RTI (h)(s)
Health Solutions

Survival Network Meta-analysis: Hazard Ratios Versus Reconstructed Survival Data

Adrian Vickers
RTI Health Solutions, Manchester, United Kingdom

BACKGROUND

- There are currently no clear guidelines from health care authorities on how to conduct network meta-analysis (NMA) on survival endpoints.

OBJECTIVE

This research aims to compare the two leading methods to conduct NMAs on survival outcomes and obtain estimates of mean survival times:

- NMA fitted to summary hazard ratio data
- NMA fitted to reconstructed patient-level data

METHODS

Hazard Ratio NMA

- This followed the method described for a Bayesian NMA by Woods et al. (2010).[1]
- Models were fitted with fixed and random effects.
- Hazard ratios were applied to a model fitted to the reference treatment for the study that contained the main treatment under investigation to give predictions for the other treatments.
- Because of the presence of long-term survivors, hazard estimates were restricted to be greater than those predicted from a model fitted to data simulated from the general population.
- Model selection was based on deviance information criteria.

Reconstructed Patient-Level Data NMA

- This followed the method described by Jansen (2011).[2]
- Patient-level data were reconstructed as described by Guyot et al. (2012).[3]
- A variety of first-order and second-order fractional polynomials with different power functions and models with fixed scale and shape, random scale and fixed shape, and random scale and random shape were conducted.
- Second-order fractional polynomial models gave the best fit but flattened before reaching zero. For the first case study, hazard rates were estimated after follow-up through the use of a flexible spline-based model fitted to an external 5-year data set. After this point, hazard rates from a model fitted to general population data were used. For the second study, comparable long-term data were not available; instead the reference treatment predictions from the NMA were used to anchor the distributions.
- Model selection was based on deviance information criteria.

THE NETWORK OF EVIDENCE

- Table 1 presents the number of studies in the network that did not report Kaplan-Meier estimates and the number of studies that were found to have significant nonproportional hazard rates.
- A similar degree of bias between the proportion of studies not presenting Kaplan-Meier estimates compared with the proportion of studies found to contain significant nonproportional hazard rates was apparent in both case studies.

Table 1. Possible Bias in the Networks of Evidence for the Two Case Studies

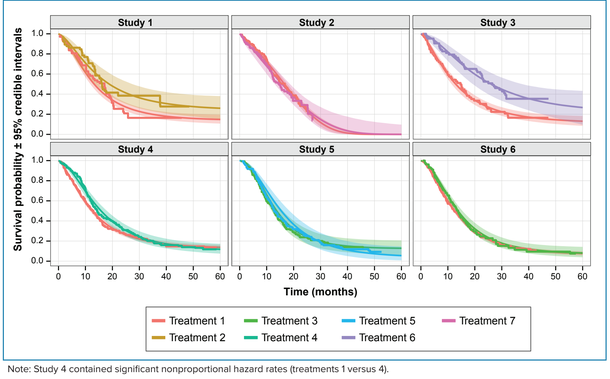
Study	Endpoint	Number of Studies	Number of Studies Without Kaplan-Meier Estimates	Significant Nonproportional Hazard Ratios
Case study 1	Overall survival	6	0	1
	Progression-free survival	6	2	1
Case study 2	Overall survival	24	3	2
	Progression-free survival	17	4	4

RESULTS

Case Study 1

- Figures 1, 2, and 3 present the results from the fractional polynomial NMAs.
  - Figure 1 shows that the predictions gave a good fit.
  - Figure 2 provides further evidence of nonproportional hazard ratios (some lines are not horizontal).
  - Figure 3 shows the predicted overall survival by treatment.

Figure 1. Predicted Overall Survival From the Fractional Polynomial NMA With Kaplan-Meier Estimates



Note: Study 4 contained significant nonproportional hazard rates (treatments 1 versus 4).

Figure 2. Hazard Ratios Relative to the Reference Treatment (Treatment 1) From the Fractional Polynomial NMA

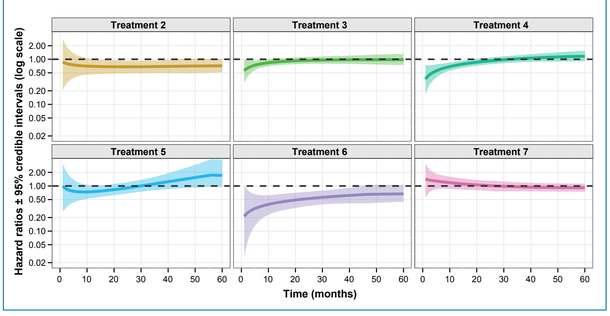
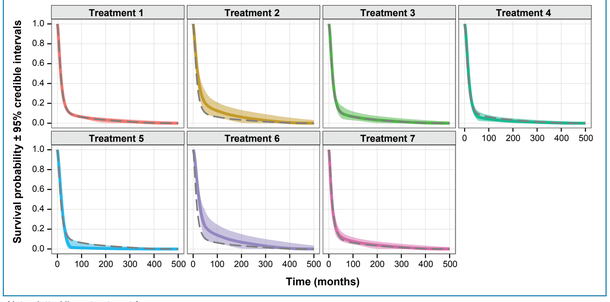


Figure 3. Predicted Overall Survival From the Fractional Polynomial NMA, by Treatment

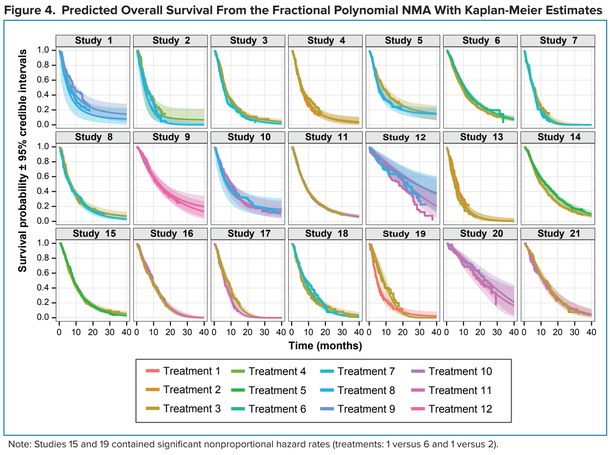


Note: dotted line = treatment 1.

Case Study 2

- Figures 4, 5, and 6 present the results from the fractional polynomial NMAs.
  - Figure 4 shows that the predictions for most study arms gave a good fit.
  - Figure 5 provides further evidence of nonproportional hazard ratios (some lines are not horizontal).
  - Figure 6 shows the predicted overall survival by treatment.

Figure 4. Predicted Overall Survival From the Fractional Polynomial NMA With Kaplan-Meier Estimates



Note: Studies 15 and 19 contained significant nonproportional hazard rates (treatments: 1 versus 6 and 1 versus 2).

Figure 5. Hazard Ratios Relative to the Reference Treatment (Treatment 1) From the Fractional Polynomial NMA

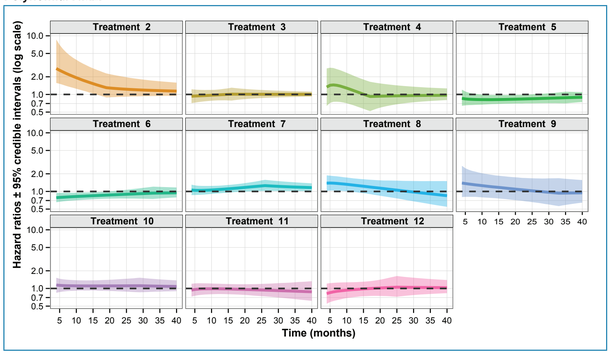
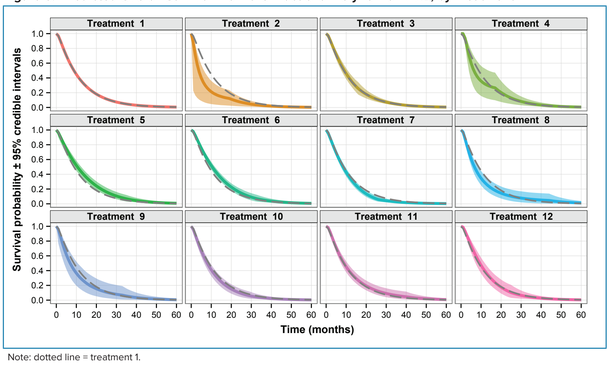


Figure 6. Predicted Overall Survival From the Fractional Polynomial NMA, by Treatment



Note: dotted line = treatment 1.

Predicted Mean Survival Times

- Some differences were observed for the relative difference with the reference treatment.
- The differences appeared to have been due to the lack of fit caused by making the proportional hazard assumption for all treatments in the NMA.

Case Study 1

- Four treatments from the hazard ratio NMA had an improvement in overall survival of at least 3 months.
- Two treatments from the fractional polynomial NMA had an improvement in overall survival of at least 3 months.

Case Study 2

- Two treatments in the hazard ratio NMA had an improvement in overall survival of at least 3 months.
- No treatments in the fractional polynomial NMA had an improvement in overall survival of at least 3 months.

CONCLUSIONS

- Survival estimates from hazard ratio NMAs are sensitive to which trial is selected to supply the reference treatment data. In addition, although a model fitted to this study arm might give plausible predictions, it does not necessarily mean that applying hazard ratios will give plausible predictions for other treatments.
- Where networks of evidence contain a large number of studies, there is a high probability that one or more comparisons may contain nonproportional hazard ratios.
- The fractional polynomial approach can produce survival curves that fit the data well and, with further adjustments, give long-term plausible extrapolations.
- However, publication bias may be introduced into a meta-analysis by including only studies that report Kaplan-Meier charts. Studies that do not achieve the expected results may present only summary data.
- Ideally, both methods are required to give a full picture of the relative efficacy between treatments.
  - Where parts of the networks contain sufficient Kaplan-Meier data, we can rely on the fractional polynomial results.
  - Where networks contain studies that have not reported Kaplan-Meier estimates, then an NMA based on hazard ratios may also be required.

REFERENCES

1. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Med Res Methodol. 2010 Jun 10;10:54.
2. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011 May 6;11:61.
3. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Feb 1;12:9.

CONTACT INFORMATION

Adrian Vickers, PhD
Director, Data and Design Strategy

RTI Health Solutions
2nd Floor, The Pavilion
Towers Business Park
Wilmslow Road
Didsbury
Manchester, M20 2LS, United Kingdom

Presented at: ISPOR 21st Annual International Meeting, May 21-25, 2016, Washington, DC, United States