

Article

Not peer-reviewed version

---

# Computation of The Mann-Whitney Effect under Parametric Survival Copula Models

---

Kosuke Nakazono , Yu-Cheng Lin , Gen-Yih Liao , Ryuji Uozumi , [Takeshi Emura](#) \*

Posted Date: 26 March 2024

doi: 10.20944/preprints202403.1554.v1

Keywords: censoring; copula; Hand's paradox; potential outcome; Mann-Whitney effect; stress-strength model; two-sample comparison; survival analysis; survival function; treatment effect



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Article

# Computation of The Mann-Whitney Effect under Parametric Survival Copula Models

Kosuke Nakazono <sup>1</sup>, Yu-Cheng Lin <sup>2</sup>, Gen-Yih Liao <sup>3</sup>, Ryuji Uozumi <sup>4</sup> and Takeshi Emura <sup>5,\*</sup>

<sup>1</sup> Research Center for Medical and Health Data Science, The Institute of Statistical Mathematics, Tokyo, Japan; nakazono@ism.ac.jp

<sup>2</sup> Department of Information Management, Chang Gung University, Taoyuan, Taiwan; yoyolin0822@gmail.com

<sup>3</sup> Department of Information Management, Chang Gung University, Taoyuan, Taiwan; gyliao@gmail.com

<sup>4</sup> Department of Industrial Engineering and Economics, Tokyo Institute of Technology, Tokyo, Japan; uozumi.r.ab@m.titech.ac.jp

<sup>5</sup> Biostatistics Center, Kurume University, 67 Asahi-machi, Kurume, Japan

Research Center for Medical and Health Data Science, The Institute of Statistical Mathematics, Tokyo, Japan

\* Correspondence: takeshiemura@gmail.com

**Abstract:** The Mann-Whitney effect is a measure for comparing survival distributions between two groups. The Mann-Whitney effect is interpreted as the probability that a randomly selected subject in a group survives longer than a randomly selected subject in the other group. Under the independence assumption of two groups, the Mann-Whitney effect can be expressed as the traditional integral formula of survival functions. However, when the survival times in two groups are not independent each other, the traditional expression of the Mann-Whitney effect has to be modified. In this article, we propose a copula-based approach to compute the Mann-Whitney effect with parametric survival models under dependence of two groups, which may arise in the potential outcome framework. In addition, we develop a Shiny web app that can implement the proposed method via simple commands ([https://nkosuke.shinyapps.io/shiny\\_survival/](https://nkosuke.shinyapps.io/shiny_survival/)). Through a simulation study, we show the correctness of the proposed calculator. We apply the proposed methods to two real datasets.

**Keywords:** censoring; copula; Hand's paradox; Mann-Whitney effect; potential outcome; stress-strength model; survival analysis; survival function; treatment effect; two-sample comparison

**MSC:** 62-04; 62D20; 62F10; 62N01; 62N03; 62N05

## 1. Introduction

When comparing the survival times of two independent groups, the Mann-Whitney parameter plays an important role in the two-sample problem ([1]). The Mann-Whitney parameter, say  $p$ , is defined as the probability that a random subject from one group (with survival time  $T_1$  in group 1) survives longer than an independent random subject from the other group (with survival time  $T_2$  in group 2), plus one-half the probability that the two subjects survive at the same time:

$$p = \mathbb{P}(T_1 > T_2) + \frac{1}{2}\mathbb{P}(T_1 = T_2). \quad (1)$$

The Mann-Whitney effect relates to important statistical ideas, such as, the Mann-Whitney test ([2]), hazard ratios, and *win ratio* ([3]). The Mann-Whitney test examines the null hypothesis  $H_0 : p = 1/2$  v.s.  $H_1 : p \neq 1/2$ . The hazard ratio is the main effect measure of a Cox proportional hazards model, which is a typical statistical model in survival analysis. The win ratio  $w$  is given by the odds of  $p$ ; that is,  $w = p/(1 - p)$ . That is,  $p > 1/2$ , or equivalently  $w > 1$ , implies a protective survival effect for group 1.

The problem of estimating the parameter  $p$  plays an important part in survival analysis. The basic idea was first studied by [4]. They illustrated an attractive relationship between the Mann-Whitney

statistic and the stress-strength model. [1] first proposed a nonparametric estimator for  $p$  under independent censoring. Since then, this topic has been investigated by several researchers. In the following, we refer to some recent studies in the field of survival analysis. [5] modified Efron's estimator for  $p$  under small sample sizes. [6] proposed a copula-graphic estimator for  $p$  and suggested the Mann-Whitney test to compare two survival distributions in the presence of dependent censoring. [7] introduced the Bayesian estimation of  $p$  for the log-Lindley distribution. [8] proposed estimating the Mann-Whitney effects in factorial clustered data. [9] developed methodologies for constructing fixed-accuracy confidence intervals of  $p$  when  $T_1$  and  $T_2$  follow geometric and the exponential distributions, respectively. [10] studied a estimation procedure of the stress-strength model for the two independent unit-half-normal distributions with different shape parameters. [11] investigated the effect of dependence of the variables on  $p$  in the stress-strength model with the exponential margins. [12] proposed a group sequential method for estimating the Mann-Whitney parameter. [13] studied the estimator of  $p$  in point, interval, and Bayesian estimations when the stress variables follow geometric and Lindley distribution. All the methods assumed that  $T_1$  and  $T_2$  are independent.

When  $T_1$  and  $T_2$  are independent of each other and continuous, one can estimate  $p$  with the marginal distributions based on the following integral:

$$p = - \int_0^{\infty} S_1(t) dS_2(t).$$

That is, one can estimate  $p$  by estimating two marginal survival functions  $S_1$  and  $S_2$ . However, this is not the case when  $T_1$  and  $T_2$  are dependent; the phenomenon is sometimes called "Hand's paradox" ([14]). This showed that the paradox arises when  $T_1$  and  $T_2$  are regarded as potential outcomes in the framework of causal inference. Therefore,  $p$  in the integral cannot be interpreted as the true treatment effect. Besides, dependence of outcomes from observation to observation is well-known in factorial designs and cross-over designs ([15]).

Since  $p$  is not identifiable solely from independently sampled data, [16] suggested a bound for  $p$  under all possible dependence structures for  $T_1$  and  $T_2$ . Alternatively, [17] reformulated  $p$  such that it can be identified from randomized treatment assignments. However, to estimate the true  $p$ , we must model the bivariate survival function of  $T_1$  and  $T_2$ . Copula is often used to model joint distributions of dependent survival times ([18], [19]).

In this article, we propose a model for the bivariate survival function by using parametric copulas and parametric marginal distributions. We then derive a new formula for computing  $p$  by a one-dimensional integral. We also propose a new formula for  $p$  under the restricted follow-up. To make the proposed computation method for  $p$  to be easily performed by users, we develop a Shiny-based web app. Furthermore, we validate the accuracy of the proposed computation method and Shiny web app by simulations. We finally illustrate the proposed method by two real datasets.

The rest of the paper is organized as follows. In Section 2, we review copula-based models and introduce several well-known copula families. In this section, we show that one can compute  $p$  by Theorem in [20], and we extend the theorem to compute  $p$  when the follow-up time is restricted up to time  $\tau$ . In Section 3, we introduce a Shiny web app in the R that can compute  $p$  via simple commands. In Section 4, we describe a simulation study to show the correctness of the proposed calculator for  $p$ . In Section 5, we illustrate a meaningful application of our proposed method using survival data.

## 2. Proposed Method

In this section, we first introduce copula-based bivariate survival models for  $T_1$  and  $T_2$ . We then propose our method for computing the Mann-Whitney effect  $p$  in Equation (1) under the copula models.

## 2.1. Copula Models for Dependent Survival Time

According to [21], any bivariate distribution function for  $(T_1, T_2)$  can be formulated by using a copula. A bivariate copula is a bivariate distribution function for two uniform variables on  $[0, 1]$  ([22], [23]). Let  $T_1$  and  $T_2$  be continuous survival times with marginal survival functions  $S_1$  and  $S_2$ , respectively. Initially, we model the bivariate survival function of  $T_1$  and  $T_2$  using a copula  $C$ :

$$\mathbb{P}(T_1 > t_1, T_2 > t_2) = C(S_1(t_1), S_2(t_2)). \quad (2)$$

This representation is useful since two marginal survival functions  $S_1$  and  $S_2$  are separated from the dependence structure  $C$ .

We will consider the following well-known families of bivariate copulas.

1. The independence copula:

$$C(u, v) = uv.$$

2. The Clayton copula ([24]):

$$C_\theta(u, v) = \max \left( (u^{-\theta} + v^{-\theta} - 1)^{-1/\theta}, 0 \right), \quad \theta \in [-1, \infty) \setminus \{0\}.$$

3. The Gumbel copula ([25]):

$$C_\theta(u, v) = \exp \left\{ -[(-\log u)^{\theta+1} + (-\log v)^{\theta+1}]^{\frac{1}{\theta+1}} \right\}, \quad \theta \in [0, \infty).$$

4. The Frank copula ([26]):

$$C_\theta(u, v) = -\frac{1}{\theta} \log \left( 1 + \frac{(e^{-\theta u} - 1)(e^{-\theta v} - 1)}{e^{-\theta} - 1} \right), \quad \theta \in (-\infty, \infty) \setminus \{0\}.$$

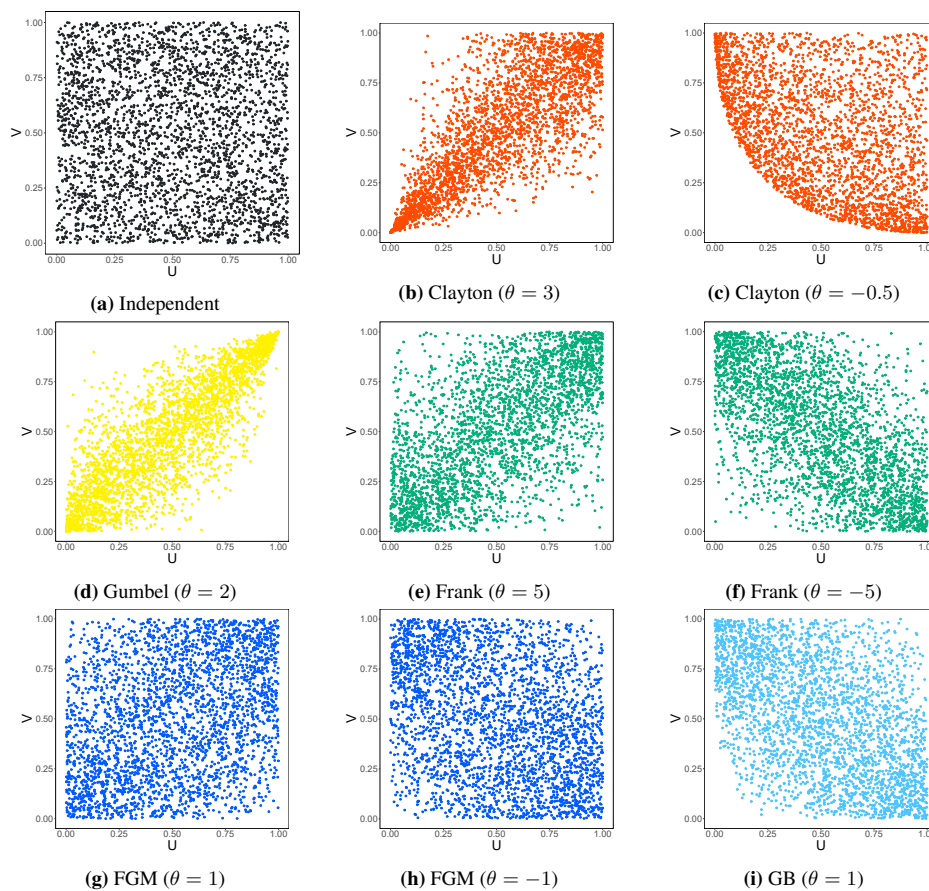
5. The Farlie-Gumbel-Morgenstern (FGM) copula ([27]):

$$C(u, v) = uv + \theta uv(1-u)(1-v), \quad \theta \in [-1, 1].$$

6. The Gumbel-Barnett (GB) copula ([22], [28], [29]):

$$C(u, v) = uv \exp(-\theta \log u \log v), \quad \theta \in [0, 1].$$

In Figure 1, we present scatterplots generated from various copulas with parameter  $\theta$ . The Clayton copula (Figure 1 (b), (c)) shows lower tail dependence, the Gumbel copula (Figure 1 (d)) shows upper tail dependence, Frank copula (Figure 1 (e), (f)) shows symmetric dependence around the median, and the FGM copula (Figure 1 (g), (h)) is similar to the Frank copula. Unlike other copulas, the GB copula exhibits negative dependence only (Figure 1 (i)).



**Figure 1.** Scatter plots of 3,000 data points generated from the copula distribution with parameter  $\theta$ .

These copulas have been applied to survival data and other data analyses. The Clayton copula was applied to survival data with dependent censoring. For instance, [30] modeled dependence between survival and dependent censoring times in the survival data of tuberculosis cure. The Clayton, Gumbel, and Frank copula were also applied to dependently censored data in clinical trials or observational studies ([31], [32], [33]). The Gumbel, Frank, and FGM copulas were often used in competing risks models on survival data analysis ([34], [35], [36]). Copulas were also applied to multivariate meta-analysis; [37] and [38] proposed a bivariate Clayton, FGM and Gumbel models for bivariate meta-analysis. The Gumbel-Barnett copula has the simple form and is suitable for modeling negative dependence ([22], [28]). Therefore, it is important to consider a variety of copulas for dependent survival times.

To see the strength of dependence in a copula,  $\theta$  can be transformed to Kendall's tau,  $\tau$ . Kendall's tau is a well-known measure to assess the dependence between two variables. Under the copula model (2), Kendall's tau for  $T_1$  and  $T_2$  is expressed as

$$\text{Kendall's } \tau = 4 \int_0^1 \int_0^1 C_\theta(u, v) C_\theta(du, dv) - 1.$$

Kendall's  $\tau$  does not depend on the marginals, and is solely determined by the copula. Therefore, it is advantageous over the Pearson correlation for  $T_1$  and  $T_2$ . Kendall's  $\tau$  of each copula is expressed as follow.

1. The independence copula:

$$\text{Kendall's } \tau = 0.$$



2. The Clayton copula:

$$\text{Kendall's } \tau = \frac{\theta}{\theta + 2}, \quad \theta \in [-1, \infty) \setminus \{0\}.$$

3. The Gumbel copula:

$$\text{Kendall's } \tau = \frac{\theta}{\theta + 1}, \quad \theta \in [0, \infty).$$

4. The Frank copula:

$$\text{Kendall's } \tau = 1 - \frac{4}{\theta} + \frac{4D_\theta}{\theta}, \quad \text{where } D_\theta = \frac{1}{\theta} \int_0^\theta \frac{x}{\exp(x) - 1} dx, \quad \theta \in (-\infty, \infty) \setminus \{0\}.$$

5. The FGM copula:

$$\text{Kendall's } \tau = \frac{2}{9}\theta, \quad \theta \in [-1, 1].$$

6. The GB copula:

$$\text{Kendall's } \tau = 1 - \frac{4}{\theta} \int_0^1 t(1 - \theta \log t) \log(1 - \theta \log t) dt, \quad \theta \in [0, 1].$$

## 2.2. Proposed Method for Computing $p$

In this section, we propose a new formula for computing  $p$  under the survival copula model (2). Let  $U = S_1(T_1)$  and  $V = S_2(T_2)$ . For computing  $p$ , we will use the conditional distribution function for  $U$  given  $V = v$ , which is the partial derivative of  $C$  with respect to  $v$ :

$$C^{[0,1]}(u, v) = \mathbb{P}(U \leq u \mid V = v) = \frac{\partial C(u, v)}{\partial v}.$$

Then, by slightly modifying Theorem of [20],  $p$  can be expressed as the univariate integral on  $[0, 1]$ :

$$\begin{aligned} p &= \mathbb{P}(T_1 > T_2) + \frac{1}{2} \mathbb{P}(T_1 = T_2) \\ &= \mathbb{P}(S_1(T_1) < S_1(T_2)) = \mathbb{P}(U < S_1(S_2^{-1}(V))) = \mathbb{E} \left[ \mathbb{P}(U < S_1(S_2^{-1}(V)) \mid V) \right] \\ &= \int_0^1 C^{[0,1]}(S_1(S_2^{-1}(v)), v) dv. \end{aligned} \quad (3)$$

We note that Theorem of [20] is not directly applicable to the survival copula model (2) since that theorem is designed for the copula model  $\mathbb{P}(T_1 \leq t_1, T_2 \leq t_2) = C(1 - S_1(t_1), 1 - S_2(t_2))$ .

Equation (3) with aforementioned copulas is computed by the following formulas:

1. The Clayton copula

$$p = \int_0^1 v^{-\theta-1} \left( \{S_1(S_2^{-1}(v))\}^{-\theta} + v^{-\theta} - 1 \right)^{-\frac{1}{\theta}-1} dv.$$

2. The Gumbel copula

$$\begin{aligned} p &= \int_0^1 \left\{ \exp \left\{ -[(-\log S_1(S_2^{-1}(v)))^{\theta+1} + (-\log v)^{\theta+1}]^{\frac{1}{\theta+1}} \right\} \right. \\ &\quad \times \left. \left[ (-\log(S_1(S_2^{-1}(v))))^{\theta+1} + (-\log(v))^{\theta+1} \right]^{-\frac{\theta}{\theta+1}} \frac{(-\log(v))^\theta}{v} \right\} dv. \end{aligned}$$

## 3. The Frank copula

$$p = \int_0^1 \frac{e^{-\theta v} (e^{-\theta S_1(S_2^{-1}(v))} - 1)}{(e^{-\theta} - 1) + (e^{-\theta S_1(S_2^{-1}(v))} - 1)(e^{-\theta v} - 1)} dv.$$

## 4. The FGM copula

$$p = \int_0^1 \left\{ S_1(S_2^{-1}(v)) + \theta S_1(S_2^{-1}(v)) (1 - S_1(S_2^{-1}(v))) (1 - 2v) \right\} dv.$$

## 5. The GB copula

$$p = \int_0^1 \left\{ S_1(S_2^{-1}(v)) (1 - \theta \log S_1(S_2^{-1}(v))) v^{-\theta \log S_1(S_2^{-1}(v))} \right\} dv.$$

In order to compute  $p$  by the above formulas, we need to specify  $S_1$ ,  $S_2$ , and  $\theta$ . One can specify  $S_1$  and  $S_2$  by continuous parametric models that will be discussed in Section 2.4. One can try different values for  $\theta$  in a sensitivity analysis. Note that the above calculations are not applicable for discrete parametric models for  $S_1$  and  $S_2$ .

2.3. Computing  $p$  with Follow-Up Time

For survival data, the follow-up period is often limited. When a subject survives longer than the follow-up period, one may treat the survival time of the subject as equal to the follow-up period ([5], [39], [40]). In this section, we assume that every subject has a common follow-up time  $\tau$ . This means that we define the Mann-Whitney effect for  $\min(T_1, \tau)$  and  $\min(T_2, \tau)$ . We now obtain  $p$  with follow-up time  $\tau$  from the following theorem, a straightforward expansion of Theorem in [20].

**Theorem 1.** *The Mann-Whitney effect  $p$  with a follow-up time  $\tau$  is written as the univariate integral:*

$$\begin{aligned} p_\tau &= \mathbb{P}(\min(T_1, \tau) > \min(T_2, \tau)) + \frac{1}{2} \mathbb{P}(\min(T_1, \tau) = \min(T_2, \tau)) \\ &= \mathbb{P}(T_1 > T_2, T_2 < \tau) + \frac{1}{2} \mathbb{P}(T_1 > \tau, T_2 > \tau) \\ &= \mathbb{P}(U < S_1(S_2^{-1}(V)), V > S_2(\tau)) + \frac{1}{2} C(S_1(\tau), S_2(\tau)) \\ &= \int_{S_2(\tau)}^1 C^{[0,1]}(S_1(S_2^{-1}(v)), v) dv + \frac{1}{2} C(S_1(\tau), S_2(\tau)). \end{aligned} \quad (4)$$

Equation 4 with different copulas is computed by the following formulas:

## 1. The Clayton copula

$$p_\tau = \int_{S_2(\tau)}^1 \left\{ v^{-\theta-1} \left( \{S_1(S_2^{-1}(v))\}^{-\theta} + v^{-\theta} - 1 \right)^{-\frac{1}{\theta}-1} \right\} dv + \frac{1}{2} (S_1(\tau)^{-\theta} + S_2(\tau)^{-\theta} - 1)^{-1/\theta}.$$

## 2. The Gumbel copula

$$\begin{aligned} p_\tau &= \int_{S_2(\tau)}^1 \left\{ \exp \left\{ -[(-\log S_1(S_2^{-1}(v)))^{\theta+1} + (-\log v)^{\theta+1}]^{\frac{1}{\theta+1}} \right\} \right. \\ &\quad \times \left[ (-\log(S_1(S_2^{-1}(v))))^{\theta+1} + (-\log(v))^{\theta+1} \right]^{-\frac{\theta}{\theta+1}} \frac{(-\log(v))^{\theta}}{v} \left. \right\} dv \\ &\quad + \frac{1}{2} \exp \left\{ -[(-\log S_1(\tau))^{\theta+1} + (-\log S_2(\tau))^{\theta+1}]^{\frac{1}{\theta+1}} \right\}. \end{aligned}$$

## 3. The Frank copula

$$p_{\tau} = \int_{S_2(\tau)}^1 \frac{e^{-\theta v} \left( e^{-\theta S_1(S_2^{-1}(v))} - 1 \right)}{(e^{-\theta} - 1) + \left( e^{-\theta S_1(S_2^{-1}(v))} - 1 \right) (e^{-\theta v} - 1)} dv \\ + \frac{1}{2} \left( -\frac{1}{\theta} \log \left( 1 + \frac{(e^{-\theta S_1(\tau)} - 1)(e^{-\theta S_2(\tau)} - 1)}{e^{-\theta} - 1} \right) \right).$$

## 4. The FGM copula

$$p_{\tau} = \int_{S_2(\tau)}^1 \left\{ S_1(S_2^{-1}(v)) + \theta S_1(S_2^{-1}(v)) \left( 1 - S_1(S_2^{-1}(v)) \right) (1 - 2v) \right\} dv \\ + \frac{1}{2} (S_1(\tau)S_2(\tau) + \theta S_1(\tau)S_2(\tau)(1 - S_1(\tau))(1 - S_2(\tau))).$$

## 5. The GB copula

$$p_{\tau} = \int_{S_2(\tau)}^1 \left\{ S_1(S_2^{-1}(v)) \left( 1 - \theta \log S_1(S_2^{-1}(v)) \right) v^{-\theta \log S_1(S_2^{-1}(v))} \right\} dv \\ + \frac{1}{2} (S_1(\tau)S_2(\tau) \exp(-\theta \log S_1(\tau) \log S_2(\tau))).$$

## 2.4. Marginal Survival Distributions

To compute  $p$  and  $p_{\tau}$ , we considered following three parametric distributions as the marginal survival distributions of group  $j \in \{1, 2\}$ :

## 1. The exponential distribution:

$$S_j(t) = \exp(-\lambda_j t), \quad \lambda_j > 0, \\ S_i(S_j^{-1}(v)) = \exp\left(\frac{\lambda_i}{\lambda_j} \log v\right).$$

where  $\lambda_j$  is a rate parameter.

## 2. The Weibull distribution:

$$S_j(t) = \exp(-\lambda_j t^{k_j}), \quad \lambda_j > 0, k_j > 0, \\ S_i(S_j^{-1}(v)) = \exp\left(-\lambda_i \left(-\frac{\log v}{\lambda_j}\right)^{\frac{k_i}{k_j}}\right).$$

where  $\lambda_j$  is a scale parameter and  $k_j$  is a shape parameter.

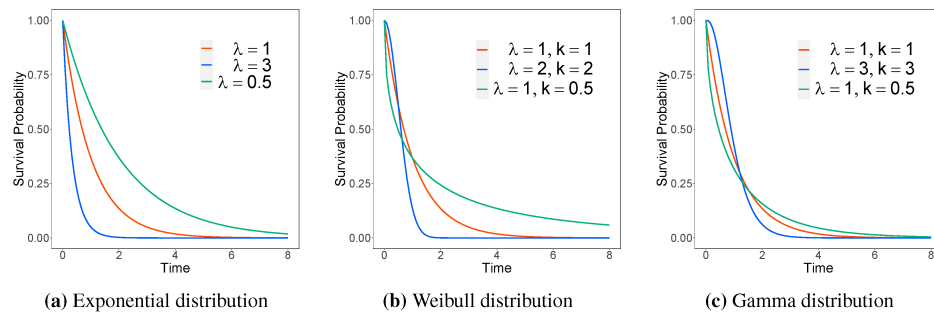
## 3. The gamma distribution:

$$S_j(t) = 1 - \frac{\gamma(k_j, \lambda_j t)}{\Gamma(k_j)}, \quad \lambda_j > 0, k_j > 0.$$

where  $\lambda_j$  is a scale parameter and  $k_j$  is a shape parameter, and  $\Gamma(k)$  is the gamma function, and  $\gamma(k, \lambda t) = \int_0^{\lambda t} x^{k-1} e^{-x} dx$  is the lower incomplete gamma function. The gamma distribution has no simple closed-form expression for the inverse survival function. Therefore, one can use approximations for the inverse survival function. In Section 3, we use the R function “*qgamma*” to calculate the quantile function of the gamma distribution.



In Figure 2, we present survival curves of three parametric distributions, the exponential, Weibull, and gamma distributions with different parameters. These plots show that these distributions can represent almost any continuous survival curve that will be encountered in practice.



**Figure 2.** Survival-curve plots of the parametric distribution functions.

**Example 1.** Let the marginals  $S_1(t), S_2(t)$  be the exponential distributions with parameter  $\lambda_1 = 1, \lambda_2 = 2$  and  $T_1$  and  $T_2$  are independent. Then by Theorem 1 with  $\tau = \infty$ ,  $p$  is given by

$$\begin{aligned} p &= \int_0^1 C^{[0,1]}(S_1(S_2^{-1}(v)), v) dv \\ &= \int_0^1 \exp\left(\frac{\lambda_1}{\lambda_2} \log v\right) dv = \frac{\lambda_2}{\lambda_1 + \lambda_2} = \frac{2}{3}. \end{aligned}$$

□

**Example 2.** Let the marginals  $S_1(t), S_2(t)$  be the exponential distributions with parameter  $\lambda_1 = 1, \lambda_2 = 2$  and  $C(u, v)$  be the Clayton copula with parameter  $\theta = 3$ . Then Kendall's  $\tau$  is given by

$$\text{Kendall's } \tau = \frac{\theta}{\theta + 2} = 0.6$$

and by Theorem 1 with  $\tau = \infty$ ,  $p$  is given by

$$\begin{aligned} p &= \int_0^1 C^{[0,1]}(S_1(S_2^{-1}(v)), v) dv \\ &= \int_0^1 v^{-\theta-1} \left( v^{-\theta \frac{\lambda_1}{\lambda_2}} + v^{-\theta} - 1 \right)^{-\frac{1}{\theta}-1} dv \\ &= \int_0^1 v^{-4} \left( v^{-3 \frac{\lambda_1}{\lambda_2}} + v^{-3} - 1 \right)^{-\frac{4}{3}} dv = 0.84. \end{aligned}$$

When  $\tau < \infty$ ,  $p_\tau$  is given by

$$\begin{aligned} p_\tau &= \int_0^1 C^{[0,1]}(S_1(S_2^{-1}(v)), v) dv + \frac{1}{2} \mathbb{P}(\min(T_1, \tau) = \min(T_2, \tau)) \\ &= \int_{e^{-2\tau}}^1 v^{-4} \left( v^{-3 \frac{\lambda_1}{\lambda_2}} + v^{-3} - 1 \right)^{-\frac{4}{3}} dv + \left( e^{-3\tau} + e^{-6\tau} - 1 \right)^{-\frac{1}{3}}. \end{aligned}$$

When  $\tau = 0.5$ ,  $p_\tau = 0.68$ . Here, we computed the last two equations by a numerical integration by the R function "integrate".

□

Parameters for the marginal distributions can be estimated by maximum likelihood estimators (MLEs) when the survival data are available in two groups (Section 5).

### 3. Software and Web App

We developed a Shiny-based web app to implement the proposed method of computing  $p$ . The Shiny app is available at ([https://nkosuke.shinyapps.io/shiny\\_survival/](https://nkosuke.shinyapps.io/shiny_survival/)) and can be used by any environment, including smartphones. Using this web app, users can choose a marginal survival distribution, copula, and the relevant parameters to compute  $p$ . Our web app is easy to use without knowledge of the R.

#### 3.1. Input

We considered three marginal survival distributions; the exponential, Weibull, and gamma distributions. We considered the Clayton, Gumbel, Frank, FGM, and GB copulas. One can choose marginal distributions and copulas, set their parameters, and choose the language displayed on the screen in the input panels on the left-hand of our app (Figure 3). Furthermore, one can set a follow-up time  $\tau$  with a slider bar. In Figure 3, we set the marginal survival distribution = "Exponential Distribution",  $\lambda_1 = 0.5$ ,  $\lambda_2 = 0.25$ ,  $\tau = 4.5$ , copula = "Clayton",  $\theta = 1.5$  and the language displayed on the screen "English".

#### 3.2. Output

This app displays several formulas, survival curves of each group,  $p$ ,  $p_\tau$ , and Kendall's  $\tau$ . These formulas include marginal and bivariate survival functions and formulas of  $p$  and  $p_\tau$  based on the input values. The theoretical values of  $p$  and  $p_\tau$  are displayed together with survival curves.

Figure 3 displays the web app. In this settings, we have the output  $p = 0.22$ ,  $p_\tau = 0.27$ , Kendall's  $\tau = 0.429$ .

#### Select and Display Results

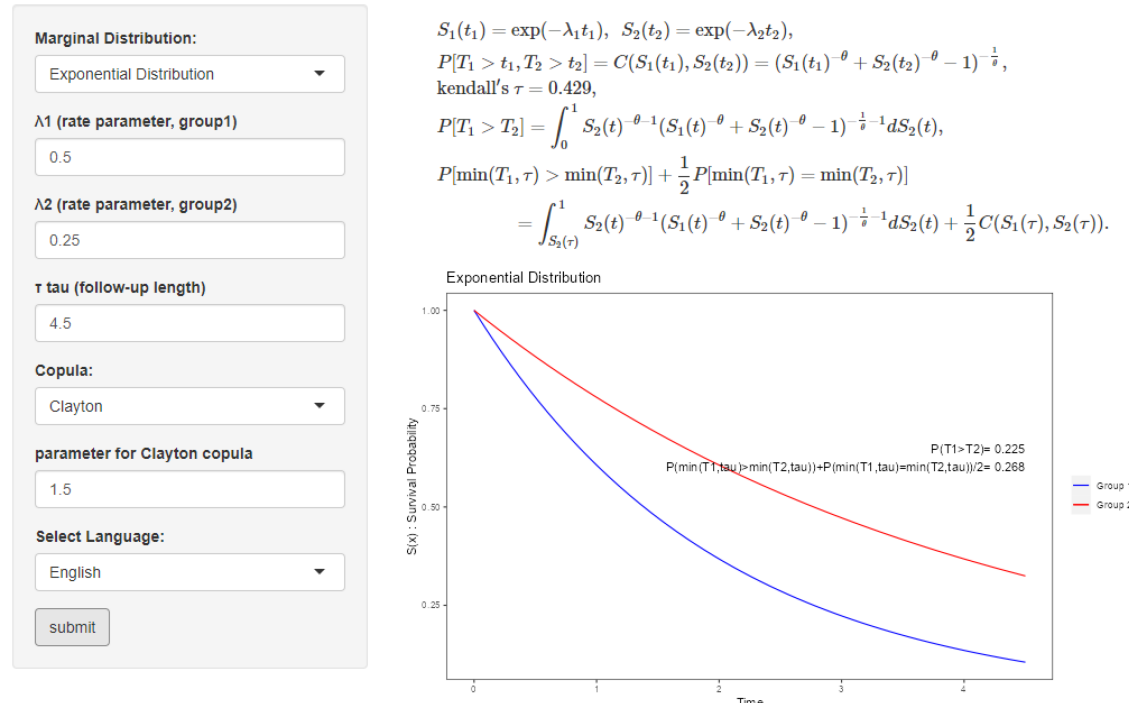


Figure 3. The web app showing the results for computing  $p$  and  $p_\tau$ .

### 4. Simulation Studies

To show the correctness of the proposed calculator for  $p$ , we conducted a simulation study. For the simulation study, we set the marginal survival functions to be the exponential distributions with  $(\lambda_1, \lambda_2) = (1, 2)$ , the Weibull distributions with  $(\lambda_1, k_1, \lambda_2, k_2) = (1, 0.5, 2, 1)$ , and the gamma

distributions with  $(\lambda_1, k_1, \lambda_2, k_2) = (1, 1.5, 2, 2)$ . Furthermore, we set the copula parameters, the Clayton copula with  $\theta = 1, 5$  or  $10$ , the Gumbel copula with  $\theta = 0$  or  $4$ , the Frank copula with  $\theta = -5, 1$ , or  $5$ , the FGM copula with  $\theta = -1, 0$ , or  $1$ , the GB copula with  $\theta = 0.5$ , or  $1$ , and follow-up time  $\tau = 0.5, 2$ , or  $5$ . We generated  $100,000$  pairs  $(T_{i1}, T_{i2}), i = 1, \dots, M$ , where  $M = 100,000$ , from the bivariate survival function based on the aforementioned settings, and calculated the Monte Carlo simulation values defined as,

$$p_{\tau, \text{sim}} = \frac{1}{M} \sum_{i=1}^M \left[ \mathbb{1}(\min(T_{i1}, \tau) > \min(T_{i2}, \tau)) + \frac{1}{2} \mathbb{1}(\min(T_{i1}, \tau) = \min(T_{i2}, \tau)) \right].$$

Table 1 shows that the simulation values are nearly equal to the theoretical values computed by the formula of Theorem 1 for every setting. In conclusion, our simulations show that Theorem 1 is correct, and the Shiny web app based on Theorem 1 is reliable.

**Table 1.** Comparison of the theoretical value and the simulation value for calculating  $p_{\tau}$  defined in Theorem 1.

Distribution	Copula	$\theta$	Kendall's $\tau$	$\tau = 0.5$								$\tau = 2$		$\tau = 5$	
				$\lambda_1$	$k_1$	$\lambda_2$	$k_2$	$p_{\tau, \text{theory}}$	$p_{\tau, \text{sim}}$	$p_{\tau, \text{theory}}$	$p_{\tau, \text{sim}}$	$p_{\tau, \text{theory}}$	$p_{\tau, \text{sim}}$	$p_{\tau, \text{theory}}$	$p_{\tau, \text{sim}}$
Exponential	Clayton	1	0.33	1	-	2	-	0.645	0.643	0.737	0.738	0.744	0.746	0.744	0.746
		5	0.71	1	-	2	-	0.704	0.706	0.872	0.872	0.881	0.883	0.881	0.883
		10	0.83	1	-	2	-	0.746	0.745	0.920	0.921	0.930	0.930	0.930	0.930
	Gumbel	0	0.00	1	-	2	-	0.629	0.631	0.666	0.666	0.666	0.665	0.666	0.665
		4	0.80	1	-	2	-	0.798	0.799	0.961	0.961	0.970	0.969	0.970	0.969
	Frank	-5	-0.46	1	-	2	-	0.615	0.615	0.622	0.622	0.622	0.622	0.622	0.622
		1	0.11	1	-	2	-	0.636	0.636	0.684	0.684	0.685	0.685	0.685	0.685
		5	0.46	1	-	2	-	0.674	0.674	0.771	0.768	0.773	0.772	0.773	0.772
	FGM	-1	-0.22	1	-	2	-	0.617	0.617	0.633	0.634	0.633	0.631	0.633	0.631
		0	0.00	1	-	2	-	0.629	0.629	0.666	0.666	0.666	0.666	0.666	0.666
		1	0.22	1	-	2	-	0.642	0.641	0.699	0.697	0.700	0.702	0.700	0.702
	GB	0.5	-0.21	1	-	2	-	0.623	0.624	0.642	0.643	0.642	0.641	0.642	0.641
		1	-0.36	1	-	2	-	0.617	0.616	0.629	0.628	0.629	0.632	0.629	0.632
Weibull	Clayton	1	0.33	1	0.5	2	1	0.497	0.496	0.594	0.589	0.603	0.602	0.603	0.602
		5	0.71	1	0.5	2	1	0.482	0.480	0.644	0.645	0.653	0.654	0.653	0.654
		10	0.83	1	0.5	2	1	0.472	0.472	0.645	0.645	0.654	0.653	0.654	0.653
	Gumbel	0	0.00	1	0.5	2	1	0.511	0.509	0.560	0.562	0.562	0.562	0.562	0.562
		4	0.80	1	0.5	2	1	0.425	0.424	0.584	0.585	0.593	0.594	0.593	0.594
	Frank	-5	-0.46	1	0.5	2	1	0.528	0.530	0.542	0.541	0.542	0.543	0.542	0.543
		1	0.11	1	0.5	2	1	0.505	0.504	0.566	0.565	0.569	0.572	0.569	0.572
		5	0.46	1	0.5	2	1	0.486	0.486	0.592	0.595	0.597	0.597	0.597	0.597
	FGM	-1	-0.22	1	0.5	2	1	0.521	0.523	0.548	0.549	0.549	0.551	0.549	0.551
		0	0.00	1	0.5	2	1	0.511	0.509	0.560	0.563	0.562	0.562	0.562	0.562
		1	0.22	1	0.5	2	1	0.501	0.503	0.572	0.574	0.575	0.577	0.575	0.577
	GB	0.5	-0.21	1	0.5	2	1	0.519	0.520	0.549	0.546	0.549	0.548	0.549	0.548
		1	-0.36	1	0.5	2	1	0.526	0.526	0.545	0.545	0.545	0.545	0.545	0.545
Gamma	Clayton	1	0.33	1	1.5	2	2	0.529	0.529	0.651	0.649	0.679	0.678	0.679	0.678
		5	0.71	1	1.5	2	2	0.530	0.528	0.763	0.763	0.809	0.810	0.809	0.810
		10	0.83	1	1.5	2	2	0.534	0.533	0.817	0.816	0.862	0.863	0.862	0.863
	Gumbel	0	0.00	1	1.5	2	2	0.530	0.530	0.611	0.612	0.615	0.614	0.615	0.614
		4	0.80	1	1.5	2	2	0.545	0.546	0.813	0.813	0.853	0.853	0.853	0.853
	Frank	-5	-0.46	1	1.5	2	2	0.532	0.530	0.584	0.584	0.584	0.583	0.584	0.583
		1	0.11	1	1.5	2	2	0.530	0.529	0.622	0.622	0.628	0.628	0.628	0.628
		5	0.46	1	1.5	2	2	0.530	0.530	0.679	0.679	0.694	0.692	0.694	0.692
	FGM	-1	-0.22	1	1.5	2	2	0.531	0.533	0.591	0.591	0.592	0.591	0.592	0.591
		0	0.00	1	1.5	2	2	0.530	0.529	0.611	0.610	0.615	0.614	0.615	0.614
		1	0.22	1	1.5	2	2	0.529	0.529	0.631	0.631	0.639	0.640	0.639	0.640
	GB	0.5	-0.21	1	1.5	2	2	0.531	0.532	0.597	0.598	0.598	0.598	0.598	0.598
		1	-0.36	1	1.5	2	2	0.532	0.532	0.589	0.592	0.590	0.588	0.590	0.588

## 5. Numerical Examples

In this section, we apply our proposed methods to a tongue cancer dataset and a prostate cancer dataset. Before analyzing the real datasets, we introduce basic notations and ideas for estimating  $p$  by using censored data. Let  $T_{ij}, j = 1, 2, i = 1, \dots, n_j$  be survival times,  $C_{ij}, j = 1, 2$  be censored times,  $t_{ij} = \min(T_{ij}, C_{ij}), j = 1, 2$  be observed time, and  $\Delta_{ij} = 1(T_{ij} \leq C_{ij}), j = 1, 2$  be event indicator. What we observe is  $t_{ij}$  and  $\Delta_{ij}$ . That is,  $\Delta_{ij}$  is 0 or 1 according to whether  $t_{ij}$  is a censored time or a survival time. As the exponential distribution is shown to fit well for  $T_{i1}$  and  $T_{i2}$ , we obtained MLE of the exponential hazard rate  $\hat{\lambda}_j, j = 1, 2$  by

$$\hat{\lambda}_j = \frac{\sum_{i=1}^{n_j} \Delta_{ij}}{\sum_{i=1}^{n_j} t_{ij}}, j = 1, 2.$$

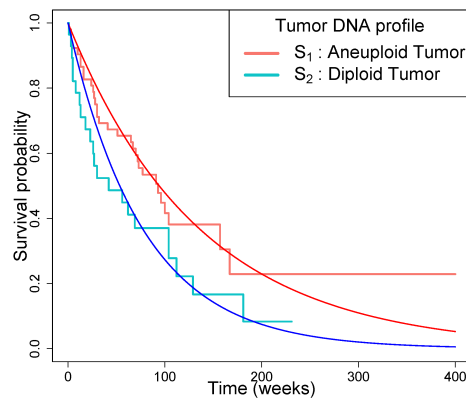
Then, by applying the values of the MLE to the proposed Shiny web app, we obtained the estimators  $\hat{p}$  and  $\hat{p}_\tau$ , where  $\tau$  was chosen appropriately (Sections 5.1 and 5.2). On the other hand, under the independence assumption of  $T_{i1}$  and  $T_{i2}$ , the naïve estimator of  $p$  is

$$\begin{aligned} \hat{p}^{\text{KM}} &= - \int_0^\infty \hat{S}_1^\pm(t) d\hat{S}_2(t), \\ \hat{p}_\tau^{\text{KM}} &= - \int_0^{\hat{S}_2^{-1}(\tau)} \hat{S}_1^\pm(t) d\hat{S}_2(t) + \frac{1}{2} \hat{S}_1^\pm(\tau) \hat{S}_2^\pm(\tau), \end{aligned}$$

where  $\hat{S}_i^\pm(t) = [\hat{S}_i(t+) + \hat{S}_i(t-)]/2$  and  $\hat{S}_i(t)$  is a Kaplan-Meier (KM) estimator. However, this estimate is subject to the independence of two groups. Therefore, the proposed estimator is useful to examine the sensitivity under a variety of dependence structures via copulas.

### 5.1. Tongue Cancer Data

The tongue dataset is available in the R package *KMsurv*. It has 80 observations and contains: type (Tumor DNA profile: 1 = aneuploid tumor, 2 = diploid tumor), time (Time to death or on-study time (weeks)), and death (Event indicator: 0 = alive, 1 = dead). It contains  $n_1 = 52$  observations in aneuploid cancer group ( $j = 1$ ), and  $n_2 = 28$  observations in diploid cancer group ( $j = 2$ ). We considered the follow-up time  $\tau = \min_i \{\max_j t_{ij} \Delta_{ij}\}$  and obtained  $\tau = 167$ . The tongue cancer data resulted in  $\hat{\lambda}_1 = 0.00736, \hat{\lambda}_2 = 0.0130$  and  $\hat{p}_\tau^{\text{KM}} = 0.615$ . In Figure 4, the KM estimators of each groups and the estimated exponential survival curves are plotted. We conducted sensitivity analyses using copula-based approach. We calculated  $\hat{p}$  by Theorem 1 under weak, strong positive, and negative independences. We calculated  $\hat{p}_\tau$  via the web app (Section 3). Figure 5 shows the output under the independent, Clayton, Gumbel, Frank, FGM, and GB copula with parameter  $\theta \in \{1, 5\}$  (the Clayton),  $\theta = 4$  (the Gumbel),  $\theta \in \{-5, 5\}$  (the Frank),  $\theta \in \{-1, 1\}$  (the FGM),  $\theta \in \{0.5, 1\}$  (the GB). The results under all copulas are summarized in Table 2. We obtained the  $\hat{p}_\tau$  ranged from 0.600 to 0.862 and concluded that a subject in DNA-aneuploid tumor group survives longer than in DNA-diploid tumor group. This conclusion did not change under any dependence structures we conducted.



**Figure 4.** KM estimators for DNA-aneuploid tumor and DNA-diploid tumor group and exponential survival curves with MLE of exponential hazard rates,  $\hat{\lambda}_1 = 0.00736$ ,  $\hat{\lambda}_2 = 0.0130$

### Select and Display Results

**Marginal Distribution:**  
Exponential Distribution

**$\lambda_1$  (rate parameter, group1)**  
0.00736

**$\lambda_2$  (rate parameter, group2)**  
0.0130

**$\tau$  tau (follow-up length)**  
167

**Copula:**  
Clayton

**parameter for Clayton copula**  
1

**Select Language:**  
English

submit

$$S_1(t_1) = \exp(-\lambda_1 t_1), \quad S_2(t_2) = \exp(-\lambda_2 t_2),$$

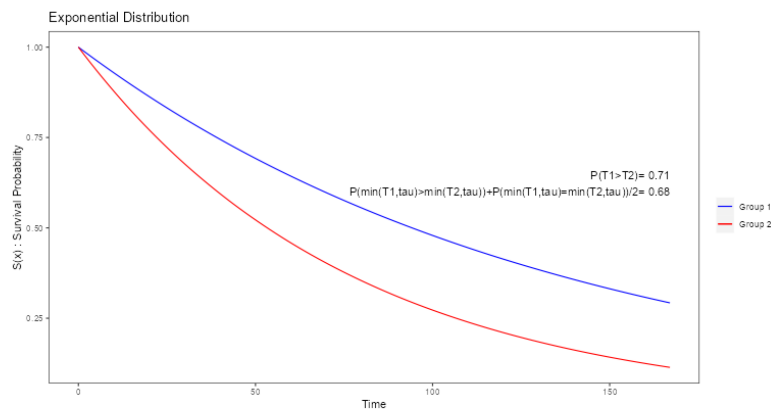
$$P[T_1 > t_1, T_2 > t_2] = C(S_1(t_1), S_2(t_2)) = (S_1(t_1)^{-\theta} + S_2(t_2)^{-\theta} - 1)^{-\frac{1}{\theta}},$$

$$\text{kendall's } \tau = 0.333,$$

$$P[T_1 > T_2] = \int_0^1 S_2(t)^{-\theta-1} (S_1(t)^{-\theta} + S_2(t)^{-\theta} - 1)^{-\frac{1}{\theta}-1} dS_2(t),$$

$$P[\min(T_1, \tau) > \min(T_2, \tau)] + \frac{1}{2} P[\min(T_1, \tau) = \min(T_2, \tau)]$$

$$= \int_{S_2(\tau)}^1 S_2(t)^{-\theta-1} (S_1(t)^{-\theta} + S_2(t)^{-\theta} - 1)^{-\frac{1}{\theta}-1} dS_2(t) + \frac{1}{2} C(S_1(\tau), S_2(\tau)).$$



**Figure 5.** Example for the tongue cancer dataset on the web app. This setting is marginal distribution: “Exponential”,  $\lambda_1 = 0.00736$ ,  $\lambda_2 = 0.0130$ ,  $\tau = 167$ , copula: “Clayton”, copula parameter:  $\theta = 1$ , and language: “English”.

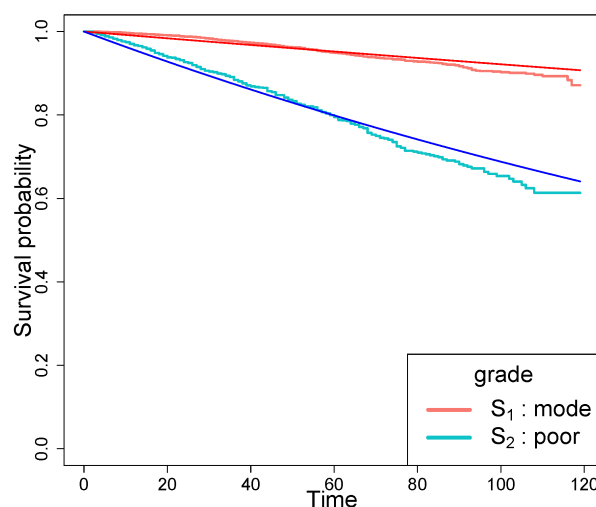
**Table 2.** Estimates  $\hat{p}_\tau(\tau = 167)$  for fitting the KM estimator (independent) and with the exponential marginal survival distributions (the independent, Clayton, Gumbel, Frank, FGM, GB copulas) for the tongue cancer dataset.

Copula	marginal distribution	$\theta$	$\hat{p}$	$\hat{p}_\tau(\tau = 167)$
Independent	KM estimator	-	-	0.632
Independent	exponential	-	0.638	0.633
Clayton	exponential	1	0.709	0.676
		5	0.856	0.799
Gumbel	exponential	4	0.906	0.862
Frank	exponential	-5	0.600	0.600
		5	0.733	0.714
FGM	exponential	-1	0.609	0.609
		1	0.666	0.658
GB	exponential	0.5	0.617	0.617
		1	0.606	0.606

## 5.2. Prostate Cancer Data

The prostate cancer data is available in the R package *asaur* ([41]). It has 14,294 observations and contains: grade (moderately differentiated and poorly differentiated), survTime (time from diagnosis to death or last date known alive), and status (Event indicator: 0 = censored, 1 = death from prostate cancer). It contains  $n_1 = 10,988$  observations in moderately differentiated group ( $j = 1$ ), and  $n_2 = 3,306$  observations in poorly differentiated group ( $j = 2$ ).

The prostate cancer data resulted in  $\hat{\lambda}_1 = 0.000817, \hat{\lambda}_2 = 0.00374, \tau = 108$ , and  $\hat{p} = 0.679$ . In Figure 6, we plot the KM estimators of each group and estimated exponential survival curves. We calculated  $\hat{p}_\tau^{\text{KM}}$  by Theorem 1 with copulas and several parameters. We calculated  $\hat{p}_\tau$  under the independent, Clayton, Gumbel, Frank, FGM, and GB copulas with parameter  $\theta \in \{1, 5\}$  (the Clayton),  $\theta = 4$  (the Gumbel),  $\theta \in \{-5, 5\}$  (the Frank),  $\theta \in \{-1, 1\}$  (the FGM),  $\theta \in \{0.5, 1\}$  (the GB) via the web app (Figure 7). The results for all scenarios are summarized in Table 3. We obtained the  $\hat{p}_\tau$  ranged from 0.623 to 0.665 and concluded that a subject in moderately differentiated group survives longer than in poorly differentiated group. The range of  $\hat{p}_\tau$  is narrower than one of tongue cancer dataset. The results may be caused by the distinct difference of survival curves between two groups, the short follow-up time for two groups and large sample size.



**Figure 6.** KM estimators for mode grade and poor grade group and exponential survival curves with MLE of exponential hazard rates,  $\hat{\lambda}_1 = 0.000817, \hat{\lambda}_2 = 0.00374$ .



Select and Display Results

Marginal Distribution:  
Exponential Distribution

A1 (rate parameter, group1)  
0.000817

A2 (rate parameter, group2)  
0.00374

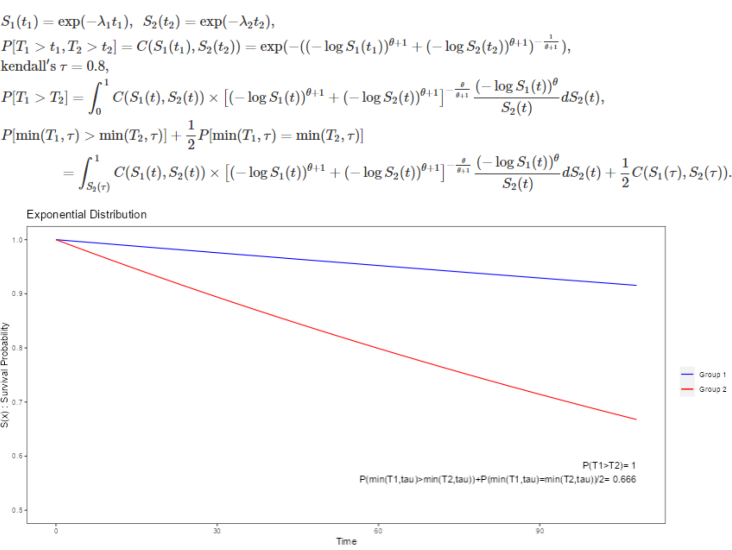
τ tau (follow-up length)  
108

Copula:  
Gumbel

parameter for Gumbel copula  
4

Select Language:  
English

submit



**Figure 7.** Example for the tongue cancer dataset on the web app. This setting is marginal distribution: “Exponential”,  $\lambda_1 = 0.00081, \lambda_2 = 0.00374, \tau = 108$ , copula: “Gumbel”, copula parameter:  $\theta = 4$ , and language: “English”.

**Table 3.** Estimates  $p_\tau(\tau = 108)$  for fitting the KM estimator (independent) and  $p_\tau(\tau = 108)$  with the exponential marginal survival distributions (the independent, Clayton, Gumbel, Frank, FGM, GB copulas) for the prostate cancer dataset.

Copula	marginal distribution	$\theta$	$\hat{p}$	$\hat{p}_\tau(\tau = 108)$
Independent	KM estimator	-	-	0.679
Independent	exponential	-	0.821	0.625
Clayton	exponential	1	0.889	0.626
		5	0.958	0.635
Gumbel	exponential	4	0.997	0.665
Frank	exponential	-5	0.753	0.624
		5	0.924	0.632
FGM	exponential	-1	0.777	0.623
		1	0.865	0.626
GB	exponential	0.5	0.786	0.624
		1	0.764	0.623

6. Conclusion

The Mann-Whitney effect has been widely used for survival analysis, which can provide the meaningful measure for treatment effects for survival outcomes. However, the Mann-Whitney effect may not be interpreted as the true treatment effect under dependence of two survival times. In this article, we proposed a parametric copula-based approach for estimating the Mann-Witney effect  $p$  under dependence structures for two survival times. We derived the formulas of  $p$  under a variety of copulas and marginal survival functions. We also introduced a web-based calculator for  $p$  for users. Simulation studies demonstrated the correctness of the proposed calculator for  $p$  under a variety of the parametric marginal survival distributions and copulas. The results of data analyses show that the proposed method gives possible changes of  $p$  under various dependence and enables to examine the sensitivity.

In the examples of real datasets, we obtained  $p_\tau$  under the Clayton, Gumbel, Frank, FGM, GB copulas with varying parameters. The value of  $p_\tau$  ranged from 0.600 to 0.862 in tongue cancer dataset, from 0.623 to 0.665 in prostate cancer dataset. We obtained the narrow ranges whose lower bound did

not include the null value of  $1/2$ . The result is consistent with previous studies that Hand's paradox does not occur under strictly monotonic effect ([14], [42]). While more complex dependence structures with various copulas might be considered, the conclusion may not change much.

The main limitation of the present article is that we only discussed the "parametric" approach. However, in practice, researchers may use the "semi-" or "non-parametric" approach. In future work, we will examine the method of computing  $p$  without parametric assumptions. Another extension is to include covariates or secondary outcomes in the model, which help obtain narrow bounds for treatment effects ([43]). Another limitation is that only one-parameter copulas are implemented. There are multi-parameter copulas that deserve attention ([22], [44], [28]).

**Funding:** This research was funded by [JSPS KAKENHI] grant number [22K11948] and grant number [20H04147].

## References

1. Efron, B. The two sample problem with censored data. Proceedings of the fifth Berkeley symposium on mathematical statistics and probability, 1967, Vol. 4, pp. 831–853.
2. Mann, H.B.; Whitney, D.R. On a test of whether one of two random variables is stochastically larger than the other. *Ann. Math. Statistics* **1947**, *18*, 50–60. <https://doi.org/10.1214/aoms/1177730491>, doi:10.1214/aoms/1177730491.
3. Pocock, S.J.; Ariti, C.A.; Collier, T.J.; Wang, D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *European Heart Journal* **2011**, *33*, 176–182, [<https://academic.oup.com/eurheartj/article-pdf/33/2/176/17154440/ehr352.pdf>]. <https://doi.org/10.1093/eurheartj/ehr352>, doi:10.1093/eurheartj/ehr352.
4. Birnbaum, Z.W. On a use of the Mann-Whitney statistic. Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability, 1954–1955, vol. I. Univ. California Press, Berkeley-Los Angeles, Calif., 1956, pp. 13–17.
5. Dobler, D.; Pauly, M. Bootstrap- and permutation-based inference for the Mann-Whitney effect for right-censored and tied data. *TEST* **2018**, *27*, 639–658. <https://doi.org/10.1007/s11749-017-0565-z>, doi:10.1007/s11749-017-0565-z.
6. Emura, T.; Hsu, J.H. Estimation of the Mann-Whitney effect in the two-sample problem under dependent censoring. *Comput. Statist. Data Anal.* **2020**, *150*, 106990, 17. <https://doi.org/10.1016/j.csda.2020.106990>, doi:10.1016/j.csda.2020.106990.
7. Biswas, A.; Chakraborty, S.; Mukherjee, M. On estimation of stress-strength reliability with log-Lindley distribution. *J. Stat. Comput. Simul.* **2021**, *91*, 128–150. <https://doi.org/10.1080/00949655.2020.1807549>, doi:10.1080/00949655.2020.1807549.
8. Rubarth, K.; Sattler, P.; Zimmermann, H.G.; Konietzschke, F. Estimation and Testing of Wilcoxon-Mann-Whitney Effects in Factorial Clustered Data Designs. *Symmetry* **2022**, *14*. <https://www.mdpi.com/2073-8994/14/2/244>, doi:10.3390/sym14020244.
9. Hu, J.; Zhuang, Y.; Goldiner, C. Fixed-accuracy confidence interval estimation of  $P(X < Y)$  under a geometric-exponential model. *Jpn. J. Stat. Data Sci.* **2021**, *4*, 1079–1104. <https://doi.org/10.1007/s42081-021-00122-2>, doi:10.1007/s42081-021-00122-2.
10. de la Cruz, R.; Salinas, H.S.; Meza, C. Reliability Estimation for Stress-Strength Model Based on Unit-Half-Normal Distribution. *Symmetry* **2022**, *14*. <https://www.mdpi.com/2073-8994/14/4/837>, doi:10.3390/sym14040837.
11. Patil, D.; Naik-Nimbalkar, U.V.; Kale, M.M. Effect of Dependency on the Estimation of  $P[Y > X]$  in Exponential Stress-strength Models. *Austrian Journal of Statistics* **2022**, *51*, 10–34. <https://www.ajs.or.at/index.php/ajs/article/view/1293>, doi:10.17713/ajs.v51i4.1293.
12. Nowak, C.P.; Mütze, T.; Konietzschke, F. Group sequential methods for the Mann-Whitney parameter. *Stat. Methods Med. Res.* **2022**, *31*, 2004–2020. <https://doi.org/10.1177/09622802221107103>, doi:10.1177/09622802221107103.
13. Singh, B.; Nayal, A.S.; Tyagi, A. Estimation of  $P[Y < Z]$  under Geometric-Lindley model. *Ricerche di Matematica* **2023**, pp. 1–32.

14. Hand, D.J. On Comparing Two Treatments. *The American Statistician* **1992**, *46*, 190–192, [\[https://www.tandfonline.com/doi/pdf/10.1080/00031305.1992.10475881\]](https://www.tandfonline.com/doi/pdf/10.1080/00031305.1992.10475881). <https://www.tandfonline.com/doi/abs/10.1080/00031305.1992.10475881>, doi:10.1080/00031305.1992.10475881.
15. Cochran, W.G.; Cox, G.M. *Experimental designs*; John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London, 1957; pp. xiv+617. 2nd ed.
16. Fan, Y.; Park, S.S. Sharp bounds on the distribution of treatment effects and their statistical inference. *Econometric Theory* **2010**, *26*, 931–951. <https://doi.org/10.1017/S0266466609990168>, doi:10.1017/S0266466609990168.
17. Fay, M.P.; Brittain, E.H.; Shih, J.H.; Follmann, D.A.; Gabriel, E.E. Causal estimands and confidence intervals associated with Wilcoxon-Mann-Whitney tests in randomized experiments. *Stat. Med.* **2018**, *37*, 2923–2937. <https://doi.org/10.1002/sim.7799>, doi:10.1002/sim.7799.
18. Emura, T.; Matsui, S.; Rondeau, V. *Survival analysis with correlated endpoints*; SpringerBriefs in Statistics, Springer, Singapore, 2019; pp. xvii+118. <https://doi.org/10.1007/978-981-13-3516-7>, doi:10.1007/978-981-13-3516-7.
19. Li, D.; Hu, X.J.; Wang, R. Evaluating association between two event times with observations subject to informative censoring. *J. Amer. Statist. Assoc.* **2023**, *118*, 1282–1294. <https://doi.org/10.1080/01621459.2021.1990766>, doi:10.1080/01621459.2021.1990766.
20. Emura, T.; Pan, C.H. Parametric likelihood inference and goodness-of-fit for dependently left-truncated data, a copula-based approach. *Statist. Papers* **2020**, *61*, 479–501. <https://doi.org/10.1007/s00362-017-0947-z>, doi:10.1007/s00362-017-0947-z.
21. Sklar, M. Fonctions de répartition à  $n$  dimensions et leurs marges. *Publ. Inst. Statist. Univ. Paris* **1959**, *8*, 229–231.
22. Nelsen, R.B. *An introduction to copulas*, second ed.; Springer Series in Statistics, Springer, New York, 2006; pp. xiv+269. <https://doi.org/10.1007/s11229-005-3715-x>, doi:10.1007/s11229-005-3715-x.
23. Geenens, G. (Re-)Reading Sklar (1959); A Personal View on Sklar's Theorem. *Mathematics* **2024**, *12*. <https://www.mdpi.com/2227-7390/12/3/380>, doi:10.3390/math12030380.
24. Clayton, D.G. A model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence. *Biometrika* **1978**, *65*, 141–151. <https://doi.org/10.1093/biomet/65.1.141>, doi:10.1093/biomet/65.1.141.
25. Gumbel, E.J. Distributions des valeurs extrêmes en plusieurs dimensions. *Publ. Inst. Statist. Univ. Paris* **1960**, *9*, 171–173.
26. Frank, M.J. On the simultaneous associativity of  $F(x, y)$  and  $x + y - F(x, y)$ . *Aequationes Math.* **1979**, *19*, 194–226. <https://doi.org/10.1007/BF02189866>, doi:10.1007/BF02189866.
27. Morgenstern, D. Einfache Beispiele zweidimensionaler Verteilungen. *Mitteilungsbl. Math. Statist.* **1956**, *8*, 234–235.
28. Chesneau, C. On the Gumbel-Barnett extended Celebioglu-Cuadras copula. *Jpn. J. Stat. Data Sci.* **2023**, *6*, 759–781. <https://doi.org/10.1007/s42081-023-00220-3>, doi:10.1007/s42081-023-00220-3.
29. Toparkus, A.M.; Weißbach, R. Testing Truncation Dependence: The Gumbel-Barnett Copula, 2024, [\[arXiv:stat.ME/2305.19675\]](https://arxiv.org/abs/2305.19675). <https://doi.org/10.48550/arXiv.2305.19675>.
30. Schneider, S.; dos Reis, R.C.P.; Gottselig, M.M.F.; Fisch, P.; Knauth, D.R.; Vigo, A. Clayton copula for survival data with dependent censoring: an application to a tuberculosis treatment adherence data. *Stat. Med.* **2023**, *42*, 4057–4081. <https://doi.org/10.1002/sim.9858>, doi:10.1002/sim.9858.
31. Sun, T.; Ding, Y. Copula-based semiparametric regression method for bivariate data under general interval censoring. *Biostatistics* **2021**, *22*, 315–330. <https://doi.org/10.1093/biostatistics/kxz032>, doi:10.1093/biostatistics/kxz032.
32. Moradian, H.; Larocque, D.; Bellavance, F. Survival forests for data with dependent censoring. *Stat. Methods Med. Res.* **2019**, *28*, 445–461. <https://doi.org/10.1177/0962280217727314>, doi:10.1177/0962280217727314.
33. Farzana, W.; Basree, M.M.; Diawara, N.; Shboul, Z.A.; Dubey, S.; Lockhart, M.M.; Hamza, M.; Palmer, J.D.; Iftikharuddin, K.M. Prediction of Rapid Early Progression and Survival Risk with Pre-Radiation MRI in WHO Grade 4 Glioma Patients. *Cancers* **2023**, *15*. <https://www.mdpi.com/2072-6694/15/18/4636>, doi:10.3390/cancers15184636.

34. Escarela, G.; Carrière, J.F. Fitting competing risks with an assumed copula. *Stat. Methods Med. Res.* **2003**, *12*, 333–349. <https://doi.org/10.1191/0962280203sm335ra>, doi:10.1191/0962280203sm335ra.
35. Chen, Y.H. Semiparametric marginal regression analysis for dependent competing risks under an assumed copula. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **2010**, *72*, 235–251. <https://doi.org/10.1111/j.1467-9868.2009.00734.x>, doi:10.1111/j.1467-9868.2009.00734.x.
36. Shih, J.H.; Emura, T. Likelihood-based inference for bivariate latent failure time models with competing risks under the generalized FGM copula. *Comput. Statist.* **2018**, *33*, 1293–1323. <https://doi.org/10.1007/s00180-018-0804-0>, doi:10.1007/s00180-018-0804-0.
37. Shih, J.H.; Konno, Y.; Chang, Y.T.; Emura, T. Estimation of a common mean vector in bivariate meta-analysis under the FGM copula. *Statistics* **2019**, *53*, 673–695. <https://doi.org/10.1080/02331888.2019.1581782>, doi:10.1080/02331888.2019.1581782.
38. Shih, J.H.; Konno, Y.; Chang, Y.T.; Emura, T. Copula-Based Estimation Methods for a Common Mean Vector for Bivariate Meta-Analyses. *Symmetry* **2022**, *14*. <https://www.mdpi.com/2073-8994/14/2/186>, doi:10.3390/sym14020186.
39. Dobler, D.; Pauly, M. Factorial analyses of treatment effects under independent right-censoring. *Stat. Methods Med. Res.* **2020**, *29*, 325–343. <https://doi.org/10.1177/0962280219831316>, doi:10.1177/0962280219831316.
40. Emura, T.; Ditzhaus, M.; Dobler, D.; Murotani, K. Factorial survival analysis for treatment effects under dependent censoring. *Stat. Methods Med. Res.* **2024**, *33*, 61–79. <https://doi.org/10.1177/09622802231215805>, doi:10.1177/09622802231215805.
41. Moore, D.F. *Applied survival analysis using R*; Vol. 473, Springer, 2016.
42. Greenland, S.; Fay, M.P.; Brittain, E.H.; Shih, J.H.; Follmann, D.A.; Gabriel, E.E.; Robins, J.M. On causal inferences for personalized medicine: how hidden causal assumptions led to erroneous causal claims about the *D*-value. *Amer. Statist.* **2020**, *74*, 243–248. <https://doi.org/10.1080/00031305.2019.1575771>, doi:10.1080/00031305.2019.1575771.
43. Yin, Y.; Cai, Z.; Zhou, X.H. Using secondary outcome to sharpen bounds for treatment harm rate in characterizing heterogeneity. *Biom. J.* **2018**, *60*, 879–892. <https://doi.org/10.1002/bimj.201700049>, doi:10.1002/bimj.201700049.
44. SUSAM, S.O. A multi-parameter Generalized Farlie-Gumbel-Morgenstern bivariate copula family via Bernstein polynomial. *Hacettepe Journal of Mathematics and Statistics* **2022**, *51*, 618–631. <https://doi.org/10.15672/hujms.993698>, doi:10.15672/hujms.993698.

**Disclaimer/Publisher’s Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.