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Time-varying NMAs in HTA: A challenge of interpretation

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Disclaimers

- An employee of the University of Bristol
- An employee of ConnectHEOR

Overview

- Why might we need a time-varying NMA?
- The challenge of interpretation
- What information do decision-makers need to see?
- A nod to some alternative methods

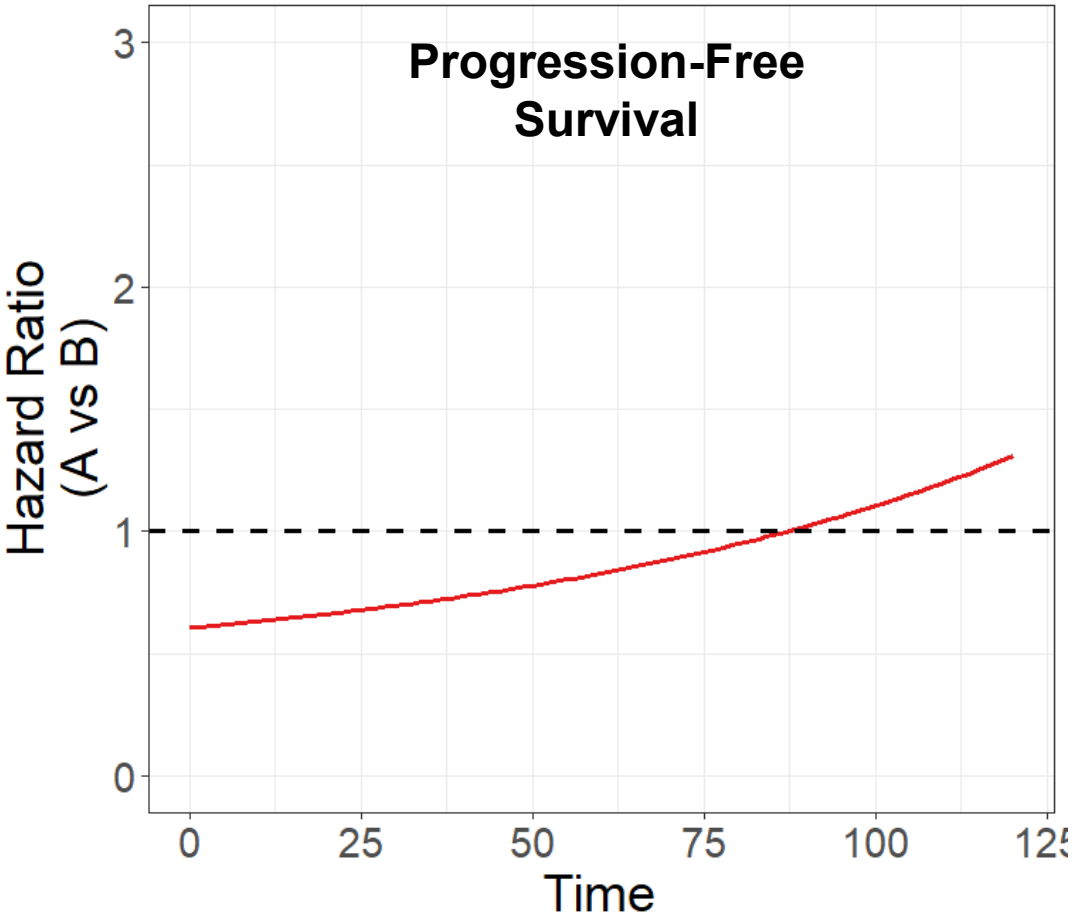
Why a time-varying NMA?

Proportional hazards assumption violated

- Interpretation of a single HR is unhelpful
- Pooling HRs from studies with different follow-ups will give biased HR
- Cannot assume same HR persists into the future (issue for extrapolation)

Time-varying NMA allows us to relax this whilst synthesising multiple studies of multiple treatments (with various follow-ups)

Poll: What does this time-varying hazard ratio tell us about the effect of Treatment A vs Treatment B?



A. A is beneficial over B and the treatment effect is constant over time
B. A is beneficial over B in the short-term, but becomes detrimental in the long-term
C. Is this a marginal or conditional HR?
D. I don't know

The Challenge of Interpretation

Time-varying treatment effect

Changes in distributions of unobserved "frailty factors" over time

Non-collapsibility

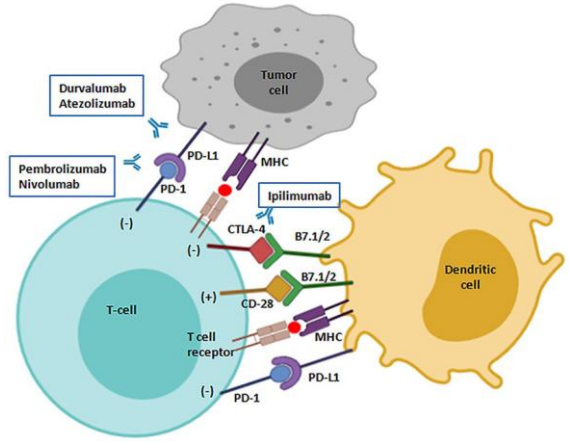
These are rarely properly considered in relation to time-varying NMA outputs when making decisions in HTA, or in HTA methods guidance

Reasons for proportional hazards violations
Time-varying treatment effect

- Treatment waning
- Delayed onset

…but we ideally need a biological/clinical rationale to justify the presence of this

E.g. Immunotherapies have a delayed effect versus chemotherapy since the immune system takes time to be stimulated to target cancer cells



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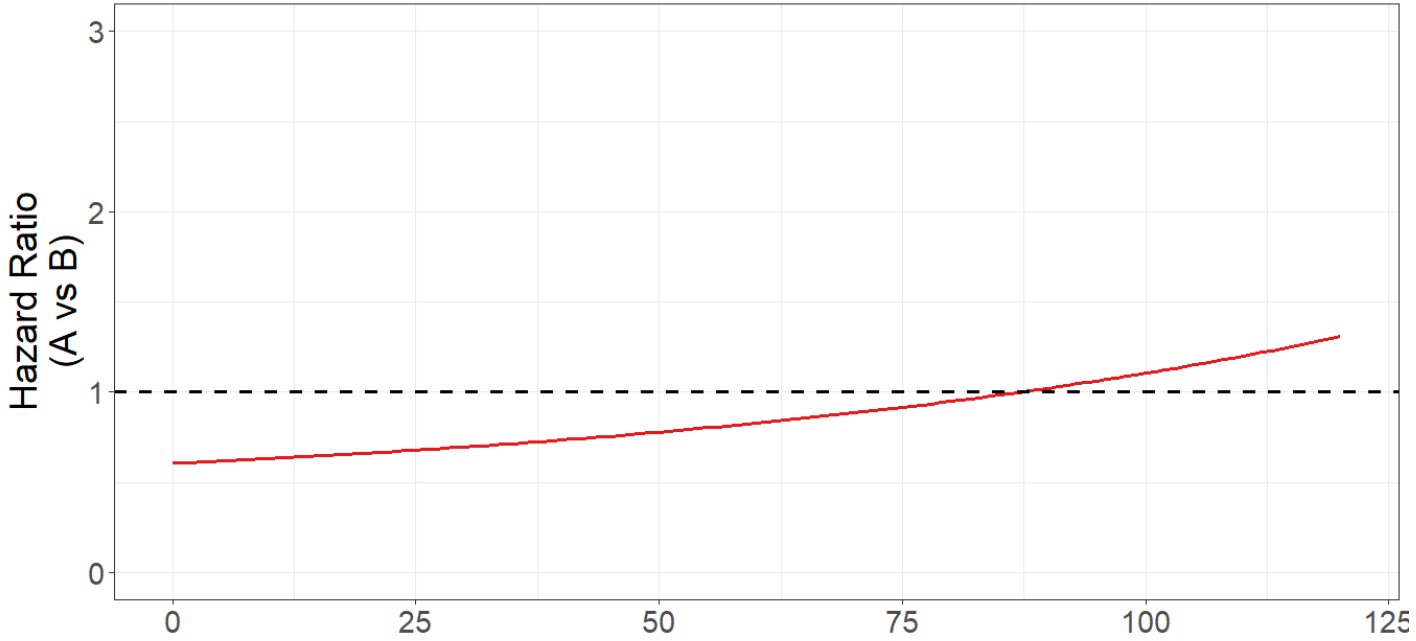
Reasons for proportional hazards violations

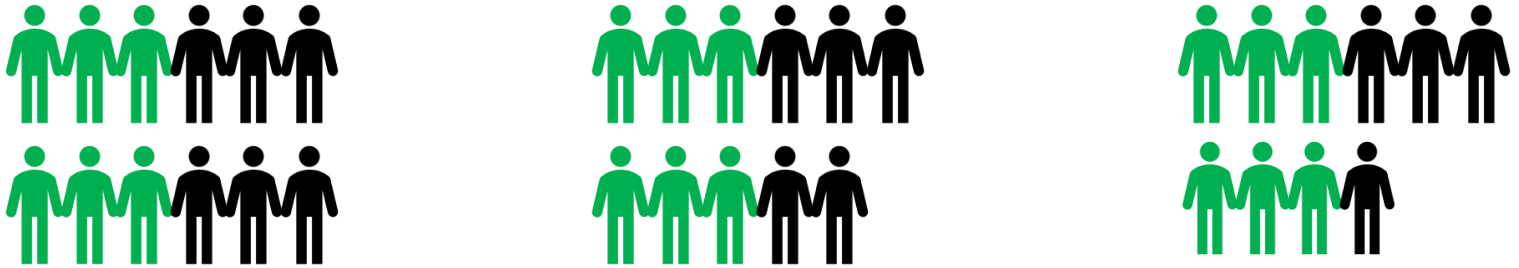
Changes in distribution of “frailty factors”

“Hazards of Period-Specific and Weighted Hazard Ratios”
Bartlett et al. 2020



Treatment A

Treatment B

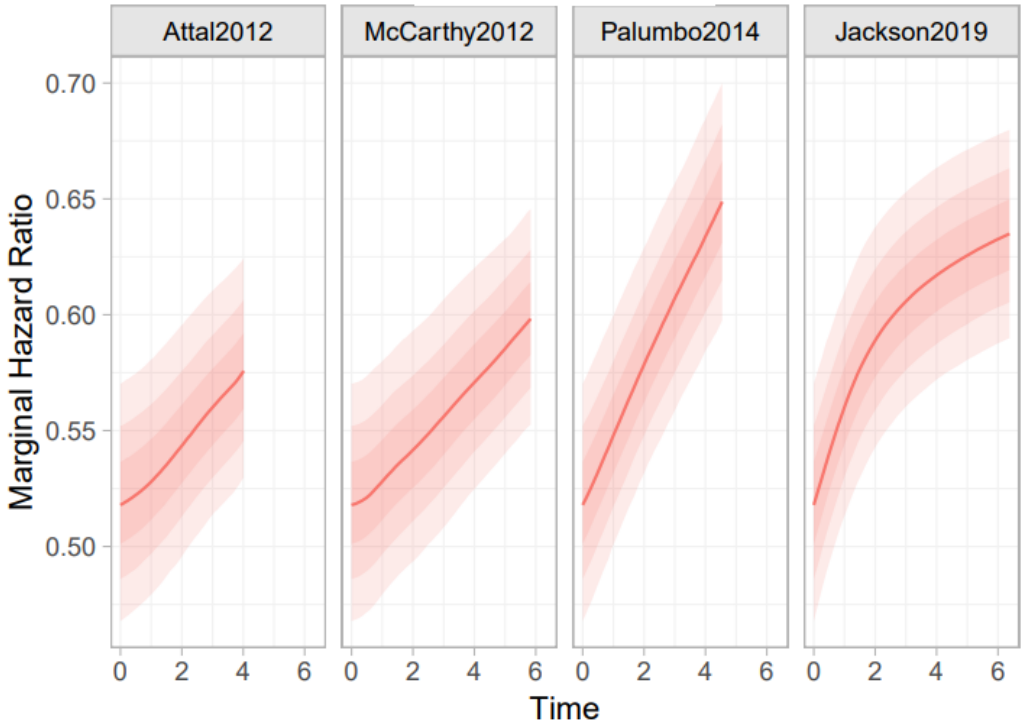


Reasons for proportional hazards violations
Non-collapsibility

If a model assumes PH conditional on a set of covariates (prognostic or effect modifying) then PH cannot hold for the marginal hazards (Phillippo et al. 2025)

- ML-NMR fit to multiple myeloma dataset from
- Adjust for 4 prognostic factors
- Assumes PH *conditional on these covariates*
    - Supported by model fit within each study

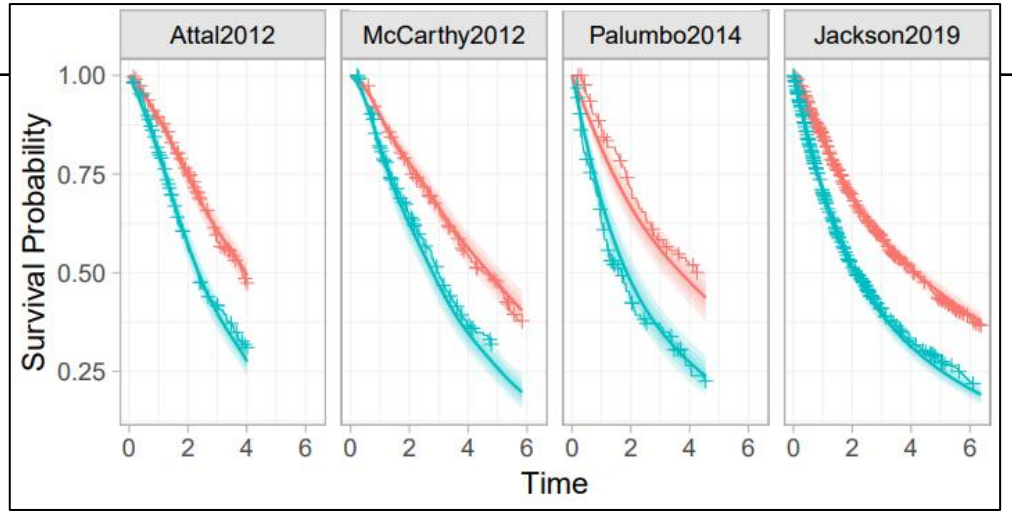
This means we are modelling a single constant HR for each treatment comparison, conditional on some prognostic factors



multinma NDMM vignette: https://dmphillippo.github.io/multinma/articles/example_ndmm.html

When do decision-makers expect to see a time-varying NMA?

- Detailed assessment of PH in included studies…clear evidence of violation
- Clinical justification for time-varying TE

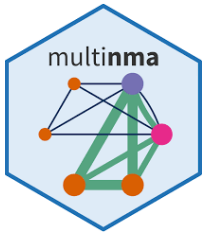


What results must be presented?

1. Fit of predicted survival curves to study-level data
   – If fit is poor then why? Would a more flexible method provide better fit?
2. Confirmation of model convergence
3. Plots of marginal HRs over time (but beware of over-interpretation)
4. **A detailed and clear explanation of how NMA results are incorporated into the model**
   – How is the baseline/NHM estimated
   – How are treatment effects applied
   – Extrapolation

A nod to some alternative methods

- M-spline NMA (Phillippo et al. 2025)
  - Flexible spline on log-hazard
  - Integrates to monotonically increasing I-spline (cumulative hazard)



- RMST NMA (Daly et al. 2021)
  - Mentioned in JCA
  - Not ideal when studies have very different duration of follow-up
  - Requires additional extrapolation for use in CEA

Summary

Analysis of time-to-event data is challenging when we can't make a PH assumption

Range of additional assumptions and approaches

(Not inherently a problem, but demands **very clear justification**)

Don't overinterpret time-varying HRs

References

Bartlett et al. (2020) The Hazards of Period Specific and Weighted Hazard Ratios. *Stat Biopharm Res,* https://doi.org/10.1080/19466315.2020.1755722

Daly et al. (2021) A non-parametric approach for jointly combining evidence on progression free and overall survival time in network meta-analysis. *Stat Med,* https://doi.org/10.1002/jrsm.1539

Phillippo et al. (2025) Effect modification and non-collapsibility together may lead to conflicting treatment decisions: A review of marginal and conditional estimands and recommendations for decision-making, *Res Synth Meth*, https://doi.org/10.1017/rsm.2025.2

Phillippo et al. (2025) Network Meta-Analysis of survival outcomes with non-proportional hazards using flexible M-splines. https://arxiv.org/abs/2509.10383