

Hemoglobin Trajectories and All-Cause Mortality in Critically Ill Hemodialysis Patients with chronic kidney disease: A Retrospective Cohort Study

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Abstract

Background

Anemia management in critically ill hemodialysis (HD) patients with chronic kidney disease (CKD) primarily relies on static hemoglobin (Hb) measurements, which fail to capture clinically meaningful dynamic changes. This study aimed to identify distinct longitudinal Hb trajectory patterns during the first 30 days of intensive care unit (ICU) admission and evaluate their associations with short- and long-term all-cause mortality in this vulnerable population.

Methods

This retrospective cohort study analyzed 1,384 maintenance HD patients from the MIMIC-IV database (2008–2019). Latent class growth modeling (LCGM) was applied to serial Hb measurements within 30 days post-ICU admission to define trajectory subgroups. Key mortality covariates were selected using the least absolute shrinkage and selection operator (LASSO) regression. Multivariable Cox models, adjusted for these covariates, assessed associations with mortality at 30, 60, 90, and 365 days. Multivariable Cox proportional hazards models adjusted for these covariates and validated for the proportional hazards assumption via Schoenfeld residual test were used to assess associations between Hb trajectories and mortality at 30, 60, 90, and 365 days. Subgroup analyses and missing data impact assessment were conducted to verify result robustness.

Results

Three distinct Hb trajectories were identified: “Stable-Low”(37.6%), “Moderate-Dcline” (55.9%), and “Rapid-Deterioration” (6.5%). LASSO regression selected seven key covariates for adjustment. Compared to “Stable-Low”, “Rapid-Deterioration” was associated with a 63% increased 30-day mortality risk (adjusted HR[aHR] = 1.63, 95% CI: 1.07–2.49) and a 68% increased risk of 60-day mortality (aHR = 1.68, 95% CI: 1.14–2.48, $P = 0.009$), but this excess risk attenuated over time and became non-significant at 90 days and 365 days. In contrast, the “Moderate-Dcline”group exhibited a persistent 35% increased risk of 60-day mortality (aHR = 1.35, 95% CI: 1.09–1.67, $P = 0.006$) and a significant 24% increased risk of 90-day mortality (aHR = 1.24, 95% CI: 1.01–1.51, $P = 0.039$). Subgroup analyses confirmed the robustness of the associations and indicated that the risk associated with “Rapid-Deterioration” was significantly greater in patients aged ≥ 65 years (P for interaction = 0.026).

Conclusion

Dynamic Hb trajectories during the early ICU period provide superior, time-sensitive prognostic stratification compared to static values. The “Rapid-Deterioration” pattern should prompt urgent

evaluation for acute complications, while "Moderate-Divide" indicates a need for long-term management optimization, supporting a shift towards trajectory-informed care.

Introduction

Anemia is a pervasive and clinically significant comorbidity in patients with end-stage renal disease (ESRD), affecting over 90% of those undergoing maintenance hemodialysis (HD) [1, 2]. Its pathophysiology is multifactorial, stemming from inadequate erythropoietin (EPO) production, functional iron deficiency, chronic inflammation, and shortened red blood cell (RBC) survival, with contributions from recurrent blood loss and hemolysis induced by the dialysis procedure itself [3, 4]. This condition imposes a substantial systemic burden, as hemoglobin (Hb) levels persistently below 10 g/dL are associated with exacerbated cardiovascular morbidity, diminished quality of life, and increased mortality[5–7]. Paradoxically, aggressive anemia correction targeting Hb levels > 11.5 g/dL may elevate the risk of adverse events, including arteriovenous fistula thrombosis and cardiovascular mortality, highlighting the precarious therapeutic balance required in this population [2].

Patients on maintenance HD represent a uniquely vulnerable cohort at exceptionally high risk for critical illness, frequently necessitating intensive care unit (ICU) admission due to life-threatening complications such as cardiovascular events, severe infections, and volume overload [8]. In this high-acuity setting, anemia management becomes even more complex. Hb concentration, while a well-established prognostic marker, is not a static parameter in HD patients [9, 10]. It undergoes dynamic fluctuations influenced by acute changes in fluid status, variable responsiveness to erythropoiesis-stimulating agents (ESAs), dialytic prescriptions, and the profound inflammatory milieu characteristic of critical illness[9, 10]. These fluctuations reflect a complex, real-time interplay between underlying pathophysiology and therapeutic interventions.

Despite the dynamic nature of Hb in critically ill HD patients, current clinical practice and prognostic assessment predominantly rely on isolated, static measurements. This approach fails to capture the longitudinal *pattern* of Hb change, which may encapsulate critical prognostic information beyond a single value,such as the rate of decline, stability, or recovery. While studies in stable outpatient HD populations have linked greater Hb variability to poor outcomes, the prognostic significance of specific, empirically derived Hb trajectories in the critical care setting remains inadequately characterized. This represents a significant knowledge gap, as understanding whether a patient's Hb is rapidly deteriorating, slowly declining, or remaining stable could offer a more nuanced, dynamic, and timely perspective on risk stratification and potentially guide more personalized management.

Therefore, this study aimed to characterize distinct longitudinal Hb trajectory patterns during the first 30 days following ICU admission in critically ill HD patients, utilizing Latent Class Growth Modeling (LCGM). We further sought to examine the independent association of these trajectory phenotypes with all-cause mortality at 30, 60, 90, and 365 days. By integrating longitudinal trajectory analysis with time-to-event

outcomes, this research seeks to move beyond static assessment and provide a dynamic framework for understanding mortality risk in this vulnerable population.

Materials and Methods

Study Population and Data Acquisition

Data for this analysis were extracted from the Medical Information Mart for Intensive Care (MIMIC-IV, version 3.0), a comprehensive repository housing records of over 70,000 intensive care unit (ICU) admissions at Beth Israel Deaconess Medical Center, Boston, MA, between 2008 and 2019[11]. Access to the database required completion of the "CITI Data or Specimens Only Research" training program via the National Institutes of Health website, and research-specific data extraction approval was obtained (Certificate for Zhang: ID: 65677952).

The study cohort consisted of first-time ICU admissions with CKD receiving HD. CKD population was established based on the International Classification of Diseases, ICD-9 codes (585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9) and the International Classification of Diseases, ICD-10 codes (N18, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9), as documented by hospital staff at the time of patient discharge[12]. HD population was defined as having diagnostic codes of HD in ICD-9 code (3995). Eligibility criteria included a baseline Hb measurement on admission and at least three serial Hb recordings within the first 30 days post-admission. Patients were excluded if they had multiple ICU admissions, were aged < 18 years, or had an ICU stay of < 72 hours. Cohort identification and extraction of relevant clinical data were performed using Structured Query Language (SQL) via PostgreSQL (version 13.0) and Navicat software (version 17.0)[13]. Demographic data included age, sex. Vital signs included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), temperature, oxygen saturation (SpO₂). Laboratory indicators included red blood cell count (RBC), hematocrit (HCT), Hb, platelet count (PLT), white blood cell count (WBC), bicarbonate (HCO₃), blood urea nitrogen (BUN), calcium, creatinine (Cr), sodium (Na), potassium (K), international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT). Hb levels measured within 30 days of admission were extracted for trajectory analysis, while other laboratory data were limited to measurements taken on the first hospital day. Documented comorbidities included myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease (CVD), chronic pulmonary disease (CPD), liver disease, diabetes mellitus (DM), and malignant cancer. Clinical severity scores assessed were the Charlson Comorbidity Index (CCI), Acute Physiology Score III (APS III), Simplified Acute Physiology Score II (SAPS II), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA). Therapeutic measures included the use of vasopressors, mechanical ventilation support, and packed red blood cell transfusion. The primary endpoint was all-cause mortality at 30, 60, 90, and 365 days. Adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, variables with > 5% missing data were excluded from analyses, while those with < 10% missing data were handled using multiple imputation[14]. We used the Multiple Imputation by Chained Equations algorithm with predictive mean

matching, generating 50 imputed datasets to achieve > 99% relative efficiency. For continuous and categorical variables, we applied Bayesian linear regression ("norm") and logistic/multinomial regression ("logreg"/"polyreg"), respectively. The imputation convergence was verified through trace plot examination and the R-hat statistic (< 1.1) [15].

Identification of Hb Trajectory Subgroups

The R package "lcmm" (version 2.0.2) was utilized to identify heterogeneous Hb trajectories via Latent Class Growth Modeling (LCGM) [16]. A latent class mixed model was applied for longitudinal data analysis, and a parametric survival model with a class-specific Weibull distribution was used to characterize the baseline hazard function [16]. Trajectory modeling was based on Hb data collected within the initial 30 days after ICU admission. We evaluated both linear and quadratic functional forms for the time variable to optimize trajectory modeling. Quadratic terms were included to capture potential acceleration or deceleration in Hb changes, reflecting scenarios such as non-linear decline during acute illness. Model selection was guided by the following criteria: lower values of the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) were used to indicate superior model fit; a significant P-value (< 0.05) from the Lo-Mendell–Rubin adjusted likelihood ratio test was considered evidence in favor of adding an additional trajectory class; and visual inspection of the trajectory plots was conducted to ensure clinical interpretability of the identified patterns [17]. The optimal number of trajectory subgroups was determined by evaluating maximum log-likelihood, AIC, BIC, sample-adjusted BIC (SABIC), entropy, and average posterior probability [18, 19]. Models with lower AIC, BIC, and SABIC values, combined with higher log-likelihood and entropy, were deemed optimal. Robust subgroup classification required an average posterior probability $\geq 70\%$, and only models with each subgroup containing $> 3\%$ of participants were retained for further analysis [20].

Covariates Screening Strategy

First, least absolute shrinkage and selection operator (LASSO) regression was used to identify key features associated with mortality as covariates. STATA software v15.0 was employed for candidate variable screening, with model fit assessed using AIC. Selection criteria included AIC minimization and candidate variable parsimony via 10-fold cross-validation with a 1 standard deviation (1SD) penalty coefficient (λ) [21, 22]. Second, covariate screening was informed by prior literature, clinical expertise, and the absence of multicollinearity (defined as a Variance Inflation Factor [VIF] > 5) [23].

Statistical Analysis

Continuous variables were presented as means (normally distributed) or medians (non-normally distributed), with between-group differences tested using the Kruskal-Wallis test. Categorical variables were expressed as frequencies and percentages (%), analyzed via chi-square or Fisher's exact tests as appropriate. The association between Hb trajectory class membership and mortality at each time point

was evaluated using multivariable Cox proportional hazards models. The proportional hazards assumption was verified for all models using Schoenfeld residuals[24]. Survival distributions were visualized using Kaplan-Meier curves. Subgroup analyses and multivariable Cox regression using the original dataset without missing data imputation were performed as sensitivity assessments. All statistical analyses were conducted using R Statistical Software (v4.2; R Foundation) and Free Statistics Platform (v2.1.1; China). Statistical significance was defined as a two-tailed $P < 0.05$ [25].

Results

Baseline Characteristics

The study cohort comprised 1,384 critically ill patients undergoing maintenance hemodialysis. The participant selection flowchart is presented in Supplementary Fig. 1. Table 1 details the baseline demographic, clinical, and laboratory characteristics, stratified by 365-day survival status.

Table 1

Baseline demographic characteristics of the study population stratified by 365-day mortality.

Age(years)	Total (n = 1384)	Survivor (n = 763)	Non-Survivor (n = 621)	p
	63.8 ± 15.1	61.5 ± 15.5	66.8 ± 14.1	< 0.001
Sex(n,%)				0.314
Female	553 (40.0)	314 (41.2)	239 (38.5)	
Male	831 (60.0)	449 (58.8)	382 (61.5)	
HR(beats/min)	86.7 ± 16.9	86.6 ± 16.8	86.8 ± 17.1	0.748
SBP(mmHg)	118.0 ± 19.7	121.8 ± 20.1	113.4 ± 18.3	< 0.001
DBP(mmHg)	59.8 ± 12.0	61.5 ± 12.5	57.7 ± 10.9	< 0.001
RR(breaths/min)	19.7 ± 4.3	19.4 ± 4.1	20.0 ± 4.4	0.011
Temperature(°C)	36.7 ± 0.7	36.8 ± 0.7	36.6 ± 0.7	< 0.001
RBC(×10 ¹² /L)	3.3 ± 0.7	3.3 ± 0.7	3.3 ± 0.7	0.326
HCT(%)	28.3 ± 5.9	28.4 ± 6.0	28.3 ± 5.9	0.692
HB(g/dL)	9.4 ± 1.9	9.4 ± 2.0	9.3 ± 1.9	0.2
PLT(×10 ⁹ /L)	151.0 (97.0, 213.2)	158.0 (109.5, 216.0)	139.0 (78.0, 209.0)	< 0.001
WBC(×10 ⁹ /L)	12.6 (8.6, 18.2)	12.0 (8.4, 17.5)	13.1 (8.8, 19.2)	0.029
Glucose(mg/dL)	132.6 (108.5, 168.4)	131.0 (108.4, 161.7)	135.8 (109.0, 174.4)	0.121
Spo2(%)	96.9 ± 2.5	97.0 ± 2.3	96.8 ± 2.8	0.116
Aniongap(mmol/L)	20.6 ± 5.9	20.8 ± 6.0	20.4 ± 5.8	0.277
Bicarbonate(mmol/L)	20.1 ± 5.8	20.1 ± 5.7	20.0 ± 5.9	0.86
Crea(mg/dL)	4.4 (2.6, 6.7)	5.1 (3.2, 7.5)	3.8 (2.2, 5.5)	< 0.001
Bun(mg/dL)	49.0 (33.0, 74.2)	51.0 (34.0, 76.5)	46.0 (30.0, 72.0)	0.022

Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.

Age(years)	Total (n = 1384)	Survivor (n = 763)	Non-Survivor (n = 621)	p
	63.8 ± 15.1	61.5 ± 15.5	66.8 ± 14.1	< 0.001
Calcium(mg/dL)	8.0 ± 1.1	7.9 ± 1.2	8.0 ± 1.1	0.556
Chloride(mmol/L)	99.2 ± 6.6	99.0 ± 6.5	99.4 ± 6.7	0.234
Sodium(mmol/L)	135.4 ± 5.3	135.4 ± 5.1	135.3 ± 5.5	0.655
Potassium(mmol/L)	5.1 ± 1.1	5.2 ± 1.2	5.0 ± 1.0	0.004
INR(ratio)	1.4 (1.2, 2.0)	1.4 (1.2, 1.8)	1.6 (1.3, 2.2)	< 0.001
PT(seconds)	15.9 (13.6, 21.1)	15.2 (13.3, 19.9)	17.3 (14.1, 23.3)	< 0.001
APTT(seconds)	38.3 (31.1, 57.5)	35.6 (30.6, 52.3)	42.6 (32.6, 63.1)	< 0.001
vasopressor(n,%)				< 0.001
No	647 (46.7)	408 (53.5)	239 (38.5)	
Yes	737 (53.3)	355 (46.5)	382 (61.5)	
Ventilation(n,%)				< 0.001
No	590 (42.6)	357 (46.8)	233 (37.5)	
Yes	794 (57.4)	406 (53.2)	388 (62.5)	
Transfusion(n,%)				0.357
No	1368 (98.8)	756 (99.1)	612 (98.6)	
Yes	16 (1.2)	7 (0.9)	9 (1.4)	
MI(n,%)				0.002
No	1119 (80.9)	639 (83.7)	480 (77.3)	
Yes	265 (19.1)	124 (16.3)	141 (22.7)	
CHF(n,%)				< 0.001
No	818 (59.1)	481 (63)	337 (54.3)	

Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.

Age(years)	Total (n = 1384)	Survivor (n = 763)	Non-Survivor (n = 621)	p
	63.8 ± 15.1	61.5 ± 15.5	66.8 ± 14.1	< 0.001
Yes	566 (40.9)	282 (37)	284 (45.7)	
PVD(n,%)				0.011
No	1122 (81.1)	637 (83.5)	485 (78.1)	
Yes	262 (18.9)	126 (16.5)	136 (21.9)	
CVD(n,%)				0.414
No	1234 (89.2)	685 (89.8)	549 (88.4)	
Yes	150 (10.8)	78 (10.2)	72 (11.6)	
COPD(n,%)				0.058
No	974 (70.4)	553 (72.5)	421 (67.8)	
Yes	410 (29.6)	210 (27.5)	200 (32.2)	
DM(n,%)				0.547
No	994 (71.8)	553 (72.5)	441 (71)	
Yes	390 (28.2)	210 (27.5)	180 (29)	
Cancer(n,%)				< 0.001
No	1232 (89.0)	706 (92.5)	526 (84.7)	
Yes	152 (11.0)	57 (7.5)	95 (15.3)	
CCI(score)	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	8.0 (6.0, 10.0)	< 0.001
APSIII(score)	68.0 (53.0, 90.2)	63.0 (50.0, 82.5)	75.0 (58.0, 100.0)	< 0.001
SAPII(score)	46.0 (36.0, 55.2)	43.0 (34.0, 52.0)	49.0 (39.0, 59.0)	< 0.001
OASIS(score)	37.0 (29.0, 46.0)	35.0 (28.0, 44.0)	39.0 (32.0, 48.0)	< 0.001

Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.

Age(years)	Total (n = 1384)	Survivor (n = 763)	Non-Survivor (n = 621)	p
	63.8 ± 15.1	61.5 ± 15.5	66.8 ± 14.1	< 0.001
SOFA(score)	8.0 (5.0, 10.0)	7.0 (5.0, 10.0)	8.0 (6.0, 11.0)	< 0.001
Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.				

Compared to survivors, non-survivors were significantly older and exhibited greater physiological derangement, as reflected in higher severity-of-illness scores (APS III: 75.0 vs. 63.0; SOFA: 8.0 vs. 7.0) and more frequent utilization of vasoactive drugs and mechanical ventilation (all $P < 0.001$). Non-survivors also had higher platelet counts, more pronounced coagulation abnormalities (elevated INR, PT, and APTT), and a higher prevalence of cancer (all $P < 0.001$). In contrast, no significant differences were observed between survivors and non-survivors in admission hemoglobin levels (9.3 vs. 9.4 g/dL, $P = 0.2$) or serum bicarbonate concentrations (20.0 vs. 20.1 mmol/L, $P = 0.86$).

Identification of Hemoglobin Trajectory Subgroups

Model fit indices for the Latent Class Growth Modeling (LCGM) are presented in Table 2. The three-class solution was selected as optimal, demonstrating a superior balance between statistical fit and clinical interpretability. It yielded lower information criteria (AIC = 20077.9, BIC = 20182.6) compared to the two-class model. The model's entropy was 0.72, exceeding the conventional threshold of 0.70, and the average posterior probabilities for class assignment were robust (Class 1: 0.91; Class 2: 0.75; Class 3: 0.75). Although models specifying four or five classes showed marginally improved fit indices (AIC = 20021.9 and AIC = 20018.0, respectively), they resulted in subgroups comprising less than 5% of the cohort (specifically, one subgroup contained only 2.1% of patients in the 4-class model, and two subgroups contained 2.1% and 5.3% in the 5-class model), which were deemed too small for reliable clinical inference and were therefore rejected.

Table 2
Metrics for determining the optimal trajectories.

Trajectory(n)	Loglikelihood	AIC	BIC	SABIC	Entropy
2	-10032.40965	20094.81931	20173.3103	20125.66116	0.447447016
3	-10018.95264	20077.90528	20182.55995	20119.02775	0.719912427
4	-9985.93593	20021.87186	20152.69019	20073.27494	0.592372036
5	-9979.001542	20018.00308	20174.98508	20079.68678	0.604926811
Trajectory(n)	Class1(%)	Class2(%)	Class3(%)	Class4	Class5(%)
2	87.42774566	12.57225434	NA	NA	NA
3	37.57225434	55.92485549	6.502890173	NA	NA
4	19.50867052	39.16184971	36.92196532	4.407514451	NA
5	6.213872832	44.14739	42.19653179	2.095375723	5.346820809
Trajectory(n)	PP1	PP2	PP3	PP4	PP5
2	0.8546	0.7907	NA	NA	NA
3	0.9109	0.7465	0.7507	NA	NA
4	0.7827	0.7796	0.76	0.7576	NA
5	0.6931	0.7468	0.7549	0.7321	0.7324
AIC, akaike information criterion; BIC: bayesian information criteria; SABIC: sample-adjusted information criteria; PP, Posterior probability					

The three identified hemoglobin trajectory patterns over the 30-day period are illustrated in Fig. 1. Class 1 (“Stable-Low”; n = 520, 37.6%) was characterized by hemoglobin levels consistently maintained within a narrow, near-physiological range (8.0–9.0 g/dL) with minimal fluctuation. Class 2 (“Moderate-Degradation”; n = 774, 55.9%) exhibited an approximately linear decrease from an initial 11.0 g/dL at ICU admission to 9.0 g/dL by day 30. Class 3 (“Rapid-Deterioration”; n = 90, 6.5%) demonstrated a pronounced, accelerated decline from 13.0 g/dL to 8.0 g/dL over the same period. The rate of hemoglobin depletion was markedly steeper in Class 3 compared to both Class 1 and Class 2.

Clinical Characteristics of Hemoglobin Trajectory Subgroups

Baseline characteristics stratified by the three Hb trajectory classes are detailed in Table 3. Patients in Class 3 were significantly younger than those in Class 1 or Class 2 (median 56.9 vs. 63.4 and 65.0 years, respectively; $P < 0.001$). Despite their younger age, they presented with heightened markers of acute physiological stress, including significantly higher heart rate, respiratory rate, and anion gap (all $P < 0.001$ compared to other classes). Hematological profiles revealed distinctive patterns. Class 3 had the highest

admission Hb level (12.1 ± 2.5 g/dL), contrasting with lower levels in Class 1 (8.2 ± 1.2 g/dL) and Class 2 (9.8 ± 1.7 g/dL) ($P < 0.001$). This group also exhibited the most pronounced coagulation abnormalities, with higher median INR (1.6 vs. 1.4 and 1.5) and PT (17.8 vs. 15.2 and 16.4 s) ($P < 0.001$). Clinically, Class 3 patients had the highest rates of vasoactive drug use (61.1%) and mechanical ventilation (67.8%). Mortality rates increased progressively across trajectory classes. The 60-day mortality was highest in Class 3 (35.6%), intermediate in Class 2 (32.2%), and lowest in Class 1 (24.6%) ($P = 0.006$). Conversely, the CCI was lowest in Class 3 (median 6), compared to Class 1 (median 7) and Class 2 (median 7) ($P < 0.001$), suggesting that acute physiological insults, rather than chronic comorbidity burden, predominantly influenced outcomes in the rapid-deterioration group.

Table 3
Baseline demographic characteristics of the study population stratified by classes.

Variables	Total (n = 1384)	Class1 (n = 520)	Class2 (n = 774)	Class3 (n = 90)	p
Age(years)	63.8 ± 15.1	63.4 ± 14.4	65.0 ± 15.2	56.9 ± 16.7	< 0.001
Sex(n,%)					0.009
Female	553 (40.0)	222 (42.7)	308 (39.8)	23 (25.6)	
Male	831 (60.0)	298 (57.3)	466 (60.2)	67 (74.4)	
HR(beats/min)	86.7 ± 16.9	86.5 ± 16.0	85.8 ± 16.9	94.9 ± 20.5	< 0.001
SBP(mmHg)	118.0 ± 19.7	120.1 ± 19.6	117.0 ± 19.5	115.3 ± 21.2	0.008
DBP(mmHg)	59.8 ± 12.0	59.4 ± 12.1	59.4 ± 11.7	64.9 ± 12.4	< 0.001
RR(breaths/min)	19.7 ± 4.3	19.8 ± 4.4	19.4 ± 4.1	21.4 ± 4.6	< 0.001
Temperature(°C)	36.7 ± 0.7	36.8 ± 0.6	36.7 ± 0.7	36.8 ± 0.9	0.033
RBC(×10 ¹² /L)	3.3 ± 0.7	2.9 ± 0.5	3.4 ± 0.6	4.3 ± 0.8	< 0.001
HCT(%)	28.3 ± 5.9	25.1 ± 3.7	29.6 ± 5.6	36.2 ± 7.6	< 0.001
HB(g/dL)	9.4 ± 1.9	8.2 ± 1.2	9.8 ± 1.7	12.1 ± 2.5	< 0.001
PLT(×10 ⁹ /L)	151.0 (97.0, 213.2)	154.0 (100.0, 222.2)	151.5 (96.2, 208.0)	146.5 (91.0, 211.0)	0.428
WBC(×10 ⁹ /L)	12.6 (8.6, 18.2)	12.4 (8.1, 17.8)	12.6 (8.8, 17.9)	13.8 (9.6, 22.0)	0.053
Glucose(mg/dL)	132.6 (108.5, 168.4)	128.5 (107.3, 166.2)	133.0 (109.4, 167.8)	143.7 (115.7, 192.1)	0.08
Spo2(%)	96.9 ± 2.5	97.1 ± 2.0	96.9 ± 2.6	96.0 ± 4.3	< 0.001
Aniongap(mmol/L)	20.6 ± 5.9	20.3 ± 5.6	20.6 ± 5.9	22.8 ± 7.0	0.001
Bicarbonate(mmol/L)	20.1 ± 5.8	20.0 ± 5.7	20.4 ± 5.8	17.5 ± 5.2	< 0.001

Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.

Variables	Total (n = 1384)	Class1 (n = 520)	Class2 (n = 774)	Class3 (n = 90)	p
Crea(mg/dL)	4.4 (2.6, 6.7)	4.7 (3.1, 7.0)	4.3 (2.3, 6.5)	3.3 (1.9, 5.5)	< 0.001
Bun(mg/dL)	49.0 (33.0, 74.2)	60.0 (37.0, 87.0)	45.0 (30.0, 67.0)	39.0 (31.0, 59.8)	< 0.001
Calcium(mg/dL)	8.0 ± 1.1	7.9 ± 1.1	8.0 ± 1.1	7.7 ± 1.4	0.002
Chloride(mmol/L)	99.2 ± 6.6	99.4 ± 6.7	99.0 ± 6.5	99.5 ± 7.1	0.449
Sodium(mmol/L)	135.4 ± 5.3	135.3 ± 5.4	135.4 ± 5.2	135.4 ± 5.6	0.863
Potassium(mmol/L)	5.1 ± 1.1	5.1 ± 1.1	5.1 ± 1.1	5.3 ± 1.3	0.172
INR(ratio)	1.4 (1.2, 2.0)	1.4 (1.2, 1.8)	1.5 (1.2, 2.1)	1.6 (1.3, 2.5)	< 0.001
PT(seconds)	15.9 (13.6, 21.1)	15.2 (13.4, 19.5)	16.4 (13.7, 21.9)	17.8 (14.3, 25.4)	< 0.001
APTT(seconds)	38.3 (31.1, 57.5)	35.9 (30.6, 48.3)	39.2 (31.7, 62.3)	46.6 (32.5, 70.5)	< 0.001
vasopressor(n,%)					0.029
No	647 (46.7)	265 (51)	347 (44.8)	35 (38.9)	
Yes	737 (53.3)	255 (49)	427 (55.2)	55 (61.1)	
Ventilation(n,%)					0.042
No	590 (42.6)	238 (45.8)	323 (41.7)	29 (32.2)	
Yes	794 (57.4)	282 (54.2)	451 (58.3)	61 (67.8)	
Transfusion(n,%)					0.025
No	1368 (98.8)	510 (98.1)	770 (99.5)	88 (97.8)	
Yes	16 (1.2)	10 (1.9)	4 (0.5)	2 (2.2)	
MI(n,%)					0.296
No	1119 (80.9)	428 (82.3)	615 (79.5)	76 (84.4)	
Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.					

Variables	Total (n = 1384)	Class1 (n = 520)	Class2 (n = 774)	Class3 (n = 90)	p
Yes	265 (19.1)	92 (17.7)	159 (20.5)	14 (15.6)	
CHF(n,%)					0.123
No	818 (59.1)	322 (61.9)	439 (56.7)	57 (63.3)	
Yes	566 (40.9)	198 (38.1)	335 (43.3)	33 (36.7)	
PVD(n,%)					0.005
No	1122 (81.1)	441 (84.8)	604 (78)	77 (85.6)	
Yes	262 (18.9)	79 (15.2)	170 (22)	13 (14.4)	
CVD(n,%)					0.629
No	1234 (89.2)	469 (90.2)	685 (88.5)	80 (88.9)	
Yes	150 (10.8)	51 (9.8)	89 (11.5)	10 (11.1)	
COPD(n,%)					0.812
No	974 (70.4)	371 (71.3)	541 (69.9)	62 (68.9)	
Yes	410 (29.6)	149 (28.7)	233 (30.1)	28 (31.1)	
DM(n,%)					0.565
No	994 (71.8)	373 (71.7)	552 (71.3)	69 (76.7)	
Yes	390 (28.2)	147 (28.3)	222 (28.7)	21 (23.3)	
Cancer(n,%)					0.011
No	1232 (89.0)	446 (85.8)	705 (91.1)	81 (90)	
Yes	152 (11.0)	74 (14.2)	69 (8.9)	9 (10)	
CCI(score)	7.0 (5.0, 9.0)	7.0 (6.0, 9.0)	7.0 (5.0, 9.0)	6.0 (4.0, 8.8)	< 0.001
APSIII(score)	68.0 (53.0, 90.2)	67.0 (53.0, 87.0)	68.0 (52.0, 92.0)	76.0 (50.5, 102.0)	0.216
Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.					

Variables	Total (n = 1384)	Class1 (n = 520)	Class2 (n = 774)	Class3 (n = 90)	p
SAPII(score)	46.0 (36.0, 55.2)	45.0 (37.0, 56.0)	46.0 (36.0, 55.0)	44.5 (35.0, 60.0)	0.951
OASIS(score)	37.0 (29.0, 46.0)	36.0 (29.0, 44.0)	37.0 (29.0, 46.0)	43.5 (31.2, 51.0)	0.003
SOFA(score)	8.0 (5.0, 10.0)	8.0 (5.0, 10.0)	8.0 (6.0, 11.0)	8.5 (5.2, 12.0)	0.106
30-day mortality, (n,%)					0.088
No	1058 (76.4)	412 (79.2)	583 (75.3)	63 (70)	
Yes	326 (23.6)	108 (20.8)	191 (24.7)	27 (30)	
60-day mortality, (n,%)					0.006
No	975 (70.4)	392 (75.4)	525 (67.8)	58 (64.4)	
Yes	409 (29.6)	128 (24.6)	249 (32.2)	32 (35.6)	
90-day mortality, (n,%)					0.018
No	927 (67.0)	372 (71.5)	499 (64.5)	56 (62.2)	
Yes	457 (33.0)	148 (28.5)	275 (35.5)	34 (37.8)	
365-day mortality, (n,%)					0.185
No	763 (55.1)	303 (58.3)	411 (53.1)	49 (54.4)	
Yes	621 (44.9)	217 (41.7)	363 (46.9)	41 (45.6)	
Abb: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO2, oxygen saturation; RBC, red blood cell; HCT, hematocrit; HB, hemoglobin; PLT, platelet; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CCI, Charlson Comorbidity Index; APS III, Acute Physiology Score III; SAP II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.					

Identification of Candidate Covariates

To identify key predictors of mortality for model adjustment, we performed variable selection using the LASSO regression. The analysis, conducted on the entire cohort, employed 10-fold cross-validation to determine the optimal penalty parameter (λ). The optimal λ value ($\lambda = 0.036$), corresponding to one standard error above the minimum cross-validation error, resulted in a parsimonious model with seven non-zero coefficient variables (Figs. 2).

The final candidate covariates selected by LASSO were then assessed for potential collinearity using variance inflation factor (VIF) analysis. All selected variables demonstrated VIF values below the threshold of 5 (range: 1.03–1.50), indicating the absence of significant multicollinearity. No significant interactions were detected among the covariates in preliminary analyses. The characteristics and estimated effect sizes of these seven variables, which were ultimately included in the final multivariable COX models, are detailed in Table 4. They comprised the three Hb trajectory classes (with “Class 1” as the reference) and four additional clinical parameters: serum creatinine, body temperature, systolic blood pressure, and the Charlson Comorbidity Index, along with two severity markers: the APS III score and vasopressor use.

Table 4
Covariate characteristics eventually included in multivariable COX model.

Variable	β	HR.95%CI	p	VIF	Co-linearity
Class	0.012				
Class1		1(Ref)			
Class2		1.36 (1.1 ~ 1.68)	0.005		
Class3		1.59 (1.08 ~ 2.34)	0.019		
Creatinine	-0.102	0.82 (0.79 ~ 0.85)	< 0.001	1.042	0
Temperature	-0.06	0.7 (0.6 ~ 0.8)	< 0.001	1.032	0
SBP	-0.009	0.98 (0.97 ~ 0.98)	< 0.001	1.029	0
APSIII	0.013	1.02 (1.02 ~ 1.02)	< 0.001	1.099	0
INR	0.016	1.13 (1.08 ~ 1.18)	< 0.001	1.049	0
Vasopressor use	0.026	1.01 (1.01 ~ 1.02)	< 0.001	1.496	0
CCI	0.048	1.08 (1.05 ~ 1.12)	< 0.001	1.493	0
Abb: Hazard Ratio,HR;95% confidence interval ,95% CI; VIF,Variance Inflation ; Temperature, temperature; SBP, systolic blood pressure; APS III, Acute Physiology Score III; INR, international normalized ratio; CCI, Charlson Comorbidity Index.Factor .					

Association Between Hb Trajectories and Mortality

Multivariable Cox proportional hazards models were constructed to assess the independent association of Hb trajectory class membership with all-cause mortality at different time points, adjusting for the covariates identified through LASSO regression. The results are detailed in Table 5. Distinct time-dependent mortality patterns were observed across the trajectory classes. Using Class 1 (“Stable-Low”) as the reference, Class 3 (“Rapid-Deterioration”) was associated with a significantly elevated risk of 30-day mortality with adjusted hazard ratio (aHR) = 1.63, 95% confidence interval (CI: 1.07–2.49; P = 0.024). However, this excess risk attenuated over longer follow-up, becoming non-significant at 90 days (aHR =

1.32, 95% CI: 0.90–1.92; $P = 0.154$) and 365 days (aHR = 1.13, 95% CI: 0.81–1.58; $P = 0.475$). A significant trend of risk reduction over time was observed for this class (P for trend = 0.003).

Table 5
Multivariable logistic regression analyses of the association of class with mortality.

Outcome	Item	Crude model		Adjusted model	
		HR	95%CI	HR	95%CI
30-day mortality	Class1	1(Ref)		1(Ref)	
	Class2	1.22 (0.97 ~ 1.55)	0.093	1.21 (0.95 ~ 1.53)	0.12
	Class3	1.56 (1.02 ~ 2.38)	0.039	1.63 (1.07 ~ 2.49)	0.024
	p for trend	1.24 (1.03 ~ 1.49)	0.022	1.25 (1.03 ~ 1.5)	0.021
60-day mortality	Class1	1(Ref)		1(Ref)	
	Class2	1.36 (1.1 ~ 1.68)	0.005	1.35 (1.09 ~ 1.67)	0.006
	Class3	1.59 (1.08 ~ 2.34)	0.019	1.68 (1.14 ~ 2.48)	0.009
	p for trend	1.3 (1.1 ~ 1.53)	0.002	1.32 (1.12 ~ 1.56)	0.001
90-day mortality	Class1	1(Ref)		1(Ref)	
	Class2	1.31 (1.07 ~ 1.6)	0.009	1.24 (1.01 ~ 1.51)	0.039
	Class3	1.47 (1.01 ~ 2.13)	0.043	1.32 (0.9 ~ 1.92)	0.154
	p for trend	1.25 (1.07 ~ 1.46)	0.004	1.18 (1.01 ~ 1.39)	0.034
365-day mortality	Class1	1(Ref)		1(Ref)	
	Class2	1.19 (1.01 ~ 1.41)	0.039	1.16 (0.98 ~ 1.37)	0.086
	Class3	1.2 (0.86 ~ 1.67)	0.29	1.13 (0.81 ~ 1.58)	0.475
	p for trend	1.14 (1 ~ 1.3)	0.053	1.11 (0.97 ~ 1.27)	0.134
Adjusted model was adjusted for Creatinine, Temperature, Systolic Blood Pressure, Acute Physiology Score III, International Normalized Ratio, vasopressor use, Charlson Comorbidity Index.					
Abb: HR, hazard ratioe; 95% CI, 95% confidence interval.					

In contrast, Class 2 (“Moderate-Decline”) demonstrated a persistent elevation in mortality risk. The association was strongest for 60-day mortality (aHR = 1.35, 95% CI: 1.09–1.67; $P = 0.006$) and remained significant for 90-day mortality (aHR = 1.24, 95% CI: 1.01–1.51; $P = 0.039$). The mortality risk in this class did not show a significant trend of attenuation over the follow-up period (P for trend > 0.05).

Kaplan-Meier Survival Analysis

The proportional hazards assumption of the multivariable Cox models was verified using Schoenfeld residuals. The P -values for the Schoenfeld residual test at 30, 60, 90, and 365 days were 0.546, 0.410, 0.349, and 0.074, respectively, all greater than 0.05, indicating that the proportional hazards assumption was satisfied. Kaplan-Meier survival curves were generated to visualize the unadjusted survival differences among the three hemoglobin trajectory classes at 30, 60, 90, and 365 days. Consistent survival stratification was observed across all time points (Fig. 3). Class 1 demonstrated the most favorable survival probability, followed by Class 2, with Class 3 consistently exhibiting the poorest outcomes. Log-rank tests quantified these visual differences. Statistically significant differences in survival distributions were confirmed at 60 days ($P = 0.0065$) and 90 days ($P = 0.015$). A trend toward separation was evident at 30 days, though it did not reach statistical significance ($P = 0.069$). By 365 days, while the survival curves continued to show clear visual separation, with 365-day survival probabilities of approximately 58.3% (Class 1), 53.1% (Class 2), and 54.4% (Class 3) based on the number at risk, the overall log-rank test did not indicate a statistically significant difference ($P = 0.11$). The most pronounced early decline in survival probability was observed in Class 3, temporally coinciding with its period of most rapid hemoglobin depletion.

Sensitivity Analyses

To evaluate the robustness of our primary findings, we conducted two sensitivity analyses: subgroup analyses and an assessment of the impact of missing data handling.

Pre-specified subgroup analyses were performed for 60-day mortality (Table 6). A statistically significant interaction was observed for age (P for interaction = 0.026). Among patients aged ≥ 65 years, Class 3 was associated with a substantially increased mortality risk (HR = 3.00, 95% CI: 1.80–5.00). In contrast, no significant association was found for Class 3 in patients aged < 65 years (HR = 0.99, 95% CI: 0.55–1.81). The associations for Class 2 remained consistently elevated across both age groups (HR ~ 1.23–1.44). No significant effect modification was detected for sex, baseline disease severity (as measured by CCI, APS III, or SOFA scores), or the presence of specific comorbidities (CVD, COPD, DM) (all P for interaction > 0.05). The trajectory-mortality association was generally consistent across these subgroups, with hazard ratios for Class 3 ranging from 1.31 to 3.00 and for Class 2 from 1.27 to 1.44.

Table 6
Subgroup analysis for 60-day mortality.

Variable		Total	Event (%)	HR (95%CI)	p for interaction
Sex	Female				0.885
	Class1	222	53 (23.9)	1(Ref)	
	Class2	308	99 (32.1)	1.4 (1.01 ~ 1.96)	
	Class3	23	9 (39.1)	1.83 (0.9 ~ 3.71)	
	Trend	553	161 (29.1)	1.38 (1.05 ~ 1.82)	
	Male				
	Class1	298	75 (25.2)	1(Ref)	
	Class2	466	150 (32.2)	1.33 (1.01 ~ 1.75)	
	Class3	67	23 (34.3)	1.49 (0.93 ~ 2.38)	
	Trend	831	248 (29.8)	1.26 (1.02 ~ 1.54)	
Age	< 65				0.026
	Class1	274	63 (23)	1(Ref)	
	Class2	360	99 (27.5)	1.23 (0.9 ~ 1.69)	
	Class3	58	13 (22.4)	0.99 (0.55 ~ 1.81)	
	Trend	692	175 (25.3)	1.09 (0.86 ~ 1.38)	
	≥ 65				
	Class1	246	65 (26.4)	1(Ref)	
	Class2	414	150 (36.2)	1.44 (1.08 ~ 1.93)	
	Class3	32	19 (59.4)	3 (1.8 ~ 5)	

Age, categorized by median; CCI (Charlson Comorbidity Index), categorized by median; APS III (Acute Physiology Score III), categorized by median; SOFA (Sequential Organ Failure Assessment), categorized by median; CVD (cerebrovascular disease), categorized by median; COPD (chronic obstructive pulmonary disease), categorized by median; DM (diabetes mellitus), categorized by median.

Variable		Total	Event (%)	HR (95%CI)	p for interaction
CCI	Trend	692	234 (33.8)	1.6 (1.26 ~ 2.03)	0.928
	Class1	187	40 (21.4)	1(Ref)	
	Class2	292	83 (28.4)	1.37 (0.94 ~ 2)	
	Class3	50	17 (34)	1.76 (1 ~ 3.1)	
	Trend	529	140 (26.5)	1.34 (1.03 ~ 1.75)	
≥ 7					
	Class1	333	88 (26.4)	1(Ref)	0.117
	Class2	482	166 (34.4)	1.36 (1.05 ~ 1.76)	
	Class3	40	15 (37.5)	1.54 (0.89 ~ 2.66)	
	Trend	855	269 (31.5)	1.3 (1.06 ~ 1.61)	
	APSI	< 68			
	Class1	263	37 (14.1)	1(Ref)	0.117
	Class2	368	89 (24.2)	1.8 (1.23 ~ 2.65)	
	Class3	46	14 (30.4)	2.33 (1.26 ~ 4.31)	
	Trend	677	140 (20.7)	1.6 (1.22 ~ 2.1)	
	≥ 68				
	Class1	257	91 (35.4)	1(Ref)	
	Class2	406	160 (39.4)	1.14 (0.88 ~ 1.48)	
	Class3	44	18 (40.9)	1.31 (0.79 ~ 2.17)	
Age, categorized by median; CCI (Charlson Comorbidity Index), categorized by median; APS III (Acute Physiology Score III), categorized by median; SOFA (Sequential Organ Failure Assessment), categorized by median; CVD (cerebrovascular disease), categorized by median; COPD (chronic obstructive pulmonary disease), categorized by median; DM (diabetes mellitus), categorized by median.					

Variable		Total	Event (%)	HR (95%CI)	p for interaction
SOFA	Trend	707	269 (38)	1.14 (0.93 ~ 1.41)	0.078
	< 8				
	Class1	254	42 (16.5)	1(Ref)	
	Class2	373	93 (24.9)	1.56 (1.08 ~ 2.24)	
	Class3	35	14 (40)	2.82 (1.54 ~ 5.16)	
	Trend	662	149 (22.5)	1.63 (1.23 ~ 2.16)	
	≥ 8				
	Class1	266	86 (32.3)	1(Ref)	
	Class2	401	156 (38.9)	1.27 (0.97 ~ 1.65)	
	Class3	55	18 (32.7)	1.08 (0.65 ~ 1.79)	
Trend	722	260 (36)	1.13 (0.93 ~ 1.39)		
CVD	No				0.591
	Class1	469	113 (24.1)	1(Ref)	
	Class2	685	222 (32.4)	1.41 (1.12 ~ 1.77)	
	Class3	80	28 (35)	1.58 (1.05 ~ 2.39)	
	Trend	1234	363 (29.4)	1.32 (1.11 ~ 1.57)	
	Yes				
	Class1	51	15 (29.4)	1(Ref)	
	Class2	89	27 (30.3)	1.01 (0.54 ~ 1.9)	
Age, categorized by median; CCI (Charlson Comorbidity Index), categorized by median; APS III (Acute Physiology Score III), categorized by median; SOFA (Sequential Organ Failure Assessment), categorized by median; CVD (cerebrovascular disease), categorized by median; COPD (chronic obstructive pulmonary disease), categorized by median; DM (diabetes mellitus), categorized by median.					

Variable		Total	Event (%)	HR (95%CI)	p for interaction
COPD	Class3	10	4 (40)	1.62 (0.54 ~ 4.89)	0.828
	Trend	150	46 (30.7)	1.15 (0.69 ~ 1.93)	
	Class1	371	87 (23.5)	1(Ref)	
	Class2	541	168 (31.1)	1.39 (1.07 ~ 1.8)	
	Class3	62	20 (32.3)	1.49 (0.92 ~ 2.43)	
	Trend	974	275 (28.2)	1.29 (1.06 ~ 1.57)	
	Yes				
	Class1	149	41 (27.5)	1(Ref)	
	Class2	233	81 (34.8)	1.29 (0.89 ~ 1.89)	
DM	Class3	28	12 (42.9)	1.76 (0.93 ~ 3.35)	0.724
	Trend	410	134 (32.7)	1.31 (0.99 ~ 1.75)	
	Class1	373	91 (24.4)	1(Ref)	
	Class2	552	178 (32.2)	1.38 (1.07 ~ 1.78)	
	Class3	69	26 (37.7)	1.73 (1.12 ~ 2.67)	
	Trend	994	295 (29.7)	1.34 (1.11 ~ 1.62)	
	Yes				
	Class1	147	37 (25.2)	1(Ref)	
	Age, categorized by median; CCI (Charlson Comorbidity Index), categorized by median; APS III (Acute Physiology Score III), categorized by median; SOFA (Sequential Organ Failure Assessment), categorized by median; CVD (cerebrovascular disease), categorized by median; COPD (chronic obstructive pulmonary disease), categorized by median; DM (diabetes mellitus), categorized by median.				

Variable		Total	Event (%)	HR (95%CI)	p for interaction
	Class2	222	71 (32)	1.31 (0.88 ~ 1.94)	
	Class3	21	6 (28.6)	1.18 (0.5 ~ 2.8)	
	Trend	390	114 (29.2)	1.2 (0.87 ~ 1.65)	
Age, categorized by median; CCI (Charlson Comorbidity Index), categorized by median; APS III (Acute Physiology Score III), categorized by median; SOFA (Sequential Organ Failure Assessment), categorized by median; CVD (cerebrovascular disease), categorized by median; COPD (chronic obstructive pulmonary disease), categorized by median; DM (diabetes mellitus), categorized by median.					

Variables with > 10% missing data (e.g., lactate, height) were excluded from the primary analysis, and remaining missing values were handled via multiple imputation (Supplementary Table 1). To test the sensitivity of our results to this approach, we replicated the primary multivariable Cox regression models using the original, non-imputed dataset (under a missing-at-random assumption) and compared the effect estimates (Supplementary Table 2).

The comparative analysis revealed a high degree of consistency between the imputed (Table 5) and non-imputed models. For the key findings: the elevated 30-day mortality risk associated with Class 3 remained statistically significant in both analyses (adjusted HR = 1.63 vs. 1.53), and the elevated 60-day mortality risk associated with Class 2 was also consistently significant (adjusted HR = 1.35 vs. 1.21). Some expected attenuation in effect size and slight variation in P-values were observed in the non-imputed model (e.g., Class 3's 90-day mortality: imputed HR = 1.32, P = 0.154; non-imputed HR = 1.33, P = 0.171), but the confidence intervals overlapped substantially. Crucially, the direction, magnitude, and temporal pattern of all associations were preserved. These findings confirm that the primary results regarding trajectory-based mortality risk are robust to the method of handling missing data.

Discussion

This study, through latent class growth modeling, identified three distinct longitudinal Hb trajectories during the first 30 days of ICU admission in critically ill HD patients: stable-low, moderate-decline, and rapid-deterioration. The key finding is that these dynamic patterns convey differential, time-specific prognostic information that cannot be inferred from a single Hb measurement, especially given the lack of significant difference in admission Hb between survivors and non-survivors. Notably, patients in the rapid-deterioration trajectory exhibited a significant 63% increased risk of 30-day mortality, a risk that attenuated over time. In contrast, the moderate-decline trajectory was associated with a persistent elevation in mortality risk, particularly at 60 days. These findings underscore the critical importance of monitoring Hb trends, rather than isolated values, for nuanced risk stratification in this vulnerable population, moving beyond the static paradigm of anemia assessment.

Our results align with the established association between anemia severity/variability and adverse outcomes in HD patients [6, 7]. The observed link between Hb variability and mortality in maintenance HD patients is conceptually extended by our work, which defines specific, clinically interpretable patterns of change (trajectories) rather than a summary metric of variability [26]. More importantly, we demonstrate that different trajectories are associated with distinct temporal risk profiles (acute, attenuating vs. persistent), suggesting divergent underlying mechanisms. This refines the understanding of Hb dynamics from a general risk marker to a potential indicator of specific pathophysiological states. The unique temporal risk profiles that acute, attenuating risk in rapid-deterioration versus persistent risk in moderate-decline suggest distinct underlying pathophysiological drivers.

The steep Hb decline and the associated early peak in 30-day mortality observed in the rapid-deterioration trajectory strongly suggest the presence of acute, potentially reversible hematological insults. Several mechanisms likely contribute to this pattern. First, hemodialysis itself can induce hemolysis through mechanical shear stress, a recognized but often under-appreciated complication [27]. Second, occult bleeding, particularly gastrointestinal or related to vascular access, presents a major challenge in critically ill HD patients, whose systemic symptoms may mask classic signs of hemorrhage [28]. This predisposition is exacerbated by uremia-related hemostatic dysfunction [29, 30] and the routine use of anticoagulation during dialysis [31]. Third, the initially elevated hemoglobin levels seen in some patients in this group may reflect hemoconcentration due to hypovolemia; subsequent fluid resuscitation can unmask the underlying anemia through hemodilution [32]. The attenuation of mortality risk beyond 30 days is a critical finding, as it implies that patients who survive the initial acute insult (e.g., controlled bleeding, resolved hemolysis, or stabilized volume status) may not carry the same long-term risk burden as those with chronic, progressive anemia. This pattern highlights the reversible nature of the primary driver in this trajectory.

In contrast, the moderate-decline trajectory, characterized by a steady, linear decrease in Hb, suggests an underlying state of chronic hematological dysfunction and ESA hyporesponsiveness, largely driven by persistent inflammation [33, 34]. In long-term hemodialysis patients, a sustained inflammatory milieu—fueled by recurrent exposure to dialysis membranes, circulating uremic toxins, and immune dysregulation—fundamentally disrupts erythropoietic homeostasis [33]. Mechanistically, proinflammatory cytokines such as IL-6 suppress erythropoietin production and promote hepcidin synthesis, leading to functional iron deficiency [35, 36]. Concurrently, cytokines like TNF- α can directly inhibit erythroid progenitor proliferation and differentiation [37]. This creates a vicious cycle: inflammation begets ESA resistance, often necessitating higher doses of ESAs or intravenous iron, which may paradoxically amplify oxidative stress and further entrench the inflammatory state [35, 38]. Consequently, this trajectory reflects a sustained, difficult-to-reverse pathophysiological burden, explaining its association with a persistent, non-attenuating elevation in mortality risk.

Our identification of a significant age interaction provides crucial clinical nuance. The pronounced mortality risk associated with the rapid-deterioration trajectory was almost exclusively confined to patients aged ≥ 65 years (HR = 3.00). This finding likely reflects the diminished physiological reserve

characteristic of older adults and aligns with the broader phenotype of frailty [39]. The ageing cardiovascular system exhibits reduced cardiac output and impaired tissue oxygen extraction, critically limiting compensatory responses to acute anemia. Furthermore, cumulative endothelial damage and accelerated vascular calcification in elderly HD patients impair microcirculatory adaptation to Hb fluctuations, compromising tissue perfusion [40]. Therefore, an acute Hb decline interacts synergistically with age-related vulnerabilities to dramatically amplify mortality risk, underscoring the need for heightened vigilance and aggressive management in older patients exhibiting this trajectory.

The strengths of this study include the novel application of trajectory modeling to characterize dynamic Hb changes in a large, well-defined cohort of critically ill HD patients, utilizing high-resolution clinical data. The robustness of our findings is strengthened by comprehensive sensitivity analyses. However, several limitations warrant consideration. First, the retrospective, observational design precludes causal inference, and residual confounding cannot be excluded. Most notably, due to the absence of key variables such as the etiology of ESRD, duration of dialysis, specific dosing and frequency of ESA and intravenous iron supplementation, and dialysis adequacy (Kt/V), these factors may influence the association between Hb trajectories and outcomes. Second, despite the substantial sample size, the data were derived from a single center (Beth Israel Deaconess Medical Center), which may introduce selection bias due to regional variations and differences in clinical practice patterns, potentially limiting the generalizability of the findings. Finally, while the model identifies distinct prognostic patterns, the clinical implementation of real-time trajectory-based monitoring requires prospective validation.

This study provides a dynamic, trajectory-aware framework for risk stratification that has direct clinical implications. For patients identified with a rapid-deterioration trajectory, especially the elderly, clinicians should prioritize prompt investigation for acute bleeding, hemolysis, and careful volume assessment. For those with a moderate-decline pattern, the management focus should shift toward optimizing ESA responsiveness and addressing underlying chronic inflammation and iron dysregulation. Future research must externally validate these Hb trajectory phenotypes in diverse, multi-center cohorts. Prospective interventional studies are needed to determine whether early, trajectory-informed management protocols can improve clinical outcomes. Ultimately, integrating real-time Hb trajectory analytics into clinical decision support systems may facilitate earlier, more individualized therapeutic strategies for anemia in this high-risk population.

Conclusion

This study demonstrates that longitudinal hemoglobin trajectories provide a clinically actionable framework for risk stratification in critically ill hemodialysis patients. The rapid-deterioration phenotype calls for prompt evaluation of acute etiologies such as hemorrhage or hemolysis, especially in elderly individuals. Conversely, the moderate-decline phenotype indicates a need for sustained management of chronic inflammation and ESA hypo-responsiveness. Transitioning from static Hb measurements to dynamic trajectory-based assessment thus enables timely, phenotype-specific interventions and supports a shift toward personalized anemia management in this high-risk population.

Abbreviations

chronic kidney disease (CKD); Hemodialysis (HD); Intensive Care Unit (ICU); Erythropoietin (EPO); Red Blood Cell (RBC); Hemoglobin (Hb); Erythropoiesis-Stimulating Agent (ESA); Latent Class Growth Modeling (LCGM); Medical Information Mart for Intensive Care (MIMIC-IV); Structured Query Language (SQL); Heart Rate (HR); Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Respiratory Rate (RR); Oxygen Saturation (SpO₂); Hematocrit (HCT); Platelet Count (PLT); White Blood Cell Count (WBC); Bicarbonate (HCO₃); Blood Urea Nitrogen (BUN); Creatinine (Cr); Sodium (Na); Potassium (K); International Normalized Ratio (INR); Prothrombin Time (PT); Activated Partial Thromboplastin Time (APTT); Myocardial Infarction (MI); Congestive Heart Failure (CHF); Peripheral Vascular Disease (PVD); Cerebrovascular Disease (CVD); Chronic Pulmonary Disease (CPD); Diabetes Mellitus (DM); Charlson Comorbidity Index (CCI); Acute Physiology Score III (APS III); Simplified Acute Physiology Score II (SAPS II); Oxford Acute Severity of Illness Score (OASIS); Sequential Organ Failure Assessment (SOFA); Strengthening the Reporting of Observational Studies in Epidemiology (STROBE); Akaike Information Criterion (AIC); Bayesian Information Criterion (BIC); Sample-Adjusted BIC (SABIC); Least Absolute Shrinkage and Selection Operator (LASSO); Standard Deviation (SD); Variance Inflation Factor (VIF); Hazard Ratio (HR); Adjusted Hazard Ratio (aHR); Confidence Interval (CI).

Declarations

Authors' contributions

F.L., Y.T. and J.D. made substantial contributions to the conception and design of the work and drafted the manuscript. J.Z., H.L. and X.W. contributed to data acquisition, statistical analysis, and interpretation. L.H., F.D. and X.G. contributed to data interpretation and critical revision of the manuscript. W.R. performed data curation (organization, cleaning, and validation). L.L. and J.F. contributed to drafting and substantive revision of the work. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The MIMIC-IV database was approved by the Institutional Review Boards (IRBs) of Beth Israel Deaconess Medical Center (BIDMC) and the Massachusetts Institute of Technology (MIT), which granted a waiver of

informed consent due to the retrospective nature of the study and the use of de-identified data. As this study involves the analysis of secondary, fully anonymized data from a publicly available source, additional approval from an Institutional Review Board (IRB) or ethics committee was not required, nor was additional informed consent required.

Data availability

Publicly available datasets were analyzed in this study. These data can be found at the datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession numbers can be found at: <https://physionet.org/content/mimiciv/2.0/>

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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41. Legend.

Figures

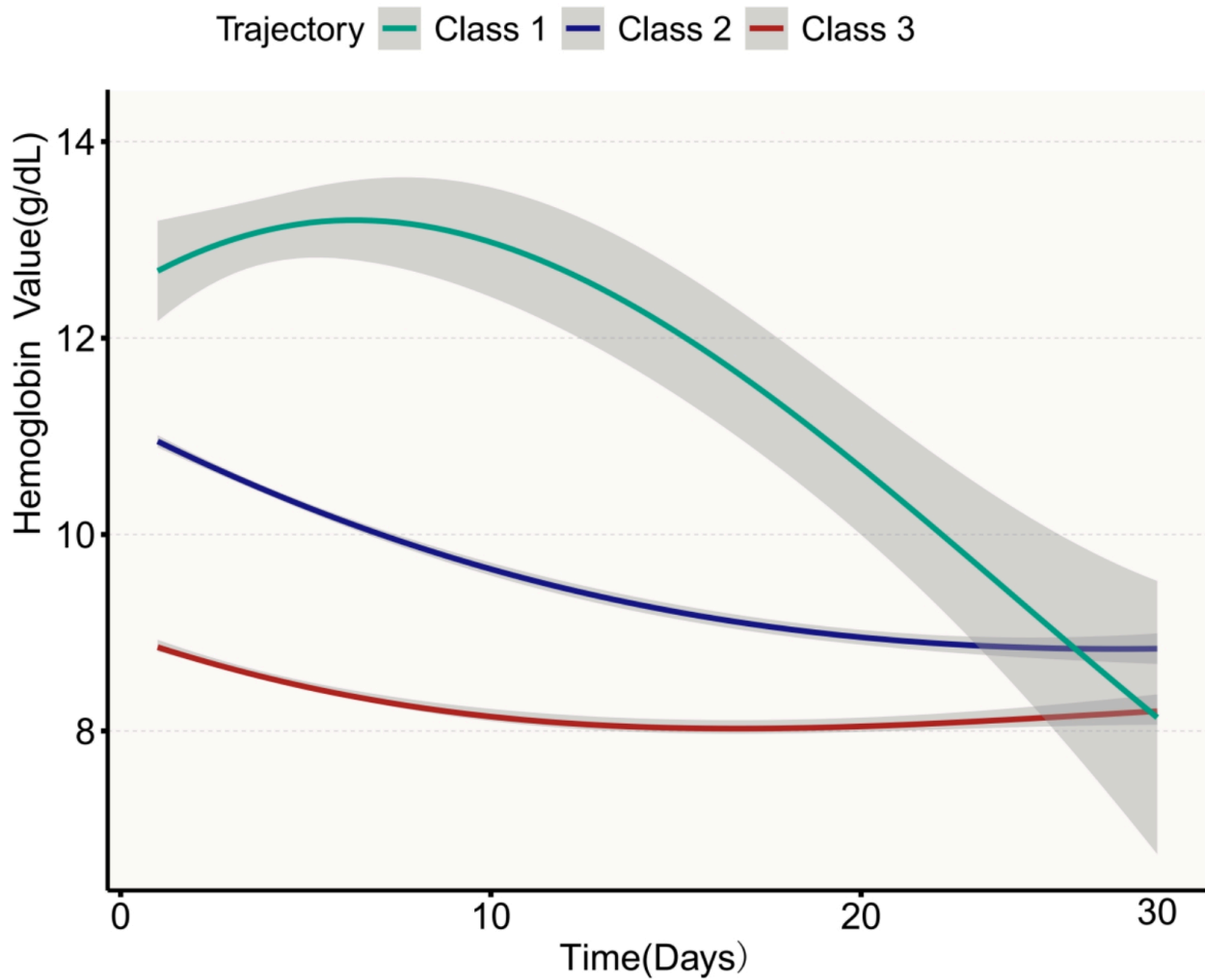


Figure 1

shows the trajectories of hemoglobin (g/dL) over time for three classes. Three groups are shown with the same color scheme: Class 1 (green), Class 2 (purple), Class 3 (red). The shaded area around class trajectory lines denotes the 95% confidence band.

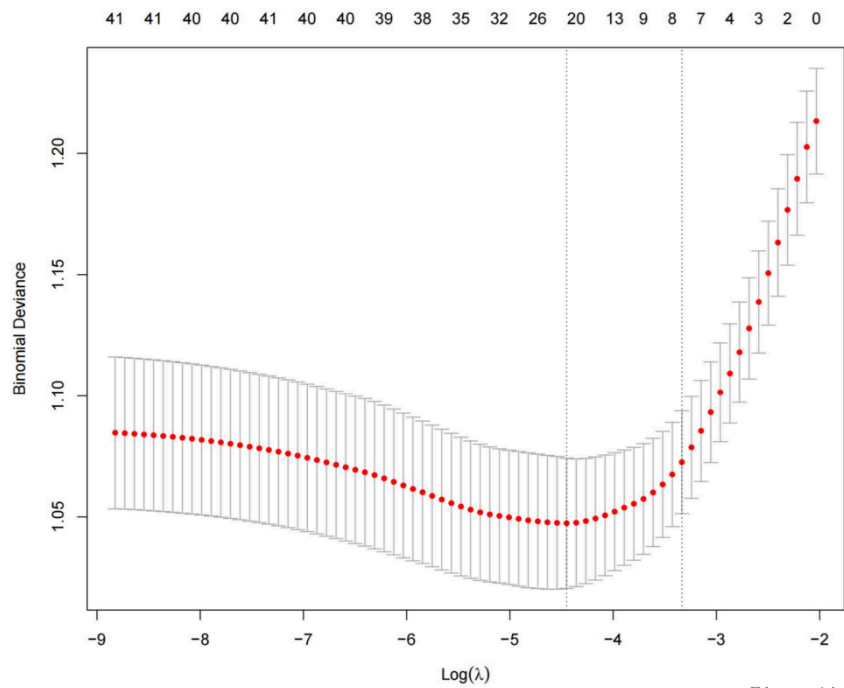


Figure1A

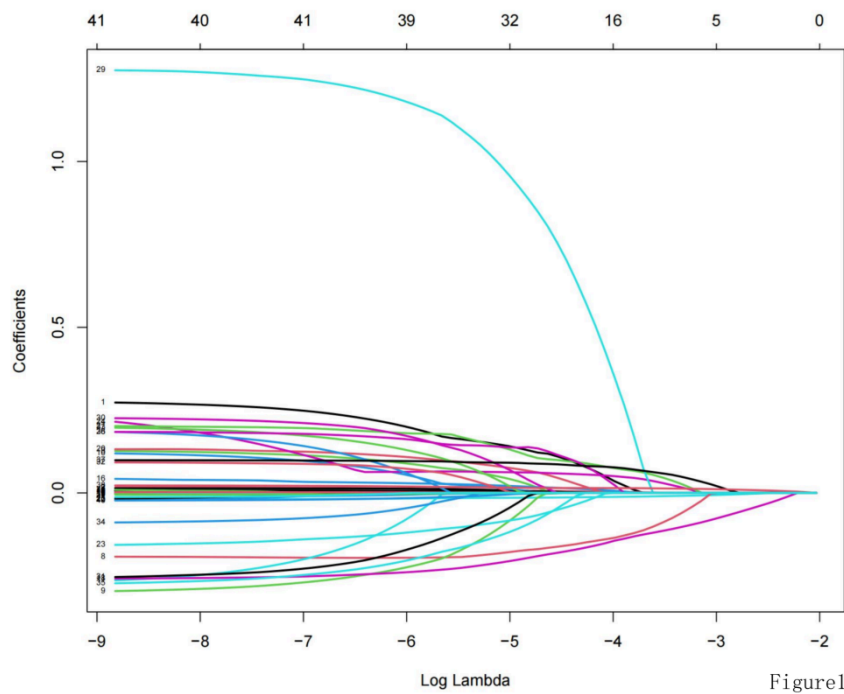


Figure1B

Figure 2

Coefficient paths for predictors selected by Lasso regression.

Figure 2A. Lasso regression coefficient paths and cross-validation selection.

Figure 2A shows the paths of standardized coefficients for predictors as a function of log lambda ($\log_{10}(\lambda)$) in Lasso regression. The red points highlight the estimated coefficients for selected variables. The y-axis denotes the standardized coefficient (β), and the x-axis shows $\log_{10}(\lambda)$. Vertical dashed lines indicate the value of $\log_{10}(\lambda)$ corresponding to the cross-validated optimal λ .

Figure 2B. Top predictors selected by Lasso regression.

Figure 2B shows the coefficients for the top predictors selected by Lasso regression. Each line represents a predictor; coefficients are standardized. Positive coefficients indicate an increased hazard of mortality (harmful factors), negative indicate a decreased hazard of mortality (protective factors). The y-axis shows the standardized coefficients, and the x-axis lists the predictor variables.

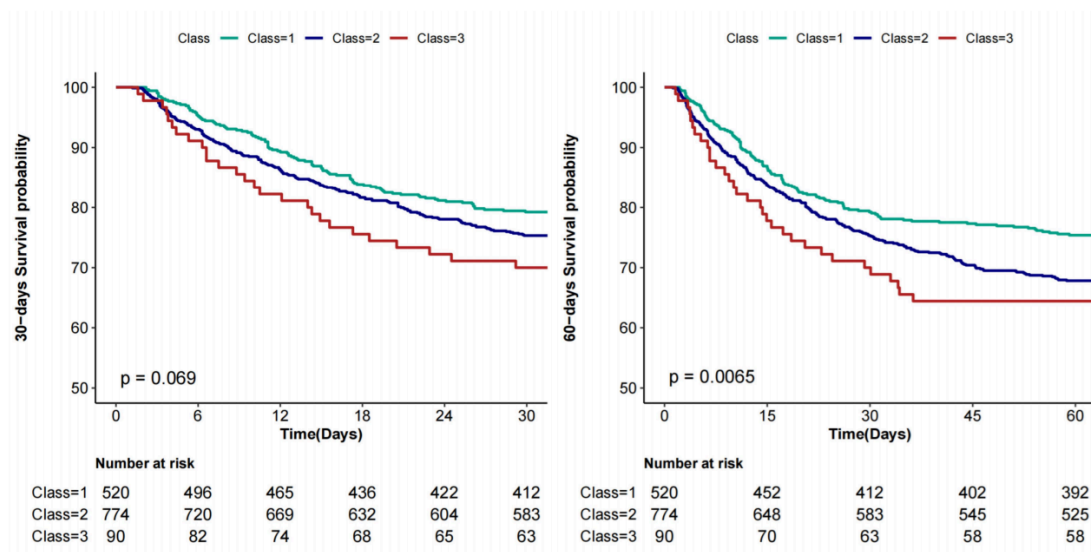


Figure3A

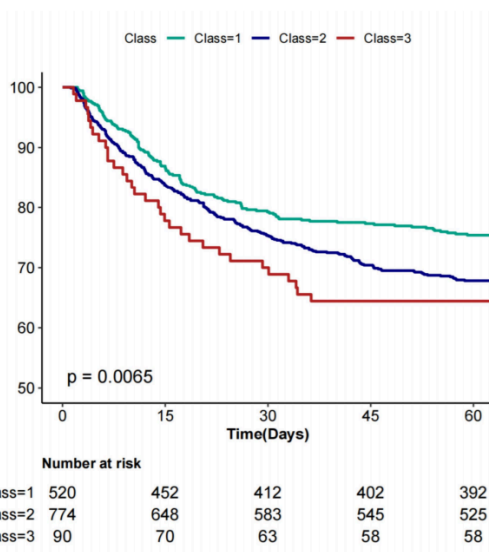


Figure3B

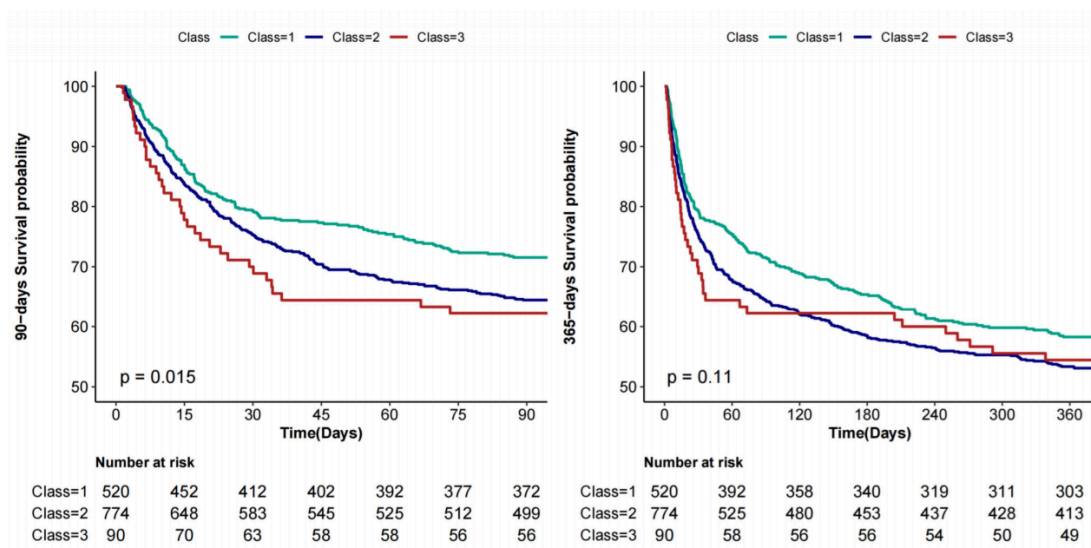


Figure3C

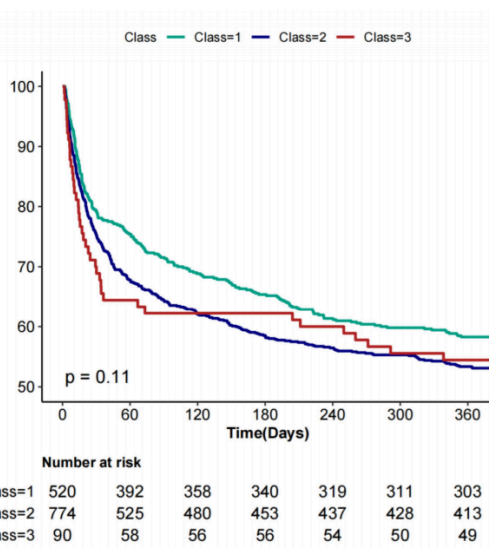


Figure3D

Figure 3

Survival curves by class across multiple time horizons.

Figure 3A shows the 30-day all-cause survival probability by class. The three curves correspond to Class 1 (green), Class 2 (purple), Class 3 (red). p-values reflect log-rank tests for differences between groups. At bottom, the table shows the number at risk per time point for each class; Figure 3B shows the 60-day

all-cause survival probability by class. Same color coding as above; Figure 3C shows the 90-day all-cause survival probability by class. Color coding as above; Figure 3D shows the 365-day all-cause survival probability by class. Color coding as above.

Supplementary Files

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- [SFigure1.Flowchartofstudypopulation.pdf](#)
- [STable1Missingdata.docx](#)
- [STable2.Multivariablelogisticregressionanalysesoftheassociationofclasswithmortality..docx](#)