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ORIGINAL ARTICLE

Individual participant data from digital sources informed and improved precision in the evaluation of predictive biomarkers in Bayesian network meta-analysis

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Abstract

Objectives: We aimed to develop a network meta-analytic model for the evaluation of treatment effectiveness within predictive biomarker subgroups, by combining evidence from individual participant data (IPD) from digital sources (in the absence of randomized controlled trials) and aggregate data (AD).

Study Design and Setting: A Bayesian framework was developed for modeling time-to-event data to evaluate predictive biomarkers. IPD were sourced from electronic health records, using a target trial emulation approach, or digitized Kaplan-Meier curves. The model is illustrated using two examples: breast cancer with a hormone receptor biomarker, and metastatic colorectal cancer with the Kirsten Rat Sarcoma (KRAS) biomarker.

Results: The model allowed for the estimation of treatment effects in two subgroups of patients defined by their biomarker status. Effectiveness of taxanes did not differ in hormone receptor positive and negative breast cancer patients. Epidermal growth factor receptor inhibitors were more effective than chemotherapy in KRAS wild type colorectal cancer patients but not in patients with KRAS mutant status. Use of IPD reduced uncertainty of the subgroup-specific treatment effect estimates by up to 49%.

Conclusion: Utilization of IPD allowed for more detailed evaluation of predictive biomarkers and cancer therapies and improved precision of the estimates compared to use of AD alone.

Keywords: IPD network meta-analysis; Network meta-regression; Predictive biomarker; Colorectal cancer; Breast cancer; One-stage Bayesian hierarchical model

1. Introduction

Predictive biomarkers and associated targeted therapies are at the center of precision medicine; therefore, they are of great interest to patients, researchers, pharmaceutical companies, and health-care decision-makers. Novel cancer therapies are often more effective in patients who harbor a specific biomarker, which may lead to greater gains for such patients in terms of overall survival (OS) and/or health-related quality of life. For example, the aromatase inhibitors, such as letrozole and anastrozole, have shown to be effective treatments in breast cancer patients who are hormone receptor positive (HR+ve) [1,2].

Randomized controlled trials (RCTs) are considered the 'gold standard' approach when evaluating treatment

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What is new?

Key findings

- We developed a one-stage Bayesian meta-analytic model that estimates the relative treatment effects in binary predictive biomarker subgroups simultaneously using time-to-event data.

What this adds to what was known?

- Combination of IPD and AD to inform effectiveness of therapies has added value compared to using AD alone.

What is the implication and what should change now?

- In the absence of IPD from published RCTs in biomarker predictive subgroups, IPD can be sourced by emulating target trials from electronic health records or by digitizing Kaplan-Meier curves.

efficacy [3]. However, limitations due to cost, safety or ethical considerations could hinder undertaking RCTs, thus limiting their sizes or numbers. Information from multiple RCTs comparing different treatments can be synthesized using network meta-analysis (NMA) [4–6] to obtain estimates of relative treatment effects of all competing therapies.

In situations where RCTs report relative treatment effects within biomarker subgroups, NMA can be undertaken within each subgroup. If the subgroup analysis is not reported in the RCTs, but the proportion of patients recruited within each subgroup is known, a network meta-regression (NMR) could be considered [7,8]. Such analysis, however, is prone to ecological bias [9]. When individual participant data (IPD) are available, this issue can be alleviated by carrying out an IPD NMA [10] or they can be combined with aggregate data (AD) to estimate the treatment effects [11,12].

Proctor et al. [13] developed an NMR method for combining evidence from IPD and AD to estimate the indirect treatment effect in binary biomarker subgroups using a binary response from published RCTs. In this paper, we build on this method by developing a one-stage IPD-AD NMA model for the synthesis of IPD and AD to estimate treatment effects on time-to-event outcomes within subgroups of patients harboring a specific biomarker type.

2. Materials and methods

This section discusses the source of data used in this study, and our one-stage NMA model for estimating the relative treatment effects within two biomarker subgroups simultaneously by synthesising mixture of IPD and AD.

2.1. Illustrative examples and sources of data

The first example estimates the relative effectiveness of therapies in advanced breast cancer (ABC) patients within HR+ve and hormone receptor negative (HR-ve) subgroups. The HR+ve subgroup includes patients who are progesterone and/or estrogen positive, while the HR-ve subgroup includes patients who are progesterone and estrogen negative. AD were extracted from a systematic review carried out by Ghersi et al. [14], who investigated the effectiveness of taxanes (X) used as monotherapy or in combination with chemotherapy (CX). The IPD were sourced by emulating target trials from synthetic electronic health records (EHRs). The target trial protocol and procedures are reported in Appendix 1.

The second example aimed to estimate the treatment effects of therapies targeted on Vascular Endothelial Growth Factor (VEGF) and epidermal growth factor receptor (EGFR) administered to patients with metastatic colorectal cancer (mCRC) within patient defined by the Kirsten Rat Sarcoma (KRAS) biomarker - either wild type (WT) or mutant (MT) KRAS status. Summary data for the mCRC example were obtained from the systematic review by Poad et al. [15], who reported the efficacy of anti-VEGF therapies plus C (VEGF + C) vs. C and anti-EGFR therapies plus C (EGFR + C) vs. C. All RCTs reported aggregate level data. However, IPD were obtained from trials of EGFR + C by digitizing the Kaplan Meier curves for subgroups of patients (with KRAS-WT and KRAS-MT) using the method by Guyot et al. [16].

In both case studies, the end point of interest was OS measured as hazard ratios (HRs). Data for both examples and the relevant references are listed in Appendix 1. The selected examples were partly based on the availability of the dataset but also on our previous knowledge of the two examples. We were aware of the predictive property of the KRAS biomarker for the effectiveness of EGFR inhibitors in colorectal cancer [17] and therefore we used this as a good illustrative example of the method. For the ABC case study, we were aware, from previous review by Umemneku-Chikere et al. [2], that the effect of treatment in the subgroups of hormone receptor is underreported, so utilizing EHR data aimed to extend the evidence base that would include IPD with more detailed level of information on the biomarker.

2.2. Network meta-analytic model

Our one-stage NMA model allows for the simultaneous synthesis of data at either aggregate level or individual participant level. Information on the biomarker status is included directly from studies with IPD available and as the proportion of biomarker positive patients where only

ADs were available. The model assumes that no subgroup analyses were reported for treatment effects within the biomarker groups, but such information can be easily incorporated in the model by treating the subgroups as individual studies with proportions of biomarker positive equal to one or zero. The first part of the model describes the contribution of the IPD to the model, the second part describes how the AD are modeled and this is followed by a discussion of how the two parts of the model are combined.

2.2.1. Part I: NMA model for IPD studies

To model the treatment effect at IPD, we model time-to-event data assuming a Weibull distribution. This is a flexible distribution which reduces to an exponential distribution in the presence of constant hazard, but the model could be adapted easily by assuming alternative distributions. For patient i in study j, time-to-event follows a Weibull distribution with a shape parameter γ_j and a scale parameter λ_{ij}

$$t_{ij} \sim Weibull\left(\gamma_j, \lambda_{ij}\right). \tag{1}$$

The log hazard (λ_{ij}), depends on the biomarker status X_{ij} of the patient (with $X_{ij}=0$ for biomarker negative patients and $X_{ij}=1$ for biomarker positive patients) and the treatment they receive T_{ij} (zero for the baseline treatment k and one for the active treatment arm l that are specific to study j);

$$\log\left(\lambda_{ij}\right) = \mu_{-ve,j} + \beta_{ij}X_{ij} + \delta_{-ve,j,kl}T_{ij} + \Delta_{j,kl}\,X_{ij} * T_{ij} \tag{2}$$

In this regression model, $\mu_{-ve,j}$ and $\delta_{-ve,j,kl}$ are the baseline treatment effect and the relative treatment effect (log hazard ratio of treatment l vs. k) respectively, in study j for biomarker negative patients. For biomarker positive patients, the baseline and relative treatment effects in the study j are $\mu_{+ve,j}$ and $\delta_{+ve,j,kl}$ respectively, such that:

and
$$\beta_{ij} = \mu_{+ve,j} - \mu_{-ve,j} \tag{3}$$

$$\Delta_{j,kl} = \delta_{+ve,j,kl} - \delta_{-ve,j,kl} \tag{4}$$

Treatments k and l are specific to study j. The relative effects are assumed exchangeable within each biomarker subgroup (and within each treatment contrast), thus:

$$\delta_{-ve,j,kl} \sim N\left(md_{-ve,kl}, \tau^2\right) \text{ and } \delta_{+ve,j,kl} \sim N\left(md_{+ve,kl}, \tau^2\right)$$

As in standard NMA, the mean effects $md_{-ve,kl}$ and $md_{+ve,kl}$ within each treatment contrast l vs. k are assumed to satisfy the consistency assumption, namely:

$$md_{-ve,kl} = d_{-ve,l} - d_{-ve,k} \tag{5}$$

$$md_{+ve,kl} = d_{+ve,l} - d_{+ve,k} \tag{6}$$

For each biomarker subgroup. The parameters $d_{-ve,k}, d_{-ve,l}, d_{+ve,k}, d_{+ve,l}$ are so called basic parameters, specific to the biomarker group, representing the effect of treatments k or l relative to the reference treatment in the network numbered as 1 and $d_{-ve,1}, d_{+ve,1} = 0$. In our implementation, prior distributions placed on the parameters specific to this part of the model are:

$$\gamma_j \sim Gamma\,(1, 0.01)$$

$$\mu_{+ve,j} \sim N(0, 100), \mu_{-ve,j} \sim N(0, 100)$$

2.2.2. Part II: NMA model for AD studies

To allow for the assumption of normality of the treatment effects ($y_{j,kl}$), these were represented using the log hazard ratio scale and were then used in the model along with the corresponding standard deviations (σ_j). We incorporated the information on the proportion of patients that are biomarker positive through the NMR. The normally distributed treatment effect ($y_{j,kl}$) for each study j is an estimate of a true treatment effect $\delta_{j,kl}$, such that:

$$y_{j,kl} \sim N\left(\delta_{j,kl}, \sigma_j^2\right)$$

Between two treatment arms comparing treatments k and l ($k \neq l$ and $k, l = 1, \ldots, n_t$, with n_t – number of treatments in the network). The true effects are assumed to follow a common distribution within each treatment contrast kl

With $\delta_{j,kl} \sim N\left(md_{j,kl}, \tau^2\right)$

$$md_{j,kl} = d_{-ve,l} - d_{-ve,k} + (\overline{\beta}_l - \overline{\beta}_k) * ppos_j, \tag{7}$$

The basic parameters $d_{-ve,k}$ and $d_{-ve,l}$ correspond to the effects of treatments k and l in the biomarker negative group, as in the first part of the model for IPD studies. The parameters $\overline{\beta}_l$ and $\overline{\beta}_k$ are the study-level metaregression coefficients corresponding to the proportion of biomarker positive participants in study j, denoted $ppos_j$. This results in the basic parameters for the biomarker positive group being given by:

$$d_{+ve,k} = d_{-ve,k} + \overline{\beta}_k$$

$$d_{+ve,l} = d_{-ve,l} + \overline{\beta}_l$$

Prior distributions are placed on the parameters specific to this part of the model:

$$\overline{\beta}_k, \overline{\beta}_l \sim N(0, 100)$$

2.2.3. Part III: combination of IPD and AD

We combined IPD and AD models via the shared basic parameters $d_{-ve,l}$, $d_{+ve,l}$, $d_{-ve,k}$, $d_{+ve,k}$, which are informed by both sets of studies. We place prior distributions on the parameters common to both above parts of the model:

$$d_{-ve,k}, d_{-ve,l} \sim N(0, 100)$$

$$\tau \sim U(0, 2)$$

The WinBUGS code for the model is provided in Appendix 2.

2.3. Application to illustrative examples

We analyzed the data in our illustrative examples using three models. For the ABC example, Model 1 is the NMR model described in Section 2.2.2 (with additional prior distributions listed in Section 2.2.3). It utilizes AD reported in the RCTs alone. We explored the added value of using external IPD from EHRs by incorporating the data in Models 2 and 3. Model 2 is a two-stage IPD-NMA, where in stage one we analyze IPD for each study independently and use the resulting log HRs and corresponding standard deviations, together with those from AD studies, as inputs to NMR Model 1 [18]. When analyzing IPD for each study j, we use the Weibull model described in Equations (1)–(4) and by placing prior distributions:

$$\delta_{-ve,j,kl} \sim N(0, 100) \text{ and } \delta_{+ve,j.kl} \sim N(0, 100)$$

In addition to those for $\mu_{+ve,j}$, $\mu_{-ve,j}$ and γ_j.

Model 3 is a one-stage NMA, as described in Section 2.2.1–2.2.3 combining IPD and AD from all available studies.

In the mCRC example, the IPD come from some of the RCTs. We, therefore, include data from all studies in all three models and illustrate the added value of more granularity of information when utilizing IPD. Model 1 is the two-stage NMR using mixed population on some of the digitized IPD (EGFR + C vs. C), Model 2 is the NMR of RCTs data at AD level with biomarker subgroups for all EGFR + C trials, and Model 3 is our one-stage NMA.

3. Results

3.1. Breast cancer case study

Ten target trials were emulated (five comparing X vs. C and five comparing CX vs. C). A summary table of the target trials is reported in Appendix 1. AD from thirteen RCTs was extracted from Ghersi et al. [14]. The RCTs did not report subgroup analyses for the hormone receptor biomarker status. All the IPD and AD studies have mixed populations of HR+ve and HR-ve patients. The IPD were combined with AD, resulting in a network of 23 trials presented in Fig. 1.

The results for the ABC example are reported in Fig. 2A for the HR + ve patients and Fig. 2B for the HR-ve patients. In Model 1, the treatment effects were obtained with substantial uncertainty. The addition of data from EHRs in Model 2 resulted in reduced uncertainty in both biomarker subgroups. For example, in the HR+ve subgroup, the HR for CX vs. X was 1.10 (95% credible interval [CrI]: 0.62, 1.84) using AD alone, and 1.04 (95% CrI: 0.69, 1.56) when IPD were included as AD. This corresponded to a 28.7% reduction in the width of the CrI. However, there was a

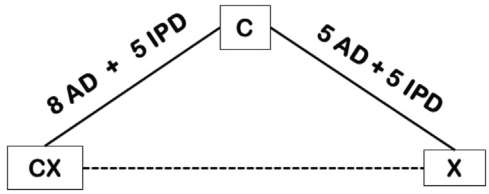

Fig. 1. Network diagram of RCTs (marked as AD) and target trials (marked as IPD) for overall survival in the Breast Cancer case study. The solid lines illustrate treatment comparisons that have been evaluated directly, and the dashed line corresponds to the indirect effect. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

further substantial reduction in uncertainty, of 49% in the width of the CrI, when including data from the target trials at IPD level (Model 3); to HR = 0.99 (95% CrI: 0.67, 1.29), where there was direct information on biomarker status of individual patients. Inclusion of target trial data at the IPD level reduced uncertainty by 29% of the width of the CrI compared to the two-stage approach. In the HR-ve patients, there was only a small reduction in uncertainty when introducing EHR data at AD level; for example, 13.3% reduction in the width of the CrI for CX vs. X (Model 2). However, there was a substantial reduction in uncertainty when utilizing data from target trials at IPD level (Model 3), with 33% reduction compared to using RCT data alone, and 29.7% reduction compared to the two-stage approach. The treatment effect estimates for all three treatment contrasts were similar for the HR+ve and HR-ve patients regardless of modeling strategy, indicating no predictive effect of the biomarker on the three therapies.

3.2. Colorectal cancer example

In this example, 15 RCTs were extracted from the review by Poad et al. [15]. Five RCTs evaluated the treatment effect of VEGF + C vs. C and these studies recruited mixed patients with KRAS-WT and KRAS-MT. 10 RCTs evaluated the treatment effect of EGFR + C vs. C and these studies had either mixed or KRAS-WT patients only. All datasets were combined to form a network plot (Fig. 3) of 15 studies.

The results for the mCRC example are presented in Fig. 4A for KRAS-WT patients and Fig. 4B for patients with KRAS-MT. In contrast to the breast cancer example, all available data were from RCTs and the results from all models presented are based on the data from all 15 RCTs. We present the results of three analyses with gradual increase of the level of information on the biomarker status. When data from six trials of EGFR + C were used to provide treatment effects for mixed biomarker populations (along with the proportions of biomarker status) in a two-stage NMR presented in Model 1, the treatment effects for the subgroups were obtained with large uncertainty. When including data at the subgroup level from all EGFR + C trials in Model 2, the uncertainty was

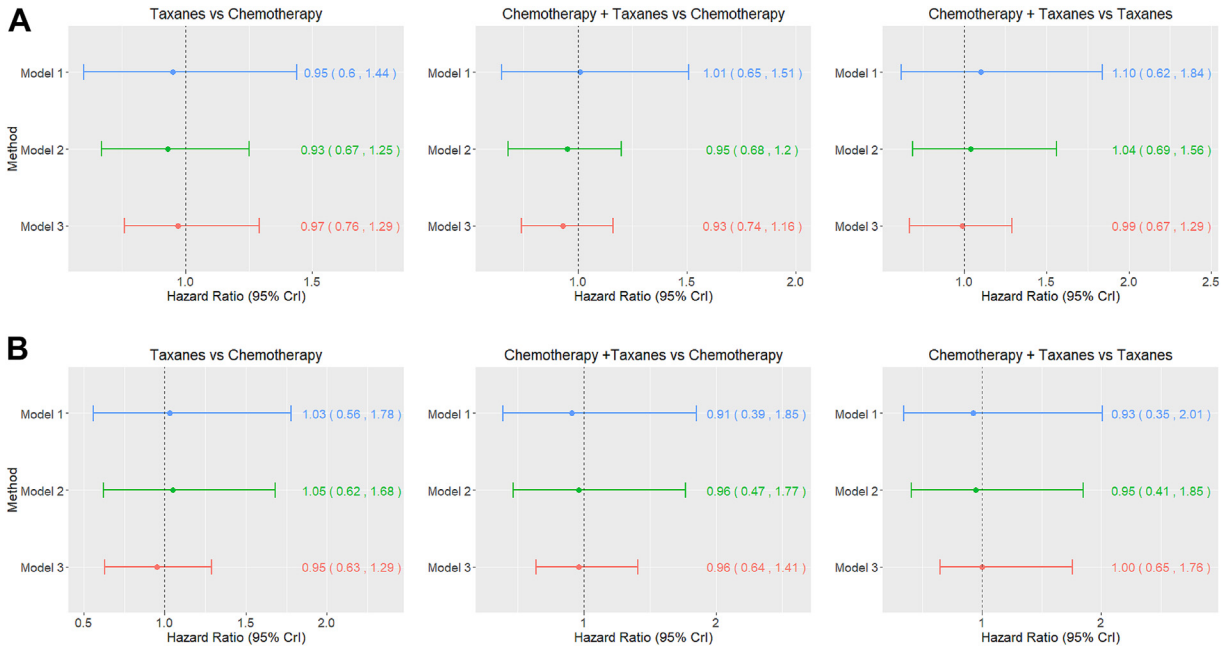

Fig. 2. Treatment effect estimates for overall survival in breast cancer example; (A) for the hormone receptor positive patients, and (B) for the hormone receptor negative patients. Model 1: NMR of RCT data [Blue], Model 2: two-stage IPD NMA with effects for mixed biomarker population calculated at the first stage [Green], and Model 3: one-stage IPD NMA [Red]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

substantially reduced; especially for the treatment effects of EGFR + C vs. C, where more granularity of information was introduced for the biomarker status. The results of Model 2 correspond to the AD level NMR using effects reported by the trials. The same results were obtained when using IPD in two-stage IPD meta-analysis with subgroup analyses conducted at the first stage (see Appendix 1). Model 3 represents the results of one-stage IPD meta-analysis where digitized data from the six RCTs of mixed populations and four RCTs of KRAS-WT only were used as IPD. Not much further improvement was noted and the differences in the results compared to Model 2 are likely due to normality assumption made when calculating standard errors for AD level NMR in Model 2.

There was a meaningful positive treatment effect of EFGR + C compared to C for the KRAS-WT patients with HR = 0.86 (95% CrI: 0.81, 0.95), but not for the KRAS-MT patients (HR = 1.03; 95% CrI: 0.91, 1.1) in the final analysis.

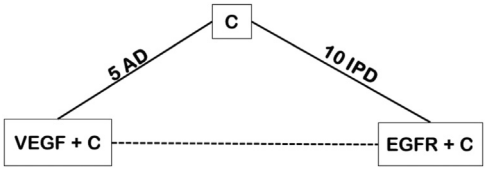

Fig. 3. Network plot of RCTs for overall survival in the colorectal cancer case study. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

We developed a one-stage NMA model that allows for IPD to be combined with AD to estimate the treatment effects in subgroups of patients defined by a biomarker status. This method uses a Bayesian framework to model time-to-event outcomes such as OS or progression-free survival. When subgroup analyses are not reported by RCTs, IPD are required to disentangle information on treatment effectiveness that may depend on the biomarker status. We utilized two approaches to generating IPD; using EHRs or digitizing Kaplan-Meier curves from RCTs that report such curves for each biomarker subgroup. This exercise did not uncover any predictive effect of the biomarker, but it did show more precise estimates, and therefore potential of the method for scenarios where RCT data are limited, in particular pertaining to the biomarker status.

Inclusion of external EHR data at IPD level to existing published RCT data at aggregate level resulted in improved precision (in terms of the width of the 95% CrIs) of treatment effect estimates as seen in the ABC example. In the mCRC example, the level of uncertainty reflected differences in granularity of information on the biomarker status when using data from the same RCTs, with largest uncertainty seen when treatment effects for mixed populations were used in NMR and much reduced uncertainty when treatment effects were obtained in subgroups for all RCTs. Our one-stage model estimated similar results as the two-stage NMA (with effects in all subgroups estimated in the

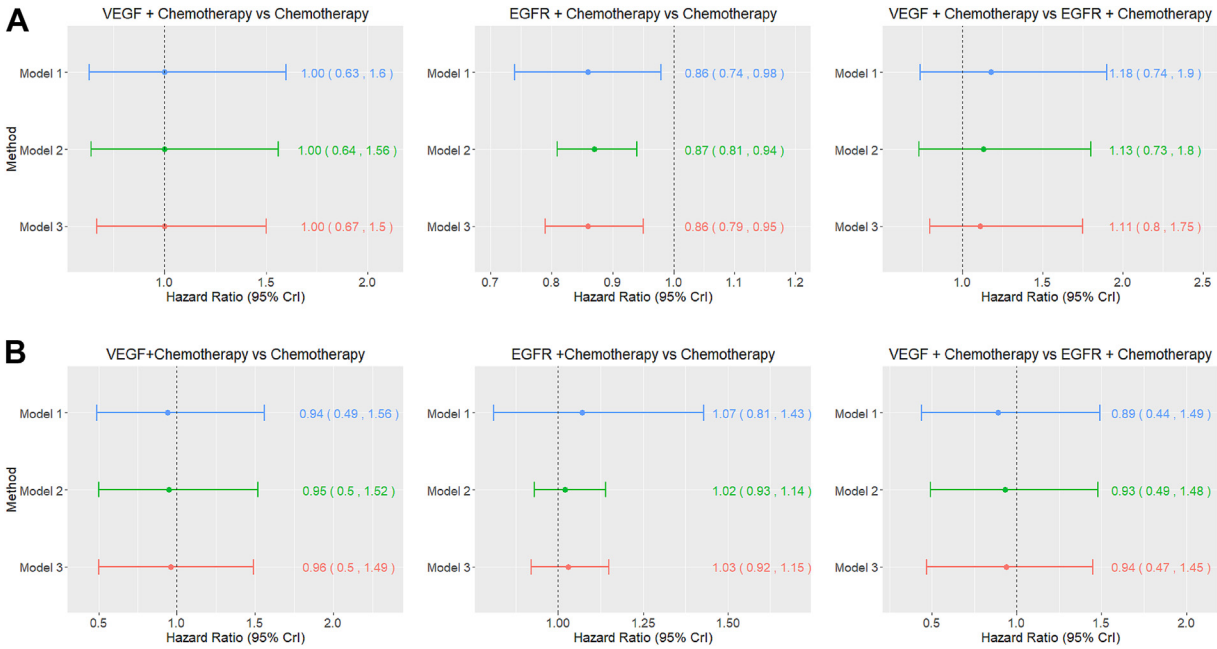

Fig. 4. Treatment effect estimates for overall survival in the metastatic colorectal cancer case study: (A) for KRAS WT biomarker subgroup, and (B) for KRAS MT biomarker subgroup. Model 1: two-stage IPD NMA with effects for mixed biomarker populations in EGFR + C trials calculated at the first stage [Blue], Model 2: NMR of RCT data at AD level with biomarker subgroups for all EGFR + C trials [Green], and Model 3: one-stage IPD NMA [Red]. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

first stage), supporting previous similar findings [19], as well as AD level only NMR (where all AD represented subgroups). Thus, our one-stage NMA serves as alternative approach to the two-stage NMA modeling approach and may prove very useful when results in subgroups are not reported but IPD for at least a proportion of studies are available.

When a predictive biomarker is not known in early trials, subgroup analyses are not performed, but access to IPD from some RCTs may be possible and the method can be useful to explore the effectiveness of the therapies in such subgroups. Such scenario did apply to the KRAS biomarker in mCRC; initially EGFR inhibitors were developed to target EGFR biomarker in mCRC patients and KRAS subgroups were not reported. Only subsequently KRAS was discovered as predictive biomarker in this setting and the design of trials changed to either trial of mixed population with subgroups reported or to enrichment trials of KRAS WT patients alone [17]. Retrospective subgroup analyses were then conducted on majority of the earlier trials. Before such retrospective analysis is conducted, the method may be useful if access to some IPD is possible. Estimates obtained from the mCRC example support prior research showing that EGFR therapies are effective in patients in the KRAS-WT patients but not in patients with KRAS-MT [17]. However, the use of digitized Kaplan-Meier curves as a source of IPD may mean that there could be some discrepancies with the original data.

Emulating trials from EHRs is still a relatively novel approach, in the context of meta-analysis and a careful consideration need to be given to issues of selection bias and potential confounding. A recent study, aimed to emulate 35 existing RCTs [20], has identified discrepancies between the treatment effect estimates from emulated trials and some of the corresponding original RCTs. Such discrepancies could influence variability in the estimated treatment effects when such estimates are incorporated in a meta-analysis. These discrepancies may have been due to issues with data quality or differences in patient populations, and occasionally issues with emulating a proxy to placebo control arm. In addition, some of the variability could be possibly attributed to changes in the EHRs given the time of analysis. However, following the target trial protocol should ensure that the effect of any potential bias or confounding is minimized. Another limitation is that the IPD in the ABC example were emulated from a synthetic dataset (Simulacrum) based on the Systemic Anti-Cancer Treatment (SACT) dataset rather than from the original SACT data. We used the data to illustrate our methodology, but the estimates obtained may not be clinically meaningful. Furthermore, where possible, use of IPD from RCTs should be prioritized and EHRs could be considered an alternative source of data. Our model is an NMR model; hence it is prone to ecological bias. However, the availability of IPD for a proportion of studies helps to alleviate this issue.

In our method, we used a Weibull proportional hazards regression model for our time-to-event data. Other parametric methods: for example, using exponential, gamma, Gompertz or log-logistic distributions, could also be used.

The model assumes proportional hazards, which is a known limitation, but this could be relaxed by adopting an Accelerated Failure Time or flexible parametric modeling approach.

Due to the star-shaped geometry of networks in both examples, it was difficult to assess the accuracy of the treatment effect estimate for the indirect comparison. This is a common issue in NMA with star-shaped network, when assessing consistency. The method, however, is applicable to more robust network structures where methods are available for assessing consistency.

5. Conclusion

Inclusion of IPD in a one-stage approach to NMR of time-to-event data allowed for increased precision in the estimation of treatment effects within biomarker subgroups compared to two-stage approach where only aggregate level information on the biomarker status was available. The method is particularly useful when subgroup analyses according to the biomarker status are not reported.

CRediT authorship contribution statement

Chinyereugo M. Umemneku-Chikere: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing − original draft, Writing − review & editing. **Lorna Wheaton:** Investigation, Resources, Writing − review & editing. **Heather Poad:** Investigation, Resources, Writing − review & editing. **Devleena Ray:** Investigation, Resources, Writing − review & editing. **Ilse Cuevas Andrade:** Investigation, Resources, Writing − review & editing. **Sam Khan:** Investigation, Resources, Writing − review & editing. **Paul Tappenden:** Conceptualization, Writing − review & editing, Funding acquisition. **Keith R. Abrams:** Conceptualization, Methodology, Writing − review & editing, Formal analysis, Funding acquisition, Supervision. **Rhiannon K. Owen:** Conceptualization, Methodology, Writing − review & editing, Formal analysis, Funding acquisition, Supervision. **Sylwia Bujkiewicz:** Conceptualization, Methodology, Formal analysis, Project administration, Funding acquisition, Supervision, Investigation, Resources, Writing − review & editing.

Data availability

Data will be made available on request.

Declaration of competing interest

S.B. is a member of the NICE Decision Support Unit (DSU). She has served as a paid consultant, providing methodological advice, to NICE, Roche, RTI Health Solutions and IQVIA, has received payments for educational events from Roche and has received research funding from European Federation of Pharmaceutical Industries & Associations (EEPIA) and Johnson & Johnson. R.K.O. is a member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, member of the NICE Decision Support Unit (DSU), and associate member of the NICE Technical Support Unit (TSU). She has served as a paid consultant providing unrelated methodological advice to AstraZeneca, Cogentia Healthcare Ltd, Daiichi Sankyo, NICE, Norwegian Institute of Public Health, Roche, and Vifor Pharma. She reports teaching fees from the Association of British Pharmaceutical Industry (ABPI) and the University of Bristol. K.R.A. is a member of the National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee, member of the NICE Decision Support Unit (DSU), and the NICE Technical Support Unit (TSU). He has served as a paid consultant, providing unrelated methodological advice to Abbvie, AstraZeneca, Bayer, Bristol-Meyers Squibb, Medtronic, NICE/DHSC, Novartis, Pfizer, and Roche, and has received research funding from Bayer, Association of the British Pharmaceutical Industry (ABPI), European Federation of Pharmaceutical Industries & Associations (EFPIA), Pfizer, Sanofi, and Swiss Precision Diagnostics. He is a Partner and Director of Visible Analytics Limited, a Health Technology Assessment (HTA) consultancy company. P.T. is a member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, and a member of the NICE Decision Support Unit (DSU). He reports teaching fees from the Association of British Pharmaceutical Industry (ABPI).

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Supplementary data

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