Joint Survival Modeling in Rare Diseases: Validating Applicability and Considering Sample Size Challenges

MSR181

View all Parexel's posters at ISPOR Europe 2024

De T[1], Tate AE[2], Chepynoga K[3], Sharpe DJ[4], Kerr J[4], Payer T[4], Vanderpuye-Orgle J[5]

[1]Parexel International, Cupertino, USA, [2]Parexel International, Amsterdam, Netherlands, [3]Parexel International, Hørsholm, Denmark, [4]Parexel International, Madrid, Spain, [5]Parexel International, Billerica, USA

Aim

Understand how small sample sizes, typical of rare disease studies, affect the performance of joint survival models.

Background

- **Joint survival modeling** integrates longitudinal data with time-to-event outcomes to account for correlations between continuous biomarkers and survival. This model effectively reduces bias, especially in cases of censored data or missing values, by considering both outcomes simultaneously [1].
  - However, applications to studies in rare diseases, where small sample sizes are liable to give rise to issues of model instability and high uncertainty, are currently scarce.
- **Cushing syndrome** (neoplastic hypercortisolism) is a rare endocrine disorder due to an ACTH-secreting tumor or from a benign or malignant adrenal neoplasia [2]. **Nonneoplastic hypercortisolism** (Pseudo-Cushing syndrome) is clinically similar, but arises from other causes [3]:
  - **Cushing phenotype** - Alcohol use, kidney disease, neuropsychiatric disorders, etc.
  - **Non-Cushing's phenotype** - Starvation equivalent disorders
- We aim to assess the feasibility of joint survival modeling in rare disease studies, using a simulated dataset representing the effects of **age at baseline**, **sex,** and regularly measured **low-density lipoprotein (LDL) cholesterol** on **disease recurrence** over five years in Nonneoplastic hypercortisolism

Methods

- We simulated datasets based on reported associations between the covariates and survival outcomes in literature [4-7] with a **sample size of 500 patients** and generated **subsets of 200, 150, 100, 75, 50, and 25 patients.**
- First, a **linear mixed effects** model was created with time-varying LDL cholesterol as the outcome. Sex and time were fixed effects on the gradient, and there were patient-level random effects on the intercept and gradient
- Next, a **Cox proportional hazards model** was fit with recurrence as an outcome and age at baseline, sex, and disease phenotype as baseline covariates.
- A **joint survival model** was estimated by maximum likelihood using the JM package [1], using Cox and linear mixed effects models for the event and longitudinal sub-models, respectively

Results

- The joint survival model estimated reasonable values of baseline covariate effects and longitudinal association on disease recurrence for the complete dataset (N=500)
- **Event sub-model estimates were unstable with decreasing sample size**, especially for N<150, even though the simulated dataset reflects robust association between recurrence and time-varying LDL (R2 = 0.7) [5]
- Additionally, the model uncertainty increased with the decreasing sample size, although, for the LDL association parameter, the uncertainty remained surprisingly modest even at small sample sizes

Figure 1. Quantile–Quantile plots [A]

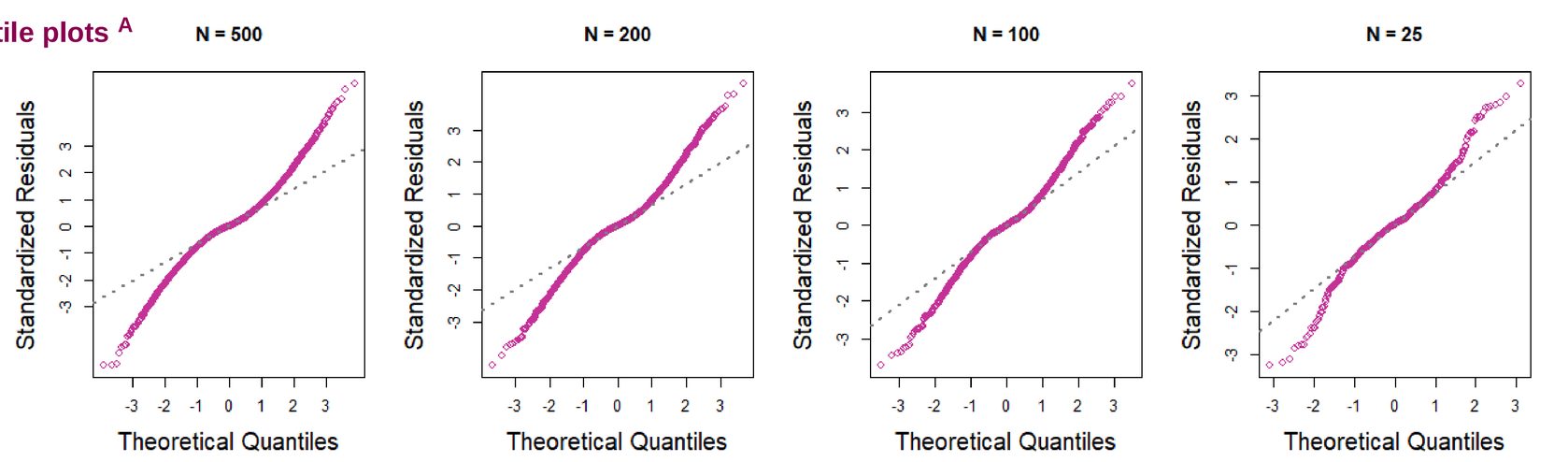
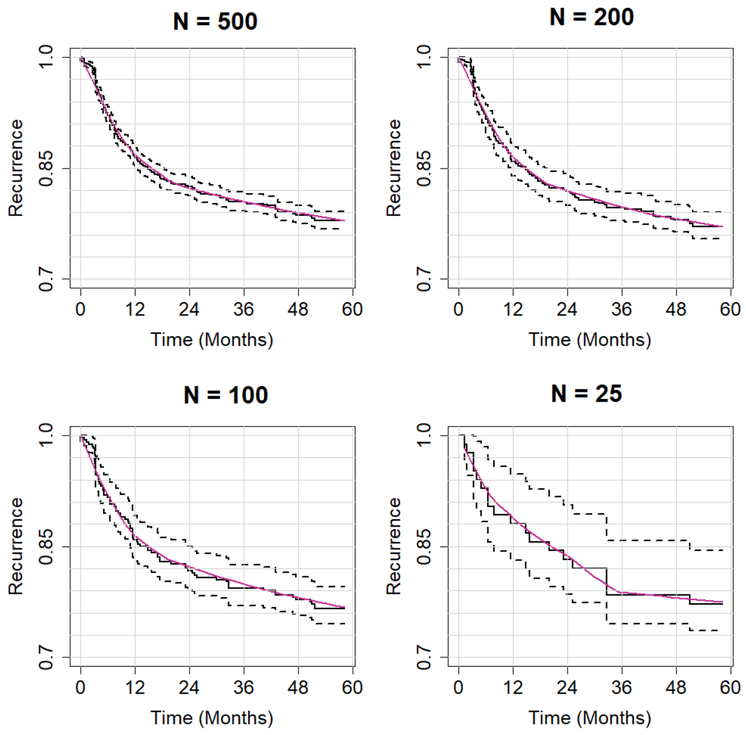


Figure 2. Marginal Survival



Estimated marginal survival curve with 95% CI (Black solid line with black dotted line) with the true Kaplan-Meier curve in purple. As the sample size decreases the model becomes less certainty, as shown by the area between the dotted lines increasing.

Table 1. Estimates for selected parameters (log hazard ratios [HR]) of the event sub-model in the joint survival model, with varying sample size N [B]

	N = 500	N = 200	N = 150	N = 100	N = 75	N = 50	N = 25
	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value	HR (95% CI) P-value
Joint model	0.037 (0.036 - 0.038) <0.001*	0.031 (0.03 - 0.033) <0.001*	0.019 (0.017 - 0.021) <0.001*	-0.027 (-0.03 - -0.025) <0.001*	-0.034 (-0.038 - -0.031) <0.001*	0.037 (0.034 - 0.04) <0.001*	0.048 (0.044 - 0.052) <0.001*
Non-Cushing's phenotype	-0.819 (-1.055 - -0.582) <0.001*	-0.502 (-0.859 - -0.145) 0.006*	-0.5 (-0.897 - -0.103) 0.013*	-0.395 (-0.856 - 0.065) 0.092	-0.018 (-0.663 - 0.628) 0.957	0.154 (-0.42 - 0.728) 0.598	-0.272 (-1.16 - 0.616) 0.548

[A] These plots assess the model fit through comparing the quantiles of the model's standard residuals to the theoretical quantiles of a standard normal distribution. The dotted line represents perfect normality, while the dots represent residual values. Dots which fit closely to the diagonal line indicate that the residuals follow a normal distribution and support the model's assumption

[B] The table shows the log hazard ratios from the fit of the joint model as well as non-Cushing's phenotype status in the Cox Regression. A significant value for the joint model indications that the time-varying covariate (LDL cholesterol) was associated with recurrence.

Conclusions

- Estimates of baseline and longitudinal effects on event times from joint survival models were highly unstable at small sample sizes
  - The model instability indicates that the underlying likelihood function could be improved by employing an informative prior distribution in a Bayesian framework to yield a smooth posterior distribution. Future studies examine joint modeling in rare diseases using this framework.
- **Estimation of simple joint models may still be feasible for modest sample sizes (e.g., N=100-200) when associations are strong**.
  - Researchers must consider increased variability, event scarcity, risk of overfitting, and power and sensitivity when deciding to implement joint models

© 2024 Parexel International (MA) Corporation

REFERENCES

[1] Rizopoulos, Dimitris. "Dynamic predictions and prospective accuracy in joint models for longitudinal and time-to-event data." Biometrics 67.3 (2011): 819-829.

[2] Nishioka, Hiroshi, and Shozo Yamada. "Cushing's disease." Journal of clinical medicine 8.11 (2019): 1951.

[3] Findling, James W., and Hershel Raff. "Recognition of nonneoplastic hypercortisolism in the evaluation of patients with cushing syndrome." Journal of the Endocrine Society 7.8 (2023): bvad087.

[4] Bou Khalil, Roula, et al. "Sequential hormonal changes in 21 patients with recurrent Cushing's disease after successful pituitary surgery." European Journal of Endocrinology 165.5 (2011): 729-737.Variables

[5] Colao, Annamaria, et al. "A 12-month phase 3 study of pasireotide in Cushing's disease." New England Journal of Medicine 366.10 (2012): 914-924.

[6] Qiao, Nidan, Brooke Swearingen, and Nicholas A. Tritos. "Cushing's disease in older patients: presentation and outcome." Clinical endocrinology 89.4 (2018): 444-453.

[7] Zhang, Peng, et al. "Trends in LDL-C and non-HDL-C levels with age." Aging and disease 11.5 (2020): 1046.

www.parexel.com