ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Risk Factors For Development Of Refeeding Syndrome-Like Hypophosphatemia In Critically Ill Children In Zagazig University Hospitals

Dina Gamal Abdel Mohsen[1],NahedKhater[1], Dalia A. Rahman[1], andAbeer Abd Alla[1]
[1]Pediatrics Department, Faculty of Medicine, Zagazig University, Alsharquia, Egypt.
Correspondence: dr.dinagamal2020@gmail.com

Abstract
Background: Hypophosphatemia is a metabolic disturbance with potentially serious complications and is often unrecognized in critically ill children. Symptoms of hypophosphatemia are unspecific in the majority of cases and include fatigue and irritability, severe hypophosphatemia (less than 1.0 mg/dl) may lead to more serious problemssuch as reduced diaphragmatic contractility and cardiac arrhythmias.
Aim of the Study: Estimate the incidence of hypophosphatemia in critically ill children, study its clinical effects and risk factors in patients during their stay in PICU.
Patients and Methods:A case-control study that was conducted over a period of one year, from June 2018 to May 2019, at PICU of Pediatrics Department, Zagazig University Hospitals.The study included 180 subjects that were classified into two groups, each of 90 subjects as follows;patients group, which included 90 cases,and the control group, which included 90 healthy infants and children.
Results:There was a statistically significant difference between the studied groups regarding weight, height percentile, ESR and CRP, hemoglobin level, TLC, PT, INR, alkaline phosphatase a serum, serum creatinine, PH, serum phosphorus level, presence of hypophosphatemia as 20% had hypophosphatemia, number of patients with hypophosphatemia, percent change in serum phosphorus, percent change in serum potassium, degree of hypophosphatemia and either duration of hospital stays and duration of MV.
Conclusion: The apparent acceptable cause of hypophosphatemia in our study is delayed TPN decision and sepsis. Mild to moderate hypophosphatemia developed in PICU. Hypophosphatemia was associated with prolongation of the duration of PICU stay and bad outcomes.
Keyword: Hypophosphatemia; Critical Ill children; Risk factors.

1. Introduction

Hypophosphatemia is a metabolic disturbance with potentially serious complications and is often unrecognized in critically ill children [1].Phosphate ions are critical for bone mineralization and play a vital role in a number of other biological processes such as signal transudation, nucleotide metabolism, adenosine triphosphate (ATP) production, and enzyme regulation[2].

Symptoms of hypophosphatemia are unspecific in the majority of cases and include fatigue and irritability, severe hypophosphatemia (less than 1.0 mg/dl) may lead to more serious problemssuch as reduced diaphragmatic contractility, cardiac arrhythmias, myocardial reduction, and severe congestive cardiac insufficiency in the postoperative period of cardiac surgery [3], leukocyte dysfunction and neuromuscular disturbance [4]

Potential risk factors for the development of hypophosphatemia in critically ill children include malnutrition, starvation for more than 3days, sepsis [5], catecholamine's administration, antacids, B2 agonist administration, trauma, diuretic, steroid therapy [6], excessive parenteral glucose administration and respiratory alkalosis[7].

2. Patients and Methods:

2.1. Study design:

This study was a case-control study that was conducted over a period of one year, from June 2018 to May 2019, at PICU of Pediatrics Department, Zagazig University Hospitals.

2.2. Study Subjects:

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

The study included 180 subjects that were classified into two groups, each of 90 subjects as follows:

A. Patients group: included 90 cases who attended the PICU Pediatrics department faculty of Medicine Zagazig University.
B. Control group: included 90 healthy infants and children.

2.2.1. Inclusion criteria:

Both genders are included, age above one month and below 18 years, Presentation with critically illness and ICU admission, and PICU admission more than seven days.

2.2.2. Exclusion criteria

Malnutritioned patients presented with chronic diseases such as renal, hepatic, and cardiac diseases, diabetic ketoacidosis, acute renal failure, hemodynamic instability, patients outside age group, oncology cases and starved patients, and those who stayed less than seven days and patients who refused to be enrolled in this study.

2.2.3. Patients consent

Written informed consent was obtained from all patients or their parents before inclusion in the study after describing and explaining the whole study design. Moreover, the study was approved by the local ethical committee.

2.3. Methodology:

All patients were subjected to the following:

a- Full history taking:

- Present history; for critical illness, history of using medication especially which has a significant effect on phosphorus level(catecholamines, antacids, steroids, and diuretics.
- Past history of previous admission, chronic illness, drug intake and operation.
- Family history: similar condition, consanguinity and socioeconomic state.

b- Full general examination:

- Includes weight for age and height for age, vital signs and appearance, activity

c- Complete local examination:

- Cardiovascular system, central nervous system, musculoskeletal system, respiratory system and abdominal examination.

d- Investigation:

- Routine laboratory investigations include:
- Liver function tests (serum albumin, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase), kidney function tests (serum creatinine, blood urea nitrogen) and random blood sugar (RBS) **(Cobas 8000, Roche diagnostics)**.
- Complete blood count (CBC) measured by (**Sysmex XN 2000, SIEMENS).**
- C- reactive protein (CRP) **(Cobas 8000, Roche diagnostics)** and erythrocyte sedimentation rate.
- Bleeding profile (prothrombin time(PT), international normalized ratio(INR) measured by **(CA 1500 Sysmex)**.

Serum electrolytes and minerals level (potassium, sodium, calcium, phosphorus, and magnesium) **(Cobas 8000, Roche diagnostics)**. Patients were classified according to serum phosphorus level into normal phosphorus level 2.5-4.5 mg/dl, mild hypophosphatemia with serum phosphorus 2-2.5 mg/dl, moderate hypophosphatemia 1-2 mg/dl and sever hypophosphatemia <1 mg/dl)

2.3.1. Statistical Analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using the Chi-square test and Fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Mann Whitney test (used with non-normally distributed data) was used to compare medians of two groups, and an independent sample t-test (used with normally distributed data) was used to compare the means of two groups. To compare medians of more than two groups over time, Kruskal Wallis test was used. To compare the change in parametric data within one group before and after, paired-sample t-test is used. To compare change in non-parametric data within one group before and after, Wilcoxon signed-rank test is used. Spearman rank correlation coefficient was used to assess the strength and direction of a linear relationship between two variables. The levelof statistical significance was set at 5% ($P<0.05$). A highly significant difference was present if $p\leq0.001$.

3. Results:

Table (1): Correlation between the studied groups regarding demographic and anthropometric characteristics:

Anthropometric measures	**Groups** **Patient group** **N=90 (%)**	**Control group** **N=90 (%)**	**Test** **Z / t**	**p**
BMI (kg/m^2):				
Mean ± SD	15.38±1.65	15.24±1.64	t (0.604)	0.547
Median (Range)	14.88(12.86-21.63)	14.87(12.86-21.63)		
Demographic characteristics	**Groups** **Patient group** **N=90 (%)**	**Control group** **N=90 (%)**	**Test** **χ^2 / t**	**p**
Weight percentiles				
5-10th	6 (6.6%)	0 (0.0%)		
10-25th	5 (5.5%)	12 (13.3%)		
25-50th	20 (22.2%)	26 (28.8%)	16.3	0.006*
50-75th	45 (50%)	28 (31.3%)		
75-90th	12 (13.3%)	20 (22.2%)		
90-97th	2 (2.2%)	4 (4.4%)		
Height percentiles				
5-10th	10 (11.1%)	0 (0.0%)		
10-25th	5 (5.5%)	5 (5.5%)		
25-50th	15 (16.6%)	28 (31.3%)	25.5	<0.001*
50-75th	23 (25.5%)	39 (43.3%)		
75-90th	31 (34.4%)	13 (14.4%)		
90-97th	6 (6.7%)	5 (5.5%)		
Gender:				
Male	49 (54.4)	46 (51.1)	0.201	0.654
Female	41 (45.6)	44 (48.9)		
Age (years):				
Mean ± SD	3.73 ± 3.53	3.48 ± 3.35	z 0.406)	0.685
Range	3 (3 month – 11yrs)	3 (3 month – 13yrs)		

χ^2 Chi-square test t Independent sample t-test Z Mann Whitney test

Table 1 demonstrates that there was a statistically non-significant difference between the studied groups regarding age or gender.
There was a statistically significant difference between the studied groups regarding weight, height percentile.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table (2): Correlation between the studied groups regarding blood picture, ESR, and CRP on admission and after seven days of hospital stay:

Acute phase reactants	Groups Patients group Mean ± SD	Median (Range)	Control group Mean ± SD	Median (Range)	Test Z	p
ESR on admission (mm/hour)	29.98±9.47	32(14-46)	6.84±1.96	7(3-12)	11.6	<0.001**
ESR after 7 days (mm/hour)	19.73±6.89	20(2-35)				
P (Wx)	<0.00 1**					
CRP admission (mg/dl)	16.03 ± 26.51	3 (1 – 89.7)	2.02 ± 0.553	2 (1 – 3)	5.103	<0.001**
CRP after7 days (mg/dl)	16.13 ± 26.51	3 (1 – 85.5)				
P (Wx)	0.823					
CBC	**Groups Patients group Mean ± SD**	**Range**	**Control group Mean ± SD**	**Range**	**Test t**	**p**
Hemoglobin on admission (g/dl)	10.39 ± 0.9	9 – 11.9	14.12 ± 1.28	11.6 – 16.6	22.665	<0.001**
Hemoglobin after 7 days (g/dl)	10.43 ± 1.14	8.3 – 12.9				
P (paired t)	0.593					
TLC on admission ($\times 10^3$/ul)	6.53 ± 1.88	2.1 –6.9	4.43 ± 1.39	3.5 –9.5	8.524	<0.001**
TLC after7 days ($\times 10^3$/ul)	6.74 ± 1.78	2.1 – 8.2				
P (paired t)	0.397					

****p≤0.001 is statistically highly significant t Independent sample t-test Wx Wilcoxon signed-rank test Z Mann Whitney test**

Table 2clarifies that there was a statistically significant difference between the studied groups regarding ESR and CRP on admission. In the patients' group, there was a significant decrease in ESR after 7days, while there was a non-significant change in CRP after seven days.

There was a statistically significant difference between the studied groups regarding hemoglobin level and TLC on admission. There was a non-significant change in hemoglobin level or TLC in the patients' group after seven days.

Table (3): Comparison between the studied groups regarding liver function tests and bleeding profile on admission and after seven days of hospital stay:

Bleeding profile	Groups Patients group Mean ± SD	Range	Control group Mean ± SD	Range	Test t	p
PT on admission (sec.)	15.4 ± 2.52	11 – 19.9	12.228 ± 0.678	11 – 13.5	11.564	<0.001**
PT after 7 days (sec.)	15.35 ± 2.64	10.8 – 21				

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

P (paired t)	0.544					
INR on admission	1.24 ± 0.24	0.8 – 1.7	0.95 ± 0.09	0.8 – 1.1	10.448	<0.001**
INR after 7 days	1.24 ± 0.27	0.7 – 1.8				
P (paired t)	0.899					
Liver function tests	**Groups**				**Test**	
	Patients group		**Control group**		**t/Z**	**p**
	Mean ± SD	**Range**	**Mean ± SD**	**Range**		
RBS on admission (mg/dl)	118.59 ± 10.53	100 – 140	106.24 ± 19.48	80 – 140	5.29	<0.001**
RBS after 7 days (mg/dl)	116.24 ± 21.35	73 - 152				
P (paired t)	0.073					
AST on admission (u/l)	25.73 ± 8.86	11 – 40	23.98 ± 8.43	10 – 40	1.361	0.175
AST after 7 days (u/l)	25.51 ± 8.81	10 – 43				
P (paired t)	0.195					
ALT on admission (u\l)	29.73 ± 14.69	7 – 56	31.57 ± 15.24	7 – 56	0.822	0.412
ALT after 7 days (u/l)	29.98 ± 15.05	7 – 59				
Albumin on admission (g/dl)	3.42 ± 0.56	2.1 – 4.3	3.98 ± 0.56	2.5 – 4.5	6.708	<0.001**
Albumin after7 days (g/dl)	3.09 ± 0.59	1.8 – 4.1				
	<0.001**					
P (paired t)	0.264					
Alkaline phosphatase on admission (u/l)	192.88 ± 93.02	205.5 (44–349)	90.93 ± 31.23	88.5 (40 – 147)	Z 7.224)	<0.001**
Alkaline phosphatase after7 days (u/l)	100.56 ± 35.24	101 (44 – 201)				
P (WX)	<0.001**					

****p≤0.001 is statistically highly significant t Independent sample t-test significant Z Mann Whitney test Wx Wilcoxon signed-rank test significant RBS random blood sugar**

Table 3 shows that there was a statistically significant difference between the studied groups regarding PT and INR on admission. In the patients' group, there was a non-significant change in PT or INR after seven days.

There was a statistically significant difference between the studied groups regarding alkaline phosphatase and serum albumin on admission. While, there was a non-significant difference between them regarding liver enzymes (AST, ALT) on admission.

In the Patients group, there was a significant change in alkaline phosphatase and serum albumin after 7days, while there was a non-significant change in liver enzymes (ALT or AST) after seven days.

There was a statistically significant difference between the studied groups regarding RBS on admission. In the Patients group, there was a non-significant change in RBS after seven days.

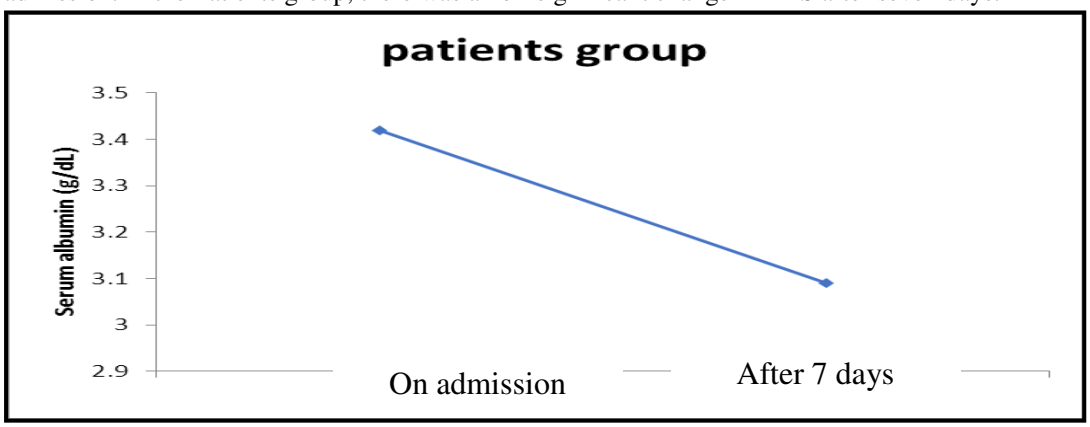

Fig. (1): Multiple line graph showing serum albumin on admission and after 7 days among the patients groups.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

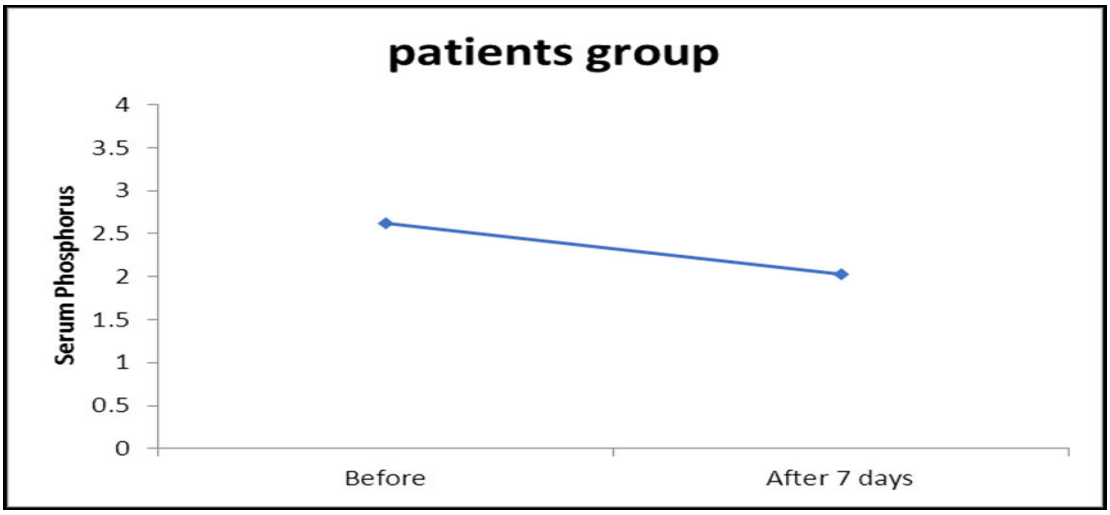

Fig. (2): Multiple line graph showing serum phosphorus levels in patients group on admission and after 7 days.

Table (4): Correlation between the studied groups regarding phosphorus level on admission and after 7 days of hospital stay:

Phosphorus	**Groups**				**Test**	
	Case group		**Control group**		**t**	**p**
	Mean ± SD	**Range**	**Mean ± SD**	**Range**		
On admission	2.62± 0.115	2.41 – 2.8	3.415 ± 0.577	2.91 – 4.54	12.805	<0.001**
After 7days	2.027 ± 0.299	1.51 – 2.49				
P (paired t)	<0.001**					

****p≤0.001 is statistically highly significant t Independent sample t-test**

Table 4 shows that there was a statistically significant difference between the studied groups regarding serum phosphorus level on admission. In the patients' group, there was a significant decrease in serum phosphorus level after seven days.

Table (5): Grading of the studied groups regarding presence of hypophosphatemia:

Serum phosphorus	**Groups**		**Test**	
	Patients group	**Control group**	χ^2	**p**
	N (%)	**N (%)**		
On admission:				
Mild hypo	18 (20%)	0 (0%)	Fisher	<0.001**
Normal	72 (80%)	90 (100%)		
After 7 days				
Moderate Hypo	42 (46.7%)		143.73	<0.001**
Mild hypo	48 (53.3%)			
Normal	0 (0%)			
p	<0.001**			

****p≤0.001 is statistically highly significant**

On admission After 7 days

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table 5confirmsa significant difference in the patients' group regarding the presence of hypophosphatemia as 20% had hypophosphatemia on admission, and all patients had hypophosphatemia after 7 days. None of the control groups had hypophosphatemia.

There was a statistically significant increase in the number of patients with hypophosphatemia among the Patients group on admission and after seven days.

Table (6): Relation between percent change in serum phosphorus and gender:

	Mean ± SD	Median (range)	Z	p
Gender:				
Male	22.05±12.89	23.05(1.63-44.89)	0.304	0.761
Female	22.91±11.73	22.22(4.96-42.44)		

KW Kruskal Wallis test Z Mann Whitney test

Table 6 shows that there was a statistically non-significant difference between percent change in serum phosphorus and gender p=0.761.

Table (7): Correlation between percent change in serum phosphorus and both percent change in blood electrolytes, minerals, and alkaline phosphatase in the studied patients:

Percent change in	Percent change in serum phosphorus	
	R	p
Calcium	0.047	0.658
Sodium	-0.05	0.637
Potassium	-0.208	0.049*
Alkaline phosphatase	-0.164	0.123

r Spearman correlation coefficient p>0.05 is statistically non-significant

Table 7 shows a statistically significant negative correlation between percent change in serum phosphorus and percent change in serum potassium. There was a statistically non-significant correlation between percent change in serum phosphorus and percent change in either sodium, calcium or alkaline phosphatase.

Table (8): Relation between hypophosphatemia and CRP on admission and after7 days of hospital stay:

CRP	Hypophosphatemia Mild	Moderate	Test	
	Median (range)	Median (range)	Z	p
On admission	2.6 (1.1 – 86.6)	3.5 (1 – 89.7)	- 1.711	0.087
After 7 days	2.4 (1 – 85.5)	3.5 (1 – 85.5)	-1.639	0.101

Z Mann Whitney test

Table 8demonstrates that there was no statistically significant difference between percent change in serum phosphorus and CRP.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Table (9): Relation between hypophosphatemia and both duration of hospital stays and duration of mechanical ventilation:

Parameter	Hypophosphatemia Mild N=48	Moderate N=42	Test t	p
Duration of Hospital stay: Mean ± SD	10.458 ± 2.625	10.381 ± 2.4909	0.145	0.885
Duration of MV: Mean ± SD	6.9 ± 2.628	6.83 ± 3.425	0.101	0.92

t Independent sample t-test

Table 9 shows that there was non-significant relation between the degree of hypophosphatemia and either duration of hospital stays and duration of MV.

Table (10): linear regression of potassium variables associated with percent change in serum phosphorus among the studied patients:

	Unstandardized Coefficients		Standardized Coefficients	t	p
	β	SE	β		
Percent change in serum potassium	-0.469	0.232	-0.21	2.018	0.047*

SE standard error

Table 10 clarifies that Percent change in serum potassium is significantly associated with the percent change in serum phosphorus (unstandardized β=- 0.469, p<0.05).

Table (11): Relation between hypophosphatemia and normal cases of patients group on admission regarding the duration of hospital stay and duration of mechanical ventilation:

Parameter	Hypophosphatemia N=18	Normo-phosphatemia N=72	Test t	p
Hospital stay:				
Mean ± SD	14.58 ± 2.625	9.81 ± 2.19	7.92	<0.001
Range	10 - 20	8 – 15		
MV days:				
Mean ± SD	10.9 ± 2.28	5.83 ± 1.25	12.8	<0.001
range	9 - 13	6 - 8		

t Independent sample t-test

Table 11 shows that there was a highly significant relationship between the degree of hypophosphatemia and either duration of hospital stays and duration of MV.

Table (12): Relation between hypophosphatemia and normal cases of patients group regarding drugs used in PICU:

Parameter	Hypophosphatemia	Normo-phosphatemia	Test

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

	N=18	N=72		p
Outcome:	N (%)	N (%)		
Discharged (n=69)	2 (11.1%)	67 (93.1%)	FET	<0.001
Expired (n=21)	16 (88.9%)	5 (6.9%)		

There was a highly significant relationship between the degree of hypophosphatemia and the bad outcome of patients.

**** P-value <0.001 is highly significant**

Table 12displaysa statistically significant relation between hypophosphatemia and drugs used for treatment in PICU, as most of the patients received furosemide (90%), dopamine (77.8%), and steroid (88.8%).

4. Discussion

Hypophosphatemia is a metabolic disturbance with potentially serious complications and is often unrecognized in critically ill children [1].

Phosphate is a constituent of various intermediate compounds involved in key physiological processes such as adenosine triphosphate, 2,3 diphosphoglycerate, and intracellular chemical messengers (e.g., cyclical adenosine monophosphate, cyclical guanosine monophosphate). Electrolyte disorders frequently develop in critically ill patients during the course oftheir stay in PICU. Phosphate disturbance is one of those frequently encountered electrolyte disorders. These are at increased risk of morbidity. Hypophosphatemia is a metabolic disturbance with potential serious complications and is often unrecognized in critically ill children (CIC) [1].

Symptoms of hypophosphatemia is unspecific in the majority of cases and include fatigue and irritability, severe hypophosphatemia (less than 1.0 mg/dl) may lead to more serious problemssuch as reduced diaphragmatic contractility, cardiac arrhythmias, myocardial reduction, and severe congestive cardiac insufficiency in the postoperative period of cardiac surgery [3].

Our study aimed to estimate the prevalence of hypophosphatemia and identify risk factors and outcomes associated with this disturbance in children admitted to our PICU, Pediatrics Department, Faculty of Medicine, Zagazig University.

In this case-control study, hypophosphatemia was common in critically ill children. The prevalence of hypophosphatemia among critically ill children admitted to PICU was 20%, as we detect 18 patients out of 90 CIC on admission. By follow-up of patients group after sevendays, we found that all patients developed hypophosphatemia, the prevalence of mild hypophosphatemia was 53.3% (48 patients out of 90 CIC) and prevalence of moderate hypophosphatemia was 46.7% (42 patients out of 90 CIC). Our prevalence was higher than **De Menezes et al. (2006)** [8]as they found that76 %(32 of the 42children) reported in a retrospective study conducted in CIChad hypophosphatemia, also **Shah et al., (2016)** [9].Found that the prevalence of hypophosphatemia was 71.6 % in the first ten days of admission; however, **Berndt et al. (2005)** [2] found that the prevalence of hypophosphatemia exceeded 50% in their study, and **Rady and Khalek Mohamed (2014)** [10] found that prevalence of hypophosphatemia on day 1 was 58% (n=42/72).

Seven percent of the patients (n=5) developed hypophosphatemia during their PICU stay, and 12.5% (n=9) of children who were hypophosphatemic at day 1 remained hypophosphatemic at day 7, while 8% (n=6) recovered from hypophosphatemia with treatment. The apparent acceptable cause of developing all patients group of our study hypophosphatemia after seven days was increased reliance on total parenteral nutrition as all patient was on parenteral nutrition for at least seven days also sepsis had a role.

In a review of clinical studies done on hypophosphatemia in a pediatric intensive care unit (PICU) patients, **Landenperg and Shoenfeld (2001)** [5] explain the development of hypophosphatemia, saying thatpotential risk factors for the development of hypophosphatemia in critically ill children include

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

malnutrition**,** starvation for more than 3days, sepsis. Also,**Rady and Khalek Mohamed (2014)** [10] revealed that hypophosphatemia was a common problem in PICU and was associated with the presence of respiratory complaints, higher PIM, and increased starvation days. These factors might be considered as risk factors for hypophosphatemia in critically ill children, mainly when they occur together.

In our study, we found that chest problems (pneumonia, pneumothorax, pleural effusion, and pulmonary edema) complicated by respiratory failure account for 60% (54patients out of 90 CIC), which were the highest percentage of the cause of admission, followed by sepsis that account for 22.3% (20 patients out of 90 CIC) than heart failure 15.5%(14 patients out of 90 CIC) lastly head trauma 2.2%(2patients out of 90 CIC). **Rady and Khalek Mohamed (2014)** [10] found that 56% of patients presenting with respiratory disorders were hypophosphatemic. Similarly, **Santana e Menses et al. (2009)** [1] found that patients diagnosed with respiratory disease were more likely to have hypophosphatemia than other subjects. Also,**Fiaccadori et al. (1994)** [11]found that 25% of adult patients admitted to the ICU with the chronic obstructive pulmonary disease were found to be hypophosphatemia. **Kilic et al. (2012)** [12]explain that the adding-on effect of hypophosphatemia to their respiratory problems might be attributed to the fact that hypophosphatemia is known to lead to muscle weakness and hypotonia.

In our study, we found a highly significant relationship between the degree of hypophosphatemia and duration of using mechanical ventilation as all patients admitted to PICU were mechanically ventilated from the start for a period ranged (6 to 13 days) with a median of 8 days, so hypophosphatemia seems to be the apparent cause of prolonged need of ventilator support and difficult early weaning, this confirmed the results of the study done by **Rady and Khalek Mohamed, (2014)**[10]that reportedhypophosphatemic patients were more likely ventilated and to spend more days on ventilation than normophosphatemic patients as thirty-five percent (n=25) of all children were mechanically ventilated. Also,**El Shazly et al. (2017)**[13] found an independent association between hypophosphatemia and prolonged mechanical ventilation as most patients were hypophosphatemia before the need for mechanical ventilation, so hypophosphatemia leads to prolonged ventilator support. In contrast,**Souza de Menezes et al. (2006)** [14] found that there was no significant association between hypophosphatemia and the use of mechanical ventilation. This might be explained by **Subramanian, and Khardori (2000)** [15], who suggested that hypophosphatemia causes deficiency in the intermediary compounds for energy production, such as adenosine triphosphate and 2,3-diphosphoglycerate and alterations in energy metabolism, which may lead to respiratory muscle weakness and consequent worsening of respiratory insufficiency, also**Aubier et al., (1985)** [16]found that the difficulty of weaning patients from mechanical ventilation is because of reduced efficiency of respiratory, muscular contraction.

Hypophosphatemia affects the duration of PICU stay, and we found a highly significant negative correlation between the degree of hypophosphatemia and duration of hospital stay as the duration of hospital stay was ranged from 8 to 20 days with a median of 12 days. This agreed with **Kilic et al. (2012)** [12]and **Shah et al. (2016)** [9], who reported that hypophosphatemia was associated with prolonged PICU length of stay > 6 days). Also,**El Shazly et al. (2017)** [13] found that there was a highly significant difference between the normophosphatemic group and the hypophosphatemic group regarding PICU stay, and **Rady and Khalek Mohamed (2014)** [10] found that those with the normal serum phosphorus level were discharged earlier than those with hypophosphatemia (discharged rather than died).

Our results revealed a highly significant association between hypophosphatemia and bad outcome of patients during the study period as 21 patients died during the study, 16 of them (88.9%) were hypophosphatemic on admission while 93.1% who survived were normophosphatemic on admission. This agreed with the study done by **Manary et al. (1998)** [17] and **Souza de Meneses et al. (2006)** [14]; patients with normal serum phosphorus levels on admission had better outcomes (discharged rather than died).Also,**Solomon and Kirby (1990)** [18], **Shor et al., (2006)** [19],and**Sakhawey et al. (2015)** [20]found that the Intensive care unit mortality rate was significantly higher in patients who presented with hypophosphatemia at ICU admission or developed hypophosphatemia on the day of ICU admission compared with patients without hypophosphatemia.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

As regards the demographic data, this study includes 90 critically ill children, their median Age 3 years (range 3months to 11years), (54.4%) of them were males and (45.6%) were females. There was astatistically non-significant correlation between percent change in serum phosphorus and both genderp=0.761, patients' age, and anthropometric measures. Also, the control group included 90 healthy children, their median Age 3 years (range 3months to 13years), (51.1%) of them were males, and (48.9%) were females. There was a statistically significant difference between the studied groups regarding weight and height percentiles. However,**Basri et al. (2012)** [21] found that hypophosphatemia was more common in female patients (67%) compared to male patients (33%), while **Shahsavarinia et al. (2016)** [22] found no significant difference in the incidence of hypophosphatemia regarding sex: in males (54.2%) and (45.8) in females.

In the present study, CRP was statistically significantly higher on admission in the patients' group than the control group. There was a non-significant change in CRP in the patients' group after seven days of the PICU stay. There was a statistically non-significant negative correlation between percent change in serum phosphorus and CRP level on admission. This agreed with **Rady and Khalek Mohamed (2014)** [10],whofound that CRP and positive cultures correlated significantly with hypophosphatemia. Also,**Antachopoulos et al. (2002)** [23]foundthat studying acute infectious disease in pediatrics, not including critically ill children, demonstrated a significant negative correlation between serum level of phosphate and CRP. Also,**Barak et al. (1998)** [24]indicate that infections and sepsis were correlated with hypophosphatemia.

Regarding ESR, it was statistically significantly higher in the patients' group than the control group on admission. There was a significant decrease in ESR in the patients' group after seven days of the PICU stay.

CBC findings showed a statistically significant difference in hemoglobin level and TLC on admission between patients and controls, most probably due to sepsis. In the patients' group, there was a non-significant change in hemoglobin or TLC after seven days of the PICU stay. This was explained by **Solomon and Kirby (1990)** [18], who found that the decline in levels of 2,3-diphosphoglycerate triggered by hypophosphatemia increases hemoglobin's affinity for oxygen, thereby causing tissue hypoxia and leading to changes in erythrocytes and leukocyte functions, hemolytic anemia, platelet dysfunction, and thrombocytopenia. Also,**Sharma et al. (2019)** [25]found that hypophosphatemia cause thrombocytopenia, impaired clotting processes, and reduced leukocyte phagocytosis; hemolysis also can occur.

Also, kidney function tests showed a statistically significant difference between the studied groups regarding serum creatinine on admission (in the patients' group than in the control group). But there was a statistically non-significant difference between the studied groups regarding BUN on admission. In the patients' group, there was a non-significant change in serum creatinine or BUN over time.

The liver function tests showed a statistically significant difference between the studied groups regarding serum albumin (lower in patients group) (3.42±0.56 vs. 3.98 ± 0.56) and alkaline phosphatase (higher in patients group) (192.88 ± 93.02 vs. 90.93 ± 31.23) on admission. On the other hand, there was a non-significant difference between them in liver enzyme levels (ALT, AST) on admission. In the patients' group, there was a significant change in alkaline phosphatase and serum albumin over time. While, there was a non-significant change in liver enzyme levels (ALT, AST) after seven days of PICU stay. This was explained by **Foly et al. (1990)** [26]demonstrate the etiology of hypoalbuminemia in CIC, which may involve a number of mechanisms such as imbalance between albumin synthesis and degradation, increase capillary leakage, and altered intravascular. Tissue albumin distribution, also Horowit and Tai ,(2007) [27] found that inflammatory disorders can accelerate catabolism of albumin while simultaneously decrease its production. **Murray et al. (1988)** [28]demonstrate thatlow serum albumin concentration correlates with the increasing length of hospital stay in PICU and complications such as ventilator dependency.

The glycemic profile revealed a statistically significant difference between the studied groups by monitoring the random blood sugar (RBS) on admission (higher in patients group may be due to stress hyperglycemia). In the patients' group, there was a non-significant change in RBS over time.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Also, the bleeding profile showed a statistically significant difference between the studied groups regarding PT and INR on admission (higher in the patients' group than the control group but still within normal ranges). In the patient group, there was a non-significant change in PT or INR after seven days of the PICU stay.

Regarding blood electrolytes and minerals, there was a statistically non-significant difference between the studied groups regarding serum sodium, potassium, or calcium on admission. In the patients' group, there was a non-significant change in sodium or potassium; however, disturbance in phosphate homeostasis is often linked to abnormalities in calcium and bone mineralization.Therefor in this study, in the patients' group, serum calcium was significantly decreased after seven days than on admission (9.72±0.98 and 9.36±0.98) but still within normal ranges. Also, there was a statistically significant decrease in serum phosphorus on admission in the patients' group than in the control group (2.62 ± 0.115 and 3.915 ± 0.577). However, there was a significant decrease in phosphorus in the patients' group over time; also, there was no statistically significant difference among younger patients (less than three years) and older ones regarding the level of serum phosphorus on admission or after seven days. There was a statistically significant negative correlation between the percent change in serum phosphorus and that of serum potassium among the patients' group. There was a statistically non-significant correlation between percent change in serum phosphorus and percent change in either serum calcium or sodium. **Rady and Khalek Mohamed (2014)** [10] found that the mean serum phosphorus level was (3.5 mg/dl for day 1; 3.7 mg/dl for day 7). The mean serum phosphorus level was significantly lower in those less than three years old when compared to those above 3yrs old. **De Menezes et al. (2006)** [8]found that 32 of the 42 patients had hypophosphatemia (76.2 %), and the median level was 3.1 ± 0.7 mg/dL in their study. **Shah et al. (2016)** [9] estimated phosphate levels at D1 and D3, the median (range) serum phosphate concentrations on D1 and D3, were 3.7 (2.9, 4.4) mg/dl and 3.2 (2.5, 3.9) mg/dl respectively.

The arterial blood gases (ABG) for our patients' group were within normal on admission and after seven days, PH (7.32 ± 0.043 and. 7.399 ± 0.031), Hco3 (25.3±4.6 and 24.3±3.12), Pco2 (35 ± 4.37 and 34.967 ± 4.98). There was no significant change in the patients' group regarding Pco2, Hco3, and PH.

Our study revealed a significant association between drugs that had an effect onthe level of phosphorus like steroids, dopaminergic drugs, and furosemides used in PICU and hypophosphatemia. In contrast, **Rady and KhalekMohamed (2014)** [10]found that none of the drugs known to deplete serum phosphorus levels as a side effect to their use (catecholamines, antacids, anticonvulsants, steroids, diuretics) showed association with hypophosphatemia. On the contrary, **Santana e Meneses et al. (2009)** [1], in their study in PICU in 2009, found that dopamine was associated with hypophosphatemia and attributed this to increased urinary phosphorus excretion. Also, **Subramanian and Khardori (2000)** [15] reported the association between hypophosphatemia and diuretics or steroids.

Funding: No funding was received for this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References:

1. **Santana e Meneses JF, Leite HP, De Carvalho WB et al., (2009):** Hypophosphatemia in critically ill children: prevalence and associated risk factors. PediatrCrit Care Med., 10(2): 234-238.
2. **Berndt TJ, Schiavi S and Kumar R (2005):** "Phosphatonins" and the regulation of phosphorus homeostasis. Am J Physiol Renal Physiol 289(6): F1170-F1182
3. **Heames RM and Cope RA (2006): Hypophospatemia** causing profound cardiac failure after cardiac surgery. Anaesthesia 61(12): 1211-1213.
4. **Gassbeek A and Meinders AE (2005):** Hypophosphatemia: an update on its etiology and treatment. Am J Med 118(10): 1094-1101.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

5. **Landenberg PVandShoenfeld Y (2001):** new approaches in the diagnosis of sepsis. Isr Med Assoc J 3(6): 439-442.
6. **De Menezes FS, Leite HP, Fermandez J, Benzecry SG and de Carvalho WB (2004):** Hypophospatemia in critically ill children. Rev Hosp Clin Fac Med Sao Paulo 59(5):306-311.
7. **Thomas C and Fourrier F (2003):** Hypophosphoremiesen reanimation. Reanimation12:280-287.
8. **De Menezes FS, Leite HP, Fernandez J, Benzecry SG and de Carvalho WB (2006):**Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med; 21(4): 235-9.
9. **Shah SK, Irshad M, Gupta N, Kabra SK and Lodha R (2016):** Hypophosphatemia in critically ill children: Risk factors, outcome and mechanism. Indian J. Pediatr.; 83(12): 1379-1385.
10. **Rady HI and Khalek Mohamed KA (2014):** Prevalence and Risk Factors of Hypophosphatemia in Pediatric Intensive Care Unit. J AnesthCrit Care Open Access; 1(6): 00033.
11. **Fiaccadori E, Coffrini E, Fracchia C, Rampulla C and Montagna T (1994):** Hypophosphatemia and phosphorus depletion in respiratory and peripheral muscles of patients with respiratory failure due to COPD. Chest; 105(5): 1392-1398.
12. **Kilic O, Demirkol D, Ucsel R, Citak A and Karabocuoglu M (2012):** Hypophosphatemia and its clinical implications in critically ill children: A retrospective study. Journal of Critical Care; 27: 474-479.
13. **El Shazly AN, Soliman DR, Assar EH, Behiry EG and Ahmed IAG (2017):** Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes. Annals of Medicine and Surgery; 21: 118-123.
14. **Souza de Menezes F, Leite HP, Fernandez J et al., (2006):** Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med., 21(4): 235-239.
15. **Subramanian R and Khardori R (2000):** severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. Medicine (Baltimore) 79(1): 1-8. 6.
16. **Aubier M, Murciano D, Lecogguic Y, Viires N, Jacquens, et al., (1985):** Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med 313(7): 420-424.18.
17. **Manary MJ, Hart CA, Whyte MP. (1998):** Severe hypophosphatemia in children with kwashiorkor is associated with increased mortality. J Pediatr; 133(6):789-791.
18. **Solomon SM and Kirby DF (1990):** The Refeeding Syndrome: A Review. JPEN J Parenter Enteral Nutr; 14(1): 90-97.
19. **Shor R, Halabe A, Rishver S et al., (2006):** Severe Hypophosphatemia in Sepsis as a Mortality Predictor. Ann Clin Lab Sci., 36(1): 67-72.
20. **Sakhawey A, Alawady S and Razek A (2015):** Effect of phosphate level on the outcome of critically ill patients in the intensive care unit. J Am Sci., 11: 82-88.
21. **Basri MN, Janattul AJ, Azrina MR et al., (2012):** Hypophosphatemia in the intensive care unit: incidence, predictors and management. IMJM. 11(1): 31-36.
22. **Shahsavarinia K, Motazedi Z, Mahmoudi L et al., (2016):** Hypophosphatemia in critically ill children. J Anal Res Clin Med., 4(3): 153-157.
23. **Antachopoulos C, Margeli A, Giannaki M, Bakoula C, Liakopoulou T, et al., (2002):** Transient hypophosphatemia associated with acute infectious disease in pediatric patients. Scand J Infect Dis 34(11): 836- 839.
24. **Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, et al., (1998):** Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. Am J Med 104(1): 40-47
25. **Sharma, S., Hashmi, M. F., and Castro, D. (2019):** Hypophosphatemia. In StatPearls [Internet]. StatPearls Publishing.
26. **Foley EF, Borlase BC, Dzik WH, Bistrian BR and Benotti PN.(1990):** Albumin supplementation in the critically ill. A prospective, randomized trial. Arch Surg; 125:73942.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

27. **Horowitz IN and Tai K.(2007):** Hypoalbuminemia in critically ill children. Archives of pediatrics & adolescent medicine. Nov 1; 161(11):1048-52.
28. **Murray MJ, Marsh HM, Wochos DN, Moxness KE, Offord KP and Callaway CW. (1988):** Nutritional assessment of intensive-care unit patients. Mayo Clin Proc.;63:1106–15.