Comparison of restricted mean survival time using copula graphic estimator under dependent censoring

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Comparison of restricted mean survival time using copula graphic estimator under dependent censoring

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Abstract

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Restricted Mean Survival Time (RMST) is defined as the area under the survival curve up to a prespecified time point. It can be interpreted as the average survival time from time 0 to a specific follow-up time, providing a simple and clinically meaningful way to interpret survival comparisons between groups. The RMST can provide useful information for comparing two survival curves when the proportional hazards (PH) assumption is not met, such as when the survival curves cross or when the separation between them is delayed. In survival analysis, the time to the occurrence of a specific event of interest is often incompletely observed. That is, for some subjects, the time to the event of interest is unknown, which is referred to as censoring. When this censoring is dependent on survival time, it can lead to biased estimates of the survival function and hazard rates. To address this issue, copula has been proposed as an effective method for modeling dependencies between multivariate data. This paper estimates the survival function using a copula graphic (CG) estimator based on copula models, considering dependent censoring, and compares the RMST of two survival curves. To compare the RMST of two survival curves, we assume that the difference in RMST between the two curves is zero. Using the bootstrap method, we estimate the confidence interval for the RMST difference and calculate the type I error. To address the issue of not being able to define the survival function for bootstrap samples, we consider four methods. Through extensive simulations, we aim to provide accurate and correct interpretations of survival analysis results for each scenario.

Key words: Restricted mean survival time, Copula graphic estimator, Dependent censoring, Type 1 error

1. Introduction

Restricted Mean Survival Time (RMST) is defined as the area under the survival curve up to a prespecified time point. It can be interpreted as the average survival time from time 0 to a specific follow-up time, providing a simple and clinically meaningful way to interpret survival comparisons between groups. The RMST can provide useful information for comparing two survival curves when the proportional hazards (PH) assumption (i.e., the ratio of two hazard functions remains constant over time) is violated, such as when the survival curves cross or when the separation between them is delayed (Royston and Parmar 2011; 2013).

In survival analysis, the time to the occurrence of a specific event of interest is often incompletely observed. That is, for some subjects, the time to the event of interest is unknown, which is referred to as censoring. When this censoring is dependent on survival time, it can lead to biased estimates of the survival function and hazard rates. To address this issue, copula has been proposed as an effective method for modeling dependencies between multivariate data (Sklar 1959). Sklar's theorem clarifies that a copula can utilize marginal distributions to represent the joint distributions of random variables. This approach is particularly useful in analyzing survival data under dependent censoring. Additionally, Kendall’s tau, a well-known non-parametric rank invariant measure proposed by Kendall (1938), characterizes the overall association between variables within a copula.

There are several methods for estimating RMST. The Kaplan-Meier (KM) method and Cox PH are the most used methods in survival analysis and are suitable for estimating RMST. To allow for more general survival time distributions, flexible parametric models have been introduced (Royston and Parmar 2002). These methods estimate RMST in the same way as the KM and Cox PH models. Another method is the pseudo-observation method (Anderson *et al.* 2004). However, these methods estimate the survival curve based on the assumption that event times and censoring times are independent. In the presence of dependent censoring, Inverse Probability of Censoring Weighting (IPCW) is a method used to adjust for the effects of censoring. However, IPCW requires the strong assumption of "no unmeasured confounders." This assumption can be challenging to meet in practice, and failing to account for all relevant confounders can lead to biased results (Robins and Rotnitzky 1992).

In this paper, we compare two survival curves under dependent censoring. Bivariate survival data are generated from a copula model to set the data generation scenarios. To compare the two survival curves, we estimate the variance using a non-parametric bootstrap method and calculate the confidence intervals and type I error. We propose methods to address the issue where the survival function cannot be defined because the last observed time does not reach the pre-specified time point during the bootstrap process. The copula graphic (CG) estimator, based on the copula model, is used to estimate the survival function. The CG estimator provides unbiased information when the copula model between survival time and censoring is correctly specified.

The purpose of this paper is to compare the RMST of two survival curves under dependent censoring through extensive simulation studies. We aim to provide accurate and correct interpretations of survival analysis results for each scenario and identify important considerations for estimating the true survival function.

2. Background

2.1 Proportional hazards assumption

2.1.1 Definition of proportional hazards assumption

Common statistical method for comparing two survival curves is the Cox proportional hazards model. This method operates under the proportional hazards (PH) assumption. The PH assumption means that the hazard ratio between two groups (e.g., treatment and control) remains constant over time. The PH assumption can be expressed using the following hazard function:

$$h(t|Z) = h_0(t)\exp\left(\beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_p Z_p\right)$$

where $h(t|Z)$ is hazard function at time t given covariates Z, $h_0(t)$ is the baseline hazard function when all covariates Z is zero, $Z_1, Z_2, \dots, Z_p$ are covariates, and $\beta_1, \beta_2, \dots, \beta_P$ are the coefficients of the covariates.

The PH assumption means that the hazard ratio between two individuals with covariate values Z_A and Z_B is given by the following:

$$\frac{h(t|Z_A)}{h(t|Z_B)} = \frac{h_0(t)\exp(\beta_1 Z_{A1} + \beta_2 Z_{A2} + \cdots + \beta_p Z_{Ap})}{h_0(t)\exp(\beta_1 Z_{B1} + \beta_2 Z_{B2} + \cdots + \beta_p Z_{Bp})}$$

$$= \exp\left(\beta_1(Z_{A1} - Z_{B1}) + \beta_2(Z_{A2} - Z_{B2}) + \cdots + \beta_p(Z_{Ap} - Z_{Bp})\right)$$

This ratio remains constant over time t, which is the essence of the PH assumption, allowing for effective estimation of the hazard ratio.

However, when the PH assumption is violated, that is, in situations of non-proportional hazards, the Cox PH model produce biased estimates and incorrect. For example, in cardiovascular disease randomized clinical trials, a more aggressive or invasive strategy may be associated with higher initial procedural risk but lower long-term risk. Conversely, in drug trials, the treatment effect may appear several months or years after treatment initiation. In such cases, the hazard ratio is not constant over time, and the overall hazard ratio may fail to adequately summarize the treatment effect (Gregson, John, et al. 2019).

2.1.2 Non-proportional hazards situations

Common situations where the PH assumption is violated include delayed effect, diminishing effect and crossing curve. Figure 1 illustrates the scenarios for proportional hazards and non-proportional hazards along with their corresponding survival curves. In (b) delayed effect scenarios, the treatment does not exert its effect immediately, resulting in a lag period, and the hazard functions diverge later in the follow-up period. Conversely, in (c) diminishing effect scenarios, the treatment provides a short-term benefit but loses its effect towards the end of the follow-up period, causing the hazard functions to converge and the effect to diminish. Lastly, in (d) crossing curve scenarios, the treatment may lead to a higher incidence of events initially, but it provides a benefit over the entire follow-up period, resulting in crossing hazard functions (Knezevic, A., and S. Patil. 2020).

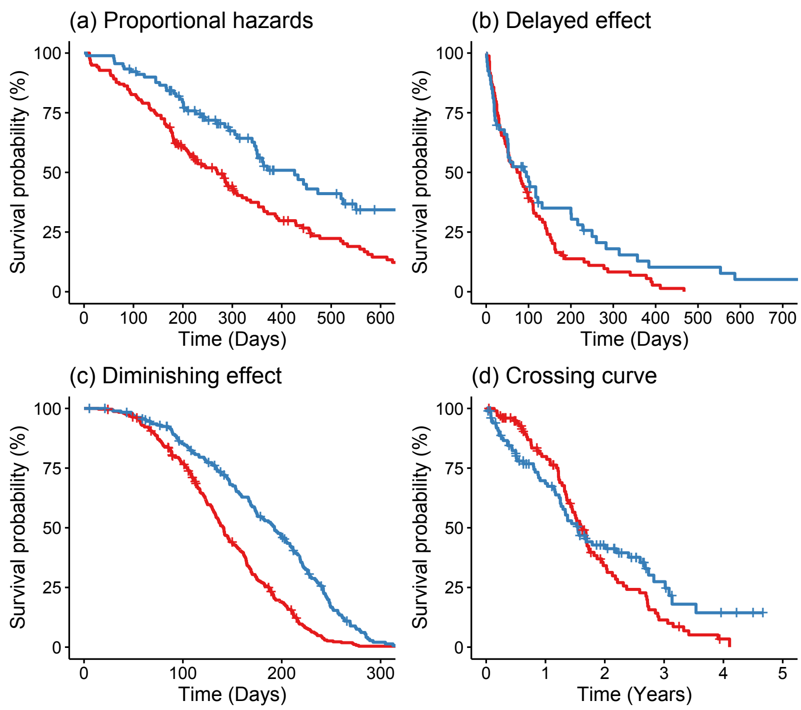

Figure 1 Situations of non-proportional hazards

2.2 Dependent censoring

The purpose of survival analysis is to estimate the time until a specific event of interest (e.g., death or recovery). However, the event time is often incompletely observed, meaning that the time at which the event of interest occurs is unknown for some subjects. This phenomenon is known as censoring.

Typically, survival data is analyzed under the assumption that censoring is unrelated to the event of interest. In fact, survival analysis tools such as the Kaplan-Meier (KM) estimator and Cox regression handle censoring under the assumption that event times and censoring times are statistically independent. However, when censoring is related to dropout or withdrawal due to worsening symptoms, it can introduce bias into the statistical analysis results. This type of dropout is known as informative dropout. Generally, when the time of the event of interest is censored by a mechanism related to the event, this phenomenon is called dependent censoring.

Figure 2 illustrates the potential bias that can occur in the presence of dependent censoring. This figure shows the KM estimate and the actual survival when all event times are observed. As expected, the KM estimator overestimates the actual survival probability. Therefore, it is essential to use appropriate methodologies that account for dependent censoring to avoid biased results (Willems, S. J. W., et al. 2018).

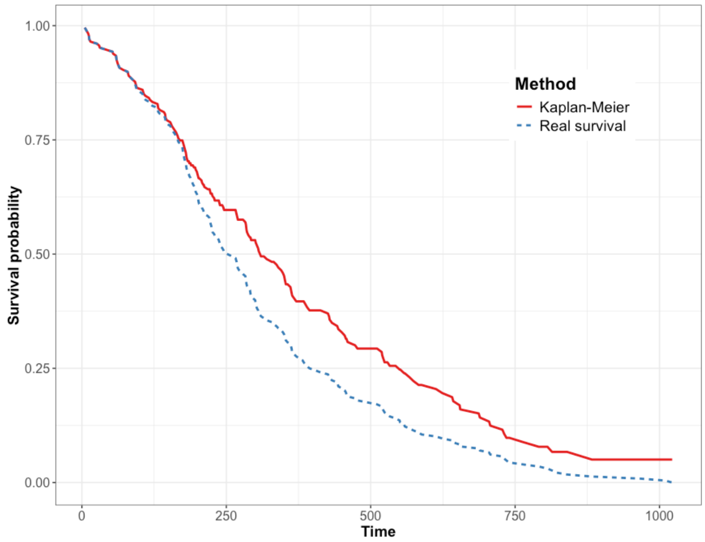

Figure 2 Real survival curve and Kaplan–Meier estimation in the presence of dependent censoring

2.3 Copula

A copula is a function that connects two random variables by specifying their dependency structure between them.

Let's denote the survival time X and the censoring time Y. Also, let $S_X(x) = Pr(X > x)$ and $S_Y(y) = Pr(Y > y)$ be the marginal survival functions for X and Y. We consider a bivariate survival function as follows:

$$Pr(X > x, Y > y) = C_\theta\{S_X(x), S_Y(y)\} \tag{2.1}$$

where a function C_θ is referred to as a copula and a parameter θ represents the degree of dependence between X and Y. Through this model, the dependency between X and Y is described by copula C_θ.

2.3.1 Bivariate copula

A bivariate copula is defined as a bivariate distribution function with marginal distributions that are uniform on the interval $[0,1]$. Let $C_\theta : [0,1]^2 \mapsto [0,1]$ be a bivariate copula indexed by a parameter θ. All bivariate copulas satisfy the following conditions:

Condition 1 (C1)

$$C_\theta(u,0) = C_\theta(0,v),\ C_\theta(u,1) = u, \text{ and } C_\theta(1,v) = v$$
$$\text{for } 0 \le u \le 1 \text{ and } 0 \le v \le 1$$

Condition 2 (C2)

$$C_\theta(u_2,v_2) - C_\theta(u_2,v_1) - C_\theta(u_1,v_2) + C_\theta(u_1,v_1) \ge 0$$
$$\text{for } 0 \le u_1 \le u_2 \le 1 \text{ and } 0 \le v_1 \le v_2 \le 1$$

C1 requires the marginal distributions to be uniform, and C2 requires C_θ to generate probability mass in the region $[u_1,u_2] \times [v_1,v_2]$.

For a copula C_θ, we can consider a pair of random variables (V, W) such that $\Pr(V \le u, W \le v) = C_\theta(u, v)$. If we define the pair of random variables (X, Y) as $X = S_X^{-1}(U)$ and $Y = S_Y^{-1}(W)$, then their bivariate survival function satisfies equation (2.1).

The following copulas satisfy C1 and C2.

The Clayton copula (Clayton 1978):

$$C_\theta(u, v) = \left(u^{-\theta} + v^{-\theta} - 1\right)^{-\frac{1}{\theta}}, \qquad \theta > 0.$$

The Gumbel copula (Gumbel 1960):

$$C_\theta(u, v) = \exp\left[-\left\{(-logu)^{\theta+1} + (-logv)^{\theta+1}\right\}^{\frac{1}{\theta+1}}\right], \qquad \theta \ge 0.$$

The Frank copula (Frank 1979):

$$C_\theta(u, v) = -\frac{1}{\theta}\log\left\{1 + \frac{\left(e^{-\theta u} - 1\right)\left(e^{-\theta v} - 1\right)}{e^{-\theta} - 1}\right\}, \qquad \theta \ne 0.$$

The Joe copula (Joe 1993):

$$C_\theta(u, v) = 1 - \left\{(1-u)^\theta + (1-v)^\theta - (1-u)^\theta(1-v)^\theta\right\}^{\frac{1}{\theta}}, \qquad \theta \ge 0$$

Table 1 Generator for Clayton, Gumbel, Frank, and Joe copula

Copula	**Parameter**	**Generator** $\phi_\theta(t)$
Clayton	$\theta > 0$	$\frac{t^{-\theta} - 1}{\theta}$
Gumbel	$\theta \geq 0$	$\{-\log(t)\}^{\theta+1}$
Frank	$\theta \neq 0$	$-\log\left(\frac{e^{\theta t} - 1}{e^{-\theta} - 1}\right)$
Joe	$\theta \geq 0$	$-\log\{1 - (1 - t)^{\theta}\}$

An *Archimedean copula* is defined as follows:

$$C_\theta(u, v) = \phi_\theta^{-1}(\phi_\theta(u) + \phi_v(u))$$

where the function $\phi_\theta: [0, 1] \longmapsto [0, \infty]$ is the generator function of the copula, which is continuous and strictly decreasing from $\phi_\theta(0) > 0$ to $\phi_\theta(1) = 0$.

If $\phi_\theta \equiv \lim_{t \downarrow 0} \phi_\theta(t) = \infty$, the generator function ϕ_θ is called a strict generator function. Under these conditions, C_θ satisfies C1. To satisfy C2, the generator function ϕ_θ must be convex. This is assumed $\frac{d\phi_\theta(t)}{dt} < 0$ and $\frac{d^2\phi_\theta(t)}{dt^2} > 0$ for $t \in (0, 1)$, with $\phi_\theta(1) = 0$ and $\phi_\theta(0) = \infty$.

Table 1 summarizes the generator functions of the Clayton, Gumbel, Frank, and Joe copula, which have strict generator functions.

2.3.2 Kendall's tau

Kendall's tau, denoted by τ, is a well-known measure for assessing the dependency between X and Y, which is defined by

$$\tau = Pr\{(X_2 - X_1)(Y_2 - Y_1) > 0\} - Pr\{(X_2 - X_1)(Y_2 - Y_1) < 0\}$$

where (X_1, Y_1) and (X_2, Y_2) are pairs drawn from the model (2.1).

Kendall's tau can be expressed using the copula C_θ as follows:

$$\tau_\theta = 4\int_0^1 \int_0^1 C_\theta(u, v) C_\theta(du, dv) - 1$$

Table 2 summarizes τ_θ for the Clayton, Gumbel, Frank and Joe copula.

Table 2 Kendall's tau for Clayton, Gumbel, Frank, and Joe copula

Copula	**Parameter**	**Kendall's tau: τ_θ**
Clayton	$\theta > 0$	$\frac{\theta}{\theta+2}$
Gumbel	$\theta \geq 0$	$\frac{\theta}{\theta+1}$
Frank	$\theta \neq 0$	$1-\frac{4}{\theta}\left(1-\frac{1}{\theta}\int_0^\theta \frac{t}{e^t-1}dt\right)$
Joe	$\theta \geq 0$	$1-4\int_0^\infty \frac{t(1-e^{-t})^{\frac{2}{\theta}-2}e^{-2t}}{\theta^2}dt$

3. Method

3.1 Restricted Mean Survival Time (RMST)

Restricted Mean Survival Time (RMST) is defined as the area under the survival curve up to a pre-specific time point. It represents the average survival time from time 0 to a particular follow-up time, providing an intuitive and clinically meaningful way to interpret survival differences between groups. The RMST can offer valuable information for comparing two survival curves, especially when the PH assumption is violated.

The RMST of the random variable X, denoted by $\mu(t^*)$, is the mean of the survival time $T = \min(X, t^*)$ constrained by a pre-specified fixed time point $t^* > 0$. This is equivalent to the area under the survival curve $S(t)$ from $t = 0$ to $t = t^*$:

$$\mu(t^*) = E(T) = E[\min(X, t^*)] = \int_0^{t^*} S(t)dt$$

When X represents the time until death, $\mu(t^*)$ can be considered the expected life up to t^*- years.

In clinical trials involving two groups – each characterized by their respective survival functions $S_0(t)$ and $S_1(t)$ for the treatment and control groups – the difference in the RMST between the two groups is defined as follows:

$$\Delta(t^*) = \int_0^{t^*} S_1(t)dt - \int_0^{t^*} S_0(t)dt$$
$$= \int_0^{t^*} [S_1(t) - S_0(t)]dt \qquad (3.1)$$

The difference, denoted $\Delta(t^*)$, is the area between the two survival curves.

To compare two survival curves, we can perform testing for the null hypothesis $H_0: \Delta(t^*) = 0$.

3.2 Copula graphic (CG) estimator

In survival data analysis, it is common to begin by plotting the KM survival curve, which graphically summarizes the survival times of patients. However, under dependent censoring, the KM estimator can provide biased information about survival. If the copula function between survival time and censoring is correctly specified, then the survival curve with the copula graphic (CG) estimator can provide unbiased information about survival and allow for the accurate calculation of the RMST.

Let's denote the survival time X and the censoring time Y. Consider an *Archimedean copula* (copulas such as Clayton, Frank, and Gumbel, which possess a generator function) model:

$$Pr(X > x, Y > y) = \phi_\theta^{-1}[\phi_\theta\{S_X(x)\} + \phi_\theta\{S_Y(y)\}]$$

where $\phi_\theta : [0,1]^2 \longmapsto [0,\infty]$ is a generator function, which is continuous and strictly decreasing from $\phi_\theta(0) > 0$ to $\phi_\theta(1) = 0$, $S_X(x) = Pr(X > x)$ and $S_Y(y) = Pr(Y > y)$ are the marginal survival functions.

Let's denote the survival data as $(t_i, \delta_i), i = 1, \dots, n$, where $t_i = \min(X_i, Y_i)$, $\delta_i = I(X_i \le Y_i)$, and $I(\cdot)$ is the indicator function. If all observed data are distinct, that is, $t_i \ne t_j$ whenever $i \ne j$, the survival function can be estimated using the following the CG estimator:

$$\bar{S}_X(x) = \phi_\theta^{-1}\left[\sum_{t_i<x,\delta_i=1} \phi_\theta\left(\frac{n_i - 1}{n}\right) - \phi_\theta\left(\frac{n_i}{n}\right)\right], \qquad 0 \le t \le \max_i(t_i)$$

where $n_i = \sum_{l=1}^{n} I(t_l \ge t_i)$ is the number of individuals at risk at time t_i. $\bar{S}_X(x) = 1$ if no death has occurred by time x, and $\bar{S}_X(x)$ is not defined after $\max(t_i)$.

3.3 Calculation of the confidence interval for the difference in RMST

To calculate the type I error for the null hypothesis $H_0\colon \Delta_{origin}(t^*) = 0$, we estimate the variance and calculate the confidence interval. However, due to the difficulty of asymptotic variance estimation under dependent censoring, we use the non-parametric bootstrap method.

Assume that there are n_i subjects, then for $i = 1, 2$ and $j = 1, \dots, n_i$, t_{ij} and δ_{ij} represent the observed event time and censoring indicator for the j-th subject in the i-th group.

The following steps outline the procedure for estimating the variance using the bootstrap method and calculating the confidence interval:

Step1: Generate datasets using the bootstrap method

The bootstrap samples are formed by independently resampling $t_{ij}^{(k)}$ and $\delta_{ij}^{(k)}$ for all groups. The following is bootstrap samples B_k:

$$B_k\colon \left\{ \left(t_{ij}^{(k)}, \delta_{ij}^{(k)} \right) \right\}_{j=1}^{n_i}$$

where $k = 1, \dots, b$ is the bootstrap sample index.

Step2: Calculate the RMST for each group and the difference in the RMST

For each bootstrap sample, calculate the RMST for each group up to the t^* and obtain the difference in RMST. The following are the RMST for each group, $\hat{\mu}_1^{(k)}$ and $\hat{\mu}_2^{(k)}$, and their difference, $\hat{\Delta}^{(k)}(t^*)$:

$$\hat{\mu}_1^{(k)} = \int_0^{t^*} \bar{S}_1^{(k)}(t)dt \ , \ \hat{\mu}_2^{(k)} = \int_0^{t^*} \bar{S}_2^{(k)}(t)dt$$

$$\hat{\Delta}^{(k)}(t^*) = \bar{\mu}_1^{(k)} - \bar{\mu}_2^{(k)}$$

where the survival function $\bar{S}_i^{(k)}$ is the CG estimator under dependent censoring.

Step3: Estimate the variance for the difference between two RMST and calculate the confidence interval

The variance estimator for the true RMST difference $\Delta_{origin}(t^*)$ is given by

$$\hat{\sigma}^2(t^*) = \frac{1}{b-1}\sum_{k=1}^{b}\left(\hat{\Delta}^{(k)}(t^*) - \Delta_{origin}(t^*)\right)^2$$

After obtaining the variance estimator, the normality-based $(1-\alpha)\times 100\%$ confidence interval for $\Delta_{origin}(t^*)$ is calculated as follows:

$$CI_{1-\alpha} = \left[\Delta_{origin}(t^*) - z_{1-\frac{\alpha}{2}}\sqrt{\hat{\sigma}^2(t^*)}, \Delta_{origin}(t^*) + z_{1-\frac{\alpha}{2}}\sqrt{\hat{\sigma}^2(t^*)}\right]$$

where $z_{1-\frac{\alpha}{2}}$ is the $(1-\alpha/2)$-quantile of $N(0,1)$.

During the process of generating $\hat{\Delta}^{(k)}(t^*)$, a numerical issue may arise where $\bar{S}_i^{(k)}(t)$ is not defined because the last observed event time does not reach the t^* due to censoring. To address this issue, the following four methods can be considered (Horiguchi and Uno 2020):

Method 1: Ignoring the inestimable cases

The first method is to ignore cases where $\hat{\Delta}^{(k)}(t^*)$ cannot be calculated. In this approach, resampling must be repeated to obtain k estimates. This method is simple, but it may take a long computation time to obtain k estimates.

Method2: Extending the survival curve to t^*

The second method is to extend the survival curve to the t^*, so that $\bar{S}_i^{(k)}(t)$ can be defined for all k $(k = 1, \dots, b)$. However, this method has the limitation of potentially overestimating RMST.

Method3: Switching the last censored observation to the event observation

The third method is to convert the last censored observation into an event occurrence observation when the survival function cannot be estimated at the t^*. However, this method has the limitation of potentially underestimating RMST.

Method4: Averaging RMSTs derived from Methods 2 and 3

The fourth method is a combination of methods 2 and 3. This method takes the average of the two RMSTs calculated using methods 2 and 3, thereby mitigating the biases that occur in each method.

4. Simulation study

In this section, we conduct a simulation study to compare two survival curves under dependent censoring.

4.1 Data generation

The probability density function and survival function of the *Weibull* distribution are as follows:

$$f(t) = \alpha\lambda t^{\alpha-1}\exp(-\lambda t^{\alpha})$$

$$S(t) = \exp\left(-\lambda t^{\alpha}\right)$$

where $\alpha > 0$ is a shape parameter, and $\lambda > 0$ is a scale parameter. The shape parameter determines the form of the distribution, and the scale parameter adjusts the spread of the distribution.

We generate survival data (t_{ij}, δ_{ij}), $i = 1, \ldots, n$ and $j = 1, 2$ from two random variables $X_{ij} \sim Weibull(\lambda_j, \alpha)$ and $Y_{ij} \sim Weibull(\lambda'_j, \alpha)$ defined by a bivariate copula. To generate this data, we use the *Copula.surv* R package, which generates bivariate survival data from copula models.

4.2 Simulation setting

The true parameter values set in our simulation study are as follows: the shape parameter $\alpha = 2$, the scale parameters $\lambda_1, \lambda_1' \in \{0.52, 0.375\}$, $\lambda_2, \lambda_2' \in \{0.175, 0.081, 0.155, 0.375\}$, and Kendall's tau $\tau_\theta \in \{0.2, 0.5, 0.8\}$. Table 3 summarizes the true copula parameter values for each Kendall's tau using Table 2 from Section 2.

The α, λ_1, λ_1', λ_2, and λ_2' were set such that for $i = 1$, the censoring rates are 20% and 50%, and for $i = 2$, the censoring rates are 10%, 20%, 25% and 50%, with the median of the observed event times approximating 1 year. Additionally, in each simulation setting scenario, we designated the time point at which the survival probability on the survival curve reaches 10% as t^*.

Table 3 True copula (Clayton, Gumbel, and Frank) parameter values for Kendall's tau

Kendall's tau τ_θ	**Copula parameter θ**		
	Clayton	Gumbel	Frank
0.2	0.5	0.25	1.86
0.5	2	1	5.75
0.8	8	4	18.2

The approximate true values for λ_1, λ_1', λ_2, λ_2', and t^* are obtained through the following process. First, set a sum of the two groups' sample size $N = n_1 + n_2$ to 1,000,000 ($n_1 = n_2 = 500{,}000$). Then, generate survival data according to Section 4.1. From the generated data, find the true values that approximate the pre-specified values of the censoring rates and the median of the observed event times. This process is repeated 1000 times to calculate the average value. This approach is often used when the true values cannot be easily obtained from the data generation mechanism. Moreover, this process is also used to calculate the $\Delta_{origin}(t^*)$.

Table 4 All scenarios for data generation settings

Scenario	Copula	Kendall's tau τ_θ	Sample size	Censoring rate (%)
I	Clayton	(0.2, 0.5, 0.8)	(50, 100, 500)	(20, 20), (20, 10)
				(50, 50), (50, 25)
II	Gumbel	(0.2, 0.5, 0.8)	(50, 100, 500)	(20, 20), (20, 10)
				(50, 50), (50, 25)
III	Frank	(0.2, 0.5, 0.8)	(50, 100, 500)	(20, 20), (20, 10)
				(50, 50), (50, 25)

Table 4 summarizes all data generation scenarios. The Scenario I-III are broadly categorized into three scenarios based on the copula models (Clayton, Gumbel, and Frank copula) used to generate survival data. For each copula model, three different true Kendall's tau $\tau_\theta = 0.2, 0.5, 0.8$ are applied, and three different sample sizes $N = 50, 100, 500$ are examined. In each case, the sample size is equally divided for $i = 1, 2$ as n_i. For each of these granular data generation scenarios, two cases are considered: one with relatively light censoring rates $(20\%, 20\%), (20\%, 10\%)$ and the other with relatively heavy censoring rates $(50\%, 50\%), (50\%, 25\%)$ for both groups. Ultimately, 54 scenarios for the data generation settings are prepared.

For the original data in each scenario, 1,000 bootstrap samples are generated to estimate the variance. For each of these bootstrap samples, another 1,000 bootstrap samples are generated to 1,000 confidence intervals for the true RMST difference and compute the type I error for the null hypothesis $H_0: \Delta_{origin}(t^*) = 0$. To estimate the survival function, the CG estimator is used with the assumed copula models (Clayton, Frank, and Gumbel copula), considering three different Kendall's tau $\tau_\theta = 0.2, 0.5, 0.8$ for each copula model. Additionally, the KM estimator is also considered. To address the issue of the survival function not being defined during the bootstrap process, we consider the Methods 2-4 from Section 3.3.

4.3 Simulation result

The simulation results present the type I error for all data generation setting scenarios using the KM estimator and the CG estimator, considering three assumed copula models (Clayton, Frank, and Gumbel copula) with three different Kendall's tau values applied to each copula model.

Table 5-22 presents the results for Scenario I, Appendix Tables 1-9 present the results for Scenario II, and Appendix Tables 10-18 present the results for Scenario III. Similar results were observed across all scenarios. Additionally, in all tables, the assumed copula model that correctly specified the true model showed lower type I error compared to when the models were incorrectly specified, but the differences were not significant. There were also no significant differences between the results of Methods 2-4.

When the true Kendall's tau is 0.2, the type I error remains stable with light or equal censoring rates. However, as the difference in censoring rates increases, the type I error rises, especially when Kendall's tau is incorrectly specified, and this increase becomes more pronounced with larger sample sizes. Similarly, when the true Kendall's tau is 0.8, the type I error remains stable with light or equal censoring rates, but it increases as the difference in censoring rates grows and the misspecified with Kendall's tau becomes larger. However, the increase in type I error is much greater in this case compared to the previous case. In Table 22, when the assumed copula is Gumbel and Kendall's tau is 0.2, the type I error is 0.921, indicating a complete mismatch between the two survival curves. In contrast, when the assumed copula is Clayton and Kendall's tau is 0.8, the type I error is 0.049, showing a significant result.

When the censoring rates are light or equal, the KM estimator did not show significant differences from the CG estimator. However, as mentioned in Section 2.2, both survival curves are likely to be overestimated, potentially leading to no change in the RMST difference.

The simulation study results indicate that when the difference in censoring rates is relatively large, correctly specifying the true copula model and parameters enables accurate and correct interpretation of survival analysis results. This importance is particularly emphasized as the true copula parameter increases.

Table 5 Type I error of the assumed copula for scenario I with τ_θ=0.2, sample size 50, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.059	0.058	0.06	0.056	0.054	0.054
	0.2	0.06	0.06	0.06	0.056	0.057	0.057
Clayton	0.5	0.054	0.055	0.055	0.058	0.058	0.058
	0.8	0.057	0.058	0.058	0.064	0.064	0.064
	0.2	0.059	0.059	0.059	0.054	0.054	0.054
Frank	0.5	0.057	0.057	0.057	0.059	0.06	0.06
	0.8	0.058	0.058	0.058	0.062	0.063	0.063
	0.2	0.06	0.06	0.06	0.054	0.054	0.054
Gumbel	0.5	0.055	0.055	0.055	0.059	0.059	0.059
	0.8	0.057	0.057	0.057	0.063	0.064	0.063

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 6 Type I error of the assumed copula for scenario I with τ_θ=0.2, sample size 50, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.056	0.063	0.063	0.071	0.069	0.072
	0.2	0.05	0.054	0.052	0.057	0.059	0.058
Clayton	0.5	0.043	0.045	0.043	0.06	0.06	0.06
	0.8	0.031	0.034	0.032	0.073	0.073	0.074
	0.2	0.051	0.052	0.052	0.057	0.059	0.058
Frank	0.5	0.043	0.044	0.044	0.056	0.057	0.058
	0.8	0.033	0.035	0.034	0.073	0.074	0.074
	0.2	0.051	0.055	0.053	0.059	0.061	0.062
Gumbel	0.5	0.045	0.047	0.045	0.055	0.055	0.057
	0.8	0.033	0.037	0.037	0.074	0.076	0.076

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 7 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 50, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.062	0.062	0.062	0.068	0.067	0.067
	0.2	0.065	0.065	0.065	0.067	0.067	0.067
Clayton	0.5	0.067	0.067	0.067	0.064	0.064	0.064
	0.8	0.063	0.063	0.063	0.067	0.067	0.067
	0.2	0.066	0.066	0.066	0.066	0.066	0.066
Frank	0.5	0.063	0.062	0.062	0.066	0.066	0.066
	0.8	0.063	0.063	0.063	0.067	0.067	0.067
	0.2	0.066	0.066	0.066	0.069	0.069	0.069
Gumbel	0.5	0.063	0.062	0.063	0.064	0.064	0.064
	0.8	0.059	0.059	0.059	0.062	0.062	0.062

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 8 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 50, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.059	0.056	0.059	0.116	0.114	0.117
	0.2	0.058	0.061	0.06	0.091	0.091	0.091
Clayton	0.5	0.057	0.056	0.057	0.057	0.058	0.057
	0.8	0.05	0.051	0.051	0.057	0.057	0.057
	0.2	0.058	0.058	0.058	0.092	0.092	0.092
Frank	0.5	0.05	0.05	0.05	0.058	0.058	0.058
	0.8	0.05	0.049	0.049	0.056	0.058	0.057
	0.2	0.056	0.058	0.057	0.098	0.095	0.097
Gumbel	0.5	0.049	0.048	0.049	0.06	0.059	0.06
	0.8	0.051	0.051	0.051	0.058	0.059	0.059

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 9 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 50, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.06	0.06	0.06	0.067	0.067	0.067
	0.2	0.059	0.059	0.059	0.068	0.068	0.068
Clayton	0.5	0.062	0.062	0.062	0.062	0.062	0.062
	0.8	0.067	0.067	0.067	0.065	0.065	0.065
	0.2	0.06	0.06	0.06	0.068	0.068	0.068
Frank	0.5	0.063	0.063	0.063	0.064	0.064	0.064
	0.8	0.067	0.067	0.067	0.064	0.064	0.064
	0.2	0.062	0.062	0.062	0.067	0.067	0.067
Gumbel	0.5	0.066	0.066	0.066	0.062	0.062	0.062
	0.8	0.069	0.069	0.069	0.066	0.066	0.066

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 10 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 50, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.061	0.06	0.064	0.27	0.265	0.27
	0.2	0.06	0.06	0.06	0.202	0.201	0.202
Clayton	0.5	0.058	0.058	0.058	0.102	0.103	0.102
	0.8	0.052	0.052	0.052	0.061	0.061	0.061
	0.2	0.06	0.058	0.06	0.203	0.203	0.203
Frank	0.5	0.054	0.054	0.054	0.108	0.109	0.109
	0.8	0.051	0.051	0.051	0.061	0.061	0.061
	0.2	0.062	0.062	0.062	0.209	0.208	0.209
Gumbel	0.5	0.057	0.056	0.057	0.114	0.115	0.115
	0.8	0.052	0.052	0.052	0.068	0.067	0.068

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 11 Type I error of the assumed copula for scenario I with τ_{θ}=0.2, sample size 100, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.065	0.065	0.065	0.071	0.071	0.071
	0.2	0.066	0.066	0.066	0.069	0.069	0.069
Clayton	0.5	0.066	0.066	0.066	0.065	0.065	0.065
	0.8	0.066	0.066	0.066	0.075	0.075	0.075
	0.2	0.067	0.067	0.067	0.067	0.067	0.067
Frank	0.5	0.065	0.065	0.065	0.068	0.068	0.068
	0.8	0.064	0.064	0.064	0.076	0.076	0.076
	0.2	0.066	0.066	0.066	0.066	0.066	0.066
Gumbel	0.5	0.065	0.065	0.065	0.069	0.069	0.069
	0.8	0.067	0.067	0.067	0.078	0.078	0.078

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 12 Type I error of the assumed copula for scenario I with τ_θ=0.2, sample size 100, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.062	0.061	0.064	0.085	0.081	0.084
	0.2	0.059	0.059	0.059	0.063	0.064	0.063
Clayton	0.5	0.06	0.06	0.06	0.081	0.082	0.082
	0.8	0.055	0.055	0.055	0.151	0.151	0.151
	0.2	0.061	0.061	0.061	0.064	0.064	0.064
Frank	0.5	0.058	0.061	0.06	0.071	0.071	0.071
	0.8	0.056	0.056	0.056	0.142	0.143	0.143
	0.2	0.06	0.06	0.06	0.065	0.065	0.065
Gumbel	0.5	0.057	0.058	0.058	0.069	0.071	0.07
	0.8	0.058	0.057	0.057	0.143	0.143	0.143

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 13 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 100, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.067	0.067	0.067	0.07	0.07	0.07
	0.2	0.065	0.065	0.065	0.069	0.069	0.069
Clayton	0.5	0.066	0.066	0.066	0.069	0.069	0.069
	0.8	0.06	0.06	0.06	0.065	0.065	0.065
	0.2	0.066	0.066	0.066	0.071	0.071	0.071
Frank	0.5	0.067	0.067	0.067	0.067	0.067	0.067
	0.8	0.061	0.061	0.061	0.062	0.062	0.062
	0.2	0.067	0.067	0.067	0.07	0.07	0.07
Gumbel	0.5	0.066	0.066	0.066	0.068	0.068	0.068
	0.8	0.065	0.065	0.065	0.062	0.062	0.062

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 14 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 100, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.07	0.07	0.07	0.174	0.174	0.174
	0.2	0.065	0.066	0.065	0.098	0.098	0.098
Clayton	0.5	0.058	0.059	0.058	0.058	0.058	0.058
	0.8	0.051	0.051	0.051	0.093	0.093	0.093
	0.2	0.065	0.066	0.065	0.108	0.108	0.108
Frank	0.5	0.062	0.062	0.062	0.058	0.058	0.058
	0.8	0.056	0.056	0.056	0.086	0.086	0.086
	0.2	0.064	0.064	0.064	0.116	0.116	0.116
Gumbel	0.5	0.061	0.061	0.061	0.063	0.063	0.063
	0.8	0.057	0.056	0.057	0.085	0.085	0.085

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 15 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 100, and light censoring rate

Assumed copula		Censoring rate (%)					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.059	0.059	0.059	0.065	0.065	0.065
	0.2	0.058	0.058	0.058	0.059	0.059	0.059
Clayton	0.5	0.059	0.059	0.059	0.055	0.055	0.055
	0.8	0.06	0.06	0.06	0.057	0.057	0.057
	0.2	0.056	0.056	0.056	0.06	0.06	0.06
Frank	0.5	0.059	0.059	0.059	0.058	0.058	0.058
	0.8	0.059	0.059	0.059	0.058	0.058	0.058
	0.2	0.057	0.057	0.057	0.06	0.06	0.06
Gumbel	0.5	0.058	0.058	0.058	0.057	0.057	0.057
	0.8	0.057	0.057	0.057	0.056	0.056	0.056

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 16 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 100, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.052	0.053	0.053	0.449	0.449	0.449
	0.2	0.057	0.057	0.057	0.304	0.304	0.304
Clayton	0.5	0.057	0.057	0.057	0.117	0.117	0.117
	0.8	0.06	0.061	0.061	0.056	0.056	0.056
	0.2	0.053	0.053	0.053	0.312	0.312	0.312
Frank	0.5	0.054	0.054	0.054	0.134	0.134	0.134
	0.8	0.058	0.058	0.058	0.056	0.056	0.056
	0.2	0.055	0.055	0.055	0.329	0.329	0.329
Gumbel	0.5	0.061	0.061	0.061	0.14	0.139	0.139
	0.8	0.058	0.058	0.058	0.057	0.057	0.057

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 17 Type I error of the assumed copula for scenario I with τ_θ=0.2, sample size 500, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.053	0.053	0.053	0.058	0.058	0.058
	0.2	0.051	0.051	0.051	0.052	0.052	0.052
Clayton	0.5	0.055	0.055	0.055	0.07	0.07	0.07
	0.8	0.056	0.056	0.056	0.117	0.117	0.117
	0.2	0.051	0.051	0.051	0.052	0.052	0.052
Frank	0.5	0.052	0.052	0.052	0.07	0.07	0.07
	0.8	0.056	0.056	0.056	0.115	0.115	0.115
	0.2	0.052	0.052	0.052	0.05	0.05	0.05
Gumbel	0.5	0.049	0.049	0.049	0.067	0.067	0.067
	0.8	0.053	0.053	0.053	0.117	0.117	0.117

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 18 Type I error of the assumed copula for scenario I with τ_θ=0.2, sample size 500, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.047	0.047	0.047	0.131	0.131	0.131
	0.2	0.047	0.047	0.047	0.045	0.045	0.045
Clayton	0.5	0.045	0.045	0.045	0.235	0.235	0.235
	0.8	0.043	0.043	0.043	0.63	0.63	0.63
	0.2	0.048	0.048	0.048	0.055	0.055	0.055
Frank	0.5	0.047	0.047	0.047	0.142	0.142	0.142
	0.8	0.044	0.044	0.044	0.568	0.568	0.568
	0.2	0.046	0.046	0.046	0.055	0.055	0.055
Gumbel	0.5	0.05	0.05	0.05	0.127	0.127	0.127
	0.8	0.048	0.048	0.048	0.565	0.565	0.565

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 19 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 500, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.047	0.047	0.047	0.089	0.089	0.089
	0.2	0.047	0.047	0.047	0.063	0.063	0.063
Clayton	0.5	0.047	0.047	0.047	0.048	0.048	0.048
	0.8	0.052	0.052	0.052	0.062	0.062	0.062
	0.2	0.045	0.045	0.045	0.064	0.064	0.064
Frank	0.5	0.046	0.046	0.046	0.05	0.05	0.05
	0.8	0.05	0.05	0.05	0.068	0.068	0.068
	0.2	0.046	0.046	0.046	0.064	0.064	0.064
Gumbel	0.5	0.049	0.049	0.049	0.053	0.053	0.053
	0.8	0.051	0.051	0.051	0.065	0.065	0.065

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 20 Type I error of the assumed copula for scenario I with τ_θ=0.5, sample size 500, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.057	0.057	0.057	0.603	0.603	0.603
	0.2	0.055	0.055	0.055	0.276	0.276	0.276
Clayton	0.5	0.054	0.054	0.054	0.046	0.046	0.046
	0.8	0.048	0.048	0.048	0.244	0.244	0.244
	0.2	0.058	0.058	0.058	0.311	0.311	0.311
Frank	0.5	0.056	0.056	0.056	0.062	0.062	0.062
	0.8	0.051	0.051	0.051	0.197	0.197	0.197
	0.2	0.055	0.055	0.055	0.337	0.337	0.337
Gumbel	0.5	0.054	0.054	0.054	0.07	0.07	0.07
	0.8	0.053	0.053	0.053	0.176	0.176	0.176

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 21 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 500, and light censoring rate

Assumed copula		**Censoring rate (%)**					
		(20, 20)			(20, 10)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.058	0.058	0.058	0.074	0.074	0.074
	0.2	0.054	0.054	0.054	0.06	0.06	0.06
Clayton	0.5	0.055	0.055	0.055	0.049	0.049	0.049
	0.8	0.05	0.05	0.05	0.05	0.05	0.05
	0.2	0.054	0.054	0.054	0.055	0.055	0.055
Frank	0.5	0.054	0.054	0.054	0.048	0.048	0.048
	0.8	0.052	0.052	0.052	0.052	0.052	0.052
	0.2	0.055	0.055	0.055	0.056	0.056	0.056
Gumbel	0.5	0.053	0.053	0.053	0.049	0.049	0.049
	0.8	0.055	0.055	0.055	0.053	0.053	0.053

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 20% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.175, 2)$. The group with a 10% censoring rate has a survival distribution following the $Weibull(0.52, 2)$ and a censoring distribution following the $Weibull(0.081, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Table 22 Type I error of the assumed copula for scenario I with τ_θ=0.8, sample size 500, and heavy censoring rate

Assumed copula		**Censoring rate (%)**					
		(50, 50)			(50, 25)		
Copula	Kendall's tau	Method 2	Method 3	Method 4	Method 2	Method 3	Method 4
Kaplan-Meier		0.061	0.061	0.061	0.985	0.985	0.985
	0.2	0.06	0.06	0.06	0.897	0.897	0.897
Clayton	0.5	0.059	0.059	0.059	0.371	0.371	0.371
	0.8	0.049	0.049	0.049	0.049	0.049	0.049
	0.2	0.059	0.059	0.059	0.904	0.904	0.904
Frank	0.5	0.058	0.058	0.058	0.447	0.447	0.447
	0.8	0.053	0.053	0.053	0.051	0.051	0.051
	0.2	0.055	0.055	0.055	0.921	0.921	0.921
Gumbel	0.5	0.056	0.056	0.056	0.512	0.512	0.512
	0.8	0.053	0.053	0.053	0.054	0.054	0.054

Note. Scenario I consists of simulation data generated from the *Clayton* copula model. The group with a 50% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival distribution following the $Weibull(0.375, 2)$ and a censoring distribution following the $Weibull(0.155, 2)$. Method 2-4 are techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

5. Conclusion

In this paper, we explained that RMST provides a simple and clinically meaningful interpretation for comparing two survival curves, especially when the PH assumption is violated. Additionally, we discussed that when censoring in survival analysis is dependent on survival time, bias can occur in the process of estimating the survival function. To address this issue, we introduced copulas and Kendall's tau, a copula parameter, as effective methods for modeling dependencies between multivariate data.

In this simulation study, we compare the RMST of two survival curves under dependent censoring. The data generation setting scenarios are broadly divided into three categories based on the copula models (Clayton, Gumbel, and Frank), and for each scenario, three copula parameters and four censoring rates are set, resulting in a total of 54 scenarios. To calculate the confidence interval for the RMST difference, we estimated the variance using a non-parametric bootstrap method. During the bootstrap process, we considered three methods to address the issue where the survival function could not be defined because the last observed time did not reach the pre-specified time point. The copula-based CG estimator was used to estimate the survival function.

The study results showed that correctly specifying the copula model resulted in slightly more favorable type I error, and there were no significant differences among the results of Methods 2-4. When the difference in censoring rates was relatively large, incorrectly specifying the copula parameters could lead to inaccurate and incorrect interpretation of survival analysis results. This is especially important when the true copula parameter is large, indicating the importance of correctly specifying the copula parameters. Therefore, the study demonstrates that correctly specifying the assumed copula and its parameters can reduce bias in estimating the true survival function.

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Appendices

Appendix Table 1 Type I error of the assumed copula for scenario II with τ_θ=0.2 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.069	0.067	0.071	0.07
	0.2	0.067	0.066	0.05	0.059
Clayton	0.5	0.065	0.066	0.045	0.059
	0.8	0.063	0.064	0.041	0.084
	0.2	0.066	0.065	0.053	0.057
Frank	0.5	0.063	0.064	0.046	0.056
	0.8	0.063	0.065	0.041	0.083
	0.2	0.065	0.064	0.052	0.057
Gumbel	0.5	0.066	0.065	0.049	0.058
	0.8	0.063	0.066	0.039	0.083

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 2 Type I error of the assumed copula for scenario II with τ_θ=0.5 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.062	0.068	0.068	0.124
	0.2	0.065	0.067	0.065	0.087
Clayton	0.5	0.06	0.063	0.061	0.062
	0.8	0.06	0.061	0.051	0.072
	0.2	0.064	0.068	0.06	0.092
Frank	0.5	0.058	0.063	0.061	0.064
	0.8	0.06	0.06	0.06	0.075
	0.2	0.063	0.07	0.064	0.094
Gumbel	0.5	0.059	0.065	0.059	0.065
	0.8	0.06	0.062	0.059	0.074

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 3 Type I error of the assumed copula for scenario II with τ_θ=0.8 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.067	0.067	0.055	0.32
	0.2	0.07	0.069	0.054	0.224
Clayton	0.5	0.069	0.068	0.054	0.107
	0.8	0.066	0.066	0.049	0.06
	0.2	0.07	0.069	0.053	0.232
Frank	0.5	0.069	0.068	0.055	0.113
	0.8	0.067	0.067	0.05	0.058
	0.2	0.069	0.068	0.054	0.24
Gumbel	0.5	0.069	0.068	0.055	0.118
	0.8	0.067	0.067	0.049	0.059

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 4 Type I error of the assumed copula for scenario II with τ_{θ}=0.2 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.063	0.06	0.059	0.072
	0.2	0.056	0.07	0.054	0.063
Clayton	0.5	0.056	0.076	0.054	0.114
	0.8	0.058	0.082	0.047	0.193
	0.2	0.052	0.067	0.054	0.061
Frank	0.5	0.054	0.075	0.046	0.102
	0.8	0.059	0.08	0.046	0.187
	0.2	0.057	0.067	0.054	0.062
Gumbel	0.5	0.056	0.07	0.047	0.094
	0.8	0.058	0.08	0.047	0.186

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 5 Type I error of the assumed copula for scenario II with τ_θ=0.5 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.062	0.073	0.065	0.137
	0.2	0.06	0.067	0.054	0.077
Clayton	0.5	0.058	0.057	0.049	0.061
	0.8	0.058	0.056	0.049	0.114
	0.2	0.06	0.066	0.058	0.086
Frank	0.5	0.053	0.056	0.049	0.065
	0.8	0.057	0.054	0.048	0.102
	0.2	0.06	0.068	0.057	0.079
Gumbel	0.5	0.059	0.061	0.047	0.063
	0.8	0.059	0.055	0.051	0.107

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 6 Type I error of the assumed copula for scenario II with τ_θ=0.8 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.064	0.063	0.058	0.45
	0.2	0.063	0.063	0.059	0.296
Clayton	0.5	0.059	0.062	0.058	0.113
	0.8	0.058	0.059	0.049	0.055
	0.2	0.062	0.065	0.059	0.323
Frank	0.5	0.057	0.06	0.061	0.147
	0.8	0.058	0.057	0.048	0.055
	0.2	0.064	0.065	0.061	0.308
Gumbel	0.5	0.061	0.062	0.056	0.13
	0.8	0.058	0.059	0.052	0.059

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 7 Type I error of the assumed copula for scenario II with τ_θ=0.2 and sample size 500 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.058	0.064	0.066	0.119
	0.2	0.06	0.061	0.067	0.069
Clayton	0.5	0.058	0.075	0.066	0.327
	0.8	0.057	0.129	0.054	0.737
	0.2	0.063	0.057	0.063	0.062
Frank	0.5	0.058	0.069	0.069	0.199
	0.8	0.054	0.123	0.057	0.669
	0.2	0.062	0.056	0.066	0.062
Gumbel	0.5	0.054	0.074	0.065	0.19
	0.8	0.054	0.124	0.06	0.693

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 8 Type I error of the assumed copula for scenario II with τ_θ=0.5 and sample size 500 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.05	0.084	0.06	0.629
	0.2	0.05	0.07	0.056	0.229
Clayton	0.5	0.051	0.051	0.061	0.066
	0.8	0.049	0.052	0.057	0.384
	0.2	0.051	0.071	0.054	0.281
Frank	0.5	0.048	0.055	0.059	0.063
	0.8	0.05	0.049	0.057	0.334
	0.2	0.051	0.072	0.056	0.3
Gumbel	0.5	0.05	0.055	0.058	0.06
	0.8	0.048	0.051	0.059	0.342

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 9 Type I error of the assumed copula for scenario II with τ_θ=0.8 and sample size 500 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.054	0.053	0.054	0.998
	0.2	0.052	0.052	0.054	0.939
Clayton	0.5	0.053	0.052	0.054	0.398
	0.8	0.053	0.053	0.058	0.054
	0.2	0.051	0.052	0.055	0.948
Frank	0.5	0.052	0.052	0.052	0.486
	0.8	0.051	0.051	0.058	0.052
	0.2	0.052	0.052	0.057	0.955
Gumbel	0.5	0.051	0.051	0.056	0.521
	0.8	0.051	0.051	0.057	0.053

Note. Scenario II consists of simulation data generated from the *Gumbel* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 10 Type I error of the assumed copula for scenario III with τ_θ=0.2 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.069	0.065	0.066	0.067
	0.2	0.063	0.067	0.059	0.051
Clayton	0.5	0.063	0.066	0.047	0.06
	0.8	0.063	0.066	0.039	0.084
	0.2	0.062	0.066	0.059	0.053
Frank	0.5	0.067	0.062	0.053	0.056
	0.8	0.062	0.067	0.044	0.086
	0.2	0.062	0.068	0.059	0.052
Gumbel	0.5	0.066	0.063	0.05	0.056
	0.8	0.061	0.068	0.044	0.085

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 11 Type I error of the assumed copula for scenario III with τ_θ=0.5 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.07	0.076	0.068	0.117
	0.2	0.066	0.072	0.064	0.082
Clayton	0.5	0.066	0.06	0.059	0.065
	0.8	0.061	0.062	0.056	0.07
	0.2	0.068	0.071	0.062	0.087
Frank	0.5	0.065	0.064	0.06	0.06
	0.8	0.062	0.061	0.057	0.068
	0.2	0.067	0.073	0.062	0.085
Gumbel	0.5	0.064	0.061	0.058	0.062
	0.8	0.061	0.061	0.058	0.07

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 12 Type I error of the assumed copula for scenario III with τ_θ=0.8 and sample size 50 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.066	0.064	0.058	0.29
	0.2	0.068	0.068	0.055	0.212
Clayton	0.5	0.07	0.066	0.056	0.096
	0.8	0.069	0.066	0.052	0.06
	0.2	0.07	0.065	0.056	0.225
Frank	0.5	0.07	0.067	0.056	0.109
	0.8	0.067	0.066	0.052	0.062
	0.2	0.068	0.069	0.054	0.214
Gumbel	0.5	0.069	0.065	0.054	0.107
	0.8	0.068	0.067	0.051	0.059

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 13 Type I error of the assumed copula for scenario III with τ_θ=0.2 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.057	0.063	0.067	0.069
	0.2	0.053	0.059	0.061	0.073
Clayton	0.5	0.059	0.071	0.058	0.108
	0.8	0.058	0.081	0.047	0.186
	0.2	0.051	0.059	0.064	0.064
Frank	0.5	0.051	0.066	0.06	0.092
	0.8	0.055	0.079	0.053	0.176
	0.2	0.051	0.058	0.063	0.063
Gumbel	0.5	0.055	0.065	0.059	0.096
	0.8	0.056	0.081	0.053	0.175

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 14 Type I error of the assumed copula for scenario III with τ_θ=0.5 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.062	0.073	0.065	0.137
	0.2	0.06	0.067	0.054	0.077
Clayton	0.5	0.058	0.057	0.049	0.061
	0.8	0.058	0.056	0.049	0.114
	0.2	0.06	0.066	0.058	0.086
Frank	0.5	0.053	0.056	0.048	0.065
	0.8	0.057	0.054	0.048	0.102
	0.2	0.06	0.068	0.057	0.079
Gumbel	0.5	0.059	0.061	0.047	0.063
	0.8	0.059	0.055	0.051	0.107

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 15 Type I error of the assumed copula for scenario III with τ_θ=0.8 and sample size 100 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.064	0.063	0.058	0.45
	0.2	0.063	0.063	0.059	0.296
Clayton	0.5	0.059	0.062	0.058	0.113
	0.8	0.058	0.059	0.049	0.055
	0.2	0.062	0.065	0.059	0.323
Frank	0.5	0.057	0.06	0.061	0.147
	0.8	0.058	0.057	0.048	0.055
	0.2	0.064	0.065	0.061	0.308
Gumbel	0.5	0.061	0.062	0.056	0.13
	0.8	0.058	0.059	0.052	0.059

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 16 Type I error of the assumed copula for scenario III with τ_θ=0.2 and sample size 500 using Method 4

Assumed copula		Censoring rate (%)			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.056	0.064	0.059	0.124
	0.2	0.059	0.06	0.066	0.067
Clayton	0.5	0.052	0.07	0.064	0.295
	0.8	0.055	0.119	0.05	0.69
	0.2	0.058	0.06	0.062	0.063
Frank	0.5	0.051	0.072	0.07	0.17
	0.8	0.054	0.119	0.057	0.633
	0.2	0.056	0.059	0.06	0.061
Gumbel	0.5	0.051	0.07	0.068	0.173
	0.8	0.051	0.117	0.058	0.623

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 17 Type I error of the assumed copula for scenario III with τ_θ=0.5 and sample size 500 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.055	0.089	0.057	0.546
	0.2	0.057	0.075	0.054	0.208
Clayton	0.5	0.055	0.048	0.051	0.063
	0.8	0.052	0.05	0.056	0.352
	0.2	0.053	0.071	0.055	0.274
Frank	0.5	0.051	0.049	0.056	0.06
	0.8	0.049	0.055	0.056	0.281
	0.2	0.057	0.073	0.053	0.252
Gumbel	0.5	0.055	0.049	0.053	0.057
	0.8	0.053	0.051	0.054	0.29

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

Appendix Table 18 Type I error of the assumed copula for scenario III with τ_θ=0.8 and sample size 500 using Method 4

Assumed copula		**Censoring rate (%)**			
Copula	Kendall's tau	(20, 20)	(20, 10)	(50, 50)	(50, 25)
Kaplan-Meier		0.057	0.069	0.046	0.99
	0.2	0.06	0.064	0.042	0.91
Clayton	0.5	0.059	0.061	0.046	0.348
	0.8	0.053	0.054	0.049	0.051
	0.2	0.061	0.067	0.041	0.929
Frank	0.5	0.052	0.055	0.053	0.499
	0.8	0.051	0.052	0.055	0.056
	0.2	0.06	0.064	0.042	0.922
Gumbel	0.5	0.053	0.056	0.047	0.442
	0.8	0.052	0.052	0.053	0.049

Note. Scenario III consists of simulation data generated from the *Frank* copula model. The group with a 20% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 10% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. The group with a 50% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.375, 2)$. The group with a 25% censoring rate has a survival dist. following the $Weibull(0.375, 2)$ and a censoring dist. following the $Weibull(0.155, 2)$. Method 4 is techniques described in Section 3.3 to address issues arising when estimating the RMST difference from bootstrap samples.

국 문 요 약

종속적 중도절단 하에서 코퓰라 그래픽 추정기를 이용한 제한 평균 생존 시간 비교

제한 평균 생존 시간은 미리 정해진 시점까지의 생존 곡선 아래 면적으로 정의된다. 이는 시간 0 부터 특정 추적 시점까지의 평균 생존 시간으로 해석될 수 있으며, 그룹 간 생존 비교를 해석하는 데 있어 간단하고 임상적으로 의미 있는 방법을 제공한다. 특히, 제한 평균 생존 시간은 생존 곡선이 교차하거나 두 곡선 간의 분리가 지연되는 경우와 같이 비례 위험 가정이 위배되었을 때 두 생존 곡선을 비교하는 데 유용한 정보를 제공할 수 있다. 생존 분석에서 특정 관심 사건 발생까지의 시간은 종종 불완전하게 관찰된다. 즉, 일부 피험자의 경우 관심 사건 발생까지의 시간이 알려지지 않으며, 이를 중도절단이라고 한다. 이 중도절단이 생존 시간에 종속될 때, 생존 함수와 위험률 추정치에 편향을 초래할 수 있다. 이러한 문제를 해결하기 위해, 다변량 데이터 간의 종속성을 모델링하는 효과적인 방법인 코퓰라가 제안되었다. 본 논문은 종속적 중도절단을 가정하여 코퓰라 모델을 기반으로 한 코퓰라 그래픽 추정기를 사용하여 생존 함수를 추정하고 두 생존

곡선의 제한 평균 생존 시간을 비교한다. 두 생존 곡선의 제한 평균 생존 시간을 비교하기 위해, 두 생존 곡선 간 차이가 없다고 가정한다. 부트스트랩 방법을 사용하여 제한 평균 생존 시간 차이에 대한 신뢰 구간을 계산하고 제 1 종 오류를 구한다. 이때, 부트스트랩 샘플에 대해 생존 함수를 정의할 수 없는 문제를 해결하기 위해 네 가지 방법을 고려한다. 광범위한 시뮬레이션을 통해 각 시나리오의 생존 분석 결과에 대한 정확하고 올바른 해석을 제공하는 것을 목표로 한다.

핵심되는 말: 제한 평균 생존 시간, 코퓰라 그래픽 추정기, 종속적 중도절단, 제 1종 오류