The Importance of Jointly Analyzing Quality of Life and Survival: Insights from a Simulation Study

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INTRODUCTION

Patient-Reported Outcomes (PROs) are a key innovation in clinical research, providing direct insights into patients' perception of symptoms and quality of life (QoL).[1] Beyond their role in measuring well-being, PROs have also shown consistent associations with survival. Nonetheless, they are often analyzed separately from survival, which may lead to biased estimates of treatment effects and loss of clinical information. PROs in fact are only collected from surviving patients and early mortality among those with lower QoL can lead to an overestimation of average QoL, distorting perceived treatment effects. Moreover, survival models that rely only on baseline PRO values may fail to capture crucial changes in QoL that might correlate with prognosis.[2] Joint models (JMs), which combine the analysis of repeated measurements and time-to-event data, were developed to address these issues.[3] However, their use in practice remains limited.[4]

AIM

This simulation study aimed to explore the interplay between QoL and survival under different scenarios and to compare traditional approaches, such as Cox models, with and without time-dependent covariates, with the JM in terms of accuracy and robustness.

METHODS

Six scenarios with 500 samples of 1,500 patients (750 treated, 750 controls) were simulated by combining three different treatment impacts on QoL (worsening, no change, improvement over time) with two survival settings (a halving of mortality vs. no direct survival benefit). The follow-up period was set at 5 years and divided into monthly intervals. In each interval, a linear mixed effect model (LMM) was used to generate QoL score for each patient. The probability of death within each interval was simulated considering the treatment arm and the current QoL score, assigning the same risk to everyone with the same profile. Informative censoring was introduced by modeling a lower probability of being observed during intervals when subjects had lower QoL scores. Additional scenarios without informative censoring were also simulated to assess how models' performances were affected by the QoL–survival association independently of observation bias. Three statistical approaches were applied: a univariate Cox model with only the treatment variable, an extended Cox model with QoL as a time-dependent covariate, and a JM with a Weibull survival component and a LMM for QoL. Performances were compared through mean estimates of treatment and QoL effects on survival in terms of hazard ratio (HR), bias, standard error, and 95% coverage probability (CP).

RESULTS

Even a modest association between QoL and survival (e.g., HR QoL=0.96) significantly influenced mortality patterns. Mortality increased when treatment had negative impacts on QoL even in the context of a direct survival benefit. Conversely, positive effects on QoL further amplified survival benefits. In the main scenarios with informative censoring, the univariate Cox model, while accurate if treatment had no impact on QoL, tended to overestimate the protective effect of treatment on survival when it was positively associated with QoL, sometimes even indicating a benefit where none existed. Conversely, when treatment negatively affected QoL, the model either underestimated its protective effect on survival or suggested harm where there was none. This pattern highlighted the potential for misinterpretation in clinical settings, where changes in QoL might be mistakenly attributed to treatment effects on survival. The extended Cox model showed mild improvement in certain scenarios but consistently failed to accurately estimate the protective effect of QoL on survival, leading to substantial bias. In contrast, JM consistently produced accurate, unbiased estimates with CPs near 95%, reflect-

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ing its robustness in all scenarios, even with a simplified structure that included only a random intercept (Table1). In the absence of informative censoring, the extended Cox model was able to accurately estimate the effect of QoL on survival when treatment positively influenced QoL and was better than the JM in terms of CP. However, it continued to perform poorly in estimating the treatment effect on survival, showing consistent bias and low CP across most scenarios. The JM remained the most reliable approach, although its performance slightly decreased, likely due to a less clearly defined QoL–survival association.

CONCLUSIONS

JMs offer a more accurate and comprehensive approach for analyzing PROs and survival, capturing both direct and indirect treatment effects. Their capacity to integrate multiple dimensions of patient data make them valuable for analyzing chronic conditions where PROs and survival are linked. Even modest interdependencies can meaningfully influence outcomes and ignoring them may lead to misleading conclusions. Their use should be prioritized in both randomized and observational studies to ensure a valid inference and a deeper understanding of treatment effects.

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Table 1. Estimated treatment and QoL effects on survival (HR trt and HR QoL) across different simulated scenarios.

(HR trt, $\beta_{timetrt}$)	Model	HR trt	95% CP HR trt	HR QoL	95% CP HR QoL
(0.5, -0.333)	Univariate Cox	0.85	0	-	-
	Extended Cox	0.74	0.104	1.03	0
	JM	0.50	0.946	0.96	0.936
(0.5, 0)	Univariate Cox	0.50	0.936	-	-
	Extended Cox	0.74	0.086	1.02	0
	JM	0.50	0.922	0.96	0.964
(0.5, 0.333)+	Univariate Cox	0.33	0.112	-	-
	Extended Cox	1.12	0	1.01	0
	JM	0.54	0.948	0.95	0.924
(1, -0.333)	Univariate Cox	1.65	0	-	-
	Extended Cox	1.04	0.976	1.03	0
	JM	1.02	0.926	0.96	0.946
(1,0)	Univariate Cox	1.01	0.960	-	-
	Extended Cox	1.00	0.992	1.02	0
	JM	1.00	0.960	0.96	0.950
(1, 0.333)+	Univariate Cox	0.67	0.026	-	-
	Extended Cox	1.39	0.214	1.01	0
	JM	1.08	0.940	0.95	0.904

worsening QoL +improving QoL
Legend: CP, coverage probability; HR, hazard ratio; JM, joint model; QoL, quality of life; trt, treatment.

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