Development of a Diagnostic Evaluation Framework of Correlated Biomarkers for Survival Outcome Using Nested Copula Models

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Abstract

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Robust evaluation of biomarker performance for survival outcomes is critical in precision medicine, particularly when multiple, dependent biomarkers are involved. Traditional regression-based approaches typically focus on marginal effects and overlook inter-marker dependencies, often treating them merely as sources of multicollinearity.

To address this limitation, we propose a diagnostic evaluation framework based on fully nested Archimedean copulas (FNACs), which flexibly model the joint distribution of two dependent biomarkers and a survival outcome. FNACs accommodate hierarchical, asymmetric dependence, enabling simultaneous modeling of both inter-marker and marker–outcome relationships within a unified probabilistic framework. This approach is particularly useful for evaluating the contribution of a new biomarker in the presence of an already established one.

The framework employs two complementary strategies: conditional evaluation, which quantifies the added value of a new biomarker given an existing one; and joint evaluation, which assesses their combined utility using an *and-classifier* that defines positive cases as those exceeding predefined thresholds for both biomarkers. These strategies support tailored interpretation depending on the clinical objectives and biomarker characteristics.

Simulation studies across varying censoring levels, prediction time horizons, and copula families (Frank, Clayton, Gumbel) demonstrate the framework's accuracy in estimating performance metrics and recovering the true dependence structure. Application to the Mayo Clinic PBC dataset further illustrates its practical utility in real-world clinical settings.

Keyword: Nested copula models, Biomarker performance evaluation, Time-dependent AUC, Survival Analysis

1. Introduction

1.1. Background

Accurate evaluation of biomarkers for survival outcomes is fundamental, especially in the era of precision medicine, where risk stratification and early diagnosis rely heavily on quantitative measures derived from biological indicators. In many real-world clinical scenarios, a new biomarker is assessed not in isolation but in the context of one or more pre-established biomarkers. These biomarkers often exhibit non-negligible interdependence due to shared biological pathways, overlapping measurement mechanisms, or underlying disease processes(Heagerty & Zheng, 2005). However, traditional modeling approaches often incorporate these biomarkers as fixed covariates in regression-based frameworks, with an emphasis on estimating their marginal effects on survival. Within this paradigm, the intrinsic dependencies among biomarkers are typically ignored or regarded as sources of multicollinearity, which can result in biased or inefficient estimates of diagnostic performance and potentially undermine the clinical interpretability of the model.

Two complementary approaches can be considered when evaluating a new biomarker in the presence of an established one. First, the conditional evaluation assesses the diagnostic value of the new biomarker, given the information contained in the existing ones; for example, assessing the utility of CA19-9 after adjusting for CEA in pancreatic cancer prognosis. Second, the joint evaluation approach considers the combination of multiple markers using a logical structure, such as an *and-classifier*, which may better reflect the clinical decision-making process when multiple criteria are required to define a high-risk subject. These complementary strategies provide flexibility in evaluating biomarker utility, whether incrementally or in combination, depending on clinical objectives.

To formally quantify the added value of a new biomarker, summary indices such as the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) have been widely used. These measures compare a baseline model and an extended model incorporating the new biomarker, focusing on improvements in risk classification and discrimination. However, it is important to note that the NRI and IDI do not assess the intrinsic predictive performance of the biomarker itself. Rather, they assess the incremental contribution of a biomarker when added to a specific prediction model. Moreover, both NRI and IDI are highly sensitive to the choice of baseline model, which can substantially influence the magnitude and interpretation of the estimated improvement. Numerous studies have emphasized that these measures should be interpreted with caution to avoid

conflating model improvement with the marker's inherent diagnostic capacity(Cook, 2007; Pencina et al., 2008; Pepe & Janes, 2011; Pepe et al., 2004).

Several extensions of the ROC curve have been proposed to capture covariate-specific diagnostic accuracy. For example, conditional ROC curves estimate performance at fixed values of a covariate, and covariate-adjusted ROC curves are obtained by averaging conditional ROCs across the distribution of the covariate. These approaches have been particularly useful in settings involving population heterogeneity, such as multicenter studies or matched case-control designs (Pepe et al., 2013).

In this study, we define conventional diagnostic tools—such as the ROC curve and risk function—as functionals of the joint distribution derived from a copula model. By doing so, we propose a copula-based diagnostic framework that provides greater flexibility in modeling complex covariate structures. Copula models are particularly advantageous in this context, as they allow for the separate modeling of marginal distributions and dependence structures, yielding several methodological benefits. First, copulas allow each biomarker to retain its own marginal distribution, including skewness and heavy tails, by independently modeling the margins. Second, they can flexibly accommodate complex and asymmetric dependence structures, which are often present in biomedical data but poorly captured by standard regression models(Joe, 1997; Nelsen, 2006). Third, once a joint distribution is specified through a copula, conditional distributions and key probabilities can be derived analytically, enabling the direct estimation of diagnostic quantities, such as risk functions and ROC-related metrics, without full access to empirical data.

Recent studies have explored the use of copula models in evaluating diagnostic performance. For instance, Escarela et al. (2023) applied copula-based modeling to capture the joint distribution of a single biomarker and survival time, enabling estimation of ROC and predictiveness curves under censoring. Melo et al. (2020) employed copulas to analyze paired diagnostic tests, allowing for flexible modeling of inter-test dependence and accurate AUC estimation. Zhang and Shao (2020) further extended copula approaches by employing vine structures to simulate high-dimensional dependencies among multiple markers. While these studies demonstrate the feasibility of copula-based evaluation, they are limited in scope: either addressing only bivariate associations or requiring extensive simulation to approximate realistic joint structures.

Building on these developments, the present study proposes a diagnostic evaluation framework based on fully nested Archimedean copulas (FNACs), which allows for

hierarchical and non-exchangeable modeling of the joint distribution among two dependent biomarkers and a survival outcome. This approach simultaneously captures intra-marker dependence and biomarker-to-survival associations within a unified probabilistic structure, offering a theoretically grounded and computationally tractable means to evaluate biomarker performance under censoring.

1.2. Objective and Outline

The primary objective of this study is to develop a diagnostic evaluation framework that leverages fully nested Archimedean copulas (FNACs) to flexibly model the joint distribution of two correlated biomarkers and a right-censored survival outcome. FNACs are particularly well suited for this purpose as they enable the modeling of hierarchical, non-exchangeable dependence structures, reflecting realistic scenarios where biomarker-to-survival associations differ in strength from biomarker-to-biomarker dependencies. Within this framework, we implement two distinct evaluation strategies:

- **Conditional evaluation**, which quantifies the diagnostic value of a new biomarker given the information from an existing one; and
- **Joint evaluation**, which assesses the combined discriminatory ability of multiple biomarkers using an *and-classifier* strategy.

To achieve these aims, the paper is organized as follows. First, we introduce the theoretical foundations of nested copulas, focusing on the structure and properties of fully nested Archimedean constructions. We then specify the joint distribution of the two biomarkers and survival time using a nested copula formulation and define marginal distributions to ensure model identifiability. Model parameters are estimated via maximum likelihood estimation (MLE), and model adequacy is evaluated through goodness-of-fit criteria such as AIC and BIC to guide copula family selection.

We define a set of diagnostic performance measures—including conditional and joint versions of the time-dependent true and false positive rates and the risk function—derived directly from the estimated joint distribution. These measures are designed to reflect both discrimination and predictiveness in a manner that is robust to censoring and complex dependence. The framework is evaluated through simulation studies involving 1,000 replicated datasets (n = 250) under various copula types (Clayton, Frank, Gumbel) and censoring levels (20%, 50%, 80%). Performance is assessed via bias and Mean Squared Error (MSE) at clinically relevant time quantiles (25th, 50th, and 75th percentiles of survival time).

To demonstrate the practical applicability of our method, we apply the proposed framework to the Mayo Clinic Primary Biliary Cirrhosis (PBC) dataset. This real-data application illustrates how the model can be implemented in clinical settings and how the resulting diagnostic measures can support medical decision-making.

In summary, this study contributes a unified, interpretable, and computationally feasible diagnostic evaluation framework that extends conventional tools by accounting for complex dependence and censoring. By embedding conditional and joint assessment strategies within a copula-based joint modeling approach, our method offers a promising tool for biomarker validation in modern survival analysis.

2. Literature Review

2.1. Fully Nested Archimedean Copulas

Copula functions offer a flexible and theoretically grounded framework for modeling the joint distribution of multiple random variables while separately accounting for their marginal behaviors and their mutual dependencies. According to Sklar's theorem(Sklar, 1959), any multivariate cumulative distribution function $F(x_1, \dots, x_n)$ with continuous marginals $F_1(x_1), \dots, F_n(x_n)$ can be uniquely expressed using a copula function C as

$$\mathrm{F}(x_1, \dots, x_n) = C\big(F_1(x_1), \dots, F_n(x_n)\big) = \mathrm{C}(u_1, \dots, u_n)$$

where $u_k = F_k(x_k) \in [0,1] \; for \; each \; k = 1, \dots n$. Thus, Copula C captures the dependence structure among the variables, independent of their marginal distributions.

This formulation implies exchangeability among variables; that is, the dependence is symmetric and invariant under permutations. However, this assumption imposes a significant limitation in many applied settings, where variables (e.g., biomarkers) may exhibit asymmetric or hierarchical dependencies. Therefore, modeling all variables under a single homogeneous dependence function can be overly restrictive and unrealistic.

To address this issue, researchers have proposed fully nested or asymmetric copulas as a generalization of standard copulas(Embrechts et al., 2003; Joe, 1997; Nelsen, 2006; Whelan, 2004), which accommodate nonexchangeable structures. A fully nested copula with n variables is defined recursively as

$$C(u_1, \dots, u_n) = C_1\big(u_1, C_2\big(u_2, \dots C_{n-1}(u_{n-1}, u_n)\big) \dots\big)$$

where $C_1, \dots, C_{n-1}$ is itself a copula, resulting in a total of $n-1$ nested copulas for an n-dimensional model.

When each component copula is chosen from the Archimedean family, the construction can be expressed in the following functional form (Equation (1)), which defines a **Fully Nested Archimedean Copula (FNAC)**.

$$C_1\left(u_1, C_2\left(u_2, \dots C_{n-1}(u_{n-1}, u_n)\right) \dots\right)$$
$$= {\varphi_{\theta_1}}^{-1}(\varphi_{\theta_1}(u_1) + \varphi_{\theta_1}({\varphi_{\theta_2}}^{-1}\left(\varphi_{\theta_2}(u_2) + \cdots + {\varphi_{\theta_{\mathrm{n}-1}}}^{-1}\left(\varphi_{\theta_{\mathrm{n}-1}}(u_{\mathrm{n}-1}) + \varphi_{\theta_{\mathrm{n}-1}}(u_{\mathrm{n}})\right) \dots\right) \quad (1)$$

Each Archimedean copula is typically expressed as

$$\mathrm{C}(u, \mathrm{v}; \theta) = {\varphi_\theta}^{-1}\left(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\right) \quad (2)$$

where $\varphi_\theta: [0,1] \to [0, \infty]$ is a convex decreasing function.

Thus, a FNAC with n variables involve $n-1$ dependence parameters $\theta_1, \dots, \theta_{n-1}$ corresponding to $C_1, \dots, C_{n-1}$. To ensure the validity of the hierarchical structure, these parameters must satisfy a strict ordering constraint(Nelsen, 2006):

$$\theta_1 < \cdots < \theta_{n-1}. \quad (3)$$

This constraint preserves the complete monotonicity of the composite generator functions and ensures that more deeply nested variable pairs exhibit a stronger dependence. If this condition is violated, the composite generator may become non-invertible, making it mathematically impossible to define a valid joint distribution. Therefore, it is essential to incorporate this constraint during the parameter estimation.

For three variables $U_1, U_2, U_3 \in [0,1]$, FNAC takes the form, representing the three-dimensional structure implied by Equation (1):

$$C_1\left(u_1, C_2(u_2, u_3)\right) = {\varphi_{\theta_1}}^{-1}\left(\varphi_{\theta_1}(u_1) + \varphi_{\theta_1} \circ {\varphi_{\theta_2}}^{-1}\left(\varphi_{\theta_2}(u_2) + \varphi_{\theta_2}(u_3)\right)\right) \quad (4)$$

which corresponds to the nesting order [1,2,3], meaning $U2$ and $U3$ are first grouped and then joined with $U1$. In the trivariate case, three valid nesting structures exist— [1,2,3], [2,1,3], and [3,1,2]—each of which encodes a distinct dependence hierarchy. These alternatives allow flexibility in specifying which variable pairs are more strongly associated, and the appropriate structure can be selected based on the model fit criteria or prior domain knowledge.

2.2. Archimedean Copulas and Their Derivatives

The Archimedean copula is widely used because of its tractability and closed-form structure. In this study, we employ three copula families from the Archimedean class—Clayton, Gumbel, and Frank—to construct fully nested Archimedean copulas (FNACs). Each of these families is characterized by a distinct generator function $\varphi_\theta(\mathrm{t})$, which governs the dependence structure, including aspects such as tail dependence, asymmetry, and Kendall's τ(Table 1)(Nelsen, 2006).

Each of these generators satisfies the required properties for Archimedean copulas: $\varphi_\theta(0) = \infty$, $\varphi_\theta(1) = 0$, strict monotonicity, and a convex decreasing function with parameter θ.

To compute the copula density and perform likelihood-based inference, we require the first and second derivatives of the copula function in equation (2) with respect to u and v. These derivatives depend on the generator function and its inverses, which are given in closed form for the three Archimedean Copulas(Genest & MacKay, 1986; Schmitz, 2003).

Table 1. Families of Archimedean Copulas

	Clayton	Frank	Gumbel
Parameter	$\theta \geq 0$	$\theta \neq 0$	$\theta \geq 1$
Generator $\varphi_\theta(\mathrm{t})$	$t^{-\theta} - 1,$	$-\log\left(\frac{\exp(-\theta t) - 1}{\exp(-\theta) - 1}\right)$	$(-\log t)^\theta$
$\varphi_\theta{}^{-1}(t)$	$(t+1)^{-1/\theta}$	$-\frac{1}{\theta}\log\left(\exp(-t)\left(\exp(-\theta) - 1\right) + 1\right)$	$\exp\left(-t^{\frac{1}{\theta}}\right)$
Kendall's $\boldsymbol{\tau}$	$\frac{\theta}{\theta+2}$	$1 - \frac{4}{\theta} + \frac{4}{\theta^2}\int_0^\vartheta \frac{t}{e^t - 1}dt$	$1 - \frac{1}{\theta}$
Tail Dependence	Strong on the lower tail	Symmetry	Strong on the upper tail

3. Proposed Method

3.1. Notation

First, we define a general setting and notation for our method. Let $M1$ and $M2$ denote two continuous biomarkers, and let T represent the true survival time, which is subject to right-censoring. The marginal cumulative distribution functions (CDFs) are defined as follows

$$\mathrm{F}_{M1}(m1) = P(M1 \le m1), \mathrm{F}_{M2}(m2) = P(M2 \le m2), \mathrm{F}_T(t) = P(T \le t),$$

and the corresponding survival function is given by $S_t(\mathrm{t}) = 1 - \mathrm{F}_t(t)$. Then let

$$u1 = \mathrm{F}_{M1}(m1), u2 = \mathrm{F}_{M2}(m2), u3 = \mathrm{S}_T(t).$$

The corresponding probability density functions (PDFs) are as follows

$$f_{M1}(m1) = d\mathrm{F}_{M1}(m1)/dm1$$

$$f_{M2}(m2) = d\mathrm{F}_{M2}(m2)/dm2$$

$$f_t(t) = d\mathrm{F}_t(t)/dt.$$

Suppose we observe n independent subjects. For each subject $i = 1, \dots, n$, let $(m1_i, m2_i)$ be the observed two biomarker values, and T_i denote the true survival time. Let W_i denote an independent right-censored time. Then the observed time X_i and event indicator δ_i can be obtained as

$$X_i = \min(W_i, T_i), \qquad \delta_i = I(T_i = X_i). \tag{5}$$

For a bivariate copula $C_\theta(\mathrm{u}, \mathrm{v}) = {\varphi_\theta}^{-1}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)$, we denote its partial derivatives as

$${C^{[1]}}_\theta(\mathrm{u}, \mathrm{v}) = \partial C_\theta(\mathrm{u}, \mathrm{v})/\partial u$$

$${C^{[1,1]}}_\theta(\mathrm{u}, \mathrm{v}) = \partial^2 C_\theta(\mathrm{u}, \mathrm{v})/\partial u \partial v$$

$$C^{[2]}{}_{\theta}(\mathrm{u},\mathrm{v}) = \partial^2 C_{\theta}(\mathrm{u},\mathrm{v})/\partial^2 u$$

$$C^{[1,2]}{}_{\theta}(\mathrm{u},\mathrm{v}) = \frac{\partial^3 C_{\theta}(\mathrm{u},\mathrm{v})}{\partial u \partial^2 v}.$$

These derivative terms are used to derive diagnostic measures and likelihood-based estimations.

3.2. Model Specification

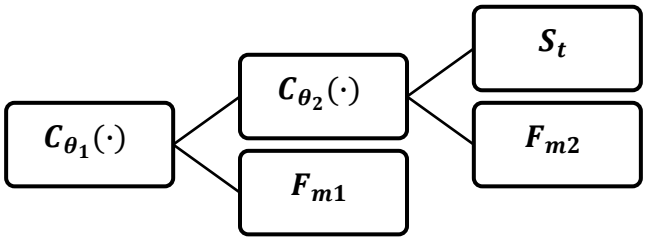

Figure 1. FNAC model structure

We propose a diagnostic evaluation framework for a new biomarker in the presence of an existing one using a **fully nested Archimedean copula (FNAC)**. Building on the general FNAC formulation defined in Equation (4), we specify the joint distribution of the two biomarkers and survival time by incorporating the hierarchical dependence structure illustrated in Figure 1. Accordingly, the joint distribution function of $(\mathrm{M1}, \mathrm{M2}, \mathrm{T})$ is given by

$$\mathrm{H}(\mathrm{m1}, \mathrm{m2}, \mathrm{t}) = \Pr(\mathrm{M1} \leq \mathrm{m1}, \mathrm{M2} \leq \mathrm{m2}, \mathrm{T} > \mathrm{t})$$

$$= \mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) = C_{\theta_1}\left(u1, C_{\theta_2}(u2, u3)\right). \quad (6)$$

The child copula C_{θ_2} captures the dependence between biomarker M2 and survival time T, whereas the parent copula C_{θ_1} models the dependence between biomarker M1 and joint value (M2, T). This formulation reflects the clinical assumption that higher biomarker values are associated with shorter survival and supports the use of popular copula families that are well suited for modeling positive dependence(Chaieb et al., 2006).

Valid nesting requires $\theta_1 < \theta_2$, reflecting the general condition in Equation (3), which ensures that the inner(child) copula exhibits a stronger dependence than the outer(parent) copula. This structural constraint, where the inner copula must capture a stronger dependence than the outer one, plays a central role in our modeling strategy. We assigned Marker 2 (M2) as a known strong biomarker owing to its direct and strong association with

survival outcomes. Thus, the child copula C_{θ_2} is used to capture this high dependence. On the other hand, Marker 1 ($M1$) is regarded as a new or candidate marker, whose diagnostic value is to be evaluated in the presence of $M2$. This design enables us to explicitly assess the diagnostic value of a new biomarker in the presence of an established biomarker within a coherent probabilistic framework that accounts for complex dependence structures.

To complete the joint model specification, we specified the marginal distributions of the biomarkers and survival time. To accommodate potential asymmetry and skewness in biomarker measurements(Van Domelen et al., 2021), we assumed that $M1$ and $M2$ each followed a skew-normal distribution. Specifically, the probability density function (PDF) of $M1$ and $M2$ is given by(Azzalini, 1985)

$$f_{m1}(\mathrm{m1};\boldsymbol{\omega}) = \frac{2}{\omega_2}\phi\left(\frac{m1-\omega_1}{\omega_2}\right)\phi\left[\omega_3\left(\frac{m1-\omega_1}{\omega_2}\right)\right] \tag{7}$$

$$f_{m2}(\mathrm{m2};\boldsymbol{\alpha}) = \frac{2}{\alpha_2}\phi\left(\frac{m2-\alpha_1}{\alpha_2}\right)\phi\left[\alpha_3\left(\frac{m2-\alpha_1}{\alpha_2}\right)\right] \tag{8}$$

where $(\mathrm{m1},\mathrm{m2}) \in \mathbb{R}^2, \boldsymbol{\omega} = (\omega_1,\omega_2,\omega_3), \boldsymbol{\alpha} = (\alpha_1,\alpha_2,\alpha_3)$ with $(\omega_1,\alpha_1) \in (-\infty,\infty)^2$, $(\omega_2,\alpha_2) \in (0,\infty)^2$ and $(\omega_3,\alpha_3) \in (-\infty,\infty)^2$, representing the location, scale, and shape parameters, respectively. Here, $\phi(\cdot)$ denotes the standard normal probability density function.

For the survival time T, we assume a Weibull distribution, which is widely used in survival analysis because of its flexibility in modeling hazard shapes. The cumulative distribution function (CDF) of the Weibull distribution is defined as follows

$$\mathrm{F}_t(t;\boldsymbol{\lambda}) = 1 - \exp\left\{-\left(\frac{t}{\lambda_2}\right)^{\lambda_1}\right\} \tag{9}$$

where $\mathrm{t} \in (0,\infty)$, $\lambda_1 \in (0,\infty)$ is the shape parameter, and $\lambda_2 \in (0,\infty)$ is the scale parameter.

3.3. Maximum Likelihood Estimation

Under the assumed fully nested Archimedean copula model and specified marginal distributions, the observed likelihood function is given by(Lawless, 2003):

$$\mathrm{L}(\boldsymbol{\theta}, \boldsymbol{\omega}, \boldsymbol{\alpha}, \boldsymbol{\lambda}) = \prod_{i=1}^{n} \left[-\frac{\partial^3 H(x,y,z)}{\partial x \partial y \partial z} \Big|_{(x,y,z)=(m1_i, m2_i, x_i)} \right]^{\delta_i} \times \left[\frac{\partial^2 H(x,y,z)}{\partial y \partial z} \Big|_{(x,y,z)=(m1_i, m2_i, x_i)} \right]^{1-\delta_i}$$

Here, the parameters are defined as

$\boldsymbol{\theta}$: dependence parameters in Equation (6),

$\boldsymbol{\omega}, \boldsymbol{\alpha}$: parameters of the skew-normal distributions for two biomarkers in Equation (7) and (8), respectively,

$\boldsymbol{\lambda}$: parameters of the Weibull distribution for survival time in Equation (9).

For censored observations ($\delta_i = 0$), the likelihood contribution involves the joint probability of survival beyond t and observed biomarkers:

$$\frac{\partial^2 H(m1, m2, t)}{\partial m1 \partial m2} = \frac{\partial^2 \mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right)}{\partial m1 \partial m2}$$

$$= \frac{\partial}{\partial m1}\left(\frac{\partial \mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right)}{\partial \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)} \frac{\partial \mathrm{C}_{\theta_2}(F_{m2}(\mathrm{m2}), S_t(\mathrm{t}))}{\partial F_{m2}(\mathrm{m2})} f_{m2}(\mathrm{m2}) \right)$$

$$= \frac{\partial^2 \mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right)}{\partial \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) \partial F_{m1}(\mathrm{m1})} \frac{\partial \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)}{\partial F_{m2}(\mathrm{m2})} f_{m1}(\mathrm{m1}) f_{m2}(\mathrm{m2})$$

$$= C^{[1,1]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) f_{m1}(\mathrm{m1}) f_{m2}(\mathrm{m2})$$

For an uncensored observation ($\delta_i = 1$), the likelihood contribution involves the joint density obtained as the third-order partial derivative, as follows

$$-\frac{\partial^3 H(m1, m2, t)}{\partial m1 \partial m2 \partial t}$$

$$= C^{[1,2]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) f_{m1}(\mathrm{m1}) f_{m2}(\mathrm{m2}) f_t(\mathrm{t})$$
$$+ C^{[1,1]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) C^{[1,1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) f_{m1}(\mathrm{m1}) f_{m2}(\mathrm{m2}) f_t(\mathrm{t}).$$

The model parameters were estimated by minimizing the negative log-likelihood function $-\mathrm{logL}(\boldsymbol{\theta}, \boldsymbol{\omega}, \boldsymbol{\alpha}, \boldsymbol{\lambda})$, and the standard errors (SEs) were derived from the observed information matrix, which is the negative of the Hessian matrix of the log-likelihood function evaluated at the MLEs. Specifically, the SE is computed as the square root of the diagonal entries in the inverse of the observed information matrix.

In the estimation process, we reparameterized the parameters with natural constraints. Specifically, Parameters κ constrained to $(0, \infty)$ and $(1, \infty)$ are expressed as $\exp(\kappa)$ and $\exp(\kappa) + 1$, respectively.

3.4. Joint Diagnostic Measures

First, we assessed the joint discriminatory performance of the two biomarkers, $M1$ and $M2$. This is relevant when both markers are used simultaneously in classification, such as in an and-classifier.

Given thresholds (m1, m2), we define the joint *dynamic false positive rate* (FPR) at time t as

$$\mathrm{FPR}(\mathrm{m1},\mathrm{m2},\mathrm{t}) = \Pr(\mathrm{M1} > \mathrm{m1}, \mathrm{M2} > \mathrm{m2} | \mathrm{T} > \mathrm{t}).$$

It can be shown under FNAC model given by Equation (6) that

$$\mathrm{FPR}(\mathrm{m1},\mathrm{m2},\mathrm{t})$$

$$= 1 - \frac{\Pr(\mathrm{M1} \le \mathrm{m1}, \mathrm{T} > \mathrm{t}) + \Pr(\mathrm{M2} \le \mathrm{m2}, \mathrm{T} > \mathrm{t}) - \Pr(\mathrm{M1} \le \mathrm{m1}, \mathrm{M2} \le \mathrm{m2}, \mathrm{T} > \mathrm{t})}{\Pr(\mathrm{T} > \mathrm{t})}$$

$$= 1 - \frac{\mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), S_t(\mathrm{t})\right) + \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) - H(m1, m2, t)}{S_t(\mathrm{t})}$$

which represents the probability of incorrectly classifying a subject as high-risk based on both markers when they survive beyond time t.

We define the corresponding *cumulative true positive rate* (TPR^C) and *incident True positive rate* (TPR^I) at time t as

$$\mathrm{TPR}^C(\mathrm{m1},\mathrm{m2},\mathrm{t}) = \Pr(\mathrm{M1} > \mathrm{m1}, \mathrm{M2} > \mathrm{m2} | \mathrm{T} \le \mathrm{t}) \text{ and}$$

$$\mathrm{TPR}^I(\mathrm{m1},\mathrm{m2},\mathrm{t}) = \Pr(\mathrm{M1} > \mathrm{m1}, \mathrm{M2} > \mathrm{m2} | \mathrm{T} = \mathrm{t}), \text{ respectively.}$$

These also can be shown under FNAC model given by Equation (6) that

$$\mathrm{TPR}^C(\mathrm{m1},\mathrm{m2},\mathrm{t})$$

$$= 1 - \left[F_{m1}(\mathrm{m1}) - \mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), S_t(\mathrm{t})\right) + F_{m2}(\mathrm{m2}) - \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right.$$

$$-\mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), F_{m2}(\mathrm{m2})\right) + H(m1, m2, t)\Big]/F_t(\mathrm{t})$$

and $\mathrm{TPR}^I(\mathrm{m1}, \mathrm{m2}, \mathrm{t})$

$$= 1 - C^{[1]}{}_{\theta_1}\left(S_t(\mathrm{t}), F_{m1}(\mathrm{m1})\right) - C^{[1]}{}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right)$$

$$+C^{[1]}{}_{\theta_1}\left(\mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right), F_{m1}(\mathrm{m1}),\right)C^{[1]}{}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right).$$

These definitions follow the framework proposed by (Wang & Li, 2012) and (Melo et al., 2020), which extend ROC analysis to the bivariate marker setting using dynamic definitions suited for censored survival outcomes.

Unlike in the univariate case, where the ROC curve is a function mapping FPR to TPR via an invertible relationship, in the bivariate case, the function $\mathrm{FPR}(\mathrm{m1}, \mathrm{m2}, \mathrm{t})$ is not one-to-one in general. That is, multiple threshold pairs $(\mathrm{m1}, \mathrm{m2})$ may yield the same FPR, leading to non-uniqueness of the corresponding TPR. Consequently, the traditional ROC function $\mathrm{TPR}(\mathrm{FPR}^{-1}(\mathrm{q}))$ is not well-defined.

To address this issue, (Wang & Li, 2012) proposed the concept of the bivariate ROC function by averaging the TPR values over all threshold pairs that yield a given FPR level. Specifically, we consider the inverse set:

$$B_0(q) = \{(\mathrm{m1}_0, \mathrm{m2}_0) : \mathrm{FPR}(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t}) = q\}, \qquad 0 \le q \le 1$$

Then, the bivariate *cumulative/dynamic* and *incident/dynamic* ROC functions are defined as

$$\mathrm{ROC}^{C/D}(\mathrm{q}, \mathrm{t}) = \mathrm{E}[\mathrm{TPR}^C(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t}) | \mathrm{FPR}(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t}) = q] \text{ and}$$

$$\mathrm{ROC}^{I/D}(\mathrm{q}, \mathrm{t}) = \mathrm{E}[\mathrm{TPR}^I(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t}) | \mathrm{FPR}(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t}) = q], \text{ respectively.}$$

Because the distribution of FPR values is not uniform over the threshold space $(m1, m2)$, (Wang & Li, 2012) further proposed the use of a weighted ROC (WROC) curve that accounts for the probability distribution of FPR values.

Let $Q_0 = \mathrm{FPR}(\mathrm{m1}_0, \mathrm{m2}_0, \mathrm{t})$ and $H_0(x)$ denote the cumulative distribution function (CDF) of Q_0, with corresponding density function $h_0(x) = \frac{d}{dx}H_0(x)$. Then the *cumulative/dynamic* and *incident/dynamic* WROC curve functions are defined as

$$\mathrm{WROC}^{C/D}(\mathrm{q}, \mathrm{t}) = \mathrm{ROC}^{C/D}(\mathrm{q}, \mathrm{t})h_0(q) \text{ and}$$

$$\mathrm{WROC}^{I/D}(\mathrm{q}, \mathrm{t}) = \mathrm{ROC}^{I/D}(\mathrm{q}, \mathrm{t})h_0(q), \text{ respectively.}$$

The corresponding weighted area under the curves (AUCs) are given by

$$WAUC^{C/D}(\mathrm{t}) = \int_0^1 \mathrm{ROC}^{C/D}(\mathrm{x}, \mathrm{t})h_0(x)dx \text{ and}$$

$$WAUC^{I/D}(\mathrm{t}) = \int_0^1 \mathrm{ROC}^{I/D}(\mathrm{x}, \mathrm{t})h_0(x)dx, \text{ respectively}$$

which provide scalar summaries of the joint discriminatory ability across the entire FPR spectrum, while accounting for the distributional structure of the bivariate threshold space.

We now consider the combined predictiveness of both Marker 1 and Marker 2. The joint risk function is defined as

$$\mathrm{Risk}(\mathrm{m1}, \mathrm{m2}, \mathrm{t}) = \Pr(\mathrm{T} \le \mathrm{t} | \mathrm{M1} = \mathrm{m1}, \mathrm{M2} = \mathrm{m2}).$$

It can be shown under FNAC model given by Equation (7) that

$$\mathrm{Risk}(\mathrm{m1}, \mathrm{m2}, \mathrm{t}) = 1 - \frac{\partial^2 H(m1, m2, t)/\partial m1 \partial m2}{\partial^2 \mathrm{C}_{\theta_1}(F_{m1}(\mathrm{m1}), F_{m2}(\mathrm{m2}))/\partial m1 \partial m2}$$

$$= 1 - \frac{C^{[1,1]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)}{C^{[1,1]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), F_{m2}(\mathrm{m2})\right)} \qquad (10)$$

Since $\frac{\partial^2 H(m1,m2,t)}{\partial m1 \partial m2}$

$= C^{[1,1]}{}_{\theta_1}\left(F_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) f_{m1}(\mathrm{m1}) f_{m2}(\mathrm{m2}).$

The time-dependent predictiveness surface at time t is defined as

$$\mathrm{R}(\mathrm{u1},\mathrm{u2},\mathrm{t}) = \Pr\left(\mathrm{T} \le \mathrm{t} \middle| \mathrm{M1} = {F_{m1}}^{-1}(\mathrm{u1}), \mathrm{M2} = {F_{m2}}^{-1}(\mathrm{u2})\right) \quad (11)$$

where and ${F_{m1}}^{-1}(\cdot)$, ${F_{m2}}^{-1}(\cdot)$ denote the quantile function corresponding to the marginal CDFs.

This quantity captures how both biomarkers jointly inform the individual-level risk probability at time t.

To quantify the overall predictiveness of the bivariate marker combination, we employed the Total Gain (TG), defined as $\mathrm{TG}(\mathrm{t}) = \int |R(\mathrm{u},\mathrm{t}) - \Pr(T \le t)|\, du$ for the univariate case. High total gain values were obtained when the predictiveness curve was steep, indicating a strong predictive ability. We now apply these definitions to evaluate the predictiveness of the bivariate marker combination. The total gain for joint combination of Marker 1 and Marker 2 is defined as

$$TG(\mathrm{t}) = \iint |R(u1,u2,t) - \Pr(T \le t)|\, du1 du2.$$

This measure reflects the average absolute deviation of the joint conditional risk from the marginal risk across the entire distribution of biomarker values. The TG achieves its maximum value of $2\mathrm{S}(\mathrm{t})[1 - \mathrm{S}(\mathrm{t})]$ when the risk estimates perfectly stratify individuals into extreme low- and high-risk groups(Bura & Gastwirth, 2001).

An alternative summary quantification of predictiveness is the time-varying overall standardized total gain defined by

$$STG(\mathrm{t}) = TG(\mathrm{t})/\{2\mathrm{S}(\mathrm{t})[1 - \mathrm{S}(\mathrm{t})]\}$$

which normalizes the total gain to lie between 0 and 1. Higher values of $STG(\mathrm{t})$ indicate steeper predictiveness curves and thus a stronger predictiveness of the joint biomarker model.

3.5. Conditional Diagnostic Measures

In clinical decision-making, evaluating the discriminatory ability of a new biomarker (Marker 1) in the presence of an existing validated biomarker (Marker 2) is often of particular interest, especially when Marker 2 is a controllable or clinically actionable factor. When Marker 2 is fixed at a given value m2, the performance of Marker 1 can be assessed using conditional time-dependent discrimination metrics.

The conditional dynamic false positive rate (FPR) at time t, for a threshold $m1$, conditional on $M2 = m2$, denoted by Marker 2-specific FPR, is defined as

$$\mathrm{FPR}(\mathrm{m1},\mathrm{t}|\mathrm{m2}) = \Pr(\mathrm{M1} > \mathrm{m1}|\mathrm{M2} = \mathrm{m2}, \mathrm{T} > \mathrm{t})$$

$$= 1 - \Pr(\mathrm{M1} \leq \mathrm{m1}|\mathrm{M2} = \mathrm{m2}, \mathrm{T} > \mathrm{t}).$$

It can be shown under FNAC model given by Equation (7) that

$$\mathrm{FPR}(\mathrm{m1},\mathrm{t}|\mathrm{m2}) = 1 - \frac{\partial \mathrm{H}(\mathrm{m1},\mathrm{m2},\mathrm{t})/\partial \mathrm{m2}}{\partial \mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)/\partial \mathrm{m2}}$$

$$= 1 - \frac{C^{[1]}{}_{\theta_1}\left(\mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right), F_{m1}(m1)\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)}{C^{[1]}{}_{\theta_2}(F_{m2}(\mathrm{m2}), S_t(\mathrm{t}))}.$$

The corresponding conditional Cumulative True positive rate (TPR^C) and Incident True positive rate (TPR^I) can be defined as

$$\mathrm{TPR}^C(\mathrm{m1},\mathrm{t}|\mathrm{m2}) = \Pr(\mathrm{M1} > \mathrm{m1}|\mathrm{M2} = \mathrm{m2}, \mathrm{T} \leq \mathrm{t}) \text{ and}$$

$$\mathrm{TPR}^I(\mathrm{m1},\mathrm{t}|\mathrm{m2}) = \Pr(\mathrm{M1} > \mathrm{m1}|\mathrm{M2} = \mathrm{m2}, \mathrm{T} = \mathrm{t})$$

which are denoted as the marker 2-specific TPR^C and TPR^I, respectively.

Based on the survival copula $C^{(S)}$ given in (Nelsen, 2006) as

$$C^{(S)}(u, v) = u + v - 1 + C(1 - u, 1 - v)$$

where $(u, v) \in [0,1] \times [0,1]$, we can derive the expressions for TPR^C and TPR^I under the FNAC model in Equation (6) as

$$\mathrm{TPR}^C(\mathrm{m1}, \mathrm{t}|\mathrm{m2}) = 1 - \frac{\partial\left(\mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), F_{m2}(\mathrm{m2})\right) - \mathrm{H}(\mathrm{m1}, \mathrm{m2}, \mathrm{t})\right)/\partial \mathrm{m2}}{\partial\left(F_{m2}(\mathrm{m2}) - \mathrm{C}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right)\right)/\partial \mathrm{m2}}$$

$$= 1 - \frac{C^{[1]}{}_{\theta_1}\left(F_{m2}(\mathrm{m2}), F_{m1}(\mathrm{m1})\right) - C^{[1]}{}_{\theta_1}\left(\mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right), F_{m1}(\mathrm{m1})\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)}{1 - C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)}$$

and

$$\mathrm{TPR}^I(\mathrm{m1}, \mathrm{t}|\mathrm{m2}) = 1 - \frac{\partial\left(\mathrm{C}_{\theta_1}\left(F_{m1}(\mathrm{m1}), F_{m2}(\mathrm{m2})\right) - \mathrm{H}(\mathrm{m1}, \mathrm{m2}, \mathrm{t})\right)/\partial \mathrm{m2}\, \partial \mathrm{mt}}{\partial\left(F_{m2}(\mathrm{m2}) - \mathrm{C}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right)\right)/\partial \mathrm{m2}\, \partial \mathrm{mt}}$$

$$= 1 - \Big[C^{[2]}{}_{\theta_1}\left(\mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(t)\right), F_{m1}(\mathrm{m1})\right) C^{[1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right) C^{[1]}{}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right)$$

$$+ C^{[1]}{}_{\theta_1}\left(\mathrm{C}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(t)\right), F_{m1}(\mathrm{m1})\right) C^{[1,1]}{}_{\theta_2}\left(F_{m2}(\mathrm{m2}), S_t(\mathrm{t})\right)\Big] / C^{[1,1]}{}_{\theta_2}\left(S_t(\mathrm{t}), F_{m2}(\mathrm{m2})\right).$$

Two main definitions of time-dependent ROC curves have been proposed in the survival analysis literature (Heagerty and Zheng, 2005). The Marker 2-specific *cumulative/dynamic* ROC curve at time t is defined as the plot of

$$[\mathrm{FPR}(\mathrm{m1}, \mathrm{t}|\mathrm{m2}), \mathrm{TPR}^C(\mathrm{m1}, \mathrm{t}|\mathrm{m2})], \{m1, m2\} \in \mathbb{R}$$

and the corresponding Marker 2-specific *cumulative/dynamic* ROC function is

$$\mathrm{ROC}^{C/D}(\mathrm{q}, \mathrm{t}|\mathrm{m2}) = \mathrm{TPR}^C[\mathrm{FPR}^{-1}(\mathrm{q}, \mathrm{t}|\mathrm{m2}), \mathrm{t}|\mathrm{m2}],$$

where $\mathrm{FPR}^{-1}(\mathrm{q}, \mathrm{t}|\mathrm{m2}) = inf_{m1}\{m1 : FP(m1, t|m2) < q\}$.

Similarly, the Marker 2-specific *incident/dynamic* ROC curve at time t is defined as the plot of

$$[\mathrm{FPR}(\mathrm{m1}, \mathrm{t}|\mathrm{m2}), \mathrm{TPR}^I(\mathrm{m1}, \mathrm{t}|\mathrm{m2})], \{m1, m2\} \in \mathbb{R}$$

and the corresponding Marker 2-specific *incident/dynamic* ROC function is

$$\mathrm{ROC}^{I/D}(\mathrm{q},\mathrm{t}|\mathrm{m2}) = \mathrm{TPR}^{I}[\mathrm{FPR}^{-1}(\mathrm{q},\mathrm{t}|\mathrm{m2}),\mathrm{t}|\mathrm{m2}].$$

The area under each curve is given by

$$AUC^{C/D}(\mathrm{t}|\mathrm{m2}) = \int_0^1 \mathrm{ROC}^{C/D}(\mathrm{x},\mathrm{t}|\mathrm{m2})dx \text{ and}$$

$$AUC^{I/D}(\mathrm{t}|\mathrm{m2}) = \int_0^1 \mathrm{ROC}^{I/D}(\mathrm{x},\mathrm{t}|\mathrm{m2})dx.$$

These ROC and AUC metrics represent the discrimination ability of Marker 1 when Marker 2 is fixed at a specific value m2, that is, in a Marker 2- specific population.

If the marginal distribution of Marker 2, given the survival status, is known or can be estimated, then Marker2-adjusted discrimination measures can be obtained. The adjusted ROC(AROC) is defined as the average Marker 2-specific ROC function by integrating over the distribution of $M2$.

The adjusted *dynamic* FPR at time t is

$$AFPR(\mathrm{m1},\mathrm{t}) = \int \mathrm{FPR}(\mathrm{m1},\mathrm{t}|\mathrm{m2})\,\mathrm{d}F_{m2|T\geq t}(\mathrm{m2}),$$

The adjusted *cumulative* TPR at time t is

$$A\mathrm{TPR}^{C}(\mathrm{m1},\mathrm{t}) = \int \mathrm{TPR}^{C}(\mathrm{m1},\mathrm{t}|\mathrm{m2})\,\mathrm{d}F_{m2|T<t}(\mathrm{m2}),$$

and the adjusted *incident* TPR at time t is

$$\mathrm{ATPR}^{I}(\mathrm{m1},\mathrm{t}) = \int \mathrm{TPR}^{I}(\mathrm{m1},\mathrm{t}|\mathrm{m2})\,\mathrm{d}F_{m2|T=t}(\mathrm{m2}).$$

Using these, the adjusted *cumulative/dynamic* ROC function and AUC are:

$$\mathrm{AROC}^{C/D}(\mathrm{q},\mathrm{t}) = \mathrm{ATPR}^{C}[\mathrm{AFPR}^{-1}(\mathrm{q},\mathrm{t}),\mathrm{t}] \text{ and}$$

$$AAUC^{C/D}(\mathrm{t}) = \int_0^1 \mathrm{AROC}^{C/D}(\mathrm{x},\mathrm{t})dx, \text{ respectively.}$$

The adjusted *incident/dynamic* ROC function and AUC are as follows

$$\mathrm{AROC}^{I/D}(\mathrm{q},\mathrm{t}) = \mathrm{ATPR}^{I}[\mathrm{AFPR}^{-1}(\mathrm{q},\mathrm{t}),\mathrm{t}] \text{ and}$$

$$AAUC^{I/D}(\mathrm{t}) = \int_0^1 \mathrm{AROC}^{I/D}(\mathrm{x},\mathrm{t})dx, \text{ respectively.}$$

Based on the definition of the time-dependent joint risk function and predictiveness surface in Equations (10) and (11), we consider the conditional predictiveness of Marker 1 given Marker 2. If the marginal distribution of Marker 2 is known, the adjusted risk function for Marker 1 at time t can be computed by averaging with respect to the distribution of Marker 2 across Marker 2 levels as follows

$$\mathrm{ARisk}(\mathrm{m1},\mathrm{t}) = \int \mathrm{Risk}(\mathrm{m1},\mathrm{m2},\mathrm{t})\,\mathrm{d}F_{m2}(\mathrm{m2}).$$

The corresponding adjusted predictiveness curve at time t is defined as

$$\mathrm{AR}(\mathrm{u1},\mathrm{t}) = \int \mathrm{R}(\mathrm{u1},\mathrm{u2},\mathrm{t})\,\mathrm{du2}.$$

We now consider the total gain for Marker 1 given Marker 2 which is defined as

$$\mathrm{TG}(\mathrm{t}|\mathrm{m2}) = \int |P(T \le t|M1 = m1, M2 = m2) - P(T \le t|M2 = m2)|\, dF_{m1}(\mathrm{m1})$$

$$= \int |R(\mathrm{u1},\mathrm{u2},\mathrm{t}) - R(\mathrm{u2},\mathrm{t})|\, du1$$

where $R(\mathrm{u2},\mathrm{t}) = P\left(T \le t \middle| \mathrm{M2} = {F_{m2}}^{-1}(\mathrm{u2})\right)$.

Similarly, we define the adjusted total gain for Marker 1 by Marker 2 as

$$\mathrm{ATG}(\mathrm{t}) = \int |AR(\mathrm{u1},\mathrm{t}) - \mathrm{AR}(\mathrm{t})|\, du1$$

where $\mathrm{AR}(\mathrm{t}) = \int R(\mathrm{u2},\mathrm{t})\,\mathrm{du2}$ denotes the cumulative density function averaged over the Marker 2 distribution.

The corresponding standardized total gain is as follows

$$\mathrm{ASTG(t)} = \mathrm{ATG(t)} \,/\, \{2(1-\mathrm{AR(t)})\mathrm{AR(t)}\}$$

where $1-\mathrm{AR(t)}$ represents the survival function averaged over the Marker 2 distribution.

3.6. Goodness-of-fit Evaluation

To assess the goodness-of-fit of the proposed copula model and guide the selection of an appropriate dependence structure, we employ both Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (Joe, 2015). These metrics quantify the trade-off between model fit and complexity:

$$AIC = -2l(\hat{\psi}) + 2k \tag{12}$$

$$BIC = -2l(\hat{\psi}) + klog(n) \tag{13}$$

where $l(\hat{\psi})$ is the log-likelihood based on the estimated model parameters $\hat{\psi}$, k is the number of model parameters, and n is the sample size. Lower values of AIC or BIC indicate better fit, and thus these criteria are used to compare alternative copula families fitted to the same dataset.

In addition to these quantitative criteria, residual-based visual diagnostics can be used to assess model adequacy. These diagnostics are derived from the conditional distributions implied by the fitted copula model and allow for graphical evaluation of potential model misspecification. We first can consider residuals for assessing distribution of survival time T given biomarkers $M1$ and $M2$. Let

$$\hat{\Lambda}_{\mathrm{i}} = -log\left[\hat{S}(t_i|M1 = m1_i, M2 = m2_i)\right]$$

denote the estimated conditional cumulative hazard given the two biomarkers, evaluated at the observed time t_i with

$$\hat{S}(t|M1 = m1, M2 = m2) = \frac{C^{[1,1]}{}_{\theta_1}\left(\hat{F}_{m1}(\mathrm{m1}), \mathrm{C}_{\theta_2}\left(\hat{F}_{m2}(\mathrm{m2}), \hat{S}_t(\mathrm{t})\right)\right) C^{[1]}{}_{\theta_2}\left(\hat{F}_{m2}(\mathrm{m2}), \hat{S}_t(\mathrm{t})\right)}{C^{[1,1]}{}_{\theta_1}\left(\hat{F}_{m1}(m1), \hat{F}_{m2}(m2)\right)}$$

If $\hat{S}_{\Lambda}(\Lambda)$ denotes the Kaplan-Meier for the transformed cumulative hazards $\hat{\Lambda}_{\mathrm{i}}$, then a plot of $\log\left[-\log\hat{S}_{\Lambda}(\hat{\Lambda}_{\mathrm{i}})\right]$ versus $\log(\hat{\Lambda}_{\mathrm{i}})$ should lie approximately on a straight line under correct model specification.(Cox & Snell, 1968)

Next, we assess two types of the conditional Residuals of the biomarkers: Residuals of $M1|M2,\ T$ and Residuals of $M2|M1,\ T$.

These are defined according to the censoring status δ_i, as follows:

$$r_{M1|M2,T}(m1_i, m2_i, t_i)$$
$$= \delta_i \hat{P}(M1 \leq\ m1_i | M2 = m2_i, T = t_i)$$
$$+ (1 - \delta_i)\hat{P}(M1 \leq\ m1_i | M2 = m2_i, T > t_i)$$

$$= \delta_i \frac{\partial^2 H(m1_i, m2_i, t_i)/\partial m2_i \partial t_i}{\partial^2 C_{\theta_2}(m2_i, t_i)/\partial m2_i \partial t_i} + (1 - \delta_i)\frac{\partial H(m1_i, m2_i, t_i)/\partial m2_i}{\partial C_{\theta_2}(m2_i, t_i)/\partial m2_i}$$

$$r_{M2|M1,T}(m1_i, m2_i, t_i)$$
$$= \delta_i \hat{P}(M2 \leq\ m2_i | M1 = m1_i, T = t_i)$$
$$+ (1 - \delta_i)\hat{P}(M2 \leq\ m2_i | M1 = m1_i, T > t_i)$$

$$= \delta_i \frac{\partial^2 H(m1_i, m2_i, t_i)/\partial m1_i \partial t_i}{\partial^2 C_{\theta_1}(m1_i, t_i)/\partial m1_i \partial t_i} + (1 - \delta_i)\frac{\partial H(m1_i, m2_i, t_i)/\partial m1_i}{\partial C_{\theta_1}(m1_i, t_i)/\partial m1_i}$$

Following the method of (Dunn & Smyth, 1996), we compute normalized quantile residuals:

$$\Phi^{-1}\left(r_{M1|M2,T}(m1_i, m2_i, t_i)\right), \qquad \Phi^{-1}\left(r_{M2|M1,T}(m1_i, m2_i, t_i)\right)$$

where Φ^{-1} is the inverse standard normal CDF. These residuals should follow a standard normal distribution under correct model specification. Accordingly, Q–Q plots can be used to visually assess whether the fitted model adequately captures the conditional distributions.

4. Simulation study

4.1. Simulation Design

To evaluate the proposed copula-based framework for discrimination and predictiveness assessment, we conducted comprehensive simulation studies under various conditions. Specifically, we aimed to (i) assess the ability of the model selection criteria to correctly identify the true copula family, (ii) evaluate the accuracy and robustness of model-based performance measures under correct model specification, and (iii) compare the proposed FNAC-based estimators with conventional approaches under both correctly and mis-specified dependence structures.

We examined combinations of data-generating copula families (Clayton, Frank, Gumbel), and censoring rates (20%, 50%, 80%). Each scenario was replicated 1,000 times with a sample size of *n=250*. The simulation process consisted of the following four steps:

Step 1: Data Generation from FNAC

We generated a random vector $\{(u1_i, u2_i, u3_i) \in [0,1]^3, \mathrm{i} = 1, \dots, 250\}$ from a fully nested Archimedean copula (FNAC) using one of the copula families: Frank, Clayton, or Gumbel(Hofert, 2011; McNeil, 2008). The FNAC structure adheres to the hierarchical form described in Equation (6).

The dependence parameters θ_1 and θ_2 were chosen such that the corresponding Kendall's tau values were approximately 0.5 (parent copula) and 0.8 (child copula), respectively, representing moderate to strong dependence.

Step 2: Transformation to Original Scale

The uniform samples were transformed using the inverse CDFs of the specified marginals:

$$m1_i = {F_{M1}}^{-1}(u1_i)$$

$$m2_i = {F_{M2}}^{-1}(u2_i)$$

$$t_i = {F_T}^{-1}(1 - u3_i)$$

$F_{M1}(m1)$and $F_{M2}(m2)$ were taken as the skewed-normal distribution characterized in Equation (7) and (8) with parameters $\boldsymbol{\omega} = (\omega_1, \omega_2, \omega_3) = (1,1,5)$, $\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3) = (2,2,4)$, respectively. $F_T(t)$ was taken as the Weibull represented in Equation (9) with parameters $\boldsymbol{\lambda} = (\lambda_1, \lambda_2) = (2,1)$.

Step 3: Incorporation of Random Censoring

Right-censoring was imposed by generating censoring time $\mathrm{W}\sim\mathrm{Weibull}(\lambda_1, \lambda_3)$, where λ_3 was calibrated to achieve target censoring rates of 20%, 50%, and 80%. The observed time and event indicator defined in Equation (5) can be obtained.

Step 4: Model Fitting and Performance Evaluation

Each simulated dataset was fitted using the proposed FNAC model via maximum likelihood estimation (MLE), incorporating known marginals. Based on the estimated model parameters $\hat{\psi}$, we computed the following time-dependent diagnostic measures, all of which were evaluated at survival time quantiles of 0.25, 0.5, and 0.75.

- Conditional and joint ROC functions (*C/D* and *I/D*)
- Area under the curve (AUC)
- Conditional and joint risk functions
- Standardized Total Gain (STG)

For model selection, the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) represented in Equations (12) and (13) were used to identify the copula family. Bias or Relative bias and mean squared error (MSE) were computed for all measures.

In our comparative analyses with existing approaches, the primary focus was placed on estimating predictiveness function $R(u1, u2, t)$ for evaluating predictiveness and the time-dependent ROC function $FP(u1, u2, t)$ and $\mathrm{TP}^C(u1, u2, t)$ defined under the *cumulative/dynamic (C/D)* framework. There are defined as $FP(u1, u2, t) = \mathrm{FPR}\left(F_{m1}{}^{-1}(\mathrm{u1}), F_{m2}{}^{-1}(\mathrm{u2})\right)$ and $\mathrm{TP}^C(u1, u2, t) = \mathrm{TPR}^C\left(F_{m1}{}^{-1}(\mathrm{u1}), F_{m2}{}^{-1}(\mathrm{u2})\right)$. For comparison of the risk functions, we used two standard regression-based approaches: the Cox proportional hazards model, which estimates hazard ratios under the proportionality assumption and provides baseline survival estimates through partial

likelihood; and the parametric Weibull regression model, which directly models the survival time distribution using a Weibull hazard function. For both models, the estimated survival probabilities were used to compute time-dependent risk curves across the quantiles of marker values. Two standard nonparametric estimators were used for the comparison of ROC functions: the Kaplan–Meier–based method by Heagerty et al. (2000) and the IPCW estimator(Uno et al., 2007), both designed to handle right-censored survival data.

4.2. Simulation Results

The simulation results were summarized across the three copula families, varying censoring levels, and prediction time quantiles. As shown in Table 2, copula selection was perfect (100%) when the true model was either Clayton or Gumbel across all censoring levels. In contrast, under 20% censoring, only 41.6% of the datasets generated under the Frank copula were correctly identified, with 58.4% misclassified, mainly as Gumbel. Specifically, for the mis-specified FNAC with Gumbel, 771 out of 1,000 replicates resulted in boundary estimates for the dependence parameter, effectively reducing to the independence copula. This indicates that the symmetric dependence structure inherent to the Frank copula was either poorly detected or estimated to be very weak in the presence of light censoring. As the censoring increased to 50% and 80%, the selection accuracy for Frank improved to 100%.

When the copula model was correctly specified [Tables 3–11], the proposed FNAC framework consistently achieved low relative bias and MSE in estimating both predictiveness and discrimination measures. For both the Clayton and Frank models, the predictiveness measures such as R, AR, STG and $ASTG$ demonstrated strong robustness regardless of the censoring proportion or prediction horizon. However, the Gumbel-based estimation showed a slightly inflated bias in certain scenarios. For example, in Table 9, under 20% censoring, $AR(0.5, t = 0.75)$ had a relative bias of 0.082, and STG had a relative bias of 0.405 at t = 0.75, highlighting the difficulty of capturing upper-tail dependence under scenarios with light right censoring. Discrimination measures including $AROC, AAUC$, $WROC$, and $WAUC$, were also accurately estimated under correct model specification, with relative Bias and MSE generally below 0.05 for Clayton and Frank models. However, under Gumbel, the adjusted and the weighted indices showed greater variability. For example, in Table 9, under 20% censoring, $WROC\ I/D$(0.25,t=0.5) had a relative bias of -0.108 and $WROC\ C/D$(0.5,t=0.75) exhibited a relative bias of 0.161, once again reflecting the sensitivity of upper-tail dependent structures to right censoring.

Tables [12, 15, 18, 21, 24, 27, 30, 33, 36] present the bias and mean squared error (MSE) of the estimated predictiveness function values for each methodological approach under each simulation scenario. In contrast, Tables [13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, 29, 31, 32, 34, 35, 37, 38] summarize the bias and MSE associated with the ROC function estimation. The FNAC model with a correctly specified copula unsurprisingly outperformed across all settings, yielding the lowest bias and MSE for both the predictive and ROC functions. For risk estimation, the FNAC approach yielded particularly accurate

results for both the Clayton and Frank copula structures. Even under the Gumbel family with 20% censoring, FNAC outperformed the parametric methods, and its accuracy remained the highest at higher censoring levels (≥50%). Regarding ROC function estimation, FNAC achieved comparable or improved performance relative to standard nonparametric methods, including Kaplan–Meier (KM) and inverse probability of censoring weighting (IPCW), particularly with substantial censoring.

In the mis-specified setting, the performance of the FNAC models varied depending on the true underlying copula structure. When the true model was Clayton, the FNAC model mis-specified with the Frank copula still exhibited relatively low bias and MSE—often outperforming the Cox and Weibull models in estimating the risk function. However, the Gumbel-based FNAC frequently failed to converge to a valid copula structure, reverting to the independence copula owing to boundary parameter estimates (e.g., 932 out of 1,000 cases under Clayton with 20% censoring and 691 out of 1,000 under Frank with 50% censoring). This indicates that Gumbel-based models under these settings failed to capture or only weakly captured the dependence inherent in the actual structure. Consequently, their performance under the independence copula assumption deteriorated and closely resembled that of the Cox and Weibull models, which do not account for inter-marker dependence. Similar patterns were observed when the true copula was Frank. Mis-specified FNAC models using Clayton performed relatively well, but Gumbel reverted to independence, yielding unstable estimates. Interestingly, when Gumbel was the true copula, the performance difference between the correct and mis-specified models was not substantial. However, the discrimination performance was generally inferior to that of the KM and IPCW estimators under copula mis-specification, highlighting the importance of correct copula selection when focusing on ROC-based classification.

Table 2. Copula Selection Accuracy (%)

	Clayton	**Frank**	**Gumbel**
20% censoring	100	41.6	100
50% censoring	100	98.1	100
80% censoring	100	100	100

Table 3. Bias and MSE of Discrimination and Predictiveness Measures under Clayton FNAC Model (n = 250, 20% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.168	-0.012	0.000	0.387	-0.004	0.001	0.653	0.002	0.001
AR (0.5,t)	0.188	-0.011	0.000	0.414	-0.002	0.001	0.669	0.002	0.001
ASTG(t)	0.069	0.012	0.000	0.046	0.015	0.000	0.028	0.015	0.000
STG(t)	0.693	0.001	0.000	0.782	0.001	0.000	0.862	0.002	0.000
Discrimination measures									
AROC I/D(0.25,t)	0.297	0.009	0.006	0.269	-0.008	0.005	0.203	-0.002	0.005
AROC I/D(0.5,t)	0.474	-0.002	0.006	0.417	0.001	0.008	0.308	-0.016	0.007
AROC C/D(0.25,t)	0.342	0.008	0.007	0.386	-0.006	0.007	0.431	0.001	0.008
AROC C/D(0.5,t)	0.517	-0.002	0.006	0.528	0.000	0.007	0.528	-0.006	0.006
AAUC I/D(t)	0.738	0.002	0.000	0.739	0.002	0.000	0.732	0.004	0.000
AAUC C/D(t)	0.758	0.003	0.000	0.799	0.003	0.000	0.852	0.003	0.000
WROC I/D(0.25,t)	0.864	0.001	0.013	0.556	-0.006	0.006	0.223	-0.001	0.001
WROC I/D(0.5,t)	0.573	0.000	0.007	0.323	-0.002	0.004	0.114	-0.010	0.001
WROC C/D(0.25,t)	0.927	0.000	0.015	0.644	-0.006	0.007	0.284	-0.001	0.002
WROC C/D(0.5,t)	0.583	0.000	0.008	0.335	-0.002	0.004	0.120	-0.010	0.001
WAUC I/D(t)	0.543	0.001	0.000	0.359	0.001	0.000	0.154	-0.003	0.000
WAUC C/D(t)	0.615	0.000	0.000	0.532	-0.001	0.000	0.431	-0.002	0.000

Table 4. Bias and MSE of Discrimination and Predictiveness Measures under Clayton FNAC Model (n = 250, 50% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.104	-0.013	0.000	0.250	-0.007	0.000	0.466	-0.002	0.001
AR (0.5,t)	0.118	-0.013	0.000	0.275	-0.006	0.000	0.492	-0.001	0.001
ASTG(t)	0.077	0.005	0.000	0.060	0.007	0.000	0.039	0.010	0.000
STG(t)	0.661	0.004	0.001	0.730	0.003	0.001	0.808	0.003	0.000
Discrimination measures									
AROC I/D(0.25,t)	0.302	-0.007	0.006	0.290	0.001	0.006	0.247	0.001	0.006
AROC I/D(0.5,t)	0.487	0.003	0.006	0.451	0.000	0.007	0.388	0.019	0.007
AROC C/D(0.25,t)	0.328	-0.006	0.006	0.360	0.001	0.007	0.393	0.000	0.008
AROC C/D(0.5,t)	0.512	0.003	0.006	0.518	0.000	0.006	0.526	0.013	0.006
AAUC I/D(t)	0.734	0.003	0.000	0.740	0.002	0.000	0.738	0.003	0.000
AAUC C/D(t)	0.744	0.003	0.000	0.774	0.003	0.000	0.814	0.003	0.000
WROC I/D(0.25,t)	0.955	-0.003	0.014	0.747	-0.001	0.010	0.452	0.001	0.004
WROC I/D(0.5,t)	0.666	0.004	0.011	0.472	0.002	0.007	0.251	0.022	0.003
WROC C/D(0.25,t)	1.001	-0.004	0.015	0.825	-0.003	0.012	0.538	0.000	0.006
WROC C/D(0.5,t)	0.673	0.004	0.011	0.483	0.002	0.007	0.261	0.022	0.003
WAUC I/D(t)	0.596	0.001	0.000	0.474	0.001	0.000	0.294	0.001	0.000
WAUC C/D(t)	0.639	0.000	0.000	0.584	0.000	0.000	0.502	-0.001	0.000

Table 5. Bias and MSE of Discrimination and Predictiveness Measures under Clayton FNAC Model (n = 250, 80% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.041	-0.012	0.000	0.099	-0.009	0.000	0.200	-0.005	0.001
AR (0.5,t)	0.047	-0.014	0.000	0.113	-0.011	0.000	0.222	-0.006	0.001
ASTG(t)	0.085	-0.005	0.000	0.078	-0.006	0.000	0.066	-0.006	0.000
STG(t)	0.626	0.010	0.001	0.658	0.009	0.001	0.708	0.008	0.001
Discrimination measures									
AROC I/D(0.25,t)	0.302	-0.005	0.007	0.304	-0.004	0.005	0.294	0.011	0.004
AROC I/D(0.5,t)	0.502	-0.004	0.008	0.490	0.004	0.005	0.463	0.001	0.006
AROC C/D(0.25,t)	0.312	-0.005	0.008	0.329	-0.004	0.006	0.348	0.011	0.005
AROC C/D(0.5,t)	0.511	-0.004	0.008	0.513	0.004	0.004	0.516	0.001	0.005
AAUC I/D(t)	0.725	0.004	0.000	0.733	0.003	0.000	0.739	0.003	0.000
AAUC C/D(t)	0.728	0.004	0.000	0.743	0.004	0.000	0.764	0.003	0.000
WROC I/D(0.25,t)	1.041	0.005	0.020	0.967	0.005	0.018	0.814	0.008	0.013
WROC I/D(0.5,t)	0.767	0.001	0.013	0.673	0.002	0.010	0.534	0.004	0.008
WROC C/D(0.25,t)	1.062	0.004	0.020	1.011	0.004	0.019	0.884	0.007	0.015
WROC C/D(0.5,t)	0.771	0.001	0.013	0.680	0.002	0.011	0.545	0.003	0.009
WAUC I/D(t)	0.646	0.001	0.000	0.600	0.001	0.000	0.517	0.001	0.000
WAUC C/D(t)	0.662	0.001	0.000	0.640	0.001	0.000	0.603	0.000	0.000

Table 6. Bias and MSE of Discrimination and Predictiveness Measures under Frank FNAC Model (n = 250, 20% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.174	-0.009	0.000	0.394	-0.004	0.000	0.652	0.000	0.000
AR (0.5,t)	0.183	-0.009	0.000	0.415	-0.003	0.000	0.675	0.000	0.000
ASTG(t)	0.062	0.015	0.000	0.040	0.016	0.000	0.040	0.010	0.000
STG(t)	0.777	0.003	0.000	0.820	0.003	0.000	0.820	0.004	0.000
Discrimination measures									
AROC I/D(0.25,t)	0.347	0.008	0.008	0.238	0.011	0.004	0.140	-0.011	0.003
AROC I/D(0.5,t)	0.530	-0.011	0.008	0.382	0.013	0.008	0.234	0.015	0.009
AROC C/D(0.25,t)	0.449	0.007	0.008	0.443	0.006	0.005	0.418	-0.004	0.006
AROC C/D(0.5,t)	0.612	-0.008	0.007	0.566	0.009	0.006	0.510	0.009	0.008
AAUC I/D(t)	0.779	0.004	0.000	0.722	0.006	0.000	0.630	0.010	0.000
AAUC C/D(t)	0.817	0.005	0.000	0.829	0.005	0.000	0.822	0.007	0.000
WROC I/D(0.25,t)	0.906	0.000	0.011	0.504	0.005	0.003	0.193	0.000	0.000
WROC I/D(0.5,t)	0.575	0.001	0.004	0.297	-0.002	0.001	0.103	0.005	0.000
WROC C/D(0.25,t)	0.981	-0.001	0.012	0.607	0.003	0.004	0.280	-0.003	0.001
WROC C/D(0.5,t)	0.586	0.001	0.004	0.314	-0.002	0.001	0.119	0.004	0.000
WAUC I/D(t)	0.563	0.001	0.000	0.323	0.001	0.000	0.128	-0.001	0.000
WAUC C/D(t)	0.679	0.000	0.000	0.556	0.000	0.000	0.434	-0.002	0.000

Table 7. Bias and MSE of Discrimination and Predictiveness Measures under Frank FNAC Model (n = 250, 50% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.107	-0.010	0.000	0.259	-0.006	0.000	0.471	-0.003	0.000
AR (0.5,t)	0.113	-0.010	0.000	0.273	-0.006	0.000	0.494	-0.002	0.001
ASTG(t)	0.076	0.010	0.000	0.050	0.012	0.000	0.038	0.011	0.000
STG(t)	0.749	0.004	0.000	0.800	0.004	0.000	0.824	0.004	0.000
Discrimination measures									
AROC I/D(0.25,t)	0.383	0.007	0.007	0.304	-0.004	0.010	0.204	-0.006	0.003
AROC I/D(0.5,t)	0.569	0.003	0.006	0.466	0.002	0.006	0.338	-0.006	0.007
AROC C/D(0.25,t)	0.446	0.006	0.007	0.451	-0.005	0.010	0.435	-0.002	0.004
AROC C/D(0.5,t)	0.617	0.003	0.005	0.591	0.002	0.004	0.554	-0.003	0.007
AAUC I/D(t)	0.790	0.004	0.000	0.759	0.005	0.000	0.697	0.007	0.000
AAUC C/D(t)	0.806	0.005	0.000	0.824	0.005	0.000	0.829	0.006	0.000
WROC I/D(0.25,t)	1.062	-0.004	0.018	0.740	0.004	0.006	0.397	0.005	0.002
WROC I/D(0.5,t)	0.686	0.004	0.006	0.453	0.010	0.003	0.225	0.000	0.001
WROC C/D(0.25,t)	1.116	-0.005	0.019	0.831	0.002	0.007	0.500	0.002	0.003
WROC C/D(0.5,t)	0.694	0.004	0.006	0.467	0.010	0.003	0.242	-0.001	0.001
WAUC I/D(t)	0.646	0.000	0.000	0.463	0.001	0.000	0.255	0.001	0.000
WAUC C/D(t)	0.719	0.000	0.000	0.630	0.000	0.000	0.517	-0.001	0.000

Table 8. Bias and MSE of Discrimination and Predictiveness Measures under Frank FNAC Model (n = 250, 80% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.040	-0.013	0.000	0.102	-0.012	0.000	0.207	-0.009	0.000
AR (0.5,t)	0.043	-0.014	0.000	0.107	-0.013	0.000	0.218	-0.009	0.000
ASTG(t)	0.094	0.006	0.000	0.077	0.008	0.000	0.057	0.013	0.000
STG(t)	0.706	0.007	0.001	0.746	0.006	0.001	0.788	0.005	0.001
Discrimination measures									
AROC I/D(0.25,t)	0.417	0.002	0.007	0.388	0.004	0.008	0.326	0.008	0.006
AROC I/D(0.5,t)	0.612	0.005	0.005	0.573	0.004	0.005	0.503	0.000	0.008
AROC C/D(0.25,t)	0.439	0.003	0.007	0.448	0.004	0.008	0.447	0.006	0.006
AROC C/D(0.5,t)	0.624	0.006	0.005	0.617	0.004	0.004	0.603	0.000	0.006
AAUC I/D(t)	0.787	0.006	0.000	0.791	0.005	0.000	0.772	0.005	0.000
AAUC C/D(t)	0.785	0.007	0.000	0.805	0.006	0.000	0.820	0.005	0.000
WROC I/D(0.25,t)	1.227	-0.007	0.025	1.069	0.002	0.018	0.840	0.000	0.011
WROC I/D(0.5,t)	0.825	0.002	0.009	0.696	0.005	0.006	0.524	0.005	0.004
WROC C/D(0.25,t)	1.252	-0.007	0.026	1.121	0.001	0.019	0.922	-0.002	0.012
WROC C/D(0.5,t)	0.829	0.002	0.009	0.704	0.005	0.006	0.537	0.005	0.004
WAUC I/D(t)	0.731	0.000	0.000	0.652	0.001	0.000	0.523	0.002	0.000
WAUC C/D(t)	0.759	0.000	0.000	0.722	0.000	0.000	0.660	0.000	0.000

Table 9. Bias and MSE of Discrimination and Predictiveness Measures under Gumbel FNAC Model (n = 250, 20% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.185	0.021	0.000	0.396	0.059	0.001	0.651	0.073	0.003
AR (0.5,t)	0.190	0.036	0.000	0.417	0.084	0.002	0.676	0.082	0.004
ASTG(t)	0.042	**0.437**	0.000	0.043	**0.417**	0.000	0.047	**0.405**	0.000
STG(t)	0.830	-0.045	0.002	0.792	-0.054	0.002	0.770	-0.052	0.002
Discrimination measures									
AROC I/D(0.25,t)	0.304	-0.066	0.008	0.186	**-0.108**	0.007	0.128	-0.056	0.002
AROC I/D(0.5,t)	0.484	-0.036	0.010	0.315	-0.055	0.009	0.231	-0.060	0.009
AROC C/D(0.25,t)	0.525	-0.036	0.008	0.431	-0.044	0.010	0.386	-0.024	0.006
AROC C/D(0.5,t)	0.661	-0.021	0.007	0.545	-0.025	0.007	0.487	-0.026	0.008
AAUC I/D(t)	0.767	-0.011	0.000	0.679	-0.013	0.000	0.611	-0.012	0.000
AAUC C/D(t)	0.851	-0.002	0.000	0.816	-0.002	0.000	0.791	0.002	0.000
WROC I/D(0.25,t)	0.861	-0.069	0.016	0.467	-0.069	0.004	0.207	-0.009	0.001
WROC I/D(0.5,t)	0.535	0.044	0.006	0.283	0.068	0.002	0.113	**0.121**	0.001
WROC C/D(0.25,t)	0.972	-0.050	0.017	0.597	-0.022	0.005	0.311	0.067	0.002
WROC C/D(0.5,t)	0.556	0.050	0.007	0.307	0.087	0.003	0.131	**0.161**	0.001
WAUC I/D(t)	0.527	-0.010	0.000	0.294	-0.005	0.000	0.134	0.021	0.000
WAUC C/D(t)	0.716	-0.013	0.000	0.553	-0.016	0.000	0.428	-0.009	0.000

Table 10. Bias and MSE of Discrimination and Predictiveness Measures under Gumbel FNAC Model (n = 250, 50% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.119	0.015	0.000	0.266	0.029	0.001	0.471	0.041	0.001
AR (0.5,t)	0.121	0.019	0.000	0.276	0.042	0.001	0.496	0.055	0.002
ASTG(t)	0.042	**0.276**	0.000	0.042	**0.266**	0.000	0.044	**0.256**	0.000
STG(t)	0.847	-0.021	0.001	0.813	-0.026	0.001	0.784	-0.028	0.001
Discrimination measures									
AROC I/D(0.25,t)	0.391	-0.015	0.007	0.245	-0.033	0.004	0.165	-0.011	0.006
AROC I/D(0.5,t)	0.581	-0.007	0.008	0.403	-0.026	0.008	0.286	-0.016	0.006
AROC C/D(0.25,t)	0.585	-0.003	0.006	0.480	-0.009	0.005	0.414	0.004	0.009
AROC C/D(0.5,t)	0.718	-0.001	0.006	0.608	-0.008	0.005	0.524	0.001	0.005
AAUC I/D(t)	0.811	0.001	0.000	0.727	-0.001	0.000	0.657	-0.001	0.000
AAUC C/D(t)	0.865	0.006	0.000	0.836	0.004	0.000	0.807	0.005	0.000
WROC I/D(0.25,t)	1.054	-0.033	0.017	0.678	-0.033	0.006	0.376	-0.026	0.002
WROC I/D(0.5,t)	0.648	0.030	0.006	0.422	0.042	0.003	0.223	0.040	0.001
WROC C/D(0.25,t)	1.144	-0.029	0.019	0.802	-0.018	0.007	0.503	0.003	0.003
WROC C/D(0.5,t)	0.664	0.031	0.006	0.446	0.046	0.003	0.246	0.050	0.001
WAUC I/D(t)	0.638	0.000	0.000	0.421	-0.004	0.000	0.238	-0.006	0.000
WAUC C/D(t)	0.787	-0.001	0.000	0.644	-0.003	0.000	0.511	-0.004	0.000

Table 11. Bias and MSE of Discrimination and Predictiveness Measures under Gumbel FNAC Model (n = 250, 80% Censoring)

	t0.25			t0.5			t0.75		
	True value	Relative bias	MSE	True value	Relative bias	MSE	True value	Relative bias	MSE
Predictiveness measures									
AR(0.25,t)	0.048	0.036	0.000	0.114	0.023	0.000	0.218	0.016	0.000
AR (0.5,t)	0.048	0.036	0.000	0.115	0.024	0.000	0.224	0.018	0.001
ASTG(t)	0.043	0.074	0.000	0.042	0.073	0.000	0.042	0.071	0.000
STG(t)	0.860	-0.002	0.000	0.848	-0.002	0.000	0.823	-0.001	0.001
Discrimination measures									
AROC I/D(0.25,t)	0.586	0.004	0.009	0.401	0.007	0.008	0.281	-0.007	0.005
AROC I/D(0.5,t)	0.742	0.007	0.005	0.590	0.008	0.008	0.448	-0.002	0.005
AROC C/D(0.25,t)	0.683	0.006	0.006	0.591	0.009	0.006	0.508	0.005	0.005
AROC C/D(0.5,t)	0.782	0.007	0.002	0.722	0.006	0.006	0.638	0.003	0.004
AAUC I/D(t)	0.881	0.005	0.000	0.815	0.007	0.000	0.750	0.008	0.000
AAUC C/D(t)	0.864	0.006	0.000	0.866	0.007	0.000	0.844	0.008	0.000
WROC I/D(0.25,t)	1.332	0.002	0.025	1.069	-0.002	0.012	0.781	0.002	0.006
WROC I/D(0.5,t)	0.794	0.018	0.008	0.658	0.017	0.005	0.488	0.017	0.003
WROC C/D(0.25,t)	1.381	0.001	0.026	1.156	-0.003	0.014	0.898	0.002	0.007
WROC C/D(0.5,t)	0.802	0.018	0.008	0.673	0.016	0.005	0.510	0.016	0.003
WAUC I/D(t)	0.802	0.003	0.000	0.648	0.003	0.000	0.481	0.002	0.000
WAUC C/D(t)	0.887	0.003	0.000	0.793	0.004	0.000	0.685	0.005	0.000

Table 12. Comparison of Bias and MSE of Risk function (True model: Clayton, n=250, 20% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.018	0.000	0.028	0.001	0.000	0.000	0.000	0.000	0.014	0.000
R(0.5,0.25,t)		0.000	0.023	0.001	0.034	0.001	0.000	0.000	0.000	0.000	0.018	0.000
R(0.25,0.5,t)		0.020	0.022	0.001	0.041	0.002	0.000	0.000	-0.014	0.000	0.025	0.001
R(0.5,0.5,t)		0.025	0.028	0.001	0.049	0.003	0.000	0.000	-0.017	0.000	0.040	0.002
R(0.25,0.25,t)	t0.5	0.002	0.100	0.011	**0.140**	0.021	0.000	0.000	0.001	0.000	**0.113**	0.014
R(0.5,0.25,t)		0.002	**0.123**	0.016	**0.167**	0.029	0.000	0.000	0.001	0.000	**0.139**	0.021
R(0.25,0.5,t)		0.229	0.000	0.003	0.065	0.007	-0.004	0.001	-0.065	0.005	0.069	0.007
R(0.5,0.5,t)		0.277	0.000	0.004	0.066	0.007	-0.004	0.001	-0.070	0.006	**0.122**	0.017
R(0.25,0.25,t)	t0.75	0.121	**0.289**	0.087	**0.325**	**0.108**	-0.002	0.001	0.054	0.004	**0.333**	**0.113**
R(0.5,0.25,t)		0.142	**0.343**	**0.122**	**0.369**	**0.140**	-0.002	0.001	0.073	0.006	**0.381**	**0.148**
R(0.25,0.5,t)		0.949	**-0.223**	0.053	**-0.208**	0.045	0.001	0.000	-0.031	0.001	**-0.216**	0.047
R(0.5,0.5,t)		0.975	**-0.172**	0.031	**-0.170**	0.030	0.001	0.000	-0.013	0.000	**-0.138**	0.019

†In 932 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 13. Comparison of Bias and MSE of FPR (True model: Clayton, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.597	0.001	0.001	0.001	0.001	0.002	0.001	**-0.111**	0.013	0.003	0.001
FP(0.5,0.25,t)		0.384	0.001	0.001	0.001	0.001	0.001	0.000	-0.076	0.006	0.005	0.001
FP(0.25,0.5,t)		0.348	0.001	0.001	0.001	0.001	0.001	0.000	-0.071	0.005	0.028	0.001
FP(0.5,0.5,t)		0.257	0.001	0.001	0.001	0.001	0.001	0.000	-0.046	0.002	0.013	0.001
FP(0.25,0.25,t)	t0.5	0.462	0.001	0.002	0.001	0.002	0.002	0.001	**-0.101**	0.011	0.005	0.001
FP(0.5,0.25,t)		0.254	-0.001	0.001	-0.001	0.002	0.001	0.000	-0.067	0.005	0.004	0.001
FP(0.25,0.5,t)		0.146	0.000	0.001	0.001	0.001	0.001	0.000	-0.035	0.001	0.065	0.005
FP(0.5,0.5,t)		0.096	-0.001	0.001	-0.001	0.001	0.001	0.000	-0.024	0.001	0.032	0.001
FP(0.25,0.25,t)	t0.75	0.175	0.002	0.002	0.003	0.002	0.000	0.000	-0.045	0.002	**0.107**	0.013
FP(0.5,0.25,t)		0.072	0.001	0.001	0.001	0.001	0.000	0.000	-0.024	0.001	0.059	0.004
FP(0.25,0.5,t)		0.004	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.078	0.006
FP(0.5,0.5,t)		0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.038	0.002

†In 932 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 14. Comparison of Bias and MSE of TPR (True model: Clayton, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.977	0.000	0.001	0.000	0.000	0.000	0.000	0.001	0.000	-0.013	0.000
TP(0.5,0.25,t)		0.838	0.000	0.003	0.001	0.003	0.001	0.000	0.057	0.004	0.050	0.003
TP(0.25,0.5,t)		0.971	0.001	0.001	0.001	0.001	0.000	0.000	0.005	0.000	-0.031	0.001
TP(0.5,0.5,t)		0.834	0.000	0.003	0.001	0.003	0.001	0.000	0.060	0.004	0.039	0.002
TP(0.25,0.25,t)	t0.5	0.964	0.000	0.000	0.001	0.000	0.000	0.000	-0.007	0.000	-0.049	0.003
TP(0.5,0.25,t)		0.781	0.003	0.002	0.005	0.002	0.001	0.001	0.034	0.002	-0.007	0.001
TP(0.25,0.5,t)		0.925	0.001	0.001	0.003	0.001	0.001	0.000	0.000	0.000	-0.097	0.010
TP(0.5,0.5,t)		0.756	0.003	0.002	0.006	0.002	0.001	0.001	0.039	0.002	-0.035	0.002
TP(0.25,0.25,t)	t0.75	0.925	0.001	0.001	0.005	0.001	0.000	0.000	-0.040	0.002	-0.089	0.008
TP(0.5,0.25,t)		0.680	0.001	0.002	0.012	0.002	0.000	0.000	-0.021	0.001	-0.026	0.001
TP(0.25,0.5,t)		0.714	0.001	0.001	0.023	0.002	-0.001	0.000	-0.046	0.002	-0.036	0.002
TP(0.5,0.5,t)		0.564	0.001	0.002	0.022	0.002	0.000	0.000	-0.016	0.001	0.001	0.001

†In 932 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 15. Comparison of Bias and MSE of Risk function (True model: Clayton, n=250, 50% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.012	0.000	0.016	0.000	0.000	0.000	0.000	0.000	0.007	0.000
R(0.5,0.25,t)		0.000	0.015	0.000	0.019	0.000	0.000	0.000	0.000	0.000	0.009	0.000
R(0.25,0.5,t)		0.008	0.018	0.000	0.026	0.001	0.000	0.000	-0.005	0.000	0.011	0.000
R(0.5,0.5,t)		0.010	0.021	0.001	0.030	0.001	0.000	0.000	-0.006	0.000	0.018	0.000
R(0.25,0.25,t)	t0.5	0.000	0.047	0.003	0.071	0.005	0.000	0.000	0.001	0.000	0.046	0.002
R(0.5,0.25,t)		0.000	0.058	0.004	0.084	0.008	0.000	0.000	0.001	0.000	0.058	0.004
R(0.25,0.5,t)		0.054	0.051	0.003	0.092	0.009	-0.002	0.000	-0.021	0.001	0.067	0.005
R(0.5,0.5,t)		0.067	0.059	0.004	**0.105**	0.012	-0.002	0.000	-0.022	0.001	**0.108**	0.012
R(0.25,0.25,t)	t0.75	0.006	**0.177**	0.033	**0.211**	0.046	0.000	0.000	0.012	0.000	**0.182**	0.035
R(0.5,0.25,t)		0.007	**0.213**	0.047	**0.247**	0.063	0.000	0.000	0.016	0.000	**0.225**	0.053
R(0.25,0.5,t)		0.459	-0.086	0.016	-0.047	0.009	-0.004	0.002	-0.066	0.006	-0.061	0.009
R(0.5,0.5,t)		0.534	-0.099	0.018	-0.065	0.010	-0.004	0.002	-0.046	0.004	-0.010	0.006

†In 943 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 16. Comparison of Bias and MSE of FPR (True model: Clayton, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.629	0.001	0.001	0.001	0.001	0.001	0.001	-0.089	0.009	-0.020	0.001
FP(0.5,0.25,t)		0.420	0.000	0.001	0.000	0.001	0.000	0.000	-0.062	0.004	-0.005	0.001
FP(0.25,0.5,t)		0.400	0.000	0.001	0.000	0.001	0.001	0.000	-0.059	0.004	0.010	0.001
FP(0.5,0.5,t)		0.303	0.001	0.001	0.001	0.001	0.000	0.000	-0.038	0.002	0.006	0.000
FP(0.25,0.25,t)	t0.5	0.552	0.002	0.001	0.002	0.002	0.002	0.001	-0.088	0.009	-0.028	0.002
FP(0.5,0.25,t)		0.337	0.001	0.001	0.001	0.002	0.001	0.000	-0.063	0.004	-0.017	0.001
FP(0.25,0.5,t)		0.277	0.002	0.001	0.002	0.002	0.001	0.000	-0.044	0.002	0.018	0.001
FP(0.5,0.5,t)		0.197	0.002	0.001	0.002	0.001	0.001	0.000	-0.031	0.001	0.003	0.000
FP(0.25,0.25,t)	t0.75	0.396	0.001	0.003	0.001	0.004	0.001	0.001	-0.078	0.007	0.003	0.001
FP(0.5,0.25,t)		0.203	0.000	0.002	0.000	0.003	0.000	0.000	-0.053	0.003	0.009	0.001
FP(0.25,0.5,t)		0.077	0.001	0.001	0.001	0.001	0.000	0.000	-0.010	0.000	0.091	0.009
FP(0.5,0.5,t)		0.047	0.000	0.001	0.000	0.001	0.000	0.000	-0.008	0.000	0.049	0.003

†In 943 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 17. Comparison of Bias and MSE of TPR (True model: Clayton, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.980	0.001	0.001	0.001	0.001	0.000	0.000	0.002	0.000	-0.004	0.000
TP(0.5,0.25,t)		0.852	-0.001	0.004	0.000	0.007	0.000	0.000	0.059	0.004	0.072	0.006
TP(0.25,0.5,t)		0.976	0.001	0.001	0.001	0.001	0.000	0.000	0.004	0.000	-0.015	0.000
TP(0.5,0.5,t)		0.849	0.000	0.004	0.000	0.007	0.000	0.000	0.060	0.004	0.065	0.005
TP(0.25,0.25,t)	t0.5	0.973	0.001	0.001	0.002	0.001	0.000	0.000	-0.002	0.000	-0.028	0.001
TP(0.5,0.25,t)		0.818	0.003	0.003	0.006	0.004	0.001	0.001	0.048	0.003	0.027	0.001
TP(0.25,0.5,t)		0.961	0.002	0.001	0.003	0.001	0.000	0.000	0.000	0.000	-0.066	0.005
TP(0.5,0.5,t)		0.810	0.003	0.003	0.007	0.004	0.001	0.001	0.050	0.003	0.003	0.001
TP(0.25,0.25,t)	t0.75	0.957	0.002	0.001	0.005	0.001	0.000	0.000	-0.016	0.000	-0.063	0.004
TP(0.5,0.25,t)		0.755	0.003	0.002	0.018	0.004	0.000	0.001	0.015	0.001	-0.010	0.001
TP(0.25,0.5,t)		0.881	0.004	0.002	0.023	0.002	0.001	0.000	-0.019	0.001	-0.097	0.010
TP(0.5,0.5,t)		0.709	0.004	0.003	0.028	0.004	0.001	0.001	0.017	0.001	-0.030	0.002

†In 943 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 18. Comparison of Bias and MSE of Risk function (True model: Clayton, n=250, 80% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.005	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.002	0.000
R(0.5,0.25,t)		0.000	0.006	0.000	0.007	0.000	0.000	0.000	0.000	0.000	0.003	0.000
R(0.25,0.5,t)		0.002	0.009	0.000	0.010	0.000	0.000	0.000	-0.001	0.000	0.003	0.000
R(0.5,0.5,t)		0.003	0.010	0.000	0.012	0.000	0.000	0.000	-0.001	0.000	0.005	0.000
R(0.25,0.25,t)	t0.5	0.000	0.016	0.000	0.021	0.000	0.000	0.000	0.000	0.000	0.010	0.000
R(0.5,0.25,t)		0.000	0.019	0.000	0.024	0.001	0.000	0.000	0.000	0.000	0.013	0.000
R(0.25,0.5,t)		0.008	0.025	0.001	0.034	0.001	0.000	0.000	-0.002	0.000	0.015	0.000
R(0.5,0.5,t)		0.010	0.029	0.001	0.039	0.002	0.000	0.000	-0.001	0.000	0.027	0.001
R(0.25,0.25,t)	t0.75	0.000	0.043	0.002	0.054	0.003	0.000	0.000	0.001	0.000	0.034	0.001
R(0.5,0.25,t)		0.000	0.051	0.003	0.063	0.004	0.000	0.000	0.002	0.000	0.044	0.002
R(0.25,0.5,t)		0.031	0.059	0.004	0.077	0.007	-0.001	0.000	-0.005	0.000	0.045	0.002
R(0.5,0.5,t)		0.038	0.067	0.005	0.087	0.008	-0.001	0.000	-0.001	0.000	0.079	0.007

†In 899 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 19. Comparison of Bias and MSE of FPR (True model: Clayton, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.658	0.001	0.001	0.001	0.001	0.001	0.001	-0.075	0.006	-0.040	0.002
FP(0.5,0.25,t)		0.455	0.000	0.001	0.000	0.001	0.000	0.001	-0.051	0.003	-0.012	0.001
FP(0.25,0.5,t)		0.448	0.001	0.001	0.001	0.001	0.000	0.001	-0.050	0.003	-0.007	0.001
FP(0.5,0.5,t)		0.348	0.001	0.001	0.001	0.001	0.000	0.000	-0.029	0.001	0.000	0.000
FP(0.25,0.25,t)	t0.5	0.631	0.001	0.001	0.000	0.002	0.001	0.001	-0.077	0.007	-0.049	0.003
FP(0.5,0.25,t)		0.423	0.001	0.001	0.001	0.002	0.000	0.001	-0.054	0.003	-0.025	0.001
FP(0.25,0.5,t)		0.404	0.001	0.001	0.000	0.002	0.000	0.001	-0.047	0.003	-0.013	0.001
FP(0.5,0.5,t)		0.307	0.001	0.001	0.000	0.002	0.000	0.000	-0.030	0.001	-0.012	0.001
FP(0.25,0.25,t)	t0.75	0.580	0.002	0.002	0.000	0.004	0.001	0.001	-0.079	0.007	-0.049	0.003
FP(0.5,0.25,t)		0.366	0.001	0.002	0.001	0.004	0.000	0.001	-0.058	0.004	-0.027	0.001
FP(0.25,0.5,t)		0.322	0.002	0.002	0.002	0.003	0.001	0.000	-0.040	0.002	0.002	0.001
FP(0.5,0.5,t)		0.234	0.002	0.001	0.002	0.003	0.000	0.000	-0.028	0.001	-0.005	0.000

†In 899 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 20. Comparison of Bias and MSE of TPR (True model: Clayton, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Gumbel†)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.982	0.001	0.002	0.000	0.005	0.000	0.000	0.003	0.000	0.004	0.000
TP(0.5,0.25,t)		0.865	0.002	0.010	0.002	0.022	0.000	0.000	0.062	0.004	0.094	0.009
TP(0.25,0.5,t)		0.979	0.002	0.002	0.000	0.005	0.000	0.000	0.003	0.000	-0.001	0.000
TP(0.5,0.5,t)		0.863	0.003	0.010	0.002	0.023	0.000	0.000	0.062	0.004	0.090	0.009
TP(0.25,0.25,t)	t0.5	0.980	0.002	0.001	0.001	0.003	0.000	0.000	0.002	0.000	-0.006	0.000
TP(0.5,0.25,t)		0.853	0.000	0.005	0.003	0.016	0.000	0.001	0.059	0.004	0.071	0.006
TP(0.25,0.5,t)		0.976	0.003	0.002	0.001	0.003	0.000	0.000	0.001	0.000	-0.023	0.001
TP(0.5,0.5,t)		0.850	0.001	0.006	0.003	0.016	0.000	0.001	0.059	0.004	0.060	0.004
TP(0.25,0.25,t)	t0.75	0.976	0.003	0.002	0.003	0.002	0.000	0.000	-0.001	0.000	-0.022	0.001
TP(0.5,0.25,t)		0.830	0.004	0.005	0.014	0.013	0.001	0.001	0.052	0.003	0.043	0.003
TP(0.25,0.5,t)		0.967	0.006	0.004	0.005	0.002	0.000	0.000	-0.004	0.000	-0.057	0.004
TP(0.5,0.5,t)		0.825	0.007	0.006	0.015	0.013	0.001	0.001	0.051	0.003	0.021	0.001

†In 899 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 21. Comparison of Bias and MSE of Risk function (True model: Frank, n=250, 20% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.010	0.000	0.018	0.000	0.000	0.000	0.007	0.000	0.001	0.000
R(0.5,0.25,t)		0.000	0.013	0.000	0.021	0.001	0.000	0.000	0.008	0.000	0.001	0.000
R(0.25,0.5,t)		0.004	0.028	0.001	0.045	0.002	0.000	0.000	0.025	0.001	0.032	0.001
R(0.5,0.5,t)		0.005	0.034	0.001	0.054	0.003	0.000	0.000	0.035	0.001	0.040	0.002
R(0.25,0.25,t)	t0.5	0.003	0.083	0.008	**0.105**	0.012	0.000	0.000	0.074	0.006	0.007	0.000
R(0.5,0.25,t)		0.004	**0.102**	0.011	**0.126**	0.017	0.000	0.000	0.090	0.009	0.008	0.000
R(0.25,0.5,t)		0.176	0.077	0.009	**0.107**	0.013	-0.003	0.001	**0.101**	0.011	0.076	0.007
R(0.5,0.5,t)		0.218	0.084	0.010	**0.114**	0.015	-0.002	0.001	**0.139**	0.021	0.089	0.010
R(0.25,0.25,t)	t0.75	0.194	**0.202**	0.044	**0.204**	0.044	-0.001	0.001	**0.211**	0.046	-0.024	0.002
R(0.5,0.25,t)		0.233	**0.231**	0.058	**0.228**	0.056	-0.001	0.001	**0.231**	0.056	-0.034	0.003
R(0.25,0.5,t)		0.920	**-0.114**	0.016	**-0.144**	0.023	0.001	0.000	**-0.165**	0.028	-0.053	0.004
R(0.5,0.5,t)		0.960	-0.092	0.010	**-0.122**	0.016	0.001	0.000	**-0.116**	0.014	-0.039	0.002

†In 771 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 22. Comparison of Bias and MSE of FPR (True model: Frank, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.562	0.000	0.001	0.001	0.001	0.001	0.001	0.042	0.002	0.010	0.001
FP(0.5,0.25,t)		0.359	0.000	0.001	0.000	0.001	0.001	0.000	0.028	0.001	0.023	0.001
FP(0.25,0.5,t)		0.338	0.001	0.001	0.001	0.001	0.000	0.000	0.037	0.002	0.023	0.001
FP(0.5,0.5,t)		0.253	0.000	0.001	0.000	0.001	0.001	0.000	0.013	0.000	0.013	0.001
FP(0.25,0.25,t)	t0.5	0.421	0.001	0.002	0.001	0.002	0.001	0.001	0.054	0.004	0.007	0.001
FP(0.5,0.25,t)		0.216	0.000	0.001	0.000	0.001	0.000	0.000	0.043	0.002	0.032	0.001
FP(0.25,0.5,t)		0.130	0.001	0.001	0.001	0.001	0.000	0.000	0.070	0.005	0.033	0.001
FP(0.5,0.5,t)		0.082	0.000	0.001	0.000	0.001	0.000	0.000	0.039	0.002	0.026	0.001
FP(0.25,0.25,t)	t0.75	0.168	-0.001	0.002	0.000	0.002	-0.001	0.000	**0.110**	0.013	0.014	0.001
FP(0.5,0.25,t)		0.063	-0.001	0.001	0.000	0.001	-0.001	0.000	0.065	0.004	0.023	0.001
FP(0.25,0.5,t)		0.006	0.000	0.000	0.000	0.000	0.000	0.000	0.060	0.004	0.010	0.000
FP(0.5,0.5,t)		0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.030	0.001	0.006	0.000

†In 771 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 23. Comparison of Bias and MSE of TPR (True model: Frank, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.980	0.000	0.000	0.000	0.000	0.000	0.000	-0.015	0.000	-0.007	0.000
TP(0.5,0.25,t)		0.901	0.004	0.002	0.005	0.002	0.001	0.000	-0.019	0.001	-0.055	0.004
TP(0.25,0.5,t)		0.979	0.000	0.000	0.000	0.000	0.000	0.000	-0.029	0.001	-0.014	0.000
TP(0.5,0.5,t)		0.900	0.004	0.002	0.005	0.002	0.001	0.000	-0.028	0.001	-0.059	0.004
TP(0.25,0.25,t)	t0.5	0.956	-0.001	0.001	0.001	0.000	0.000	0.000	-0.038	0.002	0.002	0.000
TP(0.5,0.25,t)		0.815	0.002	0.002	0.006	0.002	0.001	0.000	-0.049	0.003	-0.020	0.001
TP(0.25,0.5,t)		0.930	-0.001	0.001	0.001	0.001	0.001	0.000	-0.087	0.008	-0.008	0.000
TP(0.5,0.5,t)		0.799	0.001	0.002	0.006	0.002	0.002	0.000	-0.078	0.007	-0.028	0.002
TP(0.25,0.25,t)	t0.75	0.888	0.000	0.001	0.008	0.001	0.001	0.000	-0.048	0.003	0.036	0.002
TP(0.5,0.25,t)		0.674	0.001	0.002	0.018	0.002	0.001	0.000	-0.030	0.001	0.044	0.003
TP(0.25,0.5,t)		0.702	0.001	0.001	0.024	0.002	-0.001	0.000	-0.025	0.001	0.079	0.007
TP(0.5,0.5,t)		0.579	0.001	0.002	0.026	0.003	0.000	0.000	-0.025	0.001	0.055	0.004

†In 771 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 24. Comparison of Bias and MSE of Risk function (True model: Frank, n=250, 50% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.005	0.000	0.008	0.000	0.000	0.000	0.002	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.006	0.000	0.010	0.000	0.000	0.000	0.003	0.000	0.000	0.000
R(0.25,0.5,t)		0.001	0.012	0.000	0.020	0.000	0.000	0.000	0.008	0.000	0.006	0.000
R(0.5,0.5,t)		0.001	0.015	0.000	0.024	0.001	0.000	0.000	0.011	0.000	0.007	0.000
R(0.25,0.25,t)	t0.5	0.000	0.031	0.001	0.045	0.002	0.000	0.000	0.023	0.001	0.000	0.000
R(0.5,0.25,t)		0.000	0.038	0.002	0.054	0.003	0.000	0.000	0.028	0.001	0.000	0.000
R(0.25,0.5,t)		0.021	0.070	0.005	0.099	0.010	0.000	0.000	0.070	0.005	0.026	0.001
R(0.5,0.5,t)		0.026	0.085	0.008	**0.117**	0.014	0.000	0.000	0.099	0.011	0.030	0.001
R(0.25,0.25,t)	t0.75	0.012	**0.142**	0.022	**0.161**	0.028	0.000	0.000	**0.126**	0.017	-0.004	0.000
R(0.5,0.25,t)		0.015	**0.172**	0.032	**0.192**	0.039	0.000	0.000	**0.153**	0.025	-0.006	0.000
R(0.25,0.5,t)		0.427	-0.025	0.009	-0.010	0.006	-0.001	0.002	-0.020	0.005	-0.001	0.002
R(0.5,0.5,t)		0.507	-0.036	0.009	-0.026	0.006	0.000	0.002	0.008	0.005	-0.022	0.003

†In 691 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 25. Comparison of Bias and MSE of FPR (True model: Frank, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.596	0.001	0.001	0.001	0.001	0.000	0.001	0.017	0.001	0.033	0.002
FP(0.5,0.25,t)		0.401	0.001	0.001	0.002	0.001	0.000	0.000	0.012	0.001	0.039	0.002
FP(0.25,0.5,t)		0.390	0.001	0.001	0.001	0.001	0.000	0.000	0.020	0.001	0.036	0.002
FP(0.5,0.5,t)		0.304	0.001	0.001	0.001	0.001	0.000	0.000	0.002	0.000	0.023	0.001
FP(0.25,0.25,t)	t0.5	0.514	0.001	0.001	0.001	0.002	0.000	0.001	0.016	0.001	0.031	0.002
FP(0.5,0.25,t)		0.304	0.000	0.001	0.001	0.002	0.000	0.000	0.014	0.001	0.047	0.003
FP(0.25,0.5,t)		0.263	0.001	0.001	0.001	0.001	0.000	0.000	0.025	0.001	0.030	0.001
FP(0.5,0.5,t)		0.187	0.000	0.001	0.001	0.001	0.000	0.000	0.007	0.000	0.026	0.001
FP(0.25,0.25,t)	t0.75	0.356	0.000	0.002	0.001	0.004	0.000	0.001	0.039	0.002	0.030	0.002
FP(0.5,0.25,t)		0.167	0.000	0.002	0.002	0.002	0.000	0.000	0.038	0.002	0.049	0.003
FP(0.25,0.5,t)		0.065	0.000	0.001	0.001	0.001	-0.001	0.000	0.078	0.006	0.023	0.001
FP(0.5,0.5,t)		0.038	0.001	0.001	0.001	0.001	0.000	0.000	0.044	0.002	0.019	0.000

†In 691 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 26. Comparison of Bias and MSE of TPR (True model: Frank, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.984	-0.001	0.001	0.000	0.001	0.000	0.000	-0.006	0.000	-0.009	0.000
TP(0.5,0.25,t)		0.920	0.002	0.002	0.003	0.004	0.000	0.000	0.004	0.000	-0.067	0.005
TP(0.25,0.5,t)		0.983	-0.001	0.001	0.000	0.001	0.000	0.000	-0.013	0.000	-0.011	0.000
TP(0.5,0.5,t)		0.919	0.002	0.003	0.003	0.004	0.000	0.000	0.000	0.000	-0.068	0.005
TP(0.25,0.25,t)	t0.5	0.973	0.000	0.001	0.001	0.001	0.000	0.000	-0.023	0.001	-0.006	0.000
TP(0.5,0.25,t)		0.872	0.004	0.002	0.008	0.003	0.001	0.000	-0.030	0.001	-0.051	0.003
TP(0.25,0.5,t)		0.969	0.001	0.001	0.001	0.001	0.000	0.000	-0.054	0.003	-0.009	0.000
TP(0.5,0.5,t)		0.870	0.004	0.002	0.009	0.003	0.001	0.000	-0.049	0.003	-0.054	0.004
TP(0.25,0.25,t)	t0.75	0.943	0.001	0.001	0.008	0.001	0.000	0.000	-0.044	0.002	0.008	0.000
TP(0.5,0.25,t)		0.776	0.003	0.002	0.028	0.004	0.001	0.000	-0.040	0.002	-0.009	0.001
TP(0.25,0.5,t)		0.877	0.003	0.002	0.024	0.002	0.001	0.000	-0.082	0.007	0.019	0.001
TP(0.5,0.5,t)		0.739	0.003	0.002	0.037	0.005	0.002	0.000	-0.064	0.005	-0.006	0.001

†In 691 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 27. Comparison of Bias and MSE of Risk function (True model: Frank, n=250, 80% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.002	0.000	0.003	0.000	0.000	0.000	0.001	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.002	0.000	0.003	0.000	0.000	0.000	0.001	0.000	0.000	0.000
R(0.25,0.5,t)		0.000	0.005	0.000	0.006	0.000	0.000	0.000	0.002	0.000	0.000	0.000
R(0.5,0.5,t)		0.000	0.006	0.000	0.007	0.000	0.000	0.000	0.003	0.000	0.000	0.000
R(0.25,0.25,t)	t0.5	0.000	0.007	0.000	0.011	0.000	0.000	0.000	0.004	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.009	0.000	0.013	0.000	0.000	0.000	0.005	0.000	0.000	0.000
R(0.25,0.5,t)		0.001	0.017	0.000	0.025	0.001	0.000	0.000	0.011	0.000	0.000	0.000
R(0.5,0.5,t)		0.001	0.021	0.001	0.030	0.001	0.000	0.000	0.017	0.000	0.000	0.000
R(0.25,0.25,t)	t0.75	0.000	0.026	0.001	0.034	0.001	0.000	0.000	0.018	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.032	0.001	0.041	0.002	0.000	0.000	0.023	0.001	0.000	0.000
R(0.25,0.5,t)		0.008	0.059	0.004	0.075	0.006	0.000	0.000	0.047	0.003	-0.001	0.000
R(0.5,0.5,t)		0.011	0.072	0.006	0.089	0.009	0.001	0.000	0.071	0.006	-0.002	0.000

†In 625 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 28. Comparison of Bias and MSE of FPR (True model: Frank, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.629	0.000	0.001	0.000	0.001	0.000	0.001	-0.008	0.001	0.043	0.002
FP(0.5,0.25,t)		0.443	0.001	0.001	0.001	0.001	0.000	0.000	-0.003	0.000	0.042	0.002
FP(0.25,0.5,t)		0.440	0.001	0.001	0.000	0.001	-0.001	0.000	-0.001	0.001	0.042	0.002
FP(0.5,0.5,t)		0.355	0.001	0.001	0.001	0.001	0.000	0.000	-0.011	0.001	0.023	0.001
FP(0.25,0.25,t)	t0.5	0.599	0.001	0.001	0.000	0.002	0.001	0.001	-0.012	0.001	0.044	0.003
FP(0.5,0.25,t)		0.404	0.001	0.001	0.001	0.002	0.001	0.000	-0.007	0.000	0.049	0.003
FP(0.25,0.5,t)		0.394	0.001	0.001	0.000	0.002	0.000	0.000	-0.004	0.000	0.041	0.002
FP(0.5,0.5,t)		0.308	0.001	0.001	0.001	0.002	0.001	0.000	-0.015	0.001	0.027	0.001
FP(0.25,0.25,t)	t0.75	0.544	0.001	0.001	0.001	0.004	0.001	0.001	-0.008	0.001	0.046	0.003
FP(0.5,0.25,t)		0.337	0.001	0.001	0.002	0.003	0.001	0.000	0.001	0.000	0.058	0.004
FP(0.25,0.5,t)		0.309	0.001	0.001	0.001	0.003	0.000	0.000	0.008	0.001	0.038	0.002
FP(0.5,0.5,t)		0.227	0.001	0.001	0.000	0.003	0.001	0.000	-0.004	0.000	0.031	0.001

†In 625 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 29. Comparison of Bias and MSE of TPR (True model: Frank, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Gumbel†)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.987	0.000	0.001	0.003	0.001	0.000	0.000	0.001	0.000	-0.013	0.000
TP(0.5,0.25,t)		0.936	0.002	0.005	0.005	0.011	0.000	0.000	0.026	0.001	-0.081	0.007
TP(0.25,0.5,t)		0.987	0.001	0.001	0.003	0.001	0.000	0.000	-0.002	0.000	-0.013	0.000
TP(0.5,0.5,t)		0.936	0.003	0.005	0.005	0.011	0.000	0.000	0.024	0.001	-0.081	0.007
TP(0.25,0.25,t)	t0.5	0.984	0.000	0.001	0.001	0.002	0.000	0.000	-0.007	0.000	-0.012	0.000
TP(0.5,0.25,t)		0.921	0.002	0.004	0.005	0.009	0.001	0.000	0.005	0.000	-0.078	0.007
TP(0.25,0.5,t)		0.984	0.001	0.002	0.001	0.002	0.000	0.000	-0.018	0.000	-0.012	0.000
TP(0.5,0.5,t)		0.921	0.003	0.004	0.005	0.009	0.001	0.000	-0.002	0.000	-0.078	0.007
TP(0.25,0.25,t)	t0.75	0.977	0.001	0.002	0.003	0.001	0.000	0.000	-0.019	0.000	-0.010	0.000
TP(0.5,0.25,t)		0.890	0.005	0.004	0.013	0.009	0.001	0.000	-0.018	0.001	-0.068	0.005
TP(0.25,0.5,t)		0.975	0.004	0.003	0.004	0.002	0.000	0.000	-0.048	0.003	-0.009	0.000
TP(0.5,0.5,t)		0.889	0.007	0.005	0.014	0.009	0.001	0.000	-0.035	0.002	-0.068	0.005

†In 625 out of 1,000 replications, the Gumbel copula estimation defaulted to the independence copula due to the parameter reaching the boundary.

Table 30. Comparison of Bias and MSE of Risk function (True model: Gumbel, n=250, 20% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.003	0.000	0.004	0.000	0.000	0.000	0.000	0.000	0.001	0.000
R(0.5,0.25,t)		0.000	0.004	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.001	0.000
R(0.25,0.5,t)		0.004	0.015	0.000	0.021	0.001	0.003	0.000	0.000	0.000	0.030	0.001
R(0.5,0.5,t)		0.004	0.018	0.000	0.025	0.001	0.004	0.000	0.000	0.000	0.038	0.002
R(0.25,0.25,t)	t0.5	0.012	0.025	0.001	0.035	0.001	0.010	0.000	-0.008	0.000	-0.002	0.000
R(0.5,0.25,t)		0.014	0.031	0.001	0.043	0.002	0.012	0.000	-0.009	0.000	-0.002	0.000
R(0.25,0.5,t)		0.201	0.006	0.002	0.038	0.003	0.016	0.001	-0.019	0.001	0.046	0.003
R(0.5,0.5,t)		0.245	-0.001	0.002	0.040	0.003	0.030	0.002	-0.016	0.001	0.057	0.005
R(0.25,0.25,t)	t0.75	0.263	-0.006	0.003	0.010	0.002	0.042	0.003	-0.058	0.005	-0.095	0.010
R(0.5,0.25,t)		0.303	-0.001	0.004	0.020	0.003	0.049	0.004	-0.056	0.005	**-0.106**	0.013
R(0.25,0.5,t)		0.864	-0.024	0.004	-0.026	0.003	-0.027	0.001	0.051	0.003	0.007	0.001
R(0.5,0.5,t)		0.916	-0.026	0.002	-0.025	0.002	-0.013	0.000	0.043	0.002	0.007	0.000

Table 31. Comparison of Bias and MSE of FPR (True model: Gumbel, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.549	0.000	0.001	0.001	0.001	0.052	0.004	0.019	0.001	0.015	0.001
FP(0.5,0.25,t)		0.343	0.001	0.001	0.001	0.001	0.029	0.001	0.020	0.001	0.034	0.002
FP(0.25,0.5,t)		0.327	0.000	0.001	0.000	0.001	0.040	0.002	0.026	0.001	0.029	0.001
FP(0.5,0.5,t)		0.235	0.000	0.001	0.000	0.001	0.026	0.001	0.030	0.001	0.030	0.001
FP(0.25,0.25,t)	t0.5	0.415	0.000	0.002	0.000	0.002	0.051	0.003	-0.001	0.001	0.002	0.001
FP(0.5,0.25,t)		0.216	0.000	0.001	0.000	0.001	0.022	0.001	-0.008	0.000	0.027	0.001
FP(0.25,0.5,t)		0.136	0.000	0.001	0.000	0.001	0.030	0.001	-0.007	0.000	0.022	0.001
FP(0.5,0.5,t)		0.082	-0.001	0.001	-0.001	0.001	0.016	0.000	-0.002	0.000	0.023	0.001
FP(0.25,0.25,t)	t0.75	0.189	0.001	0.002	0.001	0.002	0.042	0.002	-0.025	0.001	-0.014	0.001
FP(0.5,0.25,t)		0.080	0.001	0.001	0.001	0.001	0.015	0.000	-0.019	0.001	0.003	0.000
FP(0.25,0.5,t)		0.015	0.000	0.000	0.000	0.000	0.011	0.000	-0.009	0.000	-0.001	0.000
FP(0.5,0.5,t)		0.007	0.000	0.000	0.000	0.000	0.005	0.000	-0.004	0.000	0.001	0.000

Table 32. Comparison of Bias and MSE of TPR (True model: Gumbel, n=250, 20% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.976	0.000	0.000	0.001	0.000	0.000	0.000	0.008	0.000	-0.002	0.000
TP(0.5,0.25,t)		0.909	0.001	0.002	0.002	0.002	-0.003	0.000	0.011	0.000	-0.056	0.004
TP(0.25,0.5,t)		0.975	0.001	0.001	0.001	0.000	-0.002	0.000	0.008	0.000	-0.008	0.000
TP(0.5,0.5,t)		0.909	0.001	0.002	0.002	0.002	-0.004	0.000	0.012	0.000	-0.060	0.004
TP(0.25,0.25,t)	t0.5	0.938	0.001	0.001	0.003	0.001	0.000	0.000	0.024	0.001	0.022	0.001
TP(0.5,0.25,t)		0.790	0.002	0.002	0.007	0.002	-0.007	0.001	0.046	0.003	0.012	0.001
TP(0.25,0.5,t)		0.901	0.000	0.001	0.004	0.001	-0.009	0.000	0.039	0.002	0.025	0.001
TP(0.5,0.5,t)		0.768	0.001	0.002	0.008	0.002	-0.011	0.001	0.055	0.004	0.012	0.001
TP(0.25,0.25,t)	t0.75	0.860	0.001	0.001	0.010	0.001	0.000	0.000	0.040	0.002	0.066	0.005
TP(0.5,0.25,t)		0.649	0.002	0.001	0.019	0.002	-0.006	0.001	0.057	0.004	0.077	0.007
TP(0.25,0.5,t)		0.683	0.001	0.001	0.025	0.002	0.003	0.001	0.059	0.004	**0.104**	0.012
TP(0.5,0.5,t)		0.556	0.001	0.002	0.025	0.002	-0.002	0.001	0.070	0.006	0.089	0.009

Table 33. Comparison of Bias and MSE of Risk function (True model: Gumbel, n=250, 50% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.001	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.001	0.000	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.5,t)		0.000	0.004	0.000	0.005	0.000	0.000	0.000	0.000	0.000	0.006	0.000
R(0.5,0.5,t)		0.000	0.004	0.000	0.006	0.000	0.000	0.000	0.000	0.000	0.007	0.000
R(0.25,0.25,t)	t0.5	0.001	0.006	0.000	0.009	0.000	0.001	0.000	-0.001	0.000	-0.001	0.000
R(0.5,0.25,t)		0.001	0.007	0.000	0.011	0.000	0.001	0.000	-0.001	0.000	-0.001	0.000
R(0.25,0.5,t)		0.025	0.022	0.001	0.035	0.002	0.006	0.000	-0.009	0.000	0.019	0.001
R(0.5,0.5,t)		0.031	0.026	0.001	0.042	0.002	0.009	0.000	-0.010	0.000	0.022	0.001
R(0.25,0.25,t)	t0.75	0.034	0.023	0.001	0.031	0.001	0.012	0.000	-0.022	0.001	-0.026	0.001
R(0.5,0.25,t)		0.041	0.029	0.001	0.040	0.002	0.015	0.001	-0.025	0.001	-0.031	0.001
R(0.25,0.5,t)		0.417	-0.074	0.012	-0.061	0.008	0.000	0.002	0.024	0.004	0.001	0.003
R(0.5,0.5,t)		0.490	-0.090	0.014	-0.071	0.009	0.012	0.002	0.030	0.004	-0.012	0.003

Table 34. Comparison of Bias and MSE of FPR (True model: Gumbel, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.583	0.000	0.001	0.000	0.001	0.027	0.002	0.025	0.002	0.035	0.002
FP(0.5,0.25,t)		0.385	0.001	0.001	0.001	0.001	0.017	0.001	0.029	0.001	0.049	0.003
FP(0.25,0.5,t)		0.379	0.000	0.001	0.000	0.001	0.024	0.001	0.033	0.002	0.047	0.003
FP(0.5,0.5,t)		0.285	0.000	0.001	0.000	0.001	0.017	0.001	0.038	0.002	0.043	0.002
FP(0.25,0.25,t)	t0.5	0.503	0.000	0.001	-0.001	0.002	0.026	0.002	0.012	0.001	0.026	0.001
FP(0.5,0.25,t)		0.293	0.000	0.001	0.000	0.002	0.012	0.001	0.009	0.001	0.047	0.003
FP(0.25,0.5,t)		0.257	-0.002	0.001	-0.002	0.002	0.019	0.001	0.013	0.001	0.034	0.002
FP(0.5,0.5,t)		0.173	-0.002	0.001	-0.002	0.001	0.011	0.000	0.017	0.001	0.037	0.002
FP(0.25,0.25,t)	t0.75	0.356	0.000	0.002	-0.001	0.004	0.021	0.001	-0.008	0.001	0.012	0.001
FP(0.5,0.25,t)		0.174	0.000	0.002	0.000	0.002	0.006	0.000	-0.014	0.001	0.031	0.001
FP(0.25,0.5,t)		0.080	-0.001	0.001	0.000	0.001	0.012	0.000	-0.019	0.000	0.006	0.000
FP(0.5,0.5,t)		0.045	-0.001	0.001	-0.001	0.001	0.005	0.000	-0.010	0.000	0.010	0.000

Table 35. Comparison of Bias and MSE of TPR (True model: Gumbel, n=250, 50% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.986	0.010	0.000	0.000	0.001	0.001	0.000	0.002	0.000	-0.009	0.000
TP(0.5,0.25,t)		0.944	**-0.107**	0.012	0.003	0.002	0.002	0.000	-0.005	0.000	-0.080	0.007
TP(0.25,0.5,t)		0.985	-0.047	0.002	0.001	0.001	0.001	0.000	0.002	0.000	-0.011	0.000
TP(0.5,0.5,t)		0.944	**-0.191**	0.037	0.003	0.002	0.002	0.000	-0.005	0.000	-0.081	0.007
TP(0.25,0.25,t)	t0.5	0.963	0.033	0.001	0.002	0.001	0.002	0.000	0.014	0.000	0.005	0.000
TP(0.5,0.25,t)		0.864	-0.028	0.001	0.009	0.003	0.002	0.000	0.028	0.001	-0.033	0.002
TP(0.25,0.5,t)		0.957	-0.019	0.000	0.003	0.001	0.000	0.000	0.018	0.000	0.005	0.000
TP(0.5,0.5,t)		0.861	**-0.108**	0.012	0.009	0.003	0.001	0.000	0.030	0.001	-0.034	0.002
TP(0.25,0.25,t)	t0.75	0.920	0.076	0.006	0.013	0.001	0.002	0.000	0.030	0.001	0.032	0.001
TP(0.5,0.25,t)		0.748	0.089	0.009	0.034	0.004	0.000	0.001	0.052	0.003	0.029	0.002
TP(0.25,0.5,t)		0.844	0.094	0.010	0.030	0.003	-0.003	0.000	0.052	0.003	0.059	0.004
TP(0.5,0.5,t)		0.705	0.048	0.003	0.043	0.005	-0.002	0.001	0.065	0.005	0.042	0.003

Table 36. Comparison of Bias and MSE of Risk function (True model: Gumbel, n=250, 80% censoring)

		True value	Semi-parametric (Cox PH)		Parametric (Weibull)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
R(0.25,0.25,t)	t0.25	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.5,t)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.5,t)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.25,t)	t0.5	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.5,t)		0.000	0.001	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.5,t)		0.000	0.002	0.000	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.25,t)	t0.75	0.000	0.001	0.000	0.002	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.5,0.25,t)		0.000	0.002	0.000	0.003	0.000	0.000	0.000	0.000	0.000	0.000	0.000
R(0.25,0.5,t)		0.009	0.007	0.000	0.010	0.000	0.001	0.000	-0.007	0.000	-0.006	0.000
R(0.5,0.5,t)		0.011	0.008	0.000	0.012	0.000	0.001	0.000	-0.008	0.000	-0.008	0.000

Table 37. Comparison of Bias and MSE of FPR (True model: Gumbel, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
FP(0.25,0.25,t)	t0.25	0.616	0.001	0.001	0.000	0.001	0.005	0.001	0.027	0.002	0.043	0.003
FP(0.5,0.25,t)		0.429	0.001	0.001	0.001	0.001	0.005	0.001	0.032	0.002	0.048	0.003
FP(0.25,0.5,t)		0.429	0.000	0.001	0.000	0.001	0.005	0.001	0.035	0.002	0.048	0.003
FP(0.5,0.5,t)		0.338	0.000	0.001	0.000	0.001	0.006	0.000	0.041	0.002	0.036	0.002
FP(0.25,0.25,t)	t0.5	0.586	0.000	0.001	0.000	0.002	0.005	0.001	0.022	0.001	0.041	0.003
FP(0.5,0.25,t)		0.388	0.001	0.001	0.001	0.002	0.003	0.000	0.026	0.001	0.052	0.003
FP(0.25,0.5,t)		0.383	0.000	0.001	0.000	0.002	0.005	0.001	0.027	0.001	0.043	0.003
FP(0.5,0.5,t)		0.289	0.000	0.001	0.000	0.002	0.004	0.000	0.033	0.001	0.038	0.002
FP(0.25,0.25,t)	t0.75	0.531	0.000	0.001	-0.001	0.004	0.004	0.001	0.015	0.001	0.038	0.002
FP(0.5,0.25,t)		0.323	0.000	0.001	0.000	0.004	0.002	0.000	0.015	0.001	0.056	0.004
FP(0.25,0.5,t)		0.300	-0.001	0.002	-0.002	0.003	0.003	0.000	0.016	0.001	0.035	0.002
FP(0.5,0.5,t)		0.210	-0.001	0.001	-0.001	0.002	0.002	0.000	0.021	0.001	0.037	0.002

Table 38. Comparison of Bias and MSE of TPR (True model: Gumbel, n=250, 80% censoring)

		True value	Heagerty (Kaplan Meier)		Uno (IPCW)		FNAC (Correctly specified)		FNAC (Frank)		FNAC (Clayton)	
			Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
TP(0.25,0.25,t)	t0.25	0.994	-0.012	0.000	0.000	0.001	0.000	0.000	0.000	0.001	-0.020	0.001
TP(0.5,0.25,t)		0.978	-0.093	0.009	0.001	0.004	0.001	0.000	0.001	0.004	**-0.123**	0.016
TP(0.25,0.5,t)		0.994	0.021	0.000	0.000	0.001	0.000	0.000	0.000	0.001	-0.020	0.001
TP(0.5,0.5,t)		0.978	-0.080	0.006	0.001	0.004	0.001	0.000	0.001	0.004	**-0.123**	0.016
TP(0.25,0.25,t)	t0.5	0.986	-0.003	0.000	0.002	0.001	0.001	0.000	0.002	0.001	-0.015	0.000
TP(0.5,0.25,t)		0.946	-0.062	0.004	0.009	0.004	0.003	0.000	0.009	0.004	**-0.104**	0.012
TP(0.25,0.5,t)		0.986	0.029	0.001	0.002	0.001	0.001	0.000	0.002	0.001	-0.015	0.000
TP(0.5,0.5,t)		0.946	-0.048	0.002	0.009	0.004	0.003	0.000	0.009	0.004	**-0.104**	0.012
TP(0.25,0.25,t)	t0.75	0.971	0.012	0.000	0.006	0.002	0.002	0.000	0.006	0.002	-0.006	0.000
TP(0.5,0.25,t)		0.891	-0.007	0.000	0.024	0.008	0.005	0.000	0.024	0.008	-0.071	0.006
TP(0.25,0.5,t)		0.969	0.047	0.002	0.007	0.002	0.001	0.000	0.007	0.002	-0.004	0.000
TP(0.5,0.5,t)		0.890	0.009	0.000	0.024	0.008	0.005	0.000	0.024	0.008	-0.069	0.006

5. Illustration : Application to PBC data

To illustrate the practical applicability of the proposed framework, we applied our model to data from the Mayo Clinic trial in Primary Biliary Cirrhosis (PBC), conducted between 1974 and 1984. This dataset, available in the 'survival' package, consists of 312 patients diagnosed with PBC, a progressive autoimmune liver disease that often requires liver transplantation as a definitive treatment. Thus, the ability to accurately identify high-risk patients is critical for clinical decision-making related to transplantation.

Previous work by Bansal and Heagerty (2019) developed two linear predictors using Cox regression models. The first, referred to as 4-cov, included orthogonal polynomials of degree 1 for albumin and age, the natural logarithm of prothrombin time, and a binary edema status variable (indicating the presence of edema despite diuretic therapy). The second predictor, mayo, augments the 4-cov model by including the natural logarithm of bilirubin, thereby aligning with the original Mayo risk score.

In this application, we used the 4-cov score as an established biomarker (denoted $M2$) and evaluated the discriminative and predictive ability of the natural logarithm of bilirubin as a new candidate biomarker ($M1$). This setup allowed us to assess the diagnostic performance of bilirubin in the presence of the 4-cov score using our copula-based conditional and joint evaluation framework.

Among the 312 patients, 125 (40%) died during follow-up, and 19 underwent liver transplantation. To evaluate biomarker performance in predicting mortality, transplanted patients were treated as censored at the time of transplantation. The median survival time was 3,395 days, and the Kaplan–Meier estimates of survival at 1, 4, and 6 years were 92.9%, 75.2%, and 67.7%, respectively.

Table 39. Comparison of Goodness-of-fit

	Frank	Clayton	Gumbel
Log-likelihood	1928.315	1971.42	1877.759
AIC	-3836.63	-3924.84	-3739.52
BIC	-3832.65	-3921.26	-3736.33

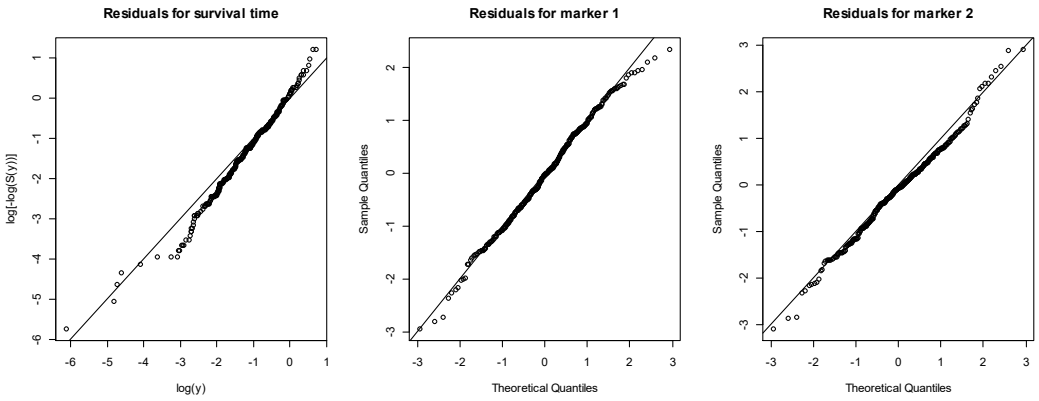

Figure 2. Conditional residual plots under Gumbel-based FNAC

Table 40. MLE estimates under Gumbel-based FNAC

	Estimates	SE
θ_1	1.345	0.233
θ_2	1.489	0.243
ω_1	-0.710	0.061
$\log(\omega_2)$	0.236	0.049
ω_3	5.926	1.245
α_1	8.857	0.062
$\log(\alpha_2)$	0.224	0.048
α_3	4.611	0.771
$\log(\lambda_1)$	0.060	0.073
$\log(\lambda_2)$	3.596	0.078

We fitted the proposed fully nested Archimedean copula (FNAC) model using each of the following copula families: Frank, Clayton, and Gumbel. The marginals were modeled using skew-normal distributions for the biomarkers and a Weibull distribution for survival time. Model fitting was conducted via maximum likelihood estimation, and model comparison based on the AIC and BIC indicated that the Gumbel copula provided the best fit among the candidates (Table 40). Residual diagnostic plots were examined to visually assess the goodness-of-fit of the model under Gumbel (Figure 2), which indicated an

adequate model fit. Parameter estimates under the Gumbel-based FNAC model were obtained as shown in Table 41. Kendall's tau were estimated based on the dependence parameters with $\tau_1 = 0.257, \tau_2 = 0.328$. This suggests moderate intra-marker dependence and slightly weaker marker-to-outcome dependence, both of which are appropriately accommodated within the nested copula structure.

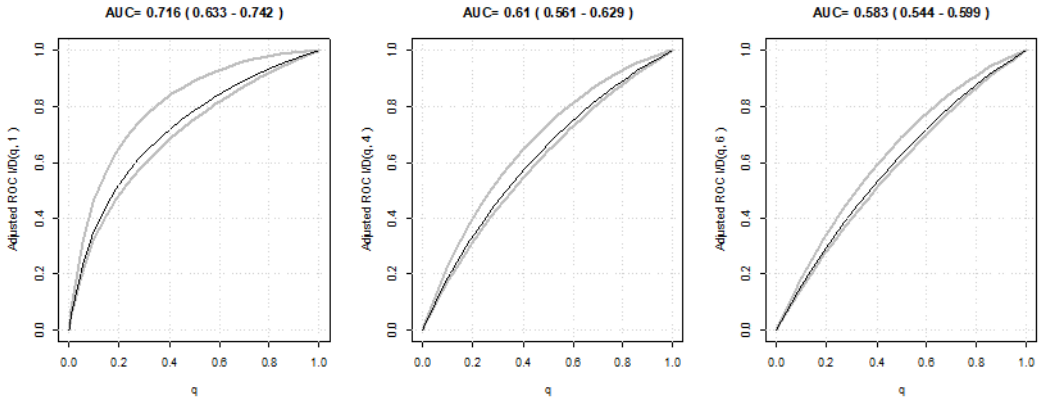

Figure 3. Estimate of adjusted ROC I/D and AUC of bilirubin with 95%CI

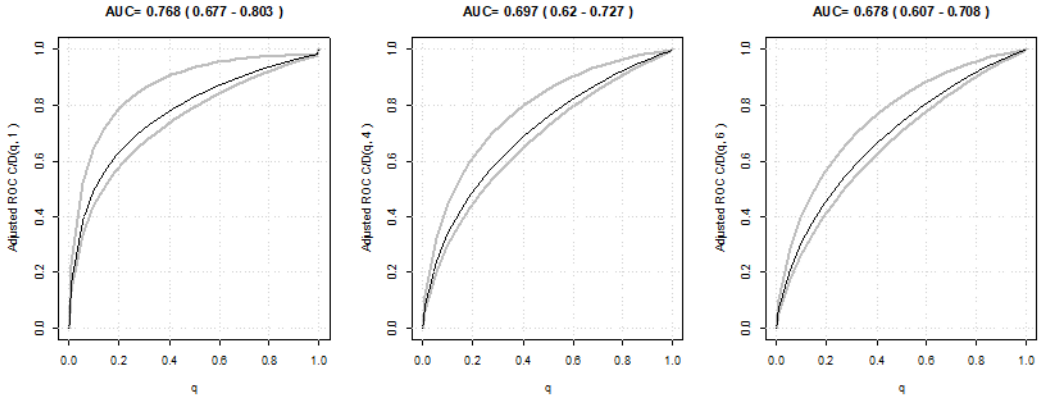

Figure 4. Estimate of adjusted ROC C/D and AUC of bilirubin with 95%CI

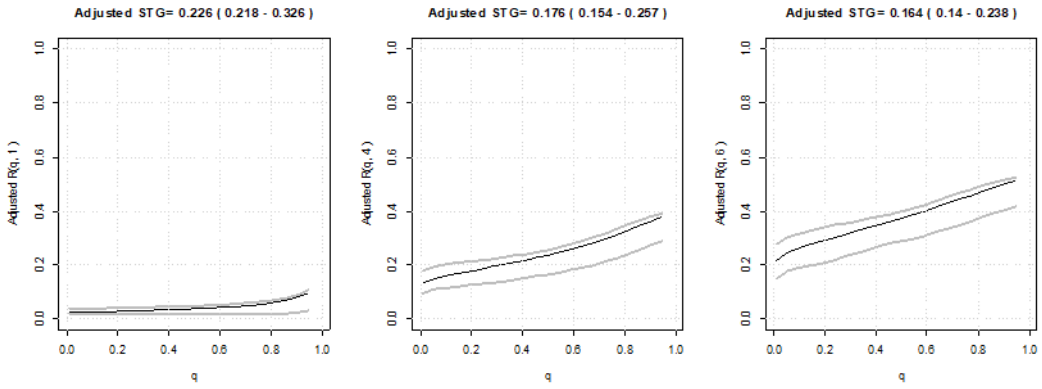

Figure 5. Estimate of adjusted Predictive curve and STG of bilirubin with 95%CI

Adjusted ROC curves and associated AUC values were estimated under both the incident/dynamic (I/D) and cumulative/dynamic (C/D) frameworks (Figures 3, 4). Under the I/D framework, the AUC at year 1 was relatively high but it decreased over time. In contrast, the C/D framework yielded consistently higher AUC values across all time points, with an AUC of 0.768 (95% CI: 0.687–0.803) at year 1, decreasing to 0.678 (95% CI: 0.615–0.713) at year 6.

We also evaluated the adjusted predictiveness function (AR) and the adjusted standardized total gain ($ASTG$), which summarizes the global predictiveness. As shown in Figure 5, the adjusted STG values at years 1, 4, and 6 were 0.226 (95% CI: 0.218–0.326), 0.176 (95% CI: 0.154–0.257), and 0.164 (95% CI: 0.140–0.238), respectively. This decreasing trend suggests a diminishing prognostic value of bilirubin as the follow-up time increases, consistent with the AUC patterns.

We further evaluated joint discrimination and predictiveness using an *and* classifier that combined $M1$ and $M2$. Under the I/D framework (Figure 6), the joint model provided limited gain compared to the univariate ROC based on the 4-cov model, with AUC values consistently lower across the 1-year, 4-year, and 6-year horizons.

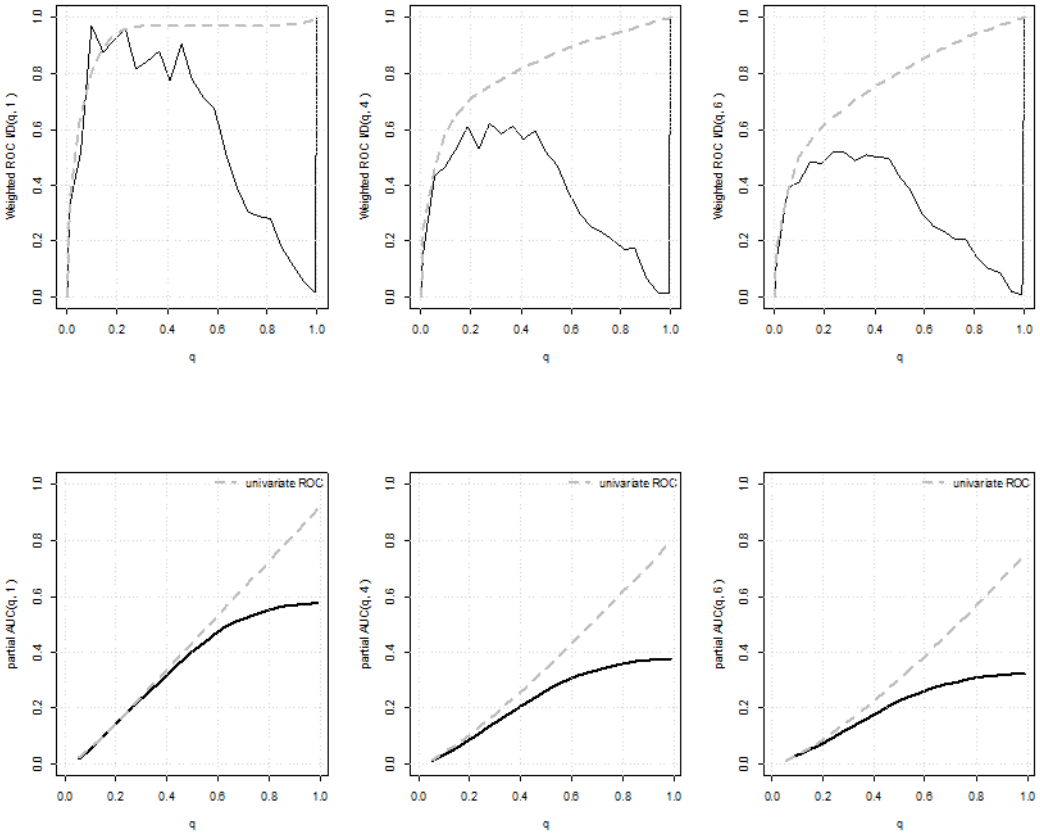

Figure 6. Estimate of weighted ROC I/D and AUC of 4-cov and bilirubin

However, under the C/D framework (Figure 7), the joint ROC curves showed an improvement in the high-specificity region. In this region, the partial AUCs suggested an enhanced discriminative ability.

For joint predictiveness, the STG values were estimated as 0.415, 0.335, and 0.316 at 1, 4, and 6 years, respectively (Figure 8), showing a declining trend consistent with previous findings. These results demonstrate the significant predictive value of the ‘and’ combined marker, especially during early follow-up.

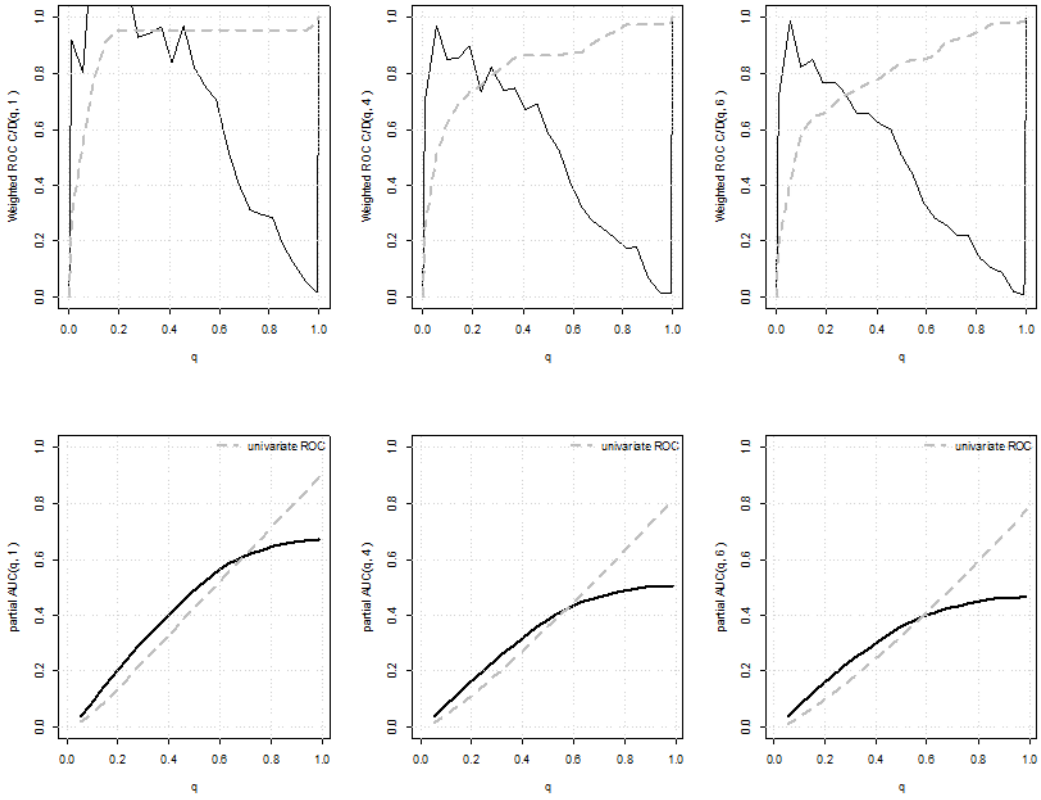

Figure 7. Estimate of weighted ROC C/D and AUC of 4-cov and bilirubin

The FNAC framework flexibly yields diagnostic measures that incorporate complex dependence structures that capture both intra-marker and marker-to-outcome dependence. As a result, bilirubin contributed to early risk stratification after adjusting for the 4-cov score. In addition, when evaluated in conjunction with the 4-cov model using an and-combination rule, bilirubin helped identify individuals who would be misclassified as high-risk.

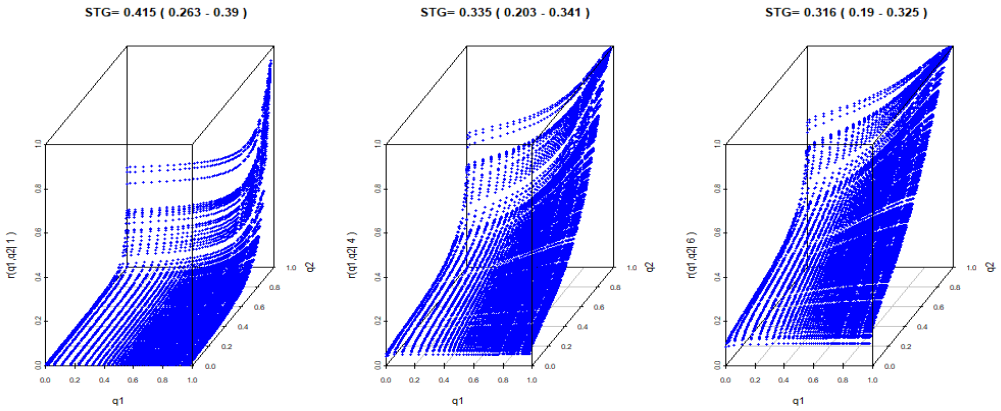

Figure 8. Estimate of Predictiveness surface of 4-cov and bilirubin

6. Conclusion and Discussion

In this study, we proposed a diagnostic evaluation framework for survival outcomes involving two dependent biomarkers using fully nested Archimedean copulas (FNACs). The model captures both intra-marker and marker-to-survival dependencies within a unified joint probabilistic structure and allows two complementary evaluation strategies: conditional and joint. Through simulation studies conducted across various censoring levels and copula families, as well as an application to real-world clinical data, we demonstrated the practical utility and interpretability of the copula-based framework for biomarker evaluation under complex dependency structures.

The proposed FNAC framework showed strong performance in identifying the correct copula structure based on the AIC and BIC. In nearly all simulation scenarios, the true copula family was identified with perfect accuracy (100%), except in cases where the model failed to adequately capture the dependence structure and was reduced to an independence copula. Performance, in terms of bias and Mean Squared Error(MSE), was optimal when the copula family was correctly specified. However, under Gumbel models with moderate censoring, FNAC-Gumbel exhibited slightly inflated bias and MSE. This appears to stem from the inherent difficulty of estimating upper-tail dependence under right-censoring, which effectively truncates the survival distribution's upper tail. Addressing this limitation may require alternative tail modeling or censoring-robust estimation strategies.

We further examined the estimation performance of key diagnostic quantities—specifically, the risk function and the time-dependent ROC function. FNAC models correctly specified with the true copula family consistently outperformed standard methods across all scenarios, even under the more challenging Gumbel setting. Interestingly, even mis-specified FNAC models yielded competitive results in estimating the risk function when the dependence structure was at least partially captured. In contrast, time-dependent ROC estimation was more sensitive to model misspecification, often resulting in diminished accuracy. This discrepancy likely arises because risk estimation is largely influenced by marginal distributions, while ROC-based discrimination depends more critically on the precision of conditional distributions.

Model misspecification had further implications in the Gumbel scenarios. FNAC models often failed to converge to a valid dependence structure and instead reverted to an independence copula. Consequently, the estimates in such cases resembled those from conventional approaches, such as Cox regression or Weibull models, which assume no explicit dependence between markers. This convergence pattern reinforces the importance of modeling dependence, even when the copula family is not precisely specified, to avoid misleading or oversimplified diagnostic conclusions.

The nested nature of the FNAC model, while structurally elegant, imposes important constraints. The nesting condition, which requires that the inner copula (linking biomarker and outcome) have stronger dependence than the outer copula (between biomarkers), may limit its applicability. In settings where the added biomarker demonstrates substantially weaker diagnostic value than the existing one, this assumption may be violated. Nevertheless, such situations are relatively uncommon in practice, as most novel biomarkers are proposed based on preliminary evidence suggesting at least moderate utility. In this context, the FNAC structure remains a practical choice for many real-world applications.

To ensure identifiability and analytic tractability, we implemented the FNAC model using three well-known Archimedean copula families—Clayton, Frank, and Gumbel. These families were chosen for their ability to represent a range of tail dependencies and their mathematical convenience. We limited our analysis to homogeneous nesting structures (e.g., Clayton–Clayton), which are well defined and computationally stable. While extensions to heterogeneous or asymmetric copula structures have been proposed in the literature, these present substantial challenges. Many combinations are not mathematically valid or lead to near-independence structures, and the complexity of modeling margins under censoring further compounds these difficulties. As shown by Joe (1997) and Serinaldi and Grimaldi (2007), asymmetric and mixture copula models offer promising theoretical generalizations, but practical implementation remains nontrivial, especially in censored survival data settings.

Despite these challenges, our framework provides several notable advantages. First, both conditional and joint diagnostic measures can be derived from a single joint model without the need for constructing linear predictors. This allows the evaluation of biomarkers on their original measurement scale. Second, our approach retains all marker values and all event or censoring times, avoiding the loss of information often encountered in conventional regression-based summaries. Third, all diagnostic quantities—such as risk

and ROC functions—are derived directly from the joint distribution of the biomarkers and the outcome. No normality assumption is imposed on the biomarkers, and their non-Gaussian, flexible distributions contribute meaningfully to the interpretation of their diagnostic performance.

In summary, the proposed FNAC-based framework provides a unified and flexible methodology for evaluating biomarkers in the presence of censoring and inter-marker dependence. Our findings underscore the critical importance of capturing dependence structures, particularly for accurate risk estimation, and highlight the potential of nested copula models to enhance diagnostic accuracy in survival analysis. Although the model imposes structural constraints and relies on a limited set of copula families, it remains computationally feasible and interpretable in practice. As methodological developments in nested and mixture copula modeling continue to advance, the practical scope of such frameworks is expected to expand, offering valuable tools for biomarker evaluation in clinical and epidemiological research.

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Appendix

This appendix provides general formulas for the derivatives of Archimedean copula functions and their generators, which are essential for constructing likelihood contributions in parametric copula models. These expressions are also relevant for deriving diagnostic measures based on the FNAC model.

A.1. General Derivatives of the Inverse Generator

Let $\varphi_\theta(t)$ be a generator of an Archimedean copula with an inverse $\varphi_\theta{}^{-1}(t)$. The following identities describe the derivatives of $\varphi_\theta{}^{-1}$ with respect to t:

$$\frac{\partial}{\partial t}\varphi_\theta{}^{-1}(t) = \frac{1}{\varphi_\theta{}'(\varphi_\theta{}^{-1}(t))}$$

$$\frac{\partial^2}{\partial t^2}\varphi_\theta{}^{-1}(t) = \frac{-\varphi_\theta{}''(\varphi_\theta{}^{-1}(t))}{(\varphi_\theta{}'(\varphi_\theta{}^{-1}(t)))^3}$$

$$\frac{\partial^3}{\partial t^3}\varphi_\theta{}^{-1}(t) = \frac{-\varphi_\theta{}'''\left(\varphi_\theta{}^{-1}(t)\right)\varphi'\left(\varphi_\theta{}^{-1}(t)\right)+3\left\{\varphi_\theta{}''\left(\varphi_\theta{}^{-1}(t)\right)\right\}^2}{\{\varphi_\theta{}'(\varphi_\theta{}^{-1}(t))\}^5}.$$

A.2. Derivatives of the Bivariate Archimedean Copula

Recall that $\mathrm{C}(u,\mathrm{v})$ is defined in Equation (2) as an Archimedean copula with a generator φ_θ. The first-order partial derivative of the copula with respect to u is obtained by applying the chain rule as follows

$$\frac{\partial \mathrm{C}(\mathrm{u},\mathrm{v})}{\partial u} = \varphi_\theta{}^{-1'}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\varphi_\theta{}'(u) = \frac{\varphi_\theta{}'(u)}{\varphi_\theta{}'\big(\mathrm{C}(u,\mathrm{v})\big)}.$$

The second-order derivative with respect to u is derived as

$$\frac{\partial^2 \mathrm{C}(\mathrm{u},\mathrm{v})}{\partial u^2} = \varphi_\theta{}^{-1''}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\big(\varphi_\theta{}'(u)\big)^2 + \varphi_\theta{}^{-1'}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\varphi_\theta{}''(u)$$

$$= -\frac{\varphi_\theta{}''(\mathrm{C}(u,\mathrm{v}))\big(\varphi_\theta{}'(u)\big)^2}{\{\varphi_\theta{}'(\mathrm{C}(u,\mathrm{v}))\}^3} + \frac{\varphi_\theta{}''(u)}{\varphi_\theta{}'(\mathrm{C}(u,\mathrm{v}))}.$$

The mixed second-order partial derivative with respect to u and v is similarly derived as

$$\frac{\partial \mathrm{C}(\mathrm{u},\mathrm{v})}{\partial u\,\partial v} = {\varphi_\theta}^{-1\prime\prime}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\varphi_\theta{}'(u)\varphi_\theta{}'(v) = -\frac{\varphi_\theta{}''(\mathrm{C}(u,\mathrm{v}))\varphi_\theta{}'(u)\varphi_\theta{}'(v)}{\{\varphi_\theta{}'(\mathrm{C}(u,\mathrm{v}))\}^3}.$$

Continuing this process, the third-order mixed derivative with respect to u and twice with respect to v is expressed as follows

$$\frac{\partial^2 \mathrm{C}(\mathrm{u},\mathrm{v})}{\partial u\,\partial \mathrm{v}^2} = {\varphi_\theta}^{-1\prime\prime\prime}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\varphi_\theta{}'(u)\big(\varphi_\theta{}'(v)\big)^2 + {\varphi_\theta}^{-1\prime\prime}\big(\varphi_\theta(\mathrm{u}) + \varphi_\theta(\mathrm{v})\big)\varphi_\theta{}'(u)\varphi_\theta{}''(v)$$

$$= \frac{-\varphi_\theta{}'''\big(\mathrm{C}(u,\mathrm{v})\big)\varphi_\theta{}'\big(\mathrm{C}(u,\mathrm{v})\big) + 3\{\varphi_\theta{}''(\mathrm{C}(u,\mathrm{v}))\}^2}{\{\varphi_\theta{}'(\mathrm{C}(u,\mathrm{v}))\}^5}\varphi_\theta{}'(u)\left(\varphi_\theta{}'(v)\right)^2 - \frac{\varphi_\theta{}''(\mathrm{C}(u,\mathrm{v}))\varphi_\theta{}'(u)\varphi_\theta{}''(v)}{\{\varphi_\theta{}'(\mathrm{C}(u,\mathrm{v}))\}^3}.$$

A.3. Derivatives of Generator Functions for the three copula types

We summarize the symbolic derivatives of the generator functions $\varphi_\theta(t)$ for three commonly used Archimedean families: Clayton, Frank and Gumbel.

For the Clayton copula, the generator is given by

$$\varphi_\theta(\mathrm{t}) = t^{-\theta} - 1, \text{ where } \theta \geq 0.$$

Differentiating this expression, we obtain the first derivative as

$$\varphi_\theta{}'(\mathrm{t}) = (-\theta)t^{-\theta-1},$$

the second derivative as

$$\varphi_\theta{}''(\mathrm{t}) = (-\theta)(-\theta-1)t^{-\theta-2},$$

and the third derivative as

$$\varphi_\theta{}'''(\mathrm{t}) = (-\theta)(-\theta-1)(-\theta-2)t^{-\theta-3}.$$

For the Frank copula, the generator is defined as

$$\varphi_\theta(\mathrm{t}) = -\log\left(\frac{\exp(-\theta t)-1}{\exp(-\theta)-1}\right), \text{ where } \theta \neq 0.$$

The first derivative with respect to t is given by

$$\varphi_\theta{}'(\mathrm{t}) = \frac{\theta \exp(-\theta t)}{\exp(-\theta t)-1}.$$

Taking the second derivative, we obtain

$$\varphi_\theta{}''(\mathrm{t}) = \frac{\theta^2 \exp(-\theta t)}{(\exp(-\theta t)-1)^2}$$

and the third derivative is

$$\varphi_\theta{}'''(\mathrm{t}) = \frac{\theta^3 \exp(-\theta t)\,(\exp(-\theta t)+1)}{(\exp(-\theta t)-1)^3}.$$

For the Gumbel copula, the generator takes the form

$$\varphi_\theta(\mathrm{t}) = (-\log t)^\theta, \text{ where } \theta \geq 1.$$

The first derivative is derived as

$$\varphi_\theta{}'(\mathrm{t}) = (-\theta/t)(-\log t)^{\theta-1}.$$

Differentiating one more, we obtain the second derivative

$$\varphi_\theta{}''(\mathrm{t}) = \frac{\theta(\theta-1)}{t^2}(-\log t)^{\theta-2} + \frac{\theta}{t^2}(-\log t)^{\theta-1},$$

and the third derivative is given by

$$\varphi_\theta{}'''(\mathrm{t}) = -\frac{\theta(\theta-1)(\theta-2)}{t^3}(-\log t)^{\theta-3} - \frac{3\theta(\theta-1)}{t^3}(-\log t)^{\theta-2} - \frac{2\theta}{t^3}(-\log t)^{\theta-1}.$$

Abstract in Korean

네스티드 코퓰라 모형을 이용한 상관 바이오마커의 생존 예후 진단 성능 평가 체계 개발

정밀의료에서 생존 예후를 예측하기 위한 바이오마커의 성능을 정밀하게 평가하는 것은 매우 중요하며, 특히 상호 종속적인 다중 바이오마커가 포함된 경우 그 중요성이 더욱 부각된다. 기존의 회귀 기반 접근법은 일반적으로 주변 효과(marginal effect)에 초점을 맞추고 바이오 마커 간 종속성을 단순한 다중공선성의 원인으로 간주하여 이를 무시하는 경향이 있다.

이러한 한계를 극복하기 위해, 본 연구에서는 두 개의 상호 종속적인 바이오마커와 생존시간의 공동 분포를 유연하게 모델링할 수 있는 완전 중첩 아키메디언 코퓰라(FNAC: Fully Nested Archimedean Copulas) 기반의 진단 평가 프레임워크를 제안한다. 이 프레임워크는 위계적(hierarchical), 비대칭적(asymmetric) 종속성을 수용할 수 있어, 바이오 마커 간 및 바이오 마커–생존시간 간의 관계를 하나의 통합된 확률 모델 내에서 동시에 반영할 수 있다. 이에, 기존 바이오 마커가 존재하는 상황에서 새로운 마커의 추가적인 진단 가치를 평가하는 데 특히 적합하다.

프레임워크는 두 가지 보완적인 전략으로 구성된다. 첫째, 조건부 평가(conditional evaluation)는 기존 마커가 주어진 상황에서 새로운 마커의 추가 기여도를 정량화한다. 둘째, 공동 평가(joint evaluation)는 두 마커가 모두 사전에 정의된 임계값을 초과할 때만 양성으로 판단하는 ‘AND-분류기’를 기반으로 두 마커의 결합된 진단 성능을 평가한다. 이러한 전략은 임상적 목표와 마커 특성에 따라 유연한 해석을 가능하게 한다.

Frank, Clayton, Gumbel 코퓰라를 포함한 다양한 종속 구조, 중도절단 비율, 예측 시점을 고려한 시뮬레이션을 통해 본 모델이 성능 지표를 정확하게 추정하고 참된 종속 구조를 복원하는 능력이 있음을 확인하였다. 마지막으로, Mayo Clinic 의 PBC 데이터를 적용한 실제 사례 분석을 통해 본 프레임워크의 실제 활용 가능성과 임상적 적용 잠재력을 입증하였다.

주요용어: 네스티드 코퓰라 모형, 바이오마커 평가, 시간종속 AUC, 생존분석