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The Influence of Hypophosphatemia on ICU Outcomes in Elderly Critically Ill Patients

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Abstract

Objective: Hypophosphatemia is a critical condition in intensive care settings, often linked to adverse clinical outcomes. Elderly patients, due to factors such as malnutrition, comorbidities, and altered renal function, are vulnerable to this condition. This study aimed to evaluate the incidence, associated factors, and clinical implications of hypophosphatemia in elderly critically ill patients.

Materials and Methods: A retrospective cohort study was conducted in a tertiary intensive care unit (ICU) between January 2020 and December 2022. Patients aged ≥65 years were divided into two groups: hypophosphatemic and non-hypophosphatemic. Hypophosphatemia was defined as a serum phosphate level <2.5 mg/dL.

Results: Among 433 elderly critically ill patients, the incidence of hypophosphatemia was 18.5%. Logistic regression analysis identified cardiac decompensation as the reason for ICU admission [odds ratio (OR): 2.33, 95% confidence interval (CI): 1.09-4.95, p=0.028]; absence of renal injury according to the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification (OR: 3.83, 95% CI: 2.19-6.71, p<0.001); hypokalemia (OR: 2.61, 95% CI: 1.46-4.69, p=0.001); and hypoalbuminemia (OR: 2.61, 95% CI: 1.46-4.67, p=0.01) as independent risk factors for hypophosphatemia. Subgroup analysis revealed a higher prevalence of hypophosphatemia of 32.8%, in patients without renal injury according to the RIFLE classification. However, hypophosphatemia was not associated with adverse clinical outcomes, including the requirement of mechanical ventilation, an increased ICU length of stay, or higher mortality, even after excluding patients with renal injury according to the RIFLE classification.

Conclusion: Contrary to expectations, this study found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Although current literature has emphasized the association between hypophosphatemia and negative clinical outcomes, our study did not demonstrate this association, suggesting, hypophosphatemia is an indicator of disease severity rather than a risk factor for mortality.

Keywords: Clinical geriatrics, elderly critical ill, geriatric care management hypophosphatemia, intensive care management, mortality, refeeding syndrome

Introduction

Phosphate is an essential anion for cellular function, including energy production, cell membrane integrity, and muscle function, making its deficiency particularly detrimental in critically ill patients (1-4). Several studies have emphasized the association between hypophosphatemia and adverse clinical outcomes in intensive care unit (ICU) settings. (2-5). The mechanical ventilation (MV) requirement is significantly higher in hypophosphatemic patients, indicating more severe respiratory compromise (4). Longer ICU and hospital stays in patients with hypophosphatemia compared to those with normal phosphate levels have been demonstrated (2,4). Some studies have shown the link between hypophosphatemia and increased mortality in ICU patients (5). However, recent meta-analyses concluded that hypophosphatemia is an indicator of disease severity rather than an independent risk factor for mortality (1,6).

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Critically ill patients, including postoperative, septic, and trauma patients, are known to be at risk of hypophosphatemia due to decreased intestinal absorption, redistribution of extracellular fluids to intracellular compartments, increased consumption in catabolic phases, increased renal excretion, and iatrogenic complications of renal replacement therapy (RRT) (2-7). The incidence of hypophosphatemia in this patient group varies widely, with some studies reporting rates as high as 28-60% (1). Hypophosphatemia often coexists with other electrolyte abnormalities, such as hypokalemia and hypomagnesemia, complicating the clinical picture. Additionally, low serum albumin levels, indicative of poor nutritional status, are frequently observed in patients with hypophosphatemia (4). Elderly patients are particularly vulnerable to hypophosphatemia due to factors such as malnutrition and associated refeeding syndrome, impaired renal function, and the use of medications like diuretics, steroids, and some antimicrobials that can contribute to phosphate depletion (7-10). Understanding the prevalence and implications of hypophosphatemia in the elderly population is crucial for improving patient outcomes. In the current literature, few studies reveal the clinical consequences of hypophosphatemia, especially in elderly critically ill patients. With this study, we aimed to reveal the incidence of hypophosphatemia, concurrent electrolyte disorders, associated factors, and outcomes in the elderly critically ill population.

Materials and Methods

Study Design and Setting

This retrospective cohort study was carried out in the nine-bed tertiary medical ICU at Gazi University Hospital between January 2020 and December 2022. The research protocol was approved by the Local Ethics Committee of Gazi University, Faculty of Medicine, (approval number: 996621, research code number: 2024-1132, date: 09.07.2024). Informed consent was not obtained as the data were collected retrospectively. This study protocol also complied with the Declaration of Helsinki.

Participants

Critically ill patients were included if they were ≥65 years old. Patients were excluded if they died within 24 hours, were transferred from other ICUs, or had recurrent ICU admissions. Patients without serum phosphate levels on admission to the ICU were also excluded from the study.

Data Collection

Epidemiological and laboratory data were retrieved from electronic hospital systems and medical archives. We collected demographic details, including age, gender, ICU admission causes, comorbidities, and clinical severity assessments such as the Glasgow Coma Scale, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) Score, as well as the infection source in septic patients. Additionally, data regarding the clinical parameters related to ICU admission, RRT requirement , and nutritional support, albumin replacement, length of ICU stay, and ICU mortality rates were documented.

The APACHE II, RIFLE, and SOFA scores were computed within the initial 24 hours of ICU admission to assess the severity of the illness. Hypophosphatemia was defined as a serum phosphate level under 2.5 mg/dL (<0.81 mmol/L) on ICU admission (11). The other electrolyte disorders were also defined according to the lower limit of the reference laboratory of Gazi University Hospital: hypokalemia as a serum potassium level was under 3.5 mEq/L, hypomagnesemia as a serum magnesium level was under 1.3 mg/dL, and hypoalbuminemia as a serum albumin level was under 3.0 g/dL on ICU admission.

Statistics

Continuous variables were reported as mean ± standard deviation or median with interquartile range, depending on their distribution. Categorical variables were summarized as frequencies and percentages. The Mann-Whitney U test was used to compare the medians of continuous variables, and the chi-squared test was used to compare categorical variables. Patients were categorized into two groups based on the presence of hypophosphatemia. Data were compared between both hypophosphatemic and non-hypophosphatemic patients. Due to the higher prevalence of renal injury in non-hypophosphatemic patients according to the RIFLE classification, a subgroup analysis was performed on non-hypophosphatemic patients without renal injury at ICU admission due to the higher prevalence of renal injury, was performed on patients without renal injury based on the RIFLE classification at ICU admission. Variables associated with ICU mortality were also analyzed and provided in a supplementary file. Logistic regression analysis was used to determine independent risk factors for hypophosphatemia and ICU mortality. A p-value of <0.05 was considered statistically significant. All analyses were performed using the SPSS statistical program version 22.0 (IBM Corp., New York, NY).

Results

Six hundred seventy-nine ICU admissions were detected during the study period. After excluding patients aged under 65, those who stayed less than 24 hours, and those with recurrent ICU admissions, 433 patients were included in further statistical analysis. The baseline characteristics and ICU-related data according to hypophosphatemia on ICU admission are given in Tables 1 and 2. Hypophosphatemia prevalence was 18.5% within the study population. In terms of reasons for ICU admission, cardiac decompensation was observed more frequently in

hypophosphatemic patients, while renal failure was detected at a higher rate in non-hypophosphatemic patients (cardiac decompensation 13.8% vs. 2.6%, p=0.02, renal failure 28.8% vs. 54.7%, p<0.001) (Table 1). According to the RIFLE classification at ICU admission, the risk, injury, loss, and end-stage renal disease categories were higher in non-hypophosphatemic patients (p-values, respectively 0.045, 0.053, 0.014, and <0.017) (Table 1). The two groups had no difference in the requirement for MV, nutritional support, albumin replacement, ICU mortality, length of ICU stay, and length of hospital stay prior to ICU admission (Table 1). When laboratory findings on ICU admission were compared, blood urea nitrogen (BUN), creatinine, potassium, magnesium, and albumin were significantly lower among hypophosphatemic patients (Table 2). Based on the evaluation of risk factors associated with hypophosphatemia on ICU admission using logistic regression analysis, cardiac decompensation as a reason for ICU admission [odds ratio (OR) 95% confidence interval (CI): 2.33 (1.09-4.95)], p=0.028), absence of renal injury according to RIFLE classification (OR 95% CI: 3.83 (2.19-6.71), p<0.001), hypokalemia (OR 95% CI: 2.61 (1.46-4.69), p=0.001), and hypoalbuminemia (OR 95% CI: 2.61 (1.46-4.67), p=0.01) were defined as independent variables related to hypophosphatemia (Table 3).

In the subgroup analysis evaluating 146 patients without renal injury according to the RIFLE classification on admission to the ICU, hypophosphatemia prevalence was 32.8% within the subgroup population. No statistically significant relationship was found between hypophosphatemia and either the reasons for ICU admission or comorbidities. Unlike in the overall study population, the subgroup analysis revealed that hypophosphatemic patients without renal injury according to the RIFLE classification had a significantly higher SOFA Score and a longer hospital stay prior to ICU admission (p-values of 0.015 and 0.016, respectively) (Table 4). In the subgroup analysis, hypophosphatemia was not significantly associated with nutritional support, requirement of MV, ICU mortality , or length of ICU stay (p-values, respectively 0.528, 0.239, 0.121, 0.140 and 0.393) (Table 4). When laboratory findings on ICU admission were compared, BUN, creatinine, potassium, and albumin were significantly lower among hypophosphatemic patients (Table 5). Based on the logistic regression analysis of factors associated with hypophosphatemia at ICU admission within the subgroup, the SOFA Score (OR 95% CI:1.069 (0.945-1.210), p=0.288), the length of hospital stay prior to ICU admission (OR 95% CI:1.006 (0.962-1.051), p=0.794), hypoalbuminemia (OR 95% CI:1.597 (0.577-4.417), p=0.367) or hypokalemia (OR 95% CI:1.385 (0.576-3.332), p=0.467) were not identified as independent risk factors for hypophosphatemia. Serum creatinine (OR 95% CI, 0.238 (0.074-0.769), p=0.016) and pH (OR 95%CI, 230.616 (3.244-16394.30), p=0.012) were defined as independent variables related to hypophosphatemia.

Detailed information on the comparison of clinical characteristics and laboratory findings of the overall study cohort based on ICU mortality is also provided in Supplemantary Tables 1, 2, and 3 of the supplemental file.

Table 1. Comparison of baseline characteristics and ICU-related data according to hypophosphatemia on ICU admission in elderly critically ill patients

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Baseline characteristics and ICU admission data				
Age*	77 (71-83)	77 (71-84)	76 (70-83)	0.852
Gender, n (%)				
Female	198 (45.7)	32 (40)	166 (47)	0.266
Male	235 (54.3)	48 (43.4)	187 (53)	
APACHE II Score*	20 (16-27)	21 (16-26)	20 (16-27)	0.800
SOFA Score*	6 (3-9)	6 (3-8)	6 (4-9)	0.305
Glasgow Coma Scale*	13 (8-15)	12 (9-15)	13 (8-15)	0.414
Length of ICU stay (day)*	16 (8-31)	18 (9-33)	16 (8-31)	0.628
Length of hospital stay prior to ICU admission (day)*	2 (0-8)	3 (1-9)	1 (0-8)	0.203
Reason for ICU admission, n (%)				
Sepsis	225 (52)	40 (50)	185 (52.5)	0.621
Renal failure	216 (49.9)	23 (28.8)	193 (54.7)	**<0.001**
Respiratory failure	243(56.1)	46 (57.5)	197 (55.8)	0.906
Cardiac decompensation	103 (23.8)	11 (13.8)	92 (2.6)	**0.02**
Acute GI disorders	46 (10.6)	1 (12.5)	36 (10.2)	0.553

Table 1. Continued

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Acute hepatobiliary disease	38 (8.8)	8 (10)	30 (8.6)	0.667
Acute neurological disorders	54 (12.5)	9 (11.2)	45 (12.7)	0.852
Metabolic disturbances	16 (3.7)	2 (2.5)	14 (4)	0.747
Surgery	13 (3)	1 (1.3)	12 (3.4)	0.477
Trauma	7 (1.6)	0	7 (2)	0.357
Comorbidities, n (%)				
Chronic renal disease	127 (29.3)	10 (12.5)	117 (32.1)	**<0.001**
Pulmonary disease	156 (36)	34 (42.5)	122 (34.6)	0.190
Cardiac disorders	315 (72.7)	48 (60)	267 (75.6)	**0.003**
Gastroenterological	23 (5.3)	4 (5)	19 (5.4)	1.0
Neurological	105 (24.2)	25 (31.3)	80 (22.7)	0.114
Rheumatological	43 (9.9)	8 (9.6)	35 (9.9)	0.991
Endocrinological	161 (37.2)	23 (28.8)	138 (39.1)	0.095
Malignancy	149 (34.4)	35 (43.8)	114 (32.3)	0.156
Concomitant shock with septic patients, n (%)	193 (44.6)	36 (45)	157 (44.5)	0.892
Source of sepsis, n (%)				
Respiratory system	90 (20.8)	22 (27.5)	68 (19.3)	0.11
Urinary tract	74 (17.1)	12 (15)	62 (17.6)	0.461
BSI	74 (17.1)	15 (18.8)	59 (16.7)	0.854
Abdominal	22 (5)	3 (3.8)	19 (5.4)	0.579
Soft tissue	12 (2.8)	3 (3.8)	9 (2.5)	0.705
Others	3 (1)	0	3 (1)	1.0
RIFLE stage, n (%)				
Risk	109 (25.2)	13 (16.3)	96 (27.2)	**0.045**
Injury	64 (14.8)	6 (7.5)	58 (16.4)	0.053
Failure	83 (19.2)	10 (12.5)	73 (20.7)	0.115
Loss	11 (2.5)	3 (3.8)	10 (3.1)	**0.014**
Endstage	32 (7.4)	1 (1.2)	31 (8.8)	**0.017**
Nutritional support, n (%)				
Parenteral	34 (7.9)	9 (11.3)	25 (7.1)	0.25
Enteral	250 (57.7)	52 (65)	198 (56.1)	0.161
Requirement of respiratory support, n (%)				
Invasive mechanical ventilation	224 (51.7)	42 (52.5)	182 (51.6)	0.928
Non-invasive mechanical ventilation	98 (22.6)	18 (22.5)	80 (22.7)	0.949
HFNO	22 (5.1)	6 (7.5)	16 (4.5)	0.269
Requirement of RRT, n (%)				
Hemodialysis	110 (25)	10 (12.5)	100 (28.3)	**0.003**
CRRT	86 (6.9)	13 (16.3)	73 (20.7)	0.348
Albumin Replacement, n (%)	149 (34.4)	30 (37.5)	119 (33.7)	0.570
ICU mortality, n (%)	197 (45.5)	37 (46.3)	160 (45.3)	0.881

*Median (25^{th} percentile-75^{th} percentile).
APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

Table 2. Baseline laboratory findings according to hypophosphatemia on ICU admission in elderly critically ill patients*

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Blood urea nitrogen (mg/dL)	42 (27.8-62.3)	28 (19.6-44)	46 (30-60)	**<0.001**
Creatinine (mg/dL)	1.58 (0.95-2.72)	0.91 (0.6-1.31)	1.76 (1.08-2.92)	**<0.001**
Sodium (mEq/L)	139 (134-142)	140 (136-144)	138 (134-142)	**0.006**
Potassium (mEq/L)	4.05 (3.55-4.67)	3.6 (3.3-4.14)	4.14 (3.6-4.8)	**<0.001**
Chlorine (mEq/L)	103 (99-108)	105 (100-110)	102 (98-107)	**0.007**
Calcium (mg/dL)	9.1 (8.5-9.6)	9 (8.2-9.5)	9.1 (8.5-9.6)	0.062
Phosphorus (mg/dL)	3.6 (2.8-4.9)	2.05 (1.8-2.3)	4 (3.2-5.3)	**0.000**
Magnesium (mg/dL)	1.9 (1.7-2.2)	1.8 (1.6-2.3)	2 (1.7-2.2)	**0.003**
Alanine transaminase (U/L)	23 (13-51)	25 (16-48)	23 (12-53)	0.28
Aspartat transaminase (U/L)	34 (19-71)	36 (22-67)	32 (19-73)	0.84
Lactate dehidrogenase (U/L)	302 (217-468)	280 (199-408)	310 (224-484)	**0.04**
Total bilirubin (mg/dL)	0.92 (0.59-1.62)	0.84 (0.57-1.47)	0.92 (0.59-1.63)	0.5
Direct bilirubin (mg/dL)	0.28 (0.15-0.7)	0.27 (0.16-0.55)	0.28 (0.15-0.74)	0.98
Albumin (g/dL)	2.6 (2.3-3.0)	2.4 (2.15-2.8)	2.7(2.3-3.1)	**0.001**
Blood gase sampling				
pH	7.36 (7.29-7.44)	7.42 (7.35-7.47)	7.35 (7.27-7.42)	**<0.001**
HCO_3 (mEq/L)	20.8 (16.9-25.4)	23.9 (19.7-27)	20 (16.4-25)	**<0.001**
Lactate (mmol/L)	2 (1.3-3.4)	1.9 (1.3-3.1)	2.1 (1.3-3.5)	0.499
White blood cell count (/µl)	10530 (6910-15700)	10545 (6920-15085)	10530 (6910-15800)	0.931
C-reactive protein (mg/L)	97.2 (42.5-171)	94.6 (44-160)	98 (42-179)	0.67
Procalcitonin (ng/mL)	0.93 (0.28-3.97)	0.7 (0.21-3.37)	0.96 (0.31-3.97)	0.07

*Median (25^{th} percentile-75^{th} percentile).
HCO_3: Bicarbonate ICU: Intensive care unit

Table 3. Multivariate analysis of independent risk factors for hypophosphatemia in elderly patients on ICU admission

	Adjusted OR (95% CI)	p
Cardiac decompensation as a reason for ICU admission	**2.33 (1.09-4.95)**	**0.028**
The absence of renal injury according to RIFLE classification	**3.83 (2.19-6.71)**	**<0.001**
Requirement of hemodialysis	0.57 (0.26-1.21)	0.142
Hypokalemia	**2.61 (1.46-4.69)**	**0.001**
Hypomagnesemia	0.72 (0.13-3.94)	0.704
Hypoalbuminemia	**2.61 (1.46-4.67)**	**0.01**

ICU: Intensive care unit, RIFLE: Risk, Injury, Failure, Loss and End-stage Kidney Disease OR: Odds ratio, CI: Confidence interval

Table 4. Comparison of baseline characteristics and ICU-related data according to hypophosphatemia in elderly critically ill patients without renal injury according to the RIFLE classification on ICU admission

	All patients (n=146)	Hypophosphatemic patients (n=48)	Non-hypophosphatemic patients (n=98)	p
Baseline characteristics and ICU admission data				
Age*	76 (70-82)	78 (71-84)	75 (70-81)	0.239
Gender, n (%)				**0.198**
Female	78 (53.4)	22 (45.8)	53 (57.1)	
Male	68 (46.6)	26 (54.2)	42 (42.9)	
APACHE II Score*	18 (14-22)	19 (16-24)	17 (13-22)	0.179
SOFA Score*	4 (2-6)	5 (3-7)	3 (2-6)	**0.015**

Table 4. Continued

	All patients (n=146)	Hypophosphatemic patients (n=48)	Non-hypophosphatemic patients (n=98)	p
Glasgow Coma Scale*	14 (9-15)	12 (9-15)	14 (9-15)	0.127
Length of ICU stay (day)*	7 (7-14)	9 (4-21)	7 (4-11)	0.393
Length of hospital stay prior to ICU admission (day)*	2 (0-9)	3 (1-10)	1 (0-6)	**0.016**
Reason for ICU Admission, n (%)				
Sepsis	56 (38.6)	20 (41.7)	36 (37.1)	0.596
Respiratory failure	96 (66.2)	29 (60.8)	67 (69.1)	0.30
Cardiac decompensation	31 (21.4)	8 (16.7)	23 (23.7)	0.33
Acute GI disorders	18 (12.4)	8 (16.7)	10 (10.3)	0.275
Acute hepatobiliary disease	11 (7.6)	5 (10.4)	6 (5.2)	0.179
Acute neurological disorders	18 (12.4)	5 (10.4)	13 (13.4)	0.608
Metabolic disturbances	4 (2.8)	0 (0)	4 (4.1)	0.302
Surgery	6 (4.1)	1 (2.1)	5 (5.2)	0.382
Trauma	1 (0.7)	0 (0)	1 (1.0)	1.00
Comorbidities, n (%)				
Pulmonary disease	68 (47.2)	22 (46.8)	46 (47.4)	1.00
Cardiac disorders	97 (67.4)	27 (57.4)	70 (72.2)	0.077
Gastroenterological	6 (4.2)	4 (8.5)	2 (2.1)	0.089
Neurological	44 (30.6)	16 (34.0)	28 (28.9)	0.527
Rheumatological	4 (2.8)	0 (0)	4 (4.1)	0.304
Endocrinological	45 (31.3)	10 (21.3)	35 (36.1)	0.072
Malignancy	53 (37.1)	22 (46.8)	31 (32.3)	0.091
Concomitant shock with septic patients, n (%)	43 (29.9)	17 (36.2)	26 (26.8)	0.250
Source of sepsis, n (%)				
Respiratory system	31 (21.2)	14 (29.1)	17 (17.3)	0.186
Urinary tract	19 (13.1)	4 (8.3)	15 (15.3)	0.061
BSI	17 (11.6)	7 (3.5)	17 (17.3)	0.723
Abdominal	19 (13.0)	4 (8.3)	15 (15.3)	1.00
Soft tissue	4 (7.5)	1 (2)	3 (3.0)	0.627
Others	0	0	0	
Nutritional support, n (%)				
Parenteral	12 (8.3)	5 (3.9)	7 (8.1)	0.528
Enteral	85 (59)	31 (66)	54 (55.7)	0.239
Requirement of respiratory support, n (%)				
Invasive mechanical ventilation	70 (48.6)	27 (57.4)	43 (44.3)	0.140
Non-invasive mechanical ventilation	35 (24.3)	12 (25.5)	23 (23.7)	0.811
HFNO	9 (6.3)	3 (6.4)	6 (6.2)	1.00
Requirement of RRT, n (%)				
Hemodialysis	14 (9.7)	4 (8.3)	10 (10.3)	1.00
CRRT	13 (9.0)	4 (8.3)	9 (9.3)	1.00
Albumin replacement, n (%)	46 (32.2)	19 (40.4)	27 (28.1)	0.139
ICU mortality, n (%)	54 (37.0)	22 (45.8)	32 (32.7)	0.121

*Median (25^{th} percentile-75^{th} percentile).
APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease GI: Gastrointestinal.

Table 5. Baseline laboratory findings according to hypophosphatemia in elderly critically ill patients without renal injury according to the RIFLE classification on ICU admission*

	All patients (n=433)	Hypophosphatemic patients (n=80)	Non-hypophosphatemic patients (n=353)	p
Blood urea nitrogen (mg/dL)	28 (19-38.5)	24 (15.7-30.4)	29 (20.7-40)	**0.025**
Creatinine (mg/dL)	0.85 (0.6-1.07)	0.75 (0.53-0.94)	0.92 (0.65-1.14)	**0.004**
Sodium (mEq/L)	140 (136-142)	140 (137-143)	139 (135-141)	0.067
Potassium (mEq/L)	3.8 (3.5-4.38)	3.6 (3.3-4.05)	3.87 (3.5-4.5)	**0.007**
Chlorine (mEq/L)	103 (98-108)	105 (100-110)	101 (98-107)	**0.027**
Calcium (mg/dL)	9.0 (8.3-9.4)	8.8 (8.3-9.3)	9.0 (8.2-9.5)	0.160
Phosphorus (mg/dL)	3.0 (2.4-3.8)	2.1 (1.9-2.4)	3.5 (3-4.3)	**0.000**
Magnesium (mg/dL)	1.8 (1.7-2.1)	1.8 (1.7-2.1)	1.85 (1.7-2.1)	0.593
Alanine transaminase (U/L)	22.5 (16-44.5)	19 (12-33)	29 (17-49)	0.121
Aspartat transaminase (U/L)	30 (18-49)	33 (23-55)	29 (17-49)	0.314
Lactate dehidrogenase (U/L)	273 (214-428)	294 (247-401)	269 (211-434)	0.809
Total bilirubin (mg/dL)	0.78 (0.51-1.33)	0.78 (0.54-1.47)	0.77 (0.51-1.33)	0.736
Direct bilirubin (mg/dL)	0.21 (0.13-0.4)	0.25 (0.16-0.48)	0.2 (0.12-0.35)	0.084
Albumin (g/dL)	2.6 (2.3-3.1)	2.4 (2.05-2.8)	2.4 (2.7-3.1)	**0.005**
Blood gase sampling				
pH	7.41 (7.35-7.46)	7.43 (7.36-7.47)	7.40 (7.32-7.46)	**0.017**
HCO_3 (mEq/L)	25.1 (20.3-29.3)	25.2 (22.4-28.5)	25 (19.7-30.6)	0.623
Lactate (mmol/L)	1.6 (1.2-2.4)	1.6 (1.3-2.4)	1.6 (1.2-2.4)	0.993
White blood cell count (/µl)	104420 (6410-15640)	10545 (6610-16455)	7500 (15400-10420)	0.659
C-reactive protein (mg/L)	82 (28-174)	97.8 (31-155)	77.7 (24.5-137)	0.330
Procalcitonin (ng/mL)	0.34 (0.14-1.1)	0.37 (0.14-1.36)	0.31 (0.14-1.02)	0.797

*Median (25^{th} percentile-75^{th} percentile).
HCO_3: Bicarbonate RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

Discussion

Our analysis has several important findings that clarify the incidence and importance of hypophosphatemia in the critically ill elderly population. The hypophosphatemia incidence was 18.5% within the study population. Independent risk factors for hypophosphatemia include cardiac decompensation as a reason for ICU admission, absence of renal injury according to RIFLE classification, hypokalemia, and hypoalbuminemia. The subgroup analysis demonstrated that hypophosphatemia was more prevalent in the absence of concomitant renal injury according to the RIFLE classification, and was associated with a longer hospital stay prior to ICU admission and a higher SOFA score. We also found that hypophosphatemia is not associated with adverse clinical outcomes, such as the requirement of MV, increased length of ICU stay, or increased mortality; even in the subgroup analysis excluding patients with renal injury according to the RIFLE classification.

In our study, which focused exclusively on elderly critically ill patients, we determined the incidence of hypophosphatemia to be 18.5%. After excluding the patients with renal injury based on the RIFLE classification at ICU admission, the incidence of hypophosphatemia was 32.8%. Several studies have reported hypophosphatemia rates as high as 28-60% in adult critically ill populations (1,4,12). The difference in rates is predominantly due to the study population and the serum phosphate level threshold. (4,6,13). Our study distinguishes itself from previous literature by targeting a specific cohort. As the population ages, elderly patients now account for the vast majority of patients admitted to ICUs (14,15). Elderly patients are particularly vulnerable to hypophosphatemia due to factors such as malnutrition, comorbidities, altered renal function, various medications leading to phosphate depletion, and risk of refeeding syndrome (7-9). Contrary to expectations, this study found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Although existing literature has demonstrated hypophosphatemia in hospitalized geriatric populations at a rate of 7-14%, this discrepancy can be attributed to the varying cutoffs used for hypophosphatemia (8,16). In this study, the cutoff for hypophosphatemia is 2.5 mg/dL (<0.81 mmol/L) according to the lower limit of reference laboratory, whereas <0.68 mmol/L and 0.77 mmol/L were defined for previous studies, respectively (9,16).

Hypophosphatemia often coexists with other electrolyte abnormalities. Suzuki et al. (13) demonstrated the relationship between hypophosphatemia and other electrolyte disturbances (4). They found that hypophosphatemic patients had lower potassium and calcium concentrations, and a higher incidence of alkalemia. They also reported that in patients without any episodes of hyperphosphatemia, a lower minimum serum albumin level and a lower maximum creatinine level were significantly and independently associated with hypophosphatemia (13). These results were very similar to the results of our study. Our study demonstrates that hypophosphatemia in elderly critically ill patients is associated with lower serum levels of potassium, calcium, magnesium, and albumin, as well as elevated pH and bicarbonate (HCO_3) levels. These findings may partly reflect differences in renal impairment between groups. Notably, patients with hypophosphatemia had a significantly lower incidence of renal impairment according to the RIFLE classification, along with reduced BUN and creatinine levels. Subgroup analysis of patients without renal injury supported this trend, showing persistently lower levels of BUN, creatinine, potassium, and albumin in the hypophosphatemic group. Furthermore, multivariate analysis identified absence of renal injury, hypokalemia, and hypoalbuminemia, as independent predictors of hypophosphatemia at ICU admission.

Contrary to previous studies, our findings suggest that admission to the ICU due to cardiac decompensation is an independent factor associated with hypophosphatemia (3,4,10). While earlier research has shown that surgical patients are less likely to develop hypophosphatemia and that patients with hypophosphatemia are more prone to infections and sepsis upon ICU admission, these studies did not establish a significant correlation between hypophosphatemia and underlying diseases (4,10,3). The discrepancy in our results may be attributed to the characteristics of our study population, which primarily consisted of elderly critically ill patients admitted to the ICU for medical, rather than surgical, reasons. Age-related chronic cardiac conditions are commonly observed in this population. Hypophosphatemia occurs in approximately 13% of patients with heart failure and may result from reduced oral intake, ongoing pharmacological treatments, concomitant electrolyte disturbances, and increased sympathetic nervous system activity (17,18). It has been shown to impair cardiac muscle contraction by disrupting adenosine triphosphate synthesis and to induce ventricular arrhythmias, thereby potentially contributing to the development or worsening of heart failure (19,20,21). Although our retrospective design precluded detailed data collection on diuretic regimens, increased renal excretion of phosphorus, potassium, and calcium due to diuretic therapy may also explain the lower levels of these electrolytes observed in hypophosphatemic patients (22).

In the geriatric population, both hypophosphatemia and hypoalbuminemia are commonly associated with malnutrition (8,9,13,16,23). Ensuring adequate caloric intake upon hospitalization, however, can increase the risk of refeeding syndrome and refeeding-associated hypophosphatemia (9,24). Our study aligns with this literature, highlighting hypoalbuminemia and hypokalemia as independent risk factors for hypophosphatemia. Additionally, the subgroup analysis of patients without renal injury according to the RIFLE classification further supports this link, as the hypophosphatemic group exhibited higher prevalence of hypokalemia and hypoalbuminemia, and prolonged hospital stays prior to ICU admission, and prolonged hospital stays. The fact that nutritional risk scores specific to the geriatric population, along with the lack of available data on caloric intake before ICU admission due to the retrospective nature of the study prevents us from demonstrating this relationship. In this respect, designing large-scale, multicenter prospective studies would be beneficial.

The most important result of our study, which differs from the current literature, is that hypophosphatemia is not associated with adverse clinical outcomes, such as prolonged MV duration, increased length of ICU stay, or increased mortality in elderly critically ill patients (3,4,25,26). This discrepancy from the existing literature may be attributed to our exclusive focus on the geriatric population, differences in the defined threshold for hypophosphatemia, as well as the inclusion of patients with hyperphosphatemia in our cohort. Our research recruited patients from the tertiary university medical ICU, providing a more specific and in-depth analysis tailored to this subgroup. In this study, there were two main reasons for including hyperphosphatemic patients. The first was to reveal the exact incidence of hypophosphatemia in the elderly critically ill population. The second was to assess whether hypophosphatemia alone is a risk factor for adverse clinical outcomes in a patient group characterized by high risk of malnutrition and reduced renal function. Nevertheless, in the subgroup analysis excluding patients with renal impairment at admission based on the RIFLE classification, hypophosphatemia was not found to be associated with adverse clinical outcomes in elderly critically ill patients. Previous studies have also demonstrated that the disease severity scores were high in hypophosphatemic patients (12,13). The disease severity scores, such as APACHE II and SOFA Scores, did not differ between hypophosphatemic and non-hypophosphatemic patients in our study population, but the SOFA Score was found to be high in hypophosphatemic patients without renal injury. This finding may reflect that hypophosphatemia indicates disease severity rather than an independent risk factor for mortality (1,2,14).

Study Limitations

Although the findings of this study have important clinical implications for the management of elderly critically ill patients, it is important to acknowledge several limitations of our research. The major limitation of this study is its retrospective design, which prevents a comprehensive assessment of patients' nutritional status and caloric intake both prior to and during their ICU stay, thereby hindering an objective evaluation of the association between hypophosphatemia and refeeding syndrome. Additionally, the study lacks detailed information on fluid management strategies, diuretic regimens, steroid use, catecholamines, and aminoglycosides, all of which can contribute to hypophosphatemia. Finally, the generalizability of the results is inherently limited by the single-center nature of the cohort.

Conclusion

Contrary to expectations, we found that hypophosphatemia incidence is not higher in elderly critically ill patients than in the general ICU population. Likewise, it was not correlated with negative clinical outcomes in ICU settings. Admission to the ICU for cardiac decompensation, along with hypoalbuminemia and hypokalemia as independent risk factors for hypophosphatemia, highlights the need for careful evaluation of hypophosphatemia in this population. Additionally, multicenter prospective studies in mixed ICU populations are required to better elucidate the relationship between hypophosphatemia and malnutrition in elderly critically ill patients.

Ethics

Ethics Committee Approval: The research protocol was approved by the Local Ethics Committee of Gazi University, Faculty of Medicine, (approval number: 996621, research code number: 2024-1132, date: 09.07.2024).

Informed Consent: Informed consent was not obtained as the data were collected retrospectively.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.B.D., K.İ., B.H., M.T., G.A., Concept: N.B.D., K.İ., Design: N.B.D., K.İ., Data Collection or Processing: N.B.D., K.İ., B.H., Analysis or Interpretation: N.B.D., K.İ., M.T., G.A., Literature Search: N.B.D., K.İ., B.H., Writing: N.B.D., K.İ., M.T., G.A.

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Supplementary Table 1. Comparison of baseline characteristics and ICU-related data according to ICU mortality

	All patients (n=433)	Survivors (n=236)	Non-survivors (n=197)	p
Baseline characteristics and ICU admission data				
Age*	77 (70-83)	77 (71-83)	76 (69-84)	0.437
Gender, n (%)				
Female	198 (45.7)	119 (50.4)	79 (40.1)	**0.032**
Male	235 (54.3)	117 (49.6)	118 (59.9)	
APACHE II Score	20 (16-27)	18 (15-22)	26 (20-32)	**<0.001**
SOFA Score	6 (3-9)	5 (3-7)	9 (6-12)	**<0.001**
Glasgow Coma Scale*	13 (8-15)	14 (12-15)	10 (5-14)	**<0.001**
Length of ICU stay (day)*	6 (3-15)	6 (3-10)	8 (4-20)	**0.003**
Reason of ICU admission, n (%)				
Sepsis	225 (52)	81 (34.3)	144 (73.1)	**<0.001**
Renal failure	216 (50)	109 (46.2)	107 (54.3)	0.085
Respiratory failure	243 (56.1)	123 (52.1)	120 (60.9)	**0.06**
Cardiac decompensation	103 (23.8)	55 (23.3)	48 (24.4)	0.784
Acute GI disorders	46 (10.6)	22 (9.3)	24 (12.1)	0.331
Acute hepatobiliary disease	38 (8.7)	20 (8.5)	18 (9.1)	0.802
Acute neurological disorders	54 (12.5)	28 (11.8)	26 (13.2)	0.668
Metabolic disturbances	16 (3.7)	9 (3.8)	7 (3.6)	1.0
Surgery	13 (3)	7 (6)	6 (3)	1.0
Trauma	7 (1.6)	4 (1.7)	3 (1.5)	1.0
Comorbidities, n (%)				
Chronic renal disease	127 (29.3)	58 (24.6)	69 (35)	0.972
Pulmonary disease	156 (36.0)	89 (37.7)	67 (34)	0.421

Supplementary Table 1. Continued

	All patients (n=433)	Survivors (n=236)	Non-survivors (n=197)	p
Cardiac disorders	315 (72.7)	167 (69.5)	148 (75.1)	0.313
Gastroenterological disorders	23 (5.3)	9 (3.8)	14 (7.1)	0.129
Neurological	105 (24.2)	62 (26.3)	43 (21.8)	0.277
Rheumatological	13 (3)	8 (3.3)	5 (2.5)	0.603
Endocrinological	161 (37.2)	90 (38.1)	71 (36)	0.617
Malignancy	149 (34.4)	59 (25)	90 (45.7)	**<0.001**
Concominant shock with septic patients, n (%)	194 (44.8)	55 (23.3)	139 (70.5)	**<0.001**
Source of sepsis, n (%)				
Respiratory system	90 (20.8)	24 (10.2)	66 (33.5)	**0.003**
Urinary tract	74 (17.1)	36 (15.3)	38 (19.2)	**0.016**
BSI	74 (17.1)	28 (11.9)	46 (23.3)	0.133
Abdominal	22 (5.1)	11 (4.7)	11 (5.6)	0.212
Soft tissue	12 (2.8)	5 (2.1)	7 (3.6)	0.368
Others	3 (1)	0	3 (1.5)	0.290
RIFLE stage, n (%)				
Risk	109 (25.2)	61 (25.8)	48 (24.3)	0.711
Injury	64 (14.8)	32 (13.6)	32 (16.2)	0.438
Failure	83 (19.2)	33 (14)	50 (25.4)	**0.003**
Loss	11 (2.5)	10 (4.2)	1 (0.5)	**0.014**
Endstage	32 (7.4)	12 (5.1)	20 (10.2)	**0.045**
Nutritional support, n (%)				
Parenteral	34 (7.9)	14 (5.9)	20 (10.2)	0.101
Enteral	250 (57.7)	125 (53)	125 (63.5)	0.031
Requirement of respiratory support, n (%)				
Invasive mechanical ventilation	224 (51.7)	50 (21.2)	174 (88.3)	**<0.001**
Non-invasive mechanical ventilation	98 (22.6)	64 (27.1)	34 (17.2)	**0.013**
HFNO	22 (5.1)	11 (4.7)	11 (5.6)	0.655
Requirement of RRT, n (%)				
Hemodialysis	110 (25.4)	42 (17.8)	68 (34.5)	**<0.001**
CRRT	86 (19.9)	9 (3.8)	77 (39)	**<0.001**
Albumin replacement, n (%)	149 (34.4)	51 (21.6)	98 (49.7)	**<0.001**

*Median (25^{th} percentile-75^{th} percentile).
APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, ICU: Intensive care unit, BSI: Bloodstream infection, HFNO: High flow nasal oxygen, RRT: Renal replacement therapy, CRRT: Continuous renal replacement therapy, RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease

Supplementary Table 2. Baseline laboratory findings according to ICU mortality*

	All patients (n=433)	Survivors (n=236)	Non-survivors (n=197)	p
Blood urea nitrogen (mg/dL)	42 (28-61)	39 (24-60)	46 (32-64)	**0.005**
Creatinine (mg/dL)	1.58 (0.95-2.72)	1.41 (0.93-2.65)	1.76 (0.96-2.84)	0.264
Sodium (mEq/L)	139 (134-142)	139 (135-142)	138 (134-142)	0.333
Potassium (mEq/L)	4.05 (3.55-4.6)	3.99 (3.5-4.65)	4.12 (3.57-4.71)	0.389
Chlorine (mEq/L)	103 (99-108)	103 (99-107)	103 (98-108)	0.740
Calcium (mg/dL)	9.1 (8.5-9.6)	9.1 (8.54-9.5)	9.2 (8.4-9.6)	0.462
Phosphorus (mg/dL)	3.6 (2.8-4.9)	3.5 (2.7-4.5)	3.9 (2.9-5.5)	**0.023**
Magnesium (mg/dL)	1.9 (1.7-2.2)	1.9 (1.7-2.2)	2.0 (1.7-2.2)	0.195
Alanine transaminase (U/L)	23 (13-51)	20 (12-33)	29 (16-72)	**<0.001**
Aspartat transaminase (U/L)	34 (19-71)	28 (18-52)	42 (22-105)	**<0.001**
Lactate dehidrogenase (U/L)	362 (217-468)	265 (202-369)	371 (267-577)	**<0.001**
Total bilirubin (mg/dL)	0.92 (0.59-1.62)	0.79 (0.55-1.32)	1.13 (0.65-1.95)	**<0.001**
Direct bilirubin (mg/dL)	0.28 (0.15-0.7)	0.22 (0.13-0.46)	0.41 (0.2-1.06)	**<0.001**
Albumin (g/dL)	2.6 (2.3-3.0)	2.8 (2.4-3.3)	2.5 (2.2-2.8)	**<0.001**
Blood gase sampling				
pH	7.36 (7.29-7.44)	7.38 (7.32-7.45)	7.34 (7.25-7.42)	**<0.001**
HCO_3 (mEq/L)	20.8 (16.9-25.4)	22.4 (18.4-26.5)	19.5 (15-23.8)	**<0.001**
Lactate (mmol/L)	2 (1.3-3.4)	1.75 (1.1-2.8)	2.3 (1.6-4.8)	**<0.001**
White blood cell count (10^3/µl)	10530 (6910-15700)	10500 (7000-14800)	10700 (6700-16900)	0.537
C-reactive protein (mg/L)	97.2 (42.5-171)	81 (29-154)	117 (71-188)	**<0.001**
Procalcitonin (ng/mL)	0.93 (0.28-3.97)	0.58 (0.21-3.11)	1.44 (0.41-5.2)	**<0.001**

*Median (25^{th} percentile-75^{th} percentile).
HCO_3: Bicarbonate

Supplementary Table 3. Multivariate analysis of independent risk factors for ICU mortality in elderly critically ill patients

	Adjusted OR (95% CI)	p
Gender	1.22 (0.65-2.27)	0.538
APACHE II Score	**1.09 (1.04-1.15)**	**0.001**
SOFA Score	1.04 (0.93-1.17)	0.455
Sepsis as a reason for ICU admission	**2.08 (1.10-3.92)**	**0.025**
Respiratory failure as a reason for ICU admission	1.51 (0.77-2.94)	0.232
Malignancy for comorbidities	**2.60 (1.34-5.06)**	**0.005**
The absence of renal injury according to RIFLE classification	1.53 (0.75-3.14)	0.244
Requirement of MV	**8.0 (3.89-16.47)**	**<0.001**
Requirement of RRT	**3.74 (1.86-7.54)**	**<0.001**
pH	0.19 (0.1-3.18)	0.250
Lactate level	1.02 (0.89-1.16)	0.826
Hypoalbuminemia	**2.4 (1.16-4.96)**	**0.018**

APACHE: Acute Physiology and Chronic Health Evaluation ICU: Intensive care unit, MV: Mechanical ventilation, RRT: Renal replacement therapy, SOFA: Sequential Organ Failure Assessment OR: Odds ratio, CI: Confidence interval