MSR83

A Quantitative Bias Analysis Framework for Real-World Comparative-Effectiveness Studies using Bayesian Data Augmentation and Restricted Survival

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• Introduction

- Real-world comparative-effectiveness studies can generate evidence of relative efficacy for novel clinical treatments, when implementation of a randomised controlled trial is infeasible.
- However, non-random treatment assignment and unrecorded confounding variables can lead to residual bias in the form of unmeasured confounding[1].
- Quantitative bias analysis (QBA) has been recommended to investigate the potential impact of unmeasured confounding on a study's conclusions[2].
- As many novel treatments now involve complex mechanisms of action or delivery, survival trends frequently violate the proportional hazards (PH) assumption[3]. Therefore, flexible QBA methods are required which can be applied under PH violation. However, there is a lack of such methods.

• Objectives

- Develop a flexible QBA framework which is valid under PH violation.
- Assess the proposed framework's ability for accurate and precise effect estimation which is adjusted for unmeasured confounding.
- Design and implement a simulation study to perform this assessment under PH violation and different forms of unmeasured confounding.

• Methods

QBA Framework

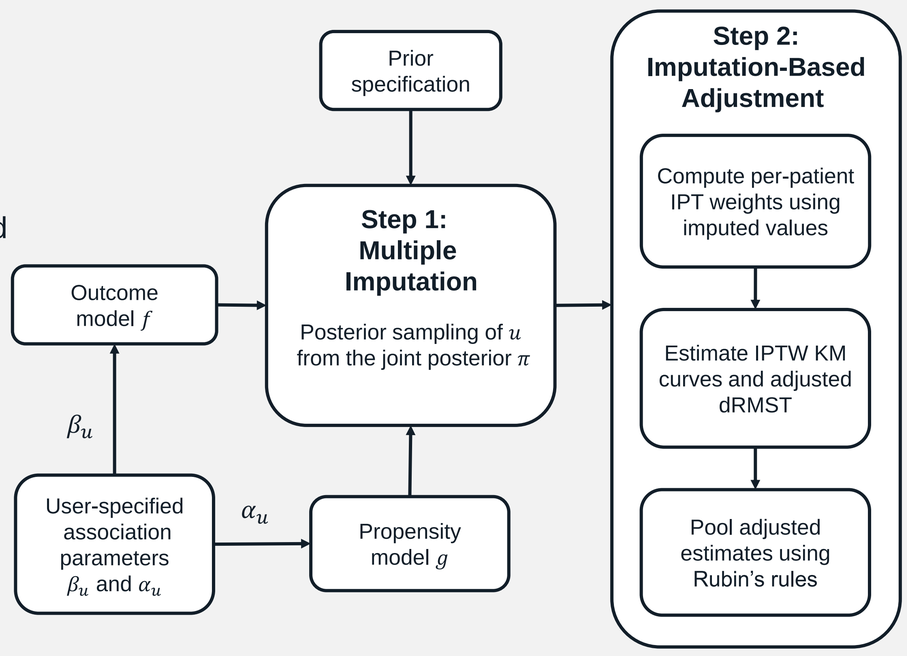
- The difference in restricted mean survival time (dRMST) has been proposed as an alternative to the hazard ratio (HR) when the PH assumption is violated[4].
- Therefore, we proposed a two-step QBA framework (Figure 1) which assess the sensitivity of dRMST to unmeasured confounders u.
- In step 1, multiple imputation (MI) of u with user-specified association parameters β_u and α_u is implemented.
- By combining Bayesian data augmentation[5] with Markov chain Monte Carlo sampling, imputed values are drawn from the joint posterior π given below:

$$\pi(\theta, u|t, z, \dots) \propto f(t|\theta, u, z, \beta_u, \dots)g(z|u, \alpha_u, \dots)p(u)p(\theta)$$

Outcome model | Propensity model | Prior specification

- In step 2, imputation-based adjustment of dRMST is implemented through inverse probability of treatment weighted (IPTW) Kaplan-Meier (KM) curves.

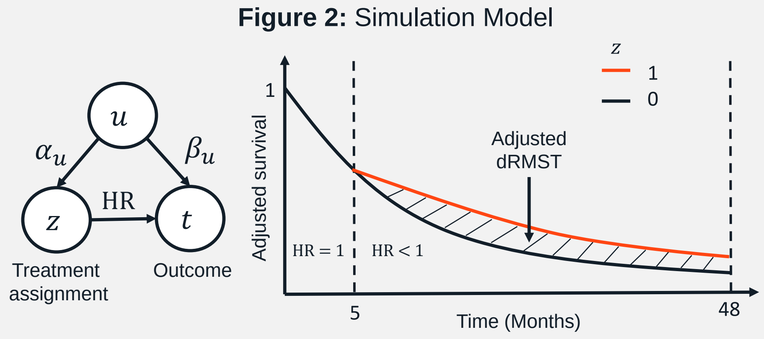
Figure 1: Proposed QBA Framework. Steps 1 and 2 are iterated for different values of β_u and α_u and the sensitivity of the dRMST examined.



Simulation Study

- Data was simulated using a delayed treatment effect model with exponential survival and a binary confounder $u \sim$ Bernoulli(0.5) (Figure 2).

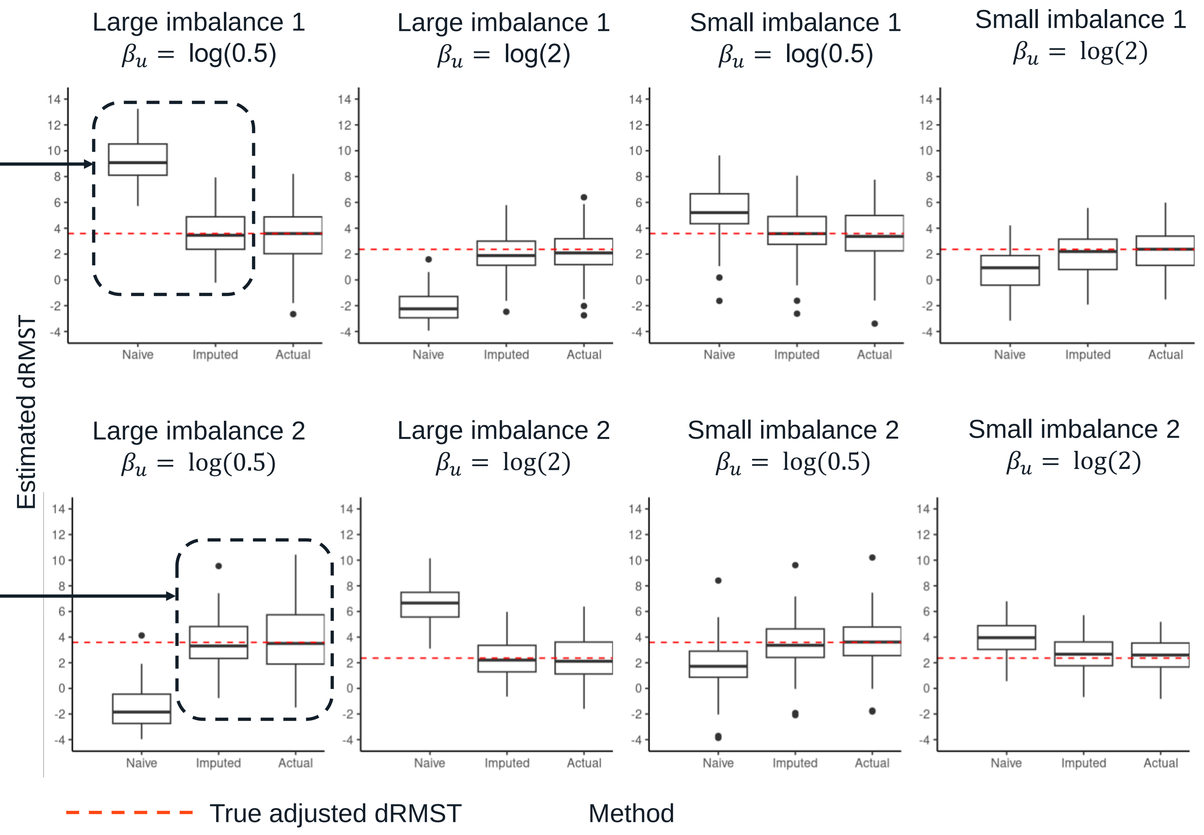
Figure 2: Simulation Model



- Imputation-based adjustment (Imputed) was compared against adjustment using the actual simulated u (Actual) and a naive analysis where confounding was ignored (Naive).
- Regression parameters β_u and α_u were varied across 8 scenarios to simulate 100 datasets of 300 patients each. 1000 imputations were drawn for each dataset using the statistical software JAGS[6].

• Results

Figure 3: Comparison of estimated dRMST between all 3 methods.



Ignoring the presence of confounding in the naive analysis led to bias, which imputation-based adjustment corrected.

Comparable ability to recover the true dRMST was observed between imputation-based adjustment and actual adjustment across all scenarios.

Table 1: Comparison of bias and standard error (SE) between imputation-based adjustment (Imputed) and actual adjustment (Actual).

		Bias[1,2]		SE[1]	
α_u[3]	β_u[4]	Imputed	Actual	Imputed	Actual
Small 1	$\log(0.5)$	0.12	-0.207	1.957	1.914
	$\log(2)$	-0.330	-0.110	1.423	1.399
Small 2	$\log(0.5)$	-0.140	0.065	1.949	1.905
	$\log(2)$	0.299	0.133	1.399	1.366
Large 1	$\log(0.5)$	0.012	-0.065	2.667	2.328
	$\log(2)$	-0.283	-0.268	1.911	1.701
Large 2	$\log(0.5)$	-0.040	0.122	2.671	2.337
	$\log(2)$	-0.022	-0.056	1.863	1.673

1: Averaged over 100 simulations. 2: Bias is defined as estimate – truth.
3: Parameters for the logistic propensity model: Values induce the following imbalances:
Small 1: $\Pr(Z = 1|\, U = 1) = 0.4$. Small 2: $\Pr(Z = 1|\, U = 1) = 0.6$.
Large 1: $\Pr(Z = 1|\, U = 1) = 0.2$. Large 2: $\Pr(Z = 1|\, U = 1) = 0.8$.
4: Conditional log(HR) capturing the effect of u on survival: Values correspond to a either a doubling (log(2)) or a halving of the hazard (log(0.5)).

• Conclusions

- Imputation-based adjustment using Bayesian data augmentation can accurately recover the adjusted dRMST when confounding variables are unmeasured.
- Hence, our proposed QBA framework can correctly identify the characteristics required by an unmeasured confounder to overturn a study's conclusions.
- Therefore, our proposed QBA framework is a valid sensitivity analysis to investigate the robustness of real-world comparative-effectiveness studies displaying PH violation, when unmeasured confounding is suspected.
- The proposed QBA framework is modular in nature and can be implemented under a wide range of non-PH settings, effect measures, and adjustment methods.
- Bayesian modelling allows for the inclusion of prior information into the analysis.
- Future work will investigate further the performance of our proposed QBA framework under different simulation scenarios and apply the framework to empirical data.

• References

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