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

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MSR83

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 in real-world data sources can lead to residual bias in the form of unmeasured confounding[1].
- If suspected, 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.

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].

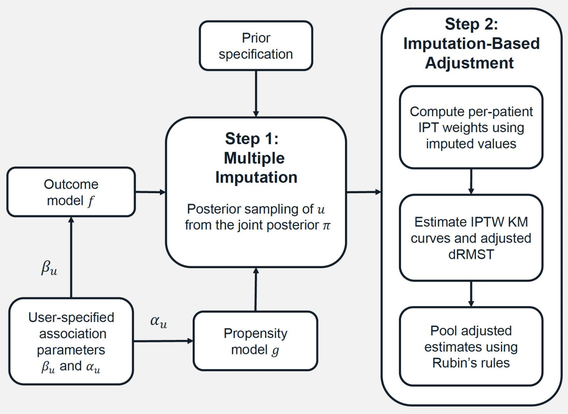
- Therefore, we proposed a two-step QBA framework (Figure 1) which assess the sensitivity of dRMST to unmeasured confounders u.
- In step 1, multiple imputation (MI) of u with user-specified association parameters β_u and α_u is implemented.
- By combining Bayesian data augmentation[5] with Markov chain Monte Carlo sampling, imputed values are drawn from the joint posterior π given below:

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

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.

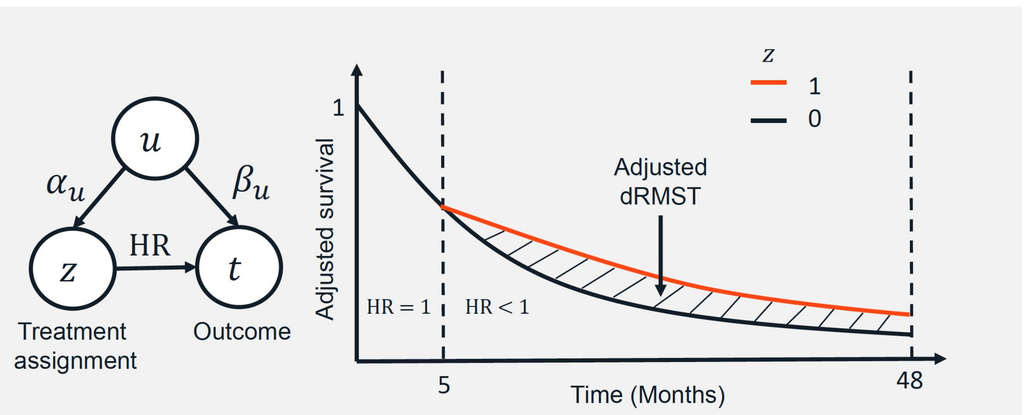
Figure 1: Proposed QBA Framework. Steps 1 and 2 are iterated for different values of β_u and α_u and the sensitivity of the dRMST examined.



Simulation Study

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

Figure 2: Simulation Model



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.

Results

Figure 3: Comparison of estimated dRMST between all 3 methods

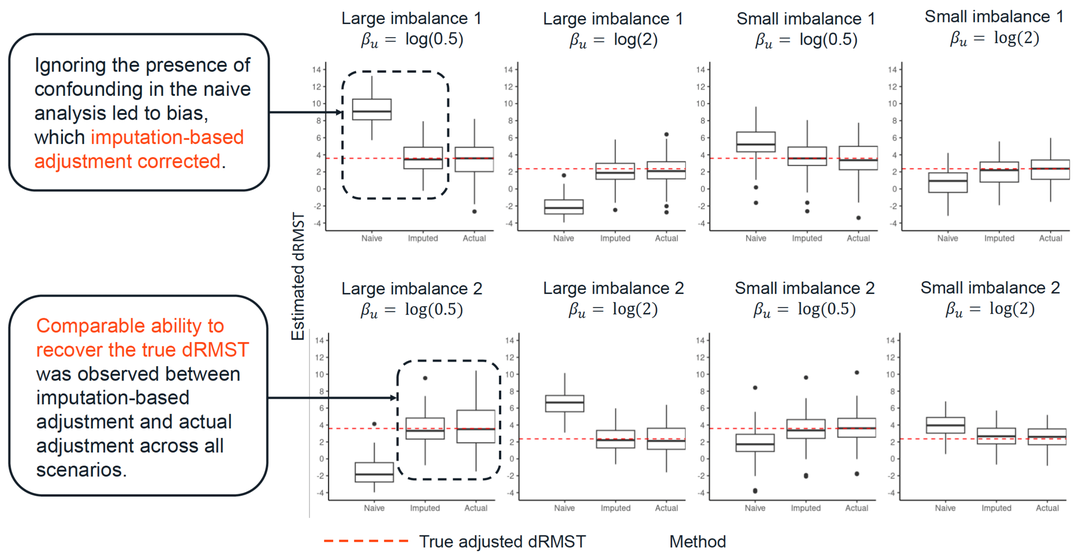


Table 1: Comparison of bias and standard error (SE) between imputation-based adjustment (Imputed) and actual adjustment (Actual).

		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 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.

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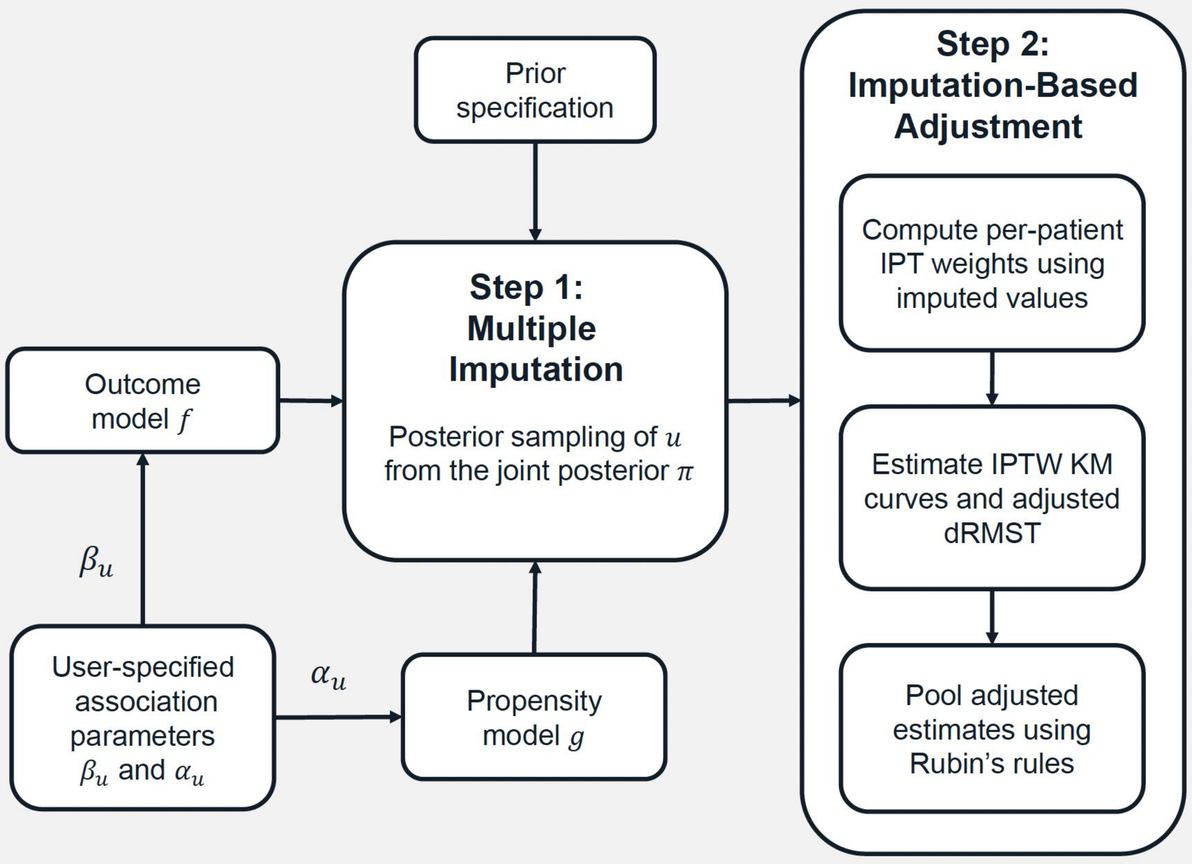

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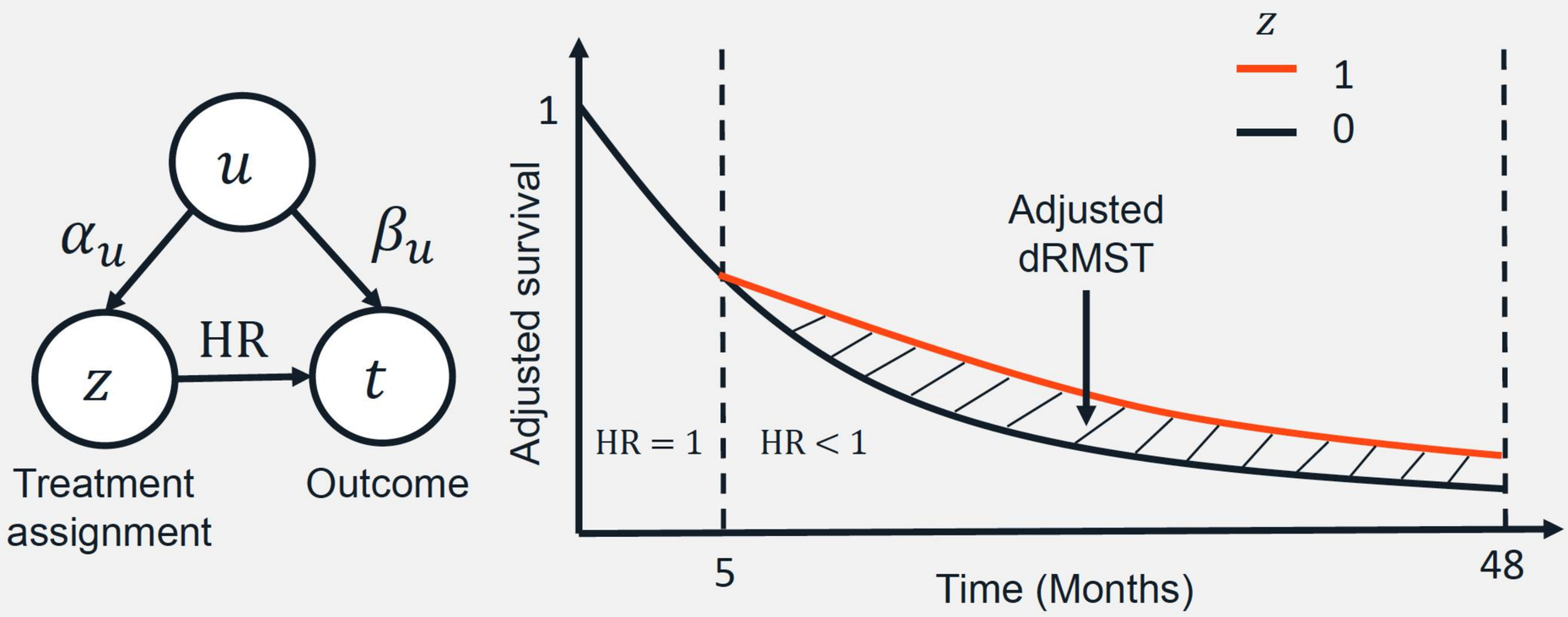

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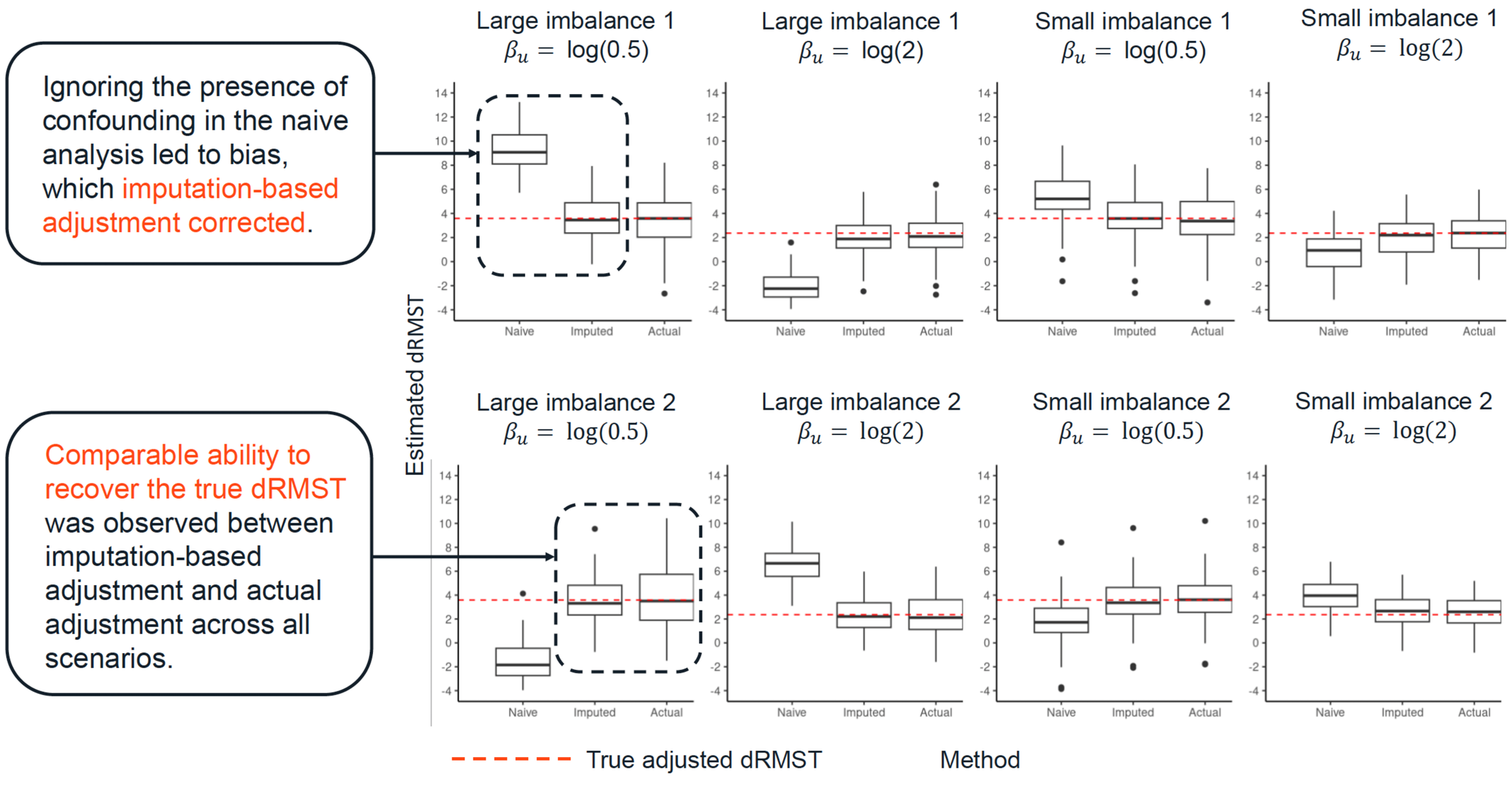

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