Surviving Unanchored Indirect Comparisons: An Extension of Multilevel Unanchored Meta-Regression (ML-UMR) for Survival Analyses

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Background

- Unanchored comparisons are common in health technology assessment (HTA) when only single-arm or disconnected evidence is available.
- Differences in baseline characteristics across studies can bias naïve comparisons, necessitating the use of population-adjusted indirect comparison (PAIC) methods.[1-2]
- Existing unanchored PAIC methods (i.e., matching-adjusted indirect comparison [MAIC], simulated treatment comparison [STC]) are limited to pairwise comparisons and often estimate effects only in the comparator population, limiting decision relevance.[1-2]
- Multilevel unanchored meta-regression (ML-UMR) extends multilevel network meta-regression (ML-NMR) to unanchored settings, enabling joint synthesis of individual patient data (IPD) and aggregate-level data (AgD) and transport to decision-relevant target populations.[3-4]
- Extension of ML-UMR to time-to-event outcomes is needed, as survival endpoints are common in HTA and introduce additional complexities (e.g., censoring, time-varying hazards, reconstruction of Kaplan-Meier [KM] data).[4]

Objectives

- To extend ML-UMR to time-to-event outcomes and evaluate its performance in a simulation study under varying levels of population imbalance and effect modification.

Methods

ML-UMR for Comparisons of Survival Outcomes

- Following the general ML-NMR framework by Phillippo et al., 2025, ML-UMR can be extended to time-to-event outcomes using parametric survival models, as shown in **Table 1** (e.g., Weibull, Gompertz, log-logistic).[5]
- ML-UMR models survival that is conditional on covariates and integrates over study-specific covariate distributions to link IPD and AgD and enable transport to target populations.
- At the individual level, survival outcomes are modeled via a linear predictor:

$$\eta_{ik} = \alpha_k + x_i^T \beta_k$$

- For treatments with IPD, each individual i contributes the standard conditional survival likelihood:

$$\mathcal{L}_{ik|x}^{IPD} = h_k(t_i \mid x_i)^{\delta_i} S_k(t_i \mid x_i)$$

- For comparator studies with only AgD, pseudo-IPD are reconstructed from published Kaplan–Meier curves (e.g., via Guyot's method), yielding (t_i, δ_i) .
- Aggregate likelihood contributions are obtained by marginalizing over the covariate distribution in the AgD study:

$$\mathcal{L}_{ik}^{AgD} = \int h_k(t_i \mid x)^{\delta_i} S_k(t_i \mid x) f_k(x)\, dx$$

- Typically, no closed-form solution exists, so this integral is approximated using numerical methods (e.g., quasi–Monte Carlo).
- IPD and AgD are combined in a unified likelihood assuming conditional independence:

$$\mathcal{L}_{\text{joint}} = \prod_{i \in IPD} \mathcal{L}_{ik|x}^{IPD} \prod_{i \in AgD} \mathcal{L}_{ik}^{AgD}$$

Table 1. General Survival Model Formulations

Type of Model	General Formulation
PH	$h_k(t \mid x_i) = h_{0k}(t)\exp(\eta_{ik})$
AFT	$\log(T_i) = \eta_{ik} + \sigma\epsilon_i$

Abbreviations: AFT = accelerated failure time; PH = proportional hazards.
Note: α_k is the baseline (intercept) for treatment k; x_i is the vector of baseline covariates for individual i; β_k are treatment-specific covariate effects; $\eta_{ik} = \alpha_k + x_i^T\beta_k$ is the linear predictor. $h_k(t \mid x_i)$ and $S_k(t \mid x_i)$ denote the hazard and survival functions, respectively, with $h_{0k}(t)$ the baseline hazard. In the AFT model, T_i is the event time, σ is a scale parameter, and ϵ_i is a random error term with a specified distribution.

Methods (continued)

- After model estimation, treatment effects can be transported to a decision-relevant target population, $\tilde{P}$.
- Marginal relative effects (e.g., restricted mean survival time [RMST] or hazard ratios [HRs]) are calculated from marginal survival $S_k(t \mid \tilde{P})$ and the hazard function $h_k(t \mid \tilde{P})$.
- Let $f_{\tilde{P}}(x)$ denote the covariate distribution of the target population.

$$S_k(t \mid \tilde{P}) = \int S_k(t \mid x) f_{\tilde{P}}(x)\, dx$$

$$h_k(t \mid \tilde{P}) = \frac{\int h_k(t \mid x) S_k(t \mid x) f_{\tilde{P}}(x)\, dx}{\int S_k(t \mid x) f_{\tilde{P}}(x)\, dx}$$

Simulation Study

- A simulation study evaluated ML-UMR for unanchored survival comparisons using two disconnected, single-arm studies:
  - Treatment A (index; IPD)
  - Treatment B (comparator; AgD only)
- Survival times were generated from Weibull models with common shape parameter r=1.5. The baseline hazard was calibrated such that the median survival for treatment B with X=0 was 2 years; a true conditional HR=0.6 was applied for treatment A (vs B), corresponding to improved survival (median ≈ 2.8 years for X=0).
- A binary prognostic factor X was imbalanced across studies, with $P(X=1)$=0.30 in the index population and 0.70 in the comparator population.
- ML-UMR was fit under the shared prognostic factor assumption (SPFA), where the prognostic covariate X has the same effect on the outcome (log-hazard scale); misspecification was induced by varying the effect of X for treatment B (**Table 2**).
- Simulations used n=1000 per study, 10% uniform censoring, and 150 Monte Carlo replications.
- Performance was assessed using bias and 95% credible interval (CrI) coverage for marginal time-varying log HRs and RMST-based estimands in the index and comparator populations.
- RMST was evaluated over a time horizon of τ=3, and marginal log HRs were evaluated at prespecified times from 0.25 to 3.0 years.

Table 2. Simulation Scenarios

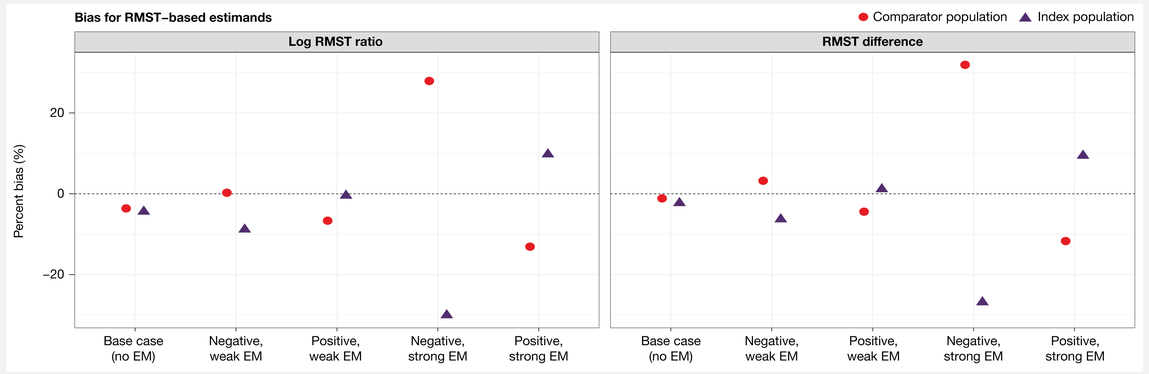
Scenario	Relative HR_X (B vs A)	PF Effect (HR_X) for A	PF Effect (HR_X) for B	Interpretation
Base case (no EM)	0%	1.00	1.00	No effect modification; SPFA holds
Negative, weak EM	-10%	1.00	0.90	Weak negative deviation from shared PF effect
Positive, weak EM	+10%	1.00	1.10	Weak positive deviation from shared PF effect
Negative, strong EM	-50%	1.00	0.59	Strong negative deviation from shared PF effect
Positive, strong EM	+50%	1.00	1.41	Strong positive deviation from shared PF effect

Abbreviations: EM = effect modification; HR = hazard ratio; PF = prognostic factor; SPFA = shared prognostic factor assumption.
Note: HR_X denotes the hazard ratio associated with covariate X. Effect modification is introduced by varying HR_X for treatment B relative to treatment A, while ML-UMR assumes a shared effect under SPFA.

Results

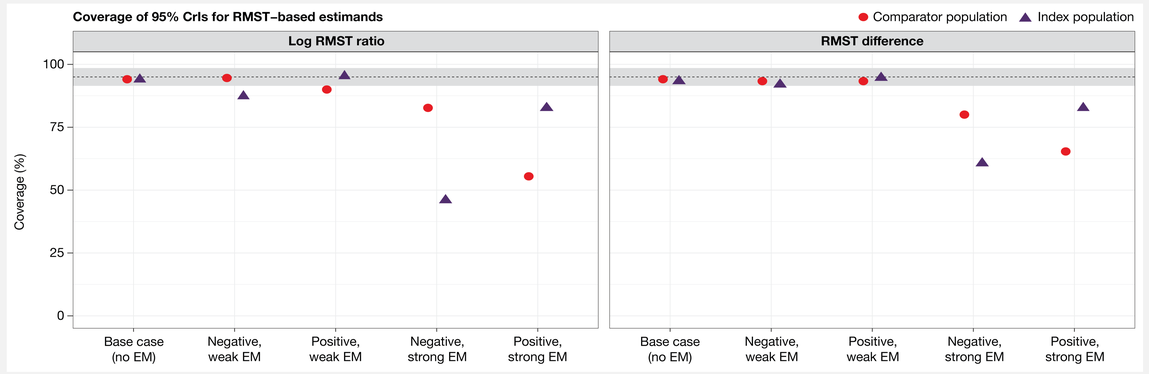
- **No effect modification (EM; SPFA holds):** RMST-based measures were accurately recovered in both populations, with relatively low bias (|bias| ≲ 0.01–0.02) and near-nominal coverage (~93%–96%).
- **Weak EM (±10%):** RMST difference and log RMST ratio remained relatively robust, with modest bias (generally <10%) and coverage ranging from ~87%–95%. Some attenuation was observed for transported effects in the index population.
- **Strong EM (±50%):** Performance deteriorated substantially. Bias increased markedly (often >25%–30% for index-population RMST measures), and coverage declined to ~45%–80%, depending on direction and population.
- **Time-varying log HRs:** A similar pattern was observed (**Figures 1–2**). Bias was minimal under no EM (<1%) with ~95% coverage, moderate under weak EM (≈1%–12%), and substantial under strong EM (often >30%–50% in the index population). Under strong EM, coverage frequently fell below 60% and approached 0% at later time points.

Figure 1. Percent Bias for RMST Log Ratios and Differences



Abbreviations: EM = effect modification; RMST = restricted mean survival time.
Percent bias reflects deviation of the estimated treatment effect from the true effect (values closer to 0 indicate lower bias). Under weak EM, bias remained modest, whereas under strong EM bias increased in both populations; the direction of EM determined whether bias was positive or negative in each population.

Figure 2. Coverage of 95% CrIs For RMST Log Ratios and Differences



Abbreviations: EM = effect modification; RMST = restricted mean survival time.
Empirical coverage probabilities of 95% CrIs for RMST-based measures. Coverage is near nominal when the shared prognostic factor assumption holds, but declines under strong EM.

Conclusions

- ML-UMR can be extended to unanchored comparisons of time-to-event outcomes and enables estimation of survival-based treatment effects in multiple target populations.
- When the SPFA holds, ML-UMR provides valid estimates (low bias, near-nominal coverage).
- Under EM, performance deteriorates. The magnitude and direction of EM influence both the direction and extent of bias across populations.
- These findings highlight that valid transport of survival effects in unanchored settings depends critically on strong, often untestable assumptions.

References

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