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Joint analysis of longitudinal measurements and spatially clustered competing risks HIV/AIDS data

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Abstract

The joint modeling of repeated measurements and time-to-event provides a general framework to describe better the link between the progression of disease through longitudinal measurements and time-to-event outcome. In the survival data, a sample of individuals is frequently grouped into clusters. In some applications, these clusters could be arranged spatially, for example, based on geographical regions. There are two benefits of considering spatial variation in these data, enhancing the efficiency and accuracy of the parameters estimations, and investigating the survivorship spatial pattern. On the other hand, in survival data, there is a situation that subjects are supposed to experience more than one type of event potentially, but the occurrence of one type of event prevents the occurrence of the others. In this article, we considered a Bayesian joint model of longitudinal and competing risks outcomes for spatially clustered HIV/AIDS data. The data were from a registry-based study carried in Hamadan Province, Iran, from December 1997 to June 2020. In this joint model, a linear mixed effects model was used for the longitudinal submodel and a cause-specific hazard model with spatial and spatial-risk random effects was used for the survival submodel. Also, a latent structure was defined by random effects to link both event times and longitudinal processes. We used a univariate intrinsic conditional autoregressive (ICAR) distribution and a multivariate ICAR distribution for modeling the areal spatial and spatial-risk random effects, respectively. The performance of our proposed model using simulation studies and analysis of HIV/AIDS data were assessed.

KEYWORDS

Bayesian approach, competing risks, joint model, longitudinal data, spatial random effect

1 | INTRODUCTION

In biomedical researches, data on repeated measurements and time-to-event are usually observed simultaneously. The joint modeling of these two outcomes provides a general framework to describe better the link between the progression of disease through longitudinal measurements such as biomarkers and time-to-event outcomes such as diagnosis of the disease or death. Also, the efficiency of parameters estimation of survival and longitudinal submodels such as treatment effect on two endpoints is increased by the joint modeling that incorporates all information simultaneously especially if outcomes are associated strongly.[1] In a joint model, a latent structure that is defined by sharing random effects links

both event time and longitudinal processes.[2] The joint modeling of longitudinal and time-to-event data has been considered extensively during the past two decades in statistical researches, and several studies have reviewed approaches and software programs for analyzing these data.[2-8]

Although some researches about a standard joint model on a single biomarker and a single clinical event have been published, in practice data structures are more complex. For example, in some studies, in the longitudinal process instead of one longitudinal outcome multiple longitudinal outcomes were assessed in a joint modeling framework.[9,10] In the survival process, there is a situation that subjects are supposed to experience more than one type of event potentially, but the occurrence of one type of event prevents the occurrence of the others. The joint modeling method has also been extended to this situation, where there are competing risks event time data.[11,12]

On the other hand, in the survival process, individuals are frequently grouped into clusters, for example, based on health centers, and geographical regions. There is a spatial correlation between data of subjects who are from various regions since those who are from nearer regions are more similar in social and environmental aspects than those who are from farther regions.[13] Incorporating this correlation results in more precise results. In addition, analyzing these data could result in some beneficial results such as identifying residents who are in need of strengthening public health services or indicating inequalities in the geographic allocation of health resources.

In epidemiology and biostatistics researches, survival models using spatial random effects in the clustered survival data have been widely used. For instance, in two studies, a spatial survival model using the classical[13] and Bayesian inference[14] was applied. For interval-censored data[15] and arbitrarily censored data,[16] two spatial survival models were proposed. In one study, the cause-specific hazard model with spatial random effects was applied in competing risks data.[17] More recently, several competing risks models for the spatio-temporally correlated data were proposed.[18]

In the joint modeling context, recently, Martins et al.[19] applied a model for joint modeling longitudinal and survival data with the spatial random effects. In another study, Martins et al.[20] employed joint survival-cure and longitudinal models along with spatial random effects. More recently, Niekerk et al.[21] proposed the joint models of competing risks and longitudinal data with various structures such as spatial random effects and non-linear longitudinal trajectories within the class of latent Gaussian models which have computational advantage and can be fitted using the R-INLA package.

To the extent of our knowledge, no joint model for longitudinal measurements and spatially correlated competing risks data in the Bayesian framework has been proposed. Thus, our main concern is carrying out a survival analysis, considering for: (i) a time-varying covariate, (ii) a competing risks model, and (iii) a spatial clustering among regions. In this article, we considered a linear mixed effects model as the longitudinal submodel and a cause-specific hazard model with spatial and spatial-risk random effects as the survival submodel. The motivation of our new model in the HIV/AIDS data is to assess effect of treatment and prognostic factors on hazards of AIDS and mortality post-HIV infection, while taking into account spatial heterogeneity. Also, the within-subject patterns of change of CD4, the relationship between features of CD4 profiles and hazards of AIDS and mortality post-HIV infection, and the patterns of geographic inequalities in hazards of AIDS and mortality post-HIV infection could be assessed in our new model.

The remainder of this article is written as follows. The motivation of our spatial joint model that was HIV/AIDS data is explained in Section 2. Section 3 presents our proposed model, consisting of the notations, submodels, distributions of areal spatial and spatial-risk random effects, likelihood function, the prior and posterior distributions, and comparison criteria between models. In Section 4, the performance of our model using two simulation studies is assessed. An analysis of the HIV/AIDS data is presented in Section 5. Finally, Section 6 illustrates a summary and a discussion of future research fields.

2 | THE HIV/AIDS DATA

The data were from a registry-based study carried in Hamadan Province, the west of Iran, from December 1997 to June 2020. In this study, there were information for 592 patients, however, based on including criteria mentioned next, information of 400 HIV-positive patients were included in our analysis. The following independent variables were available in health records in the HIV counseling clinics: age at the first visit that is classified into three categories (0-24, 25-44, and 45-74 years), sex, co-infection with tuberculosis (TB), and antiretroviral treatment (ART). Also, patients' health records are employed to collect data including date of HIV diagnosis, date of AIDS diagnosis, date of death, and the patient's district of residence. Information about a patient's vital status was checked on June 30, 2020, by active contact with the patient. The mean time of follow-up was 4.99, from 1 to 18 years. The mean age of patients was 33.35, from birth to 74 years. The number of HIV/AIDS individuals per Hamadan District (22 districts) was

TABLE 1 Estimation results for the first simulation study with low censoring rate

		$n_k = 15, n = 240$				$n_k = 25, n = 400$				$n_k = 50, n = 800$			
		Estimate	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**
Censoring rate 20%	Longitudinal process												
	$\beta_{11} = 1$	1.025	0.025	0.002	1	0.971	−0.028	0.001	1	0.968	−0.031	0.001	1
	$\beta_{12} = 1$	0.972	−0.027	0.001	1	1.059	0.059	0.003	0.998	1.020	0.020	0.0005	1
	$\beta_{13} = 1$	0.963	−0.036	0.003	1	1.061	0.061	0.005	1	1.065	0.065	0.004	1
	$\beta_{14} = 1$	0.985	−0.014	0.026	0.956	0.989	−0.010	0.014	0.954	0.998	−0.001	0.006	0.970
	$\sigma^2 = 1$	1.003	0.003	0.001	0.952	1.002	0.002	0.001	0.932	1.001	0.001	0.0003	0.944
	Survival process												
	Risk 1												
	$\beta_{21}^{(1)} = 0.6$	0.607	0.012	0.016	0.972	0.651	0.085	0.016	0.946	0.619	0.033	0.005	0.978
	$\beta_{22}^{(1)} = -0.4$	−0.467	0.168	0.084	0.972	−0.397	−0.006	0.041	0.994	−0.337	−0.156	0.022	1
	$\gamma^{(1)} = 0.7$	0.814	0.164	0.027	0.838	0.786	0.122	0.015	0.846	0.752	0.074	0.006	0.888
	Risk 2												
	$\beta_{21}^{(2)} = -0.3$	−0.369	0.230	0.017	0.944	−0.281	−0.060	0.008	1	−0.277	−0.073	0.003	0.994
	$\beta_{22}^{(2)} = 0.7$	0.641	−0.084	0.051	0.956	0.729	0.042	0.028	0.966	0.743	0.062	0.016	0.944
	$\gamma^{(2)} = 0.5$	0.561	0.123	0.012	0.892	0.556	0.112	0.007	0.866	0.530	0.061	0.003	0.906
	Random effects												
	$\Sigma_{b11} = 1$	1.008	0.008	0.004	1	0.917	−0.082	0.009	0.958	0.890	−0.109	0.013	0.956
	$\Sigma_{b22} = 1$	0.919	−0.080	0.096	0.960	0.865	−0.134	0.078	0.928	0.794	−0.205	0.073	0.904
	$\Sigma_{b12} = 0.5$	0.501	0.002	0.017	0.986	0.472	−0.054	0.009	0.990	0.473	−0.052	0.005	0.956
	$\Lambda_{11} = 1$	1.177	0.177	0.129	1	1.113	0.113	0.080	1	1.184	0.184	0.092	1
	$\Lambda_{22} = 1$	1.206	0.206	0.109	1	1.241	0.241	0.123	1	1.099	0.099	0.039	1
	$\Lambda_{12} = 0.5$	0.177	−0.644	0.139	1	0.246	−0.507	0.083	1	0.253	−0.492	0.090	1
	$\sigma_w^2 = 1$	0.863	−0.136	0.091	0.936	0.979	−0.020	0.087	0.966	0.991	−0.008	0.053	0.980

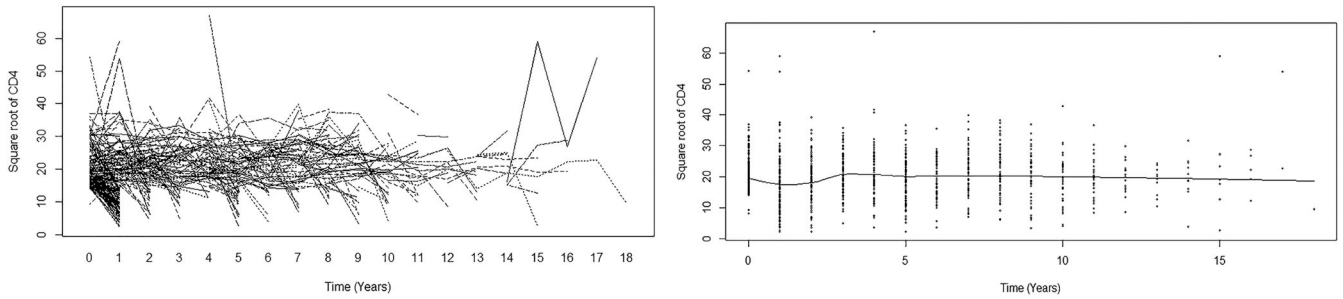

FIGURE 1 Longitudinal trajectories of CD4 measurements (left) and the overall mean trajectory of CD4 (right)

presented in the supplementary material (Table 1). In our analysis, 29 patients with missing information about the state of residency were excluded. Also, there was a variation between the sample size of different districts so that the largest number of patients belonged to the district in which the capital of province is located.

The outcome in the longitudinal submodel was the number of CD4 T-lymphocytes measured over time since the time of HIV diagnosis. The CD4 measurement times varied irregularly across patients. Moreover, patients who their CD4 were measured at least two times were included in this study. In other words, 124 patients with one CD4 measure were excluded. The frequency of CD4 measurements varied between 2 and 9 times over the follow-up period. The mean of CD4

TABLE 2 Estimation results for the first simulation study with medium censoring rate

		$n_k = 15, n = 240$				$n_k = 25, n = 400$				$n_k = 50, n = 800$			
		Estimate	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**
Censoring rate 40%	Longitudinal process												
	$\beta_{11} = 1$	1.019	0.019	0.001	1	0.990	−0.009	0.001	1	0.973	−0.026	0.001	1
	$\beta_{12} = 1$	0.959	−0.040	0.002	1	1.031	0.031	0.001	1	0.980	−0.019	0.0005	1
	$\beta_{13} = 1$	0.967	−0.032	0.002	1	1.014	0.014	0.001	1	1.049	0.049	0.003	1
	$\beta_{14} = 1$	0.986	−0.013	0.020	0.970	0.986	−0.013	0.012	0.970	0.991	−0.008	0.006	0.972
	$\sigma^2 = 1$	1.001	0.001	0.001	0.938	1.004	0.004	0.001	0.944	1.002	0.002	0.0003	0.956
	Survival process												
	Risk 1												
	$\beta_{21}^{(1)} = 0.6$	0.596	−0.006	0.023	0.964	0.670	0.116	0.016	0.952	0.573	−0.044	0.007	0.948
	$\beta_{22}^{(1)} = -0.4$	−0.425	0.062	0.089	0.984	−0.465	0.164	0.055	0.962	−0.375	−0.061	0.026	0.992
	$\gamma^{(1)} = 0.7$	0.838	0.197	0.044	0.858	0.843	0.205	0.033	0.748	0.778	0.111	0.010	0.828
	Risk 2												
	$\beta_{21}^{(2)} = -0.3$	−0.349	0.163	0.019	0.958	−0.306	0.021	0.009	0.988	−0.320	0.066	0.004	0.958
	$\beta_{22}^{(2)} = 0.7$	0.780	0.115	0.075	0.948	0.750	0.072	0.044	0.946	0.743	0.061	0.019	0.962
	$\gamma^{(2)} = 0.5$	0.636	0.273	0.035	0.798	0.589	0.178	0.015	0.846	0.550	0.101	0.005	0.852
	Random effects												
	$\Sigma_{b11} = 1$	1.105	0.105	0.016	0.985	0.871	−0.128	0.019	0.912	0.891	−0.108	0.013	0.910
	$\Sigma_{b22} = 1$	1.074	0.074	0.140	0.989	0.787	−0.212	0.103	0.876	0.872	−0.127	0.054	0.912
	$\Sigma_{b12} = 0.5$	0.525	0.051	0.028	0.981	0.357	−0.285	0.029	0.908	0.491	−0.016	0.005	0.976
	$\Lambda_{11} = 1$	1.207	0.207	0.159	1	1.183	0.183	0.141	1	1.185	0.185	0.122	1
	$\Lambda_{22} = 1$	1.316	0.316	0.214	1	1.195	0.195	0.113	1	1.082	0.082	0.040	1
	$\Lambda_{12} = 0.5$	0.151	−0.696	0.169	0.996	0.182	−0.635	0.124	1	0.260	−0.479	0.086	1
	$\sigma_w^2 = 1$	0.928	−0.071	0.132	0.938	0.857	−0.142	0.103	0.912	0.840	−0.159	0.066	0.900

exams was 3.21, bringing about a total of 1277 observations for all patients. The CD4 counts distribution by explanatory variables indicates right skewness, so the square root transformation of CD4 cell counts was used in the proposed model. The longitudinal trajectories of $\sqrt{\text{CD4}}$ measurements for all individuals and the overall mean trajectory were shown in Figure 1. We observed a large variation in the baseline $\sqrt{\text{CD4}}$ in the left figure. The right figure showed that the trend of patients' CD4 cell count does not change over time. Also, an increasing missing data was observed over the follow-up period, because of AIDS, mortality post-HIV infection, or dropout for different reasons.

Two outcomes in the survival submodel were investigated. The first outcome was time interval between HIV diagnosis and AIDS diagnosis, in years, so the event of interest is AIDS progression. The second outcome was time interval between HIV diagnosis and mortality post-HIV infection. In HIV/AIDS disease, some of patients die before AIDS, because of that, mortality post-HIV infection is considered as competing risk.[22] The patients who were lost to follow-up or did not experience these two outcomes until June 30, 2020, are considered as censored. Therefore, patients are divided into three categories by the final outcome classification: those who progressed to AIDS (64.8%), those who died before AIDS (8.0%), and those who were censored (27.2%). It is worth mentioning that 39 patients were primarily diagnosed with AIDS that were excluded in this study because their CD4 were measured after AIDS diagnosis. There was at least 1 year between HIV diagnosis and AIDS diagnosis for patients in our analysis. Figure 2 plotted the unadjusted estimates of the cumulative incidence curve for the risks of AIDS and mortality post-HIV infection. As seen, patients show a higher risk of AIDS than mortality post-HIV infection over the follow-up time. Also, a few mortalities post-HIV infection occurs after 10 years, and its cumulative incidence function plateaus.

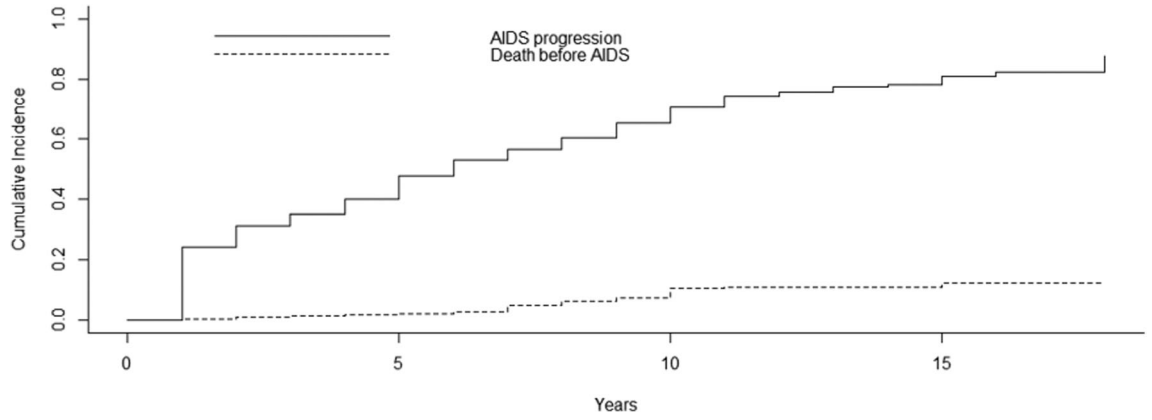

FIGURE 2 The Aalen-Johansen estimates of the cumulative incidence functions for AIDS progression and death before AIDS

3 | JOINT MODEL FORMULATION

Our spatial joint model consists of two separate models for each component: a linear mixed effects model and a competing risks model. Then the distribution function of two submodels is linked together via random effects to allow for the estimation of parameters of both longitudinal and survival processes, simultaneously. Let assume n individuals in a sample come from K regions. Also, the number of individuals in each region is n_k where $k = 1, \dots, K$ and $\sum_{k=1}^{K} n_k = n$.

For the survival part, let $C_{ik} = (T_{ik}, \nu_{ik})$ be competing risks data for the ith individual living in the kth region, $i = 1, \dots, n_k$, where T_{ik} represents event time or censoring time. Event type indicator or ν_{ik} takes a value from $\{0, 1, \dots, G\}$, with $\nu_{ik} = 0$ representing a censored event and $\nu_{ik} = g$, representing that the ikth individual fails from the gth type of event, where $g = 1, \dots, G$. For the longitudinal part, let $\boldsymbol{Y}_{ik} = (y_{ik1}, \dots, y_{ikn_{ik}})$, where $y_{ikj} \equiv y_{ik}(t_{ikj})$ the longitudinal outcomes measured intermittently for the ikth individual at some set of times $\{t_{ikj} \leq T_{ik}; i = 1, \dots, n_k, k = 1, \dots, K, j = 1, \dots, n_{ik}\}$. Also n_{ik} is the number of repeated measurements of the longitudinal response for the ikth individual and can be different for each individual. To describe the intra-subject evolution of longitudinal responses over time for the ikth individual, we define the observed value as the true value with error, that is, $y_{ik}(t_{ikj}) = y^{*}_{ik}(t_{ikj}) + \varepsilon_{ik}(t_{ikj})$.

Furthermore, the censoring mechanism in survival process is presumed to be non-informative. Also, the mechanism of missing responses in longitudinal process caused by reasons except the occurrence of events is presumed to be ignorable.

3.1 | Longitudinal submodel

For the ikth individual, we assume the longitudinal responses $\boldsymbol{Y}_{ik}$ follow a linear mixed effects model with both fixed effects and subject-level random effects as

$$\boldsymbol{Y}_{ik} = \boldsymbol{Y}^{*}_{ik} + \boldsymbol{\varepsilon}_{ik} = \mathbf{X}^{T}_{1ik}\boldsymbol{\beta}_1 + \mathbf{Z}^{T}_{ik}\mathbf{b}_{ik} + \boldsymbol{\varepsilon}_{ik}. \tag{1}$$

Generally, in a linear mixed effects model, a simple structure is assumed for random effects such as random intercept and linear random slope. The fixed effects are assumed by a polynomial regression or a spline regression. $\boldsymbol{\beta}_1$ is a $p \times 1$ vector of fixed effects corresponding $n_{ik} \times p$ covariate matrix $\mathbf{X}^{T}_{1ik}$, $\mathbf{b}_{ik}$ is a $q \times 1$ vector of random effects corresponding $n_{ik} \times q$ design matrix $\mathbf{Z}^{T}_{ik}$, and $\boldsymbol{\varepsilon}_{ik}$ is a $n_{ik} \times 1$ vector of measurement errors. We assumed the measurement errors have a normal distribution, $\varepsilon_{ik}(t_{ikj}) \sim N(0, \sigma^2)$ for all $t_{ikj} \geq 0$ and $\varepsilon_{ik}(t_{ikj})$ is independent of $\varepsilon_{ik}(t_{ikj'})$. We further assumed a multivariate normal distribution for the random effects, $\mathbf{b}_{ik}$, that is, $\mathbf{b}_{ik} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_b)$ and also the vector of $\boldsymbol{\varepsilon}_{ik}$ was assumed to be independent of $\mathbf{b}_{ik}$. No spatial structure is assumed for the longitudinal responses. In the HIV/AIDS data, $\sqrt{\text{CD4}}$ measurements are considered as a time-varying covariate with the error of measurement that should be longitudinally modeled. Note that both AIDS and mortality post-HIV infection could cause non-ignorable missing responses for the measurements of CD4.

3.2 | Survival submodel with random effects

For analyzing competing risks data different models have been proposed in the last three decades.[23,24] In this study, we assume the cause-specific proportional hazard model as follows:

$$h_{ik}^{(g)}(t|\mathbf{x}_{2ik}) = \lim_{dt\to 0}\frac{P(t \le T_{ik} < t+dt, \nu_{ik} = g|T_{ik} \ge t, \mathbf{x}_{2ik})}{dt} = h_0^{(g)}(t)\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)}), \tag{2}$$

where $h_0^{(g)}(t)$ is an baseline risk and $\boldsymbol{\beta}_2^{(g)} = (\beta_{21}^{(g)}, \beta_{22}^{(g)}, \dots, \beta_{2m}^{(g)})^T$ is a $m\times 1$ vector of parameters related to $m\times 1$ vector of independent variables $\mathbf{x}_{2ik} = (x_{2ik1}, x_{2ik2}, \dots, x_{2ikm})^T$ for the gth type of event. Let $\boldsymbol{\beta}_2 = (\boldsymbol{\beta}_2^{(1)^T}, \boldsymbol{\beta}_2^{(2)^T}, \dots, \boldsymbol{\beta}_2^{(G)^T})^T$ be a $Gm\times 1$ vector of regression coefficients for all event types. In practice, the vectors $\mathbf{x}_{1ik}$ and $\mathbf{x}_{2ik}$ may have the same components. In the cause-specific hazard model, for estimating risk of each event, other event types are presumed as censored as well as subjects who become lost to follow-up. However, in some conditions, patients who experience other event types are censored informatively. Thus, the assumption of independent censoring would not be sensible in the competing risks setting. For instance, in the HIV/AIDS data, it is possible that factors that influence the probability of AIDS as an event of interest could influence the probability of mortality post-HIV infection as an event of competing risk. Because of that, the random effects $\boldsymbol{V}_{ik} = (V_{ik}^{(1)}, \dots, V_{ik}^{(G)})^T$ are included in the cause-specific hazard model to consider the correlation between time to the event of interest and time to the informative censoring; for more information, see Huang and Wolfe [25] and Christian et al.[26] Also, the latent association between longitudinal and competing risks data is modeled through the association between the random effects $\mathbf{b}_{ik}$ and $\boldsymbol{V}_{ik}$. We consider these random effects through (2), as

$$h_{ik}^{(g)}(t|\mathbf{x}_{2ik}, V_{ik}^{(g)}) = h_0^{(g)}(t)\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)}). \tag{3}$$

In the submodel of survival, $\boldsymbol{V}_{ik}$, was assumed to follow a multivariate normal distribution, that is, $\boldsymbol{V}_{ik} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_V)$ where $\boldsymbol{\Sigma}_V$ is a $G\times G$ covariance matrix. Finally, it is assumed that the $\mathbf{b}_{ik}$ and $\boldsymbol{V}_{ik}$ for the ikth individual are correlated such that the $\mathbf{b}_{ik}$ and $\boldsymbol{V}_{ik}$ jointly have a multivariate normal distribution:

$$N\left(\begin{pmatrix}\mathbf{0}\\ \mathbf{0}\end{pmatrix}, \begin{pmatrix}\boldsymbol{\Sigma}_b & \boldsymbol{\Sigma}_{bV}\\ \boldsymbol{\Sigma}_{bv}^T & \boldsymbol{\Sigma}_V\end{pmatrix}\right). \tag{4}$$

But, the simplest structure for random effects in a survival submodel is $V_{ik}^{(g)} = \boldsymbol{\gamma}^{(g)^T}\mathbf{b}_{ik}$, that the q-dimensional vector of $\boldsymbol{\gamma}^{(g)}$ quantifies the strength of association between longitudinal responses with the risk of gth type of event. For instance, by a linear mixed effects model for CD4 counts with linear time effect and random intercept, $\gamma^{(g)}$ quantifies the effect of CD4 to the risk of gth type of event. Hence, for one unit increase in the random intercept of CD4 counts for the ikth patient, the relative hazard of AIDS is $\exp(\gamma^{(1)})$, and similarly, $\exp(\gamma^{(2)})$ is the relative hazard for mortality post-HIV infection. Also, it can be seen in this example that the direction of correlation between two risks dependent on the sign of two parameters $\gamma^{(1)}$ and $\gamma^{(2)}$ and that, as $|\gamma^{(1)}|$ and $|\gamma^{(2)}|$ closer to each other, the magnitude of correlation between competing risks increases. However, when profiles of longitudinal outcome are described by more than a single coefficient, $\boldsymbol{\gamma}^{(g)}$ do not have a direct interpretation. Note that $\boldsymbol{\gamma}^{(g)} = 0$ indicates a separated analysis of longitudinal and survival processes and also ignores a potential correlation between competing risks in the survival process.

On the other hand, a survival model along with spatial random effects was considered in this study since patients were from various districts. As mentioned earlier, patients who are from the same district or neighboring districts have shared or alike medical care and risk factors. Let $\boldsymbol{W} = (W_1, \dots, W_K)^T$ be the spatial random effects that W_k indicates unobserved heterogeneity for the kth district. Hence, Equation (3) with spatial random effects, is as follows:

$$h_{ik}^{(g)}(t|\mathbf{x}_{2ik}, V_{ik}^{(g)}, W_k) = h_0^{(g)}(t)\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)} + W_k). \tag{5}$$

Further examination of the HIV/AIDS data was shown in Figure 3. The estimates of the cumulative incidence of AIDS and mortality post-HIV infection risks for two Hamadan districts were plotted in the left figure. As observed, the

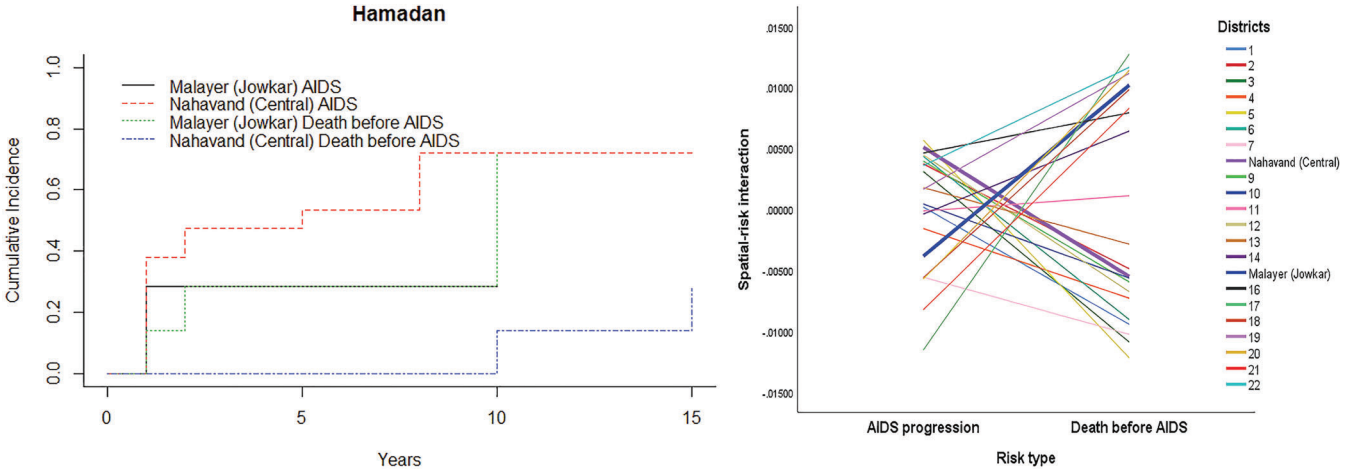

FIGURE 3 Analysis of the HIV/AIDS data to display spatial-risk interaction term [Colour figure can be viewed at wileyonlinelibrary.com]

cumulative incidence function of AIDS is higher than mortality post-HIV infection in Jowkar district of Malayer county (the southeast of Hamadan Province). By contrast, similar patterns were seen for the cumulative incidence probability of AIDS and mortality post-HIV infection in Central district of Nahavand county (the south of Hamadan Province). These two districts in the HIV/AIDS data have been selected to show spatial-risk interaction. Let $\boldsymbol{\delta} = (\delta_1^{(1)}, \ldots, \delta_K^{(G)})^T$ be spatial-risk interaction effects that $\delta_k^{(g)}$ indicates the unobserved heterogeneity for the gth type of event, nested within the kth district. Again, these interaction effects through (5) are introduced as

$$h_{ik}^{(g)}(t|\mathbf{x}_{2ik}, V_{ik}^{(g)}, W_k, \delta_k^{(g)}) = h_0^{(g)}(t)\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)} + W_k + \delta_k^{(g)}). \tag{6}$$

Finally, for the baseline hazard function, the simplest approach is to consider a parametric form. Another approach is to use a nonparametric baseline hazard proposed by the celebrated Cox model.[27] However, the Cox model does not allow fully hierarchical modeling of stratum specific baseline hazards. Another approach is flexible modeling the integrated baseline hazard as a mixture of monotone functions. Implementation of this idea was described by Gelfand and Mallick[28] and also by Carlin and Hodges[29] for stratum-specific baseline hazards. We assumed in our proposed model, an exponential function, hence, the model (6) can be substituted by:

$$h_{ik}^{(g)}(t|\mathbf{x}_{2ik}, V_{ik}^{(g)}, W_k, \delta_k^{(g)}) = \exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)} + W_k + \delta_k^{(g)}). \tag{7}$$

The exponential distribution is a one-parameter distribution that assumes exponential function in (7) as a constant hazard λ_{ik}^g.

3.3 | Spatial and spatial-risk random effects

In this study, for the spatial and spatial-risk random effects, an areal approach was applied. Let $\boldsymbol{W} = (W_1, \ldots, W_K)^T$ be the spatial random effects that W_k indicates unobserved heterogeneity for the kth district. Also, let $\boldsymbol{\delta} = (\boldsymbol{\delta}_1^T, \ldots, \boldsymbol{\delta}_K^T)^T$ be the spatial-risk random effects where $\boldsymbol{\delta}$ is $KG \times 1$ with each $\boldsymbol{\delta}_k = (\delta_k^{(1)}, \ldots, \delta_k^{(G)})^T$ being random effects for the G event types in the kth district. A conditional autoregressive (CAR) distribution for areal data in a univariate case is usually used.[30] Hence, the CAR model is as

$$P(W_k|\boldsymbol{W}_{-k}, \sigma_w^2) = N\left(\alpha\sum_{k\sim k'} b_{kk'}W_{k'}, \sigma_w^2\right), \quad k, k' = 1, \ldots, K, \tag{8}$$

where $\boldsymbol{W}_{-K}$ is the vector of random effects for all districts except the district k, and $k \sim k'$ shows that districts k and k' are neighbors.[31] Also, σ_w^2 and α are conditional variance and smoothing parameter, respectively. By Brook expansion,[32] the joint distribution is as

$$\boldsymbol{W} : N(\mathbf{0}, \sigma_w^2[\boldsymbol{D}(\boldsymbol{I} - \alpha\boldsymbol{B})]^{-1}), \tag{9}$$

If $\boldsymbol{D} = diag(m_k)$ where m_k is the number of neighbors for the kth district, $\boldsymbol{B} = \boldsymbol{D}^{-1}\boldsymbol{B}_w$ where $\boldsymbol{B}_w$ is the adjacency matrix ($b_{w_{kk}} = 0, b_{w_{kk'}} = 1$ if districts k and k' share a border), and $\alpha = 1$ are assumed the intrinsic conditional autoregressive (ICAR) model is obtained.[33] In this study, we used the ICAR distribution for $\boldsymbol{W}$ as

$$\boldsymbol{W} : N(\mathbf{0}, \sigma_w^2\boldsymbol{\Sigma}_w^{-1}), \tag{10}$$

where $\boldsymbol{\Sigma}_w = (\boldsymbol{D} - \boldsymbol{B}_w)$ is a $K \times K$ matrix.

Multivariate areal models are the best choice for analyzing multivariate areal data like information about some diseases in the same regions. The reason behind this is that some diseases may have similar or different risk factors and the occurrence of one disease might lead to or prevent the occurrence of other diseases in one region. As a result of this, multivariate models bring about capturing both variations: between multivariate components and between regions.[34,35] In other words, multivariate models could be applied to modeling the spatial-disease interaction effects.[35]

In this study, a multivariate intrinsic CAR (MICAR) distribution for the spatial-risk interaction effects, $\boldsymbol{\delta}$, was applied. Following Mardia,[36] the multivariate CAR (MCAR) distributions for $\boldsymbol{\delta}$ yield the form

$$P(\boldsymbol{\delta}_k|\boldsymbol{\delta}_{-k}, \boldsymbol{\Gamma}_k^{-1}) = N\left(\boldsymbol{R}_k \sum_{k\sim k'} \boldsymbol{B}_{kk'}\boldsymbol{\delta}_{k'}, \boldsymbol{\Gamma}_k^{-1}\right), \quad k, k' = 1, \ldots, K. \tag{11}$$

Following Brook's lemma,[32] a joint distribution of $\boldsymbol{\delta}$ is as

$$\boldsymbol{\delta} : N(\mathbf{0}, [\boldsymbol{\Gamma}(\boldsymbol{I} - \boldsymbol{B}_R)]^{-1}). \tag{12}$$

If $\boldsymbol{R}_k = \alpha\boldsymbol{I}_{G\times G}$ and $\boldsymbol{\Gamma} = \boldsymbol{D} \otimes \boldsymbol{\Lambda}^{-1}$ are assumed then the joint distribution (12) can be written more simply. Also, if $\boldsymbol{D}, \boldsymbol{B}$ and α are postulated as the ICAR distribution then the MICAR model is achieved. Therefore, the joint distribution for $\boldsymbol{\delta}$ is as

$$\boldsymbol{\delta} : N(\mathbf{0}, (\boldsymbol{\Sigma}_w^{-1} \otimes \boldsymbol{\Lambda})), \tag{13}$$

where $\boldsymbol{\Sigma}_w = (\boldsymbol{D} - \boldsymbol{B}_w)$ is a $K \times K$ matrix and hence $\boldsymbol{\Sigma}_w^{-1} \otimes \boldsymbol{\Lambda}$ is a $KG \times KG$ matrix. Moreover, $\boldsymbol{\Lambda}$ is a $G \times G$ positive definite and symmetric matrix, which is defined as the variance-covariance matrix of the risk effects and controls a correlation between competing risks in survival process in any given district. Consider that, for the spatial-risk interaction term in this model the covariance matrix is modeled as the Kronecker product of covariance matrices of spatial effects and risk effects.[37] For covariance matrix of interaction term, the Kronecker product of two covariance matrices of main effects was proposed by Clayton.[38]

Finally, an important key point is that sum to zero constraints have to be used to guarantee identifiability of the spatial and spatial-risk random effects. The new versions of BUGS for Windows, automatically imposes the sum-to-zero constraint numerically by recentring the W_k and $\delta_k^{(g)}$ samples around their own mean at the end of each iteration.[39]

3.4 | Likelihood

The likelihood function of the joint model of longitudinal and spatial competing risks survival has two parts of longitudinal and survival processes that share the random effects and covariates. These random effects consider a correlation between measurements in longitudinal process, a correlation between competing risks in the survival process, and also an association between these two types of processes. Hence, conditional on all independent variables and the $\mathbf{b}_{ik}$ and $\boldsymbol{V}_{ik}$ random effects competing risks are independent of each other and the longitudinal responses.

Let $\theta = (\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \rho^{(g)}, \sigma^2, \boldsymbol{\Sigma}_b, \boldsymbol{\Sigma}_V, \sigma_w^2, \boldsymbol{\Lambda}; g = 1, \ldots, G)$ represents all parameters, and $(\boldsymbol{Y}_{ik}, C_{ik}, \mathbf{X}_{ik}; i = 1, \ldots, n_k, k = 1, \ldots, K)$ denotes the observed data, and $\boldsymbol{U} = (\mathbf{b}_{ik}, \boldsymbol{V}_{ik}, \boldsymbol{W}, \boldsymbol{\delta}; i = 1, \ldots, n_k, k = 1, \ldots, K)$ represents all the random effects; therefore, the likelihood function for this model is factorized as

$$\begin{aligned} L(\theta \mid \boldsymbol{Y}, \boldsymbol{C}, \mathbf{X}) &\propto \prod_{k=1}^{K}\prod_{i=1}^{n_k} f(\boldsymbol{Y}_{ik}, C_{ik}|\theta, \mathbf{X}_{ik}) \\ &= \prod_{k=1}^{K}\prod_{i=1}^{n_k} \int f(\boldsymbol{Y}_{ik}|C_{ik}, \theta, \mathbf{X}_{ik}, \boldsymbol{U})\, f(C_{ik}|\theta, \mathbf{X}_{ik}, \boldsymbol{U})\, f(\boldsymbol{U}|\theta, \mathbf{X}_{ik})\, d\boldsymbol{U} \\ &= \prod_{k=1}^{K}\prod_{i=1}^{n_k} \int f(\boldsymbol{Y}_{ik}|\theta, \mathbf{X}_{ik}, \boldsymbol{U})\, f(C_{ik}|\theta, \mathbf{X}_{ik}, \boldsymbol{U})\, f(\boldsymbol{U}|\theta, \mathbf{X}_{ik})\, d\boldsymbol{U}, \end{aligned} \tag{14}$$

where $f(\boldsymbol{Y}_{ik}|\theta, \mathbf{X}_{ik}, \boldsymbol{U})$ and $f(C_{ik}|\theta, \mathbf{X}_{ik}, \boldsymbol{U})$ denote the distributions of longitudinal responses and competing risks data, respectively. The longitudinal responses distribution is that

$$\prod_{j=1}^{n_{ik}} (2\pi\sigma^2)^{-1/2} \exp\left[-\frac{(Y_{ikj} - \mathbf{x}_{1ik}^T(t_{ikj})\boldsymbol{\beta}_1 - \mathbf{z}_{ik}^T(t_{ikj})\mathbf{b}_{ik})^2}{2\sigma^2}\right], \tag{15}$$

and the corresponding competing risks survival data distribution is

$$\prod_{g=1}^{G}\left[\begin{array}{l}[\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)} + W_k + \delta_k^{(g)})]^{I(\nu_{ik}=g)} \\ \times \exp\left[-\int_0^{t_{ik}} \exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + V_{ik}^{(g)} + W_k + \delta_k^{(g)})dt\right]\end{array}\right]. \tag{16}$$

For instance, the likelihood for $\boldsymbol{\theta}$, conditional on the observed responses and covariates is expressed as follows, if $\mathbf{b}_{ik} = (\mathrm{b}_{1ik}, \mathrm{b}_{2ik})^T$, $\mathbf{Z}_{1ik}^T\mathbf{b}_{ik} = \mathrm{b}_{1ik} + \mathrm{b}_{2ik}t_{ikj}$, and $\boldsymbol{\gamma}^{(g)} = (\gamma^{(g)}, \gamma^{(g)})^T$, $V_{ik}^{(g)} = \gamma^{(g)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik})$.

$$\prod_{k=1}^{K}\prod_{i=1}^{n_k} \int \left[\begin{array}{l}\prod_{j=1}^{n_{ik}} (2\pi\sigma^2)^{-1/2} \exp\left[-\frac{(Y_{ikj} - \mathbf{x}_{1ik}^T(t_{ikj})\boldsymbol{\beta}_1 - \mathrm{b}_{1ik} - \mathrm{b}_{2ik}t_{ikj})^2}{2\sigma^2}\right] \times \\ \prod_{g=1}^{G}\left[\begin{array}{l}[\exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + \gamma^{(g)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik}) + W_k + \delta_k^{(g)})]^{I(\nu_{ik}=g)} \times \\ \exp\left[-\int_0^{t_{ik}} \exp(\mathbf{x}_{2ik}^T\boldsymbol{\beta}_2^{(g)} + \gamma^{(g)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik}) + W_k + \delta_k^{(g)})dt\right]\end{array}\right]\end{array}\right] f(\boldsymbol{U}|\theta, \mathbf{X}_{ik})\, d\boldsymbol{U}. \tag{17}$$

3.5 | Bayesian approach

The standard non-informative prior distributions for parameters of spatial joint model were considered as follows: In the longitudinal process for the regression coefficients, $\boldsymbol{\beta}_1$, the measurement error variance, σ^2, and the variance-covariance matrix of $\boldsymbol{\Sigma}_b$, a multivariate normal, $N(\mathbf{0}, \boldsymbol{\Sigma}_{\beta_1})$, an inverse gamma, $IG(a_1, b_1)$ and an inverse Wishart, $IW(\boldsymbol{\Psi}_1, \psi_1)$, priors were taken respectively. Also, in the survival process for the coefficients of $\boldsymbol{\beta}_2$, and the coefficients of $\boldsymbol{\gamma}^{(g)}$, a multivariate normal, $N(\mathbf{0}, \boldsymbol{\Sigma}_{\beta_2})$, and a multivariate normal $N(\mathbf{0}, \boldsymbol{\Sigma}_{\gamma})$ priors were taken respectively. Also, for the variance parameter of σ_w^2, and variance-covariance matrix of $\boldsymbol{\Lambda}$, an inverse-gamma, $IG(a_2, b_2)$, and an inverse Wishart, $IW(\boldsymbol{\Psi}_2, \psi_2)$, priors were used respectively. $\boldsymbol{\Psi}_1$ is a 2×2 positive definite matrix and $\boldsymbol{\Psi}_2$ is a $G \times G$ positive definite matrix. ψ_1 and ψ_2 are degrees of freedom. For our proposed model, the posterior distribution is indicated by $\pi(\boldsymbol{\theta} \mid \boldsymbol{Y}, \boldsymbol{C}, \mathbf{X})$, so that

$$\begin{aligned} L(\theta \mid \boldsymbol{Y}, \boldsymbol{C}, \mathbf{X}) \times \pi(\boldsymbol{\beta}_1|\boldsymbol{\Sigma}_{\beta_1}) \times \pi(\sigma^2|a_1, b_1) \times \pi(\boldsymbol{\Sigma}_b|\boldsymbol{\Psi}_1, \psi_1) \times \pi(\boldsymbol{\beta}_2|\boldsymbol{\Sigma}_{\beta_2}) \times \pi(\boldsymbol{\gamma}^{(g)}|\boldsymbol{\Sigma}_{\gamma}) \\ \times \pi(\sigma_w^2|a_2, b_2) \times \pi(\boldsymbol{\Lambda}|\boldsymbol{\Psi}_2, \psi_2). \end{aligned} \tag{18}$$

Statistical analysis and mapping of results were implemented using R package R2OpenBUGS and GeoBUGS software. The OpenBUGS code for the final model of data analysis section was presented in the supplementary material.

We considered two summary measures for model selection as follows: the deviance information criterion (DIC) and the log pseudo-marginal likelihood (LPML). In the Bayesian joint modeling framework, these two criteria are two

well-known Bayesian criteria for comparing models.[40] The DIC criterion depends on the posterior distribution of deviance and an effective number of parameters p_D. The difference in DIC values between models is important. LPML statistic is calculated using the conditional predictive ordinate (*CPO*) statistic, as

$$\text{LPML} = \sum_{ik} \log(CPO_{ik}). \tag{19}$$

A model with a minimum value of DIC and a maximum value of LPML suggests the best model between competing models.

4 | SIMULATION STUDY

Several scenarios were conducted in the first simulation study to evaluate the performance of our model. Scenarios consisted of different levels of sample size ($n_k = 15, n_k = 25, n_k = 50$) and censoring rate (low, medium, and high). In each of these scenarios, the number of 500 datasets was generated. Also, an area contains 16 spatial regions on a 4×4 lattice was assumed for each dataset. With the structure of equal sample sizes in each region, datasets were generated with different levels of total sample size ($n = 240, n = 400, n = 800$). Two covariates were used for generating each dataset. A continuous covariate ($\mathbf{x}_1$) and a binary categorical covariate ($\mathbf{x}_2$) were simulated from a standard normal distribution and a Bernoulli distribution with a success probability of 0.5, respectively. The longitudinal measurements were generated from the following a random intercept and slope linear mixed model

$$Y_{ikj} = \beta_{11} + \beta_{12}\mathrm{x}_{11ik} + \beta_{13}\mathrm{x}_{12ik} + \beta_{14}t_{ikj} + \mathrm{b}_{1ik} + \mathrm{b}_{2ik}t_{ikj} + \varepsilon_{ikj},$$

with the scheduled visit time of $t_{ikj} = (0, 0.05, 0.1, \ldots, 0.5)$. The measurement error was considered as $\varepsilon_{ik}(t_{ikj}) : N(0, 1)$. Also, the regression coefficients were assumed as $\beta_{11} = 1, \beta_{12} = 1, \beta_{13} = 1,$ and $\beta_{14} = 1$. The random effects b_{1ik} and b_{2ik} were generated from a multivariate normal with a mean $\mathbf{0}$ and a 2×2 variance-covariance matrix, $\boldsymbol{\Sigma}_b$, that $\boldsymbol{\Sigma}_{b11} = 1, \boldsymbol{\Sigma}_{b22} = 1,$ and $\boldsymbol{\Sigma}_{b12} = 0.5$, and then were centered around its mean. Two competing risks with constant baseline hazards of 0.2 were simulated for each dataset. The same continuous and binary covariates as used in the longitudinal submodel were also used in the survival submodel. The event time of each individual was generated by total hazard rate.[41] The sum of hazard rates of both events, $\lambda_{ik}(t) = \lambda^{(1)}_{ik}(t) + \lambda^{(2)}_{ik}(t)$, was considered as the total hazard rate. In each region, the hazard rates for two events were considered as follows:

$$\lambda^{(1)}_{ik}(t|\mathbf{x}_{2ik}, \mathrm{b}_{ik}) = \exp(\beta^{(1)}_{21}\mathrm{x}_{2ik1} + \beta^{(1)}_{22}\mathrm{x}_{2ik2} + \gamma^{(1)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik}) + W_k + \delta^{(1)}_k),$$
$$\lambda^{(2)}_{ik}(t|\mathbf{x}_{2ik}, \mathrm{b}_{ik}) = \exp(\beta^{(2)}_{21}\mathrm{x}_{2ik1} + \beta^{(2)}_{22}\mathrm{x}_{2ik2} + \gamma^{(2)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik}) + W_k + \delta^{(2)}_k).$$

Then, the type of event was defined by a Bernoulli trial with the probability $\mathrm{P}_1 = {}^{\lambda^{(1)}}\!/_{\lambda}$ for the event of type 1 and $\mathrm{P}_2 = {}^{\lambda^{(2)}}\!/_{\lambda}$ for the event of type 2. The true values of regression coefficients were supposed as $\beta^{(1)}_{21} = 0.6, \beta^{(1)}_{22} = -0.4$ for risk 1 and $\beta^{(2)}_{21} = -0.3, \beta^{(2)}_{22} = 0.7$ for risk 2. The association between longitudinal and survival processes was generated by setting $V^{(g)}_{ik} = \gamma^{(g)}(\mathrm{b}_{1ik} + \mathrm{b}_{2ik})$. The parameters $\boldsymbol{\gamma}^{(g)}$ were considered as $\gamma^{(1)} = 0.7$ for risk 1 and $\gamma^{(2)} = 0.5$ for risk 2. This setting makes a positive correlation between competing risks and also, a relatively strong correlation between survival and longitudinal processes. The spatial random effects, W_k, from the ICAR distribution were generated that variance parameter was set as $\sigma^2_w = 1$. The spatial-risk interaction effects, $\delta^{(g)}_k$, from the MICAR distribution were generated that variance-covariance matrix of $\boldsymbol{\Lambda}$, was set as $\Lambda_{11} = 1, \Lambda_{22} = 1$ and $\Lambda_{12} = 0.5$. For random effects W_k and $\delta^{(g)}_k$, matrix of $\boldsymbol{\Sigma}^*_w$ was introduced where $\boldsymbol{\Sigma}^*_w = 0.99 \times \boldsymbol{\Sigma}_w + diag(0.01)$, to be invertible their dispersion matrix. Also, for identifiability of random effects, the generated values were centered around their mean. The times above the $(1 - \alpha)$-quantile of sample survival times were considered as censored times. With this setup, the rates of risk 1 and risk 2 were approximately 30% and 50% for low censoring rate, 25% and 35% for medium censoring rate, and also, 15% and 25% for high censoring rate. Longitudinal measurements after observed or censored times were missing. The mean of longitudinal measurements was 8.8, 7.6, and 4.9 per subject for low, medium, and high censoring rates, respectively.

To show the benefits of our proposed model, four models were selected for model comparison in the second simulation study, as follows:

Model I: Separate analysis without spatial and spatial-risk random effects.
Model II: Separate analysis with spatial and spatial-risk random effects.
Model III: Joint analysis without spatial and spatial-risk random effects.
Model IV: Joint analysis with spatial and spatial-risk random effects.

In fact, the first model is the model that accounts for the correlation between repeated measures but neither for the correlation between event times, nor the correlation between longitudinal and event times data, nor the spatial correlation among the regions, and nor the correlation between risks in any given region. The second model is the model that only incorporates the correlation between repeated measures, the spatial correlation among the regions, and the correlation between risks in any given region. The third model is the model that accounts for the correlation between repeated measures, the correlation between competing risks, and also the correlation between longitudinal and event times data. The fourth model is the full model that we proposed in this article and accounts for all correlations in data including correlation between repeated measures, the correlation between event times, the correlation between longitudinal and event times data, the spatial correlation among the regions, and the correlation between risks in any given region.

In this study, we generated 500 datasets with sample size $n = 400$ under low censoring rate using the fourth model, and then we analyzed these datasets with the separate and joint analyses incorporating and ignoring spatial and spatial-risk random effects.

For convergence of the MCMC chain of fitted model, two plots of trace and auto-correlation, and also, Gelman-Rubin's diagnostic test[42] were checked. The last method recommends that two or more parallel chains be generated, each with different starting values. For each MCMC chain, the first 2000 iterations were discarded as a burn-in and 20 000 iterations were retained for the inference. The posterior point estimate, relative bias, mean square error (MSE), and coverage rate (CP) for each parameter were obtained. The relative bias and square error criteria are calculated as:

$$\text{Rel.Bias}(\theta) = \left(\frac{\widehat{\theta}_i}{\theta} - 1\right), \quad \text{SE}(\theta) = (\widehat{\theta}_i - \theta)^2.$$

4.1 | Simulation results

The results of all scenarios in the first simulation study were shown in Tables 1–3. Regarding regression coefficients in the longitudinal and survival components, the estimates in all scenarios were close to true values. However, when the censoring becomes heavier, estimates of the regression coefficients in survival component exhibit slightly larger relative biases toward values larger in magnitude, while those for the parameters in the longitudinal component are robust to the change in censoring rate. Also, our spatial joint model was not robust to varying proportions of censoring in terms of estimates of variance-covariance matrices $\mathbf{\Sigma}_b$ and $\mathbf{\Lambda}$. For example, the covariance matrix $\mathbf{\Sigma}_b$ have relatively biased estimates for censoring rate of 60% under sample size of $n = 240$. The estimates of Λ_{12} exhibit larger relative biases for censoring rate of 60% under all sample sizes. It is worth highlighting that, our proposed model overall performed well in terms of the measurement error variance, σ^2, and the variance parameter of σ_w^2. We note that, the estimate of $\boldsymbol{\gamma}$ were not relatively reliable for the censoring rate of 60% under the sample size of $n = 240$. The results of the first simulation study for our proposed model showed that as the right-censoring becomes heavier, the MSEs for variance parameter of σ_w^2, variance-covariance matrices $\mathbf{\Sigma}_b$ and $\mathbf{\Lambda}$ and other parameters in the survival submodel increase while the MSEs for the regression coefficients and the measurement error variance in the longitudinal submodel are robust to this change. Also, the results showed that as the sample size increases the relative biases and MSEs decrease. Hence, our model has consistency property. Finally, the coverage probability of all parameters of model except $\boldsymbol{\gamma}$ was close to 0.95 for nine scenarios.

The results of the second simulation study were shown in Table 4. In this simulation study, the data were generated from model IV and we wanted to show how the parameters estimates and the MSEs could be affected if the correlations in this model are ignored. In fact, we misspecified models I, II, and III for the survival time by ignoring $\mathbf{b}_{ik}$ or/and $\delta_k^{(g)}$ and W_k. As the results showed models I and II underestimate the time-dependent covariate effect in the longitudinal submodel severely while model IV provides a greater gain in efficiency for the estimators of β_{14}. Also, model IV provided more reliable estimates (less relative bias) for $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}_2$ in survival submodel than other models. Consequently, if random effects of $\mathbf{b}_{ik}$, $\delta_k^{(g)}$, and W_k are not considered, this heterogeneity converts to bias in the fixed effects. The variance-covariance matrix $\mathbf{\Sigma}_b$ and their MSEs were estimated poorer by models I and II than models III and IV. This shows that we can

TABLE 3 Estimation results for the first simulation study with high censoring rate

		$n_k = 15, n = 240$				$n_k = 25, n = 400$				$n_k = 50, n = 800$			
		Estimate	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**	**Estimate**	**Rel. bias**	**MSE**	**CP**
Censoring rate 60%	Longitudinal process												
	$\beta_{11} = 1$	1.006	0.006	0.002	1	0.942	−0.057	0.004	0.998	0.999	0.0001	0.0005	1
	$\beta_{12} = 1$	1.024	0.024	0.001	1	0.987	−0.012	0.001	1	1.022	0.022	0.0006	1
	$\beta_{13} = 1$	0.985	−0.014	0.002	1	1.114	0.114	0.014	0.998	1.004	0.004	0.0007	1
	$\beta_{14} = 1$	1.026	0.026	0.030	0.956	1.010	0.010	0.014	0.980	0.981	−0.018	0.008	0.948
	$\sigma^2 = 1$	1.002	0.002	0.001	0.970	1.002	0.002	0.001	0.948	1.001	0.001	0.0003	0.926
	Survival process												
	Risk 1												
	$\beta_{21}^{(1)} = 0.6$	0.692	0.154	0.044	0.952	0.716	0.194	0.036	0.920	0.653	0.089	0.012	0.950
	$\beta_{22}^{(1)} = -0.4$	−0.525	0.312	0.154	0.985	−0.252	−0.367	0.098	0.990	−0.355	−0.111	0.036	0.984
	$\gamma^{(1)} = 0.7$	0.913	0.305	0.082	0.759	0.871	0.244	0.048	0.764	0.803	0.147	0.018	0.800
	Risk 2												
	$\beta_{21}^{(2)} = -0.3$	−0.287	−0.043	0.031	0.981	−0.256	−0.144	0.014	0.990	−0.276	−0.078	0.007	0.990
	$\beta_{22}^{(2)} = 0.7$	0.788	0.126	0.132	0.941	0.806	0.151	0.069	0.942	0.767	0.095	0.029	0.964
	$\gamma^{(2)} = 0.5$	0.649	0.299	0.044	0.788	0.616	0.232	0.026	0.822	0.560	0.120	0.009	0.854
	Random effects												
	$\Sigma_{b11} = 1$	0.881	−0.118	0.018	0.936	0.952	−0.047	0.005	0.992	0.909	−0.090	0.009	0.816
	$\Sigma_{b22} = 1$	0.726	−0.273	0.139	0.928	0.989	−0.010	0.082	0.972	0.931	−0.068	0.056	0.956
	$\Sigma_{b12} = 0.5$	0.297	−0.404	0.056	0.924	0.477	−0.045	0.014	0.968	0.479	−0.041	0.007	0.966
	$\Lambda_{11} = 1$	1.369	0.369	0.354	1	1.114	0.114	0.100	1	1.175	0.175	0.108	1
	$\Lambda_{22} = 1$	1.285	0.285	0.256	0.996	1.254	0.254	0.193	1	1.181	0.181	0.092	1
	$\Lambda_{12} = 0.5$	0.083	−0.833	0.240	1	0.123	−0.753	0.184	0.998	0.153	−0.693	0.157	0.998
	$\sigma_w^2 = 1$	0.874	−0.125	0.135	0.894	0.762	−0.237	0.134	0.962	1.018	0.018	0.087	0.972

improve the estimation efficiency in the survival process by combing the information of the longitudinal process. Model IV which utilizes information from three components longitudinal, survival, and spatial, had more precise estimates for most parameters than other models based on the MSE criterion. Also, as it was shown in Table 4, the performance of model IV was better with respect to the coverage rates for the most parameters. Finally, the DIC value from four models was close, but for model IV was better.

5 | ANALYSIS OF THE HIV/AIDS DATA

The covariates age ($\mathbf{x}_1$), sex ($\mathbf{x}_2$), co-infection with tuberculosis ($\mathbf{x}_3$), and antiretroviral treatment ($\mathbf{x}_4$) were included in both longitudinal and survival submodels of the spatial joint model (Table 5). For the longitudinal submodel, a linear mixed model was considered as:

$$\sqrt{\text{CD4}}_{ikj} = \beta_{11} + \beta_{12}\text{x}_{1ik} + \beta_{13}\text{x}_{2ik} + \beta_{14}\text{x}_{3ik} + \beta_{15}\text{x}_{4ik} + \beta_{16}t_{ikj} + \text{b}_{1ik} + \text{b}_{2ik}t_{ikj} + \epsilon_{ikj}.$$

The $\sqrt{\text{CD4}}$ measurements after both AIDS and mortality post-HIV infection were considered as non-ignorable missing that these missing values cannot be accounted for in the linear mixed model alone. As our results of simulation showed the separate analysis underestimate the time-dependent covariates effect in the longitudinal submodel severely, which could also be due to violation of the missing-at-random assumption in this analysis.

TABLE 4 Model comparison results based on the second simulation study

	Model I			Model II			Model III			Model IV		
	Rel. bias	**MSE**	**CP**	**Rel. bias**	**MSE**	**CP**	**Rel. bias**	**MSE**	**CP**	**Rel. bias**	**MSE**	**CP**
Longitudinal process												
$\beta_{11} = 1$	−0.030	0.001	1	−0.029	0.001	1	−0.026	0.001	1	−0.023	0.001	1
$\beta_{12} = 1$	0.007	0.0002	1	0.007	0.0003	1	0.008	0.0003	1	0.009	0.0003	1
$\beta_{13} = 1$	0.044	0.003	1	0.044	0.003	1	0.052	0.003	1	0.050	0.003	1
$\beta_{14} = 1$	−0.236	0.068	0.512	−0.236	0.068	0.516	0.067	0.019	0.934	−0.012	0.013	0.964
$\sigma^2 = 1$	0.001	0.0006	0.948	0.001	0.0006	0.946	−0.001	0.0006	0.946	0.0005	0.0006	0.954
Survival process												
Risk 1												
$\beta_{21}^{(1)} = 0.6$	−0.165	0.016	0.786	−0.139	0.013	0.870	0.013	0.009	0.972	0.003	0.009	0.972
$\beta_{22}^{(1)} = -0.4$	−0.010	0.033	0.980	0.034	0.032	0.988	−0.179	0.043	0.998	−0.020	0.047	0.998
$\gamma^{(1)} = 0.7$	–	–	–	–	–	–	0.121	0.015	0.850	0.073	0.010	0.924
Risk 2												
$\beta_{21}^{(2)} = -0.3$	0.047	0.005	0.964	0.047	0.004	0.972	0.059	0.006	0.978	0.037	0.005	0.986
$\beta_{22}^{(2)} = 0.7$	−0.040	0.022	0.954	−0.006	0.022	0.954	0.032	0.025	0.968	0.078	0.027	0.956
$\gamma^{(2)} = 0.5$	–	–	–	–	–	–	0.271	0.025	0.528	0.122	0.008	0.878
Random effects												
$\Sigma_{b11} = 1$	−0.170	0.031	0.484	−0.170	0.031	0.496	−0.153	0.025	0.878	−0.118	0.016	0.942
$\Sigma_{b22} = 1$	−0.200	0.103	0.922	−0.201	0.102	0.924	0.226	0.147	0.916	−0.137	0.077	0.918
$\Sigma_{b12} = 0.5$	−0.336	0.08	0.766	−0.336	0.038	0.754	−0.253	0.029	0.854	−0.102	0.011	0.942
$\Lambda_{11} = 1$	–	–	–	0.032	0.049	1	–	–	–	0.165	0.118	1
$\Lambda_{22} = 1$	–	–	–	0.214	0.123	1	–	–	–	0.163	0.083	1
$\Lambda_{12} = 0.5$	–	–	–	−0.525	0.096	1	–	–	–	−0.505	0.088	1
$\sigma_w^2 = 1$	–	–	–	−0.133	0.095	0.916	–	–	–	−0.061	0.083	0.960
DIC	12 333.72			12 189.98			12 052.22			11 956.80		

Regarding the survival submodel, the conditional cause-specific hazard model for risks of AIDS and mortality post-HIV infection was specified as:

$$h_{ik}^{(1)}(t|\mathbf{x}_{ik}, \mathrm{b}_{ik}) = \exp\left(\beta_{21}^{(1)} + \beta_{22}^{(1)}\mathrm{x}_{1ik} + \beta_{23}^{(1)}\mathrm{x}_{2ik} + \beta_{24}^{(1)}\mathrm{x}_{3ik} + \beta_{25}^{(1)}\mathrm{x}_{4ik} + \sum_{s=1}^{2}\gamma_s^{(1)}\mathrm{b}_{sik} + W_k + \delta_k^{(1)}\right),$$

$$h_{ik}^{(2)}(t|\mathbf{x}_{ik}, \mathrm{b}_{ik}) = \exp\left(\beta_{21}^{(2)} + \beta_{22}^{(2)}\mathrm{x}_{1ik} + \beta_{23}^{(2)}\mathrm{x}_{2ik} + \beta_{24}^{(2)}\mathrm{x}_{3ik} + \beta_{25}^{(2)}\mathrm{x}_{4ik} + \sum_{s=1}^{2}\gamma_s^{(2)}\mathrm{b}_{sik} + W_k + \delta_k^{(2)}\right).$$

We analyzed the HIV/AIDS data using a variety of spatial joint models with different forms for longitudinal, survival, and spatial components. The parameters estimate of the proposed models were obtained using 100 000 iterations following the first 2000 iterations as a burn-in and with a spacing of 5 iterations. Trace, auto-correlation, and history plots were used for checking the convergence the MCMC chains. The same as the simulation study section, two parallel MCMC chains were executed, and the convergence of parameter estimates were examined by Gelman-Rubin's statistics that for all parameters were from 1.0 to 1.1. The mean and SD of all parameters in addition to hazard ratios (HR) for the regression coefficients in survival submodel were obtained.

In order to examine the effect of hyperprior specification, we carried out a sensitivity analysis regarding the prior distribution. The prior distribution for each parameter was changed leaving the rest of parameters with the same distributions

TABLE 5 Demographic characteristics of the study patients by their final outcome

	Alive or lost to follow up		AIDS		Mortality post-HIV infection		Total	
Variable	Number (109)	Percent (27.2)	Number (259)	Percent (64.8)	Number (32)	Percent (8.0)	Number (400)	Percent (100)
Gender								
Male	73	24.5	198	66.4	27	9.1	298	74.5
Female	36	35.3	61	59.8	5	4.9	102	25.5
Age								
0 to 24	19	37.3	27	52.9	5	9.8	51	12.8
25 to 44	81	26.7	197	65.0	25	8.3	303	75.8
45 to 74	9	19.6	35	76.1	2	4.3	46	11.5
Tuberculosis infection								
No	105	28.1	239	63.9	30	8.0	374	93.5
Yes	4	15.4	20	76.9	2	7.7	26	6.5
Antiretroviral therapy								
No	8	28.6	9	32.1	11	39.3	28	7.0
Yes	101	27.2	250	67.2	21	5.6	372	93.0

TABLE 6 Candidate models for the HIV/AIDS data analysis, bold number shows the best fit

Model	Longitudinal component	Survival component	Spatial component	LPML	DIC
I	b_1	$\gamma^{(g)}(b_1)$	–	−2281.36	10 430
II	$b_1 + b_2 t$	$\gamma^{(g)}(b_1 + b_2)$	–	−2306.88	10 410
III	$b_1 + b_2 t$	$\gamma_1^{(g)} b_1 + \gamma_2^{(g)} b_2$	–	−2220.69	9720
IV	b_1	$\gamma^{(g)}(b_1)$	W_k	−2281.19	10 430
V	$b_1 + b_2 t$	$\gamma^{(g)}(b_1 + b_2)$	W_k	−2290.13	10 200
VI	$b_1 + b_2 t$	$\gamma_1^{(g)} b_1 + \gamma_2^{(g)} b_2$	W_k	−2248.83	9912
VII	b_1	$\gamma^{(g)}(b_1)$	$\delta_k^{(g)}$	−2281.59	10 430
VIII	$b_1 + b_2 t$	$\gamma^{(g)}(b_1 + b_2)$	$\delta_k^{(g)}$	−2308.27	10 400
IX	$b_1 + b_2 t$	$\gamma_1^{(g)} b_1 + \gamma_2^{(g)} b_2$	$\delta_k^{(g)}$	−2253.64	9859
X	b_1	$\gamma^{(g)}(b_1)$	$W_k + \delta_k^{(g)}$	−2282.50	10 430
XI	$b_1 + b_2 t$	$\gamma^{(g)}(b_1 + b_2)$	$W_k + \delta_k^{(g)}$	−2296.08	10 280
XII	$b_1 + b_2 t$	$\gamma_1^{(g)} b_1 + \gamma_2^{(g)} b_2$	$W_k + \delta_k^{(g)}$	**−2217.18**	**9632**

in model. We used vague but proper prior distribution as follows: $\boldsymbol{\beta}_1 \sim N(\mathbf{0}, 1000\boldsymbol{I})$; $\boldsymbol{\beta}_2 \sim N(\mathbf{0}, 1000\boldsymbol{I})$; $\boldsymbol{\gamma}^{(g)} \sim N(\mathbf{0}, 1000\boldsymbol{I})$; and $\sigma^2 \sim IG(0.01, 0.01)$. Sensitivity analyses showed that the estimates of these parameters are not affected by the different hyperpriors. Also, for $\boldsymbol{\Sigma}_b$ and $\boldsymbol{\Lambda}$, only $IW(1000\boldsymbol{I}_{2\times2}, 80)$ and $IW(0.1\boldsymbol{I}_{2\times2}, 10)$, respectively, lead to acceptable convergence behavior in HIV/AIDS data. With regard to the prior distribution for σ_w^2, we used different inverse gamma priors, suggested by Silva et al[43] as follows: $IG(0.5, 0.0005)$, $IG(0.001, 0.001)$, $IG(0.01, 0.01)$, $IG(0.1, 0.1)$, $IG(2, 0.001)$, $IG(0.2, 0.0004)$, and $IG(10, 0.25)$. The results showed that prior of $IG(0.5, 0.0005)$ exhibits a pattern of convergence.

Table 6 compared 12 models using DIC and LPML criteria. The criteria both for all models were near, however, model XII that introducing two parameters $\gamma^{(1)}$ and $\gamma^{(2)}$ with spatial and spatial-risk random effects, showed somewhat better criteria values. This could propose spatial effects in the HIV/AIDS data. Also, despite the spatial component, models with intercept and slope random effects as well as two parameters $\gamma^{(1)}$ and $\gamma^{(2)}$ exhibited better comparison measures values. Therefore, model XII is the best spatial joint model and the summary measures of all its parameters were presented in Table 7.

TABLE 7 Posterior estimation results of model XII for the HIV/AIDS data

		$\sqrt{\text{CD4}}$ trajectory		AIDS		Mortality post-HIV infection	
Variable	**Category**	**Mean (SD)**	**(95% credible interval)**	**Mean (SD)**	**Hazard ratio (95% credible interval)**	**Mean (SD)**	**Hazard ratio (95% credible interval)**
Intercept Gender		14.72 (1.32)	(12.15, 17.32)	−2.47 (0.21)	0.08 (0.05, 0.12)	−5.11 (0.63)	0.007 (0.001, 0.01)
Gender							
	Male	Reference					
	Female	0.35 (0.98)	(−1.58, 2.28)	0.17 (0.15)	1.21 (0.87, 1.61)	0.12 (0.56)	1.31 (0.35, 3.28)
Age							
	0 to 24	Reference					
	25 to 44	0.01 (1.26)	(−2.54, 2.44)	0.36 (0.21)	1.47 (0.95, 2.23)	0.18 (0.56)	1.42 (0.42, 4.02)
	45 to 74	1.47 (1.63)	(−1.76, 4.61)	1.10 (0.26)	**3.14 (1.77, 5.15)**	−0.13 (0.96)	1.34 (0.10, 5.14)
Tuberculosis infection							
	No	Reference					
	Yes	−0.17 (1.79)	(−3.71, 3.37)	0.58 (0.24)	**1.85 (1.08, 2.86)**	−0.02 (0.89)	1.39 (0.14, 4.50)
Antiretroviral therapy							
	Yes	Reference					
	No	−1.17 (1.65)	(−4.37, 2.03)	−1.02 (0.35)	0.38 (0.17, 0.69)	1.82 (0.47)	**6.39 (2.49, 15.99)**
Time		0.88 (0.18)	(0.53, 1.25)	–	–	–	–
σ^2	–	40.96 (1.86)	(37.47, 44.77)	–	–	–	–
Σ_{b11}	–	11.27 (1.61)	(8.53, 14.83)	–	–	–	–
Σ_{b12}	–	−1.26 (0.46)	(−2.24, −0.41)	–	–	–	–
Σ_{b22}	–	3.95 (0.32)	(3.36, 4.63)	–	–	–	–
$\gamma_1^{(g)}$	–	–	–	0.06 (0.05)	–	−0.17 (0.15)	–
$\gamma_2^{(g)}$	–	–	–	0.12 (0.07)	–	−0.36 (0.22)	–
Spatial component							
Λ_{11}		0.013 (0.007)	(0.004, 0.037)				
Λ_{12}		−0.0006 (0.005)	(−0.012, 0.011)				
Λ_{22}		0.014 (0.008)	(0.004, 0.037)				
σ_w^2		0.007 (0.024)	(0.0002, 0.059)				

Note: Bold values indicates the confidence interval.

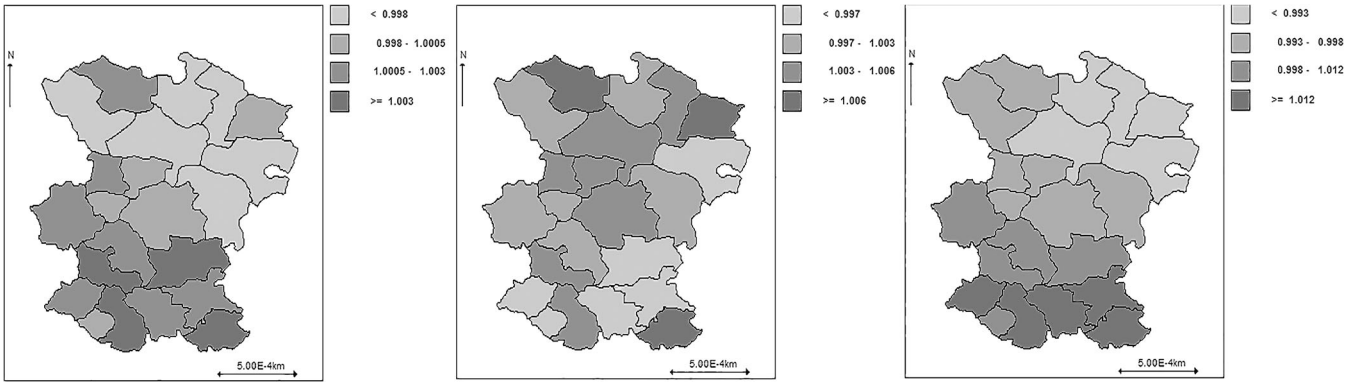

FIGURE 4 Maps of spatial relative risks of both risks (left), spatial relative risks of AIDS (middle), and spatial relative risks of death before AIDS (right) in the HIV/AIDS data based on model XII

The posterior estimates of model XII showed that none of the predictors had a significant effect on the CD4 count mean. Also, based on the HR estimates, the relationships between age at the first visit and TB co-infection with the risk of AIDS were significant. Among independent variables, only antiretroviral therapy had a significant relationship with risk of mortality post-HIV infection. In other words, the risk of AIDS was higher in patients aged above 44 years than patients aged 0 to 24 years. Also, the risk of mortality post-HIV infection was higher in patients who did not receive antiretroviral therapy than those who received antiretroviral therapy, such that the adjusted HR was 6.39. Also, based on the posterior estimates of $\boldsymbol{\gamma}^{(g)}$, the direction of correlation between two risks was inverse. The lower CD4 counts during the follow-up were related to a higher risk of mortality post-HIV infection and a lower risk of AIDS, although these relationships were not significant.

The estimations of spatial-risk interaction, $\delta_k^{(g)}$ were plotted in Figure 3 (right figure). The patterns of both risks between different districts were different, for example in districts of Jowkar and Central that were pointed out in Section 3.2. Also, these estimations were represented in the form of a map in Figure 4. The estimations of spatial relative risk for both risks were represented in the left map ($\exp(W_k)$). In this map, districts in the southeast, south, and southwest regions were with a higher risk (4 out of 22 districts), and districts in the northeast, north, and northwest regions were with a lower risk (6 out of 22 districts). In the following, the spatial-risk interaction term was mapped. The estimations of spatial relative risk for AIDS ($\exp(\delta_k^{(1)})$) and mortality post-HIV infection ($\exp(\delta_k^{(2)})$) were shown in the middle and right maps, respectively. As displayed in Figure 4, for risk of AIDS, three districts with higher risk were in the southeast, northeast, and northwest regions, and six districts with lower risk were in the northwest, southeast, and southwest regions. Also, for risk of mortality post-HIV infection, the high-risk districts were in the south region (4 out of 22 districts) and the low-risk districts were in the north, and northeast regions (5 out of 22 districts).

The values of spatial random effects for both risks, AIDS, and mortality post-HIV infection were in ranges (−0.007, 0.007), (−0.011, 0.005), and (−0.012, 0.012), respectively. Therefore, according to these small values of random effects regional variation had insignificant effects on both risks. The posterior coefficient of correlation between two risks was estimated −0.0003 proposing a weak shared geographical pattern.

6 | DISCUSSION

Over the last decades, in biomedical studies, longitudinal and survival joint modeling has become increasingly popular due to the fact that it is of interest in itself both in terms of the new insight obtained and the data structure. The introduction of spatial random effects in joint modeling adds a new tool for analyzing these data. In this article, we proposed a joint model for longitudinal and spatially clustered competing risks data. According to our knowledge, this proposed model is new in joint analysis and gives some information that would be helpful for health care organizations. Because the understanding of geographical inequalities in the area of HIV/AIDS disease could play an important role in successful surveillance programs and help to prevent new HIV infections.

The censoring mechanism in our survival process was presumed to be non-informative. However, there could be dependent censoring by disease-related or treatment-related dropouts, such as those due to worsening disease. In this

situation, dependent censoring can be treated as one of the G competing risks.[44,45] Also, our model allowed both non-ignorable monotone missing data caused by AIDS or mortality post-HIV infection and ignorable missing data (missing-at-random) at intermittent visit times. Hence, it is possible to have two types of missing data for the longitudinal measurements after the event times in our model. There is also other model framework in the joint modeling literature if, the survival time depends on the true, but unobserved CD4 counts. For example, Gruttola and Tu proposed a linear mixed model for the longitudinal measurements with a log-normal model for the drop-out mechanism that the random effects were included in the drop-out linear predictor.[46] Recently, another study proposed the alternative shared random effect model under missing at random drop out. The proposed model relates drop-out to both the longitudinal data and the random effects.[47]

In HIV disease, when the response is a survival of the patient, there is a terminal outcome (death), and an intermediate nonterminal outcome (AIDS) for a patient. When there is an intermediate nonterminal event in data we are faced with the semi-competing risks data.[48] Hence, HIV/AIDS data could be analyzed by methods for semi-competing risks data that specify dependence between the nonterminal and terminal events times (eg, multistate models). However, if information about the time and type of the first event is considered, then this data could be considered as classical competing risks.[49] Hence, when interest is in the time from HIV infection to AIDS diagnosis, mortality post-HIV infection is a competing risk.[22]

Our simulation studies showed that the performance of proposed model, in which the two outcomes, as well as spatial and spatial-risk random effects, are incorporated simultaneously, was better in terms of efficiency and accuracy of parameters estimation compared to the other models. Furthermore, simulation studies showed that in the joint model efficiency of random effects estimation in the survival submodel is improved. Also, the results of these studies showed that some parameters estimations were poorly affected by the censoring rate. Nevertheless, as the sample size increased, the estimates were slightly improved. Hence, our proposed model is a promising choice with a reasonable number of subjects in each region.

For our HIV/AIDS data, the trajectory of $\sqrt{\text{CD4}}$ measurements was better captured by both intercept and slope random effects. Also, the adjusted relationships for the CD4 count mean were not statistically significant for all independent variables. According to the posterior estimates of adjusted HR, there were significant associations between age at the first visit and TB co-infection with the risk of AIDS. Also, there was a significant association between antiretroviral therapy with risk of mortality post-HIV infection.

There are some limitations in this study that should be mentioned. First, the geostatistical frailty model was not used because the exact geographic areas were not available in our dataset. Second, our HIV/AIDS dataset was for one Province in Iran and unfortunately, we did not have access to the HIV/AIDS dataset at the country-level.

Finally, there are some ways that our spatial joint model could be extended. First, in this article, a parametric proportional hazard model was assumed for both risks, but a semiparametric model within the proportional odds structure can be used. Second, the t distribution for measurement errors can be examined instead of a normal distribution to account for a long tail. Third, in our spatial joint model, the linear mixed submodel could be developed to the multivariate and generalized linear mixed effects model. Fourth, our proposed model could be developed to the survival data with semi-competing risks. Several models for analyzing the clustered semi-competing risks data were proposed in literature.[50,51] More recently, Zhang et al.[52] proposed a Bayesian joint modeling of longitudinal and semi-competing risks data.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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