Original Research Article

Hyperphosphatemia-a predictor of poor prognosis among patients with sepsis or septic shock

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ABSTRACT

Background: Sepsis is a life-threatening organ dysfunction resulting from dysregulated host responses to infection. Serum phosphorus level was closely related to the occurrence and prognosis of kidney disease and cardiovascular disease. It is of vital importance to re-evaluate the association between serum Phosphorus level and mortality in patients with sepsis and different septic subgroups. This study aims to examine the association of serum phosphorous levels with clinical outcomes among patients with sepsis.

Methods: This study included 100 cases and was conducted at KIMS hospital Bangalore. Patients were included in the study as per inclusion criteria. SOFA scoring and APACHE-II scoring was done on first day of admission and serum phosphorus levels were sent. Patients were categorised according to phosphorous levels normal range (2.5-4.5mg/dl). Patients were followed up till primary and secondary outcome.

Results: Of the 100 patients in this study 53 patients had normophosphatemia, 17 patients had hypophosphatemia, 30 patients had hyperphosphatemia. Comparison of mean APACHE-II scores, mean length of ICU stay (in days), mean length of hospital stay (in days), serum creatinine levels, between 3 groups was statistically significant.

Conclusions: Hyperphosphatemia on first ICU admission day indicates poor clinical outcome among patients with sepsis or septic shock. Therefore, when patients are on ICU admission and under treatment, clinicians should pay more attention to the change of serum phosphate.

Keywords: Hypophosphatemia, Hyperphosphatemia, Mortality, Serum phosphate

INTRODUCTION

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a serious health care issue recognized worldwide.[1]

In 2016, the third international consensus definition for sepsis and septic shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction resulting from dysregulated host responses to infection, which offers greater consistency for epidemiologic studies and clinical trials.[2]

Despite advances in the monitoring and treatment of critically ill patients, sepsis remains the leading cause of hospitalization and death in the intensive care unit (ICU).[3] In the early stages of sepsis, systemic and complex inflammation and anti-inflammatory reactions are vital in the pathophysiological process, and it is closely related to the increased risk of death.[4] It is crucial to identify high-risk patients with poor prognosis in the early stages of sepsis and provide timely and adequate interventions. A lot of efforts have been made in studying sensitive biomarkers. However, identifying these high-risk patients is still challenging.[5]

Phosphate participates in many physiological processes in the human body and is regulated by multiple organs, including the kidneys, bones, and digestive system.[6] However, phosphate metabolism in the body usually cannot be accurately regulated in the course of acute diseases. Therefore, abnormalities in serum phosphorus levels are fairly common in critically ill patients.

Various studies have shown that the serum phosphorus level was closely related to the occurrence and prognosis of kidney disease and cardiovascular disease; however, studies on the relationship between phosphorus level and sepsis are few.[7]

For instance, in Shor et al study, severe hypophosphatemia in sepsis increased the risk of death by nearly 8-fold.[8] In contrast, in Miller et al study, they concluded that patients with hyperphosphatemia had higher 28-day in-hospital mortality while those with hypophosphatemia did not.[9]

Moreover, the heterogeneity of disease severity and classification are great in intensive care units (ICUs). Thus, it is of vital importance to re-evaluate the association between serum phosphorus and mortality in patients with sepsis and different septic subgroups.

This study aims to examine the association of serum phosphorous levels with clinical outcomes among patients with sepsis.

METHODS

Study type

This was a prospective observational study conducted at KIMS hospital Bangalore.

Study period

The study was conducted from September 2021 to October 2022.

Selection criteria

Patients aged >18 years, diagnosed with sepsis and sequential organ failure assessment (SOFA) score ≥2 were included in the study. Patients aged <18 years of age, patients with chronic kidney disease on hemodialysis and patients who stay in ICU for less than 24 hours were excluded from the study.

Procedure

Patients were included in the study as per inclusion criteria. SOFA scoring and Acute Physiology and Chronic Health Evaluation (APACHE) II scoring were done on the first day of admission, and serum phosphorus levels were sent. Patients were categorized according to phosphorus levels in the normal range (2.5-4.5 mg/dl).

Patients were followed up until primary and secondary outcomes.

Data collection

The following data were extracted from the prospectively collected ICU database: age, gender, admission category (medical, surgical, and non-operative trauma or non-operative and post-operative), chronic comorbidities (chronic liver disease, chronic cardiovascular disease, chronic respiratory disease, chronic renal disease, and chronic immunosuppression) as defined by the APACHE system, history of diabetes mellitus, presence of sepsis or septic shock on admission, presence of acute kidney injury, need for mechanical ventilation, and vasopressor use.

Ethical approval

The study protocol was approved by the institutional ethics committee.

Statistical analysis

Statistical analysis was performed using IBM-SPSS ver 26. Descriptive statistics were used to summarize patient characteristics. Categorical variables were presented as frequencies and percentages, and continuous variables were presented as mean ± standard deviation or median (interquartile range). The chi-square test or Fisher's exact test was used to compare categorical variables, and the t-test or Mann-Whitney U test was used to compare continuous variables between groups. Logistic regression analysis was used to identify factors associated with the primary and secondary outcomes. A $p<0.05$ was considered statistically significant.

RESULTS

Of the 100 patients in this study 53 patients had normophosphatemia, 17 patients had hypophosphatemia, 30 patients had hyperphosphatemia.
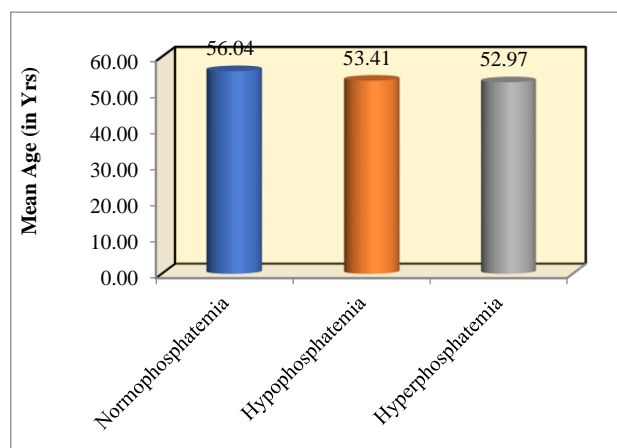

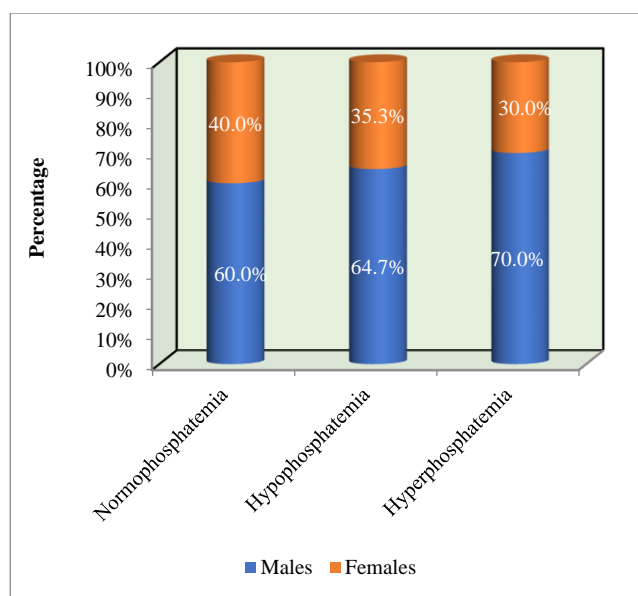**Figure 1: Age wise distribution of study subjects.**

Figure 2: Gender wise distribution of study subjects.

Mean age of the patients in normophosphatemia group was 56.04±15.06, in hypophosphatemia group 53.41±14.46 and in hyperphosphatemia group was 52.97±13.38 (Figure 1). majority of patients were males in all the groups 33 (60%) males in normophosphatemia group, 11 (64.7%) in hypophosphatemia group, and 21 (70%) in hyperphosphatemia group (Figure 2).
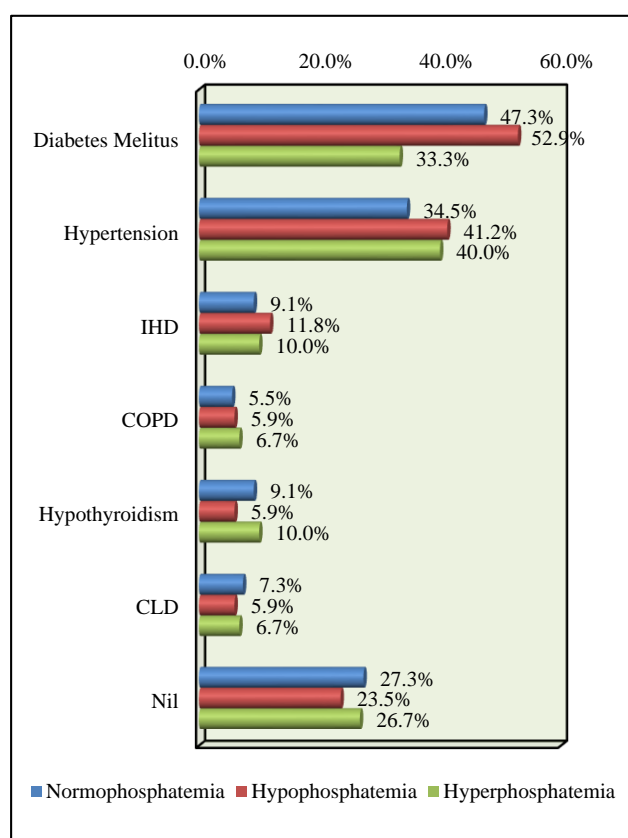

Figure 3: Presence of different comorbidity between 3 groups.

Comparison of different comorbidities in all the three groups was done using Chi square test, majority of patients had diabetes mellitus in in all the groups, followed by hypertension and other comorbidities (Figure 3).

Comparison of mean APACHE-II scores between 3 groups was done using Kruskal Wallis test followed by Dunn's post hoc test, mean value in normophosphatemia group was 17.85±4.37, hypophosphatemia group 19.00±5.01 and in hyperphosphatemia group was 22.23±5.42. P value was statistically significant between all the groups, and in hypophosphatemia and hyperphosphatemia group (Table 1).

Comparison of mean length of ICU stay (in days) between 3 groups was done using Kruskal Wallis test followed by Dunn's post hoc test, mean value in normophosphatemia group 2.87±0.92 hypophosphatemia group 2.65±0.79 and in hyperphosphatemia group was 3.90±1.06. P value statistically significant between all groups, and in hypophosphatemia and hyperphosphatemia group (Table 2).

Comparison of mean length of hospital stay (days) between 3 groups done using Kruskal Wallis test followed by Dunn's post hoc test, mean value in normo-phosphatemia group 6.25±2.18, hypophosphatemia group 7.00±2.67 and in hyperphosphatemia group 7.87±3.57. P value statistically significant between all groups, and in hypo and hyperphosphatemia group (Table 3).

Comparison of mean serum creatinine levels between 3 groups was done using Kruskal Wallis test followed by Dunn's post hoc test, mean value in normo-phosphatemia group 1.54±0.99, hypophosphatemia group 1.23±0.38 and in hyperphosphatemia group was 2.11±1.30. P value statistically significant between all groups, and in hypo and hyperphosphatemia group (Table 3).
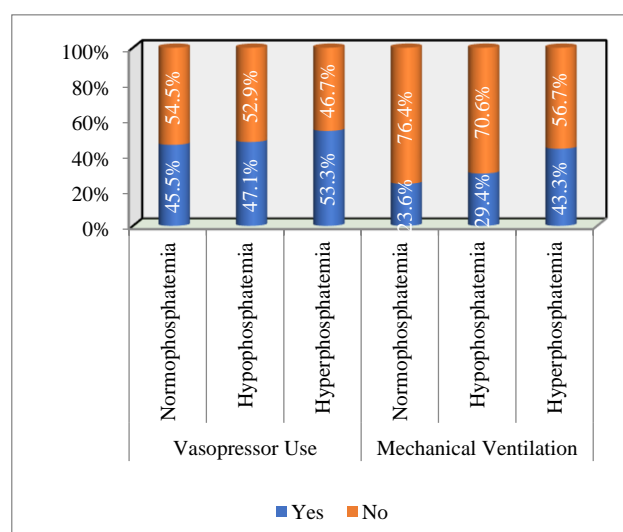

Figure 4: Use of vasopressure and mechanical ventilation between 3 groups.
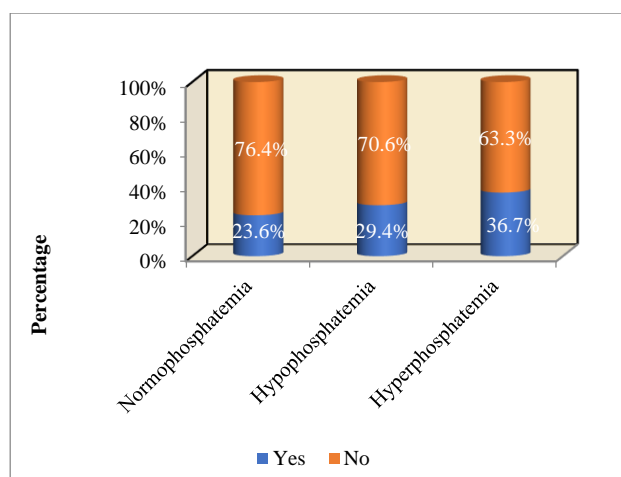
Figure 5: In-hospital mortality rate between 3 groups.

Vasopressor use done in 25 (45.5%) in normo-phosphatemia group, in 8 (47.1%) in hypophosphatemia group and 16 (53.3%) in hype-rphosphatemia group. Mechanical ventilation done in 13 (23.6%) in normo-phosphatemia group, 5 (29.4%) in hypo-phosphatemia group and 13 (43.3%) in hyperphosphatemia group (Figure 4).

Out of hundred patients twenty-eight succumbed to death in hospital, eleven (36.7%) from hyperphosphatemic group, thirteen (23.6%) from normophosphatemia group, four (29.4%) from hypophosphatemic group (Figure 5).

The patients in hyperphosphatemic group had higher APACHE-2, higher in hospital mortality, increased use of vasopressors and mechanical ventilation, longer intensive care unit stay and overall hospital stay.

Table 1: Comparison of mean APACHE-II scores between 3 groups using Kruskal Wallis test followed by Dunn's post hoc test.

Groups	N	Mean	SD	Min	Max	P value	Sig. diff	P value
Normophosphatemia	55	17.85	4.37	10	31		N vs H1	0.56
Hypophosphatemia	17	19.00	5.01	13	31	0.001	N vs H2	0.001
Hyperphosphatemia	30	22.23	5.42	13	35		H1 vs H2	0.03

Table 2: Comparison of mean length of ICU stay (days) between 3 groups using Kruskal Wallis test followed by Dunn's post hoc test.

Groups	N	Mean	SD	Min	Max	P value	Sig. diff	P value
Normophosphatemia	55	2.87	0.92	2	5		N vs H1	0.44
Hypophosphatemia	17	2.65	0.79	2	4	<0.001	N vs H2	<0.001
Hyperphosphatemia	30	3.90	1.06	2	6		H1 vs H2	<0.001

Table 3: Comparison of mean length of hospital stay (days) between 3 groups using Kruskal Wallis Test followed by Dunn's post hoc test.

Groups	N	Mean	SD	Min	Max	P value	Sig. diff	P value
Normophosphatemia	55	6.25	2.18	2	11		N vs H1	0.21
Hypophosphatemia	17	7.00	2.67	2	10	0.02	N vs H2	0.03
Hyperphosphatemia	30	7.87	3.57	2	14		H1 vs H2	0.35

Table 4: Comparison of mean serum creatinine levels between 3 groups using Kruskal Wallis test followed by Dunn's post hoc test.

Groups	N	Mean	SD	Min	Max	P value	Sig. diff	P value
Normophosphatemia	55	1.54	0.99	0.6	5.4		N vs H1	0.46
Hypophosphatemia	17	1.23	0.38	0.7	2.1	0.01	N vs H2	0.03
Hyperphosphatemia	30	2.11	1.30	1.0	5.6		H1 vs H2	0.03

DISCUSSION

In our study out of 100 patients 53 patients had normophosphatemia, 17 patients had hypophosphatemia, 30 patients had hyperphosphatemia.

In the study by Liu et al (19.6%) hypophosphatemia and 2158 cases (11.2%) hyperphosphatemia, 811 (17%) cases in the study by Wang et al were classified as hypophosphatemia, 188 (13%) cases in the study by Shmeylan et al were classified as hypophosphatemia.[10-12]

Several studies have shown an association between hypophosphatemia and increased mortality.[13,14] It has also been suggested that hypophosphatemia only reflects the severity of the disease and does not increase mortality.[15]

Two recent studies have both concluded that hyperphosphatemia is an independent risk factor for death, not hypophosphatemia. Wang et al studied the initial values of serum phosphate in 4767 septic patients after admission to the ICU, which showed that hyperphosphatemia was significantly associated with in

hospital mortality, the association between hypophosphatemia and in-hospital mortality was not significant.[11] Shmeylan et al studied the initial value of serum phosphate in 1422 septic patients after admission to ICU.[12] The results showed that hyperphosphatemia was significantly associated with hospital mortality. There was no significant correlation between hypophosphatemia (<2.5 mg/dl) as well as hospital mortality.

In our study the patients in hyperphosphatemic group had higher APACHE-II score, higher in hospital mortality, increased use of vasopressors and mechanical ventilation, longer ICU stay, and overall hospital stay.

Haider and her (his) colleagues conducted a cross-sectional study and found that hyperphosphatemia was usual in patients in the emergency room and associated with patient mortality.[16] Two studies conducted by Miller and Harbi reported that hyperphosphatemia was also associated with increased mortality in patients with mechanical ventilation or sepsis.[12]

Whether higher Pi was a direct cause of increased mortality, or a marker of disease severity is still unclear. More research studying the potential mechanisms and assessing the potential benefits of lowering serum Pi are needed.

The limitations of our study include that data were collected in a single tertiary medical centre which may limit the generalization of our findings. Hyperphosphatemia might be a marker of higher severity of illness and thus the association with higher mortality.

CONCLUSION

Hyperphosphatemia on first ICU admission day indicates poor clinical outcome among patients with sepsis or septic shock. Both hypophosphatemia and hyperphosphatemia are present in some proportion in sepsis. Therefore, when patients are on ICU admission and under treatment, clinicians should pay more attention to the change of serum phosphate in critically ill elderly

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