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**ORIGINAL ARTICLE**

# Frequency, Risk Factors, and Clinical Implications of Hypophosphatemia in Critically Ill Patients: A Prospective Observational Study from a Tertiary Care Intensive Care Unit

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## ABSTRACT

**Background:** Hypophosphatemia is a frequent but underrecognized electrolyte disturbance in critically ill patients and may contribute to respiratory, cardiovascular, and metabolic dysfunction. Data from low- and middle-income countries remain limited regarding its prevalence, risk factors, and clinical consequences.

**Objective:** To determine the frequency of hypophosphatemia among critically ill patients, identify associated clinical and therapeutic risk factors, and evaluate its relationship with laboratory parameters, ventilatory requirements, and in-hospital mortality.

**Methods:** This prospective observational study was conducted in the Medical Department Allama Iqbal Memorial Teaching Hospital KMSMC Sialkot. One hundred consecutive adult patients were enrolled. Serum phosphate was measured on days 1, 3, and 10 of hospitalization. Hypophosphatemia was defined as serum phosphate <2.5 mg/dL and severe hypophosphatemia as <1.5 mg/dL. Demographic data, diagnoses, medication exposure, ventilatory support, laboratory findings, and outcomes were recorded. Statistical analysis was performed using SPSS version 10.

**Results:** Hypophosphatemia was observed in 16% of patients, while severe hypophosphatemia occurred in 3%. The highest prevalence was noted among patients with diabetic ketoacidosis (27.3%), septicemia (21.9%), and respiratory failure (19%). Hypophosphatemic patients had significantly lower serum calcium and albumin levels ($p < 0.05$). Among non-survivors, 37.5% had hypophosphatemia, and two-thirds required mechanical ventilation. However, serum phosphate levels were not independently associated with mortality.

**Conclusion:** Hypophosphatemia is a common metabolic abnormality in critically ill patients, particularly in those with sepsis, respiratory failure, and diabetic ketoacidosis. Routine monitoring may facilitate early identification and timely correction to support respiratory and metabolic stability.

**Keywords**: Hypophosphatemia, Critical illness, Intensive care unit, Respiratory failure, Electrolyte imbalance

## INTRODUCTION

Phosphate is an essential intracellular anion that plays a fundamental role in cellular metabolism, membrane integrity, nucleic acid synthesis, and energy transfer through adenosine triphosphate (ATP) generation. It is also critically involved in oxygen delivery via its effect on erythrocyte 2,3-diphosphoglycerate, regulation of acid–base balance, and neuromuscular function.[1,2] In healthy individuals, phosphate homeostasis is tightly regulated by intestinal absorption, renal excretion, and bone buffering, mediated by parathyroid hormone, vitamin D, and fibroblast growth factor-23.[3-5] In critically ill patients, however, these regulatory mechanisms are frequently disrupted, rendering phosphate balance highly vulnerable to acute metabolic and therapeutic perturbations.

Hypophosphatemia is one of the most common but underrecognized electrolyte abnormalities in intensive care units (ICUs). Its reported prevalence varies widely, ranging from 10% to over 40% in critically ill populations, depending on patient characteristics, illness severity, and diagnostic thresholds used.[6-8] Despite its high frequency, hypophosphatemia often remains undetected unless actively sought, as its clinical manifestations-such as muscle weakness, respiratory failure, impaired myocardial contractility, hemolysis, and neurological disturbances-are frequently nonspecific and may overlap with features of the underlying critical illness[9].

The pathophysiology of hypophosphatemia in critical illness is multifactorial. Redistribution of phosphate into cells, increased renal excretion, and reduced intestinal absorption all contribute to its development.[10-13] Conditions such as sepsis, diabetic ketoacidosis, respiratory alkalosis, hepatic failure, and malnutrition are strongly associated with intracellular phosphate shifts mediated by insulin, catecholamines, and alkalemia.[14-17] Additionally, commonly employed ICU therapies-including glucose infusions, β2-agonists, corticosteroids, diuretics, antacids, and total parenteral nutrition-further exacerbate phosphate depletion by promoting cellular uptake or renal losses.[18]

Among critically ill patients, hypophosphatemia has been linked to clinically significant complications. Phosphate deficiency impairs diaphragmatic contractility, decreases respiratory muscle strength, and has been associated with prolonged mechanical ventilation and weaning failure.[19-21] Cardiovascular consequences include reduced myocardial performance, arrhythmias, and hypotension, while hematologic effects include hemolysis and impaired leukocyte function, predisposing to infection and poor wound healing.[22,23] Collectively, these physiological derangements suggest that hypophosphatemia may contribute to adverse clinical outcomes in the ICU setting.

Several studies have demonstrated an association between hypophosphatemia and increased morbidity, length of ICU stay, and mortality, although the independence and strength of this relationship remain debated.[11] Some investigators propose that hypophosphatemia primarily reflects illness severity rather than acting as a direct causal factor in poor outcomes, whereas others suggest that timely recognition and correction may improve respiratory and metabolic stability, particularly in high-risk subgroups such as patients with sepsis, diabetic ketoacidosis, and respiratory failure.[24,25]

Despite its recognized clinical relevance, data regarding the prevalence, etiological factors, and outcome associations of hypophosphatemia in critically ill populations from low- and middle-income countries remain limited. Variations in nutritional status, disease burden, and treatment practices may influence phosphate dynamics and clinical consequences, underscoring the need for region-specific evidence to guide monitoring and management strategies.

The present prospective observational study was therefore designed to determine the frequency of hypophosphatemia among critically ill patients admitted to the Medical Intensive Care Unit of Allama Iqbal Memorial Teaching Hospital Sialkot, to identify associated clinical and therapeutic risk factors, and to evaluate its relationship with laboratory parameters, ventilatory requirements, and in-hospital mortality. By systematically characterizing phosphate disturbances in this high-risk population, this study aims

to contribute clinically relevant data that may support early detection strategies and inform metabolic management protocols in critically ill patients.

## METHODOLOGY

This prospective observational study was conducted in the Medical Department Allama Iqbal Memorial Teaching Hospital KMSMC Sialkot. A total of 100 consecutive adult patients admitted to the MICU were enrolled. Patients were included if they had critical medical illnesses known to predispose to electrolyte disturbances, including diabetic ketoacidosis, respiratory failure, chronic obstructive airway disease or asthma, septicemia, hyperalimentation, acute respiratory alkalosis, hepatic coma, hypothermia, malignancies, hyperparathyroidism, and malabsorption syndromes. Patients receiving glucocorticoids, antacids, bronchodilators, diuretics, inotropic support, mechanical ventilation, or parenteral nutrition were also included.

` Serum phosphate concentrations were assessed as part of routine biochemical monitoring. Normal serum phosphate was defined as 2.5–4.5 mg/dL. Hypophosphatemia was defined as serum phosphate levels <2.5 mg/dL, while severe hypophosphatemia was defined as phosphate levels <1.5 mg/dL. Serum phosphate was measured on days 1, 3, and 10 of hospitalization when applicable, and the lowest recorded value during the hospital stay was used for analysis. Concurrent measurements of serum calcium and albumin were performed on the same samples. Additional laboratory parameters including hemoglobin, blood urea nitrogen, serum creatinine, total leukocyte count, and arterial blood gases were obtained as clinically indicated. Demographic data, clinical features, primary diagnoses, medication history, ventilatory support, and patient outcomes were documented using a standardized proforma.

Biochemical analyses were carried out using the Dade Dimension automated chemistry analyzer with Flex reagent kits for serum phosphate and calcium measurements. Serum albumin was measured manually using the LAB system. Serum phosphate estimation was based on the phosphomolybdate reduction method, whereby inorganic phosphate forms a complex with molybdate in an acidic medium and is reduced by p-methylaminophenol sulfate and bisulfite to yield a chromogen measured at 340 nm using a bichromatic endpoint technique.

Statistical analysis was performed using SPSS version 10. Numerical variables were expressed as means ± standard deviations. One-way analysis of variance (ANOVA) was applied to compare phosphate levels across disease groups, while independent sample t-tests and Chi-square tests were used to assess associations between serum phosphate levels and clinical as well as laboratory variables. A p-value <0.05 was considered statistically significant.

## RESULTS

A total of 100 critically ill patients admitted to the Medical Intensive Care Unit were included. The mean age was 51.2 ± 17.4 years (range: 16–91 years). There were 61 (61%) males and 39 (39%) females. Overall, 34 (34%) patients died during hospitalization, while 66 (66%) were discharged alive.

During hospitalization, 16 patients (16%) developed hypophosphatemia (serum phosphate <2.5 mg/dL). The overall mean serum phosphate concentration was 3.27 ± 0.79 mg/dL (range: 1.8–5.1 mg/dL). Severe hypophosphatemia (<1.5 mg/dL) was observed in 3 (3%) patients.

Respiratory failure was the most frequent admitting diagnosis (42%), followed by septicemia (32%), chronic obstructive airway disease/asthma (24%), hepatic coma (26%), diabetic ketoacidosis (11%), malignancy (10%), and respiratory alkalosis (19%). Sixty-five percent of patients presented with shortness of breath, and 38% required mechanical ventilation.

Hypophosphatemia was most frequently observed among patients with respiratory failure (19%), septicemia (21.9%), respiratory alkalosis (15%), chronic obstructive airway disease/asthma (16.7%), diabetic ketoacidosis (27.3%), hepatic coma (9.1%), and renal failure (20%). Patients with renal failure demonstrated comparatively higher serum phosphate levels.

During admission, 60% of patients received antacids, 50% β2-agonists, 53% glucose infusion, 33% total parenteral nutrition, 28% corticosteroids, and 11% diuretics. Although 56.3% of patients with hypophosphatemia were receiving β2-agonists, the association was not statistically significant ($p > 0.05$).

Patients with hypophosphatemia had significantly lower serum calcium and albumin levels, whereas hemoglobin levels were not significantly different between groups.

Among the 34 non-survivors, 6 patients (37.5%) had hypophosphatemia. Septicemia was the most frequent diagnosis among these patients (66.6%), followed by respiratory failure (50%). Two-thirds of hypophosphatemic non-survivors required mechanical ventilation. Serum phosphate levels were not independently associated with mortality ($p > 0.05$). However, admission with shortness of breath was significantly associated with increased mortality ($p = 0.014$).

Table 1. Baseline Characteristics of the Study Population

| Variable | Value |
|---|---|
| Total patients | 100 |
| Mean age (years) | 51.2 ± 17.4 |
| Male sex | 61% |
| Female sex | 39% |
| Mortality | 34% |
| Hypophosphatemia prevalence | 16% |
| Mean serum phosphate (mg/dL) | 3.27 ± 0.79 |
| Mechanical ventilation | 38% |
| Shortness of breath on admission | 65% |

Table 2. Distribution of Hypophosphatemia Across Disease Groups

| Disease Group | Total Patients | Hypophosphatemia n (%) |
|---|---|---|
| Diabetic ketoacidosis | 11 | 3 (27.3) |
| Septicemia | 32 | 7 (21.9) |
| Respiratory failure | 42 | 8 (19.0) |
| COAD/asthma | 24 | 4 (16.7) |
| Respiratory alkalosis | 19 | 3 (15.0) |
| Hepatic coma | 26 | 2 (9.1) |
| Renal failure | 5 | 1 (20.0) |

Table 3. Laboratory Comparison by Serum Phosphate Status

| Parameter | Hypophosphatemia (<2.5 mg/dL) | Normal (≥2.5 mg/dL) | p-value |
|---|---|---|---|
| Serum calcium (mg/dL) | Low | Normal | <0.05 |
| Serum albumin (g/dL) | Low | Normal | <0.05 |
| Hemoglobin (g/dL) | 12.50 ± 2.21 | 12.90 ± 2.14 | >0.05 |

## DISCUSSION

This study demonstrates that hypophosphatemia is a common biochemical abnormality among critically ill patients admitted to the medical intensive care unit, affecting 16% of the study population. The observed prevalence is consistent with previously reported ICU-based studies, which have documented hypophosphatemia in 10–40% of critically ill patients, underscoring its clinical relevance as a frequently overlooked electrolyte disturbance. The relatively high mean age and predominance of respiratory and septic etiologies in our cohort reflect the typical demographic and diagnostic patterns seen in tertiary-care ICUs, further supporting the generalizability of our findings.

The highest burden of hypophosphatemia was observed among patients with diabetic ketoacidosis, septicemia, and respiratory failure. These conditions are well known to precipitate intracellular phosphate shifts due to insulin therapy, respiratory alkalosis, increased cellular uptake, and cytokine-mediated metabolic alterations. In particular, insulin-induced cellular uptake of phosphate in diabetic ketoacidosis and the enhanced renal phosphate losses seen in sepsis likely contributed to the increased prevalence observed in these subgroups. These mechanisms

emphasize the vulnerability of metabolically stressed patients to phosphate depletion and highlight the need for routine surveillance in such high-risk clinical settings.

Patients with hypophosphatemia in this study exhibited significantly lower serum calcium and albumin levels, reflecting the interrelated disturbances in mineral metabolism commonly encountered in critical illness. Hypoalbuminemia, a marker of systemic inflammation and malnutrition, may further exacerbate phosphate deficiency by impairing gastrointestinal absorption and increasing renal losses. Conversely, hemoglobin levels were not significantly affected, suggesting that the degree of hypophosphatemia observed was insufficient to influence erythrocyte metabolism or that confounding critical illness–related factors masked its hematological effects.

Although hypophosphatemia was not found to be an independent predictor of mortality, a substantial proportion of non-survivors demonstrated low phosphate levels, particularly among those with septicemia and respiratory failure requiring mechanical ventilation. This finding aligns with existing literature suggesting that hypophosphatemia may serve more as a marker of disease severity rather than a direct cause of mortality. Nevertheless, the association between hypophosphatemia and increased ventilatory requirements is clinically significant, as phosphate deficiency has been shown to impair diaphragmatic contractility, reduce respiratory muscle strength, and contribute to prolonged ventilator dependence.

Medication-related factors, including β2-agonists, glucose infusions, total parenteral nutrition, corticosteroids, and antacids, were commonly used in the study population and are known to influence phosphate balance through intracellular shifts and renal losses. Although β2-agonist use was more frequent among hypophosphatemic patients, the association did not reach statistical significance, possibly due to the limited sample size. Nonetheless, the high prevalence of such therapies reinforces the importance of anticipating phosphate depletion in critically ill patients receiving these treatments.

Collectively, these findings highlight hypophosphatemia as a prevalent and clinically meaningful metabolic abnormality in critically ill patients, particularly among those with sepsis, respiratory failure, and diabetic ketoacidosis. Routine monitoring and timely correction of serum phosphate levels may help mitigate respiratory compromise and support overall metabolic stability in the ICU setting. Larger prospective studies are warranted to further elucidate the causal relationships between phosphate disturbances and adverse clinical outcomes and to define evidence-based thresholds for therapeutic intervention.

## CONCLUSION

Hypophosphatemia is a frequent and clinically relevant electrolyte abnormality among critically ill patients admitted to the medical intensive care unit. In this study, it affected one-sixth of patients, with the highest burden observed in individuals with diabetic ketoacidosis, septicemia, and respiratory failure. Although serum phosphate levels were not independently associated with mortality, a considerable proportion of non-survivors exhibited hypophosphatemia and required mechanical ventilation, highlighting its close association with disease severity and respiratory compromise. The significant coexistence of hypocalcemia and hypoalbuminemia further reflects the complex metabolic disturbances of critical illness. Given its potential to impair respiratory muscle function and prolong ventilatory dependence, routine surveillance of serum phosphate in high-risk ICU populations is warranted. Early detection and timely correction may improve metabolic stability and support better clinical outcomes, particularly in resource-limited healthcare settings.

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