A General Framework for IPD Meta-Analysis of Competing Risks Data with Flexible Parametric Survival Models: Estimation, Prediction and Software

PT5

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Objectives

Individual Patient Data (IPD) meta-analysis of competing risks data enables pooling of individual-level information across outcomes and trials to precisely estimate treatment effects, adjust for covariates, and support extrapolation beyond observed follow-up. Existing frameworks rely on fixed-effect only, semi-parametric models that limit plausibility. We propose a general frequentist and Bayesian framework for one-step IPD meta-analysis of competing risks data using flexible parametric cause-specific hazard models.

Methods

We extend the one-step stratified IPD meta-analysis approach of Meddis et al. [1] to accommodate flexible parametric cause-specific hazard models within a unified framework. By modelling each cause separately, we isolate treatment effects on each competing event. Study heterogeneity is captured through stratified baseline hazards with optional random treatment effects. Treatment-covariate interactions and non-proportional hazards are estimable within the same model.

Bayesian estimation is also considered, enabling prior incorporation across the cause-specific hazard structure and full posterior uncertainty propagation. Standardized predictions allow population-level inference on cause-specific hazard and cumulative incidence functions, and marginal treatment comparisons.

Features

- ✓ Flexible parametric survival models
- ✓ Time-dependent treatment effects
- ✓ Multilevel effects (e.g., trial-specific treatment effects)
- ✓ Simultaneous estimation of multiple competing endpoints
- ✓ Frequentist or Bayesian with the same syntax
- ✓ Survival extrapolation
- ✓ Trial-specific predictions

Next Steps

- ❑ Meta-regression with copulas for aggregate patient data
- ❑ Expanded post-estimation functionality

Conclusion

A flexible parametric approach to IPD meta-analysis of competing risks data enables robust cause-specific estimation, clinically interpretable predictions, and Bayesian uncertainty quantification - addressing key limitations of existing methods. Open-source software in both Stata and R is freely available at reddooranalytics.se/software.

Applied Example: Nasopharyngeal carcinoma

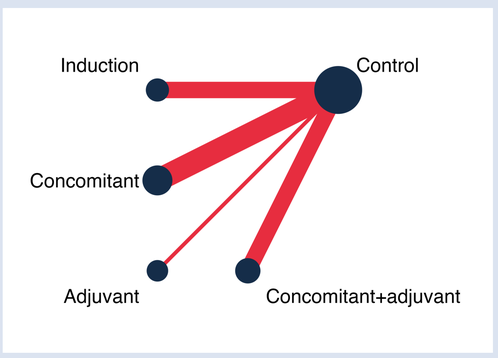


Figure 1: Network plot for the types of chemotherapy treatment modalities in the example.

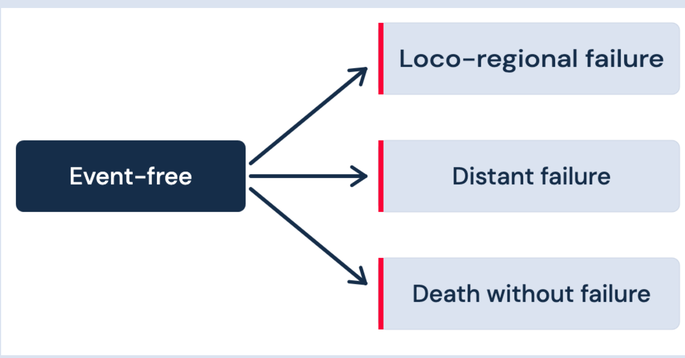


Figure 2: Multistate plot describing the three competing events in the example.

We illustrate the framework using data from 23 trials in patients with nasopharyngeal carcinoma, comparing the effect of chemotherapy added to radiotherapy across four scheduling modalities: *Adjuvant, Concomitant, Concomitant+Adjuvant*, and *Induction*.

Loco-regional failure was the primary endpoint with distant relapse and death without failure as competing events. Flexible parametric models offer improved fit over semi-parametric alternatives, smooth cumulative incidence function estimation, and seamless extrapolation beyond trial follow-up.

The dataset used is openly available from [1].

```
fit <- merlin(outcomes = list( # List of the models for each competing event(outcome)
    loco     = merlin_outcome(
                  formula = Surv(failure_time, failure_type == "Loco-regional failure") ~
                            trtgrp + trial + ns(age, 3) +
                            (trt|trial),       # Random effect of treatment by trial
                  family  = "rp", df = 3,      # Royston-Parmar with 3 df
                  tde     = ~ trtgrp + trial), # Time-dependent treatment effects, trial-specific baselines
    distant = merlin_outcome([…]), # Similar models for the other event types (details omitted)
    death   = merlin_outcome([…])
  ), data = d)
# Ex: Predict cumulative incidence for loco-regional recurrence, accounting for the other competing events
pred <- predict(fit, newdata = d[1, ], type = "cif", outcome = "loco", times = 1:15, se = TRUE)
```

Example outputs

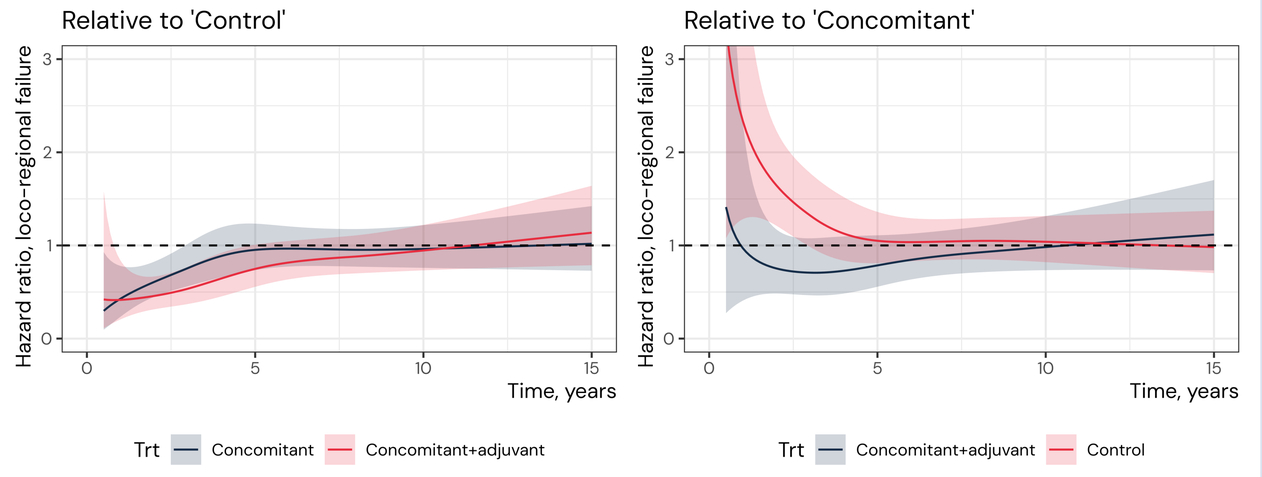


Figure 3: Estimated time-dependent hazard ratios for loco-regional failure between example treatment groups Control, Concomitant, and Concomitant+Adjuvant. The reference group can be easily changed for predictions. Left: Relative to Control. Right: Relative to Concomitant.

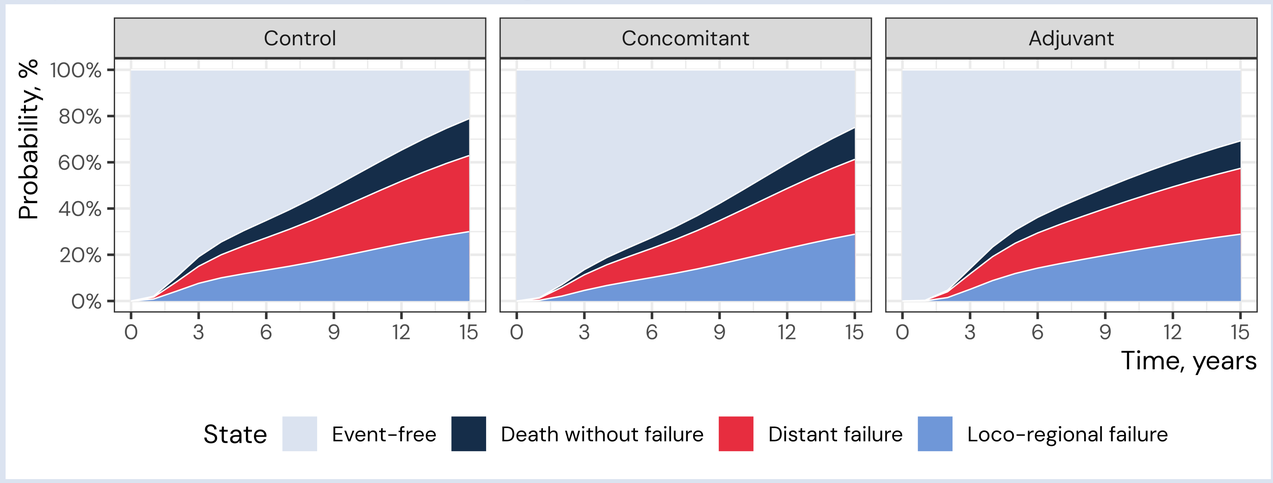


Figure 4: Estimated marginal state occupancy probabilities for example treatment groups Control, Concomitant, and Adjuvant. Standardized to Trial 1. Multiple endpoints can be compared simultaneously.

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[1] Meddis A, Latouche A, Zhou B, Michiels S, Fine J. Meta-analysis of clinical trials with competing time-to-event endpoints. Biometrical Journal. 2019;1–12. doi: 10.1002/bimj.201900103

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