BMC Medical Research Methodology

RESEARCH

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Computationally efficient Bayesian inference for semi-parametric joint models of competing risks survival and skewed longitudinal data using integrated nested Laplace approximation

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Abstract

Background Joint modeling is widely used in medical research to properly analyze longitudinal biomarkers and survival outcomes simultaneously and to guide appropriate interventions in public health. However, such models become increasingly complex and computationally intensive when accounting for multiple features of these outcomes. The need for computationally efficient methods in joint modeling of competing risks survival outcomes and longitudinal biomarkers is particularly critical in clinical and epidemiological settings, where prompt decision-making is essential. Moreover, there is very little literature on joint modeling of competing risks survival and skewed longitudinal data using Integrated Nested Laplace Approximations (INLA), despite its growing popularity in Bayesian inference. This paper presents a computationally efficient inference approach for modeling competing risks survival and skewed longitudinal data using INLA.

Methods We propose cause-specific competing risks joint models with a semi-parametric mixed-effects longitudinal submodel and second-order random walk baseline hazards. The proposed models are reformulated as latent Gaussian models to enable efficient Bayesian inference using INLA. The INLA approach and its R packages are also presented. Various smoothing spline functions, distributions, and association structures were evaluated for both approaches. The INLAjoint and R2WinBUGS R packages were employed for the INLA and Markov-Chain Monte-Carlo (MCMC) approaches, respectively, to approximate the posterior marginals of the proposed joint models. Model comparisons and performance evaluations were performed using the deviance information criterion, relative bias, coverage probability, and root mean squared error.

Results We evaluated the computational efficiency and estimation performance of the INLA and MCMC approaches using real-world chronic kidney disease (CKD) follow-up data and an extensive confirmatory simulation study. We also conducted several model comparisons by considering different specifications related to smoothing spline

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approximations, non-Gaussian (skewed) distributions, and association structures to identify the best-fitting models for the CKD data and ensure robust statistical inference.

Conclusion The application and simulation results revealed that both approaches provide accurate statistical estimation and inference. However, INLA significantly reduces the computational burden of the proposed joint models.

Keywords Competing risks-Longitudinal data, Joint modelling, Bayesian inference, INLAjoint, R2WinBUGS, Chronic kidney disease

Introduction

In public health research and applications, such as in chronic kidney disease (CKD) follow-up studies, patients often face multiple potential events (e.g., progression to end-stage renal disease (ESRD), death, kidney transplantation, and cardiovascular events). One of these events can change or prevent the likelihood of the primary event of interest happening. This scenario leads to the presence of competing risks in survival analysis, and assuming other competing events as independent censoring can lead to biased survival estimates and invalid statistical inferences [1, 2]. In a follow-up study, the time-to-event process of a certain cause may be associated with the process of the longitudinal markers. This can also affect the probability of survival or the estimates of the hazard rate for an event of interest. Thus, to fully understand and accurately predict how risk factors affect the time until an event of interest, it is necessary to accurately model survival data with competing risks and longitudinal markers using a joint modeling approach.

Joint modeling is popular and widely used in epidemiological and clinical research to properly model longitudinal biomarkers and survival outcomes and to take appropriate interventions for public health. Several studies have been conducted on the modeling of survival and longitudinal data jointly to understand and capture their underlying association. Most of the previous studies involving joint modeling consider a single failure event in the survival process; see, for example [3–6], , among others. Other recent studies also further consider competing risks in the survival data process while developing their joint model to produce unbiased results [7–10].

The methods of estimation are another key differentiation from previous studies on joint modeling. Many of the earliest literature on joint modeling of longitudinal-survival data used the likelihood approach [1, 7, 11–16] to estimate parameters, while more recent studies widely employed the Bayesian approach; see, e.g., [6, 10, 17–23], among others due to its ability to incorporate prior knowledge, flexibility, dynamic prediction, and easy in handling of uncertainty and complex models.

The need for computationally efficient methods in joint modeling of competing risks survival outcomes and longitudinal biomarkers is particularly critical in clinical and epidemiological settings, where prompt decision-making is essential for public health. For example, in the management of CKD, prompt and precise prediction of patient outcomes can guide treatment plans and enhance patient care. Additionally, in the Bayesian paradigm, the approach used to approximate the statistical inference is another key point in fitting complex joint models to escape from intensive computational time. Most Bayesian joint models of competing risks survival and longitudinal data rely on the Markov-Chain Monte-Carlo (MCMC) method to approximate the Bayesian inference. Despite their flexibility, the MCMCs are frequently too computationally expensive for large datasets or complicated models, which limits their usefulness in real-time applications. Thus, in order to facilitate quicker and scalable analyses in clinical and epidemiological research, very recent development in joint modeling considers the integrated nested Laplace approximation (INLA) due to its computational benefit and accuracy [e.g., 10, 17, 23, 24].

INLA provides a fast approximation by utilizing the structure of latent Gaussian models (LGMs), as stated by [25]. According to the literature, these two prominent approaches have their own advantages and limitations. The MCMC approach is a flexible, stochastic sampling method for Bayesian inference and is applicable to a broad range of models. However, it is computationally intensive and requires convergence diagnosis for models with high-dimensional structures. Whereas the INLA approach is a fast, deterministic method and accurate for specific model classes, such as LGMs, it is restricted within the scope of LGMs. Despite the substantial computing benefits that INLA provides, its use is restricted to LGMs. The MCMC approach is still the most flexible and accurate option, and remains the best available method for complex models that cannot be easily transformed into LGMs, such as those with complex hierarchical structures or non-Gaussian random effects, as stated by [10]. While acknowledging the continued relevance of MCMC for broader cases, this study focuses on situations where INLA's conditions are met, taking advantage of its computational efficiency.

This current study is methodologically motivated by the work of [26], titled "A Semi-parametric Bayesian

Joint Modelling of Skewed Longitudinal and Competing Risks Failure Time Data," which utilized the MCMC technique, as well as by those the aforementioned recent studies that employed INLA to fit their proposed models. The original work of [26] proposed joint models that simultaneously considered longitudinal data with skew distributions, nonlinear time effects, survival data with competing risks, and different association structures in the formulation of the joint models, using a Bayesian approach with the MCMC technique. Due to the complexity of these models, approximation of the target posterior distributions required a large number of iterations (more than 70,000) to achieve convergence, making the model-fitting process computationally expensive.

To address these challenges, this study aims to reformulate and refit the original work using INLA, evaluating its advantages over MCMC in terms of computational speed and accuracy. In addition, there is very little literature on the joint modeling of competing risks survival and skewed longitudinal data using INLA, despite its growing popularity in Bayesian inference. Furthermore, skewed (long-tailed) longitudinal data, which are frequently found in biomedical follow-up studies, can further complicate joint modeling because the commonly used approaches of transforming the data and assuming Gaussian distributions can lead to biased results. Thus, this study also aims to address this gap, evaluate INLA's performance compared to MCMC, and shed light on its applicability for complex joint models in biomedical research.

Although this paper emphasizes the computational advantages of INLA in modeling competing risks and longitudinal CKD data, its effectiveness beyond computational speed has been well established in the literature. [17] provides a foundational discussion on its accuracy in Bayesian inference for latent Gaussian models (LGMs). Specifically, recent studies have demonstrated INLA's suitability for (joint) survival and longitudinal models [10, 23, 25, 27]. As long as joint models can be expressed within the LGM framework, INLA naturally accommodates structured additive predictors, allowing flexible incorporation of nonlinear covariate effects, time-varying associations, multiple longitudinal outcomes, spatial components, and shared random effects, which are essential features for capturing the dependence between longitudinal and survival processes via joint modelling [27]. INLA also supports flexible association structures in the formulation of joint models [27, 28].

Methods

In this study, we considered a competing risks joint model with a semi-parametric mixed-effects submodel to jointly model the competing risks survival and skewed longitudinal data. The proposed Bayesian joint models are formulated as LGMs to enable efficient Bayesian inference using INLA. The INLA approach and its R packages are also presented.

The joint models for competing Risks-Longitudinal data

Let T_{ir}^{*} represent the true event time between the beginning of the follow-up and the occurrence of the r^{th} event type for the i^{th} subject. Note that in this follow-up study, we assume that there are r different competing event (risk) types, and that a subject can experience any of these events during the study period or be censored. Let C_i denotes the censoring time for subject i $(i = 1, \ldots, m)$. Then, the observed event time for subject i is defined as $T_i = \min(T_{i1}^{*}, \ldots, T_{ir}^{*}, C_i)$, and let ω_i denotes an event indicator with values $\omega_i \in \{0,1, \ldots, r\}$, where $\omega_i = 0$ indicates a censoring event, and $\omega_i = r$ represents the r^{th} event that a subject experiences during the study period. Furthermore, let y_{ij} denote the longitudinal response measured for the i^{th} subject at the j^{th} follow-up time; $j = 1, \ldots, m_i$.

A cause-specific competing risk joint model is proposed in this study to model the hazard of the r^{th} event type at time t, $\lambda_{ir}(t;.)$, the longitudinal response, and associated baseline (possibly time varying) covariates, given by:

$$\lambda_{ir}(t;\, \boldsymbol{x}_i,\, \boldsymbol{\psi}_i) = \lambda_{0r}(\mathrm{t}) \exp\left(\boldsymbol{\beta}_r^{T} \boldsymbol{x}_i + \boldsymbol{\alpha}_r^{T} \boldsymbol{\psi}_i\right), \quad (1)$$

with corresponding density function

$$f_r(t_i, \omega_i | \, \boldsymbol{x}_i,\, \boldsymbol{\psi}_i;\, \boldsymbol{\theta}_T) = \left\{\lambda_{0r}(t_i) \exp\left(\boldsymbol{\beta}_r^{T} \boldsymbol{x}_i + \boldsymbol{\alpha}_r^{T} \boldsymbol{\psi}_i\right)\right\}^{\omega_i}$$

$$\times \exp\left(-\int_0^t \sum\nolimits_{r=1}^{R} \lambda_{0r}(\mathrm{v}) \exp\left(\boldsymbol{\beta}_r^{T} \boldsymbol{x}_i + \boldsymbol{\alpha}_r^{T} \boldsymbol{\psi}_i\right) dv\right) \quad (2)$$

and likelihood function

$$L(t|\boldsymbol{x},\, \boldsymbol{\psi}\,;\, \boldsymbol{\theta}_T) = \prod\nolimits_{i=1}^{m} \left[\prod\nolimits_{r=1}^{R} f_r(t_i, \omega_i | \, \boldsymbol{x}_i,\, \boldsymbol{\psi}_i;\, \boldsymbol{\theta}_T)\right], \quad (3)$$

where $\lambda_{0r}(\mathrm{t})$ is the corresponding baseline hazard function; the parameter vectors $\boldsymbol{\beta}$ and $\boldsymbol{\alpha}$ quantify, respectively, the fixed effects of covariates $\boldsymbol{x}_i$ that are possibly associated with the hazard of the r^{th} event type, and the level of association between the hazard of the r^{th} event type and the random process of the longitudinal response $\boldsymbol{\psi}_i$ at time t. Here $\boldsymbol{\psi}_i$ can be subject-specific random effects, a linear combination of random effects, current value of the longitudinal outcome, or current slope, depending on the appropriate association structure that will be chosen in the formulation of the joint model. This linear predictor of the random process of the longitudinal outcome can be obtained from the following

semi-parametric mixed-effects longitudinal submodel, which is given by

$$\boldsymbol{y}_i = (\boldsymbol{\beta} + \boldsymbol{\phi}_i)\,\boldsymbol{Z}_i + f(\boldsymbol{H}_i) + \boldsymbol{\epsilon}_i, \tag{4}$$

where $\boldsymbol{y}_i = (y_{i1}, \ldots, y_{im_i})^T$; $\boldsymbol{\beta}$ and $\boldsymbol{\phi}_i$ parameter vectors corresponding to the fixed and random effects of the design matrix $\boldsymbol{Z}_i$; $\boldsymbol{\epsilon}_i$ is a vector of measurement errors for the i^{th} individual; and $f(\boldsymbol{H}_i)$ is an unknown (non-parametric) function which represents the random (smooth) effects of random covariates $\boldsymbol{H}_i$ including the measurement time $\boldsymbol{t}_i$ of the longitudinal response $\boldsymbol{y}_i$. We included this non-parametric function in the model to properly treat non-linear trajectories of the longitudinal response over some covariates, such as measurement time, model it more flexibly. The function f can be defined as a linear combination of the fixed and random effects spline basis functions, $\Psi(\boldsymbol{H}_i)\ and\ \Xi(\boldsymbol{H}_i)$, with associated parameters $\boldsymbol{\kappa}$ and $\boldsymbol{\vartheta}_i$, respectively, as follows:

$$f(\boldsymbol{H}_i) = f(\Psi(\boldsymbol{H}_i), \Xi(\boldsymbol{H}_i)) = \boldsymbol{\kappa}^T \Psi(\boldsymbol{H}_i) + \boldsymbol{\vartheta}_i^T \Xi(\boldsymbol{H}_i). \tag{5}$$

Thus, model (4) can be given by

$$\boldsymbol{y}_i = (\boldsymbol{\beta} + \boldsymbol{\phi}_i)\,\boldsymbol{Z}_i + \boldsymbol{\kappa}^T \Psi(\boldsymbol{H}_i) + \boldsymbol{\vartheta}_i^T \Xi(\boldsymbol{H}_i) + \boldsymbol{\epsilon}_i \tag{6}$$

$$\boldsymbol{\varepsilon}_i \sim S(\boldsymbol{\mu}, \boldsymbol{\Sigma}_\varepsilon, \boldsymbol{\delta}), \quad \boldsymbol{b}_i = (\boldsymbol{\phi}_i, \boldsymbol{\vartheta}_i)^T \sim N(0, \boldsymbol{\Sigma}_{b_i}).$$

where $S(\boldsymbol{\mu}, \boldsymbol{\Sigma}_\epsilon, \boldsymbol{\delta})$ denotes a skew distribution (skew-t or skew-normal) assumed for $\boldsymbol{\epsilon}_i$, with skewness parameter $\boldsymbol{\delta}$, to account for an asymmetric distribution of a longitudinal outcome. $N(0, \boldsymbol{\Sigma}_{b_i})$ represents a Gaussian distribution assumed for random effects, with variance-covariance matrix $\boldsymbol{\Sigma}_{b_i}$. More details on the specifications of the smoothing functions can be found in the previous study [26, 29].

In standard joint models of survival-longitudinal data, the baseline hazard is left unspecified. However, to add more flexibility and accommodate different hazard shapes over time, recent literature considers different approaches (e.g., Gompertz baseline function, spline approaches) to approximate the baseline hazard function. In this study, we consider the smoothing spline function for the baseline hazard. Furthermore, we also consider a spline-based approach (a regression spline) to approximate the unknown (non-parametric) function $f(\boldsymbol{H}_i)$ incorporated in the longitudinal submodel (4).

Bayesian inference and INLA

The Bayesian approach, using the Markov-Chain Monte-Carlo (MCMC) technique, provides a reasonable advancement over the likelihood approach by accounting for parameter uncertainties through prior information incorporation and allowing for more flexible fitting of complex joint models. However, these MCMC approaches may require substantial computational time to accurately approximate the target posterior marginals. To address this computational issue, the recent literature suggests the use of a more flexible and faster approximation method known as INLA [17, 30]. In this study, the proposed competing risks joint model should be formulated as a Latent Gaussian Model (LGM) to enable the use of INLA for fast Bayesian inference. This approach allows for the efficient fitting of complex models.

Formulation of the joint models as LGMs

An LGM is a particular subset of hierarchical Bayesian additive models, which include Bayesian generalized linear models, mixed models, spatial and spatiotemporal models, and dynamic models [17]. It is characterized by a hierarchical structure involving the likelihood of the observed variables, a latent Gaussian field, and prior distributions of hyperparameters. The likelihood defines the connection between the observed and latent variables, while the latent field, which includes linear predictors (or a linear combination of all Gaussian variables) in addition to the fixed and random effects components, captures dependencies or random correlations/effects. The prior distributions of the hyperparameters (the variance-covariance of random effects, the variance of model error, the association parameters, ...) control the behavior of the model. LGMs assume that the latent field is conditionally independent, given the observed data and hyperparameter priors.

Mathematically, these expressions can be defined as follows: Let $\mathcal{D} = \{\boldsymbol{y}, \boldsymbol{T}, \omega, \boldsymbol{Z}\}$ denotes set of all the observed competing risks event times and longitudinal data used in the proposed joint models; $\boldsymbol{\zeta} = \{\boldsymbol{\eta}, \boldsymbol{\beta}, \boldsymbol{\beta}_r^T, \boldsymbol{\alpha}_r^T, \boldsymbol{f}_i, \boldsymbol{\psi}_i, \boldsymbol{\kappa}\}$ represent latent variables corresponding to those proposed joint models; and let $\boldsymbol{\Theta} = (\boldsymbol{\theta}_l^T, \boldsymbol{\theta}_r^T)^T$ be the hyperparameters associated with the longitudinal ($\boldsymbol{\theta}_l$) and competing risks ($\boldsymbol{\theta}_r$) models. Note that from the set of the latent variables, the notation $\boldsymbol{\eta} = \{\eta_{ir}^c, \eta_i^l\}$, with $\eta_{ir}^c = \boldsymbol{\beta}_r^T \boldsymbol{x}_i + \boldsymbol{\alpha}_r^T \boldsymbol{\psi}_i(t)$ and $\eta_i^l = \boldsymbol{Z}_i\boldsymbol{\beta} + f(\boldsymbol{H}_i|\boldsymbol{\psi}_i; \boldsymbol{\kappa})$, represents the set of linear predictors from the competing risks joint model (1) and longitudinal submodel (6), respectively.

Then, the posterior for the joint model (1) can be given by

$$\begin{aligned}\pi(\zeta, \Theta|\mathcal{D}) &\propto f(\zeta, \mathcal{D}|\boldsymbol{\Theta}) \times \pi(\boldsymbol{\Theta}) \\ &\approx \pi(\boldsymbol{\zeta}|\boldsymbol{\Theta})\,\pi(\boldsymbol{\Theta}) \prod_{i=1}^{M} f(\mathcal{D}_i|\boldsymbol{\zeta}_i; \boldsymbol{\Theta}),\end{aligned} \tag{7}$$

where $L(\mathcal{D}|\boldsymbol{\zeta}, \boldsymbol{\Theta}) = \prod_{i=1}^{M} f(\mathcal{D}_i|\boldsymbol{\zeta}_i, \boldsymbol{\Theta})$ is the likelihood of the observed variables; $\pi(\boldsymbol{\Theta})$ is the prior distribution of the hyperparameters; and $\pi(\boldsymbol{\zeta}|\boldsymbol{\Theta})$ is the latent Gaussian random field, which admits conditional independence. The main aim here in latent Gaussian modeling is to approximate the posterior marginals $\pi(\boldsymbol{\zeta}_i|\mathcal{D})$, $\pi(\boldsymbol{\Theta} \mid \mathcal{D})$, and $\pi(\theta_j \mid \mathcal{D})$. This approximation can be easily and accurately done using INLA [17].

The INLA approach

As stated above, Bayesian inference with MCMC sampling techniques may require substantial computational time to accurately approximate the posterior marginals and flexibly fit the proposed semi-parametric competing risks-longitudinal joint model, which is an advanced but complex model. However, INLA [17] can accurately and quickly approximate the marginal posteriors and fit the models as long as they are expressed as LGMs.

The INLA is an alternative and attractive approach used to perform fast and accurate Bayesian inference for LGMs. It uses Laplace approximations and efficient numerical integrations. Recently, the INLA approach also considers variational Bayes with a Laplace approximation to further enhance accuracy and efficiency while flexibly fitting latent Gaussian models [24]. In comparison to the use of numerical approximation of integrals of complex models, the INLA approach is specifically designed to utilize the advantage of the structure of LGMs with minimal cost in speed.

The INLA methodology involves several stages to efficiently approximate posterior marginals. First, the marginal posteriors of the hyperparameters are obtained by integrating out fixed and random effects using Laplace approximation with a smart gradient approach as a recent advancement for optimization. The conditional posteriors of the latent field, given the hyperparameters, can be approximated in the second stage by using either a second nested Laplace approximation or an implicit variational Bayes correction to improve computational efficiency, see [23] for more details.

R package: inlajoint

The original and core R package for the INLA methodology is R-INLA. It is a popular R package widely used to approximate Bayesian inference with INLA for a wide range of LGMs. However, it should be noted that the R-INLA package might be challenging to express models as LGMs if their structure is complex [23]. In particular, this limitation arises when manually specifying multi-dimensional integrals of the joint likelihood with respect to random effects in complex joint models since INLA was not specifically designed for joint longitudinal-survival models. In our implementation, therefore, we utilized the R package INLAjoint, which is an extension of R-INLA designed specifically for fitting joint models. INLAjoint is a user-friendly wrapper for R-INLA, designed to simplify joint model specification without introducing new statistical functionality/methodology. This package, developed by [10], is a straightforward, easy-to-use interface and enables fitting joint models of longitudinal and survival outcomes. INLAjoint also provides efficient and accurate approximations, similar to R-INLA, allowing users to consider different association structures in joint modeling and allowing them to control and specify prior distributions for parameters. Thus, in this study, we used INLAjoint (version 24.3.25) to fit the proposed competing risks joint model.

Model comparison

Conducting model comparison in joint modeling of competing risks-longitudinal data is crucial to identifying the best-fitting and most parsimonious model that accurately captures the association between the competing risks-longitudinal outcomes. In this study, the comparison of models has been done with three aims: (1) to compare joint models using INLA to select the optimal association structure, (2) to compare INLA models with MCMC models to evaluate their performance in approximating Bayesian inference, and (3) to compare models with different spline smoothing functions and asymmetric distributions to flexibly and accurately capture the non-linear (skewed) longitudinal trajectories.

Regarding association structures (parameterizations) choice, in this study, we considered current value (CV), current slope (CS), and shared random effects (SRE) parameterizations based on their prevalence in the joint modeling literature [6, 15, 31–39] and our prior study [26]. The INLAjoint package allows to easily implement these parameterizations, including two additional ones (CV_CS & SRE_ind). The last two parameterizations were not included in the comparison because of CV_CS produced relatively unstable results in INLAjoint during preliminary analyses, and SRE_ind significantly slowed MCMC computations due to the high-dimensional random effects from spline basis functions and the intercept. Thus, the comparison of joint models with different association structures (parameterizations) using INLA can be conducted as follows:

- **JM-CV**: Competing risks-longitudinal joint model with current value (the linear predictor $\boldsymbol{\eta}_i^L$) parametrization:

$$\boldsymbol{\alpha}_k^T \boldsymbol{\psi}_i = \alpha_k \eta_i^L,\ k = E,\ D,\ \eta_i^L = (\boldsymbol{\beta} + \boldsymbol{\phi}_i)\boldsymbol{Z}_i + \boldsymbol{\kappa}^T \Psi(\boldsymbol{H}_i) + \vartheta_i^T \Xi(\boldsymbol{H}_i),$$

where E and D stand for ESRD and death events, respectively.

- **JM-CS**: Competing risks-longitudinal joint model with current slope parametrization:

$$\boldsymbol{\alpha}_k^T \boldsymbol{\psi}_i = \alpha_k \left(\frac{d}{dt_{ij}} \left(\eta_i^L \right) = \eta\, \prime_i^L \right),\ k = E,\ D.$$

- **JM-SRE**: Competing risks-longitudinal joint model with shared random effects parametrization (sharing a set of all random effects together with a single association coefficient α):

$$\boldsymbol{\alpha}_k^T \boldsymbol{\psi}_i = \alpha_k \boldsymbol{b}_i,$$
$$where\ \boldsymbol{b}_i = (\phi_{i0},\ \vartheta_{i1},\ \vartheta_{i2},\ \vartheta_{i3})^T,\ \ k = E,\ D.$$

The deviance information criterion (DIC), widely applicable Bayesian information criterion (WABIC), and computation time are used to address the first and third model comparison objectives. A model with the smallest DIC is chosen as the best-fitted model. To address the second model comparison objective (the main focus of this study), i.e., to assess the behavior of the estimators of these methods and compare their performance using simulation studies, we compute the relative bias, the root mean square error, and the coverage probability of the credible intervals in addition to the computation time.

Real data analysis: CKD

Description of the data

This study focuses on chronic kidney disease (CKD) longitudinal and failure time survival data collected at the University of Gondar Comprehensive Specialized Hospital in Ethiopia. These CKD data included patient profiles from medical records (charts) gathered retrospectively from June 2014 to June 2022. The data include patients with three or more visits and exclude those with acute kidney injury, fewer than three visits, started hemodialysis, or improving kidney function. Thus, this study included 198 CKD patients who met the inclusion-exclusion criteria and had complete longitudinal-competing risks survival data to illustrate the proposed methods. Specifically, the data include key variables such as estimated glomerular filtration rate (eGFR) as a longitudinal outcome, time-to-competing events (death or end-stage renal disease), and time-to-right censoring, baseline and repeatedly measured covariates (such as age, gender, diabetes, hypertension, serum creatinine, and systolic/diastolic blood pressure). The descriptive statistics show that the average age of the patients was 55.1 years, and 56.6% of them were male. At baseline diagnosis time, 23.81% and 34.4% of the patients had diabetes and hypertension, respectively. During follow-up, 31.2% of the patients developed end-stage renal disease (ESRD), 21.2% died, and the remaining 47.6% were right-censored. The median follow-up time was 16.97 months (with min = 3 and max = 18). The follow-up time intervals varied across patients and were influenced by comorbid conditions and disease severity. The longitudinal outcome (eGFR) characteristics, including the trajectories showing nonlinear patterns and skewed distributions, demonstrated the requirement of an advanced methodological approach to be used to analyze the data (Fig. 1).

The overall survival curve (survival probability of a patient free from experiencing either ESRD or a death event beyond a specified time) and the cumulative incidence of the patients are presented in Fig. 2. The figure clearly demonstrates a fast-decreasing probability of surviving from either of the two events and a rapidly increasing likelihood of the occurrence of both of the failure events over follow-up time.

Model and Bayesian inference specifications

The specification of the proposed models depends on the available CKD data. The time-to-ERD and time-to-death events are used as competing risks survival outcomes. The follow-up time for patients who did not experience either of the failure events by the end of the study, as well as for those who withdrew/lost to follow-up from the study, is considered as right-censoring time. To specify the longitudinal submodel (6), we utilized the log-transformed eGFR as a longitudinal outcome to account for its asymmetric (skewed) distribution. In addition, to take into account the non-linear trajectories of the longitudinal outcome over time, the covariate time effect is modeled non-parametrically in the longitudinal submodel using regression splines with three basis functions. Hypertension and diabetes are included in both models as covariates. Thus, models (1) and (6) are specified as follows:

$$\begin{aligned} &\lambda_{iE}(t) = \lambda_{0E}(\mathrm{t}) \exp\left(\eta_{iE}^c\right), \\ &where\ \ \eta_{iE}^c = \beta_{1E} HTN_i + \beta_{2E} Diab_i + \alpha_E^T \psi_i \end{aligned}$$

$$\begin{aligned} &\lambda_{iD}(t) = \lambda_{0D}(\mathrm{t}) \exp\left(\eta_{iD}^c\right), \\ &where\ \eta_{iD}^c = \beta_{1D} HTN_i + \beta_{2D} Diab_i + \alpha_D^T \psi_i \end{aligned} \tag{8}$$

$$\begin{aligned} &\log(y_{ij}) = \eta_{ij}^L + \varepsilon_{ij}, \\ &where\ \eta_{ij}^L = \beta_0 + \phi_{i0} + \beta_1 HTN_{ij} + \beta_2 Diab_{ij} + (\kappa + \vartheta_i)\, \mathbf{SB}(t_{ij}), \end{aligned}$$

.

in which $\lambda_{iE}(t)$ and $\lambda_{iD}(t)$ are hazard rates for the events ESRD and death at time t, respectively; $\mathrm{SB}(t_{ij})$ denotes the spline basis functions of the random time effects t_{ij}; and the function ψ_i can be the current value of the longitudinal outcome, the current slope,

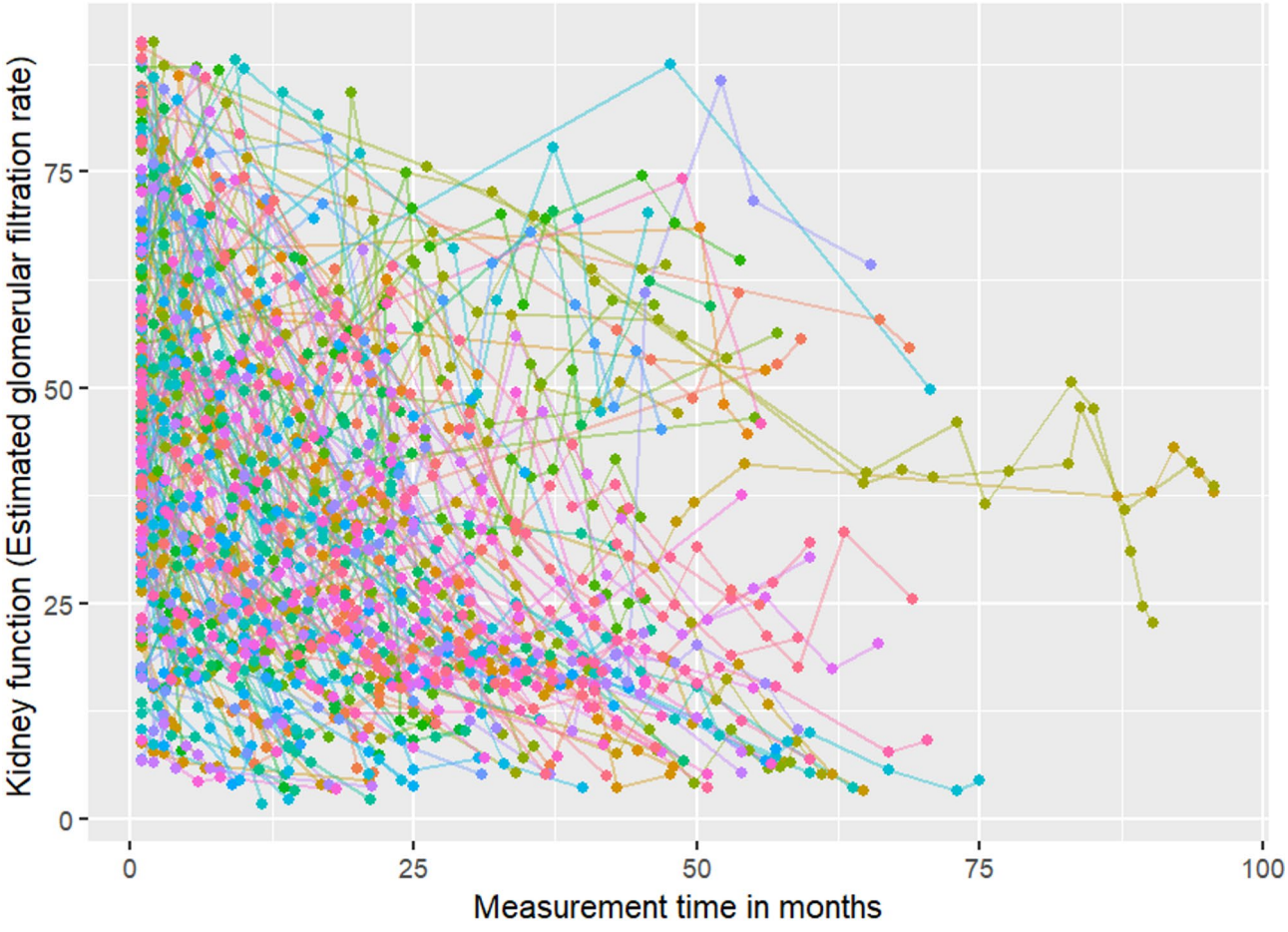

Fig. 1 Kidney function trajectories for 189 CKD patients. The figure depicts asymmetric (skewed) distributions and nonlinear trajectories of kidney functions of the patients over time

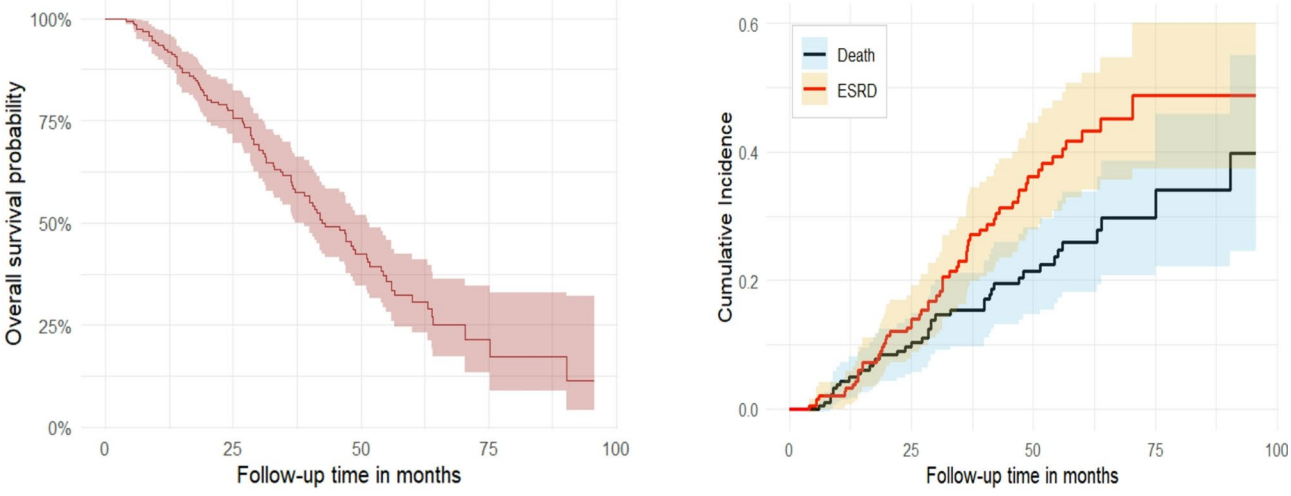

Fig. 2 Patients' overall survival (**a**) and cumulative incidence (**b**)

the current value and current slope, or shared random effects. The random intercept ϕ_{i0} and the spline basis function coefficients $\boldsymbol{\vartheta}_i = (\vartheta_{i1}, \vartheta_{i2}, \vartheta_{i3})^T$ together form the full random effects vector $\boldsymbol{b}_i = (\phi_{i0}, \vartheta_{i1}, \vartheta_{i2}, \vartheta_{i3})^T$, which captures subject-specific variations in the longitudinal outcome and links them to the hazard of the r th competing risk process. For example, the shared random effects association function can be described as: $\boldsymbol{\alpha}_k^T \boldsymbol{\psi}_i = \alpha_k \boldsymbol{b}_i$, where $k \in \{E, D\}$. A smooth spline function based on a random walk with 2nd-order differences was used to approximate each baseline hazard function with fifteen intervals set to partition the observed failure time. A Gaussian distribution is assumed for the random effects. The measurement error in the longitudinal submodel, ϵ_{ij}, can be assumed to follow lognormal and skew-normal distributions in the INLA approach, and skew-normal and skew-t distributions in the MCMC approach. These assumptions account for the non-linear (skewed) nature of the longitudinal outcome y_{ij} and enable robust inference [26, 35, 39–41]. To specify, for example, the skew-t (ST) distribution and conduct the MCMC using WinBUGS, we adopt a stochastic representation by hierarchically introducing random variables S_{ij} and w_i [35, 40]. This can be expressed as $y_{ij} \sim N(\eta_{ij}^l + \delta\left(S_{ij} - g(\upsilon), \frac{1}{w_i}\sigma^2\right)$, where the function $g(\upsilon) = \sqrt{\upsilon/\pi}\frac{\Gamma\{(\upsilon-1)/2\}}{\Gamma(\upsilon/2)}$. Here, δ and υ denote the skewness and degrees of freedom parameters, respectively, obtained from the skew-t distribution. Note that to align the MCMC specification more closely with the specification of joint models in the INLAjoint package and facilitate comparison, we slightly modified the methods from the original paper. Specifically, we adjusted the way the shared random effects association structure and the stochastic representation of the skew-t and skew-normal distributions are specified. Additionally, baseline covariates such as age and sex are excluded from the specification of both the competing risks and longitudinal models because they were not statistically significant in the original work. These modifications may have led to minor variations in some parameter estimates.

To specify Bayesian inference, prior distributions for the MCMC technique using R2WinBUGS package in R are considered as follows: weakly informative Gaussian priors were assumed for the fixed-effect parameters of the longitudinal submodel and the competing risks-longitudinal joint models. Gamma priors were assumed for the piecewise baseline hazards. Exponential (truncated) prior was assumed for the degrees of freedom. Inverse-Wishart (IW) and inverse-Gamma priors were used as priors for the variance-covariance parameters of the random effects and measurement error. More detailed specifications of these priors with mathematical notations can be found in [26]. Prior distributions for the INLA are chosen as follows: similar to MCMC, weakly informative (close to non-informative) independent Gaussian prior distributions (with mean = 0, precision = 0.01) are used for the fixed effect parameters, and the latent field, as specified by default in INLAjoint. An inverse-Wishart prior distribution was assumed for the variance-covariance matrix of the random effects. For the baseline hazard functions, random walks of order two priors are assumed. Penalizing complexity priors [42] are assumed for the precision parameter of the random walks and the precisions of other hyperparameters. Initial values for INLAjoint are set to default values. As stated in the method section, notably, the INLA package in R also allows users to modify the default prior distributions based on their preferences. For instance, fixed and random effects default priors $N(mean = 0, preci = 0.01)$ and $IW(r = 10, R = 1)$ can be modified by using control arguments such as *priorFixed* and *priorRandom*, respectively.

Table 1 Comparison of longitudinal submodels with different numbers of spline basis functions to fit the application CKD data using the INLA approach

Longitudinal submodels	Comparison tools		
	DIC	WABIC	Error variance
LModel.2Sp	10062.83	10098.65	0.0678
LModel.3Sp	10054.23	10088.66	0.0674
LModel.4Sp	10055.32	10089.64	0.0674

Model fitting results

For the longitudinal outcome, we proposed a semi-parametric mixed-effects submodel with a regression spline approximation for the nonparametric function of the time effect. Before fitting the proposed joint models, it is necessary to compare and select the best-fitting longitudinal submodel for the CKD data. This involves evaluating different numbers of spline basis functions that accurately approximate the non-linear time effects on the longitudinal outcome using the INLA approach. Thus, in this study, we compared three longitudinal models: longitudinal models with two (LModel.2Sp), three (LModel.3Sp), and four (LModel.4Sp) spline basis functions. The results presented in Table 1 demonstrate that the longitudinal submodel with 3 spline basis functions (LModel.3Sp) has the lowest values of DIC (10,054.23), WABIC (10,088.66), and model error variance (0.0674) compared to the other models. Therefore, it was selected as the best-fitting model. This is because regression splines could provide a low-dimensional (reducing the number of parameters), flexible, and computationally efficient approximation of nonparametric functions in linear mixed-effect models

Next, using the selected longitudinal submodel (LModel.3Sp), we compared the best-fitting joint model for the competing risks-longitudinal CKD data by considering different association structures based on the INLA approach. As described in the Model Comparison section, joint models with different parameterizations were considered for comparison to properly capture the relationship between the competing risks and longitudinal outcomes. These models were fitted and compared using the same distribution family, the lognormal distribution, for the longitudinal outcome. Table 2 presents the results of this comparison and shows that the joint competing risks-longitudinal model with shared random effects parameterization (JM-SRE) has the lowest values of DIC (1180.12) and WABIC (854.20) compared to the other joint models. Note that, for the MCMC approach, a joint model with shared random-effects parameterization was also selected as the best model.

Finally, the joint model with shared random effects parameterization (JM-SRE) was identified as the best-fitting model for the CKD data using the INLA approach. This model was further used to compare its results with those obtained using the MCMC approach. In this study, we proposed using skew distributions for the longitudinal outcome eGFR to account for its skewed trajectories. However, since the ST distribution is not included in the default distribution families of R-INLA, we used the log-normal (LN) and skew-normal (SN) distributions for the INLA approach. For the MCMC approach, both SN and ST distributions were considered to ensure a good fit for the joint models.

To stabilize within- and between-subject variations in the eGFR process and to speed up the Bayesian inference approximations, logarithm-transformed eGFR data were used in the joint model fitting (i.e., we assumed eGFR∼LN and *log*(eGFR)∼SN/ST). For the MCMC approach, we ran three chains, each with 90,000 iterations and a burn-in of 45,000, using WinBUGS software in R to approximate the target posterior distribution and achieve convergence. We retained every 30th MCMC sample from the remaining 45,000 iterations, resulting in 4,500 samples of each of the unknown posterior parameters. All the joint models using both posterior approximation approaches were fitted on an *HP ProBook 450 G9 Notebook laptop* with the following specifications: a *12th Gen Intel(R) Core(TM) i7-1255U* processor, *1700 MHz*, *10 cores*, and *16 GB* of RAM.

The results in Table 3 demonstrate the fitting of joint competing risks-longitudinal models with an SRE association structure and different distributions for the CKD data, using both the INLA and MCMC approaches. These models were evaluated using flexible and computationally efficient inferential approaches while considering different distributions to describe the non-linear (irregular) trajectories of the longitudinal outcome (eGFR) over

Table 2 Joint competing risks-longitudinal models with different parameterizations to fit the application CKD data using the INLA approach

Par	Joint models								
	JM-CV			JM-CS			JM-SRE		
	ME	Sd	CI (95%)	ME	Sd	CI (95%)	ME	Sd	CI (95%)
β_0	3.838	0.038	3.763, 3.913	3.813	0.027	3.759, 3.866	3.831	0.038	3.756, 3.905
β_1	-0.149	0.022	-0.193, -0.106	-0.215	0.026	-0.266, -0.165	-0.145	0.022	-0.188, -0.102
β_2	-0.138	0.063	-0.261, -0.014	-0.150	0.047	-0.241, -0.058	-0.133	0.063	-0.256, -0.009
κ_1	-1.031	0.112	-1.251, -0.811	-1.597	0.271	-2.129, -1.065	-0.955	0.109	-1.170, -0.741
κ_2	-3.084	0.241	-3.561, -2.615	-3.395	0.552	-4.477, -2.312	-3.299	0.239	-3.771, -2.833
κ_3	-3.949	0.395	-4.729, -3.181	-4.286	0.635	-5.531, -3.042	-4.346	0.545	-5.415, -3.278
σ^2_ϵ	0.068	0.003	0.062, 0.074	0.112	0.005	0.103, 0.121	0.059	0.003	0.054, 0.065
$\sigma^2_{\phi_i}$	0.186	0.026	0.142, 0.243	0.271	0.174	0.143, 0.711	0.186	0.026	0.138, 0.241
$\sigma^2_{\vartheta_{1i}}$	1.067	0.279	0.637, 1.712	13.155	11.939	4.617, 41.677	0.982	0.250	0.583, 1.555
$\sigma^2_{\vartheta_{2i}}$	5.285	1.641	2.914, 9.280	28.700	26.641	9.237, 93.001	6.250	1.752	3.608, 10.315
$\sigma^2_{\vartheta_{3i}}$	10.634	3.602	5.31, 18.99	0.179	0.129	0.044, 0.503	12.714	3.988	6.702, 21.939
β_{E1}	1.630	0.473	0.702, 2.557	2.519	0.469	1.600, 3.438	1.359	0.450	0.476, 2.242
β_{E2}	1.503	0.402	0.716, 2.291	1.445	0.409	0.643, 2.248	1.707	0.402	0.920, 2.495
β_{D1}	2.099	0.634	0.857, 3.343	2.936	0.674	1.615, 4.258	2.076	0.620	0.860, 3.291
β_{D2}	2.380	0.501	1.398, 3.362	2.114	0.524	1.086, 3.142	2.601	0.491	1.637, 3.564
α_E	-1.710	0.235	-2.184, -1.259	-9.957	4.726	-19.07 -0.462	-1.790	0.244	-2.281, -1.319
α_D	-1.556	0.246	-2.056, -1.087	-6.203	5.334	-16.97 4.031	-1.542	0.236	-2.013, -1.083
DIC	1185.06			1508.95			1180.12		
WABIC	858.89			1189.77			854.20		

Par Parameter, *ME* Mean estimate, *Sd* Standard deviation, *CI* Credible interval

Table 3 Joint model fitting for the CKD data using INLA and MCMC approches

	INLAjoint						R2WinBUGS (MCMC)					
	JM-SRE_LN			JM-SRE_SN			JM-SRE_SN			JM-SRE_ST		
Par	ME	Sd	CI (95%)	ME	Sd	CI (95%)	ME	Sd	CI (95%)	ME	Sd	CI (95%)
β_0	3.831	0.038	3.756, 3.905	3.812	0.037	3.739, 3.885	4.265	0.048	4.165, 4.358	3.952	0.048	3.855, 4.042
β_1	-0.145	0.022	-0.188, -0.102	-0.137	0.020	-0.177, -0.097	-0.142	0.022	-0.185, -0.099	-0.148	0.021	-0.192, -0.107
β_2	-0.133	0.063	-0.256, -0.009	-0.124	0.061	-0.244, -0.004	-0.161	0.069	-0.296, -0.021	-0.136	0.073	-0.271, 0.013
κ_1	-0.955	0.109	-1.170, -0.741	-0.886	0.101	-1.084, -0.689	-0.9148	0.1057	-1.12, -0.685	-0.945	0.122	-1.151, -0.683
κ_2	-3.299	0.239	-3.771, -2.833	-3.025	0.212	-3.444, -2.614	-2.529	0.1456	-2.81, -2.25	-2.717	0.142	-3.018, -2.476
κ_3	-4.346	0.545	-5.415, -3.278	-3.954	0.338	-4.624, -3.296	-3.087	0.294	-3.661, -2.539	-3.439	0.260	-3.951, -2.992
σ^2_ε	0.059	0.003	0.054, 0.065	0.062	1.188	0.056, 0.069	0.0134	0.003	0.008, 0.021	0.0118	0.0028	0.007, 0.018
$\sigma^2_{\varphi_i}$	0.186	0.026	0.138, 0.241	0.176	0.025	0.131, 0.229	0.189	0.024	0.147, 0.241	0.184	0.026	0.138, 0.241
$\sigma^2_{\vartheta_{1i}}$	0.982	0.250	0.583, 1.555	0.792	0.221	0.447, 1.313	0.8418	0.224	0.4935, 1.382	0.8215	0.2209	0.3887, 1.282
$\sigma^2_{\vartheta_{2i}}$	6.250	1.752	3.608, 10.315	4.433	1.337	2.403, 7.618	2.733	0.6372	1.823, 4.287	3.259	0.6037	2.122, 4.502
$\sigma^2_{\vartheta_{3i}}$	12.714	3.988	6.702, 21.939	8.850	3.170	4.293, 16.387	4.849	1.312	2.904, 7.953	6.235	1.501	3.324, 9.085
δ	-	-	-	-0.576	0.070	-0.702, -0.427	-0.383	0.018	-0.418, -0.346	-0.324	0.024	-0.369, -0.276
υ	-	-	-	-	-	-	-	-	-	3.145	0.146	3.004, 3.525
β_{E1}	1.359	0.450	0.476, 2.242	1.284	0.456	0.388, 2.178	1.711	0.556	0.602, 2.79	1.524	0.569	0.358, 2.559
β_{E2}	1.707	0.402	0.920, 2.495	1.727	0.404	0.936, 2.521	1.867	0.608	0.715, 3.108	1.839	0.630	0.696, 3.174
β_{D1}	2.076	0.620	0.860, 3.291	2.095	0.627	0.864, 3.325	2.315	0.722	0.895, 3.739	2.340	0.722	0.927, 3.740
β_{D2}	2.601	0.491	1.637, 3.564	2.635	0.495	1.665, 3.605	2.685	0.614	1.542, 3.936	2.648	0.612	1.526, 3.92
α_E	-1.790	0.244	-2.281, -1.319	-1.764	0.259	-2.277, -1.256	-1.792	0.401	-2.675, -1.112	-1.777	0.441	-2.757, -1.038
α_D	-1.542	0.236	-2.013, -1.083	-1.577	0.259	-2.090, -1.068	-1.019	0.366	-1.801, -0.359	-0.957	0.373	-1.742, -0.301
DIC	1180.12			-8354.73			5734.98			5524.22		
Co.time	56.96			191.02			6725.15			8154.09		

Co. time Computation time (in seconds)

time and its relationship with the hazards of competing failure events in CKD patients.

In general, all joint models, whether fitted using the INLA or MCMC methods and with different distributional specifications, provided significant and closely related estimates (mean, standard deviation, and 95% credible intervals) for the parameters they share. None of the proposed methods produced results that were inconsistent with reality. However, the methods differed in terms of computational time and the estimated values of some parameters. The INLA approach, implemented using INLAjoint, achieved significantly lower computation times (averaging 56.96 and 191.02 s for the lognormal and skew-normal joint models, respectively) compared to the MCMC approach, implemented using R2WinBUGS (averaging 6,725.15 and 8,154.09 s for the skew-normal and skew-t joint models, respectively). Overall, the INLA approach was, on average, 60 times faster than the MCMC approach in fitting the proposed joint models.

Regarding estimation, most of the fixed-effects parameter estimates were approximately similar across all methods. Figure 3 also shows how the INLAjoint and R2WinBUGS closely and accurately approximated the posterior marginals of the fixed effects parameters. While the slightly wider spread of the MCMC curves observed in Fig. 3 indicates that it captures a bit more uncertainty in parameter estimation compared to INLA, the overall similarity confirms that INLA also offers a reliable approximation for Bayesian inference in the joint modeling of competing risks and skewed longitudinal data. However, substantial variations were observed in the estimates of the fixed effects of κ_2 and κ_3 (the second and third spline basis functions of time) and their random effects variances ($\sigma^2_{\vartheta_{2i}}$ and $\sigma^2_{\vartheta_{3i}}$) between the INLA-joint and R2WinBUGS approximations. The INLAjoit produced larger estimates for these variables, as well as for the measurement error variance (σ^2_ϵ), while R2WinBUGS yielded relatively smaller variance estimates. Specifically, INLAjoint with the lognormal distribution provided overestimated results. In contrast, INLAjoint with the skew-normal distribution yielded estimates that were relatively closer to those of R2WinBUGS.

Notably, due to significant skewness estimates and relatively smaller variance estimates, the INLA approach with the SN distribution and the MCMC approach with the ST distribution outperformed the other models. The smaller DIC value further confirms that the joint model with the ST distribution is superior in the MCMC approach, while the joint model with the SN distribution is superior in the INLA approach. It is worth noting that INLA does not include the ST distribution among its default distribution families, and thus, we did not consider it in the INLA approach. In summary, although the ST joint model (JM-SRE ST) fitted by R2WinBUGS produced robust results, the INLA approach with the SN distribution (JM-SRE SN) achieved the lowest DIC value (-8354.96) and the shortest computation time. Therefore,

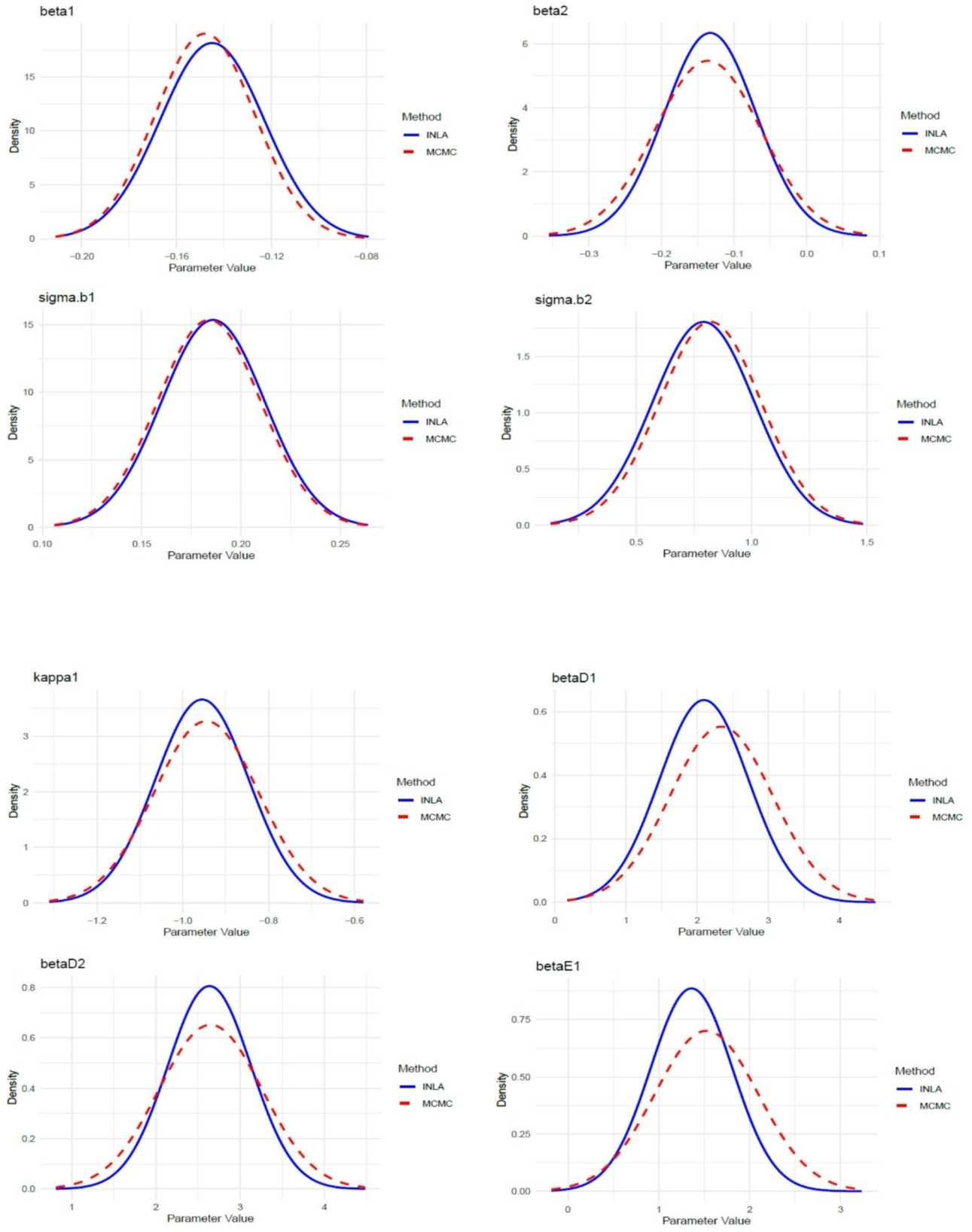

Fig. 3 Posterior marginal densities of selected parameters based on the INLA and MCMC approximations. The plots show strong agreement between the two approaches, with both providing nearly identical central parameter estimates and significant overlap in their posterior distributions

the results of the JM-SRE SN model with the INLA method will be used for further parameter interpretation and discussion.

Regarding the interpretation of the results, we first highlight the significance of jointly modelling the competing risks and longitudinal CKD outcomes. The estimates of the association parameters (the alphas) are significantly different from zero, demonstrating the benefit of using a joint modeling approach for the CKD follow-up data. The negative estimate indicates that there is an inverse relationship between the hazard of experiencing either of the competing failure events (death and/or ESRD) and the longitudinal outcome, log(eGFR). For instance, $\widehat{\alpha}_{E1} - 1.76$ $(HR = 0.17,\ 95\%\,\mathrm{CI}:\ 0.10,\ 0.28)$ indicates that the log-hazard ratio for a unit increase in log(eGFR) was −1.76. This means that a one-unit increase in log(eGFR) was associated with an 83% decrease ($95\%\,CI:\ 72\%,\ 90\%$) in the hazard of experiencing end-stage renal disease, assuming other covariates are held constant.

Next, we highlight the statistically significant contribution of employing skew distributions in the proposed models. The results of the joint models with skew distributions in both approaches show that the estimate for the skewness parameter (δ) is significantly different from zero. These models also yielded relatively robust variance estimates and outperformed other models, demonstrating the importance of accounting for skewness in the longitudinal data. Furthermore, the estimates of the covariates included in both the longitudinal and competing risks models are significantly different from zero on both outcomes. The negative estimates of β_1 and β_2 indicate that hypertension and diabetes are negatively associated with the log(eGFR).

In addition, for example, the positive estimates of β_{E1} and β_{D2} indicate that hypertension and diabetes are also positively associated with the risks of experiencing end-stage renal disease and death, respectively. This means that a CKD patient with hypertension or diabetes has a higher risk of experiencing either of those failure events compared to those without hypertension or diabetes.

Confirmatory simulation studies

In this study, we conduct intensive simulation studies to assess the performance of the proposed methods using **INLAjoint** as well as **R2WinBUGS**. Specifically, we evaluate the validity of the INLA approach in approximating the statistical inference for the proposed joint models within the Bayesian paradigm, and compare its performance with an MCMC approach.

Simulation design

We compare the performance of the INLA approximation of Bayesian inference using the INLAjoint R package (*version: 24.3.25*) with the MCMC sampling approach using the R package R2WinBUGS (*version 2.1–22.1*, released on 2024-02-05). The MCMC method uses the Gibbs sampler or the Metropolis-Hastings (M-H) algorithm within a Gibbs sampler. R2WinBUGS is able to run BUGS models by interfacing with WinBUGS/OpenBUGS from R. WinBUGS (or OpenBUGS) is a Bayesian analysis software that uses an MCMC sampling technique and fits hierarchical (multilevel) models, mixed models with multivariate skew distributions (non-linear mixed models), models with missing data, measurement errors, and joint models of longitudinal survival data with ease and convenience. One key advantage of this software is that it does not require specifying or deriving the full conditional distribution of each parameter to sample using MCMC with the Gibbs sampler. Instead, it only requires clearly specifying the likelihood functions of the data, their density functions, and the prior distributions. Other MCMC programs like JAGS can also use the basic functions of WinBUGS because they use closely related function/model specifications.

Similar to the CKD application, the simulated data include one longitudinal outcome and two competing risks survival data. Two binary covariates were generated from Bernoulli(0.44) and Bernoulli(0.24) distributions. The competing risks and longitudinal data were simulated from the proposed competing risks joint model (1) and the semi-parametric mixed-effects longitudinal submodel (6), respectively. To maintain the skewed nature of the application longitudinal data, the model error was simulated from a $ST(mean = -0.4,\ sd = 0.05,\ df = 3.15)$ based on the application parameter estimates. We considered the following different scenarios in the simulation by taking into account the effects of specifications of distributional assumptions, sample size, number of chains, and iterations:

- Scenario 1: Different distributions for both approaches were used to mimic the application that contains skewed longitudinal data.
- Scenario 2: Different sample sizes for the INLA approach: 200 and 400 study subjects with 15 equal follow-up times (i.e., 3000 and 6000 total repeated measurements) were considered to assess the sample size effect and to ensure sufficient longitudinal trajectories for subjects.
- Scenario 3: Different numbers of chains and iterations for the stochastic (MCMC) approach: The application's longitudinal data exhibit a skewed distribution, which may require longer iterations and more chains to account for their impact on convergence. Therefore, we consider (a) a single chain with 10,000 iterations, of which 5,000 iterations were discarded and a thinning of 5, and (b)

three chains with 30,000 iterations, of which 20,000 were discarded and a thinning of 10.

The prior and MCMC specifications were similar to the specifications used in the application section.

Simulation results

We simulated 500 datasets for each scenario with the specified number of subjects and repeated measurements. To assess the behavior of the estimators of these methods and compare their performance, we computed the relative bias (RB), the root mean square error (RMSE), the 95% coverage probability (CP) of the credible intervals, and the computation time (Comput.time). The summary results of the simulation are presented in Tables 4 and 5, which include the computed estimation performance metrics, such as RB, RMSE, CP, and Com. time. The simulation results in Table 4 were based on the same sample size (m = 400, with 15 follow-up times and a total of 6,000 repeated measurements) for both approaches. The MCMC approach, on the other hand, had three chains with 30,000 iterations, which included the discarded and thinned iterations.

In terms of accuracy, both the INLA and MCMC approaches with different specifications provided nearly identical and accurate statistical estimation and inference, with low relative bias and high coverage probability. They differed only slightly across distributions, sample sizes, number of chains, and iterations. More specifically, the methods (scenarios) with a large sample size in the INLA approach and with many chains and long iterations in the MCMC approach resulted in relatively higher CP and lower RB and RMSE for some parameters. Additionally, the MCMC approach with skew-t distribution demonstrated slightly more accurate and robust estimates for the variances and some parameters, as observed in the application part.

However, in terms of computational efficiency, the INLAjoint approach significantly outperforms the R2WinBUGS approach.

Discussion and conclusion

Most previous studies on the joint modeling of survival-longitudinal data with multiple characteristics have faced substantial computational challenges, in addition to a lack of available software for handling more complex survival-longitudinal data. Recent studies have focused on developing methods that approximate Bayesian statistical inference for joint modeling with reduced computational intensity. Among these, the Integrated Nested Laplace Approximation (INLA) methodology has gained substantial attention due to its low computational burden [28]. In this paper, we adopted an INLA approach to efficiently and accurately approximate Bayesian statistical inference for semi-parametric joint models of competing risks survival and skewed longitudinal data.

We utilized the INLAjoint R package to approximate the posterior marginals of the proposed joint models. The INLAjoint package is user-friendly and allows for fitting joint models with numerous hyperparameters, including those for the variance-covariance of random effects, measurement error variance, skewness, and association parameters. For comparison purpose, we also employed the WinBUGS software via the R2WinBUGS package as an MCMC approach to evaluate and compare the performance of the INLA method. Both application and simulation studies were conducted to achieve our objectives. The proposed methods were illustrated using real-world chronic kidney disease (CKD) follow-up data and validated through confirmatory simulation studies.

Several model comparisons were performed to ensure robust and valid statistical results. The Deviance Information Criterion (DIC), Widely Applicable Bayesian Information Criterion (WABIC), and computation time were used as comparison metrics. Moreover, relative bias (RB), coverage probability (CP), and root mean squared error (RMSE) were computed in the simulation studies to evaluate model performance. First, we compared longitudinal submodels with different numbers of spline basis functions to accurately capture the non-linear time effect on the longitudinal outcome using the INLA approach. A semi-parametric mixed-effects longitudinal submodel with three spline basis functions was selected for constructing the joint models with cause-specific competing risks hazard submodels. Next, joint models with different parameterizations (association structures) were fitted and compared using the INLA approach. The joint model with shared random effects parameterization was identified as the best-fitting model based on lower DIC and WABIC values. Finally, we compared joint models with different non-Gaussian distributions using both the INLA (INLAjoint) and MCMC (R2WinBUGS) approaches to accurately fit the competing risks-longitudinal CKD data. As presented in the result section, joint models with shared random effects and skew distributions were selected as the best-fitting models for the CKD data using both approaches. The R2WinBUGS approach required substantially longer computation time to approximate the posteriors of the proposed joint models, whereas the INLAjoint method accomplished the approximations (model fittings) within a fraction of time. Specifically, INLAjoint was roughly 60 times faster than R2WinBUGS, despite the latter being a flexible and widely used software for Bayesian inference in joint longitudinal-survival models. This finding aligns with previous studies highlighting the computational advantages of INLA [28].

Table 4 Simulation results using INLA and MCMC approaches with varied distributions (Scenario 1)

Approach	INLAjoint						R2WinBUGS					
Distribution	Gaussian			Skew-Normal			Skew-Normal			Skew-t		
Par & TV	RB	RMSE	CP	RB	RMSE	CP	RB	RMSE	CP	RB	RMSE	CP
$\beta_0 = 3.98$	-0.017	0.069	87.8	0.021	0.085	89.4	-0.025	0.107	86.7	-0.020	0.128	89
$\beta_1 = -0.08$	0.044	0.004	94.4	0.031	0.002	94.8	0.108	0.050	94.7	-0.072	0.049	94.4
$\beta_2 = -0.15$	0.006	0.001	94.6	0.036	0.005	95	0.001	0.054	94.8	0.034	0.056	95
$\kappa_1 = -1.12$	0.071	0.079	89	-0.098	0.110	84.4	-0.131	0.187	76.6	0.068	0.141	89.9
$\kappa_2 = -3.35$	-0.049	0.147	89.6	0.018	0.059	92.8	0.091	0.403	74.2	-0.060	0.322	91.1
$\kappa_3 = -3.52$	-0.024	0.079	88.2	0.031	0.108	91	-0.010	0.124	93.9	-0.024	0.149	90.5
$\sigma^2_\epsilon = 3.10$	0.121	0.374	99.8	0.118	0.365	99.6	-0.073	0.215	82.7	-0.031	0.259	94.4
$\sigma^2_{\phi_i} = 0.07$	0.236	0.016	90.6	0.207	0.014	94.8	0.009	0.022	95.5	0.073	0.026	94.2
$\sigma^2_{\vartheta_{i1}} = 0.85$	-0.144	0.122	90	-0.098	0.083	92.2	0.181	0.300	88.9	0.032	0.238	94.7
$\sigma^2_{\vartheta_{i2}} = 2.21$	-0.039	0.086	95.4	0.133	0.293	91.2	0.020	0.616	95.3	-0.005	0.691	94.5
$\sigma^2_{\vartheta_{i3}} = 2.90$	-0.056	0.162	93.6	-0.004	0.010	95.4	0.068	0.419	91.5	0.007	0.362	94.9
$\beta_{1E} = 1.50$	0.123	0.185	88	0.115	0.173	88.2	-0.073	0.199	92.3	-0.073	0.197	92.5
$\beta_{2E} = 0.80$	0.267	0.214	86.8	0.204	0.163	88.6	-0.171	0.236	89.1	-0.166	0.229	89.2
$\beta_{1D} = 1.75$	0.104	0.183	90.2	0.063	0.111	93.4	-0.047	0.245	93.9	-0.059	0.268	93.1
$\beta_{2D} = 2.20$	0.056	0.124	93.6	0.044	0.098	93	-0.010	0.237	94.6	-0.021	0.241	94.6
$\alpha_E = -3.65$	0.078	0.441	92	0.061	0.347	93.4	-0.116	0.297	93.8	-0.129	0.327	93
$\alpha_D = -2.53$	0.267	0.675	89.8	0.187	0.473	93.2	-0.201	0.473	92.4	-0.101	0.271	94.2
Comput.time	26.2			227.31			6425			8534		
DIC	22,671			22,618			40,551			40,464		

Par Parameters, *TV* True value

Although INLA provides computationally efficient alternative to MCMC for approximate Bayesian inference for a wide class of latent Gaussian models (LGMs), including joint modelling of biomedical follow-up data, it has some structural and distributional limitations that must be carefully considered. First, INLAjoint currently offers limited support for more flexible skewed or heavy-tailed distributions in modeling longitudinal outcomes. This is particularly relevant in biomedical studies, where outcomes, e.g., viral load or CD4 count in HIV/AIDS, often exhibit skewness or heavy tails [35, 39, 43]. For instance, distributions like the skew-t that commonly used to capture such characteristics, is not supported in existing INLA implementations (e.g., INLAjoint). In our CKD application, INLAjoint did not allow the specification of a skew-t distribution for the longitudinal submodel, whereas MCMC-based approaches (e.g., via R2WinBUGS) were able to accommodate this. Ignoring such distributional features may lead to model misspecification and biased parameter estimates [35, 39, 40]. Second, INLA strictly depends on Gaussian latent processes and requires models to be expressed as LGMs with Gaussian priors on the latent field [17]. However, there are several complex models that require more rigorous estimation methods with higher computational demands. For instance, joint models with non-Gaussian random effects, nonlinear mixed-effects submodels, and heavy tails (extreme skewness) which often arise in biomedical modeling [10, 28]. These models typically do not yield closed-form solutions, especially when involving ordinary differential equations, making INLA unsuitable. Third, even within models compatible with LGM structure, implementation challenges remain. Some advanced joint models: such as quantile joint models and those with high-dimensional spatial random effects, are difficult to fit with INLAjoint. These often require custom model formulations, extensive prior tuning, and substantial user expertise to fit in R-INLA. For many applied researchers, particularly those without deep familiarity with R-INLA, MCMC approaches may offer a more practical and transparent solution. A more detailed review of the limitations of INLA is provided in [10, 28]. Given these limitations of INLA, the MCMC approach remains a more flexible and reliable method for approximating posterior distributions, despite its higher computational cost.

Future research could further explore alternative joint model formulations and comparisons for complex competing risks–longitudinal outcomes and assess their limitations and trade-offs using INLA. Additionally, unlike MCMC, INLA is a deterministic approach that provides accurate approximations for Bayesian inference in LGMs without relying on iterative sampling [17, 44]. However, its reliance on Gaussian approximations for latent fields may introduce bias in complex joint models with non-Gaussian posteriors. As suggested by one of the reviewers, future work should evaluate the risk of premature convergence in INLA (e.g., convergence to local modes) and its trade-offs with accuracy, particularly in high-dimensional or non-linear joint models. Accordingly, we recommend future research on joint longitudinal-survival models with diverse features to systematically explore these issues.

After conducting model comparisons, we then used the selected best-fitting joint models to assess the relationship between the longitudinal and competing risks outcomes, as well as the effects of other covariates on both outcomes. The results presented in Table 3 showed that the longitudinal outcome (eGFR) and competing risks failure events (death and ESRD) have a negative association. Specifically, a CKD patient had an 83% lower risk of experiencing end-stage renal disease when their kidney function measure (the *log*(eGFR)) increased by one unit (mL/min/1.73 m^2). Covariates such as hypertension, diabetes, and measurement time were negatively associated with eGFR, demonstrating that a CKD patient with hypertension or diabetes had a higher risk of experiencing either of the failure events compared to other CKD patients without these comorbidities. Furthermore, a CKD patient with hypertension or diabetes had a significantly higher risk of developing ESRD or dying compared to those without these comorbidities.

A confirmatory simulation studies was conducted for further evaluation of the performance of the proposed methods. Some performance assessment metrics such as RB, CP, RMSE, and computation time were computed. The simulation results also confirmed that the INLA approach produced accurate estimates (low RB and RMSE, high CP) comparable to the MCMC approach, while substantially reducing the computational burden. These findings align with previous studies supporting INLA as an accurate approximation method in joint modeling. For instance, prior research has demonstrated that INLA can approximate posterior marginals with high accuracy, similar to MCMC and other likelihood-based approaches such as frailtypack, JMbayes2, and rstanarm [10, 44].

In conclusion, we have proposed an INLA-based methodology to conduct a fast and accurate statistical inference for Bayesian semi-parametric joint models of competing risks survival and skewed longitudinal data with flexible distributions and parameterizations. The application to CKD data and simulation results demonstrate that this work contributes substantially to properly and efficiently treating complex competing risks survival and skewed longitudinal follow-up data.

Table 5 Simulation results using INLA and MCMC approaches with different sample sizes (Total Observations), Number of Chains, and Iterations (Scenarios 2 & 3)

Approach	INLAjoint (Skew-Normal)						R2WinBUGS (Skew-t)					
m, chain, & iteration	m = 200 (M = 3000)			m = 400 (M = 6000)			Chain = 1, iter = 10,000			Chain = 3, iter = 30,000		
Par & TV	RB	RMSE	CP	RB	RMSE	CP	RB	RMSE	CP	RB	RMSE	CP
$\beta_0 = 3.98$	0.019	0.075	89.8	0.021	0.085	89.4	-0.024	0.123	76.5	-0.020	0.128	89
$\beta_1 = -0.08$	1.196	0.096	71.8	0.031	0.002	94.8	-0.107	0.051	95.2	-0.072	0.049	94.4
$\beta_2 = -0.15$	0.226	0.034	93.2	0.036	0.005	95	0.025	0.055	95.2	0.034	0.056	95
$\kappa_1 = -1.12$	0.206	0.231	72.4	-0.098	0.110	84.4	0.067	0.133	89.5	0.068	0.141	89.9
$\kappa_2 = -3.35$	-0.036	0.121	92.2	0.018	0.059	92.8	-0.067	0.284	83.3	-0.060	0.322	91.1
$\kappa_3 = -3.52$	0.012	0.043	94.6	0.031	0.108	91	-0.087	0.328	89.4	-0.024	0.149	90.5
$\sigma^2_\epsilon = 3.10$	0.031	0.097	99.4	0.118	0.365	99.6	-0.019	0.151	91.9	-0.031	0.259	94.4
$\sigma^2_{\phi_i} = 0.07$	0.270	0.019	92.8	0.207	0.014	94.8	0.097	0.028	92.6	0.073	0.026	94.2
$\sigma^2_{\vartheta_{i1}} = 0.85$	0.738	0.627	75	-0.098	0.083	92.2	0.038	0.277	95.4	0.032	0.238	94.7
$\sigma^2_{\vartheta_{i2}} = 2.21$	0.449	0.992	80.6	0.133	0.293	91.2	0.035	0.671	94.5	-0.005	0.691	94.5
$\sigma^2_{\vartheta_{i3}} = 2.90$	0.009	0.025	95.2	-0.004	0.010	95.4	0.012	0.373	95.7	0.007	0.362	94.9
$\beta_{1E} = 1.50$	0.189	0.284	86.2	0.115	0.173	88.2	-0.082	0.194	92.4	-0.073	0.197	92.5
$\beta_{2E} = 0.80$	0.276	0.220	88.6	0.204	0.163	88.6	-0.165	0.240	89.5	-0.166	0.229	89.2
$\beta_{1D} = 1.75$	0.019	0.034	93.8	0.063	0.111	93.4	-0.064	0.256	92.4	-0.059	0.268	93.1
$\beta_{2D} = 2.20$	0.005	0.011	94.4	0.044	0.098	93	0.029	0.237	93.6	-0.021	0.241	94.6
$\alpha_E = -3.65$	0.105	0.596	91.6	0.061	0.347	92	-0.312	0.594	90	-0.129	0.327	93
$\alpha_D = -2.53$	0.245	0.621	89.2	0.187	0.473	93.2	-0.229	0.521	91.2	-0.101	0.271	94.2

m sample size, *M* total repeated measurements

Acknowledgements
We would like to thank the University of Gondar Comprehensive Specialized Hospital for providing access to the data used in this study. This work is partially based upon research supported by the RDP grant at the University of Pretoria, the South Africa National Research Foundation (NRF) Ref.: RA210106581084, grant No. 150170, and the South African DST-NRF-MRC SARChI Research Chair in Biostatistics (Grant No. 114613). Opinions expressed and conclusions arrived at are those of the author and are not necessarily to be attributed to the NRF and SAMRC.

Author contributions
Conceptualization and methodology: MMF, DGC and NNR; software, data curation, and analysis: MMF; supervision, draft review, and validation: DGC and NNR. All authors reviewed and approved the final version of the manuscript.

Funding
Not applicable.

Data availability
The real-world chronic kidney disease (CKD) dataset used to demonstrate the proposed methods is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study received ethical clearance from the Institutional Ethical Review Board of the University of Gondar (IRBUoG), Ethiopia (Ref. VP/RTT/05/777/2022). Given the retrospective nature of the study, which utilized anonymized secondary data from medical records without direct patient involvement, the IRBUoG waived the requirement for individual informed consent. All methods in this study were conducted in adherence to all applicable ethical guidelines and regulatory standards (including the Helsinki Declaration), with a primary emphasis on methodological advancement.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 26 March 2025 / Accepted: 12 August 2025
Published online: 02 September 2025

References

1. Rizopoulos D. Joint models for longitudinal and time-to-event data: with applications in R. CRC; 2012.
2. Bakoyannis G, Touloumi G. Practical methods for competing risks data: a review. Stat Methods Med Res. 2012;21(3):257–72.
3. Tsiatis AA, Davidian M. Joint modeling of longitudinal and time-to-event data: an overview. Statistica Sinica. 2004;14:809–34.
4. Rizopoulos D, Ghosh P. A bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event. Stat Med. 2011;30(12):1366–80.
5. Mauff K, Steyerberg E, Kardys I, Boersma E, Rizopoulos D. Joint models with multiple longitudinal outcomes and a time-to-event outcome: a corrected two-stage approach. Stat Comput. 2020;30:999–1014.
6. Azarbar A, Wang Y, Nadarajah S. Simultaneous bayesian modeling of longitudinal and survival data in breast cancer patients. Commun Statistics-Theory Methods. 2021;50(2):400–14.
7. Williamson PR, Kolamunnage-Dona R, Philipson P, Marson AG. Joint modelling of longitudinal and competing risks data. Stat Med. 2008;27(30):6426–38.
8. Li N, Elashoff RM, Li G, Saver J. Joint modeling of longitudinal ordinal data and competing risks survival times and analysis of the NINDS rt-PA stroke trial. Stat Med. 2010;29(5):546–57.
9. Baghfalaki T, Kalantari S, Ganjali M, Hadaegh F, Pahlavanzadeh B. Bayesian joint modeling of ordinal longitudinal measurements and competing risks survival data for analysing Tehran lipid and glucose study. J Biopharm Stat. 2020;30(4):689–703.
10. Rustand D, van Niekerk J, Krainski ET, Rue H. Joint modeling of multivariate longitudinal and survival outcomes with the R package inlajoint. ArXiv Preprint ArXiv:2402.08335;2024.
11. Song X, Davidian M, Tsiatis AA. A semiparametric likelihood approach to joint modeling of longitudinal and time-to-event data. Biometrics. 2002;58(4):742–53.
12. Wang J, Luo S, Li L. Dynamic prediction for multiple repeated measures and event time data: an application to parkinson's disease. Annals Appl Stat. 2017;11(3):1787.
13. Yang W, Xie D, Pan Q, Feldman HI, Guo W. Joint modeling of repeated measures and competing failure events in a study of chronic kidney disease. Stat Biosci. 2017;9:504–24.
14. Rajeswaran J, Blackstone EH, Barnard J. Joint modeling of multivariate longitudinal data and competing risks using multiphase sub-models. Stat Biosci. 2018;10:651–85.
15. Teixeira L, Sousa I, Rodrigues A, Mendonça D. Joint modelling of longitudinal and competing risks data in clinical research. REVSTAT-Statistical J. 2019;17(2):245–64. https://doi.org/10.57805/revstat.v17i2.
16. Bhattacharjee A, Vishwakarma GK, Banerjee S. Joint modeling of longitudinal and time-to-event data with missing time-varying covariates in targeted therapy of oncology. Commun Statistics: Case Stud Data Anal Appl. 2020;6(3):330–52.
17. Rue H, Martino S, Chopin N. Approximate bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J Royal Stat Soc Ser B: Stat Methodol. 2009;71(2):319–92.
18. Huang X, Li G, Elashoff RM. A joint model of longitudinal and competing risks survival data with heterogeneous random effects and outlying longitudinal measurements. Stat Interface. 2010;3(2):185–95.
19. Baghfalaki T, Ganjali M, Berridge D. Robust joint modeling of longitudinal measurements and time-to-event data using normal/independent distributions: a bayesian approach. Biom J. 2013;55(6):844–65. https://doi.org/10.1002/bimj.201200272.
20. Das K. A semiparametric bayesian approach for joint modeling of longitudinal trait and event time. J Appl Stat. 2016;43(15):2850–65.
21. Zhang H, Huang Y. Quantile regression-based bayesian joint modeling analysis of longitudinal-survival data, with application to an AIDS cohort study. Lifetime Data Anal. 2019;25(1):1–30.
22. Sheikh MT, Ibrahim JG, Gelfond JA, Sun W, Chen MH. Joint modelling of longitudinal and survival data in the presence of competing risks with applications to prostate cancer data. Stat Model. 2020;20(5):1–25. https://doi.org/10.1177/1471082X20944620.
23. Alvares D, Van Niekerk J, Krainski ET, Rue H, Rustand D. Bayesian survival analysis with INLA. Stat Med. 2024;43(20):3975–4010.
24. Van Niekerk J, Bakka H, Rue H, Schenk O. New frontiers in bayesian modelling using the INLA package in R. J Stat Softw. 2021;100(2):1–28.
25. Van Niekerk J, Bakka H, Rue H. Joint models as latent Gaussian models—not reinventing the wheel. ArXiv. 2019;ArXiv:1901.09365.
26. Ferede MM, Mwalili S, Dagne G, Karanja S, Hailu W, El-Morshedy M, et al. A semiparametric bayesian joint modelling of skewed longitudinal and competing risks failure time data: with application to chronic kidney disease. Mathematics. 2022;10(24):4816.
27. Niekerk Jv, Bakka H, Rue H. Competing risks joint models using R-INLA. Stat Modelling. 2021;21(1–2):56–71.
28. Rustand D, Van Niekerk J, Krainski ET, Rue H, Proust-Lima C. Fast and flexible inference for joint models of multivariate longitudinal and survival data using integrated nested Laplace approximations. Biostatistics. 2024;25(2):429–48.
29. Ferede MM, Dagne GA, Mwalili SM, Bilchut WH, Engida HA, Karanja SM. Flexible bayesian semiparametric mixed-effects model for skewed longitudinal data. BMC Med Res Methodol. 2024;24(1):56.
30. Martino S, Riebler A. Integrated nested Laplace approximations (INLA). arXiv preprint. 2019; arXiv:190701248.
31. Deslandes E, Chevret S. Joint modeling of multivariate longitudinal data and the dropout process in a competing risk setting: application to ICU data. BMC Med Res Methodol. 2010;10:1–13.

32. Andrinopoulou ER, Rizopoulos D, Takkenberg JJ, Lesaffre E. Joint modelling of two longitudinal outcomes and competing risk data. Stat Med. 2014;33(18):3167–78.
33. Andrinopoulou ER, Rizopoulos D, Takkenberg JJ, Lesaffre E. Combined dynamic predictions using joint models of two longitudinal outcomes and competing risk data. Stat Methods Med Res. 2017;26(4):1787–801.
34. Rue M, Andrinopoulou ER, Alvares D, Armero C, Forte A, Blanch L. Bayesian joint modeling of bivariate longitudinal and competing risks data: an application to study patient-ventilator asynchronies in critical care patients. Biom J. 2017;59(6):1184–203.
35. Lu T. Simultaneous inference for semiparametric mixed-effects joint models with skew distribution and covariate measurement error for longitudinal competing risks data analysis. J Biopharm Stat. 2017;27(6):1009–27.
36. Armero C, Forte A, Perpi¯n´an H, Sanahuja MJ, Agust´ı S. Bayesian joint modeling for assessing the progression of chronic kidney disease in children. Stat Methods Med Res. 2018;27(1):298–311.
37. Hickey GL, Philipson P, Jorgensen A, Kolamunnage-Dona R. A comparison of joint models for longitudinal and competing risks data, with application to an epilepsy drug randomized controlled trial. J Royal Stat Soc Ser A: Stat Soc. 2018;181(4):1105–23.
38. [Mwanyekange J, Mwalili S, Ngesa O. Bayesian inference in a joint model for longitudinal and time to event data with Gompertz baseline hazards. 2018.
39. Zhang H, Huang Y. Bayesian joint modeling for partially linear mixed-effects quantile regression of longitudinal and time-to-event data with limit of detection, covariate measurement errors and skewness. J Biopharm Stat. 2021;31(3):295–316.
40. Sahu SK, Dey DK, Branco MD. A new class of multivariate skew distributions with applications to bayesian regression models. Can J Stat. 2003;31(2):129–50.
41. Ferede MM, Mwalili SM, Dagne GA. A mixed-effects joint model with skew-t distribution for longitudinal and time-to-event data: a bayesian approach. Commun Math Biol Neurosci. 2023;2023:Article-ID.
42. Simpson D, Rue H, Riebler A, Martins TG, Sørbye SH. Penalising model component complexity: A principled, practical approach to constructing priors. 2017.
43. Castro LM, Wang WL, Lachos VH, In´acio de Carvalho V, Bayes CL. Bayesian semiparametric modeling for HIV longitudinal data with censoring and skewness. Stat Methods Med Res. 2019;28(5):1457–76.
44. Rustand D, van Niekerk J, Rue H, Tournigand C, Rondeau V, Briollais L. Bayesian Estimation of two-part joint models for a longitudinal semicontinuous biomarker and a terminal event with INLA: interests for cancer clinical trial evaluation. Biom J. 2023;65(4):2100322.

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