ORIGINAL ARTICLE

Frequency and Risk Factors of Hypophosphatemia in Patients Admitted to Emergency Intensive Care Unit in Zagazig University Hospitals

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Abstract

Background: Inorganic phosphate is a major electrolyte that participates in many functional and integral processes in the human body. Low Pi levels may lead to multiple organ dysfunction. It is estimated to occur in 40–80% of intensive care unit (ICU) patients. However, it may be ignored during the initial evaluation in ICU.

Materials and methods: This prospective cross-sectional study included 500 adult ICU cases in two groups; a group with normal Pi levels and a group with hypophosphatemia. All admitted patients were subjected to full history taking, and clinical, laboratory, and radiological evaluation. Collected data were coded, processed, and analyzed using statistical package for social sciences (SPSS) software.

Results: Among 500 adult ICU patients; 56.8% had normal phosphate levels while the remaining 43.2% had low phosphate levels. Patients in the hypophosphatemia group were associated with a significantly higher Acute Physiological and Chronic Health Evaluation (APACHE II) score, a longer hospital and ICU stay, a higher incidence of mechanical ventilation use with a longer duration on it, and a significantly higher mortality rate.

Conclusion: Risk factors for hypophosphatemia include a higher APACHE II score, longer stay in the hospital and ICU, a higher ratio of mechanical ventilation, and a higher mortality rate.

Keywords: Accidental poisoning, Acute hypoxemic respiratory failure, Adolescent, Cardiac output blood pressure.

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Highlights

- Among 500 adult ICU patients, 56.8% patients had normal phosphate (Pi) levels, while the remaining 43.2% patients had low Pi levels.
- Patients of the hypophosphatemia group were associated with a significantly higher APACHE II score, a longer hospital and ICU stay, a higher incidence of mechanical ventilation use with a longer duration on it, and a significantly higher mortality rate.

Introduction

Inorganic phosphate is a major electrolyte that participates in many functional and integral processes in the human body. It is important for adenosine triphosphates (ATP) formation; the cornerstone for energy production in the body. Also, Pi is a major component of cell membrane phospholipids and nucleic acids.[1,2] Inorganic phosphate is considered normal between 2.5 and 4.5 mg/dL, and below 2.5 mg/dL (0.65 mmol/L) is considered low; known as hypophosphatemia. It is further classified into mild, moderate, and severe hypophosphatemia; defined as Pi below 1.5 mg/dL (0.32 mmol/L).[1,3]

Low Pi levels may lead to multiple organ dysfunction; including encephalopathy, and respiratory and circulatory failure due to diaphragm and myocardial dysfunction.[4,5] Hypophosphatemia develops due to low intake of Pi with abnormal intestinal absorption, increase renal loss, and redistribution between different body compartments, in addition to loss during renal replacement therapy.[1,6,7] It occurs mainly in most trauma cases and critically ill patients.[8] Also, it occurs in the postoperative period of most surgeries; it occurs after cardiac surgeries and nearly all cases after hepatic surgery, in addition to, diabetic ketoacidosis (DKA), sepsis, and refeeding syndrome in an ICU patients, and continuous renal replacement therapy. It may be explained by the intake of glucose-containing solutions, insulin administration, catecholamines, and diuretics use during hospitalization.[9–13]

Hypophosphatemia may worsen the condition of hospitalized patients or lead to their death. It depends on several associated factors, which have not been determined so far.[14] Low Pi level, is a major problem in ICU patients, however, it may be ignored during the initial assessment of hospitalized patients. The prevalence of hypophosphatemia may show high variability in the medical

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literature according to many factors such as defective reporting of ICU patients data, poor detection of cases (cases are mainly asymptomatic), and the difference of threshold of low Pi, and the nature of the disease. In cases of liver surgery or after re-nutrition in ICU patients, the incidence of hypophosphatemia is 100% by a threshold below 0.80 mmol/L. However, hypophosphatemia is estimated to occur in 40–80% of ICU patients[9,15–17]

As Pi is mainly an intracellular electrolyte, serum level does not reflect the exact amount in body stores; hence, clinical manifestations do not correlate with the degree of hypophosphatemia.[18] It does not manifest except with a severe decrease in serum levels, as respiratory and muscular symptoms appear below 0.5 mmol/L, while neurological and cardiovascular symptoms appear below 0.3 mmol/L.[16,19]

Treatment of hypophosphatemia depends mainly on the treatment of the cause. Oral Pi supplementation is needed only in symptomatic cases with Pi depletion. It is better than the intravenous (IV) route, as the IV route leads to Ca deposition in many tissues (calcification), so, it is only indicated in cases of severe hypophosphatemia.[12,20]

As hypophosphatemia leads to higher morbidities and mortality in ICU patients with difficult detection; it is important to estimate the frequency and risk factors contributing to this condition. Hence, in this cross-sectional study, we aim to determine the frequency, clinical outcomes, and risk factors of hypophosphatemia in patients in the emergency ICU.

Materials and Methods

Inclusion Criteria

We included all patients admitted to the emergency ICU with normal Pi levels, from 1 January 2019 to 31 June 2019 (6 months duration).

Exclusion Criteria

We excluded patients with hypophosphatemia or hyperphosphatemia at the time of admission.

Ethics

The study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Zagazig University, Egypt. We respected the privacy of all included patients, ensuring that the collected data were not used for any other purposes, also, at any time patients could withdraw from the study. All participants gave informed written consent before participating in this study.

Study Methodology

We conducted a cross-sectional study including 500 adult ICU cases in the emergency ICU at the department of anesthesia and surgical intensive care, at Zagazig University Hospitals, Faculty of Medicine, Zagazig University, Egypt. All admitted patients were subjected to full history taking, clinical examination, laboratory, and radiological evaluation; in addition to these tests, 12-leads electrocardiogram (ECG), Glasgow coma scale (GCS), and APACHE II. score At the time of admission to the ICU, all 500 patients' laboratory tests showed normal Pi levels, but, with later evaluation, hypophosphatemia was detected in a group of them, so, we divided the study population into two groups; normal Pi group (group N) and low Pi group (group H).

Patients' history included; demographic data such as age, sex, special habits of medical importance, and cause of admission to emergency ICU, in addition to, associated chronic disease and state of current diseases such as diabetes mellitus (DM), hypertension, chronic obstructive pulmonary disease (COPD), heart diseases, renal and liver diseases, psychiatric disorders, and malignancy. As for clinical examination, it included all vital signs (blood pressure, pulse, respiratory rate, temperature).

Regarding laboratory and radiological evaluation, it comprised of complete blood count (CBC), liver function tests (LFT), kidney functions tests (KFT), arterial blood gases (ABG), and serum electrolytes [sodium (Na), potassium (K), calcium (Ca), and Pi] at the time of admission; Pi level was estimated using the phosphomolybdate method by Beckman AU5800, with a reference range of 2.5–4.5 mg/dL. In addition, patients were evaluated by abdominal ultrasound, chest X-ray, and specific investigation based on patients' condition. At the time of admission, patients' PO_4 levels were measured daily.

Statistical Analysis

Collected data were coded, processed, and analyzed using SPSS, version 22, for Windows® (IBM SPSS, Inc., Chicago, IL, USA). The Shapiro–Wilk test was used for testing the normal distribution of data.

Qualitative data were represented as frequency and percentage using the Chi-square test (χ^2) to calculate the difference between qualitative variables as indicated. Quantitative data were expressed as mean ± standard deviation (SD) or median (M, range). To compare between two independent groups, we used the independent samples *t*-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Univariate and multivariate logistic regression analysis was used to test the associated covariate and independent risk factors for mortality. For all used tests, significance was tested and expressed as the probability (*p*). The $p \leq 0.05$ was considered significant.

Results

Patients' Characteristics

In our cross-sectional study, we included 500 adult ICU patients in two groups: Group N (284 cases (56.8%) with normal Pi level) and group H (216 cases (43.2%) with hypophosphatemia). Table 1 summarizes all characteristics of included patients. The median age of included patients was 49 and 53 years in groups N and H, respectively, and most of them were males. Diabetes mellitus was reported in 61.9 and 53.2% of cases in groups N and H, respectively; considering it the most common comorbidity followed by hypertension and heart failure. Moreover, smoking was reported in 46.1 and 49.2% of cases in groups N and H, respectively. Postoperative monitoring represented the most common cause of ICU admission; accounting for 38.1% of cases in the normal Pi group and 41.2% of cases in the other group. The second most common cause was sepsis followed by respiratory failure, in addition to cardiovascular diseases, neurological diseases, and shock. Statistical analysis showed no significant difference between both study groups regarding age, sex, associated morbidity, and cause of admission to ICU; $p > 0.05$.

Furthermore, APACHE II score that comprises 12 routine physiological measurements were assessed during the first 24 hours after admission to ICU. It ranges from 0 to 71 points; higher scores imply severely diseased patients with a higher risk of mortality. Patients with low Pi levels (group H) had a significantly higher APACHE II score compared to the normal Pi group (group N); with a median of 24 and 18, respectively, for the two groups;

Table 1: Characteristics of included patients in the two study groups

Items	*Group N (normal Pi level) n = 284*	*Group H (hypophosphatemia) n = 216*	*p-value*
Age (years)	49 (18–83)	53 (20–87)	0.680
Sex			
Male	170 (59.9%)	138 (63.8%)	0.163
Female	114 (40.1%)	78 (36.2%)	
BMI (kg/m^2)	30.35 ± 3.89	29.83 ± 4.46	0.552
Associated comorbidities			
Smokers	131 (46.1%)	106 (49.2%)	0.172
DM	176 (61.9%)	115 (53.2%)	0.069
Hypertension	129 (45.4%)	111 (51.4%)	0.125
Heart failure	39 (13.7%)	44 (20.4%)	0.098
Cause of admission to ICU			
Postoperative	108 (38.09%)	89 (41.11%)	0.487
Sepsis	78 (27.48%)	62 (30.10%)	0.356
Respiratory failure	25 (8.78%)	17 (7.12%)	0.639
Cardiovascular diseases	19 (6.69%)	15 (6.74%)	0.842
Neurological diseases	12 (4.18%)	9 (4.11%)	1
Shock	23 (8.09%)	18 (8.21%)	0.937
Other causes	19 (6.69%)	6 (2.61%)	0.283
APACHE II score	18 (2–38)	24 (7–47)	<0.001
GCS	13 (7–15)	11 (6–14)	0.325
Vital signs			
Pulse	87.14 ± 21.17	90.34 ± 19.48	0.096
Mean arterial pressure	61.64 ± 13.09	64.33 ± 15.68	0.362
Respiratory rate	22 (14–31)	23 (15–34)	0.127
Temperature	38.46 ± 3.23	39.09 ± 2.98	0.068
Nutritional status			
No nutrition support therapy	87 (30.6%)	74 (34.3%)	0.373
Parenteral	78 (27.5%)	53 (24.5%)	0.265
Enteral	53 (18.7%)	45 (20.8%)	0.114
Enteral + parenteral	66 (23.2%)	44 (20.4%)	0.253
Serum electrolytes measurements			
K (mEq/L)	4.9 ± 1.51	4.2 ± 1.12	0.004*
Na (mEq/L)	144.4 ± 15.61	141.53 ± 14.28	0.461
Ca (mg/dL)	8.52 ± 0.32	8.75 ± 0.41	0.387
Pi (mg/dL)	3.16 ± 0.54	2.06 ± 0.36	<0.001**
CBC			
RBCs (10^6/mL)	4.19 ± 0.65	4.55 ± 0.81	0.064
Hemoglobin	12.31 ± 2.32	12.85 ± 2.49	0.390
WBCs (10^3/mL)	8.24 ± 1.07	9.14 ± 2.98	0.492
PLTs (10^6/mL)	218.5 (120–388)	186.5 (106–412)	0.492
Liver and kidney function tests			
Albumin	3.18 ± 0.40	3.21 ± 0.49	0.193
Bilirubin	0.85 (0.21–1.5)	0.95 (0.3–3.6)	0.608
ALT	32 (18–1136)	45 (17–1198)	0.070
AST	32 (16–927)	28 (19–1592)	0.668
INR	1.32 ± 0.32	1.25 ± 0.23	0.376
Serum creatinine	0.83 ± 0.20	0.89 ± 0.26	0.136

Categorical data are expressed as numbers (percentage within the group); Continuous data expressed as median (range) or mean ± SD. ALT, alanine aminotransferase; APACHE II, acute physiology and chronic health evaluation II; AST, aspartate aminotransferase; BMI, body mass index; DM, diabetes mellitus; GCS, Glasgow coma scale; INR, international normalized ratio; K, potassium; Na, sodium; P, probability; PLTs, platelets; RBC, red blood cells; WBCs, white blood cells

Table 2: Clinical outcomes of the two groups

	Group N (normal Pi level) n = 284	*Group H (hypophosphatemia) n = 216*	*p-value*
Length of hospital stay/day	13.5 (7–40)	22.4 (10–52)	<0.001**
Length of ICU stay/day	2.5 (1.5–10.4)	8.5 (3.2–28.5)	<0.001**
Percentage of MV/day	107 (37.7%)	155 (71.8%)	<0.001**
Duration of MV/day	1.1 (0.6–4.8)	4.5 (1.8–10.9)	<0.001**
Percentage of mortality/ICU stay	62 (21.8%)	139 (64.4%)	<0.001**

**Statistically significant when $p < 0.05$. Categorical data are expressed as numbers (percentage within the group); Continuous data expressed as mean ± SD or median (range). MV, mechanical ventilation; P, probability

Table 3: Univariate and multivariate analysis of predictors of mortality

		Multivariate analysis		
Variables	*Univariate analysis*	*B*	*95% CI*	*p-value*
Age	0.287			
Gender	0.391			
APACHE II score	<0.001*	1.824	1.273–2.982	0.043*
GCS	0.182			
K level	0.071			
Pi level	<0.001*	2.176	1.78–2.835	0.0.31*
Length of hospital stay	0.011*	1.517	1.241–2.28	0.054
Length of ICU stay	0.001*	0.736	0.428–1.328	0.165
Percentage of MV	0.031*	0.528	0.398–1.05	0.362
Duration of MV	0.03*	1.68	1.13–2.97	0.04*

*Statistically significant when $p < 0.05$. APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; GCS, Glasgow coma scale

$p < 0.001$. However, the GCS and vital signs measurements did not significantly differ between both groups; $p > 0.05$.

As for nutritional status, nearly 30% of patients in group N and 34% of patients in group H required no nutritional support therapy. On the other hand, only 23 and 20% of patients required enteral plus parenteral nutrition in groups N and H, respectively.

Regarding serum electrolyte levels, K significantly decreased in the hypophosphatemia group compared to the normal Pi group; ($p = 0.004$), while, Na and Ca did not differ significantly between both groups; ($p > 0.05$). Similarly, the results of CBC, LFT, and KFT showed no significant difference between both groups.

Clinical Outcomes

Evaluated clinical outcomes included the duration of hospital and ICU stay (days), number of patients who needed mechanical ventilation, duration of mechanical ventilation (days), and mortality rate in ICU patients. As shown in Table 2, patients of the hypophosphatemia group revealed a significantly longer hospital and ICU stay compared to patients with normal Pi levels; with a median of 22.4 and 8.5 days in the two groups, respectively; $p < 0.001$. Moreover, compared to patients with normal Pi levels, there was a significantly higher incidence of mechanical ventilation use in the hypophosphatemia group (155 patients; 71.8%), in addition to a significantly longer duration using it (median of 4.5 days); $p < 0.001$. Moreover, a total of 139 patients (64.4%) in the hypophosphatemia group died, which is a significantly higher incidence compared to only 62 patients (21.8%) in the normal Pi group; $p < 0.001$.

Predictors of Hypophosphatemia

To determine the risk factors (predictors) of hypophosphatemia in patients admitted to the emergency ICU, a univariate analysis was done, revealing that APACHE II score, hospital stay duration, ICU stay duration, the need for mechanical ventilation, and the duration of the ventilator were significant risk factors for the development of hypophosphatemia; $p < 0.05$). In addition, multivariate analysis was done revealing that only APACHE II and duration on the mechanical ventilator were the only significant factors (Table 3).

Discussion

Critically ill ICU patients, frequently develop electrolyte disturbances that require routine and meticulous monitoring at the time of admission and during the period of stay for early detection and correction.[21] Hypophosphatemia represents one of the frequently developed electrolyte disturbances, especially in critically ill patients with many risk factors. Hoffmann et al.[22]reported that among 861 cases of hypophosphatemia, 45% of them were ICU population. Similarly, another study reported that hypophosphatemia occurs in 30 to 50% of critically ill patients including the ICU population.[17] The exact risk factors, the clinical outcomes, and the role of correction in these patients are still questionable.[23] However, low Pi levels can be used as a severity indicator and a prognostic factor in sepsis patients.[10]

Hypophosphatemia develops mainly postoperatively. It may be explained by the occurrence of respiratory alkalosis, insulin, and diuretic use.[24,25] In critically ill patients it could be explained by the redistribution of Pi between body compartments, in addition to, decreased intestinal absorption, and increased renal loss, especially with renal replacement therapy.[26] Also, a higher incidence is observed in patients with DKA, sepsis, and postoperative period, as high as 34% of cardiac surgeries,[25] and nearly in all patients after major hepatic surgeries.[9,15]

In our cross-sectional study, we found that among 500 patients admitted to the emergency ICU with normal Pi levels, a total of 216 patients (43.2%) developed hypophosphatemia which is a great incidence to be considered while assessing the ICU population for electrolyte disturbances. Apart from vital data, laboratory outcomes, and systemic comorbidities; patients with low Pi levels showed significantly longer hospital and ICU stay, in addition to a higher incidence of mechanical ventilation use and longer durations on it, they revealed a higher mortality rate. Moreover, we found that APACHE II score and duration on the mechanical ventilator were the only significant independent predictors of hypophosphatemia in ICU patients.

In their study, Suzuki et al.[18] reported that 710 (26%) patients out of 2,730 critically ill patients developed hypophosphatemia. In addition, Wang et al.[14] reported that 53% of their cohort had hypophosphatemia. Also, multiple studies found that hypophosphatemia occurs in 2.2 to 3.3% of general hospital populations, with 0.2 to 0.4% developing severe hypophosphatemia.[27–30] Regarding the age and sex of ICU patients, Wang et al.[14] and Marik et al.[31] found no significant difference between the two groups regarding age ($p = 0.77$), which is consistent with our results. On the other hand, Suzuki et al.[18] reported a significant difference between the two groups regarding gender ($p = 0.02$). Males represented 54% of cases in the hypophosphatemic group and 61% of patients without hypophosphatemia, which differs from what we found. We found that sex did not significantly differ between the two groups ($p = 0.163$).

These variations may be explained by several factors; the variation of the threshold below which Pi is considered low and the test used to measure Pi in different medical centers, in addition to, the duration of admission in ICU, the medical condition, and the demographics of patients.

As for the duration of mechanical ventilation, Marik et al.[31] reported that hypophosphatemia was associated with a significantly longer duration using a mechanical ventilator (10.5 for the hypophosphatemia group vs 7.1 days for the other group; $p = 0.04$), and longer ICU stay (12.1 for hypophosphatemia group vs 8.2 days for the other group; $p = 0.01$); this is consistent with our results.

We found that APACHE II and duration on the mechanical ventilator were the only significant independent predictors of hypophosphatemia in critically ill patients. APACHE II score comprises 12 routine physiological measurements assessed during the first 24 hours after admission to ICU. It ranges from 0 to 71 points; higher scores imply severely diseased patients with a higher risk of mortality. Wang et al.[14] reported that the APACHE II score was significantly higher in the hypophosphatemic cases (25.64 vs 17.02 in the other groups – $p < 0.001$) which is similar to our results. On the other hand, another study reported that the APACHE II score did not significantly differ between the two groups ($p > 0.05$).[31]

Multiple studies show an association between hypophosphatemia and increased mortality.[32,33] Shor et al. reported that severe hypophosphatemia could be used as a mortality indicator, as patients with severe hypophosphatemia had higher mortality than those without severe hypophosphatemia (80.8% vs 34.5%, $p = 0.001$).[10] Moreover, severe hypophosphatemia has been reported to predict an increase in mortality rate up to eightfold in sepsis patients.[10] Similarly, Wang et al.[14] reported significantly higher 28-day mortality rates in the hypophosphatemic cases (35.3 vs 24% of cases in the other group – $p < 0.001$). Furthermore, another study reported that both ICU and hospital mortality were significantly increased in hypophosphatemic cases.[18]

However, in other studies, hypophosphatemia has not been associated with increased mortality after cardiac surgery[25] and in DKA.[34] Moreover, the role of hypophosphatemia in ICU mortality has not been established yet; it may be used as an indicator for the increased susceptibility of death associated with different causative factors rather than a single independent etiology, also, the protective role of Pi correction is still questionable.[16] It was reported that hypophosphatemia was associated with a longer hospital stay, but was not identified as an independent indicator of mortality in the ICU population.[18,35]

In their 2021 meta-analysis, Sin et al.[36] identified several factors that may interfere with the interpretation of the results of the studies about hypophosphatemia. The major limitation in establishing the evidence is that the definition of hypophosphatemia varies between different studies. They included 12 articles in their meta-analysis, one of the studies defined hypophosphatemia as below 0.048 mmol/L,[25] while another one defined it as below 0.94 mmol/L,[37] with different values in between. This may overestimate or underestimate the true incidence of hypophosphatemia. However low threshold may avoid late detection of low phosphate levels with subsequent protection from further morbidity and mortality. Also, they found that some authors estimated the long-term mortality while others estimate the short-term mortality. This greatly influences the true incidence of mortality in ICU patients. Moreover, some authors consider that many factors play a significant role in mortality incidence, so, they consider hypophosphatemia as a marker, not as an independent factor for mortality.

Strength

We think our study poses certain strength points; we included only patients with normal phosphate levels at the time of admission to avoid the contributing factors before the time of admission. Also, to be more specific, we included only critically ill patients. Also, we assessed patients' outcomes for six months, which may represent a reasonable period for the evaluation of outcomes.

Limitations

As an observational study, we think that the major limitation of our study is the inability to confirm the causal relationship between risk factors and the disease. Also, the sample size was relatively small and conducted at a single medical center and represented only a limited age-group which limits the generalizability of the study findings to the general population.

Recommendations

So, we recommend the conduction of multicentric and international studies to detect the true prevalence and risk factors in patients with different characteristics and to address an updated approach to hypophosphatemia in critically ill patients, as well as the association of hypophosphatemia with morbidity and mortality, and the effect of the correction of this electrolyte disorder.

Conclusion

Apart from vital data, laboratory outcomes, and systemic comorbidities, patients with low Pi levels showed significantly longer hospital and ICU stays, a higher incidence of mechanical ventilation use, and longer durations on it, in addition to, higher mortality rates. Moreover, we found that APACHE II score and duration on the mechanical ventilator were the only significant independent predictors of hypophosphatemia in ICU patients.

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