

## The Association of Serum Calcium and Risk of Morbidity and Mortality in ICU-Admitted Patients

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### Abstract

**Background:** Calcium is one of the essential electrolytes in humans, and hypocalcemia is one of the most common disorders in surgical and internal medicine patients requiring ICU. Therefore, we decided to investigate the clinical relationship of calcium level with the rate of mortality and related morbidities, such as sepsis, various organ failures, the need for mechanical ventilation, and the length of stay in the intensive care unit (ICU).

**Methods:** A total of 61 patients admitted to the ICU of Shahid Mohammadi Hospital from 2019 to 2020 were included in the study. After collecting information related to calcium deficiency, patients' mortality, the need for mechanical ventilation and the duration of mechanical ventilation, serum albumin, magnesium, and potassium level, and SOFA and APACHE II prognostic scoring systems; the data were entered into SPSS software and subjected to statistical analysis.

**Results:** Out of 61 patients included in the present research, 37 were women, and 24 were men. In our study, 26.1% of the patients died during hospitalization, and 34.8% needed mechanical ventilation, which was a significant number. Serum calcium level was significant in the examined sepsis and kidney failure patients, but no other significant item was observed in the other patients, including COVID-19 patients. There was a significant relationship between serum calcium level in the studied patients with serum albumin level and SOFA score, but there was no significant relationship between the duration of hospitalization and the need for a ventilator; calcium and potassium serum level and their APACHE score ( $P$ -value  $>0.05$ ). In addition, the serum level of magnesium in the studied patients had no significant relationship with any of the variables of mortality, sepsis, liver and kidney failure, and the need for mechanical ventilation.

**Conclusions:** This study showed a significant relationship between serum calcium level with serum albumin level and SOFA score. There was no significant relationship between serum calcium level with the duration of hospitalization, the need for a ventilator, and the APACHE score. Also, the serum calcium level was not significant for any of the parameters in COVID-19 patients.

**Keywords:** Hypocalcemia, Mortality, ICU

## Introduction

The human body requires calcium as one of its necessary electrolytes. Cellular processes like signaling, hormone secretion, glycogen metabolism, and cell division are all controlled by this electrolyte. The stability of the cell wall and the formation of clots are two important functions that extracellular calcium serves in addition to providing intracellular calcium [1]. One of the most prevalent conditions among surgical and internal medicine patients requiring ICU care is hypocalcemia [2]. A prevalent biochemical abnormality, hypocalcemia can manifest itself in a variety of ways, from being asymptomatic in moderate cases to presenting as an acute life-threatening crisis in severe cases. Parathyroid hormone (PTH), vitamin D, and calcitonin [3] are the primary hormones responsible for keeping the serum calcium concentration within a restricted range (2.1 to 2.6 mmol/L). Vitamin D deficiency, vitamin D resistance, or post-surgical hypoparathyroidism (PSHP) are the common causes of hypocalcemia. It can also be because of hypothyroidism due to autoimmune disease or genetic causes of renal disease or hepatic failure inducing vitamin D deficiency, pseudo-hypoparathyroidism or pseudo-hypoparathyroidism and hypomagnesemia or hypermagnesemia [3, 4].

The reported prevalence varies significantly among the studied populations [2]. The prevalence of hypocalcemia in children is 74.12%, and in adults, it is 88.15% [5]. Acute hypocalcemia can lead to severe symptoms and the need for hospitalization, while patients who gradually develop hypocalcemia are mostly asymptomatic [3]. Paresthesia, muscle spasms, muscle cramps, and tetany are common manifestations of hypocalcemia [3, 6]. Laryngospasm, neuromuscular irritation, cognitive disturbance, personality disturbances, protracted QT, and electrocardiographic variations that resemble a cardiac attack or failure are additional symptoms of hypocalcemia [6].

The reduction of serum ionized calcium causes many complications, and that is because calcium plays an essential role in various cellular functions, including myocardial and muscle contraction, vascular tone, enzyme activity, hormone secretion, neurotransmitter, membrane potential, blood coagulation, and intracellular messenger [5]. Calcium disorders are common in ICU and CKD patients and are associated with increased mortality and morbidity [7]. Patients with sepsis are at high risk of calcium deficiency related to bacteremia and the effect on the secretion and function of parathyroid hormones [2]. Approximately 50 % of unbound ionized calcium is physiologically active, and the remainder of total serum calcium is protein-bound. Before validating a diagnosis of hypercalcemia or hypocalcemia, the serum calcium concentration must be adjusted in terms of albumin levels [3]. Among critically ill individuals, even in the ICU, the monitoring of ionized calcium is strongly advised; because any change of the serum pH affects calcium binding to albumin [8, 9]. Therefore, we attempted to identify the clinical correlation between calcium level and mortality and morbidities related to it, such as sepsis and various organs failure, including kidney and liver, the demand for mechanical ventilation, the duration of hospitalization in the ICU, and if possible, provide suitable treatment solutions.

## Methods

This cross-sectional study was conducted on 61 patients hospitalized in Shahid Mohammadi Hospital's ICU, BandarAbbas, Iran, for 12 months, from September 2019 to September 2020.

Patients were included in the study based on the inclusion and exclusion criteria and were studied until the primary outcomes appeared.

This study is approved under the ethical approval code of IR.HUMS.REC.1399.548, and all participants signed the written informed consent.

The inclusion criteria were as follows:

- Age above 18 years
- Patients whose serum calcium level is measured in the first 48 hours of hospitalization in the ICU
- Furthermore, the exclusion criteria were:
  - Pregnancy and breastfeeding
  - intravenous nutrition
  - palliative care
  - Patients who are taking calcium supplements.
  - Dialysis patients
  - Patients with acute kidney failure

Primary outcomes included death, sepsis, renal failure, liver dysfunction or failure; and secondary outcomes included the duration of hospitalization in the intensive care unit, the need for mechanical ventilation and the duration of mechanical ventilation, serum albumin level, serum calcium level, serum potassium level, and SOFA and APACHE II prognostic scoring systems.

The Sequential Organ Failure Assessment or SOFA score was developed to assess the acute morbidity of critical illness at a population level [10, 11]. In addition, the gold standard for assessing disease severity in ICUs worldwide is acute physiology and chronic health evaluation II (APACHE II) [12-14].

The research tool in the present study was the background information such as age, sex, weight, height, BMI, medications, concomitant diseases, and Glasgow coma (GCS), which were recorded in the checklist prepared by the researcher. Information related to liver function, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total and direct bilirubin (INR), serum albumin, calcium, and potassium were evaluated, and SOFA and APACHE scores were calculated and recorded in the checklist.

A 5 ml venous blood sample was taken from participants during the first 48 hours of admission. The blood samples were transferred into vacutainer tubes and were centrifuged within 30 to 45 min of collection. All biochemical analyses were performed using a Selectra 2 auto-analyzer at the Shahid Mohammadi Hospital laboratory on the day of blood collection. The serum level of Ca was measured using Xylidyl Blue photometric method (Pars Azmoon Inc., Tehran, Iran). The normal values range for serum Ca level was 8.5 to 10 mmol/L. The enzymatic colorimetric technique was used to determine albumin and potassium concentrations. Also, aspartate aminotransferase (AST), ala-

nine transaminase (ALT), and alkaline phosphatase (ALP) were measured using the enzymatic colorimetric test. Analyses were performed using commercial kits (Pars Azmoon Inc., Tehran, Iran). The scores of two scoring systems, including SOFA and APACHE II, were determined using a standard calculator previously explained in detail.

After collecting the data, they were entered into SPSS version 23 software. Moreover, the observations were described using descriptive statistical methods (frequency and percentage distribution tables, mean and standard deviation, and graph drawing). Then, according to the normality or non-normality of the

quantitative data, they were analyzed by independent t-tests and Pearson's correlation coefficient.

### Results

The present article studied 61 patients admitted to Shahid Mohammadi Hospital's ICU. The mean age of the investigated subjects was 52.66, with a standard deviation of 16.21. The minimum age of the patients was 19 years, and the maximum age was 69 years. According to the obtained information, out of 61 cases, 37 were women, and 24 were men. The patients' information is described in detail in Table 1.

**Table 1: Demographic information of the studied patients**

Variable	Frequency(Percentage)	standard deviation
Gender	24 (34.8) male	
	37 (53.6) female	
age		52.66 ±16.21
Weight		70.73±13.63
Height		156.26±12.18
BMI		25.93±4.62

**Table 2: Laboratory information of the studied patients**

Laboratory findings	± Standard deviation	Findings	± Standard deviation
AST	51.84 ± 39.57	WBC	8.78 ± 5.16
ALT	42.62 ± 25.82	HCT	33.91 ± 7.72
ALP	230.62 ± 164.68	Plt	217.36 ± 111.48
Bili T	1.16 ± 1.59	Alb	3.60 ± 0.87
Bili D	0.54 ± 1.05	Ca	8.90 ± 0.72
INR	1.18 ± 0.24	Mg	2.32 ± 0.56
BUN	55.79 ± 54.22	K	4.37 ± 0.88
Cr	1.67 ± 1.91	Vit D	23.74 ± 21.34
Na	138.46 ± 4.76		

**Table 3: Data for evaluated patients**

Variable		Frequency (Percentage)	Mean ± standard deviation
Drug Hx	Negative	43 (62.3)	
Mechanical ventilation	Positive	26 (37.7)	
	Negative	45 (65.2)	
Hospitalization results	Positive	24 (34.8)	
	Recovery	51 (73.9)	
COVID-19	Mortality	18 (26.1)	
	Negative	42 (60.9)	
Heart rate			92.71 ± 18.48
Breathing rate			19.05 ± 5.13
body temperature			36.98 ± 0.59
SatO2			90.71 ± 7.42
GCS			13.53 ± 3.21
Duration of mechanical ventilation			8.60 ± 6.98
Duration of hospitalization			9.43 ± 8.04

The information in Table 3 is related to the hospitalization records of the studied patients. Eighteen patients (1.26%) died during hospitalization, and twenty-four (34.8%) needed mechanical ventilation. The average number of days of hospitalization in

the ICU was  $9.43 \pm 8.04$  days. Also, the average number of days patients were under mechanical ventilation was  $8.60 \pm 6.98$ . As well as, 27 patients (39.1%) were positive for COVID-19.

**Table 4: Determining the relationship between serum calcium level and primary finding**

Variable	Hypocalcemia	Average rank		Test statistics independent t	P-value
		Average	Deviation		
Mortality	Positive	1.333	0.51	0.364	0.47
	Negative	1.254	0.43	0.417	
Sepsis	Positive	1	0	-0.622	0.006
	Negative	1.17	0.38	-0.110	
Liver failure	Positive	0	0	-2.312	0.126
	Negative	0.07	0.27	-0.709	
Kidney failure	Positive	0	0	-3.215	0.021
	Negative	0.142	0.35	-0.985	
Mechanical ventilation	Positive	1.5	0.54	0.720	0.39
	Negative	1.3	0.47	0.811	
Covid-19	Positive	1.5	0.54	0.72	0.44
	Negative	1.3	0.47	0.65	

The relationship between serum calcium and mortality, sepsis, liver and kidney failure, and the demand for mechanical ventilation and patients experiencing COVID-19 infection was determined using an independent t-test. Based on the obtained

information, the serum calcium level was significant among individuals experiencing sepsis and renal failure ( $P < 0.05$ ). The serum calcium level was not significant in COVID-19 patients, and no other significant item was observed.

**Table 5: Determining the relationship between serum calcium level and secondary outcome.**

Variable	Serum calcium level	
	The correlation coefficient	P-value
Mechanical ventilation duration	0.126	0.280
Hospitalization period	0.223	0.301
Albumin	-0.642	0.000
Mg	0.043	0.723
K	-0.009	0.943
SOFA	0.247	0.04
APACHE	0.089	0.206

\*SOFA: Sequential Organ Failure Assessment

\*APACHE: Acute Physiology and Chronic Health Evaluation

Pearson's correlation coefficient was employed to determine the relationship between serum calcium concentration and hospitalization mode and the need for a ventilator, serum albumin, magnesium and potassium levels, SOFA, and APACHE scores of the

studied patients. In our study, there is a significant relationship between serum calcium level, serum albumin level, and SOFA score ( $P > 0.05$ ), but there was no significant relationship with other variables.

**Table 6: Determining the relationship between serum calcium level and primary outcomes in patients hospitalized in ICU based on covid-19 infection.**

Contracting covid	Variable		average rank		Independent t-test statistic	P-value	
			mean	standard deviation			
			mean	standard deviation			
negative	Mortality	negative	2.30	0.53	-0.832	0.410	
		Positive	2.49	0.91			
	sepsis	negative	2.26	0.54	-1.628	0.111	
		Positive	2.63	0.84			
	liver failure	negative	2.34	0.53	-0.960	0.343	
		Positive	2.55	0.77			
	Kidney failure	negative	2.31	0.54	-1.270	0.211	
		Positive	2.58	0.71			
	Mechanical ventilation	negative	2.36	0.52	-0.522	0.605	
		Positive	2.48	0.87			
	Positive	Mortality	negative	2.30	0.52	0.270	0.789
			Positive	2.25	0.24		
sepsis		negative	2.27	0.45	-0.528	0.602	
		Positive	2.45	0.21			
liver failure		negative	2.22	0.52	0.193	0.849	
		Positive	2.16	0.15			
Kidney failure		negative	2.15	0.50	-1.613	0.119	
		Positive	2.57	0.30			
Mechanical ventilation		negative	2.22	0.65	0.011	0.991	
		Positive	2.21	0.37			

An Independent t-test was used to determine the relationship between magnesium serum level and mortality, sepsis, liver and kidney failure, and the demand for mechanical ventilation based on COVID-19 disease. Regarding the obtained data, the serum magnesium level in the studied patients had no significant relationship with any of the variables of mortality, sepsis, liver and kidney failure, and the demand for mechanical ventilation based on the COVID-19 disease ( $P>0.05$ ).

### Discussion

In this cross-sectional study, the relationship between hypocalcemia and morbidity and mortality in the Bandar Abbas Shahid Mohammadi Hospitals' ICU in 2019 has been investigated. Sixty-nine patients were included according to the inclusion criteria and were examined until the first results of this issue appeared. The researcher collected demographic information of the patients and other required information such as magnesium and potassium levels. Finally, all the collected information was subjected to statistical analysis.

In our research, 26.1% of 18 patients died during hospitalization, and 24 (34.8%) needed mechanical ventilation, which was a significant number. Serum calcium level was significant in the examined sepsis and kidney failure patients, but no other significant items were observed. There is a significant relationship

between serum calcium level, serum albumin level, and SOFA score. There was no significant relationship between the duration of hospitalization and the need for a ventilator, calcium and potassium serum level, and their APACHE ( $P>0.05$ ). In addition, the serum level of magnesium in the studied patients had no significant relationship with any of the variables of mortality, sepsis, liver and kidney failure, and the demand for mechanical ventilation based on COVID-19 disease.

The hypocalcemia clinical course among critically ill participants was examined in the research conducted by Steele et al. (2013) on 1038 patients hospitalized in the ICU. 55.2% of patients had hypocalcemia, which was severe in 6.2% of them. Severely hypocalcemic patients were compared with normocalcemic or mildly hypocalcemic patients, but there was no difference in mortality between the groups [2].

To investigate the calcium disorder, C. Sauter et al. (2015) conducted a cross-sectional investigation on 8,270 participants hospitalized in the Inselspital Bern Switzerland's emergency department. It was observed that a total of 264 patients demised, 150 patients experiencing hypocalcemia, and seven patients experiencing hypercalcemia demised compared to 104 patients with normal calcium. According to his study results, hypocalcemia and hypercalcemia are associated with increased 28-day in-hos-



pital mortality in unselected emergency department admissions [7].

In a different study, Sanaei et al. discovered that there was no substantial correlation between adjusted and ionized calcium but a substantial correlation between overall and ionized calcium. Hypocalcemia was found to be an indicator of illness severity and risk of death in his research of 100 patients hospitalized in Imam Reza and Shohada hospitals' ICUs. It was recommended that doctors test ionized calcium in critically ill patients because disturbances of ionized calcium levels are probably an indicator of mortality and disease severity [1]. Another related study in 2022 by Wencheng He et al. was conducted on 5761 competent patients with sepsis, encompassing 2689 receiving calcium supplementation and 3072 without calcium supplementation. The first ICU admission's ICA was the main emphasis of the study, demonstrating that it was substantially associated with death rate among individuals with sepsis, moderate hypocalcemia may be defensive in individuals with sepsis, and calcium intake may have either favorable or unfavorable consequences on mortality based on the severity of the disease. Decisions about calcium supplementation may benefit from using the SOFA score as a diagnostic indicator; however, they suggested that additional evidence is required to find more accurate results [15]. Lower calcium levels were related to the enhanced death rate in randomized emergency department hospitalizations, according to the findings of research conducted by Vroonhof et al. on a total of 1806 adult patients [16].

Additionally, hypocalcemia on hospitalization and mortality were not observed to be significantly correlated in a number of earlier studies [17-22]. Individuals experiencing severe hypocalcemia have been reported to show a substantially higher mortality rate, and the investigators of numerous studies have concluded that this relationship is therapeutically considerable [5, 3, 24]. Additionally, it should be mentioned that parenteral calcium administration may be detrimental. This idea is evidenced by empirical models of sepsis, where calcium administration is linked to an elevated death rate [25, 26].

One of the limitations of this study was that the information of some patients was distorted in different parts of the file. Also, due to the COVID-19 epidemic, the variety of patients in Bandar Abbas Shahid Mohammadi Hospital was reduced. Considering the existence of studies with a longer duration, it is suggested that future studies be conducted in more extended periods and that a larger population being studied so that the results can be cited better. Also, regarding the prevention of hypocalcemia, family doctors have a critical obligation in controlling hypocalcemia and hyperparathyroidism. Finding the etiology of hypocalcemia is the first step in treatment, which is supplemented with vitamin D and calcium metabolites. Thiazide diuretics and other alternatives that successfully treat hypocalcemia and mitigate manifestations can be introduced to additionally improve the course of treatment. Current treatment for hypothyroidism is ineffective, and it is linked to significant alterations in serum calcium levels as well as the risks of hypercalciuria, kidney failure, and hypercalcemia. Physicians should aggressively treat and accurately monitor patients after assessing and identifying

the hypocalcemia etiology [27].

## Conclusions

This research demonstrated a substantial correlation between serum calcium concentration with serum albumin level and SOFA score. There was no significant relationship between serum calcium level with the duration of hospitalization, the need for a ventilator, and the APACHE score. Also, the serum calcium level was insignificant for any of the parameters in COVID-19 patients.

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