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Clinical outcome of critically ill patients with thrombocytopenia and hypophosphatemia in the early stage of sepsis

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Abstract

Background: Hypophosphatemia and thrombocytopenia may both be independent risk factors for the development of multiple organ failure and correlate well with the severity of sepsis. In the present study we wanted to analyze the potential clinical role and prognostic significance of both early hypophosphatemia and thrombocytopenia on clinical outcomes of critically ill ICU patients with severe sepsis

Methods: We analyzed the clinical data, including the outcome of critically ill ICU patients with severe sepsis who presented during a 5 year period with early hypophosphatemia and thrombocytopenia.This study was retrospective and single centre. All clinical and laboratory data was collected from the patients' ICU and hospital electronic records. All laboratory measurements were done on admission and during the ICU stay.

Results: The included patients were distributed into one of three study groups based on the presence of hypophosphatemia and/or thrombocytopenia during the first 24 hours of admission to the ICU: group 1 — early hypophosphatemia; group 2 — early hypophosphatemia and thrombocytopenia and group 3 — early thrombocytopenia. The ICU mortality rate was significantly higher in groups 2 and 3 (25.9% and 22% vs. 9.3%, respectively, $P = 0.034$). An APACHE II score > 27, a TISS score > 25 following the first 24 hours of ICU stay , an age higher than 70, male gender and total parenteral nutrition were independent predictors of ICU and hospital mortality in this study population.

Conclusion: It may be considered that hypophosphatemia and thrombocytopenia in the early stage of sepsis, even when severe and coexisting, reflect the degree of initial illness severity of sepsis. However, further investigations need to be done for a better understanding of the potential clinical role of these features in the septic critically ill population.

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Key words: sepsis, severe sepsis, septic shock; sepsis, outcome; hypophosphatemia, thrombocytopenia

Sepsis is associated with multiple organ dysfunction and high mortality, even with optimal management [1]. Early diagnosis and better monitoring may improve clinical outcomes. Hypophosphatemia and thrombocytopenia are both independent risk factors for the development of multiple organ failure and correlated well with the severity of sepsis [2, 3].

Hypophosphatemia has been reported as one of the early findings of severe sepsis/septic shock [4, 5]. Moreover, it has been recognized as an independent risk factor for the development of cardiac arrhythmias and a high mortality rate in septic patients. Aggressive treatment of hypophosphatemia might significantly decrease the incidence of arrhythmias and improve prognosis [6, 7].

Thrombocytopenia has been recognized as a common component of multiple organ dysfunction syndrome (hematologic system) in severe sepsis [8]. The prevalence of thrombocytopenia is even higher in septic shock because of a high occurrence of DIC (about 50 %) [9]. Moreover, thrombocytopenia was found to be an independent prog-

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nostic marker of high mortality and prolonged ICU stay in septic patients [10].

In the present study, we analyzed the potential clinical role and prognostic significance of both early hypophosphatemia and thrombocytopenia on clinical outcomes of critically ill ICU patients with severe sepsis who presented during a 5 year period.

METHODS

This study was retrospective and single centre. The Human Research and Ethics Committee at Soroka Medical Center approved this study (RN 0264-12).Since the study was retrospective, the patients' informed consent was not needed.

We collected clinical, laboratory and microbiological data from all severe septic patients hospitalized in our general ICU (GICU) at Soroka Medical Centre between January 2005 and June 2011. Sepsis, septic shock and severe sepsis were defined according to the International Guidelines of the 2012 Surviving Sepsis Campaign [1].

All adult (age > 18 years) severe septic patients hospitalized in GICU of Soroka Medical Centre for more than 3 days were included into the study.

All patients who were hospitalized less than 3 days in the GICU were excluded. Moreover, patients whose medical records contained insufficient data were excluded from the study.

All clinical data was collected from the patients' ICU and hospital electronic records. We selected demographic data, underlying co-morbidities, microbiological data, duration of ICU and hospital stay, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Therapeutic Intervention Scoring System (TISS) scores.

The laboratory data was collected from Lab Database Electronic System including serum blood phosphorus and platelet count, serum blood calcium, urea, and creatinine blood levels, haemoglobin, white blood cell count and pH of arterial blood on admission and during the ICU stay. The following data from the patients' ICU stay were also recorded: insulin treatment, type of nutrition and administration of vasopressors or other inotropic support modalities.

The included patients were distributed into one of three study groups based on the presence, during the ICU stay, of early hypophosphatemia without thrombocytopenia — group 1; patients with early hypophosphatemia and thrombocytopenia — group 2; and patients with early thrombocytopenia without hypophosphatemia — group 3.

Early hypophosphatemia was defined as a serum phosphorus level less than 2.5 mg dL^{-1} (0.8 mmol L^{-1}) during the first 24 hours of ICU stay. Early thrombocytopenia was defined as a serum platelet count less than 150 G L^{-1} during the first 24 hours of ICU stay.

Statistical analyses were performed using IBM SPSS Statistics 23 (IBM Corp., Armonk, USA). Continuous variables were evaluated for normal distribution using a histogram and Q-Q plot. Normally distributed continuous variables were reported as a mean and SD while non-normally distributed variables were reported as a median and interquartile range. Normally continuous variables were compared between groups using ANOVA with the Scheffe post-hoc test. Non-normally distributed variables were compared using the Kruskal-Wallis test and the Mann-Whitney test. Categorical variables were compared between groups using the Chi-square test or Fisher's exact test. Associations between ICU and hospital mortality and study groups were described using Kaplan-Meier curves. Univariate and multivariate cox regression analyses were used to evaluate the crude and adjusted hazard ratios. Variables with $P < 0.1$ on the univariate analysis and demographic data were included in the multivariate analysis. The results are presented as a hazards ratio (HR), with confidence intervals (CI). A *P*-value of less than 0.05 represents a statistically significant finding.

RESULTS

The clinical and laboratory data of 240 critically ill patients admitted with sepsis during the study period were analyzed. A total of 170 patients were included in the study, whereas 70 patients were excluded on the basis of the exclusion criteria Group 1 consisted of 75 patients with early hypophosphatemia; group 2 consisted of 54 patients with early hypophosphatemia and thrombocytopenia; and group 3 consisted of 41 patients with early thrombocytopenia. The significant epidemiological data and clinical characteristics of the study patients are shown in Table 1.

The groups were similar with regard to age, gender, and underlying medical conditions (Table 1).

Primary bacteraemia as the septic etiology had a higher prevalence in groups 2 and 3 compared to group 1 ($P = 0.041$). There was no difference in other etiologies of sepsis between the study groups (Table 1).

According to the group's definition, the platelet count was significantly lower in both groups with thrombocytopenia compared to group 1 ($P < 0.001$). The serum phosphorus level was significantly lower in groups 1 and 2 with hypophosphatemia compared to group 3 ($P < 0.001$) (Table 2).

Serum calcium and glucose levels, arterial blood pH, urea, creatinine, white cell count and hemoglobin were similar among all the patients' groups (Table 2). No difference in insulin treatment, vasopressive therapy or length of ICU and hospital stay was found between the study groups (Table 3). Patients in groups 2 and 3 had a significantly higher percentage of total parenteral nutrition (TPN) compared to group 1 ($P = 0.032$). The APACHE II and TISS scores were

Table 1. Patients' demographic data and underlying condition. Age in years expressed in median (IQR). The remaining data in numbers of patients and (%)

	Group 1 (n = 75)	Group 2 (n = 54)	Group 3 (n = 41)	*P*-value
Age	52 (36–72)	60.5 (32.7–72.2)	64 (32.5–73)	0.822
Male sex	48 (64)	32 (59)	20 (48.8)	0.281
Admission diagnosis[a]:				
Pneumonia	36 (48)	20 (37)	12 (29.3)	0.125
Intra-abdominal sepsis	27 (36)	20 (37)	17 (41.5)	0.84
Primary bacteremia	5 (6.7)	10 (18.5)	9 (22)	0.041
Wound infection	2 (2.7)	2 (3.7)	3 (7.3)	0.47
Meningitis	5 (6.7)	2 (3.7)	0 (0)	0.28
Underlying condition:				
Diabetes mellitus (type 2)	15 (20)	13 (24.1)	8 (19.8)	0.16
Hypertension	16 (21.3)	12 (21.9)	9 (22.02)	0.8
COPD/Asthma	4 (5.3)	3 (5.5)	4 (9.7)	0.67
CIHD	18 (21)	14 (25.9)	10 (25.7)	0.51
Other[b]	22 (29)	14 (24.1)	10 (22)	0.42

[a]Admission diagnosis also characterize the potential source of sepsis
[b]"Other" past medical history include: obesity, benign prostate hypertrophy (BPH), dyslipidemia, chronic anemia,s/p CVA, dementia, chronic atrial fibrillation, peripheral vascular disease (PVD), hypo-/hyperthyroidism
COPD — chronic obstructive pulmonary disease; CIHD — chronic ischemic heart disease

Table 2. Laboratory data of study group patients; pH and Hb values expressed as median ± SD, other as (median (IQR). Platelet count in G L^{-1}, WBC count in G L^{-1}, phosphorus and calcium concentration in mmol L^{-1}, glucose, creatinine and urea levels — in mg dL^{-1}, haemoglobin in g dL^{-1}

	Group 1 (n = 75)	Group 2 (n = 54)	Group 3 (n = 41)	*P*-value
Platelets[a]	154 (121–191)	70 (60–74)	67 (57–72)	< 0.001
Phosphorus[b]	0.48 (0.44–0.54)	0.51 (0.48–0.54)	0.99 (0.89–1.2)	< 0.001
WBC	17 (12–21)	13 (5–23)	17 (11–21)	0.471
Serum glucose	144 (123–177)	154 (123–195.7)	134 (115–165)	0.132
Serum calcium	1.1 (1–1.1)	1 (0.97–1.1)	1 (1–1)	0.053
Serum creatinine	0.8 (0.7–0.9)	0.9 (0.7–1.0)	0.8 (0.6–1.0)	0.443
Serum urea	36 (27–45)	44 (31–58)	40 (29–58)	0.034
pH arterial blood	7.33 ± 0.07	7.30 ± 0.07	7.32 ± 0.07	0.449
Hemoglobin	11.7 ± 1.8	11.2 ± 1.9	11.09 ± 1.6	0.178

[b]Platelets' count presented as median (IQR) during first 96 hours of ICU admission. Note: there was no difference in platelet count between groups 1 and 2, $P = 0.163$
[a]Serum phosphorus presented as median (IQR) during first 96 hours of ICU admission. Note: there was no difference in serum phosphorus level between groups 2 and 3, $P = 0.165$

significantly lower in group 1 patients compared to groups 2 and 3 (Table 3).

The ICU mortality rate was significantly higher in group 2 and 3 vs. group 1 (25.9% and 22% vs. 9.3%, respectively) (Fig. 1). A multivariate analysis of survival and the risk factors of ICU mortality critically ill septic patients with early hypophosphatemia and thrombocytopenia demonstrated that the adjusted HR (4.03 with 95% CI: 1.37–11.8, $P = 0.01$) of group 3 was even higher which means a finally higher mortality rate in group 3 (Table 4).

There was no difference in the hospital mortality rate between study groups ($P = 0.1$) (see also Fig. 1B). The results of multivariate Cox regression analysis of critically ill severely septic patients with early hypophosphatemia and thrombocytopenia are shown in Table 4. An APACHE II score > 27, a TISS score >25 (Tables 4 and 5) during the first 24 hours of ICU stay, an age higher than 70 years, male gender and TPN were independent predictors of ICU mortality in this study population.

During the ICU stay, group 1 patients demonstrated higher survival rates compared to groups 2 and 3 (Fig. 1 and Table 4).

Table 3. Clinical outcome endpoints and treatment. APACHE II, TISS scores, ICU and hospital stay (in days) are expressed in median (IQR). The remaining data in numbers of patients and (%)

	Group 1 (n = 75)	Group 2 (n = 54)	Group 3 (n = 41)	*P*-value
Insulin treatment	26 (34.7)	17 (31.5)	13 (31.7)	0.91
TPN	15 (20)	22 (40.7)	14 (34.1)	0.032
Vasopressor use	36 (48)	32 (59.3)	16 (39)	0.141
APACHE II score[a] (median [IQR])	25 (22–27)	27 (25–29)	26 (22–30)	0.001
TISS score[a]	23 (22–25)	25 (23–28)	24 (21–27)	0.002
ICU stay	13 (6–29)	17 (9–32)	10 (4–27)	0.11
Hospital stay	27 (15–45)	28 (17–39)	25 (12–33)	0.23

TPN — total parenteral nutrition
aAPACHE II and TISS scores were calculated on first 24 hours of ICU stay. APACHE II score was found statistically significant between group 1 and group 2 ($P < 0.0001$). There was no difference in APACHE score between group 1 and 3, between group 2 and 3. Similar, TISS score was found significantly low in group 1 compared to group 2 ($P < 0.0001$); there was no difference in TISS score between group 1vs. 2, 3

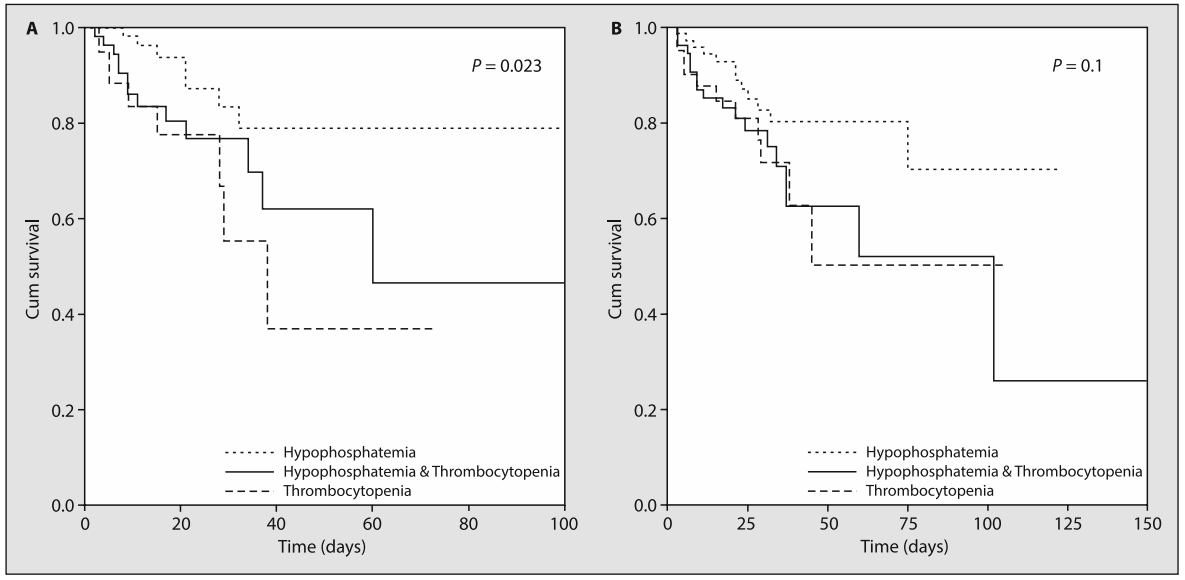

Figure 1. A — Kaplan-Meier cumulative survival curve for ICU stay in septic patients with early hypophosphatemia (group 1, dot line), early hypophosphatemia and thrombocytopenia (group 2, full line) and early thrombocytopenia (group 3, dash line). **B** — Kaplan-Meier cumulative survival curve for ICU (1A) and hospital (1B) stay in septic patients with early hypophosphatemia (group 1, dot line), early hypophosphatemia and thrombocytopenia (group 2, full line) and early thrombocytopenia (group 3, dash line)

DISCUSSION

In the present study we demonstrated a higher mortality in septic patients with early hypophosphatemia and thrombocytopenia. A high APACHE and TISS scores, older age, male gender and TPN were found to be independent predictor factors for in-ICU and hospital mortality in this critically ill population. Hypophosphatemia is a frequent electrolyte disturbance in critically ill patients, including the septic population [4, 11, 12]. Gram-negative bacteremia in particular is strongly associated with hypophosphatemia [13]. The major mechanisms of hypophosphatemia in the ICU population are inadequate intake caused by malnutrition/malabsorption, the redistribution of phosphate into cells and the loss of phosphate from the body (urinary loses with diuretics, drug poisoning etc.) [4, 11, 12]. In the acute phase of sepsis, the main cause of hypophosphatemia is believed to be redistribution across the cell membrane [14]. The precise mechanism responsible for the shift of phosphate into cells in sepsis includes high serum levels of catecholamines such as epinephrine and norepinephrine, whether endogenous or exogenous. These induce a shift of phosphate into the intracellular space, the administration of glucose and insulin which stimulates carbohydrate metabolism, leading to the transport of phosphate into the cells, respiratory alkalosis-induced increase of intracellular pH causing phosphate to enter the cell. Additionally, renal

Table 4. Multivariate and univariate analysis of risk factors of ICU mortality critically ill septic patients with early hypophosphatemia and thrombocytopenia

	Survival		Crude HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
	No (n = 30)	Yes (n = 140)				
Group 1[a]	7 (23.3%)	68 (48.5%)	1	0.034	1	0.03
Group 2[a]	14 (46.6%)	40 (28.5%)	2.4 (1.0–6.2)		1.5 (0.59–4.03)	0.36
Group 3[a]	9 (30%)	32 (22.9%)	3.6 (1.35–9.8)		4.03 (1.37–11.8)	0.01
Ph	7.28 (7.24–7.37)	7.33 (7.27–7.38)	0.10 (0.01–3.82)	0.13		
Glucose (mg dL^{-1})	142 (120–195)	144 (122–183)	1.0 (1.0–1.01)	0.68		
Calcium (mmol L^{-1})	1 (0.97–1.1)	1 (1–1.1)	0.1 (0.01–0.63)	0.03	0.05 (0.01–3.6)	0.17
Urea (mg dL^{-1})	46 (35–57)	36 (27.5–53)	1 (0.9–1.02)	0.53		
Creatinine (mg dL^{-1})	0.9 (0.6–1.1)	0.8 (0.7–0.9)	2.8 (0.6– 13.2)	0.19		
Hb (g dL^{-1})	11.4 (10.2–12.3)	11.1 (9.9–12.8)	0.9 (0.77–1.1)	0.37		
WBC (G L^{-1})	17 (5–21.2)	17 (11–21)	1.00 (0.99–1.01)	0.33		
Insulin	15 (50%)	109 (78%)	1.9 (0.89–3.83)	0.1	1.26 (0.56–2.8)	0.56
TPN	18 (60%)	34 (24.2%)	5.1 (2.44–10.7)	0.01	2.9 (1.19–7.27)	0.02
APACHE	30 (27–33)	25 (22–28)	1.2 (1.16–1.38)	0.01	1.2 (1.09–1.3)	0.01
TISS	27 (24–30)	24 (22–26)	1.2 (1.14–1.37)	0.01	1.2 (1.12–1.47)	0.01
Age	74 (53–86)	52 (31–68)	1.04 (1.02–1.06)	0.01	1.03 (1.01–1.06)	0.02
Males	20 (66.7%)	95 (67.9%)	1.5 (0.7–3.39)	0.27	3.7 (1.5–9.01)	0.01
Vasopressor use	27 (90%)	67 (47.8%)	6.4 (1.9–21.2)	0.01	3.2 (0.9–11.3)	0.07
Diagnosis on admission:						
Pneumonia	7 (23.3%)	70 (50%)		0.39		
Peritonitis	15 (50%)	53 (37.8%)	2.47 (1.0–6.08)	0.04		
Bacteremia	6 (20%)	23 (16%)	1.3 (0.41–4.13)	0.65		
Wound infection	1 (3.3%)	7 (5%)	1.09 (0.13–8.9)	0.93		
Meningitis	1 (3.3%)	8 (5.7%)	1.11 (0.13–9.1)	0.9		

[a]Group 1 – early hypophosphatemia; group 2 — early hypophosphatemia and thrombocytopenia; and group 3 — early thrombocytopenia

excretion of phosphate is increased by metabolic acidosis and by many drugs [11–14]. The clinical symptoms of hypophosphatemia involve the respiratory (respiratory muscle weakness leads to failure to wean patients from mechanical ventilation), cardiovascular (reversible myocardial dysfunction), neurologic (central and peripheral neuropathies) and hematologic (anaemia, reduced white cells and platelet function) systems [4, 11–14]. Hypophosphatemia may develop within different stages of sepsis [6, 8]. Several previously published papers have reported that severe hypophosphatemia is a strong predictor of increased mortality in sepsis [2, 15]. However, in a recent large retrospective observational study by Suzuki *et al.* [7] hypophosphatemia was not found to be an independent risk factor for ICU and hospital mortality, but most likely a general marker of illness severity.

Similarly to hypophosphatemia, thrombocytopenia was demonstrated as one of the most common laboratory findings in ICU patients, especially in sepsis [10, 16]. The major mechanisms responsible for thrombocytopenia in ICU patients are multifactorial and may include increased immune or non-immune platelet destruction or decreased production, hemodilution and platelet sequestration [16]. Thrombocytopenia in critically ill septic patients, especially in those with septic shock, leads to a higher incidence of bleeding, DIC and greater transfusion requirements [17]. In contrast to hypophosphatemia, thrombocytopenia was found to be a strong risk factor for high mortality rates in the ICU, also among septic patients [10, 18]. Thrombocytopenia was found to be more common on admission to the ICU (during first 4 days); however, the mortality rate was greater in the thrombocytopenic patients after two weeks of ICU stay [18].

In our study, we analyzed the clinical outcomes of critically ill patients with severe sepsis who presented with hypophosphatemia and/or thrombocytopenia on admission to the ICU.

In the present paper, the overall ICU mortality rate in study group 1, 2 and 3 was 9.3%, 25.9% and 22% respectively. After a multivariate analysis of survival and risk factors of ICU mortality in critically ill septic patients with early hypophosphatemia and thrombocytopenia , mortality was found to be even higher in group 3 (Table 4). Our findings support previously published data [9,19] regarding the ICU

mortality rate of septic patients with hypophosphatemia (30–40% and even up to 80 % in severe hypophosphatemia) and thrombocytopenia (up to 30%). Despite significant laboratory degree of thrombocytopenia (especially in group 2), none of patients developed clinical features or was treated by urgent platelets transfusions. In our study, the highest ICU mortality rate was demonstrated in severe septic patients with both hypophosphatemia and thrombocytopenia on admission to the ICU (group 2). In contrast to previously published studies, neither hypophosphatemia, nor thrombocytopenia in the early stage of sepsis, were found to be a risk factor for ICU mortality in our study (Table 4). TPN and vasopressors administration, age > 50 years, male gender, APACHE II > 27 and TISS > 25 in critically ill severely septic patients with both hypophosphatemia and thrombocytopenia in the early stages were in fact independent risk factors for ICU and in-hospital mortality. These findings correlate well with previous data about higher APACHE II, TISS scores and older age as well-known, independent risk factors for ICU mortality [7]. TPN in itself was not demonstrated as an independent risk factor for ICU mortality in septic, critically ill patients. However, glucose variability (GV) was found to be associated with increased mortality in critically ill patients treated with TPN [20].

Vasopressors usage in critically ill septic patients is usually a marker of hemodynamic instability that reflects severity of the illness, progressing to multiple organ failure [1].

Our study has a number of limitations. The main limitation is its retrospective design and small number of patients. The study was performed in single General ICU on a septic population only while the other ICU population (cardiac, neuro, trauma) patients were not presented. Since our study is retrospective, the influence of directed, active control of hypophosphatemia and thrombocytopenia could not be estimated or taken into account. The significance of our results on long-term outcomes is unclear because the study did not incorporate a follow-up of the study patients after hospital discharge.

CONCLUSIONS

Hypophosphatemia and thrombocytopenia are common clinical features in the early stage of severe sepsis. Based on the present findings, we may consider that both of them, even when severe and coexisting, reflect the degree of initial illness severity of sepsis rather than provide independent prognostic factors and had any predictive value of patients' clinical outcome. We believe that a future prospective, multicenter study should be carried out to better analyze the potential clinical role of hypophosphatemia and thrombocytopenia in septic the critically ill population.

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