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Serum Phosphate Level in Patients with Septic Shock

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ABSTRACT

Objective: To determine the association and impact of serum phosphate on outcomes and ICU-mortality in patients with sepsis and septic shock.

Study Design: Prospective analytical study.

Place and Duration of Study: Department of Medicine and Intensive Care, Pak-Emirates Military Hospital Rawalpindi, Pakistan, from Jan to Jun 2023.

Methodology: Patients of either gender aged 18 to 70 years admitted with sepsis or septic shock in medical HDU and ICU were included. Sequential Organ Failure Assessment (SOFA) score, Acute Physiology, Age and Chronic Health Evaluation (APACHE-II) score and serum phosphate levels were noted within first 24 hours of admission. Impact of serum phosphate on disease severity and association with in-hospital mortality was analyzed with Odds ratio.

Results: Three hundred patients of sepsis or septic shock were admitted with mean age 46.93±13.57 years, including 170(56.7%) males and 130(43.3%) females. Respiratory system was main focus of infection in 110(36.7%) patients, followed by gastrointestinal system in 73(24.3%). Eighty (26.7%) patients expired among which 42(41.2%) had raised serum phosphate levels, 27(31.1%) had low phosphate and 11(9.9%) had normal phosphate levels (p<0.005). Odds ratio for in-hospital mortality showed higher phosphate levels within 24 hours of admission was associated with higher in-hospital mortality OR; 1.55 [95% CI 0.852-2.838], p=0.149.

Conclusion: Hyperphosphatemia is a predictor of disease severity and linked with higher odds of in-hospital mortality in comparison to normal or low phosphate levels.

Keywords: Acute Physiology, Age and Chronic Health Evaluation (APACHE-II), Hyperphosphatemia, Infection, Phosphate levels, Septic Shock, Sepsis, Sequential Organ Failure Assessment (SOFA).

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INTRODUCTION

Sepsis is a host response to an infective stimulus. leading to severe organ damage. Septic shock is a sequelae and complication of sepsis associated with marked metabolic derangements leading to significant circulatory compromise.[1,2] According to recent data, there are around 49 million documented cases of sepsis and 11.9 million sepsis-related deaths which is around 19.8% of all deaths globally.[3] Sepsis and septic shock has been declared a health priority by World Health Organization (WHO) due to an incidence of 20-35% worldwide of sepsis-related deaths which increases with advancing age, reaching up to 45% of overall mortality.[4,5] Sepsis is related to marked metabolic abnormalities, which can act as markers of sepsis severity.[6]

Changes in serum phosphate level are also an important metabolic abnormality in critically ill septic patients.[7] In sepsis, phosphate derangement occurs which also impacts disease severity as well as recovery and mortality. Normal phosphate levels of 2.5 - 4.5 mg/dL are mandatory for normal cellular functioning. Both hypo (< 2.5 mg/dL) and hyperphosphatemia (> 4.5 mg/dL) has been observed in sepsis and septic shock leading to increased severity and mortality.[8] Hypophosphatemia is considered as an early indicator of infection and also associated with morbidity in critically ill patients. It is usually observed in sepsis, metabolic alkalosis, ketoacidosis, re-feeding syndromes, trauma and post-surgical patients.[9] On the other hand, hyperphosphatemia is highly associated with disease severity and increased mortality in critically ill patients. It also leads to worsening heart failure and increased all-cause mortality.[10]

There are limited local studies related to serum phosphate effect on outcome in sepsis patients. Therefore, the purpose of this study was to ascertain the association of serum phosphate in patients of sepsis and septic shock with disease severity and in-hospital mortality.

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METHODOLOGY

This prospective analytical study was carried out in the Department of Medicine, PEMH Rawalpindi from Jan 2023 to Jul 2023 over a period of 6 months following approval from Institutional Ethical Committee (IEC: ER/524/23).

Inclusion Criteria: Patients of either gender with age 18 to 70 years, admitted in medical HDU or ICU with clinical and laboratory evidence of sepsis or septic shock were included.

Exclusion Criteria: Pregnant women, patients undergoing neurosurgical procedure, acute myocardial infarction (MI), pre-existing chronic kidney disease (CKD), parathyroid disease, patients on vitamin-D supplements, terminal illness, those with a malignancy and on chemotherapy were excluded.

Sample size was 246 calculated using online WHO sample size calculator taking reported 19.8 million incident cases of sepsis.[3] Three hundred patients admitted in Medical High Dependency Unit (HDU) and Intensive Care Unit (ICU) at our setup, with sepsis or septic shock, were enrolled in the study after informed consent, using non-probability consecutive sampling.

All patients admitted to medical HDU and ICU meeting the criteria of Sepsis-3 (The Third International Consensus Definitions for Sepsis and Septic Shock) were enrolled to determine association of serum phosphate levels with disease severity and mortality.[11] For clinical operationalization, sepsis was considered as organ dysfunction secondary to infection with SOFA (Sequential Organ Failure Assessment) score of 2 or more, and septic shock as patients with sepsis having circulatory collapse needing vasopressor support to maintain mean arterial pressure (MAP) of 65mmHg or more, and serum lactate levels > 18 mg/dL in the absence of hypovolemia.12 Serum phosphate levels were checked in all patients within 24 hours of admission to correlate with disease severity. Severity of disease was determined by using SOFA score, and Acute Physiology, Age and Chronic Health Evaluation (APACHE-II) score within 24 hours of admission. Also, in-hospital mortality was assessed and correlated with serum phosphate levels.

For assessment and analysis purpose, serum phosphate levels were labeled as normophosphatemia (2.5-4.5 mg/dL), hypophosphatemia (< 2.5 mg/dL), and hyperphosphatemia (>4.5 mg/dL). Phosphate levels were correlated with disease severity, complications, recovery and in-hospital mortality. Variables like patient`s age, gender, disease severity, SOFA and APACHE-II score, recovery time and mortality were noted in all patients for analysis.

Categorical data were presented as number and percentage whereas continuous variables as Mean±SD. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 23. Odds ratio was calculated for phosphate levels and sepsis severity correlation. The statistical significance between categorical variables was calculated using Chi-square test and a *p*-value of ≤ 0.05 was taken as statistically significant.

RESULTS

A total of three hundred (n=300) patients with sepsis or septic shock were admitted and included in study, with a mean age 46.93±13.57 years. One hundred and seventy (56.7%) were male and 130 (43.3%) were female. Respiratory system was main focus of infection in most of the patients (n=110, 36.7%), followed by gastrointestinal (GIT) in 73(24.3%), genitourinary (GUT) in 32(10.7%), neurological in 44(14.7%), and hematological in 31(10.3%) patients. For purpose of analysis patients were divided in three groups on basis of serum phosphate levels as Normophosphatemia (2.5-4.5 mg/dL) which was observed in 111(37.0%) patients, Hypophosphatemia (< 2.5 mg/dL), seen in 87 (29.0%) and Hyperphosphatemia (> 4.5 mg/dL), which was observed in 102 (34.0%) patients. Increased levels of serum lactate (> 18.5 mg/dL) were seen in 96 (32.0%) patients of shock and 114(38.0%) patients required vasopressor support to maintain MAPs > 65mmHg. Out of total 300 sepsis patients 73(24.3%) patients were ventilated within 24 hours of admission and mean ICU stay was noted to be 7.29±2.40 days. (Table-I).

It was observed in this study that hyperphosphatemia was associated with higher SOFA score, with 10 to 24 (mortality 40-90%) was observed in 52 (51.0%) patients with hyperphosphatemia and 11 (12.7%) patients with hypophosphatemia (p<0.05). The APACHE-II score of > 24 (associated with 40-90% mortality) was observed in 46(45.1%) patients with hyperphosphatemia and 12(13.8%) patients with hypophosphatemia (p<0.05). Also, increased levels of serum lactate were seen in 6(62.8%) patients with hyperphosphatemia, as compared to hypo-phosphatemia (n=21, 24.1%) patients or normal phosphate levels (n=11, 9.9%) patients (p<0.05). Similarly, the need of vasopressor to maintain MAP >

65mmHg was higher in patients with hyperphosphatemia 66 (64.7%) (p<0.05). It was also observed that patients with hyperphosphatemia had higher incidence of in-hospital mortality owing to severe disease in comparison to normal or low levels of serum phosphate. A total of 80(26.7%) patients expired secondary to sepsis, among which 42(41.2%) had raised serum phosphate levels, 27(31.1%) had low phosphate and 11(9.9%) had normal phosphate levels (p<0.005).

Table-I: Basic Parameters of Study Participants (n=300)

Basic Parameters		values
Age (mean years ± SD)		46.93 ± 13.57
Gender	Male	170 (56.7%)
	Female	130 (43.3%)
Infection source	Respiratory	110 (36.7%)
	Gastrointestinal	73 (24.3%)
	Genitourinary	32 (10.7%)
	Neurological	44 (14.7%)
	Hematological	31 (10.3%)
	Miscellaneous	10 (3.3%)
SOFA score (0-24)	2-9	236 (78.7%)
	11-24	64 (21.3%)
APACHE-II score (0-71)	0-24	241 (80.3%)
	25-71	59 (19.7%)
Phosphate Levels	Normal (2.5-4.5 mg/dL)	111 (37.0%)
	Hypophosphatemia (< 2.5 mg/dL)	87 (29.0%)
	Hyperphosphatemia (> 4.5 mg/dL)	102 (34.0%)
Lactate	Normal (4.5-18.5 mg/dL)	204 (68.0%)
	Raised (> 18.5 mg/dL)	96 (32.0%)
Vasopressor	Yes	114 (38.0%)
	No	186 (62.0%)
Ventilated	Yes	73 (24.3%)
	No	227 (75.7%)
ICU stay in days	Mean ± SD	7.29 ± 2.40
	< 6 days	129 (43.0%)
	> 6 days	171 (57.0%)
Outcome	Recovered	220 (73.3%)
	Expired	80 (26.7%)

**SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology, Age and Chronic Health Evaluation, ICU: intensive Care Unit*

Odds ratio was calculated for mortality secondary to serum phosphate levels and it showed that odds of higher mortality were observed in raised phosphate levels checked within 24 hours of admission OR; 1.55 [95% CI 0.852-2.838], p=0.149. (Table-II).

DISCUSSION

Phosphate is an important electrolyte of human body and vital component of cell membrane involved in vital physiological functions including energy metabolism, oxygen supply, signal transduction, membrane transport, bone mineralization and urinary buffer system.[13] SOFA scores and APACHE-II scores at first day of admission indicates the severity of disease and risk of mortality as a SOFA score > 10 and an APACHE-II score > 24 is associated with higher in-hospital mortality of 40-95%. This study showed that patients with higher SOFA scores (>10) and APACHE-II score (>24) on 1st day of admission were at increased risk of severe disease and mortality. Bauer *et al*. reported in a cohort study that in critically ill patients with sepsis, 1-point increase in average SOFA score in the background of hyperphosphatemia, is associated with 1.3-3.3% increased mortality.[14] In source of infection, respiratory system was most common focus of infection leading to sepsis and septic shock in 110(36.7%) patients followed by gastrointestinal system in 73(24.3%) as seen in Figure-1). Prest *et al*. reported in his study that highest age-adjusted mortality rate per 1,000,000 persons in respect to source of infection was 111.8 for respiratory system infections followed by 46.7 for GIT infection and 52 for GUT sepsis.[15]

Table-II: Odds Ratio of Mortality Associated with Phosphate Levels (n=189)

		Serum Phosphate		Total
		Hyperphosphatemia n=102 n (%)	Hypophosphatemia n=87 n (%)	
In-Hospital Mortality	Yes	42 (41.2%)	27 (31.1%)	69
	No	60 (58.8%)	60 (68.9%)	120

Odds of Death in Hyperphosphatemia = (42/60) = 0.70
Odds of Death in Hypophosphatemia = (27/60) = 0.45
Odds Ratio (OR) = Odds in Hyperphosphatemia / Odds in Hypophosphatemia
OR = 0.70/0.45 = 1.55 [95% CI 0.852-2.838], p=0.149

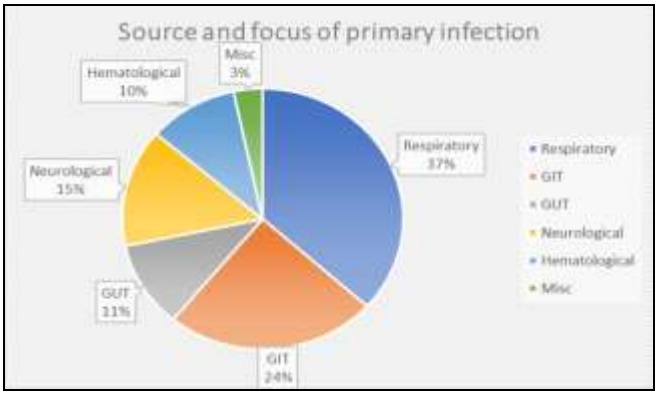

Figure-1: Focus of Infection Leading to Sepsis in Patients (n=300) *GIT: Gastrointestinal Tract, GUT: Genitourinary Tract, Misc. Miscellaneous

Al-Harbi *et al*. concluded in a cohort study that critically ill patients with hyperphosphatemia had high ICU mortality with adjusted Odds ratio (aOR

1.68, 95% CI 1.61-2.42, p=0.007) in comparison to normophosphatemia.[16] Similarly, in a retrospective cohort study by Black *et al*. it was reported that septic patients in ICU with highest quartile phosphate levels had higher mortality as compared to other quartile phosphate with 2.4 times higher odds of deaths.[17] In our study it was also seen that patients with higher serum phosphate levels (> 4.5 mg/dL) had higher in-hospital mortality 42(52.5%) out of total 80 expired patients secondary to severe sepsis and septic shock (Figure-2). Miller *et al*. documented that time-weighted hyperphosphatemia in critically ill patients had higher incidence of Simplified Acute Physiology Score (SAPS) III score and septic shock with significantly higher 28-day mortality with serum phosphate levels >3.5 mg/dL.[18]

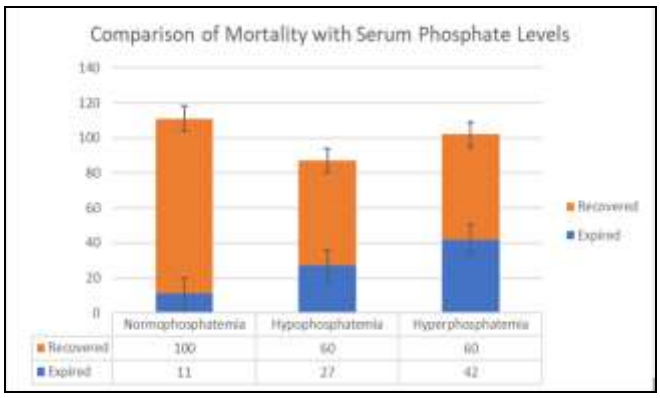

Figure-2: Comparison of Mortality with Serum Phosphate Levels

Li *et al*. reported that serum inorganic phosphate was an independent factor and predictor of in-hospital mortality with relative risk RR 1.11, [95%CI 1.08-1.23, p<0.01] regardless of age, gender, focus of infection, renal function, and vasopressor use.[19] Also he concluded that 1mg/dl rise in serum phosphate level was associated with 11% increase in-hospital mortality.[19] Xu *et al*. reported that serum phosphate levels during first 2 days of admission in ICU linked hyperphosphatemia with higher 28-day mortality as compared to hypophosphatemia group, noted as first day 32.9% vs 16.3% and second day 36.3% vs 14.7% mortality respectively.[20] Jung *et al*. explained by multivariate Cox model that hyperphosphatemia in sepsis secondary to kidney disease was significantly associated with higher 28-day mortality and 90 day mortality with HR 1.05, [95%CI 1.02-1.08], p=0.001.21 It was observed in our study that hyperphosphatemia is linked with higher mortality and higher odds of death with OR 1.55 [95% CI 0.852-2.838], p=0.149. Similarly, Cheungpesitporn et al. documented that serum phosphate levels was a prominent predictor of in-hospital mortality with Odds ratio of 1.60 [95% CI 1.25-2.05], 1.60 [95% CI 1.29-1.97] and 3.89 [95% CI 3.20-4.74] with serum phosphate levels of < 2.5, 3.5-4.8 and > 4.9 mg/dL respectively.[22]

LIMITATIONS OF STUDY

Our study has certain limitations, the most important being the limited sample size and single center study. This study ruled out the effect of kidney and parathyroid disease which could be confounding factors in determining serum phosphate levels in patients with sepsis. Also, only serum phosphate levels of within first 24 hours of admission were noted and we did not study the effect and trend of serum phosphate levels during complete ICU stay in association with prognosis. Study was done at single center, and only medical causes of sepsis was included admitted in medical HDU and ICU.

CONCLUSION

Hyperphosphatemia within 24 hours of admission was an independent factor of disease severity and strong predictor of higher incidence and odds of mortality as compared to normal or low phosphate levels. Hypophosphatemia was also observed in the background of sepsis but association with severity of disease and mortality was not significantly observed.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AF & BAB: Data acquisition, data analysis, critical review, approval of the final version to be published.

SWHN & AM & ASD: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AA & AZ & MI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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