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Competing-Risks Survival Analysis
Research Article

Parametric model for correlated survival data in the presence of competing risks and interval censoring

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Abstract

Interval censoring in survival analysis occurs when the event time is known only to lie within a specific time window. In addition, some studies involve multiple mutually exclusive types of events, commonly referred to as competing risks. This article proposes a parametric modeling approach for the cumulative incidence function in the presence of competing risks, interval censoring, and clustered observations. The proposed methodology extends existing parametric models by incorporating within-cluster dependence through a generalized estimating equations framework with an independence working correlation structure. The performance of the method is evaluated through simulation studies considering small-sample settings. The results indicate mixed but generally satisfactory estimation properties under the scenarios examined. Lastly, the proposed approach is illustrated using a real dataset concerning dental trauma. The methodology provides a practical framework for analyzing correlated interval-censored competing-risks data.

Keywords: GEE · Incidence function · Sandwich estimator · Weibull model · working correlation matrix

Mathematics Subject Classification: Primary 62N02 · Secondary 62N01

1. Introduction

Traumatic dental injuries (TDIs) are unexpected and acute events caused by an abrupt impact, primarily to the anterior teeth. They can be considered a neglected public health concern because of their high prevalence worldwide, their complex, prolonged, and expensive treatment, and their great impact on the quality of life of patients and their families [1]. TDI can simultaneously affect the mineralized tissues of the tooth, its supporting structures, and the dental pulp, with a multitude of possible trauma scenarios and complex healing patterns. The motivating data for this article originated from a longitudinal study conducted at the dental trauma clinic at the Federal University of Minas Gerais, Brazil. That study aimed to evaluate pulp prognosis as well as its prognostic factors in permanent luxated teeth.

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Pulp response after an acute TDI depends on the competition between the ingrowth of a neurovascular supply into the traumatized pulp tissue and bacterial invasion. The final pulp outcome can be pulp death (necrosis) or revascularization with the maintenance of pulp vitality, eventually followed by pulp canal obliteration (PCO). There are intermediate processes in pulpal response. Conclusive diagnosis of the pulp status can only be achieved in the long term. Therefore, survival analysis is used in clinical dental studies to account for the different probabilities of the event by considering variations in the observation periods [2]. In this study, there are three mutually exclusive possible events: maintenance of vitality, necrosis, and PCO. As it was not possible to specify an exact date of occurrence for the event, a time window between the follow-up appointments of the patient gave rise to interval-censored observations. Thus, as the same patient may have more than one traumatized tooth, characterized as a cluster, the outcomes were measured for each one.

The first issue in the present dataset is the competing risk aspect of observed outcomes. The lack of differentiation between event types might generate biased estimators related to the covariate effects and lead to inaccurate interpretations of results. Several methods have been proposed for analyzing competing risk data. Early work primarily focused on estimating and modeling cause-specific risk or the instantaneous risk of an event [3]. To study covariate effects on the cumulative probability of a particular cause, with independent individuals, in [4], a proportional sub-distribution risk model was proposed. It has a direct correspondence with the cumulative incidence function (CIF). An additive risk model was explored in [5]. The second aspect to be considered is that the timing of the event was not accurately observed. However, it was known to occur within a time window, that is, between two clinical visits, configuring interval-censored observations. Interval-censored competing-risks data can arise frequently in many applications. A parametric model for the CIF was proposed [6] for right-censored competing risk data using Weibull and Gompertz distributions. A parametric regression model was presented in [7] using the Gompertz distribution in the same scenario. In [8], the models presented in [6, 7] were extended to the case of competing risks with interval-censored data.

Lastly, competing-risks data cannot be considered independent. Hence, appropriate methods are needed to explain the correlation among subjects within the same cluster. The unknown dependence structure, within the cluster, requires appropriate regression methods, which consider correlations in a robust way to allow valid inference for the effects of the covariates on incidence function of the event of interest. Conditional and marginal models represent two alternative strategies for modeling the data of competing risks in clusters. Conditional models specify random effects to measure correlations between failure observations and have a cluster-specific interpretation of the fixed coefficients [9]. In this approach, frailty models have gained great prominence [10, 11]. Although such models are flexible, insofar as they explicitly model heterogeneity among clusters, valid inferences for the fixed-effects parameters necessarily depend on the correct specification of the frailty distribution. However, the marginal model specifies the impact of covariates across the entire population of clusters, without the need to specify unobserved correlation structure [12]. This model is computationally less intensive and, especially in the context of our application, has a population-level interpretation. In the competing-risks setting, a marginal subdistribution model and an estimation strategy assuming an independent working correlation structure for right-censored data were proposed in [13].

A sandwich variance estimator accommodates the dependence within the cluster. In [14], a sandwich variance estimator for observations in interval-censored clusters was developed. They used the model with an independence working correlation matrix in a survival analysis, that is, without competing risks. With this estimator, inferences to the marginal regression models are generally robust to assumptions of intra-cluster correlations. Another work on multi-state survival analysis with complex censoring is presented in [15].

To the best of our knowledge, statistical methodologies that simultaneously consider the structure of competing risks, clusters, and interval censoring, have not been investigated in the existing literature. Thus, we present a parametric model for correlated data in the presence of competing risks and interval censoring. The variance of the parameter estimates is corrected for clustering using a sandwich estimate.

The remaining article is organized as follows. In Section 2, we present the model for interval-censored competing risks data proposed in [8]. Section 3 proposes a methodology that extends the work introduced in [8] to include correlated data. In Section 4, the exponential and Weibull models are presented as specific cases. Simulation studies are conducted to evaluate small sample properties of the model in Section 5. In Section 6, we illustrate the proposed methodology using real dental trauma data. Section 7 states our conclusions.

2. Background and interval-censored competing-risks data

Suppose that T is an event time with K competing risks or cause of failure. Let $C \in \{1, \ldots, K\}$ indicate the cause of failure. The joint distribution of (T, C) is completely specified through either the CIF, $F_k(t)$, or by the cause-specific hazards, $\lambda_k(t)$, for $k = 1, \ldots, K$ [16]. The cumulative incidence function for event k is defined by

$$F_k(t) = P(T \leq t, C = k), \quad k = 1, \ldots, K.$$

This cumulative incidence function corresponds to the probability of occurrence of cause k of failure in the presence of the other competing causes. It is also known that

$$F_k(t) = \int_0^t \lambda_k(u) S(u) \mathrm{d}u, \tag{1}$$

where $S(t) = P(T > t) = \exp(-\int_0^t \sum_{l=1}^K \lambda_l(u) \mathrm{d}u)$ is the survival function of all causes and

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t, C = k | T > t)}{\Delta t}, \quad k = 1, \ldots, K,$$

is the cause-specific hazard function for risk k, $\lambda_k(t)$ determining the instantaneous failure rate for an event of type k at time t in the presence of the other competing risks. Thus, the CIF can be written as a function of specific cause functions for all K failure causes.

There are different ways to parametrically model the cumulative incidence function. The most used is the direct modeling of the cumulative incidence function, introduced in [6], and the approach is the so-called indirect parameterization method, in which separate parametric models are assumed for the specific cause risk functions [3].

Interval-censored data occur naturally in studies of diseases where the symptoms of interest are not directly observable, and laboratory or clinical examinations are required for detection. The exact time to the event of interest T is not directly observed but is known to fall within a time interval $[L, R]$, such that $0 < L \leq T \leq R < \infty$. In the scenario involving competing risks, the likelihood contribution for failure k in the interval is given by $P(T \in [l, r], C = k) = F_k(r) - F_k(l)$ [8].

Consider for individual i a random censoring interval $[L_i, R_i]$, where L_i denotes the left and R_i the right endpoint. We define $\Delta_{ik} = I(L_i \leq T \leq R_i, C = k)$, for $k = 1, \ldots, K$ and $i = 1, \ldots, n$, Thus, $\Delta_{ik} = 1$ indicates that individual i experienced cause k during the interval $[L_i, R_i]$. For right-censored observations, the failure type is considered unknown, that is, $R_i = \infty$, so defining $\Delta_{i0} = 1$.

As it is not possible to observe (T, C) directly, but $Y = (L, R, \Delta)$, the observations (L_i, R_i) are independent of (T, C) and the distribution of (L_i, R_i) does not contain the parameters that govern the law of (T, C). Let $Y_1, \ldots, Y_n$ be a random sample of n independently and identically distributed copies of Y. The log-likelihood function for interval-censored competing risk data can be written in terms of the cumulative incidence functions by means of [8]

$$\log(L(\Theta)) = \sum_{i=1}^{n} \log(l(Y_i; \Theta)), \tag{2}$$

where Θ is the vector consisting of total model parameters of $\Theta_1 \cup \cdots \cup \Theta_K$ and $l(Y_i; \Theta)$, which equals the expression stated as

$$l(Y_i; \Theta) = \prod_{k=1}^{K} (F_k(R_i; \Theta_k) - F_k(L_i; \Theta_k))^{\Delta_{ik}} \left(1 - \sum_{k=1}^{K} F_k(L_i; \Theta_k)\right)^{\Delta_{i0}}.$$

3. Methodological results: extended model for correlated data

The likelihood function defined in (2) was built considering a simple random sample of the population. In our context, in addition to the presence of competing risks and interval censoring, we have the existence of clusters. It causes dependence among individuals within the same cluster, but the independence among clusters remains valid. Thus, in the context of dependent data, we can use the approach of marginal models. Marginal models only consider covariate coefficients, considering the correlation within the cluster as a nuisance parameter. The estimation relies on the generalized estimating equations (GEE) approach proposed in [12].

To model dependent, right-censored, survival data including covariates, a GEE approach that allows statistical inference to be made for the marginal distributions while treating dependence among cluster members as perturbation parameters was derived in [17]. More specifically, the method specifies the marginal distributions independently of the association structure. In addition, it leaves unspecified the nature of the dependence among the survival times of the events of cluster members. The parameters of the marginal model are estimated using maximum likelihood (ML) under the assumption of independence. It was called the independence working correlation model in [17]. In the second step, the standard errors (SEs) of the estimators are established by using a correction through the sandwich variance.

Consider n clusters, where cluster i has m_i individuals, for $i = 1, \ldots, n$, so there are $\sum_{i=1}^{n} m_i = m$ subjects in the entire sample. Let T_{ij} be the failure time for individual j in cluster i, for $j = 1, \ldots, m_i$, so that it is only known that the event time T_{ij} belongs to an interval, say $[L_{ij}, R_{ij}]$. Define $\Delta_{ijk} = I(L_{ij} < T_{ij} < R_{ij}, C_{ij} = k)$, for $k = 1, \ldots, K$, so that if $\Delta_{ijk} = 1$ indicates individual j in cluster i experienced cause k during the interval $[L_{ij}, R_{ij}]$. For the case of right-censored observations, the failure type is considered unknown, thus defining $\Delta_{ij0} = 1$. Assuming that the failure times T_{ij} are independent and adopting the independence working model, the cluster contribution to the independent-working likelihood function becomes equal to

$$l(Y_i; \Theta) = \prod_{j=1}^{m_i} \prod_{k=1}^{K} (F_k(R_{ij}; \Theta_k) - F_k(L_{ij}; \Theta_k))^{\Delta_{ijk}} \left(1 - \sum_{k=1}^{K} F_k(L_{ij}; \Theta_k)\right)^{\Delta_{ij0}}. \tag{3}$$

Under the usual regularity conditions and assuming independent clusters, the estimating function can be written as the sum of the cluster-specific contributions

$$U(\Theta) = \sum_{i=1}^{n} U_i(\Theta),$$

where $U_i(\Theta)$ denotes the contribution from cluster i. Define

$$A(\Theta) = \sum_{i=1}^{n} A_i(\Theta), \quad A_i(\Theta) = -\frac{\partial U_i(\Theta)}{\partial \Theta^\top}, \quad B(\Theta) = \sum_{i=1}^{n} U_i(\Theta) U_i(\Theta)^\top.$$

Then, $\widehat{\Theta}$ is asymptotically normally distributed, with covariance matrix consistently estimated by the sandwich covariance estimator given by

$$\widehat{\mathrm{Var}}(\widehat{\Theta}) = A(\widehat{\Theta})^{-1} B(\widehat{\Theta}) A(\widehat{\Theta})^{-1}. \tag{4}$$

In this expression, $A(\widehat{\Theta})$ is the observed negative derivative of the cluster-level estimating functions and $B(\widehat{\Theta})$ is an empirical matrix associated with the cluster score contributions. Expressions for the first and second derivatives of the function presented in (3) are presented in Appendix A.

Therefore, in parametric modeling, we specify the models for the marginal distributions but leave the nature of the dependency between cluster members completely unspecified. The parameters in the marginal models are then estimated using the likelihood function associated with the one that assumes the independence of the members (even if this assumption is incorrect). In the present case, it is the equation given in (3), which is the product of the marginal likelihoods of each individual in the dataset. The model-based covariance matrix of $\widehat{\Theta}$ is estimated by the negative inverse Hessian, whereas the robust covariance matrix is estimated by the expression formulated in (4). The corresponding model-based and robust standard errors are obtained as the square roots of the diagonal elements of the respective estimated covariance matrices.

In this work, we model the cumulative incidence function using the indirect approach, for which the exponential and Weibull models are considered for the marginal distributions. Without loss of generality, consider only two failure causes, for $k = 1, 2$. The extension for K failure causes is immediate.

4. Exponential and Weibull models

Considering the exponential model for the cause specific hazard function, we have $S_k(t; \alpha_k) = \exp(-\alpha_k t)$ and $\lambda_k(t; \alpha_k) = \alpha_k$, for $k = 1, 2$. The parameterization of the cumulative incidence function stated in (1) reduces to

$$F_1(t; \Theta) = \int_0^t \alpha_1 \prod_{k=1}^{2} \exp(-\alpha_k u) \mathrm{d}u = \frac{\alpha_1}{\alpha_1 + \alpha_2} \left(1 - \exp\left(-\sum_{k=1}^{2} \alpha_k t\right)\right),$$

$$F_2(t; \Theta) = \int_0^t \alpha_2 \prod_{k=1}^{2} \exp(-\alpha_k u) \mathrm{d}u = \frac{\alpha_2}{\alpha_1 + \alpha_2} \left(1 - \exp\left(-\sum_{k=1}^{2} \alpha_k t\right)\right),$$

where $\Theta = (\alpha_1, \alpha_2)$.

In the estimation of the parameters of interest, we use the log-likelihood function defined in (3) assuming both within and between cluster independence. The log-likelihood function for the exponential model has the form given by

$$
\begin{aligned}
\log(L(\Theta)) &= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(F_1(R_{ij};\Theta)-F_1(L_{ij};\Theta)\right)+\Delta_{ij2}\log\left(F_2(R_{ij};\Theta)-F_2(L_{ij};\Theta)\right)\right.\\
&\quad \left. +\,\Delta_{ij0}\log\left(1-\sum_{k=1}^{2}F_k(L_{ij};\Theta)\right)\right)\\
&= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\left(\exp\left(-\sum_{k=1}^{2}\alpha_k L_{ij}\right)-\exp\left(-\sum_{k=1}^{2}\alpha_k R_{ij}\right)\right)\right)\right.\\
&\quad +\Delta_{ij2}\log\left(\frac{\alpha_2}{\alpha_1+\alpha_2}\left(\exp\left(-\sum_{k=1}^{2}\alpha_k L_{ij}\right)-\exp\left(-\sum_{k=1}^{2}\alpha_k R_{ij}\right)\right)\right)\\
&\quad \left. +\,\Delta_{ij0}\log\left(1-\sum_{k=1}^{2}F_k(L_{ij};\Theta)\right)\right). \qquad (5)
\end{aligned}
$$

To maximize $\log(L(\Theta))$, one can use, for example, the Newton-Raphson algorithm. For this, we need the score function obtained by calculating the derivative of $\log(L(\Theta))$ with respect to the parameter vector Θ. The expressions for first and second derivatives of the function formulated in (5) are presented in Appendix A.

There is also the option of modeling the cumulative incidence function using a Weibull distribution for the cause-specific hazard rate given by $S_k(t;\alpha_k,\tau_k) = \exp(-(\alpha_k t)^{\tau_k})$ and $\lambda_k(t;\alpha_k,\tau_k) = \tau_k\alpha_k^{\tau_k}t^{\tau_k-1}$, for $k=1,2$, where $\alpha_k > 0$ is the rate (inverse-scale) parameter and $\tau_k > 0$ is the shape parameter. In this case, parameterized version of the cumulative incidence function established in (1), with $k=1,2$, has the form $F_1(t;\Theta) = \int_0^t \exp\left(-(\alpha_1 u)^{\tau_1}-(\alpha_2 u)^{\tau_2}\right)\tau_1\alpha_1^{\tau_1}u^{\tau_1-1}\mathrm{d}u$ and $F_2(t;\Theta) = \int_0^t \exp\left(-(\alpha_1 u)^{\tau_1}-(\alpha_2 u)^{\tau_2}\right)\tau_2\alpha_2^{\tau_2}u^{\tau_2-1}\mathrm{d}u$, where $\Theta=(\alpha_1,\tau_1,\alpha_2,\tau_2)$. The integrals defining F_1 and F_2 do not have closed-form solutions in the general case such that $\tau_1\neq\tau_2$, and therefore require numerical integration. Again, in the estimation of the parameters of interest, we propose to use the log-likelihood function stated in (3). Assuming both within and between cluster independence, the log-likelihood function for the Weibull model has the form expressed as

$$
\begin{aligned}
\log(L(\Theta)) &= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(F_1(R_{ij};\Theta)-F_1(L_{ij};\Theta)\right)\right.\\
&\quad \left. +\,\Delta_{ij2}\log\left(F_2(R_{ij};\Theta)-F_2(L_{ij};\Theta)\right)+\Delta_{ij0}\log\left(1-\sum_{k=1}^{2}F_k(L_{ij};\Theta)\right)\right)\\
&= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(\int_0^{R_{ij}}\exp\left(-(\alpha_1 u)^{\tau_1}-(\alpha_2 u)^{\tau_2}\right)\tau_1\alpha_1^{\tau_1}u^{\tau_1-1}\,\mathrm{d}u\right.\right.\\
&\qquad \left. -\int_0^{L_{ij}}\exp\left(-(\alpha_1 u)^{\tau_1}-(\alpha_2 u)^{\tau_2}\right)\tau_1\alpha_1^{\tau_1}u^{\tau_1-1}\,\mathrm{d}u\right)
\end{aligned}
$$

$$
\begin{aligned}
&+ \Delta_{ij2} \log\Bigg(\int_0^{R_{ij}} \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_2 \alpha_2^{\tau_2} u^{\tau_2 - 1}\, \mathrm{d}u \\
&\qquad\qquad - \int_0^{L_{ij}} \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_2 \alpha_2^{\tau_2} u^{\tau_2 - 1}\, \mathrm{d}u \Bigg) \\
&+ \Delta_{ij0} \log\left(1 - \sum_{k=1}^{2} F_k(L_{ij}; \Theta)\right)\Bigg). \qquad (6)
\end{aligned}
$$

Estimates of unknown parameters cannot be obtained in closed forms and a numerical method is required to compute them. One may use Newton-Raphson or Broyden–Fletcher–Goldfarb–Shanno (BFGS) methods or their variants to maximize the function stated in (6). Expressions for first and second derivatives of the function given in (6) are presented in Appendix A. To examine covariate effects on the response, it is necessary to include a regression structure. In survival analysis, the heterogeneity among the individuals is explained by covariates or explanatory variables. To build the regression model, we introduce covariate $\boldsymbol{x}$ assuming that the parameter α_k depends on the covariates through $\alpha_k = \exp(\vec{\beta}_k^\top \boldsymbol{x})$ in the log-likelihood function $\log(L(\Theta))$. Here, $\boldsymbol{x} = (X_1, \ldots, X_p)$ and $\vec{\beta}_k^\top = (\beta_{k1}, \ldots, \beta_{kp})$ are the vector of regression coefficients. All parameters are simultaneously included in log-likelihood function defined in (5) for the exponential model, and in (6) for the Weibull one. To obtain the ML estimates of unknown parameters, a system of score equations is derived. For the exponential model, the system of score equations is stated as $\partial \log(L(\Theta))/\partial \vec{\beta}_k = 0$ and, for the Weibull model, it is given by $\partial \log(L(\Theta))/\partial \vec{\beta}_k = 0$ and $\partial \log(L(\Theta))/\partial \tau_k = 0$. The score functions are subsequently set to zero and solved using an iterative procedure such as the Newton-Raphson algorithm to find the ML estimates.

5. Simulation study

A Monte Carlo study is conducted using the R language [18] to assess the finite sample performance of our methodology. The maximization of the log-likelihood function presented in (2) is conducted using the BFGS quasi-Newton nonlinear optimization algorithm implemented in the optim routine available in R. Different scenarios are considered. For all of them, there are $K = 2$ causes of failure, $n \in \{100, 500, 1000\}$ and $m_i = 4$, for $i = 1, \ldots, n$. The covariates are generated, X_1 from a Bernoulli (0.5) and X_2 from a standard normal distribution. The lifetimes and event labels are simulated according to the parameters $\Theta = (\beta_{11}, \beta_{12}, \beta_{21}, \beta_{22}) = (0.3, 0.3, 0.3, 0.3)$. For the exponential model, we have

$$\lambda_k(t; \boldsymbol{x}_{ij}) = \exp(\beta_{k1} X_{1ij} + \beta_{k2} X_{2ij}). \qquad (7)$$

For the Weibull model, we get

$$\lambda_k(t; \boldsymbol{x}_{ij}) = \tau_k t^{\tau_k - 1} (\exp(\beta_{k1} X_{1ij} + \beta_{k2} X_{2ij}))^{\tau_k}, \qquad (8)$$

where

$$\Theta = (\beta_{11}, \beta_{12}, \tau_1, \beta_{21}, \beta_{22}, \tau_2) = (0.1, 0.1, 2.0, 0.1, 0.1, 2.0)$$

and τ_k is the shape parameter, β_{k1} and β_{k2} are the covariate effects, for $i = 1, \ldots, n$ and $k = 1, 2$. The generation of the simulated data sets is summarized in Algorithm 1.

Algorithm 1 Generation of the simulated data sets

Require: Number of clusters n, cluster size m_i, frailty θ_k and interval bound b, for $k = 1, 2$

for each cluster $i = 1, \ldots, n$ **do**

  Generate a common frailty term $\omega_{ik} \sim \text{Gamma}(\theta_k, \theta_k)$, for $k = 1, 2$, following [19]

  for each individual $j = 1, \ldots, m_i$ **do**

    Generate the individual covariate vector $\boldsymbol{x}_{ij} = (X_{1ij}, X_{2ij})^\top$, where $X_{1ij} \sim \text{Bernoulli}(0.5)$ and $X_{2ij} \sim \text{N}(0, 1)$.

    Specify the cause-specific hazards $\lambda_1(t; \boldsymbol{x}_{ij})$ and $\lambda_2(t; \boldsymbol{x}_{ij})$ from the expressions given in (7) or (8) ▷ following [20]

    Simulate the failure time T_{ij} with all-cause hazard $\omega_{i1}\lambda_1(t; \boldsymbol{x}_{ij}) + \omega_{i2}\lambda_2(t; \boldsymbol{x}_{ij})$

    Assign $C_{ij} = 1$ with probability $\omega_{i1}\lambda_1(t; \boldsymbol{x}_{ij})/(\omega_{i1}\lambda_1(t; \boldsymbol{x}_{ij}) + \omega_{i2}\lambda_2(t; \boldsymbol{x}_{ij}))$; otherwise set $C_{ij} = 2$.

    Generate an independent right-censoring time $V_{ij} \sim \text{U}[0, 1]$ and set $t_{ij} = \min(T_{ij}, V_{ij})$

    if the individual is right-censored **then**

      Set $L_{ij} = t_{ij}$ and $R_{ij} = \infty$

    else

      Set $L_{ij} = 0.0001$ and draw $R_{ij} = v$ with $v \sim \text{U}[0.1, b]$, extending the interval until $t_{ij} \in [L_{ij}, R_{ij}]$

    end if

  end for

end for

Ensure: Clustered interval-censored competing-risks data $\{(L_{ij}, R_{ij}, \Delta_{ij})\}$

Each dataset is analyzed using the methodology proposed in Section 3. Each simulation result displayed in this section is based on $N = 1000$ simulated datasets. The performance of all point estimators is compared numerically in terms of their average estimate, empirical variance, its asymptotic counterpart, and mean square error (MSE) values. Moreover, the coverage probability (CP) of 95% confidence intervals is computed for interval estimates.

The average of parameter estimates is computed as $\widehat{\theta} = \sum_{i=1}^{N} \widehat{\theta}_i/N$, providing an estimate of the expected value of the coefficient values for N simulations. The relative bias (RB) is obtained by taking the difference between $\widehat{\theta}$ and θ, the true population parameter value, divided by θ, such that $\text{RB} = (\widehat{\theta} - \theta)/\theta$.

The empirical variance is computed by $\text{Var}(\widehat{\theta}) = \sum_{i=1}^{N}(\widehat{\theta}_i - \widehat{\theta})^2/(N-1)$ and MSE is calculated by $\text{MSE}(\theta) = \sum_{i=1}^{N}(\widehat{\theta}_i - \theta)^2/N$. The model-based covariance matrix of $\widehat{\Theta}$ is estimated by the negative inverse Hessian matrix. The robust covariance matrix of $\widehat{\Theta}$ is estimated by the sandwich estimator defined in (4). The corresponding model-based and robust standard errors are obtained as the square roots of the diagonal elements of their respective estimated covariance matrices. The simulation study results are presented in Tables 1 to 6 and Figures 1 to 6 in Appendix B.

As shown in Tables 1 and 2, except for the Weibull shape parameters, the mean estimates are close to the true value of the parameters. As the number of clusters increases, the MSE and RB decrease. However, estimators of the Weibull shape parameters are biased and show very slow convergence rate. Furthermore, for the regression coefficients, the sandwich SE is close to the empirical SE, indicating that the proposed approach effectively makes a correction for the cluster correlation. Their CPs are close to the nominal level of 0.95, indicating an adequate normal approximation of the estimates for the normal distribution.

The effect of the interval size was evaluated by generating different scenarios with larger windows. The results are presented in Tables 3 and 4, for the exponential and Weibull models. Except for the Weibull shape parameters, the mean estimates are close to the true value but the MSE, RB, and SE are larger when compared with Scenario I. Furthermore, for the regression coefficients, the sandwich SE is very close to the empirical SE and their CPs are near the nominal level of 0.95. Note that when we increase the correlation within the cluster, the parameter estimates have a slightly greater bias; see Tables 5 and 6.

Table 1. Scenario I for the exponential model, where $\omega_{ik} \sim \text{Gamma}(2,2)$, inducing weak within-cluster correlation (Kendall tau = 0.20), and interval widths generated from U(0.1, 0.3), SE_1, SE_2 are model-based and robust-based standard errors and CP_1, CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.3$	0.276	0.008	-0.081	0.084	0.075	0.079	0.915	0.925
$\beta_{12} = 0.3$	0.271	0.008	-0.097	0.084	0.075	0.080	0.895	0.913
$\beta_{21} = 0.3$	0.271	0.008	-0.097	0.082	0.075	0.080	0.917	0.931
$\beta_{22} = 0.3$	0.270	0.007	-0.099	0.081	0.075	0.080	0.908	0.929
				500 clusters				
$\beta_{11} = 0.3$	0.281	0.005	-0.064	0.058	0.053	0.056	0.921	0.926
$\beta_{12} = 0.3$	0.281	0.005	-0.064	0.056	0.053	0.056	0.915	0.937
$\beta_{21} = 0.3$	0.281	0.005	-0.064	0.057	0.053	0.056	0.913	0.939
$\beta_{22} = 0.3$	0.281	0.005	-0.064	0.057	0.053	0.056	0.911	0.934
				1000 clusters				
$\beta_{11} = 0.3$	0.289	0.003	-0.036	0.037	0.033	0.036	0.921	0.946
$\beta_{12} = 0.3$	0.289	0.003	-0.036	0.036	0.033	0.036	0.925	0.940
$\beta_{21} = 0.3$	0.289	0.003	-0.036	0.037	0.033	0.036	0.923	0.949
$\beta_{22} = 0.3$	0.289	0.003	-0.036	0.037	0.033	0.036	0.921	0.946

Table 2. Scenario I for the Weibull model, where $\omega_{ik} \sim \text{Gamma}(2,2)$, inducing weak within-cluster correlation (Kendall tau = 0.20), and interval widths were generated from U(0.1, 0.3), SE_1, SE_2 are model-based and robust-based standard errors and CP_1 and CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.1$	0.099	0.007	-0.008	0.092	0.097	0.095	0.976	0.997
$\beta_{12} = 0.1$	0.105	0.008	0.049	0.091	0.097	0.091	0.976	0.998
$\beta_{21} = 0.1$	0.103	0.007	0.034	0.094	0.098	0.096	0.976	0.994
$\beta_{22} = 0.1$	0.105	0.008	0.048	0.093	0.098	0.097	0.981	0.996
$\tau_1 = 2.0$	0.930	1.179	-0.535	0.181	0.165	0.168	0.032	0.032
$\tau_2 = 2.0$	0.924	1.189	-0.538	0.175	0.179	0.179	0.026	0.026
				500 clusters				
$\beta_{11} = 0.1$	0.102	0.006	0.030	0.085	0.096	0.089	0.980	0.999
$\beta_{12} = 0.1$	0.102	0.006	0.023	0.088	0.097	0.095	0.982	0.999
$\beta_{21} = 0.1$	0.103	0.006	0.032	0.089	0.098	0.091	0.978	0.999
$\beta_{22} = 0.1$	0.100	0.006	-0.001	0.088	0.097	0.090	0.981	0.999
$\tau_1 = 2.0$	0.950	1.154	-0.525	0.167	0.126	0.157	0.045	0.046
$\tau_2 = 2.0$	0.941	1.162	-0.529	0.171	0.174	0.172	0.077	0.077
				1000 clusters				
$\beta_{11} = 0.1$	0.101	0.005	0.030	0.082	0.096	0.084	0.980	0.999
$\beta_{12} = 0.1$	0.101	0.005	0.018	0.084	0.094	0.086	0.982	0.999
$\beta_{21} = 0.1$	0.102	0.005	0.028	0.087	0.095	0.086	0.978	0.999
$\beta_{22} = 0.1$	0.100	0.004	-0.001	0.083	0.092	0.085	0.981	0.999
$\tau_1 = 2.0$	0.980	1.141	-0.515	0.147	0.106	0.137	0.055	0.056
$\tau_2 = 2.0$	0.972	1.131	-0.519	0.141	0.148	0.142	0.077	0.077

The empirical SE is slightly greater but the sandwich SE is still close to it. In all scenarios, increasing the number of clusters leads to less biased regression-coefficient estimators and CPs closer to the nominal level. In Tables 4 and 6 for the Weibull model, estimators of the shape parameters are biased and show very slow convergence rate as happened in Table 2.

Table 3. Scenario II for the exponential model with the same structure as in Table 1, except that the interval widths were increased using U(0.1, 0.5), SE_1, SE_2 are model-based and robust-based standard errors and CP_1 and CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.3$	0.269	0.009	-0.104	0.087	0.075	0.080	0.892	0.906
$\beta_{12} = 0.3$	0.268	0.009	-0.106	0.084	0.075	0.080	0.912	0.927
$\beta_{21} = 0.3$	0.268	0.009	-0.108	0.085	0.075	0.080	0.887	0.906
$\beta_{22} = 0.3$	0.268	0.009	-0.107	0.081	0.075	0.080	0.906	0.934
				500 clusters				
$\beta_{11} = 0.3$	0.278	0.006	-0.073	0.066	0.063	0.066	0.906	0.922
$\beta_{12} = 0.3$	0.278	0.006	-0.073	0.065	0.063	0.064	0.902	0.919
$\beta_{21} = 0.3$	0.278	0.006	-0.073	0.065	0.063	0.064	0.918	0.929
$\beta_{22} = 0.3$	0.278	0.006	-0.073	0.064	0.063	0.063	0.907	0.908
				1000 clusters				
$\beta_{11} = 0.3$	0.285	0.004	-0.049	0.046	0.043	0.046	0.926	0.942
$\beta_{12} = 0.3$	0.285	0.004	-0.049	0.045	0.043	0.044	0.922	0.949
$\beta_{21} = 0.3$	0.285	0.004	-0.049	0.045	0.043	0.044	0.928	0.949
$\beta_{22} = 0.3$	0.285	0.004	-0.049	0.044	0.043	0.044	0.927	0.948

Table 4. Scenario II for the Weibull model with the same structure as in Table 2, except that the interval widths were increased using U(0.1, 0.5), SE_1, SE_2 are model-based and robust-based standard errors and CP_1 and CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.1$	0.108	0.008	0.077	0.098	0.097	0.098	0.973	0.996
$\beta_{12} = 0.1$	0.107	0.009	0.068	0.097	0.096	0.097	0.965	0.992
$\beta_{21} = 0.1$	0.108	0.009	0.076	0.096	0.096	0.096	0.973	0.996
$\beta_{22} = 0.1$	0.109	0.008	0.087	0.094	0.096	0.094	0.974	0.995
$\tau_1 = 2.0$	0.940	1.165	-0.530	0.205	0.156	0.159	0.048	0.044
$\tau_2 = 2.0$	0.942	1.158	-0.529	0.197	0.115	0.115	0.043	0.043
				500 clusters				
$\beta_{11} = 0.1$	0.101	0.008	0.007	0.088	0.096	0.089	0.966	0.996
$\beta_{12} = 0.1$	0.105	0.007	0.049	0.092	0.095	0.094	0.972	0.996
$\beta_{21} = 0.1$	0.101	0.008	0.014	0.093	0.095	0.094	0.977	0.998
$\beta_{22} = 0.1$	0.105	0.007	0.045	0.094	0.096	0.094	0.976	0.996
$\tau_1 = 2.0$	0.962	1.144	-0.519	0.188	0.125	0.153	0.044	0.047
$\tau_2 = 2.0$	0.959	1.131	-0.521	0.190	0.279	0.209	0.078	0.075
				1000 clusters				
$\beta_{11} = 0.1$	0.101	0.006	0.007	0.085	0.093	0.087	0.966	0.996
$\beta_{12} = 0.1$	0.102	0.006	0.019	0.088	0.092	0.090	0.972	0.996
$\beta_{21} = 0.1$	0.101	0.006	0.014	0.089	0.091	0.089	0.977	0.998
$\beta_{22} = 0.1$	0.101	0.006	0.015	0.090	0.092	0.090	0.976	0.996
$\tau_1 = 2.0$	0.982	1.135	-0.509	0.178	0.112	0.145	0.044	0.047
$\tau_2 = 2.0$	0.979	1.127	-0.511	0.181	0.179	0.177	0.078	0.048

6. Application to the dental study

The proposed methodology is illustrated with a real dataset from a study carried out at the Dental Trauma Program of the School of Dentistry of the Federal University of Minas Gerais, which aimed to evaluate pulp prognosis of 427 luxated permanent teeth from 224 patients. These data presented some characteristics that must be considered in the statistical analysis.

The first refers to the existence of competing risks as there is more than one possible outcome for the pulpal response, namely: maintenance of vitality ($k = 1$), necrosis ($k = 2$), and pulp canal obliteration - PCO ($k = 3$). The second characteristic is the presence of clusters because in some cases, the same patient has more than one luxated tooth. In addition, it was not possible to specify an exact date of occurrence of the event. Hence, a time interval between the follow-up appointments of the patient was selected.

Table 5. Scenario III for the exponential model with the same structure as in Table 1, except that the intra-cluster correlation was increased (Kendall tau = 0.85) by using $\omega_{ik} \sim \text{Gamma}(1/11, 1/11)$, SE_1, SE_2 are model-based and robust-based standard errors and CP_1 and CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.3$	0.269	0.010	-0.103	0.086	0.076	0.087	0.919	0.926
$\beta_{12} = 0.3$	0.269	0.010	-0.103	0.086	0.075	0.085	0.912	0.914
$\beta_{21} = 0.3$	0.269	0.010	-0.103	0.086	0.076	0.085	0.911	0.935
$\beta_{22} = 0.3$	0.269	0.010	-0.103	0.086	0.075	0.087	0.912	0.915
				500 clusters				
$\beta_{11} = 0.3$	0.276	0.008	-0.081	0.058	0.050	0.056	0.901	0.925
$\beta_{12} = 0.3$	0.276	0.008	-0.081	0.058	0.051	0.056	0.901	0.929
$\beta_{21} = 0.3$	0.276	0.008	-0.081	0.058	0.051	0.056	0.911	0.937
$\beta_{22} = 0.3$	0.276	0.008	-0.081	0.058	0.050	0.056	0.911	0.931
				1000 clusters				
$\beta_{11} = 0.3$	0.287	0.006	-0.043	0.038	0.031	0.037	0.931	0.944
$\beta_{12} = 0.3$	0.287	0.006	-0.043	0.038	0.032	0.037	0.931	0.948
$\beta_{21} = 0.3$	0.287	0.005	-0.043	0.038	0.032	0.037	0.931	0.949
$\beta_{22} = 0.3$	0.287	0.006	-0.043	0.038	0.031	0.037	0.931	0.947

Table 6. Scenario III for the Weibull model with the same structure as in Table 2, except that the intra-cluster correlation was increased (Kendall tau = 0.85) by using $\omega_{ik} \sim \text{Gamma}(1/11, 1/11)$, SE_1, SE_2 are model-based and robust-based standard errors and CP_1 and CP_2 are the corresponding CPs.

	$\widehat{\beta}$	MSE	RB	SE	SE_1	SE_2	CP_1	CP_2
				100 clusters				
$\beta_{11} = 0.1$	0.108	0.008	0.077	0.098	0.097	0.096	0.973	0.996
$\beta_{12} = 0.1$	0.107	0.009	0.068	0.095	0.096	0.096	0.965	0.992
$\beta_{21} = 0.1$	0.108	0.009	0.076	0.095	0.096	0.097	0.973	0.996
$\beta_{22} = 0.1$	0.109	0.008	0.087	0.092	0.096	0.094	0.974	0.995
$\tau_1 = 2.0$	0.940	1.165	-0.530	0.208	0.196	0.199	0.018	0.040
$\tau_2 = 2.0$	0.942	1.158	-0.529	0.199	0.115	0.115	0.033	0.033
				500 clusters				
$\beta_{11} = 0.1$	0.101	0.007	0.007	0.096	0.096	0.090	0.966	0.996
$\beta_{12} = 0.1$	0.105	0.008	0.050	0.092	0.095	0.094	0.972	0.986
$\beta_{21} = 0.1$	0.101	0.008	0.014	0.091	0.095	0.093	0.977	0.988
$\beta_{22} = 0.1$	0.105	0.007	0.050	0.092	0.095	0.093	0.976	0.986
$\tau_1 = 2.0$	0.962	1.154	-0.521	0.198	0.155	0.171	0.014	0.077
$\tau_2 = 2.0$	0.959	1.151	-0.520	0.195	0.179	0.179	0.078	0.078
				1000 clusters				
$\beta_{11} = 0.1$	0.101	0.007	0.007	0.088	0.086	0.088	0.966	0.996
$\beta_{12} = 0.1$	0.103	0.007	0.030	0.090	0.093	0.091	0.972	0.996
$\beta_{21} = 0.1$	0.101	0.006	0.013	0.090	0.093	0.090	0.977	0.998
$\beta_{22} = 0.1$	0.102	0.006	0.020	0.091	0.092	0.091	0.976	0.996
$\tau_1 = 2.0$	0.992	1.124	-0.504	0.188	0.150	0.165	0.014	0.070
$\tau_2 = 2.0$	0.989	1.123	-0.506	0.191	0.170	0.170	0.078	0.078

A total of 21.25% of the data were subject to right censoring and 78.75% were interval-censored. Regarding the pulp diagnosis variable, 32.97% presented vitality ($k = 1$), 32.60% necrosis ($k = 2$), and 13.19% PCO ($k = 3$). Six covariates were included in the study: gender (44% female and 56% male), age (mean 15.5 years), type of luxation (33.33% subluxation+concussion, 37% lateral, 15.75% extrusive, and 13.92% intrusive), concomitant injuries other than luxations (17.22% yes and 82.78% no), diameter of the apical foramen (32.23% open and 67.77% closed), and emergency treatment (60.9% yes and 39.1% no). We fitted the exponential and Weibull regression models based on methodology presented in Section 3.

The results concerning the coefficient estimates, along with the robust sandwich SE, are reported in Table 7. The p-value associated with each covariate is calculated using the Wald test. Table 7 shows that the estimates of the τ parameter are close to 1 for the event of vitality.

Table 7. Parameter estimates from exponential and Weibull models of the CIF for three competing causes in the dental trauma study data.

	Exponential model								
	Vitality ($k = 1$)			Necrosis ($k = 2$)			PCO ($k = 3$)		
Covariates	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Age	0.0018	0.0009	0.0541	0.0023	0.0008	0.0044	-0.0076	0.0036	0.0364
Gender (Male)	0.1645	0.2356	0.4850	0.2914	0.2377	0.2200	0.3011	0.3613	0.4050
Luxation (Ext+Lat)	-0.1460	0.2384	0.5402	0.2664	0.2807	0.3426	0.9291	0.4384	0.0341
Luxation (Int)	-0.7403	0.4175	0.0762	1.0220	0.3112	0.0010	-0.0082	0.7028	0.9907
Assoc. injury (Yes)	-0.9781	0.3469	0.0048	1.4430	0.2064	<0.0001	-0.4273	0.5140	0.4060
Apical Diam. (open)	-0.0345	0.2181	0.8740	-0.2684	0.2437	0.2710	0.6228	0.3444	0.0706
Emerg. Treat. (yes)	-0.3077	0.2626	0.2410	-0.0335	0.2716	0.9020	-0.2561	0.4202	0.5420
	Weibull model								
Age	0.0220	0.0114	0.0539	0.0281	0.0098	0.0044	-0.0915	0.0437	0.0364
Gender (Male)	0.1701	0.2355	0.4750	0.2857	0.2383	0.2310	0.3045	0.3609	0.3990
Luxation (Ext+Lat)	-0.3495	0.2221	0.1155	0.1747	0.2550	0.4930	0.9848	0.3994	0.0137
Luxation (Int)	-0.7467	0.4187	0.0745	1.0205	0.3102	0.0010	-0.0078	0.7028	0.9911
Assoc. injury (Yes)	-0.9822	0.3469	0.0046	1.4520	0.2073	<0.0001	-0.4302	0.5140	0.4030
Apical Diam. (open)	-0.0027	0.2837	0.9920	-0.4569	0.3597	0.2040	0.8663	0.3661	0.0180
Emerg. Treat. (yes)	-0.3454	0.2446	0.1580	-0.0355	0.2616	0.8020	-0.3366	0.4621	0.4660
τ	1.2250	0.1381	0.1033	0.5050	0.2561	0.0533	1.8370	0.2967	0.0048

Note that the hypothesis $\tau = 1$ is rejected for the events necrosis and PCO. Therefore, there is favorable evidence supporting the Weibull model for necrosis and PCO, and the exponential one for vitality at the 10% significance level. In this latter case, as expected, both models yield similar results.

Age and at least one luxation category are associated with each of the three events at the 10% significance level. Associated injury is significant for vitality and necrosis, and lastly, the diameter of the apical foramen is relevant for the occurrence of PCO. Experimental evidence suggests that teeth with wider apical foramen are more likely to experience vascular ingrowth and nerve regeneration, which allows for the preservation of pulp vitality. Clinical data confirmed this premise and also demonstrated that the risk of pulp necrosis increased with the severity of luxation and the presence of concomitant crown fractures. Furthermore, clinical studies have shown that PCO is more frequently observed in injuries that involve the displacement of immature permanent teeth [21, 22, 23].

7. Conclusions

We proposed a GEE-type procedure for clustered competing-risks models with interval-censored data. Our approach is based on a marginal parametric likelihood for independent data and uses the sandwich variance for the estimates. The proposed approach is appealing because of its computational simplicity and the population-level interpretation of its parameters. The simulation study showed that our proposed methods perform well for finite data sets. Three scenarios were considered based on exponential and Weibull parametric structures. Whereas the regression-coefficient estimators presented adequate finite-sample properties, the Weibull shape-parameter estimators were biased and showed a very slow convergence rate. A limitation of the proposed methodology is precisely this biased estimation and slow convergence of the Weibull shape parameters, which suggests caution in small samples. We illustrated the application of our methodology with a real study of dental trauma demonstrating its practical importance. It can also be used in many other practical situations.

This work opens numerous avenues for related future research. The most interesting one seems to be considering a semi-parametric model, that is, a Cox-type approach. Another promising research direction is using splines instead of fixed coefficients for continuous covariates. We are presently working on the semi-parametric extension and wish to report the results in a future article. This study provides a basis for future research aimed at identifying patterns and trends in this field, in line with the work presented in [24].

Appendix A: Technical results

A.1. Derivatives

The parameter estimates involve calculating the first and second order derivatives of the function stated in (3) for the assumed parametric model. Hence, in general, considering $G_k(\Theta_k) = (F_k(R_{ij};\Theta_k) - F_k(L_{ij};\Theta_k))$ in the expression defined in (3), we have that

$$\log(l(y_i;\Theta)) = \sum_{j=1}^{m_i}\sum_{k=1}^{K} \Delta_{ijk}\log(G_k(\Theta_k)) + \Delta_{ij0}\log\left(1 - \sum_{k=1}^{K} F_k(L_{ij};\Theta_k)\right).$$

Therefore, we get

$$\frac{\partial \log(l(y_i;\Theta))}{\partial\Theta_k} = \sum_{j=1}^{m_i}\frac{\Delta_{ijk}}{G_k(\Theta_k)}\frac{\partial G_k(\Theta_k)}{\partial\Theta_k} - \frac{\Delta_{ij0}}{1-\displaystyle\sum_{r=1}^{K} F_r(L_{ij};\Theta_r)}\frac{\partial F_k(L_{ij};\Theta_k)}{\partial\Theta_k}, \tag{9}$$

where $\partial G_k(\Theta_k)/\partial\Theta_k = \partial F_k(R_{ij};\Theta_k)/\partial\Theta_k - \partial F_k(L_{ij};\Theta_k)/\partial\Theta_k$. From the expression established in (9), we have that the second order derivatives are stated as

$$\begin{aligned}
\frac{\partial^2 \log(l(y_i;\Theta))}{\partial\Theta_k^2} &= \sum_{j=1}^{m_i}\Delta_{ijk}\left(\frac{\partial^2 G_k(\Theta_k)/\partial\Theta_k^2}{G_k(\Theta_k)} - \left(\frac{\partial G_k(\Theta_k)/\partial\Theta_k}{G_k(\Theta_k)}\right)^2\right)\\
&\quad - \Delta_{ij0}\left(\frac{\partial^2 F_k(L_{ij};\Theta_k)/\partial\Theta_k^2}{1-\sum_{r=1}^{K} F_r(L_{ij};\Theta_r)} + \left(\frac{\partial F_k(L_{ij};\Theta_k)/\partial\Theta_k}{1-\sum_{r=1}^{K} F_r(L_{ij};\Theta_r)}\right)^2\right),\\
\frac{\partial^2 \log(l(y_i;\Theta))}{\partial\Theta_k\partial\Theta_{k'}} &= \sum_{j=1}^{m_i}\Delta_{ijk}\left(\frac{\partial^2 G_k(\Theta_k)}{\partial\Theta_k\partial\Theta_{k'}\,G_k(\Theta_k)} - \frac{\partial G_k(\Theta_k)/\partial\Theta_k\partial G_k(\Theta_k)/\partial\Theta_{k'}}{(G_k(\Theta_k))^2}\right)\\
&\quad - \Delta_{ij0}\left(\frac{\partial^2 F_k(L_{ij};\Theta_k)}{\partial\Theta_k\partial\Theta_{k'}\left(1-\sum_{r=1}^{K} F_r(L_{ij};\Theta_r)\right)} + \frac{\partial F_k(L_{ij};\Theta_k)/\partial\Theta_k\partial F_k(L_{ij};\Theta_k)/\partial\Theta_{k'}}{\left(1-\sum_{r=1}^{K} F_r(L_{ij};\Theta_r)\right)^2}\right).
\end{aligned}$$

Then, we reach $\partial\log(L(\Theta))/\partial\Theta_k = \sum_{i=1}^{n}\partial\log(l(y_i;\Theta))/\partial\Theta_k$.

A.2. Derivatives for the exponential model

Considering the presence of two competing risks, that is, $k = 1, 2$, we have for the exponential model without covariates that

$$\begin{aligned}
F_1(t;\Theta) &= \int_0^t \alpha_1\prod_{k'=1}^{2}\exp(-\alpha_k u)\mathrm{d}u = \int_0^t \alpha_1\exp\left(-\sum_{k=1}^{2}\alpha_k u\right)\mathrm{d}u = \frac{\alpha_1}{\alpha_1+\alpha_2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right),\\
F_2(t;\Theta) &= \int_0^t \alpha_2\prod_{k'=1}^{2}\exp(-\alpha_k u)\mathrm{d}u = \int_0^t \alpha_2\exp\left(-\sum_{k=1}^{2}\alpha_k u\right)\mathrm{d}u = \frac{\alpha_2}{\alpha_1+\alpha_2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right),
\end{aligned}$$

where $\Theta = (\alpha_1, \alpha_2)$. The first order derivatives of $F_1(t;\Theta)$ are given by

$$\frac{\partial F_1(t;\Theta)}{\partial\alpha_1} = \frac{\alpha_2}{(\alpha_1+\alpha_2)^2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right) + \frac{\alpha_1 t}{\alpha_1+\alpha_2}\exp\left(-\sum_{k=1}^{2}\alpha_k t\right),$$

$$\frac{\partial F_1(t;\Theta)}{\partial\alpha_2} = -\frac{\alpha_1}{(\alpha_1+\alpha_2)^2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right) + \frac{\alpha_1 t}{\alpha_1+\alpha_2}\exp\left(-\sum_{k=1}^{2}\alpha_k t\right).$$

The second order derivatives of $F_1(t;\Theta)$ are presented as

$$\frac{\partial^2 F_1(t;\Theta)}{\partial\alpha_1^2} = \frac{\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left(2(\alpha_2^2+\alpha_1\alpha_2)t-(\alpha_1\alpha_2^2+2\alpha_1^2\alpha_2+\alpha_1^3)t^2+2\alpha_2\right)-\frac{2\alpha_2}{(\alpha_1+\alpha_2)^3},$$

$$\frac{\partial^2 F_1(t;\Theta)}{\partial\alpha_2^2} = \frac{\alpha_1\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left((-\alpha_1^2-\alpha_2^2-2\alpha_1\alpha_2)t^2-2(\alpha_1+\alpha_2)t-2\right)+\frac{2\alpha_1}{(\alpha_1+\alpha_2)^3},$$

$$\frac{\partial^2 F_1(t;\Theta)}{\partial\alpha_1\partial\alpha_2} = \frac{\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left((\alpha_2^2-\alpha_1^2)t-(\alpha_1\alpha_2^2+2\alpha_1^2\alpha_2+\alpha_1^3)t^2-\alpha_1+\alpha_2\right)+\frac{\alpha_1-\alpha_2}{(\alpha_1+\alpha_2)^3}.$$

The first order derivatives of $F_2(t;\Theta)$ are formulated as

$$\frac{\partial F_2(t;\Theta)}{\partial\alpha_2} = \frac{\alpha_1}{(\alpha_1+\alpha_2)^2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right)+\frac{\alpha_2 t}{\alpha_1+\alpha_2}\exp\left(-\sum_{k=1}^{2}\alpha_k t\right),$$

$$\frac{\partial F_2(t;\Theta)}{\partial\alpha_1} = -\frac{\alpha_2}{(\alpha_1+\alpha_2)^2}\left(1-\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)\right)+\frac{\alpha_2 t}{\alpha_1+\alpha_2}\exp\left(-\sum_{k=1}^{2}\alpha_k t\right).$$

The second order derivatives of $F_2(t;\Theta)$ are defined as

$$\frac{\partial^2 F_2(t;\Theta)}{\partial\alpha_2^2} = \frac{\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left(2(\alpha_1^2+\alpha_1\alpha_2)t-(\alpha_2\alpha_1^2+2\alpha_2^2\alpha_1+\alpha_2^3)t^2+2\alpha_1\right)-\frac{2\alpha_1}{(\alpha_1+\alpha_2)^3},$$

$$\frac{\partial^2 F_2(t;\Theta)}{\partial\alpha_1^2} = \frac{\alpha_2\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left((-\alpha_1^2-\alpha_2^2-2\alpha_1\alpha_2)t^2-2(\alpha_1+\alpha_2)t-2\right)+\frac{2\alpha_2}{(\alpha_1+\alpha_2)^3},$$

$$\frac{\partial^2 F_2(t;\Theta)}{\partial\alpha_1\partial\alpha_2} = \frac{\exp\left(-\sum_{k=1}^{2}\alpha_k t\right)}{(\alpha_1+\alpha_2)^3}\left((\alpha_1^2-\alpha_2^2)t-(\alpha_2\alpha_1^2+2\alpha_2^2\alpha_1+\alpha_2^3)t^2-\alpha_2+\alpha_1\right)+\frac{\alpha_2-\alpha_1}{(\alpha_1+\alpha_2)^3}.$$

From the expression stated in (3), we have that the log-likelihood function for the exponential model is given by

$$\begin{aligned}\log(L(\Theta)) &= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(F_1(R_{ij};\Theta)-F_1(L_{ij};\Theta)\right)+\Delta_{ij2}\log\left(F_2(R_{ij};\Theta)-F_2(L_{ij};\Theta)\right)+\right.\\ &\qquad \left.+\,\Delta_{ij0}\log\left(1-\sum_{k=1}^{2}F_k(L_{ij};\Theta)\right)\right)\\ &= \sum_{i=1}^{n}\sum_{j=1}^{m_i}\left(\Delta_{ij1}\log\left(\frac{\alpha_1}{\alpha_1+\alpha_2}\left(\exp\left(-\sum_{k=1}^{2}\alpha_k L_{ij}\right)-\exp\left(-\sum_{k=1}^{2}\alpha_k R_{ij}\right)\right)\right)\right.+\\ &\qquad +\Delta_{ij2}\log\left(\frac{\alpha_2}{\alpha_1+\alpha_2}\left(\exp\left(-\sum_{k=1}^{2}\alpha_k L_{ij}\right)-\exp\left(-\sum_{k=1}^{2}\alpha_k R_{ij}\right)\right)\right)+\end{aligned}$$

$$+ \Delta_{ij0} \log\left(1 - \sum_{k=1}^{2} F_k(L_{ij};\Theta)\right)\Bigg).$$

The first-order derivatives of the log-likelihood function are given by

$$\frac{\partial \log(L(\Theta))}{\partial \alpha_1} = \sum_{i=1}^{n}\sum_{j=1}^{m_i}\Bigg(\Delta_{j1}\left(\frac{R_j \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right) - L_j \exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right)}{\exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right) - \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right)} + \frac{\alpha_2}{\alpha_1(\alpha_1+\alpha_2)}\right)$$

$$+\Delta_{j2}\left(\frac{R_j \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right) - L_j \exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right)}{\exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right) - \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right)} - \frac{1}{(\alpha_1+\alpha_2)}\right) - \Delta_{j0} L_j\Bigg),$$

$$\frac{\partial \log(L(\Theta))}{\partial \alpha_2} = \sum_{i=1}^{n}\sum_{j=1}^{m_i}\Bigg(\Delta_{j1}\left(\frac{R_j \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right) - L_j \exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right)}{\exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right) - \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right)} - \frac{1}{(\alpha_1+\alpha_2)}\right)$$

$$+\Delta_{j2}\left(\frac{R_j \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right) - L_j \exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right)}{\exp\left(-\sum_{k=1}^{2}\alpha_k L_j\right) - \exp\left(-\sum_{k=1}^{2}\alpha_k R_j\right)} + \frac{\alpha_1}{\alpha_2(\alpha_1+\alpha_2)}\right) - \Delta_{j0} L_j\Bigg).$$

A.3. Derivatives for the Weibull model

Considering the Weibull model and the presence of two competing risks, that is, $k = 1, 2$, we have

$$F_1(t;\Theta) = \int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_1 \alpha_1^{\tau_1} u^{\tau_1 - 1} \mathrm{d}u,$$

$$F_2(t;\Theta) = \int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_2 \alpha_2^{\tau_2} u^{\tau_2 - 1} \mathrm{d}u,$$

where $\Theta = (\alpha_1, \tau_1, \alpha_2, \tau_2)$. The integrals defining F_1 and F_2 do not have closed-form solutions in the general case such that $\tau_1 \neq \tau_2$, and therefore require numerical integration.

The first order derivatives of F_1 and F_2, about α_k and τ_k, are established as

$$\frac{\partial F_1(t;\Theta)}{\partial \alpha_k} = \frac{\partial}{\partial \alpha_k}\int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_1 \alpha_1^{\tau_1} u^{\tau_1 - 1} \mathrm{d}u,$$

$$\frac{\partial F_1(t;\Theta)}{\partial \tau_k} = \frac{\partial}{\partial \tau_k}\int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_1 \alpha_1^{\tau_1} u^{\tau_1 - 1} \mathrm{d}u,$$

$$\frac{\partial F_2(t;\Theta)}{\partial \alpha_k} = \frac{\partial}{\partial \alpha_k}\int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_2 \alpha_2^{\tau_2} u^{\tau_2 - 1} \mathrm{d}u,$$

$$\frac{\partial F_2(t;\Theta)}{\partial \tau_k} = \frac{\partial}{\partial \tau_k}\int_0^t \exp\left(-(\alpha_1 u)^{\tau_1} - (\alpha_2 u)^{\tau_2}\right) \tau_2 \alpha_2^{\tau_2} u^{\tau_2 - 1} \mathrm{d}u.$$

Appendix B: Additional simulation results

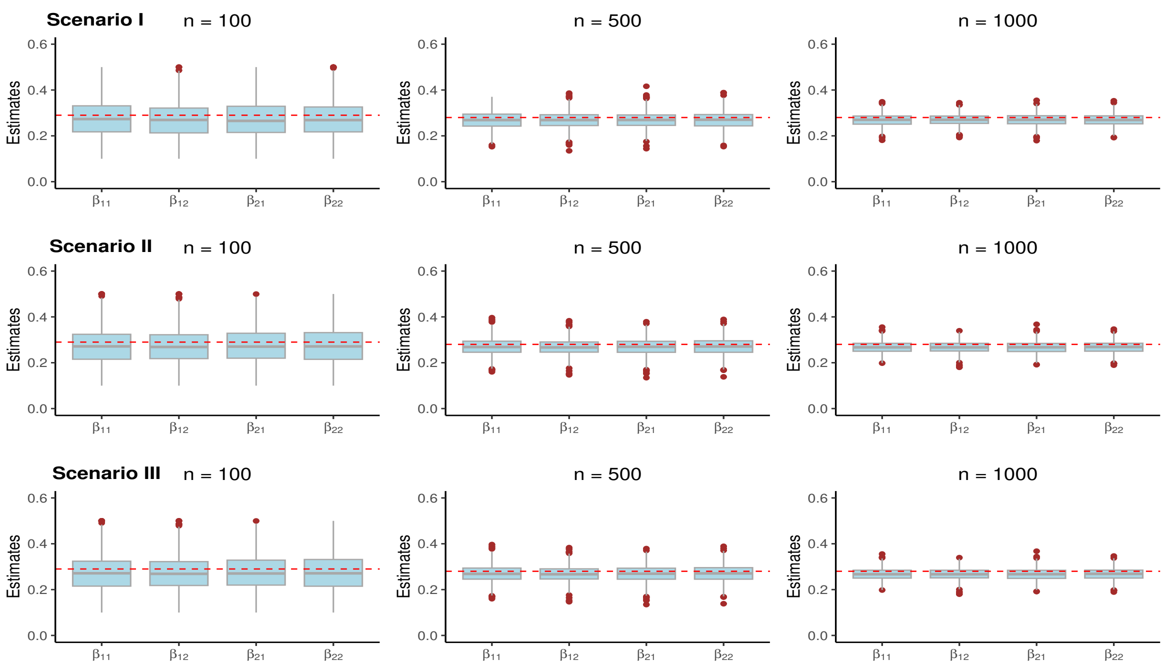

Figure 1. Empirical mean estimates of the parameters of the exponential model.

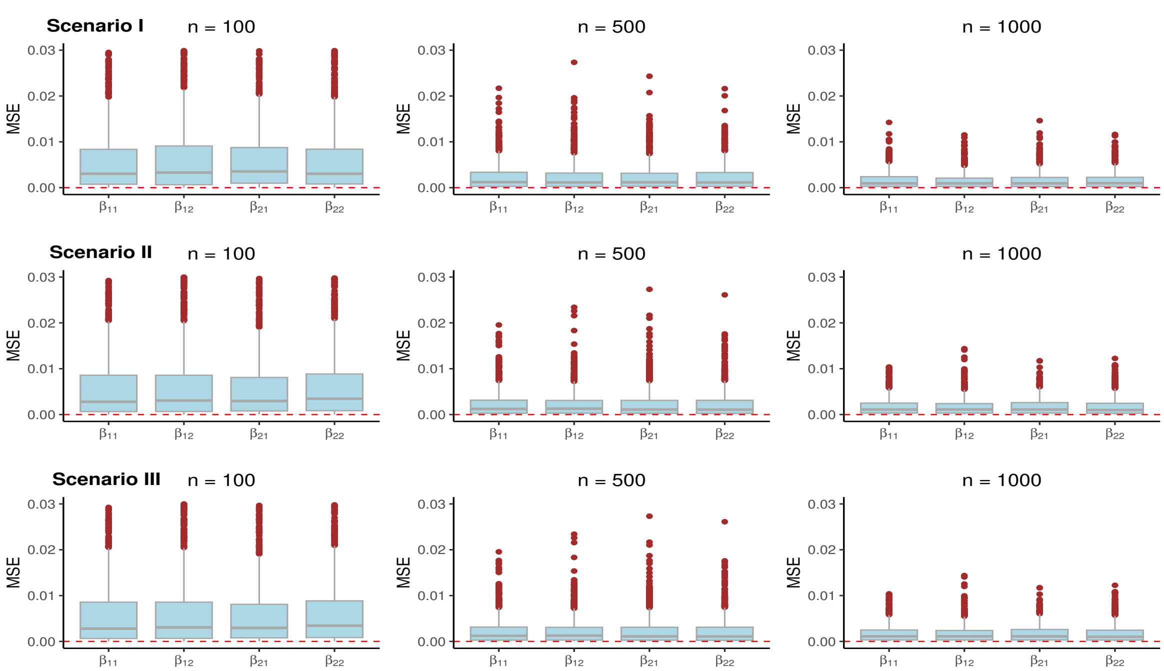

Figure 2. Empirical MSE of the estimators of the exponential model.

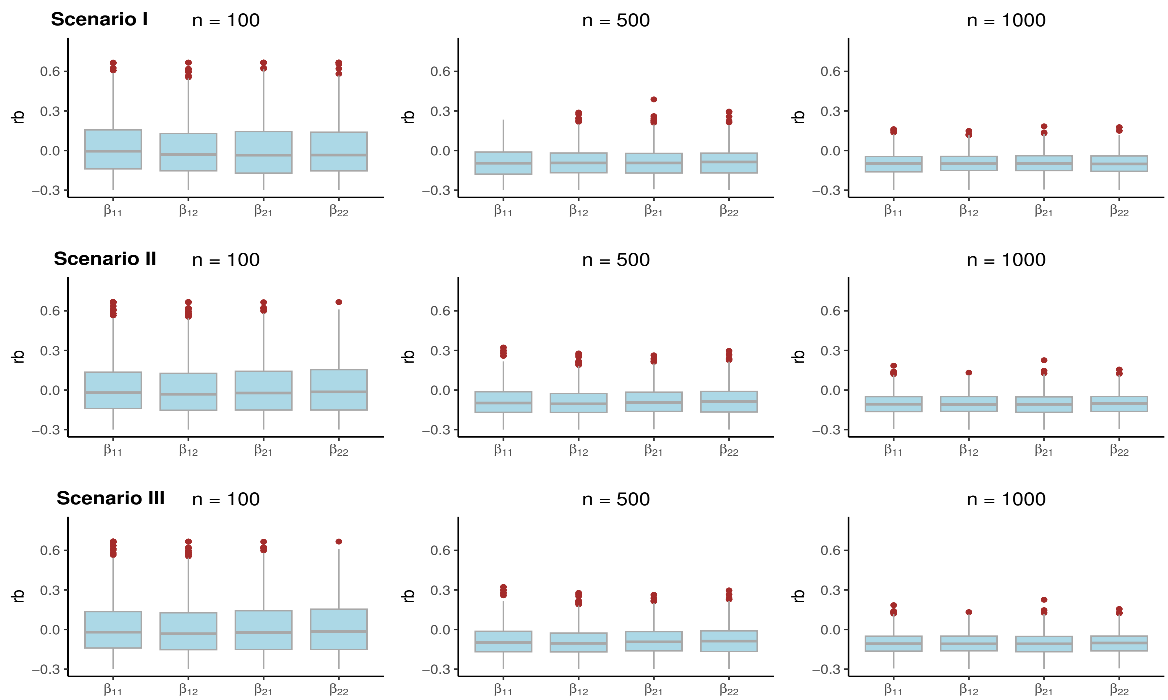

Figure 3. Empirical RB of the estimators of the exponential model.

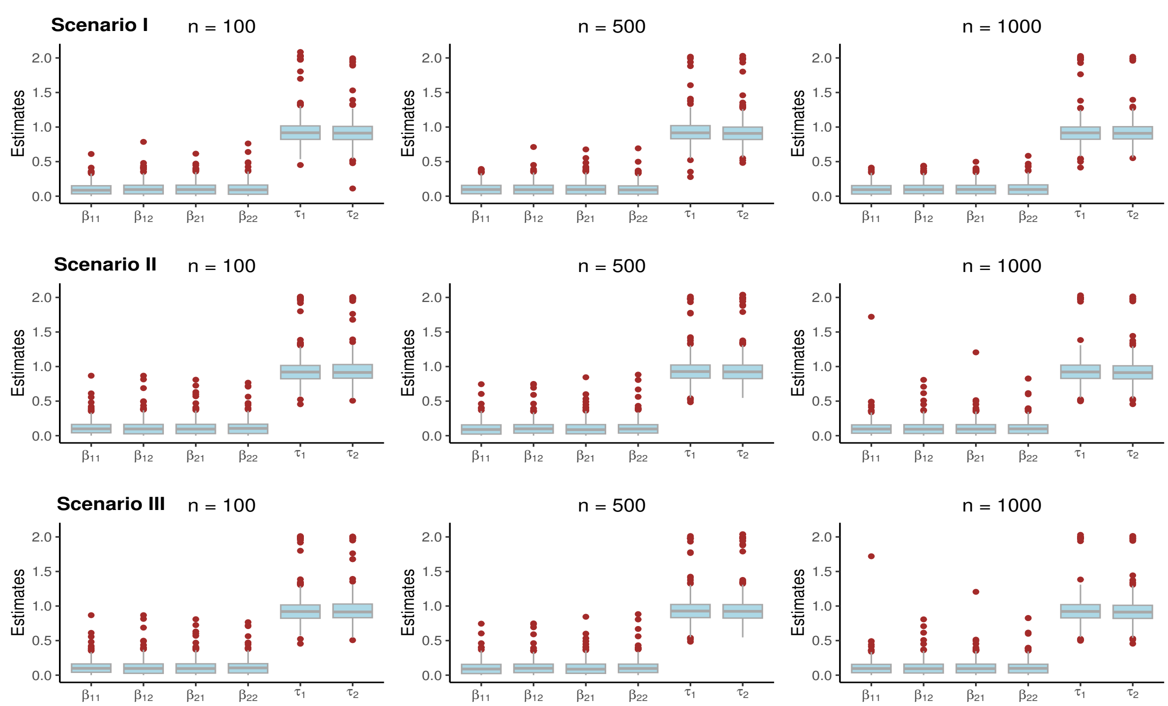

Figure 4. Empirical mean estimates of the parameters of the Weibull model.

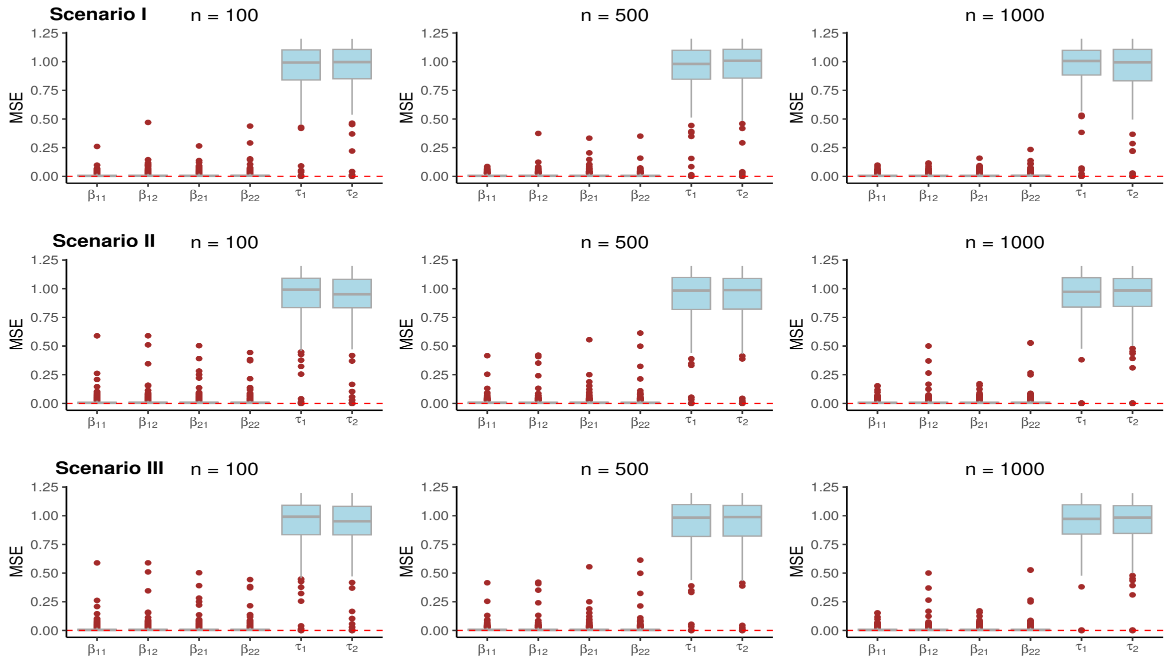

Figure 5. Empirical MSE of the estimators of the Weibull model.

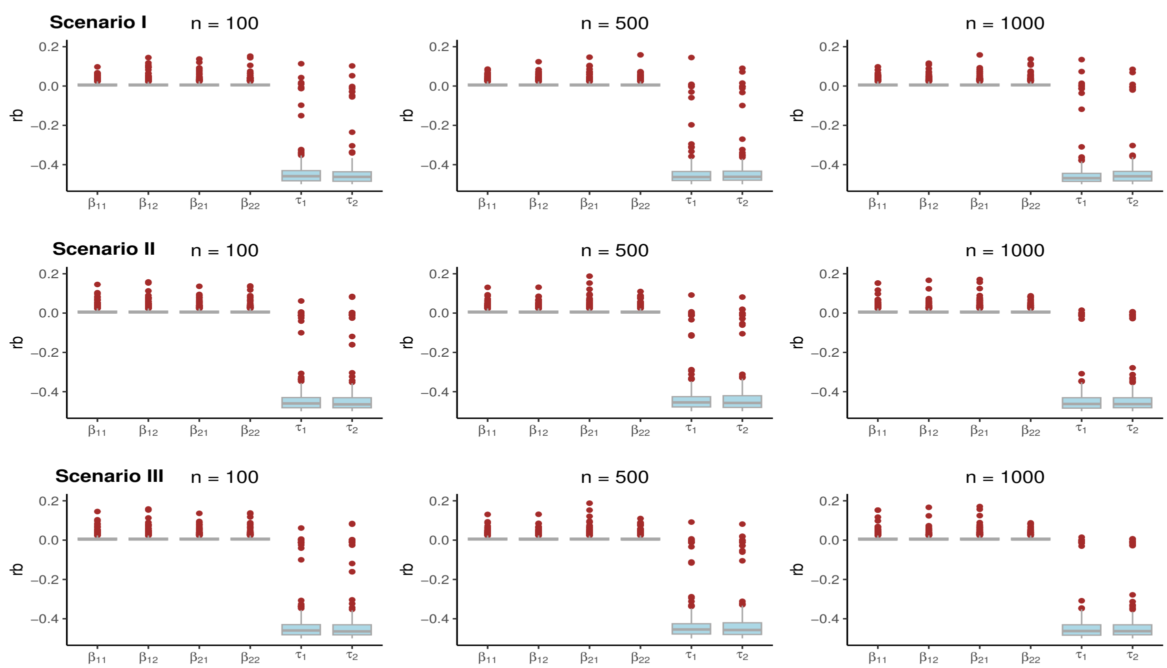

Figure 6. Empirical RB of the estimators of the Weibull model.

Statements

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Author contributions

Conceptualization: M.A.F. Rodrigues, E.A. Colosimo, and J.V. Bastos. Data curation: M.A.F. Rodrigues, J.V. Bastos, and S.C. Coste. Formal analysis: M.A.F. Rodrigues and E.A. Colosimo. Investigation: M.A.F. Rodrigues, E.A. Colosimo, and J.V. Bastos. Methodology: M.A.F. Rodrigues and E.A. Colosimo. Software: M.A.F. Rodrigues. Supervision: E.A. Colosimo and J.V. Bastos. Validation: M.A.F. Rodrigues and E.A. Colosimo. Visualization: M.A.F. Rodrigues, E.A. Colosimo, and J.V. Bastos. Writing – original draft: M.A.F. Rodrigues, E.A. Colosimo, and J.V. Bastos. Writing – review and editing: M.A.F. Rodrigues, E.A. Colosimo, J.V. Bastos, and S.C. Coste. All authors have read and agreed to the published version of the article.

Conflicts of interest

The authors declare no conflict of interest.

Data and code availability

The code used to reproduce the analyses and results presented in this article is publicly available in the public repository github.com/augustomarcio/Parametric-Model. The repository contains all scripts, data processing workflows, and documentation required to ensure full reproducibility of the study's findings.

Declaration on the use of artificial intelligence (AI) technologies

The authors declare that no generative AI was used in the preparation of this article.

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Open access statement

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