

Clayton Copula Gamma Weibull Distribution for Modeling Semi-Competing Risk Bone Marrow Transplant Data

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ABSTRACT

Semi-competing risks data arise frequently in survival analysis when individuals are subject to two related events: a non-terminal event and a terminal event, where the occurrence of the terminal event prevents the subsequent observation of the non-terminal event, whereas the reverse is not true. This asymmetric dependence structure is particularly relevant in medical studies, including bone marrow transplant (BMT) data, where the onset of acute graft-versus-host disease (acute GVHD) may be associated with the time to death. Conventional survival models often analyze each event time separately and therefore may fail to capture the underlying dependence structure adequately, especially when the marginal distributions differ in form and the dependence is nonlinear. To address this limitation, the present study proposes a new joint distribution based on the Clayton copula combined with Gamma and Weibull marginal for modeling semi-competing risks data. Specifically, the non-terminal event time T_1 is assumed to follow a Gamma distribution, while the terminal event time T_2 is assumed to follow a Weibull distribution, and their dependence is modeled through the Clayton copula. The study derives the main statistical properties of the proposed Clayton Copula Gamma–Weibull model, including the joint cumulative distribution function, joint probability density function, survival function, and hazard function. Model parameters are estimated using the maximum likelihood method. The proposed model is then applied to bone marrow transplant data from the Semi Comp Risks package, involving (137) patients, where acute GVHD is treated as the non-terminal event and death as the terminal event. Goodness-of-fit results for the marginal distributions indicate that the Gamma distribution provides an adequate fit for T_1 , while the Weibull distribution adequately fits T_2 . Furthermore, comparison among alternative copula-based specifications shows that the proposed Gamma–Weibull Clayton copula model achieves the best performance, with the highest log-likelihood and the lowest AIC and BIC values. The Cramér–von Mises copula goodness-of-fit test also supports the adequacy of the proposed model. The results demonstrate that the Clayton copula effectively captures positive lower-tail dependence between acute GVHD occurrence and death time, providing a more realistic representation of the temporal association between the two events. In addition, the close agreement between theoretical and maximum likelihood estimated survival values confirms the stability and practical suitability of the model. Overall, the proposed Clayton Copula Gamma–Weibull distribution offers a flexible and efficient framework for analyzing semi-competing risks data and provides a valuable statistical tool for studying complex dependent event-time outcomes in medical applications.

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1. Introduction

Semi-competitive risk data are complex in survival analysis because they involve a non-terminal event that may precede or coincide with the terminal event, while the occurrence of the terminal event precludes the observation of the non-terminal event afterward. This type of data makes the assumption of time independence unrealistic in many medical applications, particularly in bone marrow transplant data, where the time of onset of immune complications such as acute graft-versus-host disease (GVHD) is directly or indirectly related to time of death. Although traditional survival analysis models can represent each event individually using appropriate MARGINAL DISTRIBUTIONS, they often fail to accurately characterize the inter-term dependency structure, especially when the relationship is non-linear or tail-centered. Hence the need for more flexible models, such as copula models, which separate MARGINAL DISTRIBUTIONS from the dependency structure and allow for the construction of a combined distribution capable of representing the true relationship between

the two events. The research problem lies in the inadequacy of traditional or constrained covariate models to describe the dependency between the time of the non-final event and the time of the final event in semi-competing risk data, especially when the MARGINAL DISTRIBUTIONS of the two events differ in form and behavior.

COPULA is a fundamental tool in probability theory and statistics, providing a flexible mathematical framework for representing the dependency structure between random variables in multidimensional models. It enables the separation of the study of the MARGINAL DISTRIBUTIONS of each individual variable from the study of the dependency structure between them, by linking these different MARGINAL DISTRIBUTIONS within a common function that describes their interrelationship. The COPULA is distinguished by its ability to handle non-homogeneous MARGINAL DISTRIBUTIONS, meaning that all variables do not necessarily have to follow the same type of distribution, unlike some traditional multidimensional distributions such as the multivariate normal distribution or the multidimensional Pareto distribution, which may assume symmetry or certain constraints on the form of the distributions. It is a methodologically effective alternative to traditional models, as it allows for a more precise characterization of dependency structures, including nonlinear dependencies and tail dependencies. This enhances the efficiency of statistical modeling in analyzing complex interactions between random variables. Therefore, COPULA is particularly important in many practical applications, especially in risk management, finance, insurance, data analysis, and medicine, where relationships between variables are highly complex and heterogeneous.

[Sklar \(1959\)](#) was the first to lay the mathematical foundation for the theory of correlation between multidimensional distributions and their functions, which he named the Copula function. [Clayton \(1978\)](#) then proposed one of the most famous of these functions, called the Clayton Copula. Later, [Fine et al. \(2001\)](#) employed the Clayton Copula function in the analysis of semi-competing risk data, using this function to correlate the time of the non-final event with the time of the final event in order to describe the degree of correlation or dependence between events and their timing. In doing so, they established a fundamental starting point for building a model of the Copula function that can describe the strength of the dependence between events and their timing. [Han et al. \(2023\)](#) proposed Methods for estimating correlation using copula models for controlled survival data were presented. Estimation algorithms based on the pseudo-likelihood method were discussed, the theoretical properties of the proposed methods were explained, and their efficiency was evaluated through Monte Carlo simulation studies. The methods were applied to a real dataset of 137 patients who underwent bone marrow transplantation, 81 of whom died after leukemia recurrence, while only two died without recurrence. The data for the remaining 54 patients were incomplete and designated T1 as the time from transplantation to leukemia recurrence, and T2 as the time from transplantation to death. The accuracy and effectiveness of the estimates were demonstrated through simulation experiments in different controlled situations. For real data, the copula function was found to be very suitable for analyzing complex survival data.

[Novianti et al. \(2021\)](#) used the Clayton Copula function to analyze the relationship between the COVID-19 outbreak and maximum temperature in Jakarta, Indonesia, using daily data including cumulative and new cases and deaths related to COVID-19, in addition to maximum temperature data from the Kemuyuran Air Station in Jakarta during the period from March 13 to August 31, 2020. A strong correlation was found between maximum temperature and the COVID-19 pandemic based on the Clayton Copula model, and small values of the coefficients in the Copula function indicate a weak correlation between COVID-19 and maximum temperature.

[Tang et al. \(2013\)](#) proposed a new development of the Clayton Copula family by suggesting a two-parameter bivariate copula instead of the traditional single-parameter formula. This aimed to provide a more flexible model for representing inter-variable dependency structures, particularly in reliability analysis applications. They concluded that the proposed model represents a more flexible and efficient generalization of the Clayton two-parameter copula, offering better performance in inter-event dependency modeling while maintaining the original copula's theoretical structure as a special case. The significance of this research stems from the importance of modeling semi-competing risk data, which appears in many medical applications, especially in survival studies related to bone marrow transplant patients, where different medical events overlap and the relationship between them is not independent. Understanding the relationship between the time of onset of acute graft-versus-host disease (GVHD) and time of death is crucial in medical statistical analysis, as it plays a significant role in interpreting disease progression and evaluating treatment outcomes. The research is also significant for its use of Copula models, particularly the Clayton Copula model, which provides a flexible framework for separating MARGINAL DISTRIBUTIONS from the inter-variable dependency structure. This allows for more accurate modeling of complex time relationships compared to traditional models. Furthermore, the research presents a new combined model based on the Gamma and Weibull distributions, offering a more efficient statistical tool for representing and analyzing real data. In practical terms, the proposed model helps improve the understanding of the time-dependent relationship between medical events and provides more accurate statistical results applicable to medical studies, survival analysis research, and semi-competitive risk data. This research aims to construct a Clayton-Copula Gamma-Weibull joint probability distribution to represent the dependency relationship between the time to non-final event and the time to final

event in semi-competing risk data. This is achieved by linking different MARGINAL DISTRIBUTIONS using the Clayton-Copula correlation function, where the non-final event time (T1) is represented by a Gamma distribution and the final event time (T2) by a Weibull distribution. The fundamental statistical properties of this distribution are then derived, such as the joint probability density function, the cumulative distribution function, the survival function, and the joint risk function. The research also seeks to estimate the model parameters using the maximum likelihood method and evaluate its suitability for real-world bone marrow transplant patient data. This is done by comparing theoretical results with experimental estimates and conducting fitting tests to verify the proposed model's ability to more accurately and realistically represent the dependency structure between the time to acute GVHD and the time to death within the framework of semi-competing risk data analysis.

2. Semi-Competing Risks Data

Competing risks are a concept in survival analysis. They occur when an individual is exposed to more than one possible event, and the occurrence of one of these events prevents or changes the probability of the occurrence of the other events. Mathematically, it is assumed that there are K competing events with times that cannot be directly observed, which we denote as $T_1, T_2, \dots, T_K$. However, these times cannot all be observed at the same time. Rather, we observe only the time $T = \min(T_1, T_2, \dots, T_K)$, which is the time of the first event that occurs, in addition to the variable $\varepsilon \in \{1, 2, \dots, K\}$ that determines the type of event that actually occurred. This means that the observed data is the pair T, ε . Semi-competing risks are an extension of competing risks data, and they arise when an individual is exposed to two possible events, one of which is a non-terminal event and the other a terminal event, such that the terminal event can monitor or prevent the observation of the non-terminal event, while the non-terminal event does not have the ability to monitor or prevent the occurrence of the terminal event. This asymmetric property is the distinguishing feature between semi-competing risks and competitive risk, in which all events are final and mutually exclusive.

3. The Copula Function

This is a powerful tool for describing the interdependence of random variables. It was introduced by Sklar (1959) and has gained significant importance in various fields such as finance, insurance (Joo et al., 2020), hydrology, genetics, neuroscience, environmental science, communications, and reliability engineering (Chesneau, 2024). It is a multivariable cumulative distribution function where the marginal probability distribution for each variable is defined on the interval $[0, 1]$ (Peres et al., 2020, 1). The term is derived from the Latin word (COPULA) meaning to connect or link and is used to describe or model the interdependence (or correlation) between random variables, i.e., the shared relationship or interaction between different variables. It is a means of understanding how variables affect each other, even though each variable has its own probability distribution (Schmidt, 2007). It is an important function in statistics, serving as a valuable tool for statisticians for two main reasons: first, as a means of studying the relationship between variables regardless of the units of measurement; and second, as a starting point for constructing families of bivariate distributions (Ahmed et al., 2021). The foundation of copula theory rests on Sklar's Theorem, which states that any multivariate distribution can be resolved into its MARGINAL DISTRIBUTIONS, allowing researchers and practitioners to independently analyze dependency behaviors, thus contributing to a more accurate understanding of complex data.

4. Mathematical Model for Copula Function

Let us have a random variable vector $X = (X_1, X_2, \dots, X_d)$ for each of which has a continuous cumulative distribution function $p(X \leq x_i) = F_i(X_i)$. By using the probability integral transform on each component of the random vector, we obtain a new random vector as follows (Berg & Bakken, 2005; Durante & Sempi, 2005; Joo et al., 2020):

$$U = (U_1, U_2, \dots, U_d)$$

where $U_i = F_i(X_i)$ for all $i = 1, 2, \dots, d$, which has regular MARGINAL DISTRIBUTIONS, i.e. $U_i \sim \text{uniform}(0,1)$

The copula function is a joint cumulative distribution function (Joint CDF) of the random vector $U = (U_1, U_2, \dots, U_d)$ that determines the joint distribution of these variables, i.e., where:

$$C(U) = C(u_1, u_2, \dots, u_d) = p(U \leq u_1, U \leq u_2, \dots, U \leq u_d) = F_i(X_i)$$

Which contains all the information related to the dependency structure between the components of vector X , while the boundary distribution functions $F_i(X_i)$ contain all the information related to the MARGINAL DISTRIBUTIONS of the variables X_i .

The range of this function is $I^d = [0, 1]^d$ and its corresponding range is $[0, 1]$, where I^d is the space consisting of all

possible points that can take values within the interval $[0, 1]$ in each component of the d -dimensional space. This is called the unit square of d -dimensional space, which is $I \times I \times \dots \times I$, used to denote a d -dimensional domain or a set of d pairs of values, and which represents the Cartesian product of the d domain, which may represent a set of values used to relate multidimensional probability distributions $X_1, X_2, \dots, X_d$ of multiple distributions (Durante & Sempi, 2005; Geenens, 2024).

This means that the cumulative distribution of COPULA must take into account the special equality relating to the probability of random variables falling within a multidimensional rectangle, a condition that ensures that COPULA provides valid probabilities, i.e., the probabilities cannot be negative (non-negative). Using the principle of the inverse of the cumulative function $F_i^{-1}(X_i)$ to generate random samples from the general classes of multidimensional probability distributions, the required sample can be constructed from the COPULA function as follows:

$$(X_1, X_2, \dots, X_d) = p\left(F_1^{-1}(U_1), F_2^{-1}(U_2), \dots, F_d^{-1}(U_d)\right)$$

Then,

$$C(u_1, u_2, \dots, u_d) = p(X_1 \leq F_1^{-1}(u_1), X_2 \leq F_2^{-1}(u_2), \dots, X_d \leq F_d^{-1}(u_d))$$

The COPULA function has the following properties:

- Since cumulative distribution functions (cdfs) are always increasing, $C(u_1, u_2, \dots, u_d)$ increases for each u_i component.
- The marginal distribution of component i is obtained by setting $u_j = 1$ for each $i \neq j$, and it must be uniformly distributed as follows:

$$C(1, \dots, 1, u_i, \dots, 1) = u_i$$

- For every $a_i \leq b_i$, the probability is:
- $p(U_1 \in [a_1, b_1], \dots, U_d \in [a_d, b_d])$

It must be non-negative and lead to a trigonometric inequality, as follows:

$$\sum_{i_1=1}^2 \dots \sum_{i_d=1}^2 (-1)^{i_1 + \dots + i_d} C(u_{1,i_1}, \dots, u_{d,i_d}); u_{j1} = a_j, u_{j2} = b_j$$

- If we have a d -dimensional COPULA function, then $C(1, u_1, \dots, u_{d-1})$, i.e., holding one component in place, the resulting function is also a $d-1$ -dimensional COPULA function. This property makes high-dimensional COPULA functions easier to analyze, because it allows us to study simpler cases (such as two-dimensional capillaries) and then extend from them into broader inferences relating to multi-dimensional copulas. Any function that meets these characteristics is a copula function. Figure (1) shows the copula function with dimension d .

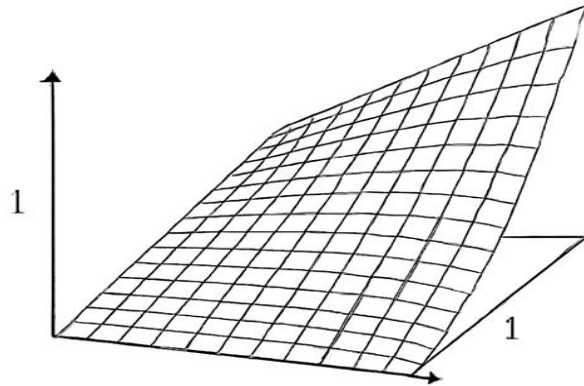


Figure 1: Graph of a d -dimension Copula Function

5. Sklar's Theorem

This theorem, introduced by Sklar (1959), lays the foundation for understanding how copula functions are used in statistics and probability modeling. It highlights how a copula function can be used to couple a joint distribution function to univariate marginal distributions. It is the basis of coupling theory and a cornerstone in many statistical applications (Geenens, 2024). The theorem states that a copula function is a single function when the marginal distributions are continuous. This ensures that, in the case of continuous distributions, a single copula function can be used to couple the marginal distributions in a specific way (Torgersen, 1974). It states that any joint distribution function can be represented

as a copula function that couples the joint distribution functions of the marginal distributions for each random variable, thus facilitating dependency analysis between variables. In other words, if you have marginal distribution functions for two variables, Sklar's theorem allows you to construct a joint distribution function using a copula function. This theorem is of great importance because it allows the separation of complex co-variances into their simpler components (marginal and COPULA distributions), thus facilitating the understanding of the relationship between random variables. It also provides an effective method for studying the dependencies between different variables, making it a powerful tool in fields such as financial risk management, statistical analysis, and probability modeling. This is especially true if the marginal distribution functions are continuous, as the COPULA distribution is unique, which enhances the accuracy of statistical models (Durante & Sempi, 2005).

Let F be the cumulative distribution function with dimension d , with univariate boundary cumulative functions $F_1, F_2, \dots, F_d$, A_j refer to the range of F_j such that $F_j := F_j(\bar{R})$, $j=1, 2, \dots, d$. Therefore, there exists a function C for every $(x_1, x_2, \dots, x_d) \in \bar{R}^d$ such that C is uniquely determined on $A_1 \times A_2 \times \dots \times A_d$ when $F_1, F_2, \dots, F_d$ is continuous.

The copula function can be obtained from equation (1) as follows:

$$F(x_1, x_2, \dots, x_d) = C(F_1(x_1), F_2(x_2), \dots, F_d(x_d)) \quad (1)$$

F_i^{-1} is pseudo-inverse of F_i , which refers to the function that can be used to invert the cumulative distribution function F_i when we don't need to invert the distribution function directly, but rather pseudo-inversely, such that

$$F_i^{-1} = \inf\{t \mid F_i(t) \geq s\} \quad (2)$$

Where s in the equation is a probability value between 0 and 1, representing the probability for which we want to invert the distribution function. Therefore, copula is a primary method for transforming a random variable $(X_1, X_2, \dots, X_d)$ into another random variable:

$$(U_1, U_2, \dots, U_d) = (F_1(x_1), F_2(x_2), \dots, F_d(x_d)) \quad (3)$$

With uniform MARGINAL DISTRIBUTIONS on I , inter-component dependencies are preserved. Uniform MARGINAL DISTRIBUTIONS on $[0,1]$ are a type of allocation used to make each component in a multidimensional space follow a uniform distribution, but the copula itself describes the interdependencies between these components. When we say that inter-component dependencies are preserved, we mean that even though uniform MARGINAL DISTRIBUTIONS are used, the interdependencies between random variables are not lost and remain as they were in the original distribution. According to this theory, any COPULA can be combined with different one-dimensional distribution functions to obtain a distribution function with a dimension d using equation (3). Therefore, capillaries can be used to model cases requiring a different distribution for each component, providing a valid alternative to many traditional multidimensional distribution functions such as the Gaussian, Pareto, Gamma, and others (Durante & Sempi, 2005).

6. Clayton Copula

This is one of the functions used to correlate multidimensional random variables and determine the relationships between their distributions, especially in statistical modeling of dependent (correlated) data. It is primarily used in models that deal with correlations between variables that may be asymmetric (Embrechts et al., 2003).

There are several methods for constructing a COPULA function (Sklar/Elliptical, Archimedean, Hierarchical, and Empirical). One of the methods that describe dependency clearly and accurately is the Archimedean method, which relies on a generator function denoted by $\psi(t)$. This generator function controls the dependency structure between the variables. It is a function with a range of $[0, \infty)$ domain of $[0, 1]$ (Embrechts et al., 2003; Müller & Scarsini, 2005), $\psi(t): [0, \infty) \rightarrow [0, 1]$

The function is convex to ensure that 2-increasing condition ensures non-negativity. It is monotonically increasing and reversible, and $t \in [0, 1]$ because φ must be decreasing, φ^{-1} then increases. This ensures that the copula is not decreasing with the order of probabilities if both u and v increase and satisfy the condition that $\psi(1) = 0$, $\lim_{t \rightarrow \infty} \psi(t) = 0$ to ensure that φ does not exceed 1 at $t=0$, the value of θ increases as it grows, resulting in $u=0$ and $v=0$ at the extremes $\varphi^{-1}(0^+) = \infty^+$. Then,

$$C(0, v) = \varphi(\varphi^{-1}(0) + \varphi(v)) = \varphi(\infty^+) = 0, \text{ and}$$

$$C(u, 0) = \varphi(\varphi^{-1}(u) + \varphi(0)) = \varphi(\infty^+) = 0$$

This is a boundary behavior for copula because we want the margins $C(u, 1) = u$ and $C(1, v) = v$, we observe that $\varphi^{-1}(1) =$ because $\varphi(0) = 1$. That is, the zero point in the range of φ corresponds to the 1 point in its domain. Therefore,

$$\begin{aligned} C(u, v) &= \varphi^{-1}(\varphi(u) + \varphi(1)) \\ &= \varphi^{-1}(\varphi(u)) = u \end{aligned}$$

$$\begin{aligned} C(u, v) &= \varphi^{-1}(\varphi(1) + \varphi(v)) \\ &= \varphi^{-1}(\varphi(v)) = v \end{aligned}$$

If $\varphi(0) = 1$ is not satisfied, we will not obtain regular margins, and the function will fail to be capacitive. This is all to ensure that $C \neq 0$, and then the binary copula function is then defined as follows:

$$C(u, v) = \psi(\psi^{-1}(u) + \psi^{-1}(v)) \quad (4)$$

If we use $\varphi = \psi^{-1}(u)$, we get the follows:

$$C(u, v) = \varphi^{-1}(\varphi(u) + \varphi(v)) \quad (5)$$

The standard form of the Clayton copula function is derived, assuming $\theta > 0$, from the following perfect generative function (McNeil & Nešlehová, 2009):

$$\varphi(t) = t^\theta - 1; t \in (0, 1]$$

The reason for using this function in constructing the COPULA is that it controls the degree of nonlinear dependence between variables. When θ is close to zero, t^θ approaches 1 for each $t \in [0, 1]$, and therefore $\varphi(t) = 0$. In this case, $\varphi(u_1) + \varphi(u_2)$ remains constant, and consequently, $C(u, v) \approx u_1 u_2$, i.e., a very weak or near-independence dependence. As θ increases, t^θ decreases more rapidly as t approaches 0. This means that small values of u_1 , i.e., extreme events in the lower tail become more clustered, which is called lower-tail dependence. That is, the two variables tend to be small together and have low concurrent values (Pramanik, 2024).

This means that whenever θ changes, the rate of decrease of $\varphi(t)$ changes, and the amount of contribution of each variable to the sum $\varphi(u_1) + \varphi(u_2)$ changes, and thus the shape of the curvature in the final COPULA function changes, which practically means a change in the degree and shape of the nonlinear correlation between the variables (Kato et al., 2022).

Let,

$$\begin{aligned} s &= \varphi(t) = t^\theta - 1 \Rightarrow t = (1 + s)^{-\frac{1}{\theta}} \\ \therefore \varphi^{-1}(t) &= (1 + s)^{-\frac{1}{\theta}}; s < 0 \end{aligned}$$

If we put $\varphi(u) = u^{-\theta} - 1$ and $\varphi(v) = v^{-\theta} - 1$ then,

$$\begin{aligned} C(u, v) &= \varphi^{-1}(u^{-\theta} - 1 + v^{-\theta} - 1) \\ &= \varphi^{-1}(u^{-\theta} + v^{-\theta} - 2) \end{aligned}$$

Adding 1 to the bracket inside equation (5) as a result of inverting the inverse generator function $t = (1 + s)^{-\frac{1}{\theta}}$ yields:

$$\begin{aligned} C(u, v) &= \varphi^{-1}(u^{-\theta} + v^{-\theta} - 2 + 1) \\ &= \varphi^{-1}(u^{-\theta} + v^{-\theta} - 1) \end{aligned} \quad (6)$$

7. Probability Density for Clayton Copula

We begin with the Copula function $c(u, v)$, a joint cumulative function (Joint CDF). From this function, we find the joint distribution or joint probability density (JPDF) by differentiating it. The first derivative of the function $\partial C / \partial v$, $\partial C / \partial u$ gives us the conditional cumulative function (CDF), which represents a conditional probability for one of the variables. We differentiate again because the second derivative equals the final probability density. That is, when we differentiate the first time with respect to the variable u , the function remains incomplete. We need to differentiate again with respect to the variable v to obtain the Copula density function, as follows:

$$\frac{\partial^2 c(u, v)}{\partial u \partial v} = f_{uv}(u, v) \quad (7)$$

Equation (7) called the COPULA density function, which we need when we relate the marginals distributions $f_1(t_1)$, $f_2(t_2)$ to obtain the combined probability density for times T_1 and T_2 , as follows:

We have the following Cumulative distribution function (CDF) (Clayton copula):

$$C_\theta(u, v) = (u^{-\theta} + v^{-\theta} - 1)^{-\frac{1}{\theta}} \quad (8)$$

Then, $u = F_1(t_1)$, $v = F_2(t_2)$, where $u, v \in (0, 1)$ are the distributions of random variables, each of which has a cumulative probability function. $\theta > 0$ Dependency parameter that controls the strength of the correlation between the two variables

We take the first derivative of the equation with respect to u , and again with respect to v , to obtain the Clayton copula density function, as follows:

$$\begin{aligned} A(u, v) &= (u^{-\theta} + v^{-\theta} - 1) \\ \therefore C(u, v) &= (A(u, v))^{-\frac{1}{\theta}} \\ \frac{\partial C(u, v)}{\partial u} &= -\frac{1}{\theta} (A(u, v))^{-\frac{1}{\theta}-1} \cdot \frac{\partial A(u, v)}{\partial u} \\ \therefore \frac{\partial A(u, v)}{\partial u} &= -\theta u^{-\theta-1} \\ \therefore \frac{\partial C(u, v)}{\partial u} &= \left(-\frac{1}{\theta}\right) (u^{-\theta} + v^{-\theta} - 1)^{-\frac{1}{\theta}-1} \cdot -\theta u^{-\theta-1} \\ \frac{\partial C(u, v)}{\partial u} &= u^{-(\theta+1)} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+1\right)} \end{aligned} \quad (9)$$

Now we differentiate with respect to v as follows:

$$\begin{aligned} \frac{\partial C(u, v)}{\partial v} &= -\frac{1}{\theta} (A(u, v))^{-\frac{1}{\theta}-1} \cdot \frac{\partial A(u, v)}{\partial v} \\ \therefore \frac{\partial A(u, v)}{\partial v} &= -\theta v^{-\theta-1} \\ \therefore \frac{\partial C(u, v)}{\partial v} &= \left(-\frac{1}{\theta}\right) (u^{-\theta} + v^{-\theta} - 1)^{-\frac{1}{\theta}-1} \cdot -\theta v^{-\theta-1} \\ \frac{\partial C(u, v)}{\partial v} &= v^{-(\theta+1)} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+1\right)} \end{aligned} \quad (10)$$

Now we find the second derivative to extract the Clayton copula density function as follows:

$$\begin{aligned} C(u, v) &= \frac{\partial^2 C(u, v)}{\partial u \partial v} \\ \frac{\partial^2 C(u, v)}{\partial u} &= \frac{\partial^2}{\partial u} \left(u^{-\theta-1} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+1\right)} \right) \\ &= (\theta + 1) u^{-\theta-1} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+2\right)} \end{aligned}$$

Now we extract the previous equation with respect to the variable v to find $\frac{\partial^2 C(u, v)}{\partial v}$

$$\begin{aligned} \frac{\partial^2 C(u, v)}{\partial v} &= \frac{\partial^2}{\partial v} \left(v^{-\theta-1} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+1\right)} \right) \\ &= (\theta + 1) v^{-\theta-1} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+2\right)} \\ \therefore \frac{\partial^2 C(u, v)}{\partial u \partial v} &= (\theta + 1) (uv)^{-(\theta+1)} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+2\right)} \end{aligned}$$

According to Sklar's Theorem,

$$f_{T_1, T_2}(t_1, t_2) = c(F_1(t_1), F_2(t_2)) \cdot f_1(t_1) \cdot f_2(t_2) \quad (11)$$

Therefore, the combined probability density function for u and v , based on the Clayton Copula function, becomes as follows (Adu-Ntim, 2025; Tang et al., 2013):

$$f_{T_1, T_2}(t_1, t_2) = (\theta + 1) (uv)^{-(\theta+1)} (u^{-\theta} + v^{-\theta} - 1)^{-\left(\frac{1}{\theta}+2\right)} \cdot f_1(t_1) \cdot f_2(t_2) \quad (12)$$

8. Clayton-Copula Gamma-Weibull Distribution

Let $T_1 = \{t_{11}, t_{12}, \dots, t_{1n}\}$ be a random variable with a gamma distribution in parameters α, λ , i.e., $T_1(t) \sim \text{gama}(\alpha, \lambda)$ with the following probability density function,

$$f_1(t_1) = \frac{\lambda^\alpha}{\Gamma(\alpha)} t_1^{\alpha-1} e^{-\lambda t_1}; t_1 > 0 \quad \alpha, \lambda > 0 \quad (13)$$

With Cumulative distribution function (CDF),

$$u = F_1(t_1) = \frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \quad t_1 \geq 0 \quad (14)$$

Where $\gamma(\alpha, \lambda t)$ is an incomplete gamma function (Lower Incomplete Gamma Function)

Let $T_2 = \{t_{21}, t_{22}, \dots, t_{2n}\}$ be a random variable with a Weibull distribution given the parameters k, β , i.e., $T_2(t_2) \sim \text{Weibull}(k, \beta)$ with the following probability density function,

$$f_2(t_2) = \frac{k}{\beta} \left(\frac{t_2}{\beta}\right)^{k-1} e^{-\left(\frac{t_2}{\beta}\right)^k}; t_2 > 0, k, \beta > 0 \quad (15)$$

Where k is the shape parameter, β is the scale parameter,

The Cumulative distribution function (CDF):

$$v = F_2(t_2) = 1 - e^{-\left(\frac{t_2}{\beta}\right)^k} \quad (16)$$

Using equation (12) together with Equations (13) and equation (16), we obtain the joint probability density function for the two variables T_1, T_2 .

$$\begin{aligned} \therefore f_{T_1, T_2}(t_1, t_2, \alpha, \lambda, \beta, k, \theta) &= (1 + \theta) \left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \left(1 - e^{-\left(\frac{t_2}{\beta}\right)^k} \right) \right)^{-(\theta+1)} \\ &\quad \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_2}{\beta}\right)^k} \right)^{-\theta} - 1 \right)^{-\left(\frac{1}{\theta}+2\right)} \\ &\quad \left(\frac{\lambda^\alpha}{\Gamma(\alpha)} (t_1)^{\alpha-1} e^{-\lambda t_1} \right) \left(\frac{k}{\beta} \left(\frac{t_2}{\beta}\right)^{k-1} e^{-\left(\frac{t_2}{\beta}\right)^k} \right) \\ &\quad \alpha, \beta, \lambda, k, \theta > 0, t_1, t_2 > 0 \end{aligned} \quad (17)$$

Where t_1 the first random variable (first event), t_2 : the second random variable (second event), α, k the shape parameters, β : scale parameter, λ rate parameter, θ the dependency parameter of the Clayton Copula, which controls the strength of the correlation between events.

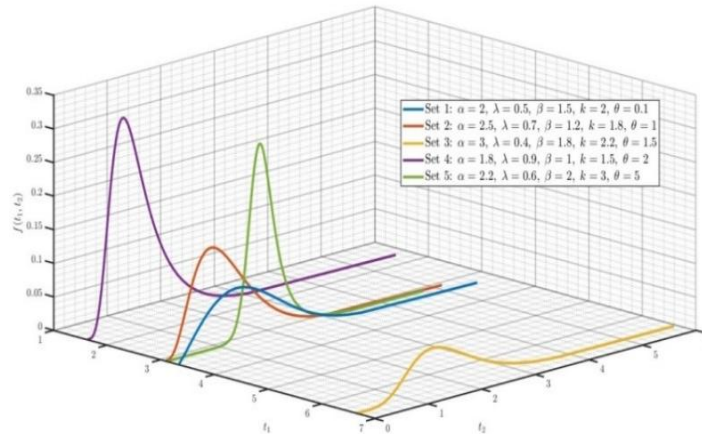


Figure 2: Shows the Curves of the Joint Probability Density Function for the Clayton-Copula Gamma-Weibull Distribution at Different Parameter Values

The figure illustrates the behavior of the co-density function $f_{T_1, T_2}(t_1, t_2)$ resulting from the correlation of the boundary distribution $T_1 \sim \text{Gamma}(\alpha, \lambda)$ and the boundary distribution $T_2 \sim \text{Weibull}(\beta, k)$ using the Clayton Copula function. The parameter θ plays a crucial role in determining the nature of the dependence between the two variables, controlling the strength of the correlation, particularly the degree of dependence in the lower tail. This means that the probability of both events occurring simultaneously at short time points increases as the value of θ increases. Its effect does not alter the MARGINAL DISTRIBUTIONS themselves but only affects the structure of the dependence between the two variables. When $\theta \rightarrow 0$, the distribution approaches independence, where the Copula becomes approximately equivalent to the product of the two MARGINAL DISTRIBUTIONS, indicating no dependence between T_1 and T_2 . The co-density is then more expansive, and no clear concentration is observed in the lower corner of the graph. When $\theta < 2$, positive correlation begins to appear at small and medium values of θ . The probability of the two variables occurring together increases, and the co-intensity gradually rises in the region near the origin, with a slight tendency towards concentration in the lower tail. When $\theta > 2$, the higher the value of θ , the stronger the positive correlation between the two variables becomes, and the correlation in the lower tail becomes clear and dominant. Sharp peaks in co-intensity appear near small values, and the probability of the two events occurring together increases in the lower extremes.

Figure (2) shows that some curves exhibit a noticeable extension in the right direction, i.e., a long right tail in the common density function. This is because the two MARGINAL DISTRIBUTIONS used the Gamma distribution for variable T_1 and the Weibull distribution for variable T_2 , are positively skewed distributions, and therefore allow for large values with relatively non-negligible probability. In the Gamma distribution, the tail's behavior is primarily determined by the rate coefficient λ , where a decrease in its value slows the exponential decrease in density, resulting in a longer right tail. Similarly, in the Weibull distribution, the value of the shape coefficient k affects the rate of decrease. Smaller values of k lead to a slower decrease in density and a greater extension of the tail. Regarding dependency, the Clayton Copula is characterized by the presence of a Lower Tail Dependence without an Upper Tail Dependence. Mathematically, the Lower Tail Dependence is measured by the coefficient $\lambda_L = 2^{-\frac{1}{\theta}}$, and this dependence increases with the increasing value of θ . However, the Clayton Copula does not generate similar dependence at large values, which means that the behavior of the right tail in the common distribution is not directly affected by the increase in θ , but remains subject to the properties of MARGINAL DISTRIBUTIONS. Accordingly, the noticeable extension of the curves in the right part of the graph can be interpreted as a direct reflection of the nature of the MARGINAL DISTRIBUTIONS, especially at values that lead to a slowing of the exponential decrease, while the effect of θ is clearly visible in the region near the origin, where the combined probability density increases as a result of the enhanced dependence in the lower tail. Thus, the tail behavior in this distribution is a result of an interaction between the shape of the MARGINAL DISTRIBUTIONS on the one hand, and the structure of the dependence on the other, with the right extension being mainly related to the MARGINAL DISTRIBUTIONS, while the concentration near small values is related to the dependence parameter θ .

The common Cumulative distribution function (CDF) for the distribution, based on equation (8), (14) and equation (16), is written as follows:

$$F_{T_1, T_2}(t_1, t_2) = \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_2}{\beta} \right)^k} \right)^{-\theta} - 1 \right)^{-\frac{1}{\theta}} \quad (18)$$

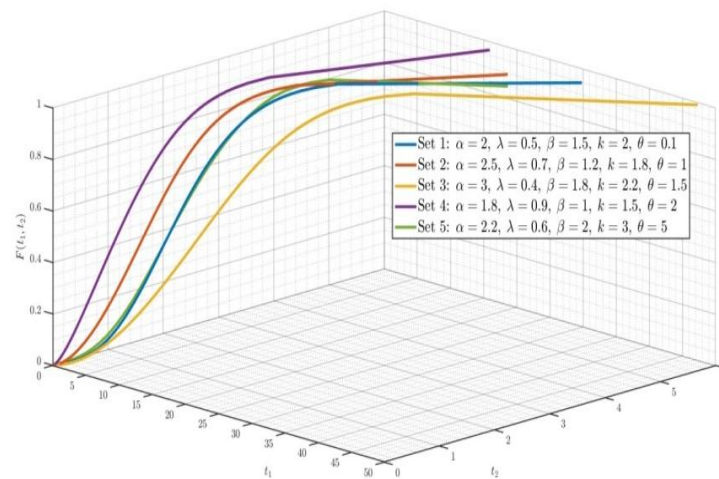


Figure 3: Shows the Curves of the Joint Cumulative distribution function (CDF) for the Clayton-Copula Gamma-Weibull Distribution at Different Parameter Values

The reliability function for the distribution is as follows:

$$R_{T_1, T_2}(t_1, t_2) = 1 - \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_2}{\beta} \right)^k} \right)^{-\theta} - 1 \right)^{-\frac{1}{\theta}} \quad (19)$$

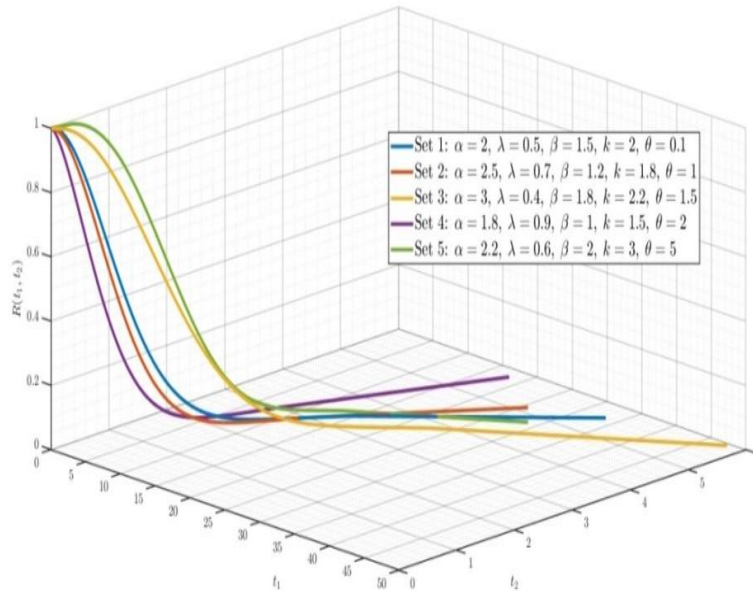


Figure 4: Shows the Curves of Reliability Function for the Clayton Copula Gamma-Weibull Distribution at Different Parameter Values

The Hazard function is as follows:

$$h_{T_1, T_2}(t_1, t_2) = \frac{f_{T_1, T_2}(t_1, t_2)}{R_{T_1, T_2}(t_1, t_2)} = \frac{(1+\theta) \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right) \left(1 - e^{-\left(\frac{t_2}{\beta} \right)^k} \right) \right)^{-(\theta+1)} \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_2}{\beta} \right)^k} \right)^{-\theta} - 1 \right)^{-\left(\frac{1}{\theta} + 2 \right)} \left(\frac{\lambda^\alpha}{\Gamma(\alpha)} (t_1)^{\alpha-1} e^{-\lambda t_1} \right) \left(\frac{k}{\beta} \left(\frac{t_2}{\beta} \right)^{k-1} e^{-\left(\frac{t_2}{\beta} \right)^k} \right)}{1 - \left(\left(\frac{\gamma(\alpha, \lambda t_1)}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_2}{\beta} \right)^k} \right)^{-\theta} - 1 \right)^{-\frac{1}{\theta}}}$$

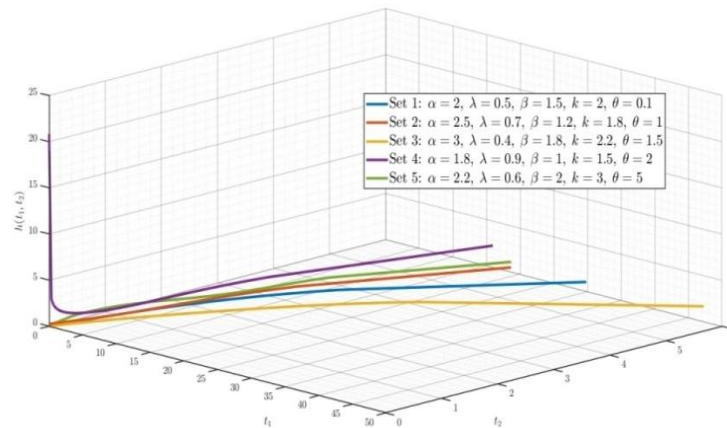


Figure 5: Shows the Curves of Hazard Function for the Clayton Copula Gamma-Weibull Distribution at Different Parameter Values

Figure (5) represents the risk function curves for the Clayton Copula Gamma-Weibull distribution, showing non-

boundary behavior when $t_1, t_2 \rightarrow 0$. This behavior reflects the intrinsic nature of the Clayton function, known for its strong dependence at small values compared to large ones. As time moves away from zero, the shape of the risk function is influenced by the boundary structure, particularly the WEIBULL distribution. If the shape parameter $k > 1$, the Whipple boundary risk increases with time, leading to a gradual upward trend in the bidirectional risk. Thus, the overall behavior of the function is characterized by a sharp initial rise due to the downward dependence, followed by a gradual increase governed by the properties of MARGINAL DISTRIBUTIONS, especially the shape parameter k . Increasing θ also raises the overall level of the function, i.e., increasing the intensity of the combined risk over time, reflecting the increasing strength of the correlation between the two events. Therefore, the binary risk function in this model can be described as unbounded at the origin, increasing with time when $k > 1$, increasing in intensity as θ increases, and clearly sensitive to the properties of the WEIBULL distribution, particularly the shape parameter that determines the pattern of risk evolution over time.

9. The maximum Likelihood Estimation

Let us have a random sample of t_1, t_2 with a Clayton Copula Gamma-Weibull distribution. Then the possibility function as follows:

$$L(\alpha, \lambda, \beta, k, \theta) = \prod_{i=1}^n \left((1 + \theta) \left(\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right) \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right) \right)^{-(\theta+1)} \left(\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1 \right)^{-\left(\frac{1}{\theta}+2\right)} \right) \left(\frac{\lambda^\alpha}{\Gamma(\alpha)} (t_{1i})^{\alpha-1} e^{-\lambda t_{1i}} \right) \left(\frac{k}{\beta} \left(\frac{t_{2i}}{\beta} \right)^{k-1} e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right) \quad (20)$$

The natural logarithm of both sides, we get:

$$\begin{aligned} l(\alpha, \lambda, \beta, k, \theta) = & n \ln(\theta + 1) - (\theta + 1) \sum_{i=1}^n \ln \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right) - (\theta + 1) \sum_{i=1}^n \ln \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right) - \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \ln \left[\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1 \right] \\ & + n \alpha \ln(\lambda) - n \ln(\alpha) + (\alpha - 1) \sum_{i=1}^n \ln(t_{1i}) - \lambda \sum_{i=1}^n \ln(t_{1i}) + n \alpha \ln(k) - n \ln(\beta) + (k - 1) \sum_{i=1}^n \ln(t_{2i}) - n(k - 1) \ln(\beta) \end{aligned} \quad (21)$$

The maximum Likelihood estimation for each parameter is obtained by solving the following system:

$$\frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \alpha} = 0, \quad \frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \lambda} = 0, \quad \frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \beta} = 0, \quad \frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial k} = 0, \quad \frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \theta} = 0$$

$$\begin{aligned} \frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \theta} = & \frac{n}{\theta + 1} - \sum_{i=1}^n \ln \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right) - \sum_{i=1}^n \ln \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right) + \frac{1}{\theta^2} \sum_{i=1}^n \ln \left[\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1 \right] \\ & - \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \frac{\ln \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right) \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \ln \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right) \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta}}{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1} \end{aligned} \quad (22)$$

$$\frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \lambda} = -(\theta + 1) \sum_{i=1}^n \frac{\frac{t_{1i}(\lambda t_{1i})^{\alpha-1} e^{-\lambda t_{1i}}}{\Gamma(\alpha)}}{\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)}} + \theta \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \frac{\left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta-1} \frac{t_{1i}(\lambda t_{1i})^{\alpha-1} e^{-\lambda t_{1i}}}{\Gamma(\alpha)}}{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1} + \frac{n\alpha}{\lambda} - \sum_{i=1}^n t_{1i} \quad (23)$$

$$\frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \alpha} = -(\theta + 1) \sum_{i=1}^n \frac{\frac{\partial \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)}{\partial \alpha}}{\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)}} + \theta \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \frac{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta-1} \frac{\partial \left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)}{\partial \alpha}}{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1} + n\lambda - n\psi(\alpha) + \sum_{i=1}^n \ln(t_{1i}) \quad (24)$$

$$\frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial \beta} = -(\theta + 1) \sum_{i=1}^n \frac{\frac{\partial}{\partial \beta} \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)}{1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k}} + \theta \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \frac{\left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta-1} \left[-\frac{k}{\beta} \left(\frac{t_{2i}}{\beta} \right)^k e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right]}{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1} + \frac{nk}{\beta} + \frac{k}{\beta} \sum_{i=1}^n \left(\frac{t_{2i}}{\beta} \right)^k e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \quad (25)$$

$$\frac{\partial l(\alpha, \lambda, \beta, k, \theta)}{\partial k} = -(\theta + 1) \sum_{i=1}^n \frac{e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \left(\frac{t_{2i}}{\beta} \right)^k \ln \left(\frac{t_{2i}}{\beta} \right)}{1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k}} + \theta \left(\frac{1}{\theta} + 2 \right) \sum_{i=1}^n \frac{\left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta-1} e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \left(\frac{t_{2i}}{\beta} \right)^k \ln \left(\frac{t_{2i}}{\beta} \right)}{\left(\frac{\gamma(\alpha, \lambda t_{1i})}{\Gamma(\alpha)} \right)^{-\theta} + \left(1 - e^{-\left(\frac{t_{2i}}{\beta}\right)^k} \right)^{-\theta} - 1} + \frac{n}{k} - n \ln(\beta) + \sum_{i=1}^n \ln(t_{2i}) - \sum_{i=1}^n \left(\frac{t_{2i}}{\beta} \right)^k \ln \left(\frac{t_{2i}}{\beta} \right) \quad (26)$$

10. Real Data Set

The Bone Marrow Transplant Data (BMT) from the (SemiCompRisks) package was used, which includes 137 patients on bone marrow transplantation (Bone Marrow Transplant Data) in years. The time of occurrence of acute graft-versus-host disease (AGVHD) was defined as the non-terminal event T_1 , which is an immune complication that may occur after bone marrow or stem cell transplantation. This occurs when the immune system cells coming from the donor (graft) recognize the patient's (host's) body tissues as foreign bodies and attack them. The time of death was defined as the terminal event T_2 , depending on the variable T_1 . Then, the Gamma and Weibull distributions were used as MARGINAL DISTRIBUTIONS for the times of the two events and these MARGINAL DISTRIBUTIONS were correlated using the Clayton-Copula function to study the time dependency between these two events.

Table (1) and Figure (6) show the fit analysis of the MARGINAL DISTRIBUTIONS for the variables T_1 and T_2 in BMT bone marrow transplant data before constructing the combined distribution using Clayton Copula.

Table 1: Results of the Fit Analysis of the MARGINAL DISTRIBUTIONS for the Variables T_1 and T_2 in BMT Bone Marrow Transplant Data Before Constructing the Combined Distribution using Clayton Copula

Variable	Marginal Distribution	KS	P-Value	AD	P-Value
(T_1)	Gamma	0.084	0.200	0.421	0.173
(T_2)	Weibull	0.091	0.148	0.537	0.119

Table (1) and Figure (6) show that the Gamma distribution is suitable for representing the borderline distribution of the non-final event time T_1 , while the Weibull distribution is suitable for representing the borderline distribution of the final event time T_2 . This is because the probability value for each test is greater than the significance level of 0.01, indicating that the null hypothesis, which states that MARGINAL DISTRIBUTIONS are suitable for the studied variables, is not supported. This verification is a crucial step before constructing the combined distribution $f(t_1, t_2)$ using Clayton Copula to study the temporal dependence between the occurrence of acute GVHD and death within the framework of semi-competing risks data.

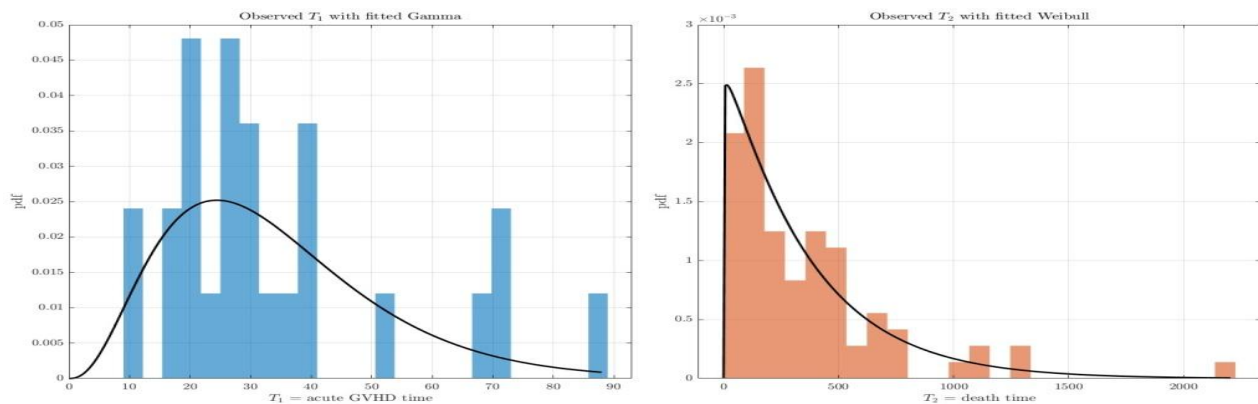


Figure 6: Examination of the Fit of the MARGINAL DISTRIBUTIONS of the Two Variables T_1 and T_2 in BMT Bone Marrow Transplant Data Before Constructing the Combined Distribution Using Clayton Copula

Table 2: Results of the Fit Test for the Common Distribution and its Basic Distributions using the Clayton-Copula Function

Distribution	Log-Likelihood	AIC	BIC	CvM*	P-Value
Gamma-Weibull Clayton Copula	-412.57	835.1	849.7	0.214	0.231
Gamma Clayton Copula	-418.9	847.8	862.4	0.342	0.071
Weibull Clayton Copula	-416.44	842.9	857.5	0.287	0.118

*Cramér-von Mises Copula Goodness-of-Fit Test

Table (2) shows that the Clayton Copula Gamma-Weibull model achieved the highest probability function value of (-412.57) and also had the lowest values for both (AIC and BIC) of (835.1 and 849.7, respectively) compared to the other distributions, indicating its superiority in representing the dependency structure of the data. Furthermore, the CvM test showed a probability value of (0.231), which is greater than the significance level of 0.01, indicating a high degree of fit for this distribution under real-world data conditions. Therefore, it can be considered a suitable model for describing the relationship between the times of two events.

Table 3 (A): Values of the Survival Function for the Theoretical, Empirical, and Maximum Likelihood Estimated

Obs.	T ₁ GVHD	T ₂ Death	S_Theoretical	S_Empirical	S_MLE
1	0.18356	5.70137	0.99768	1.00000	0.99884
2	4.38904	4.38904	0.99508	1.00000	0.99712
3	4.09863	4.09863	0.93662	0.87500	0.92927
4	0.19178	4.00548	0.83037	0.81250	0.79698
5	3.92603	3.92603	0.78133	0.62500	0.77514
6	3.77260	3.77260	0.70927	0.68750	0.68117
7	3.64384	3.64384	0.61770	0.43750	0.56898
8	0.19726	2.72877	0.57908	0.43750	0.52894
9	0.61918	0.61918	0.47224	0.31250	0.41008
10	3.28493	3.28493	0.46946	0.18750	0.40889
11	3.04384	3.04384	0.46327	0.18750	0.39262
12	0.10411	1.45205	0.42937	0.18750	0.36231
13	3.23836	3.23836	0.39184	0.12500	0.32428
14	0.10685	3.19726	0.38256	0.25000	0.31011
15	1.14521	1.14521	0.38215	0.18750	0.30114
16	1.14247	1.14247	0.30650	0.06250	0.23261
17	0.75616	0.75616	0.30360	0.18750	0.22630
18	0.07671	0.42740	0.17788	0.06250	0.11785
19	2.13973	2.13973	0.15890	0.06250	0.08928
20	0.06027	0.47123	0.14635	0.06250	0.08280
21	1.33425	1.33425	0.12820	0.06250	0.07912
22	1.96164	1.96164	0.08656	0.00000	0.04132
23	0.53151	0.53151	0.06860	0.06250	0.03712
24	1.01644	1.01644	0.05811	0.00000	0.02141
25	1.44110	1.44110	0.04122	0.00000	0.01079
26	0.24110	0.33425	0.03037	0.06250	0.01392
27	3.50411	3.50411	0.01506	0.00000	0.00178
28	0.30137	0.30137	0.01276	0.00000	0.00182
29	0.66575	0.66575	0.01097	0.06250	0.00411
30	0.23562	0.23562	0.01063	0.00000	0.00111
31	1.27671	1.27671	0.00860	0.00000	0.00309
32	0.02740	0.71781	0.00622	0.00000	0.00209
33	0.44384	0.44384	0.00557	0.00000	0.00027
34	0.71781	0.71781	0.00447	0.00000	0.00141
35	0.00274	0.00274	0.00248	0.00000	0.00031
36	0.29315	0.29315	0.00229	0.00000	0.00063
37	0.73699	0.73699	0.00229	0.00000	0.00063
38	0.95890	0.95890	0.00193	0.00000	0.00052
39	7.03836	7.03836	0.00150	0.00000	0.00038
40	6.86575	6.86575	0.00072	0.00000	0.00003
41	6.60000	6.60000	0.00053	0.00000	0.00011
42	6.07671	6.07671	0.00031	0.00000	0.00006
43	5.08767	5.08767	0.00029	0.00000	0.00005
44	5.01096	5.01096	0.00023	0.00000	0.00000
45	4.27945	4.27945	0.00014	0.00000	0.00000

Table 3 (B): Values of the Survival Function for the Theoretical, Empirical, and Maximum Likelihood Estimated

Obs.	T ₁ GVHD	T ₂ Death	S _{Theoretical}	S _{Empirical}	S _{MLE}
46	4.02740	4.02740	0.00003	0.00000	0.00000
47	3.73425	3.73425	0.00001	0.00000	0.00000
48	2.82192	2.82192	0.00001	0.00000	0.00000
49	2.35616	2.35616	0.00001	0.00000	0.00000
50	3.44658	3.44658	0.00001	0.00000	0.00000
51	0.14247	6.15342	0.00000	0.00000	0.00000
52	5.12329	5.12329	0.00000	0.00000	0.00000
53	4.92877	4.92877	0.00000	0.00000	0.00000
54	0.05479	4.68219	0.00000	0.00000	0.00000
55	4.58630	4.58630	0.00000	0.00000	0.00000
56	4.29589	4.29589	0.00000	0.00000	0.00000
57	4.18356	4.18356	0.00000	0.00000	0.00000
58	0.06849	3.62740	0.00000	0.00000	0.00000
59	2.62192	2.62192	0.00000	0.00000	0.00000
60	0.07945	2.55342	0.00000	0.00000	0.00000
61	2.32055	2.32055	0.00000	0.00000	0.00000
62	2.32329	2.32329	0.00000	0.00000	0.00000
63	5.06849	5.06849	0.00000	0.00000	0.00000
64	5.04932	5.04932	0.00000	0.00000	0.00000
65	4.20548	4.20548	0.00000	0.00000	0.00000
66	3.96438	3.96438	0.00000	0.00000	0.00000
67	3.79178	3.79178	0.00000	0.00000	0.00000
68	1.13425	1.13425	0.00000	0.00000	0.00000
69	6.03836	6.03836	0.00000	0.00000	0.00000
70	2.91233	2.91233	0.00000	0.00000	0.00000
71	0.08219	1.31781	0.00000	0.00000	0.00000
72	0.05753	0.28767	0.00000	0.00000	0.00000
73	1.75616	1.75616	0.00000	0.00000	0.00000
74	1.06849	1.06849	0.00000	0.00000	0.00000
75	0.04932	0.78904	0.00000	0.00000	0.00000
76	0.06849	1.43014	0.00000	0.00000	0.00000
77	0.04384	0.21644	0.00000	0.00000	0.00000
78	3.16712	3.16712	0.00000	0.00000	0.00000
79	1.59726	1.59726	0.00000	0.00000	0.00000
80	0.13151	0.13151	0.00000	0.00000	0.00000
81	1.18082	1.18082	0.00000	0.00000	0.00000
82	2.94247	2.94247	0.00000	0.00000	0.00000
83	1.07671	1.07671	0.00000	0.00000	0.00000
84	0.02740	0.02740	0.00000	0.00000	0.00000
85	0.14521	0.14521	0.00000	0.00000	0.00000
86	0.02740	0.21918	0.00000	0.00000	0.00000
87	0.09589	0.09589	0.00000	0.00000	0.00000
88	4.10685	4.10685	0.00000	0.00000	0.00000
89	0.09863	1.92877	0.00000	0.00000	0.00000
90	1.78904	1.78904	0.00000	0.00000	0.00000
91	0.60822	0.60822	0.00000	0.00000	0.00000
92	3.71507	3.71507	0.00000	0.00000	0.00000
93	7.23288	7.23288	0.00000	0.00000	0.00000
94	6.65753	6.65753	0.00000	0.00000	0.00000
95	6.16986	6.16986	0.00000	0.00000	0.00000
96	5.86301	5.86301	0.00000	0.00000	0.00000
97	5.84384	5.84384	0.00000	0.00000	0.00000
98	3.39178	3.39178	0.00000	0.00000	0.00000
99	4.46849	4.46849	0.00000	0.00000	0.00000
100	5.54521	5.54521	0.00000	0.00000	0.00000
101	0.08767	3.68493	0.00000	0.00000	0.00000
102	3.11233	3.11233	0.00000	0.00000	0.00000
103	2.31507	2.31507	0.00000	0.00000	0.00000
104	1.34521	1.34521	0.00000	0.00000	0.00000
105	0.44384	0.44384	0.00000	0.00000	0.00000
106	3.55616	3.55616	0.00000	0.00000	0.00000
107	0.07671	0.33151	0.00000	0.00000	0.00000
108	0.00548	0.00548	0.00000	0.00000	0.00000

Table 3 (C): Values of the Survival Function for the Theoretical, Empirical, and Maximum Likelihood Estimated

Obs.	T ₁ GVHD	T ₂ Death	S_Theoretical	S_Empirical	S_MLE
109	0.16986	0.16986	0.00000	0.00000	0.00000
110	0.72603	0.72603	0.00000	0.00000	0.00000
111	1.49863	1.49863	0.00000	0.00000	0.00000
112	0.05753	0.93425	0.00000	0.00000	0.00000
113	0.87123	0.87123	0.00000	0.00000	0.00000
114	0.53425	0.53425	0.00000	0.00000	0.00000
115	1.28493	1.28493	0.00000	0.00000	0.00000
116	0.25479	0.25479	0.00000	0.00000	0.00000
117	1.41096	1.41096	0.00000	0.00000	0.00000
118	0.50137	0.50137	0.00000	0.00000	0.00000
119	0.28767	0.28767	0.00000	0.00000	0.00000
120	0.35068	0.35068	0.00000	0.00000	0.00000
121	0.44932	0.44932	0.00000	0.00000	0.00000
122	0.35342	0.35342	0.00000	0.00000	0.00000
123	0.33425	0.33425	0.00000	0.00000	0.00000
124	0.05753	0.21918	0.00000	0.00000	0.00000
125	1.85479	1.85479	0.00000	0.00000	0.00000
126	0.20000	0.20000	0.00000	0.00000	0.00000
127	0.46027	0.46027	0.00000	0.00000	0.00000
128	0.07945	0.20274	0.00000	0.00000	0.00000
129	0.04384	0.04384	0.00000	0.00000	0.00000
130	0.67945	0.67945	0.00000	0.00000	0.00000
131	2.00548	2.00548	0.00000	0.00000	0.00000
132	0.28767	0.28767	0.00000	0.00000	0.00000
133	1.07397	1.07397	0.00000	0.00000	0.00000
134	0.10411	0.17260	0.00000	0.00000	0.00000
135	0.26575	0.26575	0.00000	0.00000	0.00000
136	0.41918	0.41918	0.00000	0.00000	0.00000
137	0.99452	0.99452	0.00000	0.00000	0.00000

Table (3) shows the values of the survival function for the hypothetical, empirical, and maximum probability Gamma-Weibull Clayton Copula co-distribution. We note that the values of S_Theoretical and S_MLE are relatively high at small times and then gradually decrease as the values of t₁ and t₂ increase. This is expected behavior and is consistent with the statistical theory of survival functions, since increasing time means a decrease in the probability of co-survival. Therefore, in the first rows, values close to one appeared, then gradually declined to very small values and approached zero at large times, which reflects that the probability of the two events not occurring together becomes very weak in long time intervals. It is also evident that the S_MLE estimated values came very close to the S_Theoretical values in most observations, indicating that the proposed model is stable and data-friendly, and that re-estimating the parameters using the S_MLE method did not change the overall structure of the model but rather improved its suitability to the actual data. Meanwhile, the S_Empirical values appeared gradually and unevenly because they depend on a limited number of complete observations, and therefore took fixed levels such as 1.00000, 0.87500, 0.81250, 0.43750, and then quickly reached zero. This is normal in non-parametric empirical estimation when the effective sample size is limited. These results also confirm the suitability of the Clayton-Copula model for this type of data, as it describes a positive dependence in the lower tail, i.e., at shorter time points, where the probability of the two events occurring together increases in the early stages of follow-up with increasing θ . A similar dependence is not observed in the upper tail. Therefore, the behavior in the right-hand side of the combined distribution remains more closely governed by the properties of the Gamma and Weibull MARGINAL DISTRIBUTIONS, particularly the positive skewness and the relatively extended right-hand tail. Thus, the table clearly demonstrates that the Gamma-Weibull combined distribution with the Clayton-Copula model accurately and consistently represents the time points of the two events. It shows a regular decrease in the co-occurrence function with time and a clear convergence between theoretical and maximum-possibility estimated values. However, the experimental estimate remains less smooth and more gradual due to the limited data available. This supports the model's suitability for describing the co-occurrence relationship between the time of acute GVHD and the time of death in bone marrow transplant patients.

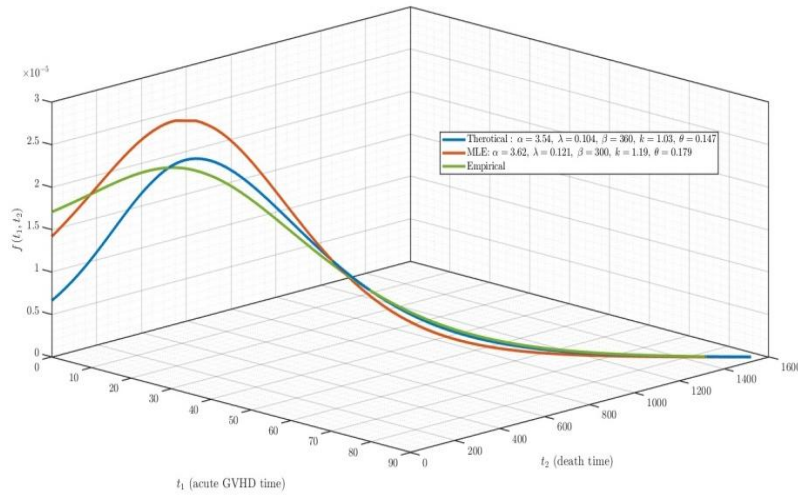


Figure 7: Joint Probability Density Function of the Clayton Copula Gamma-Weibull Distribution for the Variables T_1 and T_2 in BMT Bone Marrow Transplant Data

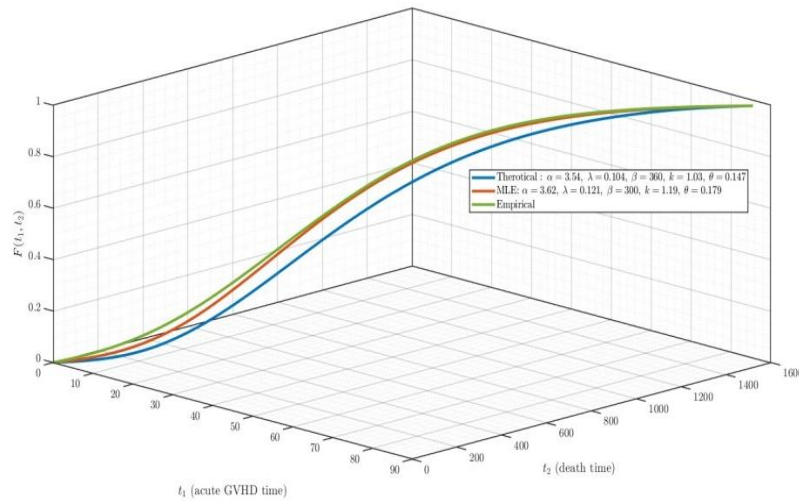


Figure 8: Joint Cumulative distribution function (CDF) of the Clayton Copula Gamma-Weibull Distribution for the Variables T_1 and T_2 in BMT Bone Marrow Transplant Data

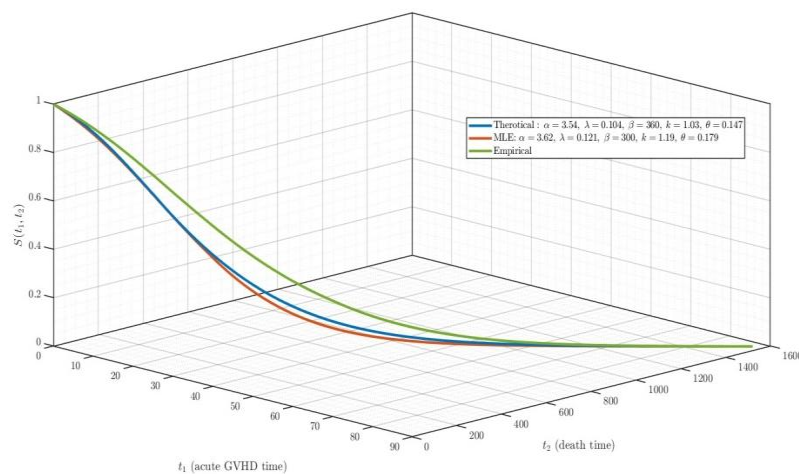


Figure 9: Joint Survival Function of the Clayton Copula Gamma-Weibull Distribution for the Variables T_1 and T_2 in BMT Bone Marrow Transplant Data

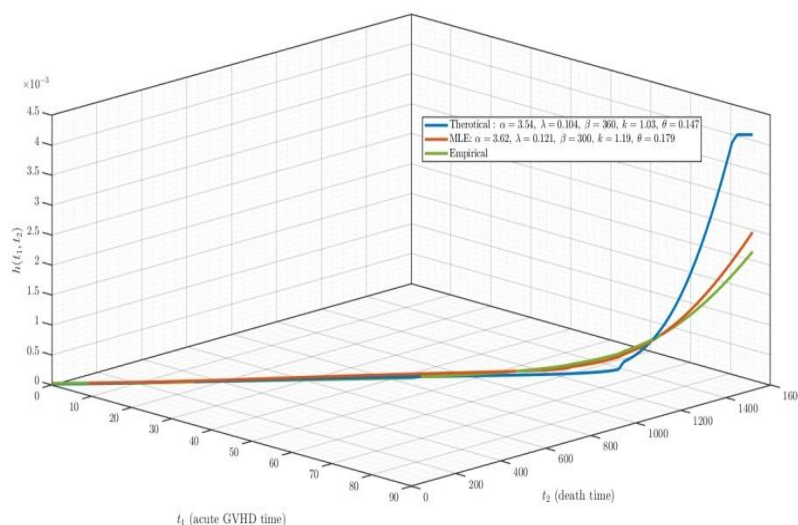


Figure 10: Joint Hazard Function of the Clayton Copula Gamma-Weibull Distribution for the Variables T_1 and T_2 in BMT Bone Marrow Transplant Data

11. Results Discussion

The research results showed that the proposed model based on the Clayton Copula Gamma-Weibull was able to represent the quasi-competing risk data for bone marrow transplant patients well, both theoretically and practically. The suitability of the MARGINAL DISTRIBUTIONS was first verified before constructing the combined distribution. It was found that the Gamma distribution was suitable for representing the non-terminal event time T_1 , which is the occurrence of acute GVHD, while the Weibull distribution was suitable for representing the terminal event time T_2 , which is death. Conformity tests such as Kolmogorov-Smirnov and Anderson-Darling supported this choice because the probability values were greater than the adopted significance level, which means that the construction of the combined model started from statistically suitable borderline distributions. The comparison of the combined models then showed that the Gamma-Weibull model, coupled with the Clayton Copula function, performed best compared to the alternative models. It achieved the highest probability function value and the lowest values for the AIC and BIC parameters. Furthermore, the Cramér-von Mises test indicated a good fit to the data, demonstrating that combining the gamma distribution for the non-final event time and the Weibull distribution for the final event time, coupled with the Clayton function, provided a more accurate representation of the underlying dependency structure. The results also showed that the dependency parameter θ /theta in the Clayton function played a crucial role in interpreting the relationship between the two events. The model clearly captured the positive lower-tail dependence, meaning that the probability of both the non-final and final events occurring simultaneously is higher at shorter time points. This aligns with the clinical nature of bone marrow transplant data, where the occurrence of early immunological complications may be associated with an increased risk of death in the early follow-up periods. By examining the joint survival function, it was found that theoretical and maximum likelihood estimated values were highly convergent, reflecting the stability of the estimates and the model's efficiency in representing the actual behavior of the data. In contrast, the empirical values appeared less smooth and more gradual due to their reliance on a limited number of complete observations, which is expected in non-parametric estimation. The joint risk function also exhibited high behavior near the origin, followed by a gradual change over time. This reflects the interaction of the dependency structure imposed by the Clayton function with the properties of borderline distributions, particularly the influence of the WEIBULL distribution in shaping the risk pattern over time. Overall, these results confirm that the proposed model is not merely a novel mathematical formulation but also a practical and flexible statistical tool for understanding the temporal relationship between the occurrence of acute GVHD and death in quasi-competing risk data. Furthermore, it provides a more realistic description of the dependency between the two events compared to traditional models that assume independence or treat each event time in isolation. This enhances its applicability in medical studies and the analysis of complex survival data.

12. Conclusions

The results of this research indicate that using Copula models provides an effective statistical framework for modeling semi-competing risks data, as these models are capable of separating MARGINAL DISTRIBUTIONS from the dependency structure. The proposed Clayton Copula Gamma-Weibull model demonstrated high efficiency in representing the co-

relationship between the time to non-final event (acute graft-versus-host disease, T_1) and the time to final event (death) in bone marrow transplant patient data. Fit tests showed that the Gamma distribution was suitable for representing the borderline distribution of the non-final event time (T_1), while the Weibull distribution was suitable for representing the borderline distribution of the final event time (T_2), thus providing a suitable statistical basis for constructing the co-distribution. The comparison of different models showed that the combined Gamma-Weibull model, associated with the Clayton-Copula function, performed best statistically compared to the other models. This was achieved by obtaining the highest possible value and the lowest values for the AIC and BIC criteria. Furthermore, the results of the Cramér-von Mises test supported its suitability for the studied data. These results indicate that the proposed model has a better ability to represent the intertime dependency structure compared to traditional models that assume independence or rely on constrained co-distributions. The results also showed that the Clayton-Copula function is able to capture the lower-tail dependence pattern between the two events, where the probability of the non-final and final events occurring together increases in the early stages. This pattern is consistent with the medical nature of bone marrow transplant data. The comparison between the theoretical values of the survival function and the values estimated using the maximum possibility method showed a high degree of convergence, indicating the stability of the model's estimates and its efficiency in representing the actual behavior of the data.

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