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ORIGINAL ARTICLE

Association between phosphorus-to-calcium ratio at ICU admission and all-cause mortality in acute pancreatitis: Insights from the MIMIC-IV database

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Abstract

Background: Serum phosphorus and serum calcium are important electrolytes in the body. The relationship between them and acute pancreatitis (AP) has been previously discussed. However, the results seem to lack credibility due to the neglect of mutual influence between them. Thus, a comprehensive indicator is needed.

Methods: In this study, AP patients with intensive care unit (ICU) treatment were extracted from Medical Information Mart for Intensive Care (MIMIC) database. The outcomes included in-hospital mortality and ICU mortality. Kaplan–Meier survival analysis, Cox proportional hazard regression model and restricted cubic spline were employed to investigate the association between the phosphorus-to-calcium ratio (PCR) index and clinical outcomes.

Results: A total of 719 AP patients (57.2% male) were enrolled. The in-hospital and ICU mortality were 11.4% and 7.5%, respectively. After adjusting for confounders, Cox proportional hazard analysis indicated patients with a higher PCR index had a significant association with in-hospital mortality (adjusted hazard ratio, 2.88; 95% confidence interval, 1.34–6.19; $p = .007$). Restricted cubic splines revealed that a progressively increasing risk of all-cause mortality was associated with an elevated PCR index.

Conclusion: The PCR index has a strong correlation with in-hospital and ICU all-cause mortality in AP, which provides a reference for clinical decision-making.

KEYWORDS

acute pancreatitis, all-cause mortality, in-hospital, MIMIC-IV database, phosphorus-to-calcium ratio

1 | INTRODUCTION

Acute pancreatitis (AP), an inflammatory injury caused by the premature activation of trypsinogen,[1] is one of the most common reasons for gastrointestinal admission. Its incidence has continued to increase over the past 20 years, with hospitalization costs surpassing $30 000 per person in the United States.[2] Given the

severity of disease, AP has a variable individual prognosis. Majority of patients with mild AP usually recover within a week after supportive treatment such as fluid resuscitation, pain management and nutritional supplement.[3] However, 20% of patients with moderate or severe acute pancreatitis (SAP) may suffer dire outcomes due to infected pancreatic and peripancreatic necrosis or organ failure.[4] It is reported that the mortality rate within this group is as high as 30%.[5] Therefore, early identification and timely intervention are of great significance to the clinical treatment of AP. Currently, multiple predictive models and scoring systems have been developed to assess the severity of AP, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), Bedside Index for the Severity in Acute Pancreatitis (BISAP), Ranson criteria and Computed Tomography Severity Index (CTSI).[6,7] The dependence of these systems on multiple variables and the requirement for image analysis limits their clinical application. Thus, a practical and economical indicator is urgently needed.

Serum phosphorus and serum calcium are commonly detected electrolytes in clinical practice. Several studies have been conducted to investigate their association with a variety of diseases,[8,9] which provides important guidelines bases for practical decision-making. Previous results have also shown that their values are closely related to the prognosis of AP. Hyperphosphatemia is regarded as a risk factor for AP.[10,11] Meanwhile, lower serum calcium levels have been revealed to be associated with longer hospital stays for AP and with persistent organ failure.[12,13] However, due to the regulation of various hormones in the body, the values of serum phosphorus and calcium often change simultaneously.[14] Therefore, using individual serum phosphorus or calcium level predictions does not ensure reliable results. A more comprehensive approach is needed.

In the current study, the concept of the phosphorus-to-calcium ratio (PCR), which is convenient for detection and can reflect the serum phosphorus and calcium levels simultaneously, is introduced. We aim to analyze the relationship between PCR index and in-hospital all-cause mortality in AP patients, with a view to providing a reference for clinical decision-making.

2 | METHODS

2.1 | Data source

This study was conducted with Medical Information Mart for Intensive Care (MIMIC), an extensive, single-center, and freely accessible clinical database hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (MIT).[15] It covers well-documented information of patients enrolled in Beth Israel Deaconess Medical Center (BIDMC), Boston, from 2008 to 2019.[15] Our study is based on the newly released one (version 2.2) updated January 6, 2023.

2.2 | Population selection criteria

Patients whose diagnostic description included "acute pancreatitis" according to the International Classification of Diseases (ICD), 9th and 10th revisions were enrolled in the study (Table S1). A total of 5894 matching hospitalization records were retrieved from the database. Based on the selection, those who were not admitted to the intensive care unit (ICU) were eliminated, and only the first ICU records were kept. Furthermore, patients meeting the following criteria were excluded: (1) patients younger than 18 years of age at admission; (2) patients with an ICU stay of less than 24 h; (3) patients with malignant tumors upon admission; (4) patients without serum phosphorus and serum calcium simultaneously measured during the first 24 h of ICU stay. Ultimately, 719 participants were enrolled in the study (Figure 1) and grouped according to the PCR index with the help of X-tile, a piece of software which can test multiple partitions and accept the best *p*-values to help researchers determine the optimal cutoff value.[16]

2.3 | Data collection

All variables involved in this study were extracted by using Structured Query Language (SQL)[17] with Navicate Premium (version 16.0.12) and PostgreSQL (version 14.4.1) software. As the main study variable, the PCR index is defined as the serum phosphorus-calcium ratio measured simultaneously for the first time within the initial 24 h after admission to ICU, aiming to reduce the interference of subsequent treatments on their values. In addition, potential confounders considered mainly included: (1) demographics, such as age and gender; (2) vital signs, including temperature, heart rate, respiratory rate, and mean arterial pressure; (3) comorbidities, including congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and renal disease; (4) clinical interventions, such as mechanical ventilation (MV) and renal replacement therapy (RRT); (5) laboratory tests, including hemoglobin, white blood cells (WBC), platelet, alanine aminotransferase (ALT), serum creatinine, serum phosphorus, and serum calcium. Similarly, these variables are also limited to values recorded during the first 24 h of ICU admission.

To avoid possible error, only variables with less than 10% missing were included in the study (Table S2). The

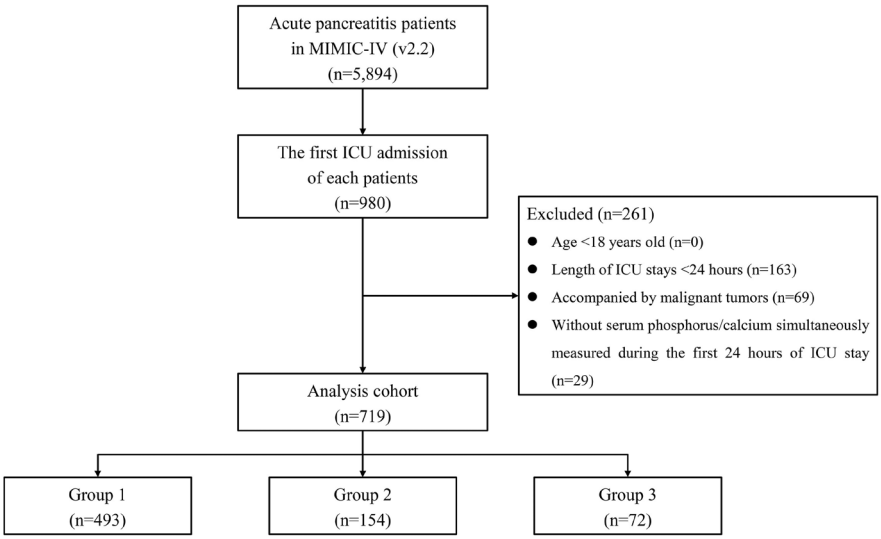

FIGURE 1 Schematic diagram of study sample selection steps. ICU, intensive care unit; MIMIC, Medical Information Mart for Intensive Care.

missing parts were processed by the "missForest" package of R software using a random forest algorithm.

2.4 | Clinical outcomes

The primary outcome of the present study was in-hospital all-cause mortality, and the second endpoint was mortality in ICU.

2.5 | Statistical analysis

Based on data distribution, continuous variables are expressed as mean ± SD or median (interquartile range). Categorical variables are displayed as numbers (%). Groups of categorical parameters were compared using the χ^2 test or Fisher's exact test. Kolmogorov–Smimov test was used to evaluate the normality of continuous parameters. The analysis of continuous variables was performed using *t*-test or analysis of variance (ANOVA) if they presented a normal distribution and using Wilcoxon rank-sum test or Kruskal–Wallis test if they were non-normal distribution. Moreover, standardized mean differences (SMD) were also used to represent the differences in variables among distinct groups. For survival analysis, Kaplan–Meier survival curve was used to depict outcome events among groups according to the PCR index and log-rank test was employed to determine statistical differences. To identify influencing factors related to all-cause mortality, both binary logistic regression and Cox proportional hazard model were applied. To ensure robustness three Cox models (including clinically associated and prognosis-relevant variables) were evaluated separately. Furthermore, we used the restricted cubic spline (RCS) method to investigate the possible nonlinear relationship between PCR index and patient outcomes.[18] Finally, subgroup analyses were conducted to investigate whether PCR index had any effect in different subgroups, including age, gender, CHF, and COPD. Two-sided $p < .05$ was considered to indicate a statistically significant difference. All analyses were performed with R software (version 4.3.2).

3 | RESULTS

3.1 | Baseline demographic and clinical characteristics

After screening, a total of 719 AP patients were enrolled in this study. The median age of the participants was 58 years (IQR: 46–72), and 411 (57.2%) of them were male. Participants had a median PCR index of 0.41 (IQR: 0.30–0.51). Participants spent an average of 12 days in the hospital and 3 days in the ICU. The in-hospital and ICU mortality rates were 11.4% and 7.5%, respectively.

X-tile plots provide a single, global assessment of every possible way of dividing a population into low-, medium-, and high-level marker expression.[16] With the application of it, when in-hospital outcomes were reviewed, participants were divided into three groups according to PCR index from smallest to largest: group 1 (0.04–0.48), group 2 (0.48–0.73), and group 3 (0.73–2.05) (Figure S1). Table 1 shows the demographic and clinical characteristics of the participants. There were no significant differences in age or gender among different groups; however, the high PCR index group had a larger proportion of therapeutic interventions such as MV and RRT than the lower. In addition, compared with patients with a low PCR index, those with a higher PCR index had significantly higher hospital mortality rates (6.7% vs. 14.3% vs. 37.5%, $p < .001$) and ICU

TABLE 1 Baseline demographic and clinical characteristics categorized by PCR index.

Variables	MIMIC-IV ($n = 719$)					
	Overall	Group 1	Group 2	Group 3	*p*-value	SMD
N	719	493	154	72		
Age (years)	58 (46–72)	56 (44–71)	61 (50–74)	60 (51–70)	.053	0.135
Male (%)	411 (57.2)	282 (57.2)	82 (53.2)	47 (65.3)	.234	0.164
Vital sign						
Temperature (°C)	37.0 (36.7–37.4)	37.0 (36.7–37.5)	36.9 (36.7–37.2)	36.7 (36.2–37.2)	<.001	0.334
Heart rate (bpm)	96 (83–108)	96 (83–109)	96 (81–107)	94 (82–105)	.611	0.076
Respiratory rate (bpm)	21 (18–24)	21 (18–24)	21 (18–24)	22 (18–25)	.320	0.102
MAP (mmHg)	81 (73–91)	83 (75–93)	77 (71–86)	76 (71–83)	<.001	0.378
Comorbidities, *n* (%)						
CHF	138 (19.2)	79 (16.0)	42 (27.3)	17 (23.6)	.005	0.184
COPD	154 (21.4)	96 (19.5)	40 (26.0)	18 (25.0)	.169	0.104
Renal disease	119 (16.6)	57 (11.6)	39 (25.3)	23 (31.9)	<.001	0.339
Clinical interventions, *n* (%)						
MV use (first 24 h)	304 (42.3)	164 (33.3)	89 (57.8)	51 (70.8)	<.001	0.531
RRT use (first 24 h)	52 (7.2)	13 (2.6)	15 (9.7)	24 (33.3)	<.001	0.590
Laboratory tests						
Hemoglobin (g/dL)	10.5 (8.8–12.0)	10.7 (9.2–12.2)	10.0 (8.3–11.7)	9.2 (7.7–10.9)	<.001	0.456
WBC (*10^9/L)	14.1 (10.1–19.8)	13.7 (9.7–19.1)	16.0 (12.1–23.2)	15.1 (10.8–20.0)	<.001	0.246
Platelet (*10^9/L)	167 (114–235)	170 (119–244)	180 (121–226)	139 (82–211)	.045	0.116
ALT (IU/L)	63.0 (26.5–181.9)	62.0 (26.0–169.0)	62.5 (27.2–184.0)	79.5 (32.2–434.8)	.038	0.233
Serum creatinine (mg/dL)	1.1 (0.8–2.2)	1.0 (0.7–1.4)	2.0 (1.0–3.4)	4.8 (3.1–6.9)	<.001	1.141
Serum phosphorus (mg/dL)	3.2 (2.3–4.1)	2.7 (2.0–3.3)	4.4 (4.0–4.9)	7.4 (5.8–8.8)	<.001	2.274
Serum calcium (mg/dL)	7.9 (7.3–8.5)	8.1 (7.4–8.5)	7.8 (7.3–8.5)	7.3 (6.2–8.1)	<.001	0.511
PCR index	0.41 (0.30–0.51)	0.34 (0.26–0.41)	0.54 (0.51–0.62)	1.00 (0.86–1.21)	<.001	2.754
Events						
LOS hospital (days)	12 (6, 22)	11 (6, 21)	12 (6, 23)	14 (8, 23)	.359	0.080
LOS ICU (days)	3 (2, 8)	3 (2, 8)	3 (2, 8)	4 (2, 9)	.044	0.110
Hospital mortality (%)	82 (11.4)	33 (6.7)	22 (14.3)	27 (37.5)	<.001	0.533
ICU mortality (%)	54 (7.5)	21 (4.3)	16 (10.4)	17 (23.6)	<.001	0.392

Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; MAP, mean arterial pressure; MV, mechanical ventilation; PCR, phosphorus-to-calcium ratio, RRT, renal replacement therapy; SMD, standard mean difference; WBC, white blood cell.

mortality (4.3% vs. 10.4% vs. 23.6%, $p < .001$). The SMD values (0.533 and 0.392, respectively) also confirm this result.

Subsequently, we analyzed the characteristics of survivors and nonsurvivors while in the hospital (Table 2). Although no significant differences in comorbidities were detected within the nonsurvival group, they did have lower platelets and higher creatinine, compared to survivors. The PCR index of the two cohorts were also significantly different (0.40 vs. 0.53, $p < .001$, SMD = 0.749). Figure S2 depicted the distribution of PCR in hospital and ICU all-cause mortality conditions, respectively.

3.2 | Kaplan–Meier survival analysis

To explore the incidence of outcome events among groups divided by X-tile, we used Kaplan–Meier survival analysis. Patients with a higher PCR index were associated with higher in-hospital and ICU mortality (log-rank $p < .001$, <0.001, respectively). In addition, 28-day mortality and 90-day mortality were discussed and similar results were obtained (Figure 2). Group 3 showed more significant differences compared to groups 1 and 2.

TABLE 2 Baseline characteristics of the survivor and nonsurvivor groups.

Variables	MIMIC-IV ($n = 719$)				
	Overall	Survivor	Non-survivor	*p*-value	SMD
N	719	637	82		
Group 1	493	460	33		
Group 2	154	132	22		
Group 3	72	45	27		
Age (years)	58 (46–72)	58 (46–72)	55 (42–66)	.087	0.224
Male (%)	411 (57.2)	361 (56.7)	50 (61.0)	.533	0.088
Vital sign					
Temperature (°C)	37.0 (36.7–37.4)	37.0 (36.7–37.4)	36.8 (36.3–37.2)	.001	0.365
Heart rate (bpm)	96 (83–108)	96 (83–109)	93 (81–105)	.525	0.063
Respiratory rate (bpm)	21 (18–24)	21 (18–24)	22 (18–25)	.165	0.149
MAP (mmHg)	81 (73–91)	82 (73–92)	77 (71–84)	.006	0.310
Comorbidities, *n* (%)					
CHF	138 (19.2)	123 (19.3)	15 (18.3)	.943	0.026
COPD	154 (21.4)	140 (22.0)	14 (17.1)	.381	0.124
Renal disease	119 (16.6)	104 (16.3)	15 (18.3)	.769	0.052
Clinical interventions, *n* (%)					
MV use (first 24 h)	304 (42.3)	258 (40.5)	46 (56.1)	.010	0.316
RRT use (first 24 h)	52 (7.2)	0 (0.0)	52 (63.4)	<.001	1.862
Laboratory tests					
Hemoglobin (g/dL)	10.5 (8.8–12.0)	10.5 (8.8–12.0)	10.2 (8.9–11.5)	.339	0.156
WBC (*10^9/L)	14.1 (10.1–19.8)	14.1 (10.2–20.0)	14.0 (9.9–19.7)	.921	0.055
Platelet (*10^9/L)	167 (114–235)	170 (117–243)	148 (89–204)	.006	0.408
ALT (IU/L)	63.0 (26.5–181.9)	62.0 (26.0–172.0)	65.0 (30.2–278.9)	.063	0.283
Serum creatinine (mg/dL)	1.1 (0.8–2.2)	1.1 (0.8–1.9)	3.2 (1.5–5.8)	<.001	0.857
Serum phosphorus (mg/dL)	3.2 (2.3–4.1)	3.2 (2.3–4.0)	4.0 (2.9–6.6)	<.001	0.682
Serum calcium (mg/dL)	7.9 (7.3–8.5)	8.0 (7.4–8.5)	7.8 (6.6–8.4)	.050	0.289
PCR index	0.41 (0.30–0.51)	0.40 (0.29–0.50)	0.53 (0.39–0.89)	<.001	0.749

Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MAP, mean arterial pressure; MV, mechanical ventilation; PCR, phosphorus-to-calcium ratio; RRT, renal replacement therapy; SMD, standard mean difference; WBC, white blood cell.

3.3 | Outcome of interests

Based on clinical experience, relevant factors were included in univariate logistic regression analysis of in-hospital all-cause mortality in AP population. As displayed in Table S3, platelet, ALT, serum creatinine, serum phosphorus, serum calcium, and PCR index were all possible influencing factors. Using Cox proportional hazard analysis, the relationship between PCR index and in-hospital mortality was further elaborated. When treating PCR index as a continuous variable, in the univariate model (hazard ratio [HR]: 5.25, 95% confidence interval [CI]: 3.26–8.46, $p < .001$), partially adjusted multivariate model (HR: 4.96, 95% CI: 3.12–7.89, $p < .001$), and fully adjusted multivariate model (HR: 2.88, 95% CI: 1.34–6.19, $p = .007$), patients with a higher PCR index were significantly associated with higher in-hospital mortality. Similarly, when viewed as a categorical variable, in three Cox proportional hazard models described above, PCR index was still considered a significant risk factor: univariate model (HR: 5.16, 95% CI: 3.09–8.62, $p < .001$), partially adjusted multivariate model (HR: 5.23, 95% CI: 3.13–8.74, $p < .001$), and fully adjusted multivariate model (HR: 3.10, 95% CI: 1.58–6.10, $p = .001$), compared to subjects in group 1, respectively. When the outcome of concern was converted to ICU mortality, similar conclusions were reached using the same models and methods (Table 3).

Furthermore, to eliminate the interference of possible nonlinear change relations on the results, the RCS

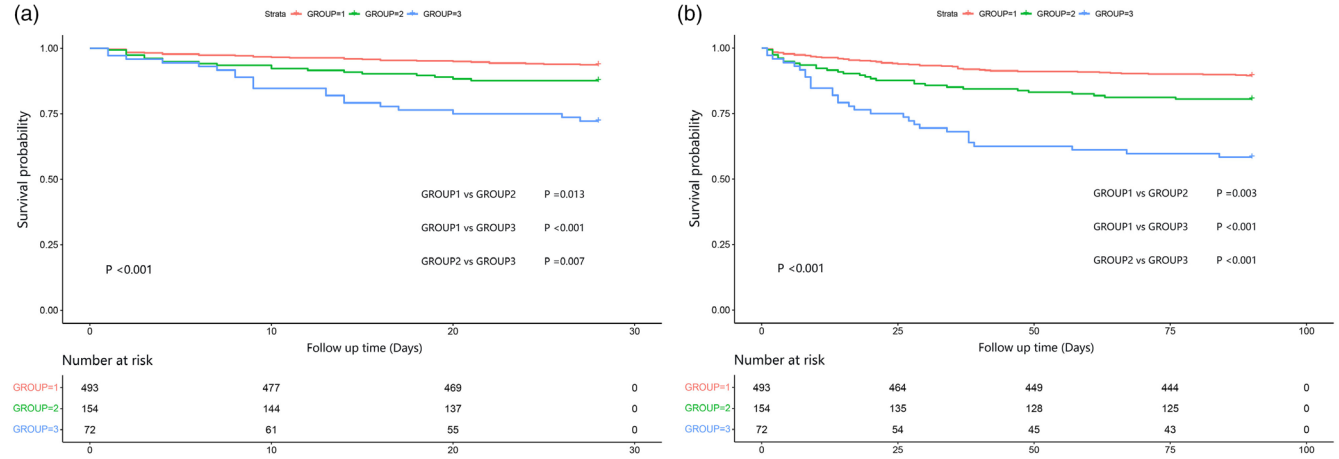

FIGURE 2 Kaplan–Meier survival analysis curves for all-cause mortality. (a) 28-day mortality; (b) 90-day mortality.

regression model was adopted. As presented in Figure 3, in RCS curves, *p*-value for nonlinearity in in-hospital and ICU mortality was .183 and .126, respectively. This suggests that the risk of these two outcomes increases linearly with the increase in the PCR index.

3.4 | Subgroup analysis

Figure 4 elucidated whether the correlation between PCR and all-cause in-hospital mortality was stable across subgroups, including age, gender, CHF, and COPD, in AP patients during hospitalization. As illustrated in the figure, when stratified analysis was performed, there was no significant interaction between the PCR index and each subgroup (*p* for interaction: .070–.849). Similarly, when considering ICU mortality as the outcome, the results remained stable (*p* for interaction: .085–.914). This further proves that the PCR index is an independent risk factor.

4 | DISCUSSION

Due to the increasing morbidity and mortality of patients with AP,[1,2] more and more attention has been paid to this condition. In recent years, researchers have conducted several studies to identify its prognostic markers, which include red cell distribution width (RDW),[19] neutrophil-lymphocyte ratio (NLR),[20] lactate-albumin ratio (LAR),[21] among others. Similarly, our study evaluated the relationship between PCR index and clinical outcomes in an AP cohort. The results indicated that a higher PCR was associated with AP hospital and ICU all-cause mortality, which may provide clinicians with a new decision-making tool.

Serum phosphate is essential for cell signaling and necessary for ATP synthesis.[22] Its correlation to the prognosis of patients with sepsis or those admitted to the ICU for various reasons has been elucidated.[23] Interestingly, the relationship between serum phosphorus levels and AP remains uncertain. In the study by Farooq et al., it was found that hypophosphatemia caused by a low-phosphorus diet increased susceptibility to alcoholic pancreatitis.[24] A similar idea was demonstrated in another study by his team, involving either caerulein injection or retrograde pancreatic duct perfusion. However, in some existing clinical studies, hyperphosphatemia has been considered a possible risk factor for AP. These associations have been observed in the context of hospital admission,[11] ICU treatment[10] or post-ERCP. It has been suggested that this is caused by the activation of extracellular purinergic metabolism in AP, which leads to an increase in the hydrolysis of nucleotides by ectonucleotidases, followed an increase in serum phosphorus.[25] Conflicting data may arise from different models, and it suggests the need for more accurate metrics.

The relationship between calcium and AP has been widely discussed. As an intracellular Ca^{2+} reservoir in acinar cells, the endoplasmic reticulum releases a large amount of Ca^{2+} into the cytoplasm when stimulated. More extracellular Ca^{2+} enters cells along with the activation of calcium-release-activated calcium regulator 1 (Orai1), resulting in persistent cytoplasmic Ca^{2+} overload,[26] which can lead to premature trypsin activation and mitochondrial stress. Additionally, studies on serum calcium suggest that hypocalcemia is independently associated with AP in cases of persistent organ failure and may serve as a potential prognostic factor.[13] Furthermore, lower serum calcium levels were related to longer hospital stays in AP patients.[12] There have also been reports of hypercalcemia-induced AP.[27] In AP, attention should continue to be paid to calcium.

TABLE 3 Cox proportional HRs for all-cause mortality.

Categories	Univariate model			Partially adjusted multivariate model			Fully adjusted multivariate model		
	HR (95% CI)	*p*-value	P for trend	HR (95% CI)	*p*-value	P for trend	HR (95% CI)	*p*-value	P for trend
Hospital mortality									
Continuous variable per unit	5.25 (3.26–8.46)	<.001		4.96 (3.12–7.89)	<.001		2.88 (1.34–6.19)	.007	
Group									
Group 1 ($N=493$)	Ref.		<0.001	Ref.		<0.001	Ref.		<0.001
Group 2 ($N=154$)	2.01 (1.17–3.47)	.012		2.13 (1.23–3.68)	.007		1.87 (1.06–3.29)	.031	
Group 3 ($N=72$)	5.16 (3.09–8.62)	<.001		5.23 (3.13–8.74)	<.001		3.10 (1.58–6.10)	.001	
ICU mortality									
Continuous variable per unit	4.76 (2.62–8.62)	<.001		4.66 (2.61–8.32)	<.001		2.48 (1.15–5.31)	.020	
Group									
Group 1 ($N=493$)	Ref.		<0.001	Ref.		<0.001	Ref.		<0.001
Group 2 ($N=154$)	2.26 (1.18–4.34)	.014		2.43 (1.26–4.69)	.008		2.11 (1.07–4.13)	.030	
Group 3 ($N=72$)	4.14 (2.18–7.89)	<.001		4.22 (2.21–8.07)	<.001		2.06 (0.87–4.91)	.102	

Note: Partially adjusted multivariate model: adjusted for age, gender, CHF and COPD. Fully adjusted multivariate model: adjusted for age, gender, CHF, COPD, WBC, ALT, and serum creatinine.

Abbreviations: ALT, platelet, alanine aminotransferase; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICU, intensive care unit; WBC, white blood cell.

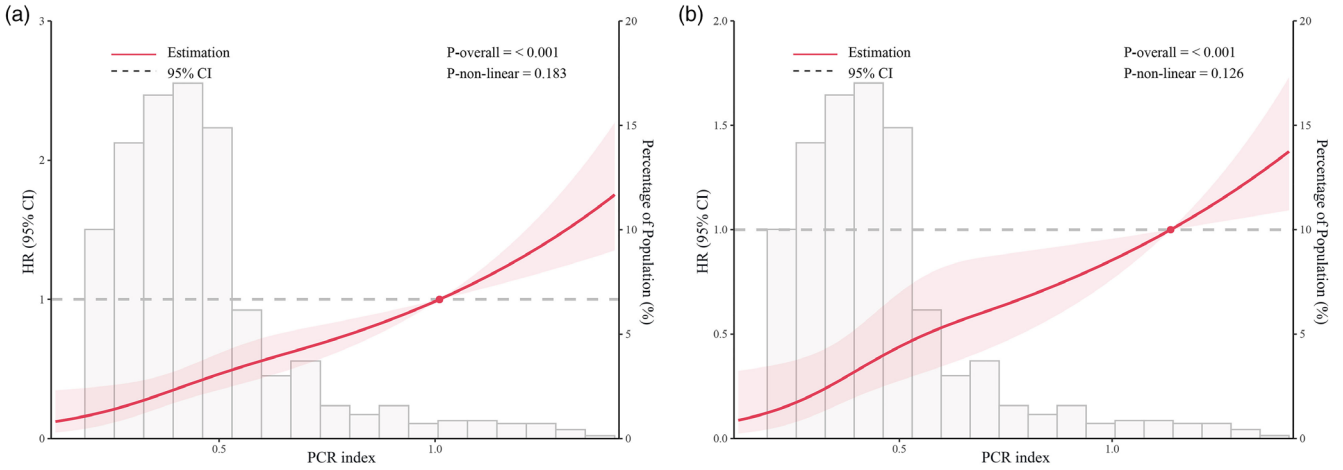

FIGURE 3 Restricted cubic spline (RCS) curve for the PCR index hazard ratio. Heavy central lines represent the estimated hazard ratios, with shaded ribbons denoting 95% CIs. The horizontal dotted lines represent the hazard ratio of 1.0. (a) RCS for hospital mortality; (b) RCS for ICU mortality. CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; PCR, phosphorus-to-calcium ratio.

(a)

Variable	Count	Percent	HR(95% CI)	P value	P for interaction
Overall	719	100	5.25 (3.26 to 8.46)	<0.001	
Age					0.146
<=60	389	54.1	4.08 (2.24 to 7.43)	<0.001	
>60	330	45.9	8.33 (3.69 to 18.81)	<0.001	
Gender					0.649
Female	308	42.8	5.87 (2.89 to 11.91)	<0.001	
Male	411	57.2	4.78 (2.50 to 9.15)	<0.001	
CHF					0.849
No	581	80.8	5.61 (3.35 to 9.38)	<0.001	
Yes	138	19.2	4.41 (1.32 to 14.71)	0.016	
COPD					0.07
No	565	78.6	4.48 (2.64 to 7.59)	<0.001	
Yes	154	21.4	16.28 (4.58 to 57.84)	<0.001	

0 2 4 6 8 10

(b)

Variable	Count	Percent	HR(95% CI)	P value	P for interaction
Overall	719	100	4.76 (2.62 to 8.62)	<0.001	
Age					0.315
<=60	389	54.1	3.63 (1.63 to 8.09)	0.002	
>60	330	45.9	6.83 (2.74 to 17.00)	<0.001	
Gender					0.914
Female	308	42.8	5.24 (2.22 to 12.34)	<0.001	
Male	411	57.2	4.94 (2.07 to 11.78)	<0.001	
CHF					0.474
No	581	80.8	4.27 (2.20 to 8.28)	<0.001	
Yes	138	19.2	9.10 (2.06 to 40.21)	0.004	
COPD					0.085
No	565	78.6	3.96 (2.06 to 7.60)	<0.001	
Yes	154	21.4	31.41 (4.89 to 201.87)	<0.001	

0 2 4 6 8 10

FIGURE 4 Forest plots of hazard ratios of the PCR index for mortality in different subgroups. (a) Hospital mortality; (b) ICU mortality. CI, confidence interval; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICU, intensive care unit; PCR, phosphorus-to-calcium ratio.

As described above, previous studies effectively support the existence of pathophysiological changes both in phosphorus and calcium in the natural course of AP, which provides guarantee for the theoretical feasibility of the association between PCR index and AP.

Multiple previous studies have demonstrated that phosphorus and calcium interact during changes in the body.[14] Parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), Klotho, and 1,25 $(OH)_2$ vitamin D are key regulators of this interaction,[28] which prompts us to take a more comprehensive view of the role of them. As a composite ratio indicator, the PCR index reflects the changes in phosphorus and calcium, considering their interaction. This represents the novelty of our research. Such applications are more common in diseases of the parathyroid gland or the skeletal system. In their study, Bestepe et al. proposed that the calcium-phosphorus ratio is a simple and inexpensive screening method for primary hyperparathyroidism.[29] A similar conclusion was reached in another study.[30] It has been reported that the specificity of the calcium-phosphorus ratio is higher than that of individual calcium and phosphorus concentration in the diagnosis of bone diseases, and the results are more reliable.[31] Additionally, the relationship between calcium-phosphorus product and coronary artery calcification score (CACS) has been noted.[32] Although there is no such discussion in the context of AP, it confirms that the form of PCR index is scientific.

In our study, the concept of PCR index was introduced into the decision of AP. Comparing the initial PCR index of survivors and nonsurvivors during the hospital stay revealed that there was indeed a difference: nonsurvivors had higher PCR index. In binary logistic regression analysis of hospital all-cause mortality in AP population, results suggested that serum phosphorus (HR: 1.39, 95% CI: 1.25–1.54, $p < .001$) and serum calcium (HR: 0.74, 95% CI: 0.60–0.91, $p = .004$) were the influential factors. Based on clinician recommendations and clinical experience, different Cox proportional hazard models reached similar conclusions, regardless of whether all-cause deaths occurred in the hospital or ICU. Furthermore, a significant linear relationship between the PCR index and hospital mortality in AP cohort was confirmed by the RCS regression model. This was consistent with the conclusions of previous studies. These results, as well as the exact pathophysiological changes and confirmed forms, support the potential of the PCR index as an effective stratification tool.

Our study had certain limitations. First, it was a single-center retrospective study based on the MIMIC-IV database. Even though we employed various methods to stabilize the results, there are still variables that we do not consider that may affect the outcomes. Further prospective cohort studies are needed to revalidate the role of the PCR index in AP. Second, mortality was the primary outcome measure. The data extracted from the database pertained to all-cause deaths, so it is impossible to accurately determine whether the death was caused specifically by AP. This could inevitably lead to slightly different conclusions.

In summary, our results extend the application of the PCR index to patients with AP. It was also demonstrated that PCR has a strong correlation with in-hospital mortality in AP, which suggests that it has significant potential as an efficient stratification tool. Monitoring the PCR index could contribute to timely and effective management of AP patients in clinical setting. However, its practical value still needs further clinical verification.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available in the MIMIC-IV database, https://physionet.org/content/mimiciv/2.2/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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