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Serum Calcium-Phosphate Product and the Risk of Kidney Replacement Therapy or In-Hospital Death in
Critically Ill Patients with Rhabdomyolysis: a Multicohort Database Study

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Abstract

Background. Rhabdomyolysis may be complicated by kidney replacement therapy (KRT) or death. We evaluated whether the early serum calcium-phosphate product ($\text{Ca} \times \text{P}$) was associated with these outcomes in critically ill adults with rhabdomyolysis.

Methods. We conducted a retrospective multicohort study using MIMIC-IV, eICU, and NWICU. Adults with maximum creatine kinase (CK) ≥ 1000 U/L during ICU hours 0–24 were eligible. Total calcium and phosphate were paired when measured within 6 h; the earliest valid pair completion time was selected, with the smallest gap used for ties. A 24-h landmark excluded KRT by 24 h, end-stage kidney disease/chronic dialysis, and ICU stay ≤ 24 h. The primary outcome was incident KRT after 24 h or in-hospital death after 24 h. Logistic models adjusted for age, sex, and $\ln(\text{CK})$.

Results. Final cohorts included 2,744 MIMIC-IV, 1,644 eICU, and 109 NWICU patients, with 541, 370, and 18 composite events. Adjusted ORs per $10 \text{ mg}^2/\text{dL}^2$ higher $\text{Ca} \times \text{P}$ were 1.416 (95% CI 1.324–1.514), 1.337 (1.246–1.434), and 1.515 (1.080–2.124), respectively. The pooled fixed-effect OR was 1.380 (1.316–1.448; $I^2=0\%$). In MIMIC-IV, restricted cubic spline analysis showed an overall association and evidence of nonlinearity (both $P<0.001$).

Conclusions. Higher early $\text{Ca} \times \text{P}$ was consistently associated with the composite of incident KRT or in-hospital death across three ICU cohorts. The nonlinear MIMIC-IV pattern supports further evaluation of $\text{Ca} \times \text{P}$ as a risk marker but does not establish causality or a treatment threshold.

Keywords: rhabdomyolysis; calcium-phosphate product; kidney replacement therapy; mortality; intensive care.

Background

Rhabdomyolysis is characterized by skeletal-muscle injury with release of intracellular constituents and may lead to acute kidney injury, electrolyte abnormalities, KRT, and death.[1–5] The McMahon risk model identified serum phosphate and calcium as separate prognostic variables in rhabdomyolysis, and critical care consensus guidance describes hyperphosphatemia and early hypocalcemia as characteristic biochemical changes.[5,8] Recent studies reinforce the clinical importance of this problem: large-scale hospitalization data link rhabdomyolysis-associated AKI with higher mortality, and ICU cohorts report substantial AKI and adverse outcomes.[13,14] Mechanistic work continues to implicate myoglobin, phosphate, calcium, and tubular injury in rhabdomyolysis-associated AKI.[15] In critically ill rhabdomyolysis, admission phosphate has been associated with subsequent AKI, while separate studies have evaluated calcium-phosphate product and the timing or modality of kidney replacement therapy.[16–19] More recent multicenter work has used complex multi-task models to estimate rhabdomyolysis outcomes.[20] Despite this progress, the literature has generally focused on AKI incidence, individual phosphate or calcium measurements, treatment timing, or complex prediction models; it has not established whether a simple early $\text{Ca} \times \text{P}$ measure is associated with a post-landmark composite of incident KRT or death across independent ICU databases.[13–20] These findings motivate evaluation of their product as a candidate marker of coupled mineral disturbance; they do not establish that $\text{Ca} \times \text{P}$ itself predicts outcomes. We therefore examined whether early $\text{Ca} \times \text{P}$ was associated with incident KRT or in-hospital death in critically ill adults with rhabdomyolysis.

Methods

Study design and population

This retrospective observational study used MIMIC-IV v3.1 [6] as the discovery cohort, eICU Collaborative Research Database v2.0 [7] as an external validation cohort, and Northwestern ICU (NWICU) database v0.1.0 [9] as a supportive validation cohort. The source databases cover admissions from 2008–2022 for MIMIC-IV, 2014–2015 for eICU, and 2020–2022 for NWICU. Adults aged ≥ 18 years with maximum CK during ICU hours 0–24 ≥ 1000 U/L were eligible; the first qualifying ICU stay per patient was retained. Patients required a valid calcium-phosphate pair and were excluded for end-stage kidney disease/chronic dialysis, KRT by ICU hour 24, or ICU stay ≤ 24 h. Follow-up began at ICU admission +24 h.

Exposure and outcomes

The exposure was total serum calcium (mg/dL) $\times$ serum phosphate (mg/dL), expressed as mg^2/dL^2 . Measurements during ICU hours 0–24 were paired when collection times differed by ≤ 6 h. The pair with the earliest completion time was selected; ties were resolved by smaller time gap and deterministic measurement-time ordering. KRT was operationalized from database-specific records of dialysis or renal replacement therapy; KRT recorded at or before ICU hour 24 was an exclusion, and the first qualifying KRT record after the 24-h landmark was counted as incident KRT. The primary outcome was incident KRT after the landmark or in-hospital death after the landmark.

Statistical analysis

Unpenalized cohort-specific logistic regression modeled the composite outcome as $\text{Ca} \times \text{P}/10 + \text{age} + \text{male sex} + \ln(\text{maximum CK during ICU hours 0–24})$; no standardization was applied. Eligibility required the exposure measurements needed to calculate $\text{Ca} \times \text{P}$, and regression analyses used complete observations for the prespecified model variables; no missing values were imputed. Cohort estimates were pooled by inverse-variance fixed effects, with DerSimonian-Laird random effects as sensitivity analysis. Cochran's Q , I^2 , τ^2 , and leave-one-out analyses assessed heterogeneity and robustness.

In MIMIC-IV, restricted cubic spline analysis used four knots at the 5th, 35th, 65th, and 95th percentiles of $\text{Ca} \times \text{P}$ (14.25, 26.04, 34.41, and 56.31 mg^2/dL^2), with the median (30.03 mg^2/dL^2) as reference. The spline

model adjusted for age, sex, and ln(CK). Likelihood-ratio tests assessed overall association and nonlinearity.

Use of AI-assisted tools

An AI language model assisted with English-language editing and document formatting only. The authors remain responsible for the methods, results, interpretation, and final text.

Supplementary methods and sensitivity analyses are provided in Additional file 1.

Results

The harmonized cohorts included 2,744 MIMIC-IV, 1,644 eICU, and 109 NWICU patients. Composite events occurred in 541 (19.7%), 370 (22.5%), and 18 (16.5%) patients. In eICU, incident KRT after 24 h occurred in 90 patients and death after 24 h in 310; in NWICU the corresponding counts were 11 and 11 (Table 1).

Higher Ca×P was associated with greater odds of the composite outcome in all cohorts (Table 2; Fig. 1). Adjusted ORs per 10 mg²/dL² were 1.416 (95% CI 1.324–1.514; P=2.64×10⁻²⁴) in MIMIC-IV, 1.337 (1.246–1.434; P=6.16×10⁻¹⁶) in eICU, and 1.515 (1.080–2.124; P=0.016) in NWICU. The pooled fixed-effect OR was 1.380 (1.316–1.448; P=1.62×10⁻³⁹); Q=1.64 (df=2, P=0.440), I²=0%, and τ²=0.

In MIMIC-IV, restricted cubic spline analysis demonstrated a significant overall association (P=5.06×10⁻²⁷) and evidence of nonlinearity (P=2.60×10⁻⁵; Fig. 2). Relative to the median Ca×P of 30.03 mg²/dL², adjusted odds rose progressively at higher Ca×P values. Confidence intervals widened toward the upper tail, indicating lower precision at very high Ca×P values; the spline was used to characterize exposure-response shape rather than define a clinical threshold.

Discussion

Across three ICU databases, higher early Ca×P was consistently associated with incident KRT or in-hospital death after a 24-h landmark. The association was similar in magnitude across cohorts, with no detectable statistical heterogeneity and stable leave-one-out estimates. These findings extend recent

observational evidence linking phosphate or calcium-phosphate measures with AKI and mortality,[16,18] complement studies of CRRT timing and kidney replacement strategies in rhabdomyolysis,[17,19] and add a parsimonious mineral marker to a field that has recently emphasized more complex prognostic models.[20]

The association is biologically plausible because rhabdomyolysis releases intracellular phosphate, kidney dysfunction may reduce phosphate clearance, and calcium concentrations change during early muscle injury. These processes are consistent with the current mechanistic framework for rhabdomyolysis-induced kidney injury, which emphasizes myoglobin-mediated tubular toxicity, hemodynamic change, oxidative stress, and mineral disturbance.[15] $\text{Ca} \times \text{P}$ may therefore integrate aspects of muscle injury, mineral disturbance, and renal handling not represented by CK alone. The nonlinear MIMIC-IV spline suggests a steeper increase in adjusted odds at higher $\text{Ca} \times \text{P}$ values, but it should not be interpreted as a treatment cutoff.

Strengths include harmonized exposure definition, a common 24-h landmark, identical adjustment, and multicohort replication. Limitations include retrospective design, residual confounding, and dependence on routinely recorded laboratory and KRT data. The models did not adjust for baseline renal function or illness severity, leaving potential confounding by kidney dysfunction, which may influence both phosphate and outcomes. Total rather than ionized calcium was used, and the NWICU sample was small. Prospective evaluation is required before clinical thresholds are proposed.

Conclusions

Higher calcium-phosphate product during the first 24 h of ICU admission was associated with greater odds of incident KRT or in-hospital death after a 24-h landmark in adults with rhabdomyolysis. The association was consistent across MIMIC-IV, eICU, and NWICU, and MIMIC-IV demonstrated a nonlinear exposure-response pattern.

Declarations

Ethics approval and consent to participate. This study was a secondary analysis of de-identified critical-care databases accessed under their applicable data-use requirements and did not involve direct patient contact or prospective enrollment. The MIMIC-IV source resource reports institutional review and waiver of individual informed consent for release of the de-identified database [6]. The eICU Collaborative Research Database is de-identified and available to credentialed users under a data-use agreement [7]. The NWICU source resource reports Northwestern University IRB approval with waiver of informed consent and authorization for data release by the Northwestern Medicine Data Steward [9].

Consent for publication. Not applicable.

Availability of data and materials. The datasets analyzed in this study are available through PhysioNet to credentialed users who meet the applicable training and data-use requirements: MIMIC-IV v3.1 (<https://doi.org/10.13026/kpb9-mt58>), eICU Collaborative Research Database v2.0 (<https://doi.org/10.13026/C2WM1R>), and Northwestern ICU (NWICU) database v0.1.0 (<https://doi.org/10.13026/s84w-1829>). Access is subject to the applicable data-use agreements and restrictions. The standard PhysioNet resource is described in reference [10], and the version-specific dataset records are cited in references [9,11,12].

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. ZY conceived and designed the study, performed data curation and statistical analysis, interpreted the results, drafted the manuscript, and takes responsibility for the integrity of the work. ZF contributed to study design, clinical interpretation of the findings, and critical revision of the manuscript. SZ contributed to clinical interpretation, literature review, and critical revision of the manuscript. All authors reviewed and approved the final manuscript.

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List of abbreviations. Ca×P, calcium-phosphate product; CI, confidence interval; CK, creatine kinase; ICU, intensive care unit; KRT, kidney replacement therapy; OR, odds ratio; RCS, restricted cubic spline.

Additional file 1

Additional file 1: Supplementary Material (DOCX). Supplementary methods, cohort-specific adjusted estimates, meta-analysis, leave-one-out analysis, quartile analyses, and a leave-one-out sensitivity analysis figure.

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Table 1. Cohort summary and outcome frequencies

Cohort	N	Ca×P median (IQR)	KRT >24 h	Death >24 h	Composite
MIMIC-IV	2744	30.03 (22.88–38.27)	177 (6.5%)	444 (16.2%)	541 (19.7%)
eICU	1644	28.16 (20.72–37.72)	90 (5.5%)	310 (18.9%)	370 (22.5%)
NWICU	109	28.48 (21.84–40.04)	11 (10.1%)	11 (10.1%)	18 (16.5%)

Values are n (%) unless otherwise indicated. Ca×P, calcium-phosphate product; IQR, interquartile range;

KRT, kidney replacement therapy. KRT and death are counted after the 24-h landmark.

Table 2. Adjusted association between Ca×P and the composite outcome

Cohort	Adjusted OR per 10 mg ² /dL ²	95% CI	P value
MIMIC-IV	1.416	1.324–1.514	2.64×10 ⁻²⁴
eICU	1.337	1.246–1.434	6.16×10 ⁻¹⁶
NWICU	1.515	1.080–2.124	0.016
Pooled (fixed)	1.380	1.316–1.448	1.62×10 ⁻³⁹

Odds ratios are per 10 mg²/dL² higher Ca×P and are adjusted for age, male sex, and ln(maximum CK during ICU hours 0–24).

Figure

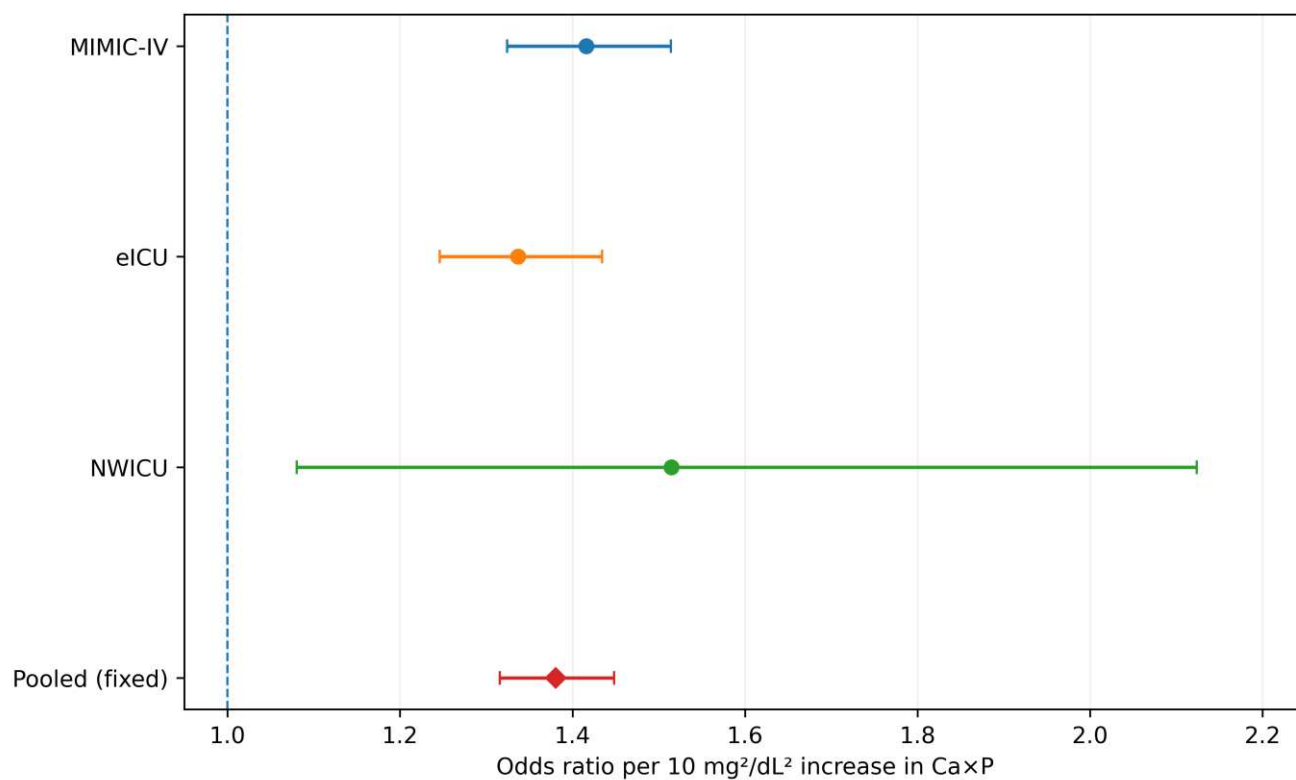


Fig. 1. Association of calcium-phosphate product with the composite outcome across cohorts. Points and horizontal lines show adjusted odds ratios and 95% confidence intervals per 10 mg²/dL² increase in Ca×P. The pooled estimate uses inverse-variance fixed-effect meta-analysis.

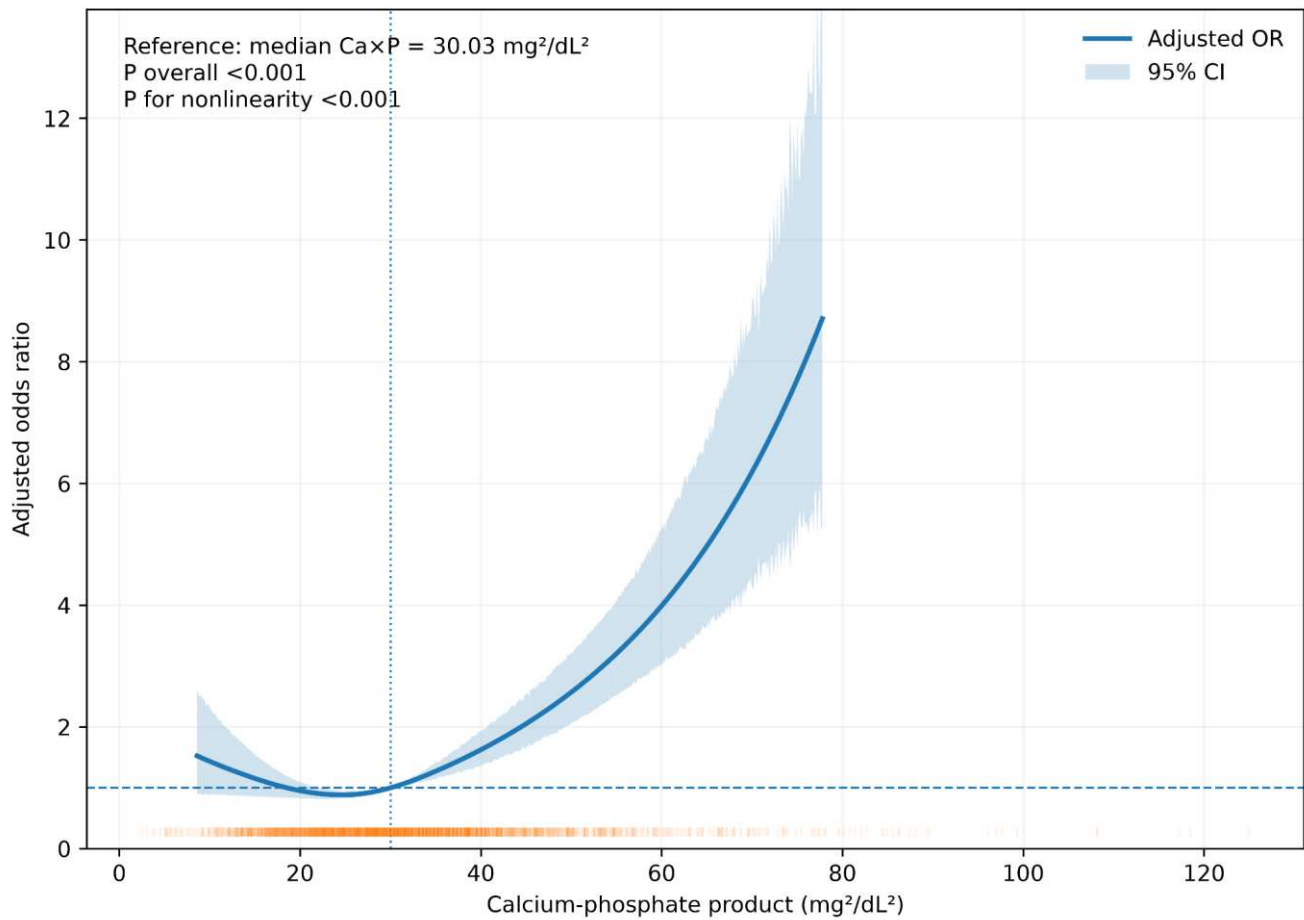


Fig. 2. Restricted cubic spline association between the calcium-phosphate product and the composite outcome in MIMIC-IV. The solid line represents adjusted odds ratios and the shaded area 95% confidence intervals. The model adjusted for age, sex, and $\ln(\text{maximum CK during ICU hours 0–24})$. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles (14.25, 26.04, 34.41, and 56.31 mg^2/dL^2), with the median (30.03 mg^2/dL^2) as reference. P for overall association <0.001 ; P for nonlinearity <0.001 . Confidence intervals widen toward the upper tail, reflecting lower precision at very high $\text{Ca} \times \text{P}$ values.

Supplementary Files

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