et al., 2021; Qadri et al., 2022; Schmitz et al., 2020), and is more reliable than isolated liver enzymes as was previous practice in Swansea (Roberts et al., 2023).

None of the observed blood biomarkers correlated with the TE-LSM, which raises a concern around test consistency. This may suggest that in high risk groups either TE or the ELF test is the superior investigation, though this study is limited by the lack of ELF testing and would be particularly useful to include in future work.. The ELF test is reliable in people with a higher BMI (Kjaergaard et al., 2024). However, the test was not used in this pilot study due to the associated expense of the test and funding limitations. This may be particularly interesting to investigate given the limitations of the other blood biomarkers used in this study in younger cohorts, such as the FIB-4 score and NFS (McPherson et al., 2017). Confirming accuracy of these blood biomarkers was not the aim of the study, and discussion is limited by the lack of biopsy data. Such an investigation would require a much larger cohort of patients, with paired liver biopsy data in this clinical setting.

It is because the FIB-4 score and TE-LSM relatively maintain accuracy in people with obesity that guidance advocates for their use in this setting (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Applying these guidelines, only one participant would be identified at risk of advanced fibrosis preoperatively. This was the participant with the greatest TE-LSM score preoperatively, suggesting the greatest degree of fibrosis. Postoperatively, the only participant identified at risk of advanced fibrosis using the FIB-4 score had an elevated TE-LSM requiring referral, and was the participant with a greater TE-LSM post-RYGB despite a normal preoperative score. Based on the TE-LSM scores, the FIB-4 score appeared to miss several people with clinically significant fibrosis. This may be related to the reduced accuracy of the FIB-4 score in younger people (McPherson et al., 2017), such as this cohort. This limitation may be avoided by use of the ELF test in future studies as discussed above. On the

other hand, the NFS identified 12 (54.5%) patients requiring referral, which may be challenging to manage alongside other preoperative considerations. Whilst the number identified at moderate or high risk using the NFS was similar as the TE-LSM, of the 12 patients identified at risk by the NFS, 5 (41.7%) had a normal TE-LSM and it missed 5 patients with elevated TE-LSM. In previous studies, the NFS triggered excess referrals, and performed poorly in people with obesity, T2D, or those younger than 35 years or older than 65 years, making it unattractive in this group (Barb et al., 2021; Ciardullo et al., 2020; McPherson et al., 2017; Qadri et al., 2022). Neither the NFS nor the FIB-4 score correlated with the TE-LSM score in this study. Applying this screening algorithm in a larger cohort of patients undergoing bariatric surgery with paired liver biopsy data may improve confidence in the proposed screening approach.

Whilst the TE-LSM may better predict the degree of hepatic fibrosis, it is not a practical first-line test. Firstly, there is the cost of the device which may be too high given current financial pressures, and its use would require trained technicians, with additional clinic time. Therefore, use of TE as a second-line test seems most appropriate (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). However, concerns around potential false negative results using the FIB-4 score in by this study emphasises the need to consider this carefully, and undertake larger pilot studies trialling the ELF test with paired liver biopsy before introducing in practice. Additionally, these findings highlight the need to consider postoperative screening, particularly following a relatively malabsorptive procedure, such as RYGB. We observed one participant with a significantly greater TE-LSM post-RYGB requiring referral despite normal preoperative scores. This case and several others, would have been missed at follow-up using the FIB-4 score only to screen preoperatively given this participant and most others had an initially normal result. Given that approximately 1 in 8 people will experience worsening hepatic fibrosis following bariatric surgery, and it is more likely in those undergoing a malabsorptive procedure (Y. Lee et al., 2019), consideration of routinely screening patients post-operatively also is needed.

There was a substantial burden of MASLD and clinically significant fibrosis in this cohort. Preoperatively, 63.6% participants had moderate-severe hepatic steatosis based on the TE-CAP score, and 50.0% had clinically significant hepatic fibrosis based on the TE-LSM. Whilst the prevalence of hepatic steatosis is high, it is lower than observed in larger studies using biopsy data. This may reflect our smaller study size, or use of non-invasive tests to define steatosis. In other studies, a TE-CAP ≥ 302 dB/m was identified in 64.8-78.0% of people undergoing bariatric surgery (Avcu et al., 2021; Yang et al., 2021), like our observation. However, the

proportion of participants in our study with clinically significant hepatic fibrosis based on TE-LSM was greater than elsewhere, with other studies identifying a TE-LSM ≥ 8.2 kPa in 6.0-13.9% of participants (Avcu et al., 2021; Yang et al., 2021). Extending the pilot study with additional liver-related clinical history (e.g. alcohol use, family history) and other biochemical tests discussed may determine whether patients undergoing bariatric surgery in South Wales do have greater fibrosis risk. Additionally, an important reflection in the interpretation of the TE-LSM both at baseline and over follow-up is that the very high baseline TE-CAP and the substantial reduction in the TE-CAP associated with weight loss over follow-up may confound the TE-LSM. This may overestimated baseline hepatic fibrosis, augmenting the reported burden of advanced fibrosis in the cohort. Moreover, given the rapid reduction in TE-CAP alongside weight loss over follow-up, the substantial change in TE-LSM may overestimate the resolution of hepatic fibrosis over this period. Given our smaller cohort and lack of liver biopsy data, it is difficult to draw conclusions on MASLD prevalence.

Given the concerns around the feasibility of TE and scanning time required, it was reassuring that patients found this approach acceptable. We observed all 22 participants reported TE was acceptable preoperatively, and all would have TE again if needed. All reported understanding the need for the scan and the result of the scan. Most reported the scan was not painful (95.5%) and that it did not take longer than expected. The previously referenced studies using TE in people undergoing bariatric surgery did not report patient feedback on TE. However, there are similar observations reported by previous studies exploring TE acceptability in people with other forms of CLD (Malekzadeh & Poustchi, 2011; Marshall et al., 2015; Matthews et al., 2019; Xia et al., 2019), and some with MASLD risk factors (Archer et al., 2024; Knight et al., 2020). Further quantitative analysis with larger numbers would be useful, and a qualitative study of patients undergoing bariatric surgery may identify themes around why patients find it acceptable and their views on MASLD screening generally as these are lacking in the literature.

Moving forward, collaboration between the WIMOS and hepatology teams within the WIMOS catchment area is needed. This would be to develop a screening pathway for MASLD to support perioperative safety, and possibly postoperative monitoring. The results of this pilot study will support these discussions, and additional pilot studies should extend to include greater patient numbers to confirm feasibility, paired liver biopsy data to confirm test accuracy, explore the cost-efficacy of various screening approaches in this cohort, and include the ELF test. Additionally, further quantitative and qualitative studies to explore the acceptability and views of such a process with patients utilising the service would be important. In the current health-

economic climate and based on current international consensus, use of simple blood tests first-line seems appropriate and feasible in this group, but work to investigate the benefits of the ELF test need to be taken before implementing a pathway. This would improve the current perioperative assessment, in which no meaningful assessment for hepatic fibrosis takes place.

8.6 Summary and limitations

In this chapter, I presented a pilot study to screen for MASLD and clinically significant hepatic fibrosis in people undergoing bariatric surgery. Additional blood tests and TE appeared feasible given all participants agreed to participate and had valid results. The use of bariatric surgery improved non-invasive measures of hepatic steatosis and fibrosis over a median 6.9-month follow-up. However, there were concerns around the consistency of the tests used and further investigation is warranted before implementing a perioperative screening approach. The process was acceptable to those who participated in this pilot study.

8.6.1 Clinical significance

The results of this study will support future discussions between the WIMOS and hepatology teams to develop an appropriate perioperative pathway. Preoperative identification of significant liver disease permits treatment to reduce perioperative risk or undertake further investigation to exclude cirrhosis-related complications such as portal hypertension or oesophageal varices which may affect patient outcomes.

8.6.2 Limitations

There are some limitations to this study:

1. The lack of biopsy data limits conclusions about the prevalence of MASLD and hepatic fibrosis in this group, and assessment of test accuracy.
2. The small sample size limits the generalisability of the results, and subsequent local pilot studies should include greater numbers.
3. The non-invasive tests used did not include patented fibrosis scores such as the ELF test. Further work to include this test is important.
4. Patient feedback was limited to a binary response to confirm general acceptability. Further work to expand this would be interesting, as would qualitative studies exploring patient views and acceptability.

Chapter Nine:

**Awareness of MASLD and views of
MASLD screening in people with diabetes
and clinicians practising diabetes &
endocrinology or primary care in Wales**

9.1 Introduction

Our understanding of MASLD as a distinct disease entity has developed rapidly in recent years (Stefan et al., 2025), though disease awareness amongst clinicians (Alqahtani et al., 2025; Bergqvist et al., 2013; Sebastiani et al., 2021), the general public (Ghevariya et al., 2014; Leung et al., 2009; Tan et al., 2021), and those at risk of MASLD (Ciardullo et al., 2021; Goh et al., 2016; Wieland et al., 2015) remains poor, highlighting an unmet public health need (Alemany-Pages et al., 2020). This lack of awareness may reflect the rapidity of our understanding and clinical interest in MASLD. Most studies exploring patient or clinician understanding of the disease were undertaken 10 years or more ago, and I am unaware of such investigation in a UK cohort. Historically, both the public and clinicians would often attribute advanced liver disease in people with no clear cause to undisclosed alcohol ingestion, despite their metabolic risk factors, highlighting stigma in CLD. Worryingly, stigma in the diagnosis of MASLD continues to be reported (Ciardullo, 2024; Schomerus et al., 2022; Younossi, AlQahtani, et al., 2024). It is in part because of the stigma felt by patients using the NAFLD nomenclature that there was a major change in the disease definition and classification (Rinella, Lazarus, et al., 2023).

It is imperative that patients understand their metabolic risk factors give rise to complications beyond the well-recognised CVD consequences of diabetes or obesity, such as stroke or MI. This is because knowing you have risk or a diagnosis of liver disease related to such risk factors can result in meaningful lifestyle changes which improve CVD risk factors (Kjaergaard et al., 2024). Better disease understanding supports patient acceptance for additional screening and investigation for MASLD (Alemany-Pages et al., 2020). Acceptance of the tests taken to screen for disease is essential when considering a screening programme, highlighted by the Wilson and Junger principles discussed previously (Wilson & Junger, 1968).

People with T1D or T2D have significantly different risk of MASLD. People with T1D have close to the population risk, though risk increases in those with greater bodyweight, age, and duration of diabetes (Souza et al., 2024). People with T2D have a two-fold increase in MASLD risk with greater risk of advanced fibrosis compared with the general population (Younossi, Golabi, et al., 2024). Previous studies highlight that people with T2D typically underestimate their MASLD risk (Ciardullo et al., 2021; Wieland et al., 2015), though there is little literature on the perceived risk of developing MASLD in people with T1D. Previous studies indicate that screening for MASLD and advanced liver disease in people with T2D or signs of metabolic dysfunction is acceptable (Allen et al., 2025; Knight et al., 2020; Lindfors et al., 2025), though I am unaware of studies exploring the views of people with T1D on MASLD screening.

In practice, hepatic fat is a common incidental finding on abdominal imaging taken for other reasons but is frequently overlooked by clinicians. One study observed that 30% of abdominal imaging incidentally reported the presence of excess hepatic fat, but only 1.6% of patients had this formally recorded as a diagnosis and only a third had further evaluation (Karhiaho et al., 2024). In practice, recognition of the negative health impact of excess hepatic fat is often overlooked, because clinicians may misinterpret this as a benign or even expected feature in people living with T2D or obesity. Naturally, this may adversely impact patient outcomes as the identification of people unknowingly living with advanced fibrosis is missed, and targeted therapies to reverse excess CVD risk and monitoring for hepatic complications are forgotten. Misunderstandings about MASLD, and its treatment amongst practising clinicians have been described (Alqahtani et al., 2025; Bergqvist et al., 2013; Sebastiani et al., 2021), though not in UK-based doctors. Moreover, in view of recent updates to screening guidelines for MASLD in people at metabolic risk such as those with T2D (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), clinician acceptability surveys in the UK would be of interest. This is because often the practicability, costs, and perceived clinical utility of screening for MASLD act as barriers to undertaking such investigations in practice (Castera et al., 2025; Lee et al., 2024; Williams, Nagaraj, et al., 2025).

In this chapter, I aim to assess the understanding of patients with diabetes and practising clinicians who frequently manage patients living with T2D in primary and secondary care about their understanding of MASLD and views around MASLD screening.

9.2 Aims of this chapter

The specific aims of this chapter are to explore the:

- i. awareness of liver disease in people with diabetes, and their views on additional tests to screen for MASLD.
- ii. awareness of MASLD amongst practising doctors in Wales, and their views on screening for MASLD

9.3 Methods

9.3.1 Study design

This is a questionnaire-based service evaluation project to explore patient and clinician understanding of MASLD, and their views on MASLD screening. Patients with T1D or T2D were asked to complete an anonymised questionnaire prior to their routine diabetes clinic appointment in SBUHB. The paper survey form and QR code used are presented in Appendix IV and discussed in chapter two. Surveys were completed September 2023-February 2024.

Clinician surveys were completed by GPs and consultants or other doctors working in diabetes and endocrinology. Surveys were advertised at professional meetings as described in chapter two, and circulated by email to these networks. The paper survey and QR code used are shown in the Appendix. Surveys were completed August 2023-April 2025.

9.3.2 Participants

Patient participants were people with T1D or T2D who were managed under secondary care services in SBUHB. Patients with other forms of diabetes were excluded. Clinicians surveyed were consultants or other doctors practising diabetes in Wales, or GPs practising in Swansea.

9.3.3 Data collection

Questionnaires were completed using paper forms in clinic or by following a QR code to an electronic version hosted using the Qualtrics website. The surveys used were described in chapter two, and presented in Appendix IV, and used a 5-point Likert scale to gauge patient responses to six statements about MASLD. In the clinician survey, participants were asked to respond to seven statements and record their response on a scale of 1 (strongly disagree) to 100 (strongly agree). Data were managed using a Microsoft Excel database.

9.3.4 Funding and ethical approval

No additional funding was received for this work. Surveys used in the study were completed voluntarily, anonymously, and did not require access to patient medical records, thereby limiting generalisability of the data. Therefore ethical approval was not required.

9.3.5 Statistical analysis

Statistical analysis was performed using SPSS, version 29 (IBM Inc., Armonk, US). Figures were produced using Microsoft Excel for Microsoft 365 (version 2503), or SPSS. Presentation of data was described in chapter two. The significance of differences in non-parametric data were determined by the Mann-Whitney U test. Statistical significance was defined as $p < 0.05$.

9.4 Results

9.4.1 Participant characteristics

Four-hundred-and-three patients with diabetes are included in the analysis. Their self-reported characteristics are presented in Table 9.1. Patients who reported they had T2D were more likely to report pre-existing liver disease than people with T1D (32 (11.8%) vs 5 (3.8%), $p<0.01$). A further 12 (3.0%) participants reported that they were previously told they had significant risk of developing liver disease (8 MASLD, 4 ALD), of whom 10/272 (3.7%) reported they had T2D and 2/131 (1.5%) had T1D ($p=0.23$).

A total of 70 clinician responses are included in the analysis, of whom 47 worked in diabetes and endocrinology (19 consultants, 3 specialty and associate specialist doctors, and 25 resident doctors), and 23 worked in general practice (18 GPs, 5 GP resident doctors).

Table 9.1: Patient characteristics

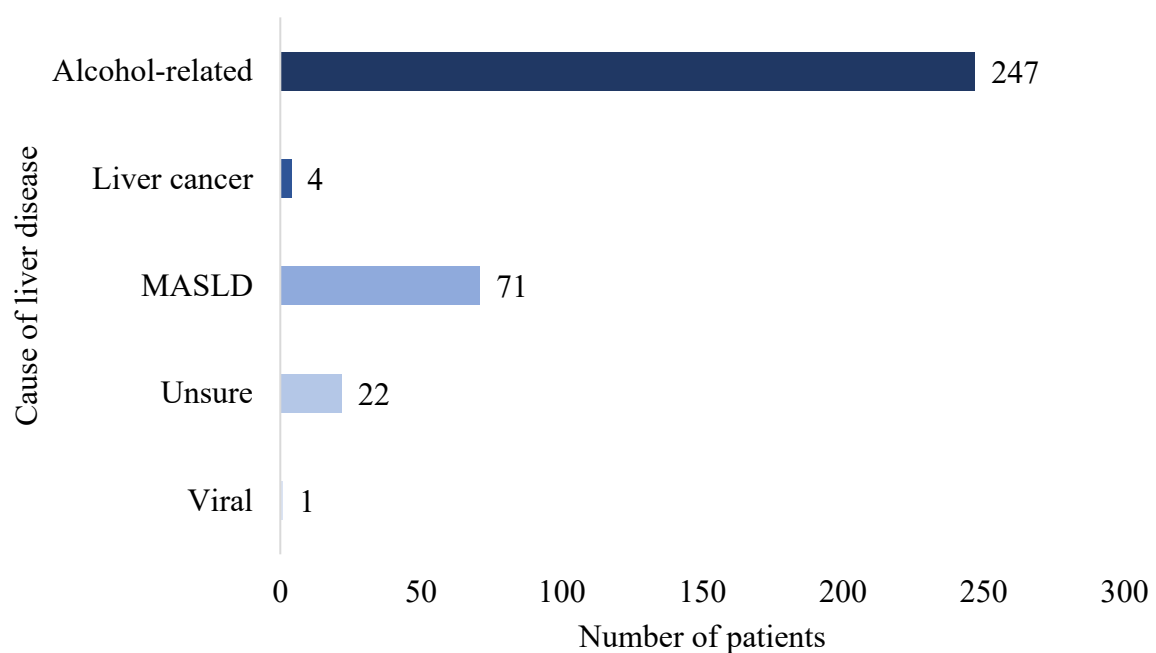
Characteristic	Total cohort (n=403)
Age (years)	57.3±14.8
Gender:	
- Male	204 (50.6%)
- Female	197 (48.9%)
- Transgender	2 (0.5%)
Type of diabetes:	
- T1D	131 (32.5%)
- T2D	272 (67.5%)
Previous diagnosis of liver disease	37 (9.2%)
- MASLD	- 32 (7.9%)
- ALD	- 2 (0.5%)
- Drug-induced	- 1 (0.3%)
- Liver cancer	- 1 (0.3%)
- PSC	- 1 (0.3%)

Self-reported characteristics of patients with diabetes in the study. Abbreviations: *ALD* alcohol-related liver disease; *MASLD* metabolic dysfunction-associated steatotic liver disease; *PSC* primary sclerosing cholangitis; *T1D* type 1 diabetes; *T2D* type 2 diabetes.

9.4.2 Awareness of liver disease in people with diabetes, and their views on additional tests to screen for MASLD

Patients with diabetes were asked what they believed to be the commonest cause of liver disease in Wales over the last 10 years. A total of 58 (14.4%) patients responded with 2 or more answers to this question and so were excluded, resulting in 345 (85.6%) respondents included. A total of 247 (71.6%) felt ALD is the commonest cause of liver disease in Wales, and 71 (20.6%) patients reported that the commonest cause of liver disease in Wales is MASLD. These data are presented in Figure 9.1.

Figure 9.1: The commonest causes of liver disease in Wales according to respondents

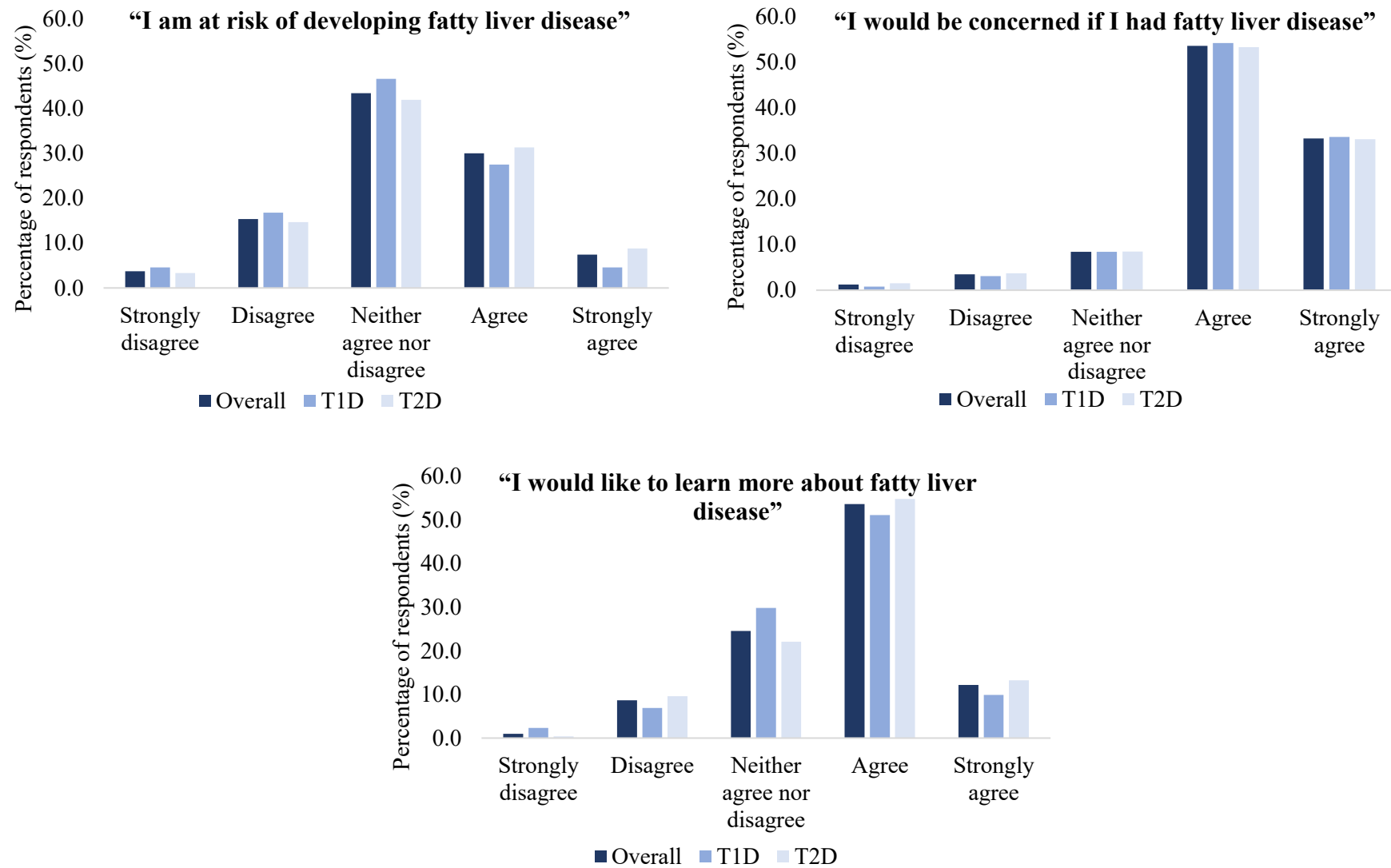


The commonest cause of liver disease in Wales according to patient responders. Abbreviation: *MASLD* metabolic dysfunction-associated steatotic liver disease.

Patients were asked to respond to statements to explore their understanding of MASLD using a 5-point Likert scale. In response to “I am at risk of developing fatty liver disease”, 151 (37.5%) responded “agree” or “strongly agree”. There was no statistically significant difference between the number of people with T1D responding “agree” or “strongly agree” compared to people with T2D (32.1 vs 40.1%, $p=0.12$). In response to “I would be concerned if I had fatty liver disease”, 350 (86.9%) responded “agree” or “strongly agree”. There was no significant difference in this response between people with T1D or T2D (86.4 vs 87.8%, $p=0.70$). In response to “I would like to learn more about fatty liver disease”, 265 (65.8%) responded “agree” or “strongly agree”. There was no statistical difference in this response between those with T1D or T2D (61.1 vs 68.1%, $p=0.17$). Data are presented in Figure 9.2.

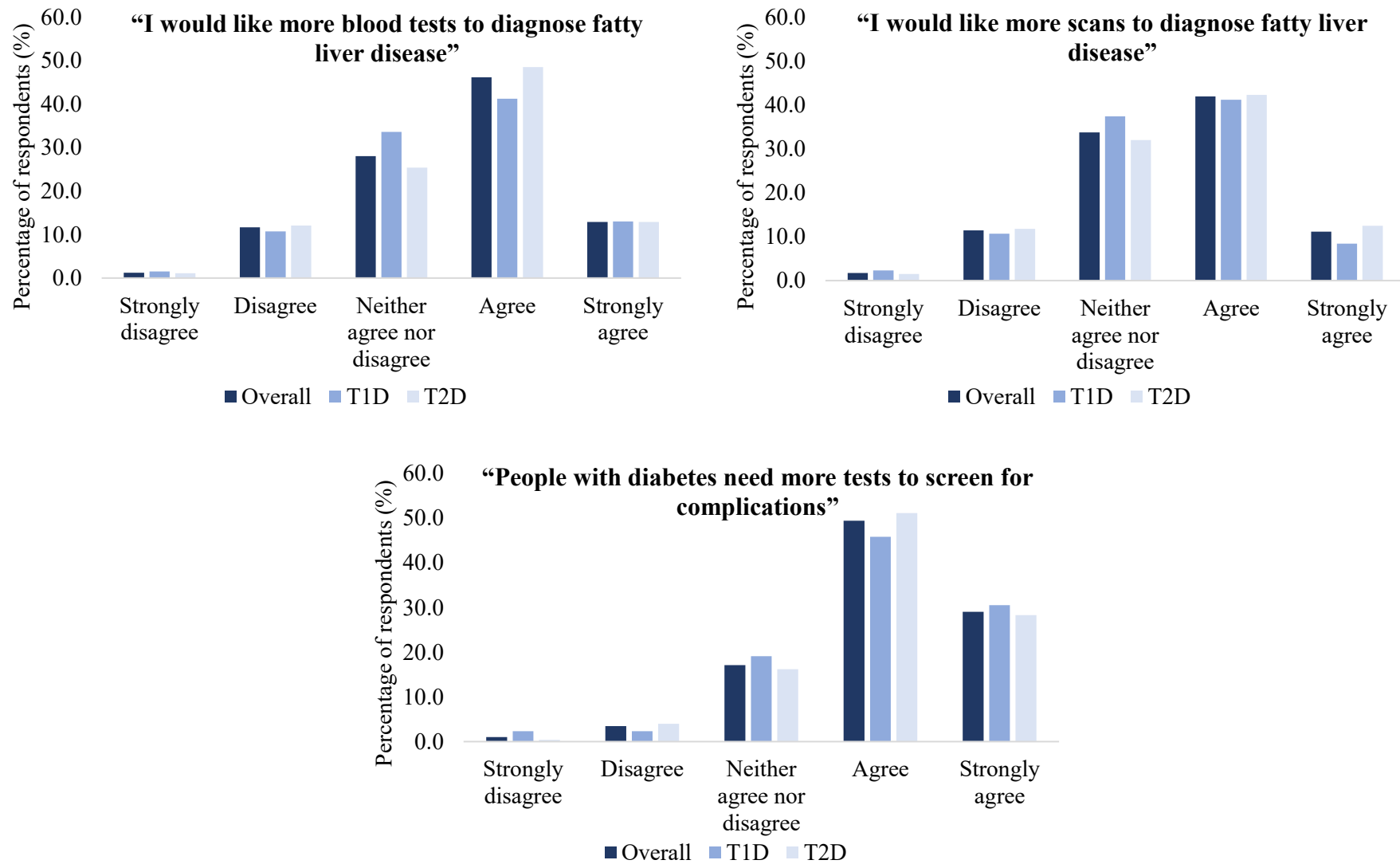
Patients were asked to respond to statements to determine their views about MASLD screening. In response to “I would like more blood tests to diagnose fatty liver disease”, 238 (59.1%) responded “agree” or “strongly agree”. There was no statistical difference between people with T1D or T2D (54.2 vs 61.4%, $p=0.17$). In response to “I would like more scans to diagnose fatty liver disease”, 214 (53.1%) responded “agree” or “strongly agree”, with no statistical difference between those with T1D or T2D (49.6 vs 54.8%, $p=0.33$). Finally, in response to “People with diabetes need more tests to screen for complications”, 316 (78.4%) responded “agree” or “strongly agree”. There was no statistical difference in this response between people with T1D or T2D (76.3 vs 79.4%, $p=0.48$). Data are presented in Figure 9.3.

Figure 9.2: Patient views about MASLD



Patient views about their risk and concern around developing MASLD. Abbreviations: *T1D* type 1 diabetes; *T2D* type 2 diabetes.

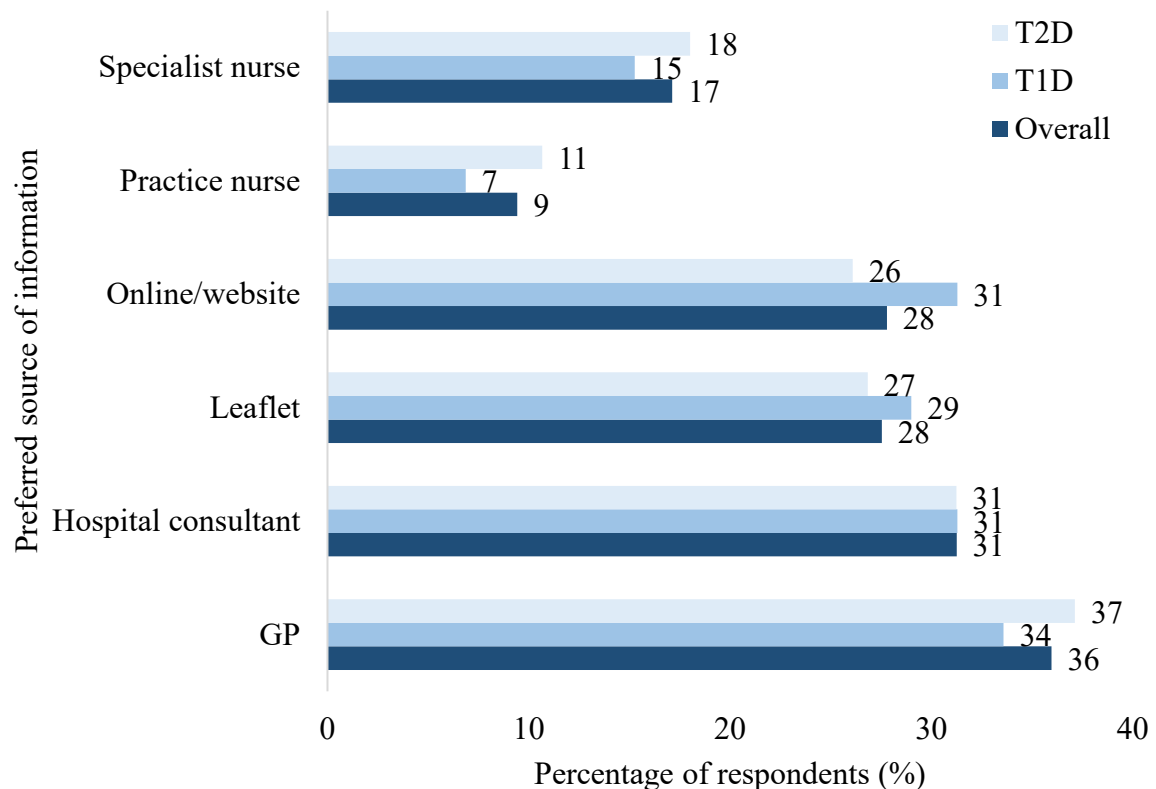
Figure 9.3: Patient views about MASLD screening



Patient views about screening for MASLD Abbreviations: *T1D* type 1 diabetes; *T2D* type 2 diabetes.

Patients who responded they would like to learn more about liver disease in diabetes were asked to cite their preferred sources of further information, and to choose as many as desired. The most popular source was the GP, followed by hospital consultant. There was no significant difference in the preferences reported by people with T1D compared to T2D. Data are presented in Figure 9.4.

Figure 9.4: Preferred sources of further information about liver disease in diabetes



Preferred sources of further information about liver disease in people with diabetes. Abbreviations: *GP* general practitioner; *T1D* type 1 diabetes; *T2D* type 2 diabetes.

9.4.3 Awareness of MASLD amongst practising doctors in Wales, and their views on screening for MASLD

Clinicians were asked to estimate the prevalence of MASLD. The median estimate in the global population was 30.0%, and in Wales 34.5%. In people with T2D the global prevalence was estimated at 51.0%. The clinicians had a median estimated MASLD prevalence in their practice of 20.0% over the last 2 weeks, with no significant difference in those practising diabetes & endocrinology compared to general practice (27.0 [11.0-39.0] vs 12.0 [9.0-24.0]%, $p=0.08$). These data are presented in Table 9.2. There were no significant differences in any of these responses by clinician speciality, presented in Figure 9.5.

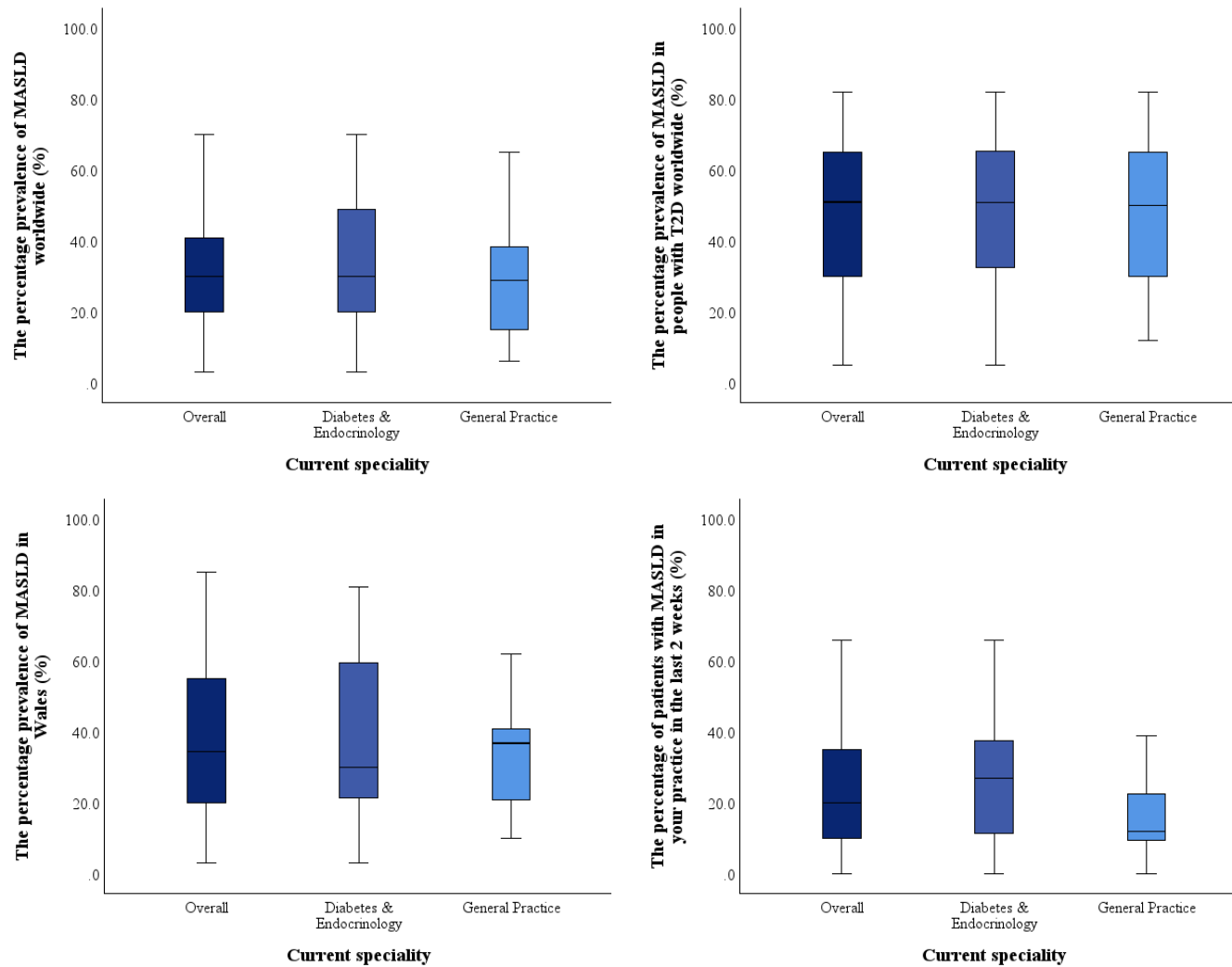
All 70 (100%) participants believed MASLD is an important health issue. Overall, 40 (57.1%) reported they would usually refer patients identified with fatty liver for further assessment, with no significant difference between those practising diabetes & endocrinology compared to general practice (27/40 (67.5%) vs 13/23 (56.5%), $p=0.38$). Twenty-eight (40.0%) reported they had made a referral regarding MASLD in the last three months, with no significant difference between those in diabetes and endocrinology or general practice (17/40 (42.5%) vs 11/23 (47.8%), $p=0.68$). Participants were asked to report which teams they had referred a patient with MASLD to in the last 3 months and could select multiple options. The referrals made by respondents are presented in Figure 9.6.

Table 9.2: Clinician responses to estimate the prevalence of MASLD

On a scale of 1-100, estimate each of the following:	Response in the total cohort (%) [n=70]
i. The percentage prevalence of MASLD worldwide:	30.0 [20.0-41.3]
ii. The percentage of prevalence of MASLD in people with T2D worldwide:	51.0 [30.0-65.3]
iii. The percentage prevalence of MASLD in Wales:	34.5 [20.0-55.5]
iv. The percentage of patients in your practice with MASLD in the last 2 week:	20.0 [10.0-35.3]

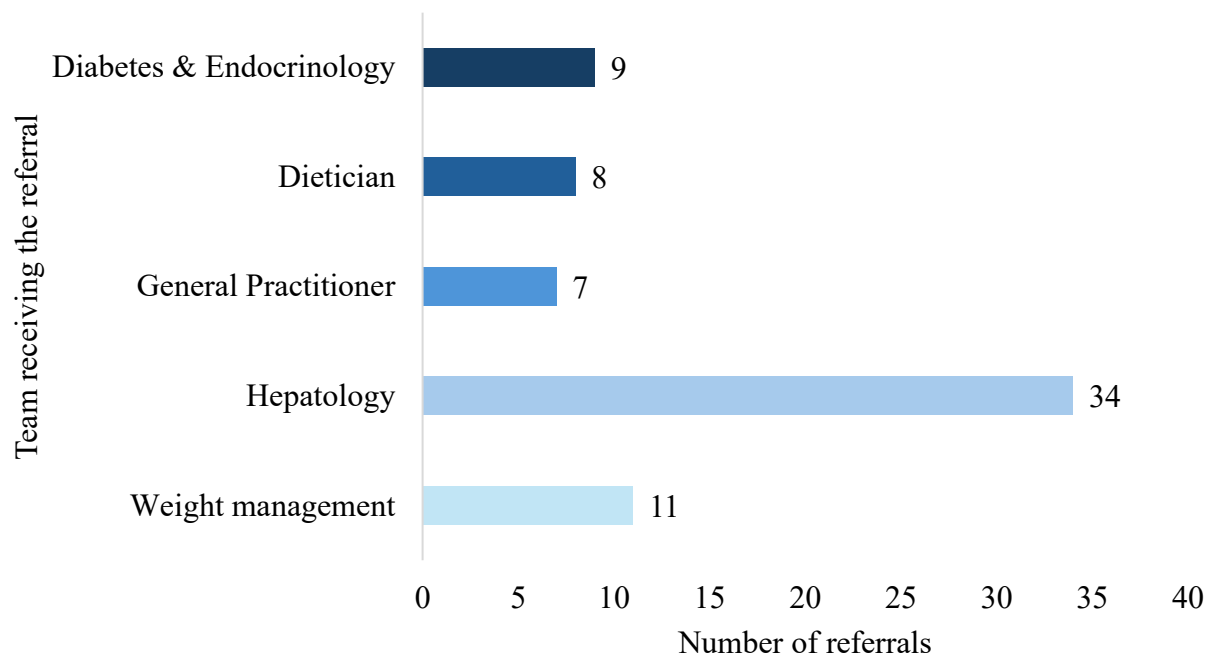
Clinician responses to estimate the prevalence of MASLD. Abbreviation: *MASLD* metabolic dysfunction-associated steatotic liver disease.

Figure 9.5: Comparing responses on MASLD prevalence by clinician speciality



Boxplots comparing the responses between clinicians practising in diabetes & endocrinology with general practice. Abbreviations: *MASLD* metabolic dysfunction-associated steatotic liver disease; *T2D* type 2 diabetes.

Figure 9.6: Teams receiving referrals for MASLD from survey participants



A bar chart presenting the teams who received referrals for patients with suspected MASLD from survey participants in the last 3 months.

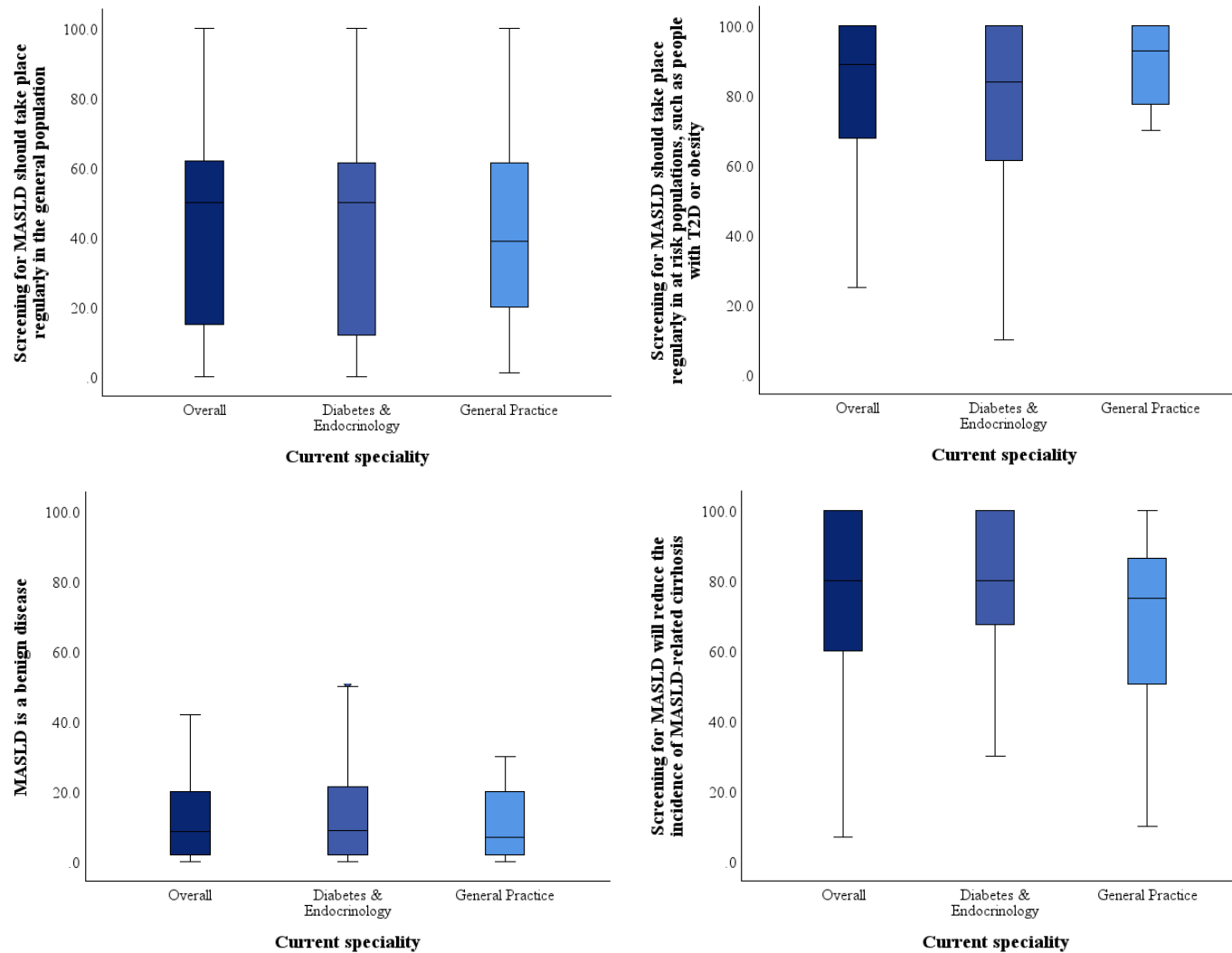
Clinicians were asked to respond to statements about MASLD screening. There were strong agreements with “screening for MASLD should take place regularly in at risk populations, such as people living with diabetes or obesity”, and “screening for MASLD will reduce the incidence of MASLD-related cirrhosis”. There was strong disagreement with “MASLD is a benign disease”. These data and responses to other statements are presented in Table 9.3. There was a significantly greater score given by clinicians practising diabetes & endocrinology compared to general practice for “additional blood tests are an appropriate screening strategy for MASLD” (74.0 [45.0-92.0] vs 56.0 [21.0-70.0], $p<0.05$), but not for any other statement. The scores attributed to each statement in those practising diabetes and endocrinology are compared to those in general practice in Figure 9.7.

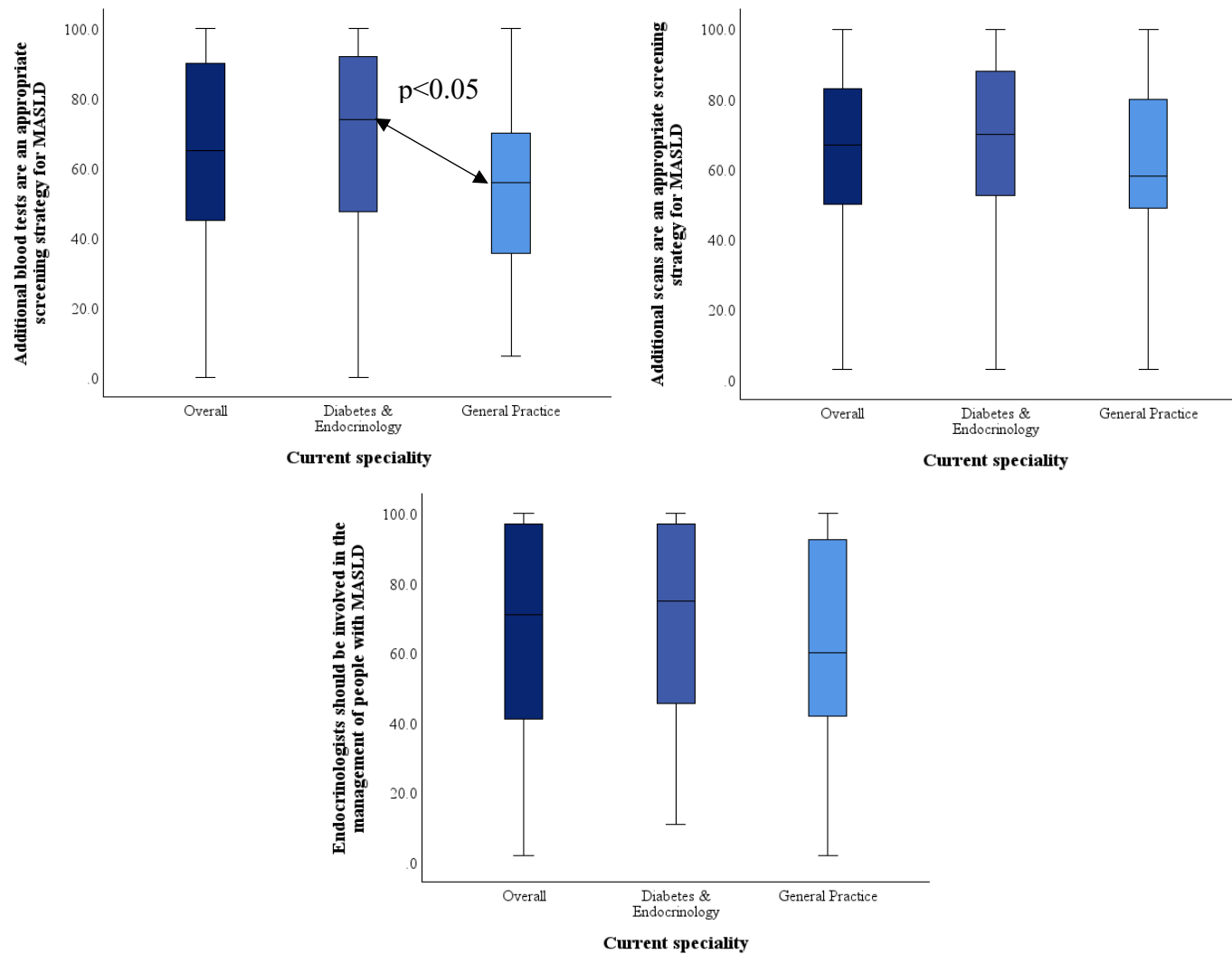
Table 9.3: Clinician responses to statements about MASLD screening

On a scale of 1-100, rate how much you agree with each of the following statements:	Response in the total cohort (%) [n=70]
i. Screening for MASLD should take place regularly in the general population:	50.0 [14.8-63.0]
ii. Screening for MASLD should take place regularly in at risk populations, such as people living with diabetes or obesity:	89.0 [66.8-100.0]
iii. MASLD is a benign disease:	8.5 [2.0-20.8]
iv. Screening for MASLD will reduce the incidence of MASLD-related cirrhosis:	80.0 [60.0-100.0]
v. Additional blood tests are an appropriate screening strategy for MASLD:	65.0 [44.8-90.0]
vi. Additional scans are an appropriate screening strategy for MASLD:	67.0 [50.0-83.3]
vii. Endocrinologists should be involved in the management of people with MASLD:	71.0 [40.8-97.5]

Clinician responses to statements about MASLD screening. Abbreviation: *MASLD* metabolic dysfunction-associated steatotic liver disease.

Figure 9.7: Comparing responses to statement about MASLD screening by clinician speciality





Boxplots comparing responses to statement about MASLD screening by clinician speciality. Abbreviations: *MASLD* metabolic dysfunction-associated steatotic liver disease; *T2D* type 2 diabetes.

9.5 Discussion

In this chapter, I sought to explore the understanding of people with diabetes and the clinicians who are frequently involved in their care about the risk of MASLD, and to explore their views about MASLD screening. This was undertaken using self-reporting, anonymous surveys using both paper-based and electronic forms as preferred by the participants.

9.5.1 Patient survey responses

In this survey, 11.8% of patients with T2D reported pre-existing liver disease, compared with 3.8% of patients with T1D, giving a three-fold increased prevalence of pre-existing liver disease in those with T2D. This is in keeping with previous investigations, in which people with T2D have a 2-3-fold greater prevalence of MASLD than people with T1D or the general population (Souza et al., 2024; Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024). However, the risk of MASLD in people with T2D is about 65% (Younossi, Golabi, et al., 2024), and in people with T1D is about 22% (Souza et al., 2024), so there is likely a significant number of people in this cohort with undiagnosed liver disease, predominantly secondary to MASLD. In chapter five, the prevalence of MASLD using TE was around two-thirds in a similar cohort with T2D in Swansea. One reason for patients not reporting they have liver disease is that they have not yet been identified to have the disease. However, some may have had previous imaging which demonstrated hepatic steatosis, but this was not communicated, or they did not undergo further evaluation. It would be interesting to explore the proportion of people in diabetes clinics locally who have MASLD on previous imaging. Previous studies indicate the lack of recognition or investigation in people with incidental hepatic steatosis or cirrhosis in other cohorts (Chu et al., 2024; Karhiahio et al., 2024; Kontrick et al., 2021; Williams, Krishnamoorthy, et al., 2022; Wright et al., 2015). Given this survey was anonymous, further investigation is not possible in this study.

More than 70% of respondents believed that ALD is the most common form of CLD in Wales, and 20% indicated MASLD is commonest. Previous studies indicate the worldwide prevalence of diagnosed ALD is 3.5-4.8% (Amonker et al., 2023; Niu et al., 2023), though studies exploring ALD epidemiology are often limited by inaccurate reporting of alcohol use by patients, and referral biases which hinder the reliability of such investigation (Younossi, Wong, et al., 2023). In people with an identified alcohol use disorder, the prevalence of ALD is about 50%, and around 13% have cirrhosis (Amonker et al., 2023). Nonetheless, ALD is the leading cause of identified cirrhosis and liver-related death globally (Devarbhavi et al., 2023; Younossi, Wong, et al., 2023). In contrast, epidemiological investigation into MASLD prevalence include

studies undertaking tests in the general population, and therefore less prone to bias. In the global population, the prevalence of MASLD sits at around 30%, 2-3-fold greater in those with T2D (Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024). In Wales, the incidence of MASLD has grown more than 10-fold over 20 years, exceeding the incidence of other forms of CLD, meaning there is now a reducing proportion of people with ALD nationally given its' own stable incidence (J. Gao et al., 2025; Pembroke et al., 2023). The discrepancy between these previous epidemiology studies and the views of patients reported in this study may be explained by at least two reasons. The first is a lack of patient awareness, given the recent progress in our understanding of MASLD which may not be well appreciated even by clinicians. Though, it may reflect the stigma which associates CLD with alcohol and other drugs of abuse (Ciardullo, 2024; Schomerus et al., 2022; Younossi, AlQahtani, et al., 2024). Such perceptions and misunderstanding may improve with the new classification of MASLD (Rinella, Neuschwander-Tetri, et al., 2023), though public health work to support patients to understand the distinction is imperative (Alemany-Pages et al., 2020). This result indicates there is scope to improve understanding of the causes of liver disease amongst people with diabetes, which is particularly relevant to their own risk.

Despite most of this cohort being diagnosed with T2D, only 37.5% felt at risk of MASLD, and this was similar in people with T1D or T2D. This does not reflect the reality of their risk of disease, which is about 65% in those with T2D and the risk in T1D is similar to the general population (Souza et al., 2024; Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024). Therefore, people with T2D underestimated their risk and people with T1D overestimated their risk. Previous studies observe that people with T2D tend to underestimate their risk of MASLD (Ciardullo et al., 2021; Wieland et al., 2015). This may highlight the lack of understanding that many in this cohort have about the causes of CLD, such as MASLD, and the association with T2D. Though, as two-thirds reported they would like to learn more about MASLD, there appears to be support for public health intervention and education. This is like a previous study which included 368 participants with metabolic risk factors attending an endocrinology clinic in the USA, in which 73% indicated interest in learning more about MASLD (Wieland et al., 2015). Nonetheless, the group appeared to consider a diagnosis of MASLD as serious, given 87.8% reported they would be worried if they were diagnosed with it. Further qualitative study to explore this would be interesting, and may uncover themes of interest. Patients may be surprised to learn that the risks associated with MASLD are primarily related to CVD risk (Angulo et al., 2015; Ng et al., 2022). Whilst there is greater risk of adverse liver outcomes,

this risk is considered lower compared with other causes of CLD. The lower risk of liver decompensation in MASLD compared with other causes of CLD was noted in recent studies from Wales (Pembroke et al., 2023), and elsewhere (Kim et al., 2024).

Most patients indicated they wanted more blood tests (61.4%), or scans (54.8%) to screen for MASLD. The preference toward blood tests may be because they already have annual blood tests for their diabetes review, so additional blood tests offer little inconvenience compared to additional scan appointments. Though, this suggests either blood tests or scans are acceptable. Previous studies indicate that CLD screening in people with metabolic risk factors such as T2D is acceptable, in a range of different settings (Allen et al., 2025; Knight et al., 2020; Lindfors et al., 2025). Acceptability of additional tests for CLD in people with T2D or obesity is also supported by feedback presented in chapter five and eight. Around 75% of patients wanted more tests to screen for diabetes complications generally. Naturally, anxieties about developing complications is high in people with diabetes (Arend et al., 2019), given the impact of CVD and microvascular complications. Though, additional investigations are a potential concern in this cohort, as they are subject to numerous routine hospital appointments already. This would be interesting to explore in qualitative research. These data indicate most patients want tests to screen for MASLD and education about MASLD, highlighting potential for public health intervention. Naturally, interventions may be best targeted to those with earlier diabetes, such as in primary care, to prevent complications developing and it would be interesting to repeat this survey in a primary care setting given the potential biases of patients in secondary care. Further information from their GP was the preferred source of information for most patients. Many cited their hospital team as a source of further information and many wanted information provided through websites, or leaflets. This highlights a need for coordinated intervention between primary and secondary care providers, probably through public health.

It is important to note the surveyed patient population was recruited entirely from secondary care, and future studies should extend to people with diabetes in primary care. Additionally, as participants completed the survey whilst attending clinic, responses may be subject to a positive response bias. However, the impact of this may have been minimised by the anonymity of responses. Future research could consider offering electronic surveys for completion at home, as this may yield different responses given the potential for biased responses, and would also support response rate monitoring.

9.5.2 Clinician survey responses

In this survey, clinicians were asked to estimate the prevalence of MASLD. The median global estimates were 30% in the general population and 51% in people with T2D. This is like the global prevalence studies indicating 30% in the general population and 65% in T2D (Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024). The respondents' estimate was slightly higher at 34.5% in Wales, and previous investigation in Wales indicates the prevalence is rising dramatically, though is similar to the global average at 30% (J. Gao et al., 2025). Nonetheless, clinicians reported a lower estimated prevalence of patients with MASLD in their own practice compared with their other estimations. There was a median estimated prevalence of 20% in their own practice, trending to a higher estimate in those practising diabetes and endocrinology (27%) compared to general practice (12%). Given respondents indicated the prevalence in the general population and in people with T2D was 30% and 51%, respectively, it is interesting that clinicians in either speciality underestimated MASLD prevalence in their own practice. In previous studies, clinicians have underestimated MASLD prevalence generally and in their practice (Bergqvist et al., 2013; Patel et al., 2018; Said et al., 2013; Sebastiani et al., 2021).

All clinicians reported that MASLD was an important condition. Over 50% reported they would usually refer such cases and 40% reported they had referred a patient with MASLD in the last 3 months, with no significant difference by speciality. There was a range of services involved, the commonest being hepatology but significant numbers were referred to weight management, diabetes and endocrinology or dietetic services. When asked to rate their agreement with "MASLD is a benign disease", there was disagreement indicated by a median score 8.5. This differs from previous studies which observed clinicians do not typically undertake investigation or referral for hepatic steatosis, and many fail to document the presence of hepatic steatosis, deranged LFTs, or even cirrhosis (Alqahtani et al., 2025; Chu et al., 2024; Karhiho et al., 2024; Williams, Krishnamoorthy, et al., 2022). Patients often report delayed or missed diagnosis and a lack of clear information from healthcare professionals (Stine et al., 2024). Given the self-reported nature of their practice, this study may be limited to self-reported biases. Moreover, on reflection, it may be better to ask "how important do you think MASLD is?" rather than ask "MASLD is a benign disease", as the framing of the question or statement can lead a positive or negative response bias. Careful consideration of the language used is important. It would also be interesting to audit the practice of primary and secondary care clinicians in these specialities, to investigate whether there are missed cases with incidental hepatic steatosis or cirrhosis. This is not possible in this study given the anonymous

surveys used. Though, the range of specialty referrals made by the clinicians surveyed is of interest. This observation highlights that a MASLD service would need multidisciplinary input, including hepatologists, endocrinologists, weight management services, specialist dietetics, and primary care providers, at least. This model has been proposed previously (Zoncape et al., 2022), and highlights the complexity of such patients (Cusi et al., 2022; EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). In keeping with international guidelines and proposed models of care, in response to “endocrinologists should be involved in the management of people with MASLD”, the median score of 71 indicated general agreement by the group. It would be interesting to extend such questions to groups of gastroenterologists and hepatologists to observe their opinion on this too. Further inter-speciality discussions are needed to develop MASLD services, and there are some services in other UK sites.

When asked about the appropriateness of general population screening, the median score of 50 suggests the respondents neither agreed nor disagreed. Participants appeared to strongly agree with targeted screening in at-risk populations such as T2D, given the median score of 89. These views are in keeping with recent international guidelines (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023), which advocate for this approach in people with T2D or obesity and 1 or more cardiometabolic risk factor. Their view does contradict current UK guidance, in which NICE continues to advocate for assessment of hepatic fibrosis only in those with incidental hepatic steatosis (NICE, 2016). These guidelines were last updated in 2016, and there is ongoing consultation to update this (NICE, 2025a). In keeping with their views on undertaking targeted MASLD screening, respondents agreed with “screening for MASLD will reduce the incidence of MASLD-related cirrhosis”, given a median score of 80. There is little evidence to support this, as screening is not yet in place for a sufficient period to investigate. However, when exploring the impact of screening for macrovascular disease risk factors and presence of microvascular complications in people with diabetes, there is a clear impact on reducing end-stage disease (Beckman & Creager, 2016). A similar impact could be expected with respect to identifying and treating MASLD, but services need to be redesigned prior to introducing a screening process to support intervention delivery.

Around two-thirds of respondents felt additional blood tests or scans would be appropriate screening tools for MASLD, and clinicians practising diabetes and endocrinology had a significantly greater agreement score to support the use of blood tests to screen for MASLD than those in primary care (74 vs 56%, $p<0.05$). The use of blood tests first is more practical and easily incorporated into existing diabetes review (Williams, Nagaraj, et al., 2025), whilst

additional scans for MASLD may provide better accuracy but would require additional hospital appointments and cost. Recent guidelines advocate for blood tests first and TE as a second-line investigation in those at risk of advanced fibrosis (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Further qualitative studies to investigate why there was a greater agreement for blood tests in those practising diabetes and endocrinology may uncover additional themes of interest around perceived accuracy and utility of different test modalities to diagnose MASLD and advanced fibrosis.

In this study, only clinicians practising primary care or diabetes & endocrinology were surveyed because these are the clinicians most likely to be responsible for undertaking a targeted MASLD testing approach in people with T2D. However, surveys of clinicians in gastroenterology, hepatology and other internal medicine specialities may be interesting also. Thematic analysis from qualitative investigation would be helpful to understand not only what clinicians think about MASLD but why they believe that, and would expand on the findings presented in this chapter.

9.6 Summary and limitations

Participants with T2D in this survey appeared to underestimate their MASLD risk, whilst those with T1D overestimated their risk. Likewise, there is likely a large proportion of patients, with T1D or T2D, living with undiagnosed MASLD given only a minority reported pre-existing liver disease. There appears to be scope for public health intervention as two-thirds of patients surveyed indicated they would like to learn more about liver disease in diabetes and most wanted additional routine blood tests or scans to screen for MASLD. Given their preferred sources of further information, a coordinated approach involving public health, primary and secondary care teams would be needed.

Clinician participants underestimated the proportion of patients under their care with MASLD, in either primary or secondary care. This is despite a good understanding of the prevalence of MASLD in the general population and in people with T2D. In practice, this may mean people with MASLD may get missed or overlooked. Nonetheless, clinicians appeared to support additional routine investigations in people with T2D for MASLD, which challenge the current approach advocated by NICE, and support international recommendations.

9.6.1 Clinical significance

The implication of these results is that a MASLD service would be supported by patients with diabetes, and by clinicians involved in their care. Most patients with diabetes indicated they want additional tests for MASLD, and the clinicians indicated people with T2D should have MASLD screening routinely. However, subsequent management of MASLD identified in people with T2D in current primary or secondary care diabetes reviews may not be adequate given the likely need for multidisciplinary input. As recognition and the subsequent referral of people with MASLD fibrosis increases, current hepatology services may become overwhelmed by the demand and benefit from a re-design to address this. Moving forward, work to develop collaborative working models across specialities between diabetes and primary care clinicians with hepatologists is needed. This would aim to improve screening for advanced fibrosis in people with T2D, whilst supporting the management of CVD risk reduction and use of specific pharmacotherapies such as SGLT-2 inhibitors or GLP-1RAs in this high-risk group to improve health outcomes. This will inevitably require multidisciplinary work, and targeted resource management to this group of patients often already seen in secondary care by both specialities.

9.6.2 Limitations

There are some limitations in this study:

- The questionnaires relied on self-reported information taken in clinic, which may be prone to a positive response bias.
- The survey only included secondary care participants who attended diabetes clinics, and there was no structured invitation model used to select patients.
- Data were not collected to report on response rates, which limits discussion around the generalisability of the findings reported in both clinician and patient surveys.
- Given participant anonymity, analyses to explore further associations is not possible.
- There is a lack of qualitative data in this chapter. Further studies should consider patient or clinician interviews to support thematic analysis and discussion.
- The number of clinician responses, particularly from primary care, mean the results presented should be interpreted cautiously and are not generalisable. Extending the survey to other localities would improve the number of responses.
- Extending the survey to clinicians practising in other specialities, particularly in gastroenterology, hepatology and internal medicine would be of interest.

Chapter Ten:

General discussion

10.1 Aims of the thesis

In this thesis, I explored the clinical application of screening for MASLD in people with T2D and obesity. This investigation was undertaken using four different studies. The first study was presented in chapters three and four and aimed to determine the accuracy of non-invasive tests to identify hepatic steatosis or hepatic fibrosis in people with biopsy-confirmed MASLD, and the bidirectional relationship between MASLD and T2D. The second study piloted a range of non-invasive tests to screen for MASLD and advanced fibrosis in people with T2D, presented in chapter five, six and seven. This study aimed to determine the prevalence of MASLD and advanced fibrosis in people with T2D, associations between blood biomarkers and TE-based measures of MASLD, and the utility of these tests to predict CVD. The third study presented in chapter eight piloted the use of non-invasive tests to screen for MASLD and advanced fibrosis in people with obesity undergoing bariatric surgery. The fourth study presented in chapter nine used questionnaires to evaluate the understanding of MASLD and views around MASLD screening of patients with T2D and doctors practising in diabetes & endocrinology or general practice. Themes of interest from these data are discussed below.

10.2 Accuracy and consistency of non-invasive tests for MASLD

10.2.1 Hepatic steatosis

In chapter three, the accuracy of blood biomarkers and TE to identify hepatic steatosis was determined using liver biopsy data in 153 people with MASLD. The HSI poorly excluded stage 2-3 hepatic steatosis, with a specificity of 3.4% at previously published thresholds and an AUC similar to chance, irrespective of T2D or BMI status. The TE-CAP had better accuracy for stage 2-3 hepatic steatosis evidenced by greater AUC on the ROC analysis. People with T2D or BMI $>36.3 \text{ kg/m}^2$ had greater optimal screening cut-off scores to identify stage 2-3 hepatic steatosis compared to people without T2D (364.5 vs 338.5 dB/m), or BMI $\leq 36.3 \text{ kg/m}^2$ (382.0 vs 347.5 dB/m). However, the ROC analysis indicated the TE-CAP was less reliable in people without T2D or BMI $>36.3 \text{ kg/m}^2$.

As discussed previously, the TE-CAP is the most accurate test in routine practice to identify hepatic steatosis, but is less reliable as BMI increases (Cao et al., 2022; Eddowes et al., 2019). These data were consistent as the TE-CAP was less accurate in people with a BMI $>36.3 \text{ kg/m}^2$. Similar to this study, other studies indicate people with T2D may require greater diagnostic thresholds to identify hepatic steatosis compared to people without T2D (Karlas et al., 2017), but I am unaware of previous studies reporting the accuracy of TE-CAP is affected by T2D status. However, it is worth noting the limitations of these sub-analyses. Twenty-one (13.7%)

participants had missing TE-CAP data, and only 4 (2.6%) had stage 0 hepatic steatosis at biopsy limiting the analysis to assess test utility to exclude disease. Only 5 (3.3%) participants had BMI <30.0 kg/m² and none had a BMI <25.0 kg/m² meaning analysis to compare accuracy by clinically relevant BMI thresholds was limited, necessitating the use of median BMI. Larger real-world study cohorts, such as by combining data with other groups in Wales, may mitigate some of these limitations and a control group without MASLD may support further analysis.

In chapter six, liver enzymes, HSI, NAFLD-LFS and TyG each correlated with the TE-CAP and had an AUC greater than chance suggesting a reassuring consistency between non-invasive tests in people with T2D. However, in their practical application, isolated liver enzymes were poorly sensitive to identify hepatic steatosis, meaning adjusted thresholds below the upper limit of normal were needed. In this analysis, an optimal ALT threshold of 25.5 U/L was identified using the Youden index to screen for hepatic steatosis, but this would ultimately identify a very high number of people at risk requiring further investigation. At previous thresholds the HSI, NAFLD-LFS and TyG demonstrated excellent sensitivity but poor specificity to identify hepatic steatosis, which improved using higher cut-off scores. The AUC for the HSI and NAFLD-LFS were similar in those with a BMI above or below the cohort mean, though was greater for the TyG in the leaner group. Clinical features of the metabolic syndrome were useful to identify hepatic steatosis risk. Diagnosis of the metabolic syndrome had a sensitivity 86.5% and specificity 41.9% to identify hepatic steatosis, with increasing prevalence of hepatic steatosis in those with a greater number of metabolic syndrome features.

It is well-established that use of ALT or AST alone to identify hepatic steatosis is impractical given most people with MASLD have normal liver enzymes, meaning screening thresholds below the upper limit of normal are needed (J. Chen et al., 2024; Lominadze & Kallwitz, 2018; Shrestha et al., 2023; Zheng et al., 2020). This leads to excess investigation, with greater costs, hospital appointments, and debatable health impact given the lack of direct association between hepatic steatosis and health outcomes (Hagstrom et al., 2017; Simon et al., 2022). This is the reason blood biomarkers were developed, to reliably exclude disease, and most include liver enzymes in their algorithms. Given both the HSI and NAFLD-LFS score additional points for presence of T2D, their use to discriminate steatosis risk in people with T2D is limited, and in this analysis led to greater screening cut-offs identified than in their previous validation studies using populations in which most did not have T2D (Kotronen et al., 2009; J. H. Lee et al., 2010). The TyG was developed to predict IR in apparently healthy subjects (Simental-Mendia et al., 2008), and in both this study and others (Zhu et al., 2025), the TyG is less useful to

discriminate hepatic steatosis risk in people with obesity. Inclusion of BMI in a modified TyG-BMI score improves accuracy for hepatic steatosis (Chang et al., 2023; M. Wang et al., 2023). Using metabolic syndrome features to identify risk of hepatic steatosis is attractive, given its simplicity. In this study and others (Jinjuvadia et al., 2017; Younossi, Koenig, et al., 2016), an increasing number of metabolic syndrome features associated with the prevalence of hepatic steatosis, and in this study metabolic syndrome diagnosis had reasonable sensitivity and specificity to identify disease. This suggests MASLD screening may be best targeted to people with >1 metabolic syndrome feature. Nonetheless, in people with T2D under hospital services, most would be screened using this approach; 189 (94.5%) had at least two metabolic syndrome features in this cohort. This study was limited by a lack of biopsy data, therefore discussion on test accuracy is limited. Further studies including people with T1D or without diabetes may be of interest to investigate the impact of having no metabolic syndrome features and evaluate measures of IR in non-diabetes populations on MASLD risk. Greater participant numbers may have supported a ROC analysis using clinically-relevant BMI thresholds.

Taken together, the results presented in chapters three and six suggest good accuracy for the TE-CAP to predict biopsy-confirmed stage 2-3 hepatic steatosis, and the HSI, NALFD-LFS, and TyG strongly associate with the TE-CAP score in a prospective cohort of people with T2D. Sub-analyses indicate the TE-CAP is less accurate in those with greater obesity, and the TyG associates less significantly with the TE-CAP in people with greater BMI. However, given the association between metabolic syndrome features and hepatic steatosis risk in this study, there may be limited gains made by investigating people with such features for hepatic steatosis and additional resource may be best used to screen for hepatic fibrosis.

10.2.2 Hepatic fibrosis

The APRI, FIB-4, and TE-LSM tests were the most accurate for advanced fibrosis in the cohort with biopsy-confirmed MASLD presented in chapter three based on their sensitivity and specificity at published thresholds, and the ROC analysis. There was no statistically significant difference in test accuracy to identify advanced fibrosis irrespective of T2D or BMI status. Consistently, the AST:ALT ratio and BARD scores performed poorly. The NFS demonstrated modest accuracy compared to the APRI, FIB-4 and TE-LSM scores, and had similar accuracy in those with or without T2D but trended to poorer accuracy in those with BMI >36.3 kg/m² compared to the leaner cohort (AUC 0.73 vs 0.84, p=0.21).

The observation that the FIB-4, APRI and TE-LSM are the most accurate tests for advanced hepatic fibrosis was made by a previous meta-analysis (Mozes et al., 2022), which reported similar AUCs for these tests as in chapter three. Two meta-analyses report the AST:ALT ratio and BARD score have poorest accuracy to identify advanced fibrosis in MASLD (Contreras et al., 2023; Mozes et al., 2022). However, previous studies suggest the APRI, FIB-4 score, and TE-LSM may be less accurate to detect cirrhosis in T2D (Bertot et al., 2018; Boursier et al., 2023; Chung et al., 2023; Ito et al., 2023). Like other studies, the results in chapter three support consistent accuracy for the APRI, and FIB-4 score in people with obesity (de Carli et al., 2020; Drolz et al., 2021; Qadri et al., 2022; Schmitz et al., 2020), and a previous meta-analysis observed similar accuracy for the TE-LSM in those with obesity (Cao et al., 2022). Given the consistent accuracy of the FIB-4 and TE-LSM in our cohort, and these tests remain the most useful biomarkers in people with T2D and obesity despite lesser accuracy in people with T2D (Boursier et al., 2023), these would be the best choice in practice (Williams, Nagaraj, et al., 2025). Though, the practicality of using TE in the annual review is limited by the additional clinic appointments needed, the cost of the device, staff training and staff time to deliver this. Therefore, using the FIB-4 first-line is most appropriate, with TE second-line (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023).

In the cohort with T2D presented in chapter six, the APRI, ELF test, FIB-4 score, and NFS were the most accurate to predict the TE-LSM (AUC 0.61-0.67), and the AST:ALT ratio and BARD score performed poorly. These results are therefore similar to those in chapter three, and other studies (Contreras et al., 2023; Mozes et al., 2022). Nonetheless, in this study the AUC observed for these biomarkers to identify hepatic fibrosis on TE was modest, and similar to the AUC observed for isolated liver enzymes (AUC 0.63-0.70). Likewise, the correlations between each liver enzyme or blood biomarker with the TE-LSM were statistically significant, though their coefficients were modest ($r=0.15-0.29$). Screening for advanced fibrosis using liver enzymes at the upper limit of the normal range was poorly sensitive (20.0-43.5%). On the ROC analysis, the optimal screening threshold for advanced fibrosis was lower than the upper limit of normal for the ALT, AST and GGT and this analysis identified a lower screening threshold for the APRI (0.17) and FIB-4 score (1.03) than their validation studies. These are similar to previous studies, which report the ALT or AST poorly discriminate risk of advanced fibrosis, and lower thresholds are needed to avoid false negative results (Lominadze & Kallwitz, 2018; Zheng et al., 2020). Other studies report that it may be appropriate to apply a lower FIB-4 threshold of 1.0 in people with T2D to sensitively identify advanced fibrosis

(Singh et al., 2024). Similarly, in the data presented in chapter three, a lower FIB-4 score screening threshold was identified for people with T2D compared to those without T2D for advanced hepatic fibrosis (1.70 vs 1.98).

In the sub-analysis investigating the impact of obesity on non-invasive test consistency, the APRI was the only biomarker to predict advanced fibrosis with a similar AUC irrespective of BMI status. There was a lower AUC identified for the FIB-4 score to predict the TE-LSM in those with BMI $>33.3 \text{ kg/m}^2$, and the NFS had a lower AUC to identify advanced fibrosis in those with BMI $<33.3 \text{ kg/m}^2$. There are mixed observations reported with respect to the impact of obesity on the accuracy of the APRI in previous studies (Alqahtani et al., 2021; de Carli et al., 2020; Ito et al., 2023; Qadri et al., 2022; Schmitz et al., 2020). The FIB-4 score observation in this study is unlike previous, in which test accuracy is reported to be similar irrespective of BMI (de Carli et al., 2020; Drolz et al., 2021; Kjaergaard et al., 2023). Though, there was a low AUC observed in both BMI groups for the FIB-4 score, which in the leaner group just reached statistical significance compared to the AUC expected by chance, and there was no significant difference between the two BMI groups. As the comparison is made with the TE-LSM, and not liver biopsy data, speculation around test accuracy is limited. Nonetheless, as the accuracy of these tests is similar by BMI status in previous studies, closer association between these non-invasive tests was expected. The AUC being greater than expected by chance for the NFS to predict the TE-LSM in those with greater BMI, but not the leaner group, was also unexpected as the NFS is less accurate with increasing BMI (Kjaergaard et al., 2023; Qadri et al., 2022). However, discussion is limited by the use of only non-invasive tests, and lack of statistical significance in the AUC between the BMI groups.

Non-invasive test consistency was also explored in chapter eight. Blood biomarkers and TE were piloted to screen for MASLD-related fibrosis perioperatively in 22 people undergoing bariatric surgery, with a mean BMI 45.0 kg/m^2 . Using the FIB-4 threshold ≥ 1.30 to identify risk of advanced fibrosis, just 1 of 11 cases with moderate-advanced fibrosis using TE were identified, suggesting lower thresholds may be needed to identify those at risk in obesity. In chapter three a lower screening threshold using a FIB-4 score of 1.05 was identified in the ROC analysis in those with BMI $>36.3 \text{ kg/m}^2$. Other studies suggest to reduce the FIB-4 score cut-off in obesity, with a score ≥ 0.88 and ≥ 1.24 to exclude stage 2 and 3 fibrosis, respectively (Green et al., 2024). Of interest, in the cohort presented in chapter eight of this thesis, eight (36.4%) participants had a score ≥ 0.88 , of whom four (50.0%) had a TE-LSM score $>8.2 \text{ kPa}$. It would be interesting and important to undertake a similar study in a larger cohort undergoing

bariatric surgery with additional blood tests, imaging and intraoperative liver biopsy to support such a strategy in local practice. This may support discussion on biomarker and TE accuracy in people with severe obesity undergoing bariatric surgery. It is a concern in this cohort given the poor correlation between the blood biomarkers with the TE-LSM. Though, the significance of this is uncertain given the small participant numbers included in this pilot study.

In summary, the APRI, FIB-4 score and TE-LSM appeared the most accurate and consistent non-invasive tests in these investigations, and were generally consistent in people with T2D or obesity. Given these observations, the application of sequential FIB-4 score and TE-LSM testing to screen for advanced fibrosis in people with T2D or obesity and ≥ 1 cardiometabolic risk factor seems appropriate, as recommended (Cusi et al., 2022; EASL-EASD-EASO, 2024; Misra et al., 2025; Rinella, Neuschwander-Tetri, et al., 2023). However, it may be appropriate to consider using lower screening thresholds than recommended in people with T2D or those undergoing bariatric surgery, warranting further investigation.

10.3 The relationship between MASLD and type 2 diabetes or obesity

In chapter four, the bidirectional associations between MASLD and T2D was investigated in people with MASLD under hepatology care. In chapter five, the prevalence of MASLD was determined in people with T2D without pre-existing liver disease, and the impact of obesity on MASLD prevalence was explored. Screening for MASLD and advanced fibrosis was piloted in people undergoing bariatric surgery, presented in chapter eight. These observations highlight the complicated relationship between these disease states, and potential for shared treatment.

In chapter four, the relationship between MASLD and T2D was investigated in 153 people with biopsy-confirmed MASLD. Seventy-three (47.7%) patients had pre-existing T2D, eight times greater than the UK prevalence of T2D (Diabetes UK, 2020). Other studies report the relative risk of T2D in people with MASLD is 2-2.5 fold the population risk (Targher et al., 2021; Younossi, Golabi, et al., 2024), though other factors may influence the apparent risk. These include frequency and severity of obesity and other metabolic syndrome features, which amplify T2D risk up to 14-fold (Sung et al., 2012). The high-risk of T2D in this cohort may be explained by unknown variables, for instance their physical activity and comorbidities, or real-world biases such as better identification of MASLD in people with T2D given their frequent healthcare contact. Even so, people with T2D had greater mean hepatic fibrosis stage than people without T2D (2.6 vs 1.7, $p < 0.001$), despite similar BMI, liver enzymes and better lipid profiles. This is established in people with T2D, who have greater steatohepatitis and fibrosis

risk (Younossi, Golabi, et al., 2023; Younossi, Golabi, et al., 2024). Those with T2D were significantly older, which is a potential confounder (He et al., 2024), as patients may have had unrecognised MASLD for a longer duration.

Over four years follow-up, there was a trend to greater CVD and malignancy-related mortality in those with T2D compared to those without T2D (12.3 vs 5.0%, $p=0.10$). This is consistent with other observations, in which people with T2D have poorer outcomes, largely from excess CVD and malignancy risk (Cusi et al., 2025; Leith et al., 2024). The trend to greater mortality in people with T2D may relate to greater hepatic fibrosis which is the strongest predictor of CVD in MASLD (Hagstrom et al., 2017; Simon et al., 2022). This underpins the rationale behind screening for advanced fibrosis in people with T2D or obesity (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Follow-up highlighted the risk of developing T2D in MASLD; a new diagnosis of T2D was observed in 25% of patients. This is four times greater than reported elsewhere (Mantovani, Petracca, et al., 2021), but may be confounded by missing HbA1c data prior to liver biopsy and differences in the prevalence of other metabolic comorbidities. Nonetheless, the high risk of T2D over follow-up highlights the degree of metabolic dysfunction present. To this end, meta-analyses investigating the impact of treating MASLD with GLP-1RAs and other T2D agents on incident diabetes risk would be of interest and may support their use in people with MASLD without T2D.

In chapter five, I piloted screening tests for MASLD and advanced fibrosis in people with T2D. These disease states were defined by a TE-CAP ≥ 302 dB/m for stage 1-3 hepatic steatosis, and a TE-LSM 8.2-9.6 kPa or ≥ 9.7 kPa for moderate or advanced fibrosis, respectively. The median TE-CAP score 324.5 dB/m was consistent with stage 2 steatosis, and median TE-LSM score 6.8 kPa was consistent with stage 0-1 fibrosis. Though, 126 (63.0%) participants had stage 1-3 hepatic steatosis consistent with MASLD given their diagnosis of T2D, and 25 (12.5%) and 46 (23.0%) had moderate or advanced fibrosis, respectively. Participants with BMI ≥ 35.0 kg/m² were more likely to have stage 1-3 hepatic steatosis (82.5%), compared to people with BMI 30.0-35.0 kg/m² (71.4%) or BMI <30.0 kg/m² (32.2%) [$p<0.001$]. Likewise, those with BMI ≥ 35.0 kg/m² had greater prevalence of moderate-advanced fibrosis (54.1%) compared to those with BMI 30.0-35.0 kg/m² (23.8%) or BMI <30.0 kg/m² (25.8%) [$p<0.01$].

The prevalence of MASLD in people with T2D is similar to a previous meta-analysis indicating the prevalence in Western Europe is 68% (Younossi, Golabi, et al., 2024). Though a greater proportion of this cohort had advanced fibrosis (23.0%), compared to the global prevalence of 11.8% in people with T2D. However, prevalence of moderate or advanced fibrosis (TE-LSM

≥ 8.2 kPa) is similar in this study as in global meta-analyses (35.5 vs 36.4%) (Younossi, Golabi, et al., 2024). Likewise, previous studies in European cohorts with T2D indicate the prevalence of MASLD or moderate-advanced fibrosis is 67.0-83.6% and 17.8-39.5%, respectively (Forlano et al., 2024; Martinez-Ortega et al., 2022; Mikolasevic et al., 2020). The study reporting lower prevalence of moderate fibrosis was in a primary care cohort of patients with T2D, with shorter T2D duration, less frequent insulin use and lower HbA1c than the cohort in chapter five (Forlano et al., 2024). The impact of obesity on MASLD prevalence and moderate-advanced fibrosis was expected. A previous meta-analysis estimated 75% of people with obesity have MASLD using several diagnostic modalities for MASLD including invasive and non-invasive tests (Quek et al., 2023), similar to the findings in chapter five in which 71.4% and 82.5% of people with BMI 30.0-35.0 kg/m² or ≥ 35.0 kg/m² had MASLD, respectively. Though, this previous meta-analysis estimated 21.6% and 6.9% of people with obesity have moderate-advanced fibrosis or advanced fibrosis, compared to 54.1% and 33.8% in this study, respectively. The disparity may be a consequence of differing population characteristics of the studies included in this meta-analysis, for example a relatively small proportion had T2D in this meta-analysis compared to this study in which all participants had T2D.

In chapter eight, I presented a pilot study including 22 participants to screen for MASLD and advanced fibrosis in people undergoing bariatric surgery. Pre-operatively, participants had a mean TE-CAP 321.2 dB/m and TE-LSM 11.2 kPa, consistent with stage 2 steatosis and stage 3 fibrosis, respectively. Based on TE, two-thirds of participants had stage 1-3 steatosis, and 50.0% had stage 2-4 fibrosis. Previous studies clearly implicate obesity as a major risk factor for MASLD and accelerated risk of steatohepatitis and advanced fibrosis (Younossi, Golabi, et al., 2023; Younossi et al., 2025). The results in chapter six indicated a similar risk of stage 1-3 steatosis, and greater risk of significant fibrosis based on TE in those undergoing bariatric surgery compared with previous studies. Other pilot studies report that in people undergoing bariatric surgery, 64.8-78.0% had TE-CAP ≥ 302 dB/m, and 6.0-13.9% have a TE-LSM ≥ 8.2 kPa (Avcu et al., 2021; Yang et al., 2021). Our results indicate a much greater risk of significant fibrosis, but as this pilot study included only 22 participants greater numbers are needed to generalise any conclusion. Moreover, no data related to alcohol intake was collected in these participants, so some may have MetALD rather than MASLD. The results do support the need to consider perioperative screening prior to bariatric surgery given the burden of disease, and highlight the relationship between MASLD and obesity which explains the growing global burden of MASLD (Younossi et al., 2025).

In the cohort with biopsy-confirmed MASLD in chapter four, there were similar improvements in liver enzymes, lipid profiles, BMI and TE-CAP in people with or without T2D. However, T2D therapies such as GLP-1RAs and SGLT-2 inhibitors associated with greater benefits in measures of MASLD compared to other treatments. It is well-evidenced that GLP-1RAs improve invasive and non-invasive measures of MASLD, including fibrosis (Souza et al., 2025; Wang et al., 2025), and SGLT-2 inhibitors improve non-invasive measures of MASLD (Song et al., 2021; Wei et al., 2021). Interestingly only 4 (2.6%) patients were prescribed pioglitazone despite NICE guidance at the time of their care supporting its off-label use. This older recommendation highlights the long recognition of the relationship between T2D and MASLD. The lack of pioglitazone use in practice is probably due to concerns of its side-effects including fluid overload, and fracture risk. Contemporary guidelines advocate for GLP-1RAs and SGLT-2 inhibitor use in people with T2D and MASLD, not pioglitazone, given the availability, efficacy and safety of newer agents (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Other shared treatment for MASLD was highlighted by the cohort with severe obesity undergoing bariatric surgery, presented in chapter eight. Associated with improvements in BMI, lipid profiles and glycaemic control, there were significant reductions in the TE-CAP and TE-LSM scores, and both scores were in the normal range at 6-12 months postoperatively. Similarly, previous systematic reviews and clinical trials support these observations, as people with severe obesity demonstrate improvements in steatohepatitis and hepatic fibrosis within 6-24 months (Hwang et al., 2024; Verrastro et al., 2023). This is alongside reductions in CVD associated with metabolic surgery, underpinning the potential impact of surgery in this group. Larger studies with longer follow-up may support the safety and efficacy of bariatric surgery in people with MASLD, and could be taken as part of larger studies trialling screening and monitoring strategies for hepatic fibrosis in people undergoing bariatric surgery.

In conclusion, the relationship between T2D and obesity with MASLD is complicated. Data presented in this investigation highlight this relationship, in which T2D associates with more advanced fibrosis, and MASLD associates with greater T2D risk. The prevalence of MASLD and advanced fibrosis in people with T2D under hospital care or in those with severe obesity undergoing bariatric surgery was similar in this investigation as in previous populations, and demonstrates the worrying burden of undiagnosed disease in these groups. Data presented in this thesis support the impact of interventions for T2D and obesity on MASLD outcomes and therefore support the rationale to screen for advanced fibrosis in people with T2D or obesity, to focus therapies which improve CVD risk and liver outcomes in these populations.

10.4 Feasibility of MASLD screening in type 2 diabetes or obesity

In this thesis, I presented the results of pilot studies to screen for MASLD and advanced fibrosis in people with T2D or obesity under hospital services. This is timely, given the ongoing national consultation by NICE to update its existing guidance on MASLD identification and management in the UK (NICE, 2016, 2025a). This update is of interest given the growing consensus that routine screening for advanced fibrosis should be undertaken in high-risk groups, such as people with T2D or obesity (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Others recommend perioperative screening for cirrhosis and additional investigation in such cases to confirm the safety of bariatric surgery in people with severe obesity (Patton et al., 2021). Pilot studies to confirm the feasibility of such processes are needed to support their implementation, and these studies are well positioned to do so.

In chapter five, the feasibility of blood biomarkers and TE was investigated in 200 people with T2D managed in hospital clinics in SBUHB. Valid blood biomarkers for hepatic steatosis were achieved in 97.5-99.0%, and valid blood biomarkers for hepatic fibrosis were achieved in 98.5-99.5% of participants. Additionally, all participants had valid TE scores, supporting feasibility. This is similar to previous studies for MASLD screening in people with T2D, in which 94.7-100% of participants had valid TE scores (Forlano et al., 2024; Martinez-Ortega et al., 2022; Mikolasevic et al., 2020). The use of blood biomarkers would be more practical than TE, given the potential to integrate this into the diabetes annual review (Williams, Nagaraj, et al., 2025). However, using blood biomarkers can be challenging. For example only 67/104 (64.4%) participants had a valid NFS in one study given issues with invalid albumin results (Martinez-Ortega et al., 2022). Work to develop pathways, is needed and should account for the additional costs of staffing (doctors, nurses, support staff), blood tests and fibroscan devices needed.

In chapter eight, the feasibility of using blood biomarkers and TE in people undergoing bariatric surgery was piloted in 22 participants. All participants had valid blood biomarkers and TE scores preoperatively for advanced fibrosis, and post-operatively, 94.4% participants had valid blood biomarkers for advanced fibrosis, and all had valid TE. Other studies with greater participant numbers have observed valid TE-LSM in 87.9-99.4% of participants (Ali et al., 2022; Avcu et al., 2021; Eilenberg et al., 2021; Garg et al., 2018; Yang et al., 2021). Reassuringly, this is supported by the acquisition of valid TE scores in all 137 participants with a BMI ≥ 30.0 kg/m² in the T2D study presented in chapter five. There remain concerns around the accuracy of TE in people with severe obesity, and the challenge of obtaining a valid TE result (Puthenpura et al., 2020), thus larger studies to corroborate these findings locally are

needed. Should NICE update its MASLD screening recommendations in obesity, such investigation may become commonplace and services need to adapt.

In conclusion, these pilot studies suggest that introducing screening for MASLD fibrosis using blood biomarkers and TE in people with T2D or severe obesity is feasible. Further work is needed to evaluate the resource required to upscale this project to implement into practice, as are larger studies involving the bariatric surgery service expanded upon below. Such a process may not be appropriate or possible to introduce into UK-based practice, until UK-based guidance supports such measures which is an ongoing national discussion.

10.5 Acceptability of screening tests for MASLD

The tests employed to screen for a disease must be acceptable to the population in which they are used (Wilson & Junger, 1968). Therefore, feedback to confirm participant acceptability of TE in the pilot studies screening for MASLD in people with T2D or obesity were sought, and presented in chapters five and eight respectively. People with diabetes managed in SBUHB and clinicians in diabetes & endocrinology or general practice were also asked to complete a questionnaire to provide their views about MASLD screening, presented in chapter nine.

Feedback provided by the participants in the pilot studies was generally positive. In the study including 200 participants with T2D, 100% reported they understood the reasons for the scan, 99.5% felt TE was an acceptable test to screen for MASLD, 99.5% would have the scan again if needed, and 98.5% reported they understood the result. Similarly, in the study including 22 people with obesity undergoing bariatric surgery, all participants reported they understood the reasons for having TE and it was an acceptable test to screen for liver disease in obesity. All reported they would have the scan again, and they understood the result of the scan. In keeping with these results, numerous studies have reported that TE is an acceptable test for most people with a range of causes or risk factors for CLD (Malekzadeh & Poustchi, 2011; Marshall et al., 2015; Matthews et al., 2019; Xia et al., 2019). Likewise, previous investigations report that screening for MASLD in people with high-risk is acceptable to both patients and clinicians, in a range of community or hospital-based environments (Allen et al., 2025; Knight et al., 2020; Lindfors et al., 2025). However, in the T2D pilot study 3.5% reported TE was painful, and 6.5% reported the scan took longer than expected. In the bariatric surgery pilot study, 4.6% considered TE painful, and 9.1% felt it took longer than anticipated.

In chapter nine, I presented data from questionnaires given to 403 patients with diabetes, and 70 doctors practising in diabetes & endocrinology or general practice. Most patients reported

they wanted more blood tests or scans for MASLD, and 75% wanted further tests to identify complications generally. In clinicians, there was strong agreement that MASLD screening should take place in people with T2D or obesity, and that screening will reduce incidence of MASLD cirrhosis. There was also agreement that appropriate strategies for screening include additional blood tests or scans, and that endocrinologists should be involved in the management of MASLD. Nonetheless, qualitative studies observe participation in liver screening associates with the degree of patient motivation, experience of the service and perceived health benefits (Archer et al., 2024). This requires clinicians to engage with patients at risk of MASLD to support their understanding of disease, the tests used, the health impact of MASLD and to agree treatment goals (Boeckmans et al., 2025). Patients attending for bariatric surgery are often highly motivated by surgery (Cohn et al., 2019), and increasingly patients with T2D are motivated by newer therapies which improve weight loss (Sims et al., 2022). Therefore there may be scope for clinician intervention in clinic, but this is frequently limited by time-pressured appointments and patients may not see a regular doctor or allied health professional which can hinder the development of patient-clinician relationships.

Only 37.5% of people with diabetes reported they felt at risk of MASLD with no significant difference between people with T1D or T2D. This is despite around two-thirds of people with T2D having MASLD (Younossi, Golabi, et al., 2024). This implies patients with T2D do not appreciate their risk of MASLD, possibly because of the focus given in practice to screening and managing microvascular and macrovascular complications. There may be opportunity for patient education as part of a coordinated public health intervention. This is supported by the respondents, in which two-thirds of patients with diabetes reported interest in learning more about MASLD. Whilst screening for disease at earlier stages of T2D, such as in primary care, would be more likely to identify reversible disease, screening at any stage may benefit. Indeed, TE itself improves patient understanding of their CLD risk and contemplation of lifestyle changes (Knight et al., 2020), which can improve health behaviours and outcomes (Kjaergaard et al., 2024). Qualitative studies in patients with T2D or obesity may identify themes of interest, and this could be considered as future work in the participants of the previous two pilot studies.

In conclusion, screening for MASLD with blood tests or TE appeared acceptable in patients with T2D or obesity, in those who responded to the clinic questionnaire and in those who participated in the pilot studies presented in this thesis. Clinicians who regularly treat people with T2D or obesity supported additional screening with blood tests or TE in people at risk of MASLD. Qualitative studies would be of interest to expand on these observations.

10.6 Clinical significance and limitations

The results presented throughout this thesis challenge current NICE guidelines on MASLD identification (NICE, 2016), and support international guidelines which advocate for MASLD screening in high-risk groups (EASL-EASD-EASO, 2024; Rinella, Neuschwander-Tetri, et al., 2023). Recognising there is likely to be a significant update in the NICE recommendations around MASLD identification and management (NICE, 2025a), the pilot studies presented in chapters five, six, seven and eight provide clinically-relevant evidence to guide the integration of a screening approach in clinical practice. Moreover, the work presented in chapters three and four provide further evidence from a local cohort with MASLD to support the accuracy of non-invasive tests for MASLD-related fibrosis, and the potential importance of frequently overlooked clinical signs of metabolic dysfunction including T2D and obesity in the case-finding approach and treatment of MASLD. Finally, the patient and clinician surveys provide local interest to support routinely screening for MASLD during the diabetes annual review process. The clinical significance of these data were discussed in each chapter of this thesis and the key points highlighted throughout this discussion chapter.

Altogether, these data emphasise the relationship between MASLD, T2D and obesity, and need for a coordinated approach from hepatologists, endocrinologists, primary care clinicians, allied health professionals, funders, and of course patients to develop strategies for screening and managing people with MASLD. There are strengths and limitations with each of the four studies presented in this thesis, which have been highlighted throughout this thesis. The key strengths and limitations are summarised in Table 10.1.

Table 10.1: Key strengths and limitations of each study presented in this thesis

Study	Strengths	Limitations
1 Chapters 3 & 4	i. Good participant numbers. ii. Patients with definite MASLD based on biopsy and other work-up. iii. Investigated a range of available non-invasive tests.	i. Retrospective design.
		ii. Missing data limited analysis.
		iii. All participants had MASLD, the lack of control group limited analysis.
		iv. Few patients with BMI <30.0 kg/m ² limited analysis of BMI impact on test accuracy.
2 Chapter 5, 6 & 7	i. Prospective design. ii. Good participant numbers. iii. 'Real-world' pilot study. iv. Trialled several available tests for MASLD assessment.	i. Lack of liver biopsy prevented analysis on test accuracy.
		ii. Did not include a control group e.g. without T2D or a primary care cohort with T2D.
		iii. Feedback was limited to binary questionnaire responses.
		iv. Lack of follow-up required use of QRISK3 to predict CVD risk instead of actual risk.
3 Chapter 8	i. Prospective design. ii. 'Real-world' pilot study. iii. Trialled several non-patented tests for MASLD.	i. Low participant numbers.
		ii. Lack of liver biopsy prevented analysis on test accuracy.
		iii. Feedback was limited to binary questionnaire responses.
		iv. Did not trial patented tests for MASLD fibrosis.
4 Chapter 9	i. Good number of patient responses. ii. Collected numerical data to support analysis.	i. Self-reported questionnaires prone to bias.
		ii. Responses were anonymous, limiting further analysis.
		iii. Lack of qualitative data.
		iv. Low number of primary care clinician responses.

The key strengths and limitations of each of the studies presented in this thesis. Abbreviations: *BMI* body mass index; *CVD* cardiovascular disease; *MASLD* metabolic dysfunction-associated steatotic liver disease; *QRISK3* QRESEARCH cardiovascular risk score-3.

10.7 Future work

Future work should seek to translate this research into practice. There is national consultation to update existing NICE guidance on MASLD (NICE, 2025a), which may recommend screening for MASLD fibrosis in people with risk factors, as recommended by American (Cusi et al., 2022; Rinella, Neuschwander-Tetri, et al., 2023), European (EASL-EASD-EASO, 2024), and most recently Asia-Pacific (Misra et al., 2025) guidelines. Locally, translation of this research into practice would start with practical steps to make it easier for clinicians to undertake such a liver assessment. There are ongoing discussions with the pathology team in Swansea to update the electronic test request system to permit direct requests for the FIB-4 score, as opposed to its individual components which then requires manual calculation. This is also being sought locally by other clinicians who monitor for liver fibrosis associated with the treatment of rheumatological or dermatological diseases. Direct requesting would improve the ease of obtaining a FIB-4 score, and remove error in its calculation.

Integrating the FIB-4 score into the current diabetes annual review bundle would further facilitate this process, and minimise missing the investigation in people with T2D who are at high-risk. However, this is a major challenge as the diabetes annual review is an all-Wales agreed bundle, meaning it would require broad agreement across the seven NHS health boards. This is complicated by numerous stakeholders in primary care, and groups in secondary care, such as hepatology and diabetes teams. This is unlikely achievable given current UK guidance recommends against routine MASLD screening, but if NICE changes this recommendation, the process may be easier. To support this discussion, we plan to undertake a cost analysis of the completed pilot study screening for MASLD-related fibrosis in people with T2D. Critically, changes in this process and the development of such pathways would require support of hepatology services. This will involve collaboration across hospital-based specialities given the nature of MASLD, and its treatment. Locally, we have worked with the hepatologist Dr Jagadish Nagaraj to develop and implement this pilot study, and I hope to expand on this work with national teams as I embark on my consultant role in the near future.

Further work is needed to integrate MASLD assessment perioperatively in people with severe obesity undergoing bariatric surgery. To support this, a larger pilot study expanding on the one undertaken in this thesis is needed. Mr Andrew Beamish (WIMOS service lead) and I have discussed the potential of further work to investigate the utility of additional blood tests, TE, MRI, and intraoperative liver biopsy in the setting of bariatric surgery in collaboration with researchers at the University of Liverpool (Professor Daniel Cuthbertson) and industry

(Echosens). This will support undertaking a safety and cost analysis to explore the impact of MASLD on patient outcomes. When designing this future work it will be essential to include hepatologists in the study design, to develop a perioperative MASLD assessment within the local bariatric surgical pathway, and strategies for follow-up monitoring and care. An extension of the screening project in people with T2D would be of interest, to identify whether measures of IR or other clinical measures impact the likelihood of developing MASLD or advanced fibrosis in people without diabetes or people with T1D. This may facilitate discussion in future about other subgroups (if any) who would benefit from screening.

Ultimately, I aspire to develop my clinical role within metabolism and diabetes as a new consultant over the next few years, and to apply what I have learned during this PhD into clinical practice. This would initially seek to integrate an assessment for MASLD in practice for patients at risk, such as those living with T2D, or obesity under the care of NHS services. This may support a more aggressive, and targeted intervention to mitigate their excess CVD risk and reverse signs of MASLD and associated fibrosis given the increasingly available and evidenced drug therapies. There is a role for clinicians in diabetes & endocrinology to support MASLD services and there are examples of this developing across the UK, such as being part of a multidisciplinary meetings within existing MASLD services or developing existing services with hepatologists in joint clinics. An integrated approach to MASLD management may best support the identification and management of treatable comorbidities, such as T2D or obesity, and other intervention to mitigate excess CVD risk in addition to the liver-related monitoring and treatment already undertaken in practice.

Appendix I:
Presentations, publications and prizes
related to this thesis

Table 11.1: Presentations related to the work presented in this thesis

Poster presentations
Diabetes UK Professional Conference (Liverpool, April 2023)
1. <u>Williams DM.</u> Ali J. Ch'ng CL. Stephens JW. Min T. <i>Greater risk of hepatic fibrosis and progressive renal disease in people with type 2 diabetes and non-alcoholic steatohepatitis at liver biopsy: A call for screening in people with type 2 diabetes</i>
2. Ali J. <u>Williams DM.</u> Ch'ng CL. Stephens JW. Min T. <i>Increased risk of developing type 2 diabetes after diagnosis of non-alcoholic steatohepatitis in people without an initial diagnosis of type 2 diabetes</i>
Swansea University Postgraduate Research Conference (Swansea, May 2023)
3. <u>Williams DM.</u> Min T. Stephens JW. <i>The bidirectional relationship between type 2 diabetes and non-alcoholic steatohepatitis: A retrospective cohort study</i>
International Diabetes Federation (Virtual, December 2023)
4. <u>Williams DM.</u> Ali J. Ch'ng CL, Williams N. Stephens JW. Min T. <i>The bi-directional relationship between type 2 diabetes and non-alcoholic fatty liver disease: A cohort study</i>
5. <u>Williams DM.</u> Ali J. Ch'ng CL, Williams N. Stephens JW. Min T. <i>The accuracy of non-invasive markers for advanced non-alcoholic fatty liver disease fibrosis in people with T2D</i>
Diabetes UK Professional Conference (London, April 2024)
6. <u>Williams DM.</u> Ch'ng CL. Williams N. Stephens JW. Min T. <i>The use of non-invasive tests for clinically significant hepatic fibrosis associated with non-alcoholic fatty liver disease in people with type 2 diabetes</i>
7. <u>Williams DM.</u> Cragg J. Ch'ng CL. Williams N. Stephens JW. Min T. <i>The real-world impact of treatments for type 2 diabetes on outcomes in people with non-alcoholic fatty liver disease</i>
British Society of Gastroenterology (Birmingham, June 2024)
8. Cragg J. <u>Williams DM.</u> Ch'ng CL. Williams N. Stephens JW. Min T. <i>P330 The real-world impact of treatments for type 2 diabetes on outcomes in people with non-alcoholic fatty liver disease</i>
9. <u>Williams DM.</u> Wilkinson L. Nagaraj J. Stephens JW. Min T. <i>P323 Routine screening for steatotic liver disease in people with diabetes: a patient survey</i>
10. <u>Williams DM.</u> Ch'ng CL. Stephens JW. Min T. <i>P351 The impact of increased body mass on non-invasive test accuracy for advanced hepatic fibrosis with metabolic dysfunction-associated steatotic liver disease</i>
11. <u>Williams DM.</u> Ch'ng CL. Stephens JW. Min T. <i>P375 The accuracy of non-invasive tests for advanced hepatic fibrosis associated with metabolic dysfunction-associated steatotic liver disease in type 2 diabetes</i>
Diabetes UK Professional Conference (Glasgow, February 2025)
12. <u>Williams DM.</u> Nagaraj J. Stephens JW. Min T. <i>Screening for steatotic liver disease and advanced fibrosis in people with type 2 diabetes: A prospective cohort study</i>
13. <u>Williams DM.</u> Wilkinson L. Nagaraj J. Stephens JW. Min T. <i>Routine screening for steatotic liver disease in people with diabetes: a patient survey</i>
Association of British Clinical Diabetologists (Newcastle, November 2025)
14. Khosho M. Gatenby A. Alismael H. <u>Williams DM.</u> Min T. <i>Cardiovascular Risk Prediction in Non-Diabetic MASLD: Insights from Liver Biopsy and QRISK3.</i>
15. Alismael H. Gatenby A. Khosho M. <u>Williams DM.</u> Min T. <i>Evaluating QRISK3 Cardiovascular Risk in Patients with Type 2 Diabetes and Biopsy-Confirmed MASLD.</i>

Oral presentations

Welsh Endocrine Diabetes Society (Cardiff, May 2023)

1. **Williams DM.** Ali J. Ch'ng CL. Williams N. Stephens JW. Min T. *The bi-directional relationship between type 2 diabetes and non-alcoholic steatohepatitis: A retrospective cohort study*

Diabetes UK Professional Conference (London, April 2024)

2. **Williams DM.** Cragg J. Ch'ng CL. Williams N. Stephens JW. Min T. *The real-world impact of treatments for type 2 diabetes on outcomes in people with non-alcoholic fatty liver disease*

Swansea University Postgraduate Research Conference (Swansea, May 2024)

3. **Williams DM.** Min T. Stephens JW. *Routine screening for steatotic liver disease in people with diabetes: a patient survey*

European Association for the Study of Diabetes (Madrid, September 2024)

4. **Williams DM.** Nagaraj J. Stephens JW. Min T. *A prospective study on the prevalence of steatotic liver disease and advanced fibrosis in people with type 2 diabetes*

The EXCHANGE patient conference (Swansea, September 2024)

5. **Williams DM.** Min T. *Screening for liver disease in people with diabetes*

Young Diabetologist and Endocrinologist Forum Wales (Cardiff, January 2025)

6. **Williams DM.** *Fatty liver disease for the endocrinologist*

Diabetes UK Professional Conference (Glasgow, February 2025)

7. **Williams DM.** Nagaraj J. Stephens JW. Min T. *Screening for steatotic liver disease and advanced fibrosis in people with type 2 diabetes: A prospective cohort study*

Swansea University Postgraduate Research Conference (Swansea, May 2025)

8. **Williams DM.** Min T. Stephens JW. *A pilot study screening for steatotic liver disease and advanced fibrosis in people with type 2 diabetes*

Welsh Endocrine Diabetes Society (Cardiff, May 2025)

9. **Williams DM.** Nagaraj J. Stephens JW. Min T. *A pilot study screening for steatotic liver disease and advanced fibrosis in people with type 2 diabetes*

All Wales Tiers 3 & 4 Weight Management Meeting (Swansea, July 2025)

10. **Williams DM.** Min T. Beamish A. Stephens JW. *A pilot study screening for liver fibrosis in people undergoing bariatric surgery*

European Association for the Study of Diabetes (Vienna, September 2025)

11. Min T. Nagaraj J. Stephens JW. **Williams DM.** *A new horizon in risk assessment: ELF test and cardiovascular health in type 2 diabetes*

Poster and oral presentations related to the work presented in this thesis at national and international meetings.

Table 11.2: Peer-reviewed publications related to the work presented in this thesis

Peer-reviewed publications	
1.	Williams, D.M.* , Roberts, R.* , Min, T., Barry, J., Stephens, J. W. (2023). Benefits in routinely measured liver function tests following bariatric surgery: A retrospective cohort study. <i>J Diabetes Metab Disord</i> , 22(2), 1763-8. https://doi.org/10.1007/s40200-023-01311-4 .
2.	Williams, D.M. , Ali, J., Cragg, J., Ch'ng, C. L., Williams, N., Stephens, J. W., Min, T. (2024). The bidirectional relationship between type 2 diabetes and metabolic dysfunction-associated steatotic liver disease: A retrospective cohort study. <i>Cureus</i> , 16(12), e75993. https://doi.org/10.7759/cureus.75993 .
3.	Williams, D.M. , Nagaraj J., Stephens, J. W., Min, T. (2025). The use of non-invasive biomarkers to screen for advanced fibrosis associated with metabolic dysfunction-associated steatotic liver disease in people with type 2 diabetes: A narrative review. <i>touchREV Endocrinol</i> , 21(1), 24-31. https://doi.org/10.17925/EE.2025.21.1.4 .
4.	Williams, D.M. , Min, T., Beamish, A., Stephens, J. W. (2025). Perioperative screening for metabolic dysfunction associated steatotic liver disease in people undergoing bariatric surgery: a pilot study. <i>Obes Surg</i> . 35(5). 1963-7. https://doi.org/10.1007/s11695-025-07810-y .
5.	Williams, D.M. , Nagaraj J, Wilkinson L, Stephens JW, Min T. (2026). Views and understanding of metabolic dysfunction-associated steatotic liver disease in patients with diabetes. <i>Diabetes Metab</i> . 52(2). 101723. https://doi.org/10.1016/j.diabet.2026.101723 .

Peer-reviewed publications related to this work to date. *denotes joint first authorship status.

Table 11.3: Prizes related to the work presented in this thesis

Prizes	
1.	Swansea University James Callaghan Research Award (2024): I was ‘highly commended’ for this award for postgraduate research students at Swansea University, with a laptop prize for the duration of my postgraduate studies.
2.	Young Diabetologist and Endocrinologist Forum Travel Award (2024): I was shortlisted for this national award presented at the Diabetes UK professional Conference in 2024.
3.	Swansea University Postgraduate Research Conference Oral Presentation Prize (2025): I was given an ‘honourable mention’ for this prize following my presentation at the Swansea University PGR conference in 2025.
4.	Welsh Endocrine Diabetes Society Best Research Award (2025): I was awarded this prize for the best original research oral presentation at the Welsh Endocrine and Diabetes Society national meeting in 2025.

Prizes received related to the work presented in this thesis.

Appendix II:
Supplementary Information for Study 2

Figure 12.1: Participant information sheet used in study 2

Participant information sheet version 2: 18-May-2023



Participant Information Sheet

The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics: A Pilot Study

IRAS number: 326341

Pencadlys Bae Abertawe / Swansea Bay Headquarters, 1 Talbot Gateway, Port Talbot, SA12 7BR.
Ffon / Tel: (01639) 683344. <https://sbuhb.nhs.wales/>

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The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics: A Pilot Study

You are being invited to take part in a research study. You are free to decide if you want to take part in this study or not. This participant information will help you decide if you want to take part. Please take time to read this document carefully. You may wish to talk to your study doctor, family or friends before deciding.

Please ask your study doctor if there is anything not clear or if you want more information and take the time you need to make your choice.

If you decide to take part in the study, you need to sign the 'Consent form'.

What is in this document?

1. Why are we doing this study?
 2. Deciding if you want to take part
 3. What will happen to you if you take part?
 4. What are the possible side effects or harms of taking part?
 5. What are the benefits of taking part?
 6. Who is involved and more information about taking part?
 7. How will information collected about you be used and who can see it?
 8. Who can you talk to for more information?
-

1. Why are we doing this study?

People with type 2 diabetes are at greater risk of several health concerns compared to people without type 2 diabetes, such as heart disease, stroke, eye problems, kidney disease and nerve damage. More recent studies show that many people with type 2 diabetes develop fatty liver disease, which increases the risk of liver irritation causing liver scarring and ultimately liver cirrhosis. Earlier stages of fatty liver disease are potentially reversible with lifestyle and diet changes, and more recent studies show some medications used for type 2 diabetes can reverse fatty liver disease. Currently there is no screening tests for this type of

liver disease in people with type 2 diabetes, and patients are often diagnosed at later stages of cirrhosis, which is currently incurable.

This study uses body measurements, additional blood tests and bedside scans of the liver to find out how many people with type 2 diabetes receiving diabetes care from specialist diabetes clinics in Swansea Bay University Health Board have this type of liver disease and whether your usual blood tests or any additional blood tests are useful to help diagnose patients with this condition. This might allow us to diagnose people with fatty liver disease more quickly, allowing these patients to be seen earlier by a liver specialist and treatment changed to prevent them developing liver cirrhosis in the future. As our understanding of the extent and cause of the link between liver disease and type 2 diabetes is currently limited, there may be further tests not included in this study, which may be useful to perform in future. You are free to decide whether we can securely store your blood tests for up to five years in order to perform any additional tests as part of future research. These additional tests will be undertaken to explore other blood test markers that may be useful to screen for liver disease in people with diabetes or for other markers, which may explain the reason that people with type 2 diabetes are more likely to develop liver disease.

2. Deciding if you want to take part

Why have I been invited to take part?

You have been invited to take part in this study because you have type 2 diabetes and are seen in specialist diabetes clinics in Swansea Bay University Health Board. Of note, pregnant women are excluded from the study.

What happens if you say 'yes'?

Your participation in this study is entirely voluntary. It is up to you to decide whether you would like to take part. If you do, you will be given this information sheet to keep and you will be asked to sign the 'Consent Form'. The original signed and dated copy will remain at the hospital and you will be given a copy to take home for future reference.

What happens if you say 'no'?

You are free to say no. If you do not take part in the study, your current and future medical care will not be affected. You will continue to be seen by the same team that you currently see now.

What happens if you change your mind and no longer want to take part?

Your participation in this study is completely voluntary and if you wish, you can withdraw from the study at any time without penalty or loss of benefits. Your decision to withdraw will not affect the relationship between you and your study or usual doctor, nor influence any future medical treatment provided for you. If you withdraw from the study, we can destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

3. What will happen to you if you take part?

A doctor taking part in the study will ask you some additional questions about your health. Some of these questions involve your alcohol intake. The doctor will then take your usual blood tests along with some additional blood tests at the same time and perform a liver scan called FibroScan in the clinic room. The whole study visit should take about 30 minutes of your time. You will be asked to attend the clinic appointment in fasting state. That means that you cannot eat or drink anything except water for 8 hours before the visit. You do not need to adjust any of your medications. A total of about 40 mL of blood (8 teaspoons full) will be taken during the visit.

The liver scan (FibroScan) usually takes around 5 minutes and measures the "stiffness" of your liver which reflects the amount of liver scarring present. This will all be done immediately following your usual clinic appointment. This scan is not invasive, using a probe and some lubricant jelly on the skin to look at the liver. During the scan, you may feel vibration and a sort of tickling on your ribs. People having this scan very rarely report that this is painful.

You may be asked to come for extra visit for another type of scan (ultrasound scan of the liver) if there is a clinical need. If you are found to have significant liver disease through any of these

tests in the clinic appointment or in any future study, you will be referred to the appropriate liver specialist for further tests.

Your details will be kept on a secure and confidential database within Swansea Bay University Health Board, and you may be contacted again in future by the study team for follow-up tests such as blood tests or liver scans to monitor for liver disease. You will also be invited to take part in the future study where your blood samples will be stored for future use.

Why are we asking you to use some of your samples for future research?

As greater understanding of the link between diabetes and liver disease develops, additional research questions may arise and additional blood tests may be useful to answer these questions and further develop our knowledge. We would like the opportunity to do more tests on your blood samples should the need arise.

Deciding if you allow some samples to be used for future research

If you agree to allow some of your samples to be stored for future research, you do not need to do anything extra. When you have your blood tests taken as part of the main study, an extra bottle containing around 5 mL of blood will be taken. There is no additional needles or puncture required for this blood test and you will not need any extra visits. Your blood sample will be stored for 5 years in the Swansea Bay Local Laboratory after the study ends and will then be destroyed in accordance with local guidance.

If you do not agree to allowing some of your samples to be stored for future research, it will not impact on your ability to take part in the main study, and it will not impact upon your usual medical care in any way. If you do not agree to take part in the future research, your samples will be handled and destroyed in accordance with local guidance and Human Tissue Act at the end of study.

What happens if you change your mind and no longer want to take part in the future research?

You can withdraw your consent to store your blood samples for future research at any time. A decision to withdraw at any time, or a decision not to take part, will not affect the standard

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of care you receive, and you will continue to be seen by the same team that you currently see now. If you withdraw, your samples will not be used in future research and will be destroyed at the end of study. Results from your samples which have already tested at the time of withdrawn consent may still be used for research purposes.

4. What are the possible side effects or harms of taking part?

This study involves additional blood tests and non-invasive scans. The main risk from taking part in this study is being found to have a previously unknown disease such as liver disease. If this is found on your tests, the study doctor will inform you and refer you to a specialist liver clinic for further evaluation and assessment. In that instance, you might be reviewed by a liver specialist doctor and/or a liver specialist nurse in the clinic. They can provide you additional information tailored to your needs. You can also request an additional review with the study doctor to go through with results and plan for further specialist evaluation. . Some patients find the bedside scan a little uncomfortable with a slight vibration from the probe but this usually a very simple and painless non-invasive scan which usually takes 5 minutes to do.

5. What are the benefits of taking part?

The benefits of taking part include the additional assessment on your liver health. This review will include the additional liver blood tests and an additional scan of your liver to look for liver disease. If there are any abnormalities found, you will be informed of these results and if needed referred for additional specialist review or additional medical therapy may be suggested. The study cannot guarantee that you will receive any direct health benefit from participating. However, it is hoped that the information gained from this study may help to treat other people with type 2 diabetes in the future.

6. Who is involved and more information about taking part?

Who is organising and funding the research study?

This study is being sponsored by Research and Development Department, Swansea Bay University Health Board. This study will be carried out in three hospital sites (Morrison Hospital, Singleton Hospital and Neath Port Talbot Hospital) within the Swansea Bay University Health Board. You will not receive payment for your participation in this study.

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Who has reviewed the study?

Before any research goes ahead it must be reviewed by an ethics committee. They make sure that the research is planned properly and is not likely to cause harm or undue distress to the participants in the study. This study protocol has been reviewed and approved by the Joint Study Review Committee, Swansea Bay University Health Board, and the Wales REC3 (Ref: 23/WA/0139)

What if something goes wrong?

Participating in the study should not put you at any increased risk of something going wrong and the additional tests are all non-invasive with very little risk of harm. However, if taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay for it. Regardless of this, if you wish to complain or have any aspect of the way you have been approached or treated during this study, the normal National Health Service complaints mechanism is available to you. Information on the complaints procedure of Swansea Bay University Health Board can be found here: <https://sbuhb.nhs.wales/about-us/complaints-feedback/complaints/>.

What happens when the study stops?

At the end of the research study visit the research doctor will discuss your scan results and let you know if any further action is needed. You will also be informed of the findings from your blood samples once the results are available.

You may be contacted in future to take part in a follow-up study for further discussions, blood tests, and/or liver scans. You can decline any further invitations to take part in this study or withdraw from the study at any time and without giving a reason.

7. How will information collected about you be used and who can see it?

Will my taking part in this study be kept confidential?

All the information about your participation in this study will be confidential. If you agree to take part in this study, your study doctor will contact your GP to let him/her know of your participation after clinic appointment by a written correspondence. You will be asked to consent for your GP to be informed of your participation.

What information about you will be collected?

During the study your study doctor will collect information about your health and certain types of personal information. This will include your name, hospital number, NHS number, contact information, sex and race. The study team may also collect information relevant for the study from other health care professionals such as your GP and specialist doctors and nurses from liver clinic. You will be asked to consent for your study doctors to contact other health care professionals.

Who will be able to see your information?

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are my choices about how my information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can I find out more about how my information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team

What will happen to the results of the research study?

The study is being undertaken for the purpose of a higher educational qualification. The findings of the study will form the basis of a higher medical research degree (MD or PhD). The results of the study will also be published in a medical journal and might be presented to other doctors and scientists with an interest in diabetes and liver disease in the UK and abroad. If reports or publications are generated from the study, you will not be identified in these.

Who can you talk to for more information?

This Participant Information Sheet and the Consent Form contains important facts, which you should consider when deciding whether you are willing to take part in this study. If, at any time, you have any questions about the study, your rights as a research participant, a study-related injury or side-effects, you should contact your research doctor on:

Name: Dr Thinzar Min, Consultant Physician (Diabetes and Endocrinology)
Address: Department of Diabetes, Neath Port Talbot Hospital, Swansea SA12 7BX
Telephone: [REDACTED]

If you would like independent information on the study before you decide whether to take part, you may contact the following person:

Name: Professor Stephen Bain, Consultant Physician
Address: Department of Diabetes, Singleton Hospital, Swansea SA6 6NL
Telephone: [REDACTED]

Thank you for reading this information sheet.

Pencadlys Bae Abertawe / Swansea Bay Headquarters, 1 Talbot Gateway, Port Talbot, SA12 7BR.
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Figure 12.2: Consent form used to participate in study 2

Consent Form Version 2 18-05-2023

IRAS ID: 326341



CONSENT FORM

Title of project: The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics: A pilot study

Principle Investigator: Dr Thinzar Min

Participant ID Number	Consultant
Date of Birth	NHS No.

Participant: Please read this form very carefully prior to signing if in agreement:

Please initial box

- I confirm I have read and understood the participant information sheet (version 2: dated May 18th, 2023) for the above study. I have had the opportunity to consider the information, ask questions and have them answered to my satisfaction. ☐
- I confirm that I understand what is required of me if I participate in the above study. ☐
- I understand that my participation is entirely voluntary, and I can choose to change my mind at any time, without giving a reason, and without any effect on my medical or surgical care, or my legal rights being affected. ☐
- I understand that responsible individuals involved in the research may look at relevant sections of my medical notes, including individuals from the NHS, Swansea University, or from regulatory authorities where it is relevant to my taking part in this research. I give permission to these individuals to have access to my records. ☐
- I agree for the research team to inform my General Practitioner of my participation in this study, including any necessary exchange of information about me between my GP and the research team. ☐
- I understand that the information collected about me as part of this research study will be held and maintained securely by the research team. ☐

I agree to take part in the study ☐

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A copy of the completed consent form should be given to the patient, placed in the site file and patient notes

Participant

I confirm that I agree to take part in the study:

_____	_____	_____
Name of participant	Date	Signature

Person seeking consent:

I confirm that I have explained the study:

_____	_____	_____
Name of person seeking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes.

The consent form used to take part in study 2.

Figure 12.3: Consent form for future research used in study 2

Future Research Consent Form Version 2 18-05-2023

IRAS ID: 326341



CONSENT FORM: FUTURE RESEARCH

The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics: A pilot study

Principle Investigator: Dr Thinzar Min

Participant ID <u>Number</u>	Consultant
Date of Birth	NHS No.

Participant: Please read this form very carefully prior to signing if in agreement:

Please initial box

- I have read and understood the participant information and agreement to use samples for future research sheet (version 2: dated May 18th, 2023) for the above study. I have had the opportunity to consider the information, ask questions and have them answered to my satisfaction. ☐
- I confirm that I understand what is required of me if I participate in the above study. ☐
- I understand that my participation is entirely voluntary, and I can choose to change my mind at any time, without giving a reason, and without any effect on my medical or surgical care, or my legal rights being affected. ☐
- I understand that my blood samples will be stored for up to five years, and may be used later as part of future research in this study and will not involve any genetic testing. ☐
- I understand that responsible individuals involved in the research may look at relevant sections of my medical notes, including individuals from the NHS, Swansea University, or from regulatory authorities where it is relevant to my taking part in this research. I give permission to these individuals to have access to my records. ☐
- I agree for the research team to inform my General Practitioner of my participation in this study, including any necessary exchange of information about me between my GP and the research team. ☐
- I understand that the information collected about me as part of this research study will be held and maintained securely by the research team. ☐

I agree to take part in the study

☐

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A copy of the completed consent form should be given to the patient, placed in the site file and patient notes

Participant

I confirm that I agree to take part in the study:

_____	_____	_____
Name of participant	Date	Signature

Person seeking consent:

I confirm that I have explained the study:

_____	_____	_____
Name of person seeking consent	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes.

The consent form used to confirm participation in future research in study 2.

Figure 12.4: The general practitioner notification letter for participants in study 2

GP Letter version 1: 30 March 2023

GP Surgery Address	Dr Thinzar Min Department of Diabetes & Endocrinology Neath Port Talbot Hospital Baglan Way, Port Talbot Swansea Bay University Health Board SA12 7BX

Date: [insert date]	Tel: [REDACTED]

Dear Dr [insert name],

RE: The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics

[Insert patient details]

I am writing to inform you that the above patient has kindly agreed to take part in a clinical study titled 'The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics'. This study is approved by the Research Ethics Committee [insert approval number] and is being conducted by the Diabetes Clinical Research Team in collaboration with the Hepatology team in Swansea Bay University Health Board (SBUHB).

The primary aim of this study is to determine the prevalence of non-alcoholic fatty liver disease (NAFLD) in people with type 2 diabetes attending secondary care diabetes clinics in SBUHB. The study also aims to determine whether additional blood tests (e.g., liver enzymes, enhanced liver fibrosis (ELF) test, measures of insulin resistance) or transient elastography (Fibroscan) taken in the diabetes clinic are useful to identify NAFLD in people with type 2 diabetes as a screening test. During this research study, no invasive tests will be undertaken, and no additional drug therapies or other investigative medicinal products will be administered. People identified at risk of advanced NAFLD will be referred to the Hepatology team in SBUHB by the Clinical Research Team. We will keep you informed of any test results and any further action that is taken during the study.

Should you have any questions or wish to have further information about this research, please do not hesitate to contact us.

Yours sincerely,

Dr David Williams MRCP Diabetes Research Fellow and Specialist Registrar in Diabetes & Endocrinology, Singleton Hospital, Sketty Lane, Sketty, Swansea, SA2 8QA. Email: [REDACTED]	Dr Thinzar Min MBBS, MSc, MD, FRCP, FHEA, PGDip Senior Clinical Lecturer, Swansea University Medical School, Grove Building, Singleton Park, Swansea, SA2 8PP Honorary Consultant, Diabetes & Endocrinology, Singleton Hospital & Neath Port Talbot Hospital Email: [REDACTED]

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The template used to notify the participants' GP of their involvement in study 2.

Figure 12.5: Case report form used for data collection in study 2

Case report form: Version 1, February 1st, 2023.

Date:

Patient initials:

The screening of non-alcoholic fatty liver disease and advanced liver fibrosis in people with type 2 diabetes in secondary care diabetes clinics: A pilot study	
Date of informed consent:	
Demographics	
Name:	Insert patient sticker here
NHS number:	
Hospital number:	
DOB:	
Sex:	
Ethnicity:	
History	
Duration of T2D diagnosis	Year of diagnosis: ____ Duration: ____ years
Past Medical History	
Past Surgical History	
Family History	
Medication history	

Social history	
Alcohol history	Current: ____ units/week
	Previous (>20g/day/<20g/day)
	Never
Smoking history	Current: ____ /day
	Previous ____ pack years
	Never
Illicit/injectable recreational drug use	Current: _____
	Previous: _____
	Never
Deprivation	Postcode: _____
	WIMD Decile: ____ WIMD Quintile: ____
Frailty	CFS ____ CCMi ____
Exclusion criteria	
Suspected alcohol dependence*:	Yes ☐ No ☐
Chronic liver disease other than NAFLD or NASH:	Yes ☐ No ☐
Family or personal history of inherited liver disease:	Yes ☐ No ☐
Previous surgical treatment of obesity:	Yes ☐ No ☐
Diabetes type other than T2D:	Yes ☐ No ☐
Current pregnancy:	Yes ☐ No ☐
Unable or unwilling to provide informed consent:	Yes ☐ No ☐
Concern study will cause participant distress:	Yes ☐ No ☐
Examination	
Height: ____ m	BMI: ____ kg/m ²
Weight: ____ kg	Blood pressure: ____ mmHg

* Suspected alcohol dependence is defined as regularly taking >20g/day alcohol in the last 3 months or as assessed using the AUDIT questionnaire

Investigations		
Urine		
Urinary albumin: ____ mg/g		
Urinary albumin: creatinine ratio: ____		
Blood		
Hb: ____ g/L	Bili: ____ μ mol/L	PT: ____ seconds
WCC: ____ $\times 10^9$ /L	TP: ____ g/L	APTT: ____ seconds
~~Rbc~~ : ____ $\times 10^9$ /L	Alb: ____ g/L	Fibrinogen: ____ g/L
MCV: ____ ~~fL~~	ALP: ____ IU/L	ELF test: ____
HbA1c: ____ mmol/mol	ALT: ____ IU/L	Fasting c peptide: ____ nmol/L
Na: ____ mmol/L	AST: ____ U/L	Fasting glucose: ____ mmol/L
K: ____ mmol/L	GGT: ____ U/L	Fasting insulin: ____ ~~μU/mL~~
Urea: ____ mmol/L	TC: ____ mmol/L	HOMA-IR: ____
~~Creat~~ : ____ ~~μmol/L~~	TG: ____ mmol/L	
eGFR: ____ mL/min/1.73m ²	LDL: ____ mmol/L	
~~CrCl~~ : ____ mL/min	HDL: ____ mmol/L	
Radiology		
Fibroscan (Date __/__/__)	CAP: ____ kPa LSM: ____ kPa IQR: ____ %	
Referred to hepatology team?	Yes ☐ No ☐	
Date & Signature		

The case report form used to support data collection in study 2.

Figure 12.6: Questionnaire used for feedback following TE in study 2

Patient feedback survey

1. Did the scan take longer than expected?
Yes ☐ No ☐
2. Was the scan painful?
Yes ☐ No ☐
3. Did you understand the reasons for having the scan?
Yes ☐ No ☐
4. Did you understand the result of the scan?
Yes ☐ No ☐
5. If asked, would you have the scan again?
Yes ☐ No ☐
6. Do you think this is an acceptable test to screen for fatty liver disease in people living with diabetes?
Yes ☐ No ☐
7. Any other feedback

Liver disease screening in people with diabetes

Thank you for completing this questionnaire, please return to reception desk or your clinic doctor.

If you have any questions, please contact:

Dr David Williams: [REDACTED]

Dr Thinzar Min: [REDACTED]

The questionnaire used by patients with T2D following TE in study 2.

Figure 12.7: Confirmation of favourable opinion from the REC Wales for study 2



Wales Research Ethics Committee 3
Cardiff

Mailing address:
Health and Care Research Wales
Castlebridge 4
15-19 Cowbridge Road East
Cardiff, CF11 9AB

email: Wales.REC3@wales.nhs.uk
website: www.hra.nhs.uk

25 May 2023

Dr Thinzar Min
Consultant Physician (Diabetes) / Senior Clinical Lecturer
Swansea Bay University Health Board
Diabetes Unit, Neath Port Talbot Hospital
Port Talbot
SA12 7BX

Dear Dr Min

Study title:	SCREENING OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND ADVANCED LIVER FIBROSIS IN PEOPLE WITH TYPE 2 DIABETES IN SECONDARY CARE DIABETES CLINICS: A PILOT STUDY
REC reference:	23/WA/0139
IRAS project ID:	326341

Thank you for your response of 24 May 2023, responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Good practice principles and responsibilities

The [UK Policy Framework for Health and Social Care Research](#) sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of [research transparency](#):

1. [registering research studies](#)
2. [reporting results](#)
3. [informing participants](#)
4. [sharing study data and tissue](#)

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: [Research registration and research project identifiers](#)).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/>

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: <https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/>

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at <https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/>.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/consultant information sheets or letters [GP-letter]	1	30 March 2023
IRAS Application Form [IRAS_Form_05042023]		05 April 2023
Letter from sponsor [Approval email]		27 January 2023
Letters of invitation to participant [Invitation-letter]	1	30 March 2023
Other [Consent-Form-Future Research]	2	18 May 2023
Other [Response from applicants]	1	23 May 2023
Participant consent form [Consent-Form-Main-study]	2	18 May 2023
Participant information sheet (PIS) [Main and Future research study]	2	18 May 2023
Referee's report or other scientific critique report [Peer-Reviewed-combined]		
Research protocol or project proposal [Study Protocol-T2DM-NAFLD]	2	06 January 2023
Response to Request for Further Information		
Summary CV for Chief Investigator (CI) [Dr.ThinzarMin-CV]	Mar-2022	
Summary CV for student [DW-CV]		
Summary CV for supervisor (student research) [Prof-Stephens CV]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

IRAS project ID: 326341 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely



Sue Byng
Approvals Specialist
On behalf of the Chair

Email: Wales.REC3@wales.nhs.uk

Enclosures: List of names and professions of members
who were present at the meeting and those who submitted written
comments
"After ethical review – guidance for researchers"

[After ethical review guidance for sponsors and investigators –
Non CTIMP Standard Conditions of Approval\]](#)

Copy to: Anne-Claire Owen

The confirmation letter received for the favourable opinion from the REC Wales to undertake study 2.

Figure 12.8: Confirmation of approval from the HRA and HCRW for study 2



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales



**Health Research
Authority**

Dr Thinzar Min
Consultant Physician (Diabetes) / Senior Clinical
Lecturer
Swansea Bay University Health Board
Diabetes Unit, Neath Port Talbot Hospital
Port Talbot
SA12 7BX

Email: HCRW.approvals@wales.nhs.uk

25 May 2023

Dear Dr Min

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title: SCREENING OF NON-ALCOHOLIC FATTY LIVER
DISEASE (NAFLD) AND ADVANCED LIVER FIBROSIS IN
PEOPLE WITH TYPE 2 DIABETES IN SECONDARY
CARE DIABETES CLINICS: A PILOT STUDY

IRAS project ID: 326341

REC reference: 23/WA/0139

Sponsor Swansea Bay University Health Board

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, [in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.](#)

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see [IRAS Help](#) for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to [obtain local agreement](#) in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "[After Ethical Review – guidance for sponsors and investigators](#)", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The [HRA website](#) also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **326341**. Please quote this on all correspondence.

Yours sincerely,
Sue Byng

Approvals Specialist

Email: HCRW.approvals@wales.nhs.uk

Copy to: Ms Anne-Claire Owen

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

<i>Document</i>	<i>Version</i>	<i>Date</i>
GP/consultant information sheets or letters [GP-letter]	1	30 March 2023
IRAS Application Form [IRAS_Form_05042023]		05 April 2023
Letter from sponsor [Approval email]		27 January 2023
Letters of invitation to participant [Invitation-letter]	1	30 March 2023
Other [Consent-Form-Future Research]	2	18 May 2023
Other [Response from applicants]	1	23 May 2023
Participant consent form [Consent-Form-Main-study]	2	18 May 2023
Participant information sheet (PIS) [Main and Future research study]	2	18 May 2023
Referee's report or other scientific critique report [Peer-Reviewed-combined]		
Research protocol or project proposal [Study Protocol-T2DM-NAFLD]	2	06 January 2023
Summary CV for Chief Investigator (CI) [Dr.Thinzar Min-CV]	Mar-2022	
Summary CV for student [DW-CV]		
Summary CV for supervisor (student research) [Prof-Stephens CV]		

IRAS project ID	326341

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
This is a single site study sponsored by the participating NHS organisation therefore there is only one site type.	The single participating NHS organisation of this type is also sponsoring the research. You should work with your sponsor R&D office to make arrangements to set up the study. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.	This is a single site study sponsored by the participating NHS organisation therefore no agreements are expected.	No external study funding has been sought	Principal Investigators are expected to be in place at participating NHS / HSC organisations where locally employed staff take responsibility for research procedures.	Where an external individual who does not already hold an NHS employment contract will be conducting any of the research activities that will be undertaken at this site type then they would be expected to hold an Honorary Research Contract. External staff holding pre-existing NHS employment contracts should obtain a Letter of Access. These should confirm Occupational Health Clearance. These should confirm [enhanced/standard] DBS checks [and appropriate barred list checks].

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.

N/A

The confirmation letter received to notify of approval from the HRA and HCRW to undertake study 2.

Figure 12.9: Confirmation of sponsor approval to commence study 2

From: Rebecca McGrath (Swansea Bay UHB - Research And Development) [REDACTED]
Sent: Monday, October 9, 2023 4:30:56 PM
To: Thinzar Min (Swansea Bay UHB - Diabetes and Endocrinology) [REDACTED]; David Williams (Morriston Hospital - W082) [REDACTED]
Cc: Tina Morgan (Swansea Bay UHB - Research & Development) [REDACTED]; Anne-Claire Owen (Swansea Bay UHB - Research & Development Department) [REDACTED]; Jemma Rogers (Swansea Bay UHB - Research & Development) [REDACTED]; Jenna Walters (Swansea Bay UHB - Laboratory Medicine) [REDACTED]; Non Gwynn (Swansea Bay UHB - Laboratory Medicine) [REDACTED]; Rachel Still (Swansea Bay UHB - Laboratory Medicine) [REDACTED]; Mark Simpson (Swansea Bay UHB - Finance) [REDACTED]; Jeffrey Stephens (Swansea Bay UHB - Diabetes) [REDACTED]; Jagadish Nagaraj (Swansea Bay UHB - Gastroenterology) [REDACTED]
Subject: 326341 NAFLD-T2DM Confirmation of Capacity and Capability from SBU LHB

Dear Chief Investigator,

RE: Study Title NAFLD-T2DM
REF: IRAS 326341

This email confirms that SWANSEA BAY UNIVERSITY HEALTH BOARD has the capacity and capability to deliver the above referenced study.

Please accept this email as confirmation of "green light" from us the sponsor.

As sponsor, we expect you to notify us of any changes/amendments to this study so that we can sign off the required Amendment tool.

Details on the Amendment process, Amendment Tool and how to apply can be found using the following link.

IRAS Help - Maintaining your approvals - Amendments for projects conducted in NHS/HSC
(<https://myresearchproject.org.uk/help/hlp/amendments.aspx>)

We may also contact you to provide other data to your study as and when required.

Please now liaise with Tina Morgan our QAO (Copied in) to arrange your study initiation and Site File set-up.

We will contact you regarding any changes to capacity, should the need arise.

If you wish to discuss further, please do not hesitate to contact us.

Many Thanks

Rebecca McGrath

Research Facilitator | Research & Development | Swansea Bay University Local Health Board
Hwylusudd Ansawdd | Ymchwil a Datblygu | Bwrdd Iechyd Lleol Prifysgol Bae Abertawe

Research & Development, Swansea Bay University Local Health Board/ Bwrdd Iechyd Lleol Prifysgol Bae Abertawe
Room 104, Floor 1, Institute of Life Science 2/ Ystafell 104, Llawr 1, Athrofa Gwyddor Bywyd 2
Swansea University/ Prifysgol Abertawe
Singleton Park/ Parc Singleton
Swansea/ Abertawe
SA2 8PP

The confirmation email received from the study sponsor to notify approval to commence study 2

Figure 12.10: Amendment tool submitted to extend study duration

Amendment Tool					For office use QC: No
v1.6 06 December 2021					
Section 1: Project Information					
Short project title:	NAFLD-T2DM				
IRAS project ID* (or REC reference if no IRAS project ID is available):	326341				
Sponsor amendment reference number:	NSAQ2				
Sponsor amendment date* (enter as DD/MM/YY):	11 October 2024				
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered):	Recruitment to the study was completed. However, analysis of blood samples are still in progress and hence the study will need to extend until 31.10.25.				
Project type (select):	Specific study Research tissue bank Research database				
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	Yes		No		
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	NHS/HSC REC Ministry of Defence (MoDREC)				
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a modified amendment (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		No		
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland	
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		No		
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		No		
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		No		
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		No		
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		No		
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		No		
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		No		
Did the study involve children OR does the amendment introduce this?:	Yes		No		
Did the study involve NHS/HSC organisations prior to this amendment?:	Yes		No		
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		No		
	England	Wales	Scotland	Northern Ireland	
Lead nation for the study:	No	Yes	No	No	
Which nations had participating NHS/HSC organisations prior to this amendment?	No	Yes	No	No	
Which nations will have participating NHS/HSC organisations after this amendment?	No	Yes	No	No	
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	Yes		No		
Section 2: Summary of change(s)					

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Study Design			
Specific change (select - only available when area of change is selected first):	Extension to study duration that will not have any additional resource implications for participating organisations - Please specify in the free text below			
Further information in particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered):	Specify new date: 31/ October/ 2025			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?:	No	Yes	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (please note that this answer may affect the categorisation for the change):	All		Some	
Add another change				

Section 3: Declaration(s) and look for submission

Declaration by the Sponsor or authorized delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name (first name and surname)*: Lisa Wakeman

Email address*: [REDACTED]

Look for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Look for submission

After locking the tool, [proceed to submit the amendment online](#). The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for information only. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																Category:		
	UK wide:						England and Wales:				Scotland:			Northern Ireland:					
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSA	Radiation Assurance	UKSW Governance	REC (MCA)	CAG	HMPs	MRA and HCRW Approval	REC (AWA)	PRPP	SPS (RAC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	
Change 1:						(Y)				(Y)									C
Overall reviews for the amendment:																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

The submitted amendment tool to extend the study duration, to permit analysis of collected samples.

Figure 12.11: Approval received from study sponsor for minor amendment

Lisa Wakeman (Swansea Bay UHB - Research And Development)

From: no-reply-IRAS <no-reply-iras@hra.nhs.uk>
Sent: 16 October 2024 15:09
To: Thinzar Min (Swansea Bay UHB - Diabetes and Endocrinology)
Subject: IRAS 326341. Amendment

You don't often get email from no-reply-iras@hra.nhs.uk. [Learn why this is important](#)

WARNING: This email originated from outside of NHS Wales. Do not open links or attachments unless you know the content is safe.

IRAS Project ID: 326341
Sponsor amendment reference: NSA02

Thank you for submitting your study amendment. In accordance with the outcome of your completed amendment tool, this amendment requires no further regulatory review. Please now share this amendment with your UK research sites, in accordance with the instructions in your completed amendment tool.

For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

For all NHS research sites in England and Wales, please now share this amendment by email directly with those sites, including both the R&D offices and research teams.

Do not reply to this email as this is an unmonitored address and replies to this email cannot be responded to or read.

This message may contain confidential information. If you are not the intended recipient please inform the sender that you have received the message in error before deleting it. Please do not disclose, copy or distribute information in this e-mail or take any action in relation to its contents. To do so is strictly prohibited and may be unlawful. Thank you for your co-operation..

Correspondence received to confirm approval of the minor amendment to extend the study duration.

Appendix III:
Supplementary Information for Study 3

Figure 13.1: Questionnaire used for feedback following bariatric surgery pilot study

Patient feedback survey:
Liver disease screening in people living with obesity.

viii. Did the scan take longer than expected?
Yes ☐ No ☐
ix. Was the scan painful?
Yes ☐ No ☐
x. Did you understand the reasons for having the scan?
Yes ☐ No ☐
xi. Did you understand the result of the scan?
Yes ☐ No ☐
xii. If asked, would you have the scan again?
Yes ☐ No ☐
xiii. Do you think this is an acceptable test to screen for fatty liver disease in people living with obesity?
Yes ☐ No ☐
xiv. Any other feedback

Thank you for completing this questionnaire, please return to reception desk or your clinic doctor.

If you have any questions, please contact:

Dr David Williams:

████████████████████

Dr Thinzar Min:

████████████████████

The questionnaire used by patients undergoing bariatric surgery in study 3 following TE in clinic.

Figure 13.2 Letter of support from the clinical director for general surgery



Sketty Lane
Swansea
SA2 8QA

Our Ref: AB/EJE/

Contact: Elizabeth J Evans
(Secretary)

Your Ref:
NHS No:

Direct Line:
Fax:

To Whom it May Concern

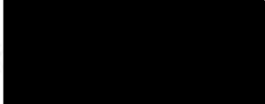
Dear

As part of quality improvement processes within the Welsh Institute of Metabolic and Obesity Surgery, additional tests for the formal assessment of pre-operative and post-operative liver disease are being introduced. This is in response to the intraoperative findings of advanced liver disease related to obesity, including cirrhosis. Identifying markers of liver disease in advance of bariatric surgery will allow us to undertake the appropriate additional tests, where indicated, including the gold standard diagnostic investigation - liver biopsy - whilst performing the bariatric surgery. As such, we will routinely collect additional blood liver tests (alanine transaminase and gamma glutamyl transferase, and international normalised ratio). We will also use fibro scan where available and combine the findings validated scoring tools including the NAFLD fibrosis score and the FIB-4 index as well as the MELD score.

As with other clinically relevant data, these results will be collected and monitored within existing audit and quality improvement processes using the existing prospectively maintained WIMOS database.

Kind regards

Yours sincerely


Professor J Barry
Clinical Director for General Surgery


Mr A Beamish
Bariatric Lead – WIMOS

The letter of support from Professor Jonathan Barry (clinical director for general surgery) and Mr Andrew Beamish (bariatric lead for the WIMOS) to undertake the pilot study. This letter was part of the application submitted to the JSRC at SBUHB to support undertaking the service evaluation project.

Figure 13.3: Confirmation email from the JSRC at SBUHB

Jeffrey Stephens (Swansea Bay UHB - Diabetes)

From: Karen Chesters (Swansea Bay UHB - Research & Development)
Sent: 13 June 2023 08:30
To: Jeffrey Stephens (Swansea Bay UHB - Diabetes)
Cc: Anne-Claire Owen (Swansea Bay UHB - Research & Development Department);
Jemma Rogers (Swansea Bay UHB - Research & Development); Lisa Wakeman
(Swansea Bay UHB - Research And Development)
Subject: RE: Service delivery proposal for R&D Item 9.4 - JSRC comments 06.06.2023
RESPONSE

Dear Jeff,

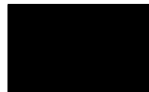
Thank you for the comprehensive information you've provided following JSRC last week.

Jemma, Steve & Dean have reviewed this & all are happy to badge your project as Service Evaluation.

There is no need for the project to come back to the committee.

Please ensure IG are aware of your planned activities.

Many Thanks



Karen Chesters
Research Facilitator | Research & Development | Swansea Bay University Health Board
Ymchwil Hwylusydd | Ymchwil a Datblygu | Bwrdd Iechyd Prifysgol Bae Abertawe (BIPBA)

Swansea Bay University Health Board / Bwrdd Iechyd Prifysgol Bae Abertawe
1st floor, Institute of Life Science 2 / Athrofa Gwyddor Bywyd 2
Swansea University / Prifysgol Abertawe
Singleton Park / Parc Singleton
SA2 8PP



The confirmation email received to confirm support from the research and development team in SBUHB to undertake the pilot study as a service evaluation project.

Appendix IV:
Supplementary Information for Study 4

Figure 14.1: Questionnaire used for the patient survey study

Liver disease survey																									
Section 1: Demographics																									
1. How old are you? _____ years 2. What is your ethnic group? _____ 3. How would you describe your gender? Man ☐ Woman ☐ Non-binary (please specify) ☐ _____ Another gender not listed here ☐ _____ Prefer not to say ☐ 4. What type of diabetes do you have? Type 1 diabetes ☐ Type 2 diabetes ☐ Other, please describe ☐ _____																									
Section 2: Liver disease awareness																									
5. Has a doctor or other health professional told you that you have any form of liver disease? Yes ☐ No ☐ 6. If yes, please tell us what type of liver disease you have (select all that apply): <table border="0"> <tr> <td>Alcohol-related ☐</td> <td>Primary biliary cholangitis (PBC) ☐</td> </tr> <tr> <td>Autoimmune hepatitis ☐</td> <td>Primary sclerosing cholangitis (PSC) ☐</td> </tr> <tr> <td>Fatty liver disease ☐</td> <td>Viral hepatitis (hepatitis B, hepatitis C) ☐</td> </tr> <tr> <td>Liver cancer ☐</td> <td>Other, please specify ☐ _____</td> </tr> </table> 7. Has a doctor or other health professional told you that you are at risk of liver disease? Yes ☐ No ☐ 8. If yes, please tell us what type of liver disease you are at risk of (select all that apply): <table border="0"> <tr> <td>Alcohol-related ☐</td> <td>Primary biliary cholangitis (PBC) ☐</td> </tr> <tr> <td>Autoimmune hepatitis ☐</td> <td>Primary sclerosing cholangitis (PSC) ☐</td> </tr> <tr> <td>Fatty liver disease ☐</td> <td>Viral hepatitis (hepatitis B, hepatitis C) ☐</td> </tr> <tr> <td>Liver cancer ☐</td> <td>Other, please specify ☐ _____</td> </tr> </table> 9. What is the commonest cause of liver disease in people living in Wales in the last 10 years? <table border="0"> <tr> <td>Alcohol-related ☐</td> <td>Primary biliary cholangitis (PBC) ☐</td> </tr> <tr> <td>Autoimmune hepatitis ☐</td> <td>Primary sclerosing cholangitis (PSC) ☐</td> </tr> <tr> <td>Fatty liver disease ☐</td> <td>Viral hepatitis (hepatitis B, hepatitis C) ☐</td> </tr> <tr> <td>Liver cancer ☐</td> <td>Other, please specify ☐ _____</td> </tr> </table>		Alcohol-related ☐	Primary biliary cholangitis (PBC) ☐	Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐	Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐	Liver cancer ☐	Other, please specify ☐ _____	Alcohol-related ☐	Primary biliary cholangitis (PBC) ☐	Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐	Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐	Liver cancer ☐	Other, please specify ☐ _____	Alcohol-related ☐	Primary biliary cholangitis (PBC) ☐	Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐	Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐	Liver cancer ☐	Other, please specify ☐ _____
Alcohol-related ☐	Primary biliary cholangitis (PBC) ☐																								
Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐																								
Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐																								
Liver cancer ☐	Other, please specify ☐ _____																								
Alcohol-related ☐	Primary biliary cholangitis (PBC) ☐																								
Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐																								
Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐																								
Liver cancer ☐	Other, please specify ☐ _____																								
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Autoimmune hepatitis ☐	Primary sclerosing cholangitis (PSC) ☐																								
Fatty liver disease ☐	Viral hepatitis (hepatitis B, hepatitis C) ☐																								
Liver cancer ☐	Other, please specify ☐ _____																								

10. If you would like to learn more about liver disease in diabetes, what would be your preferred source of information? (select all that apply)

- GP ☐ Practice nurse ☐
Hospital consultant ☐ Specialist nurse ☐
Leaflet ☐ Other, please specify ☐ _____
Online/website ☐

11. Please circle whether you strongly agree, agree, neither agree nor disagree, disagree, or strongly disagree with each of the following statements:

I am at risk of developing fatty liver disease:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

I would like more blood tests to diagnose fatty liver disease:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

I would like more scans to diagnose fatty liver disease:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

I would be concerned if I had fatty liver disease:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

I would like to learn more about fatty liver disease:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

People with diabetes need more tests to screen for complications:

Strongly agree Agree Neither agree nor disagree Disagree Strongly disagree

Alternatively, use the QR code for mobile-friendly version



Thank you for your time taking this survey.

Figure 14.2: Questionnaire used for the clinician survey study

Physician survey																	
Section 1: Demographics																	
1. What is your current grade? Consultant Physician ☐ Foundation Trainee ☐ GP ☐ GP registrar ☐ Internal Medicine Trainee ☐ Medical Registrar ☐ Specialist, Associate Specialist, and Specialty (SAS) doctors ☐ Other, please specify ☐ _____ 2. What is your current specialty? _____																	
Section 2: Awareness and screening of non-alcoholic fatty liver disease (NAFLD)																	
3. On a scale of 1 to 100, please estimate each of the following: <table border="0"> <tbody> <tr> <td>i. The percentage prevalence of NAFLD worldwide</td> <td>Score</td> </tr> <tr> <td>ii. The percentage prevalence of NAFLD in people with type 2 diabetes worldwide</td> <td>Score</td> </tr> <tr> <td>iii. The percentage prevalence of NAFLD in Wales</td> <td>Score</td> </tr> <tr> <td>iv. The percentage of patients in your practice with NAFLD in the last 2 weeks</td> <td>Score</td> </tr> </tbody> </table> 4. Do you think NAFLD is an important public health issue? Yes ☐ No ☐ 5. In patients with fatty liver identified on a scan, would you usually refer them for further assessment or treatment? Yes ☐ No ☐ 6. Have you made a referral regarding NAFLD in the last 3 months? Yes ☐ No ☐ 7. If so, to whom did you refer? (Select all that apply) <table border="0"> <tbody> <tr> <td>Diabetes & endocrinology ☐</td> <td>Hepatology team ☐</td> </tr> <tr> <td>Dietician ☐</td> <td>Weight management ☐</td> </tr> <tr> <td>GP ☐</td> <td>Other, please specify ☐ _____</td> </tr> <tr> <td>Gym ☐</td> <td></td> </tr> </tbody> </table>		i. The percentage prevalence of NAFLD worldwide	Score	ii. The percentage prevalence of NAFLD in people with type 2 diabetes worldwide	Score	iii. The percentage prevalence of NAFLD in Wales	Score	iv. The percentage of patients in your practice with NAFLD in the last 2 weeks	Score	Diabetes & endocrinology ☐	Hepatology team ☐	Dietician ☐	Weight management ☐	GP ☐	Other, please specify ☐ _____	Gym ☐	
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Dietician ☐	Weight management ☐																
GP ☐	Other, please specify ☐ _____																
Gym ☐																	

8. On a scale of 1 (strongly disagree) to 100 (strongly agree), please rate how much you agree with each of the following statements:

i.	Screening for NAFLD should take place regularly in the general population	Score
ii.	Screening for NAFLD should take place regularly in at risk populations, such as people living with diabetes or obesity	Score
iii.	NAFLD is a benign disease	Score
iv.	Screening for NAFLD will reduce the incidence of NAFLD-related cirrhosis	Score
v.	Additional blood tests are an appropriate screening strategy for NAFLD	Score
vi.	Additional scans are an appropriate screening strategy for NAFLD	Score
vii.	Endocrinologists should be involved in the management of people with NAFLD	Score

Alternatively, use the QR code for mobile-friendly version



Thank you for your time taking this survey.

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