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Assessment of Serum Phosphate in Patients with Acute Respiratory Distress Syndrome on Mechanical Ventilation and Its Effect on Disease Severity and Mortality

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ABSTRACT

Background: Acute respiratory distress syndrome (ARDS) is a severe form of respiratory failure, life-threatening condition, characterized by rapid onset of widespread inflammation in the lungs and severe hypoxemia with significant impact on the morbidity and mortality of critical care patients who have a high prevalence of hypophosphatemia because of the presence of multiple causal factors . Identification of prognostic biomarker for ARDS as serum phosphate may aid in improving survival. **Objective of the study:** Evaluate role of hypophosphatemia in disease severity and mortality. **Method:** prospective study was conducted from 1st of October 2018 to1sof June 2019, on Fifty subjects with ARDS on mechanical ventilation in the intensive care units (ICUs) of medical city hospitals in Baghdad, variable ages, variable risk factors. Serum phosphate level measured for all study sample. **Results:** Fifty patients with ARDS, 26%mild 50%moderate 24%severe severity, 56% female versus 44% male. The mean age for ARDS was 49.56 ± 20.31 years, aged >50 years (48%). Pneumonia (28%) was common risk factor. 30% hypophosphatemia versus 6% hyperphosphatemia. 60% of study patients were died. There was no significant association between severity of ARDS and S. Phosphate level ($P \geq 0.05$). There was significant association between prevalence of mortality and S. Phosphate level ($P \leq 0.05$). The cut point of S. Phosphate was 3.1 mg/dL, S. Phosphate < 3.1 mg/dL is predicator for risk of mortality as a large significant area under the curve (AUC= 71.5%) indicating significant association between S. Phosphate level and risk of mortality. S. Phosphate was 80% sensitive, 60% specific, and 72% accurate as a predictor for risk of mortality. **Conclusion:** Patients with ARDS have low serum phosphate level tend to increase mortality rate. Evaluation the serum phosphate concentration carefully and early detection of hypophosphatemia in patients with ARDS and correcting it to within normal range if possible.

Keywords: Acute Respiratory Distress Syndrome (ARDS), Hypophosphatemia, Serum Phosphate, Mortality and Prognostic Biomarker

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical condition characterized by the sudden onset of severe shortness of breath, low blood oxygen levels (hypoxemia), and widespread pulmonary infiltrates, ultimately resulting in respiratory failure (Obaid et al., 2022). ARDS results from widespread lung injury that may arise due to a variety of medical or surgical conditions. Initially referred to as "adult respiratory distress syndrome," the condition is now known as "acute respiratory distress syndrome" to reflect the fact that it can also occur in children (Kumpf et al., 2017).

ARDS typically progresses through three distinct stages: the exudative, proliferative, and fibrotic phases (Talib et al., 2022). The pathological changes begin with an acute inflammatory stage, characterized by diffuse alveolar damage. This involves the accumulation of neutrophils, macrophages, red blood cells, hyaline membranes, and protein-rich edematous fluid within the alveolar spaces. These changes are due to increased permeability of the alveolar-capillary barrier, damage to the capillaries, and disruption of the alveolar epithelial lining. This initial phase typically lasts between 4 and 7 days (Cehovic et al., 2009).

During this phase, pro-inflammatory cytokines, such as interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-α), may be locally released in the lungs by activated inflammatory cells. Damage to type II alveolar cells impairs surfactant production and recycling, which likely contributes to alveolar collapse and abnormalities in gas exchange. Additionally, coagulation system disturbances are common, leading to the formation of platelet-fibrin thrombi in small blood vessels and reduced fibrinolytic activity within the distal air spaces of the injured lungs. These processes result in pulmonary vasoconstriction and pulmonary hypertension, caused by the destruction of pulmonary capillaries. In severe cases, this can progress to right-sided heart failure (Vistisen & Larsson, 2009).

Phosphate (PO_4^{3-}) is one of the most essential anions found both inside and outside cells. While the normal concentration of phosphate in the serum ranges between 2.5 and 4.5 mg/dL, the majority of phosphate in the human body is stored in bones and soft tissues. Phosphate plays a vital role in several physiological processes, including neurological, muscular, and metabolic functions. It is a crucial component of adenosine triphosphate (ATP), which provides energy for cellular processes, and is necessary for cellular structure, including cell membranes and

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nucleic acids. Additionally, it helps maintain the redox balance of cells throughout the body (Huang et al., 2008).

Aim of the Study

To evaluate serum phosphate levels in patients diagnosed with ARDS and to investigate their relationship with disease severity and clinical outcome, particularly mortality.

METHODOLOGY

A prospective analytical study was carried out from October 1, 2018, to June 1, 2019**.** The study included fifty patients diagnosed with ARDS who were receiving mechanical ventilation in the intensive care units (ICUs) of Medical City hospitals in Baghdad**.** Diagnosis was based on clinical criteria (acute onset of symptoms within one week of a known clinical insult and no prior history of heart failure), radiological evidence (chest X-ray showing bilateral infiltrates), and hypoxemia ($PaO_2/FiO_2 \leq 300$ mmHg), in accordance with the Berlin criteria**.**

A structured paper form was used to collect data on age**,** gender, and associated risk factors**.** Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25**.** Continuous variables were compared using the independent t-test and two-tailed ANOVA as appropriate. To examine the relationship between serum phosphate levels and PaO_2/FiO_2**,** Pearson's correlation coefficient (r) was applied**.** A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1: *Distribution of study patients by cause of ARDS*

Cause of ARDS	No. (n= 50)	Percentage (%)
Pneumonia	14	28.0
Gastric Aspiration	9	18.0
Major Trauma	7	14.0
Chest Trauma	1	2.0
Sepsis	10	20.0
Disseminated Intravenous Coagulopathy	2	4.0
Acute Pancreatitis	2	4.0
Massive Blood Transfusion	1	2.0

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Burn	4	8.0

Table 2: *Distribution of study patients by fate*

Dead	30	60.0
Alive	20	40.0

The distribution of study patients by fate is shown in table 2. In this study, 60% of study patients were died.

Table 3: *Association between severity of ARDS and study patients' characteristics*

Variable	Severity of ARDS			Total (%) n= 50	P- Value
	Severe n= 12	Moderate n= 25	Mild n= 13		
Age (Years)					
< 30	1 (10.0)	7 (70.0)	2 (20.0)	10 (20.0)	**0.034**
30 – 50	8 (50.0)	6 (37.5)	2 (12.5)	16 (32.0)	
> 50	3 (12.5)	12 (50.0)	9 (37.5)	24 (48.0)	
Gender					
Male	6 (27.3)	10 (45.4)	6 (27.3)	22 (44.0)	**0.834**
Female	6 (21.4)	15 (53.6)	7 (25.0)	28 (56.0)	
Cause					
Direct cause	4 (16.7)	11 (45.8)	9 (37.5)	24 (48.0)	**0.170**
Indirect cause	8 (30.8)	14 (53.8)	4 (15.4)	26 (52.0)	

This table shows the association between severity of ARDS and study patients' characteristics. There was a significant association between severity of ARDS and study patients' age .($P \leq 0.05$).

Table 4: *Association between severity of ARDS and S. Phosphate level*

S. Phosphate level	Severity of ARDS			Total (%) n= 50	P- Value
	Severe n= 12	Moderate n= 25	Mild n= 13		

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Low	7 (46.6)	4 (26.7)	4 (26.7)	15 (30.0)	**0.082**
Normal	4 (12.5)	19 (59.4)	9 (28.1)	32 (64.0)	
High	1 (33.3)	2 (66.7)	0 (0.0)	3 (6.0)	

The table 4 shows the association between the severity of ARDS and S. Phosphate level. There was no significant association between the severity of ARDS and S. Phosphate level ($P \geq 0.05$).

Table 5: *Comparison of the mean S. Phosphate level according to the severity of ARDS*

S. Phosphate	**Severity of ARDS**			**P- Value**
	Severe Mean ± SD	**Moderate Mean ± SD**	**Mild Mean ± SD**	
	2.51 ± 1.52	3.10 ± 0.95	3.12 ± 0.85	**0.267**

The comparison in mean of S. Phosphate level according to severity of ARDS is shown in table (5). There was no significant difference in mean of S. Phosphate level regarding severity of ARDS ($P \geq 0.05$).

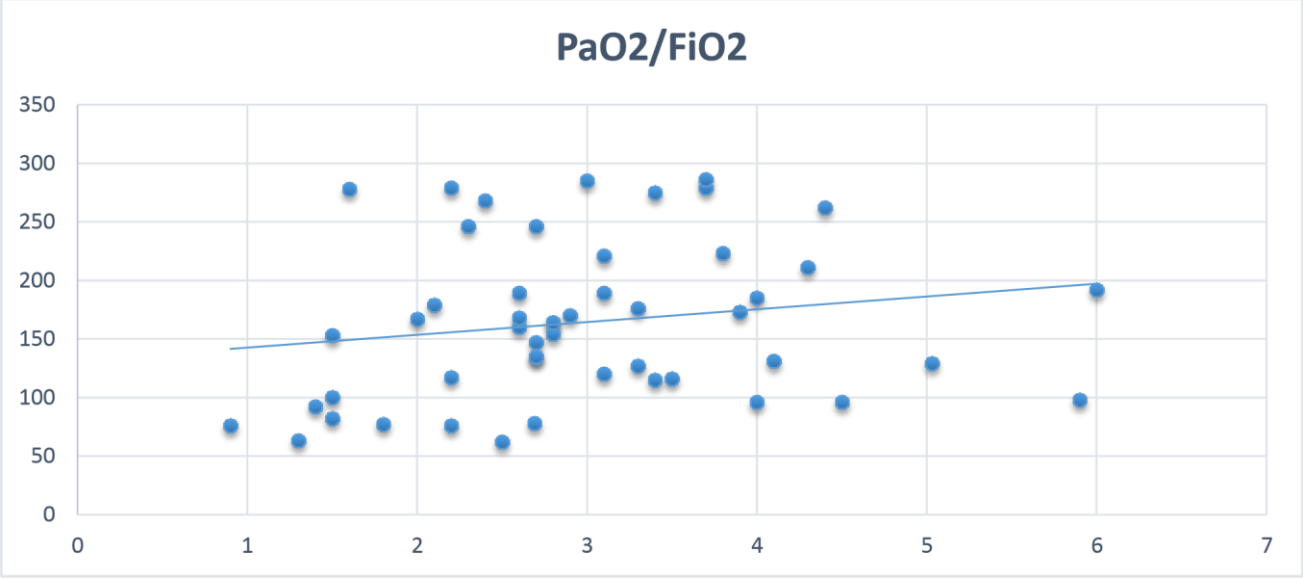

Figure 1: Correlation between S. Phosphate level and PaO_2/ FiO_2

Table 6: *Association between prevalence of mortality and study patients' characteristics*

Variable	**Mortality**		**P - Value**

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	Death (%) n= 30	Alive (%) n= 20	Total (%) n= 50	
Age (Years)				
< 30	3 (30.0)	7 (70.0)	9 (20.0)	**0.048**
30 – 50	9 (56.3)	7 (43.8)	16 (32.0)	
> 50	18 (75.0)	6 (25.0)	25 (48.0)	
Gender				
Male	13 (59.1)	9 (40.9)	22 (44.0)	**0.901**
Female	17 (60.7)	11 (39.3)	28 (56.0)	
Cause of ARDS				
Direct cause	13 (54.2)	11 (45.8)	24 (48.0)	**0.419**
Indirect cause	17(65.4)	9 (34.6)	26 (52.0)	
Severity of ARDS				
Severe	11 (91.7)	1 (8.3)	12 (24.0)	**0.035**
Moderate	12 (48.0)	13 (52.0)	25 (50.0)	
Mild	7 (53.8)	6 (46.2)	13 (26.0)	

Table 6 shows the association between prevalence of mortality and study patients characteristics. There was significant association between prevalence of mortality with study patients' age and severity of ARDS. ($P \leq 0.05$)

Table 7: *Association between prevalence of mortality and S. Phosphate level.*

S. Phosphate level	Mortality		Total (%) n= 50	P- Value
	Death n= 30	Alive n= 20		
Low	13 (86.7)	2 (13.3)	15 (30.0)	**0.033**
Normal	15 (46.9)	17 (53.1)	32(64.0)	
High	2 (66.7)	1 (33.3)	3 (6.0)	

Table 7 shows the association between the prevalence of mortality and S. Phosphate level. There was a significant association between the prevalence of mortality and S. Phosphate level ($P \leq 0.05$).

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Table 8: *Comparison between study groups by means of S. Phosphate*

S. Phosphate level	Mortality		P- Value
	Death Mean ± SD	Alive Mean ± SD	
	2.70 ± 1.14	3.37 ± 0.92	**0.035**

The comparison in mean of S. Phosphate according to fate of patients is shown in table 8. We noticed that the mean of S. Phosphate was significantly lower in died patients than that in alive (2.70 versus 3.37 mg/dL, $P \leq 0.05$).

Table 9: *Diagnostic accuracy of S. Phosphate level for predicting risk of mortality*

S. Phosphate	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	3.1	**80%**	**60%**	**75%**	**66.7 %**	**72%**

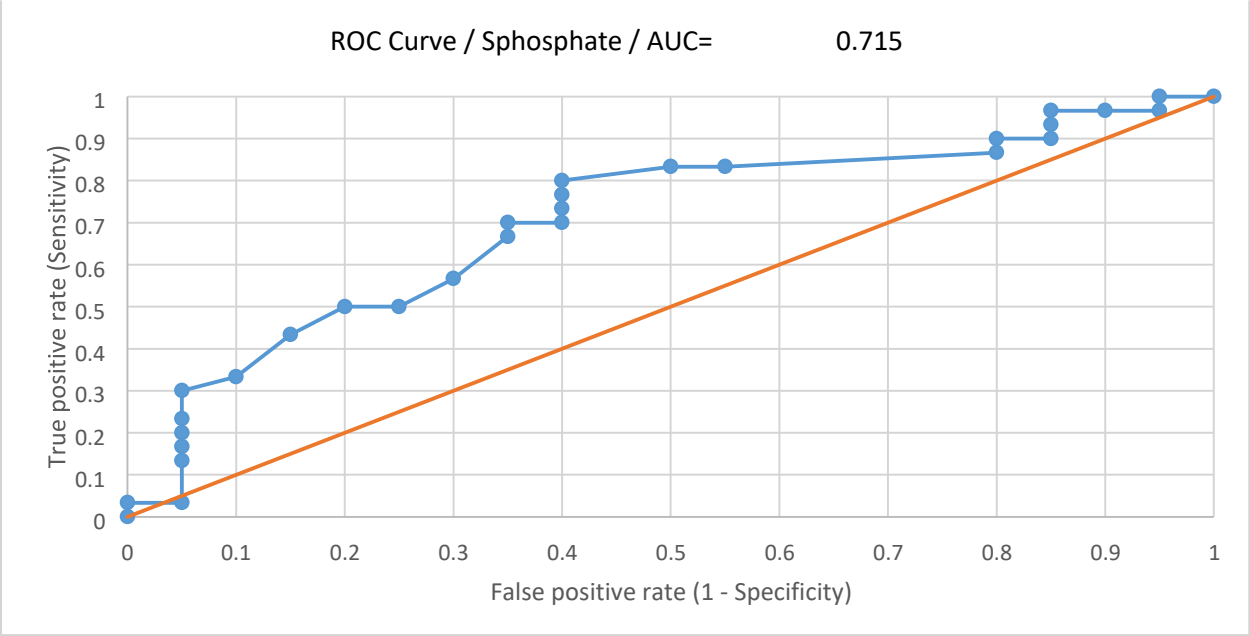

Figure 2: ROC curve for S. Phosphate level as prediction for risk of mortality

DISCUSSION

This study reports the frequency and impact of phosphate abnormalities in patients with ARDS who were on mechanical ventilation in the ICU. The incidence of hypophosphatemia in the

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current research was 30%. Similar findings were reported by Brunelli and Goldfarb, who noted that hypophosphatemia occurred in approximately 28–33% of ICU admissions (Brunelli & Goldfarb, 2007). Likewise, Doig et al. found that 37% of 2,915 patients developed hypophosphatemia during their ICU stay (Doig et al., 2009).

A relationship was observed between increasing age and the severity of ARDS in this study. However, no significant association was found between ARDS severity and serum phosphate levels or their mean values, which might be attributed to the relatively small sample size. A Scatter/Dot plot demonstrated either no correlation or only a weak positive correlation between serum phosphate levels and PaO2/FiO2 ratios.

A separate study conducted by Estenssoro et al. (2002) found hypophosphatemia (≤ 2.5 mg/dL) in 34 patients (21.5%) out of 158 with respiratory illness. In that study, hypophosphatemia did not show an association with disease severity.

The present study revealed an association between mortality and both advanced age and ARDS severity, as well as hypophosphatemia. Pneumonia was the most frequently identified cause (28%). The overall mortality rate observed was 60%. However, the data did not suggest any specific dependence on the underlying cause of ARDS. In an observational study on ARDS patients, Li et al. (2007) also reported a mortality rate of 58%. The high mortality noted in this research may reflect the specific healthcare context. The hospital where this study took place is a tertiary care center, receiving referrals from basic healthcare units and other cities. Additionally, due to ICU bed shortages, some patients with respiratory failure may experience delays in receiving ventilatory support.

ARDS is known to result from a generalized lung response to a broad range of direct or indirect insults. Bacterial and viral pneumonia are among the leading causes (Villar et al., 2007). Sepsis is the most common predisposing factor, with ARDS developing in 20–40% of patients with severe sepsis. The likelihood of ARDS increases with the accumulation of risk factors: incidence rates have been reported as 13%, 28.5%, 32%, and 50% in the presence of one, two, three, or four risk factors, respectively (Cutts et al., 2017).

The general mortality rate of ARDS ranges from 50% to 75%. Several clinical variables at the onset of ARDS are associated with poorer outcomes, including age above 60 years, severe hypoxemia (PaO2/FiO2 < 100 mmHg), extensive pulmonary infiltrates, sepsis as an underlying

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cause, chronic liver disease, extra-pulmonary organ dysfunction, overall illness severity, hypoalbuminemia, and prolonged hospital stay prior to ARDS onset (Lee et al., 2020).

Patients older than 75 years face a significantly greater mortality risk (around 60%) compared to those younger than 45 years (approximately 20%). Additionally, patients older than 60 years who have both ARDS and sepsis show a threefold increase in mortality compared to those under 60. ARDS can result from more than 60 different conditions that cause either direct or indirect lung injury. Mortality is highest in ARDS patients with sepsis and lowest in those with trauma-related ARDS. Deaths occurring early in the disease course are typically caused by the initial lung injury, while later deaths are more often due to complications such as hospital-acquired infections, multiple organ failure, and hemodynamic instability, rather than failure of gas exchange (Adrion et al., 2020).

Mortality increases with the severity of ARDS: from 11–31% in mild cases, to 33–49% in moderate cases, and 36–68% in severe cases. Three major studies found that mortality in patients with an initial PaO2/FiO2 ratio of 300 or less was comparable to those with a ratio of 200 or less. In the study by Shor et al. (2006), no significant difference in mortality was seen between moderate and severe ARDS groups (41.2% and 36.8%, respectively; $P = 0.25$).

Hypophosphatemia may directly contribute to increased mortality or reflect the overall severity of the illness. Sakhawey et al. (2012) identified a statistically significant association between severe hypophosphatemia and mortality among patients receiving ventilator support. Their retrospective study suggested that severe hypophosphatemia (phosphate <1 mg/dL) could lead to respiratory failure and was associated with a fourfold increase in death risk. Furthermore, hypophosphatemia was described as an independent risk factor for mortality in critically ill patients. Supporting these findings, other researchers, including Hoffmann et al. and Cohen et al., have also demonstrated a link between low phosphate levels and higher mortality rates (Cohen et al., 2004).

In the current study, 6% of patients exhibited hyperphosphatemia, with a maximum recorded level of 6 mg/dL. Rhabdomyolysis triggered by hypophosphatemia may have occurred due to instability in cellular membranes from ATP depletion, leading to phosphate release from damaged myocytes and subsequent increases in serum phosphate. Patients with serum phosphate levels above 6.5 mg/dL were reported to have higher mortality (Hoffmann et al., 2008).

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The phosphate cutoff value determined in this study was 3.1 mg/dL. Serum phosphate levels below this threshold were associated with increased mortality risk, showing 80% sensitivity, 60% specificity, and 72% diagnostic accuracy.

Although a level of 3.1 mg/dL falls within the standard reference range, critically ill patients often present with multi-organ failure, electrolyte disturbances, and hypoalbuminemia. They are also typically treated with medications such as antacids, diuretics, corticosteroids, and intravenous dextrose, all of which can contribute to the development of hypophosphatemia. Despite this, hypophosphatemia remains one of the most overlooked electrolyte imbalances in clinical settings. Many medical conditions and commonly used drugs can induce it. According to Arend et al. (2012), patients with serum phosphate levels below 3.1 mg/dL required more intensive medical intervention.

CONCLUSION

There is a statistically significant association between hypophosphatemia and mortality among ARDS patients. Hypophosphatemia is considered a poor prognosis.

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