



Hypocalcemia in hospitalized patients with COVID-19: roles of hypovitaminosis D and functional hypoparathyroidism

Sima Hashemipour¹ · Somaieh Kiani¹ · Pouria Shahsavari¹ · Sabereh Afshar¹ · Arefeh Ghobadi¹ · Seyyed Mohammad Reza Hadizadeh Khairkhanan¹ · Milad Badri² · Seyed Saeed Farzam³ · Hossein Sohrabi¹ · Mahyar Seddighi¹ · Rozita Bahadori¹

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Abstract

Introduction Despite the high prevalence of hypocalcemia in patients with COVID-19, very limited studies have been designed to evaluate etiologies of this disorder. This study was designed to evaluate the status of serum parameters involved in calcium metabolism in patients with COVID-19 and hypocalcemia.

Materials and methods This cross-sectional study was conducted on 123 hospitalized patients with COVID-19. Serum concentrations of PTH, 25 (OH) D, magnesium, phosphate, and albumin were assessed and compared across three groups of moderate/severe hypocalcemia (serum total calcium < 8 mg/dl), mild hypocalcemia (8 mg/dl ≤ serum total calcium < 8.5 mg/dl) and normocalcemia (serum total calcium ≥ 8.5 mg/dl). Multivariate analyses were performed to evaluate the independent roles of serum parameters in hypocalcemia.

Results In total, 65.9% of the patients had hypocalcemia. Vitamin D deficiency was found in 44.4% and 37.7% of moderate/severe and mild hypocalcemia cases, respectively, compared to 7.1% in the normal serum total calcium group ($P=0.003$). In multivariate analysis, vitamin D deficiency was independently associated with 6.2 times higher risk of hypocalcemia ($P=0.001$). Only a minority of patients with hypocalcemia had appropriately high PTH (15.1% and 14.3% in mild and moderate/severe hypocalcemia, respectively). Serum PTH was low/low-normal in 40.0% of patients with moderate/severe low-corrected calcium group. Magnesium deficiency was not associated with hypocalcemia in univariate and multivariate analysis.

Conclusion Vitamin D deficiency plays a major role in hypocalcemia among hospitalized patients with COVID-19. Inappropriately low/low-normal serum PTH may be a contributing factor in this disorder.

Keywords Hypocalcemia · COVID-19 · Vitamin D deficiency · Functional hypoparathyroidism

Introduction

Since the beginning of the COVID-19 pandemic in December 2019, other manifestations have been progressively reported in various organs in addition to the respiratory system [1]. The endocrine system is one of the targets of Coronavirus. New-onset diabetes, adrenal insufficiency, syndrome of inappropriate secretion of anti-diuretic hormone, and hypocalcemia have been reported in this disease [2–4].

Hypocalcemia is highly prevalent in COVID-19 [5–7]. Up to 80% of hospitalized patients with COVID-19 have been reported to have hypocalcemia [5]. Furthermore, hypocalcemia in COVID-19 is associated with progressive disease and poor outcomes [7, 8]. Despite being a highly prevalent disorder and its robust role in the prognosis of patients with

✉ Somaieh Kiani
kiani8825@gmail.com

¹ Metabolic Diseases Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran

² Medical Microbiology Research Center, Qazvin University of Medical Sciences, Qazvin, Iran

³ Cardiovascular Surgery, Department of Cardiology, Clinical Research Development Unit, Boalisina Hospital, Qazvin University of Medical Sciences, Qazvin, Iran

COVID-19, very limited studies have investigated the etiologies of its occurrence.

Hypocalcemia has been reported as a prevalent disorder in critically ill patients since decades ago [9, 10]. Different mechanisms such as hypoalbuminemia, disorders of PTH secretion and action, vitamin D deficiency or increased catabolism of vitamin D, and calcium precipitation are involved in the hypocalcemia of critical illness [11–13].

Despite some similarities between hypocalcemia in COVID-19 and other critical illnesses, it seems that this disorder is somehow different in COVID-19. Firstly, albeit based on limited studies, hypocalcemia is more prevalent in the acute respiratory syndrome by COVID-19 infection compared to other infections [14]; secondly, hypocalcemia in COVID-19 is not restricted to severe or critical cases and the prevalence of this disorder is high even in non-severe-COVID-19 [15].

Regarding the dearth of evidence about the etiologies of hypocalcemia in COVID-19, this prospective cross-sectional study has been designed to evaluate the contributing factors involved in this disorder.

Materials and methods

Study design and characteristics of participants

The current prospective cross-sectional study was conducted on hospitalized patients with COVID-19 in Boali education and therapeutic center, Qazvin Province, Iran, from January to April 2021. The inclusion criteria were age ≥ 18 years old, and confirmed COVID-19 by polymerase chain reaction (PCR) method. Patients with serum creatinine ≥ 2 mg/dl, known parathyroid or metabolic bone disease, advanced liver disease, or using anticonvulsants were excluded from the study. Information about demographic characteristics, comorbidities, and symptoms was collected and recorded in the questionnaire.

Serum total calcium and albumin were assessed on the first day of hospitalization, and serum samples were stored at -80 °C. Serum total calcium, magnesium, and phosphate were assessed via colorimetric method using Selectra E Chemistry Analyzer (Hoogerheide, the Netherlands) and Delta Darman Kits.

The normal range of serum total calcium was 8.5–10.5 mg/dl with inter-assay and intra-assay 1.05% and 0.95%, respectively. Normal ranges of phosphate and magnesium were 2.5–4.5 mg/dl and 1.8–2.6 mg/dl, respectively. The parathormone (PTH) and 25 (OH)D assays were performed via Electrochemiluminescence (ECL) method using the Roche/Hitachi cobas® 6000 immunoassay system and Roche Kits with a normal range of 15–65 pg/ml and 30–70 ng/ml, respectively.

The participants were divided into three groups of normal calcium (serum total calcium ≥ 8.5 mg/dl), mild hypocalcemia (serum total calcium between 8 to 8.4 mg/dl), and moderate/severe hypocalcemia (serum total calcium lower than 8 mg/dl).

Vitamin D deficiency and insufficiency were defined as the serum 25 (OH)D lower than 20 ng/ml, and between 20–29.9 ng/ml, respectively.

Corrected calcium was calculated by the formula:

$$\text{Corrected calcium(mg/dl)} = \text{serum total calcium(mg/dl)} + 0.8 \times (4 - \text{serum albumin(g/dl)})$$

Based on laboratory criteria for diagnosis of hypoparathyroidism (low or low-normal PTH level in the presence of hypocalcemia [16], the term of functional hypoparathyroidism was used for PTH level in low/low normal range in the presence of hypocalcemia [11].

Statistical analysis

The Kolmogorov–Smirnov test was run to evaluate quantitative data distribution. The comparisons of quantitative data with normal distribution, abnormal distribution, and categorical data across the three groups were conducted using Analysis of variance (ANOVA), Kruskal–Wallis, and Chi-square tests, respectively. The logistic regression analysis was performed to investigate the independent associations of serum albumin, hypovitaminosis D, PTH status, and hypomagnesemia with hypocalcemia.

Results

Totally, 132 patients were recruited in the study. The serum creatinine of nine patients was > 2 mg/dl, and they were excluded from the study, and 123 patients remained for examining the cause of hypocalcemia. Demographic characteristics and disease severity indicators are given in Table 1.

In total, 65.9% and 60.2% of the patients had low total and corrected calcium, respectively. Frequencies of mild and moderate/severe hypocalcemia were 43.1% and 22.8%, respectively (Table 2).

The analysis regarding serum parameters involved in calcium metabolism is presented in Table 2.

Serum 25 (OH)D concentration was significantly higher in patients with normocalcemia compared to hypocalcemia groups (38.2 ± 16.2 ng/ml vs. 28.7 ± 19.5 ng/ml in mild and 25.3 ± 15.6 ng/ml in moderate/severe hypocalcemia, $P=0.01$ and $P=0.004$, respectively). This difference was

Table 1 Demographic characteristics, main complains, disease severity indices, and comorbidities of patients

Age (y)	61.5 ± 16.5
Gender (male%)	57.7%
Complains	
Constitutional	60.3%
Respiratory	90.9%
Gastrointestinal	21.5%
Musculoskeletal	52.1%
O2 saturation without oxygen supply	
O2 sat > 93%	9.3%
90% ≤ O2 sat ≤ 93%	17.8%
O2 sat < 90%	72.9%
RR	
RR ≤ 20	57%
20 < RR ≤ 30	41.1%
RR > 30	1.9%
Comorbidity	
HTN	24.3%
IHD	15.7%
DM	28.7%
CKD	0.9%
CRD	6.1%

O2 sat capillary oxygen saturation, RR respiratory rate, HTN hypertension, IHD ischemic heart disease, DM diabetes mellitus, CKD chronic kidney disease, CRD chronic respiratory disease

also significant between mild low corrected calcium vs. normal corrected calcium groups ($P = 0.003$) (Table 2).

Serum albumin was significantly different in calcium groups (4.1 ± 0.3 g/dl in normal serum total calcium vs. 3.9 ± 0.3 g/dl in mild hypocalcemia, and 3.5 ± 0.2 g/dl in moderate/severe hypocalcemia, $P < 0.001$). The

comparisons of serum PTH, magnesium, and phosphate concentrations did not show any significant difference in serum total calcium or corrected calcium groups (Table 2).

The frequencies of abnormal values of the above serum parameters are represented in Fig. 1.

Regarding serum 25 (OH)D levels, 44.4% of the patients in moderate/severe and 37.7% in mild hypocalcemia groups had vitamin D deficiency. On the other hand, only 7.1% of patients in the normal serum total calcium group had vitamin D deficiency ($P = 0.003$). The frequency of vitamin D insufficiency was not significantly different across groups (Fig. 1). The frequency of vitamin D deficiency in moderate/severe hypocalcemia was nearly close to the prevalence of Iranian general population in the systematic review by Vatandost et al. with prevalence of 56% [17].

In our study, only a minority of patients with hypocalcemia had appropriately high PTH (15.1% and 14.3% in mild and moderate/severe hypocalcemia, respectively), and the frequency of high PTH was not significantly different between normal and low serum total calcium groups (14.6% in the normal calcium group) (Fig. 1).

Functional hypoparathyroidism (low or low-normal PTH in the presence of hypocalcemia) was found in 45.3% and 28.6% of mild and moderate/severe hypocalcemia cases, respectively. When we considered corrected calcium, the frequency of functional hypoparathyroidism raised to 40.0% of moderate/severe low-corrected calcium (Fig. 1).

Hypomagnesemia was found with similar frequencies in calcium groups (10.7%, 9.4%, and 14.3% in moderate/severe, mild hypocalcemia, and normal calcium groups, in that order) (Fig. 1).

Serum albumin level < 4 g/dl was found in 92.9% of moderate/severe hypocalcemia vs 47.2% and 31.0% of mild

Table 2 Demographic characteristics and serum parameters levels categorized by serum calcium and corrected calcium groups

	Serum calcium				Serum corrected calcium			
	Ca ≥ 8.5 mg/dl 42 (34.1%)	8 ≤ Ca < 8.5 mg/dl 53 (43.1%)	Ca < 8 mg/dl 28 (22.8%)	P	Ca _{correct} ≥ 8.5 mg/dl 45 (38%)	8 ≤ Ca _{correct} < 8.5 mg/dl 58 (50%)	Ca _{correct} < 8 mg/dl 13 (11.2%)	P
Age (year)	61.0 ± 16.0	59.9 ± 16.1	65.4 ± 18.0	0.357	60.4 ± 15.4	62.1 ± 16.7	59.1 ± 19.5	0.798
Gender (male%)	45.2%	60.4%	71.4%	0.082	44.4%	69.0%	46.2%	0.032
25 (OH)D (ng/ml) [†]	38.2 ± 16.2	28.7 ± 19.5	25.3 ± 15.6	0.006	37.3 ± 18.6	26.6 ± 17.0	30.0 ± 18.9	0.013
PTH (pg/ml)	32.7 (30.5)	36.1 (35.3)	45.6 (24.1)	0.318	30.9 (33.9)	37.2 (30.8)	31.1 (37.3)	NS
Magnesium (mg/dl)	2.0 ± 0.3	2.0 ± 0.2	2.1 ± 0.3	0.617	2.0 ± 0.2	2.0 ± 0.2	2.1 ± 0.2	0.553
Phosphate (mg/dl)	3.4 (1.1)	3.3 (0.7)	3.3 (0.8)	0.474	3.5 (1.0)	3.3 (1.1)	3.0 (0.6)	0.069
Albumin (g/dl) ^{††}	4.1 ± 0.3	3.9 ± 0.3	3.5 ± 0.2	< 0.001	3.9 ± 0.3	3.9 ± 0.3	4.0 ± 0.5	0.348

Variables with normal distribution are represented by mean ± SD. Variables without normal distribution (PTH and phosphate) are represented as median (interquartile). ANOVA and Kruskal–Wallis tests was used for comparing variable with normal and abnormal distributions, respectively

[†]Significant difference between mild hypocalcemia and moderate/severe hypocalcemia groups vs. normal calcium group, $P = 0.01$ and $P = 0.004$, respectively. For corrected calcium, significant difference between mild hypocalcemia vs. normal calcium groups, $P = 0.003$

^{††}Significant difference between three groups, moderate/severe vs. mild hypocalcemia and vs. normal calcium groups, $P < 0.001$, mild hypocalcemia vs. normal group, $P = 0.05$

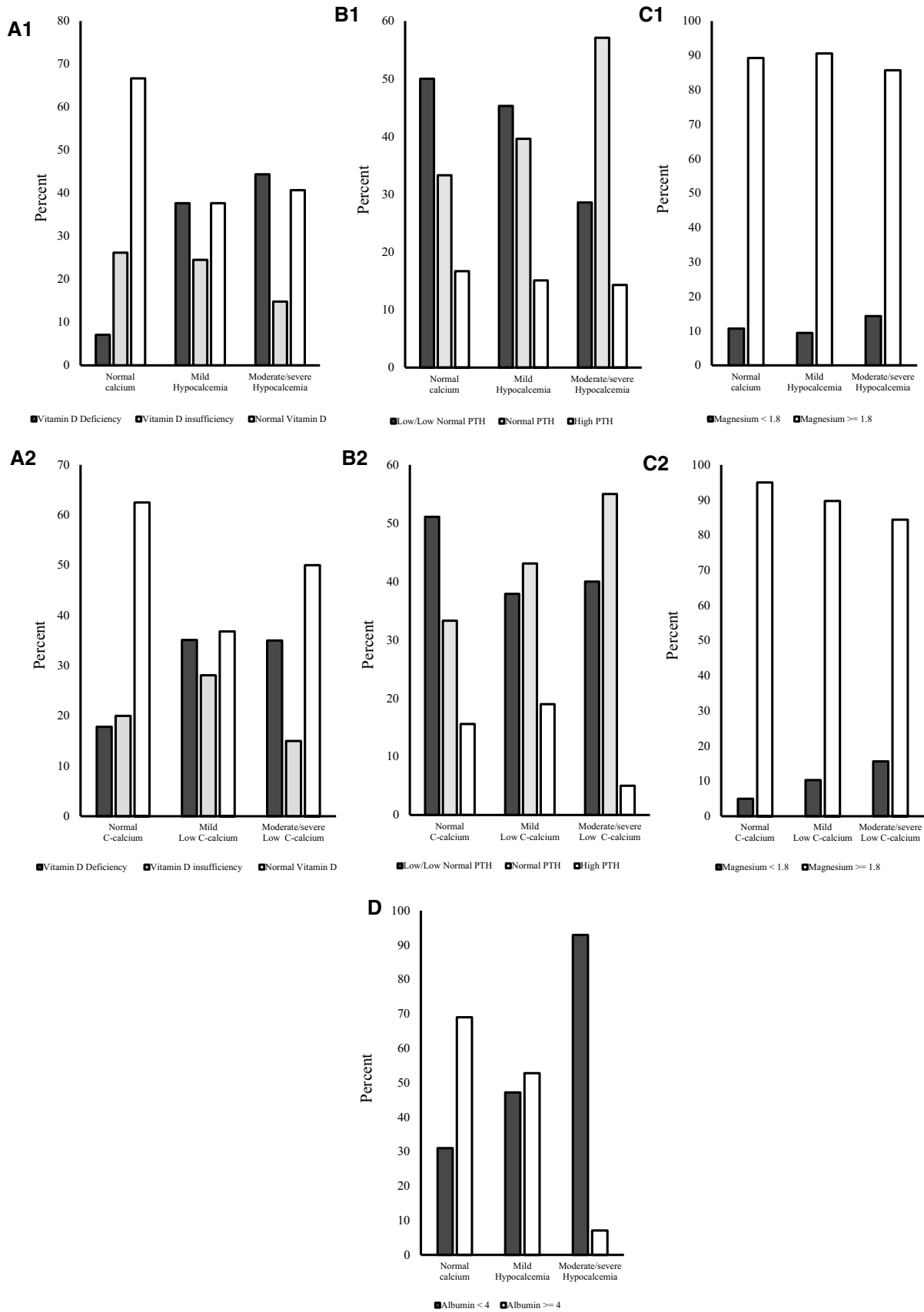


Fig. 1 Status of biochemical and hormonal variables in different degrees of hypocalcemia. **A1** Frequency of vitamin D deficiency and insufficiency in calcium groups. **A2** Frequency of vitamin D deficiency and insufficiency in corrected calcium groups. **B1** Frequency of functional hypoparathyroidism and secondary hyperparathyroidism in calcium groups. **B2** Frequency of functional hypoparathyroidism and secondary hyperparathyroidism in corrected calcium groups. **C1** Frequency of magnesium deficiency in calcium groups. **C2** Frequency of magnesium deficiency in corrected calcium groups. **D** Frequency of serum albumin < 4 mg/dl in calcium groups

hypocalcemia and normal calcium groups, respectively ($P < 0.001$) (Fig. 1).

The logistic regression analysis was performed to examine the independent roles of serum albumin, hypovitaminosis D, PTH status, and hypomagnesemia in the occurrence of hypocalcemia (Table 3).

After adjustment, vitamin D deficiency was associated with a 6.2 higher risk of hypocalcemia (CI 95% 2.0–19.5, $P = 0.002$). Furthermore, vitamin D insufficiency was associated with a 2.5 higher risk of hypocalcemia, but this association was not significant ($P = 0.098$).

Lower albumin levels were associated with low serum total calcium. For each 1 mg/dl decrease in the serum albumin from 4 mg/dl, the risk of low total calcium was increased 7.5 times (CI 95% 2.9–19.3, $P < 0.001$).

Other variables regarding hypomagnesemia, functional hypoparathyroidism or secondary hyperparathyroidism did not show any significant association with hypocalcemia.

Discussion

In the present study, about two-thirds of the patients with COVID-19 had hypocalcemia. Despite the higher frequency of relative hypoalbuminemia in the patients with hypocalcemia, the prevalence of low-corrected calcium was similarly high. Vitamin D deficiency was independently associated with about a six-times higher risk of hypocalcemia. We found a high prevalence of functional hypoparathyroidism in the patients with hypocalcemia. We did not find any role of serum magnesium disturbances in hypocalcemia.

There are some hypotheses as the causes of hypocalcemia in COVID-19 in special and critical illnesses in general. Hypoalbuminemia, vitamin D deficiency, decreased activity of 1α hydroxylase, functional hypoparathyroidism, PTH resistance, increased binding of calcium ions to unsaturated fatty acids, and virus-dependent mechanisms causing the influx of calcium into the cells are mentioned as the main reasons for hypocalcemia in COVID-19 [7, 11, 18, 19].

Vitamin D deficiency is common in critically ill patients with the reported prevalence of 40–70% [20]. Furthermore, prevalence of hypovitaminosis D is very high in patients with COVID-19. In the study by Hernández et al. about 82%

of patients with COVID-19 had vitamin D deficiency. The mean of 25 (OH)D in this study was 13.8 ± 7.2 ng/ml [21]. In Pal et al.'s study, vitamin D deficiency was seen in 97% of patients with COVID-19, and the median of 25 (OH)D was as low as 9.1 ng/ml [15]. Despite this high prevalence of vitamin D deficiency in COVID-19, the association of this abnormality with hypocalcemia of COVID-19 is less investigated. In the prospective study by Osman et al., there was no association between serum 25 (OH)D and calcium levels [22].

Functional hypoparathyroidism and resistance to PTH action have been reported as contributing factors to hypocalcemia of critical illness [23]. In animal studies, high levels of interleukin 1β induce up-regulation of calcium sensor receptors (CaSR) in the kidney and parathyroid cells. Other cytokines such as interleukin-6 and TNF- α also upregulate these receptors. These changes result in increasing sensitivity of CaSR to the serum total calcium and higher threshold of parathyroid cells for PTH secretion [24, 25]. Furthermore, magnesium deficiency can impair PTH secretion response to hypocalcemia and PTH resistance [26].

In Lind et al.'s study in septic patients with hypocalcemia, PTH level was increased in more than seventy percent of hypocalcemic patients. In a minority of the patients, PTH level remained in normal range. These patients with low PTH concentrations had significantly higher CRP and inflammatory cytokines [27].

In Hu et al.'s study conducted on patients admitted to medical intensive care unit, about ninety percent of patients had low ionized calcium. Secondary hyperparathyroidism occurred in 56% of hypocalcemic patients [28].

Surprisingly, appropriately high PTH was found in only about one-seventh of our patients with hypocalcemia. In about 40% of the patients with moderate/severe low-corrected calcium, the PTH level was low or in the lower half of the normal range. The reason of this difference between COVID-19 and above mentioned critical illnesses is not clear, but may be one of the clues of highly prevalent hypocalcemia even in non-severe COVID-19.

The serum magnesium level did not have a significant difference in hypocalcemia and normocalcemia; however, serum magnesium level is not a good indicator of intracellular magnesium [29]. Thus we cannot reject total body magnesium deficiency as a contributing factor in hypocalcemia.

Our study had some limitations. The study design was cross-sectional, so causality could not be confirmed. Another limitation was the lack of assessment of ionized calcium. We calculated corrected calcium, but this parameter does not have a good sensitivity in detecting hypocalcemia in critical illnesses [30]. The third limitation was the inability to evaluate some hypotheses about hypocalcemia in COVID-19 such as increased binding of Ca^{++} to unsaturated fatty acids and virus-dependent increased influx of Ca^{++} into the cells.

Table 3 Associations of biochemical/hormonal parameters involved in calcium metabolism with hypocalcemia

	Crude OR (CI 95%)	P	Adjusted OR (CI 95%)	P
Age	1.0 (0.9–1.0)	0.747	0.9 (0.9–1.0)	0.812
Vitamin D deficiency	4.2 (1.6–10.9)	0.002	6.2 (2.0–19.5)	0.002
Vitamin D insufficiency	1.2 (0.5–3.1)	0.604	2.5 (0.8–7.3)	0.098
Low/low normal PTH	0.7 (0.2–2.0)	0.539	0.9 (0.2–3.3)	0.690
High PTH	1.46 (0.5–4.3)	0.492	1.8 (0.5–6.7)	0.378
Hypomagnesemia	0.5 (0.2–1.7)	0.325	0.7 (0.2–2.7)	0.768
Albumin < 4 mg/dl	5.0 (2.3–10.7)	<0.001	7.5 (2.9–19.3)	<0.001

Hypocalcemia was defined as serum calcium \leq 8.5 mg/dl as dependent variable

In conclusion, the results of our study revealed the significant roles of vitamin D deficiency and the high frequency of functional hypoparathyroidism in the hypocalcemia of COVID-19.

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Declarations

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval The research protocols used in this research were approved by the ethics committee and the research council of Qazvin University of Medical Sciences, Qazvin, Iran (The ethical cod: IR.QUMS.Rec.1399.565).

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