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A Comparison of Network Meta Analysis using Hazard Ratios and RMST in Clinical Data

(Perbandingan Meta Analisis Rangkaian menggunakan Nisbah Bahaya dan RMST dalam Data Klinikal)

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ABSTRACT

Hazard Ratio based Network Meta-Analysis (NMA) has gained popularity in evidence synthesis in data with time-to-event outcomes. However, the most commonly used Cox-Proportional Hazard ratio suffers due to lack of baseline information utilization. The proportionality assumption, which assumes that ratio of the hazards between any two treatment arms or strata is constant over time for the entire duration of study, is also violated in most Cox-regression models. In the current work we demonstrate few of the alternate approaches by firstly reconstructing the time-to-event dataset from Kaplan Meier curves from results of clinical trials available in public domain using relevant software such as 'IPDfromKM' and 'DigitizeIt' and then recomputing the restricted mean survival time (RMST) estimates as well as parametric estimates assuming exponential, Weibull and Gompertz distributions to be used respectively, each in a separate NMA. The methods are compared and the advantages of each approach is highlighted. For illustration purpose, Kaplan Meier based results from four trials of Advanced Renal Cell Cancer, are used for analysis. The results of Cox-Proportional Hazard Ratio were compared with parametric distribution-based Hazard Ratio obtained in our analysis. The RMST estimates-based analysis provided additional insights. Based on the NMA, the comparative treatment landscape is provided in terms of a treatment ranking of the included combination therapies.

Keywords: Bayesian methods in meta-analysis; hazard ratio estimation; network meta-analysis; restricted mean survival time; survival analysis

ABSTRAK

Meta-Analisis Rangkaian (NMA) berasaskan Nisbah Bahaya telah memperoleh populariti dalam sintesis bukti dalam data dengan hasil masa-ke-peristiwa. Walau bagaimanapun, nisbah Bahaya Perkadaran Cox yang paling biasa digunakan terjejas disebabkan oleh kekurangan penggunaan maklumat asas. Andaian perkadaran yang mengandaikan bahawa nisbah bahaya antara mana-mana dua cabang atau strata rawatan adalah malar dari semasa ke semasa sepanjang tempoh kajian, juga dilanggar dalam kebanyakan model regresi Cox. Dalam kajian semasa, kami menunjukkan beberapa pendekatan alternatif dengan terlebih dahulu membina semula set data masa-ke-peristiwa daripada lengkung Kaplan Meier daripada keputusan ujian klinikal yang tersedia dalam domain awam menggunakan perisian yang berkaitan seperti 'IPDfromKM' dan 'DigitizeIt' dan kemudian mengira semula anggaran masa hidup min terhad (RMST) serta anggaran parametrik dengan mengandaikan taburan eksponen Weibull dan Gompertz yang akan digunakan setiap satu dalam NMA berasingan. Kaedah dibandingkan dan kelebihan setiap pendekatan diserlahkan. Untuk tujuan ilustrasi, keputusan berasaskan Kaplan Meier daripada empat percubaan Kanser Sel Renal Lanjutan, digunakan untuk analisis. Keputusan Nisbah Bahaya Berkadaran Cox telah dibandingkan dengan Nisbah Bahaya berasaskan taburan parametrik yang diperoleh dalam analisis kami. Analisis berasaskan anggaran RMST memberikan pandangan tambahan. Berdasarkan NMA, landskap rawatan perbandingan disediakan dari segi kedudukan rawatan terapi gabungan yang disertakan.

Kata kunci: Analisis kemandirian; anggaran nisbah bahaya; kaedah Bayesian dalam meta-analisis; meta-analisis rangkaian; purata masa kemandirian terhad

INTRODUCTION

Survival analysis, which is essentially time-to-event modelling, is commonly applied in time-to-event outcomes evaluation in clinical trials (Klein et al. 2018; Mills 2011). Historically, survival regression models can be broadly categorized as non-parametric, semi-parametric and

parametric models (Du et al. 2018). Survival probabilities of different strata can be evaluated using Kaplan–Meier estimator (Kaplan & Meier 1958). Since confounding variables can lead to differences in the survival probabilities, the confounding is adjusted using methods such as the Cox proportional hazards model (Collett 2023; Royston & Parmar 2002). Cox proportional hazard models are semi-parametric models as they do not use the baseline hazard (Zhang 2016), which essentially get cancelled out while generating the ratio. This has become the *de facto* method of survival analysis.

Health economic studies in oncology need indirect survival comparisons when there are many alternative drugs but when there is lack of direct head-to-head studies. In this scenario, Bayesian network meta-analysis (NMA) becomes a preferred option but often uses the proportional Hazard Ratios as endpoints for input of NMA (Kirion et al. 2023). If the proportional hazards hypothesis is not met, then alternative NMA approaches are warranted.

Parametric models have gained popularity based on the several advantages. Firstly, the simplicity of defining a parametric model requires few parameters. The survival functions and hazard functions are completely specified. Additionally, survival functions can be extrapolated easily beyond the measurement time frame of the trial data (Latimer & Adler 2022). There is scope to generalize and the models can be easily extended to deal with interval censored data (Johansen et al. 2021). However, they can suffer if model is mis-specified or if there are large deviations from assumed distribution (Bartoš, Aust & Haaf 2022). Novel parametric additive hazard model which has provision to report results on the original time instead of reporting results on the hazard scale (Voeltz et al. 2024).

From Kaplan-Meier graph results of individual clinical trials in, the Guyot algorithm, or modified versions of the algorithm, can construct approximate individual patient data (IPD) which can be referred to as 'pseudo' IPD (Guyot et al. 2012). In this paper we attempt to show the combined benefit of using digitized Kaplan-Meier survival curves to regenerate the pseudo individual patient data and recompute alternate statistical estimates such as parametric hazard ratios and Restricted Mean Survival Time estimates (RMST).

It opens up the possibility to re-analyse time-to-event data with a fresh perspective. Pooled estimates of hazard ratios (HR) in Network Meta Analysis (NMA) depend on the quality of individual study estimates of HR. A comparative analysis of the pooled estimates using NMA that are based on the semi-parametric cox regression HR, parametric Weibull HR and RMST difference (RMSTd) are presented.

This research presents an advanced analysis comparing Hazard Ratio (HR)-based Network Meta-Analysis (NMA) with Restricted Mean Survival Time (RMST)-based NMA of clinical data. The HR-based NMA evaluates relative hazards over time, while the RMST-based NMA compares restricted mean survival times up to a pre-specified time horizon tau (τ). To enhance mathematical rigor, we incorporate additional derivations and equations to support the comparative framework.

THEORETICAL FRAMEWORK

HAZARD RATIO-BASED NETWORK META-ANALYSIS

The hazard function $h_i(t)$ for a treatment arm i is given by:

$$h_i(t) = h_0\,(t)\, e^{\beta i}, \tag{1}$$

where $h_0(t)$ is the baseline hazard function and β_i is the log hazard ratio.

The survival function is:

$$S_i(t) = \exp(-\int_0^t h_i(u)du). \tag{2}$$

Expanding for the Cox model:

$$S_i(t) = S_0\,(t)^{\,e\beta i}, \tag{3}$$

where $S_0(t)$ is the baseline survival function.

The HR comparing treatments i and j is:

$$HR_{ij} = \frac{h_i(t)}{h_j(t)} = e^{\beta i - \beta j} \tag{4}$$

The log-likelihood function is:

$$\mathcal{L}(\beta|Data) = \sum_{k=1}^{n}[d_k \log h_k\,(t_k) - H_k(t_k)], \tag{5}$$

where d_k is the event indicator, and $H_k(t_k)$ is the cumulative hazard function.

RESTRICTED MEAN SURVIVAL TIME-BASED NETWORK META-ANALYSIS

RMST is defined as:

$$RMST_i\,(\tau)\int_0^{\tau} Si(t)dt. \tag{6}$$

The RMST ratio and difference are:

$$RMST_{ij}\,(\tau) = \frac{RMST_i\,(\tau)}{RMST_j\,(\tau)}, \tag{7}$$

$$\Delta RMST_{ij}(\tau) = RMST_i\,(\tau) - RMST_j\,(\tau) \tag{8}$$

The variance of the RMST estimator is:

$$\mathrm{Var}(RMST_i) = \int_0^{\tau}\left[\frac{S_i(t)}{N_i(t)}\right] dt, \tag{9}$$

where $N_i(t)$ is the number of patients at risk.
In an NMA framework, the relative effect between two treatment arms can be modelled through the hazard ratio approach. The log hazard ratio between treatment arms *i* and *j* follows a normal likelihood:

$$\log H R_{ij} \sim N\left(\log\left(\frac{h_i(t)}{h_j(t)}\right), SE^2(HR_{ij})\right), \quad (10)$$

where $SE(HR_{ij})$ represents the standard error associated with the hazard ratio.
Similarly, the RMST-based relative treatment effect is denoted by:

$$\log R\,MST_{ij}\,(\tau) \sim N\left(\log\left(\frac{RMST_i(\tau)}{RMST_j(\tau)}\right), SE^2(RMST_{ij})\right), \quad (11)$$

where $SE(RMST_{ij})$ denotes the standard error of the RMST based ratio.
The equation herewith specifies the RMST difference (RMSTd) between 2 treatment arms.
Let t^* be the truncation time (e.g., 2 years), $\mathrm{RMST}_i(t^*)$ be the restricted mean survival time for treatment *i*, $\mathrm{RMST}_j(t^*)$ be the restricted mean survival time for treatment *j*, then the Restricted Mean Survival Time Difference (RMSTD) between treatments *i* and *j* is denoted by:

$$\mathrm{RMST\ d}_{ij}(t^*) = \mathrm{RMST}_i(t^*) - \mathrm{RMST}_j(t^*) \quad (12)$$

This value represents the average additional survival time (up to *t*) that patients remain on treatment *i* compared to those on treatment *j*.

METHODS

COX-PROPORTIONAL HAZARD MODEL

The Cox proportional hazards model regression analysis is a semi-parametric model. No distribution is assumed but warrants that the effects of the stratifying variable or covariates on the survival is constant over time and have an additive effect on the hazard (Bradburn et al. 2003).

The hazard function is the basis of the Cox proportional hazards model regression. The equation herewith defined the Cox model:

$$H(t) = H_0(t)e^{b_1x_1 + b_2x_2 + \cdots + b_zx_z} \quad (13)$$

where X_1, X_2, ..., X_Z are the set of predictors and $H_0(t)$ represents the baseline hazard at time *t*.

PARAMETRIC HAZARD MODEL

The semi-parametric cox regression model relies on the impact of co-variates on hazard and on the survival distribution form. The Parametric models in time-to-event analysis offer advantages as the full maximum likelihood can be utilized for parameter estimation while the residuals can help differentiate the recorded and estimated values of time (Hosmer, Lemeshow & Sturdivant 2013).

If the base distribution is exponential with parameter λ then the survival of each individual *i* is based on

$$S_i(t) = e^b \quad (14)$$

where $b = -\lambda t\theta_i$ which is an exponential model with base hazard multiplied by *i*, which is also the proportional hazards model based on exponential distribution. Weibull regression model ensures that treatment effect can be illustrated both in terms of hazard ratios as well as event time ratio (Carroll 2003).

The cumulative incidence function (CIF) plays a key role in survival analysis specially when competing risks are present. As these functions are inherently improper, parametric modelling often involves the use of improper distributions. A commonly applied improper distribution in this context is the Gompertz distribution (Haile et al. 2016). Parametric model using Gompertz distribution have been developed for hazards model with competing risks (Rehman & Chandra 2022).

RESTRICTED MEAN SURVIVAL TIME MODEL

Restricted mean survival time (RMST) models are increasingly being employed in analysing time-to-event outcomes. Restricted Mean Survival Time (RMST) represents the total survival time up to a specific time point, calculated as the area under the survival curve. It is often considered more reliable to estimate than mean or median survival times, especially in studies with limited follow-up or incomplete data (Han & Jung 2022). The reason is twofold as RMST models do not suffer from the proportionality assumptions needed when using the hazard ratios and they provide an easier interpretation of treatment effects (Hua, Wang & Hong 2023). The between-arm difference in the RMST is avoids the proportionality assumption and also flexibility for the treatment effect to vary with time (Wei et al. 2015). A study by Petit et al. (2019) focussed on the use of the restricted mean survival time difference (rmstD) as an absolute outcome measure in a NMA and compared the results against an NMA based on HR. The ranking of 3 treatments differed based on the outcome measure used and hence calls for more work in the area to develop a robust methodology for application of rmstD. In the NMA on hepatocellular carcinoma (HCC), Celsa et al. (2023) was one the first studies that employed the RMST and highlighted lack of availability of individual-patient data as one of the study limitations.

In time-to-event analysis, with a right-censored data, for a time interval *a*, the RMST is defined as:

$$RMST\,(a) = \int_0^a S(t)dt \tag{15}$$

where $S(t) = P(T > t) = e\int_0^t \lambda(u)du$ function represents survival and λ function represents hazard.

The *RMST* (*a*) is the calculated time duration, *S(t)* over a time interval *a*. The difference of *RMST* (*a*) for 2 or more different treatments is easily interpretable in clinical pharmacology space (Royston & Parmar 2011; Uno et al. 2014). One advantage over the hazard ratio-based analysis is in case of overlapping survival curves of two or more treatment arms. While the log-rank based on hazard ratio estimates may fail to detect a difference in efficacy, the RMST based analysis can still show the overall efficacy difference (Han & Jung 2022).

NMA BASED ON SURVIVAL ANALYSIS DATA

Network meta-analysis facilitates the comparative evaluation of interventions by synthesizing treatment effect estimates from both direct head-to-head trials and indirect evidence across randomized controlled trials (Caldwell, Ades & Higgins 2005), thereby enabling robust inference on relative efficacy and safety profiles within clinical pharmacotherapy. In order to evaluate the treatments, researchers often compare groups using a measure called the hazard ratio, which comes from a statistical method known as the Cox model (Cox 1972). Newer alternatives such as the frailty models (Keiding, Andersen & Klein 1997) as well as the popular accelerated failure time (ATF) models (Wei 1992) are also employed.

NMA often use hazard ratios from Cox regression models to compare treatments based on survival time. However, other methods like fractional polynomials, parametric hazard models, and restricted mean survival time (RMST) estimates are also used to analyse and compare treatment effects (Freeman et al. 2022).

EXAMPLE DATASET FOR THE NMA

For illustration purposes, results based on survival curve from four different phase III trials of Advanced Renal Cell Cancer, have been used for analysis. The common reference arm is Sunitinib, which is the common node across the 4 trials. Though heterogeneity within and among treatment arms is expected across studies and taken care in NMA models via techniques such as random effects models, it makes interpretation hard. We selected data from only four trials and ensured that Sunitinib arm across the 4 studies were statistically in agreement, for better interpretability of the estimates from the non-Sunitinib treatment arms. The resulting network is based on the network design conceptualized by Butcher et al. (1997). Only Sunitinib and one alternate treatment arm per study were included.

We propose that the common reference arms such as Placebo or active reference arm (such as Sunitinib arm in our example) should be checked so that any study where the reference arm is significantly different should be discarded from the Network. The other inclusion criteria should ensure similar subject demographics such are age and gender across the studies as well as the disease condition/stage.

The first clinical trial study (henceforth, referred to as Study 1) compares 'Avelumab plus Axitinib' with the reference Sunitinib for advanced renal-cell carcinoma (Motzer et al. 2019). The second clinical trial study (henceforth referred to as Study 2) included compares 'Pembrolizumab plus Axitinib' to Sunitinib (Rini et al. 2019). The third clinical trial study (henceforth referred to as Study 3) compares 'Nivolumab plus Cabozantinib' with Sunitinib (Choueiri et al. 2021). The fourth clinical trial study (henceforth referred to as Study 4) compares 'Lenvatinib plus Pembrolizumab or Everolimus' with Sunitinib (Motzer et al. 2021). The Lenvatinib plus Pembrolizumab and Sunitinib arm data were included in the NMA from this study. The Lenvatinib plus Everolimus was not used to restrict the data to 2 arms only including Sunitinib arm to keep the design similar to the Bucher at al. (1997)'s method.

The results of Cox-Proportional Hazard Ratio are compared with parametric distribution-based Hazard Ratio obtained in our analysis. The RMST estimates-based analysis provided additional insights. Based on the NMA, the comparative treatment landscape is provided in terms of a treatment ranking of the included combination therapies.

$$h(t) = be^{at},\ S(t) = \exp\left(-\tfrac{b}{a}(e^{at} - 1)\right),\ L(a, b) = \prod_i b\, e^{at_i} \exp\left(-\tfrac{b}{a}(e^{at_i} - 1)\right) \tag{16}$$

THEORETICAL JUSTIFICATION AND COMPARISON

RMST ADVANTAGE WHEN CURVES CROSS

Model assumptions and practical use cases are provided for Cox PH, Weibull and RMST based models in Table 1. RMST reflects total benefit over time even when HR fails due to crossing curves. Cox-proportional hazard model may fail due to various reasons such as time-dependent treatment effect, crossing survival curves, or non-constant hazard ratios.

EXPANDED PARAMETRIC MODEL EQUATIONS

Exponential Model:

$$S(t) = e^{-\lambda t},\ h(t) = \lambda,\ L(\lambda) = \Pi_i\, \lambda e^{-\lambda t_i} \tag{17}$$

Weibull Model:

$$S(t) = e^{-\lambda t k},\ h(t) = \lambda\, kt^{k-1},\ L(\lambda, k) = \Pi_i\, \lambda k t_i^{k-1} e^{-\lambda t_i^k} \tag{18}$$

Gompertz Model:

TABLE 1. Model assumptions and practical use cases

Model	Assumptions	Interpretation	Suitability
Cox PH	PH Assumption	Moderate	Limited if PH fails
Weibull	Known form	High	Reliable under good fit
Gompertz	Monotonic hazard	Moderate	Fewer parameters
RMST	No PH required	High	Best with crossing curves

$$h(t) = be^{at},\ S(t) = \exp\left(-\frac{b}{a}(e^{at}-1)\right),\ L(a,b) = \prod_i b\, e^{at_i} \exp\left(-\frac{b}{a}(e^{at_i}-1)\right) \quad (19)$$

ALGORITHMIC FLOW OF METHODS USED

A basic flow of the diagram is provided below in Figure 1.

Algorithm 1: IPD reconstruction from KM curves

Algorithm 1 IPD reconstruction using Guyot et al.'s Method
1: Digitize KM plot to extract time and survival probability points
2: Input number at risk and event counts at intervals. Digitize KM plot to extract time and survival probability points
3: Use Guyot's algorithm to generate pseudo-IPD from digitized points
4: Validate by replotting KM curve from generated IPD

Algorithm 2: RMST estimation

Algorithm 2 Restricted mean survival time computation
1: Estimate survival function $S(t)$ using KM or parametric models
2: Set restriction time τ (e.g., 12 months)
3 Compute RMST $(\tau) = \int_0^\tau S(t)dt$ using trapezoidal integration
4: Compute variance using Greenwood's formula or bootstrap

Algorithm 3: Parametric hazard estimation

Algorithm 3 Parametric survival model fitting
1: Choose a distribution: Exponential, Weibull, or Gompertz
2: Fit model using maximum likelihood estimation
3 Derive *h(t), S(t), f(t)* and HR from parameters
4: Validate goodness of fit (e.g., via AIC/BIC)

Algorithm 4: Network Meta-Analysis (NMA)

Algorithm 4 Conducting NMA using different inputs
1: Input data: Cox HRs, Parametric HRs, or RMSTd
2: Use frequentist or Bayesian NMA model (e.g., netmeta, gemtc)
3: Model direct and indirect evidence
4: Estimate relative treatment effects and rankings

RESULTS OF NETWORK META ANALYSIS USING NETMETA

Progression Free Survival (PFS) is the selected endpoint for calculating the Hazard ratios. Using the DigitizeIt (Bartoš, Aust & Haaf 2022), the co-ordinates of x and y are extracted from the Kaplan Meier graph. The events and censoring information in available intervals along with the extracted data points are then input in the IPDfromKM (Zhou, Liu & Lee 2020). The KM plot in Figure 2 depicts that the result based on the pseudo-IPD closely matches the Hazard Ratio from the original trial results and shows difference between the arms.

The survival curves plotted matches the plot reported in the original trial results. No major departure from proportionality assumption is seen. The HR of 0.69(0.57 -0.84) is reflective of the original trial results. It can be seen that the two treatment arms are significantly different as indicated by the p-value based on the log-rank test. Similarly, the KM plot of the study 2 in Figure 3 shows that the 2 treatment arms are statistically different.

The KM plot of the study 3 in Figure 4 shows the statistical difference between the trial arms.

Although the KM plot of the study 4, Figure 5 shows that the HR is slightly higher (at 0.43) than the original HR (at 0.39) reported by the original trial results.

To evaluate any statistical difference among the Sunitinib arm of all included trials, we used the log-rank test, and plotted it to visually inspect any difference (Figure 6).

The NMA utilized cox-proportional hazard ratio was conducted via netmeta package of R. The 'HR' option was used on log scale along with log of standard error as input. The rank and cumulative rank probability which show the relative treatment rankings, have become default result measures in NMA. The treatment ranking obtained

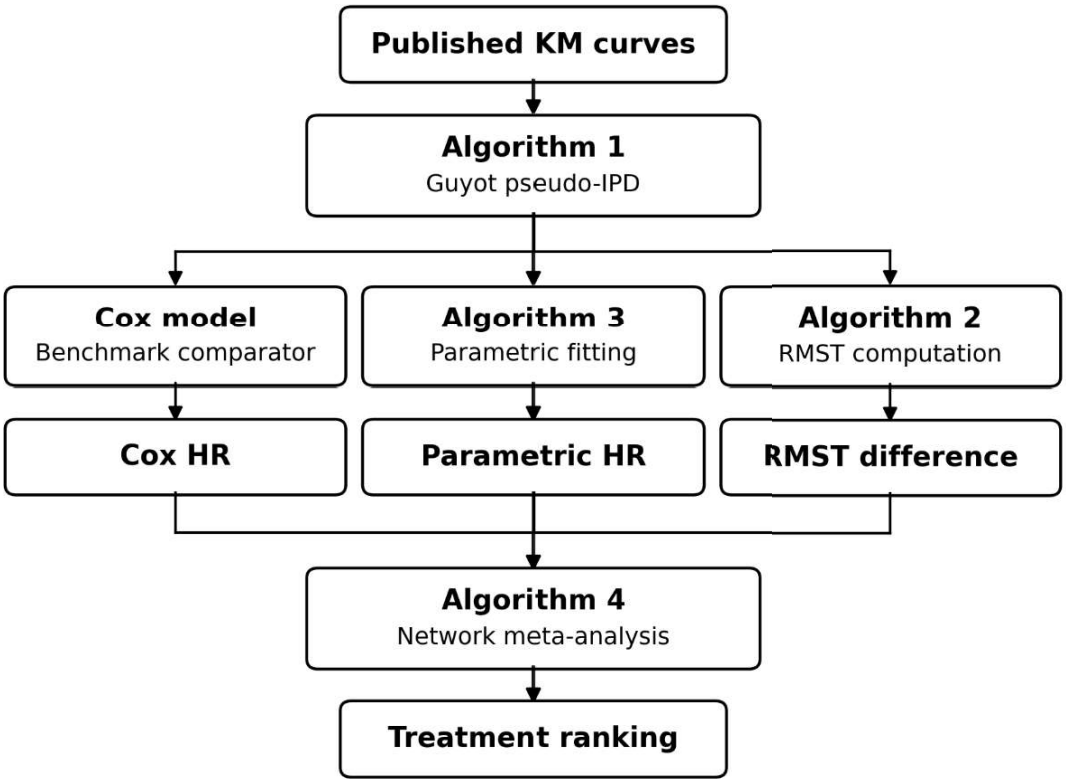
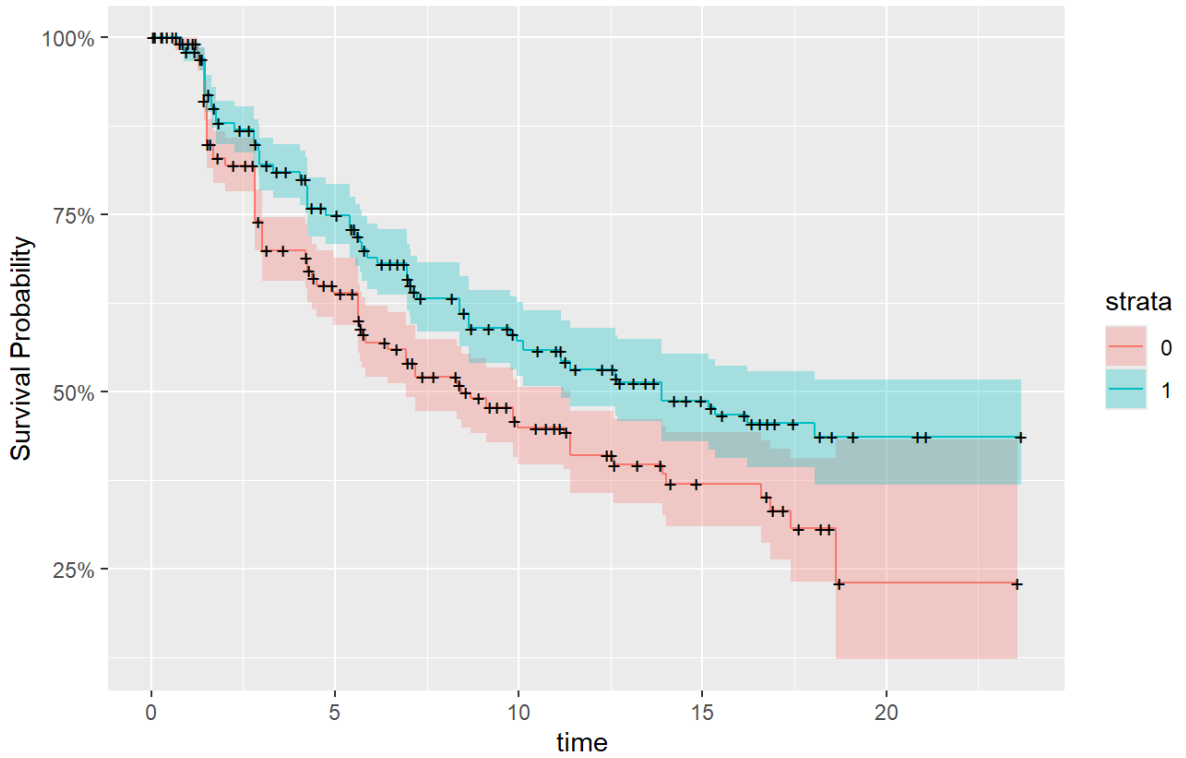
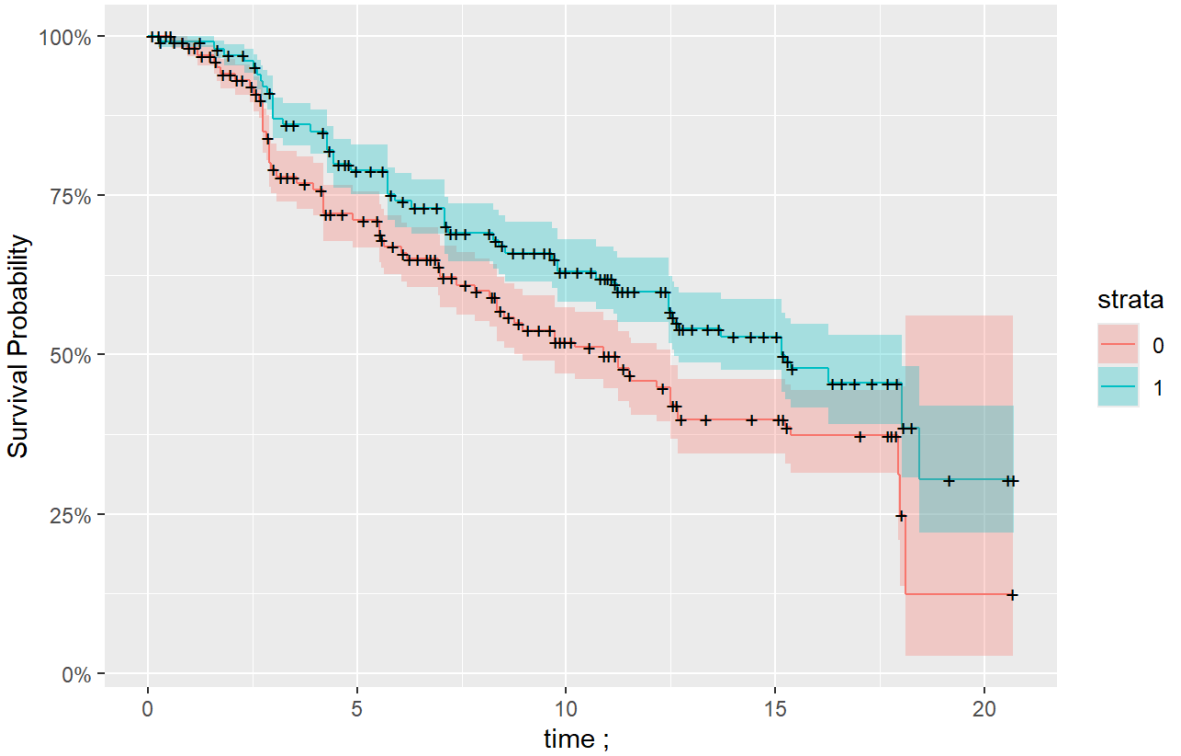


FIGURE 1. Algorithmic Flow



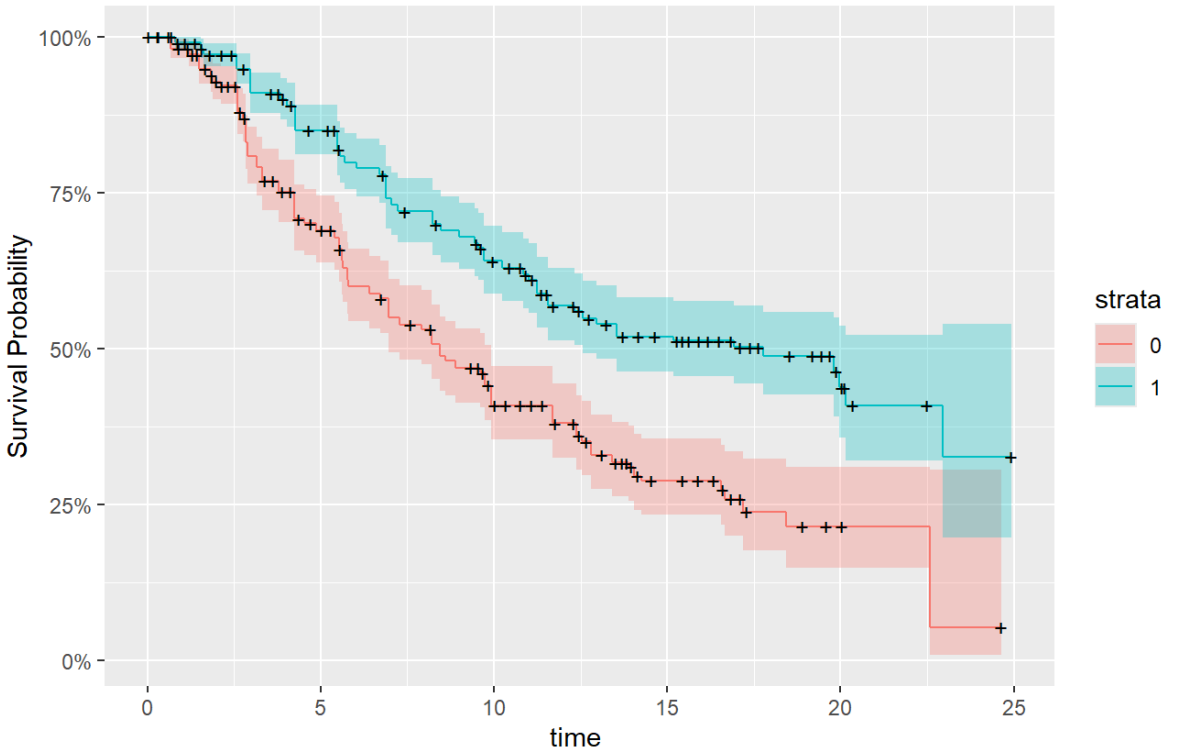
Strata = treatment- 1: Avelumab + Axitinib; 0: Sunitinib; HR: 0.69 (0.57 - 0.84) PVAL: <0.001

FIGURE 2. KM Plot: Study 1



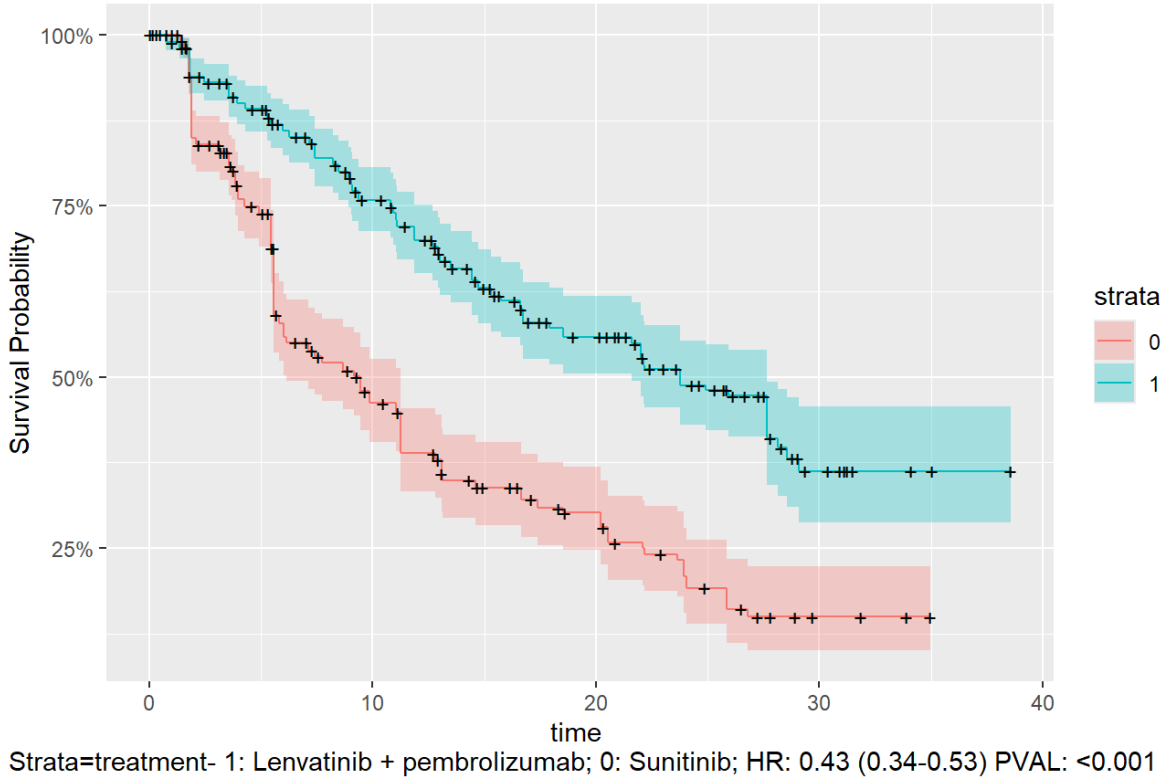
Strata = treatment- 1: Pembrolizumab + Axitinib; 0: Sunitinib; HR: 0.69 (0.56 - 0.84) PVAL: <0.001

FIGURE 3. KM Plot: Study 2



Strata = treatment- 1: Nivolumab + Cabozantinib; 0: Sunitinib; HR: 0.52 (0.42 - 0.64) PVAL: <0.001

FIGURE 4. KM Plot: Study 3



Strata = treatment- 1: Lenvatinib + pembrolizumab; 0: Sunitinib; HR: 0.43 (0.34 - 0.53) PVAL: <0.001

FIGURE 5. KM Plot: Study 4

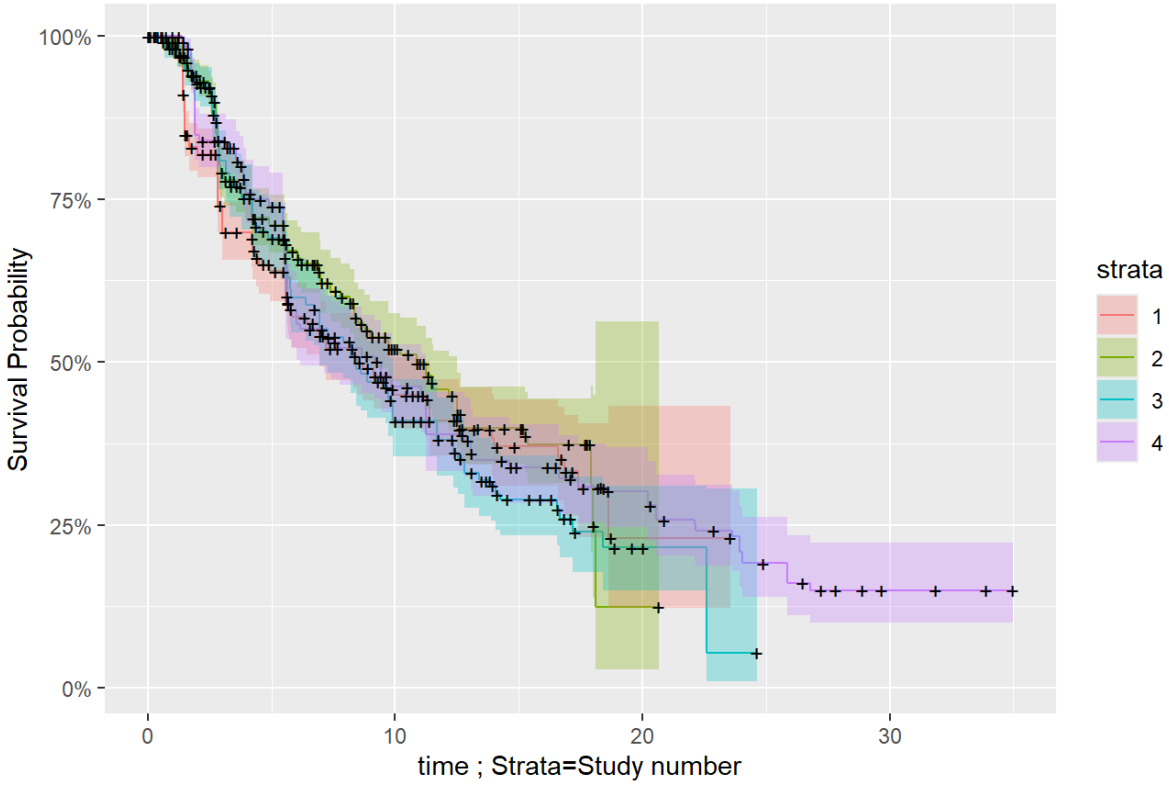


FIGURE 6. Survival plot by Sunitinib arm for each strata: study number

from the NMA is provided herewith. The netrank function is used to obtain the P-Score. It quantifies the certainty that one drug is better than another drug, averaged over all competing drugs (Harrer et al. 2021). Table 2 shows the treatment rankings based on the Cox HR input based NMA.

Similarly, the NMA based on parametric estimates of Hazard Ratios from the four studies were conducted. The NMA results from the exponential, Weibull and Gompertz distribution-based HR were obtained. The comparative hazard ratios of the comparative treatment arms from Cox-regression based HR and those obtained from the Weibull distribution-based HR are presented in Table 3 for comparison. The results are close from both the methods.

The results from NMA based on exponential and Gompertz distributions derived HR were similar. The RMST difference between the treatment arms up to 12 months were used for NMA. Figures 7 and 7 show the contrast of the treatment arm versus the active control (Sunitinib arm) in each of the 4 studies. The RMST difference (RMSTd) can be interpreted an estimate of the delay of the event/or endpoint occurrence (PFS in this example) during the included (restricted) interval and is estimated based on the difference between the areas under the two survival curves for the intervention and active control (Sunitinib) groups (Kloecker et al. 2020). The RMSTd upto month 12 is provided in Figure 6 for the study 1 trial results.

Similarly for study 4, Figure 8 is provided to show the contrast.

The RMST time on x-axis is easy to interpret and indicates the approximate survival time in the interval. Compared to the HR and log rank test-based method, this visual representation-based method is thus a good alternate. The direct-indirect plot of the NMA based on RMSTd upto month 12 is provided in Figure 9 for the study 1 trial results.

The treatment rankings based on the NMA using RMSTd up to month 12 shows that combination of Lenvatinib and Pembrolizumab is provides the best protection compared to the Sunitinib. The rankings and P-score is provided in Table 4.

RESULTS INTERPRETATION

The results indicate that in studies with one common reference arm, the results of parametric distribution-based HR can be used as an alternative to the standard cox regression-based HR. The results obtained from NMA based on both the cox HR as well as those based on the parametric HR based on Weibull (and also from exponential and Gompertz) were similar. In this example dataset, non-proportionality was graphically observed in Study 3 and Study 4.

Here the alternate RMSTd was used to conduct an NMA to check if the treatment rankings had any impact. While the proportional hazard models assume that the hazard ratio is constant over the entire duration of study, differences are observed if data is censored at different timepoints. We used the RMSTd with an interval up to 12 months. The rankings of treatment differed when

TABLE 2. Treatment ranking-Cox HR based NMA

Treatment	P-Score	Ranking
Pembrolizumab + Lenvatinib	0.97	1
Cabozantinib + Nivolumab	0.76	2
Axitinib + Avelumab	0.39	3
Axitinib + Pembrolizumab	0.38	4
Sunitinib & 0.00 & 5	0.00	5

TABLE 3. Adjusted HR from NMA based on Cox and Weibull based HR

Treatment	P-Score	Ranking
Pembrolizumab + Lenvatinib	0.4084	0.4257
Cabozantinib + Nivolumab	0.4952	0.5161
Axitinib + Avelumab	0.6753	0.6916
Axitinib + Pembrolizumab	0.6998	0.6865
Sunitinib	0.00	0.00

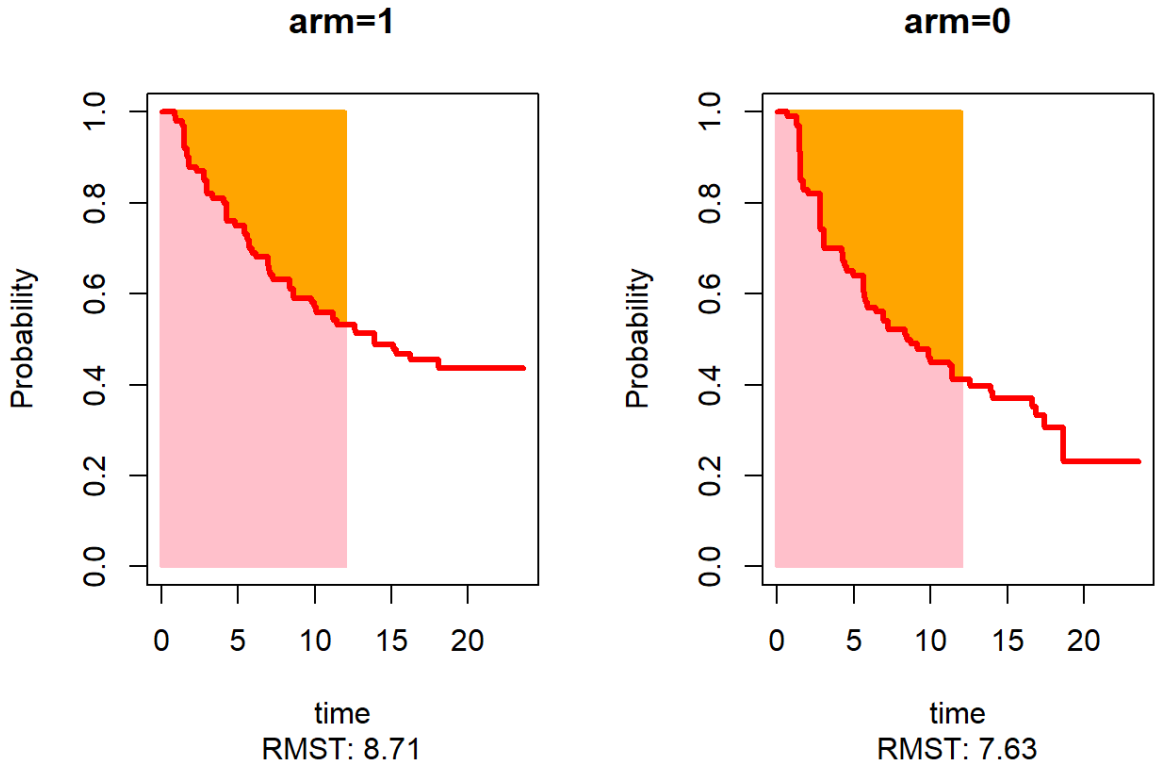


FIGURE 7. RMSTd up to month 12 for Avelumab plus Axitinib versus sunitinib}

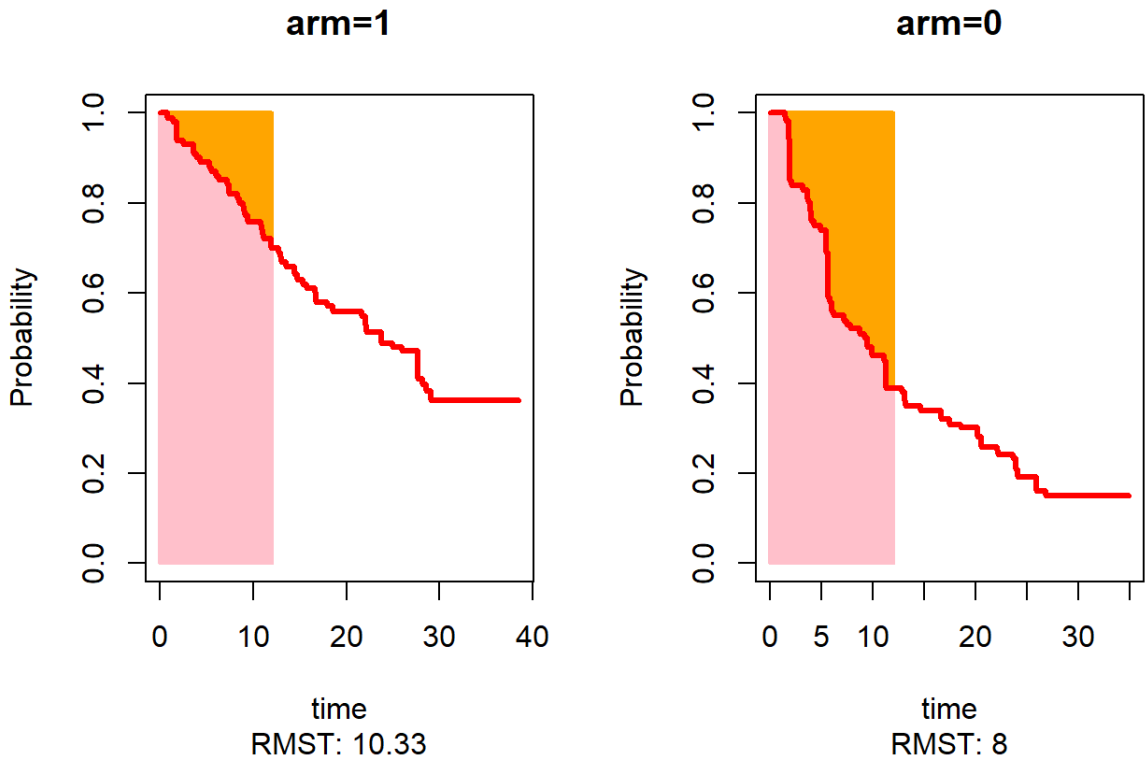


FIGURE 8. RMSTd up to month 12 for Lenvatinib plus Pembrolizumab versus Sunitinib

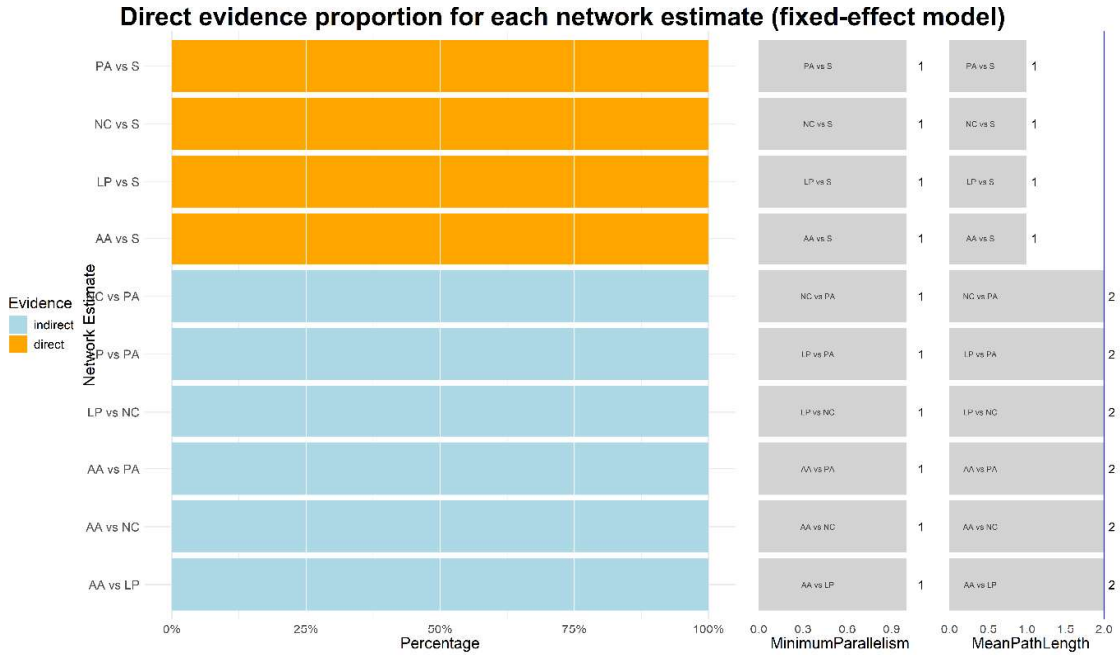


FIGURE 9. Direct-Indirect Network Plot of NMA based on RMSTd at month 12

TABLE 4. Treatment ranking-RMSTd based NMA

Treatment	P-Score	Ranking
Pembrolizumab + Lenvatinib	0.98	1
Cabozantinib + Nivolumab	0.75	2
Axitinib + Avelumab	0.42	3
Axitinib + Pembrolizumab	0.35	4
Sunitinib	0.00	5

using the RMSTd. Since the difference using RMSTd is an absolute measure of difference and is not impacted either by non-propotionality not by crossing of the survival curves, it provides us a great alternative estimate to study time-to-event data, especially in the field of NMA.

A consistency check between HR and RMST approaches can be additionally done using the following:

$$\frac{\log HR_{ij}}{\Delta RMST_{ij}(\tau)} \approx c, \tag{20}$$

where c is a scaling constant. The concordance index (C-index) is:

$$C = P(S_i(t) > S_j(t) | T_i > T_j). \tag{21}$$

CONCLUSION

NMA as a step wise additive tool to knowledge synthesis methodology for the comparison of medical interventions is well known (Zarin et al. 2017). Through the example dataset of 4 clinical trial results in the field of advanced renal cell cancer, we have demonstrated two aspects. One is that the survival plot data can be extracted via graphical and digital tools and then a reconstructed dataset that approximately mimics the anonymized individual patient data can be created. This opens up the possibility to recompute several estimates such as parametric hazard ratios and RMST estimates. This enables us to get additional insights into the data.

We showed that in presence of some non-proportional data in a network where there is one common reference arm that shows consistency among the included studies, the NMA based parametric HR based on distributions such as Weibull, is similar to that obtained using the cox-regression based HR.

RMSTd based approach gives us another absolute difference-based approach that is easier to interpret. The rankings based on the RMSTd based NMA were slightly different from those obtained via the HR based NMA. They could be beneficial in trials with delayed treatment effects or non-standard survival patterns.

LIMITATIONS

Since there are 4 studies in this NMA, the Bayesian estimates should be used to augment the findings of the Freqentist estimates. The low number of studies could be a potential limitation. The main aim of this paper was to frame rules for inclusion of studies based on consistency of the common reference arm. This study only has one common reference arm. In studies with several common treatment arms across several studies, it would be more challenging to control such heterogeneity. Attempts should be made to however study Placebo and common reference arms if present in more than 50 percent of the included studies in any NMA.

As new randomized controlled trials with similar inclusion/exclusion are available, the analysis should be repeated to check for the stability of results currently obtained in this study.

Even though randomized double blinded trials are considered as gold standard in clinical trials, they are difficult to implement in oncology trials and hence open-label trials were included in the NMA. The bias in estimates from individual studies would be similarly carried forward in the NMA.

The biggest scope for improvement is in the reconstruction of IPD. Even though the Hazard ratios from reconstructed IPD very closely match that of the original research findings, the approximation of event and censor points is an area for improvement. The choice of RMSTd estimate over the RMST ratio of treatments was arbitrary and more studies need to be conducted to conclude the best estimate to be used using the RMST approach.

R PACKAGES USED

netmeta (Balduzzi et al. 2023); dplyr; tidyverse; rjags

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