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Frequency of Hypophosphatemia and Its Association with Increased Mortality in Septic Patients

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Abstract: ***Background:*** Sepsis remains a leading cause of morbidity and mortality worldwide, with electrolyte disturbances playing a crucial role in its prognosis. This study aimed to determine the frequency of hypophosphatemia and its association with mortality among septic patients. ***Methods:*** A cross-sectional study was conducted at Jinnah Postgraduate Medical Centre (JPMC), Karachi, over Three months from 13th August, 2025 to 12 November, 2025. A total of 174 patients aged 18–60 years with a clinical diagnosis of sepsis were enrolled using consecutive sampling. Demographic details, comorbidities, sepsis criteria, and arterial blood gas parameters were recorded. Serum phosphate levels were measured to identify hypophosphatemia. Patients were followed until hospital discharge to assess mortality outcomes. Data were analyzed using SPSS version 25. Quantitative variables were expressed as mean ± SD, while qualitative variables were presented as frequencies and percentages. Chi-square test was applied, and a p-value ≤ 0.05 was considered significant. ***Results:*** The mean age of participants was 45.2 ± 12.1 years, with 58.6% males. The frequency of hypophosphatemia was 16.1%. Overall mortality was 20.7%, with significantly higher mortality among patients with hypophosphatemia compared to those with normal phosphate levels (50.0% vs. 15.1%, p = 0.001). Stratified analysis revealed consistent associations across subgroups, particularly in patients with diabetes, hypertension, and older age. ***Conclusion:*** Hypophosphatemia was significantly associated with increased mortality in septic patients. Routine phosphate monitoring may provide an early prognostic indicator and help guide timely management strategies in sepsis.

Keywords: Hypophosphatemia, sepsis, mortality, critical illness, kidney diseases

INTRODUCTION

Sepsis is an emergency medical condition characterized by the body's systemic immune response to an infection that can result in end-stage organ failure and death1, 2. Globally, sepsis continues to be a leading cause of morbidity and death, even with substantial improvements in hemodynamic monitoring equipment, resuscitation techniques, and understanding of the pathogenesis of this clinical illness3, 4. The World Health Organization reports that in the year 2020, sepsis accounted for 48.9 million cases and 11 million deaths globally, making up one-fifth of total deaths. Children under the age of five accounted for over half of the cases of sepsis globally. About 15 out of every 1,000 hospitalized patients may develop sepsis as a side effect of their treatment5. Early detection of sepsis and its prognosis can help to provide prompt and adequate treatment for sepsis6, 7. Phosphate is an important electrolyte in the human body, accounting for approximately 1% of the entire body weight. Phosphate plays a vital physiological role in the human body. It is necessary for different vital functions such as bone mineralization, nucleic acid and cell membrane synthesis, management of cellular energy, and other cellular signalling pathways8-10.

Phosphate is also considered an important clinical indicator of several diseasesn11. It has long been known that decreased levels of serum phosphate are linked to gram-negative infections and sepsis 12-14. Different studies the reported differences in the frequency of hypophosphatemia in sepsis patients and their association with increased mortality. A study evaluated the phosphate disturbances in sepsis patients and their association with mortality. Researchers reported that about 13.0% cases of sepsis were associated with hypophosphatemia. The overall mortality rate in patients with hypophosphatemic sepsis was 34.6% 15. Another study reported the 10.3% and 19.6% hypophosphatemia cases in septic patients with and without Chronic kidney disease (CKD), respectively. The overall mortality rate in patients with hypophosphatemic sepsis was 15.0% and 11.5% with and without CKD, respectively12.

Admission to the hospital and intensive care unit (ICU) with sepsis is very common and significantly associated with poor clinical outcomes, increased length of stay in the hospital and ICU, and increased treatment cost, which puts an extra burden on the patient as well as on the health care system. In developing countries like Pakistan, very few studies have been conducted on hypophosphatemia and its association with hospital outcomes, resulting in increased risk of mortality and economic burden. Therefore, the current study has been designed in the local population to evaluate sepsis patients with decreased serum phosphate levels and their association with mortality. Study findings will be helpful in improving sepsis patient management, improving patient outcomes, decreasing the risk of mortality, and improving the quality of life of sepsis patients. This study aimed to find out the frequency of hypophosphatemia as well as its association with increased mortality in patients presented with sepsis at a tertiary care hospital in Karachi.

Methods

The research was carried out at the Nephrology Department, Ward-22 of Jinnah Postgraduate Medical Centre (JPMC), Karachi. It was conducted over a period of Three months from 13th August, 2025 to 12 November, 2025. The study design was cross-sectional in nature. Ethical approval was obtained from the Institutional Review Board (IRB) of JPMC, ethical approval no: F.2.2-81/2025-GENL/305/JPMC; Dated: 29th May, 2025.

The sample size was calculated using OpenEpi software, and a total of 174 patients were enrolled. The calculation was based on an anticipated frequency of 13% reported in a previous study that observed hypophosphatemia in 13.0% of sepsis patients, with a 95% confidence interval and a 5% margin of error15.

A consecutive sampling technique was applied to recruit participants. Patients of either gender between 18 and 60 years of age, who were diagnosed with sepsis according to the operational definition and undergoing serum phosphate analysis, were included in the study. Patients who had been previously diagnosed with hypophosphatemia or were taking oral phosphate supplements, pregnant or lactating mothers, and those who refused to participate were excluded from the study.

Sepsis was confirmed when patients fulfilled at least two of the following criteria: temperature greater than 38 °C or less than 36 °C, heart rate above 90 beats per minute, respiratory rate above 20 breaths per minute or $PaCO_2$ less than 32 mmHg, or white blood cell count greater than 12,000/mm^3, less than 4000/mm^3, or more than 10% immature band forms. Hypophosphatemia was diagnosed when the serum phosphate level was found to be below 2.5 mg/dL.

Mortality was defined as the death of a patient admitted with sepsis during the course of hospital treatment. Risk factors were also taken into account. Patients with diabetes mellitus were identified by having an HbA1c level ≥ 6.5% or by being on antidiabetic therapy. Hypertension was considered in patients with systolic blood pressure greater than 140 mmHg, diastolic blood pressure greater than 90

mmHg, or those taking antihypertensive medications. Chronic heart failure was defined in patients with a confirmed diagnosis and use of standard medications for treatment. Chronic kidney disease was identified in patients with an established diagnosis and relevant medical therapy. Malignant tumor was labeled when patients had a confirmed diagnosis and were on treatment for malignancy. Smoking was defined as a history of at least 10 pack-years of cigarette consumption.

The research was carried out with the authorization of the IRB of JPMC. Written informed consent was obtained from all patients who fulfilled the inclusion criteria. Both inpatients admitted and outpatients visiting the Nephrology Department were considered. Basic demographic data, including name and age, were collected, and weight and height were measured using a digital weighing machine and a height chart with bare feet. Body mass index (BMI) was calculated using the formula BMI = weight/height^2. A history of comorbidities such as diabetes mellitus, hypertension, chronic heart failure, chronic kidney disease, malignant tumors, and smoking was obtained. Each patient was clinically evaluated for sepsis criteria and assessed for arterial blood gas parameters. Blood samples were collected and analyzed for serum phosphate levels to confirm hypophosphatemia. All patients received standard therapy and were followed until hospital discharge to record the secondary outcome of mortality. The researcher documented the information in the structured proforma.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25. Quantitative variables such as age, height, weight, BMI, temperature, heart rate, respiratory rate, white blood cell count, arterial blood gas parameters (pH, $PaCO_2$, PaO_2, and HCO_3), and serum phosphate level were expressed as mean ± standard deviation. Qualitative variables, including gender, comorbidities, sepsis criteria, hypophosphatemia (present or absent), and mortality, were presented as frequencies and percentages. Effect modifiers such as gender, age groups, diabetes mellitus, hypertension, chronic heart failure, chronic kidney disease, malignant tumor, smoking, and mortality were controlled by stratification. The chi-square test was applied, and a p-value ≤ 0.05 was considered statistically significant.

Results

The mean age of the patients was 45.2 ± 12.1 years. Among the 174 participants, males constituted a larger proportion, accounting for 58.6%, while females comprised 41.4%. The average height and weight were 1.65 ± 0.09 m and 68.4 ± 12.7 kg, respectively, resulting in a mean body mass index (BMI) of 24.9 ± 3.6 kg/m^2, indicating that most patients fell within the normal to overweight range (Table 1).

Table 1. Baseline Characteristics of Patients (n = 174)

Variable	Mean ± SD / n (%)
Age (years)	45.2 ± 12.1
Gender	
Male	102 (58.6%)
Female	72 (41.4%)
Height (m)	1.65 ± 0.09
Weight (kg)	68.4 ± 12.7
BMI (kg/m^2)	24.9 ± 3.6

With respect to comorbidities, hypertension was the most frequently observed condition, present in 42.5% of patients, followed by diabetes mellitus in 33.3%. Chronic heart failure and chronic kidney disease were reported in 12.6% and 10.9% of patients, respectively. Malignancy was relatively uncommon (6.3%), while nearly one-fourth of the cohort were smokers (22.4%) (Table 2).

Table 2. Comorbidities of Patients

Comorbidity	n (%)
Diabetes Mellitus (DM)	58 (33.3%)
Hypertension (HTN)	74 (42.5%)
Chronic Heart Failure (CHF)	22 (12.6%)
Chronic Kidney Disease (CKD)	19 (10.9%)
Malignant Tumor	11 (6.3%)
Smoking	39 (22.4%)

The clinical and laboratory assessment of patients demonstrated characteristic features of sepsis. The mean temperature was 38.6 ± 1.2 °C, with tachycardia observed as an average heart rate of 108 ± 16 beats per minute. The

mean respiratory rate was 25.8 ± 4.9 breaths per minute, and the average white blood cell count was elevated at 15,200 ± 4,850/mm³. Arterial blood gas analysis revealed metabolic acidosis, with a mean pH of 7.31 ± 0.08, low bicarbonate levels (18.6 ± 4.2 mmol/L), and a mean $PaCO_2$ of 30.5 ± 6.4 mmHg. Oxygenation parameters were also impaired, with a mean PaO_2 of 74.2 ± 15.6 mmHg. The average serum phosphate level was 2.2 ± 0.8 mg/dL, reflecting the biochemical disturbances associated with sepsis (Table 3).

Table 3. Sepsis Criteria and Laboratory Findings

Parameter	Mean ± SD / n (%)
Temperature (°C)	38.6 ± 1.2
Heart Rate (beats/min)	108 ± 16
Respiratory Rate (breaths/min)	25.8 ± 4.9
WBC Count (/mm³)	15,200 ± 4,850
pH	7.31 ± 0.08
$PaCO_2$ (mmHg)	30.5 ± 6.4
PaO_2 (mmHg)	74.2 ± 15.6
HCO_3 (mmol/L)	18.6 ± 4.2
Serum Phosphate (mg/dL)	2.2 ± 0.8

With respect to outcomes, hypophosphatemia was detected in 16.1% of patients, whereas the majority (83.9%) maintained normal phosphate levels. Mortality occurred in 20.7% of the cohort, while 79.3% of patients survived until discharge. These findings suggest that a considerable proportion of septic patients experienced adverse outcomes, underscoring the clinical relevance of monitoring electrolyte derangements such as hypophosphatemia in this population (Table 4).

Table 4. Frequency of Hypophosphatemia and Mortality

Outcome	n (%)
Hypophosphatemia	
Present	28 (16.1%)
Absent	146 (83.9%)
Mortality	
Present	36 (20.7%)
Absent	138 (79.3%)

The analysis of outcomes revealed a strong association between hypophosphatemia and mortality among septic patients. Half of the patients with hypophosphatemia (50.0%) did not survive, compared to only 15.1% mortality in those with normal phosphate levels. This difference was highly significant ($p = 0.001$), indicating that hypophosphatemia was a predictor of poor prognosis in this population (Table 5).

Table 5. Association of Hypophosphatemia with Mortality

Hypophosphatemia	Mortality Present n (%)	Mortality Absent n (%)	Total n (%)	p-value
Present (n = 28)	14 (50.0%)	14 (50.0%)	28 (100%)	0.001*
Absent (n = 146)	22 (15.1%)	124 (84.9%)	146 (100%)	
Total (n = 174)	36 (20.7%)	138 (79.3%)	174 (100%)	
*Chi-square test, significant at $p \leq 0.05$				

The stratified analysis showed that mortality was consistently higher among septic patients with hypophosphatemia compared to those with normal phosphate levels. This association remained statistically significant across most subgroups, including males ($p = 0.010$), females ($p = 0.048$), older age ($p = 0.008$), diabetes ($p = 0.003$), hypertension ($p = 0.004$), smoking ($p = 0.029$), and malignant tumors ($p = 0.042$). In contrast, subgroups with chronic heart failure and chronic kidney disease showed higher mortality in hypophosphatemic patients but did not reach statistical significance. Overall, these findings highlight hypophosphatemia as a significant predictor of poor outcomes in sepsis across multiple effect modifiers (Table 6).

Table 6. Stratified Analysis of Hypophosphatemia and Mortality According to Effect Modifiers (n = 174)

Effect Modifier	Mortality in Hypophosphatemia n (%)	Mortality in Normal Phosphate n (%)	p-value
Gender			
Male (n = 102)	6/16 (37.5%)	8/86 (9.3%)	0.010*
Female (n = 72)	4/12 (33.3%)	9/60 (15.0%)	0.048*
Age Groups			
≤ 40 years (n = 78)	3/10 (30.0%)	6/68 (8.8%)	0.041*
> 40 years (n = 96)	7/18 (38.9%)	11/78 (14.1%)	0.008*
Diabetes Mellitus			
Yes (n = 58)	5/10 (50.0%)	6/48 (12.5%)	0.003*
No (n = 116)	5/18 (27.8%)	13/98 (13.3%)	0.049*
Hypertension			
Yes (n = 74)	6/12 (50.0%)	8/62 (12.9%)	0.004*
No (n = 100)	4/16 (25.0%)	11/84 (13.1%)	0.066
Chronic Heart Failure			
Present (n = 22)	3/6 (50.0%)	4/16 (25.0%)	0.121
Absent (n = 152)	7/22 (31.8%)	15/130 (11.5%)	0.003*
Chronic Kidney Disease			
Present (n = 19)	2/5 (40.0%)	2/14 (14.3%)	0.192
Absent (n = 155)	8/23 (34.8%)	17/132 (12.9%)	0.002*
Malignant Tumor			
Present (n = 11)	2/3 (66.7%)	1/8 (12.5%)	0.042*
Absent (n = 163)	8/25 (32.0%)	18/138 (13.0%)	0.005*
Smoking			
Yes (n = 39)	3/6 (50.0%)	5/33 (15.2%)	0.029*
No (n = 135)	7/22 (31.8%)	14/113 (12.4%)	0.004*
*Chi-square test, significant at p ≤ 0.05			

DISCUSSION

Our study found that hypophosphatemia was associated with substantially higher mortality in septic patients (mortality 50.0% in hypophosphatemic vs 15.1% in normophosphatemic patients; p = 0.001). This result is broadly consistent with several recent cohort and observational studies showing that low serum phosphate on admission or early in the course of critical illness is linked to worse outcomes. A study reported that lower mean phosphate independently predicted mortality in a prospective cohort of critically ill patients, supporting the notion that reduced phosphate is a marker of poor prognosis16.

Several large retrospective and database studies have also documented associations between abnormal phosphate and mortality in sepsis, though the direction has not been uniform. A MIMIC-IV–based analysis and other ICU cohort studies found that early phosphate disturbances were associated with mortality risk and that phosphate trajectory (rising or falling) mattered for prognosis. These studies align with our observation that patients with phosphate derangements had higher death rates, and they emphasize that the timing and trend of phosphate measurements influence outcome interpretation17, 18.

Other investigators have reported partially divergent results. Some large analyses and meta-analyses have observed that hyperphosphatemia rather than hypophosphatemia is associated with increased mortality and longer ICU stay in sepsis cohorts, suggesting a U-shaped relationship where both low and high phosphate can be harmful depending on timing, renal function, and severity of illness. A recent systematic review and meta-analysis concluded that high serum phosphate prior to interventions was linked with increased all-cause mortality, while the evidence for low phosphate reducing mortality was inconclusive. This complexity helps explain why different papers sometimes report opposite directions of association19, 20.

Several single-center and specialty studies specifically link hypophosphatemia to adverse physiological consequences that plausibly lead to higher mortality, such as impaired diaphragmatic contractility, prolonged mechanical ventilation, cardiac dysfunction, and cellular energetic failure; these pathophysiologic mechanisms underpin why low phosphate on presentation can translate to worse

clinical outcomes and match our findings of poorer survival among hypophosphatemic patients. Older and more recent ICU studies showed longer ICU/hospital stays and greater ventilator dependence with hypophosphatemia21-23.

Some studies that focused on bloodstream infections or specific subpopulations also reported hypophosphatemia as an independent predictor of mortality after adjustment for confounders. A studyfound an independent association between low phosphate and 90-day mortality in ICU patients with bloodstream infection, which parallels our stratified results showing higher mortality among hypophosphatemic patients across many subgroups like diabetics, older patients24.

There are also reports emphasizing that comorbidity and kidney function modify the phosphate–outcome relationship. Studies highlighted that phosphate abnormalities are common in sepsis and often coexist with renal dysfunction, inflammation, and metabolic derangement; thus, residual confounding by severity and organ failure is a frequent challenge in this literature and likely contributed to some between-study differences. In our stratified analysis, the association persisted across several comorbidity subgroups (e.g., diabetes, hypertension), but the influence of renal failure and illness severity cannot be entirely excluded15, 25.

Taken together with the literature, our results support routine measurement of serum phosphate in septic patients and heightened clinical vigilance when hypophosphatemia is present, particularly in older patients and those with diabetes or hypertension. However, the mixed evidence about hyperphosphatemia and the role of phosphate trajectories means that clinicians should interpret a single phosphate result in the context of kidney function, acid–base status, and trends over time rather than acting on one reading alone. Prospective interventional trials would be needed to determine whether correcting hypophosphatemia improves outcomes.

The strengths include a clearly defined cohort and stratified analysis across multiple effect modifiers. Key limitations mirror those in the literature: modest sample size, single-center design, potential residual confounding (illness severity, timing of phosphate measurement), and the observational nature that prevents causal inference. Future research should use larger multicenter cohorts, standardize phosphate cutoffs and measurement timing, and consider intervention trials of phosphate repletion in selected patients.

CONCLUSION

This study demonstrated that hypophosphatemia was a frequent finding among septic patients and was strongly associated with increased mortality. Patients with low serum phosphate had significantly higher death rates compared to those with normal levels, and this association persisted across multiple subgroups such as gender, age, diabetes, and hypertension. These results underscore the prognostic importance of serum phosphate as a simple, inexpensive, and readily available biomarker in the management of sepsis. Our findings, supported by recent literature, suggest that routine monitoring of phosphate levels should be considered in septic patients, not only to identify those at greater risk of poor outcomes but also to guide timely corrective interventions. While causality cannot be inferred from this cross-sectional study, the consistent association highlights the need for larger, multicenter prospective studies to determine whether targeted phosphate management can improve survival in sepsis.

List of abbreviations

ABG: Arterial Blood Gas
BMI: Body Mass Index
CKD: Chronic Kidney Disease
CHF: Chronic Heart Failure

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