Comparison of Systemic Inflammatory Indices with the Oncotype DX® Recurrence Score and the Nottingam Prognostic Index in Early Hormone Receptor Positive Ductal Breast Cancer

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ABSTRACT:

***Background**:* Adjuvant therapy decisions in hormone receptor positive and human epidermal growth factor receptor 2 negative breast cancer are evolving. The introduction of gene panel testing has significantly reduced the number of patients recommended for chemotherapy by up to two thirds. However, these tests are expensive, highlighting the need to identify lowrisk genomic breast cancer cases before testing, which could represent a significant economic impact. The use of systemic inflammatory indices has shown promise as prognostic markers in early breast cancer. We investigated the potential utility of four systemic inflammatory indices with the Nottingham Prognostic Index to predict the Oncotype DX® recurrence scores threshold level (low score or high score), in a cohort of women aged 50 and over with node negative invasive ductal carcinoma of the breast.

***Methods**:* A retrospective review of patients who had Oncotype DX® Recurrence Score testing from 2007 to 2021 were identified. After exclusions, the final sample size was 245. Clinicopathological features were collected to calculate the Nottingham Prognostic Index. The systemic inflammatory indices were estimated from preoperative peripheral blood samples.

***Results**:* 22.4% of the cohort had a Recurrence Score in the higher risk group. This cohort had a greater percentage of grade 3 tumours, progesterone receptor negativity, higher Nottingham Prognostic Scores, and inflammatory indices ratios than the lower risk group. A decision tree incorporating the Neutrophil Lymphocyte Ratio with clinicopathological features showed potential as an indicator of a high Oncotype DX® RS score, such that further investigation is warranted to assess whether Recurrence Score testing could be triaged in certain cohorts of patients. In this cohort, 38% of patients might be able to avoid genomic testing based on the decision tree analysis.

***Conclusion**:* Utility of the inflammatory indices with clinicopathological features may help triage gene panel testing.

Keywords: Early Breast Cancer • Adjuvant; Peripheral Blood Inflammatory Markers • Oncotype DX • NPI

INTRODUCTION

The concept of personalised medicine has become forefront in many medical disciplines with the aim of tailoring treatment to individual patients. The field of breast surgical oncology has embraced this, incorporating traditional risk assessment tools such as the Nottingham Prognostic Index (NPI) with clinically validated gene expression tests to predict the risk of recurrence and to guide chemotherapy decisions in early breast cancer [1, 2]. The shift of emphasis from pathological factors, such as lymph node status, tumour size and stage, to include molecular signaling pathways and genetic signatures, aimed to represent the true heterogeneity of breast cancer more accurately.

A recent study demonstrated that prognostication was improved when clinicopathologic data was integrated with tumour genomic testing [1]. The genomic classifier investigated in this study, Oncotype DX® Recurrence Score (ODX RS), a 21-gene assay, is validated as a prognostic and predictive tool in node negative hormone receptor positive and human epidermal growth factor receptor (*HER2*) negative early breast cancer [3]. The assay measures the expression of 16 tumour related genes and 5 control genes. The Recurrence Score (RS) is calculated algorithmically, with results ranging from 0 to 100, stratifying patients into a high, intermediate, or low risk group. The score estimates prognosis and, in addition, the relative benefit of adding chemotherapy to adjuvant endocrine therapy. However, there are limitations; namely cost, borderline results, and possible treatment delay, such that less expensive and more rapid methods of prediction and prognostication would be welcome. Furthermore, the proportion of patients with ODX RS low risk ranges between 48% [4] to 64% [5], such that triaging these patients before genomic testing could result in significant savings. Indeed, a health economic analysis suggested that the cost-effectiveness of genomic testing was favourable for ODX RS in lymph node negative early breast cancer when the NPI was >3.4 [6]. Thereby highlighting the importance of considering pathological factors to screen cases where gene panel testing may be omitted..

The study explored whether this stratification proposal may be enhanced by incorporating other markers of poorer prognosis such as inflammation, as the role that inflammation plays in tumour development and progression is well recognised [7]. Systemic inflammatory markers assessed from peripheral blood samples have been evaluated as potential prognostic and predictive markers in cancer. Most research has evaluated the utility of the Neutrophil-toLymphocyte Ratio (NLR), the Platelet-to-Lymphocyte ratio (PLR), the Monocyte-toLymphocyte Ratio (MLR) and a combination of the NLR and platelet level in a Systemic Inflammation Index (SII). Studies have found, that of these ratios, the NLR may have potential as a prognostic marker for breast cancer [8] as the ratio has shown promising results in a variety of other solid malignancies [9,10]. These ratios are readily available from preoperative blood results. However, although a meta-analysis by Wei and colleagues [8] found an association between higher NLR and poor survival rate in patients with breast cancer, the authors noted significant heterogeneity in the results especially for Western populations.

The aim of this study was to explore the association between the systemic inflammatory indices SII, NLR, PLR, MLR, the NPI and the ODX RS in node negative early ductal breast cancer in patients aged 50 and older. We also sought to evaluate whether a model incorporating clinicopathological features and systemic inflammatory ratios could predict a low ODX RS, such that genomic testing may be safely omitted in certain categories of patient.

2. MATERIAL AND METHODS

2.1 Patient identification

A single centre retrospective cohort study was undertaken following local and UK ethical approval. The Hywel Dda University Health Board (HDUHB) in Southwest Wales, UK, commenced ODX RS testing in 2007, with results from three district general hospitals within the HDUHB Surgical Oncology held in one database. ODX RS testing is performed on unstained slides of formalin-fixed paraffin-embedded tissue as per manufacturer's guidelines. Female patients treated for early oestrogen receptor positive, *HER2* negative breast cancer with post-surgical RS between 2007 and 2020 were identified (n=506), and link-anonymised using unique identification numbers. Some of these individuals had been included in a decision impact and economic evaluation study in Southwest Wales [11].

2.2 Clinical data sources

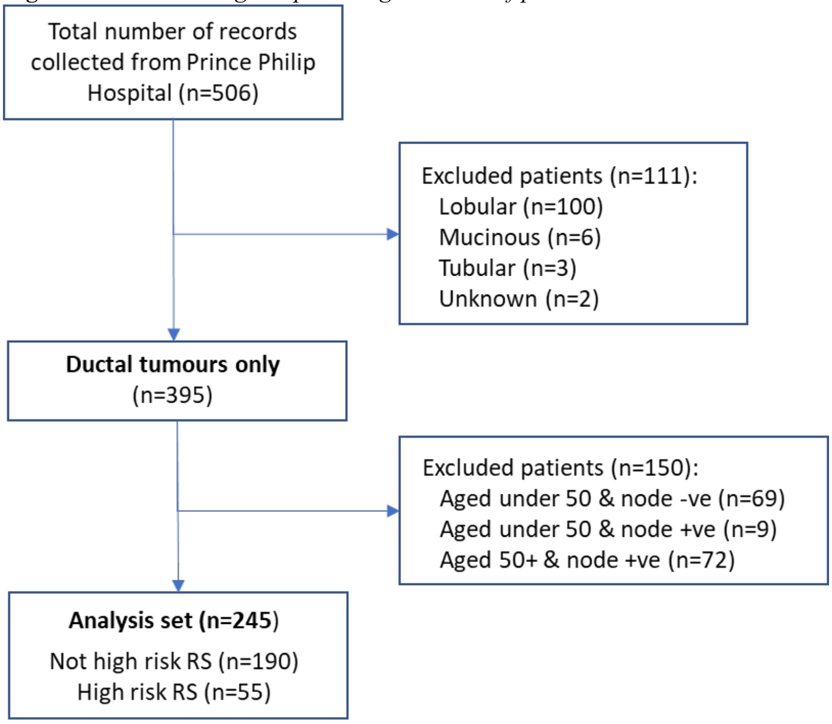
ODX RS data were recorded in a secure database. RS levels were grouped into two categories, high and non-high risk, with high being ODX RS > 25 in patients 50 years and over, levels considered working cut-offs for consideration of chemotherapy benefit in the UK following data from the TAILORx [2] and RxPONDER trials [12].

Clinicopathological reports for the cohort were retrieved. Tumour characteristics recorded included size, grade, lymph node status.The NPI was calculated for all patients using the formula: NPI = tumour size (in cm) x 0.2 + Tumour Grade (1-3) + lymph node status (1=negative, 2= one to three nodes positive, 3 = greater than four nodes positive). The groups were classified into four categories: Excellent ≤ 2.4, Good >2.4 ≤3.4, Moderate >3.4 ≤5.4, Poor > 5.4 [13].
A review of clinical records was undertaken to ascertain date of diagnosis, age at diagnosis, date last seen (follow-up period), dates of recurrence, date of death and cause of death.

The preoperative Full Blood Count (FBC) was used to calculate the NLR, MLR, PLR and SII for each patient in the cohort. The SII was calculated using the formula Neutrophil Count x Platelet count/Lymphocyte count (N/L x P).

Exclusion criteria included ODX RS testing for preinvasive histology (Ductal Carcinoma insitu (DCIS)), lobular or any of the special histology types, mixed ductal or ductal with mucinous features. Mixed ductal lobular histology cases were included in the ductal cohort. Patients receiving testing in the axillary node positive setting, subjects lost to follow-up and cases with no preoperative peripheral blood analysis recorded were also excluded. All patients included in the study were female and aged 50 years and over. The database included 395 ductal patients, after exclusion of nodal positivity (n=72) and patients aged less than 50 years (n=78), 245 cases were available for analysis (Figure 1).

Figure 1 *STROBE Diagram providing overview of patient selection*



2.3 Ethics

This study received ethical approval by IRAS Dulwich REC 262537 and HDUHB on 20th October 2020.

2.4 Data availability statement

Requests for copies of the dataset will be considered by the authors.

2.5 Statistical analyses

The outcome measure was the ODX RS being classed as high (≥26) or not high (<26) for the target age group (≥50 years).

All categorical and binary variables were described as counts and percentages. Medians and their interquartile range statistics were calculated for all continuous variables. Univariate logistic regression models were developed to assess the individual effects of grade, *PR*, NPI group, size, NLR, PLR, SII and MLR.

All continuous variables used in the logistic regression models were first transformed into normalised Z-scores with a mean of 0 and a standard deviation of 1. This enabled a consistent interpretation of the effect of a unit change for variables having very different measurement scales, as some ranged from 0 to 2, while others ranged from 115 to 5020. We avoided dichotomising these continuous variables with cut points to preserve the ability to treat them as continuous variables. As continuous variables, we could estimate the effect for each unit increase. For the variables that were transformed into Z scores that then meant the effect of each increase of one standard deviation. The Shapiro-Wilk test and visual inspection of the histograms were used to establish normality of the untransformed variables. Tukey's ladder of powers identified the best transformation for variables which did not exhibit a normal distribution.

For categorical variables, the largest category in terms of patient numbers was used as the baseline category, as this provided the greatest stability in the estimates.

Multivariable logistic regression models were employed to adjust for all covariates simultaneously. To investigate whether using the summary measures SII and NPI obscured important effects relating to their components, four models were assessed: SII and NPI, SII and

NPI components, SII components and NPI, SII components and NPI components. The final model choice was based on an assessment of the area under the ROC curve, the classification accuracy and the goodness of fit of the model. The goodness of fit was assessed by applying Pearson chi-square test. Visuals of the goodness of fit and of the regression diagnostics were used to evaluate the fit of the final model [14]. Covariate combinations that appeared to be substantially different to the norm in the regression diagnostics plots were investigated.
All analyses were conducted in Stata 18 [15].

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RESULTS

The number of patients in the cohort with an ODX RS greater than 25 was 22.45% (Table 1). This group were more likely to have grade 3 tumours, *PR* negativity; and to have a moderate, rather than good or excellent NPI score, than the non-high risk group. The high risk group also had slightly larger tumours and higher medians for NLR, PLR, SII and MLR; although the interquartile ranges were similar for the two ODX RS category groups.

Table 1: Patient and tumour characteristics

		Oncotype DX recurrence score category		**All**
		Not high risk	**High risk**	
		N (%)	N (%)	n (%)
Patients		190 (77.55%)	55 (22.45)	245
Grade	1	30 (15.8)	1 (1.8)	31 (12.7)
	2	131 (69.0)	24 (43.6)	155 (63.3)
	3	29 (15.3)	30 (54.6)	59 (24.1)
ER	Positive	190 (100)	55 (100)	245 (100)
PR	Positive	172 (90.5)	30 (54.6)	202 (82.5)
HER2	Negative	190 (100)	55 (100)	245 (100)
NPI	Excellent	16 (8.4)	0 (0.0)	16 (6.5)
	Good	78 (41.1)	12 (21.8)	90 (36.7)
	Moderate	96 (50.5)	43 (78.2)	139 (56.7)
		Median (IQR)	Median (IQR)	Median (IQR)
Age	(years)	62 (57 to 68)	64 (59 to 67)	63 (57 to 68)
Size	(cm)	2.1 (1.5 to 2.5)	2.2 (1.9 to 2.5)	2.1 (1.5 to 2.5)
NLR		2.26 (1.72 to 3.00)	3.08 (1.77 to 3.78)	2.33 (1.75 to 3.29)
PLR		139.3 (115.0 to 182.5)	150.0 (109.6 to 190.0)	140.7 (113.9 to 185.5)
SII		623.7 (464.3 to 883.2)	835.6 (516.8 to 1251.7)	653.9 (471.7 to 960.2)
MLR		0.22 (0.18 to 0.29)	0.23 (0.18 to 0.33)	0.22 (0.18 to 0.29)

The Shapiro-Wilk test and histograms suggested none of the continuous variables being considered for the model were normally distributed. Inspection of Tukeys ladder of powers plots and tests indicated 1/sqrt transformations for NLR and MLR, sqrt transformation for PLR and the log transformation for size and SII. The Z scores for NLR and MLR were reversed to enable evaluation of the effect of increases in size of NLR and MLR.

The models within NPI components, rather than NPI, performed best (Table 2). Of those two models, the model with SII components, rather than SII, had slightly better performance and was taken forward as the main model. ***Table 2**: Four multivariable model summary*

Model	Area under the ROC curve	Correctly classified %	Pearson Chi-square goodness of fit test	Notes
SII & NPI	0.77	80.8	p=0.49	NPI group I (Excellent) perfectly predicted DX score group so 16 records dropped from the model
SII & NPI components	0.83	81.6	p=0.85	
SII components & NPI	0.78	82.1	p=0.13	NPI group I (Excellent) perfectly predicted DX score group so 16 records dropped from the model
SII components & NPI components	0.84	83.3	p=0.53	

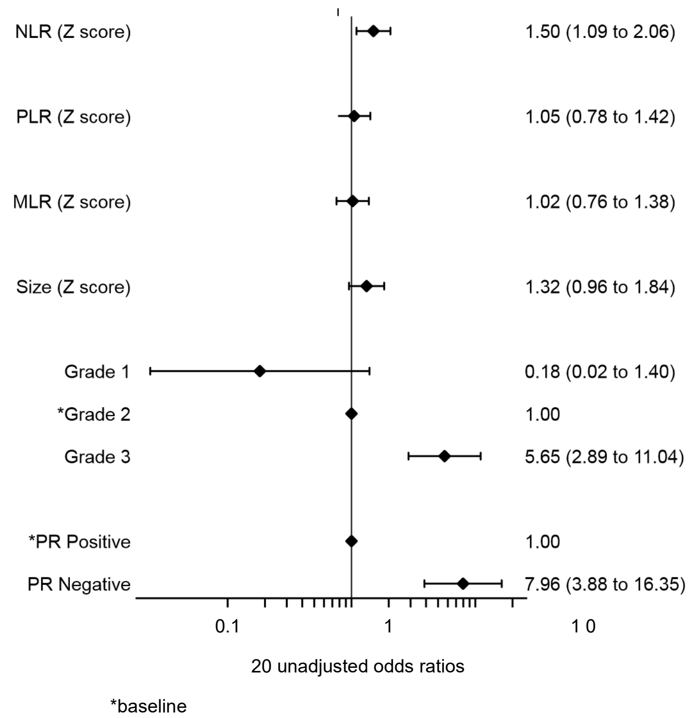
Univariate logistic regression models for all the variables to be included in the multivariable model showed that, on their own, only NLR, grade and *PR* status were significant predictors of ODX RS category (Table 3, Figure 2). Each increase in NLR of one standard deviation increased the chance of having a high risk ODX RS (OR 1.50, 95% CI 1.09 to 2.06). Grade three tumours were more likely (OR=1.73, 95% CI=1.06 to 2.40) to have a high risk ODX RS than grade 2. The large odds ratio for being *PR* negative (OR=7.96, 95% CI=3.88 to 16.34) suggested *PR* status to be an important indicator of ODX RS category.

***Table 3**: Univariate logistic regression*

Variable		Coefficient (β)	SE	Wald χ^2	P value	Odds Ratio	95% CI
NLR (Z score)		0.408	0.161	2.5	0.01	1.50	1.09 to 2.06
PLR (Z score)		0.050	0.153	0.32	0.75	1.05	0.78 to 1.42
MLR (Z score)		0.022	0.154	0.14	0.89	1.02	0.76 to 1.38
Size (Z score)		0.281	0.167	1.69	0.09	1.32	0.96 to 1.84
Grade	1	-1.704	1.040	-1.64	0.10	0.18	0.02 to 1.40
	(Baseline) 2	0.000				1.00	
	3	1.731	0.342	5.06	<0.01	1.73	1.06 to 2.40
Progesterone receptor status	Negative	2.074	0.367	5.65	<0.01	7.96	3.88 to 16.34

(Baseline) Positive	0.000	1.00

Figure 2: *Univariate logistic regression models odds ratios*



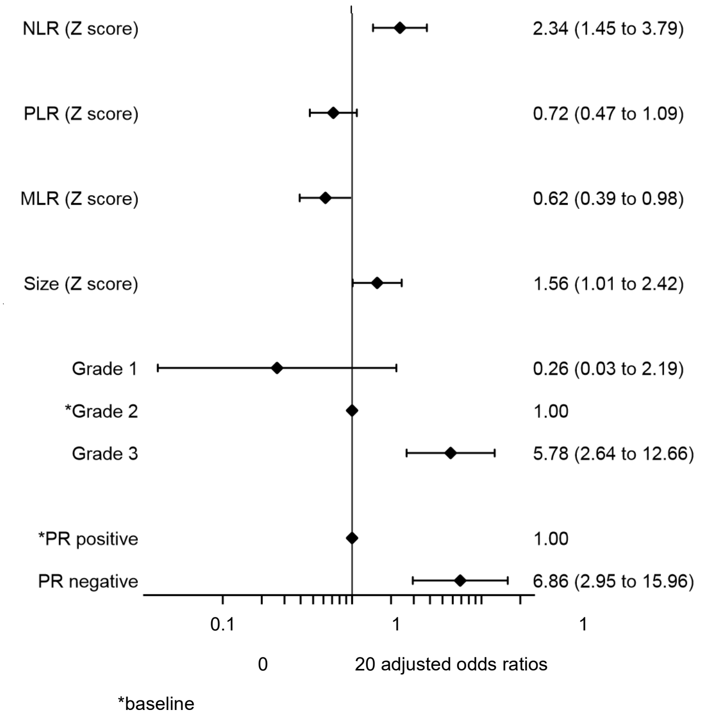
The three significant variables in the univariate analyses were also significant in the multivariable logistic regression model. However, in the presence of the other variables, MLR and size were also significant predictors, leaving only PLR as not significant (Table 4, Figure 3). The odds ratios for NLR and grade suggested even stronger effects when the additional variables were considered. There was a slight reduction in the effect of *PR* status, although it retained the biggest odds ratio in the model.

Table 4: *Multivariable logistic regression model*

Variable		**Coefficient (β)**	**SE**	**Wald**	**P χ^2 value**	**Odds Ratio**	**95% CI**
NLR (Z score)		0.8520.245		3.48	<0.01	2.341.45 to 3.79	
PLR (Z score)		-0.3340.214		-1.56	0.12	0.720.47 to 1.09	
MLR (Z score)		-0.4750.234		-2.03	0.04	0.620.39 to 0.98	
Size (Z score)		0.4470.223		2.01	0.04	1.561.01 to 2.42	
Grade	1	-1.3361.084		-1.23	0.22	0.260.03 to 2.20	
	(Baseline) 2	0.000				1.00	
	3	1.7550.400		4.39	<0.01	2.64 to 5.7812.66	

Progesterone receptor status	Negative	1.9250.431	-8.06	<0.01	2.95 to 6.8615.96
	(Baseline) Positive	0.000			1.00
Constant		-2.3160.287			

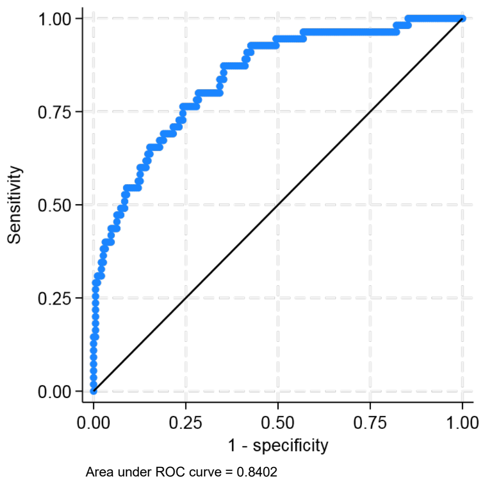
Figure 3: *Multivariable logistic regression model odds ratios*



There were 245 observations with 245 covariate patterns in this dataset. The Pearson chisquare goodness of fit test indicated a good fit of the model (*p*=0.53). As a precaution, due to the observations each representing a unique covariate pattern, the Hosmer-Lemeshow test was also conducted and indicated a good fit of the model (*p*=0.72).

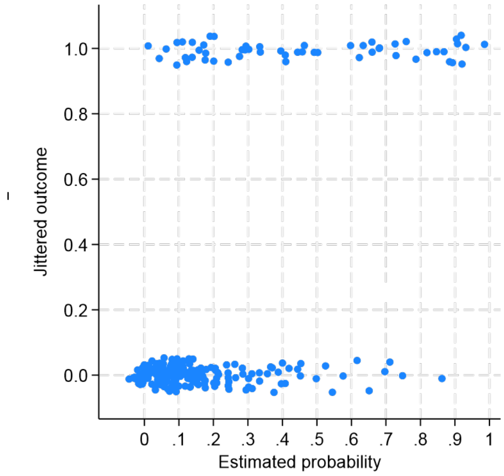
The area under the Receiver Operating Characteristic (ROC) curve (0.84) suggested the model had excellent discriminatory powers (Figure 4).

Figure 4*: Area under the ROC curve*



Plots of the predicted values showed the model was good at predicting those with non-highrisk RS scores, with those patients very much clustered to the low end of the estimated probability scale (Figure 4). The model was not so good at predicting those with high risk RS scores, which were spread right across the estimated probability scale.

Figure 5: Estimated probability against actual outcomes



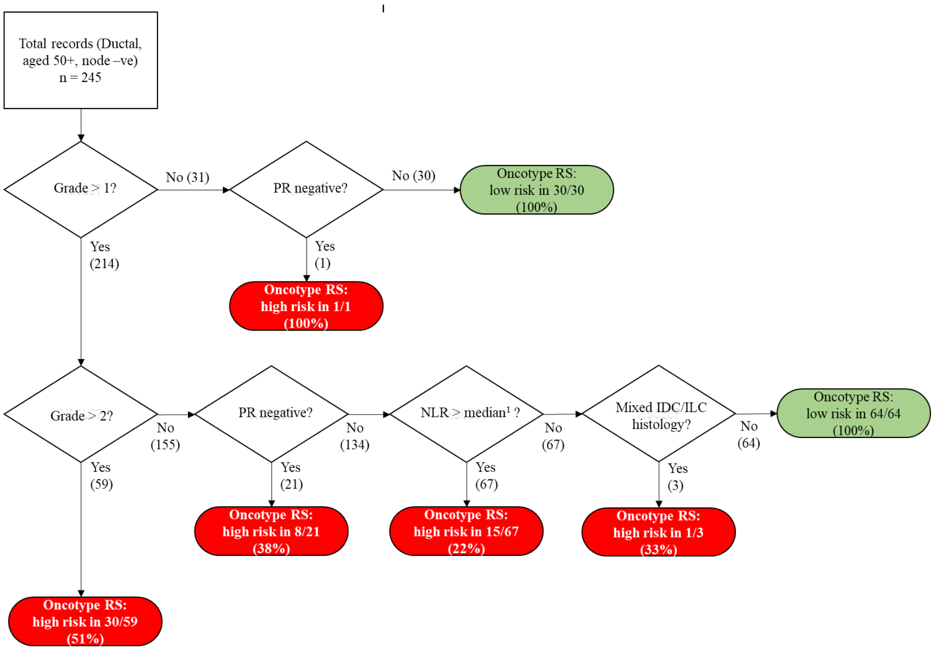
Inspection of plots of the estimated probabilities against leverage (Figure S1), change in Pearson chi-square (Figure S2), change in deviance (Figure S3), Cook's distance (Figure S4) and change in Pearson chi-square weighted by Cook's distance (Figure S5), indicated 12 covariate patterns that may have been poorly fitted by the model (see supplementary material).

None of the covariate patterns investigated seemed clinically implausible and all records were retained in the model.

Decision tree

Inspection of the predicted values for the range of covariate combinations revealed that grade 1 tumours were always low risk unless they were *PR* negative. Grade 2 tumours were always negative when all three of these characteristics were present: *PR* positive; lower than median NLR; not of mixed histology. Grade 3 tumours had no obvious differentiating factors within this dataset. To see whether these results could be applied to triage testing in IDC, a decision tree was developed from this information. The findings suggest that if these observations can be demonstrated within a wider and more diverse patient population, then almost 40% of patients could be screened out of testing (Fig 6). This has the potential to improve clinical workflow, and in addition, would represent a significant economic benefit.

Figure 6: Decision tree



[1] median for ductal, aged 50+ node –ve, grade 2, PR +ve = 2.3155

DISCUSSION

Although decisions surrounding the use of adjuvant chemotherapy in early *ER* positive and *HER2* negative breast cancer continue to evolve, it is becoming increasingly evident that integration of clinicopathological features with molecular scores can improve prognostication and stratification and clinical decision making [16, 17]. Whilst some genomic assays incorporate clinicopathological factors (MammaPrint, EndoPredict, Breast cancer Index, Prosigna), it is recognised that there can be discrepancies between the clinical risk scores and genomic scores [18]. The RS-pathology and clinical (RSPC) model, which include clinical factors such as age, tumour type, size, and grade with the genomic results, has been shown to downgrade intermediate recurrence scores to low scores, although studies indicate that the RSPC did not affect the high RS category [1, 2]. This was also noted in our study, as the model could not predict high RS. However, as demonstrated in other studies, our results show that over two thirds of patients (77.55%) had a non high RS, suggesting that if this cohort could be triaged into genomic screening/no genomic screening this would represent significant cost savings and improve clinical workflow.

The use of systemic inflammatory indices, most notably the NLR, has shown promise as prognostic markers in early breast cancer [8, 19, 20]. We investigated the potential utility of four systemic inflammatory indices with the NPI to predict the ODX RS threshold level (low score or high score), in a cohort of women aged 50 and over with node negative IDC. The study demonstrated that on univariate regression testing, only NLR, *PR* negativity and tumour grade were predictors of ODX RS. The association with *PR* receptor status is expected as *PR* status is one of the components of the RS assay. Tumour grade is used in other genomic assays as outlined above and has been shown to be prognostically relevant even in the era of molecular testing [21], as seen in our results.

We investigated the utility of a multivariate model to predict ODX RS using the components of summary scores. As expected, this provided better fitting models than using the summary scores. The final multivariable model suggested that NLR, MLR, size, grade and *PR* status were all important predictors of ODX RS category. All final model variables except MLR and size were also significant in their respective univariate models. We used a standardised measure of the distribution of the scores rather than absolute cut points. This has both technical merit as it eliminates the arbitrary binary decision of a cut-point, and practical benefit as it enables a better comparison of the effects of measures of very different scales. The final multivariate model fitted the data well by all conventional measures, but it is evident that prediction of high ODX RS was not improved. Given this model considers a relatively small set of markers compared to Oncotype DX® Recurrence Score testing, this is expected. However, it has highlighted the potential of tumour Grade, *PR* status and NLR as possible predictors of a low ODX RS which was explored further. This analysis, presented as a decision tree, suggests that patients fell into two categories. The first category represented 38% of the cohort, those patients were either Grade 1 and *PR* positive, or Grade 2 and *PR* positive, with lower NLR. There were no mixed IDC/lobular histology within this group. None of these cases had a high ODX RS.

With 77.55% of patients in this group receiving a low ODX RS, and given the cost of the test, removing the need to test any subgroup could result in significant savings [6]. Following further research, if the ODX RS for a third of patients could be predicted by Grade, *PR* status and NLR this would result in a simple method to triage ODX RS testing in women aged 50 and above with node negative IDC, which would translate into a considerable economic benefit. A recent study by Faria et al [20] classified patients into three groups of relapse based on Eastern Cooperative Oncology Group Performance Score (ECOG-PS), presence of comorbidities, tumour and nodal stage, *PR* status and NLR. The results of this study suggest that the combination of clinicopathological features and the NLR may have potential as a prognostic model. These findings are in line with the GEICAM substudy [22], which also noted an association between prognosis and high NLR; although, this was in patients with *ER* negative and *HER2* positive breast cancer.

The findings of this decision tree suggest that there may be potential for prognostication in the adjuvant setting of early invasive ductal carcinoma of the breast.

Limitations

The study has several limitations aside from the retrospective cohort design, with the potential for selection bias. The population in this study was ethnically homogenous and from a single institution which may limit the applicability of the findings to other geographical regions, thereby affecting the overall generalisability. Indeed, in December 2023, only 2.3% of the population of Southwest Wales were registered as Black, Asian and minority ethnic groups [23]. To address this limitation, it is important that future research includes larger, multicentre studies with more diverse populations to validate and extend our findings.

This study evaluated the use of systemic inflammatory indices calculated from preoperative peripheral blood samples. These indices are easily obtained and, as they are part of general preoperative assessment, there is no cost implication. However, there are a number of limiations when interpreting these parameters. Standardisation of thresholds in the literature is not consistent. The inflammatory indices can vary with age and ethnicity, and some patients in the study may have had concurrent morbidities, or be on medication that could have influenced the preoperative haematological parameters. These confounding factors may potentially have influenced the inflammatory indices levels. However, as our cohort was ethnically homogenous, the indice ratios in this study may be less varied.

Currently genomic testing in patients with invasive lobular breast cancer is performed in line with testing in other histological subtypes of breast cancer. Our study did not include patients with invasive lobular breast carcinoma (ILC), as studies have shown that most lobular cancers have a low to intermediate RS on ODX RS testing [24], with high RS typically, although not exclusively, found in patients with pleomorphic ILC. In addition, prognostication with NPI in lobular cases may also be limited, as the majority of ILC cases are grade 1 or 2, with only approximately 10% grade 3 [25]. This limitation can be compounded by difficulties with grading ILC, as pathological features such as tubule formation, atypia, nuclear pleomorphism and mitotic count are generally uniform in classical ILC [26]. However, we included cases with ductal/lobular carcinoma, and as some studies suggest that this histological subtype may be more histologically similar to lobular carcinoma, this could have confounded our results [27].

In Southwest Wales, ODX RS testing is requested after discussion in the multidisciplinary team meeting (MDT). High risk cases assessed on clinicopathological factors are often considered for chemotherapy with no testing, and individuals who are unable to, or have expressed a wish to avoid chemotherapy, will have been excluded from testing. This may have introduced selection bias. After exclusions, the cohort size was significantly reduced. A larger cohort may have improved the validity of the results.

CONCLUSION

Prognostication and prediction are important considerations in the adjuvant setting in early breast cancer. Combination of clinicopathological factors with multigene assay scores for a more personalised risk stratification, may allow a more tailored approach to treatment. This study investigated the association between the ODX RS, NPI and the systemic inflammatory indices and developed a decision tree incorporating grade, NLR and *PR* status to triage genomic testing. The results suggest that this decision tree may identify cases of IDC where genomic testing can be omitted. Prospective studies are needed to evaluate this decision tree further.

Ethics

Ethical approval for the study was obtained from REC Dulwich on 6th October 2020. IRAS ID 262537**,** REC reference number 20/LO/0850.

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No funding was received for the study.

CRediT authorship contribution statement

Anita Huws: Conceptualisation; Data curation; Investigation; Writing – original draft, review and editing.
Gareth Davies: Software; Data curation; Methodology; Results; Formal analysis; Visualisation; Writing – review and editing.
Paul Lewis: Writing – review and editing;
Claire Morgan: Writing – review and editing;

Declaration of Competing Interest

The authors have no Competing Interests to declare

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Supplementary Documents

The most extreme values towards the upper corners were investigated along with those that seemed some distance from the general patterns. They could be clearly separated into four groups:

1. Nine patients with the strong predictors of lower risk ODX RS (*PR* positive and Grade 2) giving them a low predicted probability but with a higher risk RS. Seven of these nine had lower than average NLR and MLR scores, both of which would have suggested lower risk ODX RS.
2. One grade 3 patient with a strong predictor of lower risk ODX RS (*PR* positive) giving them a low predicted probability but actually having a high risk RS.
3. One *PR* negative patient with a strong predictor of lower risk ODX RS (Grade 1) giving them a low predicted probability but with a high risk RS.
4. One patient with strong predictors of a high risk ODX RS (Grade 3 and *PR* negative) giving a high predicted probability but with a low risk RS. This patient had lower than average values for NLR, PLR, MLR and tumour size, though not exceptionally so.

Figure S1: *Estimated probability against leverage*

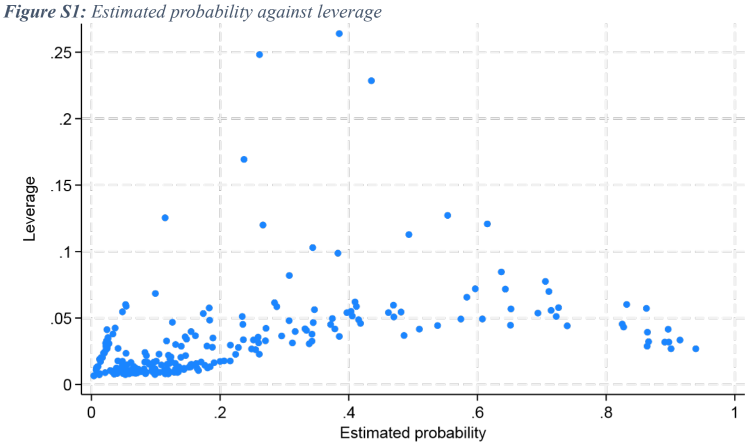

Figure S2: *Estimated probablitity against change in Pearson Chi-square*

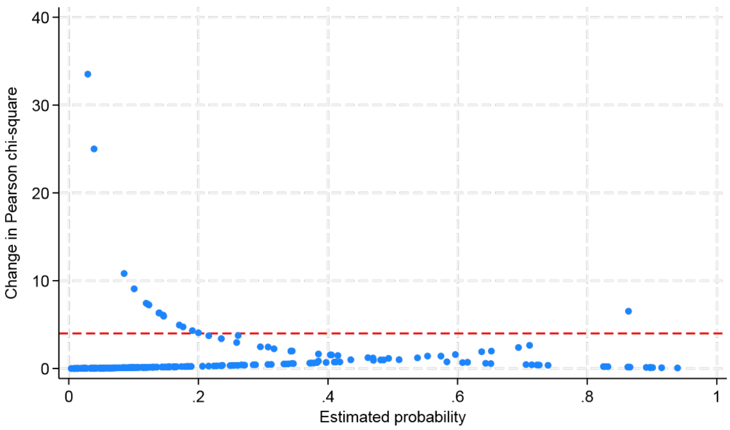

Figure S3: *Estimated probablity against change in deviance*

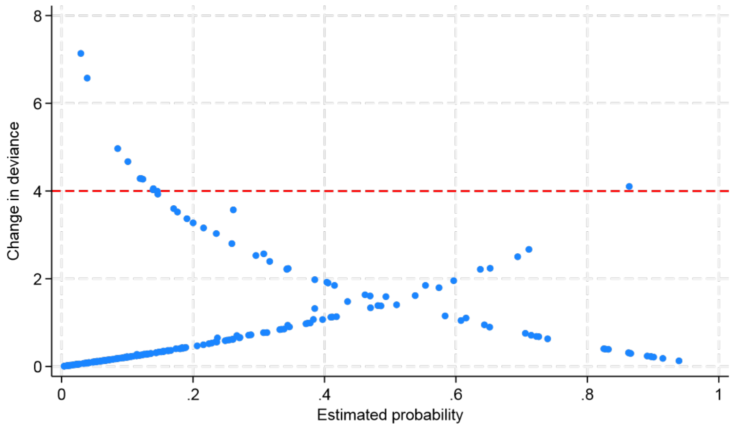

Figure S4: Estimated probability against Cook's distance

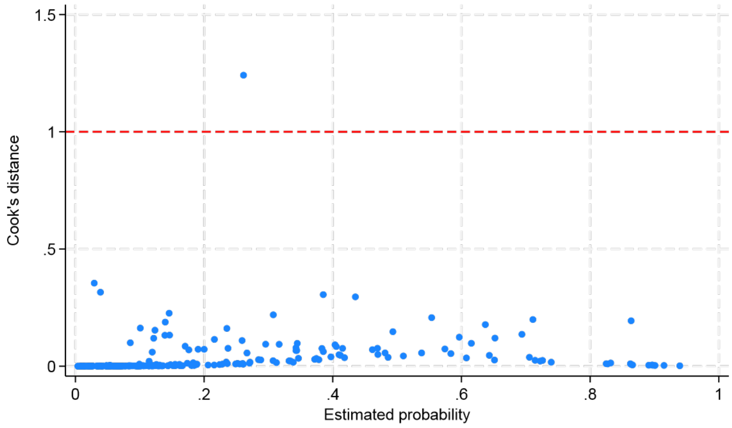

Figure S5: Estimated probability against change in Pearson's Chi-square, weighted by Cook's distance.