A Comparison of statistical models for clustered survival data in multicenter clinical trials

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Introduction

Background

Conducting multinational or multicenter clinical trials is a popular method of drug efficacy analysis these days. In many cases, the number of centers is large, but only a few patients are included in each center, and the ratio of treatment group to control group in a stratum is imbalanced. An appropriate model should be selected through statistical modeling when analyzing such data. Also, stratified analysis should be performed when many centers exist. When the functional form of baseline hazards is unknown for each center, Glidden (2004) showed that the marginal hazard ratio is biased in a Cox proportional hazards model. Thus, more complex methods are required to analyze such clustered data of patients. In this situation, a stratified cox model or frailty model can be considered.

Purpose

1. To check why estimates are highly biased in unstratified analysis when the stratified analysis is the correct procedure.
2. To show through simulation whether a stratified Cox model or a random effects model is more appropriate under various scenarios.

Method

• **Cox's Proportional Hazards Models**

$$h(t|Z_j) = h_0(t)\exp(\beta Z_j)$$

The log partial likelihood function

$$LL(\beta) = \sum_{\ell=1}^{D}\sum_{k=1}^{p}\beta_k Z_{(\ell)k} - \sum_{\ell=1}^{D}\ln\left[\sum_{j\in R(t_\ell)}\exp\left(\sum_{k=1}^{p}\beta_k Z_{jk}\right)\right]$$

• **Stratified Proportional Hazards Models**

$$h_{ij}(t|Z_{ij}(t)) = h_{0i}(t)\exp\left(\beta^* Z_{ij}(t)\right)$$

The log partial likelihood function

$$\mathrm{LL}(\beta) = \sum_{i=1}^{s}\sum_{\ell=1}^{D}\sum_{k=1}^{p}\beta_k Z_{(i\ell)k} - \sum_{i=1}^{s}\sum_{\ell=1}^{D}\log\left[\sum_{j\in R(t_{i\ell})}\exp\left(\sum_{k=1}^{p}\beta_k Z_{ijk}\right)\right]$$

• **Gamma Frailty Model**

$$h_{ij}(t|Z_{ij}) = h_0(t)\exp(\beta^{**}Z_{ij})\,u_i, u_i \sim Gamma\left(\frac{1}{\theta}, \theta\right)$$

The log likelihood function

$$LL_{FULL} = LL_1(\theta) + LL_2(\beta, H_0)$$

$$LL_1(\theta) = -G\left[\frac{1}{\theta}\log(\theta) + \log\Gamma\left(\frac{1}{\theta}\right)\right] + \sum_{=1}^{G}\left[\frac{1}{\theta} + D_i - 1\right]\log u_i - \frac{u_i}{\theta}$$

$$LL_2(\beta, H_0) = \sum_{i=1}^{s}\sum_{j=1}^{n_i}\delta_{ij}\left[\beta' Z_{ij} + \log h_0(T_{ij})\right] - u_i H_0(T_{ij})\exp(\beta' Z_{ij})$$

** i : stratum, j : individual

Struthers & Kalbfleisch (1986) showed that $\frac{1}{n}l(\beta,\infty)$ converges in probability to the concave function $H(\beta)$ which has a unique maximum at $\beta = \beta^*$. In the case of model misspecified,
True model : $Y_i(t)\lambda_1(t)\exp(\alpha_1 Z_{i1} + \alpha_2 Z_{i2})$, Assumed model : $Y_i(t)\lambda_0(t)\exp(\beta Z_{1i})$

For the case $\alpha_1 > 0$ or $\alpha_1 < 0$,

$$h(\beta) = \int_0^\infty E\{Z_1\lambda(t;Z)G(t;Z)\}dt - \int_0^\infty \frac{E\{Z_1 e^{\beta Z_1 + \alpha_2 Z_2}G(t;\ Z)\}}{E\{e^{\beta Z_1 + \alpha_2 Z_2}G(t;Z)\}}E\{\lambda(t;Z)G(t;Z)\}dt\,,$$

where $G(t;Z) = C(t;Z_1)\exp\left\{-e^{\alpha^T Z}\Lambda_1(t)\right\}$ and $\lambda(t;Z) = \exp(\alpha^T Z)\,\lambda_1(t)$.

Since $h(\alpha_1) = 0$ and $\frac{dh(\beta)}{d\beta} < 0$ for all β, therefore $h(\beta)$ is a monotone decreasing function of β which crosses the x axis at $\beta = \alpha_1$. It can be shown that $h(\beta^*) > 0$ and therefore $\beta^* < \alpha_1$.

Simulation study

Data generation

- Only single covariate Z ($Z = 1$: Treatment group, $Z = 0$: Control group).
- Two type of survival time

① Based on Gamma frailty, $h_0(\mathrm{t}) \sim \mathrm{Weibull}(\lambda = 1, \alpha = 2)$, $u_i \sim \Gamma\left(2, \frac{1}{2}\right)$

$$T^* = \left[-\frac{\log(s)}{u_i\lambda\exp(\beta Z_{ij})}\right]^{\frac{1}{\alpha}}$$

② Based on stratified Cox model, $h_{0i}(\mathrm{t}) \sim \mathrm{Weibull}(\lambda = 1, \alpha_i = 0.5 \sim 2)$

$$T^{**} = \left[-\frac{\log(s)}{\lambda\exp(\beta Z_{ij})}\right]^{\frac{1}{\alpha_i}}$$

Where s is a random variable with $s \sim unif(0,1)$

- Balance case : the ratio of treatment group to control group in a stratum is 1:1.
- Imbalance case (depend on strata)
  - $k/2$: maintain the 1:1 ratio
  - $k/4$: 80% of patients are assigned to treatment groups
  - $k/4$: 80% of patients are assigned to control groups

Simulation setting

Parameters	Values
Censoring rates	25%, 75%
True beta (β)	0, -0.3, -0.5
The number of stratum (k)	4, 8, 20, 100
Total observation (N)	400, 2000

For each scenario, we repeat 1,000 independent simulation runs.

The performance measures
Mean estimate (Estimate), mean bias (Bias), mean squared error (MSE; the mean of the squared bias), empirical standard deviation of the parameter estimate (SD), mean estimated standard error (SE). The empirical power (or type I error when β=0) tested by Wald statistics of the above was also compared. The mean is based on 1,000 replicates.

Result

We presented the results of $\beta = -0.5$, censoring rates $= 25\%$ only (other results are similar). In all scenarios, bias existed when the unadjusted Cox model is performed. In contrast, stratified Cox model does not generate bias, no matter which model is correct model. In the case of the frailty model, we found that there was no bias when the data was generated based on the gamma frailty model, and that bias existed when the data was generated on the stratified Cox model basis. It was also confirmed that the bias would large if a small number of samples were assigned in the stratum. However, the stratified Cox analysis showed that if the balance between treatment group and control group within the stratum was broken, the standard error would be larger than other models. In other words, stratified Cox model was able to confirm that it was well-fitting without significant impact on the form of baseline. In comparison, the frailty model was able to identify that the bias would occur if the multiply form on the baseline did not satisfied.

Figure1. The estimates of regression coefficients in simulation setting1

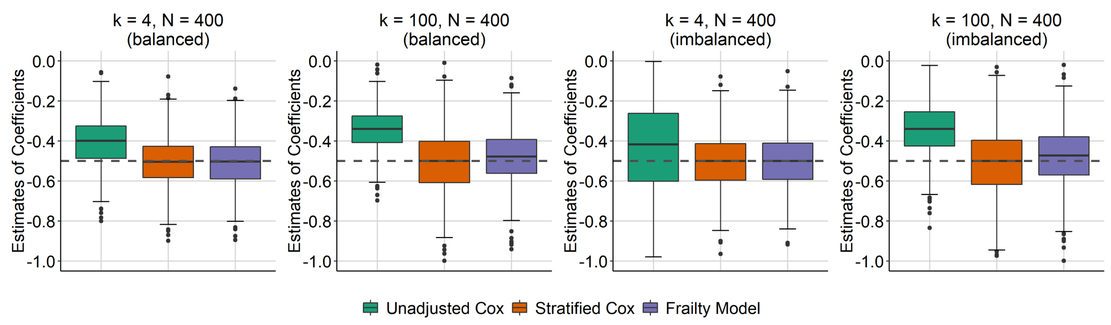

Figure2. The estimates of regression coefficients in simulation setting2

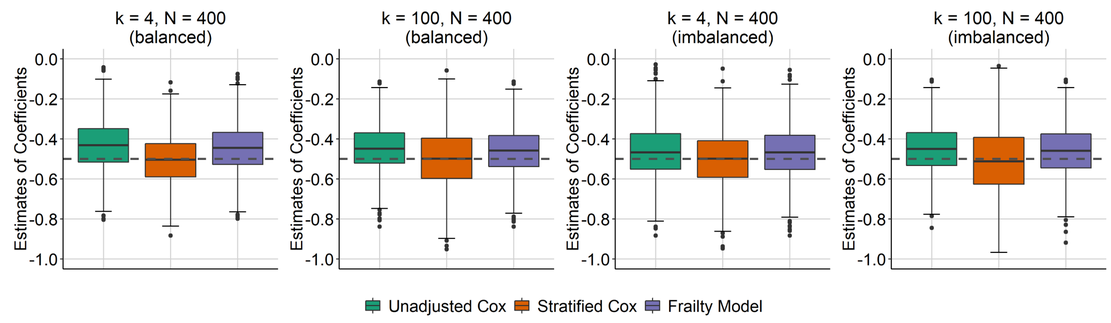

Figure3. The estimates of Standard Error in simulation setting1

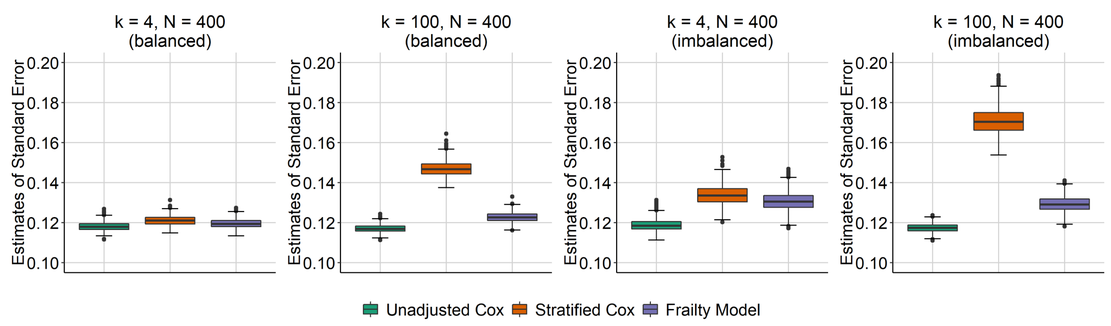

Figure4. The estimates of Standard Error in simulation setting2

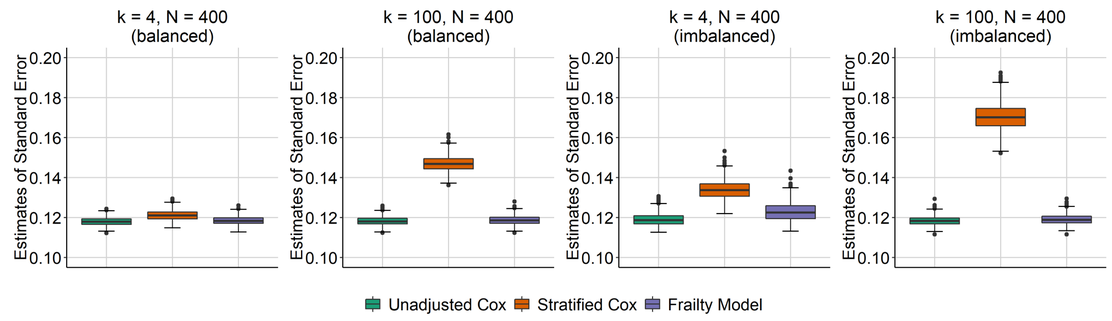

Table1. Power of the simulation setting1

N	k	Balanced			Imbalanced		
		Unadjusted Cox	Stratified Cox	Frailty Model	Unadjusted Cox	Stratified Cox	Frailty Model
400	4	0.940	0.991	0.991	0.746	0.961	0.969
	8	0.907	0.987	0.990	0.735	0.960	0.965
	20	0.898	0.985	0.989	0.784	0.946	0.960
	100	0.872	0.927	0.968	0.810	0.853	0.941

Table2. Power of the simulation setting2

N	k	Balanced			Imbalanced		
		Unadjusted Cox	Stratified Cox	Frailty Model	Unadjusted Cox	Stratified Cox	Frailty Model
400	4	0.962	0.987	0.973	0.947	0.967	0.961
	8	0.973	0.990	0.980	0.958	0.969	0.960
	20	0.970	0.985	0.973	0.962	0.951	0.967
	100	0.967	0.936	0.970	0.969	0.855	0.971

Conclusion & Discussion

- In all scenarios, bias existed when the unadjusted Cox model is performed.
- When conducting multinational or multicenter clinical trials, stratified Cox model or frailty model should be used instead of using unadjusted Cox model.
- Especially, model selection is important if many centers exists and the balance of the treatment group in the stratum is not satisfied.