Hypocalcemia Increase the Severity of the Clinical Degree of Covid-19 Patients

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ABSTRACT

Introduction: Coronavirus Disease 2019 (Covid-19) can cause electrolyte imbalances, one of which is hypocalcemia. Hypocalcemia has been identified as a predictor of the severity of Covid-19. This research aimed to determine the correlation between hypocalcemia and the clinical degrees of Covid-19 patients at UNS Hospital.
Method: This study used a cross-sectional design with a population of Covid-19 patients treated at the Covid-19 ward at UNS Hospital in 2020-2022. Samples were collected from medical records by purposive sampling technique that met the inclusion and exclusion criterias.
Results: There were 90 cases of hypocalcemia in Covid-19 patients. Mild hypocalcemia (88.9%) was found more than severe hypocalcemia (11.1%). Hypocalcemia was more common in male sex (54.4%), aged 46-65 years (70%), and in moderate clinical degree (31.1%). The Kolmogorov-Smirnov statistical test results showed a significant correlation between hypocalcemia and the clinical degree of Covid-19 with p=0.009 (p<0.05). The Spearman statistical test results showed that there was a fairly strong and statistically significant correlation between hypocalcemia and the clinical degree of Covid-19 where r=0.310 and p=0.003 (p<0.05).
Conclusion: There is a fairly strong and statistically significant unidirectional correlation between hypocalcemia and the clinical degree of Covid-19 patients.
Keywords: hypocalcemia; clinical degree; Covid-19

INTRODUCTION

An unknown upper respiratory infection case appeared in Wuhan, Hubei, China at the end of 2019. A new variant of the beta coronavirus was found to be the cause of this infection. Severe acute respiratory syndrome coronavirus 2 or abbreviated as SARS-CoV-2 is the name of the virus that causes cases of upper respiratory tract infections. The name was given by WHO on February 11, 2020. The virus can infect humans and cause a disease called Coronavirus Disease 2019 or abbreviated to Covid-19. On May 11, 2020, WHO declared Covid-19 a pandemic due to its rapid spread[1]. WHO reports there was over 304 million confirmed cases of Covid-19 worldwide with the number of death over 5.4 million cases as of January 9, 2022[2].

Many studies have reported that Covid-19 causes electrolyte imbalances. Electrolyte imbalance caused by renin–angiotensin–aldosterone system (RAAS) dysregulation, gastrointestinal disturbances, and renal tubular dysfunction due to SARS-CoV-2 invasion[3]. Severe Covid-19 had significantly lower sodium, potassium, and calcium concentrations in the meta-analysis[4].

Previous studies have shown that hypocalcemia is more common in more severe Covid-19 clinical conditions. Hypocalcemia or low calcium levels have been identified as an indicator of the Covid-19 severity. The study compared total calcium levels with the clinical degree of Covid-19[5]. In addition, other studies comparing serum albumin-corrected calcium levels with poor prognosis showed that Covid-19 patients with hypocalcemia require ICU and mechanical ventilators with a higher frequency, have a higher frequency of death and longer hospitalization time[6]. Hypocalcemia patients have higher D-dimer and lower lymphocytes levels so that their disease condition is more severe[7]. The hypocalcemia hypothesis in Covid-19 was explained by potential pathophysiological factors including the mechanism of interaction of calcium and the virus during the infectious process. Vitamin D deficiency, acute and chronic nutritional imbalances during critical illness can predispose to hypocalcemia. In addition, an increase in the level of unbound and unsaturated fatty acids (UFA) due to the inflammatory process can provoke the occurrence of hypocalcemia[8].

Meanwhile, there were also studies showing that hypocalcemia has no correlation with the severity of Covid-19. The study compared total and ionized calcium levels with non-severe and severe Covid-19 conditions[9]. In addition, other studies have shown that hypocalcemia is also common in Covid-19 patients with a non-severe degree[10].

The difference in the results of these studies was the background for researchers to conduct research on hypocalcemia. Previous studies did not execute comorbid whereas comorbid is one of the factors that can affect the severity of Covid-19. Therefore, researchers used the Charlson Comorbidity Index (CCI) to execute comorbid in order to reduce the causal bias of disease severity. In addition, researchers also assessed the level of hypocalcemia experienced by Covid-19 patients. This study aimed to determine the correlation between hypocalcemia and the clinical degrees of Covid-19 patients at UNS Hospital.

METHODS

This study was conducted by observational analytical method. This study used a cross-sectional design. This study was conducted in the Covid-19 Ward of Universitas Sebelas Maret Hospital from March to July 2022. The study subjects were Covid-19 patients with hypocalcemia in the Covid-19 Ward of Universitas Sebelas Maret Hospital in 2020-2022. Samples were collected from medical records by purposive sampling technique that met the inclusion and exclusion criteria. The inclusion criteria were mild to critical Covid-19 patients, hypocalcemia, and ages 15-64 years. While the exclusion criteria were CCI ≥ 4 and incomplete medical records. Total sample was 90 patients. Data analysis was conducted by Chi Square test and Spearman test. Health Research Ethics Commission of Regional Public Hospital Dr. Moewardi has granted ethical clearance on April 7, 2022 under number 434/IV/HREC/2022.

RESULTS

Patient Characteristics

Based on a study of 90 Covid-19 patients at Universitas Sebelas Maret Hospital which can be seen in Table 1, hypocalcemia was found more in the male sex (54.4%) and at the age of 45-65 years (70%). The Covid-19 patients who experienced the most hypocalcemia were patients with a moderate clinical degree (31.1%). Hypocalcemia found in this study was mostly mild hypocalcemia (88.9%) with an average calcium level of 0.96 mmol/L.

Table 1. Patient characteristics

Characteristics	Number (Patient)	Percentage
Gender		
Male	49	54.4%
Female	41	45.6%
Age (year)		
15-25	5	5.6%
26-45	22	24.4%
46-65	63	70%
Clinical Degree		
Mild	16	17.8%
Moderate	28	31.1%
Severe	23	25.55%
Critical	23	25.55%
Hypocalcemia Level		
Mild (0.9-1.1 mmol/L)	80	88.9%
Severe (<0.9 mmol/L)	10	11.1%

Correlation Between Hypocalcemia and Covid-19 Clinical Degree

The statistical test results resulted that the research data did not fulfill the Chi Square test requirements, so an alternative test was conducted. The alternative test was the Kolmogorov-Smirnov test as seen in Table 2. The test results showed that the p value <0.05, namely 0.009. It meant that the correlation between hypocalcemia and the clinical degree of Covid-19 patients at Universitas Sebelas Maret Hospital was significant.

Table 2. Kolmogorov-Smirnov test results

Hypocalcemia	Covid-19 Clinical Degree				Total	p value
	Mild	Moderate	Severe	Critical		
Mild	16	28	18	18	80	0.009
Severe	0	0	5	5	10	
Total	16	28	23	23	90	

Spearman test in Table 3 showed that the p value <0.05, namely 0.003. It meant that the correlation between hypocalcemia and the clinical degree of Covid-19 patients at Universitas Sebelas Maret Hospital was significant. The correlation coefficient value was 0.310. It meant that hypocalcemia and the clinical degree of Covid-19 patients had a moderate correlation. Furthermore, the correlation coefficient with a positive value indicated that there was a unidirectional correlation between hypocalcemia and the clinical degree of Covid-19 patients. It meant that the high level of hypocalcemia (decreased calcium levels), affected the severity of the clinical degree.

Table 3. Spearman test results

	Covid-19 Clinical Degree	
	r	P value
Hypocalcemia	0.310	0.003
Age	0.111	0.298
Gender	-0.049	0.650

Table 3 showed that age and gender did not have significant correlation with the Covid-19 clinical degree. It was because the value of p>0.05 was 0.298 and 0.650 respectively. The correlation coefficient value of the age and the Covid-19 clinical degree variables was 0.111. It showed a weak and unidirectional correlation. Meanwhile, the correlation coefficient for the gender and the Covid-19 clinical degree variables was -0.049. It indicated that the correlation was low and bidirectional. The correlation coefficient value of these two variables was lower than hypocalcemia where hypocalcemia had a stronger correlation to the Covid-19 clinical degree than age and gender. Based on these results, age and gender did not affect the Covid-19 clinical degree.

DISCUSSION

Based on the results, male Covid-19 patients had more hypocalcemia than female patients, namely 49 male patients (54.4%) and 41 female patients (45.6%). It was similar to Pani et al. who found that hypocalcemia cases in women were lower than men. Hypocalcemia cases with Covid-19 in male patients were between 28% to 34% than female patients, namely 16% to 32%. This difference was associated with the vitamin D or calcium supplements consumption in women who are more often for osteoporosis prevention[11].

Based on age, the most common hypocalcemia was in the elderly (46-65 years), namely 63 patients (70%). Previous studies revealed that Covid-19 patients aged 65 years or older had more hypocalcemia, namely 198 people than patients with normal calcium levels, namely 118 people[12]. Aging affects the decrease in calcium levels[13]. Older people are more likely to have osteoporosis and decreased calcium absorption[14]. Increasing age will decrease liver and kidney function so that serum levels of 25-hydroxyvitamin-D (25(OH)D) in the human body decrease. These conditions lead to impaired intestinal calcium absorption, thereby affecting the recovery of blood calcium[15].

Based on the Covid-19 clinical degree, hypocalcemia was more common in moderate degree (31.1%). It contrasted with previous studies that found that hypocalcemia was more common in severe degree (53.8%) than moderate degree (46.2%)[16]. Another study divided patients into mild/moderate patients and severe/critical patients. There were 80.9% of severe/critical Covid-19 patients with below normal calcium levels and lower than mild/moderate patients, namely 41%[14]. If this research results were divided into two categories, there were more severe/critical hypocalcemia cases (51.1%) than mild/moderate cases (48.9%). Calcium homeostasis is related to vitamin D and the PTH-calcium axis. It was very common for critical illness to have PTH dysfunction. Therefore, critically sick patients often had hypocalcemia[14]. In addition, hypocalcemia was related to a poor prognosis in critically sick patients[17].

Based on the hypocalcemia level, there were more Covid-19 patients with mild hypocalcemia than severe hypocalcemia. It was similar to previous studies that revealed that mild hypocalcemia in Covid-19 patients was higher than moderate hypocalcemia patients, namely 56.8% of 74.7% of hypocalcemia cases[18]. In general, mild hypocalcemia was evident in SARS and Ebola patients[16].

The statistical test results indicated that hypocalcemia had a significant correlation with the Covid-19 clinical degree. The positive correlation coefficient indicated a unidirectional correlation. It meant that the high level of hypocalcemia (low calcium level) affected the severity of the clinical degree. Data analysis showed that severe and critical Covid-19 patients had severe hypocalcemia. Meanwhile, mild and moderate patients only had mild hypocalcemia. These findings proved that patient's clinical degree will be more severe if the calcium level is lower. Previous studies stated that patients with severe Covid-19 infection with risk of ICU admission and death had lower calcium levels[16]. These findings were consistent with another study who stated that patients with lower serum calcium levels had worse clinical variables, septic shock, higher multiorgan failure, and 28-day mortality[18]. In addition, there were also studies that have found that besides severity, in the early stages

of viral infection, all cases displayed low calcium levels. However, lower calcium levels were indicated by severe/critical cases than mild/moderate cases[14].

Hypocalcemia correlated with inflammatory conditions[19]. Coronavirus Disease 2019 can interfere with the immune system and cause a cytokine storm[20]. Cytokines can impair calcium receptor expression so that there is an imbalance in serum calcium levels[19]. Increased activation of inflammation and inflammatory mediators, such as IL-1β, IL-6, and TNF can be affected by alterations in intracellular calcium homeostasis[14]. Increased CASR could assist interleukin-6 to reduce serum calcium concentrations[21]. Calcium also had a correlation with multiorgan injury, especially in severe and critical cases. Therefore, balanced calcium was essential for maintaining normal organ function. IL-6 inhibitors are useful for blocking the effect of IL-6 on serum calcium and avoiding multiorgan damage in patients with low calcium levels[14].

Hypocalcemia patients usually have higher D-dimer and lower lymphocytes levels, so that their disease condition is more severe[7]. Low calcium levels cause a significant increase in D-dimer levels[22]. These conditions resulted in more inflammatory responses in hypocalcemia patients so that calcium levels could be thought to affect disease severity[7]. The CRP level of Covid-19 patients with low serum calcium was higher. The prognosis of critically ill patients can be estimated using CRP and D-Dimer parameters. Therefore, serum calcium levels can be correlated with the prognosis of Covid-19 patients[18]. Hospitalized SARS-CoV-2 infection patients often had low calcium. In addition, patients had vital clinical implications, such as musculoskeletal, cardiovascular, psychiatric, and neurological side effects. However, currently, calcium measurement and supplementation in hospitalized SARS-CoV-2 infected patients were not considered by the international Covid-19 management[12].

This research had several limitations. First, this research used cross-sectional research, and the data source was medical records so that other factors that affect the patient's calcium levels, such as vomiting, low intake, or medications previously consumed were not considered. Second, the research design did not compare data with Covid-19 patients without hypocalcemia. Third, there was a confounding variable, namely race, because this correlation cannot be explained with the Covid-19 clinical degrees. Fourth, the sample was small. For these reasons, the results accuracy of this research required to be confirmed by prospective or retrospective clinical studies that compare hypocalcemia Covid-19 patients and Covid-19 patients without hypocalcemia on a larger scale. Further research is expected to exclude other factors that cause hypocalcemia, such as low intake and vomiting symptoms which in general can cause electrolyte imbalances including hypocalcemia. It was conducted to minimize bias. Further research can also compare hypocalcemia and other inflammatory parameter such as lymphocytes, D-Dimer, CRP, and IL-6 to confirm hypocalcemia as a severity predictor.

CONCLUSION

Hypocalcemia and the clinical degree of Covid-19 patients have a significant correlation and there is a moderate and unidirectional correlation whereby high levels of hypocalcemia (decreased calcium levels) increase the severity of the clinical degree. The most common cases of hypocalcemia were found in Covid-19 patients at Universitas Sebelas Maret Hospital was mild hypocalcemia, namely the patient was male, older, and had a moderate clinical degree.

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