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Serum phosphate is associated with mortality among patients admitted to ICU for acute pancreatitis

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Abstract

Background and Aims: Routine laboratory tests can be useful predictors in the early assessment of the severity and mortality of acute pancreatitis (AP). The aim of this study was to evaluate the accuracy of clinical and laboratory parameters for the prediction of mortality among patients admitted to the intensive care unit (ICU) for AP.

Methods: We conducted a retrospective analysis of prospectively collected data from Beth Israel Deaconess Hospital made publicly available to examine the relationship between routine clinical and laboratory parameters with respect to mortality for AP. Cox proportional hazard ratio was used to evaluate the impact of several routine laboratory markers on mortality. Receiver operation characteristic (ROC) curve was performed to determine the accuracy of diagnosis of laboratory tests by using area under curve (AUC) for the respective analysis.

Results: In total, 499 patients were admitted to the ICU for AP. Several factors for predicting mortality in AP at admission were identified in the multivariate analysis: alkaline phosphatase hazard ratio (HR) = 1.00 (1.00–1.00, $p = 0.024$), anion gap HR = 1.09 (1.00–1.20, $p = 0.047$), bilirubin total HR = 1.11 (1.06–1.17, $p < 0.001$), calcium total HR = 0.59 (0.42–0.84, $p = 0.004$), phosphate HR = 1.51 (1.18–1.94, $p = 0.001$), potassium HR = 1.91 (1.03–3.55, $p = 0.041$), white blood cells HR = 1.04 (1.00–1.07, $p = 0.028$). The AUC of serum phosphate level for mortality was 0.7 in the ROC analysis. The optimal cut-off value of serum phosphate level for prediction of mortality was 3.78 mg/dl (sensitivity, 0.58; specificity, 0.78).

Conclusion: In this large cohort, we identified baseline serum phosphate as the most valuable single routine laboratory test for predicting mortality in AP. Future prospective studies are required to confirm these results.

KEYWORDS
mortality, pancreatitis, risk factors, serum phospahte

Key Points

- This is the first study that evaluates the role of serum phosphate at baseline for predicting the mortality of acute pancreatitis (AP) in intensive care unit (ICU).
- This study found that serum phosphate is a useful laboratory marker for predicting the mortality of AP independently of other known factors.
- This study found that serum phosphate value greater than 3.78 mg/dl within the first 24 h after admission in the ICU could predict mortality (area under curve = 0.7, $p < 0.001$, sensitivity 58%; specificity 77%).

INTRODUCTION

Acute pancreatitis (AP) was found to be the most frequent principal discharge diagnosis for hospitalization related to a gastrointestinal disease in the United States in 2012.[1] Individual estimates of the incidence of AP range from 10 to 78 per 100,000 per year.[2–6] AP is an inflammatory disease, generally benign. However, approximately a fifth of cases are clinically severe characterized by the development of multiple system organ failure and/or necrotic changes of the pancreas and peripancreatic areas and are associated with an increased morbidity and mortality.[7] Mortality for severe form varies from 10% to 85%.[8–14] Patients with severe AP represent the largest group of patients with intensive care unit (ICU) stays longer than 1 month in various studies. For instance, in Scotland, between 2008 and 2010, 5% of all offered intensive care beds were occupied by patients with AP.[15]

Consequently, prediction of the severity of the disease and mortality at an early stage is very important for appropriate management, which may consequently decrease morbidity and mortality. Numerous prognostic factors for mortality in AP have been developed including the bedside index for severity in AP (BISAP), acute physiology and chronic health evaluation (APACHE II), the computed tomography severity index (CTSI), as well as systemic inflammatory response syndrome (SIRS).[16] However, data available for predicting the mortality of patients with AP, especially severe presentation within the setting of ICU, is limited. Therefore, we aimed to assess the predictability value of mortality of simple routine factors in patients with AP admitted to the ICU.

MATERIAL AND METHODS

Study design

Retrospective analysis of prospectively collected data from Beth Israel Deaconess Hospital made publicly available.

Study population

We used the Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC-III (version 1.4)) database, developed conjointly by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT), Cambridge, MA, United States, and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC) in Boston in the United States. This large, single-center database contains the information of 46,520 critically ill patients admitted to BIDMC from 2001 to 2012 and has detailed information about ICU patient stays, including high-resolution monitoring data, therapeutic interventions including medications, hydrations, and procedures, discharge summaries, laboratory data, and radiology reports. Given the fact that all patients were de-identified in a Health Insurance Portability and Accountability Act-compliant manner, the institutional review boards (IRBs) of BIDMC and MIT approved the use of the MIMIC-III database.[17,18] It is possible to access this database by passing an examination and obtaining the certification. One author (AH) obtained access and was responsible for the data extraction. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. A written informed consent was obtained from each patient included in the study. Since the study was an analysis of an anonymized publicly available database with pre-existing IRB approval, IRB approval from our institution was exempted.

We included adult patients admitted directly to the ICU from the emergency department with AP. Patients with AP were identified based on the ICD-9 code (577.1), and confirmed by elevated serum amylase and/or lipase greater than three times the upper limit of normal (ULN), and/or finding on CT abdomen consistent with AP. Furthermore, patients' cases were manually rechecked by two independent investigators.

The data were collected from the observation charts of patients both clinical and demographics. The baseline characteristics of patients including age, sex, alcohol consumption, comorbidities, and the etiology of AP were explored and compared between survivor and non-survivor groups. The laboratory data at admission and severity scores including SOFA, APS III, and OASIS were also evaluated. Early death was defined as death occurring within the first week (<7 days) and a late death after 7 days from ICU admission.

Statistical analysis

Statistical analysis was performed by including monitored variables to observe the impact of clinical and biological risk factors on mortality in AP. All statistical analyses were performed using R software

TABLE 1 Baseline characteristics of the study population

N		Overall *N* = 499	Survivor (*n* = 453)	Non-survivor (*n* = 46)	*p*
Age, *n* (%)	Less than 50	166 (33.3)	157 (34.7)	9 (19.6)	0.093
	Between 50 and 65	142 (28.5)	128 (28.3)	14 (30.4)	
	More than 65	191 (38.3)	168 (37.1)	23 (50.0)	
Ethnicity (%)	African American	52 (10.4)	50 (11.0)	2 (4.3)	0.009
	Caucasian	337 (67.5)	311 (68.7)	26 (56.5)	
	Other	110 (22.0)	92 (20.3)	18 (39.1)	
Etiology (%)	Alcohol	132 (26.6)	120 (26.6)	12 (26.7)	0.230
	Drug	12 (2.4)	12 (2.7)	0 (0.0)	
	Gallstones	181 (36.5)	165 (36.6)	16 (35.6)	
	Hypertriglyceridemia	7 (1.4)	7 (1.6)	0 (0.0)	
	Idiopathic	86 (17.3)	74 (16.4)	12 (26.7)	
	Post-ERCP	29 (5.8)	25 (5.5)	4 (8.9)	
	Other	49 (9.9)	48 (10.6)	1 (2.2)	
Time to ICU admission (h)		13.11 (49.26)	13.92 (51.37)	5.03 (15.18)	0.249
First episode (%)		251 (66.8)	224 (65.1)	27 (84.4)	0.044
Gender (%), male		277 (55.5)	250 (55.2)	27 (58.7)	0.764
Intensive care unit	CCU	21 (4.2)	20 (4.4)	1 (2.2)	0.755
	CSRU	12 (2.4)	12 (2.7)	0 (0.0)	0.550
	MICU	341 (68.6)	305 (67.5)	36 (80.0)	0.119
	SICU	127 (25.6)	119 (26.3)	8 (17.8)	0.282
	TSICU	59 (11.9)	53 (11.7)	6 (13.3)	0.939
Hospital LOS, mean (SD)		13.98 (12.67)	14.42 (13.02)	9.63 (7.21)	0.014
ICU LOS, mean (SD)		7.96 (11.24)	7.86 (11.56)	8.95 (7.42)	0.528
Marital status (%)	Married	211 (42.3)	190 (41.9)	21 (45.7)	0.041
	Separated	38 (7.6)	34 (7.5)	4 (8.7)	
	Single	157 (31.5)	150 (33.1)	7 (15.2)	
	Other	93 (18.6)	79 (17.4)	14 (30.4)	

Abbreviations: CCU, coronary care unit; CSRU, cardiac surgery recovery unit; ICU, intensive care unit; LOS, length of stay; MICU, medical intensive care unit; SICU, surgical intensive care unit; TSICU, trauma/surgical intensive care unit.

(www.cranR.com). Continuous data were expressed as means (SDs) and analyzed using independent samples' *t*-tests of Mann–Whitney U-test when appropriate. Categorical variables are described in absolute numbers and in percentages and analyzed using chi-square tests. A Cox proportional-hazards model was used to identify risk factors affecting survival. Variables with a *p*-value of <0.20 in univariate analysis were considered into the multivariable analysis, and non-significant factors were removed using the backward-selection procedure. Finally, receiver operation characteristics (ROC) curve was performed to determine the accuracy of diagnosis of laboratory tests by using area under curve (AUC) for the respective analysis. Statistical significance was defined as $p < 0.05$. Data were extracted by structured query language with pgAdmin4 PostgreSQL 9.6 and RPostgreSQL package.

RESULTS

Clinical characteristics

A total of 499 patients were admitted to the ICU for AP. Patient selection process is depicted in supplementary File 1. Table 1 shows the patient demographics, admission laboratory data, and outcomes of the overall AP population and study cohort. Etiology of AP was biliary (181, 36.5%), alcohol (132, 26.6%), idiopathic (86, 17.3%), medication (12, 2.4%), post-ERCP (29, 5.8%), and others (49, 9.9%). Two hundred seventy-seven patients (55.5%) were male. A first-episode pancreatitis was observed in 251 (66.8%). The mean hospital and ICU stay were 14.0 (12.7) and 8.0 (11.2) days, respectively. In-hospital mortality was 46/499 (9%). The mean SOFA score

TABLE 2 Univariate analysis of the clinical characteristics according to in-hospital mortality

		Survivors (n = 453)	Non-survivors (n = 46)	p
Heart rate, mean (SD)		96.44 (18.93)	96.98 (18.51)	0.853
Respiratory rate, mean (SD)		20.51 (4.64)	23.28 (4.38)	<0.001
Mean Glasgow, mean (SD)		5.67 (6.36)	5.07 (6.02)	0.539
Glasgow Coma Scale (GCS)	Verbal reponse, mean (SD)	1.64 (2.10)	1.52 (1.99)	0.722
	Eyes, mean (SD)	1.49 (1.70)	1.39 (1.58)	0.693
	Movements, mean (SD)	2.54 (2.77)	2.15 (2.58)	0.367
NIBP diastolic, mean (SD)		66.07 (14.51)	58.31 (14.62)	0.001
NIBP mean, mean (SD)		82.61 (14.33)	74.25 (14.76)	<0.001
NIBP systolic, mean (SD)		125.82 (19.70)	113.41 (19.19)	<0.001
Weight, kg mean (SD)		86.23 (25.08)	87.94 (24.35)	0.659
SOFA, mean (SD)		4.01 (3.51)	8.96 (4.37)	<0.001
APS III, mean (SD)		26.16 (14.22)	44.20 (15.15)	<0.001
OASIS, mean (SD)		15.18 (4.90)	17.80 (5.36)	0.001
Temperature °C, mean (SD)		37.14 (0.71)	36.92 (0.85)	0.050
Comorbidities	Cancer (%)	6 (1.3)	5 (10.9)	<0.001
	CHF (%)	92 (20.3)	10 (21.7)	0.970
	Dementia (%)	7 (1.5)	1 (2.2)	1.000
	DM (%)	127 (28.0)	11 (23.9)	0.673
	DMcx (%)	11 (2.4)	2 (4.3)	0.770
	HIV (%)	9 (2.0)	2 (4.3)	0.609
	Mild liver disease (%)	69 (15.2)	9 (19.6)	0.577
	Severe liver disease (%)	18 (4.0)	4 (8.7)	0.267
	Mets (%)	5 (1.1)	3 (6.5)	0.030
	Myocardial infarction (%)	27 (6.0)	6 (13.0)	0.126
	Paralysis (%)	2 (0.4)	0 (0.0)	1.000
	PUD (%)	11 (2.4)	0 (0.0)	0.588
	Pulmonary (%)	65 (14.3)	10 (21.7)	0.263
	PVD (%)	20 (4.4)	1 (2.2)	0.737
	Renal (%)	50 (11.0)	10 (21.7)	0.059
	Rheumatic (%)	12 (2.6)	1 (2.2)	1.000
	Stroke (%)	18 (4.0)	3 (6.5)	0.664

Abbreviations: APS III, Acute Physiology Score III; CHF, congestive heart failure; DM, diabetes mellitus; DMcx, diabetes mellitus with complication; ICU, intensive care unit; LOS, length of stay; Mets, metastasis; NIBPm, non-invasive blood pressure; OASIS, Oxford Acute Severity of Illness Score; PUD, peptic ulcer disease; PVD, peripheral vascular disease; SOFA, Sequential Organ Failure Assessment.

was 4.0 (3.5) for survivors and 8.9 (4.3) for non-survivors. The first cause of AP was gallstone in 181 patients (36.5%) followed by alcohol in 132 patients (26.6%). The causes of pancreatits were not statistically different when comparing survivors to non-survivors.

The clinical characteristics of patients with AP according to in-hospital mortality are described in Table 2. Systolic, mean, and diastolic blood pressures at admission were significantly lower in the non-survivor group than in the survivor group. On the contrary, respiratory rate, SOFA, APSIII, and OASIS scores were higher among non-survivors than among survivors. Oncological diseases were more frequently observed among non-survivors than among survivors. Other factors did not significantly differ between groups.

TABLE 3 Univariate analysis of the biological variables according to in-hospital mortality

	Survivors (n = 453)	Non-survivors (n = 46)	p
Alanine aminotransferase U/L	216.43 (750.02)	242.10 (439.48)	0.822
Alkaline phosphatase U/L	138.35 (120.73)	193.05 (179.59)	0.006
Anion gap	15.02 (3.72)	17.53 (6.68)	<0.001
Aspartate aminotransferase U/L	315.98 (1250.83)	384.62 (658.13)	0.717
Bicarbonate mmol/L	22.18 (4.51)	19.34 (4.91)	<0.001
Bilirubin total mg/dl	2.02 (2.73)	4.47 (7.09)	<0.001
Calcium total mmol/L	7.89 (0.87)	7.66 (0.76)	0.082
Chloride mmol/L	106.17 (5.95)	106.01 (7.63)	0.866
Creatinine mg/dl	1.51 (1.63)	2.39 (2.05)	0.001
Glucose mg/dl	141.29 (60.22)	156.71 (58.59)	0.098
Hematocrit %	33.86 (5.43)	33.12 (6.05)	0.387
Magnesium mg/dl	1.93 (0.34)	1.92 (0.30)	0.830
Phosphate mg/dl	3.13 (1.37)	4.33 (1.87)	<0.001
Platelet count/mm^3	228.74 (129.83)	202.71 (143.90)	0.200
Potassium mmol/L	4.01 (0.55)	4.42 (0.65)	<0.001
Sodium mmol/L	139.30 (4.40)	138.36 (6.07)	0.186
Blood urea nitrogen, mmol/L	25.83 (23.02)	38.09 (22.72)	0.001
White blood cells/mm^3	13.68 (7.59)	16.35 (11.56)	0.032

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 4 Univariate analysis of the treatments received according to in-hospital mortality

	Survivors (n = 453)	Non-survivors (n = 46)	p
Dialysis (%)	37 (8.2)	17 (37.0)	**<0.001**
Mechanical ventilation (%)	166 (36.6)	32 (69.6)	**<0.001**
Non-invasive mechanical ventilation (%)	7 (1.5)	1 (2.2)	1.000
Vasopressor (%)	103 (22.8)	32 (69.6)	**<0.001**

Biological characteristics

Laboratory studies at admission of patients with AP according to in-hospital mortality are shown in Table 3. Non-survivors had higher anion gap, alkaline phosphatase, total bilirubin, creatinine, phosphate, potassium, blood urea nitrogen (BUN), plasma concentrations and WBC count, and lower bicarbonate plasma concentration than survivors. Other factors did not significantly differ between groups.

Treatments received

The comparison of the treatments according to in-hospital mortality is shown in Table 4. Non-survivors required significantly more frequently mechanical ventilation, renal replacement therapy, and vasopressors use.

Univariate and multivariate analysis of prognostic factor

The results of the Cox regression analysis of factors associated with in-hospital mortality are presented in Table 5. Among the serum markers, alkaline phosphatase, anion gap, bilirubin total, calcium total, phosphate, and white blood cells were independent prognostic factors for mortality due to AP. Serum markers with an AUC significantly different from 0.5 were alanine aminotransferase, alkaline phosphatase, anion gap, aspartate aminotransferase, bilirubin total, creatinine, phosphate, potassium, and BUN. The sensitivity and

TABLE 5 Multivariable Cox regression

		HR (univariable)	HR (multivariable)
Age	Less than 50	0.54 (0.23-1.24, $p = 0.144$	-
	Between 50 and 65	1	-
	More than 65	1.23 (0.63-2.38, $p = 0.548$)	-
Respiratory rate		1.10 (1.05-1.16, $p < 0.001$)	1.16 (1.08-1.24, $p < 0.001$)
Mean NIBP		0.96 (0.93-0.98, $p < 0.001$)	0.97 (0.95-1.00, $p = 0.057$)
Temperature °C		0.64 (0.41-0.97, $p = 0.038$)	0.67 (0.40-1.11, $p = 0.118$)
Alkaline phosphatase U/L		1.00 (1.00-1.00, p = 0.005)	1.00 (1.00-1.00, $p = 0.024$)
Anion gap		1.14 (1.08-1.21, $p < 0.001$)	1.09 (1.00-1.20, $p = 0.047$)
Bilirubin total mg/dl		1.10 (1.06-1.15, $p < 0.001$)	1.11 (1.06-1.17, $p < 0.001$)
Calcium total mmol/L		0.76 (0.56-1.04, $p = 0.085$)	0.59 (0.42-0.84, $p < 0.004$)
Creatinine mg/dl		1.19 (1.08-1.32, $p = 0.001$)	0.88 (0.68-1.14, $p = 0.347$)
Glucose mg/dl		1.00 (1.00-1.01, $p = 0.095$)	-
Hematocrit %		0.98 (0.92-1.03, $p = 0.394$)	-
Phosphate mg/dl		1.47 (1.27-1.69, $p < 0.001$)	1.51 (1.18-1.94, $p = 0.001$)
Platelet count/mm^3		1.00 (1.00-1.00, $p = 0.181$)	-
Potassium mmol/L		2.50 (1.70-3.66, $p < 0.001$)	1.91 (1.03-3.55, $p = 0.041$)
Sodium mmol/L		0.96 (0.90-1.02, $p = 0.193$)	-
Blood urea nitrogen mg/dl		1.01 (1.01-1.02, $p = 0.001$)	0.99 (0.97-1.00, $p = 0.158$)
White blood cells/mm^3		1.03 (1.00-1.06, $p = 0.029$)	1.04 (1.00-1.07, $p = 0.028$)

Abbreviation: NIBP, non-invasive blood pressure.

specificity of the prognostic variables with a significant AUC for severe AP are listed in Table 6. In the ROC analysis, serum phosphate appeared as the most valuable single routine laboratory test for predicting mortality in AP with an AUC for mortality of 0.7. The optimal cut-off value of serum phosphate level for prediction of mortality was 3.78 mg/dl. In a subgroup analysis (Table S2), we found that serum phosphate was independently associated with late phase mortality but not with the early phase.

DISCUSSION

We found several biological markers being associated with in-hospital mortality among 499 patients admitted to the ICU for AP. Among the different biological markers, we found that serum phosphate was associated with the highest prognostic value. Non-survivors had significantly higher serum phosphate than survivors. To the best of our knowledge, this observation has rarely been pointed out in previous publications dealing with the prognostic assessment of AP in conventional or ICU.

Interestingly, increased serum phosphate was independent of increased kaliemia and decreased calcemia for evaluating the risk of in-hospital mortality. Such association of hyperphosphatemia, hyperkaliemia, and hypocalcemia is observed during tumor lysis syndrome, where it is frequently associated with hyperuricemia and acute renal failure. Since severe AP is linked to the importance of pancreas tissue necrosis, one could make a parallel for the biological signature between severe AP with large tissue necrosis, and tumor lysis syndrome observed during several hemopathies.

In our study, we found that the mortality rate of AP was similar to other studies (around 10%). Mortality usually occurs at two different phases during AP. It is admitted that in the first days after ICU admission, mortality is caused by the development of multiple organ failure occurring, whereas late death, occurring after several weeks in the disease course, is secondary local complications due to pancreatic necrosis and infection.[19,20] Precise assessment of patient severity permits earlier triage to a conventional or ICU and earlier initiation of adequate effective therapy and follow-up. Multiple predictors, including clinical and laboratory markers and various more or less complex scoring systems, have been developed such as the Ranson score,[21] valid for the first 48 h, or the APACHE II[22] which is however not specific for pancreatitis. These scoring systems incorporate clinical, laboratory, and radiographic data. However, due to their complexity, attention has also focused on the role

TABLE 6 Predictive performance of serum markers as an early indicator for severe acute pancreatitis; the results from receiver operating characteristic analysis

Variable	AUC	*p*	Cut-off
Phosphate mg/dl	0.7	<0.001	3.78
Blood urea nitrogen mg/dl	0.698	<0.001	21.75
Potassium mmol/L	0.691	<0.001	4.125
Creatinine mg/dl	0.67	<0.001	1.025
Bilirubin total mg/dl	0.638	0.001	3.75
AST U/L	0.617	0.005	266.66
Anion gap	0.6	0.013	18.28
ALT U/L	0.585	0.031	61
Alkaline phosphatase U/L	0.58	0.038	121.5
Chloride mmol/L	0.5	0.504	111.66
Magnesium mg/dl	0.483	0.646	2.26
Hematocrit %	0.477	0.7	36.2
Platelet count/mm^3	0.413	0.974	385
Calcium total mmol/L	0.408	0.979	6.63
Bicarbonate mmol/L	0.34	1	7.85
White blood cells/mm^3	0.551	0.126	13.95
APS III	0.807	<0.001	35
OASIS	0.647	<0.001	20
SOFA	0.812	<0.001	5

Abbreviations: ALT, alanine aminotransferase; APS III, acute physiology score III; AST, aspartate aminotransferase; AUC, area under the curve; OASIS, Oxford Acute Severity of Illness Score; SOFA, Sequential Organ Failure Assessment.

of individual and single laboratory parameters in assessment of severity or mortality. International Association of Pancreatology and the American Pancreatic Association in their 2013 guidelines advises the use of systemic inflammatory response syndrome (SIRS) to predict severe AP at admission as well as its persistence at 48 h. In 2017, a group of international experts developed the acute Pancreatitis Activity Scoring System (PASS) to monitor the disease activity during its course.[23] The PASS system applies a quantitative weight to five clinically important parameters organ failure, intolerance to solid diet, systemic inflammatory response syndrome, abdominal pain and intravenous morphine equivalent dose. This score can be calculated sequentially during the pancreatitis admission to follow evolution of acute pancreatitis. A PASS score >140 at admission was associated with the development of moderately severe and severe pancreatitis, SIRS, and local complications, as well as prolonged length of stay and delayed resumption of oral nutrition.[24]

Data from our study demonstrate for the first time a statistically significant association between serum phosphate at baseline and mortality in ICU patient. We found an optimal serum phosphate cut-off value of 3.78 mg/dl for the prediction of mortality. In an animal study conducted by Mazzini et al., the authors found a relationship between serum phosphate and the severity of AP on animal.[25] A previous study conducted by Choi et al.[26] found serum phosphate level to be an independent risk factor for severe post-ERCP pancreatitis (OR = 1.97, $p = 0.04$). In the ROC analysis, the AUC of serum phosphate level for severe post-ERCP pancreatitis was 0.65 (95% CI: 0.56–0.75). Similarly, the authors found that the optimal cut-off value of serum phosphate level for the prediction of severe post-ERCP pancreatitis was 3.35 mg/dl (sensitivity, 0.62; specificity, 0.73).

At admission, a decrease in the intravascular volume due to fluid loss leads to the development of prerenal azotemia and increased BUN.[27] A concentration of blood urea greater than 39 mg/dl on admission is associated with increased mortality.[28] Severity scores of AP in their composition are based on high levels of urea (Ranson, Glasgow/Imrie, POP, BISAP ...). In our study, we found BUN to be associated with mortality in univariate analysis. However, this remained no longer significant on multivariate analysis in our specific ICU population. Similarly, a maximum serum creatinine greater than 1.8 mg/dl within the first 48 h after hospitalization was associated with the development of pancreatic necrosis in a previous study.[29] However, serum creatinine was found associated with an increased mortality on univariate analysis but remained not longer significant on multivariate analysis.

Regarding liver enzymes, increased total bilirubin are well-established mortality markers in ICU and are taken into consideration when calculating scores prognosis to monitor possible liver failure (SOFA).[30–32] An increase in total bilirubin and liver disease marker (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphate) was observed in the deceased patients in our study and remained significantly associated with fatal outcome on multivariate analysis.

There were several limitations to the current study. First, AP cases were identified by ICD-9 code. Thus, even though the risk is marginal, we cannot exclude that a patient was not properly coded and not found on our data. Another limitation was the inability to compare inflammatory markers (C-reactive protein or interleukins) or established prognostic factor such as BMI that were because these data were not available in the database or not collected routinely. Also, we focused in this study on patient admitted directly to ICU. Clinical, biological, and discharge summaries of non-ICU patients are not available on MIMIC-III database preventing the analysis of patients admitted initially to the floor.

Serum phosphate, BUN, creatinine, total bilirubin, AST, ALT, and alkaline phosphatase can be used as a reliable prognostic marker in predicting the mortality of AP. In the ROC analysis, the AUC of serum phosphate level for mortality has the highest value. Future prospective studies would be the cogent next step in validating its predicting value.

CONFLICT OF INTEREST

No conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Study design, data collection, statistical analysis, drafting of the article: Abdellah Hedjoudje, Frédéric Prat, Philippe Levy, Gaël Piton. *Data collection, drafting of the article*: Jad Farha, Chérifa Cheurfa, Emmanuel Weiss, Dilhana Badurdeen, Vivek Kumbhari. *Study design, quality assessment, interpretation of data drafting of the article, critical revision and final approval of the manuscript*: Philippe Levy, Frédéric Prat, Emmanuel Weiss, Gaël Piton, Vivek Kumbhari, Emmanuel Weiss.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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