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Introduction

Human Immunode ciency Virus (HIV) remains a signi - cant public health concern globally. According to WHO since the beginning of the epidemic, 85.6 million people have been infected with the Human Immunode ciency Virus (HIV), and about 40.4 million people have died of HIV. Globally, 39.0 million people were living with HIV at the end of 2022. HIV is also a public health challenge in Iran. According to the latest estimates of the United Nations Program on HIV/AIDS (UNAIDS), a total of 54,000 people were living with HIV, and 3200 people died of HIV at the end of 2020 in IRAN [1]. HIV is an infection that attacks the body's immune system, speci cally the white blood cells called CD4 cells. e CD4 count measures how many CD4 cells are present in a person's blood. A normal CD4 count in a healthy adult ranges from 500 to 1,500 cells per cubic millimeter of blood. HIV is considered to have progressed to AIDS (Acquired Immunode ciency Syndrome) when the CD4 count drops below 200 cells per cubic millimeter of blood. Monitoring CD4 counts is an important part of managing HIV infection. Low CD4 counts indicate a weakened immune system and an increased risk of opportunistic infections [2].

One of the important biomarkers that indicate the weakness of the body's immune system is the number of CD4 cells in a blood sample. Examining and testing the number of CD4 cells and their changes over time is related to the progress of HIV and the death of HIV-infected. It should be noted that the decrease in the number of cells over time can be a sign of deterioration and weakening of the immune system of HIV-infected persons [3, 4]. Observed and follow-up of patients are common in many studies. In these studies, longitudinal measurements were recorded until the time to event of interest and the time origin (baseline) was de ned as the time of HIV diagnosis. In many studies, longitudinal and time-to-event responses have been used separately. However, it should be noted that these two responses are related, and modeling them separately can lead to biased results and estimates because such an analysis ignores the association between longitudinal and time-to-event responses. erefore, the joint modeling of longitudinal and time-to-event responses can lead to unbiased estimates of the parameters describing both processes. In HIV studies, repeated measurements of the CD4 cell count and time of death are always recorded. As mentioned, the CD4 count is the most important clinical measure that indicates disease progression in HIV/AIDS patients earlier than disease or death. erefore, a joint model was used to consider the dependence between longitudinal and time-to-event responses [5, 6].

Modeling longitudinal and time-to-event data jointly assumes that the longitudinal outcome o ers extra insights into the risk of event occurrence, gaining popularity in the medical eld over recent decades. Joint models handle the relationship at the individual level and relate the longitudinal and survival components. is approach allows for the simultaneous analysis of repeated measurements of an outcome and time-to-event data in a single model. One of the key advantages of joint modeling is that it can account for the interdependence between the longitudinal and survival outcomes, allowing for a more e cient and accurate estimation of the e ects of covariates on both outcomes. is can lead to more precise estimates of the risk factors associated with disease progression and mortality in HIV patients. In this study, we explored factors associated with survival time in HIV-infected individuals using a Bayesian joint model.

Methods

Data collection

In this study, we used the information of patients who were infected with HIV in Fars Province, from June 29, 2011, to March 15, 2016, and they were followed up until May 12, 2022. Demographic and clinical characteristics of patients in the study such as gender, marital status, age, and co-infection with hepatitis B virus (HBV) have

denote the $n_i \times 1$ longitudinal response vector for the ith subject, with element Y_{ij} denoting the value of the longitudinal outcome taken at time point t_{ij}. e distribution of Y_i is

$$Y \sim Negative\,binomial(\lambda\ , \lambda\ + \frac{\lambda}{\theta}^{2})$$

- Mean: λ_i
- Variance: $\lambda_i + \frac{\lambda_i^2}{\theta}$,

where θ is the dispersion parameter. λ_i depends on the covariates via logarithmic link function as:

$$log\,(\lambda_i|b\ ) = x^t\,(t)\,\beta\ (t) + z^T b\ = \eta\ \ (t)$$

$x_i\,(t)$ and $z_i\,(t)$ denote the design vectors for the xed e ects β and the random e ects b_i, respectively. e random e ects are assumed to follow a multivariate normal distribution with mean zero and variance-covariance matrix **D**.

The survival sub-model

For the survival process, we assume that the risk for an event depends on a function of the subject-speci c linear predictor $\eta_i\,(t)$. More speci cally, we have

$$h\ \ (t) = h\ \ (t)\,exp\{w^T\,(t)\ \gamma\ + f\ \{\eta\ \ (t)\}\,\alpha\ \}$$

$h_0\,(t)$ denotes the baseline hazard function, $w_i\,(t)$ is a vector of exogenous, possi2 260>>B7 4.326812754 58.a 5 Tf ET10(ivy-10(al)]TJ2)-1210(ar)-8(i)-4.9(a)9(t)6(e)-7(s v)-10(i)EMC

Table 1 Demographic and clinical characteristics of patients in the study

Years	2011	2012	2013	2014	2015	2016	Total
No. of cases	110	144	159	132	167	43	755
No. of Death (Until 2022)	35	45	50	36	35	11	212(28.0%)
1-year survival (95% CI)	89% (83%, 95%)	94% (91%, 98%)	86% (81%, 92%)	91% (86%, 96%)	93% (90%, 97%)	91% (82%, 100%)	91% (89%, 93%)
5-year survival (95% CI)	78% (71%, 86%)	81% (74%,87%)	76% (69%, 83%)	78% (71%,85%)	84% (79%, 90%)	79% (68%, 92%)	79% (77%, 82%)
Age							
1st Qu.	27	29	28	30	30	34	29
Median	35	33	34	35	35	37	34
3rd Qu.	39	38	39	41	43	44	40
Gender							
Male	79	103	107	87	108	28	512(67.8%)
Female	31	41	52	45	59	15	243(32.2%)
Marital status							
Married	50	62	72	54			

longitudinal CD4 count measurements revealed that addiction was signi cantly associated with a decrease in CD4 count ($P < 0.0001$). Age showed a marginally almost signi cant negative e ect on CD4 count ($P = 0.0616$) and being a man ($P = 0.0358$) were associated with a decreased count of CD4 cells signi cantly.

Discussion

is research employed a Bayesian joint model to explore the relationship between the risk of mortality and the longitudinal changes in the CD4 biomarker, aiming to identify the factors in uencing the survival of individuals infected with HIV. e joint model revealed a signi cant

correlation between CD4 cell counts and mortality risk, indicating that a one-unit decrease in the Log(CD4) is associated with a 5.64-fold increase in the risk for death.

is nding aligns with a 2019 study conducted in North-West Ethiopia, which utilized joint latent class modeling to assess the survival of HIV-positive individuals based on CD4 cell counts and time-to-death [7]. ey revealed that the risk of death hinged on longitudinal CD4 counts. In another study carried out in 2019 in Iran, the result show that the joint model provided a exible framework for simultaneous studying of the e ects of covariates on the level of CD4 cell count and the risk of progression to TB and AIDS. is model also assessed the e ect of CD4 trajectory on the hazards of competing events [8].

According to the result of the joint model, in the survival sub-model: age, addiction and Hepatitis B, were statistically signi cant on the risk of death at a 95% con dence level. ese results are in line with a study conducted in 2017 in Fars province in Iran, they used Time-varying Cox regression analyses, the ndings of this study implied that some variables could play the role of risk factors in HIV patients, and shorten the patient's life span e.g. older age, female gender, unemployment, delay in HIV diagnosis, drug injection, and higher Hemoglobin levels [9].

Our nding indicates that age is associated with changes in CD4 cell counts over time. A study employing joint modeling techniques found that age, along with other factors such as weight and antiretroviral therapy

times the risk of death in females. Similarly, this result is in agreement with those observed in earlier studies [12].

progression, and treatment outcomes. Women and men often experience di erent immunological responses,

In our joint model analysis, hepatitis B infection was found to signi cantly increase the risk of mortality among HIV patients. However, its e ect on CD4 cell count in the longitudinal component of the model was not statistically signi cant. e risk of death for those with Hepatitis B was exp(0.5635) = 1.75 times that of those without hepatitis B. From a clinical perspective, hepatitis B increases the risk of AIDS or death in newly diagnosed patients, highlighting the importance of considering it as a signi cant risk factor for mortality in HIV patients, regardless of its impact on CD4 counts. e ndings were in alignment with earlier studies [17, 18].

In this study, a joint model was used to analyze the longitudinal CD4 cell count and the survival time data. e association parameter between the longitudinal and survival components was statistically signi cant. is signi cance suggests a strong association between the CD4 cell count and the survival time of HIV patients. Patients with higher CD4 cell counts have better survival prospects compared to those with lower CD4 cell counts.

Previous studies have shown that joint models in contrast to separate models can lead to unbiased and more e cient estimates of parameters [19, 20]. e use of the joint model allows for a more comprehensive understanding of the factors in uencing both the CD4 cell count and survival time, compared to using separate models. One notable limitation of this study is the absence of data regarding the antiretroviral therapy (ART) provided to the patients included in the analysis. is lack of information restricts our ability to fully understand the impact of ART on the outcomes observed.

Another limitation of this study is related to the selection of the time of HIV diagnosis as the baseline (time origin) for the analysis. While this approach allowed us to capture valuable longitudinal information on CD4 counts and other variables from the time of diagnosis, it does not account for the potential in uence of ART initiation timing. Given the changes in ART initiation protocols over the past decade ranging from initiating ART only for CD4 counts below 300 or 500 to the current universal initiation immediately after diagnosis the timing of ART initiation varied signi cantly among participants in Iran. Using ART initiation as the time origin might have provided a more precise perspective on the e ect of ART on CD4 trajectories. is limitation may a ect the interpretation of CD4 trajectories, as ART initiation is known to signi cantly in uence CD4 recovery. Consequently, our results likely re ect a combination of natural disease progression and the e ects of ART, which could not be disentangled in this analysis. Without detailed ART data, covariate group di erences in CD4 counts may also be confounded by di erences in ART initiation timing, as individuals with lower CD4 counts might have initiated ART earlier according to WHO guidelines. Future studies

Declarations

Ethics approval and consent to participate
This study utilized secondary data collected from the HIV/AIDS care system