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Hypophosphatemia as a Predictor of Clinical Outcomes in Acute Pancreatitis

A Retrospective Study

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Objective: Phosphate is crucial for cellular repair after injury and may be important in recovery following acute pancreatitis (AP). This study aimed to evaluate the association between hypophosphatemia and severity of AP.

Methods: Patients admitted with AP between 2014–2018 were identified and their records were retrospectively reviewed. Pancreatitis severity was defined using the modified Atlanta Criteria. Hypophosphatemia was defined as phosphate <2 mg/dL and was assessed at three time points: within one day, within two days, at any time during admission. The proportion of patients who developed severe AP was compared between patients with and without hypophosphatemia.

Results: Of 312 patients, 30.1% (n = 94) developed severe AP. Hypophosphatemia occurred in 25.0% overall, within one day in 19.7%, and within two days in 20.0%. A higher proportion of patients with hypophosphatemia developed severe AP (overall: 47.4% vs. 24.4%, $P < 0.001$; one day: 47.4% vs. 23.9%, $P = 0.004$; two days: 42.9% vs. 24.5%, $P = 0.01$). Patients with hypophosphatemia within one day were also more likely to have ICU admission ($P < 0.001$) and longer length of stay ($P < 0.001$).

Conclusions: Early hypophosphatemia during an admission for AP was associated with increased AP severity, ICU admission, and longer length of stay.

Key Words: acute pancreatitis, hypophosphatemia

Abbreviations: AP - acute pancreatitis, ATP - adenosine triphosphate, SIRS - systemic inflammatory response syndrome, SBP - systolic blood pressure, DBP - diastolic blood pressure, BUN - blood urea nitrogen, SpO2 - percentage oxygen saturation, FiO2 - fraction inspired oxygen, Cr - creatinine, BMI - body mass index, BISAP - bedside index for severity in acute pancreatitis, ICD - international classification of diseases, HR - heart rate, ERCP - endoscopic retrograde cholangiopancreatography

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Acute pancreatitis (AP) is a common disease with a high degree of medical and financial burden on the healthcare system. There are approximately 275,000 hospitalizations for AP within the United States per year, accounting for over $2 billion in annual healthcare spending.[1,2] Acute pancreatitis occurs because of premature activation digestive enzymes within the pancreas leading to autodigestion and inflammation. This intrapancreatic inflammation leads to localized extra-pancreatic inflammation and, in some cases, systemic organ dysfunction. Although most patients recover from pancreatitis without systemic complications, 15%–20% of patients develop a prolonged systemic inflammatory response syndrome (SIRS) and multiorgan failure.[3,4] Identifying which patients will develop persistent end organ dysfunction can be difficult for clinicians to predict[5]; however, it is important to identify these patients as severe AP carries mortality rates as high as 36%–50% compared with 4% in the general pancreatitis population.[5,6]

During the body's inflammatory response, the ability to use stored energy for cell function is crucial for recovery after injury. Adenosine triphosphate (ATP) is the main reservoir of biochemical energy within the body, and phosphate is essential for mitochondrial oxidative phosphorylation.[7] Hypophosphatemia has been shown to be associated with decreased ATP production and mitochondrial dysfunction,[8] which in turn affects the energy available for cellular recovery. In the context of AP, hypophosphatemia is a common occurrence[9,10]; however, the effects of hypophosphatemia on the clinical presentation and outcomes of AP have not been fully examined.

Prior literature has demonstrated a high proportion of hypophosphatemia in patients admitted with AP, particularly in the context of alcohol use.[9] In addition, a recent study demonstrated an association between hypophosphatemia and outcomes in acute alcohol-related pancreatitis.[10] Whether this extends to other etiologies of AP is uncertain, however. Given the limited scope of prior studies, a more comprehensive review of this relationship is warranted. We therefore performed a retrospective study to elucidate whether there is an association between hypophosphatemia and clinical outcomes in AP, inclusive of all etiologies.

MATERIALS AND METHODS

Study Population

Adults 18 years or older with an inpatient admission for AP at 1 of 3 hospitals within a tertiary referral university healthcare system from January 1, 2014, to December 31, 2018, were identified by ICD codes (577.0, K85.90, K85.1-.9). The electronic medical record was retrospectively reviewed to confirm a clinical diagnosis of AP according to the modified Atlanta Criteria, defined as meeting 2 of 3 of the following: epigastric abdominal pain, serum lipase more than 3 times the upper limit of normal, or imaging (abdominal computed tomography, ultrasound, or

magnetic resonance imaging scan) suggestive of AP. Individuals with a diagnosis of AP who had at least 1 serum phosphate level measured during their hospital admission were identified.

Individuals were excluded if they did not have phosphate measured during the hospitalization, were transferred from another hospital, or had evidence of chronic pancreatitis or pancreatic cancer. Patients with stage 4 or 5 chronic kidney disease, with a history of hyperparathyroidism, or who experienced acute burn were also excluded, as these conditions may impact phosphate levels.

Data Collection

Baseline demographic data, comorbidities, and clinical data (vital signs, body mass index [BMI], laboratory values, imaging, alcohol use, tobacco use, etiology of AP) were collected from the electronic medical record. The Charlson comorbidity index was calculated for each subject according to its published criteria.[11] Obesity was defined as a BMI ≥30 kg/m^2. The etiology of AP was categorized as alcohol related, gallstone related, or other, which included post-ERCP pancreatitis, medication-related pancreatitis, autoimmune pancreatitis, and other causes.

The following data were collected on admission: temperature, systolic blood pressure/diastolic blood pressure (SBP/DBP), heart rate, respiratory rate, percentage oxygen saturation (SpO2), fraction inspired oxygen (FiO2), mental status, hematocrit, white blood cell count, lipase, calcium, blood urea nitrogen (BUN), and creatinine (Cr). The following data were also assessed at 48 hours: SBP, DBP, SpO2/FiO2, Cr. Imaging during the patient's admission was also reviewed to assess for the presence of local peripancreatic complications or a pleural effusion, if available.

Other information regarding the hospital admission was additionally collected, including intensive care unit (ICU) admission, days in the ICU, respiratory failure requiring mechanical ventilation, renal failure requiring renal replacement therapy, circulatory failure requiring vasopressors, in-hospital mortality, and hospital length of stay.

Hypophosphatemia

We hypothesized that the presence of hypophosphatemia was most important early in AP during the period of initial inflammation and cellular repair, and hypophosphatemia would be associated with a higher rate of end organ dysfunction later in the disease process. In addition, because severe AP was defined as persistent end organ dysfunction beyond 48 hours, we evaluated phosphate levels within 24 and 48 hours. Hypophosphatemia was defined as a serum phosphate <2.0 mg/dL. This was assessed at 3 time points: within 24 hours of admission (on hospital day 0 or 1), within 48 hours of admission (on hospital day 0, 1, or 2), or at any point during hospitalization. Whether hypophosphatemia was present on initial laboratory testing or developed subsequently was evaluated. Phosphate levels were also stratified into <1.5, 1.5–2.0, 2.0–2.5, and >2.5 mg/dL to evaluate for a dose-response relationship.

Outcomes

The primary outcome was the development of severe AP during the hospitalization as defined by the revised Atlanta criteria for pancreatitis, with persistent organ failure at 48 hours.[5] The modified Marshall criteria was used to define organ failure as any of the following: shock (SBP <90 mm Hg or use of vasopressors), pulmonary insufficiency (PaO2/FiO2 <300 or surrogate SpO2/FiO2 <357), or renal failure (Cr >1.9).[12,13] Patients discharged before 48 hours were not considered to have severe AP.

Secondary outcomes assessed included BISAP score, the presence of SIRS, ICU admission, hospital length of stay, and in-hospital mortality. The BISAP score is a validated scoring system in AP that assists with identification of patients at increased risk of in-hospital mortality.[14] The scoring system uses the following parameters: BUN >25, ≥2 SIRS criteria, altered mental status, age >60 years, and presence of a pleural effusion on imaging. A BISAP score of 0–2 is associated with low risk of mortality (<2%) compared with a score of 3–5 (>15%).[14]

These outcomes were compared by hypophosphatemia status.

Statistical Analysis

Descriptive statistics were calculated for the demographic and clinical characteristics. The BISAP score was assessed as a continuous variable and as a categorical variable (as 0–2 and 3–5). Systemic inflammatory response syndrome criteria include HR >90, respirations >20, PaCO2 <32 mm Hg, temperature >38°C or <36°C, WBC >12,000 or <4000, or >10% immature neutrophils. Comparisons were performed using chi-square tests for categorical variables and *t* tests or Wilcoxon rank-sum tests for continuous variables, depending on the normality of the distribution. Cochran-Armitage tests for trend were conducted to evaluate proportions across ordered groups. Multivariable logistic regression was performed to assess the association between hypophosphatemia and outcomes after accounting for potential confounding factors, including age, sex, obesity, etiology of pancreatitis, and Charlson comorbidity index. A sensitivity analysis was also performed excluding individuals with alcohol-related pancreatitis to ensure these patients were not the primary mediator of any observed differences in outcomes. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and a 2-sided *P* value less than 0.05 was considered statistically significant. This study was approved by the Duke University Institutional Review Board.

RESULTS

Baseline Characteristics

A total of 312 patients met inclusion criteria between January 1, 2014, and December 31, 2018,. Baseline characteristics by severity of AP are shown in Table 1. The most common etiology of pancreatitis in our cohort was gallstone (33.9%) followed by alcohol (33.3%) and other etiologies (32.7%). A total of 94 patients (30.1%) developed severe AP. There were no significant differences in age, sex, race, BMI, tobacco/alcohol use, Charlson comorbidity index, or etiology of pancreatitis by severity of AP.

Overall, 25% (78 of 312) had hypophosphatemia (<2.0 mg/dL) at any point during their admission, including 38 of 193 (19.7%) and 49 of 245 (20.0%) with a serum phosphate level collected during the first 24 or first 48 hours, respectively. Individuals with hypophosphatemia were generally similar to those with serum phosphate ≥2, although they were slightly younger on average, particularly those that developed hypophosphatemia at 48-hour time point (Supplemental Table 1, http://links.lww.com/MPA/B23).

Hypophosphatemia and Severe AP

A significantly greater proportion of patients with hypophosphatemia within 24 hours (47.4%) developed severe AP compared with patients without hypophosphatemia (23.9%) (P = 0.004) (Table 2). This was also true for patients with

TABLE 1. Baseline Characteristics

	All (n = 312)	Severe AP (n = 94)	No Severe AP (n = 218)	*P*
Age, y, mean ± SD	54.1 ± 17.2	56.5 ± 18.4	53.1 ± 16.6	0.11
Sex, n (%)				0.32
Male	156 (50.0)	51 (54.3)	105 (48.2)	
Female	156 (50.0)	43 (45.7)	113 (51.8)	
Race				0.63
Black	113 (36.2)	31 (33.0)	82 (37.6)	
White	163 (52.2)	53 (56.4)	110 (50.5)	
Other	36 (11.5)	10 (10.6)	26 (11.9)	
BMI, median (IQR)	28.1 (24.2–34.2)	29.3 (25.4–35.6)	27.9 (23.7–33.7)	0.11
Obesity	126 (40.4)	42 (44.7)	84 (38.5)	0.31
Current tobacco use, n (%)	78 (25.0)	19 (20.2)	59 (27.1)	0.20
Current alcohol use, n (%)	161 (51.6)	47 (50.0)	114 (52.3)	0.71
Charlson comorbidity index, median (IQR)	2 (0–4)	2 (1–5)	2 (0–4)	0.06
Etiology of pancreatitis				0.44
Alcohol	104 (33.3)	34 (36.2)	70 (32.1)	
Gallstone	106 (33.9)	27 (28.7)	79 (36.2)	
Other	102 (32.7)	33 (35.1)	69 (31.6)	
Laboratory values				
Lipase, median (IQR)*	519 (207–1241)	798 (333–1739)	381 (166–900)	0.001
Hematocrit, median (IQR)	40.3 (36.3–44.5)	41.2 (38.0–46.8)	40.0 (36.0–43.5)	0.02
BUN, median (IQR)	14 (10–22)	18 (12–33)	13 (9–19)	<0.001
Creatinine, median (IQR)	1.0 (0.7–1.4)	1.2 (0.9–2.0)	0.9 (0.7–1.2)	<0.001
AST, median (IQR)	50 (27–154)	50 (30–145)	50 (26–158)	0.71
ALT, median (IQR)	44 (21–130)	40 (21–115)	48 (22–143)	0.56
Alkaline phosphatase, median (IQR)	92 (68–137)	88 (66–134)	92 (72–141)	0.38
Total bilirubin, median (IQR)	1.2 (0.8–2.3)	1.3 (0.9–2.5)	1.2 (0.8–2.3)	0.35
Albumin, mean ± SD	3.7 ± 0.8	3.7 ± 1.0	3.7 ± 0.7	0.93
Calcium, median (IQR)	9.0 (8.5–9.4)	8.8 (8.3–9.4)	9.0 (8.6–9.4)	0.08

*Upper limit of normal = 51 U/L.

BMI missing in n = 7, lipase missing in n = 2, BUN missing in n = 2, AST missing in n = 9, ALT missing in n = 4, alkaline phosphatase missing in n = 2, bilirubin missing in n = 7, albumin missing in n = 4, calcium missing in n = 1.

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

hypophosphatemia within 48 hours or at any time during their admission ($P = 0.01$ and $P < 0.001$, respectively). On multivariable logistic regression, this association between hypophosphatemia and severe AP persisted with adjustment for age, sex, obesity, etiology of pancreatitis, and Charlson comorbidity index, with patients with hypophosphatemia having approximately 3 times the odds of severe AP across all time points measured (Table 3). Hypophosphatemia remained associated with severe AP when alcohol-related pancreatitis was excluded (Supplemental Table 2, http://links.lww.com/MPA/B24).

We additionally found that minimum phosphate levels differed significantly by severity of pancreatitis with median minimum phosphate of 2.3 mg/dL (interquartile range [IQR], 1.5–3.0 mg/dL) and 2.9 mg/dL (IQR, 2.1–3.4 mg/dL) for patients with and without severe pancreatitis, respectively ($P = 0.001$). When minimum phosphate levels were stratified into <1.5, 1.5–2.0, 2.0–2.5, and >2.5 mg/dL to evaluate for a dose-response relationship, the proportion with severe AP was 47.6%, 47.2%, 27.6%, and 23.3%, respectively ($P_{trend} < 0.001$). This was similar when limited to the minimum value within 48 hours (42.3% vs 44.0% vs 20.6% vs 23.5%, $P_{trend} = 0.01$).

We further evaluated the relationship between severe AP and hypophosphatemia by determining whether hypophosphatemia was present on the initial laboratory testing or developed subsequently. Median initial phosphate levels did not differ between severe and nonsevere AP groups (median, 3.1 [IQR, 2.3–4.1] vs 3.0 [2.3–3.6], $P = 0.27$). In the majority of patients who developed hypophosphatemia, low phosphate levels were present on initial testing (59.0%). The group without hypophosphatemia on initial testing who later developed hypophosphatemia had a higher proportion of severe AP (62.5%) compared with those with hypophosphatemia on presentation (37.0%). Both groups had a higher proportion of severe AP compared with those without hypophosphatemia (24.4%, $P < 0.001$). This trend was similar when limited to hypophosphatemia during the first 48 hours (52.9% with severe AP vs 37.5% vs 24.5%, respectively, $P = 0.02$).

Hypophosphatemia and Other Clinical Outcomes

Hypophosphatemia was also associated with ICU admission and the presence of SIRS at all evaluated time points (Tables 2 and 3). After adjusting for demographic factors, obesity, etiology of pancreatitis, and Charlson comorbidity index, patients with hypophosphatemia had approximately 3 times the odds of SIRS and 5 times the odds of ICU admission across all time points (Table 3).

TABLE 2. Association Between Hypophosphatemia and Outcomes

	Within 24 h of Admission			Within 48 h of Admission			At Any Time During Admission		
	Phos <2 (n = 38)	Phos ≥2 (n = 155)	*P*	Phos <2 (n = 49)	Phos ≥2 (n = 196)	*P*	Phos <2 (n = 78)	Phos ≥2 (n = 234)	*P*
Severe AP, n (%)	18 (47.4)	37 (23.9)	0.004	21 (42.9)	48 (24.5)	0.01	37 (47.4)	57 (24.4)	<0.001
SIRS, n (%)	21 (55.3)	47 (30.3)	0.004	29 (59.2)	60 (30.6)	<0.001	42 (53.8)	69 (29.5)	<0.001
BISAP score, median (IQR)	1 (1–2)	1 (0–2)	0.04	1 (1–2)	2 (1–3)	0.07	1 (1–2)	1 (0–2)	0.01
BISAP >2, n (%)	7 (20.6)	16 (11.4)	0.16	8 (17.8)	22 (12.4)	0.34	13 (17.8)	26 (12.0)	0.21
ICU admission	23 (60.5)	21.9 (34)	<0.001	28 (57.1)	41 (20.9)	<0.001	43 (55.1)	44 (18.8)	<0.001
Length of stay, days, median (IQR)	8 (5–13)	4 (3–7)	<0.001	8 (4–12)	4 (3–7)	<0.001	9 (5–15)	5 (3–9)	<0.001
In-hospital mortality, n (%)	1 (2.6)	11 (7.1)	0.47	1 (2.0)	15 (7.6)	0.21	4 (5.1)	15 (6.4)	0.79

BISAP able to be calculated for n = 175/193, 223/245, 289/312.

In addition, individuals with hypophosphatemia within 24 or 48 hours were more likely to have a BISAP score >2 after adjusting for other factors (Table 3). Median length of stay was also significantly longer in individuals with hypophosphatemia (within 24 or 48 hours: 8 vs 4 days, $P < 0.001$) (Table 2). There was no association between hypophosphatemia and in-hospital mortality (Tables 2 and 3). These findings were similar when limited to non–alcohol-related etiologies of AP (Supplemental Table 2, http://links.lww.com/MPA/B24).

DISCUSSION

In this retrospective study, we observed that hypophosphatemia is associated with severe AP across diverse etiologies of pancreatitis. Among the patients in this study, approximately one-third of the patients had gallstone pancreatitis, one-third had alcohol-related pancreatitis, and one-third qualified as other, which included post-ERCP pancreatitis, medication-related pancreatitis, autoimmune pancreatitis, among others. Based on our sensitivity analysis, the association was not exclusively driven by an association with alcohol-related pancreatitis. We further demonstrated that hypophosphatemia was associated with an increased risk of poor outcomes as indicated by longer hospital length of stay and increased odds of experiencing SIRS, BISAP scores >2, and ICU admission. There were, however, no differences in in-hospital mortality.

Hypophosphatemia has a variety of causes and has been shown to affect patient outcomes, especially during times of critical illness. Etiologies of low serum phosphate include low intestinal absorption, high renal excretion, and redistribution of inorganic phosphate.[15] This can be exacerbated by conditions including respiratory alkalosis,[16] metabolic acidosis,[17] and high levels of catecholamines.[18] These scenarios all commonly occur in patients that are critically ill. In terms of outcomes in the critical care setting, for example, patients with hypophosphatemia during continuous renal replacement therapy were shown to have more ventilator days and longer vasopressor support while in the ICU.[19] Furthermore, patients admitted to the ICU with hypophosphatemia had significantly higher ICU mortality rates than those with normophosphatemia.[20]

In addition to the general critically ill population, pancreatitis has been specifically shown to be associated with low phosphate in both preclinical and clinical settings. A recently published preclinical model has shown a relationship between low phosphate and alcohol-related pancreatitis.[21] Using an experimental model where mice were fed a low phosphate diet followed by intragastric ingestion of ethanol, this study demonstrated that low phosphate levels increased susceptibility to alcohol-induced pancreatitis. At the cellular level, this relationship could be explained, at least in part, by the observation that pancreatic acinar cells had increased susceptibility to cellular injury caused by ethanol in the low phosphate state compared with control conditions. This effect was mediated by decreased mitochondrial function and cellular ATP. Similar results were observed in secretagogue-induced pancreatitis, a common experimental model of AP, and in a preclinical model of pressure-induced pancreatitis, which is analogous to gallstone- and ERCP-induced pathologies.[22] Taken together, these studies support a central role of phosphate in the pathogenesis of pancreatitis.

TABLE 3. Association Between Hypophosphatemia and Outcomes

	Phosphate <2 Within 24 h of Admission		Phosphate <2 Within 48 h of Admission		Phosphate <2 at Any Time During Admission	
	Univariable OR (95% CI)	Adjusted OR* (95% CI)	Univariable OR (95% CI)	Adjusted OR* (95% CI)	Univariable OR (95% CI)	Adjusted OR* (95% CI)
Severe AP	2.87 (1.38–5.99)	3.24 (1.49–7.04)	2.31 (1.20–4.44)	2.71 (1.35–5.41)	2.80 (1.64–4.79)	3.18 (1.81–5.58)
SIRS	2.84 (1.37–5.86)	2.92 (1.39–6.15)	3.29 (1.72–6.27)	3.46 (1.77–6.74)	2.79 (1.65–4.72)	2.94 (1.72–5.05)
BISAP >2	2.02 (0.76–5.40)	4.95 (1.38–17.78)	1.53 (0.63–3.72)	3.19 (1.08–9.44)	1.58 (0.77–3.27)	2.26 (0.99–5.19)
ICU admission	5.46 (2.57–11.59)	5.91 (2.69–13.00)	5.04 (2.60–9.78)	5.60 (2.78–11.27)	5.30 (3.05–9.23)	5.82 (3.26–10.41)
In-hospital mortality	0.35 (0.04–2.83)	0.33 (0.04–2.92)	0.25 (0.03–1.95)	0.23 (0.03–2.04)	0.79 (0.25–2.45)	0.88 (0.27–2.84)

*Adjusted for age, sex, obesity, etiology of pancreatitis, Charlson comorbidity index.

OR indicates odds ratio.

In a clinical context, a relationship between low phosphate levels and AP has been previously observed in limited case series, case reports, and 1 retrospective analysis. Sacks and Berman[9] demonstrated a correlation between AP and low phosphate levels, with two-thirds of patients who developed AP also having coincident hypophosphatemia. A case report by Rizos et al[23] also described severe hypophosphatemia in an adult with AP, which was life-threatening. Finally, Steckman et al[24] extended these observations to a case of severely low levels of serum phosphate in a patient with AP caused by gallstones. Most recently, Wagner et al[10] described the prevalence of hypophosphatemia with pancreatitis severity among 147 patients with acute alcohol-induced pancreatitis. Our study is the largest to date to examine the relationship of low phosphate levels and AP in a clinical setting and, to our knowledge, the first to look across multiple etiologies of pancreatitis.

There are, however, several limitations to our study. Although we included several hospitals, including a large tertiary academic center and 2 mid-sized community-based hospitals, which treat patients from a diverse catchment area, the study was still performed in 1 health system, which may limit the generalizability of our findings. Because of the variability of available data on patients before transfer from another hospital, patients who were transferred after being admitted elsewhere were excluded from the analysis. In addition, in our health system, phosphate levels are not routinely reported on a basic or comprehensive metabolic panel and must be ordered separately, so our findings are likely impacted by selection bias. This may account for the higher rates of severe AP in our cohort (30%) compared with prior published data (15%–20%).[3] Variability in the timing and frequency of phosphate testing in this retrospective analysis also limited our ability to fully assess the impact of the onset, chronicity, and severity of the hypophosphatemia, as well as its change over time. We are also unable to directly evaluate causal relationships between phosphate levels and pancreatitis with this study design. We specifically evaluated hypophosphatemia during 2 time points early in admission as severe AP is defined as persistent end organ dysfunction beyond 48 hours, although the relationship between the timing of hypophosphatemia and the development of severe AP remains uncertain. In an attempt to investigate chronicity, we evaluated the proportion of patients with hypophosphatemia during their admission who also had hypophosphatemia on initial testing. We found that patients with initial phosphate levels ≥2 mg/dL who later developed hypophosphatemia, perhaps indicative of more acute hypophosphatemia, had a higher proportion of severe AP than patients with hypophosphatemia on presentation or no hypophosphatemia. We also attempted to assess whether there was a dose-response relationship between hypophosphatemia and pancreatitis severity, which was not apparent. However, because of the aforementioned limitations associated with the retrospective nature of the study and variability in laboratory testing patterns, it is difficult to draw definitive conclusions from these findings, and further prospective studies of phosphate levels among patients admitted with AP, changes along their course, and differences in outcomes are needed.

In addition, although we attempted to control for comorbidities that may affect phosphate levels (eg, severe chronic kidney disease, hyperparathyroidism, burns), we were unable to assess the relationship between phosphate levels and the patients' nutritional intake, which may be important. Furthermore, although our sensitivity analysis importantly showed that the relationship of hypophosphatemia with AP severity was not driven solely by alcohol-related pancreatitis, the study was not powered to detect a difference between phosphate levels and severity of pancreatitis across different etiologies. We also lacked statistical power to evaluate the relationship between hypophosphatemia and in-hospital mortality due to few deaths. Future studies should further evaluate these associations.

Despite these limitations, the data from our study have important clinical implications. As observed in preclinical models, deficiency in phosphate has important physiologic ramifications across diverse cellular processes and multiple organ systems. Thus, it can be hypothesized that maintaining normal levels of phosphate during periods of systemic or critical illness is important for clinical recovery, particularly in patients who experience AP. Further prospective studies evaluating the relationship between phosphate levels and AP are needed.

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