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Research Paper

The Impact of Late Secondary Hyperparathyroidism on Mortality in COVID-19 Patients: A Longitudinal Study

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ABSTRACT

Background: Adverse effects of high parathormone hormone (PTH) in critical illness have been described in some studies.

Objective: The relationship between high PTH levels with mortality in hospitalized patients with COVID-19 was evaluated in the present study.

Methods: A total of 123 patients were included in the study. The patients were evaluated in phase 1 (on admission) and phase 2 (days 4-6 of hospitalization). The patients were categorized into four groups based on the PTH status in both phases: normal PTH_1/normal PTH_2 (group 1), high PTH_1/normal PTH_2 (group 2), high PTH_1/high PTH_2 (group 3), and normal PTH_1/high PTH_2 (group 4). The multiple logistic regression analysis was performed to examine the independent association of late hyperparathyroidism with mortality. After excluding ineligible participants, 115 patients in phase 1 and 96 patients in phase 2 (days 4-6 of hospitalization) were evaluated.

Findings: The level of phase 2 PTH in non-survivors was significantly higher than in survivors (57.5±40.9 pg/mL vs. 27.6±16.2 pg/mL, P=0.001). The mortality rate was significantly higher in high-PTH groups in phase 2 compared to normal-PTH groups in this phase (50% and 42.9% in groups 3 and 4 vs. 6.6% and 18.2% in PTH groups 1 and 2, respectively, P=0.007). Late hyperparathyroidism was associated with 11.4 times higher mortality risk (95% CI: 2.3-56.1, P=0.003).

Conclusion: Late hyperparathyroidism remained a significant predictor of mortality after adjusting for the main PTH secretion modulators and disease severity. Late hyperparathyroidism is an independent and strong risk factor for mortality in COVID-19. Further studies are necessary to clarify the mechanisms involved.

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1. Introduction

In critically ill patients, hypocalcemia is a common abnormality [1]. Hypocalcemia is more common in patients with infections, particularly septicemia [2]. According to the available data, this disorder is highly prevalent in hospitalized COVID-19 patients [3-5]. In some studies, a prevalence of over 80% has been reported in hospitalized COVID-19 patients [6].

Higher levels of inflammatory markers and more severe disease have been observed in COVID-19 patients with severe hypocalcemia [6, 7] The association of hypocalcemia with a higher mortality rate has been reported in some studies in patients with COVID-19 or other critical cases. However, the findings of this association are not consistent. In some studies, hypocalcemia is a strong independent predictor of mortality [4, 8, 9], but in other studies, the association of hypocalcemia with mortality is found only in univariate analysis, and after adjusting for other clinical parameters, this association has disappeared [6]. Other studies found no association between hypocalcemia and mortality in hospitalized patients with COVID-19 or other diseases [10-12].

Besides the impact of hypocalcemia on mortality, a few studies have investigated the role of the main modulator of calcium physiology, i.e. parathormone hormone (PTH), in the prognosis of patients with critical illness and hypocalcemia. Based on these limited data, secondary hyperparathyroidism predicts a poor prognosis, even in patients with mild hypocalcemia [13, 14]. Nevertheless, we do not have enough data about the association between serum PTH levels and prognosis in patients with COVID-19. The present study thus evaluated the association of PTH response to hypocalcemia with mortality in two phases of hospitalization with COVID-19.

2. Material and Methods

Study design and characteristics of participants

This prospective longitudinal study was conducted on hospitalized patients with COVID-19 at Bu Ali-Sina Hospital, Qazvin Province, Iran, from March to April 2021, for about three weeks. The inclusion criteria included age over 18 years and hospitalization for COVID-19. COVID-19 disease was confirmed by a polymerase chain reaction (PCR) test. The exclusion criteria included patients with known parathyroid or metabolic bone disease, serum creatinine ≥2 mg/dL, advanced liver disease, using anticonvulsants, and patients with unknown outcomes due to discharge by personal consent. The demographic characteristics, symptoms, and underlying diseases were recorded in a questionnaire. The clinical and laboratory data were evaluated on the first day and days 4-6 of hospitalization. The patients were categorized into four groups based on the PTH status in both phases, normal PTH_1/normal PTH_2 (group 1), high PTH_1/normal PTH_2 (group 2), high PTH_1/high PTH_2 (group 3), and normal PTH_1/high PTH_2 (group 4). The groups were compared regarding severity indices (assessed by oxygen saturation and inflammatory markers), biochemical and hormonal data, and outcomes.

Measures

Serum levels of total calcium, albumin, magnesium, phosphate, 25-Hydroxy Vitamin D (25[OH]D), PTH, and creatinine were assessed on the first day and days 4-6 of hospitalization. Physicians who managed the patients were not aware of the calcium and albumin results. The serum calcium was measured by the colorimetric method. The normal range, inter-assay, and intra-assay of the calcium assay were 8.5-10.5 mg/dL, 0.95%, and 1.05%, respectively. The PTH level assay was performed by the electrochemiluminescence (ECL) method. The normal range of PTH was 15-65 pg/mL, and the inter-assay and intra-assay were 1.2% and 2%, respectively. Details of the assays of other biochemical parameters have been previously published [15].

Corrected calcium was calculated by the following formula:

Corrected calcium (mg/dL)=serum calcium (mg/dL)+0.8×(4-serum albumin (g/dL) (Goltzman) [16].

Vitamin D deficiency and insufficiency were defined as 25(OH)D<20 ng/mL and 20 ng/mL ≤25(OH)D<30 ng/mL, respectively [17].

Statistical analysis

The data were analyzed using SPSS software version 24. The distribution normality of quantitative variables was tested using the Kolmogorov–Smirnov test. The logarithmic transformation was performed on the quantitative variables without normal distribution. A t-test and an analysis of variance (ANOVA) were performed to compare the quantitative data, and the chi-square test was used for qualitative data.

The multiple logistic regression analysis with two models was performed to examine the independent roles of variables in mortality as an outcome. Considering the similar mortality of groups 3 and 4, and the small number of patients in group 3, these two groups were combined as late hyperparathyroidism (regardless of PTH status in phase 1). In model 1, age, PTH groups, corrected calcium, creatinine, and vitamin D status were entered into the model; in model 2, variables of model 1 plus the status of oxygen saturation status and CRP level (as indicators of disease severity) were entered into the model. Pearson's correlation coefficient was used to examine the correlation of serum PTH with serum 25(OH) D at each time and simultaneous calcium with $P<0.05$ was considered significant.

3. Results

A total of 123 patients were included in the study. Of these patients, the outcomes of eight patients are unknown due to early discharge by personal consent, and predictors of mortality were evaluated in 115 patients (phase 1). For phase 2 (days 4-6 of hospitalization), 19 patients were excluded from the study, 7 patients due to early discharge, 4 patients due to decease, 3 patients due to serum creatinine rising to >2 mg/dL, and 5 patients due to missing some data, and eventually 96 patients were studied in this phase (Figure 1).

The clinical and laboratory data of the participants are categorized according to the outcome of death and are presented in Table 1. Of the 115 eligible patients, 15 patients died. Among related minerals and hormones, no relationship was observed between serum levels of total/corrected calcium, phosphate, magnesium, 25(OH)D, and mortality. Moreover, the frequencies of hypocalcemia (calculated as low corrected calcium) and vitamin D deficiency or insufficiency did not have any significant difference between a survivor and non-survivor groups (P=0.258 and P=0.634, respectively). As for PTH, the

Table 1. The clinical and laboratory data of participants categorized by the outcome of death

Variables		Mean±SD/ No. (%)			P
		Total (n=115)	Survived (n=100)	Expired (n=15)	
Age (y)		61.4±16.1	59.4±15.4	74.4±14.5	0.001
Sex (male)		64(55.7)	53(53)	11(73.3)	0.139
Complaints	Respiratory	103(89.6)	92(92)	11(73.3)	0.058
	Gastrointestina	25(21.7)	23(23)	2(13.3)	0.397
	Musculoskeletal	58(50.4)	53(53)	5(33.3)	0.155
HTN		27(23.5)	24(24)	3(0.20)	0.892
IHD		18(15.7)	14(14)	4(26.7)	0.208
DM		25(21.7)	22(22)	3(20)	0.861
COPD/Asthma		6(5.2)	6(6)	0	0.330
Oxygen saturation$_1$ †		-	-	-	0.003
O_2 Sat <90%		29(29.6)	20(23.5)	9(69.2)	-
90% ≤2 Sat ≤93%,		21(21.4)	20(23.5)	1(7.7)	-
O_2 Sat >93%		48(49)	45(52.9)	3(23.1)	-
Oxygen saturation2 ††					0.034
O_2 Sat <90%		17(19.3)	13(16.7)	4(40)	-
90%≤O_2 Sat ≤93%		20(22.7)	16(20.5)	4(40)	-
O_2Sat >93%		51(58)	49(62.8)	2(20)	-

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Variables		Mean±SD/ No. (%)			P
		Total (n=115)	Survived (n=100)	Expired (n=15)	
Laboratory data	FBS (mg/dL)	135(83.5)	132(84.5)	144(66)	0.313
	Na (meq/L)	138(5.0)	138(4.5)	139(7.0)	0.457
	K (meq/L)	4.6(0.6)	4.6(0.7)	4.5(0.7)	0.242
	Cr_1 (mg/dL)	0.9±0.3	0.9±0.2	1.1±0.4	0.056
	Cr_2 (mg/dL)	0.8±0.2	0.8±0.2	1.0±0.3	0.028
	WBC (n/mm^3)	7700(4400)	7500(3900)	7800(5200)	0.085
	CRP (mg/L)	46.4(82.1)	38.9(75.4)	120.8(169.9)	0.005
	Total $calcium_1$ (mg/dL)	8.3±0.5	8.3±0.5	8.2±0.5	0.715
	Total $calcium_2$ (mg/dL)	8.0±0.5	8.0±0.5	7.9±0.8	0.486
	Corrected Ca_1 (mg/dL)	8.4±0.4	8.4±0.4	8.4±0.3	0.907
	Low corrected $calcium_1$	69(60)	58(58)	11(73.3)	0.258
	Corrected Ca_2 (mg/dL)	8.3±0.5	8.3±0.4	8.3±0.7	0.964
Low corrected $calcium_2$		65(67.7)	57(67.1)	8(72.2)	0.705
PTH_1 (pg/mL)		36.1(29.5)	35.0(29.6)	45.0(41.5)	0.130
PTH_1>65 (pg/mL)		15(30)	11(11)	4(26.7)	0.093
PTH_2 (pg/mL)		26.2(19.2)	25.4 (16.8)	50.6(50.2)	0.001
PTH_2>65 (pg/mL)		9(9.4)	5 (5.9)	4(36.4)	0.001
Mg (mg/dL)		2.1±0.3	2.1±0.3	2.2±0.3	0.125
Phosphate (mg/dL)		3.4±0.6	3.4±0.7	3.5±1.0	0.426
25(OH)D (ng/mL)		31.3±18.1	31.9±18.1	27.2±17.5	0.343
25(OH)D groups		-	-	-	0.634
25(OH)D ≤20 (ng/mL)		32(27.8)	27(27.0)	5(33.3)	-
20<25(OH)D≤30 (ng/mL)		26(22.6)	24(24.0)	2(13.3)	-

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Quantitative data with normal and non-normal distribution are presented as Mean±SD and median (interquartile range), respectively. Logarithmic transformation was used for quantitative data without a normal distribution. Phase 2 laboratory data was collected from 96 participants. Low corrected ca: serum corrected calcium <8.5 mg/dL.

Abbreviations: HTN: Hypertension; DM: Diabetes mellitus; IHD: Ischemic heart disease; FBS: Fasting blood glucose; Cr: Creatinine; WBC: White blood cells; CRP: C-reactive protein; PTH: Paratormone; COPD: Chronic obstructive pulmonary disease; O_2: Oxygen; Na: Sodium; K: Potassium; Mg: Magnesium; 25(OH)D 25-Hydroxy: Vitamin D.

Table 2. Laboratory data and outcomes of participants categorized by paratormone (PTH) status in phases 1 and 2

Variables		Mean±SD/ No. (%)/ N				P
		Normal PTH_1, Normal PTH_2 (n=76)	High PTH_1, Normal PTH_2 (n=11)	High PTH_1, High PTH_2 (n=2)	Normal PTH_1, High PTH_2 (n=7)	
Age (y)		63.4±15.7	61.0±11.9	59.0±28.3	58.9±20.9	0.856
Sex (male)		43(56.6)	4(36.4)	0	3(42.9)	0.249
ICU admission		15(19.7)	3(27.3)	1(50)	3(42.9)	0.398
Mortality		5(6.6)	2(18.2)	1(50)	3(42.9)	0.007
Comorbidity	HTN	18(23.7)	2(18.2)	2(100)	0	0.158
	IHD	11(14.5)	1(9.1)	1(50)	2(28.6)	0.374
	DM	21(27.6)	1(9.1)	0	0	0.185
	COPD/Asthma	3(3.9)	2(18.2)	0	1(14.3)	0.234
Oxygen saturation$_1$	O_2 Sat <90%	13(17.1)	2(18.2)	0	3(42.9)	0.717
	90%≤O_2 Sat ≤93%	24(31.6)	3(27.3)	1(50)	1(14.3)	-
	O_2 Sat >93%	39(51.3)	6(54.5)	1(50)	3(42.9)	-
	Oxygen saturation$_2$	-	-	-	-	0.045
	O_2 Sat <90%	7(9.2)	4(36.3)	0	1(14.3)	-
	90%≤O_2 Sat ≤93%	20(26.3)	3(27.3)	2(100)	3(42.9)	-
	O_2 Sat >93%	49(64.5)	4(36.4)	0	3(42.9)	-
Inflammatory markers	WBC (n/mm^3)	7700(4550)	8000(4400)	12300	7450(5875)	0.334
	CRP (mg/l)	44.5(75.1)	57.2(227.5)	56.9	38.9(102.8)	0.849
Kidney function	Creatinine (mg/dl)	0.8±0.2	0.9±0.3	0.6±0.1	0.9±0.3	0.177
Minerals disorders	Hypocalcemia$_1$	42(55.3)	7(63.6)	1(50)	7(100)	0.140
	Hypocalcemia$_2$	50(65.8)	8(72.7)	0	7(100)	0.051
Vitamin D deficiency/ insufficiency	Vitamin D deficiency	20(26.3)	4(36.4)	1(50)	3(42.9)	0.514
	Vitamin D insufficiency	16(21.1)	3(27.3)	1(50)	0	-
Phosphate disorders	Hypophosphatemia	5(6.6)	2(18.2)	0	2(28.6)	0.173
	Hyperphosphatemia	2(2.6)	2(18.2)	0	0	-
	Hypomagnesemia	9(11.8)	12(18.2)	0	1(14.3)	0.882
QTC-interval	Long QTC-interval$_1$†	9(15.3)	1(12.5)	0	2(33.3)	0.611
	Long QTC-interval$_2$††	4(7.7)	0	0	1(16.7)	0.690

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Hypocalcemia: Low corrected calcium <8.5 mg/dL; Vitamin D deficiency: Serum 25(OH)D level ≤ 20 ng/mL; Vitamin D insufficiency: 20 ng/mL < serum 25(OH)D level ≤30 ng/mL; Hypophosphatemia: Serum phosphate <2.5 mg/dL; Hyperphosphatemia: Serum phosphate >4.5 mg/dL; Hypomagnesemia: Serum magnesium <1.8 mg/dL; QTC: Corrected Q-T interval; Long Q-Tc interval, Q-Tc interval ≥440 msec and ≥460 msec in males and females, respectively.

†Based on the data of 75 patients; ††Based on the data of 65 patients.

Abbreviations: HTN: Hypertension; DM: Diabetes mellitus; IHD: Ischemic heart disease; FBS: Fasting blood glucose; Cr: Creatinine; WBC: White blood cells; CRP: C-reactive protein; PTHl: Paratormone; COPD: Chronic obstructive pulmonary disease; O_2: Oxygen.

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Table 3. The crude and adjusted associations of late hyperparathyroidism with mortality

Variables	Unadjusted OR (95% CI)	P	Model 1 OR (95% CI)	P	Model 2 OR (95% CI)	P
Age (y)	1.1(1.0-1.1)	0.002	1.1(1.0- 1.1)	0.009	1.1(1.0- 1.2)	0.008
PTH group	-	0.011	-	0.009	-	0.015
Normal PTH_1, Normal PTH_2	Reference	-	Reference	-	Reference	-
High PTH_1, Normal PTH_2	3.2(0.5-18.7)	0.206	4.9(0.5-38.9)	0.169	2.6(0.2-32.0)	0.453
Normal or high PTH_1, High PTH_2	11.4(2.3-56.1)	0.003	29.9(3.3-274.9)	0.002	82.2(4.2-1603.4)	0.004
Corrected calcium[2]	1(0.3-3.9)	0.964	1.3(0.3-6.8)	0.735	2.9(0.4-19.8)	0.274
25 (OH)D group		0.644	-	0.612	-	0.494
25 (OH)D ≥30 ng/mL	Reference	-	Reference		Reference	-
20≤25(OH)D <30 ng/mL	0.5(0.1-2.5)	0.403	0.3(0.02-4.9)	0.424	0.1(0.01-4.5)	0.255
25(OH)D <20 ng/mL	1.1(0.3-3.7)	0.865	1.4(0.3-7.4)	0.719	0.9(0.1-1.7)	0.965
Creatinine2	17.7(1.6-189.9)	0.018	7.7(0.2-245.7)	0.248	2.4(0.02-325.7)	0.732
Level of hypoxia[2]		0.097	-	-	-	0.337
O_2 saturation >93%	Reference	-	-	-	Reference	-
90%<O_2 saturation ≥93%	3.8(0.8-17.4)	0.081	-	-	0.7(0.1-7.3)	0.786
O_2 saturation ≤90%	5.9(1.0-33.9)	0.047	-	-	4.1(0.4-45.5)	0.244
CRP	1.01(1.0-1.02)	0.008	-	-	1.0(0.9-1.0)	0.099

No. 1: The 1st admission day.

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No. 2: The 4-6th admission day.

Abbreviations: PTH: Paratormone; O_2: Oxygen; 25(OH)D, 25-Hydroxy: Vitamin D.

levels of this hormone on the first day of admission were not significantly different in non-survivors compared to survivors. However, the PTH level on day 4-6 of hospitalization was significantly higher in non-survivors compared to survivors (57.5±40.9 pg/mL vs. 27.6±16.2 pg/mL, P=0.001). Moreover, the frequency of non-survivor patients in phase 2 with an increased level of PTH was higher than survivors (36.4% vs. 5.9%, P=0.001).

To examine the relationship between PTH variations and other abnormalities, the participants were categorized into 4 groups, including normal PTH_1/normal PTH_2 (group 1), high PTH_1/normal PTH_2 (group 2), high PTH_1/high PTH_2 (group 3), and normal PTH_1/high PTH_2 (group 4). Among 13 patients with high PTH in phase 1, the levels of this hormone returned to normal in 11 patients. In 7 patients with normal PTH in phase 1, the PTH level increased to a higher than normal level in phase 2. In total, 9 patients had high PTH in phase 2 (Table2).

All patients in group 4 (early normal PTH and late high PTH) had low corrected calcium in phase 2, and all patients with high PTH in phase 2 (groups 3 and 4) had hypocalcemia or and hypovitaminosis D (25(OH)D<30 ng/mL) (Table 2).

The mortality rate was significantly different among the four PTH groups. Of groups with normal PTH in both phases and high PTH_1/normal PTH_2, 6.6% and 18.2% of the patients died, respectively. The mortality rate in the other two groups with high PTH in phase 2 was 50% in group 3 and 42.9% in group 4 (a significant difference was observed between the four groups, P=0.007) (Table 2).

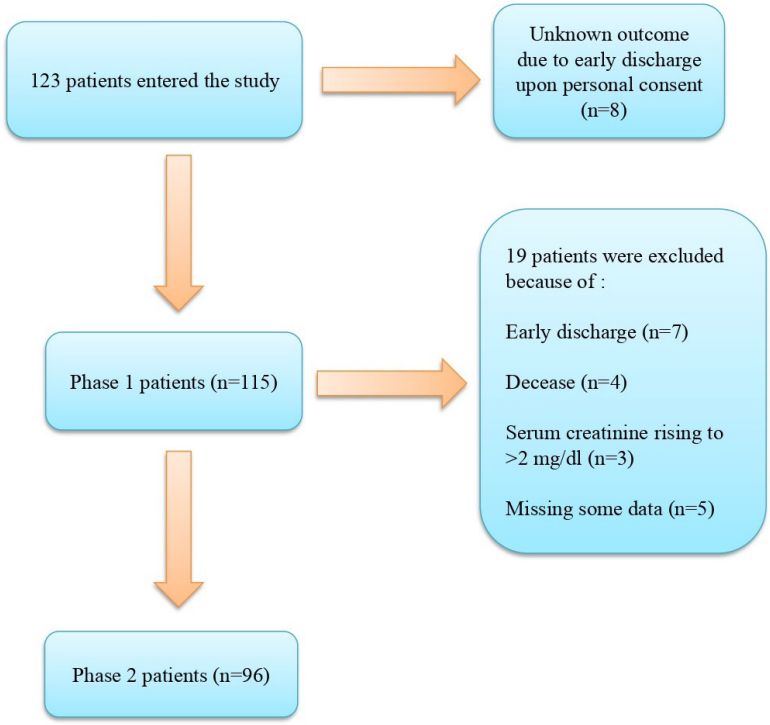

Figure 1. Flow chart of the patients participated the study.

The capillary oxygen saturation in phase 2 was slightly different among the study groups (P=0.045). (The highest frequency of severe hypoxemia, i.e. oxygen (O_2) saturation less than 90% was in group 2). The frequency of hypocalcemia in phase 2 patients was borderline significant (P=0.051), and group 4 had the highest hypocalcemia rate (100% of patients). Other parameters, including comorbidities, inflammatory markers, and mineral disorders, did not show any significant difference between PTH groups (Table 2).

Figure 2 shows the correlation of serum PTH at each time with serum 25(OH)D and calcium simultaneously. On the first day of admission, there was no correlation between serum PTH and calcium (R^2=0.0005, P=0.821). However, in phase 2 of the study, a significant correlation was observed between PTH and calcium (R^2=0748, P=0.007). On the contrary, the PTH was correlated with 25(OH)D only on the first day of admission (R^2=0.075, P=0.003).

Table 3 presents the crude and adjusted associations of late hyperparathyroidism with mortality. The patients with late hyperparathyroidism had an 11.4 times higher rate of mortality regardless of PTH levels on the first day of hospitalization (95% CI: 2.3-56.1, P=0.003). After adjusting for the main modulators of PTH secretion (serum creatinine, corrected calcium, vitamin D status, and age), the association of late hyperparathyroidism with mortality was significant (OR=29.9, 95% CI: 3.3-274.9, P=0.002). After adding the levels of hypoxia and serum CRP to model 1 (as indicators of disease severity), the association of late hyperparathyroidism with mortality remained significant (OR=82.2, 95% CI: 4.2-1603.4, P=0.004).

4. Discussion

We found no association between hypocalcemia or vitamin D deficiency and mortality. However, late hyperparathyroidism was strongly associated with mortality. The patients with late hyperparathyroidism had about a 10 times higher risk of mortality compared to those with normal PTH in each phase of the study. The association of late hyperparathyroidism with mortality was independent of the main modulators of PTH secretion and disease severity. The patients who had early hyperparathyroidism on the first day but normal PTH levels on subsequent days had similar mortality rates to patients with normal PTH levels in each phase of the study.

The association of hypocalcemia and/or vitamin D deficiency with COVID-19 mortality has been investigated in some studies. Nevertheless, as mentioned above, the results of these studies are not consistent. In some of these studies, only hypocalcemia was found to be as-

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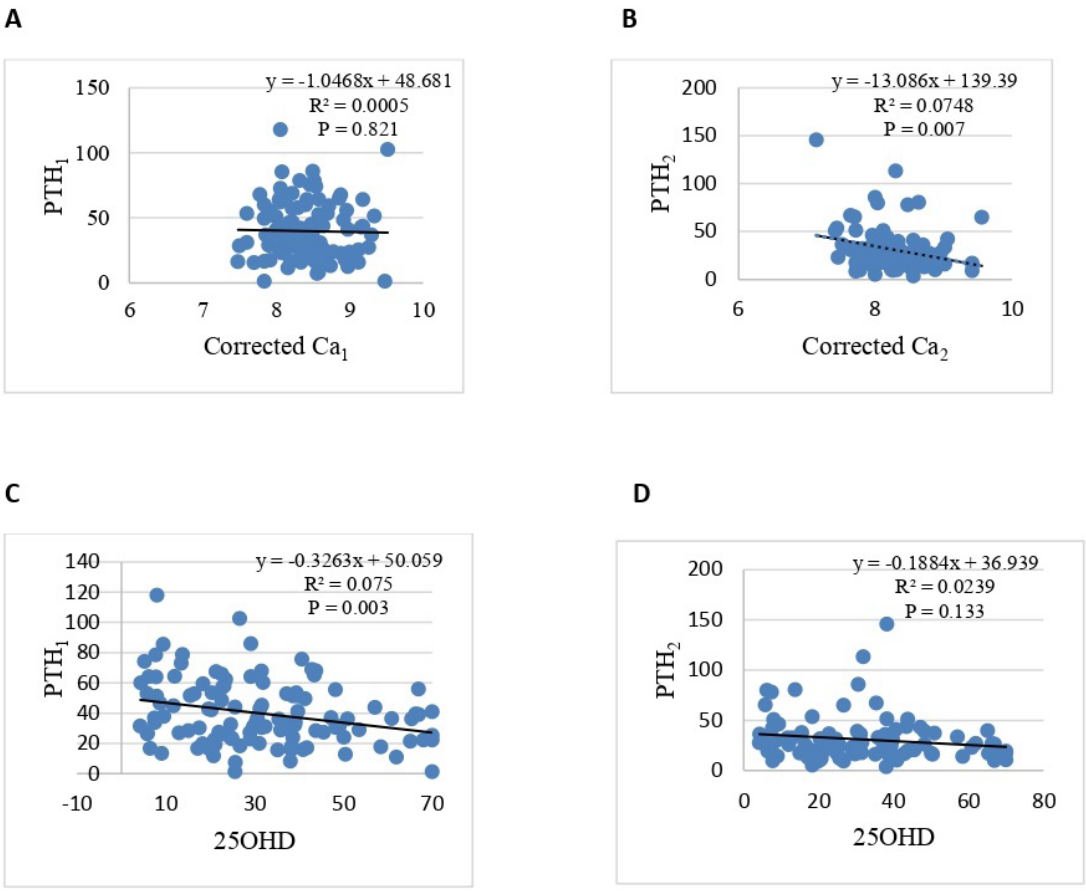

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Figure 2. Correlation of serum PTH levels at two different times with serum 25(OH)D and simultaneouscorretd calcium levels.

PTH_1: Serum PTH level at the 1st admisson day; PTH_2: Serum PTH level at the 4-6th admisson day; Corrected Ca_1: Serum calcium level at the 1st admisson day; Corrected Ca_2: Serum calcium level at the 4-6th admisson day.

sociated with the severity of COVID-19, but not with mortality [11]. In the meta-analysis by Alemzadeh et al., hypocalcemia was associated with higher mortality; however, no detailed description was observed of how the publication bias was evaluated in this study [18]. In another meta-analysis by Martha et al., the association of hypocalcemia with mortality was observed only in the form of composite outcomes of death/ICU admission/ prolonged hospitalization [7].

Some studies have reported a higher mortality rate in critically ill patients with vitamin D deficiency. In the meta-analysis by Wang et al., vitamin D deficiency was associated with a higher mortality rate. However, the cut-off of serum 25(OH)D was <20 ng/mL or lower in most of the included studies [19]. In our study, only about one-fourth of patients had vitamin D deficiency (serum 25(OH)D level ≤20 ng/mL), possibly due to widespread vitamin D usage in the Iranian people, especially during the COVID-19 pandemic. The frequency of vitamin D deficiency was slightly higher in survivors compared to non-survivors, but this difference was not significant. The lack of a significant difference between the two groups of survived and expired patients can be attributed to the small sample size and prevalent vitamin D usage among our patients.

Very few studies have been conducted on the relationship between serum PTH level and mortality in acute settings; to the best of our knowledge, no information is available on the relationship between late secondary hyperparathyroidism with mortality in patients with COVID-19. In our study, late secondary hyperparathyroidism was an independent and strong predictor of mortality. In Ardehali et al.'s study on neurosurgical patients admitted to ICU, the frequency of secondary hyperparathyroidism in patients with hypocalcemia or and hypovitaminosis D was 51.6% and 45.4%, respectively [15]. These patients

with secondary hyperparathyroidism were defined as PTH responders. The PTH responder group had higher APACHI II score, ventilator dependency, and mortality (mortality rate: 81% in the high-PTH group vs. 19% in the normal-PTH group, P=0.001). In the multiple logistic regression (adjusted for age, APACHE II score, serum calcium, albumin, phosphate, magnesium, and calorie intake), neither serum calcium nor 25(OH)D level was associated with mortality. Nevertheless, serum PTH level was independently significantly associated with mortality, and each pg/mL increase in PTH was related to 2% higher mortality [13].

In the study by Carlstedt et al., surgical and septic patients admitted to the ICU were evaluated in terms of the relationship between serum PTH and ionized calcium with the severity of illness and mortality. This study was carried out in two phases. Phase 1 involved the first day of ICU admission, and phase 2 involved the daily measurement of calcium and PTH for 1 week. The frequency of high serum PTH was similar in septic and surgical patients (both 69%). However, the trend of serum PTH levels increased in septic and decreased in surgical patients in one week. At the end of the first week, 87% of septic patients and 37% of surgical patients showed high serum PTH levels. In this study, serum PTH levels in both phases were significantly related to the APACHE II score. Nevertheless, the association of serum PTH level with mortality was found only in the second phase of the study [13].

In Hu et al.'s study of medical ICU patients, approximately half of those who had low serum ionized calcium or hypovitaminosis D (defined as 25(OH)D<30 ng/mL) had secondary hyperparathyroidism (PTH-responders). In the entire group, neither ionized calcium nor PTH was associated with mortality. However, in the hypovitaminosis D group, PTH responders had significantly higher APACHE II and mortality than non-responders [13].

In Nair et al.'s study, the levels of calcium, 25(OH) D, and PTH were measured in patients admitted to the ICU on days 1, 3, and 7 or after discharge from the ICU. About one-third of the patients with hypocalcemia or and low 25(OH)D had secondary hyperparathyroidism (PTH responders). The PTH-responder group had a higher simplified acute physiology score II (SAPS-II) compared to the non-responder group. Nevertheless, the mortality rate was not significantly different between the two groups [20].

Regarding the results of our study and the aforementioned evidence, secondary hyperparathyroidism is associated with a worse prognosis and or more severe disease in patients with a critical illness. Based on the results of our and Carlstedt et al.'s studies, late secondary hyperparathyroidism has a more profound impact on mortality [13].

Some hypotheses justify the higher mortality rate in patients with late hyperparathyroidism in the present study. PTH has been shown to have negative effects on cardiomyocytes for decades [20-22]. In cardiomyocytes, PTH binding activates G- protein receptors and causes calcium influx into the cells and calcium release from the sarcoplasmic reticulum into the cytosoles [23]. Increased intracellular calcium activates protein kinase C (PKC), which interferes with B- adrenergic activity and decreases myocardial contractility [24]. The action of PTH on vascular smooth muscle cells is different; this hormone reduces calcium influx into these cells and subsequently inhibits cAMP-dependent calcium channels and vasodilation [20, 24]. In the study by Baczynski et al. on rats, all the detrimental effects of PTH on cardiomyocytes were countered after the administration of verapamil [20]. The adverse effects of excess PTH are not confined to the bone and cardiovascular system. Lymphocytes and polymorphonuclears (PMN) have receptors for PTH, and suppressive effects of PTH on the secretion of immunoglobins and inhibition of PMN activities have been found in various studies [24, 26, 27]. The inhibitory effects of PTH have been attributed to the increased calcium influx into the immune cells by PTH, and these effects are eliminated by treatment with calcium blockers [28-32].

In the present study, the mortality rate was higher in the high PTH compared to the normal PTH group in both study phases, but this difference was statistically significant only in phase 2. Very limited studies have examined the course of PTH changes and their relationship with prognosis during acute illnesses. This finding parallels Carlstedt et al.'s study in which mortality was associated with high PTH in the following days of hospitalization [13]. Differences in modulators of PTH secretion in two phases of our study may provide some clues to the different impacts of PTH on mortality in various phases of the disease. In the present study, the PTH level on days 4-6 of hospitalization was negatively correlated with the corrected calcium level at that time. However, in the first phase of the study, we found no correlation between serum PTH and corrected calcium levels. Instead, a negative correlation was observed between serum 25(OH)D level and PTH on the first day of hospitalization. Based on these data, the modulators of PTH secretion differed in various phases of our study. The main reason for this difference is not clear, but it appears that in later days of

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hospitalization, PTH stimulation by low serum calcium or unknown other parameters leads to detrimental impacts of high PTH.

Despite these considerations and due to the design of our study, we cannot prove that the high PTH causes mortality. A high PTH may be the result of disease severity, and the higher mortality rate in patients with late hyperparathyroidism can be only a reflection of the severity of COVID-19. However, comparing various PTH groups, we did not find more severe disease in patients with late hyperparathyroidism regarding hypoxemia or inflammatory markers. Moreover, after adjusting for hypoxemia and CRP level (as severity indices), late hyperparathyroidism remained a significant predictor of mortality.

5. Conclusion

In conclusion, we found a strong association between mortality and late secondary hyperparathyroidism in patients with low corrected calcium and/or hypovitaminosis D. Considering the different impacts of hyperparathyroidism on mortality at different times of hospitalization, other studies were designed to investigate the modulators of PTH secretion in various stages of the disease, as well as molecular and cellular studies on variations of intracellular calcium (as the consequence of high PTH and the main potential mechanism for detrimental effects of high PTH), can be very beneficial. If the results of the present study are confirmed by other studies, randomized clinical trials to investigate the dual treatment with calcium (to prevent PTH stimulation) and calcium blocker drugs (to decrease the detrimental cellular effects of high PTH) are recommended.

Our study had some limitations and advantages. The main limitation of our study was the relatively small sample size, which was reflected in the wide confidence intervals of late hyperparathyroidism impact on mortality in the adjusted models. Using calculated calcium instead of measured ionized calcium is the second main limitation of our study. On the other hand, the main advantage of our study was its longitudinal design and the novel finding of the association of late hyperparathyroidism with mortality in COVID-19.

Ethical Considerations

Compliance with ethical guidelines

The study design, including its ethical aspects, was reviewed and approved by the Ethics Committee of Qazvin University of Medical Sciences (ethical approval. Code: IR.ARAKMU.REC.13400.471).

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Authors' contributions

Conceptualization, methodology: Sima Hashemipour; Investigation: Sabereh Afshar, Somaieh Kiani, and Pouria Shahsavari; Original draft: All authors; Preparation, writing, review and editing, visualization, supervision, project administration, funding acquisition: Sabereh Afshar, and Sima Hashemipour.

Conflict of interest

The authors declared that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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