

Early serum phosphate trajectories after acute kidney injury onset and their association with mortality in critically ill patients: derivation in MIMIC-IV and external evaluation in eICU-CRD

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Abstract

Background

Acute kidney injury (AKI) is a common and prognostically important complication of critical illness. Although serum phosphate abnormalities have been associated with adverse outcomes, previous studies have largely focused on single measurements rather than longitudinal patterns after AKI onset. We aimed to identify distinct serum phosphate trajectories during the first 72 hours after ICU admission among critically ill patients who developed AKI within 24 hours of ICU admission and to evaluate their associations with subsequent mortality.

Methods

This retrospective derivation and external-evaluation study used the MIMIC-IV and eICU-CRD databases. Adults who developed AKI within 24 hours after ICU admission and had serum phosphate measurements on ICU days 1–3 were included. Group-based trajectory modeling identified phosphate trajectory patterns in MIMIC-IV. The primary outcome was 28-day mortality. A 72-hour landmark analysis separated trajectory ascertainment from subsequent mortality assessment. Associations were evaluated using Kaplan–Meier analysis, multivariable Cox regression, and subgroup analyses. The MIMIC-IV-derived model was frozen and applied to eICU-CRD without refitting.

Results

Among 7,894 patients in the MIMIC-IV trajectory cohort, three phosphate trajectories were identified: low-decreasing (Trajectory 1, $n = 6,168$; 78.1%), moderate-decreasing (Trajectory 2, $n = 1,425$; 18.1%), and persistently high (Trajectory 3, $n = 301$; 3.8%). In the 72-hour landmark cohort, compared with Trajectory 1, Trajectory 2 and Trajectory 3 remained associated with higher 28-day mortality after adjustment for age, sex, Charlson Comorbidity Index, Sequential Organ Failure Assessment (SOFA) score, and AKI stage (adjusted hazard ratio [HR] 1.16, 95% confidence interval [CI] 1.03–1.30; $P = 0.018$ and adjusted HR 1.26, 95% CI 1.02–1.55; $P = 0.028$, respectively). In eICU-CRD, the frozen model classified 3,462 patients into the three trajectories with high classification performance. Trajectory 2 remained associated with 28-day mortality after adjustment for age, sex, and race/ethnicity (HR 1.44, 95% CI 1.13–1.83; $P = 0.004$).

Conclusions

Early serum phosphate trajectories characterize clinically distinct AKI phenotypes and are associated with subsequent mortality among critically ill patients. Further prospective studies are required to determine their clinical utility.

Background

Acute kidney injury (AKI) is one of the most frequent forms of acute organ dysfunction in critically ill patients and is strongly associated with adverse short- and long-term outcomes [1, 2]. Contemporary epidemiological studies have demonstrated that AKI affects more than half of critically ill patients, with mortality increasing progressively with Kidney Disease: Improving Global Outcomes (KDIGO) severity stage [1, 2]. Beyond a transient reduction in kidney function, AKI is a dynamic systemic syndrome characterized by rapidly evolving changes in renal clearance, metabolic homeostasis, inflammation, and organ interactions. Therefore, risk stratification after AKI onset may benefit from biomarkers capable of capturing these dynamic physiological changes rather than relying solely on static measurements obtained at a single time point.

Serum phosphate is a biologically plausible candidate for dynamic risk assessment in AKI. Phosphate plays essential roles in adenosine triphosphate generation, cellular energy metabolism, membrane integrity, intracellular signaling, oxygen delivery, and acid–base regulation [3]. Circulating phosphate concentrations are tightly regulated through coordinated interactions among the kidney, bone, gastrointestinal tract, parathyroid hormone, vitamin D, and fibroblast growth factor 23 (FGF23) pathways [3, 4]. Because the kidney is the primary organ responsible for phosphate excretion, acute impairment of renal function can rapidly disturb phosphate balance. Critical illness may further alter phosphate concentrations through cellular injury, intracellular–extracellular shifts, metabolic disturbances, nutritional interventions, insulin exposure, and renal replacement therapy. Serial phosphate measurements may therefore provide integrated information on renal dysfunction, cellular stress, and metabolic instability that cannot be captured by a single phosphate value.

Previous studies have reported associations between abnormal phosphate concentrations and mortality in critically ill patients and individuals with AKI. Among AKI patients receiving continuous renal replacement therapy (CRRT), higher phosphate levels were associated with greater disease severity and increased short- and long-term mortality [5–7]. Changes in phosphate concentration over time may provide additional prognostic information beyond baseline values, as increasing phosphate trajectories have been linked to poorer outcomes compared with stable or decreasing patterns [6]. However, most previous studies have focused on static phosphate measurements or predefined phosphate categories, leaving the prognostic significance of longitudinal phosphate patterns insufficiently explored.

Trajectory-based approaches provide an opportunity to characterize dynamic biomarker patterns and identify clinically meaningful phenotypes. Group-based trajectory modeling (GBTM) identifies latent subgroups of patients with similar longitudinal biomarker profiles and may reveal heterogeneity that is not apparent from baseline measurements alone [8, 9]. Recent studies have applied trajectory methods to phosphate and other metabolic biomarkers in critical illness and have reported associations between persistent metabolic abnormalities and mortality [10–12]. However, early phosphate trajectories in critically ill patients with AKI remain poorly characterized. The first several intensive care unit (ICU) days represent a clinically important period during which renal function, organ failure severity, and therapeutic interventions change rapidly. Evaluating phosphate patterns during this early window may therefore improve the identification of high-risk AKI phenotypes.

In addition, trajectory analyses introduce methodological challenges because exposure classification depends on repeated measurements collected over time. Treating the final trajectory assignment as if it were available at ICU admission may introduce immortal-time bias. A landmark approach that separates the trajectory ascertainment period from subsequent outcome assessment can help address this source of immortal-time bias [13]. Accordingly, we used a 72-hour landmark design corresponding to the completion of the first three ICU days of phosphate assessment. The present study aimed to identify early serum phosphate trajectories in critically ill patients with AKI, evaluate their associations with subsequent mortality, and assess the transportability of the derived trajectory model in an external multicenter cohort.

Methods

Study design and data sources

This retrospective observational study with trajectory derivation and external evaluation used two publicly available critical-care databases (Fig. 1). The Medical Information Mart for Intensive Care IV (MIMIC-IV) served as the derivation and primary analysis cohort and contains high-resolution electronic health record data from patients treated at Beth Israel Deaconess Medical Center [14]. The eICU Collaborative Research Database (eICU-CRD), a multicenter U.S. critical-care database containing more than 200,000 ICU admissions, was used for external evaluation [15]. Access to both databases was granted after completion of the Collaborative Institutional Training Initiative (CITI) program (author Yue Yu, certification number 33281932).

The creation and release of MIMIC-IV were approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (2001-P-001699/14) and the Massachusetts Institute of Technology (No. 0403000206), which waived the requirement for individual informed consent because of the de-identified nature of the data. eICU-CRD comprises fully de-identified data and is released under the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provision (Certification No. 1031219-2). Both databases are available to credentialed investigators under their respective data-use agreements; therefore, additional individual informed consent was not required for this secondary analysis. The study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2024, and was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [16].

Study population

Adult patients (age ≥ 18 years) were screened from first eligible ICU stays. The cohort was restricted to patients with AKI occurring within the first 24 hours after ICU admission. To permit construction of a uniform early phosphate trajectory, patients were required to have a serum phosphate value available for ICU day 1 (0–24 h), day 2 (24–48 h), and day 3 (48–72 h). Patients were further excluded if 7-, 28-, or 90-day survival information was unavailable, ICU length of stay was ≤ 3 days, or pre-existing chronic renal disease was recorded by the Charlson renal-disease indicator. For patients with multiple ICU admissions, a single index ICU stay was retained.

Diagnosis of AKI

The diagnosis of AKI follows the Kidney Disease: Improving Global Outcomes (KDIGO) criteria. AKI was diagnosis as any of the following: 1) Increase in serum creatinine (SCr) by ≥ 0.3 mg/dL ($\geq 26.5\mu\text{mol/L}$) within 48 hours. 2) Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days. 3) Urine output (Uro) < 0.5 mL/kg/h for 6 hours. AKI is calculated every time a SCr or Uro measurement occurs. The baseline SCr was defined as the lowest SCr in the past 7 days. To ensure that biochemical measurements used for subsequent analyses occurred after the onset of kidney injury, we included only patients who developed AKI within the first 24 hours after ICU admission. This temporal restriction was prespecified to establish a clear exposure–outcome sequence and minimize potential reverse causation, ensuring that early metabolic biomarkers were assessed after AKI onset rather than preceding kidney injury.

Data extraction and covariates

Data were queried from MIMIC-IV using PostgreSQL through pgAdmin (version 6.1). Structured query language (SQL) scripts retrieved demographics, ICU stay identifiers, diagnoses, severity scores, vital signs, laboratory tests, treatments, complications, and survival times. Baseline demographic characteristics, vital signs, laboratory measurements, and severity scores were defined as the earliest available values within the first 24 hours after ICU admission, reflecting patients' initial clinical status. In contrast, treatment-related variables, including CRRT, vasopressor use, antibiotic therapy, mechanical ventilation, and cumulative fluid balance, were defined as ICU exposures occurring throughout the entire ICU stay to capture subsequent organ-support requirements. Variables with more than 20% missingness were excluded from multivariable modeling. For variables with 20% or less missingness, missing values were imputed using multiple imputation by chained equations (MICE) with random-forest imputation. Under this missingness rule, the final retained analytic variables were: age, sex, race, and marital status; Charlson Comorbidity Index (CCI) and its component diagnoses (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild and severe liver disease, diabetes with and without chronic complication, paraplegia, renal disease, malignant cancer, metastatic solid tumor, and acquired immunodeficiency syndrome); severity scores including SOFA, Simplified Acute Physiology Score II (SAPS II), Acute Physiology Score III (APS III), Oxford Acute Severity of Illness Score (OASIS), systemic inflammatory response syndrome (SIRS) score, and Glasgow Coma Scale; vital signs including weight, temperature, heart rate, respiratory rate, peripheral oxygen saturation (SpO₂), and noninvasive

systolic, diastolic, and mean blood pressure; laboratory tests including hemoglobin, hematocrit, platelet count, white blood cell count, red blood cell count, red cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), creatinine, blood urea nitrogen, sodium, potassium, chloride, calcium, anion gap, bicarbonate, glucose, arterial blood gas indices (pH, arterial oxygen tension [PaO₂], arterial carbon dioxide tension [PaCO₂], base excess, and total carbon dioxide), and coagulation parameters (international normalized ratio [INR], prothrombin time [PT], and activated partial thromboplastin time [APTT]); urine-output indices; treatment variables including CRRT, vasopressor use, antibiotic therapy, mechanical ventilation, and fluid balance; and AKI stage.

Serum phosphate exposure

Serum phosphate was treated as a continuous longitudinal exposure during the early ICU course. Measurements were extracted from MIMIC-IV laboratory events (d_labitems itemid 50910, "Phosphate"; blood) and expressed in mg/dL. The conventional adult reference range of 2.5–4.5 mg/dL was used only for clinical interpretation of the resulting trajectory patterns and was not used to define the latent classes. Measurements were aligned to the ICU admission timestamp (intime) and grouped into three consecutive 24-hour intervals: 0–24, 24–48, and 48–72 hours. When more than one measurement was available within an interval, the arithmetic mean was calculated. This approach was chosen to reduce the influence of transient within-day fluctuations and isolated measurements, while providing a summary measure that more closely reflects the overall phosphate level during each 24-hour period. These three interval-specific mean values (day 1, day 2, and day 3) were used as the longitudinal measurements for trajectory modeling.

Group-based trajectory modeling

GBTM was performed under a Gaussian latent-class framework to identify subgroups with similar phosphate evolution over the first three ICU days. Candidate solutions with 2–5 classes were evaluated using polynomial functions of time. Model selection considered log likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC), sample-size-adjusted BIC (SABIC), entropy, class-specific average posterior probability (AvePP), odds of correct classification (OCC), class size, parsimony, graphical separation, and clinical interpretability. This multidimensional approach was chosen because reliance on a single fit index may overextract small or spurious classes [8, 9, 18]. AvePP > 0.70 and OCC > 5 were considered supportive of adequate classification [18, 19].

Outcomes and 72-hour landmark design

The primary outcome was all-cause mortality through day 28 after ICU admission. Secondary outcomes were mortality through days 7 and 90 after ICU admission. Because trajectory membership was determined using phosphate measurements obtained over the first 72 hours, the primary survival analysis used a landmark at ICU admission plus 72 hours (the beginning of ICU day 4) [13]. Only patients alive at the landmark were considered at risk in landmark survival models. Follow-up began at the landmark and continued until death or the prespecified endpoint measured from ICU admission, whichever occurred first. Thus, the maximum post-landmark follow-up was approximately 4, 25, and 87 days for the 7-, 28-, and 90-day outcomes, respectively. This design separates the exposure-ascertainment window from the subsequent risk window and reduces immortal-time bias.

Statistical analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range), as appropriate, and compared across trajectory groups using one-way analysis of variance or the Kruskal–Wallis test. Categorical variables were summarized as counts (percentages) and compared using the chi-square test or Fisher's exact test.

Kaplan–Meier methods and log-rank tests were used to describe post-landmark survival across phosphate trajectory groups. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs), with the low-decreasing trajectory as the reference. Four sequential Cox regression models were constructed to assess the robustness of the association between serum phosphate trajectories and mortality. Model 1 was unadjusted and included trajectory group only. Model 2 additionally adjusted for age, sex, and race to account for demographic confounding. Model 3 further adjusted for CCI [20], SOFA score [21], and AKI stage [17, 22] to account for baseline comorbidity burden, overall illness severity, and AKI severity, respectively, and was considered the primary multivariable model. Model 4 additionally included mechanical ventilation and vasopressor use as an extended adjustment model to evaluate the robustness of the association after accounting for major organ-support requirements during the ICU course. Multicollinearity was evaluated using generalized variance inflation factors (GVIFs), with prespecified concern for values equivalent to a variance inflation factor (VIF) > 5.

Prespecified exploratory subgroup analyses assessed whether the association between phosphate trajectory and 28-day mortality was consistent across clinically relevant strata: age (≤ 65 vs > 65 years), sex, race, AKI stage, SOFA score (≤ 5 vs > 5), CRRT, liver disease, vasopressor use, and mechanical ventilation. These factors were selected to represent demographic characteristics, kidney-injury severity, overall organ dysfunction, renal replacement therapy/phosphate clearance, and major organ-support requirements. Effect modification was formally evaluated using trajectory-by-subgroup interaction terms and likelihood-ratio tests; interpretation was based on the *P* value for interaction rather than on within-stratum statistical significance alone.

For external evaluation, eligible eICU-CRD patients were selected using a harmonized early-AKI and phosphate assessment framework. The $K = 3$ quadratic GBTM coefficients, class-membership priors, and residual variance derived in MIMIC-IV were frozen and applied directly to eICU patients to calculate posterior class-membership probabilities. Each patient was assigned to the class with the highest posterior probability. Classification transportability was summarized using entropy, class-specific AvePP, OCC, and class proportions. A 72-hour/day-4 landmark Cox analysis was then performed for ICU 28-day mortality.

All statistical analyses were performed using R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

Results

Study population

Among 51,983 unique ICU patients identified in MIMIC-IV, 14,590 patients without AKI were excluded. Of the remaining patients, those with AKI occurring beyond 24 hours after ICU admission, insufficient serum phosphate measurements during ICU days 1–3, ICU stay ≤ 3 days, or pre-existing chronic renal disease were excluded. The final trajectory analysis cohort comprised 7,894 patients (Fig. 2).

Missing data

Missingness patterns of candidate covariates were systematically evaluated before multivariable analysis. Among variables retained according to the prespecified missingness threshold ($\leq 20\%$), the greatest proportion of missing values was observed in arterial blood gas–related measurements, including total carbon dioxide, PaO₂, PaCO₂, pH, and base excess, with a maximum missing rate of 18.15%. Other variables with relatively higher missingness included noninvasive blood pressure measurements, fluid balance, urine output indices, and coagulation parameters, whereas most routinely collected hematological, biochemical, and demographic variables demonstrated minimal missingness (< 1%). The imputation procedure preserved the observed distributions of continuous variables, supporting the validity of the reconstructed analytic datasets. The full missing-data pattern is provided in **Table S1, Figure S1, and S2**.

Selection of the phosphate trajectory model

Final class-number selection considered information criteria, classification diagnostics, class size, and clinical interpretability. For the three-class ($K = 3$) model, log likelihood was $-34,733.50$, AIC $69,491.00$, BIC $69,574.69$, and SABIC $69,536.56$, with entropy 0.889 . Although AIC, BIC, and SABIC continued to decrease with increasing numbers of classes, the four- and five-class solutions generated very small subgroups ($1.8\% - 2.0\%$), suggesting potential over-extraction of trajectory classes, while the three-class solution retained strong classification performance (entropy 0.889 ; class-specific AvePP $0.887 - 0.965$; all OCC > 5). The three-class model provided three clinically distinct classes with class-specific AvePP values of 0.965 , 0.887 , and 0.950 and OCC values of 7.60 , 35.62 , and 477.39 . Although the smallest class accounted for 3.8% of the cohort ($n = 301$), it showed excellent classification certainty (AvePP 0.950 ; OCC 477.39) and a clinically distinct persistently high-phosphate phenotype. Therefore, the three-class model was selected as the primary trajectory model (Table 1; Additional file 1: **Table S2**).

Table 1
Metrics for determining the optimal number of phosphate trajectory classes.

No.of trajectories	Log likelihood	AIC	BIC	SABIC	entropy	Proportion of patients (%)				
						Class 1	Class 2	Class 3	Class 4	Class 5
MIMIC-IV										
1	-40387.54	80783.07	80810.97	80798.26	1.000	100.0	NA	NA	NA	NA
2	-36020.54	72057.08	72112.88	72087.45	0.942	11.4	88.6	NA	NA	NA
3	-34733.50	69491.00	69574.69	69536.56	0.889	78.1	18.1	3.8	NA	NA
4	-34266.23	68564.47	68676.05	68625.21	0.829	23.4	1.8	7.0	67.8	NA
5	-33734.02	67508.05	67647.53	67583.97	0.831	25.4	63.0	1.7	2.0	7.9

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SABIC, sample-size adjusted Bayesian information criterion; NA, not applicable; MIMIC-IV, Medical Information Mart for Intensive Care IV; eICU, eICU Collaborative Research Database. eICU class membership was assigned using frozen MIMIC-IV $K = 3$ coefficients; therefore log likelihood, AIC, BIC, and SABIC from eICU model selection are not applicable.

Characteristics of the three serum phosphate trajectories

The three-class GBTM identified clearly separated phosphate patterns during the first three ICU days (Fig. 3). Trajectory 1 (low-decreasing; $n = 6,168$, 78.1%) started at a relatively low-normal phosphate concentration and declined progressively, with fitted means of 3.330 , 2.944 , and 2.820 mg/dL on days 1, 2, and 3. Trajectory 2 (moderate-decreasing; $n = 1,425$, 18.1%) was characterized by moderately elevated phosphate that remained relatively stable between days 1 and 2 before declining on day 3 (4.881 , 4.826 , and 4.456 mg/dL). Trajectory 3 (persistently high; $n = 301$, 3.8%) showed marked hyperphosphatemia throughout the 72-hour window, increasing from day 1 to day 2 and declining only modestly by day 3 (6.877 , 7.492 , and 7.253 mg/dL) (Table 2) (Fig. 3).

Table 2
Baseline characteristics of the study population stratified by phosphate trajectory groups

Characteristic	Overall (N = 7894)	Trajectory 1 (N = 6168)	Trajectory 2 (N = 1425)	Trajectory 3 (N = 301)	P value
N	7894	6168	1425	301	
Demographics					
Age, years	66.5 (55.1–77.2)	67.2 (55.3–77.7)	65.1 (55.1–75.9)	60.8 (51.1–70.2)	< 0.001
Sex, male, n (%)	4428 (56.1)	3424 (55.5)	797 (55.9)	207 (68.8)	< 0.001
Race, n (%)					0.011
White	4966 (62.9)	3904 (63.3)	906 (63.6)	156 (51.8)	
Black	607 (7.7)	468 (7.6)	109 (7.6)	30 (10.0)	
Asian	175 (2.2)	136 (2.2)	30 (2.1)	9 (3.0)	
Other	2146 (27.2)	1660 (26.9)	380 (26.7)	106 (35.2)	
Marital status, n (%)					0.502
Married	3244 (41.1)	2543 (41.2)	575 (40.4)	126 (41.9)	
Single	2074 (26.3)	1595 (25.9)	393 (27.6)	86 (28.6)	
Other/unknown	2576 (32.6)	2030 (32.9)	457 (32.1)	89 (29.6)	
Clinical status & severity					
SOFA	5.0 (3.0–9.0)	5.0 (3.0–8.0)	8.0 (5.0–11.0)	11.0 (8.0–13.0)	< 0.001
GCS	15.0 (15.0–15.0)	15.0 (15.0–15.0)	15.0 (15.0–15.0)	15.0 (15.0–15.0)	0.362
SAPS II	40.0 (31.0–50.0)	38.0 (30.0–47.0)	47.0 (38.0–58.0)	53.0 (45.0–63.0)	< 0.001
APS III	48.0 (35.0–65.0)	44.0 (33.0–59.0)	61.0 (46.0–80.0)	74.0 (62.0–90.0)	< 0.001
OASIS	35.0 (30.0–41.0)	35.0 (29.0–41.0)	38.0 (32.0–45.0)	39.0 (33.0–45.0)	< 0.001
SIRS	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–4.0)	3.0 (3.0–4.0)	< 0.001
Charlson CCI	4.0 (3.0–6.0)	4.0 (3.0–6.0)	5.0 (3.0–6.0)	4.0 (3.0–6.0)	< 0.001
AKI stage, n (%)					< 0.001
Stage 1	786 (10.0)	696 (11.3)	78 (5.5)	12 (4.0)	
Stage 2	3950 (50.0)	3446 (55.9)	481 (33.8)	23 (7.6)	

Abbreviations: SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; APS III, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; SIRS, systemic inflammatory response syndrome; CCI, Charlson Comorbidity Index; AKI, acute kidney injury; AIDS, acquired immunodeficiency syndrome; SpO₂, peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell count; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; BUN, blood urea nitrogen; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; CO₂, carbon dioxide; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy.

Characteristic	Overall (N = 7894)	Trajectory 1 (N = 6168)	Trajectory 2 (N = 1425)	Trajectory 3 (N = 301)	P value
Stage 3	3158 (40.0)	2026 (32.8)	866 (60.8)	266 (88.4)	
Comorbidities					
Myocardial infarction, n (%)	1287 (16.3)	969 (15.7)	275 (19.3)	43 (14.3)	0.003
Congestive heart failure, n (%)	2145 (27.2)	1577 (25.6)	489 (34.3)	79 (26.2)	< 0.001
Peripheral vascular disease, n (%)	852 (10.8)	611 (9.9)	213 (14.9)	28 (9.3)	< 0.001
Cerebrovascular disease, n (%)	1483 (18.8)	1265 (20.5)	188 (13.2)	30 (10.0)	< 0.001
Dementia, n (%)	299 (3.8)	261 (4.2)	33 (2.3)	5 (1.7)	< 0.001
Chronic pulmonary disease, n (%)	2045 (25.9)	1553 (25.2)	422 (29.6)	70 (23.3)	0.001
Rheumatic disease, n (%)	289 (3.7)	222 (3.6)	55 (3.9)	12 (4.0)	0.854
Peptic ulcer disease, n (%)	251 (3.2)	181 (2.9)	54 (3.8)	16 (5.3)	0.025
Mild liver disease, n (%)	1357 (17.2)	871 (14.1)	360 (25.3)	126 (41.9)	< 0.001
Diabetes mellitus, n (%)	2051 (26.0)	1541 (25.0)	429 (30.1)	81 (26.9)	< 0.001
Diabetes without chronic complication, n (%)	1857 (23.5)	1403 (22.7)	380 (26.7)	74 (24.6)	0.006
Diabetes with chronic complication, n (%)	349 (4.4)	248 (4.0)	84 (5.9)	17 (5.6)	0.005
Paraplegia, n (%)	641 (8.1)	570 (9.2)	57 (4.0)	14 (4.7)	< 0.001
Renal disease, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	†
Malignant cancer, n (%)	1103 (14.0)	820 (13.3)	232 (16.3)	51 (16.9)	0.004
Severe liver disease, n (%)	768 (9.7)	471 (7.6)	214 (15.0)	83 (27.6)	< 0.001
Metastatic solid tumor, n (%)	504 (6.4)	388 (6.3)	99 (6.9)	17 (5.6)	0.571
AIDS, n (%)	41 (0.5)	31 (0.5)	8 (0.6)	2 (0.7)	0.768†
Vital signs					
Weight, kg	83.6 (70.0–100.0)	82.7 (69.8–99.4)	86.4 (71.0–103.7)	90.0 (75.0–106.3)	< 0.001
Temperature, °C	36.8 (36.4–37.1)	36.8 (36.4–37.2)	36.6 (36.3–37.1)	36.7 (36.4–37.1)	< 0.001
Abbreviations: SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; APS III, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; SIRS, systemic inflammatory response syndrome; CCI, Charlson Comorbidity Index; AKI, acute kidney injury; AIDS, acquired immunodeficiency syndrome; SpO ₂ , peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell count; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; BUN, blood urea nitrogen; PaO ₂ , arterial partial pressure of oxygen; PaCO ₂ , arterial partial pressure of carbon dioxide; CO ₂ , carbon dioxide; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy.					

Characteristic	Overall (N = 7894)	Trajectory 1 (N = 6168)	Trajectory 2 (N = 1425)	Trajectory 3 (N = 301)	P value
Heart rate, /min	90.0 (77.0–106.0)	89.0 (76.0–105.0)	92.0 (80.0–108.0)	94.0 (80.0–109.0)	< 0.001
Respiratory rate, /min	20.0 (16.0–24.0)	19.0 (16.0–23.0)	20.0 (16.0–26.0)	21.0 (17.0–26.0)	< 0.001
SpO ₂ , %	98.0 (95.0–100.0)	98.0 (95.0–100.0)	97.0 (94.0–100.0)	97.0 (94.0–100.0)	< 0.001
SBP, mmHg	120.0 (103.0–138.0)	121.0 (104.0–139.0)	116.0 (100.0–135.0)	116.0 (101.0–132.0)	< 0.001
DBP, mmHg	68.0 (57.0–82.0)	69.0 (58.0–82.0)	66.0 (54.0–80.0)	64.0 (54.0–77.0)	< 0.001
MBP, mmHg	81.0 (69.0–95.0)	82.0 (70.0–96.0)	79.0 (67.0–93.0)	78.0 (67.0–90.0)	< 0.001
Laboratory tests					
Hemoglobin, g/dL	11.0 (9.3–12.8)	11.3 (9.5–12.9)	10.2 (8.6–12.2)	9.3 (7.7–11.4)	< 0.001
Platelet, ×10 ⁹ /L	193.0 (135.0–262.0)	197.0 (141.0–262.0)	178.0 (111.0–265.0)	159.0 (85.0–249.0)	< 0.001
WBC, ×10 ⁹ /L	11.9 (8.4–16.5)	11.7 (8.4–16.1)	12.8 (8.6–18.2)	13.6 (8.5–19.1)	< 0.001
RBC, ×10 ¹² /L	3.7 ± 0.8	3.8 ± 0.8	3.5 ± 0.9	3.2 ± 0.9	< 0.001
Hematocrit, %	33.8 ± 7.3	34.3 ± 7.0	32.4 ± 7.9	29.8 ± 7.8	< 0.001
RDW, %	14.4 (13.4–16.0)	14.2 (13.3–15.7)	15.1 (13.9–17.0)	15.8 (14.3–18.4)	< 0.001
MCV, fL	92.0 (88.0–96.0)	92.0 (88.0–96.0)	92.0 (88.0–97.0)	92.0 (87.0–98.0)	0.003
MCHC, g/dL	32.8 ± 1.7	32.9 ± 1.6	32.5 ± 1.8	32.7 ± 1.9	< 0.001
MCH, pg	30.3 (28.7–31.8)	30.3 (28.8–31.8)	30.2 (28.5–31.8)	30.3 (28.4–32.3)	0.131
Creatinine, mg/dL	1.0 (0.7–1.3)	0.9 (0.7–1.2)	1.3 (1.0–2.0)	2.3 (1.4–4.3)	< 0.001
BUN, mg/dL	19.0 (14.0–29.0)	18.0 (13.0–25.0)	27.0 (18.0–44.0)	45.0 (26.0–74.0)	< 0.001
Sodium, mmol/L	139.0 (135.0–141.0)	139.0 (136.0–141.0)	138.0 (134.0–142.0)	137.0 (132.0–141.0)	< 0.001
Potassium, mmol/L	4.1 (3.7–4.6)	4.1 (3.7–4.5)	4.4 (3.9–4.9)	4.7 (4.1–5.3)	< 0.001
Chloride, mmol/L	104.0 (100.0–108.0)	104.0 (100.0–108.0)	103.0 (99.0–107.0)	100.0 (95.0–106.0)	< 0.001

Abbreviations: SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; APS III, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; SIRS, systemic inflammatory response syndrome; CCI, Charlson Comorbidity Index; AKI, acute kidney injury; AIDS, acquired immunodeficiency syndrome; SpO₂, peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell count; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; BUN, blood urea nitrogen; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; CO₂, carbon dioxide; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy.

Characteristic	Overall (N = 7894)	Trajectory 1 (N = 6168)	Trajectory 2 (N = 1425)	Trajectory 3 (N = 301)	P value
Calcium, mg/dL	8.3 (7.8–8.8)	8.3 (7.8–8.8)	8.3 (7.7–8.8)	8.2 (7.5–8.8)	0.194
Anion gap, mmol/L	14.0 (12.0–17.0)	14.0 (12.0–16.0)	16.0 (13.0–19.0)	19.0 (15.0–23.0)	< 0.001
Bicarbonate, mmol/L	22.0 (19.0–25.0)	23.0 (20.0–25.0)	21.0 (18.0–24.0)	19.0 (16.0–23.0)	< 0.001
Glucose, mg/dL	135.0 (110.0–174.0)	134.0 (110.0–170.0)	138.0 (110.0–186.0)	144.0 (109.0–203.0)	0.006
pH	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.3 (7.3–7.4)	7.3 (7.2–7.4)	< 0.001
PaO ₂ , mmHg	104.0 (63.0–197.0)	106.0 (65.0–200.0)	96.0 (59.0–188.0)	91.0 (60.0–159.0)	< 0.001
PaCO ₂ , mmHg	41.0 (36.0–48.0)	41.0 (36.0–48.0)	42.0 (35.0–50.0)	39.0 (33.0–46.0)	< 0.001
Base excess, mmol/L	-1.0 (-4.0–1.0)	0.0 (-4.0–1.0)	-3.0 (-7.0–0.0)	-5.0 (-9.0–-1.0)	< 0.001
Total CO ₂ , mmol/L	24.0 (21.0–28.0)	25.0 (22.0–28.0)	23.0 (19.0–27.0)	21.0 (17.0–24.0)	< 0.001
INR	1.3 (1.1–1.6)	1.3 (1.1–1.5)	1.4 (1.2–1.8)	1.6 (1.3–2.2)	< 0.001
PT, s	14.3 (12.6–17.5)	14.0 (12.5–16.8)	15.5 (13.3–19.9)	17.7 (13.9–24.2)	< 0.001
APTT, s	31.1 (27.2–39.4)	30.4 (26.9–37.5)	33.9 (28.7–46.3)	35.9 (29.3–50.5)	< 0.001
Treatments					
CRRT, n (%)	744 (9.4)	279 (4.5)	319 (22.4)	146 (48.5)	< 0.001
CRRT days	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–5.0)	< 0.001
Vasopressor use, n (%)	4093 (51.8)	2979 (48.3)	912 (64.0)	202 (67.1)	< 0.001
Antibiotic use, n (%)	6729 (85.2)	5133 (83.2)	1310 (91.9)	286 (95.0)	< 0.001
Mechanical ventilation, n (%)	5776 (73.2)	4362 (70.7)	1162 (81.5)	252 (83.7)	< 0.001
Fluid balance	2345.4 (688.5–4787.4)	2289.7 (725.1–4598.0)	2719.3 (540.7–5913.6)	2356.2 (547.5–5124.4)	0.001
Abbreviations: SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; APS III, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; SIRS, systemic inflammatory response syndrome; CCI, Charlson Comorbidity Index; AKI, acute kidney injury; AIDS, acquired immunodeficiency syndrome; SpO ₂ , peripheral oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell count; RBC, red blood cell count; RDW, red cell distribution width; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; BUN, blood urea nitrogen; PaO ₂ , arterial partial pressure of oxygen; PaCO ₂ , arterial partial pressure of carbon dioxide; CO ₂ , carbon dioxide; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; CRRT, continuous renal replacement therapy.					

Compared with patients in the low-decreasing phosphate trajectory group (Trajectory 1), those in higher phosphate trajectory groups (Trajectories 2 and 3) showed progressively worse clinical profiles, characterized by higher severity scores (SOFA, SAPS II, APS III, and OASIS), a greater proportion of stage 3 AKI, and more adverse laboratory abnormalities, including elevated creatinine, blood urea nitrogen, anion gap, and INR levels with reduced hemoglobin, platelet count,

bicarbonate, and base excess. These patients also required more intensive organ-support therapies, including CRRT, vasopressor therapy, and mechanical ventilation (Table 2).

Mortality risk associated with early serum phosphate trajectories

In the full trajectory cohort, 28-day mortality demonstrated a clear stepwise increase across phosphate trajectory groups, with rates of 19.0% in Trajectory 1, 32.2% in Trajectory 2, and 38.9% in Trajectory 3 ($P < 0.001$). Similar gradients were observed for early and longer-term outcomes, with 7-day mortality rates of 7.8%, 14.8%, and 21.6%, respectively ($P < 0.001$), and 90-day mortality rates of 25.1%, 39.0%, and 41.9%, respectively ($P < 0.001$) (Fig. 4). Kaplan–Meier analyses using the 72-hour landmark approach demonstrated consistent separation of survival curves across all follow-up periods, with the low-decreasing trajectory showing the most favorable survival and the persistently high trajectory exhibiting the highest mortality risk (log-rank $P < 0.001$ for 7-, 28-, and 90-day outcomes) (Fig. 4).

Cox regression analysis of phosphate trajectories and mortality

In the unadjusted landmark Cox model, Trajectory 2 was associated with an 80% higher hazard of death than Trajectory 1 (HR 1.80, 95% CI 1.61–2.02; $P < 0.001$), while Trajectory 3 was associated with a more than twofold higher hazard (HR 2.40, 95% CI 1.98–2.92; $P < 0.001$). Adjustment for age, sex, and race did not attenuate these associations (Trajectory 2 HR 1.86, 95% CI 1.66–2.08; Trajectory 3 HR 2.68, 95% CI 2.20–3.26; both $P < 0.001$). In the primary clinically adjusted model including age, sex, CCI, SOFA score, and AKI stage, both trajectory associations remained statistically significant but were substantially attenuated: adjusted HR 1.16 (95% CI 1.03–1.30; $P = 0.018$) for Trajectory 2 and 1.26 (95% CI 1.02–1.55; $P = 0.028$) for Trajectory 3. AKI stage showed a strong severity gradient, with stage 2 versus stage 1 HR 1.54 (95% CI 1.19–1.98) and stage 3 versus stage 1 HR 3.04 (95% CI 2.37–3.91). CCI and SOFA also remained independently associated with mortality. Results were stable in the extended model that additionally included mechanical ventilation and vasopressor use. Adjusted HRs were 1.15 (95% CI 1.02–1.30; $P = 0.020$) for Trajectory 2 and 1.28 (95% CI 1.04–1.57; $P = 0.021$) for Trajectory 3. Mechanical ventilation was associated with mortality (HR 1.38, 95% CI 1.21–1.58; $P < 0.001$), whereas vasopressor use was not independently associated after multivariable adjustment (HR 1.05, 95% CI 0.93–1.17; $P = 0.440$) (Table S3; Table S4; Table S5) (Fig. 5). No concerning multicollinearity was detected; all adjusted GVIF measures were well below the prespecified threshold (Table S6; Table S7; Table S8).

Subgroup analyses

Exploratory subgroup analyses demonstrated that the association between phosphate trajectory groups and 28-day mortality was generally consistent across clinically relevant subgroups, including age, sex, race, AKI stage, SOFA category, liver disease, vasopressor use, and mechanical ventilation. No statistically significant interactions were observed for most prespecified subgroup variables (all Pinteraction > 0.05). However, a significant interaction was identified for CRRT status (Pinteraction = 0.014). Among patients not receiving CRRT, higher phosphate trajectories were associated with increased mortality risk, with HRs of 1.67 (95% CI 1.47–1.90) for Trajectory 2 and 1.93 (95% CI 1.44–2.59) for Trajectory 3 compared with Trajectory 1. Conversely, among patients receiving CRRT, these associations were attenuated and did not reach statistical significance, with HRs of 1.17 (95% CI 0.92–1.48) and 1.24 (95% CI 0.92–1.67), respectively. These findings should be interpreted cautiously because CRRT is closely associated with AKI severity and directly influences phosphate clearance (Fig. 6).

External evaluation in eICU-CRD

A similar stepwise selection process was applied in the eICU-CRD external-evaluation cohort (Fig. 2). Among 34,801 eICU admissions linked to day-1 to day-3 phosphate data, 34,169 met an overall KDIGO AKI stage of at least 1. Restricting AKI onset to the first 24 hours yielded 19,457 patients. After requiring complete phosphate measurements on ICU days 1–3, 4,759 patients remained; exclusion of 1,297 patients with ICU length of stay ≤ 3 days resulted in a final external-evaluation cohort of 3,462 patients. Application of the frozen MIMIC-IV K = 3 trajectory model assigned 2,826 patients (81.6%) to Trajectory 1, 540 (15.6%) to Trajectory 2, and 96 (2.8%) to Trajectory 3 (Figure S3). Despite the small proportion of

Trajectory 3, classification certainty was high: entropy was 0.910 and the minimum class-specific OCC was 8.01 (Table S9; Table S10).

For mortality through day 28 after ICU admission, 384 deaths occurred in the eICU cohort. Mortality was 10.2% (288/2,826) in Trajectory 1, 15.7% (85/540) in Trajectory 2, and 11.5% (11/96) in Trajectory 3. In the unadjusted Cox model, Trajectory 2 was associated with higher mortality relative to Trajectory 1 (HR 1.45, 95% CI 1.14–1.85; $P = 0.002$), whereas Trajectory 3 was not (HR 1.16, 95% CI 0.64–2.12; $P = 0.628$). After adjustment for age, sex, and race/ethnicity, the association for Trajectory 2 remained significant (HR 1.44, 95% CI 1.13–1.83; $P = 0.004$), while the estimate for Trajectory 3 remained non-significant (HR 1.20, 95% CI 0.66–2.19; $P = 0.556$). The wide confidence interval and only 11 deaths in Trajectory 3 indicate limited precision for this comparison (**Table S11**).

Discussion

In this large retrospective derivation and external-evaluation study, we identified three distinct early serum phosphate trajectories among critically ill patients who developed AKI within 24 hours after ICU admission. The majority of patients exhibited a low-decreasing phosphate pattern, whereas approximately one fifth demonstrated a moderate-decreasing trajectory and a smaller subgroup showed persistent hyperphosphatemia. Importantly, higher phosphate trajectories were associated with increased 28-day mortality after adjustment for demographic characteristics, comorbidity burden, SOFA score, AKI stage, and organ-support therapies. These findings remained robust in the 72-hour landmark analysis, which minimized potential immortal-time bias by ensuring that trajectory classification preceded outcome assessment [13]. Furthermore, the trajectory model demonstrated good transportability in the external eICU-CRD cohort, suggesting potential applicability for early risk stratification in heterogeneous ICU populations [14, 15].

AKI is a common and clinically important complication of critical illness, affecting more than half of ICU patients and contributing substantially to short- and long-term mortality [2, 23, 24]. AKI is increasingly recognized as a dynamic clinical syndrome rather than a static decline in kidney function. Current international guidelines, including the KDIGO Clinical Practice Guideline for AKI, emphasize serial assessment of kidney function, urine output, and clinical status because AKI severity and prognosis evolve continuously over time [17, 22, 25–27]. Traditional risk assessment strategies primarily rely on static indicators, such as serum creatinine, urine output, and severity scores. However, these parameters provide only snapshots of a continuously evolving disease process. Therefore, dynamic evaluation strategies incorporating longitudinal biomarkers may provide additional prognostic information by capturing temporal changes in renal dysfunction, metabolic disturbance, inflammation, and multiple organ interactions [28–30].

Serum phosphate is biologically plausible as a dynamic biomarker in AKI because phosphate homeostasis depends strongly on renal excretion and is regulated through complex interactions involving FGF23, parathyroid hormone, vitamin D metabolism, and cellular energy pathways [3, 4, 30, 31]. During critical illness, phosphate levels may be influenced by impaired renal clearance, tissue breakdown, intracellular–extracellular shifts, nutritional interventions, acid–base abnormalities, and renal replacement therapy. Consequently, persistent phosphate elevation may reflect not only impaired kidney function but also systemic metabolic stress and disease severity. Previous studies have demonstrated that abnormal phosphate concentrations are associated with adverse outcomes in critically ill populations, including patients with sepsis, septic shock, acute ischemic stroke, and cardiovascular disease, where elevated phosphate levels have been linked to increased mortality and poor clinical outcomes [7, 32–34]. Both hypophosphatemia and hyperphosphatemia have been linked to increased mortality, although the mechanisms and clinical implications differ across populations [7, 35]. Among patients with AKI requiring CRRT, elevated phosphate concentrations and inadequate phosphate reduction were associated with higher short-term mortality, suggesting that phosphate imbalance may reflect the severity of renal dysfunction and critical illness [5, 6, 36]. However, most previous studies evaluated baseline phosphate values or predefined categories, which may overlook clinically meaningful longitudinal patterns. Our findings extend previous literature by demonstrating that phosphate trajectories after AKI onset provide prognostic information beyond individual measurements. Similar trajectory-based approaches have recently been applied in septic populations, where persistent

high phosphate trajectories were associated with increased 28-day mortality [10]. Compared with these previous studies, our investigation specifically focused on patients with early AKI and assessed phosphate evolution during the initial 72-hour period after kidney injury onset, a clinically important window characterized by rapid changes in renal function and organ support requirements. By applying GBTM, we identified latent metabolic phenotypes that may not be recognized using conventional threshold-based approaches [8, 9, 18].

The biological interpretation of these trajectory patterns deserves consideration. Patients with persistent phosphate elevation exhibited a more severe clinical phenotype, including higher AKI stage, greater SOFA scores, and increased requirements for CRRT, mechanical ventilation, and vasopressor therapy. Beyond reflecting impaired renal phosphate clearance, persistent hyperphosphatemia may represent an active marker of systemic metabolic and inflammatory dysregulation during AKI. Experimental studies have demonstrated that AKI induces rapid activation of the fibroblast growth factor 23 (FGF23)–Klotho axis, driven by inflammatory cytokines, ischemic stress, and altered phosphate metabolism [37, 38]. Excessive FGF23 signaling and phosphate accumulation may promote endothelial dysfunction, oxidative stress, inflammation, and cardiovascular injury, thereby contributing to multisystem complications associated with severe AKI [38, 39]. In addition, phosphate overload has been shown to increase calciprotein particle formation, aggravate metabolic acidosis, and enhance inflammatory responses in experimental AKI models, processes that may further impair organ recovery and increase mortality risk [40]. Therefore, persistent phosphate elevation may not simply represent reduced renal excretion but may serve as an integrated indicator of renal dysfunction, cellular stress, and systemic organ injury. Importantly, although phosphate trajectories remained independently associated with mortality after adjustment for disease severity, the association was attenuated, suggesting that phosphate dynamics are likely a marker of underlying pathophysiological burden rather than an isolated causal factor. The clinical implications of our findings should therefore be interpreted cautiously. Early identification of high-risk phosphate trajectories may help clinicians recognize AKI patients requiring closer monitoring and more intensive management. However, whether therapeutic correction of phosphate abnormalities can improve outcomes remains uncertain. Previous studies have suggested potential benefits of phosphate control strategies, including optimized renal replacement therapy, but randomized clinical trials are lacking [35, 36]. Future prospective studies should evaluate whether trajectory-guided interventions can improve patient-centered outcomes.

This study has several strengths. First, the large sample size from MIMIC-IV and independent evaluation in eICU-CRD enhance the robustness and generalizability of our findings [14, 15]. Second, longitudinal trajectory analysis provides a more comprehensive assessment of phosphate dynamics than conventional single-value approaches. Third, the use of a landmark analysis strengthens temporal inference and reduces bias associated with exposure classification [13]. Finally, external application of the frozen trajectory model demonstrated excellent classification performance, supporting the reproducibility of this approach.

Several limitations should also be acknowledged. First, the retrospective observational design prevents causal inference, and residual confounding cannot be completely excluded. Second, although the external cohort reproduced the trajectory structure, the number of deaths in the persistent high-phosphate group was limited, reducing statistical precision. Fourth, detailed information regarding phosphate supplementation, nutritional interventions, and dialysis prescriptions was unavailable. Finally, prospective studies are required to determine whether incorporating phosphate trajectories into clinical decision-making algorithms improves outcomes.

Conclusions

Among critically ill patients with AKI occurring within the first 24 hours of ICU admission, three distinct early serum phosphate trajectories were identified in MIMIC-IV. Compared with a low-decreasing trajectory, both a moderate-decreasing trajectory and a persistently high trajectory were associated with higher subsequent 28-day mortality in the 72-hour landmark analysis after adjustment for major prognostic factors. Direct application of the frozen MIMIC-IV model to eICU-CRD reproduced the three-class structure with high classification certainty and confirmed the adverse association for the

moderate-decreasing trajectory. The association for the rare persistently high trajectory was not statistically confirmed in eICU-CRD and remains imprecisely estimated. These findings support longitudinal phosphate trajectories as potential markers of evolving metabolic and renal risk in AKI while highlighting the need for larger multicenter validation of uncommon high-risk phenotypes.

Abbreviations

AIC
Akaike information criterion
AKI
Acute kidney injury
APS III
Acute Physiology Score III
APTT
Activated partial thromboplastin time
AvePP
Average posterior probability
BIC
Bayesian information criterion
CCI
Charlson Comorbidity Index
CI
Confidence interval
CITI
Collaborative Institutional Training Initiative
CRRT
Continuous renal replacement therapy
eICU-CRD
eICU Collaborative Research Database
FGF23
Fibroblast growth factor 23
GBTM
Group-based trajectory modeling
GVIF
Generalized variance inflation factor
HIPAA
Health Insurance Portability and Accountability Act
HR
Hazard ratio
ICU
Intensive care unit
INR
International normalized ratio
KDIGO
Kidney Disease:Improving Global Outcomes
MCH
Mean corpuscular hemoglobin
MCHC

Mean corpuscular hemoglobin concentration
MCV
Mean corpuscular volume
MICE
Multiple imputation by chained equations
MIMIC-IV
Medical Information Mart for Intensive Care IV
OASIS
Oxford Acute Severity of Illness Score
OCC
Odds of correct classification
PaCO₂
Arterial carbon dioxide tension
PaO₂
Arterial oxygen tension
PT
Prothrombin time
RDW
Red cell distribution width
RRT
Renal replacement therapy
SABIC
Sample-size-adjusted Bayesian information criterion
SAPS II
Simplified Acute Physiology Score II
SCr
Serum creatinine
SIRS
Systemic inflammatory response syndrome
SOFA
Sequential Organ Failure Assessment
SpO₂
Peripheral oxygen saturation
SQL
Structured query language
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
UO
Urine output
VIF
Variance inflation factor

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of two publicly available, fully de-identified critical-care databases. The creation and release of MIMIC-IV were approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (2001-P-

001699/14) and the Massachusetts Institute of Technology (No. 0403000206), with a waiver of individual informed consent. eICU-CRD is released under the HIPAA Safe Harbor provision (Certification No. 1031219-2). Database access was granted after completion of CITI training (author Yue Yu, certification number 33281932). Additional institutional ethics approval and individual informed consent were not required for this secondary analysis of de-identified data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available in the PhysioNet repository: MIMIC-IV and eICU-CRD. Access is granted to credentialed users who complete the required training and sign the respective data-use agreements. Analysis code and derived non-identifiable outputs are available from the corresponding author upon reasonable request, subject to those data-use agreements.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LW, YY, and CP contributed equally to this work and share first authorship. YL and LL, as corresponding authors, were primarily responsible for the conception and overall design of the study and supervised its conduct. LW, YY, and CP performed the data analyses, interpreted the results, and prepared the figures and tables. LW took primary responsibility for drafting the manuscript. YY obtained the required authorization to access the databases and was responsible for data acquisition and extraction. QX and YZ contributed to manuscript revision and critically reviewed its intellectual content. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work, including ensuring that any questions related to its accuracy or integrity are appropriately investigated and resolved.

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Figures

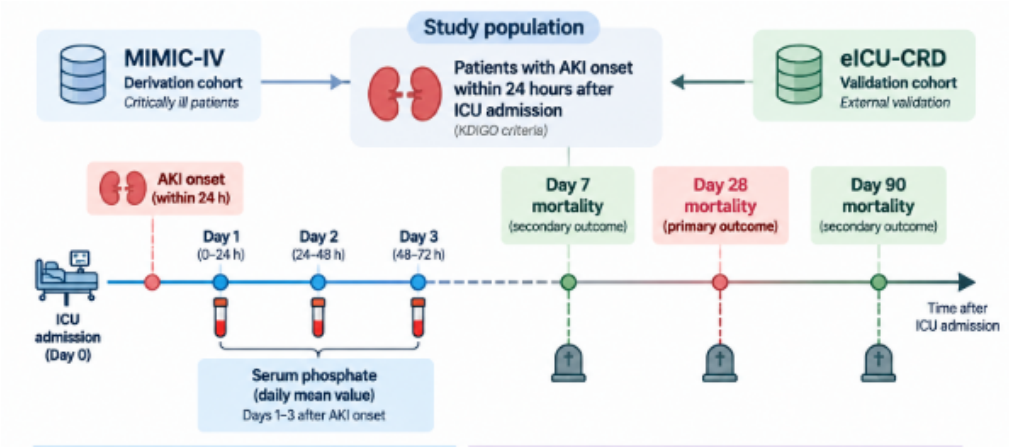


Figure 1

Study design and analytical framework.

Abbreviations:

AKI, acute kidney injury; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV; eICU-CRD, eICU Collaborative Research Database; KDIGO, Kidney Disease: Improving Global Outcomes.

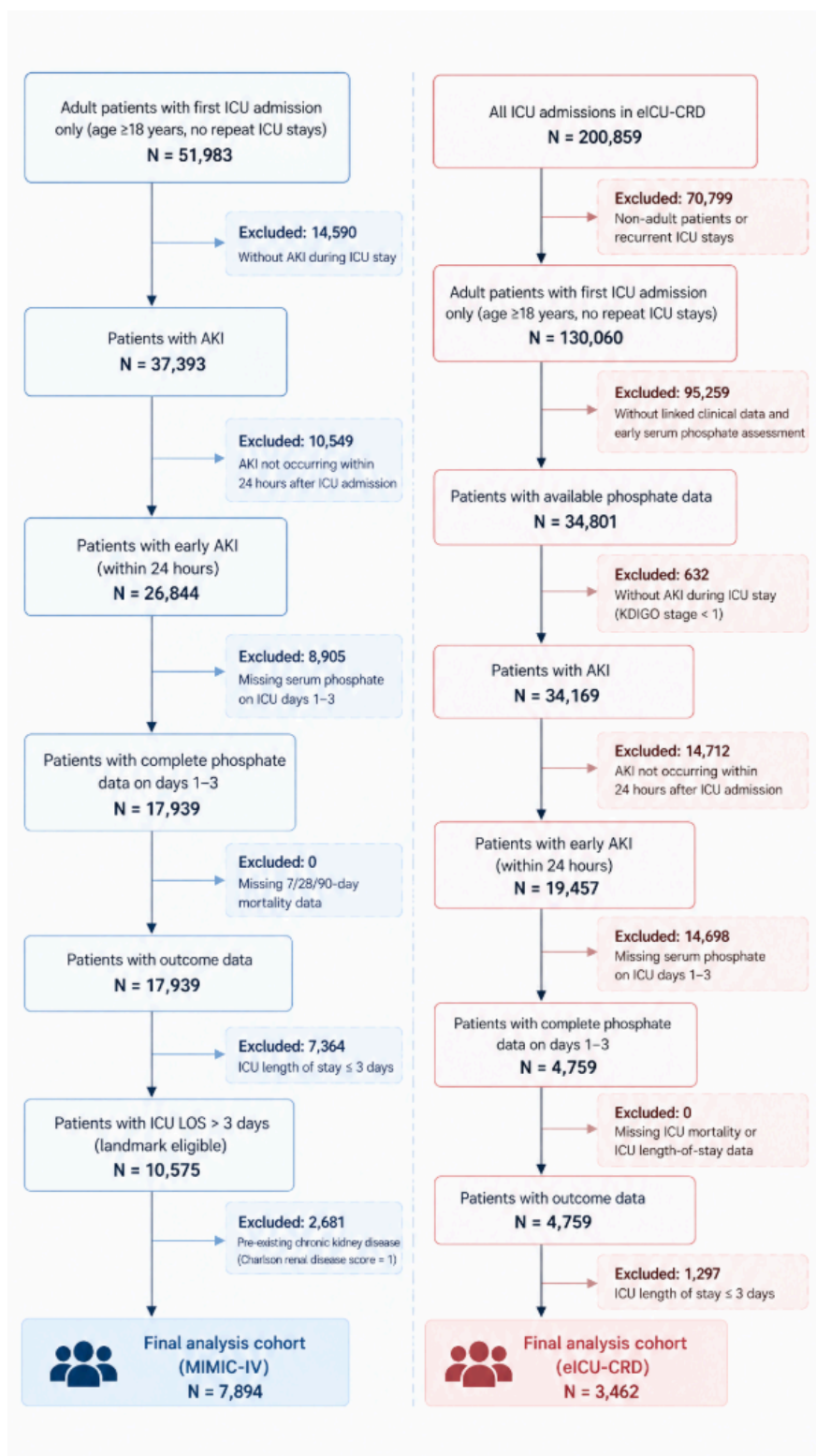


Figure 2

Flow diagram of cohort selection.

Abbreviations:

AKI, acute kidney injury; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV; eICU-CRD, eICU Collaborative Research Database; LOS, length of stay; CRRT, continuous renal replacement therapy.

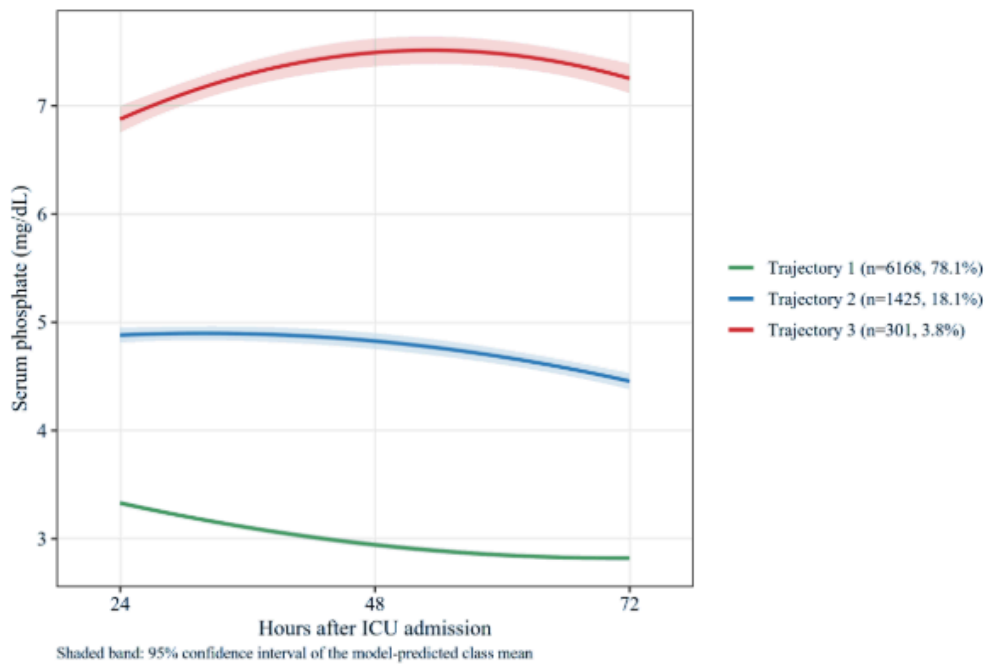


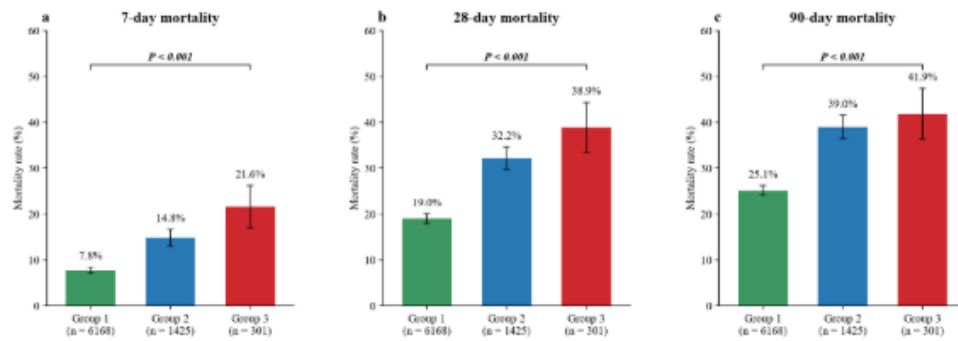
Figure 3

Early serum phosphate trajectories after AKI onset.

Abbreviations:

AKI, acute kidney injury; ICU, intensive care unit; CI, confidence interval; GBTM, group-based trajectory modeling.

A Mortality rates by phosphate trajectory



B Kaplan–Meier survival analysis by phosphate trajectory (72-hour landmark)

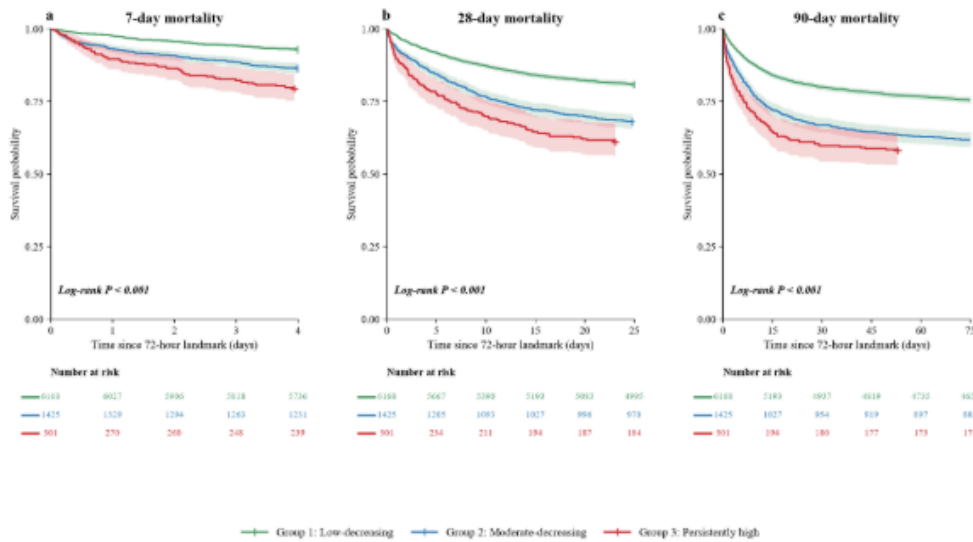


Figure 4

Association between serum phosphate trajectories and mortality outcomes.

(A) Mortality rates at 7, 28, and 90 days according to phosphate trajectory groups. (B) Kaplan–Meier survival curves using the 72-hour landmark approach for 7-day, 28-day, and 90-day mortality. Survival differences were assessed using log-rank tests.

Abbreviations:

AKI, acute kidney injury; ICU, intensive care unit; KM, Kaplan–Meier; HR, hazard ratio; CI, confidence interval.

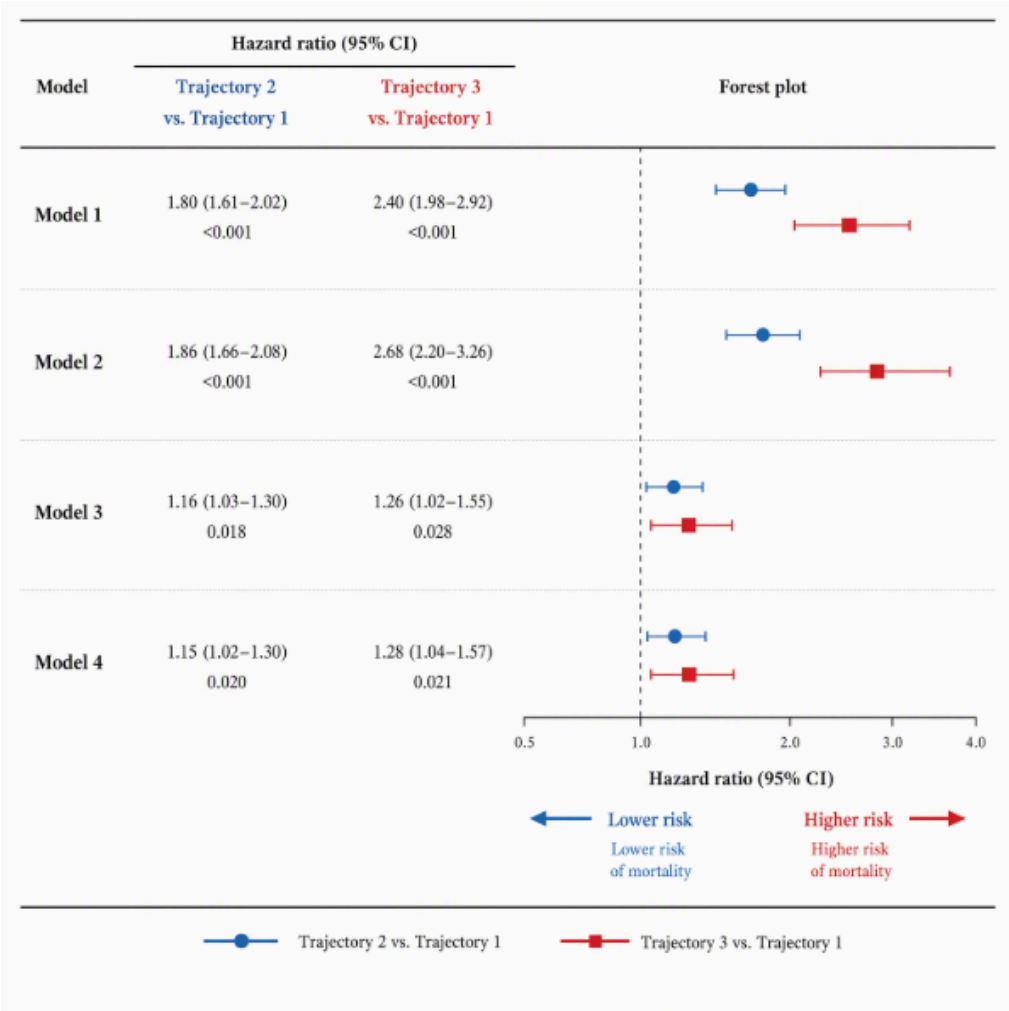


Figure 5

Multivariable Cox regression analysis of 28-day mortality according to phosphate trajectory groups.

Abbreviations:
 HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; ICU, intensive care unit.

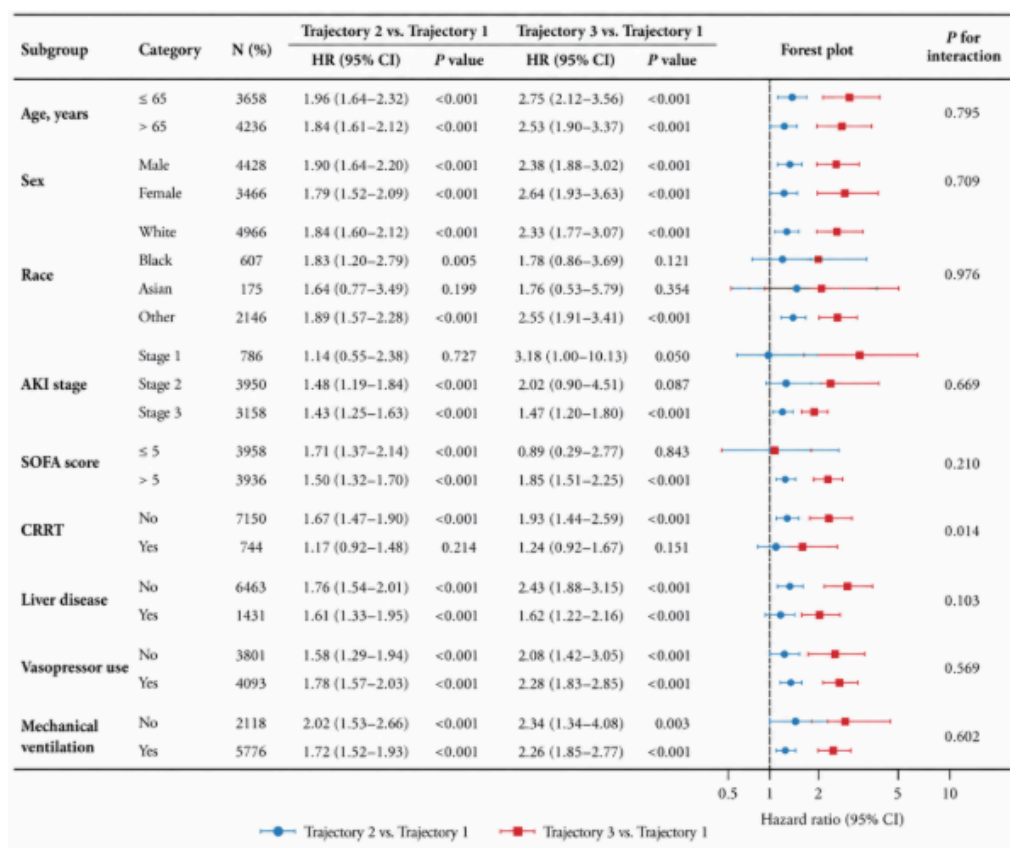


Figure 6

Subgroup analysis of the association between serum phosphate trajectories and 28-day mortality.

Abbreviations:
 HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

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