Comparative Analysis of Spline-based and Standard Frailty Models: Impact of Model Misspecification on Estimation Accuracy

Felix O. Ouma, Edwine B. Atitwa, Zakayo N. Morris and Maurice Wanyonyi

Abstract—**Survival models with random effects (frailty terms) are used in applied and biostatistical research to account for unmeasured heterogeneity. These models prevent biases resulting from the exclusion of significant covariates. However, little is known about the effects of misspecifying the baseline hazard or frailty distribution in parametric frailty models. The study used simulations to assess the impact of such misspecifications on model parameter estimates and predictions, which is essential for addressing the complexities of survival data and improving bias correction. Recurrent survival data were generated with the actual Weibull baseline hazard and accurate gamma frailty distribution. Model performance was evaluated when the baseline hazard was misspecified as exponential and the frailty distribution as inverse Gaussian or Lognormal. Both the standard and spline-based parametric frailty models were compared. Misspecifying the baseline hazard, specifically for a beta estimate, a bias for the spline-based Gamma frailty model significantly increased from 0.00207% to 194.254% when the baseline hazard is misspecified as an exponential distribution. The spline-based gamma frailty model exhibited an almost negligible bias of 0.00207% for the covariate effect (Beta) and 2.875% frailty variance (theta), outperforming the standard gamma frailty model with a bias of 6.3% for Beta and 4.0% for theta. The flexibility of the restricted cubic splines enhanced the modeling of non-linear relationships, improving the recurrence rate prediction from 1.865% to 6.211%. Therefore, care is required when choosing models to analyze recurrent survival data. Misspecification of the frailty distribution, the baseline hazard, or both can have important implications for prediction and inference in survival analysis.**

Index Terms—**Misspecification, frailty models, restricted cubic splines, recurrent events, baseline hazard, unobserved heterogeneity.**

I. Introduction

In many different disciplines, survival analysis is critical, particularly in epidemiology and biostatistics, where understanding the influence of risk factors on individual lifetime is more critical [16]. Traditional survival analysis techniques, like the semi-parametric and parametric models, have provided valuable frameworks for analyzing time-to-event data. Among these, the Cox proportional hazards model is one of the most widely used due to its flexibility and capacity to handle various covariates, including continuous and categorical variables [7].

However, these traditional models can introduce significant biases when unobserved variability exists [17]. These often rely on the assumption that all individuals in a population are homogeneous concerning their risk of experiencing an event, i.e., the hazard function is proportional and the hazard ratio is constant over time. This can lead to significant biases when unobserved variability exists [13], [30]. This study aimed to evaluate the impact of misspecifying the frailty distribution and the baseline hazard in recurrent survival data. The study specifically focused on the Gamma, Log-normal, and Inverse Gaussian frailty models.

The Cox proportional hazards model traditionally estimates the coefficients of the covariates and assesses their impact on survival outcomes [12]. However, the limitations of the Cox model become especially apparent considering recurrent survival data. This is because the covariates may inadequately capture the underlying risk dynamics over time, leading to biased estimations of treatment impacts on the recurrence of events, such as malaria episodes [25]. Traditional non-parametric and standard approaches often overlook critical components of the data structure, such as potential time-varying treatment effects, censoring, and the inherent dependence among occurrences, ultimately compromising the integrity of the analysis [14]. The concept of frailty was introduced due to this limitation to account for unobserved heterogeneity among subjects [26].

Frailty models incorporate random effects that capture latent characteristics that affect an individual's risk of experiencing an event [29]. This allows for more accurate estimates and insights regarding survival times and factors that influence them [27]. Incorporating random effects (frailty) into survival models can mitigate the limitations of the traditional models by accounting for unobserved heterogeneity, which significantly enhances the ability to analyze heterogeneous and complex data structures [4]. However, selecting a suitable frailty distribution poses a challenge, as the frailty term is usually hidden from direct observation. Misspecifying unobserved frailty can lead to biased estimates and decreased estimation efficiency, potentially resulting in erroneous conclusions [10].

In scenarios where individuals experience the same event multiple times, such as disease relapses or hospital readmissions, the challenges become more pronounced and complicate the analysis significantly [6]. Parametric methods for analyzing recurrent events often rely on assumptions of independence between occurrences, which overlook the inherent correlation between repeated events. Frailty mod-

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els thus provide a more nuanced framework for capturing this correlation by allowing individual risk to vary due to unobserved factors, which improves the understanding of recurrent event dynamics, therefore providing a better representation of how variables interact over time [1].

The emergence of flexible parametric survival models, specifically the spline-based methods, represents a significant advancement in survival analysis methodology. These models provide a more flexible way to capture the non-linear relationships between covariates and the hazard function, offering enhanced flexibility in adequately fitting complex data structures [19]. Restricted cubic splines are particularly effective in modeling the non-linear relationship between covariates and the hazard function flexibly while controlling for over-fitting [23]. Unlike polynomials, which tend to grow without bounds, the restricted cubic splines maintain a smooth curve by being linear beyond points known as the knots [20]. This allows the splines to identify intricate patterns in the data, which makes them particularly useful for survival analysis when the relationship between the log-hazard rate and the covariate is non-linear [2]. The restricted cubic spline model with K knots is denoted by:

$$f(x) = \beta_0 + \beta_1 x + \beta_2 h_1(x) + \cdots + \beta_{K+1} h_K(x) \qquad (1)$$

Where: $\beta_1, \ldots, \beta_{K+1}$ are coefficients for each spline basis function, and β_0 is the intercept. Each $h_k(x)$ represents the basis function of the spline corresponding to the k-th component. The first two terms, one and x, are linear components, while the remaining terms are non-linear transformations.

For the restricted cubic spline, the basis functions $h_K(x)$ for $K = 1, \ldots, K$ are defined based on the knots $k_1, \ldots, k_K$. They include linear components and non-linear components derived from the positions of the knots. By ensuring that the spline is linear beyond the boundary knots, this basis function helps to prevent polynomials from behaving abnormally at the extreme ends [21].

This flexibility is more important when dealing with heterogeneous populations, where the relationships between covariates and outcomes are non-linear [28]. The ability to allow for varying shapes of the hazard function based on observed characteristics, the spline-based methods can capture effectively the nuances of the relationship between predictors and event timing, which Parametric methods may inadequately address [20]. Therefore, this capability enables the fitting of models more accurately to the underlying data, leading to improved estimation and inference. However, the implications of model misspecification arising from selecting an inappropriate model for the underlying effects are profound. Such errors can give biased estimates and compromise the validity of the inferences that are drawn from the analysis [3].

Despite advanced modeling techniques in survival analysis, there has been limited comparative analysis evaluating the robustness and performance of spline-based frailty models relative to parametric frailty models under conditions of misspecification. The study conducted a thorough comparative analysis of spline-based and parametric frailty models for recurring events. By evaluating the impact of model misspecification on estimation accuracy, the study provides valuable insights that will guide researchers and practitioners in selecting appropriate survival analysis methods for their specific applications, ultimately enhancing the reliability of results in clinical and epidemiological research [15]

II. Materials and Methods

A. Study Design and Data Simulation

To evaluate frailty models under recurrent survival scenarios, this study simulated data across 1000 Monte Carlo iterations, with each dataset consisting of 200 individuals. A binary covariate x, generated from a Bernoulli distribution with probability $P(x = 1) = 0.5$, was used to simulate heterogeneity in event risk. The covariate effect was fixed at $\beta = 1.5$. Censoring times were drawn from a uniform distribution $U(0, 4)$, and the actual baseline hazard followed a Weibull distribution, with scale $\lambda = 1$ and shape $\rho = 2$. For model misspecification, an exponential baseline ($\rho = 1$) was used.

The simulated recurrent event data were generated from the following theoretical hazard model:

$$\begin{aligned} h_{ij}(t) &= h_0(t) v_i \exp(x_{ij}\beta), \\ & \quad j = 1, \ldots, n_i, \quad i = 1, \ldots, G \end{aligned} \qquad (2)$$

Here, $h_0(t)$ is the baseline hazard, v_i denotes the shared frailty term for individual i, and $x_{ij}\beta$ is the linear predictor. If the Weibull distribution is assumed for the baseline hazard, then the survival time T is generated by:

$$T = \left(\frac{-\log(u)}{\lambda v_i \exp(x_{ij}\beta)} \right)^{1/\rho} \qquad (3)$$

Where $u \sim U(0, 1)$, and the frailty term v_i is drawn from one of three distributions with mean one and variance $\theta \in \{0.1, 0.5, 2\}$: Gamma, Lognormal, or Inverse Gaussian. For the lognormal frailty, the transformation $\mu = -\theta/2$ ensures $E(v) = 1$. These distributional choices reflect common assumptions in recurrent event modeling and are guided by settings in Rodríguez-Girondo et al. (2018).

The Weibull-based frailty model then becomes:

$$\begin{aligned} h_{ij}(t) &= \lambda \rho t^{\rho - 1} v_i \exp(x_{ij}\beta), \\ & \quad j = 1, \ldots, n_i, \quad i = 1, \ldots, G \end{aligned} \qquad (4)$$

When $\rho = 1$, the Weibull model simplifies to an exponential model, serving as a comparison for model misspecification.

Three frailty distributions were evaluated: Gamma, Inverse Gaussian, and Lognormal. These distributions model unobserved heterogeneity by allowing the frailty term u_i (or v_i) to follow a distribution with unit mean and specified variance. The general form of the hazard function for individual i is given by:

$$h_i(t \mid x_i, u_i) = h_0(t) \cdot \exp(x_i\beta) \cdot u_i \qquad (5)$$

where $h_0(t)$ is the baseline hazard, x_i is the covariate vector, β the regression coefficient, and u_i the individual-specific frailty term.

To enhance model flexibility and capture non-linear covariate effects, restricted cubic splines (RCS) were employed in modeling the baseline hazard and covariate relationships.

The simulated datasets thus included survival time, censoring indicator, covariate, and cluster ID. Models were fitted using the Gamma and Inverse Gaussian frailty distributions across three baseline hazard specifications: Weibull, Exponential, and spline-based. These configurations were designed to assess robustness and accuracy under both correct and misspecified model assumptions.

1) Gamma Frailty Distribution: In the gamma frailty model, the frailty term u_i for individual i follows a gamma distribution, which introduces unobserved heterogeneity into the survival analysis. The frailty term u_i is modeled as a gamma–distributed random variable:

$$u_i \sim \text{Gamma}(\theta, \theta) \tag{6}$$

Where θ, the shape parameter, is also interpreted as the inverse of the frailty variance. The Gamma distribution is parameterized such that:

$$f(u_i) = \frac{u_i^{\theta-1} e^{-u_i/\theta}}{\Gamma(\theta)\theta^\theta}, \quad u_i > 0 \tag{7}$$

Where $\Gamma(\theta)$ represents the Gamma function, and the mean of u_i is normalized to 1 with a variance of $1/\theta$.

The survival function for individual i is;

$$S_i(t \mid u_i) = \exp(-H_i(t \mid u_i)) \tag{8}$$

The survival probability $S_i(t \mid u_i)$ represents the individual i's probability of surviving beyond time t and $H_i(t \mid u_i)$ the cumulative hazard function.

Where the cumulative hazard for individual i is:

$$H_i(t \mid u_i) = \int_0^t h_i(s \mid x_i, u_i)\, ds = H_o(t) \cdot \exp(x_i\beta) \cdot u_i \tag{9}$$

Where $H_o(t)$ is the baseline cumulative hazard function that represents the risk over time for an average individual and $x_i\beta$ is the linear predictor, where x_i are the covariates for individual i and the regression coefficients' vector is denoted by β.

The survival function is thus written as:

$$S_i(t \mid u_i) = \exp(-u_i H_o(t) \cdot \exp(x_i\beta)) \tag{10}$$

To account for the unobserved frailty, we integrate across the frailty u_i distribution to obtain the marginal survival function. The marginal survival function with covariates, which adjusts for the unobserved heterogeneity, is:

$$S_i(t \mid x_i) = \int_0^\infty S_i(t \mid u_i) f(u_i)\, du_i \tag{11}$$

The integral result in the closed-form solution for the marginal survival function is:

$$S(t \mid x) = \left(1 + \frac{H_o(t) \cdot \exp(x_i\beta)}{\theta}\right)^{-\theta} \tag{12}$$

This equation describes the marginal survival probability for individual i, considering both the observed covariates and the unobserved frailty effect.

Without covariates i.e., $x_i = 0$, the marginal survival function simplifies to;

$$S(t) = \left(1 + \frac{H_o(t)}{\theta}\right)^{-\theta} \tag{13}$$

This represents the population-level survival probability, where frailty introduces additional variation in survival times.

The marginal cumulative hazard function is the negative log of the marginal survival function:

$$H_i(t) = -\log(S_i(t)) \tag{14}$$

Which provides the overall risk of experiencing an event by time t, taking into account both observed and unobserved risk factors.

2) Inverse Gaussian frailty distribution: The inverse Gaussian frailty model assumes that the frailty term u_i for individual i follows an inverse Gaussian distribution. This type of frailty model captures the over-dispersion in the data, where individuals exhibit varying risk levels that are not directly explained by observed covariates.

Where the frailty term u_i follows an inverse Gaussian distribution, which is denoted by:

$$u_i \sim \text{InverseGaussian}(\mu = 1, \lambda = 0) \tag{15}$$

Where μ is the mean and λ is the shape parameter controlling the variability of the frailty.

The probability density function of the inverse Gaussian distribution for the frailty term u_i is:

$$f(u_i|\theta) = \sqrt{\frac{\theta}{2\pi u_i^3}} \exp\left(-\frac{\theta(u_i-1)^2}{2u_i}\right), \quad u_i > 0 \tag{16}$$

The marginal survival function is:

$$S_i(t) = \int_0^\infty S_i(t|u_i) f(u_i|\theta)\, du_i \tag{17}$$

Where $S_i(t|u_i)$ is the individual survival function conditional on frailty, and $f(u_i|\theta)$ is the inverse Gaussian frailty distribution. These integral captures the population-level heterogeneity and provide a more accurate estimate of survival probabilities by averaging over all possible values of u_i.

The marginal survival function without covariates represents the average survival probability across the distribution of the frailty parameter u_i when no covariate is considered. It reflects how the overall survival function accounts for the unobserved heterogeneity among individuals:

$$S(t) = \exp\left(1 - \frac{\sqrt{1 + 2\theta H_0(t)} - 1}{\theta}\right) \tag{18}$$

The marginal survival function with covariates represents the average survival probability when covariates are included. It adjusts the baseline hazard based on the covariate effects, while still accounting for the distribution of the frailty parameter u_i

$$S(t|x) = \exp\left(1 - \frac{\sqrt{1 + 2\theta H_0(t)\exp(\beta)} - 1}{\theta}\right) \tag{19}$$

3) Log-normal frailty distribution: The lognormal frailty distribution assumes that the frailty term u_i follows a lognormal distribution. The frailty term is modeled as $u_i = \exp(Z_i)$, where Z_i follows a normal distribution. This introduces a dependency between the survival times of individuals with shared frailty, indicating that some individuals may experience events more frequently due to unmeasured factors.

The probability density function of u_i is given by:

$$f(u_i) = \frac{1}{\sqrt{2\pi\sigma^2 u_i}} \exp\left(-\frac{(\log u_i - \mu)^2}{2\sigma^2}\right), \quad u_i > 0 \quad (20)$$

The marginal survival function $S(t)$ integrates over the distribution of frailty to account for unobserved heterogeneity. The survival function for individual i, conditional on frailty u_i is given by:

$$S_i(t|u_i) = \exp\left(-u_i H_0(t) \exp(x_i\beta)\right) \quad (21)$$

To get the marginal survival function, we integrate the conditional survival function over the frailty distribution:

$$\begin{aligned} S(t) &= \int_0^\infty \exp\left(-u_i H_0(t) \exp(x_i\beta)\right) \cdot \frac{1}{\sqrt{2\pi\sigma^2 u_i}} \\ &\quad \cdot \exp\left(-\frac{(\log u_i - \mu)^2}{2\sigma^2}\right) du_i \quad (22) \end{aligned}$$

This reflects the population-level survival probability by averaging over the unobserved frailty u_i.

The marginal survival function without covariates, i.e., $x_i = 0$, is denoted by:

$$S(t) = \int_{-\infty}^{\infty} S_i(t|\eta) f(\eta|\theta)\, d\eta \quad (23)$$

The marginal survival function with covariates is denoted by:

$$S(t|x) = \int_{-\infty}^{\infty} S_i(t|\eta,\beta) f(\eta|\theta)\, d\eta \quad (24)$$

Where:

$S_i(t|\eta,\beta)$ is the survival function that includes the covariate effect β for an individual i, at time t, given the frailty η, and $f(\eta|\theta)$ is the probability density of the frailty distribution, which is normally distributed with mean $-\theta/2$ and standard deviation of $\sqrt{\theta}$.

The survival function $S_i(t|\eta,\beta)$ is:

$$S_i(t|\eta,\beta) = \left(e^{-\lambda t^\rho e^\beta}\right)^{e^\eta} \quad (25)$$

Moreover, without covariates, the survival is given by:

$$S_i(t|\eta) = \left(e^{-\lambda t^\rho}\right)^{e^\eta} \quad (26)$$

Where $e^{-\lambda t^\rho}$ represents the baseline hazard function that is raised to the power of e^η, which indicates the impact of the frailty on the hazard. e^η, the frailty term, modifies the baseline hazard, capturing unobserved heterogeneity among individuals.

B. Restricted cubic splines (RCS)

In survival analysis, RCS are applied to model the non-linear effects of covariates on the hazard function (cumulative hazard function). For a frailty survival model, the hazard function for individual i is expressed as:

$$\begin{aligned} h_i(t|x_i,\eta_i) &= \eta_i h_0(t) \exp(\beta_0 + \beta_1 x + \beta_2 h_1(x) \\ &\quad + \cdots + \beta_{K+1} h_K(x)) \quad (27) \end{aligned}$$

Where: $h_0(t)$ represents the baseline hazard function, x is the covariate of interest. The spline terms $h_1(x), \ldots, h_K(x)$ allow for non-linear relationships between the covariate x and the log-hazard function, and η_i is the frailty term specific to individual i that introduces random effects into the hazard function, capturing the unobserved heterogeneity that might affect individual survival times.

The general mathematical formulation of each model is:

$$h_i(t|x_i,\eta_i) = \eta_i h_0(t) \exp\left(\beta_1 x_i + \sum_{j=2}^{K+1} \beta_j h_j(x_i)\right) \quad (28)$$

Where η_i is the frailty term, the spline term $h_j(x_i)$ allows for non-linear effects of the covariate x on the hazard function.

C. Baseline hazard distributions

1) Weibull distribution: The Weibull distribution is mainly used in survival analysis due to its flexibility in modeling time-to-event data. It represents increasing, constant, or decreasing hazard rates depending on its parameters. Two parameters define it: the scale parameter λ and the shape parameter ρ, where the hazard changes over time, depending on ρ.

The probability density function is:

$$f(t) = \rho\lambda^\rho t^{\rho-1} \exp(-\lambda t^\rho) \quad (29)$$

Where $t \geq 0$, $\rho > 0$. If $\rho = 1$, when the hazard rate remains constant, the Weibull distribution transforms into an exponential distribution. If $\rho > 1$, over time, the hazard rate increases, and if $\rho < 1$, the hazard rate decreases.

The hazard function for recurrent events describes the instantaneous rate at which subsequent events will occur, given that K events have already happened up to time t.

The hazard function is given by:

$$h_k(t) = \rho\lambda^\rho t^{\rho-1} \quad (30)$$

The cumulative hazard function is expressed as:

$$H_k(t) = (\lambda t)^\rho \quad (31)$$

The survival function will therefore be given by:

$$S_k(t) = \exp(-\lambda t^\rho) \quad (32)$$

2) Exponential Baseline hazard: The exponential distribution is commonly used in survival models due to its simplicity and the constant hazard rate over time assumption, meaning the probability of an event occurring is the same at any point in time, regardless of how much time has passed. The probability density function of the exponential distribution is given by:

$$f(t;\lambda) = \lambda e^{-\lambda t}, \quad t \geq 0 \quad (33)$$

Where λ is the rate parameter, which determines the constant rate at which events occur over time.

The cumulative distribution function gives the probability that the event occurs before or at time t:

$$F(t;\lambda) = P(T \leq t) = 1 - e^{-\lambda t} \quad (34)$$

The survival function shows the likelihood that the event has not occurred by time t, and is given by:

$$S(t;\lambda) = P(T > t) = 1 - F(t;\lambda) = e^{-\lambda t} \quad (35)$$

The hazard rate is given by:

$$h(t) = \lambda \quad (36)$$

Which shows that the likelihood of the event happening in the next interval of time is always the same, it is a special case of the Weibull where $\rho = 1$. The cumulative hazard function is the integral of the hazard function over time, which represents the accumulated hazard by time t:

$$H(t;\lambda) = \int_0^t h(u;\lambda)\,du = \lambda t \tag{37}$$

The cumulative hazard function grows linearly with time since the hazard rate is constant.

D. Performance Metrics

1) Bias: Bias is the measure of the difference between the estimated value and the true value; it provides insights into how far, on average, the estimated value is from the true value. Bias can be positive or negative if the estimates are consistently more than the actual value, and if the estimates are consistently less than the actual value, respectively.

$$\text{Bias}(\hat{\beta}) = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{\hat{\beta}_i - \beta_{\text{true}}}{\beta_{\text{true}}}\right) \tag{38}$$

$$\text{Bias}(\hat{\theta}) = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{\hat{\theta}_i - \theta_{\text{true}}}{\theta_{\text{true}}}\right) \tag{39}$$

2) Standard Deviation (SD): The standard deviation measures the variability or spread of the estimates around the mean value; it tells how much the estimates fluctuate from the average estimate, indicating how consistently the model estimates the parameters across simulations, hence reflecting the precision of the model.

$$\text{SD}(\hat{\beta}) = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(\hat{\beta}_i - \bar{\beta})^2} \tag{40}$$

Where:

$$\bar{\beta} = \frac{1}{n}\sum_{i=1}^{n}\hat{\beta}_i$$

Similarly, for $\hat{\theta}$:

$$\text{SD}(\hat{\theta}) = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(\hat{\theta}_i - \bar{\theta})^2} \tag{41}$$

Where:

$$\bar{\theta} = \frac{1}{n}\sum_{i=1}^{n}\hat{\theta}_i$$

3) Mean Squared Error (MSE): The MSE combines both bias and variance. It calculates the mean squared difference between the estimated and the true parameter, providing a comprehensive metric of the estimator's accuracy.

$$\text{MSE}(\hat{\beta}) = \frac{1}{n}\sum_{i=1}^{n}(\hat{\beta}_i - \beta_{\text{true}})^2 \tag{42}$$

$$\text{MSE}(\hat{\theta}) = \frac{1}{n}\sum_{i=1}^{n}(\hat{\theta}_i - \theta_{\text{true}})^2 \tag{43}$$

E. Model Comparison

The Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) are used to compare the performance of the models in survival analysis and select the best. These metrics account for the goodness of fit of the model, while penalizing for the complexity to avoid overfitting. The AIC and BIC are denoted by:

$$\text{AIC} = -2\log(L) + 2k \tag{44}$$

$$\text{BIC} = -2\log(L) + k\log(n) \tag{45}$$

Where:
$\log(L)$ is the log-likelihood of the model, k is the number of parameters in the model, and n is the sample size.

F. Hazard Ratio (HR)

HR is the measure of the relative risk of an event happening in one group as compared to another over time. It is the proportion of the hazard rates between these two groups given by:

$$HR = \frac{h_1(t)}{h_2(t)} \tag{46}$$

Where $h_1(t)$ represents the treatment group's hazard rate and $h_2(t)$ is the hazard rate for the control group.

G. Recurrence Probability

The recurrence probability quantifies the likelihood that an event has occurred by time t. It is given by:

$$P(\text{Event by time } t) = 1 - S(t) \tag{47}$$

where $S(t)$ is the survival function.

H. Software Implementation

R statistical software version 4.4.1. Was used for the analysis using the packages for survival analysis and frailty modeling (survival, frailtySurv, frailtypack, splines)

I. Ethical Considerations

The study used simulated data, for which no ethical approval was needed

J. Limitations

The models and data are based on specific assumptions, such as distribution types and parameter values, which may not fully represent real-world data.

III. RESULTS

A. Introduction

Recurrent survival data were simulated, and different frailty models fitted (Gamma, Lognormal, and inverse Gaussian). Then they assessed the impact of the models on bias, variance, mean squared error (MSE), baseline estimates, and survival probabilities. The results also included the effects of incorporating restricted cubic splines (RCS) to model the Relationship between the covariate and the hazard more flexibly.

B. Parameter Estimates

Using equations 35, 37, and 39, the bias, standard deviation, and the mean squared error (MSE) were calculated for beta estimates, respectively. Equations 36, 38, and 40 were used to calculate the theta estimates for the standard models when the sample size is 200. These parameter estimates are summarized in TABLE I.

As the accurate frailty model, the Gamma model displays a relatively small bias for both Beta and Theta estimates, with a positive bias of 0.063 for Beta and a positive bias of 0.040 for theta. If the true frailty is misspecified by an inverse Gaussian model, the bias for Beta is 0.181, indicating a more positive bias. At the same time, we get a slightly negative bias for theta estimate of -0.019. Misspecifying the frailty by a lognormal model, the bias increases significantly to 0.217 for the Beta estimates and a somewhat negative bias of -0.028 for theta estimates. The inverse Gaussian model provides the most accurate estimates for theta, showing the least MSE of 0.001 and a very low standard deviation of 0.016, although its bias for Beta is higher. The lognormal model exhibits the highest biases and MSE for both Beta and theta, suggesting it is the least preferable for accurate estimation. However, when using an exponential baseline hazard, the estimates of the Beta are generally smaller than those obtained with a Weibull baseline hazard.

For Beta estimates, the spline-based Gamma model showed an almost negligible positive bias of 0.0000207, indicating that it provides estimates close to the actual beta value; misspecifying the frailty to an inverse Gaussian model, the bias increases significantly to a positive bias of 0.1479. If the frailty model is misspecified to lognormal, the bias increases slightly to a positive bias of 0.0116, indicating more accuracy than the inverse Gaussian model. For the theta estimate, the spline-based lognormal model had the lowest positive bias of 0.0036 compared to the spline-based Inverse Gaussian model with a bias of 0.0159. The Gamma spline model had the highest bias for theta, with a positive bias of 0.02875. The gamma model with splines had a moderate SD of 0.1256; the lognormal model had the highest SD of 0.1697, indicating an increased variability in its estimates. The inverse Gaussian model with splines had the lowest SD of 0.1128, suggesting more precision than the gamma model.

Similarly, the Gamma, inverse Gaussian, and lognormal SD for theta estimates were 0.0099, 0.0045, and 0.0090, respectively. For MSE for the Beta estimate, the gamma model with splines had the very lowest MSE of 0.00091486, indicating good accuracy in its estimates. The inverse Gaussian had a considerably higher MSE of 0.0333, while the lognormal model had an MSE of 0.0261, indicating a strong overall error but less than the inverse Gaussian model. For the theta estimate, the gamma model with splines had a low MSE of 0.000000914, indicating exceptional accuracy in theta estimation. Then, the lognormal model was followed with an MSE of 0.00008653, which is still very low compared to the inverse Gaussian model with an MSE of 0.00027. When the baseline hazard distribution is exponentially distributed, the bias increases significantly, showing the model's inability to capture more variability in the data as compared to the Weibull distribution. These estimates are summarized in TABLE II

C. Baseline Hazard Estimates

The baseline estimates were calculated using equation 27 and summarized in TABLE III. At time t=0.3, the gamma model shows a relative negative bias of -0.270, indicating a slight underestimation of survival probabilities; the lognormal and inverse Gaussian models both had a negative bias of -0.779 and -0.687, respectively, indicating a significant underestimation. As the time increases to t=1, all the biases for the three models indicate underestimation to a greater extent. The gamma, inverse Gaussian, and lognormal models at t=1 had biases of -0.557, -0.815, and -0.862, respectively. For the SD at t=0.3, the lognormal model showed a lower SD of 0.0180, indicating that it provides the highest consistency among the estimates at this time point.

The inverse Gaussian model shows a lower SD of 0.020 than that of the gamma model, with an SD of 0.025. At time t=1, the lognormal model had the lowest SD of 0.098, indicating the most consistent results at this time point as compared to the Gamma and inverse Gaussian models with SDs of 0.175 and 0.107, respectively. For the MSE at time t=0.3, the gamma model had an MSE of 0.001, indicating excellent accuracy. The inverse Gaussian and lognormal models had relatively higher MSEs of 0.004 and 0.005, respectively. As the time increases to t=1, the MSE increases significantly in all the models. The Gamma, inverse Gaussian, and lognormal models had MSEs of 0.338, 0.674, and 0.752. Misspecifying the Weibull baseline hazard as an exponential baseline hazard leads to a significant overestimation of survival probabilities. When the baseline hazard is an exponential distribution, we have high variability and a poorer survival probability estimation accuracy than when the actual baseline hazard is the Weibull distribution.

At time t=0.3, the Gamma, inverse Gaussian, and lognormal models had a relative bias of -0.117, -0.486, and -0.680, respectively, indicating an underestimation of survival probabilities. At time t=1.0, all models' relative biases increased significantly to -0.491, -0.741, and -0.806, respectively, indicating a significant underestimation. For the SD at time t=0.3, the lognormal model had the lowest SD of 0.017, indicating the highest consistency among estimates. The inverse Gaussian and gamma models had an MSE of 0.034 and 0.042, respectively. At time t=1.0, the gamma model had a significantly higher SD of 0.257, with inverse Gaussian and lognormal models having an SD of 0.159 and 0.096, respectively. For the MSE at time t=0.3, the gamma model had the lowest MSE of 0.002, indicating strong accuracy in survival probability estimation. The inverse Gaussian model had an MSE of 0.003, and the lognormal had 0.004. At time t=1.0, the bias increased significantly with MSE of 0.301, 0.571, and 0.658 for the Gamma, inverse Gaussian, and lognormal models. From the results, as time increases from t=0.3 to t=1.0, the survival probability estimates significantly become less accurate across all the RCS models, with significant variability and growing error. When the baseline hazard is exponential, then we have a considerable amount of bias. See TABLE IV.

Cumulative hazard analysis between the standard and spline-modelled frailty approaches demonstrates the substantial effects that model structures have on time-based hazard estimation results. See Figures 1 and 2. Standard models that employ Gamma or Inverse Gaussian frailty distributions

TABLE I
PARAMETER ESTIMATES FOR STANDARD MODELS

Model	Baseline hazard	Bias (Beta)	SD (Beta)	MSE (Beta)	Bias (Theta)	SD (Theta)	MSE (Theta)
Gamma	Weibull	0.063	0.059	0.007	0.040	0.096	0.010
	Exponential	0.029	0.008	0.001	0.037	0.019	0.001
Inverse Gaussian	Weibull	0.181	0.104	0.043	-0.019	0.016	0.001
	Exponential	0.033	0.010	0.001	-0.019	0.003	0.000
Log-normal	Weibull	0.217	0.127	0.062	-0.028	0.067	0.005
	Exponential	0.032	0.010	0.001	-0.002	0.004	0.000

TABLE II
PARAMETER ESTIMATES FOR SPLINE-BASED MODELS

Model	Baseline Hazard	Parameter	Bias	SD	MSE
Gamma	Weibull	Beta	0.0000	0.1256	0.0009
	Exponential	Beta	1.9425	0.3106	3.8602
	Weibull	Theta	0.0288	0.0099	0.0000
	Exponential	Theta	0.0337	0.0036	0.0011
Inverse Gaussian	Weibull	Beta	0.1479	0.1128	0.0333
	Exponential	Beta	1.9597	0.2627	3.9027
	Weibull	Theta	0.0159	0.0045	0.0003
	Exponential	Theta	-0.0383	0.0799	0.0072
Log-normal	Weibull	Beta	0.0116	0.1697	0.0261
	Exponential	Beta	1.8472	0.3236	3.5062
	Weibull	Theta	0.0036	0.0090	0.0001
	Exponential	Theta	-0.0250	0.1311	0.0161

TABLE III
BASELINE HAZARD ESTIMATES FOR STANDARD MODELS

Time	Model	Baseline Hazard	Relative Bias	SD	MSE
0.3	Gamma	Weibull	-0.270	0.025	0.001
		Exponential	2.975	0.519	1.039
	Inverse Gaussian	Weibull	-0.687	0.020	0.004
		Exponential	0.579	0.105	0.040
	Log-normal	Weibull	-0.779	0.018	0.005
		Exponential	0.349	0.110	0.022
1.0	Gamma	Weibull	-0.557	0.175	0.338
		Exponential	3.444	2.212	16.262
	Inverse Gaussian	Weibull	-0.815	0.107	0.674
		Exponential	0.399	0.354	0.272
	Log-normal	Weibull	-0.862	0.098	0.752
		Exponential	0.260	0.369	0.190

TABLE IV
BASELINE ESTIMATES FOR SPLINE-BASED MODELS

Time	Model	Baseline Hazard	Relative Bias	SD	MSE
0.3	Gamma	Weibull	-0.117	0.042	0.002
		Exponential	-0.972	0.008	0.085
	Inverse Gaussian	Weibull	-0.486	0.034	0.003
		Exponential	-0.978	0.005	0.086
	Log-normal	Weibull	-0.680	0.017	0.004
		Exponential	-0.972	0.006	0.086
1.0	Gamma	Weibull	-0.491	0.257	0.301
		Exponential	-0.929	0.047	0.864
	Inverse Gaussian	Weibull	-0.741	0.159	0.571
		Exponential	-0.938	0.040	0.881
	Log-normal	Weibull	-0.806	0.096	0.658
		Exponential	-0.929	0.030	0.903

generate parallel cumulative hazard curves that differ mainly from Lognormal estimates due to the Lognormal model showing diminished heterogeneity evaluation. The spline-based models' hazard projections vary greatly because rcs-Gamma exhibits the steepest hazard increase after time 2, which displays higher sensitivity to time-dependent effects. The rcs-Log-Normal and rcs-Inverse Gaussian model estimations produce higher cumulative hazard rates than their standard versions because they understand complex nonlinear covariate effects and baseline hazard patterns.

D. Survival Probability Estimates

Using equations 10, 15, and 20, the survival probability estimates were calculated without covariates, x=0. Equations 9, 16, and 21 were used to calculate the survival probability estimates when covariates were included, x=1. See TABLE V. The gamma frailties model with x=0 shows a relative bias of 0.013, indicating a negligible bias when the covariate is not included. When the covariate is included, x=1, the relative bias increases to 0.097, suggesting a more substantial covariate influence on the survival probability estimate. The inverse Gaussian model had a relative bias of 0.050 for x=0, slightly higher than the gamma model's bias

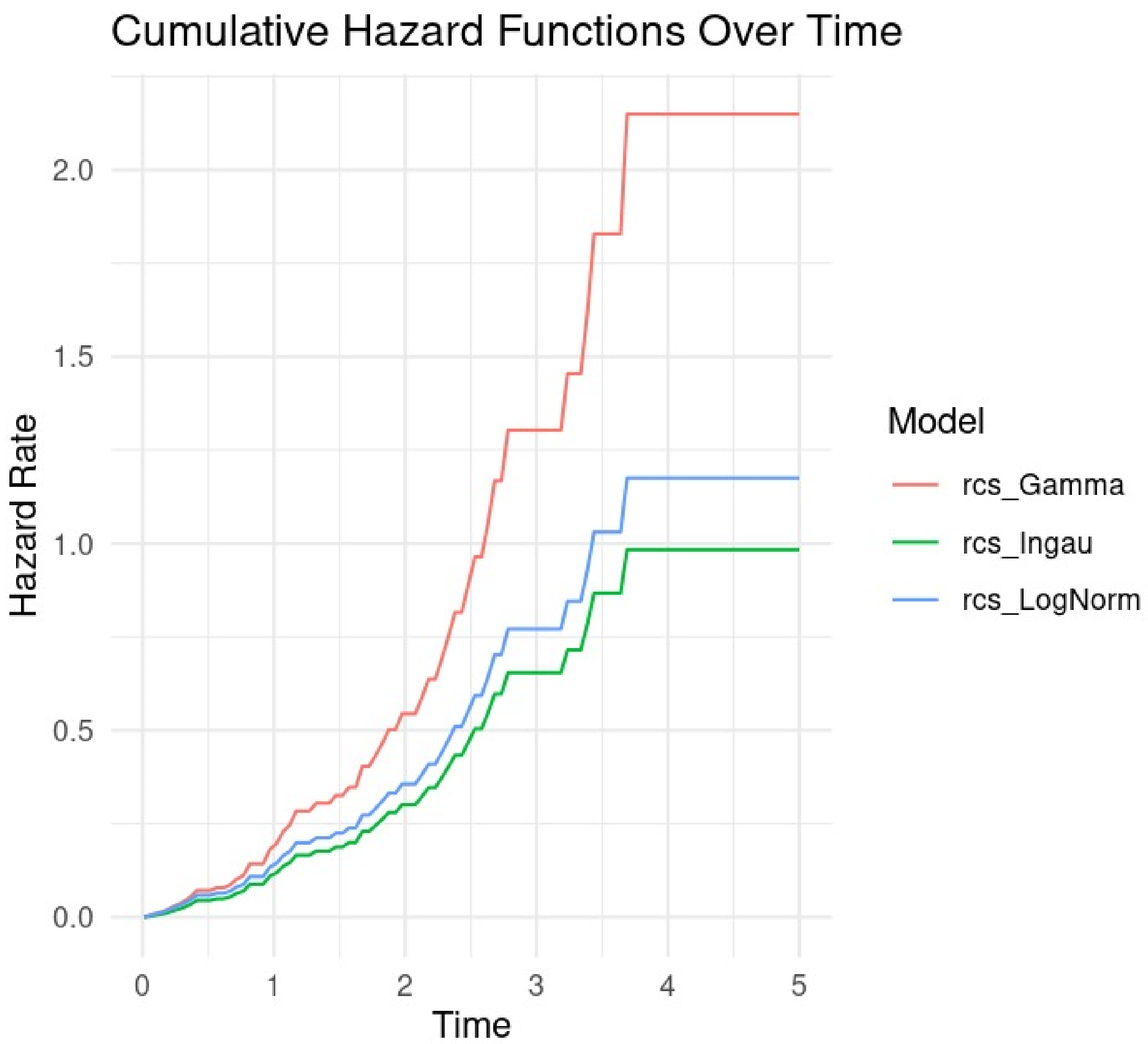

Fig. 1. Cumulative hazard functions for spline-modeled frailty models.

at this level. With x=1, the relative bias increases to 0.195, indicating a more pronounced impact of the covariate on estimates. In both models, incorporating a covariate tends to increase the relative bias. For SD, the gamma frailty model has an SD of 0.022 for x=0, indicating low variability in its survival probability estimates without the covariate; with the covariate, the SD increases to 0.047, indicating greater variability in the estimates due to the additional complexity introduced by the covariate. For the inverse Gaussian model, the SD is 0.019 for x=0, showing slightly less variability in estimates than the gamma model at the same covariate level. The SD increases to 0.042 when including the covariate, indicating increased variability. The gamma frailty model yielded an MSE of 0.001 for x=0, indicating excellent accuracy in estimating survival probabilities without the covariate. However, when x=1, the MSE rises to 0.008, indicating an increase in error when the covariate is considered. The inverse Gaussian model had an MSE of 0.002 for x=0, indicating good accuracy. Still, the error increases significantly to 0.024 with the addition of the covariate, x=1, marking the most substantial increase in error.

For the spline models. Including covariate (x = 1) in the Gamma and Inverse Gaussian frailty models caused their relative bias to increase from 0.162 to 0.616 and from 0.394 to 1.181, respectively, under the Weibull baseline. The effects of the covariate produce a significant upward shift in survival probability forecasts. The Exponential baseline produces two models that present a negative bias that reduces survival probability estimates. Implementing the Gamma-Exponential model produces reduced variability (SD = 0.028) and lower MSE (0.039) while including the covariate, which indicates more accurate predictions despite the significant bias.

When adding the covariate to the Weibull-based models, the standard deviation and Mean Squared Error generally rise, which produces more complicated and erroneous prediction estimates. The exponential models demonstrate a decrease in MSE and SD values when using covariates, while the Inverse Gaussian model shows the most substantial decrease from 0.048 to 0.022 in MSE as shown in TABLE VI. Two factors suggest that Exponential models

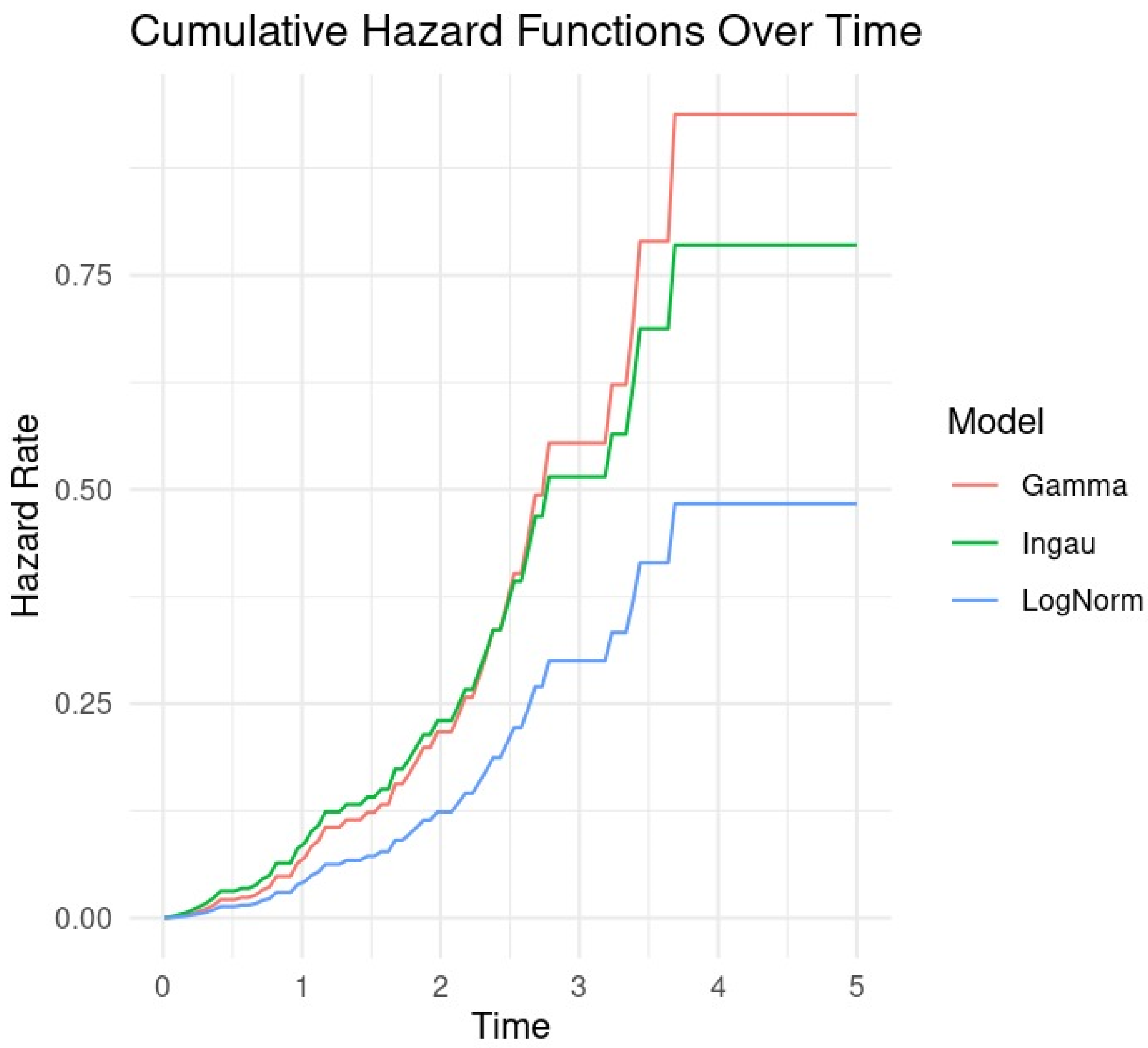

Fig. 2. Cumulative hazard functions for standard frailty models.

TABLE V
SURVIVAL PROBABILITY ESTIMATES FOR STANDARD MODELS

Method	Baseline	Rel. Bias	SD	MSE
Gamma, $x = 0$	Weibull	0.013	0.022	0.001
Gamma, $x = 0$	Exponential	-0.402	0.097	0.115
Gamma, $x = 1$	Weibull	0.097	0.047	0.008
Gamma, $x = 1$	Exponential	-0.515	0.073	0.084
Inverse Gaussian, $x = 0$	Weibull	0.050	0.019	0.002
Inverse Gaussian, $x = 0$	Exponential	-0.017	0.050	0.021
Inverse Gaussian, $x = 1$	Weibull	0.195	0.042	0.024
Inverse Gaussian, $x = 1$	Exponential	-0.250	0.062	0.022

maintain stronger performance stability alongside covariate application despite exhibiting bias. The Gamma model demonstrates superior consistency with lower error variability than the Inverse Gaussian model, particularly under the Weibull hazard condition. The results indicate that survival probability estimation depends on frailty distribution and baseline hazard rate while influencing model robustness levels.

The standard frailty models demonstrate different survival impact when compared to spline-based models. See Figures 3 and 4. According to standard models, the covariate produces a minor adjustment in the survival distribution curve, demonstrating proportional hazard effects with homogeneous risk patterns. The spline-based models demonstrate a greater distributional shift coupled with distribution flattening because they reveal more substantial and possibly nonlinear changes to the hazard function. The variable generates nonuniform hazard effects across its measurement scale because it influences survival changes based on the observation value within the range. This effect effectively restricts the cubic spline model. The superior ability of spline-based models lies in their capacity to depict covariate effects with increased

TABLE VI
SURVIVAL PROBABILITY ESTIMATES FOR SPLINE MODELS

Method	Baseline	Rel. Bias	SD	MSE
Gamma, $x = 0$	Weibull	0.162	0.087	0.017
Gamma, $x = 0$	Exponential	-0.643	0.058	0.156
Gamma, $x = 1$	Weibull	0.616	0.105	0.042
Gamma, $x = 1$	Exponential	-0.672	0.028	0.039
Inv. Gaussian, $x = 0$	Weibull	0.394	0.068	0.062
Inv. Gaussian, $x = 0$	Exponential	-0.346	0.064	0.048
Inv. Gaussian, $x = 1$	Weibull	1.181	0.097	0.128
Inv. Gaussian, $x = 1$	Exponential	-0.489	0.042	0.022

accuracy because they accommodate nonlinear effects when standard assumptions do not apply.

E. Hazard Ratios

Equation 43 was used to calculate the hazard ratios, see TABLE VII. To facilitate the interpretation of hazard ratios, we compute the percentage increase using the formula:

$$\text{Percent Increase} = (\text{HR} - 1) \times 100 \tag{48}$$

A one-unit increase in the covariate (beta estimate) for the Gamma frailty model leads to a 241.5825% increase in the hazard, which shows a strong positive effect of the covariate in the Gamma Model. Similarly, for the Inverse Gaussian and lognormal frailty models, a unit increase in the covariate corresponds to a 190.6704% and 229.3545% increase in the hazard, respectively. The theta estimate relates to the frailty effect in the models. For the Gamma frailty model, the impact of the frailty results in a 176.7657% increase in the hazard. Similarly, for the Inverse Gaussian and Lognormal frailty models, the frailty effect leads to a 179.8207% and 184.3274% increase in the risk, respectively.

TABLE VII
HAZARD RATIOS FOR THE STANDARD MODELS

Method	Baseline	Beta	Theta
Gamma	Weibull	3.4158	2.7677
Gamma	Exponential	2.7868	2.9241
Inverse Gaussian	Weibull	2.9067	2.7982
Inverse Gaussian	Exponential	2.7932	2.7954
Lognormal	Weibull	3.2935	2.8433
Lognormal	Exponential	2.7914	2.8438

For the spline-based models, see TABLE VIII. A unit increase in the covariate results in the hazard increasing by 2.565, 2.6195, and 2.323993 times for the Gamma, Inverse Gaussian, and Lognormal frailty models, respectively. For the theta estimate, the hazard increases by 2.804, 2.759, and 2.76 times due to the frailty effect in the Models, respectively. The standard models showed a higher hazard ratio for both Beta and theta estimates, which reflects a strong association between the covariate and the risk of recurrent events; however, the spline-based models moderated the Relationship, suggesting a more nuanced effect of the covariates. The frailty effect was consistent across all the models; this indicates a significant unobserved heterogeneity that influences the hazard.

F. Recurrence Rates

In the Gamma frailty model, the predicted recurrence rate at time t=0.3 is approximately 1.87% as shown in TABLE IX. This indicates that, based on the predictions of the model, 1.87% of the individuals are expected to experience a recurrence of the event. For the inverse Gaussian and Lognormal frailty models, the models predict a recurrence rate of 2.81% and 1.185%, respectively. These suggest that individuals modeled by using the Inverse Gaussian model have a higher probability of recurrence compared to the log-normal and Gamma models. Using a lognormal distribution, the individuals are least likely to experience the recurrence. The log normal model suggested a conservative estimate of recurrence rates, which indicates that it may be less suited for detecting early or frequent recurrences, unlike the inverse Gaussian model, which appeared to predict higher recurrence rates at both time points, which indicates its sensitivity to early recurrence risks.

TABLE VIII
HAZARD RATIOS FOR THE SPLINE MODELS

Model	Baseline	Beta	Theta
Gamma	Weibull	2.5653	2.8036
Gamma	Exponential	17.3504	2.7980
Inverse Gaussian	Weibull	2.6195	2.7586
Inverse Gaussian	Exponential	17.2370	2.7561
Log-normal	Weibull	2.3240	2.7601
Log-normal	Exponential	16.2305	2.7629

For the spline-based models, the recurrence rate predicted by the Gamma, Inverse Gaussian, and Lognormal frailty models at time t=0.3 is 6.211%, 3.942%, and 5.197%, respectively as illustrated in TABLE X. These recurrence rates are consistently higher than in their respective standard models, which indicates that the more flexible models allow for capturing increased risk of recurrence. Similarly, at time t=1.0, the recurrence rate increased when splines were incorporated into the models from 11.12% to 29.003%, from 12.995% to 17.075%, from 6.59% to 20.3312% for the Gamma, Inverse Gaussian, and Lognormal frailty models, respectively. The spline-based models indicate that recurrence risks are under-estimated by the standard models, especially as time progresses.

G. Application to Malaria Data

In this section, the models used in the simulations were fitted to a recurrent malaria dataset to determine how effective the models' performance could be. This was done by examining the AIC and BIC values to assess their performance and survival curves. The objective was to determine which model predicted recurrent malaria more accurately by looking at its predictive and statistical ability. The dataset consisted of 300 individuals who had experienced up to 5 events within a 2-year follow-up period. The table below shows the number of recurrent episodes. 44% of the individuals received up to 5 recurrent episodes of malaria, as shown in TABLE XI.

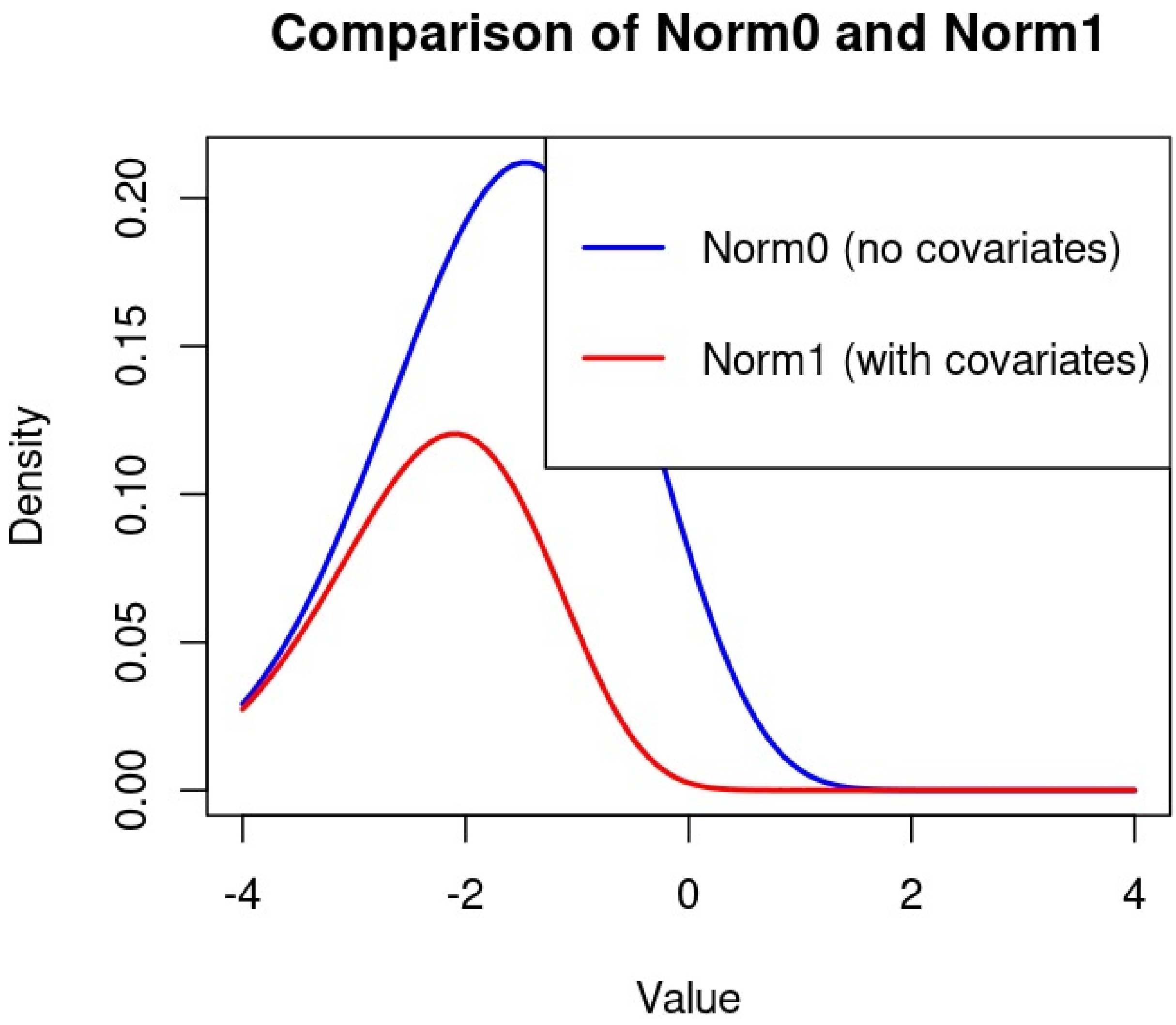

Fig. 3. Standard models distributions.

Log-likelihood, AIC, and BIC were assessed to examine how well the model performed. The standard models, Gamma, inverse Gaussian, and Lognormal distribution, had AIC values of 22932.64, 22977.98, 22953.38, respectively, as shown in TABLE XII. However, the spline-based models had a relatively lower AIC value of 22926.46, 22966.97, and 22944.70 for the spline gamma, spline inverse Gaussian, and spline lognormal. This shows that the spline-based models fitted the data well and had better predictive power than their standard counterparts, which is in line with a study by [22], [8]. For BIC values that penalize for complexity and overfitting, we had the spline models still having relatively low BIC values compared to their standard counterparts. This could be because the standard models cannot adequately represent the nonlinear patterns in hazard rates and the variations in frailty among individuals. When measuring the observed recurrence times, the spline models were the most robust and fitted the data well, as their performance was better than the Standard models. The findings are consistent with other studies highlighting how spline-based models react to complicated survival data distributions [25], [5].

Comparison to Kaplan-Meier Survival Estimates: Using Kaplan-Meier as a benchmark and plotting the survival probabilities of the standard and spline models for 2-year follow-up, all the models indicated a sharp drop in survival probability within the first 0.5 years as shown in Figure 5, revealing a higher initial recurrence rate of malaria episodes after the initial episode. For the standard models, the gamma and inverse Gaussian models mimic the Kaplan-Meier curve at the start, which indicates that they seem more able to predict the early risk of recurrence. The lognormal model indicates that the risk declines gradually, implying that it can manage situations where the disease takes longer to recur.

Cumulative Hazard Curves

However, all parametric models are not the same as the Kaplan-Meier curve for the follow-up period, which points to certain limitations in standard models. Spline-based techniques and other flexible techniques are therefore better suited to managing the nonlinear models. After only 0.5 years

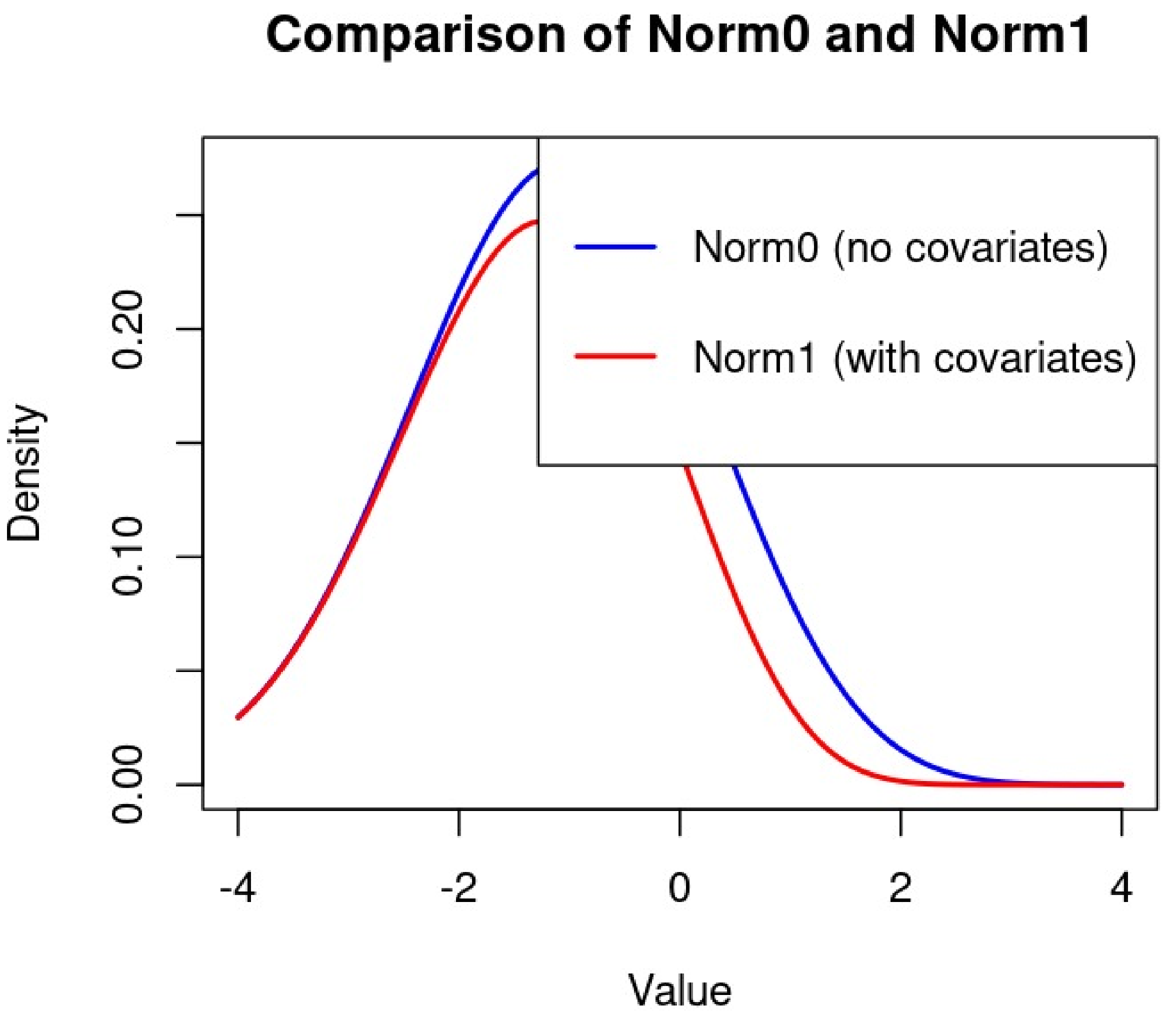

Fig. 4. Spline-based Models Distributions.

of follow-up, Spline Gamma and Spline Inverse Gaussian models have curves almost identical to the Kaplan-Meier curve as shown in Figure 6. This method foresees a longer survival period for some patients, and at the start, it yields results that differ from those produced by Kaplan-Meier. The addition of restricted cubic splines makes the model fit the data better and gives a more realistic estimate of the hazard function's initial shape.

Two-Year Recurrence Projections

Figure 7 gives the cumulative hazard for standard and spline-based frailty models over two years. Unlike the ordinary models, Spline Gamma and Inverse Gaussian models demonstrate a more gradual increase in the risk of recurrent malaria with time because they are more flexible for capturing these changes. Standard Inverse Gaussian and Standard Lognormal models instead predict more rapid and irregular hazard growth after one year, which might lead to an exaggerated risk calculation. Of special note, the Standard Gamma model has the steepest early increase in hazard, possibly because it is not as flexible in handling nonlinear trends in the data. Still, the Spline Lognormal model gives the lowest cumulative hazard over time, which points to better handling of delayed or scattered events throughout the follow-up period. This research shows that spline-based frailty models are best suited for dealing with changes in hazard through time, and help provide better estimates of malaria risk for intervention policies.

Distribution of Predicted Recurrences

The graph in Figure 8 shows how many malaria cases can be expected for people over two years. There is a sharp increase in the curve within the first 0.5 years, meaning there is an initial high risk of a recurrence, but the curve levels off as time lapses, revealing that the risk of another recurrence reduces as years go by. Such irregular patterns show the need for flexible models, such as spline-based frailty models, that deal with changing hazard rates. These recent analyses demonstrate the usefulness of using joint frailty approaches and recurrent event models: they allow for more precise and accurate estimations of the risk of being affected by malaria. It is observed clinically that, because of intense spread, early

TABLE IX
PREDICTING RECURRENCE USING STANDARD MODELS

Time	Model	Baseline	Recurrence Rate
0.3	Gamma	Weibull	0.0187
0.3	Gamma	Exponential	1.1018
0.3	Inverse Gaussian	Weibull	0.0281
0.3	Inverse Gaussian	Exponential	0.4270
0.3	Log-normal	Weibull	0.0118
0.3	Log-normal	Exponential	0.3711
1.0	Gamma	Weibull	0.1111
1.0	Gamma	Exponential	4.4430
1.0	Inverse Gaussian	Weibull	0.1299
1.0	Inverse Gaussian	Exponential	1.2596
1.0	Log-normal	Weibull	0.0659
1.0	Log-normal	Exponential	1.1594

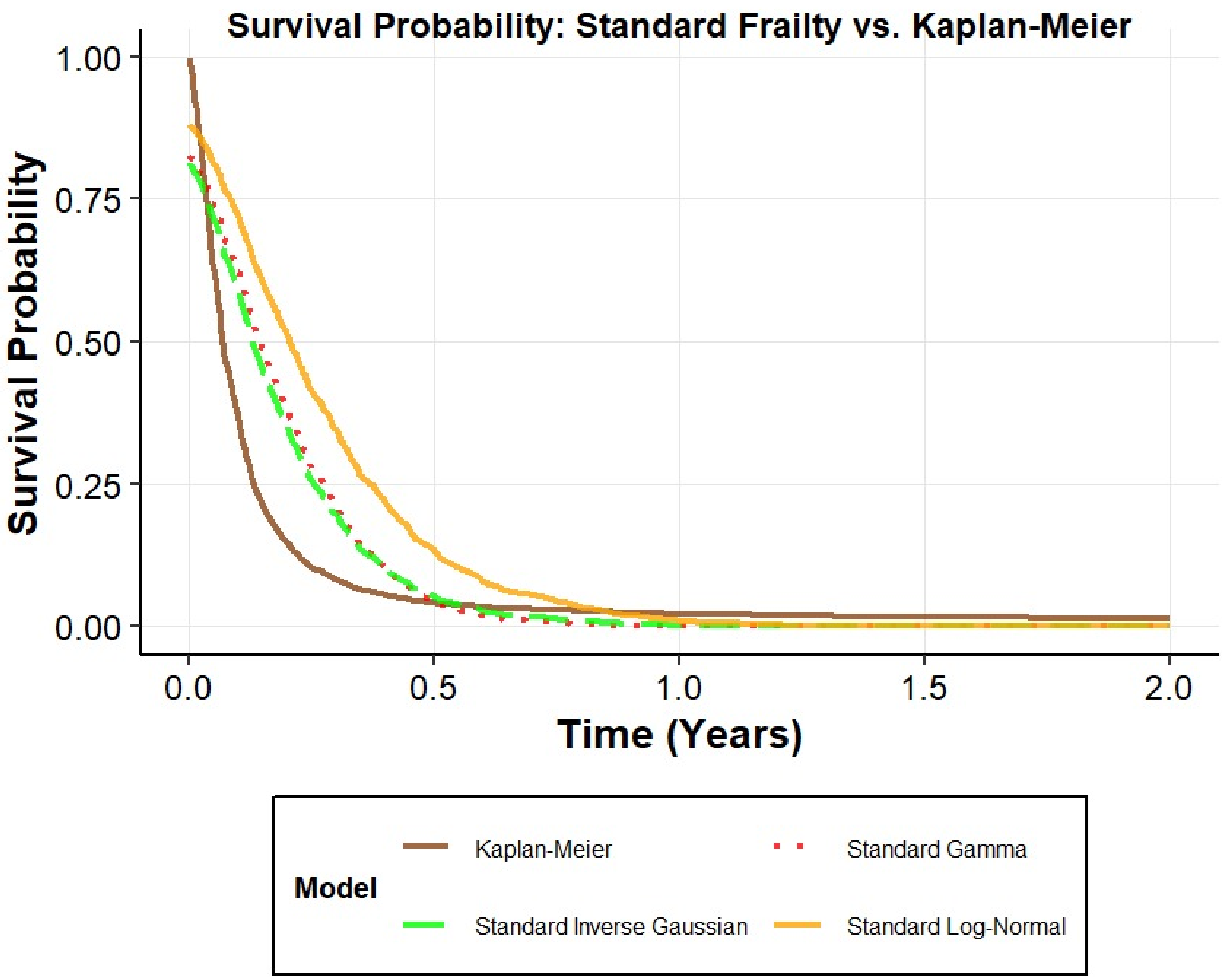

Fig. 5. Comparison of survival probabilities over a 2-year follow-up period using Kaplan-Meier estimates and standard/spline frailty models

reinfections are more common and then tend to decrease as immunity rises or specific measures are enforced.

Risk Score Predictive Accuracy

Predicting the recurrence rate for the next 2 years, we can see how much malaria is likely to recur again in the next two years using standard frailty and spline-based models, and these are shown along with the Kaplan-Meier estimate in Figure 9. The Kaplan–Meier estimate illustrates a sharp early rise up to 0.5 years, then levels out close to 1.0 in the second year, indicating that most cases of recurrence happen in the beginning. Spline Gamma and Standard Gamma fit the steep rise at the beginning, and Spline Lognormal and Spline Inverse Gaussian go slowly, missing the initial risks but converging afterward. So, even though splines allow for more flexibility, they could smooth the short-term rise in the recurrence rate. Even so, spline-based models balance the accuracy of short-term and long-term predictions, unlike the extreme change seen early on in the Standard Inverse Gaussian and Standard Lognormal modes. The results found

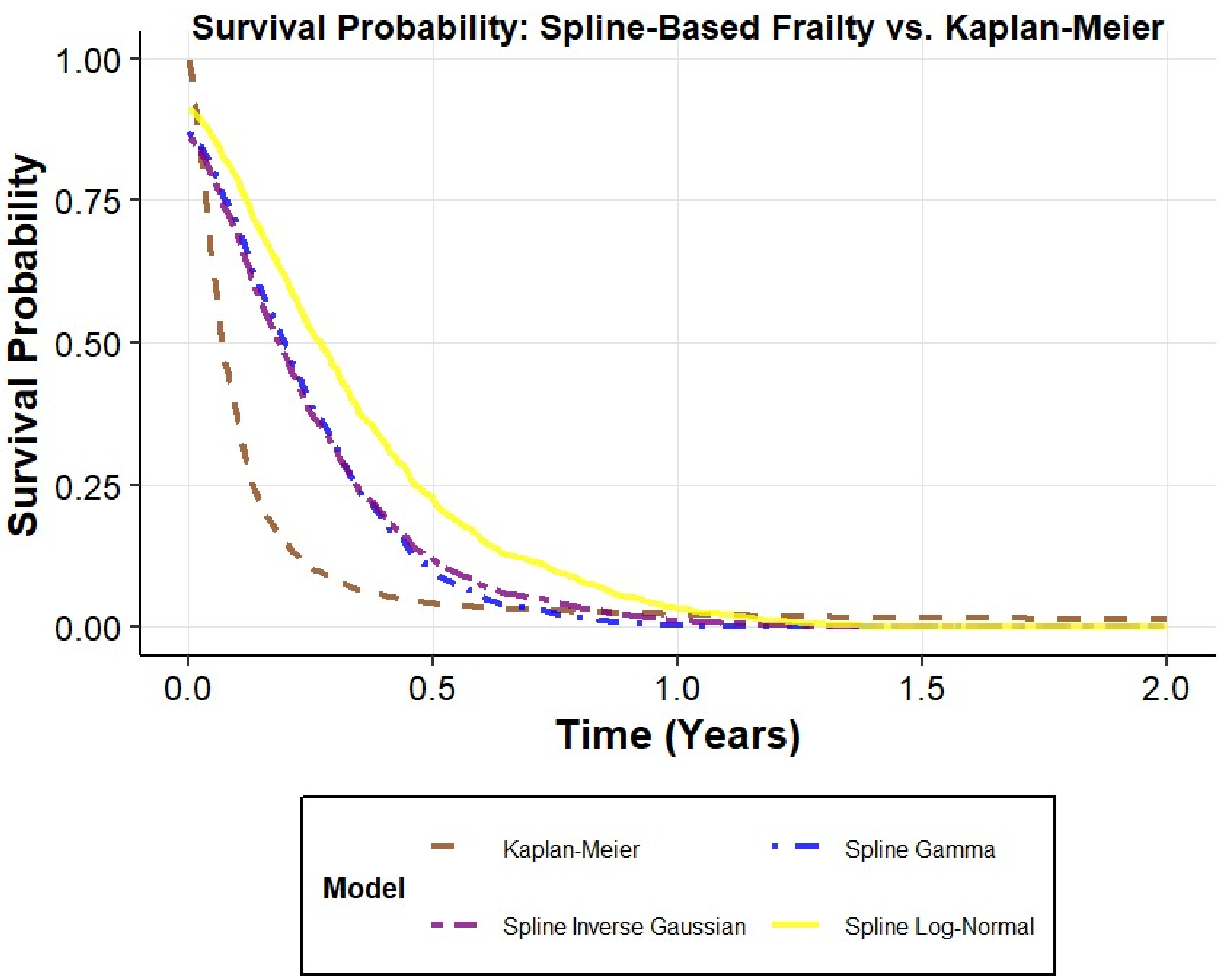

Fig. 6. Cumulative hazard curves comparing spline-based frailty models to Kaplan-Meier estimates, illustrating improved fit with restricted cubic splines

TABLE X
RECURRENCE RATES FOR SPLINE-BASED MODELS

Time	Model	Baseline	Recurrence Rate
0.3	Gamma	Weibull	0.0621
0.3	Gamma	Exponential	0.0088
0.3	Inverse Gaussian	Weibull	0.0394
0.3	Inverse Gaussian	Exponential	0.0070
0.3	Log-normal	Weibull	0.0520
0.3	Log-normal	Exponential	0.0058
1.0	Gamma	Weibull	0.2900
1.0	Gamma	Exponential	0.0986
1.0	Inverse Gaussian	Weibull	0.1708
1.0	Inverse Gaussian	Exponential	0.0825
1.0	Log-normal	Weibull	0.2033
1.0	Log-normal	Exponential	0.0642

TABLE XI
DISTRIBUTION OF MALARIA EPISODES PER INDIVIDUAL

Episodes	Frequency	Percentage
0	68	22.7%
1	34	11.3%
2	30	10.0%
3	23	7.7%
4	13	4.3%
5	132	44.0%

here are in line with those of [24], [18], who concluded that using flexible and joint models improves the risk estimation for recurrent malaria, and [22], [8], who highlighted that spline-based models well represent non-constant, flexible risks over time.

Risk Prediction Insights and Policy Implications

The histograms in Figure 10 show the estimated number of repeated malaria episodes based on a frailty model. Spline methods (top-row models) generally lead to more compact distributions that stand out, implying better predictions and less variation. Notably, both Spline Gamma and Spline Lognormal have narrow distributions that tilt to the right, representing a tendency to overpredict the number of extreme values slightly. At the same time, the standard models (bottom row) tend to produce distributions that are broader and widely dispersed. By way of example, Standard Gamma and Standard Inverse Gaussian have wider tails and less steep peaks, implying that these distributions show more variability and react to different individual risks. Such differences prove the benefit of spline modeling since it helps control overfitting and provides stable estimates of the model's parameters. It appears from these histograms that

TABLE XII
MODEL PERFORMANCE COMPARISON

Model	AIC	BIC	Log-Likelihood
Standard Gamma	22932.64	22943.37	-11464.32
Spline Gamma	22926.46	22947.94	-11459.23
Standard Inverse Gaussian	22977.98	22988.72	-11486.99
Spline Inverse Gaussian	22966.97	22988.45	-11479.49
Standard Log-Normal	22953.38	22964.12	-11474.69
Spline Log-Normal	22944.70	22966.18	-11468.35

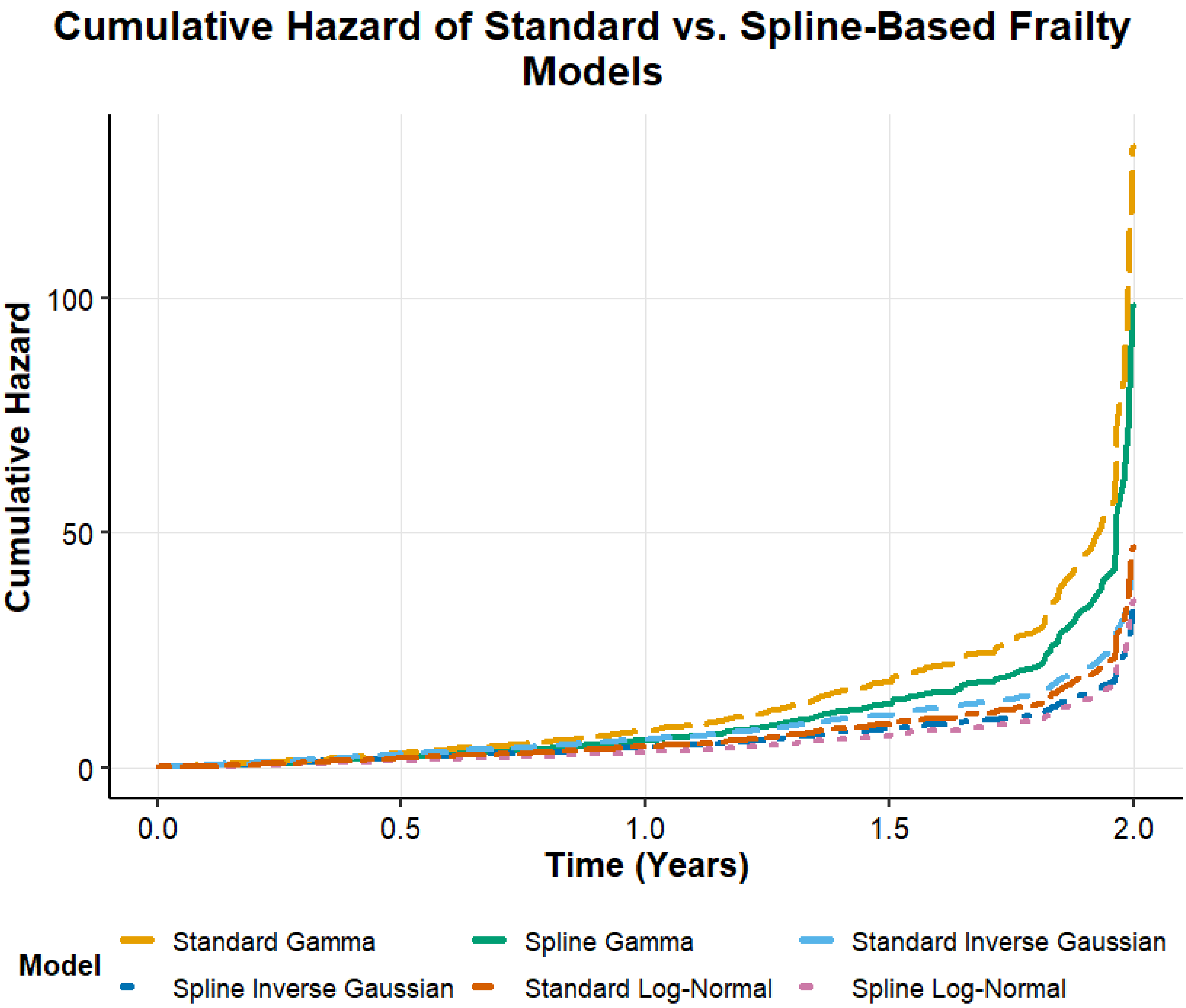

Fig. 7. Cumulative hazard functions for standard and spline-based frailty models over a 2-year follow-up period

spline-based frailty models are better suited for forecasting recurrent malaria by avoiding unexpected results and placing most of the probability in likely ranges.

Figure 11 compares each individual's risk score to the number of predicted recurrent events when Standard Gamma frailty is used. The fact that blue points lie very close to the red line implies an almost perfect linear link between risk score and event count according to Gamma's multiplicative formula. The fact that the points are gathered close to the red line proves that predictions are accurate and steady. Even though most estimates are close to the line, those at both ends may reveal that very low or high-risk people are wrongly assessed. An R^2 close to 0.997 is a good sign, but these edge pairs point to improved results when using a nonlinear model.

The graph in Figure 12 illustrates the correlation between risk scores and the expected number of recurrent malaria cases computed using the Spline Lognormal frailty model. Rather than a straight pattern, this plot initially sees an increase in events, but then the events seem to stay the same or decrease for higher scores in risk. It is clear from the trend line that the data has a curved pattern, which means it is not following a completely straight line. This demonstrates why spline modeling is beneficial since it supports the interaction of risk and event prediction. The Standard Gamma model gives more clustered prediction ranges in Survival Rate curves, whereas the spread of points in the Lognormal model seems more spread out across risk levels. In general, this type of modeling achieves more flexibility and can address how changes in risk can occur and stabilize in specific populations.

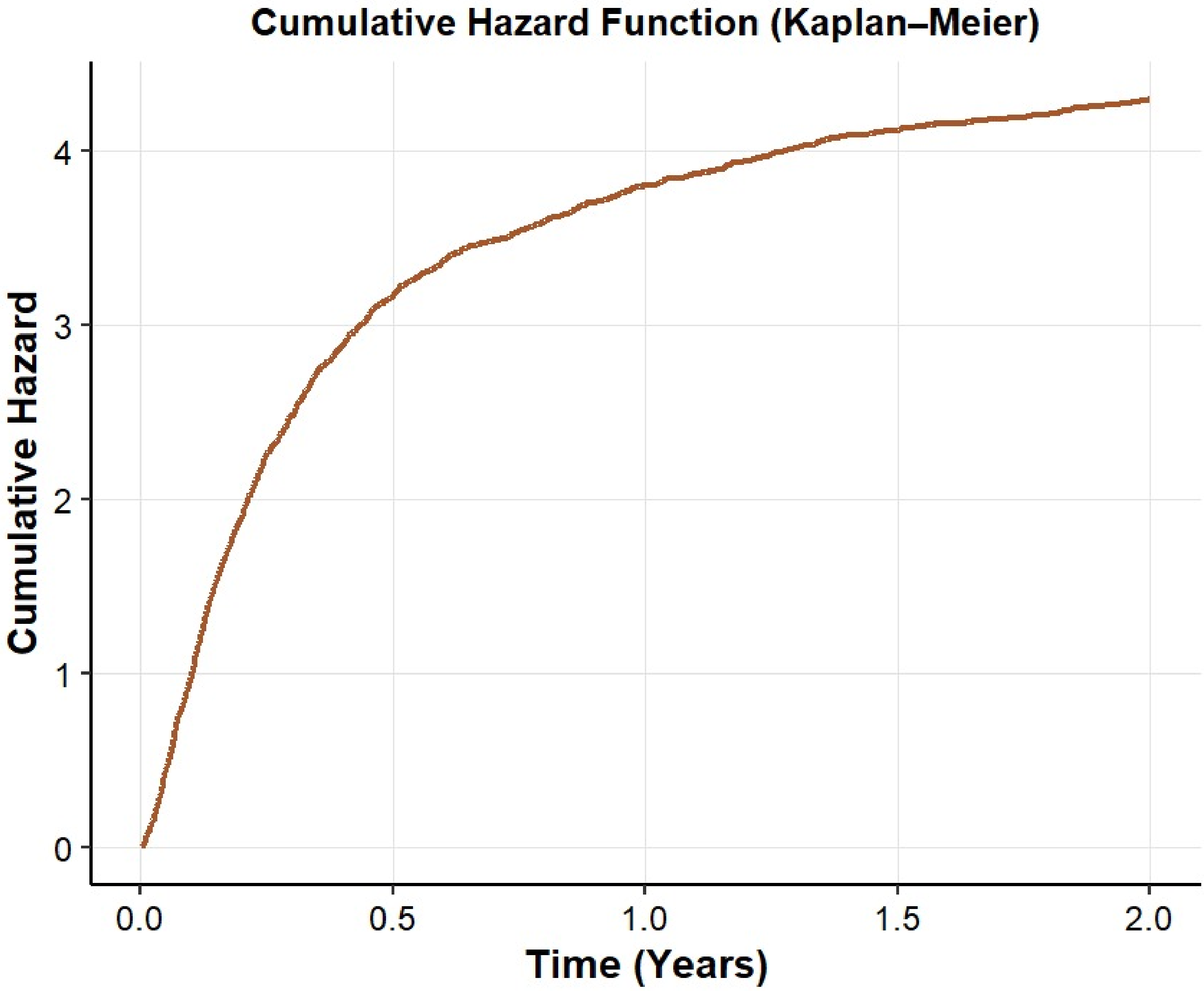

Fig. 8. Predicted recurrence probability over a 2-year follow-up for standard and spline-based frailty models

IV. Discussion

The results of this study provide important insights into the relative performance of frailty models in recurrent event survival analysis and emphasize the value of incorporating restricted cubic splines (RCS). Consistent with previous research, this study shows that the model.

Misspecification—particularly incorrect assumptions about the baseline hazard—can lead to significant inferential errors. As [10] reported, and as seen here, using an exponential rather than a Weibull baseline increases bias considerably. For example, the spline-based Gamma model's covariate effect bias spiked from 0.00207% to 194.254% under exponential misspecification, reaffirming the necessity of appropriate baseline specification.

The Gamma distribution emerged as the most reliable among the standard frailty models, with the lowest bias and mean squared error (MSE) in both the covariate and frailty variance estimates. This aligns with [4], who identified the Gamma model as particularly effective in handling unobserved heterogeneity due to its mathematical tractability and flexibility. Conversely, while the Inverse Gaussian model showed promise in estimating frailty variance—reporting the lowest MSE (0.001)—its performance on covariate effects was weaker, showing higher bias and MSE. These results reflect findings by [1], [6], who caution against using Inverse Gaussian models in covariate-driven survival scenarios.

The Lognormal model demonstrated the poorest performance overall, with the highest bias and MSE across most measures. This is consistent with [4], who noted its limited capacity to capture complex heterogeneity. The limitations of the Lognormal model became even more evident when examining long-term survival probability and baseline hazard accuracy, particularly at later time points such as $t = 1.0$, where bias and MSE increased considerably.

A key advancement shown in this study is the integration of RCS, which significantly improved model fit and accuracy. Particularly for the Gamma frailty model, including RCS-reduced bias and MSE (e.g., 0.0000207 and 0.0009, respectively) and enhanced prediction of recurrence rates—from 1.87% to 6.211%. These improvements align with the work of [23], [20], who advocated for the use of flexible parametric models in capturing non-linear dynamics in epidemiological data.

However, the benefit of RCS was not uniform across all distributions. Despite improvements, the Lognormal and Inverse Gaussian models exhibited considerable bias and

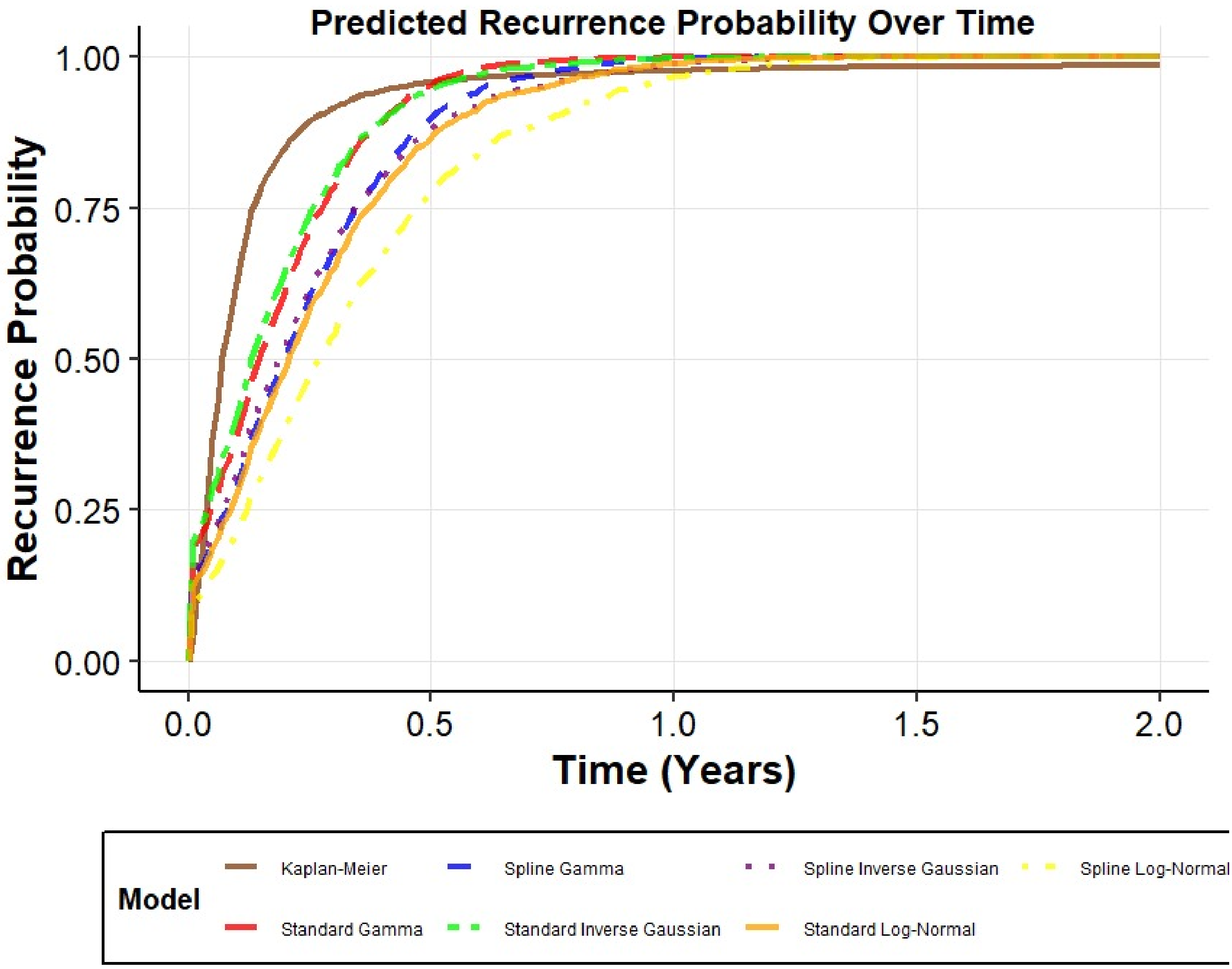

Fig. 9. Predicted recurrence probability over time using standard and spline-based frailty models, compared with the Kaplan-Meier estimate

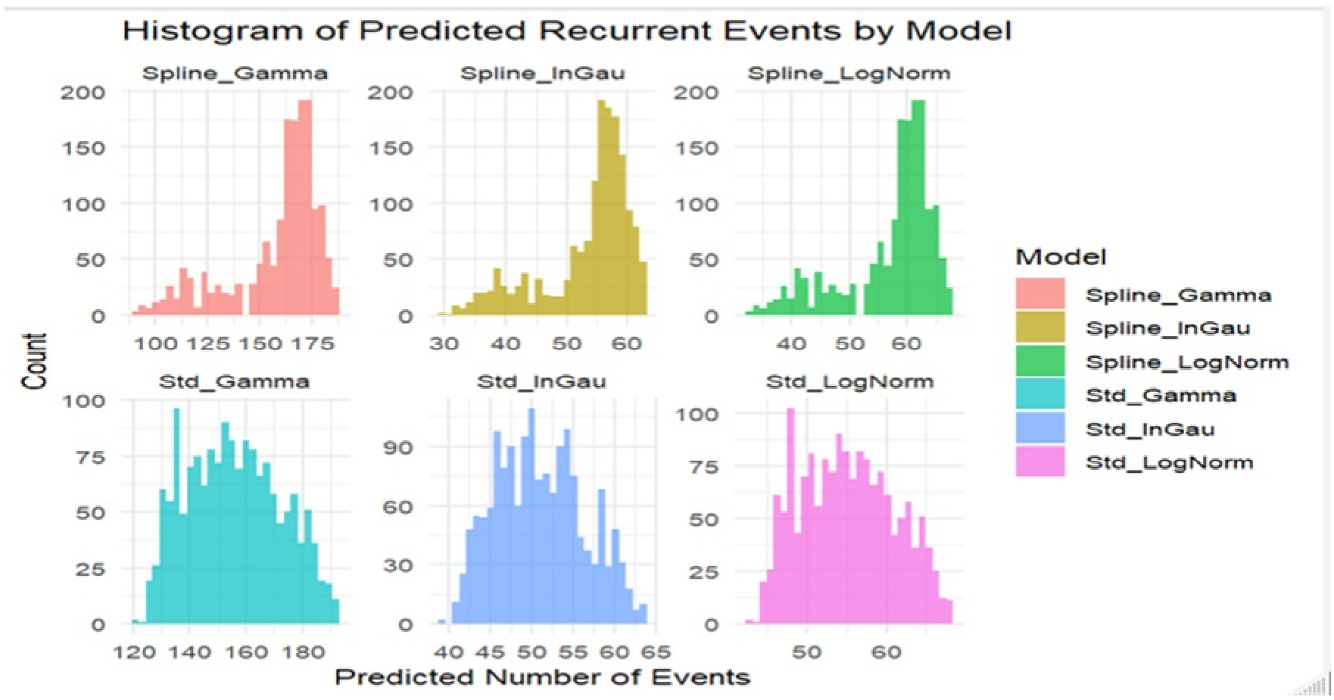

Fig. 10. Histogram of predicted recurrent malaria events by model type: spline-based (top row) vs. standard (bottom row)

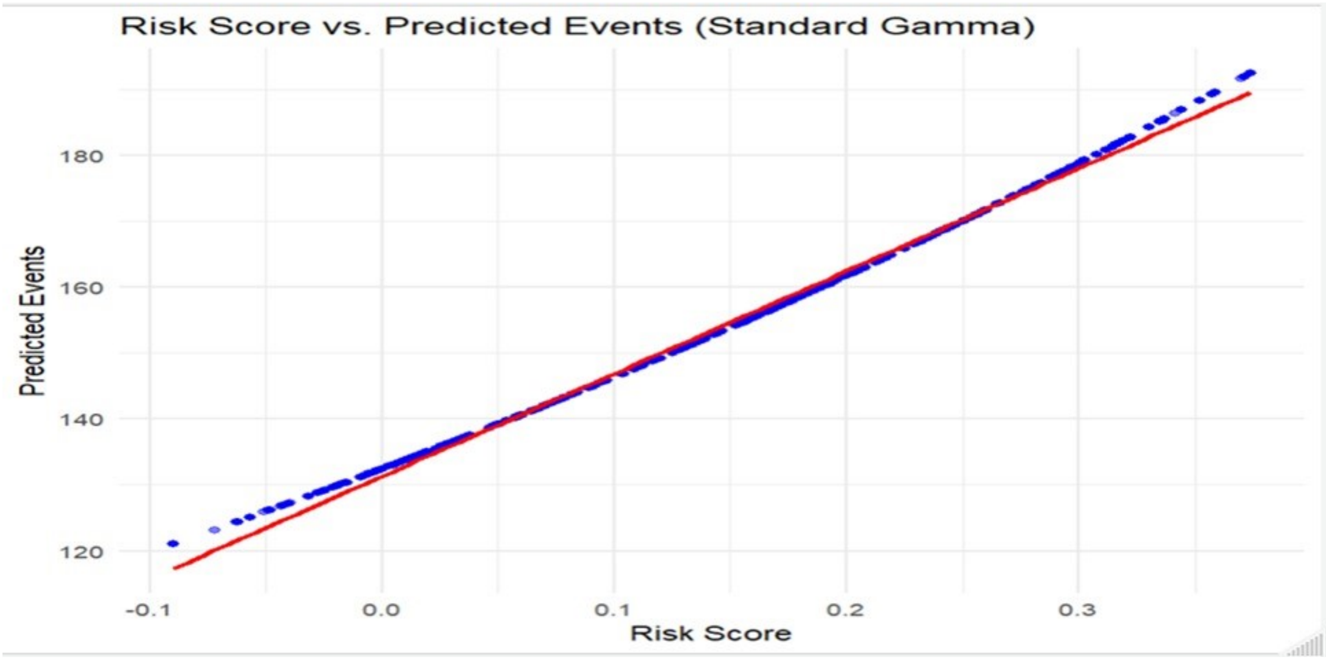

Fig. 11. Relationship between individual risk scores and predicted recurrent events using the Standard Gamma frailty model

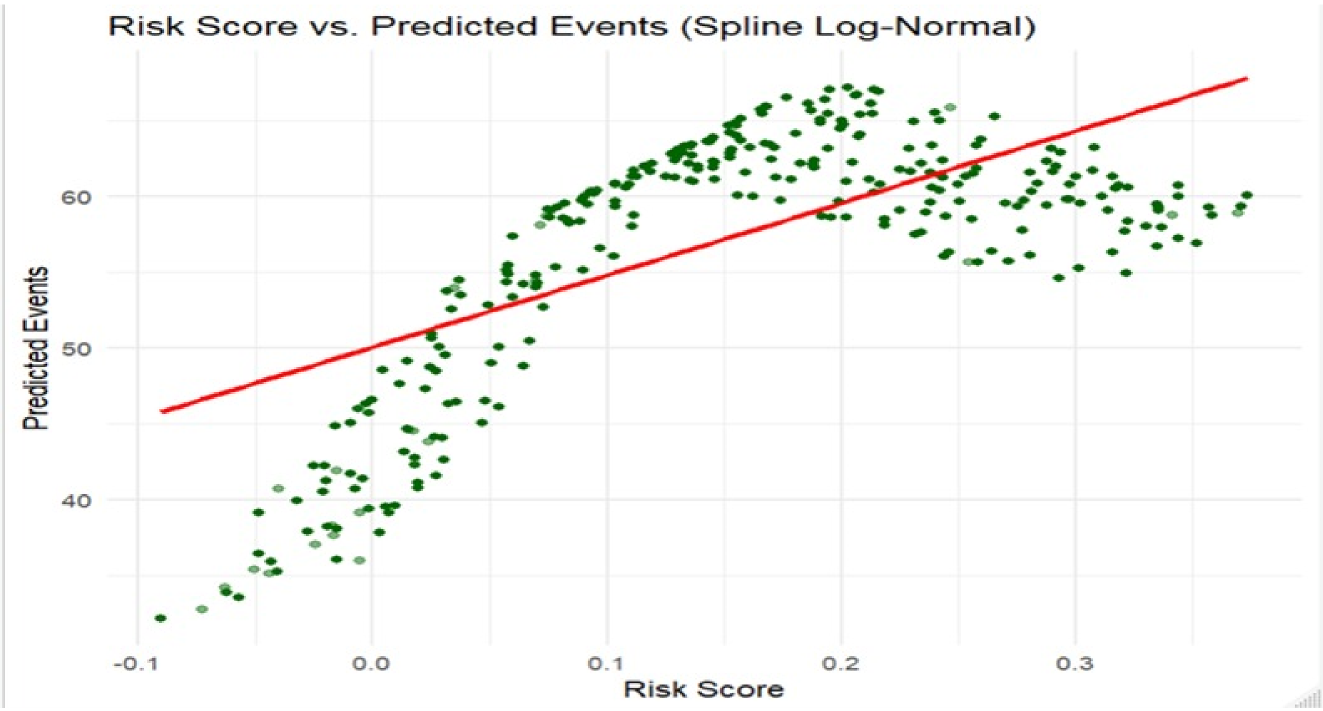

Fig. 12. Relationship between individual risk scores and predicted recurrent events using the Spline Lognormal frailty model

error in long-term baseline hazard estimation. This supports observations by [6], who emphasized the deteriorating performance of parametric frailty models over more extended follow-up periods, especially when assumptions are violated.

When covariates were included, all models showed increased bias and MSE, but the Inverse Gaussian model appeared to be the most sensitive. This further supports [10], who warned that including covariates can amplify the adverse effects of model misspecification.

Overall, the Gamma frailty model—especially when enhanced with RCS—offers the most balanced and accurate performance across key metrics, including bias, standard deviation, and MSE. This supports the position of [4], who recommends the Gamma model in situations where the underlying frailty structure is uncertain. While the Inverse Gaussian model may still be helpful when the primary goal is a precise estimation of frailty variance, its broader utility appears limited by its vulnerability to covariate influence and long-term estimation error.

The evidence also strongly supports the adoption of RCS in survival analysis frameworks, particularly for datasets with suspected non-linear covariate effects. This echoes findings by [23], [20], who champion RCS for their capacity to reveal hidden structures in survival data. However, researchers should remain cautious when applying RCS in combination with Lognormal or Inverse Gaussian frailty models for long-term projections.

These findings underscore the importance of careful model selection in recurrent survival analysis. As [1] suggests, robust modeling directly informs clinical decision-making, especially for recurrent diseases such as malaria. Future studies should explore these findings across diverse clinical settings, larger samples, and under competing risks to ensure the generalizability and practical utility of the models tested, as recommended by [4].

V. Conclusion

These results provide insights into the performance of frailty models and the effects of the restricted cubic splines in the recurrent survival analysis. The models were evaluated based on the bias, standard deviation, mean squared error, survival probabilities, and baseline hazard estimates. The results show that misspecifying the baseline hazard can lead to significant biases and skewed estimates, especially when the actual baseline hazard function is not linear. The gamma frailty model was the most reliable, exhibiting low bias and MSE for the covariate effect (Beta) and the frailty variance (theta) estimates. The inverse Gaussian model performed well for theta estimates but had higher bias and mean square error for beta estimates, which indicated a lesser accuracy in estimating the covariate effects. The lognormal model had the highest bias and mean square error for beta and theta estimates, therefore becoming the least suitable for parameter estimation. Incorporating the restricted cubic splines into the models to capture the non-linear relationship between covariates and the baseline hazard significantly improved the model's accuracy, reducing the bias and MSE, particularly for the gamma frailty model.

For the baseline hazard estimates, the models showed an increased bias and MSE as time progressed from t=0.3 to t=1.0, reflecting a reduced accuracy of survival probability estimates over time. With and without splines, the gamma frailty model outperformed the inverse Gaussian and Lognormal frailty models in estimating the baseline hazard, especially at earlier time points. When the covariates were excluded from the models, the Inverse Gaussian and gamma frailty models showed a low relative bias, SD, and MSE, exhibiting reliable survival probability estimates. However, when the covariates were included, the relative bias and MSE increased in all the frailty models. This indicates that including the covariates introduces more error and variability in the estimates. The inverse Gaussian model showed the highest increase in MSE, suggesting it was more sensitive to the covariate effects than the Gamma model.

The gamma frailty model is the most preferred choice when the accurate frailty distribution is unknown, as it generally performs better in terms of bias, SD, and MSE. The model consistently provides accurate and reliable estimates for the frailty variance and the covariate effect, especially when restricted cubic splines are incorporated. The inverse Gaussian frailty model can be helpful when precise estimation of frailty variance is the primary focus, but it is less accurate for survival probabilities and covariate effects.

The restricted cubic splines enhanced the model's flexibility and reduced bias incredibly when estimating non-linear relationships between the hazards and the covariates. The increasing bias and MSE over time in all the frailty models suggested that predictions of long-term survival probabilities become less reliable. The flexibility provided by the restricted cubic splines allowed for better modeling of non-linear relationships, enhancing the recurrence rate predictions. The spline-based Gamma frailty model was the most sensitive to predicting recurrence across both time points, becoming more valuable for high-risk groups. Incorporating RCS significantly improved the accuracy of the frailty models, particularly the Gamma frailty model, reducing bias and MSE and better capturing the non-linear relationships between the covariates and the baseline hazard over the standard models.

Practitioners and researchers should consider incorporating the restricted cubic splines into survival analysis models to improve the accuracy of capturing the non-linear relationships between covariates and hazard functions. However, caution should be taken when interpreting long-term survival estimates because predictions for extended follow-up periods might be less reliable, especially for lognormal and inverse Gaussian models.

These results emphasize the importance of suitable model selection in survival analysis and recurrence prediction in clinical decision-making. Accurate and correct modeling can inform patient management strategies by better understanding the likelihood of event recurrences. Therefore, the study underscored the importance of selecting appropriate frailty models and using flexible methods that incorporate RCS to improve the accuracy of survival estimates in recurrent event analysis. Further research into model performance across different datasets with different sample sizes and clinical scenarios is necessary to validate these findings further and refine methodologies in recurrent survival analysis.

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