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Hypophosphatemia Levels Deleteriously Affect Outcome of Patients with Severe Sepsis and Septic Shock Admitted to ICU

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Abstract

Objectives: To determine incidence of hypophosphatemia (HP) among severe sepsis/septic shock patients admitted to ICU and its impact on morbidity and mortality rates and to evaluate the impact of phosphorous supplemental therapy (PST) on such outcomes.

Patients & Methods: 65 septic shock and 252 severe sepsis patients were categorized according to at-admission inorganic phosphate (Pi) level (T0) into normophosphatemia (NP; n=238) and mild, moderate and severe HP (n= 24, 38 and 17 patients, respectively). All patients were evaluated using sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation II score (APACHE II) and gave blood sample for T0 ELISA estimation of serum Pi, human C-reactive protein (CRP) and L-lactate. Sepsis was managed according to Surviving Sepsis Campaign guidelines and dose of PST was calculated and administered on 4-hourly divided doses. Serum Pi level was re-estimated immediate and 24-hr after full dose administration. Outcomes included the 28-day ICU morbidity and mortality rates and their relation to HP severity and PST administration.

Results: PST administration increased serum Pi levels by 73 (±44.5)% of T0 level and after 24-hr serum Pi level was re-dropped in 24 patients, but still higher than T0 level and was within normal range in 55 patients. Morbidity and mortality rates were non-significantly higher among HP than NP patients and were negatively correlated with the percentage of change in serum Pi estimated 24-hr after PST. Regression analysis defined low at admission serum Pi and high SOFA score as most significant predictors for development of morbidities and mortalities during ICU stay.

Conclusion: Sepsis induces decreased levels of serum Pi and the extent of decrease increases with sepsis severity. Early detection of HP and institution of PST is mandatory to reduce morbidity and mortality rates and this reduction correlates with Pi deficit improvement.

Keywords: Hypophosphatemia; Sepsis; ICU mortality; Phosphorous supplemental therapy

Introduction

Sepsis is the terminal event for most infectious diseases [1] and is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [2]. Sepsis still evolves to a mortal outcome, one out of five cases, with no recent or specific therapy showing efficacy on patient's prognosis [3]. Sepsis is frequent and associated with high burden for patients, relatives and societies [1].

Normal adult serum inorganic phosphate (Pi) ranges between 2.5 and 4.5 mg/dl, but higher levels were estimated during childhood, adolescence and pregnancy [4]. Intracellular phosphate is actively involved in many important biochemical pathways, such as energy and nucleic acid metabolism and cellular signaling [5] and extracellular phosphate is essential for bone matrix mineralization [4].

Hypophosphatemia (HP) was defined as serum phosphate levels <2.5 mg/dl [5], but it can be graded as mild (2-2.5 mg/dl), moderate (1-1.9 mg/dl) or severe (<1 mg/dl) [6]. Despite being an infrequent event, HP can affect 2-3% of hospitalized patients and up to 28% of ICU patients [7]. HP may be due to increased renal excretion, decreased intestinal absorption [8] or shifts from extra- to intracellular compartments accompanied or not by depletion of the total phosphorus pool, and extreme catabolic states [9].

HP commonly occurs in clinical settings such as refeeding, alcoholism, diabetic ketoacidosis, malnutrition/ starvation, after surgery especially hepatectomy and in ICU [6]. Clinically, HP may be manifested by respiratory, neuromuscular, cardiac and hematologic manifestations, and the incidence and severity of these manifestations are proportional to severity of HP [10].

Pathophysiologically, HP induces inadequate supplies of high-energy phosphate with inhibition of glyceraldehyde-3-phosphate dehydrogenase, which occupies a key position in glycolysis [11] resulting in reduction of ATP and 2,3-diphosphoglycerate (DPG) levels with subsequent left-hand displacement of oxygen-hemoglobin dissociation curve, and decreased peripheral oxygen uptake and transport [12]. Depletion of DPG in erythrocytes and ATP in peripheral nerves may cause peripheral neuropathy with paresthesias [13] and in myocardial cells results in cardiomyopathy and arrhythmia with impaired left ventricular performance [14].

Brain dysfunction is a frequent and occasionally severe complication of septic shock and may be attributed primarily to direct effects of septic insult on brain or to secondary/indirect injuries [15]. Also, HP through ATP depletion may lead to metabolic encephalopathy resulting in confusion, seizures, severe ataxia and tetra-paresis [16].

Hypothesis

Patients with severe sepsis/septic shock complicated by HP are at high risk of developing morbidities other than that underlying sepsis and more vulnerable to higher mortality rate. Thus, the current study hypothesized that diagnosis and management of HP may be advantageous for reduction of morbidity and mortality rates of septic patients admitted to ICU

Objectives

The current study aimed to determine the incidence of HP among severe sepsis/septic shock patients admitted to ICU and its impact on morbidity and mortality rates of ICU septic patients, and to evaluate the impact of phosphorous supplemental therapy (PST) on such outcomes.

Setting

ICU centers at Ain Shams University Hospital.

Design

Prospective observational study.

Patients & Methods

The current study was started since June 2018 till Jan 2020 after approval of the study protocol by the Local Ethical Committee. The study intended to include all patients admitted to ICU with or developed severe sepsis or septic shock within 24-hr after admission to ICU. Sepsis was defined according to the Sepsis-3 new sepsis definition as life-threatening organ dysfunction caused by a dysregulated host response to infection [17] with organ dysfunction that can be identified as an acute change in total sequential organ failure assessment (SOFA) score ≥2 points consequent to the infection [18]. Septic shock patients were identified according to Shankar-Hari et al. [19] using the clinical criteria of hypotension requiring use of vasopressors to maintain mean blood pressure (MAP) of ≥65 mmHg and having a persisting serum L-lactate level ≥ 2 mmol/L despite adequate fluid resuscitation.

All patients admitted to ICU were eligible to evaluation for demographic and clinical data including hemodynamic data. Disease severity and its impact on body organs were evaluated using acute physiology and chronic health evaluation II score (APACHE II) [20] and SOFA [18] scores. Exclusion criteria included maintenance on immunodepressent therapy for any indication, severe hemorrhagic shock, pregnancy and refusal of nearest relative to sign the written concept for study participation. Children and adulthoods younger than 18 years and patients who were expected to die were also excluded from the study.

Management Plan

Central venous catheter was inserted for all patients enrolled in the study via the jugular or subclavian vein and gradually advanced till the tip of the catheter was positioned in the upper part of the right atrium and its position was assured by chest radiograph. Then, baseline hemodynamic parameters and central venous pressure (CVP) were estimated and were continuously monitored. Arterial blood samples were obtained anaerobically and collected in heparinized tubes for estimation of arterial blood gas and pH.

Biochemical Analyses

Two peripheral venous blood samples (5 ml) were obtained by venipuncture under complete aseptic conditions and without use of tourniquet. Blood samples were collected and numbered by an assistant who was blinded about diagnosis

A. The 1st sample was divided into three parts

1. 1st part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis for estimation of blood glucose levels using glucose oxidase method [21].
2. 2nd part was put in heparinized tube for complete blood count
3. 3rd part was put in a plain tube and serum was separated for estimation of serum levels of liver and renal function markers

B. The 2nd sample was allowed to clot and then centrifuged at 3000 rpm for 10 minutes to separate serum that was collected in sterile Eppindorff tube and stores at -80oC till be assayed using enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions and were read using a 96 well microplate ELISA reader (Dynatech. MR 7000) for estimation of:

1. Human CRP level using ELISA kit (catalogue no. ab99995, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique [22].
2. Serum phosphate (Pi) level using ELISA kit (catalogue no. ab102508, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique. Principle; Pi reacts with maltose to produce glucose which is oxidized to generate a product that reacts with the OxiRed probe to generate fluorescence [23].
3. Serum L-lactate level using ELISA kit (catalogue no. ab65331, abcam Inc., San Francisco, USA) by quantitative sandwich enzyme immunoassay technique. Principle; lactate is oxidized by lactate dehydrogenase to generate a product which interacts with a probe to produce a color [24].

Management

A. Sepsis management: Patients were managed according to guidelines of Surviving Sepsis Campaign [25]; briefly,

1. Fluid therapy: according to the national guidelines, volume used for fluid resuscitation was calculated as 30 ml/kg body weight (BW), an initial fluid bolus of 20 ml/kg BW was given over the first 30–60 minutes and remaining of the calculated volume was given within 60–120 minutes. Fluid therapy was continued depending on clinical response that included achieving MAP of >65 mmHg, reduction of heart rate and increase of urine output (UOP) to >0.5 ml/kg BW. In responders, fluid therapy was continued to the extent necessary to maintain stable circulation [26].

2. For non-responders to fluid resuscitation, vasoactive drug therapy, using nor-epinephrine as the first line therapy, was initiated in combination with continued fluid therapy aiming to achieve a CVP equal to 8–12 mmHg [27].

3. Intropics were preserved for patients with low cardiac index [28] and patients with anuria or high serum potassium levels despite of proper fluid resuscitation were subjected for renal replacement therapy.

4. Antibiotic therapy was initiated with broad-spectrum drugs until result of blood or body fluid sample culture and sensitivity test identified the infecting pathogen and the most appropriate antibiotic. Aminoglycosides and benzylpenicillin were used as standard regime except for patients who were hemodynamically and/or respiratory unstable and/or have reduced diuresis [29]. If β-lactam antibiotic therapy was indicated, it was used as monotherapy according to the national recommendations [30].

B. HP management regimen followed that used by Bech et al. [31] as follows:

1. Calculation of supplementation dose according to the equation: phosphate dose (in mmol) = 0.5 x body weight x (1.25 – [serum Pi]).

2. Preparation used: sodium-phosphate 10 ml vial supplying 4 mmol [92 mg] of sodium and 3 mmol [93 mg] of phosphorus per each ml.

3. Dilution: 25 ml of sodium-phosphate were diluted in 500 cc of dextrose 5% to provide 0.15 mmol of phosphorous and 0.2 mmol of sodium/ml.

4. Dosing: 100 ml of prepared solution was infused every 4-hr till giving the calculated supplementation dose and serum Pi was measured immediately and next morning and percentage of change in serum Pi in relation to at-admission level (T0 level).

Grouping

Patients who fulfilled the inclusion criteria were selectively divided into two groups according to estimated level of serum Pi: Control group included patients with serum Pi >2.5 mg/dl and Study group included patients having serum Pi<2.5 mg/dl and were further sub-grouped according to severity of HP into mild HP (2-2.5 mg/dl), moderate (1-1.9 mg/dl) or severe (<1 mg/dl) [6].

Study Outcome

1. Primary outcome: the 28-day ICU mortality rate (28-MR)

2. Secondary outcomes:

a. The incidence of additional morbidities.

b. The relation between 28-MR and incidence of additional morbidities and severity of HP.

c. The success rate of supplemental regimen was judged as

- The extent of increase in serum Pi levels estimated immediate and 24-hr after PST.
- The incidence of re-decrease of serum Pi during ICU stay
- The impact of serum Pi correction on the 28-MR and incidence of additional morbidities.

d. The 28-day incidence of developing new cases of HP among control group

Statistical Analysis

Obtained data were presented as mean±SD, numbers and percentages. Results were analyzed using paired t-test for inter-group comparisons, One-way ANOVA Test for intra-group comparisons and Chi-square test (X2 test). Possible relationships were investigated using Pearson linear regression analysis. The receiver operating characteristic (ROC) curve analysis was used to evaluated at-admission (T0) data as predictors for outcomes as judged by the area under the curve (AUC) that was compared versus null hypothesis that AUC=0.5. Regression analysis (Stepwise method) was used for stratification of T0 data as specific predictors for outcomes. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Through the duration of the study, since Jan 2018, 385 patients who were admitted to ICU were evaluated for enrolment criteria and 317 patients were included in the study. According to the clinical severity of sepsis, 65 patients (20.5%) had septic shock, while 252 patients (79.5%) had severe sepsis. Patients were categorized according to level of Pi estimated at time of admission into NP and HP groups that included 238 (75.1%) and 79 patients (24.9%), respectively. Among patients of NP group 65 patients had at admission serum Pi level of <3.5 mg/dl and 173 patients had level >3.5 mg/dl. According to severity of HP, patients were categorized into mild, moderate and severe HP subgroups which included 24, 38 and 17 patients, respectively (Figure 1).

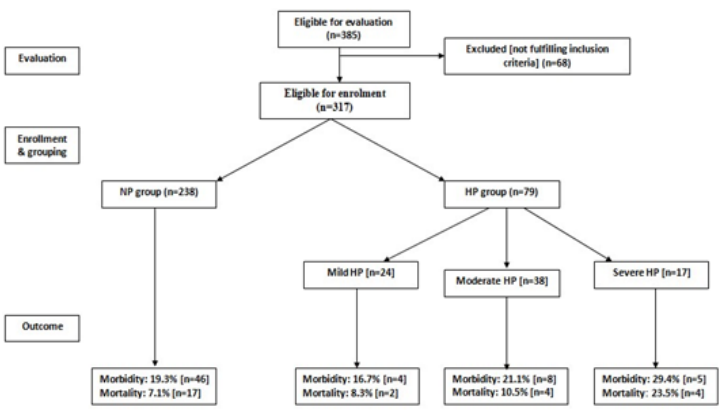

Figure 1: Consort Flow Sheet

At time of ICU admission, the frequency of patients had septic shock was significantly higher among HP patients than patients had severe sepsis. Moreover, HP patients had significantly higher mean APACHE II and SOFA scores in comparison to patients had severe sepsis, while other clinical characteristics of enrolled patients showed non-significant differences between NP and HP groups (Table 1).

Table (1): Clinical characteristics and lab findings of studied patients at time of ICU admission

Parameters	Group	NP (n= 238)	HP (n=79)	P value
Age		55.3±9.8	57.6±10.1	0.073
Sex; M:F		167:71	52:27	0.469
Weight (kg)		86.7±10	89.3±12.6	0.063
Height (cm)		167.3±4.4	166.1±5.7	0.071
BMI (Kg/m2)		31±3.7	32.4±4.8	0.093
APACHE II score		22.1±3.8	23.2±5.3	0.028
SOFA score		9.9±3.3	10.8±3.2	0.037
Need ventilation	Yes	31 (13%)	16 (20.3%)	0.117
	No	207 (87%)	63 (79.7%)	
Sepsis severity	Severe sepsis	206 (86.6%)	46 (68.2%)	<0.0001
	Septic shock	32 (13.4%)	33 (41.8%)	
Associated medical morbidities	CVD	43 (18.1%)	22 (27.8%)	0.078
	Liver	18 (7.6%)	6 (7.7%)	
	GIT	12 (5.1%)	4 (5%)	
	DM	37 (15.5%)	10 (12.7%)	
	Neurological	52 (21.8%)	20 (25.3%)	
	No	76 (31.9%)	17 (21.5%)	

Data are shown as mean, standard deviation, numbers, percentages; NP: Normo-phosphatemia, HP: Hypophosphatemia, BMI: Body mass index; APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: sequential organ failure assessment, CVD: Cardiovascular disease; GIT: Gastrointestinal disease, DM: Diabetes mellitus, p value indicates significance of difference between both groups; p<0.05 indicates significant difference; p value >0.05 indicates non-significant difference

Mean at-admission serum Pi levels (T0 level) were significantly lower, while serum lactate levels were significantly higher and serum CRP levels were non-significantly higher in septic shock patients than patient had severe sepsis. Among patients' subgroups according to serum Pi levels, at admission serum Pi levels showed significant declination among studied groups. Serum lactate levels estimated at admission, were significantly higher in HP patients in comparison to NP, with significantly higher lactate levels in samples of NP patients with mean Pi level <3.5 mg/L in comparison to NP patients had serum Pi >3.5 mg/L. On contrary, among subgroups of HP, serum lactate levels showed non-significant differences despite being higher with decreased Pi levels. On the other hand, serum CRP levels showed non-significant differences between NP and HP patients and between mild and moderate HP patients, despite being significantly higher in samples of severe HP patients in comparison to both mild and moderate HP patients (Table 2).

Table (2): At admission laboratory data of studied patients

Group	Variables		Pi (mg/L)	Lactate ()	CRP (mg/L)
According to sepsis severity	Severe sepsis (n=252)		3.33±0.87	1.38±0.31	232.3±119.2
	Septic shock (n=65)		2.41±1.03	3.19±0.79	257±118.4
	P1 value		<0.0001	<0.0001	0.136
According to serum Pi level	NP	>3.5 (n=173)	3.88±0.21	1.48±0.51	235.5±115.1
		<3.5 (n=65)	2.99±0.23	1.89±0.88	248.88±133.6
		P2	<0.00001	0.00011	0.444
		Total (n=238)	3.64±0.45	1.59±0.66	239.12±120.3
	HP	Mild (n=24)	2.24±0.09	1.95±1.11	204±89.8
		Moderate (n=38)	1.66±0.16	2.21±1.05	213.6±101.7
		P3	<0.00001	0.357	0.706
		Severe (n=17)	0.83±0.09	2.68±1.43	312.8±148.2
		P3 P4	<0.00001 <0.00001	0.071 0.172	0.0057 0.0063
		Total (n=79)	1.66±0.52	2.23±1.17	232.1±116.7
		P5	<0.00001	<0.00001	0.649

Data are shown as mean, standard deviation; Pi: inorganic phosphate, CRP: C-reactive protein; NP: normo-phosphatemia, HP: hypo-phosphatemia; P1 indicates the significance of difference between septic shock and severe sepsis patients, P2 indicates the significance of difference between NP patients sub-grouped according to serum Pi levels, P3 indicates the significance of difference versus mild HP patients, P4 indicates the significance of difference versus moderate HP patients, P5 indicates the significance of difference between total NP and HP patients

All HP patients received PTS by a mean amount of 347.4±45.2 ml and Pi levels estimated immediately after administration of the last part of the calculated dose was increased by 73 (±44.5)% of the at admission level. No patient still having severe HP, 9 patients had moderate and 11 patients had mild HP and the remaining 59 patients became NP and 3 of them had serum Pi level>3.5 mg/L. On 24-hr after administration of the calculated dose of PST, 55 (69.6%) had serum Pi level within normal range and 13 (16.4%) patients had serum Pi level >3.5 mg/L, but unfortunately, serum Pi levels re-dropped in 24 patients despite being still higher than the at-admission level, and the total extent of change was increased levels by 77.8 (±63.3) % (Table 3).

Table (3): changes of serum Pi levels after PST for hypophosphatemic patients

		At admission	Immediately after therapy	24-hr after therapy
Mild HP		24 (30.4%)	11 (13.9%)	10 (12.7%)
Moderate HP		38 (48.1%)	9 (11.4%)	10 (12.7%)
Severe HP		17 (21.5%)	0	4 (5.1%)
Normal	<3.5 (mg/L)	0	56 (70.9%)	42 (53.1%)
	>3.5 (mg/L)	0	3 (3.8%)	13 (16.4%)
Level (mg/L)		1.66±0.52	2.7±0.56	2.77±0.83
% of increase*			73±44.5	77.8±63.3

Data are shown as numbers, percentages, mean, standard deviation; HP: Hypophosphatemia, *: % of increase in relation to at-admission level;

Sixty-three patients developed additional morbidities during their ICU stay; 46 NP patients (19.3%) and 17 HP patients (21.5%) for a total morbidity rate of 19.3% and non-significantly (p=0.672) higher rate among HP than NP patients. Concerning the 28-day mortality, 27 patients (8.5%); 17 NP (7.1%) and 10 HP (12.6%) patients with a non-significantly (p=0.128) higher mortality rate among HP patients (Figure 1). Among NP patients, 31 patients (17.9%) had T0 serum Pi level >3.5 mg/L, while 15 patients (23.1%) had T0 level of <3.5 mg/L with non-significantly higher morbidity rate among patients had T0 level <3.5 mg/L. The 28-day mortality rate among patients had T0 Pi level >3.5 was 5.8%, while was 10.8% among patients had T0 level <3.5 mg/L with non-significantly (p=0.183) higher rate in the latter patients.

Concerning HP patients, after receiving PST additional morbidities were detected in 2 (8.3%), 4 (10.5%) and 4 patients (23.5%) among patients had at admission mild, moderate and severe HP, respectively with non-significant (p-0.304) difference between these patients. Similarly, mortality rates were 16.7%, 21.1% and 29.4%, respectively.

Pearson's correlation analysis showed positive significant correlation between development of new morbidities and mortalities during ICU stay and at admission high APACHE II and SOFA scores and high blood lactate and serum CRP levels, while showed negative significant correlations with at-admission serum Pi levels. ROC curve analysis excluded high serum CRP as predictor for either of development of morbidities (Figure 2a) or mortality (Figure 2b) during ICU stay, while showed that all other variables can predict these outcomes with varied significance. Regression analysis, stepwise method, defined low at admission serum Pi and high SOFA score as most significant predictors for development of additional morbidities during ICU stay, while high at admission SOFA score, serum Pi and blood lactate levels as the most significant predictors for mortalities (Table 4).

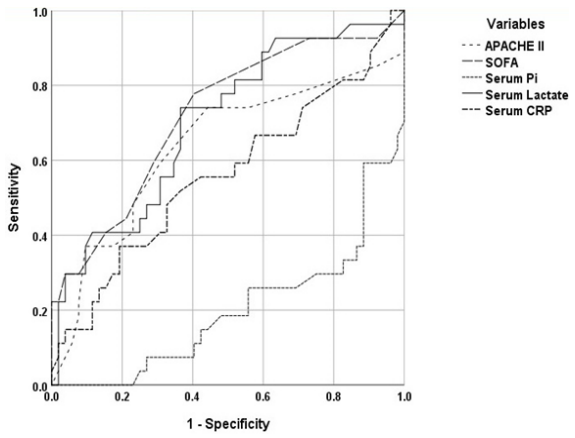

Figure 2a: ROC curve analysis of at admission variables as predictors for ICU additional morbidities

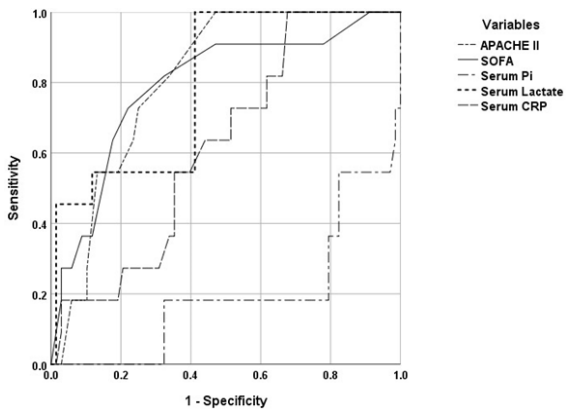

Figure 2b: ROC curve analysis of at admission variables as predictors for ICU mortality

Table (4): Statistical analyses of at admission variables as predictors for 28-day outcomes of studied patients

Statistical method	Variables	Morbidity			Mortality		
Pearson's correlation		r	p		r	P	
	APACHE II	0.247	<0.001		0.324	<0.001	
	SOFA	0.235	<0.001		0.284	<0.001	
	Pi	-0.261	<0.001		-0.214	<0.001	
	Lactate	0.195	<0.001		0.208	<0.001	
	CRP	0.211	<0.001		0.146	0.009	
ROC curve analysis		AUC (±SE)	p	95%CI	AUC (±SE)	p	95%CI
	APACHE II	0.636 (0.072)	0.048	0.495-0.778	0.809 (0.053)	0.001	0.706-0.912
	SOFA	0.722 (0.062)	0.001	0.600-0.844	0.792 (0.076)	0.002	0.644-0.940
	Pi	0.201 (0.054)	0.001	0.095-0.307	0.196 (0.077)	<0.001	0.045-0.347
	Lactate	0.701 (0.062)	0.004	0.579-0.823	0.795 (0.066)	0.002	0.666-0.925
	CRP	0.560 (0.072)	0.385	0.419-0.700	0.621 (0.078)	0.200	0.467-0.775
Regression analysis		β	p		β	p	
	SOFA	0.295	0.004		0.486	<0.001	
	Pi	-0.241	0.033		-0.387	<0.001	
	Lactate	0.281	0.007		0.448	<0.001	

r: Pearson's coefficient; AUC: Area under curve; CI: Confidence interval; β: Standardized coefficient; APACHE II: Acute Physiology And Chronic Health Evaluation II, SOFA: sequential organ failure assessment, Pi: Inorganic phosphate; CRP: C-reactive protein; p<0.05 indicates significant value; p>0.05: indicates insignificant value

Interestingly, correlation analysis detected a negative significant correlation between the percentage of change in serum Pi estimated 24-hr after end of PST and both development of additional morbidities (r=-0.298, p=0.008) and mortality (r=-0.337, p=0.002) during ICU stay.

Discussion

The current study reported an incidence of HP of about 25% of the studied septic patients admitted to ICU, this figure coincided with that previously reported by Padelli et al. [7] who found the incidence of HP rise up to 28% of ICU patients and is frequent during sepsis, and could be responsible for leucocyte dysfunction that might increase sepsis which in turn increases HP. Also, Liu et al. [32] out of a met-analysis to evaluate the relation between HP and prognosis in critically ill patients, reported 38% incidence of HP and found HP patients had higher APACHE II than NP patients with steadily increasing score with HP severity.

The current study tried to evaluate the prognostic value of at-admission estimation of serum Pi for ICU patients admitted for management of sepsis. Reliance on the at-admission level goes in hand with and supported the results obtained by Brotfain et al. [33] who found early HP in critically ill ICU patients with severe sepsis and early thrombocytopenia worsens their prognosis with increased mortality rate than those with normal Pi serum levels. Thus, early identification of HP patients and management of HP may improve outcome. In support of this assumption, statistical analyses showed negative significant correlations between development of new morbidities and mortalities during ICU stay and at admission serum Pi levels and defined low serum Pi level as the most significant predictor for high morbidity and mortality rates.

These findings are coincident with early reports that among ICU patients without any episodes of hyperphosphatemia, patients with at least one episode of HP had a higher ICU mortality than those without hypophosphatemia and non-survivors had lower minimum Pi concentrations than did survivors, so serum Pi levels have a prognostic value for mortality [34,35] and provide further support for the need for early detection of HP [33].

Moreover, the obtained results go in hand with recent reports that HP in ICU patients is associated with severity of illness, prolonged duration of mechanical ventilation; length of ICU stay, and higher mortalities [32,36] and HP was an independent risk factor for ICU 28-day mortality in the multivariate logistic regression analysis [36]. Also, Rimaz et al. [37] detected HP in 75.1% of burnt patients admitted to hospital and the highest decrease in the serum P level occurs on the 3rd and 5th days after burn, was negatively correlated with patient's mortality rate and suggested regular assessment of Pi level for the timely initiation of PST.

All HP patients received PST, administered in a dose calculated according Bech et al. [31] and significantly improved serum Pi level immediately after completion of therapy and 59 patients (74.7%) had normal level that was maintained in 55 patients (69.6%). In support of the efficacy of calculation according Bech et al. [31], Agarwal et al. [38] using the same formula for calculation reported improvement in 67.7% of patients by 35% of baseline levels with no adverse effects on renal function. Also, Engwerda et al. [39] using the same formula detected increased serum Pi to >0.60 mmol/l in 56% and 86% of patients with severe and moderate HP, respectively.

In support of the need for intervention to correct HP, Yang et al. [40] reported continuous decline of serum Pi indicates poor prognosis, and its level is one of the most important prognostic indicators for outcome of patients who admitted to ICU for severe sepsis management with progressively increasing AUC on ROC analysis for prediction of mortality with prolonged duration and severity of HP.

In line with the efficacy of PST, Padelli et al. [7] documented that treatment of HP through supplementation is simple and quickly restores normal concentration, with few adverse effects even if regularly used. Also, Song et al. [41] found PST effectively corrected renal replacement therapy-induced HP in patients developed acute kidney injury during ICU stay and amount needed and time required till correction were correlated to the deficit and Hendrix et al. [42] reported success rate of 38% of PST for resolution of HP in ICU patients maintained on continuous renal replacement therapy and concluded that aggressive supplementation strategies to correct phosphorus is warranted in such patients.

In support of the obtained results and this review of literature, correlation analysis detected a significant inverse relation between morbidity and mortality and the extent of correction of Pi deficit detected at time of admission. The reported high figure for improvement in the current study could be attributed to exclusion of patients had chronic renal disease or maintained on chronic replacement therapy during preliminary evaluation of patients.

Conclusion

Sepsis induces decreased levels of serum Pi and the extent of HP increases with the severity of sepsis. Early detection of HP and institution of PST is mandatory to reduce the incidence of additional morbidities and mortality and this reduction correlates with the extent of improvement in the deficit of Pi levels. Care must be provided during calculation of the required PST dose to guard against hyper-phosphatemia.

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