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Impact of model misspecification in survival models with frailties

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Motivation

Survival data is commonly analysed by using parametric survival models or the Cox model. Nevertheless:

1. Subjects may be exposed to different baseline risk levels
2. Subjects may be clustered (clinical trials, geographical clusters, paired organs, twin studies, ...)
3. Subjects may experience repeated events (infections, cancer recurrence, ...)

An elegant and increasingly popular approach: including in the model a multiplicative random effect that allows accounting for this unobserved heterogeneity (i.e. a *frailty*).
Further details in Hougaard (2000) and Wienke (2010).

Survival models with shared frailty

For the j^{th} individual in the i^{th} cluster:

$$h_{ij}(t) = h_0(t)\exp(X_{ij}\beta)u_i \tag{1}$$

$$h_{ij}(t) = h_0(t)\exp(X_{ij}\beta + w_i) \tag{2}$$

In a parametric world, we need to choose:

1. baseline hazard $h_0(\cdot)$: exponential, Weibull, Gompertz, flexible spline-based, ...
2. distribution of the frailty u_i (or w_i): Gamma, log-Normal, positive stable, ...

Misspecification

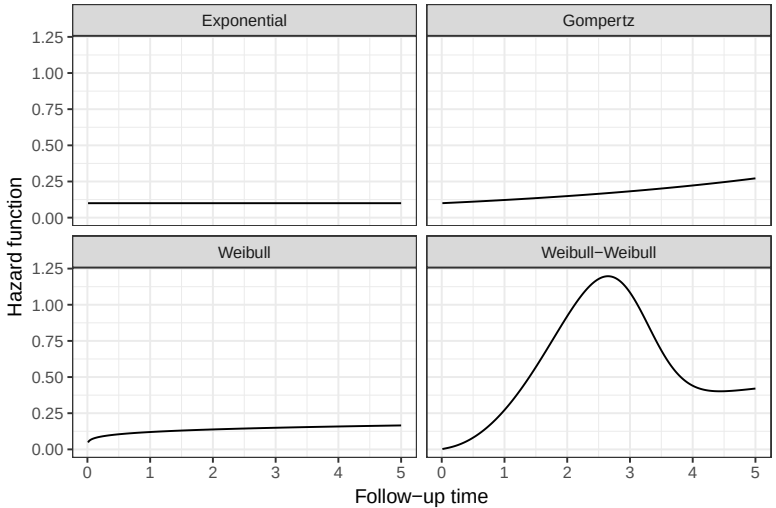
What we know:

1. The choice of the baseline hazard is often data-driven, using information criteria such as AIC and BIC
2. Relative risk estimates are insensitive to the correct specification of the baseline hazard (Rutherford, 2015)
3. Flexible parametric models (Royston, 2002) are robust to the choice of degrees of freedom for the spline function, assuming a sufficient number of degrees of freedom it is used (Rutherford, 2015)
4. The choice of frailty distribution has little impact on the estimation and testing of regression coefficients (Pickles, 1995)

A simulation study (1)

- Aim: assessing the impact of misspecifying the baseline hazard or the frailty distribution in a wide range of clinically and biologically plausible scenarios
- Data-generating mechanisms:
  - exponential baseline hazard
  - Weibull baseline hazard
  - Gompertz baseline hazard
  - mixture Weibull baseline hazard

Data-generating baseline hazard functions



A simulation study (2)

- Data-generating mechanisms:
  - Gamma and log-Normal frailty distribution
  - number of clusters (15, 50) and number of individuals per cluster (30, 100)
  - frailty variance (0.25, 0.50, 1.00)
  - log-treatment effect of -0.50
- Methods:
  - exponential, Weibull, Gompertz parametric survival models
  - Royston-Parmar model with 3 to 9 degrees of freedom
  - Royston-Parmar model using penalised likelihood
  - each model with Gamma or log-Normal frailty

A simulation study (3)

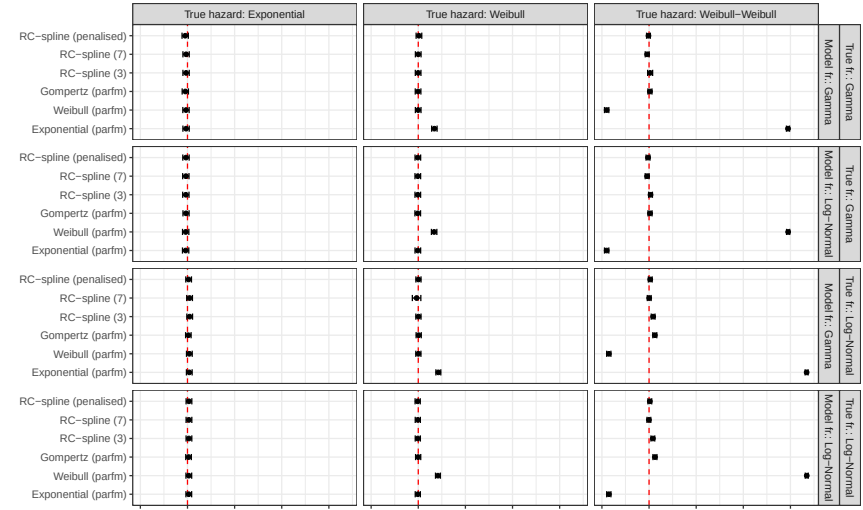
- Estimands:
  - log-treatment effect
  - frailty variance
- Performance measures:
  - bias and percentage bias
  - coverage

Results

Fully factorial design: 96 simulated scenarios. We present:

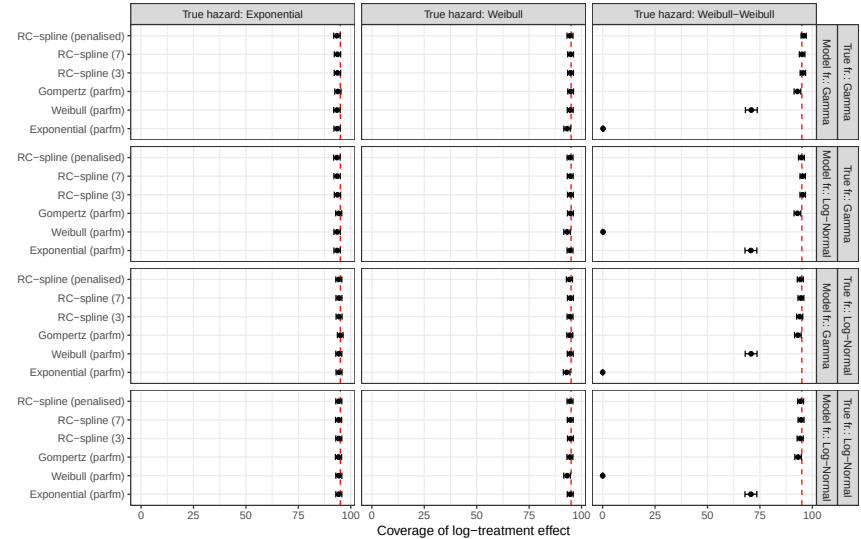
- 50 clusters of 100 individuals each, frailty variance of 0.50
- 50 clusters of 30 individuals each, mixture Weibull baseline hazard

Results: (1) bias of treatment effect

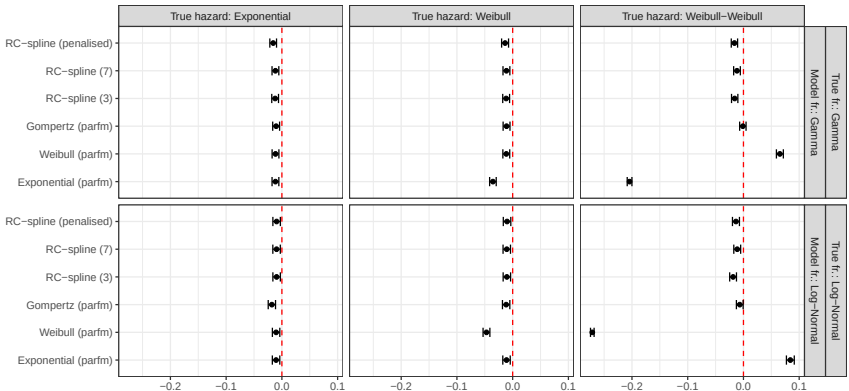


100 individuals per cluster, 50 clusters, frailty variance of 0.50, true log−treatment effect of −0.50

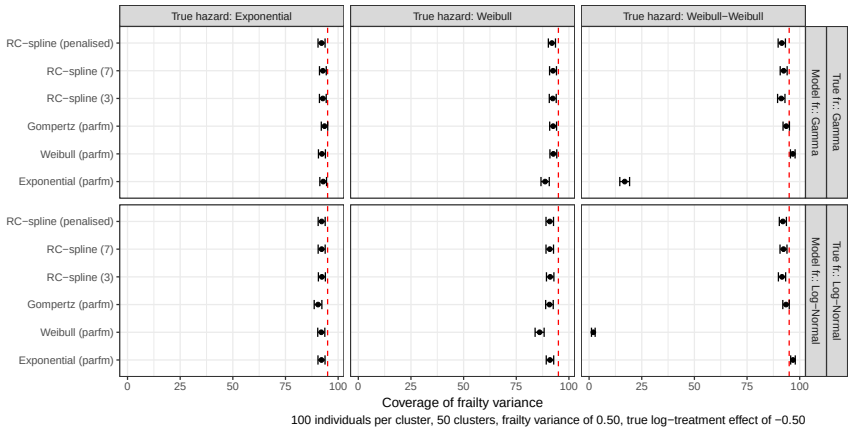
Results: (1) coverage of treatment effect



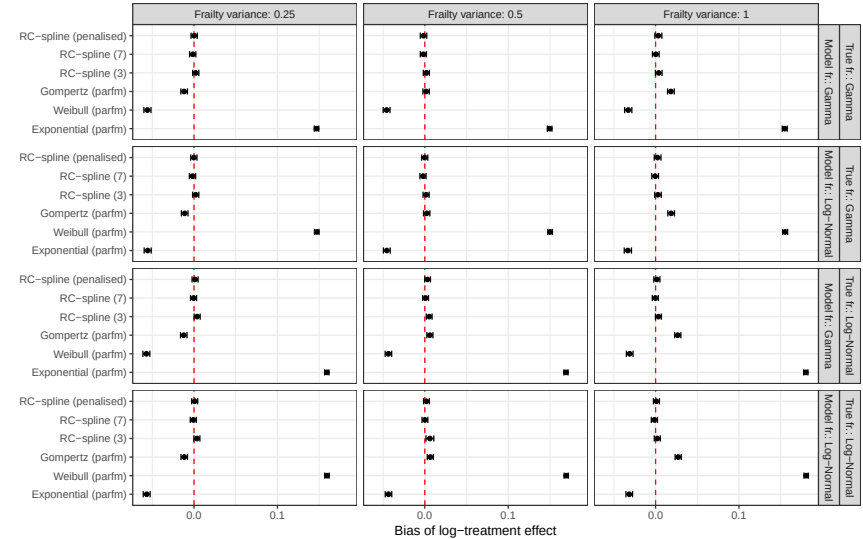
Results: (1) bias of frailty variance



Results: (1) coverage of frailty variance

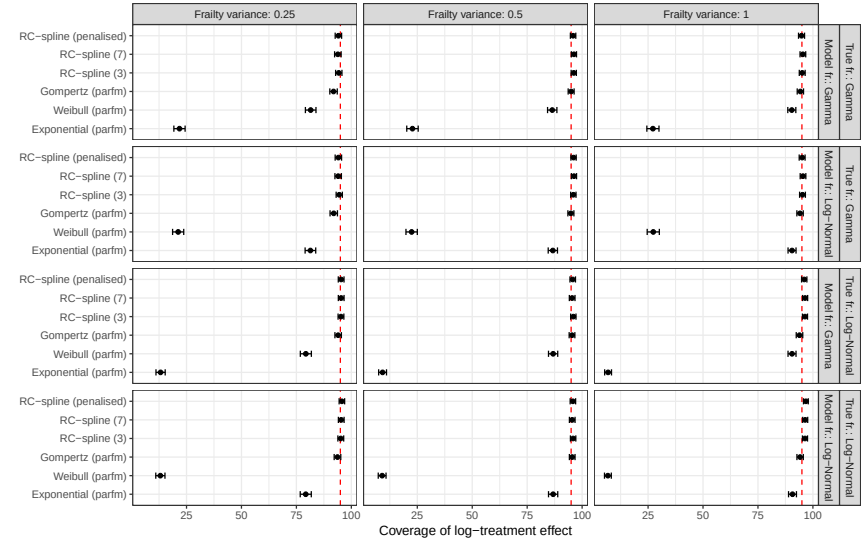


Results: (2) bias of treatment effect

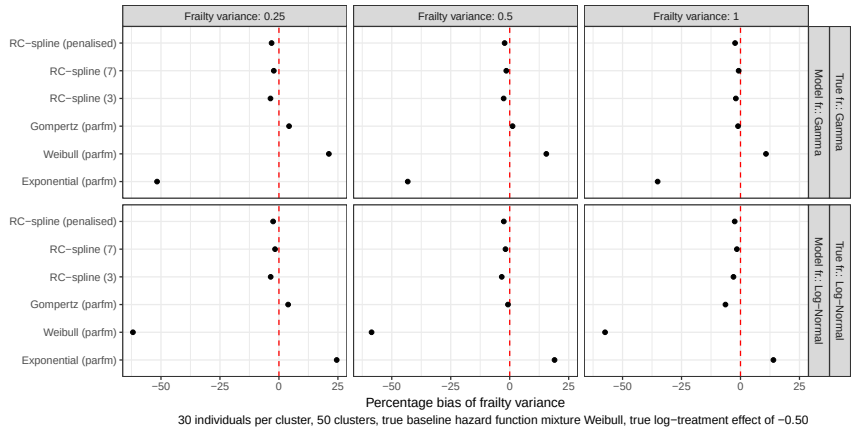


30 individuals per cluster, 50 clusters, true baseline hazard function mixture Weibull, true log−treatment effect of −0.50

Results: (2) coverage of treatment effect

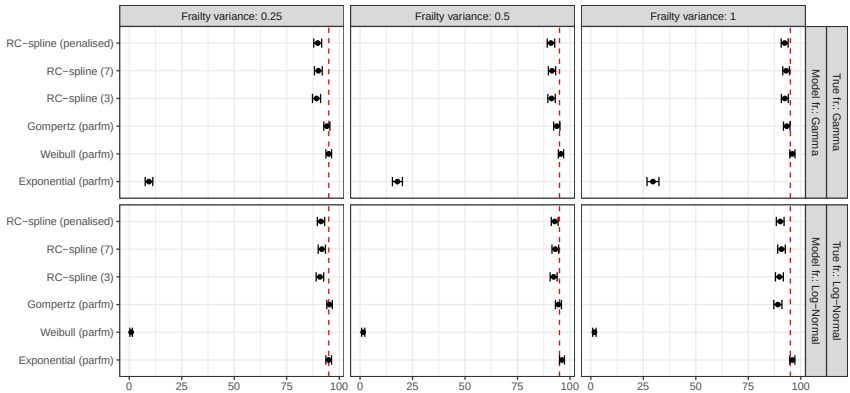


Results: (2) percentage bias of frailty variance



30 individuals per cluster, 50 clusters, true baseline hazard function mixture Weibull, true log−treatment effect of −0.50

Results: (2) coverage of frailty variance



30 individuals per cluster, 50 clusters, true baseline hazard function mixture Weibull, true log−treatment effect of −0.50

Conclusions

- Misspecification of the baseline hazard can yield markedly biased regression coefficients, irrespectively of the frailty distribution
- Misspecification of the baseline hazard can also yield biased estimates of the frailty variance, even when the frailty distribution is well specified
- Misspecification of the frailty distribution has a negligible impact on bias of regression coefficients
- Flexible parametric models tend to be quite robust to model misspecification, using both full and penalised likelihood estimation procedures
- Further simulations will provide greater insight on the topic, especially on absolute risk predictions

Next steps

1. Adding a simulation scenario with 1,000 clusters of 2 observations each: twin data
2. Adding marginal survival as estimand: ease of obtaining absolute risk predictions is one of the advantages of parametric models
3. Adding further comparisons with available software: shared frailty models with M-splines on the hazard scale estimated using penalised likelihood (R package `frailtypack`), ...

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