# Comparison of permutation tests for difference in two Restricted Means Survival Time

Bomi Kim

The Graduate School
Yonsei University
Department of Biostatistics and Computing

# Comparison of permutation tests for difference in two Restricted Means Survival Time

A Master's Thesis
Submitted to the Department of Biostatistics and Computing
and the Graduate School of Yonsei University
in partial fulfillment of the
requirements for the degree of
Master of Science

Bomi Kim

December 2023

This certifies that the master's thesis of ***Bomi Kim*** is approved.

***ChungMo Nam***: Thesis Supervisor

***Inkyung Jung***: Thesis Committee Member #1

***YunHo Roh***: Thesis Committee Member #2

The Graduate School

Yonsei University

December 2023

# Contents

# List of Tables

# List of Figures

# Abstract

Comparison of permutation tests for difference
in two Restricted Means Survival Time

Survival analysis assumes proportional hazards to compare survival functions between groups. However, these assumptions may not apply to real-world data, so the restricted mean survival time (RMST) is adopted as an alternative.

In this paper, we compare methods suitable for small sample sizes through simulation using the permutation method. We also consider the dependency between survival and censoring distributions using the Clayton and Gumbel copula functions.

We interpret that the studentized approach provides better control of type I error when the censoring distribution is different between the two groups. However, if there is a dependency between the survival and censoring distributions and the censoring distributions of the two groups are different, a studentized permutation shows that the type I error increases.

---

Key words : Restricted mean survival time, Studentized Permutation, Copula

# 1. Introduction

In survival analysis, when the proportional hazards assumption holds true, the log-rank test and proportional hazards model are used to compare the survival functions between groups. However, in actual survival data, the proportional hazards assumption may not hold. In such cases, it is easier to use methods that do not require model assumptions. Restricted mean survival time (RMST) can be used as an alternative (Royston and Parmar, 2011; 2013).

Restricted mean survival time represents the expected value of the minimum survival time until the occurrence of the event of interest and a pre-specified time point called the $\tau$. It is expressed as the area under the survival curve from time point 0 to the $\tau$. RMST is easy to interpret clinically and can be used even when the proportional hazards assumption is not satisfied (Chen et al., 2001; Royston and Parmar, 2011; 2013; Zhao et al., 2016).

If the survival curves of two groups cross, it may be difficult to ascertain significant differences between the groups using the log-rank test. However, comparing the RMSTs of the two groups allows for a valid interpretation. Furthermore, it has higher statistical power compared to the log-rank test and proportional hazards model (Tian et al., 2016).

However, applying RMST based on the characteristics observed in asymptotic tests with sufficiently large sample sizes may be challenging in small clinical trials. Additionally, if the last observed event time is shorter than the pre-specified time point when calculating

RMST, an error may occur, preventing the comparison of the difference in RMST between groups.

To address such issues, permutation methods have been used, allowing for a more accurate comparison of time-to-event outcomes in small randomized trials (Horiguchi et al., 2020). The five permutation methods involve permuting data, excluding instances where the last observed time point occurs before the pre-specified time point. The first method may be computationally time-consuming due to the exclusion process. The second method involves extending based on survival probability at the last observation time, and the third method calculates the area under the survival curve from time 0 to the last observed time. The fourth method averages RMST obtained from the second and third methods, while the last method fits a Weibull distribution to calculate RMST. However, these methods assume equal distributions between groups. In real survival data, group-specific survival or censoring distributions may differ. In cases where the survival distributions differ between groups, RMST is compared using permutation methods under the assumption of equal RMST. Moreover, to address differing censoring distributions between groups, the studentized permutation method is employed (Dizhaus et al., 2021).

This paper primarily focuses on comparing the RMST of two groups using permutation methods, which are commonly used to address distributional assumptions in cases of small sample sizes where the distribution is challenging. The paper aims to apply two permutation methods to five RMST calculation methods under the assumption of independence between survival and censoring distributions. Additionally, it investigates how these methods are applied when survival and censoring distributions are dependent, utilizing Copula functions. Furthermore, the paper examines differences between the asymptotic method and permutation method in cases with sufficiently large sample sizes.

The structure of this paper is as follows. Section 2 explains the two permutation methods: Horiguchi and Uno (2020) and Ditzhaus et al. (2021). In Section 3, various other simulations are performed, such as when the survival distribution and censoring distribution of each group are different and when there is a dependency between the two distributions. In Section 4, the results are compared when applying the actual PBC data. Finally, Section 5 concludes the paper and discusses the implications of this study.

# 2. Method

## 2.1 Notations

Assume that there are $n_i$ subjects. For $j = 1, \cdots, n_i$, $T_{ij}$ denotes the survival time for the $j$th subject and in the $i$th group, and $C_{ij}$ is the censoring time. We observe $(X_{ij}, \delta_{ij})$, where the observed event time is denoted $X_{ij} = \min(T_{ij}, C_{ij})$ and $\delta_{ij} = \mathrm{I}(X_{ij} = C_{ij})$ serves as the censoring indicator. The $\tau$ is a pre-specified time point, as a truncation time point.

The Restricted Mean Survival Time (RMST) is calculated as the expected value of the minimum between $\tau$ and $X_{ij}$. It represents the area under the survival function from time 0 to $\tau$, which can be expressed as

$$\mu_i = E\{\min(X_i, \tau)\} = \int_0^{\tau} S_i(t)dt \quad (i = 1, 2),$$

where $i$ indicates each group 1 and 2.

The difference in RMSTs between the two groups up to $\tau$ is denoted as $D(\tau)$ and is calculated as

$$D(\tau) = \int_0^{\tau} \{S_2(t) - S_1(t)\}dt$$

Under the null hypothesis $H_0 : \mu_1 = \mu_2$, we conduct a test for $D(\tau) = 0$.

## 2.2 Horiguchi and Uno (2020)

The comparison between groups is conducted based on the RMSTs of the two groups. The difference in RMST, $D(\tau)$, is proposed as a measure to assess the survival benefit of the treatment. Here, $\widehat{D}(\tau)$ is an estimator based on non-parametric estimation, defined as

$$\widehat{D}(\tau) = \int_0^{\tau} \left\{\widehat{S_2}(t) - \widehat{S_1}(t)\right\} dt$$

where $\widehat{S_1}(t)$ and $\widehat{S_2}(t)$ represent the Kaplan-Meier estimators for the survival functions of groups 1 and 2, respectively.

Let $A_i(t)$ be the cumulative hazard function for $T_i$ and let $\pi_i(t) = Pr\{min(T_i, C_i) \geq t\}$. $\widehat{A}_i(\cdot)$ represents the Nelson-Aalen estimator, and $\hat{p}_i = \frac{n_i}{n}$ denotes the fraction of the sample size $n_i$ in group $i$. This estimator converges to a zero-mean Gaussian process, $Q(\tau) = \sqrt{n}\{\widehat{D}(\tau) - D(\tau)\}$, when the sample size is sufficiently large, and the associated variance function is as follows.

$$\sigma^2(\tau) = \int_0^{\tau} \left\{\int_v^{\tau} S_1(t)\, dt\right\}^2 \frac{dA_1(v)}{p_1\pi_1(v)} + \int_0^{\tau} \left\{\int_v^{\tau} S_2(t)\, dt\right\}^2 \frac{dA_2(v)}{p_2\pi_2(v)}.$$

Therefore, the variance estimator based on the Nelson-Aalen estimator is as follows.

$$\hat{\sigma}_A^2(\tau) = \int_0^{\tau} \left\{\int_v^{\tau} \widehat{S_1}(t)\, dt\right\}^2 \frac{d\widehat{A_1}(v)}{\widehat{p_1}\widehat{\pi_1}(v)} + \int_0^{\tau} \left\{\int_v^{\tau} \widehat{S_2}(t)\, dt\right\}^2 \frac{d\widehat{A_2}(v)}{\widehat{p_2}\widehat{\pi_2}(v)}$$

The variance estimator based on Greenwood's formula for the variance of the Kaplan-Meier estimator is given by

$$\hat{\sigma}_B^2(\tau) = n\left[\sum\nolimits_{t_{1k}} \left\{\int_{t_{1k}}^{\tau} \widehat{S_1}(u)\,du\right\}^2 \frac{d_{1k}}{Y_{1k}(Y_{1k}-d_{1k})} + \sum\nolimits_{t_{2k}} \left\{\int_{t_{2k}}^{\tau} \widehat{S_2}(u)\,du\right\}^2 \frac{d_{2k}}{Y_{2k}(Y_{2k}-d_{2k})}\right]$$

In this case, $t_{ik}$ represents the distinct failure time points in group $i$ that are smaller than $\tau$, and $d_{ik}, Y_{ik}$ denote the number of observed events and the number of subjects at risk at $t_{ik}$ respectively.

Therefore, the variance estimator based on the Nelson-Aalen estimator can be expressed as:

$$\hat{\sigma}_A^2(\tau) = n\left[\sum\nolimits_{t_{1k}} \left\{\int_{t_{1k}}^{\tau} \widehat{S_1}(u)\,du\right\}^2 \frac{d_{1k}}{{Y_{1k}}^2} + \sum\nolimits_{t_{2k}} \left\{\int_{t_{2k}}^{\tau} \widehat{S_2}(u)\,du\right\}^2 \frac{d_{2k}}{{Y_{2k}}^2}\right]$$

When using the asymptotic Z-test to compare the difference in RMST, the test statistic $Z(\tau)$ is represented as $Z(\tau) = \frac{\sqrt{n}\hat{D}(\tau)}{\hat{\sigma}} \sim N(0,1)$, where $\hat{\sigma}^2(\tau)$ can be either $\hat{\sigma}_A^2(\tau)$ $or$ $\hat{\sigma}_B^2(\tau)$. This asymptotic test follows a standard normal distribution, denoted as $Z(\tau) \sim N(0,1)$. It should be noted that while the asymptotic test provides similar results to the permutation test for large sample sizes, it poses an issue of increased type I error rates for small sample sizes.

The permutation method is carried out through the following steps:

Firstly, Z and z are calculated as the test statistics and observed data, respectively. Next, under the assumption of no difference between groups under the null hypothesis, the observed data is randomly shuffled, and the test statistics are recalculated. This shuffling process is repeated M times to obtain the reference distribution $\{Z_1^*, \cdots, Z_M^*\}$. Finally, the p-value is obtained by comparing the test statistic z with the reference distribution.

When defining the RMST difference obtained through permutation as follows:

$$\left\{\widehat{D}^{(m)}(\tau) = \int_0^\tau \left\{\hat{S}_2^{(m)}(t) - \hat{S}_1^{(m)}(t)\right\} dt\,;\ m = 1,\ \cdots,\ M\right\}$$

Therefore, Horiguchi and Uno (2020) proposed the following five methods due to the numerical issues that arise when the last observed time point appears before $\tau$, which is more likely to occur with small sample sizes.

Method1: **Ignoring the inestimable cases**

- Simply ignoring the cases that we cannot calculate $\widehat{D}^{(m)}(\tau)$
- It may take a long computing time to obtain the M realizations for some observed data

Method2: **Extending the survival curves to $\tau$**

- Extending the survival curve to $\tau$, both $\hat{S}_2^{(m)}(u)$ and $\hat{S}_1^{(m)}(u)$
- This method is overestimating the RMST value

Method3: **Switching the last censored observation to the event observation**

- Switching the last censored observation to event when the survival function at $\tau$

Method4: **Averaging RMSTs derived from Methods 2 and 3**

- Combination of Method 2 and 3

Method5: **Fitting a Weibull distribution to each inestimable case**

- Survival function of either group cannot be defined in the permutations
- $\hat{S}_1^{(m)}(u)$ cannot be defined with the $m$th permutation data, we fit the data with a Weibull distribution model

### 2.3 Ditzhaus et al. (2021)

Ditzhaus et al. (2021) proposed the studentized permutation test to compare two restricted mean survival time (RMST) in a randomized trial with small sample sizes. This method was introduced to relax the general assumption that, under the null hypothesis $H_0$: $\mu_1 = \mu_2$, the censoring distribution should be equal when permuted, as it may differ. This approach aims to address a limitation of classic permutation test, where the groups to be compared need to be exchangeable data.

$$\widehat{D}(\tau) = \int_0^{\tau} \{\widehat{S_2}(t) - \widehat{S_1}(t)\}\, dt$$

The estimator $\widehat{S_i}(t)$ compares based on the normal approximation using the Kaplan-Meier estimator.

Under the assumption that $\frac{n_i}{n} \to p_i \in (0,1)$ $as$ $n \to \infty$, this have

$$\sqrt{n}\{(\hat{\mu}_1 - \hat{\mu}_2) - (\mu_1 - \mu_2)\} \xrightarrow{d} Z \sim N(0, \sigma^2),\ \ \sigma^2 = \sigma_1^2 + \sigma_2^2.$$

Additionally, the asymptotic variance of $\sqrt{n}(\hat{\mu}_i - \mu_i)$ is $\sigma_i^2$.

$A_i = -\log(S_i)$ represents the cumulative hazard rate function, and $\Delta A_i(x)$ is the $x$ increment. Furthermore, $\Delta A_i(x) = A_i(x) - A_{i\_}(x)$, $G_{i\_}(t) = P(C_{i1} \geq t)$ are examples of the left-continuous forms of $G_i, S_i$ and $A_i$, respectively denoted by $G_{i\_}, S_{i\_}$ and $A_{i\_}$. These values obtained as the Kaplan-Meier and Nelson-Aalen estimators, respectively.

$$\hat{\sigma}_i^2 = \frac{n}{n_i}\int_0^{\tau}\left\{\int_x^{\tau}\hat{S}_i(t)dt\right\}^2 \frac{1}{\{1-\Delta\hat{A}_i(x)\}\hat{S}_{i\_}\hat{G}_{i\_}} d\hat{A}_i(x).$$

$\hat{S}_{i\_}\hat{G}_{i\_} = \frac{1}{n_i}\sum_{j=1}^{n_i} 1\{X_{ij} \geq t\} = \frac{1}{n_i}Y_i(t)$, $\hat{A}(t) = \sum_{k:t_k\leq t}\frac{\Delta N(t_k)}{Y(t_k)} = \int_0^t Y(s)^{-1}\,dN(s)$ $(t \geq 0)$ is expressed, where $N_i(t)$ is the number of observed events up until $t$ in group $i$, and $Y_i(t)$ is the number of individuals under risk just before $t$ in group $i$. So $\mathrm{N(t)} = N_1(t) + N_2(t), Y(t) = Y_1(t) + Y_2(t)$.

When each value is substituted and simplified, the formula for the variance estimation can be expressed as follows:

$$\begin{aligned}\hat{\sigma}_i^2 &= \frac{n}{n_i}\int_0^{\tau}\left\{\int_x^{\tau}\hat{S}_i(t)dt\right\}^2 \frac{1}{\{1-\Delta\hat{A}_i(x)\}\frac{1}{n_i}Y_i(t)} d\hat{A}_i(x) \\ &= n\sum_{t_k\leq t}\left\{\int_x^{\tau}\hat{S}_i(t)dt\right\}^2 \frac{1}{\{1-\Delta\hat{A}_i(x)\}Y_i(t)}\end{aligned}$$

For the hypothesis test of $H_0:\ \mu_1 = \mu_2$, we obtain the value $\varphi = 1\left\{\frac{\sqrt{n}|\hat{\mu}_1-\hat{\mu}_2|}{\sigma} > z_{\frac{1-\alpha}{2}}\right\}$. If the sample size is small, there is an issue of inflated type I error.

To address this issue, permutation tests are used, which are relatively robust assuming the same survival and censoring distributions. However, since it is difficult for actual data to satisfy this assumption, a studentized permutation is proposed.

Theorem 1: The given data converges to a central normal distribution constrained by the following variance.

$$\sigma_{perm}^2 = \frac{1}{\kappa_1\kappa_2}\int_0^\tau \left\{\int_x^\tau S(t)dt\right\}^2 \frac{1}{\{1-\Delta A(x)\}y(t)} dA(x)$$

Then,

$$\underset{t\in\mathbb{R}}{SUP} \left| P\{\sqrt{n}(\hat{\mu}_1^\pi - \hat{\mu}_2^\pi) \le t \middle| (X,\delta)\} - \Phi\left(\frac{t}{\sigma_{perm}}\right)\right| \overset{P}{\rightarrow} 0 \ \ as \ \ n \rightarrow \infty$$

When the survival distributions of the two groups are the equal, and the censoring distributions are also the equal, $\sigma^2 = \sigma_1^2 + \sigma_2^2$ and $\sigma_{perm}^2$ coincide. If the censoring distribution assumptions of the two groups differ, the variance of the permutation statistic will be different. To address this, the original test statistic is augmented with an estimator of the variance from the permutated data. The superscript π denotes the mean and standard deviation for each permutation in the permuted data.

Theorem 2: The studentized permutation statistic, $\sqrt{n}(\hat{\mu}_1^\pi - \hat{\mu}_2^\pi)/\hat{\sigma}^\pi$, converges to a standard normal distribution.

$$\underset{t\in\mathbb{R}}{SUP} \left| P\left\{\frac{\sqrt{n}(\hat{\mu}_1^\pi - \hat{\mu}_2^\pi)}{\hat{\sigma}^\pi} \le t \middle| (X,\delta)\right\} - \Phi(t)\right| \overset{P}{\rightarrow} 0 \ \ as \ \ n \rightarrow \infty$$

In theorem 2, $\hat{\sigma}^\pi$ refers to the standard deviation calculated from permutated data.

# 3. Simulation

## 3.1 Data generation

Survival time is generated using Exponential, Weibull, Log-normal distributions. The survival distribution is as follows

- Exponential distribution : $f(x) = \lambda exp(-\lambda x)$

$$T_i \sim S_i \ = \ exp(-\lambda x), \qquad (i = 1, 2)$$

- Weibull distribution : $f(x) = \alpha\lambda x^{\alpha-1} exp(-\lambda x^{\alpha}), \quad (\lambda = \left(\frac{1}{\sigma}\right)^{\alpha}, \sigma \ \ is \ \ scale)$

$$T_i \sim S_i \ = \ exp\left(-\left(\frac{x}{\sigma}\right)^{\alpha}\right), \qquad (i = 1, 2)$$

- Log-normal distribution : $f(x) = \frac{\exp\left[-\frac{1}{2}(\frac{lnx-\mu}{\sigma})^2\right]}{x(2\pi)^{1/2}\sigma}$

$$T_i \sim S_i \ = \ 1 - \Phi\left[\frac{lnx - \mu}{\sigma}\right], \qquad (i = 1, 2)$$

The censoring distribution is created from Weibull, Uniform distribution. The observed event time is $T$ and $C$ is the censoring variable. Then $X_{ij} = \min(T_{ij}, C_{ij})$ is the observed event time, and $\delta_{ij} = \mathrm{I}(X_{ij} = C_{ij})$ is censoring indicator. $i$ is the group indicator, so individuals were randomly assigned to either the treatment or control group.

### 3.2 Simulation setting

When the survival and censoring distributions are independent, scenarios 1, 2, and 3 assume equal survival distributions in each group, while scenarios 4, 5, and 6 involve unequal survival distributions. The censoring distribution is represented in three cases, where the first case entails different censoring distributions in each group (Weibull (3, 18), Weibull (0.5, 40)), and the second and third cases assume the same censoring distribution for each group (case 2: Uniform (0, 25), case 3: Weibull (3, 15)).

For a sample size where the sum of the two groups' sample sizes is 30, we set $n_1$=12, 15, 18, and $n_2$=18, 15, 12 for each. Additionally, we multiply each group size by 10. The pre-specified time point, denoted as τ (>0), is set to 10.

Moreover, a permutation test is conducted under the following conditions:

First, if the maximum observation time in each group is greater than τ or if an event occurs at the maximum observation time point in either group. Second, if the larger of the maximum observation times in the two groups is greater than τ. Both of these conditions must be satisfied to proceed with the simulation for RMST.

All scenarios operate under the assumption of the null hypothesis,

$$H_0 : \ \mu_1 = \mu_2$$

being true.

Each scenario has the following survival distributions:

**Table 1. Data generation setting**

| | |
|---|---|
| Survival distribution (equal distribution in each group) | • Scenario 1 $T_{.j} \sim Exp(0.2)$<br>• Scenario 2 $T_{.j} \sim Weibull(3, 8)$<br>• Scenario 3 $T_{.j} \sim log - normal(2, 0.25)$ |
| Survival distribution (unequal distribution in each group) | • Scenario 4 $T_{1j} \sim Exp(0.2)$<br>$T_{2j} \sim piece - wise\ \ Exp$<br>Hazard function $\alpha_2 = 0.5I(t \leq \lambda_4) + 0.05I(t > \lambda_4)$<br>• Scenario 5 $T_{1j} \sim Weibull(3, 8)$<br>$T_{2j} \sim Weibull(shape, 14)$<br>• Scenario 6 $T_{1j} \sim Weibull(3, 8)$<br>$T_{2j} \sim Weibull(1.5, scale)$ |
| $n_1, n_2$ | $(12, 18), (15, 15), (18, 12)$ |
| $n_1, n_2 \ \times 10$ | $(120, 180), (150, 150), (180, 120)$ |

In scenarios 4, 5, and 6, the parameter values of group 2's survival distribution are estimated based on the value when the difference between the RMSTs of the two groups is

0. Using the equation $D(\tau) = \int_0^\tau \{S_2(t) - S_1(t)\}\, dt = 0$, we find that for scenario 4, $\lambda_4$ is 1.50, for scenario 5, the shape is 0.91, and for scenario 6, the scale is 9.86.

Furthermore, in all scenarios, we assume that the survival distribution and censoring distribution in each group are not independent. In this case, we utilize Kendall's tau, a statistic that represents the dependency between the two distributions in the Archimedean copula, to estimate the parameters of the copula function and conduct simulations for cases where the survival distributions are not independent. We use the Gumbel copula and Clayton copula, and each copula's generator function and parameter estimation are expressed as follows:

- Gumbel copula:

$$C_\theta(u_{1,} u_{2,}) = \exp\left\{-\left[(-\ln u_1)^\theta + (-\ln u_2)^\theta\right]^{1/\theta}\right\} \quad 0 \le u_{1,} u_{2,} \le 1$$

$$\tau_\theta = \frac{\theta - 1}{\theta}$$

- Clayton copula:

$$C_\theta(u_{1,} u_{2,}) = \left(u_1{}^{-\theta} + u_2{}^{-\theta} - 1\right)^{1/\theta}$$

$$\tau_\theta = \frac{\theta}{\theta + 2}$$

Using the copula R package, we set θ to 2 and generate data that considers the dependency between the two distributions. In all simulations, the RMST is calculated using the survRM2perm R package. The permutation method employs five approaches provided by the rmst2perm function in this package: Method 1: Ignoring the inestimable cases, Method 2: Extending the survival curves to $\tau$, Method 3: Switching the last censored observation to the event observation, Method 4: Averaging RMSTs derived from Methods 2 and 3, Method 5: Fitting a Weibull distribution to each inestimable case. The simulations are conducted 1000 iterations, and within each iteration, permutations are performed 2000 times.

### 3.3 Simulation result

Survival distributions in each scenario are denoted from S1 to S6, and the results for censoring cases are represented as C1 to C3. The pre-specified time point, $\tau$, is set to 10.

The permutation method involves randomly shuffling observations of both groups to generate new samples and relies on the assumption that the distributions of the two groups are equal. However, if the censoring distributions differ, the assumption of distributional similarity in permutation may not hold. In such cases, the studentized permutation method, which allows for maintaining distributional characteristics between groups while conducting tests, may be more suitable.

Under the assumption that the survival distribution and censoring distribution are independent, it can be observed that the type 1 error increases in the asymptotic method when the sample size is small (Appendix Table 1, 2). Table 2 shows the type 1 error in scenarios S1-S3, where the survival distributions of each group are equal but the censoring distributions differ (C1). In this case, when the sample sizes of the two groups are different, it can be interpreted that studentized permutation better controls the type 1 error compared to permutation. Additionally, even when the sample sizes of two groups differ, the use of the studentized statistic in the studentized permutation method results in less sensitivity to differences in sample sizes between groups.

In the case where the survival distributions of the two groups are different, a test was conducted under the null hypothesis that the RMST values of the two groups are equal.

Table 3 shows the type 1 error when the survival distributions differ, regardless of the characteristics of the censoring distribution. Overall, the interpretation is that the studentized permutation method is more suitable. Moreover, in cases of a small sample size, differences between the two permutation methods can be observed, with Method 2 showing a tendency to be overestimated and Method 3 being underestimated. When the sample size is small, situations where the last observed time point appears before $\tau$, making it challenging to calculate RMST, are more likely to occur. In such cases, the issue is directly addressed through permutation, potentially influencing the outcomes.

In Table 4, the type 1 error is presented for scenarios where the sample size is increased by a factor of 10. When the sample size becomes sufficiently large, the trends observed in scenarios with different sample sizes, as shown in Table 2, diminish. This case occurs irrespective of the characteristics of survival and censoring distributions, and the differences between permutation methods diminish, favoring asymptotic results (see Appendix Table 3 and 4).

In cases where the survival distribution and censoring distribution are dependent, simulations are conducted using the Clayton and Gumbel copula functions to determine the dependency between each distribution. The results for each copula function can be observed in Table 5 and 6. Irrespective of the similarity in survival distributions between groups. In such cases, even with a small sample size, there tends to be a reduced difference between methods observed in scenarios where survival and censoring distributions are independent. This tendency is influenced by the $\tau$ value, and therefore, the results are compared by adjusting the $\tau$ value for each scenario. When increasing the $\tau$ value to 15, there is a more frequent occurrence of cases where the last observed time point is earlier than $\tau$. This leads to variations in type 1 error among methods, as shown in Table 7 and 8.

As the sample size increases, it is anticipated that asymptotic methods, akin to scenarios where survival distribution and censoring distribution are independent, would be more suitable. The actual results also suggest that these methods effectively control type 1 error compared to permutation methods (see Table 9 and 10). The hypothesis testing is conducted under the null hypothesis that the restricted mean survival time (RMST) is equal for the two groups. This implies that, even if the survival distribution of the two groups differs, the RMST may still be equal. Regardless of the distribution characteristics of the survival function, when there is a difference in censoring distribution between groups, using copula functions to derive marginal distributions can result in significant variations. In such cases, there is a potential for an increase in type 1 errors.

**Table 2. Type1 error of the studentized and unstudentized permutation method in small sample size**

| Censoring | Survival | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| C1 | S1 | 12, 18 | 0.102 | 0.042 | 0.039 | 0.045 | 0.041 | 0.040 | 0.039 | 0.043 | 0.039 | 0.042 | 0.041 |
| | | 15, 15 | 0.101 | 0.042 | 0.056 | 0.042 | 0.057 | 0.041 | 0.057 | 0.041 | 0.057 | 0.041 | 0.057 |
| | | 18, 12 | 0.100 | 0.064 | 0.060 | 0.064 | 0.057 | 0.063 | 0.055 | 0.064 | 0.057 | 0.063 | 0.056 |
| | S2 | 12, 18 | 0.094 | 0.044 | 0.055 | 0.044 | 0.055 | 0.044 | 0.054 | 0.044 | 0.055 | 0.044 | 0.055 |
| | | 15, 15 | 0.101 | 0.064 | 0.063 | 0.066 | 0.063 | 0.066 | 0.063 | 0.066 | 0.063 | 0.066 | 0.063 |
| | | 18, 12 | 0.097 | 0.055 | 0.065 | 0.054 | 0.065 | 0.054 | 0.065 | 0.054 | 0.065 | 0.055 | 0.065 |
| | S3 | 12, 18 | 0.102 | 0.047 | 0.039 | 0.047 | 0.039 | 0.045 | 0.039 | 0.046 | 0.039 | 0.046 | 0.039 |
| | | 15, 15 | 0.073 | 0.044 | 0.049 | 0.044 | 0.050 | 0.043 | 0.050 | 0.043 | 0.050 | 0.043 | 0.050 |
| | | 18, 12 | 0.100 | 0.075 | 0.070 | 0.074 | 0.069 | 0.074 | 0.067 | 0.074 | 0.069 | 0.074 | 0.069 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Table 3. Type1 error of the studentized and unstudentized permutation method in small sample size**

| Survival | Censoring | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| S4 | C1 | 12, 18 | 0.081 | 0.045 | 0.040 | 0.043 | 0.040 | 0.041 | 0.037 | 0.042 | 0.039 | 0.042 | 0.039 |
| | | 15, 15 | 0.093 | 0.071 | 0.062 | 0.068 | 0.061 | 0.068 | 0.060 | 0.068 | 0.060 | 0.068 | 0.060 |
| | | 18, 12 | 0.115 | 0.063 | 0.090 | 0.062 | 0.089 | 0.059 | 0.087 | 0.061 | 0.088 | 0.061 | 0.088 |
| | C2 | 12, 18 | 0.087 | 0.043 | 0.041 | 0.043 | 0.036 | 0.039 | 0.035 | 0.041 | 0.036 | 0.042 | 0.035 |
| | | 15, 15 | 0.093 | 0.044 | 0.054 | 0.040 | 0.049 | 0.038 | 0.047 | 0.040 | 0.048 | 0.041 | 0.048 |
| | | 18, 12 | 0.102 | 0.055 | 0.065 | 0.050 | 0.064 | 0.047 | 0.062 | 0.049 | 0.064 | 0.050 | 0.064 |
| | C3 | 12, 18 | 0.086 | 0.042 | 0.045 | 0.041 | 0.044 | 0.041 | 0.043 | 0.041 | 0.043 | 0.041 | 0.043 |
| | | 15, 15 | 0.096 | 0.054 | 0.063 | 0.052 | 0.063 | 0.051 | 0.063 | 0.051 | 0.063 | 0.051 | 0.063 |
| | | 18, 12 | 0.073 | 0.071 | 0.050 | 0.068 | 0.049 | 0.067 | 0.048 | 0.067 | 0.048 | 0.067 | 0.049 |

Abbreviations: S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C2, Censoring distribution in both groups follow Uniform(0, 25); C3, Censoring distribution in both groups follow Weibull(3, 15); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Table 4. Type1 error of the studentized and unstudentized permutation method**

| Censoring | Survival | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| C1 | S1 | 120, 180 | **0.050** | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 |
| | | 150, 150 | **0.056** | 0.043 | 0.059 | 0.043 | 0.059 | 0.043 | 0.059 | 0.043 | 0.059 | 0.043 | 0.059 |
| | | 180, 120 | **0.055** | 0.045 | 0.056 | 0.045 | 0.056 | 0.045 | 0.056 | 0.045 | 0.056 | 0.045 | 0.056 |
| | S2 | 120, 180 | **0.060** | 0.037 | 0.056 | 0.037 | 0.056 | 0.037 | 0.056 | 0.037 | 0.056 | 0.037 | 0.056 |
| | | 150, 150 | **0.054** | 0.040 | 0.055 | 0.040 | 0.055 | 0.040 | 0.055 | 0.040 | 0.055 | 0.040 | 0.055 |
| | | 180, 120 | **0.055** | 0.071 | 0.062 | 0.071 | 0.062 | 0.071 | 0.062 | 0.071 | 0.062 | 0.071 | 0.062 |
| | S3 | 120, 180 | **0.053** | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | 150, 150 | **0.055** | 0.063 | 0.050 | 0.063 | 0.050 | 0.063 | 0.050 | 0.063 | 0.050 | 0.063 | 0.050 |
| | | 180, 120 | **0.052** | 0.058 | 0.064 | 0.058 | 0.064 | 0.058 | 0.064 | 0.058 | 0.064 | 0.058 | 0.064 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Table 5. Type1 error of the studentized permutation method with Clayton copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S2 | 12, 18 | **0.198** | **0.197** | **0.197** | **0.197** | **0.197** |
| | | | | 15, 15 | **0.186** | **0.186** | **0.186** | **0.186** | **0.186** |
| | | | | 18, 12 | **0.150** | **0.150** | **0.150** | **0.150** | **0.150** |
| | | | S5 | 12, 18 | **0.218** | **0.218** | **0.218** | **0.218** | **0.218** |
| | | | | 15, 15 | **0.239** | **0.239** | **0.239** | **0.239** | **0.239** |
| | | | | 18, 12 | **0.282** | **0.282** | **0.282** | **0.282** | **0.282** |
| | | C3 | S2 | 12, 18 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| | | | | 15, 15 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 18, 12 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | S5 | 12, 18 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | | 15, 15 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 18, 12 | 0.074 | 0.074 | 0.074 | 0.074 | 0.074 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Table 6. Type1 error of the studentized permutation method with Gumbel copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S2 | 12, 18 | **0.118** | **0.118** | **0.118** | **0.118** | **0.118** |
| | | | | 15, 15 | **0.128** | **0.128** | **0.128** | **0.128** | **0.128** |
| | | | | 18, 12 | **0.096** | **0.096** | **0.096** | **0.096** | **0.096** |
| | | | S5 | 12, 18 | **0.119** | **0.119** | **0.119** | **0.119** | **0.119** |
| | | | | 15, 15 | **0.140** | **0.140** | **0.140** | **0.140** | **0.140** |
| | | | | 18, 12 | **0.135** | **0.135** | **0.135** | **0.135** | **0.135** |
| | | C3 | S2 | 12, 18 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | | 15, 15 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| | | | | 18, 12 | 0.054 | 0.054 | 0.053 | 0.053 | 0.053 |
| | | | S5 | 12, 18 | 0.038 | 0.038 | 0.038 | 0.038 | 0.038 |
| | | | | 15, 15 | 0.054 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | | 18, 12 | 0.068 | 0.067 | 0.067 | 0.067 | 0.067 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Table 7. Type1 error of the studentized permutation method with Clayton copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S2 | 12, 18 | 0.147 | 0.148 | 0.147 | 0.147 | 0.147 |
| | | | | 15, 15 | 0.190 | 0.191 | 0.191 | 0.191 | 0.191 |
| | | | | 18, 12 | 0.164 | 0.165 | 0.165 | 0.165 | 0.165 |
| | | | S5 | 12, 18 | 0.607 | 0.603 | 0.600 | 0.602 | 0.602 |
| | | | | 15, 15 | 0.654 | 0.654 | 0.653 | 0.654 | 0.653 |
| | | | | 18, 12 | 0.671 | 0.672 | 0.671 | 0.671 | 0.671 |
| | | C3 | S2 | 12, 18 | 0.053 | 0.054 | 0.053 | 0.054 | 0.053 |
| | | | | 15, 15 | 0.052 | 0.053 | 0.052 | 0.053 | 0.052 |
| | | | | 18, 12 | 0.044 | 0.046 | 0.045 | 0.046 | 0.046 |
| | | | S5 | 12, 18 | 0.163 | 0.156 | 0.154 | 0.156 | 0.155 |
| | | | | 15, 15 | 0.232 | 0.226 | 0.223 | 0.224 | 0.226 |
| | | | | 18, 12 | 0.273 | 0.281 | 0.275 | 0.277 | 0.279 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Table 8. Type1 error of the studentized permutation method with Gumbel copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S2 | 12, 18 | 0.099 | 0.099 | 0.099 | 0.099 | 0.099 |
| | | | | 15, 15 | 0.149 | 0.149 | 0.148 | 0.148 | 0.148 |
| | | | | 18, 12 | 0.118 | 0.118 | 0.118 | 0.118 | 0.118 |
| | | | S5 | 12, 18 | 0.391 | 0.389 | 0.387 | 0.388 | 0.389 |
| | | | | 15, 15 | 0.466 | 0.465 | 0.463 | 0.463 | 0.465 |
| | | | | 18, 12 | 0.538 | 0.538 | 0.538 | 0.538 | 0.538 |
| | | C3 | S2 | 12, 18 | 0.053 | 0.053 | 0.052 | 0.052 | 0.052 |
| | | | | 15, 15 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | | 18, 12 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | | | S5 | 12, 18 | 0.167 | 0.161 | 0.160 | 0.160 | 0.161 |
| | | | | 15, 15 | 0.226 | 0.221 | 0.220 | 0.220 | 0.219 |
| | | | | 18, 12 | 0.258 | 0.258 | 0.255 | 0.257 | 0.257 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Table 9. Type1 error of the studentized permutation method with Clayton copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S2 | 120, 180 | **0.955** | 0.955 | 0.955 | 0.955 | 0.955 | 0.955 |
| | | | | 150, 150 | **0.964** | 0.965 | 0.965 | 0.965 | 0.965 | 0.965 |
| | | | | 180, 120 | **0.973** | 0.952 | 0.952 | 0.952 | 0.952 | 0.952 |
| | | | S5 | 120, 180 | **0.951** | 0.961 | 0.961 | 0.961 | 0.961 | 0.961 |
| | | | | 150, 150 | **0.960** | 0.960 | 0.960 | 0.960 | 0.960 | 0.960 |
| | | | | 180, 120 | **0.921** | 0.954 | 0.954 | 0.954 | 0.954 | 0.954 |
| | | C3 | S2 | 120, 180 | **0.059** | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | | | | 150, 150 | **0.065** | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | | 180, 120 | **0.050** | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | S5 | 120, 180 | **0.043** | 0.032 | 0.032 | 0.032 | 0.032 | 0.032 |
| | | | | 150, 150 | **0.055** | 0.061 | 0.061 | 0.061 | 0.061 | 0.061 |
| | | | | 180, 120 | **0.058** | 0.068 | 0.068 | 0.068 | 0.068 | 0.068 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Table 10. Type1 error of the studentized permutation method with Gumbel copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S2 | 120, 180 | **0.727** | 0.712 | 0.712 | 0.712 | 0.712 | 0.712 |
| | | | | 150, 150 | **0.745** | 0.737 | 0.737 | 0.737 | 0.737 | 0.737 |
| | | | | 180, 120 | **0.729** | 0.731 | 0.731 | 0.731 | 0.731 | 0.731 |
| | | | S5 | 120, 180 | **0.594** | 0.546 | 0.546 | 0.546 | 0.546 | 0.546 |
| | | | | 150, 150 | **0.589** | 0.591 | 0.591 | 0.591 | 0.591 | 0.591 |
| | | | | 180, 120 | **0.541** | 0.594 | 0.594 | 0.594 | 0.594 | 0.594 |
| | | C3 | S2 | 120, 180 | **0.043** | 0.056 | 0.056 | 0.056 | 0.056 | 0.056 |
| | | | | 150, 150 | **0.051** | 0.058 | 0.058 | 0.058 | 0.058 | 0.058 |
| | | | | 180, 120 | **0.040** | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | S5 | 120, 180 | **0.064** | 0.035 | 0.035 | 0.035 | 0.035 | 0.035 |
| | | | | 150, 150 | **0.052** | 0.042 | 0.042 | 0.042 | 0.042 | 0.042 |
| | | | | 180, 120 | **0.049** | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |

Abbreviations: S2, Survival distribution in both groups follow Weibull(3, 8); S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

# 4. Application

In this section, we apply the previously introduced method to real data from a study on head and neck cancer. The data come from a randomized clinical trial conducted by the Northern California Oncology Group (NCOG). The aim of the study was to investigate the combined effects of radiation therapy and chemotherapy on stage III or IV inoperative head and neck cancer. A total of 104 patients were randomly assigned, with 51 receiving only radiation therapy and 45 receiving a combination of radiation therapy and chemotherapy.

We aim to compare the restricted mean survival time (RMST) between the two groups using both studentized and unstudentized permutation methods. Figure 1 shows the Kaplan-Meier curves for each group, with a maximum observation time of 47 months for group 0 (only radiation therapy) and 77 months for group 1 (a combination of radiation and chemotherapy). The crossing of the two survival curves indicates a departure from the proportional hazards assumption. Therefore, comparing the survival functions of the two groups using RMST becomes meaningful.

Table 11 presents the results of RMST for the reconstructed data at $\tau = 25, 30, 35, 40, 46, 47$, utilizing five methods including the asymptotic test with Nelson-Aalen estimator and studentized and unstudentized permutations. In cases where τ closely resembles the last observed time point ($\tau = 46, 47$), a problem arises where it is not possible to calculate RMST. This situation occurred in approximately 0.15% to 0.35% of the 2000 repetitions, requiring the application of the permutation method. Additionally, during these instances, Method 1 consistently yields the smallest p-value, while Methods 2-5 provide identical p-values for each permutation (range: 0.045-0.051). Although the difference between studentized and unstudentized methods is not substantial, the studentized method tends to produce slightly smaller p-values. For smaller values of τ ($\tau = 25, 30, 35, 40$), there is no discernible difference in p-values between methods, and overall, the p-values from the asymptotic test are smaller.

The permutation method introduced earlier appears to be more advantageous in cases of small sample sizes. However, with a total of 104 participants in this dataset, relying on the results of the permutation method over asymptotic methods may pose challenges. Moreover, if the sample sizes of the two groups differ, the studentized method seems less influenced by the difference in sample sizes. Nevertheless, in this case, even though the sample sizes of the two groups are not equal, the ratio between them does not differ significantly, resulting in relatively similar outcomes between the studentized and unstudentized methods.

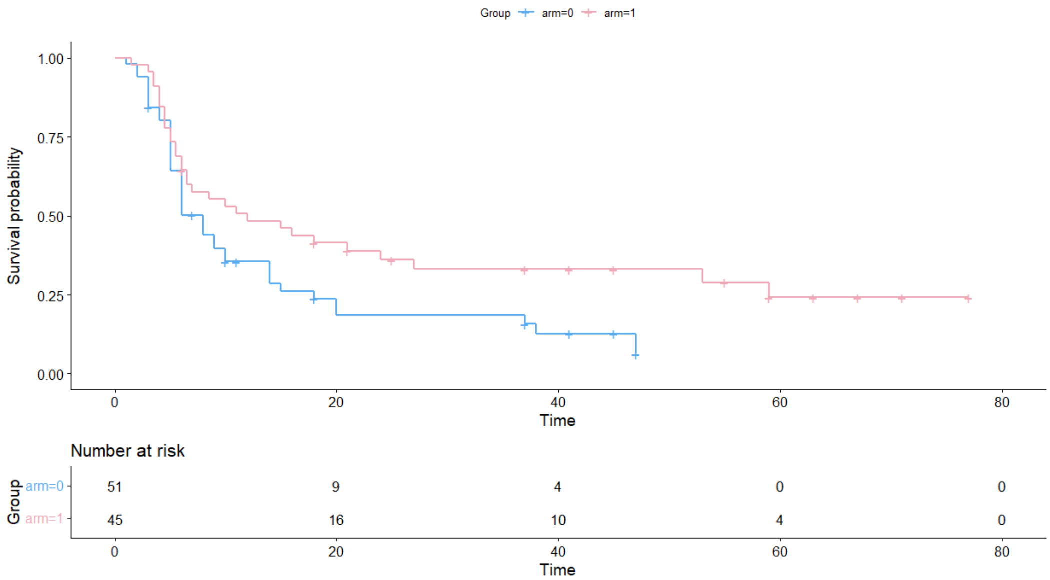


**Figure 1. Kaplan-Meier curves for the radiotherapy alone (Group, arm=0) and a combination of radiotherapy and chemotherapy (Group, arm=1) in head and neck cancer study**

**Table 11. P-values based on the studentized and unstudentized permutation method for the radiotherapy alone (Group, arm=0) and a combination of radiotherapy and chemotherapy (Group, arm=1) in head and neck cancer study**

| sample size | τ | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| 51, 45 | 25 | **0.050** | 0.062 | 0.052 | 0.062 | 0.052 | 0.062 | 0.052 | 0.062 | 0.052 | 0.062 | 0.052 |
| | 30 | **0.047** | 0.056 | 0.055 | 0.056 | 0.055 | 0.056 | 0.055 | 0.056 | 0.055 | 0.056 | 0.055 |
| | 35 | **0.050** | 0.061 | 0.060 | 0.061 | 0.060 | 0.061 | 0.060 | 0.061 | 0.060 | 0.061 | 0.060 |
| | 40 | **0.045** | 0.058 | 0.054 | 0.058 | 0.054 | 0.058 | 0.054 | 0.058 | 0.054 | 0.058 | 0.054 |
| | 46 | **0.036** | 0.044 | 0.049 | 0.045 | 0.050 | 0.045 | 0.050 | 0.045 | 0.050 | 0.045 | 0.050 |
| | 47 | **0.035** | 0.044 | 0.050 | 0.046 | 0.051 | 0.046 | 0.051 | 0.046 | 0.051 | 0.046 | 0.051 |

Abbreviations: sample size, (Group, arm=0) = 51, (Group, arm=1) = 45; Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

# 5. Conclusion

In this paper, we introduced the application of permutation methods to address issues that may arise due to small sample sizes when using restricted mean survival time (RMST) for comparing survival functions between groups. The approach by Horiguchi and Uno (2020) employs permutation methods to calculate RMST and make comparisons, specifically addressing issues that arise when the pre-specified time point $\tau$ is larger than the maximum observed time. The method proposed by Ditzhaus et al. (2021) recognizes that in real survival data, the assumption of identical distributions between groups, a common consideration in conventional permutation methods, may not hold true. To accommodate potential differences in the distributions between groups, they suggest a studentized permutation method. It's important to note that the study assumes independence between all survival and censoring distributions. To evaluate the performance of both methods under the assumption of dependence between distributions and as the sample size increased, simulations were conducted.

In the simulation, scenarios were set up with both equal and unequal survival distributions between groups, considering cases where censoring distributions were either equal or unequal. The simulations were performed by incorporating the dependence between the two distributions using copula functions. For cases with unequal and small sample sizes in each group, there was a tendency for type 1 error to increase in the asymptotic test, and the studentized method was interpreted as more advantageous than unstudentized method. Among the five methods, Method 2 (Extending the survival curves to τ) tended to overestimate, while Method 3 (Switching the last censored observation to the event observation) tended to underestimate. When the sample size was increased by a factor 10 and the same simulation process was conducted, there was minimal difference between studentized and unstudentized methods, and no significant differences were observed among the five methods. In this case, the asymptotic test was considered more suitable.

In utilizing the copula and employing the studentized method, it is observed that the type 1 error increases regardless of the difference in survival distributions for each group when the characteristics of censoring distributions differ. The asymptotic test, considered advantageous when increasing the sample size, also exhibits an increase in type 1 error when the censoring distributions differ. Furthermore, there is no significant difference among the five methods. This can be interpreted as an effect influenced by the τ value, and when the initially determined τ was increased to 15 for simulation, it showed a similar trend to the characteristics observed when survival and censoring distributions are independent.

In reviewing the simulation results and the application to real data, it is challenging to determine which method is more suitable. Due to its sensitivity to sample size, this method may be suitable for application in small clinical trials. However, determining its superiority over the asymptotic test becomes challenging as the sample size increases. Additionally, attention should be given not only to the characteristics of survival distributions between the two groups but also to differences in censoring distribution. Particularly when modeling dependence using copula functions, it is crucial to consider variations in censoring distribution. Further research is needed to compare RMST in situations characterized by these conditions.

# Appendix

**Appendix Table 1. Type1 error of the permutation method and asymptotic test for equal censoring distribution in small sample size**

| Survival | Censoring | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| S1 | C2 | 12, 18 | 0.101 | 0.043 | 0.041 | 0.043 | 0.042 | 0.041 | 0.041 | 0.042 | 0.042 | 0.042 | 0.042 |
| | | 15, 15 | 0.096 | 0.048 | 0.055 | 0.049 | 0.052 | 0.048 | 0.050 | 0.048 | 0.052 | 0.048 | 0.052 |
| | | 18, 12 | 0.117 | 0.053 | 0.070 | 0.053 | 0.068 | 0.050 | 0.067 | 0.052 | 0.068 | 0.052 | 0.068 |
| | C3 | 12, 18 | 0.093 | 0.048 | 0.051 | 0.049 | 0.048 | 0.047 | 0.048 | 0.049 | 0.048 | 0.049 | 0.048 |
| | | 15, 15 | 0.085 | 0.046 | 0.045 | 0.047 | 0.046 | 0.047 | 0.044 | 0.047 | 0.045 | 0.047 | 0.046 |
| | | 18, 12 | 0.096 | 0.038 | 0.052 | 0.039 | 0.054 | 0.038 | 0.052 | 0.039 | 0.052 | 0.039 | 0.054 |
| S2 | C2 | 12, 18 | 0.098 | 0.032 | 0.051 | 0.031 | 0.052 | 0.031 | 0.050 | 0.031 | 0.050 | 0.031 | 0.050 |
| | | 15, 15 | 0.092 | 0.060 | 0.057 | 0.059 | 0.058 | 0.058 | 0.056 | 0.058 | 0.058 | 0.059 | 0.056 |
| | | 18, 12 | 0.103 | 0.048 | 0.054 | 0.044 | 0.056 | 0.042 | 0.055 | 0.044 | 0.056 | 0.044 | 0.056 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 12, 18 | 0.081 | 0.054 | 0.039 | 0.054 | 0.039 | 0.053 | 0.038 | 0.053 | 0.038 | 0.053 | 0.038 |
| | C3 | 15, 15 | 0.088 | 0.047 | 0.062 | 0.046 | 0.059 | 0.046 | 0.058 | 0.046 | 0.058 | 0.046 | 0.058 |
| | | 18, 12 | 0.087 | 0.056 | 0.040 | 0.056 | 0.041 | 0.054 | 0.041 | 0.055 | 0.041 | 0.056 | 0.041 |
| | | 12, 18 | 0.112 | 0.045 | 0.055 | 0.047 | 0.056 | 0.045 | 0.056 | 0.046 | 0.056 | 0.047 | 0.056 |
| | C2 | 15, 15 | 0.105 | 0.061 | 0.058 | 0.061 | 0.059 | 0.061 | 0.058 | 0.061 | 0.059 | 0.061 | 0.058 |
| | | 18, 12 | 0.085 | 0.048 | 0.045 | 0.048 | 0.045 | 0.046 | 0.044 | 0.048 | 0.045 | 0.046 | 0.044 |
| S3 | | 12, 18 | 0.084 | 0.058 | 0.043 | 0.058 | 0.044 | 0.058 | 0.044 | 0.058 | 0.044 | 0.057 | 0.044 |
| | C3 | 15, 15 | 0.094 | 0.048 | 0.055 | 0.050 | 0.054 | 0.050 | 0.053 | 0.050 | 0.053 | 0.050 | 0.053 |
| | | 18, 12 | 0.094 | 0.040 | 0.051 | 0.042 | 0.051 | 0.042 | 0.051 | 0.042 | 0.051 | 0.042 | 0.051 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C2, Censoring distribution in both groups follow Uniform(0, 25); C3, Censoring distribution in both groups follow Weibull(3, 15); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Appendix Table 2. Type1 error of the permutation method and asymptotic test for unequal survival distribution in small sample size**

| Survival | Censoring | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| S5 | C1 | 12, 18 | 0.093 | 0.034 | 0.037 | 0.033 | 0.037 | 0.033 | 0.037 | 0.033 | 0.037 | 0.033 | 0.037 |
| | | 15, 15 | 0.097 | 0.052 | 0.071 | 0.052 | 0.071 | 0.052 | 0.071 | 0.052 | 0.071 | 0.052 | 0.071 |
| | | 18, 12 | 0.087 | 0.099 | 0.075 | 0.098 | 0.076 | 0.098 | 0.075 | 0.098 | 0.076 | 0.098 | 0.075 |
| | C2 | 12, 18 | 0.092 | 0.034 | 0.030 | 0.034 | 0.030 | 0.034 | 0.030 | 0.034 | 0.030 | 0.035 | 0.030 |
| | | 15, 15 | 0.091 | 0.046 | 0.050 | 0.045 | 0.050 | 0.045 | 0.050 | 0.045 | 0.050 | 0.045 | 0.049 |
| | | 18, 12 | 0.092 | 0.048 | 0.066 | 0.046 | 0.064 | 0.046 | 0.062 | 0.046 | 0.062 | 0.047 | 0.062 |
| | C3 | 12, 18 | 0.074 | 0.036 | 0.031 | 0.036 | 0.031 | 0.036 | 0.031 | 0.036 | 0.031 | 0.036 | 0.031 |
| | | 15, 15 | 0.084 | 0.054 | 0.055 | 0.054 | 0.055 | 0.054 | 0.055 | 0.054 | 0.055 | 0.053 | 0.055 |
| | | 18, 12 | 0.107 | 0.077 | 0.088 | 0.075 | 0.087 | 0.074 | 0.087 | 0.075 | 0.087 | 0.074 | 0.087 |
| S6 | C1 | 12, 18 | 0.090 | 0.037 | 0.040 | 0.036 | 0.039 | 0.036 | 0.039 | 0.036 | 0.039 | 0.037 | 0.039 |
| | | 15, 15 | 0.112 | 0.056 | 0.083 | 0.056 | 0.082 | 0.056 | 0.082 | 0.056 | 0.082 | 0.056 | 0.082 |
| | | 18, 12 | 0.126 | 0.095 | 0.098 | 0.094 | 0.096 | 0.092 | 0.095 | 0.093 | 0.096 | 0.094 | 0.096 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 12, 18 | 0.090 | 0.030 | 0.035 | 0.031 | 0.035 | 0.030 | 0.034 | 0.031 | 0.035 | 0.031 | 0.034 |
| C2 | 15, 15 | 0.100 | 0.039 | 0.049 | 0.039 | 0.047 | 0.038 | 0.046 | 0.039 | 0.046 | 0.039 | 0.045 |
| | 18, 12 | 0.103 | 0.061 | 0.069 | 0.061 | 0.070 | 0.059 | 0.067 | 0.060 | 0.070 | 0.060 | 0.069 |
| | 12, 18 | 0.085 | 0.053 | 0.043 | 0.052 | 0.044 | 0.052 | 0.044 | 0.052 | 0.044 | 0.051 | 0.044 |
| C3 | 15, 15 | 0.088 | 0.050 | 0.054 | 0.049 | 0.053 | 0.049 | 0.053 | 0.049 | 0.053 | 0.049 | 0.053 |
| | 18, 12 | 0.082 | 0.071 | 0.061 | 0.069 | 0.061 | 0.068 | 0.061 | 0.068 | 0.061 | 0.069 | 0.061 |

Abbreviations: S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C2, Censoring distribution in both groups follow Uniform(0, 25); C3, Censoring distribution in both groups follow Weibull(3, 15); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Appendix Table 3. Type1 error of the permutation method and asymptotic test for equal censoring distribution**

| Survival | Censoring | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| S1 | C2 | 120, 180 | 0.061 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 |
| | | 150, 150 | 0.055 | 0.041 | 0.049 | 0.041 | 0.049 | 0.041 | 0.049 | 0.041 | 0.049 | 0.041 | 0.049 |
| | | 180, 120 | 0.051 | 0.071 | 0.048 | 0.071 | 0.048 | 0.071 | 0.048 | 0.071 | 0.048 | 0.071 | 0.048 |
| | C3 | 120, 180 | 0.041 | 0.047 | 0.039 | 0.047 | 0.039 | 0.047 | 0.039 | 0.047 | 0.039 | 0.047 | 0.039 |
| | | 150, 150 | 0.052 | 0.040 | 0.049 | 0.040 | 0.049 | 0.040 | 0.049 | 0.040 | 0.049 | 0.040 | 0.049 |
| | | 180, 120 | 0.047 | 0.048 | 0.043 | 0.048 | 0.043 | 0.048 | 0.043 | 0.048 | 0.043 | 0.048 | 0.043 |
| S2 | C2 | 120, 180 | 0.054 | 0.047 | 0.052 | 0.047 | 0.052 | 0.047 | 0.052 | 0.047 | 0.052 | 0.047 | 0.052 |
| | | 150, 150 | 0.053 | 0.065 | 0.051 | 0.065 | 0.051 | 0.065 | 0.051 | 0.065 | 0.051 | 0.065 | 0.051 |
| | | 180, 120 | 0.046 | 0.044 | 0.040 | 0.044 | 0.040 | 0.044 | 0.040 | 0.044 | 0.040 | 0.044 | 0.040 |
| | C3 | 120, 180 | 0.057 | 0.066 | 0.053 | 0.066 | 0.053 | 0.066 | 0.053 | 0.066 | 0.053 | 0.066 | 0.053 |
| | | 150, 150 | 0.051 | 0.047 | 0.049 | 0.047 | 0.049 | 0.047 | 0.049 | 0.047 | 0.049 | 0.047 | 0.049 |
| | | 180, 120 | 0.043 | 0.046 | 0.041 | 0.046 | 0.041 | 0.046 | 0.041 | 0.046 | 0.041 | 0.046 | 0.041 |
| S3 | C2 | 120, 180 | 0.035 | 0.051 | 0.032 | 0.051 | 0.032 | 0.051 | 0.032 | 0.051 | 0.032 | 0.051 | 0.032 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 150, 150 | 0.053 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 |
| | 180, 120 | 0.055 | 0.060 | 0.054 | 0.060 | 0.054 | 0.060 | 0.054 | 0.060 | 0.054 | 0.060 | 0.054 |
| | 120, 180 | 0.051 | 0.044 | 0.047 | 0.044 | 0.047 | 0.044 | 0.047 | 0.044 | 0.047 | 0.044 | 0.047 |
| C3 | 150, 150 | 0.045 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 |
| | 180, 120 | 0.062 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 | 0.052 | 0.059 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); C2, Censoring distribution in both groups follow Uniform(0, 25); C3, Censoring distribution in both groups follow Weibull(3, 15); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Appendix Table 4. Type1 error of the permutation method and asymptotic test for unequal survival distribution**

| Survival | Censoring | sample size | Asymp | Method 1 | | Method 2 | | Method 3 | | Method 4 | | Method 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Nelson-Aalen | Stud | Un | Stud | Un | Stud | Un | Stud | Un | Stud | Un |
| S4 | C1 | 120, 180 | 0.058 | 0.056 | 0.048 | 0.056 | 0.048 | 0.056 | 0.048 | 0.056 | 0.048 | 0.056 | 0.048 |
| | | 150, 150 | 0.043 | 0.054 | 0.047 | 0.054 | 0.047 | 0.054 | 0.047 | 0.054 | 0.047 | 0.054 | 0.047 |
| | | 180, 120 | 0.065 | 0.075 | 0.082 | 0.075 | 0.082 | 0.075 | 0.082 | 0.075 | 0.082 | 0.075 | 0.082 |
| | C2 | 120, 180 | 0.060 | 0.037 | 0.043 | 0.037 | 0.043 | 0.037 | 0.043 | 0.037 | 0.043 | 0.037 | 0.043 |
| | | 150, 150 | 0.068 | 0.051 | 0.064 | 0.051 | 0.064 | 0.051 | 0.064 | 0.051 | 0.064 | 0.051 | 0.064 |
| | | 180, 120 | 0.060 | 0.058 | 0.067 | 0.058 | 0.067 | 0.058 | 0.067 | 0.058 | 0.067 | 0.058 | 0.067 |
| | C3 | 120, 180 | 0.060 | 0.036 | 0.045 | 0.036 | 0.045 | 0.036 | 0.045 | 0.036 | 0.045 | 0.036 | 0.045 |
| | | 150, 150 | 0.063 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 | 0.049 | 0.062 |
| | | 180, 120 | 0.053 | 0.061 | 0.058 | 0.061 | 0.058 | 0.061 | 0.058 | 0.061 | 0.058 | 0.061 | 0.058 |
| S5 | C1 | 120, 180 | 0.045 | 0.027 | 0.033 | 0.027 | 0.033 | 0.027 | 0.033 | 0.027 | 0.033 | 0.027 | 0.033 |
| | | 150, 150 | 0.066 | 0.055 | 0.074 | 0.055 | 0.074 | 0.055 | 0.074 | 0.055 | 0.074 | 0.055 | 0.740 |
| | | 180, 120 | 0.070 | 0.095 | 0.108 | 0.095 | 0.108 | 0.095 | 0.108 | 0.095 | 0.108 | 0.095 | 0.108 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 120, 180 | 0.056 | 0.042 | 0.033 | 0.042 | 0.033 | 0.042 | 0.033 | 0.042 | 0.033 | 0.042 | 0.033 |
| | C2 | 150, 150 | 0.059 | 0.052 | 0.050 | 0.052 | 0.050 | 0.052 | 0.050 | 0.052 | 0.050 | 0.052 | 0.050 |
| | | 180, 120 | 0.067 | 0.063 | 0.086 | 0.063 | 0.086 | 0.063 | 0.086 | 0.063 | 0.086 | 0.063 | 0.086 |
| | | 120, 180 | 0.052 | 0.025 | 0.032 | 0.025 | 0.032 | 0.025 | 0.032 | 0.025 | 0.032 | 0.025 | 0.032 |
| | C3 | 150, 150 | 0.064 | 0.048 | 0.060 | 0.048 | 0.060 | 0.048 | 0.060 | 0.048 | 0.060 | 0.048 | 0.060 |
| | | 180, 120 | 0.061 | 0.065 | 0.083 | 0.065 | 0.083 | 0.065 | 0.083 | 0.065 | 0.083 | 0.065 | 0.083 |
| | | 120, 180 | 0.053 | 0.051 | 0.040 | 0.051 | 0.040 | 0.051 | 0.040 | 0.051 | 0.040 | 0.051 | 0.040 |
| | C1 | 150, 150 | 0.042 | 0.061 | 0.052 | 0.061 | 0.052 | 0.061 | 0.052 | 0.061 | 0.052 | 0.061 | 0.052 |
| | | 180, 120 | 0.051 | 0.092 | 0.084 | 0.092 | 0.084 | 0.092 | 0.084 | 0.092 | 0.084 | 0.092 | 0.084 |
| | | 120, 180 | 0.055 | 0.038 | 0.039 | 0.038 | 0.039 | 0.038 | 0.039 | 0.038 | 0.039 | 0.038 | 0.039 |
| S6 | C2 | 150, 150 | 0.056 | 0.055 | 0.052 | 0.055 | 0.052 | 0.055 | 0.052 | 0.055 | 0.052 | 0.055 | 0.052 |
| | | 180, 120 | 0.045 | 0.060 | 0.053 | 0.060 | 0.053 | 0.060 | 0.053 | 0.060 | 0.053 | 0.060 | 0.053 |
| | | 120, 180 | 0.061 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 | 0.044 | 0.041 |
| | C3 | 150, 150 | 0.060 | 0.058 | 0.057 | 0.058 | 0.057 | 0.058 | 0.057 | 0.058 | 0.057 | 0.058 | 0.057 |
| | | 180, 120 | 0.048 | 0.067 | 0.055 | 0.067 | 0.055 | 0.067 | 0.055 | 0.067 | 0.055 | 0.067 | 0.055 |

Abbreviations: S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); C2, Censoring distribution in both groups follow Uniform(0, 25); C3, Censoring distribution in both groups follow Weibull(3, 15); Asymp, asymptotic test; Stud, studentized permutation method; Un, unstudentized permutation method

**Appendix Table 5-a. Type1 error of the studentized permutation method with Clayton copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S1 | 12, 18 | 0.067 | 0.067 | 0.067 | 0.067 | 0.067 |
| | | | | 15, 15 | 0.073 | 0.072 | 0.072 | 0.072 | 0.072 |
| | | | | 18, 12 | 0.071 | 0.072 | 0.072 | 0.072 | 0.072 |
| | | | S3 | 12, 18 | 0.161 | 0.161 | 0.161 | 0.161 | 0.161 |
| | | | | 15, 15 | 0.186 | 0.186 | 0.186 | 0.186 | 0.186 |
| | | | | 18, 12 | 0.166 | 0.166 | 0.166 | 0.166 | 0.166 |
| | | | S4 | 12, 18 | 0.060 | 0.060 | 0.059 | 0.060 | 0.060 |
| | | | | 15, 15 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 |
| | | | | 18, 12 | 0.064 | 0.064 | 0.063 | 0.064 | 0.064 |
| | | | S6 | 12, 18 | 0.228 | 0.227 | 0.226 | 0.226 | 0.226 |
| | | | | 15, 15 | 0.267 | 0.266 | 0.266 | 0.266 | 0.266 |
| | | | | 18, 12 | 0.292 | 0.291 | 0.291 | 0.291 | 0.291 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 5-b. Type1 error of the studentized permutation method with Clayton copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C2 | S1 | 12, 18 | 0.061 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 15, 15 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 18, 12 | 0.041 | 0.040 | 0.040 | 0.040 | 0.040 |
| | | | S2 | 12, 18 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 15, 15 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 18, 12 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | S3 | 12, 18 | 0.040 | 0.040 | 0.040 | 0.040 | 0.040 |
| | | | | 15, 15 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 18, 12 | 0.039 | 0.038 | 0.038 | 0.038 | 0.038 |
| | | | S4 | 12, 18 | 0.052 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | | 15, 15 | 0.047 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 18, 12 | 0.056 | 0.056 | 0.056 | 0.056 | 0.056 |

| | | | | | | |
|---|---|---|---|---|---|---|
| S5 | 12, 18 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| | 15, 15 | 0.065 | 0.065 | 0.065 | 0.065 | 0.065 |
| | 18, 12 | 0.096 | 0.094 | 0.094 | 0.094 | 0.091 |
| S6 | 12, 18 | 0.050 | 0.049 | 0.048 | 0.048 | 0.048 |
| | 15, 15 | 0.046 | 0.046 | 0.045 | 0.046 | 0.045 |
| | 18, 12 | 0.071 | 0.071 | 0.070 | 0.071 | 0.071 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 5-c. Type1 error of the studentized permutation method with Clayton copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C3 | S1 | 12, 18 | 0.038 | 0.038 | 0.038 | 0.038 | 0.038 |
| | | | | 15, 15 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 18, 12 | 0.058 | 0.058 | 0.058 | 0.058 | 0.058 |
| | | | S3 | 12, 18 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 15, 15 | 0.047 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 18, 12 | 0.054 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | S4 | 12, 18 | 0.037 | 0.037 | 0.037 | 0.037 | 0.037 |
| | | | | 15, 15 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 18, 12 | 0.065 | 0.065 | 0.065 | 0.065 | 0.065 |
| | | | S6 | 12, 18 | 0.030 | 0.029 | 0.029 | 0.029 | 0.029 |
| | | | | 15, 15 | 0.057 | 0.057 | 0.056 | 0.056 | 0.056 |
| | | | | 18, 12 | 0.081 | 0.081 | 0.081 | 0.081 | 0.081 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Appendix Table 6-a. Type1 error of the studentized permutation method with Gumbel copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S1 | 12, 18 | 0.049 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 15, 15 | 0.068 | 0.068 | 0.068 | 0.068 | 0.068 |
| | | | | 18, 12 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | S3 | 12, 18 | 0.109 | 0.108 | 0.108 | 0.108 | 0.108 |
| | | | | 15, 15 | 0.114 | 0.114 | 0.114 | 0.114 | 0.114 |
| | | | | 18, 12 | 0.131 | 0.131 | 0.129 | 0.131 | 0.131 |
| | | | S4 | 12, 18 | 0.051 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 15, 15 | 0.066 | 0.066 | 0.066 | 0.066 | 0.066 |
| | | | | 18, 12 | 0.100 | 0.100 | 0.099 | 0.100 | 0.100 |
| | | | S6 | 12, 18 | 0.111 | 0.111 | 0.111 | 0.111 | 0.111 |
| | | | | 15, 15 | 0.155 | 0.155 | 0.155 | 0.155 | 0.155 |
| | | | | 18, 12 | 0.183 | 0.183 | 0.183 | 0.183 | 0.183 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 6-b. Type1 error of the studentized permutation method with Gumbel copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C2 | S1 | 12, 18 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 15, 15 | 0.051 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 18, 12 | 0.037 | 0.037 | 0.037 | 0.037 | 0.037 |
| | | | S2 | 12, 18 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| | | | | 15, 15 | 0.061 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 18, 12 | 0.039 | 0.039 | 0.039 | 0.039 | 0.039 |
| | | | S3 | 12, 18 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | | 15, 15 | 0.051 | 0.051 | 0.051 | 0.051 | 0.051 |
| | | | | 18, 12 | 0.051 | 0.051 | 0.051 | 0.051 | 0.051 |
| | | | S4 | 12, 18 | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 |
| | | | | 15, 15 | 0.048 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 18, 12 | 0.070 | 0.067 | 0.065 | 0.066 | 0.066 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 12, 18 | 0.041 | 0.041 | 0.041 | 0.041 | 0.041 |
| S5 | 15, 15 | 0.059 | 0.059 | 0.059 | 0.059 | 0.059 |
| | 18, 12 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | 12, 18 | 0.039 | 0.039 | 0.039 | 0.039 | 0.039 |
| S6 | 15, 15 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | 18, 12 | 0.069 | 0.069 | 0.069 | 0.069 | 0.068 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 6-c. Type1 error of the studentized permutation method with Gumbel copula in small sample size**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C3 | S1 | 12, 18 | 0.067 | 0.066 | 0.065 | 0.065 | 0.065 |
| | | | | 15, 15 | 0.049 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 18, 12 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 |
| | | | S3 | 12, 18 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | | | | 15, 15 | 0.039 | 0.038 | 0.038 | 0.038 | 0.038 |
| | | | | 18, 12 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | S4 | 12, 18 | 0.036 | 0.036 | 0.036 | 0.036 | 0.036 |
| | | | | 15, 15 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | | 18, 12 | 0.065 | 0.065 | 0.065 | 0.065 | 0.065 |
| | | | S6 | 12, 18 | 0.049 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 15, 15 | 0.058 | 0.058 | 0.058 | 0.058 | 0.058 |
| | | | | 18, 12 | 0.064 | 0.064 | 0.064 | 0.064 | 0.064 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Appendix Table 7-a. Type1 error of the studentized permutation method with Clayton copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S1 | 12, 18 | 0.072 | 0.073 | 0.072 | 0.072 | 0.072 |
| | | | | 15, 15 | 0.060 | 0.062 | 0.062 | 0.062 | 0.062 |
| | | | | 18, 12 | 0.075 | 0.076 | 0.076 | 0.076 | 0.076 |
| | | | S3 | 12, 18 | 0.158 | 0.158 | 0.157 | 0.158 | 0.157 |
| | | | | 15, 15 | 0.157 | 0.157 | 0.157 | 0.157 | 0.157 |
| | | | | 18, 12 | 0.186 | 0.187 | 0.185 | 0.186 | 0.185 |
| | | | S4 | 12, 18 | 0.082 | 0.080 | 0.079 | 0.079 | 0.081 |
| | | | | 15, 15 | 0.109 | 0.107 | 0.106 | 0.106 | 0.107 |
| | | | | 18, 12 | 0.129 | 0.127 | 0.127 | 0.127 | 0.127 |
| | | | S6 | 12, 18 | 0.474 | 0.476 | 0.471 | 0.475 | 0.473 |
| | | | | 15, 15 | 0.552 | 0.552 | 0.550 | 0.552 | 0.551 |
| | | | | 18, 12 | 0.608 | 0.612 | 0.611 | 0.611 | 0.611 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 7-b. Type1 error of the studentized permutation method with Clayton copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C2 | S1 | 12, 18 | 0.050 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | | 15, 15 | 0.040 | 0.044 | 0.043 | 0.044 | 0.045 |
| | | | | 18, 12 | 0.049 | 0.054 | 0.051 | 0.053 | 0.051 |
| | | | S2 | 12, 18 | 0.057 | 0.058 | 0.058 | 0.058 | 0.058 |
| | | | | 15, 15 | 0.049 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | | 18, 12 | 0.049 | 0.054 | 0.051 | 0.053 | 0.051 |
| | | | S3 | 12, 18 | 0.048 | 0.050 | 0.049 | 0.049 | 0.049 |
| | | | | 15, 15 | 0.053 | 0.056 | 0.056 | 0.056 | 0.056 |
| | | | | 18, 12 | 0.056 | 0.056 | 0.055 | 0.056 | 0.055 |
| | | | S4 | 12, 18 | 0.048 | 0.051 | 0.047 | 0.049 | 0.049 |
| | | | | 15, 15 | 0.066 | 0.065 | 0.062 | 0.064 | 0.064 |
| | | | | 18, 12 | 0.102 | 0.096 | 0.093 | 0.093 | 0.095 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 12, 18 | 0.096 | 0.095 | 0.094 | 0.094 | 0.094 |
| S5 | 15, 15 | 0.144 | 0.136 | 0.135 | 0.136 | 0.136 |
| | 18, 12 | 0.209 | 0.211 | 0.207 | 0.209 | 0.208 |
| | 12, 18 | 0.080 | 0.081 | 0.078 | 0.080 | 0.079 |
| S6 | 15, 15 | 0.106 | 0.111 | 0.110 | 0.111 | 0.111 |
| | 18, 12 | 0.148 | 0.159 | 0.156 | 0.159 | 0.159 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 7-c. Type1 error of the studentized permutation method with Clayton copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C3 | S1 | 12, 18 | 0.043 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | | 15, 15 | 0.049 | 0.056 | 0.054 | 0.056 | 0.056 |
| | | | | 18, 12 | 0.044 | 0.052 | 0.050 | 0.050 | 0.052 |
| | | | S3 | 12, 18 | 0.059 | 0.061 | 0.059 | 0.061 | 0.059 |
| | | | | 15, 15 | 0.054 | 0.057 | 0.057 | 0.057 | 0.057 |
| | | | | 18, 12 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | S4 | 12, 18 | 0.056 | 0.053 | 0.052 | 0.052 | 0.053 |
| | | | | 15, 15 | 0.073 | 0.068 | 0.067 | 0.068 | 0.068 |
| | | | | 18, 12 | 0.097 | 0.101 | 0.095 | 0.097 | 0.099 |
| | | | S6 | 12, 18 | 0.091 | 0.091 | 0.089 | 0.090 | 0.091 |
| | | | | 15, 15 | 0.132 | 0.129 | 0.127 | 0.128 | 0.128 |
| | | | | 18, 12 | 0.182 | 0.175 | 0.173 | 0.173 | 0.173 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Appendix Table 8-a. Type1 error of the studentized permutation method with Gumbel copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S1 | 12, 18 | 0.077 | 0.077 | 0.077 | 0.077 | 0.077 |
| | | | | 15, 15 | 0.072 | 0.072 | 0.072 | 0.072 | 0.072 |
| | | | | 18, 12 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | S3 | 12, 18 | 0.094 | 0.095 | 0.095 | 0.095 | 0.095 |
| | | | | 15, 15 | 0.124 | 0.124 | 0.124 | 0.124 | 0.124 |
| | | | | 18, 12 | 0.132 | 0.132 | 0.132 | 0.132 | 0.132 |
| | | | S4 | 12, 18 | 0.066 | 0.066 | 0.065 | 0.066 | 0.066 |
| | | | | 15, 15 | 0.127 | 0.127 | 0.127 | 0.127 | 0.127 |
| | | | | 18, 12 | 0.156 | 0.156 | 0.154 | 0.155 | 0.155 |
| | | | S6 | 12, 18 | 0.319 | 0.319 | 0.318 | 0.318 | 0.318 |
| | | | | 15, 15 | 0.406 | 0.407 | 0.407 | 0.407 | 0.406 |
| | | | | 18, 12 | 0.465 | 0.467 | 0.466 | 0.466 | 0.466 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 8-b. Type1 error of the studentized permutation method with Gumbel copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C2 | S1 | 12, 18 | 0.049 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | | 15, 15 | 0.038 | 0.038 | 0.038 | 0.038 | 0.038 |
| | | | | 18, 12 | 0.048 | 0.048 | 0.047 | 0.048 | 0.047 |
| | | | S2 | 12, 18 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | | 15, 15 | 0.051 | 0.052 | 0.051 | 0.051 | 0.051 |
| | | | | 18, 12 | 0.048 | 0.048 | 0.047 | 0.048 | 0.047 |
| | | | S3 | 12, 18 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 15, 15 | 0.044 | 0.043 | 0.042 | 0.043 | 0.042 |
| | | | | 18, 12 | 0.040 | 0.040 | 0.040 | 0.040 | 0.040 |
| | | | S4 | 12, 18 | 0.048 | 0.047 | 0.046 | 0.047 | 0.046 |
| | | | | 15, 15 | 0.061 | 0.059 | 0.056 | 0.058 | 0.058 |
| | | | | 18, 12 | 0.087 | 0.086 | 0.086 | 0.086 | 0.086 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 12, 18 | 0.151 | 0.150 | 0.148 | 0.149 | 0.149 |
| S5 | 15, 15 | 0.193 | 0.188 | 0.179 | 0.184 | 0.183 |
| | 18, 12 | 0.225 | 0.226 | 0.217 | 0.222 | 0.223 |
| | 12, 18 | 0.084 | 0.082 | 0.080 | 0.081 | 0.081 |
| S6 | 15, 15 | 0.119 | 0.120 | 0.120 | 0.120 | 0.120 |
| | 18, 12 | 0.167 | 0.168 | 0.164 | 0.167 | 0.166 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 8-c. Type1 error of the studentized permutation method with Gumbel copula on $\tau = 15$**

| Copula | Kendall's tau | Censoring | Survival | sample size | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C3 | S1 | 12, 18 | 0.046 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 15, 15 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 18, 12 | 0.051 | 0.051 | 0.050 | 0.051 | 0.050 |
| | | | S3 | 12, 18 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | | | | 15, 15 | 0.041 | 0.042 | 0.041 | 0.041 | 0.041 |
| | | | | 18, 12 | 0.049 | 0.050 | 0.048 | 0.048 | 0.048 |
| | | | S4 | 12, 18 | 0.045 | 0.044 | 0.044 | 0.044 | 0.045 |
| | | | | 15, 15 | 0.068 | 0.065 | 0.065 | 0.065 | 0.065 |
| | | | | 18, 12 | 0.081 | 0.083 | 0.081 | 0.083 | 0.083 |
| | | | S6 | 12, 18 | 0.085 | 0.080 | 0.079 | 0.079 | 0.079 |
| | | | | 15, 15 | 0.138 | 0.139 | 0.136 | 0.137 | 0.136 |
| | | | | 18, 12 | 0.160 | 0.162 | 0.160 | 0.162 | 0.161 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Appendix Table 9-a. Type1 error of the studentized permutation method with Clayton copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C1 | S1 | 120, 180 | 0.340 | 0.303 | 0.303 | 0.303 | 0.303 | 0.303 |
| | | | | 150, 150 | 0.309 | 0.306 | 0.306 | 0.306 | 0.306 | 0.306 |
| | | | | 180, 120 | 0.302 | 0.331 | 0.331 | 0.331 | 0.331 | 0.331 |
| | | | S3 | 120, 180 | 0.929 | 0.930 | 0.930 | 0.930 | 0.930 | 0.930 |
| | | | | 150, 150 | 0.909 | 0.944 | 0.944 | 0.944 | 0.944 | 0.944 |
| | | | | 180, 120 | 0.920 | 0.901 | 0.901 | 0.901 | 0.901 | 0.901 |
| | | | S4 | 120, 180 | 0.128 | 0.093 | 0.093 | 0.093 | 0.093 | 0.093 |
| | | | | 150, 150 | 0.126 | 0.099 | 0.099 | 0.099 | 0.099 | 0.099 |
| | | | | 180, 120 | 0.119 | 0.137 | 0.137 | 0.137 | 0.137 | 0.137 |
| | | | S6 | 120, 180 | 0.987 | 0.985 | 0.985 | 0.985 | 0.985 | 0.985 |
| | | | | 150, 150 | 0.983 | 0.980 | 0.980 | 0.980 | 0.980 | 0.980 |
| | | | | 180, 120 | 0.977 | 0.983 | 0.983 | 0.983 | 0.983 | 0.983 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 9-b. Type1 error of the studentized permutation method with Clayton copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C2 | S1 | 120, 180 | 0.046 | 0.061 | 0.061 | 0.061 | 0.061 | 0.061 |
| | | | | 150, 150 | 0.047 | 0.059 | 0.059 | 0.059 | 0.059 | 0.059 |
| | | | | 180, 120 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | S2 | 120, 180 | 0.048 | 0.044 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 150, 150 | 0.052 | 0.044 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 180, 120 | 0.050 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | S3 | 120, 180 | 0.052 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| | | | | 150, 150 | 0.053 | 0.037 | 0.037 | 0.037 | 0.037 | 0.037 |
| | | | | 180, 120 | 0.061 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | S4 | 120, 180 | 0.050 | 0.044 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 150, 150 | 0.050 | 0.057 | 0.057 | 0.057 | 0.057 | 0.057 |
| | | | | 180, 120 | 0.056 | 0.069 | 0.069 | 0.069 | 0.069 | 0.069 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 120, 180 | 0.291 | 0.181 | 0.181 | 0.181 | 0.181 | 0.181 |
| S5 | 150, 150 | 0.264 | 0.228 | 0.228 | 0.228 | 0.228 | 0.228 |
| | 180, 120 | 0.252 | 0.275 | 0.275 | 0.275 | 0.275 | 0.275 |
| | 120, 180 | 0.063 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| S6 | 150, 150 | 0.057 | 0.066 | 0.066 | 0.066 | 0.066 | 0.066 |
| | 180, 120 | 0.068 | 0.085 | 0.085 | 0.085 | 0.085 | 0.085 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 9-c. Type1 error of the studentized permutation method with Clayton copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Clayton | 0.5 | C3 | S1 | 120, 180 | 0.056 | 0.049 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | | 150, 150 | 0.035 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | | 180, 120 | 0.061 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| | | | S3 | 120, 180 | 0.061 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |
| | | | | 150, 150 | 0.039 | 0.052 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | | 180, 120 | 0.053 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | S4 | 120, 180 | 0.053 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |
| | | | | 150, 150 | 0.059 | 0.044 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 180, 120 | 0.065 | 0.072 | 0.072 | 0.072 | 0.072 | 0.072 |
| | | | S6 | 120, 180 | 0.051 | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 |
| | | | | 150, 150 | 0.060 | 0.041 | 0.041 | 0.041 | 0.041 | 0.041 |
| | | | | 180, 120 | 0.054 | 0.078 | 0.078 | 0.078 | 0.078 | 0.078 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

**Appendix Table 10-a. Type1 error of the studentized permutation method with Gumbel copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C1 | S1 | 120, 180 | 0.269 | 0.234 | 0.234 | 0.234 | 0.234 | 0.234 |
| | | | | 150, 150 | 0.251 | 0.231 | 0.231 | 0.231 | 0.231 | 0.231 |
| | | | | 180, 120 | 0.224 | 0.239 | 0.239 | 0.239 | 0.239 | 0.239 |
| | | | S3 | 120, 180 | 0.763 | 0.739 | 0.739 | 0.739 | 0.739 | 0.739 |
| | | | | 150, 150 | 0.762 | 0.760 | 0.760 | 0.760 | 0.760 | 0.760 |
| | | | | 180, 120 | 0.718 | 0.748 | 0.748 | 0.748 | 0.748 | 0.748 |
| | | | S4 | 120, 180 | 0.149 | 0.101 | 0.101 | 0.101 | 0.101 | 0.101 |
| | | | | 150, 150 | 0.171 | 0.144 | 0.144 | 0.144 | 0.144 | 0.144 |
| | | | | 180, 120 | 0.131 | 0.142 | 0.142 | 0.142 | 0.142 | 0.142 |
| | | | S6 | 120, 180 | 0.741 | 0.686 | 0.686 | 0.686 | 0.686 | 0.686 |
| | | | | 150, 150 | 0.722 | 0.743 | 0.743 | 0.743 | 0.743 | 0.743 |
| | | | | 180, 120 | 0.682 | 0.734 | 0.734 | 0.734 | 0.734 | 0.734 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C1, Censoring distribution in each group follow Weibull(3,18), Weibull(0.5, 40); Method, studentized permutation method

**Appendix Table 10-b. Type1 error of the studentized permutation method with Gumbel copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C2 | S1 | 120, 180 | 0.055 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | | 150, 150 | 0.057 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | | 180, 120 | 0.053 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | S2 | 120, 180 | 0.055 | 0.039 | 0.039 | 0.039 | 0.039 | 0.039 |
| | | | | 150, 150 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 | 0.047 |
| | | | | 180, 120 | 0.054 | 0.052 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | S3 | 120, 180 | 0.053 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | | 150, 150 | 0.064 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |
| | | | | 180, 120 | 0.050 | 0.049 | 0.049 | 0.049 | 0.049 | 0.049 |
| | | | S4 | 120, 180 | 0.057 | 0.044 | 0.044 | 0.044 | 0.044 | 0.044 |
| | | | | 150, 150 | 0.044 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | | 180, 120 | 0.075 | 0.076 | 0.076 | 0.076 | 0.076 | 0.076 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 120, 180 | 0.085 | 0.041 | 0.041 | 0.041 | 0.041 | 0.041 |
| S5 | 150, 150 | 0.057 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | 180, 120 | 0.072 | 0.080 | 0.080 | 0.080 | 0.080 | 0.080 |
| | 120, 180 | 0.056 | 0.038 | 0.038 | 0.038 | 0.038 | 0.038 |
| S6 | 150, 150 | 0.050 | 0.042 | 0.042 | 0.042 | 0.042 | 0.042 |
| | 180, 120 | 0.059 | 0.046 | 0.046 | 0.046 | 0.046 | 0.046 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S2, Survival distribution in both groups follow Weibull(3, 8); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S5, Survival distribution in each groups follow Weibull(3, 8), Weibull(0.91, 14); S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C2, Censoring distribution in both groups follow Uniform(0, 25); Method, studentized permutation method

**Appendix Table 10-c. Type1 error of the studentized permutation method with Gumbel copula**

| Copula | Kendall's tau | Censoring | Survival | sample size | asymptotic | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Gumbel | 0.5 | C3 | S1 | 120, 180 | 0.060 | 0.056 | 0.056 | 0.056 | 0.056 | 0.056 |
| | | | | 150, 150 | 0.047 | 0.052 | 0.052 | 0.052 | 0.052 | 0.052 |
| | | | | 180, 120 | 0.058 | 0.048 | 0.048 | 0.048 | 0.048 | 0.048 |
| | | | S3 | 120, 180 | 0.054 | 0.041 | 0.041 | 0.041 | 0.041 | 0.041 |
| | | | | 150, 150 | 0.060 | 0.055 | 0.055 | 0.055 | 0.055 | 0.055 |
| | | | | 180, 120 | 0.047 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | | | S4 | 120, 180 | 0.075 | 0.041 | 0.041 | 0.041 | 0.041 | 0.041 |
| | | | | 150, 150 | 0.047 | 0.045 | 0.045 | 0.045 | 0.045 | 0.045 |
| | | | | 180, 120 | 0.055 | 0.060 | 0.060 | 0.060 | 0.060 | 0.060 |
| | | | S6 | 120, 180 | 0.065 | 0.040 | 0.040 | 0.040 | 0.040 | 0.040 |
| | | | | 150, 150 | 0.046 | 0.043 | 0.043 | 0.043 | 0.043 | 0.043 |
| | | | | 180, 120 | 0.045 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 |

Abbreviations: S1, Survival distribution in both groups follow Exp(0.2); S3, Survival distribution in both groups follow log-normal(2, 0.25); S4, Survival distribution in each groups follow Exp(0.2), piece-wise Exp; S6, Survival distribution in each groups follow Weibull(3, 8), Weibull(1.5, 9.86); C3, Censoring distribution in both groups follow Weibull(3, 15); Method, studentized permutation method

# References

Horiguchi, Miki, and Hajime Uno. "On permutation tests for comparing restricted mean survival time with small sample from randomized trials." Statistics in Medicine 39.20 (2020): 2655-2670.

Ditzhaus, Marc, Menggang Yu, and Jin Xu. "Studentized permutation method for comparing restricted mean survival times with small sample from randomized trials." arXiv preprint arXiv:2102.10186 (2021).

Royston, Patrick, and Mahesh KB Parmar. "The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt." Statistics in medicine 30.19 (2011): 2409-2421.

Royston, Patrick, and Mahesh KB Parmar. "Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome." BMC medical research methodology 13.1 (2013): 1-15.

Kaplan, Edward L., and Paul Meier. "Nonparametric estimation from incomplete observations." Journal of the American statistical association 53.282 (1958): 457-481.

Chen, Pei-Yun, and Anastasios A. Tsiatis. "Causal inference on the difference of the restricted mean lifetime between two groups." Biometrics 57.4 (2001): 1030-1038.

Zhao, Lihui, et al. "On the restricted mean survival time curve in survival analysis." Biometrics 72.1 (2016): 215-221.

Tian, Lu, et al. "Efficiency of two sample tests via the restricted mean survival time for analyzing event time observations." Biometrics 74.2 (2018): 694-702.

Janssen, Arnold, and Thorsten Pauls. "A Monte Carlo comparison of studentized bootstrap and permutation tests for heteroscedastic two-sample problems." Computational Statistics 20 (2005): 369-383.

Yan, Jun. "Enjoy the joy of copulas: with a package copula." Journal of Statistical Software 21 (2007): 1-21.

KARAKAŞ, Ayşe Metin, and Mine DOĞAN. "Archimedean Copula Parameter Estimation with Kendall Distribution Function." Journal of the Institute of Science and Technology 7.3 (2017): 187-198.

# 국 문 요 약

두 제한된 평균 생존 시간 차이에 대한

순열 검정 비교

생존 분석에서는 그룹 간의 생존 함수를 비교하기 위해 비례 위험을 가정한다. 그러나 이러한 가정은 실제 데이터에는 적용되지 않을 수 있으므로 제한된 평균 생존 시간(RMST)이 대안으로 채택된다. 본 논문에서는 순열 방법을 이용한 시뮬레이션을 통해 작은 표본 크기에 적합한 방법을 비교한다. 또한 Clayton 및 Gumbel copula 함수를 사용하여 생존 분포와 검열 분포 간의 종속성을 고려한다. 검열 분포가 두 그룹 간에 다를 때, 스튜던트화 순열 접근 방식이 제 1종 오류를 더 잘 컨트롤 한다고 해석한다. 그러나 생존 분포와 검열 분포의 종속성이 존재하고 두 그룹의 검열 분포가 다른 경우, 스튜던트화 순열에서는 제1종 오류가 증가한다는 것을 볼 수 있다.

---

핵심되는 말: 제한된 평균 생존 시간(RMST), 스튜던트화 순열, Copoula