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A Parametric Approach to Relaxing the Independence Assumption in Relative Survival Analysis

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Abstract

With known cause of death (CoD), competing risk survival methods are applicable in estimating disease-specific survival. Relative survival analysis may be used to estimate disease-specific survival when cause of death is either unknown or subject to misspecification and not reliable for practical usage. This method is popular for population-based cancer survival studies using registry data and does not require CoD information. The standard estimator is the ratio of all-cause survival in the cancer cohort group to the known expected survival from a general reference population. Disease-specific death competes with other causes of mortality, potentially creating dependence among the CoD. The standard ratio estimate is only valid when death from disease and death from other causes are independent. To relax the independence assumption, we formulate dependence using a copula-based model. Likelihood-based parametric method is used to fit the distribution of disease-specific death without CoD information, where the copula is assumed known and the distribution of other cause of mortality is derived from the reference population. We propose a sensitivity analysis, where the analysis is conducted across a range of assumed dependence structures. We demonstrate the utility of our method through simulation studies and an application to French breast cancer data.

Keywords— Competing risks, Copula, Dependence Modelling, Net survival, Relative survival

1 Introduction

Cancer patients including breast, prostate, endometrial and thyroid cancer are at higher risk of dying from heart disease and stroke than the general population. As the number of cancer survivors increases, so is the rate of cardiovascular deaths (Sturgeon *et al.*, 2019). A patient’s survival burden can be quantified either by the distribution of cancer-specific death in the presence of death from other causes or by the cancer-specific mortality in the absence of failure types other than the disease of interest. This quantity, also known as net survival (under independence assumption), is controversial but meaningful to many practitioners and researchers for comparisons of survival across populations with different background mortality.

With improvement in medical treatment and long follow-up in population-based disease registries, patients may either experience disease-specific death or death from non-disease related causes (Brinkhof *et al.*, 2010). In such competing risk settings where one death type precludes the occurrence of other types, standard methodology assumes that cause of death is known (Gichangi and Vach, 2005). In the analysis of competing risks events from registry data, accurate documentation of death is essential (Percy *et al.*, 1981; Welch and Black, 2002; and Mieno *et al.*, 2016). A challenge is that documentation either may not be available, or may be incomplete or incorrect for cause of death, resulting in problems distinguishing disease and non-disease related mortality. The issue is pronounced in Europe, where comparison of disease-specific survival across countries is of interest. The World Health Organization (World Health Organization, 1977) defines cause of death as “the disease or injury which initiated the train of morbid events leading directly to death”. However, population-based disease registries may not be harmonized across countries, leading to imprecise cause of death definitions and different levels of documentation for cause of death information. Often, the underlying cause of death may be unclear as hospital coding of cancer death may not agree with the death certificate coding. As an example, Welch and Black (2002) reported that 41% of deaths that occurred (within one month of cancer diagnosis and cancer directed surgery) were not attributable to the coded cancer in the registry. When reliable cause of death information is available, it is often located in separate databases, which may be costly to obtain and difficult to link with registry data.

Suppose that $T = \min\{T_k : k = 1, 2, 3, \dots, K\}$ is the potentially observable failure time and $\varepsilon = \{k : T = T_k\}$ the failure type where T_1, T_2, \dots, T_K , are the latent failure types associated with K failure types. In registry data,

$K = 2$ and $\varepsilon = 1$ implies death from cancer and $\varepsilon = 2$ implies death from other competing causes. Standard methods for independently right censored survival data without competing risks cannot generally be used to make inference about disease-specific survival. Under dependent competing risks, where T_1 and T_2 are dependent, the Kaplan-Meier (Kaplan and Meier, 1958) curve estimates a function of the cause-specific hazard function, defined in Section 2. The logrank test (Bland and Altman, 2004) assesses group differences between the cause-specific hazard function, while the standard proportional hazards model (Cox, 1972) formulates the effects of covariates on the cause-specific hazard function. The cumulative incidence function, defined in Section 2, gives disease-specific survival in the presence of competing events. This quantity has been widely adopted in applications, with the Aalen-Johanson estimator (Aalen and Johansen, 1978), Gray’s test (Gray, 1988), and the Fine-Gray model (Fine and Gray, 1999), providing analogs to the Kaplan-Meier curve, the logrank test, and the proportional hazards model for the cumulative incidence function. Without cause of death information, these methods are not applicable.

To address disease-specific survival without reliable cause of death information, relative survival methods have been proposed. Relative survival, $S_R(t)$, is the ratio of the observed survival rate in a group of cancer patients, during a specified period, to the expected survival rate in a general reference population, (Ederer, 1961). Mathematically,

$$S_R(t) = \frac{S_O(t)}{S_P(t)} \quad (1)$$

where at time t , $S_O(t)$ is the observed survival probability from the registry and $S_P(t)$ is the expected survival from mortality tables. Existing literature has focused exclusively on the estimation of $S_R(t)$ under the independence assumption, $T_1 \perp T_2$. Under independence, $S_O(t) = S_{T_1}(t) \cdot S_{T_2}(t)$, with $S_P(t) = S_{T_2}(t)$ which implies $S_R(t) = S_{T_1}(t)$ where $S_{T_1}(t)$ and $S_{T_2}(t)$ are the survival probabilities corresponding to T_1 and T_2 respectively. The relationship (1) can be rewritten in terms of hazard functions as $\lambda_O(t) = \lambda_E(t) + \lambda_P(t)$ (Cronin and Feuer, 2000), where $\lambda_O(t)$ is the hazard in the disease registry, $\lambda_E(t)$ is the so called excess hazard among the cancer cohort, and $\lambda_P(t)$ is the hazard from mortality tables. Under independence, $\lambda_E(t) = \lambda_{T_1}(t)$ and $\lambda_P(t) = \lambda_{T_2}(t)$, where $\lambda_{T_j}(t) = \frac{-d \log S_{T_j}(t)}{dt}$, $j = 1, 2$, are the net hazard functions for cancer and other cause mortality, respectively. The net survival probability (under independence assumption) $S_{T_1}(t)$ is the target of relative survival analysis and corresponds to a hypothetical population in which death from competing causes does not exist. It differs from the cumulative incidence function which is commonly used to quantify disease-specific survival in analyses with known cause of death information. Under dependence, $S_R(t)$ in (1) has an excess hazard (Suissa, 1999) interpretation since the estimator eliminates the effect of background risk, and is no longer the survival probability $S_{T_1}(t)$.

Relative survival method was pioneered by Berkson and Gage (1950), and Ederer *et al.* (1961) for nonparametric estimation of $S_{T_1}(t)$. A variant of this method was proposed by Hakulinen (1982) to address the bias due to heterogeneity of patient withdrawal within subgroups. Pohar Perme *et al.*, (2012) demonstrated that these classical methods may be biased under certain censoring patterns. For example, in population comparisons, such bias may arise from unmeasured covariates affecting the cancer cohort group and the reference population from which rates of expected mortality are drawn. Rebolj Kodre and Pohar Perme, (2013) studied biases associated with censoring and age distribution (at the time of cancer diagnosis) and proposed weighting corrections. Nixon *et al.* (1994) documented that event times and censoring times are dependent on the age of the patients in a cancer study. Stratified methods (Sasieni and Brentnall, 2017) based on age standardization of relative survival ratios may reduce such biases. Hakulinen *et al.*, (2011) developed alternative estimators valid under weaker assumption.

Several authors (Bolard, *et al.*, 2002; Giorgi, *et al.* 2003; Nelson *et al.*, 2007; Mahboubi, *et al.*, 2011) proposed variations of spline functions to address some of limitations of earlier methods. These models include mainly flexible parametric functions that examine the effects of covariates that potentially influence the estimation of the excess survival. Charvat *et al.*, (2016) introduced spline models for grouped data, where they fitted flexible excess hazard models to cluster data, while Rubio *et al.*, (2019) proposed extensions (beyond proportional hazard method) to the general parametrization of hazard functions and implemented flexible parametric distribution in modelling the event time. However, the above estimation methods for $S_R(t)$ do not model the dependence event times concurrently.

To relax the independence assumption, we formulate the dependence between the latent failure times distributions for death from disease and death from competing causes using copula models (Deheuevls, 1978). A copula function generates a joint distribution for the two event times, taking as input their marginal distributions. Copulas allow a broad range of dependence structures and have been employed widely in survival analysis, including bivariate event times (Oakes, 1982), competing risks with known cause of failure (Heckman and Honoré, 1989), and semi-competing risks where one event time censors the other but not vice versa (Fine *et al.*, 2001). We employ such models with competing risks data from disease registries where cause of death information is either not reliable or not available. Because the joint distribution of the latent failure times is nonparametrically nonidentifiable (Tsiatis, 1975), we treat the copula function as known. The marginal distribution of the time to disease-specific death is modelled parametrically with the distribution of death from other causes drawn from the reference population. Likelihood-based inference is proposed. Because the joint distribution is unidentifiable nonparametrically and unverifiable from the observed registry data, a sensitivity analysis is suggested in which disease-specific survival is estimated across a range of rich dependence structures, specified via the copula func-

tion. To our knowledge, this is the first attempt in modelling dependence between T_1 and T_2 in relative survival analysis.

The main purpose of this method is to provide an alternative estimator for net survival (survival in a hypothetical world where other competing causes of death do not exist) under dependence between cancer mortality and other cause mortality. This is accomplished by explicitly modelling the dependence between cancer mortality and other cause mortality. The rest of this paper proceeds as follows. In section 2, we present the data and copula model formulation for competing risks data. Section 3 describes the likelihood estimation and inference procedure without cause of death information, as well as the proposed sensitivity analysis. In section 4, we present the numerical illustrations including simulation results and application to French breast cancer data. Section 5 discusses and concludes the paper.

2 Data and Model

We begin by defining traditional endpoints for competing risk data with known cause of death. The cause-specific hazard, $\lambda_k(t)$ is the instantaneous failure rate for occurrence of event $\varepsilon = k$ at time t (Prentice et al., 1978),

$$\lambda_k(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < t + \delta t, K = k | T > t)}{\delta t} \quad (2)$$

and the cumulative incidence function $C_k(t)$ is the proportion of patients who died from cause k by time t in the presence of patients who might die from other causes. The cumulative incidence function can be expressed as $C_k(t) = P(T \leq t, \varepsilon = k) = \int_0^t \lambda_k(s) \cdot S(s) ds$ where $S(t) = P(T > t)$ is the overall survival probability. Standard competing risks methods with known cause of failure focus on estimation of $\lambda_k(t)$ and $C_k(t)$.

Without cause of death information, the registry data is simply time to death from any cause, T , which may be right censored by lost to follow up. Let C be the time to right censoring, with the common assumption being that T and C are independent. The observed data consist of $X_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$, where T_i and C_i are the failure and censoring times on individual $i = 1, 2, 3, \dots, n$. Relative survival methods employing such data do not focus on the traditional competing risks endpoints $\lambda_k(t)$ and $C_k(t)$ but rather on the latent failure time distributions with the corresponding survival functions $S_{T_1}(t)$ and $S_{T_2}(t)$.

To capture the dependence between T_1 and T_2 , we employ copula models, which completely describe the dependence structure and provide scale invariant measures of association (Venter, 2002; Müller, 1996; Bäuerle and Müller, 1998; and Denuit *et al.*, 1999). Suppose ψ is a copula generator function defined such that $\psi : [0, 1] \rightarrow [0, +\infty]$, then the j -dimensional copula function is given by $C(u_1, \dots, u_j) = \psi(\psi^{-1}(u_1), \dots, \psi^{-1}(u_j))$ with marginal distributions, $u_j = P(T_j \leq t_j) = F_{T_j}(t_j) = 1 - S_{T_j}(t_j)$, $\forall j \in \mathbb{N}$. When $j = 2$, then, the copula model for the joint distributions of T_1 and T_2 is:

$$C(u_1, u_2) = P(T_1 \leq t_1, T_2 \leq t_2) = \psi(\psi^{-1}(u_1) + \psi^{-1}(u_2)) = F_{T_1, T_2}(t_1, t_2)$$

where ψ^{-1} is the inverse of ψ and ψ satisfies the Laplace-Stieltjes transform and Bernstein (1929) theorem. McNeil and Nešlehová (2009) showed that the generator function ψ is completely monotone for non-negative random variables with $\psi(0) = 1$, $\psi'(\cdot) < 0$ and $\psi''(\cdot) < 0$.

The most widely used scale invariant measures of association to characterize dependence are Spearman's rho (ρ_S) and Kendall's tau (τ_{ken}) correlation coefficients. The connection between the latter and the copula generator function was shown by Genest and MacKay, (1986) as:

$$\tau_{ken} = 1 + 4 \int_0^1 \frac{\psi^{-1}(u)}{\psi^{-1}(u)'} du = 1 - 4 \int_0^1 u(\psi(u))^2 du$$

with ψ^{-1}' being the derivative of ψ^{-1} . While in theory, any copula may be used to link the marginal distributions of T_1 and T_2 , in this paper, we focus on two popular Archimedean copulas, indexed by a single dependence parameter θ having simple interpretations. The Gumbel copula is:

$$C(u_1, u_2) = \exp \left[-\{(-\log(u_1))^\theta + (-\log(u_2))^\theta\}^{\frac{1}{\theta}} \right] \quad (3)$$

with $\theta \in (1, +\infty)$ and the Clayton copula is:

$$C(u_1, u_2) = (u_1^{-\theta} + u_2^{-\theta} - 1)^{-\frac{1}{\theta}} \quad (4)$$

with $\theta \in (0, +\infty)$. A special case of product copula model: $C(u_1, u_2) = u_1 \cdot u_2$ is obtained when $\theta = 1$ and when $\theta \rightarrow 0$ for Gumbel and Clayton copulas respectively. The product copula model gives independence of T_1 and T_2 . When $\theta > 0$, the Clayton copula is bounded by: $C(u_1, u_2) \leq \theta(1 - u_1 - u_2) + (1 + \theta)u_1u_2$. As dependence increases, that is $\theta \rightarrow +\infty$, the Clayton copula approximates the Fréchet-Hoeffding upper bound, (Fréchet, 1951; and Hoeffding, 1940) giving perfect positive dependence.

3 Likelihood Estimation and Inference

We first formulate our model without covariates for the potentially dependent latent failure times T_1 and T_2 . In the sequel, the distribution of T_1 involves an unknown parameter η , while that of T_2 is assumed from a reference population. The distribution of T implicitly involves η via $T = \min(T_1, T_2)$. The survival function for all-cause mortality at time t given η is:

$$\begin{aligned} S_T(t|\eta) &= S_{T_1}(t|\eta) + S_{T_2}(t) - 1 + F_{T_1, T_2}(t, t|\eta) \\ &= 1 - F_{T_1}(t|\eta) - F_{T_2}(t) + F_{T_1, T_2}(t, t|\eta) \end{aligned} \quad (5)$$

with the corresponding density function using $F_T(t|\eta) = F_{T_1}(t|\eta) + F_{T_2}(t) - F_{T_1, T_2}(t, t|\eta)$

$$f_T(t|\eta) = f_{T_1}(t|\eta) + f_{T_2}(t) - f_{T_1, T_2}(t, t|\eta) \quad (6)$$

where $f_{T_1}(t|\eta) = \frac{dF_{T_1}(t|\eta)}{dt}$, $f_{T_1, T_2}(t, t|\eta) = \frac{dF_{T_1, T_2}(t, t|\eta)}{dt}$ and $f_{T_2}(t)$ is derived from the reference population. If censoring of T by C is noninformative, then the likelihood contribution for individual i is:

$$L_i = f_{X_i, \Delta_i}(X_i, \delta_i|\eta) = [f_T(X_i|\eta)]^{\delta_i} [S_T(X_i|\eta)]^{1-\delta_i} \quad (7)$$

From equation (7), the full log-likelihood function based on n independent observations is:

$$\begin{aligned} l(\mathbf{X}, \Delta|\eta) &= \sum_{i=1}^n (\delta_i * \log f_T(X_i|\eta) + (1 - \delta_i) * \log S_T(X_i|\eta)) \\ &= \sum_{i=1}^n \delta_i * \log [f_{T_1}(X_i|\eta) + f_{T_2}(X_i) - f_{T_1, T_2}(X_i, X_i|\eta)] \\ &\quad + \sum_{i=1}^n (1 - \delta_i) * \log [S_{T_1}(X_i|\eta) + S_{T_2}(X_i) - 1 + F_{T_1, T_2}(X_i, X_i|\eta)] \end{aligned} \quad (8)$$

where $(\mathbf{X}, \Delta) = (X_i, \Delta_i, i = 1, 2, 3, \dots, n)$.

We specify a parametric model for $F_{T_1}(t)$, with finite dimensional parameter of interest η . The general form of the probability density function for T_1 at time t is $f_{T_1}(t|\eta)$ with survival probability $S_{T_1}(t|\eta) = 1 - F_{T_1}(t|\eta) = \int_t^\infty f_{T_1}(s|\eta)ds$. The distribution of T_2 is assumed known and extracted from the reference population with the usual assumption that disease-specific death is negligible in this reference population (Ederer, et al. 1961). This is illustrated in the French breast cancer data analysis in section 4.2. The copula distribution linking $F_{T_1}(t|\eta)$ and $F_{T_2}(t)$ may be specified using simple parametric copula models such as the Archimedean copulas. The parameters in the copula model may be chosen for a pre-specified dependence between T_1 and T_2 , for example, Kendall's tau (τ_{ken}). In the numerical illustrations, T_1 was assumed to follow an exponentiated Weibull distribution with parameter $\eta = (\lambda, \kappa, \alpha)$ and probability density function $f(t : \lambda, \kappa, \alpha) = \alpha \frac{\kappa}{\lambda} \cdot \left(\frac{t}{\lambda}\right)^{\kappa-1} \cdot \exp\left\{-\left(\frac{t}{\lambda}\right)^\kappa\right\} \left(1 - \exp\left\{-\left(\frac{t}{\lambda}\right)^\kappa\right\}\right)^{\alpha-1}$ because of its versatility to accommodate a wide range of hazard shapes. We consider the Gumbel and Clayton copulas for the joint distribution of T_1 and T_2 as both copulas exhibit tail behaviours that mimic the mortality trend observed in the cancer registry data. The bivariate joint distribution and density functions under the Gumbel copula are given below.

$$\begin{aligned} F_{T_1, T_2}(t|\eta, t) &= \exp\left\{-\left(\left(-\log(F_{T_1}(t|\eta))\right)^\theta + \left(-\log(F_{T_2}(t))\right)^\theta\right)^{\frac{1}{\theta}}\right\} \\ f_{T_1, T_2}(t|\eta, t) &= F_{T_1, T_2}(t|\eta, t) \cdot \left(\left(-\log(F_{T_1}(t|\eta))\right)^\theta + \left(-\log(F_{T_2}(t))\right)^\theta\right)^{\frac{1}{\theta}-1} \\ &\quad \times \left(\left(-\log(F_{T_1}(t|\eta))\right)^{\theta-1} \cdot \frac{f_{T_1}(t|\eta)}{F_{T_1}(t|\eta)} + \left(-\log(F_{T_2}(t))\right)^{\theta-1} \cdot \frac{f_{T_2}(t)}{F_{T_2}(t)}\right) \end{aligned} \quad (9)$$

Under the Clayton copula, the bivariate joint distribution and density functions are:

$$\begin{aligned} F_{T_1, T_2}(t|\eta, t) &= \left(F_{T_1}(t|\eta)^{-\theta} + F_{T_2}(t)^{-\theta} - 1\right)^{-\frac{1}{\theta}} \\ f_{T_1, T_2}(t|\eta, t) &= \frac{F_{T_1, T_2}(t|\eta, t)}{\left(F_{T_1}(t|\eta)^{-\theta} + F_{T_2}(t)^{-\theta} - 1\right)} \cdot \left(\frac{f_{T_1}(t|\eta)}{F_{T_1}(t|\eta)^{\theta+1}} + \frac{f_{T_2}(t)}{F_{T_2}(t)^{\theta+1}}\right) \end{aligned} \quad (10)$$

The maximum likelihood estimator (MLE) of η can be obtained by maximizing the log-likelihood function in (8) using any optimization algorithm such as Nelder-Mead (Nelder and Mead, 1965) or better. In the simulation in section 4.1, and because the model is highly nonlinear for hazard shapes and the estimation of dependent parameter θ , we suggest using multiple starting values and taking the MLE to be the maximizer giving the largest value of the log likelihood across all starting values. Under a fixed and correctly specified copula, the

usual regularity conditions for the MLE holds and the estimator converges in probability, that is $\hat{\eta} \xrightarrow{P} \eta$ and is asymptotically normal, $\hat{\eta} \sim N(\eta, I_O(\eta)^{-1})$ with variance estimated using the inverse of the observed information matrix

$$\begin{aligned}
I_O(\hat{\eta}) &= -\frac{\partial^2 l(\mathbf{X}, \Delta | \eta)}{\partial \eta \partial \eta^T} \Big|_{\eta=\hat{\eta}} \\
&= -\left\{ \delta_i \cdot \sum_{i=1}^n \left\{ \frac{[f_T(X_i | \eta)] \cdot \left[\frac{\partial^2}{\partial \eta^2} f_T(X_i | \eta) \right] - \left[\frac{\partial}{\partial \eta} f_T(X_i | \eta) \right]^T \left[\frac{\partial}{\partial \eta} f_T(X_i | \eta) \right]}{[f_T(X_i | \eta)]^2} \right\} \right. \\
&\quad \left. + (1 - \delta_i) \cdot \sum_{i=1}^n \left\{ \frac{[S_T(X_i | \eta)] \cdot \left[\frac{\partial^2}{\partial \eta^2} S_T(X_i | \eta) \right] - \left[\frac{\partial}{\partial \eta} S_T(X_i | \eta) \right]^T \left[\frac{\partial}{\partial \eta} S_T(X_i | \eta) \right]}{[S_T(X_i | \eta)]^2} \right\} \right\} \Big|_{\eta=\hat{\eta}}
\end{aligned} \tag{11}$$

Since the dependence structure for time to disease-specific mortality (T_1) and time to other competing mortality (T_2) is nonidentifiable and unverifiable from the observed registry data, we propose a sensitivity analysis, where the analysis is conducted across a range of assumed dependence structures. The levels of dependence represent the varying levels of dependent competing mortality possible in the observed registry data. For each copula dependence structure with known θ , we estimate η with $\hat{\eta}$ and compute $F_{T_1}(t|\hat{\eta})$ to estimate relative survival. The corresponding standard errors are obtained as the square root of the Delta method variance: $Var(\widehat{S_{T_1}}(X)) = g(\widehat{S_{T_1}}(X)) \cdot I_O(\hat{\eta})^{-1} \cdot g^T(\widehat{S_{T_1}}(X))$ where $g(\eta)$ is the derivative of $S_{T_1}(t|\eta)$ with respect to η . Due to the complex nature of the likelihood, numerical approximation is used to estimate the information matrix in the numerical illustrations in Section 4.

In the presence of informative censoring where T and C are dependent, we propose conditioning on additional covariates Z in F_{T_2} , (Sasieni and Brentnall, 2017; and Pohar Perme et al., 2012), where $F_{T_2}(t|Z)$ is the conditional distribution of T_2 given Z. Such covariates might include age, sex, period, as well as other relevant demographic variables. Let Z_i be the covariate observed on individual $i = 1, \dots, n$. The log-likelihood function (8) is easily modified, where the likelihood contribution for individual $i (= 1, \dots, n)$ is (7) with $F_{T_2}(t|Z_i)$ replacing $F_{T_2}(t)$ in $f_T(X_i|\eta)$ and $S_T(X_i|\eta)$. Here, we estimate η in $F_{T_1}(t|\eta)$ conditionally on Z to mitigate against the bias (caused by informative censoring) associated with these covariates (Pohar Perme et al, 2012; and Sasieni and Brentnall, 2017, Schaffar, et al., 2017). The usual likelihood regularity conditions continue to hold, with the resulting estimator $\hat{\eta}$ being consistent and asymptotically normal with variance which may be estimated using the inverse of the observed information matrix evaluated at $\hat{\eta}$.

4 Numerical Illustrations

4.1 Simulation Studies

To evaluate the performance of our proposed method, first, we simulated a general survival time data $T_j \sim ExpWeibull(\lambda_j, \kappa_j, \alpha_j)$, and second, to mimic the French breast cancer data set for sample sizes; 1000, 2500 and 5000 with 500 replications. The latent failure times for T_j with probability density function defined above in Section 3 and parameters as in figure 1. The exponentiated Weibull distribution degenerates to a 2-parameter Weibull distribution when $\alpha = 1$. The parameters for the reparametrized Weibull distribution for T_1 were $\lambda_1 = 0.182$ and $\alpha_1 = 1.609$, while those for T_2 were $\lambda_2 = 0.742$ and $\alpha_2 = 0.693$. In the estimation of λ_1, α_1 for T_1, λ_2, α_2 are assumed known for T_2 and vice versa for the estimation of λ_2 and α_2 . Noninformative censoring times were generated from a uniform distribution $(0, \gamma)$, where γ was chosen for 10, 30 (omitted from table) and 50% censoring. We consider the Gumbel copula with Kendall's tau, $\tau_{ken} = 1 - \frac{1}{\theta} = 0, 0.25, 0.50,$ and 0.75. Initial parameter values were randomly chosen from uniform distributions, with multiple starting values (wherever possible) as described in Section 3. We also simulated data from the Clayton copula. The results are similar to those for the Gumbel copula and are described in the appendix. Tables 1, 5 and 6 show the results for estimation of the model for T_1 treating T_2 as a competing event and for T_2 treating T_1 (for brevity, tables 5 and 6 show results for selected sample sizes) as a competing event. The bias is small decreasing to zero as the sample size increases for each of the censoring levels. The empirical variance and the model based variance tend to agree and the coverage is close to the nominal 0.95 level, particularly at larger sample sizes. The empirical variance decreases as the sample size increases at roughly the expected root n rate. Table 4 shows the robust survival estimates for the mis-specified model (data simulation from exponentiated Weibull but Weibull survival estimated instead) for T_1 treating T_2 as competing risk. We presented the results for the lower, mean and upper quantiles for each of the sample sizes and dependence levels. This shows decreasing bias for increasing sample sizes for each of the quantiles.

Table 1: Estimated parameters for the exponentiated Weibull model for T_1 across samples sizes (N), dependence levels (τ_{ken}) and for 15% censoring treating T_2 as a competing event. $\hat{\eta}$: estimated parameters: λ , scale, α , and κ are shape parameters, ModB: model-based variance, EMP: empirical variance, CP: 95% coverage probability.

τ_{ken}	N	$\hat{\eta}$	Mean	Bias	ModB	EMP	CP
0.00	1000	$\hat{\lambda}$	2.936	-0.064	0.069	0.056	0.960
		$\hat{\kappa}$	4.198	0.198	8.663	3.873	0.848
		$\hat{\alpha}$	0.120	0.020	0.004	0.003	0.942
	2500	$\hat{\lambda}$	2.965	-0.035	0.025	0.023	0.949
		$\hat{\kappa}$	4.180	0.180	2.839	2.305	0.885
		$\hat{\alpha}$	0.109	0.009	0.001	0.002	0.894
	5000	$\hat{\lambda}$	2.994	-0.006	0.012	0.012	0.947
		$\hat{\kappa}$	4.264	0.264	1.446	1.250	0.947
		$\hat{\alpha}$	0.100	1.6e-4	0.001	0.001	0.931
0.25	1000	$\hat{\lambda}$	3.001	0.001	0.051	0.062	0.924
		$\hat{\kappa}$	4.912	0.912	3.042	14.274	0.922
		$\hat{\alpha}$	0.101	0.001	0.002	0.002	0.896
	2500	$\hat{\lambda}$	3.005	0.005	0.019	0.018	0.960
		$\hat{\kappa}$	4.213	0.213	0.765	0.829	0.958
		$\hat{\alpha}$	0.100	0.000	0.000	0.001	0.928
	5000	$\hat{\lambda}$	2.998	-0.002	0.009	0.008	0.960
		$\hat{\kappa}$	4.082	0.082	0.300	0.297	0.958
		$\hat{\alpha}$	0.100	1.0e-5	2.0e-4	2.5e-4	0.958
0.50	1000	$\hat{\lambda}$	3.003	0.003	0.036	0.038	0.954
		$\hat{\kappa}$	4.376	0.376	1.645	1.898	0.952
		$\hat{\alpha}$	0.100	3.3e-4	0.001	0.001	0.920
	2500	$\hat{\lambda}$	3.006	0.006	0.014	0.014	0.950
		$\hat{\kappa}$	4.147	0.147	0.439	0.523	0.938
		$\hat{\alpha}$	0.100	1.7e-5	2.6e-4	0.001	0.934
	5000	$\hat{\lambda}$	3.002	0.002	0.007	0.007	0.964
		$\hat{\kappa}$	4.072	0.072	0.185	0.187	0.948
		$\hat{\alpha}$	0.099	-5.7e-4	1.2e-4	1.4e-4	0.940
0.75	1000	$\hat{\lambda}$	3.003	0.003	0.027	0.042	0.942
		$\hat{\kappa}$	4.266	0.266	1.101	1.146	0.950
		$\hat{\alpha}$	0.102	0.002	0.001	0.007	0.926
	2500	$\hat{\lambda}$	3.006	0.006	0.011	0.010	0.942
		$\hat{\kappa}$	4.132	0.132	0.323	0.330	0.954
		$\hat{\alpha}$	0.099	-0.001	2.0e-4	2.0e-4	0.938
	5000	$\hat{\lambda}$	3.004	0.004	0.005	0.005	0.952
		$\hat{\kappa}$	4.066	0.066	0.145	0.145	0.956
		$\hat{\alpha}$	0.099	-0.001	9.7e-5	1.1e-4	0.934

Table 2: The 2, 5, 10 and 15-yr overall net survival for French women diagnosed with breast cancer between 1980 and 2011. $a : \times 10^{-2}$, $b : \times 10^{-3}$, τ_{ken} : dependence, PP: Pohar-Perme, $S_{T_1}(t)$: survival estimate at year t , SE: standard error for the relative survival estimate.

τ_{ken}	Independent Competing Risks				Dependent Competing Risks				
	0.00		0.25		0.50		0.75		
	t	PP^a	SE^b	$S_{T_1}(t)^a$	SE^b	$S_{T_1}(t)^a$	SE^b	$S_{T_1}(t)^a$	SE^b
2	95.6	96.0	6.99	95.8	6.96	95.4	7.23	94.7	7.74
5	84.8	87.4	9.01	86.6	9.10	85.5	9.31	84.0	9.53
10	71.0	72.8	11.01	71.4	10.99	69.8	10.91	68.0	10.67
15	59.5	59.5	12.22	57.9	12.08	56.3	11.74	54.9	11.19

4.2 Application to French Breast Cancer Data

In this section we analyze data from women between the ages of 18 and 96 years surviving breast cancer in France from 1980 to 2011. The data were obtained from the Institut Curie breast cancer database. This database contains records from 24,458 nonmetastatic breast cancer patients treated at the Institut Curie. Out of the 24,458 breast cancer patients, 9,885 (40.4%) died while 14,573 were alive and administratively censored on December 31st 2011. Five age group categories were considered for the estimation of relative survival. 3,970 were between the ages of 15 – 44, 6,895 between the ages of 45 – 54, 6,420 between the ages of 55 – 64, 4,675 between the ages of 65 – 74 and 2,498 were in the 75 – 99 age group category. We individually matched the observed death or censoring time in the disease cohort group with a corresponding time in the general reference population on age, sex, and year (date of diagnosis and the date of death or censored) for each participant and for each follow-up period. The background mortality data from the Human Mortality Database (<https://www.mortality.org>) was last modified on June 28, 2018. Within each follow-up year, we assumed that $\lambda_P(t)$ is piecewise constant (Dickman *et al.*, 2004) for each period up to time X . The cumulative hazard for each period based on $\lambda_P(t)$ is calculated from the background survival function at the beginning and end of the period. The cumulative hazard is then used to obtain $\lambda_P(t)$ under the piecewise constant assumption. The goal of matching in determining $\lambda_{T_2} = \lambda_P$ is to mitigate the impact of age and calendar year on potentially dependent censoring by C (Pohar Perme *et al.*, 2012). Thus, our approach is stratified by age, sex and year. We estimate 2, 5, 10, and 15–year relative survival assuming a Weibull distribution for T_1 and a Gumbel copula model with differing levels of dependence to specify the joint distribution for T_1 and T_2 . We compared our estimates with estimates from Pohar Perme *et al.* (2012), which require independence of T_1 and T_2 with $S_{T_2}(t)$ derived from the background reference population.

Tables 2 and 3 show the estimates of $S_{T_1}(t)$ for cancer mortality both overall and stratified by age. The parametric estimates under independence are similar to those from the Pohar-Perme method. This suggests that the Weibull assumption is a reasonable fit to the data. One observes that as dependence increases, cancer survival generally decreases. For a fixed dependence level, younger women tend to have higher cancer survival rates than do older women, with marked reductions for the 65-74 and 75-99 age groups. There is some instability in survival estimates at 15 years, especially for the older age groups, as evidenced by the large standard errors. This may be due to small numbers of patients at risk at longer follow-up times.

The net survival function for cancer corresponds to a hypothetical world where the only cause of death is breast cancer. This quantity can only be estimated under unverifiable dependence assumptions between T_1 and T_2 using disease registry data. To account for uncertainty in dependence, we recommend reporting a range of probabilities corresponding to differing levels of dependence. For example, using results from table 2, the overall 5 year net breast cancer survival from 1980 – 2011 is estimated to be between 84.0-87.4% under dependence ranging from Kendall’s tau equal to 0 (independence) to 0.75 (strong dependence). These cancer survival probabilities may be meaningfully compared with those in other populations having different background mortality rates and different dependence levels between T_1 and T_2 .

The sensitivity analysis was conducted across different levels of dependence representing different competing mortality potentially observable in the registry data. Figures 2 and 3 show the 2, 5, 10 and 15-yr overall net breast survival plots across a spectrum of dependence structures for women between the ages of 18 and 96-yr living in France during 2008 and 2011. As the dependence level increases, the net breast cancer survival decreases dramatically. Perhaps, this might be due to increase hazard for the patients compounding the effect of competing mortality hereby decreasing the chances of survival.

5 Discussion and Conclusion

Our model formulation for competing risk data without cause of failure information is general, permitting arbitrary but known copula functions. The distribution of other cause mortality is obtained from external reference data

(Sarfati *et al.*, 2010; Pohar Perme *et al.*, 2012; Sasieni and Brentnall, 2017). We have undertaken preliminary investigations of simultaneous estimation of the dependence parameter and the parameter in the disease-specific survival distribution. There is evidence of instability in the estimation process especially at the boundary values,

Table 3: The 2, 5, 10 and 15-yr age group specific net breast cancer survival among French women diagnosed between 1980 and 2011. $a : \times 10^{-2}$, $b : \times 10^{-3}$, τ_{ken} : dependence, PP: Pohar-Perme, $S_{T_1}(t)$: relative survival estimate at year t, SE: standard error for the relative survival estimate.

τ_{ken}	Independent Competing Risks					Dependent Competing Risks				
	t	Agegp	PP ^a	$S_{T_1}(t)^a$	SE ^b	0.25	0.50	0.75	$S_{T_1}(t)^a$	SE ^b
2	15-44	95.8	94.9	20.90	94.9	20.73	94.8	20.73	94.8	20.68
	45-54	97.1	96.6	16.44	96.5	16.13	96.3	16.27	96.2	16.40
	55-64	95.7	96.1	13.72	96.0	13.49	95.7	13.70	95.3	14.12
	65-74	95.1	97.0	08.50	96.8	08.54	96.2	09.61	95.1	11.60
	75-99	91.5	96.5	07.94	95.6	08.93	93.4	12.44	89.9	17.16
5	15-44	85.1	86.9	23.70	86.8	23.64	86.7	23.62	86.7	23.35
	45-54	88.6	90.4	19.39	90.1	19.36	89.8	19.45	89.7	19.28
	55-64	85.8	88.1	17.72	87.6	17.71	86.9	17.87	86.6	17.66
	65-74	84.1	86.9	16.71	85.8	17.01	84.2	17.71	82.5	18.09
	75-99	72.3	77.1	24.21	72.7	24.85	67.1	25.08	61.7	24.00
10	15-44	71.9	74.4	26.88	74.2	26.84	74.0	26.75	74.1	26.62
	45-54	78.3	80.1	22.83	79.6	22.80	79.2	22.73	79.2	22.34
	55-64	73.4	74.5	22.03	73.5	21.97	72.7	21.74	72.7	21.08
	65-74	68.4	67.2	25.38	65.0	25.32	63.0	24.72	62.3	23.20
	75-99	44.6	43.1	34.83	37.0	32.55	33.0	28.61	31.1	24.35
15	15-44	62.5	63.2	29.03	63.0	28.96	62.9	28.83	63.0	28.72
	45-54	70.8	70.5	25.31	69.8	25.24	69.4	25.00	69.6	24.51
	55-64	63.5	61.9	24.81	60.7	24.62	59.9	24.11	60.3	23.20
	65-74	50.3	48.7	30.06	46.2	29.46	44.7	27.92	45.3	25.47

Table 4: Robust survival probability for a misspecified exponentiated Weibull model for T_1 across samples sizes (N), dependence levels (τ_{ken}) and for 16% censoring treating T_2 as a competing event. \hat{S}_w : estimated Weibull survival probability, and associated bias at the 0.25, 0.50, and 0.75 quantiles.

τ_{ken}	N	Survival Quantiles			Bias Quantiles		
		$\widehat{sw.25}$	$\widehat{sw.50}$	$\widehat{sw.75}$	Bias.25	Bias.50	Bias.75
0.00	1000	0.373	0.532	0.751	-19.5e-4	25.4e-3	11.7e-3
	2500	0.372	0.532	0.750	-16.8e-4	26.0e-3	12.3e-3
	5000	0.372	0.532	0.751	-15.1e-4	26.1e-3	12.3e-3
0.25	1000	0.363	0.533	0.755	-14.7e-3	18.5e-3	68.6e-4
	2500	0.362	0.532	0.754	-14.2e-3	19.1e-3	74.9e-4
	5000	0.362	0.532	0.754	-13.6e-3	19.6e-3	78.0e-4
0.50	1000	0.345	0.527	0.758	-17.1e-3	17.8e-3	31.2e-4
	2500	0.345	0.527	0.758	-16.7e-3	18.4e-3	36.2e-4
	5000	0.345	0.527	0.758	-16.3e-3	18.7e-3	38.7e-4
0.75	1000	0.326	0.521	0.761	-74.6e-4	22.5e-3	-5.1e-4
	2500	0.325	0.519	0.761	-64.8e-4	23.4e-3	-1.9e-05
	5000	0.325	0.519	0.761	-61.6e-4	23.8e-3	2.1e-05

with care needed in the model specification to aid estimability of the model parameters. This is expected (see Zahl, 1997 for challenges), as there are similar issues even when the cause of failure is known. The proposed sensitivity analysis is a practical solution to this issue, providing a range of estimates across different dependence levels not requiring simultaneous estimation of the dependence parameter. The parametric model for disease-specific mortality is restrictive but may be flexible enough for applications where the hazard is smooth over time, which is the case in cancer registry data. Estimating expected hazard or the distribution of T_2 from life tables is limiting as mismatches in covariates and other stratifying variables may also induce biases, Rubio et al (2021). However, it is important to note that our estimator is robust and arguably invariant to the parameter estimates under different specifications of the copula models as shown in the parameter estimates for both Gumbel and Clayton copulas (tables 5 and 6). To relax the parametric assumption, nonparametric techniques are currently being developed for use in more complex failure patterns.

The focus of relative or net survival analysis is the distribution of the latent event time for death from disease. This endpoint has been advocated by many practitioners (Slud *et al.*, 1988; Reason, 1990; and Louzada *et al.*, 2015), as it removes the impact of other cause mortality on the risk of disease-specific mortality, permitting comparisons across populations with different background mortality. As an alternative, other work has considered estimation of the crude disease-specific survival, $C_k(t)$, using the relative survival estimates and the known reference hazard for other cause mortality (Cronin and Feuer, 2000). An analogous procedure could be implemented using our copula based estimate of the distribution of T_1 and would provide an assessment of the sensitivity of the estimator of C_k under independence of T_1 and T_2 . Such procedure would be of interest to individuals who prefer crude disease-specific mortality to net disease-specific mortality. This and time-dependent models are topics for future research.

Our proposed estimator performed well overall and by subgroup analysis. We observed that in cases of elderly patients, long-term survival decreases dramatically as expected. Perhaps this might be due to elderly patients experiencing higher expected mortality rates than younger patients particularly in terms of higher risk of death from other competing causes leading to loss of patients at longer follow-up times. This loss of information induces higher variability in net survival estimates for this elderly populations, thereby inducing a higher variability as observed in the variance. Net survival under dependence competing risk assumption is observable and does not require additive model as in the case for net survival (in hypothetical world) under the independence assumption. Our estimator modelled both the dependence between times to disease-specific event and competing risk event with covariates like age, sex, and period (date of diagnosis and date of event: death or censored). Since it's been known (Nanieli, et. al., 2012) that such covariates affect both excess and expected hazards estimates. We conditioned on these covariates (Pohar-Perme (2012) by matching cancer cohort data with registry data to alleviate biases associated with informative censoring as done in multivariable modelling techniques (Bolard, et. al., (2002), Giorgi, et. al., (2003), Lambert, et. al., (2005), Remontet, et. al., (2007)) where estimators are adjusted for life-table covariates. Researchers are encouraged to use a patients' medical history in determining the levels of competing risks and use a corresponding dependence survival estimate (independence, low, moderate or high) as a measure for disease-specific prognosis.

In conclusion, our proposed methodology provides estimates for net survival under both independent and dependent competing mortality. On the contrary, Pohar-Perme et al., (2012) estimator is only valid under the independent competing risk assumption. Additionally, Pohar-Perme et al., (2012) estimator may exceed 1 in the left tail. Schaffar et al., (2017) showed that these erratic results may occur with longer follow-up times. Our estimator provides comparable relative or net survival estimates under both independent and dependent competing risk assumptions without the need for cause of disease-specific event in the competing risks setting.

Conflict of Interest

None declared

Appendix

Simulation Results for Gumbel and Clayton Copula Models

We simulated data to mimic the French breast cancer data set for sample sizes; 1000, and 5000 with 500 replications. The latent failure times for $T_j \sim Weibull(\alpha_j, \lambda_j)$ with probability density function defined in section 3. The parameters for the Weibull distribution for T_1 were $\lambda_1 = 0.182$ and $\alpha_1 = 1.609$, while those for T_2 were $\lambda_2 = 0.742$ and $\alpha_2 = 0.693$. In the estimation of λ_1, α_1 for T_1, λ_2, α_2 are assumed known for T_2 , and vice versa for estimation of λ_2, α_2 . Noninformative censoring times were generated from a uniform distribution $(0, \gamma)$, where γ was chosen for 10, 30 and 50% censoring. We consider the Clayton copula with Kendall's tau, $\tau_{ken} = \frac{\theta}{\theta+2} = 0, 0.25, 0.50, 0.75$. Initial parameter values were randomly chosen from uniform distributions, with multiple starting values as described in section 3. The simulation results based on the Clayton copula are presented in the table 4 below.

Table 5: Gumbel Model: Estimated parameters of the Weibull model for T_1 across samples sizes (N), dependence levels (τ_{ken}) and levels of censoring (C) treating T_2 as a competing event and vice versa. $\hat{\eta}$: estimated parameters, ModB: model-based variance, EMP: empirical variance, CP: 95% coverage probability. $^a : \times 10^{-3}$.

τ_{ken}	C		0.10					0.50				
	N	$\hat{\eta}$	Mean	Bias ^a	ModB ^a	EMP ^a	CP	Mean	Bias ^a	ModB ^a	EMP ^a	CP
0.00	1000	$\hat{\lambda}_1$	0.182	-0.080	0.090	0.090	0.940	0.182	-0.290	0.150	0.170	0.928
		$\hat{\alpha}_1$	1.610	0.790	1.420	1.560	0.938	1.611	1.980	2.620	2.720	0.950
	5000	$\hat{\lambda}_1$	0.182	-0.050	0.020	0.020	0.948	0.182	0.050	0.030	0.030	0.958
		$\hat{\alpha}_1$	1.610	0.520	0.280	0.280	0.954	1.610	0.290	0.520	0.530	0.956
	1000	$\hat{\lambda}_2$	0.748	5.980	9.940	10.270	0.936	0.746	3.650	14.410	15.320	0.922
		$\hat{\alpha}_2$	0.694	0.840	6.790	7.020	0.944	0.697	4.070	8.490	0.010	0.948
5000	$\hat{\lambda}_2$	0.743	0.630	1.870	1.640	0.962	0.743	1.000	2.700	2.460	0.968	
	$\hat{\alpha}_2$	0.693	0.100	1.340	1.210	0.962	0.693	0.280	1.680	1.530	0.958	
0.25	1000	$\hat{\lambda}_1$	0.182	-0.480	0.080	0.080	0.948	0.182	-0.450	0.140	0.130	0.954
		$\hat{\alpha}_1$	1.610	1.490	1.310	1.340	0.952	1.613	3.960	2.480	2.840	0.934
	5000	$\hat{\lambda}_1$	0.182	-0.050	0.020	0.020	0.956	0.182	-0.130	0.030	0.030	0.940
		$\hat{\alpha}_1$	1.609	-0.250	0.260	0.240	0.956	1.610	0.590	0.500	0.460	0.950
	1000	$\hat{\lambda}_2$	0.753	10.920	14.700	14.430	0.938	0.760	18.430	20.460	20.810	0.946
		$\hat{\alpha}_2$	0.690	-3.170	8.240	7.930	0.954	0.687	-5.930	10.080	9.900	0.944
5000	$\hat{\lambda}_2$	0.741	-0.950	2.690	2.530	0.950	0.742	0.260	3.620	3.580	0.964	
	$\hat{\alpha}_2$	0.695	1.940	1.610	1.480	0.958	0.695	2.260	1.960	1.940	0.948	
0.50	1000	$\hat{\lambda}_1$	0.182	-0.030	0.070	0.070	0.956	0.182	-0.260	0.120	0.120	0.954
		$\hat{\alpha}_1$	1.611	2.270	1.270	1.300	0.948	1.613	3.840	2.380	2.710	0.928
	5000	$\hat{\lambda}_1$	0.182	0.010	0.010	0.020	0.946	1.824	0.040	0.020	0.030	0.956
		$\hat{\alpha}_1$	1.609	-0.340	0.250	0.240	0.954	1.610	0.450	0.480	0.510	0.932
	1000	$\hat{\lambda}_2$	0.759	17.440	19.080	20.140	0.932	0.767	25.540	25.050	25.330	0.932
		$\hat{\alpha}_2$	0.688	-5.180	9.440	9.910	0.944	0.684	-9.170	11.210	11.510	0.940
5000	$\hat{\lambda}_2$	0.740	-1.580	3.360	3.380	0.944	0.744	1.620	4.340	4.660	0.946	
	$\hat{\alpha}_2$	0.695	1.720	1.820	1.870	0.936	0.692	-0.750	2.150	2.270	0.944	
0.75	1000	$\hat{\lambda}_1$	0.182	-0.200	0.060	0.070	0.956	0.182	-0.260	0.100	0.100	0.948
		$\hat{\alpha}_1$	1.610	0.490	1.060	1.520	0.936	1.612	2.660	2.090	2.370	0.942
	5000	$\hat{\lambda}_1$	0.182	0.050	0.010	0.010	0.948	0.182	-0.020	0.020	0.020	0.952
		$\hat{\alpha}_1$	1.609	-0.010	0.210	0.210	0.944	1.609	-0.120	0.420	0.450	0.948
	1000	$\hat{\lambda}_2$	0.760	17.780	20.190	20.360	0.938	0.766	24.200	26.040	25.790	0.952
		$\hat{\alpha}_2$	0.689	-4.600	9.870	10.440	0.946	0.685	-7.510	11.580	11.590	0.956
5000	$\hat{\lambda}_2$	0.742	-0.190	3.540	3.770	0.946	0.743	0.830	4.440	4.540	0.950	
	$\hat{\alpha}_2$	0.694	0.550	1.900	1.990	0.930	0.693	0.350	2.210	2.280	0.944	

Table 6: Clayton Model: Estimated parameters of the Weibull model for T_1 across samples sizes (N), dependence levels (τ_{ken}) and levels of censoring (C) treating T_2 as a competing event and vice versa. $\hat{\eta}$: estimated parameters, ModB: model-based variance, EMP: empirical variance, CP: 95% coverage probability. $^a : \times 10^{-3}$.

τ_{ken}	C		0.10					0.50					
	N	$\hat{\eta}$	Mean	Bias ^a	ModB ^a	EMP ^a	CP	Mean	Bias ^a	ModB ^a	EMP ^a	CP	
0.00	1000	$\hat{\lambda}_1$	0.182	0.000	0.080	0.090	0.948	0.182	-0.340	0.140	0.160	0.930	
		$\hat{\alpha}_1$	1.610	0.710	1.390	1.520	0.942	1.611	1.820	2.490	2.540	0.948	
	5000	$\hat{\lambda}_1$	0.182	-0.020	0.020	0.020	0.942	0.182	0.060	0.030	0.030	0.946	
		$\hat{\alpha}_1$	1.610	0.520	0.280	0.280	0.956	1.610	0.710	0.500	0.510	0.952	
	1000	$\hat{\lambda}_1$		0.747	5.910	9.750	9.910	0.940	0.746	3.570	14.010	14.150	0.922
			$\hat{\alpha}_1$	0.694	0.780	6.720	6.950	0.948	0.696	3.840	8.360	8.590	0.956
5000		$\hat{\lambda}_1$	0.742	0.690	1.840	1.610	0.962	0.742	0.880	2.640	2.380	0.964	
		$\hat{\alpha}_1$	0.693	0.050	1.330	1.200	0.962	0.693	0.320	1.650	1.490	0.956	
0.25	1000	$\hat{\lambda}_1$	0.182	-0.010	0.070	0.080	0.952	0.182	-0.670	0.130	0.110	0.964	
		$\hat{\alpha}_1$	1.610	0.560	1.280	1.410	0.930	1.611	1.870	2.390	0.220	0.952	
	5000	$\hat{\lambda}_1$	0.182	-0.180	0.010	0.010	0.946	0.182	-0.120	0.020	0.020	0.940	
		$\hat{\alpha}_1$	1.609	-0.310	0.230	0.230	0.950	1.609	-0.030	0.430	0.450	0.958	
	1000	$\hat{\lambda}_1$		0.751	9.200	16.630	17.220	0.924	0.749	7.170	21.000	1.610	0.914
			$\hat{\alpha}_2$	0.693	0.200	8.520	8.840	0.940	0.696	2.890	10.090	10.680	0.942
5000		$\hat{\lambda}_2$	0.742	0.460	2.980	2.690	0.952	0.744	2.080	3.840	3.690	0.940	
		$\hat{\alpha}_2$	0.693	0.550	1.660	1.54	0.950	0.693	0.140	1.980	1.930	0.942	
0.50	1000	$\hat{\lambda}_1$	0.182	-0.090	0.060	0.050	0.956	0.182	-0.440	0.100	0.100	0.964	
		$\hat{\alpha}_1$	1.608	-0.980	1.030	1.090	0.952	1.612	2.580	2.020	2.060	0.968	
	5000	$\hat{\lambda}_1$	0.182	-0.180	0.010	0.010	0.936	0.182	-0.180	0.020	0.020	0.940	
		$\hat{\alpha}_1$	1.609	-0.190	0.200	0.210	0.952	1.610	0.240	0.400	0.410	0.948	
	1000	$\hat{\lambda}_2$		0.750	9.020	17.470	18.370	0.924	0.748	6.530	21.500	22.090	0.912
			$\hat{\alpha}_2$	0.693	0.390	8.850	9.390	0.928	0.696	3.120	10.350	11.080	0.930
5000		λ_2	0.742	0.070	3.170	2.870	0.948	0.744	2.400	3.970	3.760	0.944	
		α_2	0.693	0.460	1.730	1.620	0.950	0.693	-0.080	2.040	1.960	0.948	
0.75	1000	$\hat{\lambda}_1$	0.182	0.130	0.040	0.040	0.944	0.182	-0.050	0.080	0.080	0.937	
		$\hat{\alpha}_1$	1.609	0.030	7e-04	0.860	0.924	1.610	1.120	1.410	1.450	0.947	
	5000	$\hat{\lambda}_1$	0.182	-0.120	0.010	0.010	0.940	0.182	-0.040	0.020	0.020	0.948	
		$\hat{\alpha}_1$	1.609	0.040	0.140	0.160	0.936	1.610	0.780	0.270	0.320	0.926	
	1000	$\hat{\lambda}_1$		0.747	4.900	13.000	14.790	0.924	0.744	1.780	16.030	17.270	0.928
			$\hat{\alpha}_1$	0.694	1.460	8.370	9.630	0.924	0.697	4.230	9.660	10.980	0.932
5000		$\hat{\lambda}_1$	0.743	1.160	2.440	2.120	0.966	0.744	1.920	3.040	2.590	0.966	
		$\hat{\alpha}_1$	0.693	-0.090	1.650	1.490	0.970	0.693	-0.470	1.910	1.700	0.962	

References

- [1] Aalen, O. O., & Johansen, S. (1978). An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics*, 141-150.
- [2] Bäuerle, N., & Müller, A. (1998). Modeling and comparing dependencies in multivariate risk portfolios. *ASTIN Bulletin: Journal of the IAA*, 28(1), 59-76.
- [3] Berkson, J., & Gage, R. P. (1950, May). Calculation of survival rates for cancer. In *Proceedings of the staff meetings. Mayo Clinic* (Vol. 25, No. 11, p. 270).
- [4] Bernstein, S. (1929). Sur les fonctions absolument monotones. *Acta Mathematica*, 52, 1-66.
- [5] Bland, J. M., & Altman, D. G. (2004). The logrank test. *Bmj*, 328(7447), 1073.
- [6] Bolard, P., Quantin, C., Abrahamowicz, M., Esteve, J., Giorgi, R., Chadha-Boreham, H., ... & Faivre, J. (2002). Assessing time-by-covariate interactions in relative survival models using restrictive cubic spline functions. *Journal of Cancer Epidemiology and Prevention*, 7(3), 113-122.
- [7] Brinkhof, M. W., Spycher, B. D., Yiannoutsos, C., Weigel, R., Wood, R., Messou, E., ... & International epidemiological Database to Evaluate AIDS (IeDEA). (2010). Adjusting mortality for loss to follow-up: analysis of five ART programmes in sub-Saharan Africa. *PLoS one*, 5(11), e14149.
- [8] Charvat, H., Remontet, L., Bossard, N., Roche, L., Dejardin, O., Rachet, B., ... & CENSUR Working Survival Group. (2016). A multilevel excess hazard model to estimate net survival on hierarchical data allowing for non-linear and non-proportional effects of covariates. *Statistics in medicine*, 35(18), 3066-3084.
- [9] Cox, D. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society, Series B* 34, 187-200.
- [10] Cronin, K. A., & Feuer, E. J. (2000). Cumulative cause-specific mortality for cancer patients in the presence of other causes: a crude analogue of relative survival. *Statistics in medicine*, 19(13), 1729-1740.
- [11] Deheuvels, P. (1978). Caractérisation complète des lois extrêmes multivariées et de la convergence des types extrêmes. *Publ. Inst. Statist. Univ. Paris*, 23, 1-36.
- [12] Denuit, M., Lefevre, C., & Mesfioui, M. H. (1999). On s-convex stochastic extrema for arithmetic risks. *Insurance: Mathematics and Economics*, 25(2), 143-155.
- [13] de Lacerda, G. F., Howlader, N., & Mariotto, A. B. (2019). Differences in Cancer Survival with Relative versus Cause-specific Approaches: An Update Using More Accurate Life Tables. *Cancer Epidemiology and Prevention Biomarkers*, cebp-0125.
- [14] Dickman, P. W., Sloggett, A., Hills, M., & Hakulinen, T. (2004). Regression models for relative survival. *Statistics in medicine*, 23(1), 51-64.
- [15] Ederer, F. (1961). The relative survival rate: a statistical methodology. *NCI Monograph*, 6, 101-121.
- [16] Fermanian, J. D., & Scaillet, O. (2004). Some statistical pitfalls in copula modeling for financial applications.
- [17] Fine, J. P., & Gray, R. J. (1999). A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association*, 94(446), 496-509.
- [18] Fine, J. P., Jiang, H., & Chappell, R. (2001). On semi-competing risks data. *Biometrika*, 88(4), 907-919.
- [19] Fréchet, M. (1951). Sur les tableaux de corrélation dont les marges sont données. *Ann. Univ. Lyon, 3^e serie, Sciences, Sect. A*, 14, 53-77.
- [20] Genest, C., & MacKay, J. (1986). The joy of copulas: bivariate distributions with uniform marginals. *The American Statistician*, 40(4), 280-283.
- [21] Gichangi, A., & Vach, W. (2005). The analysis of competing risks data: A guided tour. *Statistics in Medicine*, 132(4), 1-41. bibitemjournal- Giorgi, R., Abrahamowicz, M., Quantin, C., Bolard, P., Esteve, J., Gouvetnet, J., & Faivre, J. (2003). A relative survival regression model using B-spline functions to model non-proportional hazards. *Statistics in medicine*, 22(17), 2767-2784.
- [22] Giorgi, R., Abrahamowicz, M., Quantin, C., Bolard, P., Esteve, J., Gouvetnet, J., & Faivre, J. (2003). A relative survival regression model using B-spline functions to model non-proportional hazards. *Statistics in medicine*, 22(17), 2767-2784.
- [23] Gray, R. J. (1988). A class of K -sample tests for comparing the cumulative incidence of a competing risk. *Annals of statistics*, 16(3), 1141-1154.
- [24] Hakulinen, T. (1982). Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics*, 933-942.
- [25] Hakulinen, T., & Tenkanen, L. (1987). Regression analysis of relative survival rates. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 36(3), 309-317.
- [26] Hakulinen, T., Seppä, K., & Lambert, P. C. (2011). Choosing the relative survival method for cancer survival estimation. *European Journal of Cancer*, 47(14), 2202-2210.

- [27] Heckman, J. J., & Honoré, B. E. (1989). The identifiability of the competing risks model. *Biometrika*, 76(2), 325-330.
- [28] Hoeffding, W. (1940). Masstabinvariante korrelationstheorie. *Schriften des Mathematischen Instituts und Instituts für Angewandte Mathematik der Universität Berlin*, 5, 181-233.
- [29] Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American statistical association*, 53(282), 457-481.
- [30] Lambert, P. C., Smith, L. K., Jones, D. R., & Botha, J. L. (2005). Additive and multiplicative covariate regression models for relative survival incorporating fractional polynomials for time-dependent effects. *Statistics in medicine*, 24(24), 3871-3885.
- [31] Lambert, P. C., Dickman, P. W., & Rutherford, M. J. (2015). Comparison of different approaches to estimating age standardized net survival. *BMC medical research methodology*, 15(1), 1-13.
- [32] Louzada, F., Cancho, V. G., & Yiqi, B. (2015). The log-Weibull-negative-binomial regression model under latent failure causes and presence of randomized activation schemes. *Statistics*, 49(4), 930-949.
- [33] Mahboubi, A., Abrahamowicz, M., Giorgi, R., Biquet, C., Bonithon-Kopp, C., & Quantin, C. (2011). Flexible modeling of the effects of continuous prognostic factors in relative survival. *Statistics in medicine*, 30(12), 1351-1365.
- [34] Makkar, N., Ostrom, Q. T., Kruchko, C., & Barnholtz-Sloan, J. S. (2018). A comparison of relative survival and cause-specific survival methods to measure net survival in cancer populations. *Cancer medicine*, 7(9), 4773-4780.
- [35] Müller, A. (1996). Orderings of risks: A comparative study via stop-loss transforms. *Insurance: Mathematics and Economics*, 17(3), 215-222.
- [36] Mieno, M. N., Tanaka, N., Arai, T., Kawahara, T., Kuchiba, A., Ishikawa, S., & Sawabe, M. (2016). Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. *Journal of epidemiology*, 26(4), 191-198.
- [37] Nelder, J. A., & Mead, R. (1965). A simplex method for function minimization. *Computer journal*, 7(4), 308-313.
- [38] Nelson, C. P., Lambert, P. C., Squire, I. B., & Jones, D. R. (2007). Flexible parametric models for relative survival, with application in coronary heart disease. *Statistics in medicine*, 26(30), 5486-5498.
- [39] Nixon, A. J., Neuberg, D., Hayes, D. F., Gelman, R., Connolly, J. L., Schnitt, S., ... & Harris, J. R. (1994). Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *Journal of Clinical Oncology*, 12(5), 888-894.
- [40] McNeil, A. J., & Nešlehová, J. (2009). Multivariate Archimedean copulas, d-monotone functions and l-norm symmetric distributions. *Annals of Statistics*, 37(5B), 3059-3097.
- [41] Oakes, D. (1982). A model for association in bivariate survival data. *Journal of the Royal Statistical Society: Series B (Methodological)*, 44(3), 414-422.
- [42] Percy, C., Stanek 3rd, E., & Gloeckler, L. (1981). Accuracy of cancer death certificates and its effect on cancer mortality statistics. *American journal of public health*, 71(3), 242-250.
- [43] Perme, M. P., Stare, J., & Estève, J. (2012). On estimation in relative survival. *Biometrics*, 68(1), 113-120.
- [44] Prentice, R. L., Kalbfleisch, J. D., Peterson Jr, A. V., Flournoy, N., Farewell, V. T., & Breslow, N. E. (1978). The analysis of failure times in the presence of competing risks. *Biometrics*, 541-554.
- [45] Reason, J. (1990). The contribution of latent human failures to the breakdown of complex systems. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences*, 327(1241), 475-484.
- [46] Rebolj Kodre, A., & Pohar Perme, M. (2013). Informative censoring in relative survival. *Statistics in medicine*, 32(27), 4791-4802.
- [47] Remontet, L., Bossard, N., Belot, A., Esteve, J., & French Network of Cancer Registries FRANCIM. (2007). An overall strategy based on regression models to estimate relative survival and model the effects of prognostic factors in cancer survival studies. *Statistics in medicine*, 26(10), 2214-2228.
- [48] Rubio, F. J., Remontet, L., Jewell, N. P., & Belot, A. (2019). On a general structure for hazard-based regression models: an application to population-based cancer research. *Statistical methods in medical research*, 28(8), 2404-2417.
- [49] Sarfati, D., Blakely, T., & Pearce, N. (2010). Measuring cancer survival in populations: relative survival vs cancer-specific survival. *International journal of epidemiology*, 39(2), 598-610.
- [50] Sasieni, P., & Brentnall, A. R. (2017). On standardized relative survival. *Biometrics*, 73(2), 473-482.
- [51] Schaffar, R., Rachet, B., Belot, A., & Woods, L. M. (2017). Estimation of net survival for cancer patients: relative survival setting more robust to some assumption violations than cause-specific setting, a sensitivity analysis on empirical data. *European Journal of Cancer*, 72, 78-83.

- [52] Slud, E. V., Byar, D. P., Schatzkin, A., Prentice, R., & Kalbfleisch, J. (1988). Dependent competing risks and the latent-failure model, *Biometrics*, Vol. 44, No. 4 (Dec., 1988), pp. 1203-1205.
- [53] Sturgeon, K. M., Deng, L., Bluethmann, S. M., Zhou, S., Trifiletti, D. M., Jiang, C., ... & Zaorsky, N. G. (2019). A population-based study of cardiovascular disease mortality risk in US cancer patients. *European heart journal*, 40(48), 3889-3897.
- [54] Suissa, S. (1999). Relative excess risk: an alternative measure of comparative risk. *American journal of epidemiology*, 150(3), 279-282.
- [55] Tsiatis, A. (1975). A nonidentifiability aspect of the problem of competing risks. *Proceedings of the National Academy of Sciences*, 72(1), 20-22.
- [56] Venter, G. G. (2002, March). Tails of copulas. In *Proceedings of the Casualty Actuarial Society* (Vol. 89, No. 171, pp. 68-113).
- [57] Welch, H. G., & Black, W. C. (2002). Are deaths within 1 month of cancer-directed surgery attributed to cancer?. *Journal of the National Cancer Institute*, 94(14), 1066-1070.
- [58] Zahl, P. H. (1997). Frailty modelling for the excess hazard. *Statistics in medicine*, 16(14), 1573-1585.

Exponentiated Weibull Hazard for $\lambda = 3$, $\kappa = 4$, $\alpha = 0.1$

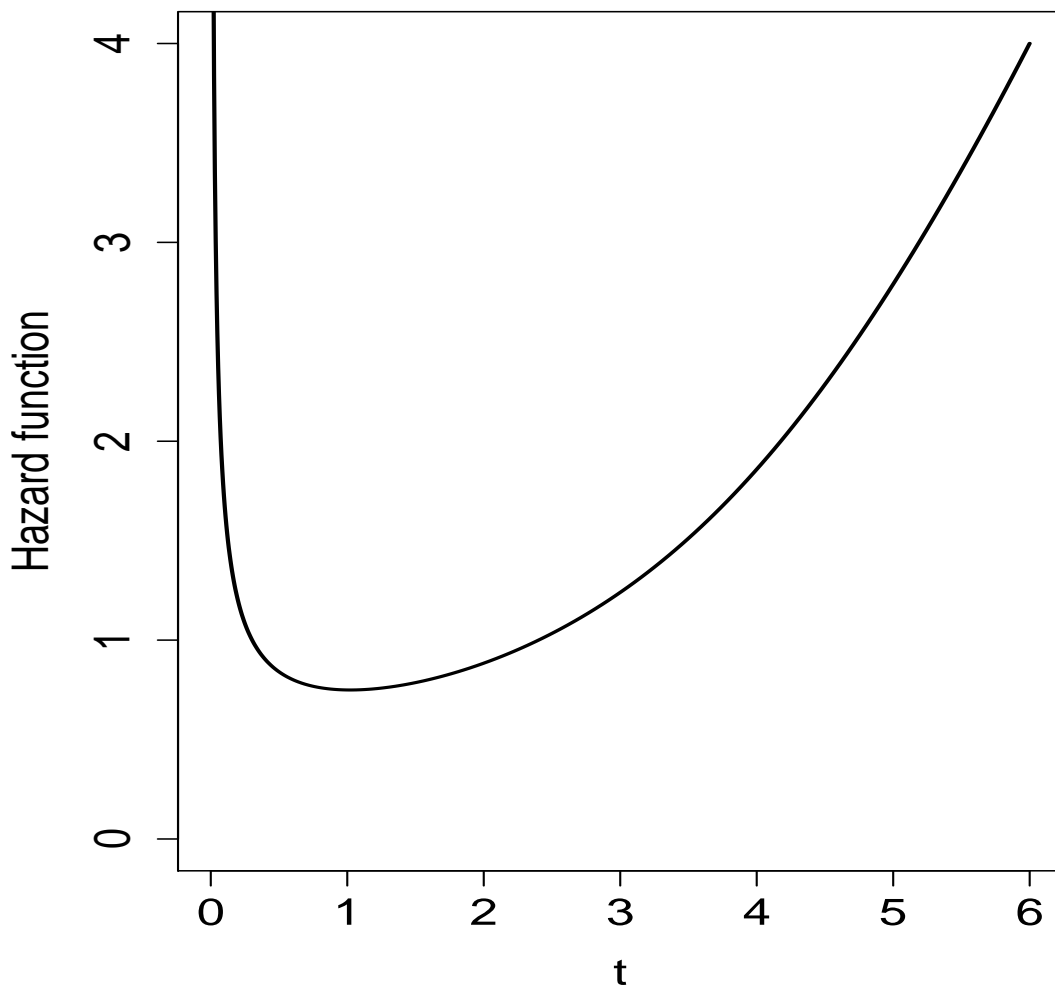


Figure 1: Bathtub shape hazard for the exponentiated Weibull distribution for the event time t

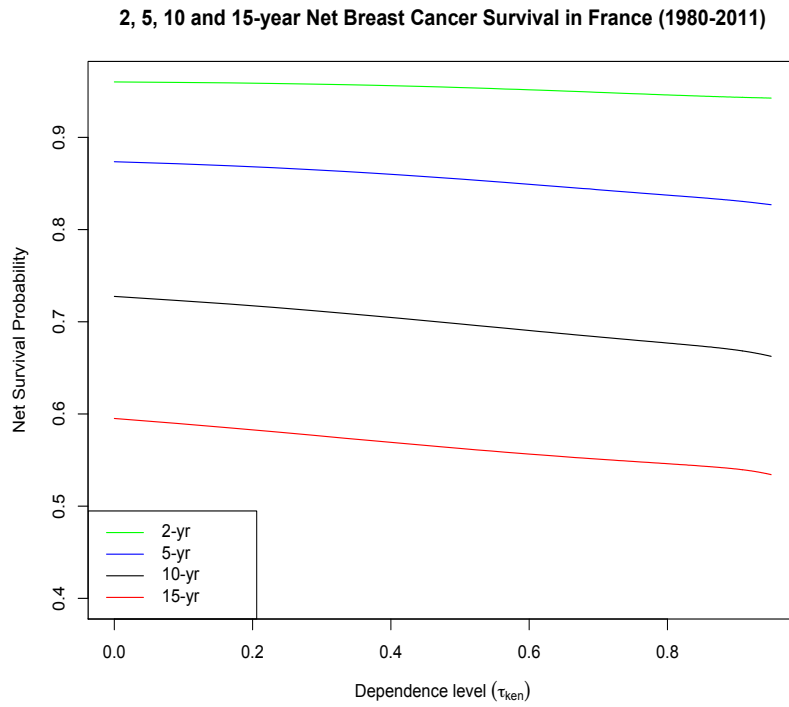


Figure 2: Sensitivity Analysis of Net Breast Cancer Survival Across a Range of Dependent Competing Mortality

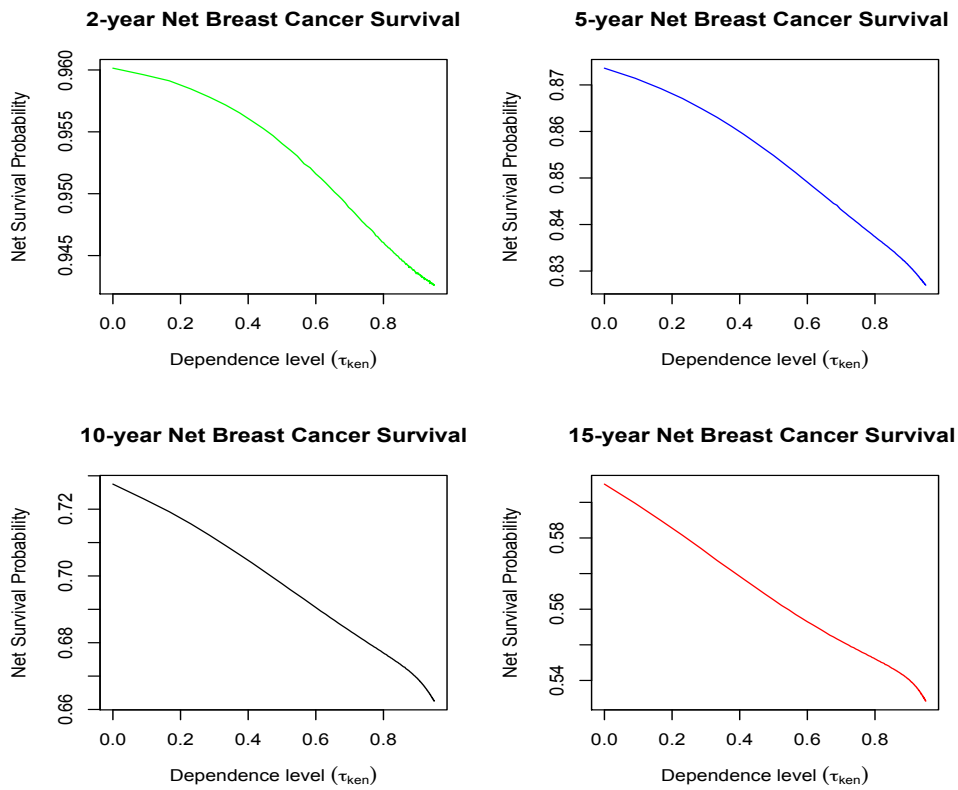


Figure 3: Changes in Net Breast Cancer Survival for Increasing Dependent Competing Risks