Original Paper

Joint Modeling of Multivariate Longitudinal Measurements and Survival Data: Application to Hemodialysis Data

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Introduction. In studies involving hemodialysis patients, repeated laboratory measurements (longitudinal data) and survival outcomes are often analyzed separately, which can lead to biased results due to ignoring measurement errors and the intrinsic dependency between the two analyses. Joint modeling has emerged as a powerful approach to handle such data. This study aims to investigate the impact of six time-varying biochemical markers, along with baseline covariates, on the survival of hemodialysis patients using a multivariate joint model.

Methods. A longitudinal cohort of 894 maintenance hemodialysis (MHD) patients, who had started dialysis between 2004 and 2023, were included. Baseline and follow-up clinical information and monthly laboratory measurements were analyzed. A multivariate linear mixed-effects model was jointly fitted with a Cox proportional hazards model to simultaneously assess the longitudinal biomarkers and time-to-event data. Analyses were performed using R software.

Results. The model indicated that older age (Hazard Ratio, HR = 1.02, $P < .001$), male gender (HR = 1.72, $P < .001$), diabetes mellitus (HR = 1.61, $P < .001$), walking disability at admission (HR = 1.78, $P < .001$), and catheter-based vascular access (HR = 1.71, $P < .001$) were significantly associated with an increased risk of mortality. Higher square root of phosphate levels (HR = 13.97, $P < .001$) were linked to increased, and higher square root of creatinine (HR = 0.32, $P < .001$), hemoglobin (HR = 0.75, $P = .009$) and albumin (HR = 0.31, $P < .001$) levels were associated with decreased mortality.

Conclusion. Findings of the joint model confirm the importance of baseline clinical risk factors and modifiable biochemical markers on the survival outcomes of hemodialysis patients.

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INTRODUCTION

Despite advances in dialysis technology, mortality rate remains high among maintenance hemodialysis (MHD) patients. Studies have shown that factors such as age, diabetes mellitus, and cardiovascular comorbidities significantly impact survival in patients undergoing MHD.[1,2] Additionally, laboratory biomarkers- including hemoglobin, phosphate, albumin, intact parathyroid hormone (iPTH), creatinine, and calcium - are frequently monitored during dialysis due to their effect on patient outcomes.[3,4]

In many clinical studies repeated measurements of these biomarkers are collected over time (longitudinal data), together with baseline clinical risk factors and variables such as type of vascular access , to investigate their association with survival outcomes. Conventionally, these data are analyzed separately which has often led to biased or inefficient estimates due to ignoring the

measurement error and interdependence between the longitudinal and survival processes.[5]

During analysis of laboratory markers over time, we typically use linear mixed-effects models. These models describe how biomarkers change on average in a population and how individual patients deviate from this average. Separately, we analyze survival data using Cox proportional hazards model, which identifies baseline factors that affect mortality risk. However, these separate analyses ignore the inherent connection between a patient's biomarker trajectory and their survival outcome. Consider a patient whose albumin levels are steadily declining. This patient is likely becoming more malnourished and frailer, and therefore has a higher risk of death. If we analyze albumin changes and mortality separately, we lose this critical link.[6]

Two specific problems arise with conventional approaches: First, measurement error is ignored. Second, informative dropout is not handled properly. Separate analyses cannot adequately account for this, leading to further bias.[7]

Joint modeling was developed specifically to address these limitations. The method consists of two connected parts:

a. A longitudinal sub-model that describes how each patient's biomarkers change over time
b. A survival sub-model that describes their risk of death at any given time

These two sub-models are linked through shared random effects. This dynamic, patient-specific information is what makes joint modeling clinically valuable and it moves beyond population averages to provide insights that can guide patient-level monitoring and intervention.[6]

The earliest applications of joint modeling were in studies of human immunodeficiency virus (HIV) using CD4 positive white blood cell counts, and since then, joint models have been applied in cardiovascular disease, cancer, and nephrology studies.[8-11]

Given the importance of repeated laboratory values in MHD patients, this study aims to jointly analyze the longitudinal trajectories of six biomarkers along with baseline clinical variables to assess their association with patient survival using multivariate joint modeling.

MATHERIALS AND METHODS

Study sample and data collection

This longitudinal cohort study consisted of 894 patients undergoing maintenance hemodialysis (MHD) at Hasheminejad Kidney Center (HKC) (Tehran, Iran). Laboratory data and clinical information of the patients were extracted from the hospital information system (HIS) and their medical records over the period from March 2004 to May 2023.

Inclusion criteria

All patients undergoing MHD at HKC at the mentioned period, who had at least one measurement of the six laboratory markers (hemoglobin, albumin, phosphate, iPTH, creatinine, and calcium) in their medical records were enrolled to the study.

Exclusion criteria

Patients with less than three months of dialysis history or patients with incomplete baseline data (age, sex, cause of ESKD) were excluded from the study.

Baseline demographic and clinical characteristics, including age at admission, gender, and presence of diabetes mellitus, walking disability, cardiovascular disease, and type of vascular access (arteriovenous fistula/graft vs. catheter) were collected at enrollment in the Hemodialysis Data Processing Software (HDPS) designed for this purpose by Artificial Intelligence Processors (AIP) Inc., 2003. Monthly laboratory tests included hemoglobin, phosphate, serum creatinine, and calcium, while iPTH was measured every three and serum albumin every six months.

Missing data were present in the longitudinal measurements, with an overall missing rate of 3.5% across all biomarkers and time points. The low rate of missing data reflects the comprehensive data collection protocols at HKC and the regularity of patient follow-up in this cohort.

The study protocol was approved by the Ethics Committee of the National Institute for Medical Research Development (IR.NIMAD.REC.1397.118), and the informed consent was waived due to the observational retrospective nature of the study.

Survival time and censored define

Survival time was defined as the time from study entry (baseline) until death from any cause. Patients were censored if they were transferred to other dialysis centers, switched to peritoneal dialysis, underwent kidney transplantation, recovered

kidney function, or still alive and on HD at the end of the study (May 2023).

Joint modeling specification

This study used joint modeling to simultaneously analyze the longitudinal and survival data. The joint model consists of two sub-models:

Longitudinal Sub-model: A multivariate linear mixed-effects model was used to describe the trajectories of the six repeated biomarkers over time. Each marker was modeled using a random intercept and random slope structure to account for within-subject variability.

Time-to-event Sub-model (Survival): A Cox proportional hazards model was applied to analyze time-to-death as the survival outcome. The proportional hazards assumption for baseline covariates in the survival sub-model was assessed using Schoenfeld residuals.

The survival and longitudinal processes were

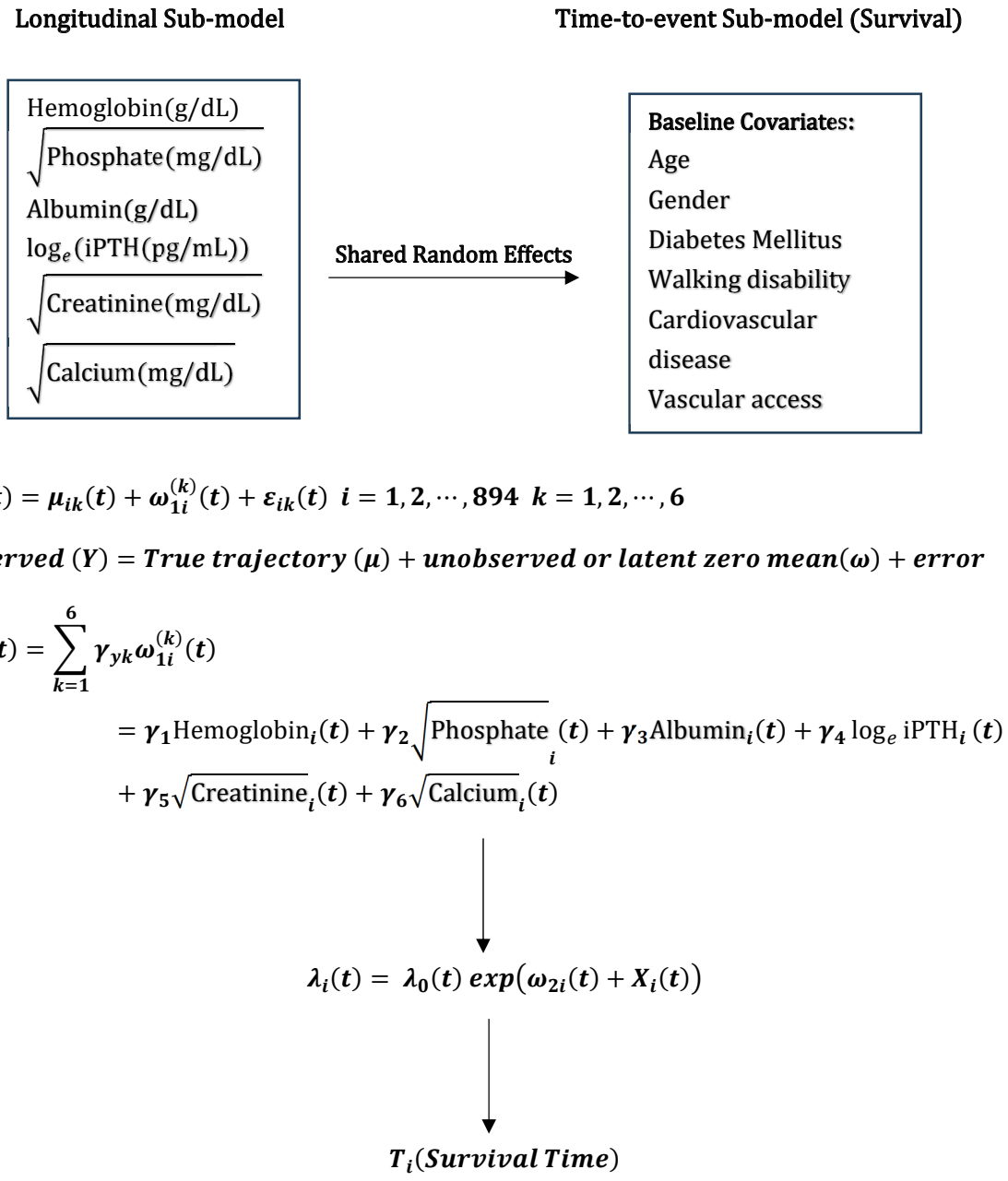

Figure 1. Multivariate Joint Model Structure for Hemodialysis Data.

linked through shared random effects.

The primary goal was to assess the association between the dynamic trajectories of the biomarkers and mortality risk. This association was captured through parameters (γ coefficients) linking each longitudinal marker to the hazard function.[12]

In order to meet the assumptions of normality required for the longitudinal sub-model, some laboratory variables were transformed prior to analysis. Square root transformation was applied to variables such as phosphate, creatinine, and calcium, while $\log_e$ transformation was used for iPTH. Multivariate Joint Model Structure for HD Data were explanted completely in Figure 1.

Statistical software

All statistical analyses were conducted using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Linear mixed-effects models for longitudinal sub-models were fitted using the nlme package, and survival analyses were performed using the survival package.[13,14] For the implementation of multivariate joint modeling of repeated measurements and time-to-event data, the joineRML package was used.[15]

RESULTS

A total of 894 MHD patients were analyzed in this study. The mean (± SD) age of patients was 56.4 (± 17.1) years, ranging from 14 to 95 years. Out of 894 patients, 338 (37.8%) were female and 556 (62.2%) were male. Overall, 342 patients (38.3%) had diabetes mellitus, and 189 (21.1%) had walking disability at the time of admission. A total of 126 patients (14.1%) had cardiovascular disease (CVD), defined as history of coronary artery disease or heart failure, and 379 (42.4%) used catheter as their vascular access, while the remaining 515 (57.6%) had AV fistula or graft. The overall rate of missing data across all biomarkers and time points was low (3.5%), with iPTH having the lowest missing rate (1.1%) and hemoglobin the highest (4.3%), consistent with less frequent measurement schedule of iPTH. The total number of longitudinal observations across all patients and biomarkers was 5,041. The median number of six-month measurement occasions per patient was 4 (interquartile range: 2-8, range: 1-31).

The correlation between laboratory biomarkers were generally weak to moderate, with the strongest correlations observed between albumin and creatinine ($r = 0.295$, $P < .001$), calcium and hemoglobin ($r = 0.188$, $P < .001$), and hemoglobin and albumin ($r = 0.208$, $P < .001$). These correlations were accounted for in the multivariate joint model through the inclusion of correlated random effects, allowing for the interdependence between biomarkers, while still obtaining efficient estimates.

The median survival time was 5.41 years (95% CI: 4.85 to 5.96). The estimated overall survival rates at 1, 2, 3, 4, 5, 10 and 15 years were 93%, 84%, 70%, 60%, 49%, and 20% and 8% respectively.

Table 1. Baseline Patients' Characteristics

	Censored		Dead		Total	
	n	%	n	%	n	%
Gender						
Female	169	37.1	169	38.5	338	37.8
Male	286	62.9	270	61.5	556	62.2
Diabetes Mellitus*						
Yes	132	29.0	210	47.8	342	38.3
No	323	71.0	229	52.2	552	61.7
Walking disability at admission						
Yes	58	12.7	131	29.8	189	21.1
No	397	87.3	308	70.2	705	78.9
Cardiovascular disease at admission						
Yes	47	10.3	79	18.0	126	14.1
No	408	89.7	360	82.0	768	85.9
Vascular access at admission						
AV Fistula or AV Graft	249	54.7	266	60.6	515	57.6
Catheter	206	45.3	173	39.4	379	42.4

*Diabetic mellitus was the major cause of kidney disease in this data set, it was used versus other cause of kidney disease.

Detailed patient characteristics and censoring status are presented in Table 1, and laboratory results stratified by survival outcome (censored vs. dead) are summarized in Table 2.

Figure 2 shows the Kaplan–Meier survival curve for the cohort of MHD patients. The plot demonstrates a gradual decline in survival probability over time, indicating the increasing risk of mortality throughout the follow-up period.

Schoenfeld residuals analysis supported the proportional hazards assumption for all covariates ($P > .05$) and global test p-value was 0.162.

Figure 3 displays the longitudinal trends of six biomarkers, stratified by survival status (censored vs. dead). Spline smoothing was used to estimate average trajectories. The patterns differ notably among survival status.

Initially, univariate joint models were fitted for each biomarker separately. In these models, hemoglobin ($\gamma = -0.396$, $P < .001$), albumin ($\gamma = -1.313$, $P < .001$), square root of creatinine ($\gamma = -0.541$, $P < .001$) and square root of calcium ($\gamma = -0.492$, $P < .001$) were significantly associated with a reduced hazard of death, while square root of phosphate ($\gamma = 1.256$, $P < .001$) and $\log_e$ (iPTH) ($\gamma = 0.204$, $P < .001$) showed positive associations with mortality risk. Table 3 shows the results of separate modeling.

In the next step, a multivariate joint model was constructed, incorporating all six longitudinal biomarkers simultaneously, along with key baseline

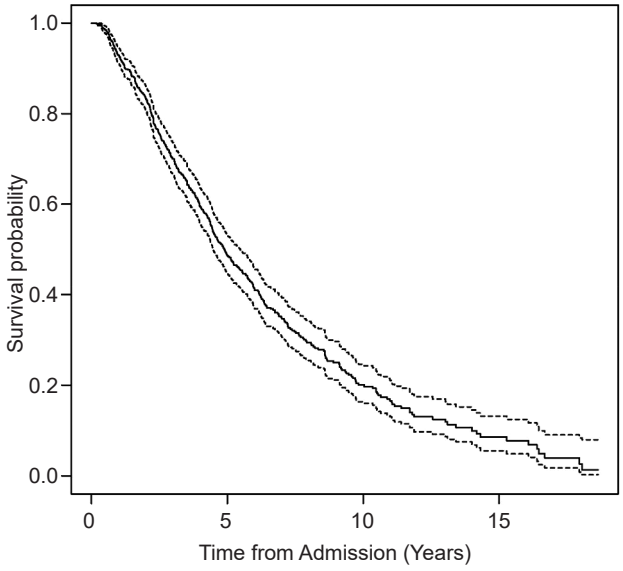

Figure 2. Kaplan-Meier Curve for Overall Survival. A pointwise 95% band (dashed lines).

Table 2. Reports of Laboratory Variables According to Censored and Dead

	Censored		Dead		Total	
	Mean ± SD	Med (Q1-Q3)	Mean ± SD	Med (Q1-Q3)	Mean ± SD	Med (Q1-Q3)
Age (year)	50.73 ± 17.59	51.2 (36.59-63.95)	62.33 ± 14.29	65.17 (54.43-72.65)	56.43 ± 17.06	58.63 (43.95-70.49)
Hemoglobin (g/dL)	10.93 ± 1.7	11 (9.9-12)	11.01 ± 1.81	11.1 (9.9-12.2)	10.97 ± 1.76	11 (9.9-12.1)
$\sqrt{\text{Phosphate (mg/dL)}}$	2.29 ± 0.33	2.28 (2.07-2.51)	2.25 ± 0.33	2.24 (2.02-2.47)	2.27 ± 0.33	2.26 (2.05-2.49)
Albumin (g/dL)	3.96 ± 0.43	4 (3.7-4.2)	3.83 ± 0.5	3.8 (3.5-4.1)	3.89 ± 0.47	3.9 (3.6-4.2)
$\log_e$ (iPTH(pg/mL))	5.6 ± 1.03	5.78 (5.02-6.33)	5.4 ± 1.02	5.48 (4.74-6.13)	5.48 ± 1.03	5.62 (4.87-6.23)
$\sqrt{\text{Creatinine (mg/dL)}}$	3.04 ± 0.47	3.03 (2.75-3.35)	2.87 ± 0.47	2.84 (2.57-3.15)	2.94 ± 0.48	2.93 (2.62-3.24)
$\sqrt{\text{Calcium (mg/dL)}}$	2.96 ± 0.16	2.98 (2.88-3.05)	2.99 ± 0.15	3 (2.91-3.08)	2.98 ± .015	2.98 (2.89-3.07)

In order to meet the assumptions of normality required for the longitudinal sub-model, square root transformation was applied to phosphate, creatinine, and calcium, while $\log_e$ transformation was used for iPTH.
Abbreviations: SD = Standard Deviation; Med = Median; Q1 = 25th percentile; Q3 = 75th percentile; iPTH = intact parathyroid hormone

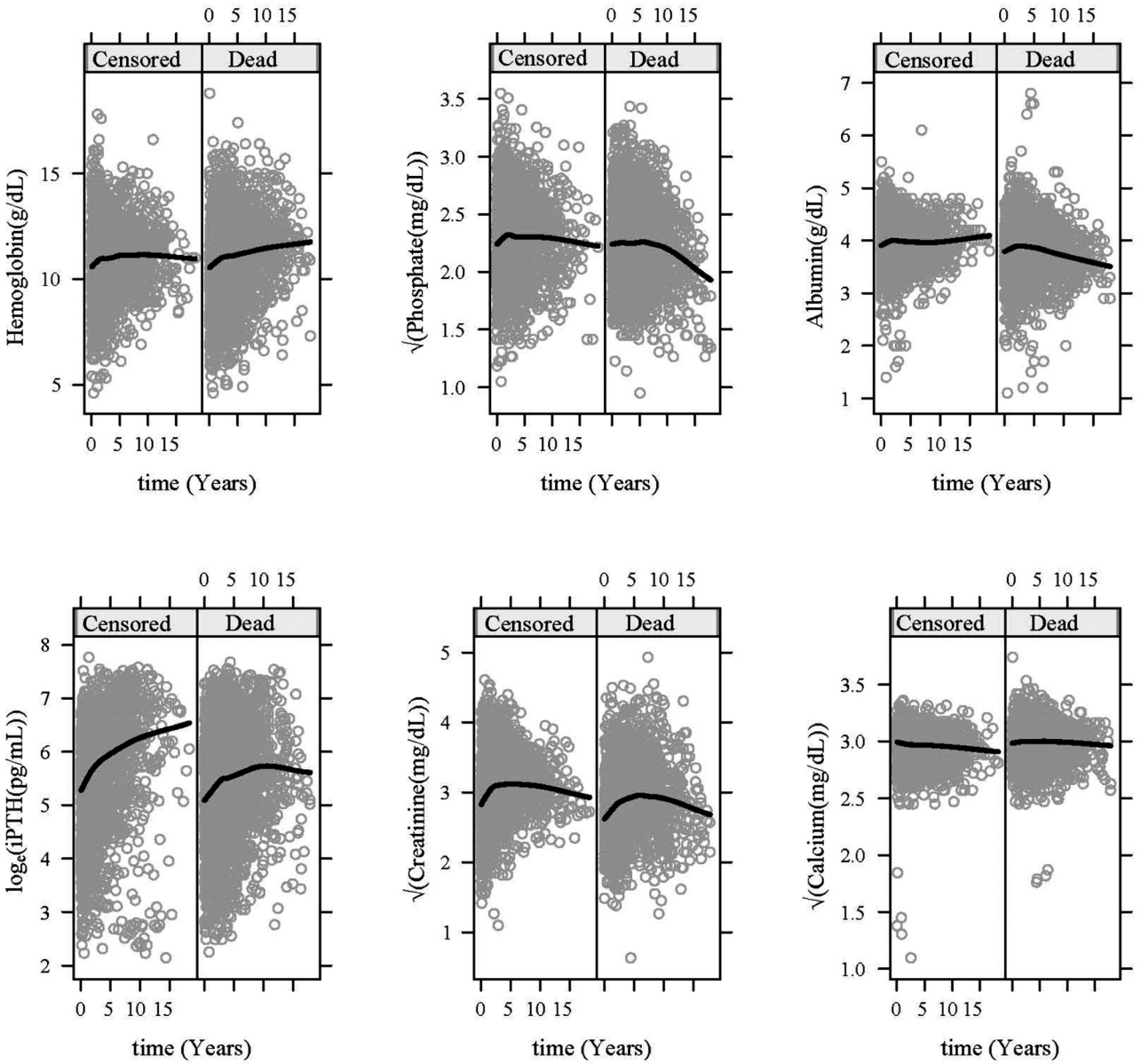

Figure 3. Longitudinal Trajectory Plots Stratified by Survival Status (Censored Vs. Dead). Spline smoothing was used to estimate average trajectories.

covariates. The survival sub-model revealed that older age (Hazard Ratio, HR = 1.023, $P < .001$), male gender (HR = 1.72, $P < .001$), diabetes mellitus (HR = 1.61, $P < .001$), walking disability (HR = 1.78, $P < .001$), and use of catheter for vascular access (HR = 1.71, $P < .001$) were all independently associated with increased mortality risk.

Regarding the time-varying biomarkers in the multivariate joint model, hemoglobin ($\gamma = -0.277$, HR = 0.75, $P = .009$), albumin ($\gamma = -1.165$, HR = 0.31, $P < .001$) and square root of creatinine ($\gamma = -1.15$, HR = 0.32, $P < .001$) remained significantly protective. Square root of phosphate ($\gamma = 2.637$, HR = 13.97, $P < .001$) was strongly associated with higher hazard of death.

Hazard ratios for biomarkers with square root or logarithmic transformations were calculated at their mean values to facilitate clinical interpretation.

Phosphate demonstrated the strongest association with mortality. At the mean phosphate level of 5.26 mg/dL, each 1 mg/dL increase was associated with an 81% higher hazard of death (HR = 1.81, 95% CI: 1.49-2.19, $P < .001$). Serum creatinine showed a protective effect. At the mean serum creatinine

Table 3. Separate Univariate Joint Models Fitted to Hemodialysis Data

	Hemoglobin			$\sqrt{\text{Phosphate}}$			Albumin		
	Estimate	**SE**	***P***	**Estimate**	**SE**	***P***	**Estimate**	**SE**	***P***
Longitudinal sub-model:									
(Intercept)	10.751	0.053	< .001	2.282	0.010	< .001	3.921	0.017	< .001
Year	0.034	0.012	.004	-0.001	0.003	.677	-0.019	0.004	< .001
Time-to-event sub-model:									
Age	0.030	0.003	< .001	0.032	0.003	< .001	0.021	0.004	< .001
Gender	0.255	0.106	.016	0.148	0.107	.167	0.181	0.103	.079
Diabetes Mellitus	0.546	0.098	< .001	0.518	0.101	< .001	0.545	0.098	< .001
Walking disability	0.585	0.113	< .001	0.639	0.116	< .001	0.459	0.115	.001
Cardiovascular disease	0.240	0.129	.061	0.174	0.127	.169	0.161	0.129	.212
Vascular access	0.602	0.102	< .001	0.690	0.104	< .001	0.531	0.104	< .001
γ	-0.396	0.067	< .001	1.256	0.358	< .001	-1.313	0.202	< .001
	$\log_e(\text{iPTH})$			$\sqrt{\text{Creatinine}}$			$\sqrt{\text{Calcium}}$		
	Estimate	**SE**	***P***	**Estimate**	**SE**	***P***	**Estimate**	**SE**	***P***
Longitudinal sub-model:									
(Intercept)	5.205	0.034	< .001	2.850	0.018	< .001	2.986	0.004	< .001
Year	0.084	0.009	< .001	0.014	0.004	.001	-0.004	0.001	< .001
Time-to-event sub-model:									
Age	0.029	0.004	< .001	0.022	0.004	< .001	0.028	0.004	< .001
Gender	0.130	0.105	.215	0.213	0.108	.049	0.114	0.104	.274
Diabetes Mellitus	0.544	0.099	< .001	0.503	0.101	< .001	0.533	0.100	< .001
Walking disability	0.590	0.114	< .001	0.513	0.113	< .001	0.560	0.113	< .001
Cardiovascular disease	0.191	0.129	< .001	0.167	0.129	.193	0.188	0.130	.147
Vascular access	0.679	0.103	< .001	0.623	0.104	< .001	0.654	0.107	< .001
γ	0.204	0.087	< .001	-0.541	0.139	< .001	-0.492	0.907	< .001

In order to meet the assumptions of normality required for the longitudinal sub-model, square root transformation was applied to phosphate, creatinine, and calcium, while $\log_e$ transformation was used for iPTH.
Abbreviations: SE = standard error; iPTH = intact parathyroid hormone; γ = The association parameter γ (gamma) indicates how strongly the current value of each biomarker is linked to instantaneous mortality risk.

value of 8.9 mg/dL, each 1 mg/dL increase was associated with a 16% reduction in mortality risk (HR = 0.84, 95% CI: 0.76-0.93, $P < .001$). Hemoglobin and albumin were both significantly associated with lower mortality rates with HR = 0.76, 95% CI: 0.62-0.93, $P = .009$ and HR = 0.31, 95% CI: 0.16-0.61, $P < .001$ respectively. All model parameter estimates are summarized in Table 4.

DISCUSSION

In this study which included 894 patients undergoing MHD , we employed a multivariate joint modeling approach to analyze 15-year survival and time-varying clinical factors. The distribution of laboratory parameters in our study population, as presented in Table 2, generally aligns with the targets recommended by the 2024 KDIGO Chronic Kidney Disease guidelines.[16]

Among baseline predictors the results highlighted increasing age, male gender, diabetes mellitus, and walking disability, and catheter-based vascular access at admission to be significantly associated with increased risk of mortality. These findings are consistent with previous studies showing the adverse impact of older age, male sex, diabetes, and suboptimal vascular access on survival in dialysis patients.[17-22] In particular, the use of catheters as vascular access has been widely associated with increased infection risk and poor outcomes.

Regarding time-varying biomarkers, the longitudinal sub-model revealed that higher phosphate levels were significantly associated with increased risk of mortality. Hemoglobin, albumin and serum creatinine also demonstrated protective associations. However, iPTH and calcium were not significantly associated with survival. These findings highlight the importance of both baseline characteristics and dynamic clinical biomarkers in predicting survival among hemodialysis patients. The significant effects of time-varying biomarkers

Table 4. Multivariate Joint Model Fitted to Hemodialysis Data

Par	Estimate	SE	z-value	*P*
Longitudinal sub-model:				
(Intercept)_ Hemoglobin	10.765	0.059	181.485	< .001
Year_ Hemoglobin	0.023	0.016	1.415	.157
(Intercept)_ $\sqrt{\text{Phosphate}}$	2.271	0.011	199.097	< .001
Year_ $\sqrt{\text{Phosphate}}$	0.005	0.004	1.370	.176
(Intercept)_ Albumin	3.916	0.019	211.554	< .001
Year_ Albumin	-0.019	0.005	-3.670	< .001
(Intercept)_ $\log_e(\text{iPTH})$	5.200	0.039	134.283	< .001
Year_ $\log_e(\text{iPTH})$	0.087	0.011	7.662	< .001
(Intercept)_ $\sqrt{\text{Creatinine}}$	2.849	0.019	151.041	< .001
Year_ $\sqrt{\text{Creatinine}}$	0.016	0.004	3.781	< .001
(Intercept)_ $\sqrt{\text{Calcium}}$	2.987	0.005	583.246	< .001
Year_ $\sqrt{\text{Calcium}}$	-0.004	0.002	-2.315	.021
Time-to-event sub-model:				
Age	0.023	0.005	4.969	< .001
Gender	0.540	0.134	4.019	< .001
Diabetes Mellitus	0.479	0.119	4.042	< .001
Walking disability	0.579	0.145	3.984	< .001
Cardiovascular disease	0.131	0.163	0.805	.420
Vascular access	0.536	0.126	4.251	< .001
γ _Hemoglobin	-0.277	0.106	-2.617	.009
γ _ $\sqrt{\text{Phosphate}}$	2.637	0.607	4.346	< .001
γ –Albumin	-1.165	0.345	-3.378	< .001
γ _ $\log_e(\text{iPTH})$	0.077	0.117	0.661	.509
γ _ $\sqrt{\text{Creatinine}}$	-1.153	0.332	-3.474	< .001
γ _ $\sqrt{\text{Calcium}}$	1.128	1.163	0.970	.322

In order to meet the assumptions of normality required for the longitudinal sub-model, square root transformation was applied to phosphate, creatinine, and calcium, while $\log_e$ transformation was used for iPTH.
Abbreviations: SE = standard error; iPTH = intact parathyroid hormone, γ = The association parameter γ (gamma) indicates how strongly the current value of each biomarker is linked to instantaneous mortality risk.

such as phosphate, hemoglobin and albumin on mortality in end-stage kidney disease (ESKD) patients have been consistently reported in the literature. Elevated serum phosphate has been widely linked to vascular calcification and cardiovascular mortality among dialysis patient populations.[17] On the other hand, the protective effects of higher hemoglobin and albumin levels observed in our study align with previous research emphasizing their roles as markers of better nutritional and hematologic status and overall patient resilience.[23,24]

Our study also revealed that higher serum creatinine levels were linked with better survival in hemodialysis patients, in concordance with studies suggesting that serum creatinine mostly reflect muscle mass rather than kidney function in dialysis patients, offering a more positive prognostic value.[25-27] A joint longitudinal-survival analysis of 408 incident hemodialysis patients showed that a slower decline in the Modified Creatinine Index (mCI), a marker of muscle mass, was linked to lower mortality (HR per 0.1 unit/year decrease = 1.04; P = .011).[25] Similarly, the MONDO cohort on more than 23,000 patients found that a simplified creatinine index, serving as a lean body mass proxy, predicted lower mortality rate (adjusted HR $\approx$ 0.81 per unit increase).[26]

These findings support the view that in dialysis patients, higher serum creatinine, when linked to muscle mass, may be a marker of better health and

improved survival, not just kidney dysfunction.

Also, our findings are consistent with our previous study on the cohort of MHD patients in HKC by Ossareh *et al.*, which evaluated 560 patients over 9 years, finding 1-, 5-, and 9-year survival rates of 91.9%, 46.3%, and 28.5%, and showed that time-dependent hypocalcemia (HR = 1.63), hypercalcemia (HR = 1.50), and hyperphosphatemia (HR = 1.68) were significantly associated with mortality, alongside with protective effects of higher HDL-C (HR = 0.67) and serum creatinine (HR = 0.71).[28] Another cohort study from HKC, also identified time-dependent laboratory factors as the key to patient survival.[29] That study found low hemoglobin, high phosphate, and high LDL-C to be significant predictors of mortality. In contrast, a higher Kt/V (dialysis adequacy) and higher serum creatinine levels were protective in patients undergoing MHD . These results mirror our joint model's emphasis on phosphate, hemoglobin, and serum creatinine as modifiable risk factors.[29]

When comparing our results with previous studies on mortality risk factors in hemodialysis patients, several important distinctions emerge that highlight the added value of our joint modeling approach. While the aforementioned studies from our center and elsewhere have consistently identified similar risk factors-age, diabetes, phosphate, hemoglobin, albumin, and serum creatinine-the methodological rigor of joint modeling provides deeper clinical insights that traditional time-dependent Cox models cannot offer.

First, there is distinguishing between level and trajectory. Traditional time-dependent Cox models typically use the most recent biomarker value or time-averaged values, treating each measurement as independent. Our joint model distinguishes between a patient's underlying true biomarker trajectory and the observed values with error.[6,29]

Second, informative dropout is handled. Patients who are sicker and at higher mortality risk inevitably drop out of the dataset due to death. Traditional methods cannot adequately address this non-random missingness, potentially biasing estimates toward the null.[5]

Third, showing the worth of multivariate versus univariate assessment. Previous studies from our center, while valuable, often examined biomarkers in separate models or adjusted for limited covariates.[28,29]

Fourth, it shows personalized dynamic predictions. Perhaps the most clinically valuable contribution of our approach is its potential for personalized medicine. While previous studies could identify group-level risk factors ("patients with high phosphate have higher mortality"), our joint model can generate individualized survival predictions that update over time as new biomarker measurements become available.[6]

Fifth, there is methodological advantages validated by consistency with literature. Importantly, while our effect estimates differ in magnitude from some previous studies, the direction and pattern of associations remain consistent with the extensive literature.[3,4,17,21-32]

These advances move the field closer to personalized medicine in dialysis care, where interventions can be tailored not just to a patient's baseline characteristics, but to the evolving trajectory of their clinical status over time.

Moreover, the development of joint modeling methods for repeated measurements and survival outcomes has been rapidly expanding in recent years, with a large number of statistical contributions in the literature.[33-36] Applications of joint models in clinical studies have also increased significantly, including in AIDS research , cardiovascular diseases , diabetes , cancer studies, and particularly in renal and dialysis research.[7-9,37-39] For example, Ratcliffe *et al.* applied a joint model in ESKD patients to study the effect of iron as a time-varying covariate on mortality.[4] Similarly, Liang Li *et al.* used a joint model to evaluate serum albumin as a longitudinal marker in MHD patients.[3] In another study on 5860 MHD patients, McCrink *et al.* used joint modeling to investigate the impact of hemoglobin variability and other covariates on survival. Their study also compared joint modeling with traditional independent models and found the joint model provided more accurate results.[31]

Taken together, our findings and the growing body of literature support the effectiveness and increasing popularity of joint modeling in nephrology and broader medical fields. The ability of this model to correct measurement error, incorporate dynamic processes, and provide personalized survival predictions, makes it a highly valuable tool for both researchers and clinicians.

This study has several limitations. First, BMI was excluded due to substantial missing data

(approximately 30%), as including it could bias the estimates. Second, dialysis vintage could not be incorporated into the joint model due to convergence issues arising from the proximity of survival times among patients. Although dialysis vintage is important in prognosis of MHD patients, our sample characteristics limited its inclusion. Future studies with larger samples and longer follow-up are warranted to address these factors.

CONCLUSION

Our findings demonstrate that older age, male gender, diabetes mellitus, walking disability, and catheter-based vascular access were significantly associated with increased mortality risk in patients undergoing MHd. Among time-varying biomarkers, higher phosphate levels were strongly associated with increased mortality (while higher, albumin, and serum creatinine) showed significant protective effects in this patient group. Calcium and iPTH did not reach statistical significance in the multivariate model. By accounting for measurement error and the inherent correlation between longitudinal trajectories and survival, joint modeling provides more accurate and clinically meaningful estimates compared to conventional separate analyses. These results highlight the importance of dynamic monitoring and targeted interventions-particularly phosphate control, nutritional support, anemia management, and preferential use of fistulas over catheters-to improve survival in this high-risk population.

FUTURE WORK

Following this study, future research could apply similar joint modeling frameworks to other chronic disease populations, such as those undergoing peritoneal dialysis, kidney transplantation, or post-acute care settings. Moreover, integrating competing risks models within the joint modeling framework may allow for evaluating situations where patients face multiple potential outcomes (e.g., death vs. transplantation). Such advanced models may offer more tailored and accurate survival predictions in clinical practice.[32,40]

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