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Original Article

Bayesian Joint Modeling of Longitudinal Pattern of WT1 Gene Expression and Survival Time in AML Patients

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Abstract

Introduction: Acute Myeloid Leukemia (AML) is a malignant hematologic neoplasm with an unfavorable prognosis. The Wilms' tumor gene (*WT1*) is a key prognostic biomarker in AML, showing longitudinal patterns that may predict survival outcomes after transplantation. This study aimed to jointly model the longitudinal changes in the *WT1* gene expression and the survival time of AML patients using a Bayesian approach.

Methods: This retrospective cohort study used data from 319 AML patients who underwent allo-HSCT and were followed up between 2008 and 2019 at the Hematology Clinic of Shariati Hospital in Tehran. For data analysis using Bayesian joint longitudinal and survival modeling, a random effects model was used for the longitudinal submodel, and a generalized hazard regression model with a Burr XII (BXII) baseline hazard function was used for the survival submodel.

Results: Results demonstrated that a higher baseline *WT1* level was significantly associated with reduced survival, increasing the hazard of death by 47.4% (HR = 1.474, 95% CI: 1.325-2.052). The longitudinal submodel revealed that *WT1* expression significantly increased by 0.169 times in patients with acute Graft-versus-Host Disease (aGVHD) and by 1.103 times in those who relapsed. The survival submodel confirmed that increased age (HR = 1.309), disease relapse (HR = 1.955), and donor type other relative and unrelated compared to sibling (HR = 1.975 and HR = 1.479, respectively) were predictors of worse survival.

Conclusion: In conclusion, elevated *WT1* expression at transplantation is a critical negative prognostic indicator in AML. Monitoring this biomarker helps identify high risk patients and can guide pre-transplant therapeutic strategies to improve survival outcomes.

Keywords: Acute Myeloid Leukemia, Bayesian approach, Hazard function, Joint model, Longitudinal, Survival

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Introduction

Acute Myeloid Leukemia (AML) is the most common adult leukemia, characterized by substantial heterogeneity that complicates prognosis and treatment planning. Given the high relapse rate, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended for many patients to reduce relapse risk and improve overall surviva.[1-3]

Transplantation outcomes are influenced by a complex interplay of patient and donor-related factors. Despite advances in transplantation, post-transplant complications, particularly acute graft-versus-host disease (aGVHD), remain significant challenges.[1] Established prognostic factors include recipient age and sex, donor-recipient sex matching, disease status at transplantation, relapse, and GVHD occurrence.[4-7]

The Wilms tumor 1 (*WT1*) gene has emerged as a key prognostic biomarker in AML. Elevated *WT1* expression in leukemic blasts identifies high-risk patients and correlates with adverse clinical outcomes.[8-10] Importantly, longitudinal patterns of *WT1* expression may provide dynamic information about post-transplant survival. However, effectively analyzing repeated *WT1* measurements alongside time-to-event outcomes requires sophisticated statistical methods that can account for the inherent relationship between these two processes.

Joint longitudinal-survival modeling offers an ideal analytical framework, enabling simultaneous assessment of biomarker trajectories and their association with clinical events.[11,12] This approach is particularly valuable in AML,

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where survival distributions are often right-skewed and a subset of patients experiences short-term mortality while others achieve long-term remission.[13,14] For the survival component, we employed a parametric regression model within the general hazard (GH) framework, which encompasses proportional hazards, accelerated failure time, and additive hazards models as special cases.[15] To capture the complex hazard patterns characteristic of AML, we utilized the three-parameter Burr XII (BXII) distribution for the baseline hazard. Unlike conventional distributions (e.g. Weibull, exponential), the BXII distribution's two shape parameters accommodate diverse hazard shapes including monotonic and unimodal patterns making it particularly suitable for modeling the long tails and skewness observed in cancer survival data.[16-20] Bayesian estimation offers distinct advantages for joint models, including avoidance of high-dimensional integration, incorporation of prior information, and straightforward implementation using freely available software without reliance on asymptotic approximations.[16] The Bayesian framework also provides full posterior distributions for all parameters, enabling more intuitive clinical interpretation.

Accordingly, this study aimed to jointly model longitudinal *WT1* expression trajectories and post-transplant survival in AML patients using a Bayesian approach with a GH survival submodel and BXII baseline hazard, to better understand the dynamic prognostic value of *WT1* and inform clinical decision making.

Materials and Methods

Data Description

This retrospective cohort study used data from the Hematology-Oncology and Stem Cell Research Center at Shariati Hospital, Tehran, Iran (affiliated with Tehran University of Medical Sciences). The study population included adult AML patients who attended the Hematology Clinic between 2008 and 2019, underwent allo-HSCT, and were followed up until the end of 2022. According to institutional protocols, all patients included were in complete remission (CR) and underwent their first allo-HSCT. Most patients received a myeloablative conditioning regimen of busulfan and cyclophosphamide (BuCy), while a few received a fludarabine based regimen. Based on the follow-up status at the end of 2022, patients who were alive or lost to follow-up were treated as censored cases, while those with documented death were considered events. A total of 405 patients were initially identified. After excluding 75 patients with missing data, seven patients diagnosed with acute promyelocytic leukemia (APL), and four non-Iranian patients, complete data from 319 patients were analyzed. As this is a retrospective cohort study, the sample size was determined by data availability rather than a priori power calculation.

WT1 expression levels were measured in peripheral blood samples collected at multiple time points throughout follow-up by quantitative real-time polymerase chain reaction (PCR). The ABL housekeeping gene was used for normalization, and *WT1* expression levels were reported as (*WT1* copies/10^4 ABL copies). Peripheral blood was selected as the sample source due to its suitability for routine, minimally invasive minimal residual disease (MRD) monitoring in AML patients.

The baseline measurement was obtained just prior to transplantation, defining time-zero for both the survival analysis and the start of the longitudinal trajectory. Subsequent measurements were performed at variable intervals as part of routine clinical follow up, with the timing of assessments determined by clinical visits rather than a fixed protocol. The number of longitudinal measurements per patient ranged from 1 to 13, reflecting differences in follow-up duration and visit frequency across individuals. This irregular measurement schedule is appropriately handled by the random effects structure of the joint model, which accommodates unbalanced longitudinal data.

Due to the skewed distribution of *WT1*, a logarithmic transformation was applied, and normality of the transformed values was confirmed by summary statistics (mean, median, skewness, kurtosis) and graphical methods (boxplots and histograms). The survival outcome was defined as the time in months from allo-HSCT to death from AML or last known follow-up, with deaths from other causes treated as right censored events.

Independent covariates extracted from medical records and prepared forms included:

- recipient age at diagnosis (years),
- donor–recipient sex match,
- donor type (sibling, other relative, unrelated),
- aGVHD status,
- remission phase (CRI/CRII),
- diagnostic time to allo-HSCT (years),
- CD3 and CD34 cell counts.

The selection of covariates was primarily hypothesis driven, based on established clinical and prognostic factors in AML and allo-HSCT literature, rather than a purely data driven algorithm. Variables included in both submodels (age, aGVHD, relapse, disease status, donor type, sex matching, CD3, CD34) were chosen *a priori* because they are well-known predictors of survival in AML patients. This approach ensures clinical relevance and avoids the pitfalls of stepwise selection methods, such as overfitting and instability, which are particularly problematic in complex models like joint models.

Joint Longitudinal and Survival Model

Joint longitudinal and survival models allow simultaneous and integrated examination of longitudinal data and time-to-event outcomes, considering the intrinsic relationship between these two processes. The theoretical foundations of joint model analysis are presented in.[21-23] These models are based on a key assumption: the conditional independence of the longitudinal and survival processes given the shared random effects. In practice, these random effects capture the within-cluster correlation in the longitudinal data and model the dynamic association between the longitudinal trajectory of biomarkers and the hazard of the event of interest. For this reason, this approach is also known as

the shared parameter model.

The structure of joint models consists of two main components:

1. Longitudinal submodel, which describes the temporal evolution of longitudinal outcomes,
2. Survival submodel, which models the time-to-event process.

Longitudinal Submodel

For the longitudinal submodel, we assume that $y_{ij} = y_i(t_j)$ is the longitudinal response variable ($WT1_{ij}$) where the *WT1* response for the ith individual i = 1,…, n is measured at time t_j j = 1,…, n_i. We also assume that x_i is the vector of independent variables for each individual. Over time, we used a random effects model:

$$y_i(t_{ij} \mid \theta_1) = m_i(t_{ij}) + \varepsilon_{ij},\ \varepsilon_{ij} \sim Normal(0, \sigma^2)$$

$$m_i(t_{ij}) = \tilde{\beta}_0 + \tilde{\beta}_1 t_{ij} + \beta X_{ij}^T + b_{0i} + b_{1i} t_{ij},\quad b_i \sim N(0, D)$$

Where $\tilde{\beta}_0$ is the intercept, $\tilde{\beta}_1$ is the slope for time points, X_{ij}^T is a vector of (possibly time-varying) covariates with coefficient vector β, and $b_i = (b_{0i}, b_{1i})^T$ is the vector of subject-specific random effects. The random effects are assumed to follow a bivariate normal distribution with mean zero and variance-covariance matrix D (often parameterized via a Cholesky decomposition), where b_{0i} is the random intercept and b_{1i} is the random slope for time. This model naturally manages unequal intervals of longitudinal measurements. The error term ε_{ij} is independent of b_i and follows a normal distribution with variance variance σ^2.

Survival Submodel

This study used the General Hazard structure to model the survival process.[15] We assume $h_0(.|\theta)$ is a parametric baseline hazard function with parameter θ, then we define the hazard function as follows:

$$h(t \mid \psi_{2i}) = h_0(t \exp\{\alpha_1 b_{1i}\} \mid \theta) \exp\left(\beta X_{ij}^T + \alpha_0 b_{0i}\right)$$

where t > 0 represents survival time, $X_i(t)$ is the vector of potentially time-dependent covariates for patient *i* with corresponding regression coefficients **β**. The terms $b_{0i}, and\ b_{1i}$ are the patient-specific random intercept and random slope, respectively, shared from the longitudinal submodel. The parameters α_0 and α_1 are association parameters that link the two submodels: α_0 quantifies the association between the patient-specific baseline *WT1* level (b_{0i}) and the log-hazard of death, while α_1 quantifies the association between the patient-specific rate of change in *WT1* (b_{1i}) and the log-hazard, with α_1 also allowing for a time-acceleration effect via the term $\exp(\alpha_1 b_{1i})$ in the time scale of the baseline hazard. The complete vector of model parameters for patient *i* is denoted as $\psi_{2i}^T = (\theta^T, \beta^T, b_i^T, \alpha_0, \alpha_1)$. Thus, the two submodels are linked through the shared random effects and association parameters, capturing the interdependence between the longitudinal biomarker trajectory and the survival outcome.

The BXII distribution was also used to model the baseline hazard function, whose hazard and survival functions are as follows:

- Survival function of the BXII distribution:

$$S_{BXII}(t; \nu, \delta) = \left(1 + t^{\nu}\right)^{-\delta}$$

- Hazard function of the BXII distribution is as follows:

$$h_{BXII}(t) = \nu\delta t^{\nu-1}\left(1 + t^{\nu}\right)^{-1}$$

Where t > 0 represents survival time, $\nu > 0$, and $\delta > 0$ are also the shape parameters of the BXII distribution. Accordingly, the final longitudinal model fitted to the data of AML patients is as follows:

$$y_i(t) = \tilde{\beta}_0 + \tilde{\beta}_1 t + \beta_1 age + \beta_2 diag_{HSCT} + \beta_3 aGVHD + \beta_4 relapse + \beta_5 diseasestatus + \beta_6 donortype + \beta_7 sexmatching + \beta_8 CD3cells + \beta_9 CD34cells + b_{0i} + b_{1i} t + \varepsilon_i(t)$$

Where yi(t) is the longitudinal response of the logarithm of the *WT1* gene expression level and ϵi(t)∼N(0, σ2). The survival model fitted to the data of AML patients is as follows:

$$h(t \mid \psi_i) = h_{0BXII}(t \exp\{\alpha_1 b_{1i}\} \mid \theta) \exp\left\{\begin{array}{l}\lambda_1 age + \lambda_2 diag_{HSCT} + \lambda_3 aGVHD + \lambda_4 relapse + \lambda_5 diseasestatus + \\ \lambda_6 donortype + \lambda_7 sexmatching + \lambda_8 CD3cells + \lambda_9 CD34cells + \alpha_0 b_{0i}\end{array}\right\}$$

Statistical Analysis

Data were initially analyzed descriptively, using mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Patient survival was estimated using Kaplan–Meier (KM) curves, and the Log-rank test was applied to compare survival probabilities between groups.

The Bayesian framework was selected for this joint modeling application due to its distinct advantages in handling complex data structures and providing more comprehensive inference.[16] Joint models involve high-dimensional random effects and intricate likelihoods that pose computational challenges for frequentist methods, which rely on numerical integration techniques that can be unstable or prohibitive. Bayesian estimation via Markov Chain Monte Carlo (MCMC) sampling circumvents these difficulties by drawing samples directly from the posterior distribution, offering greater numerical stability and modeling flexibility. Moreover, the Bayesian paradigm provides full posterior distributions for all parameters, enabling more intuitive probabilistic interpretations such as the probability that a hazard ratio exceeds a clinically meaningful threshold without relying on asymptotic approximations.[16,24] This framework also readily accommodates the complex parametric forms required for our analysis, specifically the generalized hazard structure with a Burr XII baseline distribution, which is essential for capturing the diverse hazard shapes observed in AML survival data.

For prior specification, we employed weakly informative and non-informative priors to ensure that posterior

inferences are driven primarily by the observed data while maintaining computational stability. Weakly informative priors provide minimal regularization that helps stabilize estimation, particularly for variance components and complex model parameters, without imposing strong prior beliefs. Non-informative priors allow the data to dominate the posterior distribution, ensuring that our results are not materially influenced by subjective prior choices. This approach aligns with standard Bayesian practice for complex models, where the goal is to let the empirical evidence speak while benefiting from the computational advantages that even weak priors afford in MCMC estimation.[16]

The linearity assumption for continuous predictors (age and diagnostic time to HSCT) was assessed in both submodels. For the longitudinal submodel, residuals from the linear mixed model were plotted against the predictors, and no systematic patterns were detected. For the survival submodel, Martingale residuals from a Cox model were plotted against the continuous covariates; smoothed curves did not indicate any significant departure from linearity. Based on these assessments, the linearity assumption was considered reasonable for all continuous predictors.

Patients were followed over the interval (0, T), where the *i*th patient contributed a series of longitudinal *WT1* expression measurements (*Yij*), collected at 1 to 13 follow up visits. The survival time of interest was defined as the duration from transplantation to death or last follow-up.

For the joint analysis, weakly informative and non-informative priors were applied. Specifically:

- A Gamma(10,10) prior was assumed for the shape parameters of the Burr XII (BXII) baseline hazard distribution.
- Regression coefficients in longitudinal and survival submodels were assigned Normal(0, 1000) priors.
- Error variance was modeled with an Inverse-Gamma(0.01, 0.01) prior, while random effect variances used an Inverse-Gamma(0.1, 0.1) prior.
- For the correlation structure of random effects, an LKJ(1) prior (Lewandowski–Kurowicka–Joe distribution with df = 1) was adopted.

Posterior sampling was performed using the MCMC algorithm with 20000 iterations, a burnin of 5000, and three parallel chains. Convergence was assessed via trace plots, autocorrelation plots, the effective sample size (N_eff ≥ 100 considered adequate), and the ($\hat{R}$) potential scale reduction factor (with values < 1.10 deemed acceptable, according to Gelman's recommendation.[25]) All analyses were conducted in R using the RStan package.

Results

Descriptive Results

In this Bayesian joint longitudinal–survival study, 319 AML patients were included. The mean age at transplantation was 38.51 ± 12.25 years with a median of 37.4 years (IQR: 29.9–48.0). The mean follow-up time was 32.4 ± 25.50 months, and the median follow-up time for the entire cohort was 28.2 months (IQR: 10.15–50.79 months). The mean time from diagnosis to transplantation was 9.2 ± 6.5 months, with a median of 7.7 months (IQR: 5.4–11.1). The primary event of interest was death attributable to acute myeloid leukemia; deaths from other causes were regarded as right-censored observations. The overall censoring proportion was 74.9% (239 of 319 patients). The one-year survival probability was 83% (95% CI: 78-87), two-year survival was 78% (95% CI: 72-82), five-year survival was 69% (95% CI: 63-75), and ten-year survival was 62% (95% CI: 50-72). The median *WT1* expression level was 27.1×10^4 copies/ ABL copies (IQR: 10.1–120.6). Due to the right-skewed distribution characteristic of biomarker data, the mean was substantially higher at $471.6 \pm 1198.6 \times 10^4$ copies/ABL copies. After logarithmic transformation, the median log(*WT1*) was 3.30 (IQR: 2.31–4.79) and the mean was 3.69 ± 2.19.

In this study, 191 patients (59.9%) were male, 71 (22.3%) experienced relapse, and 117 (36.7%) also experienced aGVHD. During follow-up, 76.49% of patients were in CRI status; 85% of donors were siblings, and 37% of donor–recipient pairs were male–male. Among those who died, 52.5% had CD3 counts > 284, and 65% had CD34 counts > 1.5. Descriptive characteristics of all prognostic factors are summarized in Table 1.

The Kaplan-Meier curves for overall survival and survival by aGVHD, disease relapse, disease status, donor type, recipient-donor sex match, CD3, and CD34 cell levels are presented in Figure 1. The p-values of the log-rank test between the examined groups are provided in each chart.

Figure 2 shows the individual profile plot of the longitudinal trend of *WT1* in AML patients. This figure shows the changes in *WT1* over time and provides information on the variability between *WT1* values. This figure indicates that some patients show an increase in *WT1* gene expression level, while others show unpredictable patterns.

Results of Bayesian Joint Longitudinal–Survival Modeling

The Bayesian joint longitudinal–survival model results examining the association between *WT1* expression and survival time in AML patients after allo-HSCT are summarized in Tables 2 and 3. In the longitudinal submodel, the outcome variable is the log-transformed *WT1* expression. A regression coefficient is considered statistically significant if its 95% Bayesian credible interval (CrI) does not include zero; otherwise, it is considered insignificant. In the survival submodel, the outcome is the hazard ratio (HR) for time-to-event. A covariate is considered statistically significant if the 95% CrI for the HR does not include 1, and not significant if the CrI includes 1. This criterion allows consistent interpretation of significance for both the longitudinal and survival submodels within the Bayesian joint modeling framework.

Longitudinal Submodel Results

In the longitudinal submodel, the posterior mean baseline log(*WT1*) level was 3.442, with an associated random intercept variance of 1.062. The posterior mean slope for

Table 1. Frequency Distribution of Independent Variables with Censored Observations After Allo-HSCT

Variables	Group	Censored	Event	Total
		n (%)	n (%)	n (%)
aGVHD	Yes	92 (38.49)	25 (31.25)	117 (36.68)
	No	147 (61.51)	55 (68.75)	202 (63.32)
Relapse	Yes	40 (16.74)	31 (38.75)	71 (22.26)
	No	199 (83.26)	49 (61.25)	248 (77.74)
Disease status	CRI	186 (77.82)	58 (72.50)	244 (76.49)
	CRII	53 (22.18)	22 (27.50)	75 (23.51)
Donor type	Sibling	208 (87.03)	63 (78.75)	271 (84.95)
	Other relative	13 (5.44)	8 (10.00)	21 (6.58)
	Unrelated	18 (7.53)	9 (11.25)	27 (8.46)
Sex matching (recipient-donor)	Male - Male	91 (38.08)	27 (33.75)	118 (36.99)
	Male -Female	58 (24.27)	15 (18.75)	73 (22.88)
	Female - Male	49 (20.50)	22 (27.50)	71 (22.26)
	Female - Female	41 (17.15)	16 (20.00)	57 (22.88)
CD3 cells	<284	125 (52.03)	38 (47.50)	163 (51.10)
	>284	114 (47.70)	42 (52.50)	156 (48.90)
CD34 cells	<5.1	87 (36.40)	28 (35.00)	115 (36.05)
	>5.1	152 (63.60)	52 (65.00)	204 (63.95)
		Mean ± SD	Mean ± SD	Mean ± SD
Age (year)		37.74 ± 12.09	40.60 ± 12.56	38.46 ± 12.25
Diagnostic time to Allo-HSCT (months)		9.57 ± 7.11	9.09 ± 6.23	9.21 ± 6.45

log(*WT1*) was approximately -0.003, indicating a slight decline in the mean trajectory over time; however, this decrease was not statistically significant (95% CI: -0.007 to 0.010). The variance of the random slope was 0.023, indicating substantial between-individual variability in the rate of change of *WT1* expression. A negative correlation was observed between baseline *WT1* levels and their rate of change (P = -0.579, 95% CI: -0.812 to 0.387), suggesting that higher baseline *WT1* values may be associated with steeper subsequent declines. However, the wide credible interval includes positive values and indicates substantial heterogeneity across patients, with some showing the expected inverse association while others demonstrated stable or even increasing trajectories.

After adjusting for covariates, patients with aGVHD showed an increase of 0.169 in log(*WT1*) compared to those without aGVHD (95% CI: 0.045–0.527), corresponding to approximately an 18% increase in *WT1* expression on the original scale. Similarly, patients who experienced relapse showed an increase of 1.103 in log(*WT1*) compared to those without relapse (95% CI: 0.968–1.504), corresponding to approximately a threefold increase (201%) in *WT1* expression on the original scale (Table 2).

Survival Submodel Results

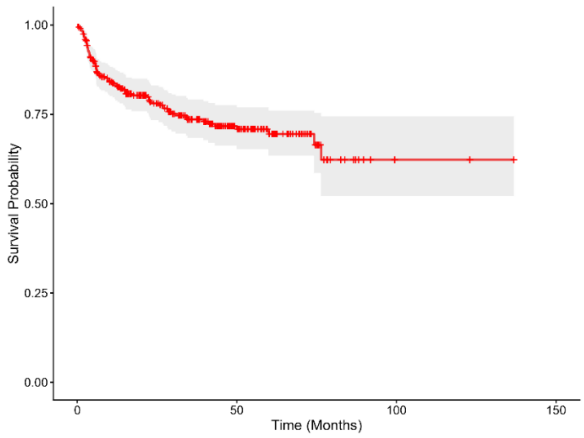
In the survival submodel, older age, relapse, and donor type were significantly associated with increased mortality risk. Each additional year of age increased the hazard of death by 30.9% (HR = 1.309, 95% CI: 1.209–1.642). Relapsed patients had nearly twice the risk of death compared with non-relapsed patients (HR = 1.955, 95% CI: 1.650–3.215). Donor type was also significant: recipients of grafts from "other relative" donors had a 2.384-fold higher risk (95% CI: 1.806–5.272), and those from unrelated donors had a 1.50-fold higher risk (95% CI: 1.136–3.293), compared with sibling donors.

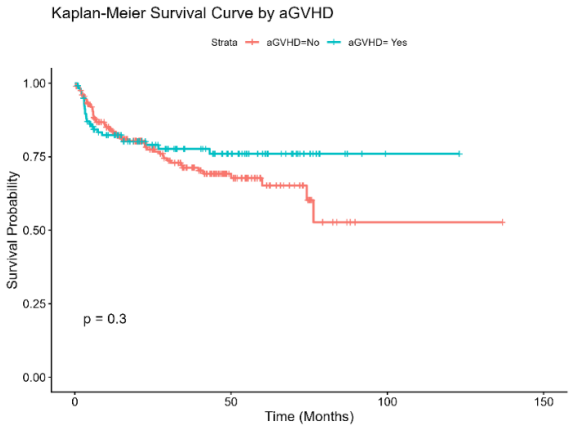
Regarding the association between *WT1* expression and survival, the posterior mean of the association parameter for baseline *WT1* (α_1 = 0.388) was positive and statistically significant, indicating that higher baseline *WT1* expression was associated with increased mortality (HR = 1.474, 95% CI: 1.325–2.052). The association parameter for the slope of *WT1* (α_2 = 1.213) was also positive, implying that increasing *WT1* levels over time corresponded to higher mortality risk; however, this effect did not reach statistical significance (HR = 1.213, 95% CI: 0.442–3.072).

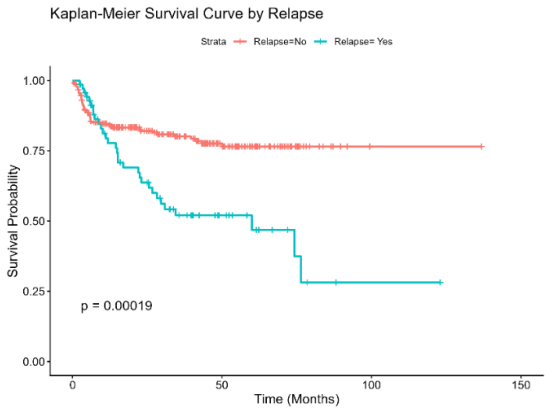
These findings suggest that while longitudinal changes in *WT1* were heterogeneous and not independently predictive of survival, baseline *WT1* expression emerged as a strong and significant prognostic biomarker for post-transplant mortality in AML patients.

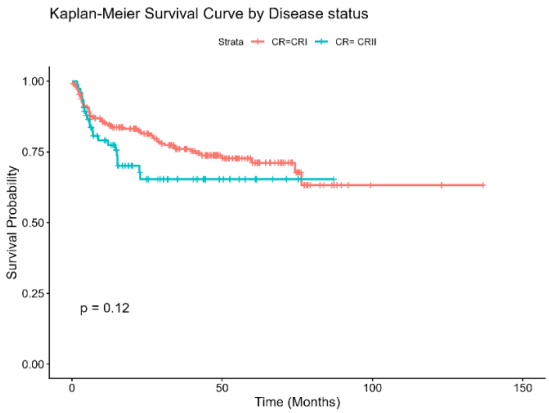
Discussion

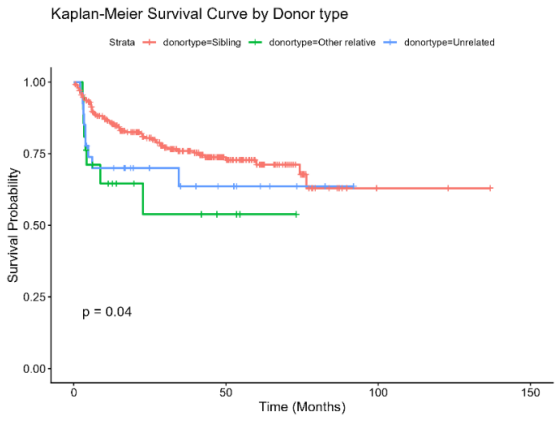
In this study, we applied a Bayesian joint modeling framework to examine the relationship between longitudinal *WT1* gene expression and survival in patients with AML undergoing allo-HSCT, combining a linear mixed effects model with a Burr XII baseline hazard distribution within a generalized hazard structure. The Bayesian approach was selected for its methodological

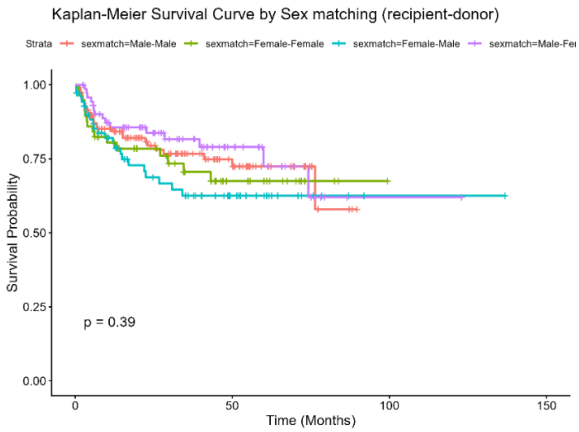


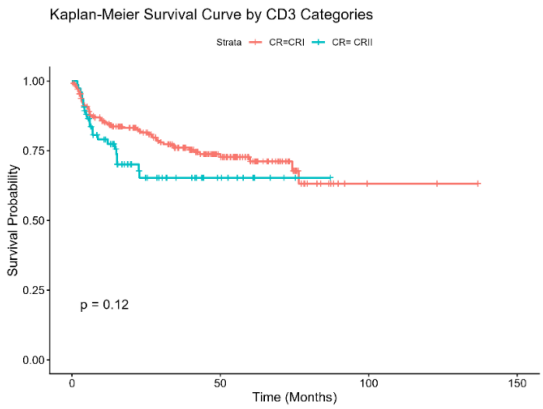












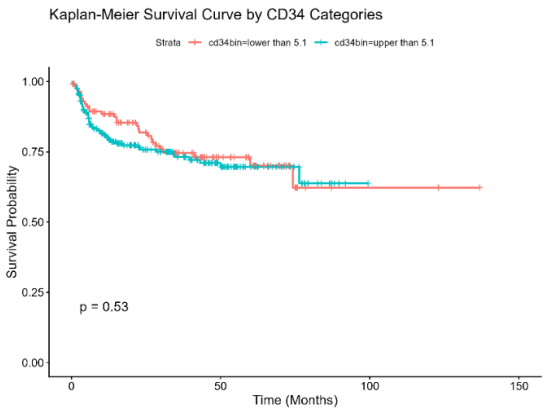


Figure 1. Kaplan-Meier Plot for the Survival Function aGVHD, Relapse, Disease Status, Donor Type, and Sex Matching (recipient-donor), CD3 and CD34 Cells Categories

Table 2. Estimated Parameters of the Longitudinal Sub-model of the Bayesian Joint Model.

Variables	Posterior Mean	Posterior Median	SE	95% CI		N_eff	$\hat{R}$
				Lower	Upper		
Intercept	3.442	3.412	0.002	3.287	3.888	9194	1.000
Obstime (month)	-0.003	-0.004	0.000	-0.007	0.010	8905	1.001
Age (year)	0.062	0.061	0.001	-0.008	0.237	9063	1.000
Diag time to HSCT (month)	0.020	0.022	0.001	-0.048	0.216	8090	1.000
CD3 cells							
<284	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>284	-0.020	-0.025	0.002	-0.139	0.322	8967	1.000
CD34 cells							
<5.1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>5.1	0.109	0.114	0.002	-0.008	0.462	8993	1.000
aGVHD							
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.169	0.166	0.002	0.045	0.527	8790	1.000
Relapse							
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.103	1.109	0.002	0.968	1.504	8457	1.000
Disease status							
CRI	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CRII	0.076	0.088	0.002	-0.077	0.513	8870	1.000
Donor type							
Sibling	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Other relative	-0.104	-0.103	0.004	-0.343	0.606	9024	1.000
Unrelated	-0.145	-0.125	0.004	-0.365	0.507	8898	1.000
Sex matching (recipient-donor)							
Male - Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female - Female	-0.011	-0.021	0.003	-0.174	0.468	9173	1.000
Female - Male	-0.208	-0.222	0.002	-0.360	0.240	9073	1.000
Male- Female	-0.388	-0.394	0.002	-0.540	0.062	8805	1.000
Random effects correlation							
RE correlation (ρ)	-0.579	-0.560	0.004	-0.812	0.387	8675	1.000
Intercept RE variance	1.062	1.052	0.001	0.980	1.301	6888	1.000
Slope RE variance	0.023	0.093	0.0001	0.014	0.047	6577	1.000
Error variance	3.625	3.535	0.002	3.491	4.033	8542	1.000

RE: random effect

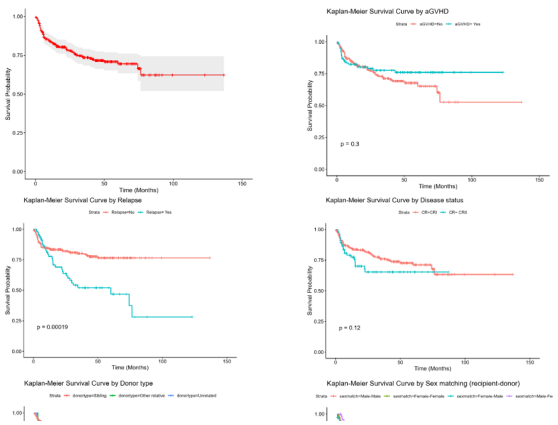


Figure 2. Individual Profile Plot of Log-transformed *WT1* Expression Over Time (Months)

advantages in handling complex joint models, providing stable parameter estimates through MCMC sampling and offering full posterior distributions without reliance on asymptotic approximations. The Burr XII distribution, with its flexible shape parameters, was chosen to accommodate the diverse hazard patterns typically observed in AML survival data. While previous studies from Iranian transplantation centers have examined prognostic factors in AML using standard survival methods, the present study offers several distinct contributions.[26-28] First, we focus on *WT1* expression levels (rather than mutations) in a general AML cohort. Second, we analyze longitudinal measurements of *WT1* (1-13 per patient) rather than single timepoint assessments, enabling examination of dynamic biomarker trajectories. Third, we employ a Bayesian joint

Table 3. Estimated Parameters of the Survival Sub-model of the Bayesian Joint Model.

Variables	Posterior Mean	Posterior Median	SE	HR	95% CI		N_eff	$\hat{R}$
					Upper	Lower		
Age (year)	0.269	0.219	0.001	1.309	1.209	1.642	8750	1.000
Diag time to HSCT (month)	0.052	0.044	0.001	1.053	0.976	1.306	8647	1.000
CD3 cells								
<284	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>284	-0.102	-0.106	0.002	0.903	0.773	1.417	9525	1.000
CD34 cells								
<5.1	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
>5.1	-0.179	-0.167	0.002	0.836	0.721	1.304	9475	1.000
aGVHD								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	-0.301	-0.313	0.003	0.740	0.622	1.219	9217	1.000
Relapse								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.671	0.673	0.003	1.955	1.650	3.215	9362	1.000
Disease status								
CRI	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
CRII	0.051	0.050	0.003	1.053	0.868	1.840	9041	1.000
Donor type								
Sibling	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Other relative	0.680	0.672	0.004	1.975	1.505	4.291	8974	1.001
Unrelated	0.405	0.412	0.004	1.499	1.136	3.293	9033	1.001
Sex matching (recipient-donor)								
Male - Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female - Female	-0.106	-0.102	0.003	0.899	0.721	1.699	9117	1.000
Female - Male	-0.015	-0.015	0.003	0.985	0.817	1.719	8839	1.000
Male- Female	-0.502	-0.503	0.003	0.606	0.490	1.114	8733	1.000
Association parameters								
Intercept RE association (α_0)	0.388	0.371	0.002	1.474	1.325	2.052	8207	1.000
Time association (α_1)	0.193	0.182	0.016	1.213	0.442	3.072	8789	1.000
Shape 1 (υ)	1.396	1.405	0.002	-	-	-	9430	1.000
Shape 2 (δ)	0.067	0.058	0.000	-	-	-	8961	1.000

modeling framework with generalized hazard structure and Burr XII baseline hazard, a sophisticated approach not previously applied to AML data. This framework uniquely quantifies the dynamic association between longitudinal *WT1* trajectories and survival while adjusting for transplant-related covariates. The novelty thus resides in applying an innovative statistical framework that yields deeper understanding of the relationship between *WT1* dynamics and post-transplant survival, advancing both biostatistical methodology and clinical oncology research.

In this study, we applied a Bayesian joint modeling framework, combining a linear mixed effects model for the longitudinal trajectory of *WT1* gene expression with a Burr XII baseline hazard distribution within a generalized hazard (GH) structure for the survival submodel in patients with AML undergoing allo-HSCT. The Bayesian approach was chosen over frequentist methods due to its methodological and computational advantages. While frequentist approaches often face limitations in estimating complex joint models, particularly when likelihood functions involve high dimensional integration, the Bayesian framework provides more stable and precise parameter estimates through Markov Chain Monte Carlo (MCMC) sampling and incorporation of prior information. Furthermore, Bayesian inference does not rely on asymptotic approximations and allows full posterior distributions to be obtained, which is particularly advantageous in biomedical studies with moderate or small sample sizes. The Burr XII distribution, with its flexible two shape parameters, was selected as a suitable choice for modeling the hazard patterns typically observed in AML survival data. While the sample size of this single-center study was adequate for the proposed analyses and yielded robust convergence diagnostics, the findings may be influenced by center-specific protocols and patient selection. Therefore, larger multicenter studies are

warranted to validate the generalizability of these results across diverse populations and treatment settings.

WT1 is widely recognized as a marker of minimal residual disease in AML, although its prognostic role continues to be investigated. Consistent with earlier studies reporting that elevated *WT1* expression at diagnosis may be associated with poorer overall survival,[29] our findings demonstrated a positive and significant association parameter for the random intercept ($\alpha_0 = 0.388$), indicating that higher baseline *WT1* expression was associated with increased mortality risk (HR = 1.474, 95% CI: 1.325–2.052). This result highlights the interdependence between the longitudinal and survival processes captured by the joint modeling framework and underscores the potential clinical value of regular *WT1* monitoring following transplantation. The negative correlation observed between the random intercept and random slope ($P = -0.579$, 95% CI: −0.812 to 0.387) suggests that patients with higher baseline *WT1* levels may tend toward steeper subsequent declines, although the wide credible interval reflects substantial heterogeneity across individuals. This observation aligns with previous research identifying *WT1* overexpression as a potential prognostic indicator in AML,[30,31] and supports the hypothesis that *WT1* may serve as a useful biomarker for risk stratification. The association between *WT1* and mortality may reflect underlying biological processes involving disease progression and treatment resistance, given the gene's role in regulating leukemic cell proliferation and differentiation. However, the observed associations could also be influenced by unmeasured clinical or biological factors.

Although the posterior mean association parameter for the random slope was positive ($\alpha_2 = 0.193$), it did not reach statistical significance (HR = 1.213, 95% CI: 0.442–3.072), indicating that longitudinal changes in *WT1* expression, when considered in isolation, were not significantly associated with overall survival in this cohort. Nevertheless, in the longitudinal submodel, both relapse and aGVHD were positively associated with elevated *WT1* levels. Relapse emerged as a particularly strong predictor of higher *WT1* expression, consistent with previous reports by Tsushima et al.[32], who reported reduced relapse rates among those who had a 3-log reduction in *WT1* mRNA, and Malagola et al.[33], who demonstrated the predictive value of pre-transplant peripheral blood *WT1* for relapse. From a clinical perspective, these findings emphasize the utility of measuring *WT1* levels at diagnosis and before transplant to identify high risk patients who may benefit from intensified therapeutic strategies or closer post-transplant monitoring. This study showed that experiencing aGVHD is associated with a significant increase in *WT1* gene expression level in AML patients. The observed association between aGVHD and elevated *WT1* levels warrants cautious interpretation. While one might hypothesize about underlying immunological mechanisms such as donor T-cell mediated immune activation or inflammatory cytokine release, the present study did not investigate these pathways directly. Similarly, although immunosuppressive therapies used in GVHD management could theoretically modulate the host immune response against residual leukemic cells, such mechanisms remain speculative based on these data. Further studies incorporating immunological markers and detailed treatment protocols are needed to explore potential biological explanations for this association.

Within the survival submodel, age at transplant, relapse, and donor type were identified as significant predictors of mortality. Older age was associated with a 30.9% increase in mortality risk per additional year, consistent with prior evidence identifying age as a major prognostic factor in AML.[32-34] One of the most significant challenges in AML treatment is post-transplant relapse, which occurs at a high incidence rate[1] and is influenced by factors such as age and disease status.[35-37] In this study, relapse nearly doubled the hazard of death (HR ≈ 2.0), reaffirming its role as a critical determinant of poor post-transplant survival. This finding, which is consistent with previous reports,[27,38-42] underscores the profound negative prognostic impact of relapse and highlights the need for clinical strategies to prevent it or manage it with aggressive interventions, including potentially a second transplantation. In line with prior studies, donor type also significantly influenced survival, with unrelated or other relative donors associated with worse outcomes than sibling donors.[43] No significant associations were observed for donor sex or disease status at transplant, consistent with previous literature.[27]

In addition to the methodological advantages discussed, the fitted model holds substantial potential for further development in future studies. One promising direction is using these models for the dynamic prediction of patient survival. With new longitudinal data for an individual patient, the probability of a survival event such as death or disease relapse can be continuously updated. This capability significantly expands the clinical applicability of statistical models in personalized medicine. For instance, by leveraging updated *WT1* gene expression levels, a customized risk profile for death or disease relapse at different post-transplantation time points can be generated for each patient. Such models can serve as valuable tools for clinicians in designing targeted interventional programs, determining the appropriate intensity of clinical follow-up, and selecting individualized treatment strategies. Moreover, extending the model to multi marker joint frameworks incorporating multiple biomarkers or imaging data could further enhance predictive accuracy and broaden its clinical utility.

The observed aGVHD–WT1 relationship might result from alloreactive T-cell activation and GVHD-related cytokine release, alongside potential impairment of anti-leukemic immunity by GVHD therapies, both of which could raise *WT1* levels.

Several limitations should be considered when interpreting these findings. First, the moderate sample size and single-center design mean that our data were derived from a specific treatment center and may not fully represent the broader population of AML patients; therefore, generalizability to other populations and healthcare settings

requires caution. Second, although *WT1* served as a key biomarker in this analysis, information on other important genetic and molecular prognostic factors including *FLT3-ITD*, *NPM1* mutations, and comprehensive cytogenetic risk profiles was not available. These variables are well-established predictors of AML outcomes and their omission may introduce unmeasured confounding, potentially affecting the estimated associations between *WT1* expression and survival. Third, data on treatment-related factors, including variations in conditioning regimens and post-transplant immunosuppressive protocols, were not incorporated into the analysis. Such variations could influence both *WT1* dynamics and survival outcomes, representing another potential source of confounding. Fourth, the absence of a standardized schedule for *WT1* measurements introduced variability in the timing and frequency of longitudinal assessments. Although the joint modeling framework is designed to accommodate irregularly spaced data, more uniform collection times could yield more precise trajectory estimates. Fifth, as with any observational study, there is potential for immortal time bias and informative dropout. Patients who survive longer necessarily contribute more measurements, and dropout may be related to disease progression, which could influence the observed longitudinal patterns. Sixth, as noted by Hernán[44], hazard ratios are conditional measures that may be affected by time-dependent selection mechanisms and should be interpreted as measures of association rather than causal effects. Finally, despite the flexibility of our Bayesian joint model, the validity of the results depends on the correctness of the underlying assumptions, including the specified random effect structure (random intercept and random slope) and the chosen link function connecting the two submodels. Violations of these assumptions could introduce bias that is difficult to assess. Future studies with prospective multicenter designs, standardized measurement protocols, comprehensive genetic and molecular profiling, detailed treatment data, and larger sample sizes are warranted to validate and extend these findings.

Conclusion

This study employed a comprehensive Bayesian approach to examine the relationship between longitudinal *WT1* gene expression and survival in patients with Acute Myeloid Leukemia (AML) following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Our results identify baseline *WT1* expression as a strong independent prognostic biomarker, significantly associated with increased mortality, whereas longitudinal changes in *WT1* alone exhibited limited predictive value. *WT1* may be a useful risk stratification tool alongside other clinical and transplant related covariates. Moreover, continuous monitoring of *WT1*, particularly in combination with additional biomarkers, has the potential to guide personalized therapeutic strategies and improve post-transplant outcomes in AML.

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Authors' Contribution

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Competing Interests

The authors declare no competing interests.

Ethical Approval

This study was found to be under the ethical principles and the national norms and standards for conducting medical research in Iran by the National Institute for Medical Research Development (NIMAD), Tehran, Iran. The approval ID is IR.NIMAD.REC.1397.251.

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