Serum magnesium in patients with severe acute respiratory syndrome coronavirus 2 from Wuhan, China

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Abstract. Objective: The aim of the study was to evaluate the significance of hypomagnesemia in patients with coronavirus disease 2019 (COVID-19) and clarify its possible pathogenesis. **Subjects and Methods**: A retrospective cohort study was conducted by reviewing 83 patients hospitalized in Guanggu district, Wuhan Third Hospital, China. Clinical histories, laboratory findings and outcome data were collected. **Results**: Eighteen patients had hypomagnesemia during hospitalization. Fourteen patients were in the critical group and six died. In the critical group, serum magnesium (0.72 ± 0.15 mmol/L) was much lower than that in the moderate and severe groups. At the same time, we also found that several indicators are correlated with the level of magnesium. The level of magnesium was positively associated with the lymphocyte count ($r = 0.203$, $P = 0.004$) and platelet count ($r = 0.217$, $P = 0.002$) but negatively related to the levels of CRP ($r = –0.277$, $P = 0.000$), LDH ($r = –0.185$, $P = 0.011$) and α-hydroxybutyrate dehydrogenase ($r = –0.198$, $P = 0.008$) in the critical group. **Conclusion**: Hypomagnesemia might increase symptoms and may be associated with mortality in COVID-19 by affecting enzyme activity and activating the inflammatory response. Thus, magnesium might play a key role in the pathogenesis of COVID-19.

Key words: COVID-19, disease severity, magnesium, mortality, inflammation

Introduction

In December 2019, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection outbreak began; it was first reported in Wuhan, China. SARS-CoV-2 causes coronavirus disease 2019 (COVID-19) and has been a critical threat to global public health. SARS-CoV-2 is a beta coronavirus closely related to two bat-derived coronaviruses, that is, SARS-CoV and MERS-CoV, both of which cause severe acute respiratory syndrome [1]. More than 150 million people have been infected by SARS-CoV-2, which has impacted society, the economy and life worldwide up to April 2021.

The characteristics of COVID-19 include fever, cough, fatigue and dyspnoea in severe cases [2, 3] and these symptoms vary from mild to severe [4]. It was easily observed that chest CT images were diffuse bilateral ground-glass opacities with or without consolidations [5].

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Patients with different severities have different prognoses, especially elderly patients with underlying diseases and the mortality rate is higher than that of other diseases [2, 6, 7].

Laboratory findings showed that leukopenia and lymphopenia were common [8]. Studies revealed that severe patients had much higher C-reactive protein levels, higher levels of myocardial damage and increased calcitonin [9, 10]. However, most of these studies focused on the relationship between the clinical manifestations of the patients, some test results and prognosis, but insufficient attention was paid to the general condition of patients, especially their serum magnesium level.

Magnesium is an essential element that plays important roles in human physiology and metabolism. It is involved in critical cellular events, including apoptosis and oxidative stress and it is also involved in over 600 enzyme reactions. Magnesium plays an important physiological role, especially in the brain, heart and skeletal muscles [11]. As discussed in the first publication on magnesium in COVID-19, deficiency of magnesium might closely relate to pathogenesis of COVID-19 [12]. Quilliot *et al*. also reported that an abnormal level of magnesium had been found in hospitalized patients with COVID-19 [13].

In order to make further study on the influence of magnesium on COVID-19, we analysed cases of COVID-19 from Wuhan, China and investigated the correlation among serum magnesium, clinical characteristics, related factors and the severity and prognosis of the patients.

Subjects and Methods

Objects

We conducted a retrospective cohort study by reviewing patients hospitalized in the Guanggu Hospital District, Wuhan Third Hospital, China. Eighty-three patients were recruited for this study and data were acquired from the hospital database. This period lasted from January 27 to March 10, 2020. The study was approved by the Ethics Committee of Wuhan Third Hospital and written informed consent was waived because of the retrospective nature of the study.

Diagnosis criteria

The patients were diagnosed with confirmed COVID-19 according to the diagnosis criteria from the fifth version of the guidelines for the Diagnosis and Treatment of COVID-19 by the National Health Commission of China [14]. Diagnostic criteria included the following:
(1) in line with epidemiological history;
(2) clinical features: fever and respiratory symptoms, with imaging features of viral pneumonia, normal or decreased white blood cell (WBC) counts in the early stage of the disease, or a decreased lymphocyte count;
(3) and aetiological evidence: respiratory tract specimens tested positive for novel coronavirus nucleic acid by RT-PCR or viral gene sequencing of respiratory specimens highly homologous to SARS-COV-2.

Clinical classification of COVID-19

According to the fifth edition of China's guidelines [14], combined with clinical manifestations, laboratory examinations, CT imaging examinations and so on, patients were divided into mild, moderate, severe and critical based on the severity of the disease using the diagnostic criteria.

Mild type
The clinical symptoms were mild with no pneumonia manifestation on imaging.

Moderate type
Fever, respiratory tract and other symptoms, with typical pneumonia on imaging.

Severe type
It should meet any of the following conditions:
(1) respiratory distress, RR $\geq$30 times/min;
(2) in the resting state, oxygen saturation $\leq$93%;
(3) arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) $\leq$300 mmHg (1 mmHg = 0.133 kPa).

Critical type

For this type, one of the following conditions should be met:

(1) respiratory failure occurs and requires mechanical ventilation;
(2) shock occurs;
(3) combinations with other organ failures requiring ICU monitoring and treatment.

Data collection

Basic information included sex, age, date of admission, survival status and clinical classification. Clinical features included whether patients had fever, respiratory symptoms, fatigue, vomiting, diarrhoea, headache and so on. We reviewed all laboratory test results regarding the counts of WBCs, lymphocytes and platelets and the levels of C-reactive protein (CRP), magnesium, lactate dehydrogenase (LDH), α-hydroxybutyrate dehydrogenase and so on. Patients' temperatures were recorded as the highest and average temperature. Laboratory results were all recorded for analysis.

Serum magnesium

For the detection of magnesium, the ion-selective electrode method was used (fully automatic chemical photoimmunoanalyzer, Centaur XPT, SIEMENS). The magnesium data were obtained from the hospital medical history database. The reference value of serum magnesium was defined according to the method used and the data available in the literature. The normal value range was 0.65-1.21mmol/L [15]. Magnesium was tested multiple times during the patient's hospitalization, mainly at admission, when the condition changes and before discharge. Hypomagnesemia was recognized as serum magnesium below the normal range once during hospitalization and hypermagnesemia was higher than the normal range.

Statistical analysis

All data were expressed as mean ± standard deviation (SD) for continuous variables and as frequencies and percentages for categorical variables. Continuous data were compared using Student's *t*-test or Wilcoxon's test, while categorical data were compared using chi-squared and Fisher's exact tests. Spearman's rank correlation techniques were used to analyse the relationships between several continuous variables. A p value of 0.05 was considered statistically significant for single comparisons. All the reported p values were two-sided. Data were analysed using SPSS 22.00 software package (SPSS Inc, Chicago, IL, USA).

Results

Basic characteristics and clinical findings

Because mild patients were admitted to the shelter hospital, this study included all moderate, severe and critical patients and they were divided into groups according to the guidelines. There were 83 patients recruited in this study, 44 females and 39 males. The average age was 62.96 ± 14.49 years old and the median age was 64 years old. The 15 patients who died (all in the critical group) were aged 73 years old and the 68 patients who survived were aged 63 years old ($P < 0.05$). Patient age, maximum temperature and average temperature were higher in the death group ($P < 0.05$). Fatigue, dyspnoea, anorexia, nausea, palpitations and headache were more common in death cases. As the severity of COVID-19 worsened, the maximum temperature and average temperature gradually increased ($P < 0.05$). Anorexia, palpitations and headache were more common in the critical group (*table 1*).

Incidence of hypomagnesemia

Eighteen patients had hypomagnesemia during hospitalization. A total of 17.65% of survivors had hypomagnesemia, while 40% of non-survivors had hypomagnesemia, which was significantly different ($P < 0.05$). The incidence of hypomagnesemia was also different in the severe classification groups. The incidence (proportion) of hypomagnesemia was 3 (12.50%), 1 (3.85%) and 14 (43.75%) in the moderate, severe and critical groups, respectively and was notably higher in the critical group ($P < 0.05$).

Magnesium and laboratory findings in COVID-19 according to survival status

The WBC, CRP, LDH, α-hydroxybutyrate dehydrogenase and lactic acid levels of non-survivors were significantly higher than those of surviving patients, while lymphocyte counts were lower (*table 2*). Magnesium was also lower in non-survivors, 0.71 ± 0.18 mmol/L, than in survivors.

Table 1. Basic characteristics and clinical findings in COVID-19.

	All	Survival		Severity		
	(n = 83)	Yes	No	Moderate	Severe	Critical
		(n = 68)	(n = 15)	(n = 25)	(n = 26)	(n = 32)
Median age IQR-yrs	64 (31 to 95)	63 (31-89)	73 (47-95)*	62 (31-80)	65 (31-84)	69 (42-95)$
Gender no./total no.(%)						
Male	44/83(%)	34/68(%)	10/15(18.18%)	11/25(%)	14/26(%)	19/32(%)
Female	39/83%)	34/68(%)	5/15(9.43%)	14/25/(%)	12/26(%)	13/32(%)
Symptoms no./total no.(%)						
Fever	73/83(87.95%)	59/68(86.76%)	14/15(93.33%)	20/25(80.00%)	23/26(88.46%)	30/32(93.75%)
T max	37.88 ± 0.90	38.10 ± 0.89	38.84 ± 0.67*	37.58 ± 0.65	37.97 ± 0.83	38.61 ± 0.84#$
T average	36.94 ± 0.33	37.01 ± 0.35	37.34 ± 0.54*	36.86 ± 0.22	36.94 ± 0.20	37.18 ± 0.44#$
Cough	68/83(81.93%)	56/68(82.35%)	12/15(80.00%)	20/25(80.00%)	22/26(84.62%)	26/32(81.25%)
Fatigue	52/83(62.65%)	39/68(57.35%)	13/15(86.67%)*	14/25(56.00%)	16/26(61.54%)	22/32(68.75%)
Dyspnea	53/83(63.86%)	40/68(58.82%)	13/15(86.67%)*	11/25(44.00%)	18/26(69.23%)	24/32(75.00%)
Anorexia	33/83(39.76%)	21/68(30.88%)	12/15(80.00%)*	6/25(24.00%)	8/26(30.77%)	19/32(59.38%)#
Nausea	16/83(19.28%)	9/68(13.24%)	7/15(46.67%)*	1/25(4.00%)	4/26(15.38%)	11/32(34.38%)
Diarrhea	12/83(14.46%)	8/68(11.76%)	4/15(26.67%)	4/25(16.00%)	2/26(7.69%)	6/32(18.75%)
Palpitations	10/83(12.05%)	3/68(4.41%)	7/15(46.67%)*	2/25(8.00%)	0/26(0.00%)	8/26(25.00%)$
Headache	9/83(10.84%)	5/68(7.35%)	4/15(26.67%)*	2/25(8.00%)	0/26(0.00%)	7/32(21.88%)$
Throat pain	12/83(14.46%)	11/68(16.18%)	1/15(6.67%)	4/25(16.00%)	3/26(11.54%)	5/32(15.63%)
Myalgia	6/83(7.23%)	5/68(7.35%)	1/15(6.67%)	1/25(4.00%)	1/26(3.85%)	4/32(12.50%)

* comparing survivors and non-survivors with COVID-19, P <0.05; #compared with the severe and critical groups of COVID-19 patients, P <0.05; $ compared with the moderate and critical groups of COVID-19 patients, P <0.05.

Magnesium and laboratory findings in COVID-19 according to disease severity

As the severity of the disease increased, lymphocyte and platelet counts decreased, while WBC, CRP, LDH, α-hydroxybutyrate dehydrogenase and lactic acid levels gradually increased (*table 3*). Platelet counts were lower in the severe and critical groups than in the moderate group. Serum magnesium was 0.72 ± 0.15 mmol/L, which was notably lower in the critical group than in the moderate and severe groups.

Correlation of magnesium and related factors in the group of critical patients with COVID-19

Serum magnesium was significantly decreased in the critical group compared with the other groups. Linear correlation was conducted between related factors and the magnesium level. Serum magnesium was negatively associated with CRP in the severe group (r = –0.270, P < 0.05). Although serum magnesium had no correlation with other laboratory findings in the moderate and severe groups (*table 4*), it was positively associated with lymphocyte (r = 0.203, P = 0.004) and platelet (r = 0.217, P = 0.002) counts but negatively related to CRP (r = –0.277, P = 0.000), LDH (r = –0.185, P = 0.011) and α-hydroxybutyrate dehydrogenase (r = –0.198, P = 0.008) in the critical group (*figure 1*).

Discussion

The aetiology of COVID-19 is clear, but its pathogenesis is rather unclear. Some risk factors

Table 2. Magnesium and laboratory findings in COVID-19 based on survival.

Item	Survival	
	Yes	No
	(n = 68)	(n = 15)
WBC ($\times 10^9$/L) *	6.55 ± 2.58	10.38 ± 5.96
Lymphocytes ($\times 10^9$/L) *	1.14 ± 0.57	0.54 ± 0.34
Platelets ($\times 10^9$/L) *	227.95 ± 90.66	154.47 ± 85.33
CRP (mg/L) *	33.82 ± 51.62	108.10 ± 101.43
Magnesium (mmol/L) *	0.80 ± 0.22	0.71 ± 0.18
LDH (IU/L) *	244.49 ± 100.43	584.47 ± 460.36
α-hydroxybutyrate dehydrogenase (IU/L) *	207.05 ± 93.19	445.56 ± 279.34
Lactic acid (mmol/L) *	3.31 ± 1.57	4.09 ± 1.85

*comparing survivors and non-survivors with COVID-19, P <0.05.

for disease severity have been reported, such as the lymphocyte count and D-dimer level. Here, we mainly discussed the relationship between the severity of COVID-19 and serum magnesium.

In the baseline information of this study, the general data were consistent with those of other reports. In this study, the median age of non-surviving patients was 73 years, which was higher than that of surviving patients. The data supported that old age was a high-risk factor for mortality and poor prognosis [7, 16, 17]. In our study, 87.95% of patients had fever and non-surviving patients had a higher temperature, a slightly higher incidence than that reported by Zhang *et al*. and Du *et al*. [2, 8]. Lymphocyte counts were lower, while lactic acid, WBC and LDH levels were higher in non-survivors, the same as was reported regarding independent risk factors for severity [18, 19].

We found a close relationship between serum magnesium levels and disease severity. The level of serum magnesium was positively associated with lymphocyte and platelet counts but negatively related to CRP, LDH and α-hydroxybutyrate dehydrogenase in critical patients. We

Table 3. Magnesium and laboratory findings according to disease severity.

Item	Disease Severity		
	Moderate	Severe	Critical
	(n = 25)	(n = 26)	(n = 32)
WBC ($\times 10^9$/L)	6.05 ± 2.12	7.13 ± 2.81*	7.87 ± 4.62$^{\$}$
Lymphocytes ($\times 10^9$/L)	1.34 ± 0.50	1.12 ± 0.66*	0.86 ± 0.51$^{\#\$}$
Platelets ($\times 10^9$/L)	256.92 ± 90.38	211.43 ± 84.42*	199.75 ± 96.79$^{\$}$
CRP (mg/L)	16.78 ± 32.66	47.14 ± 63.10*	60.49 ± 81.28$^{\$}$
Magnesium (mmol/L)	0.85 ± 0.28	0.84 ± 0.23	0.72 ± 0.15$^{\#\$}$
LDH (IU/L)	207.98 ± 80.97	247.50 ± 85.09*	389.00 ± 341.87$^{\#\$}$
α-hydroxybutyrate dehydrogenase (IU/L)	183.65 ± 79.34	210.63 ± 87.09*	312.15 ± 227.04$^{\#\$}$
Lactic acid (mmol/L)	3.11 ± 0.82	3.33 ± 0.89	3.70 ± 2.15$^{\$}$

* compared with the moderate and severe groups, P <0.05; $^{\#}$ compared with the severe and critical groups, P <0.05; $^{\$}$ compared with the moderate and critical groups, P <0.05.

Table 4. The correlation between magnesium and other laboratory findings in moderate and severe groups.

	Moderate	**Severe**		
	r	***P***	**R**	***P***
WBC	0.049	0.712	-0.013	0.895
Lymphocyte	0.078	0.556	0.02	0.843
Platelet	0.269	0.038	-0.063	0.521
CRP	-0.084	0.526	-0.27	0.005
LDH	0.109	0.416	-0.154	0.125
α-hydroxybutyrate dehydrogenase	-0.014	0.919	-0.188	0.069

found that patients with hypomagnesemia had higher mortality rates, which was similar with the finding by Damayanthi and Prabani [20]. These data indicated the importance of magnesium in the pathogenesis.

Hypomagnesemia is believed that play an important role in the pathogenesis of critical diseases. The clinical manifestations of hypomagnesemia are unspecific, including nausea, vomiting, weakness, cardiac arrhythmia and coronary spasm [21, 22]. Decreased magnesium levels could cause a higher mortality rate [23, 24]. These clinical symptoms are very common in patients with COVID-19.

Does hypomagnesemia play an important role in COVID-19? Could hypomagnesemia explain some clinical manifestations? The answer is affirmative.

Magnesium may be associated with the severity of COVID-19 and its mortality. Our data indicated that the magnesium level could be a critical indicator in COVID-19 for distinguishing critical patients from others. Other studies showed that patients with hypomagnesemia had a higher mortality rate [23, 24] in community-acquired pneumonia. Quilliot D *et al*. found that hospitalized patients for COVID-19 had high prevalence of hypomagnesemia associated to severity of disease [13]. The implication of magnesium-containing combination could significantly reduce the proportion of patients with intensive care support in older COVID-19 patients [25]. We reached a similar conclusion that deficiency of magnesium would increase the risk of mortality.

Hypomagnesemia contributed to inflammation in COVID-19. The maximum temperature and average temperature gradually increased in the severe group and in non-survivors. This reflected the intensity of the inflammatory response and correlated with the incidence of hypomagnesemia. On the other hand, serum magnesium was negatively related to CRP in critical patients and these patients had higher levels of CRP. Xiong *et al.* found that inflammatory cytokine of bronchoalveolar lavage fluid and peripheral blood mononuclear cell was increased [26]. Deficiency of magnesium could cause immune dysfunction in patients with COVID-19 [27].

Magnesium deficiency causes inflammation by activating phagocytic cells, opening calcium channels, activating N-methyl-D-aspartate (NMDA) receptors and activating nuclear factor (NF)-κB [28]. It can also promote inflammation by priming phagocytes, enhancing granulocyte oxidative burst, activating endothelial cells and increasing the levels of cytokines [29]. Magnesium inhibits the activation of macrophages and after the addition of magnesium, certain cytokines (IL-1β, IL-6 and IL-10) in the cell supernatant are inhibited [30]. Magnesium supplementation could reduce CRP levels in individuals with inflammation [31]. In other viral infections, decreased levels of magnesium can lead to defective expression of programmed cell death 1 (PD-1) and NK-activated receptors in NK and CD8+ T cells [32], thus leading to tissue injury and inflammation. These results indicated that magnesium played an important

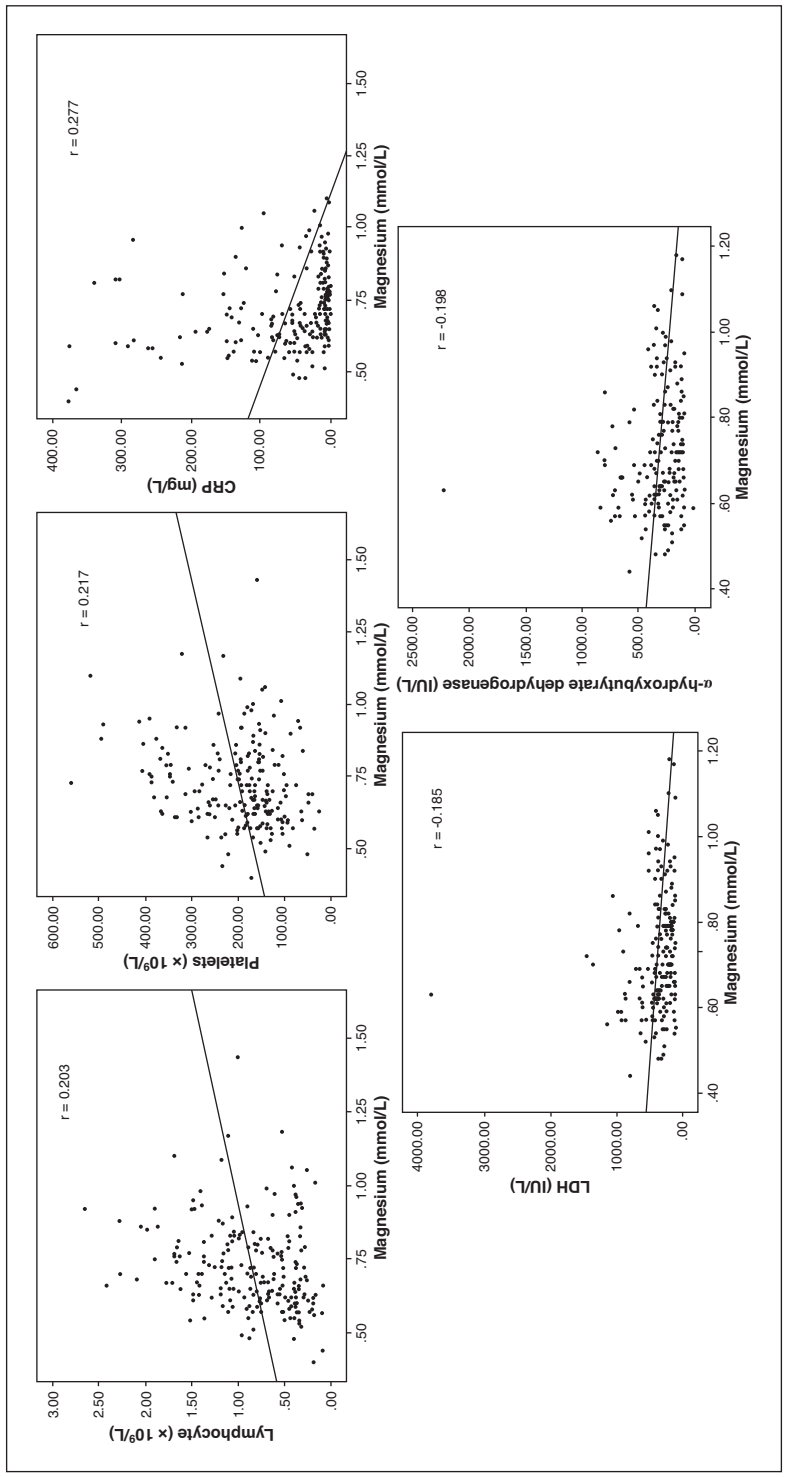

Figure 1. The relationship between magnesium and other laboratory findings in the critical group. The figure shows the relationship between magnesium and other laboratory findings in the critical groups: (a) the relationship between magnesium and lymphocyte count, $r = 0.203$, $p < 0.05$, (b) the relationship between magnesium and platelet count, $r = 0.217$, $p < 0.05$, (c) the relationship between magnesium and CRP in the critical group, $r = -0.277$, $p < 0.05$ and (d) and (e) the relationship between magnesium and LDH and α-hydroxybutyrate dehydrogenase in the critical group. (d) The relationship between magnesium and LDH, $r = -0.185$, $p < 0.05$. (e) The relationship between magnesium and α-hydroxybutyrate dehydrogenase, $r = -0.198$, $p < 0.05$.

role in the inflammatory response in the critical group of patients with COVID-19.

Hypomagnesemia may contribute to obvious changes in lymphocyte counts. Our study showed that lymphocyte count decreased in critical patients compared to other groups; furthermore, serum magnesium was positively associated with the lymphocyte count. Many studies have reported a decrease in lymphocyte count in severe groups [33, 34]. Diffuse alveolar damage and T-lymphocyte apoptosis in lymphoid organs could be observed in histopathologic features [35, 36]. As important immune cells, lymphocytes are recognized as predictors of recovery in COVID-19 [37]. CD4+ T cells slightly decreased and CD8+ T cells significantly decreased; thus, an elevated CD4/CD8 ratio could diagnosis and predict COVID-19 severity [38].

Magnesium can affect the acquisition of immune lymphocytes by regulating proliferation and development [39]. Therefore, magnesium plays an important role in maintaining the number and function of lymphocytes in COVID-19.

Magnesium is critical for maintaining platelet function and decreased magnesium might lead to platelet deficiency [40]. We revealed that magnesium was positively correlated with the platelet count in COVID-19. Chen *et al.* showed that restored levels of platelets could be a predictor for recovery in COVID-19 [37]. This could explain why critical patients had hypomagnesemia and lower levels of platelets.

Under low magnesium-induced oxidative stress, endothelium forms a state of permanent inflammation characterized by increased NF-κB activity [41] and increased risk of sudden cardiac death [42]. As a part of the myocardial enzymogram, LDH and α-hydroxybutyrate dehydrogenase were notably higher in the critical group than in the other groups in this study. Zhang *et al.* concluded that elevated LDH could be a predictor of ARDS and mortality [19]. LDH was also an independent predictor for severe COVID-19 [43]. We found that these indexes were also negatively related to magnesium. Non-survivors and critical patients had more complaints of palpitations. As hypomagnesemia may cause cardiac arrhythmia and coronary spasm, this can explain patients' palpitations. Wetterslev *et al.* had similar findings that critical patients with COVID-19 had higher prevalence of tachyarrhythmias [44]. The occurrence of common symptoms of heart failure and myocardial enzymes indicated heart damage in patients with COVID-19, which may be associated with hypomagnesemia.

Variation in magnesium levels depends on intake and consumption. The possible mechanisms of hypomagnesemia in COVID-19 might be as follows:

1) Ishimaru *et al.* revealed that the homologous virus SARS-CoV needed magnesium [45]. SARS-CoV also requires magnesium to maintain the main helical axis tunnel [46]. Magnesium intervention could modify the phenotype of the TMPRSS2 genotype, to prevent COVID-19 in early stage [47]. These findings suggested that virus SARS-CoV required magnesium not only for synthesis but also for maintaining structure. This process will require more magnesium;

2) extracellular magnesium is detected as serum magnesium, which represents only 1% of the total body magnesium [48]. Magnesium is mainly regulated by intestinal absorption and renal excretion [22], mainly dependent on magnesium daily intake [49]. Jin *et al.* also found that 11.4% of patients with COVID-19 had gastrointestinal (GI) symptoms. Of these, 22.97% were severe or critical, a higher percentage than among non-GI patients [50];

> In this study, the incidence of anorexia and nausea was higher in non-survivors, in line with the incidence of hypomagnesemia. This indicated that critical patients had these symptoms because of hypomagnesemia and these symptoms worsened the deficiency of magnesium. As non-survivors had high rates of anorexia and nausea and could not eat by themselves, this might cause insufficient magnesium intake. The application of magnesium could be a preventative strategy in populations at risk [51].

3) the key enzyme in sugar metabolism requires Mg-ATP. Because kinase ATPase, guanylate cyclase and adenylate cyclase all depend on the normal function of Magnesium ions play a role in almost every process of the cell [52]. Refeeding syndrome (RFS) is a syndrome in which critical patients suffer from eating difficulties for various reasons. RFS occurs in critically ill patients. External stressors cause a hypercatabolic response, which is quite different from that of healthy patients with RFS because of the lack of anabolism [53]. These critical patients had little intake and huge

consumption which is why patients had hypomagnesemia in COVID-19.

COVID-19 could lead to a low level of magnesium and hypomagnesemia also aggravates the condition of patients with COVID-19, leading to the development of a vicious cycle.

There were some limitations to this study. With the limitation of medical resources, our study was a retrospective and single-centre study. The number of patients enrolled was small, their condition was serious and there might be selection bias. More studies have been conducted worldwide to reveal the risk factors for COVID-19. The importance of magnesium should be noted, especially in the regulation of inflammation and the condition of the whole body.

Conclusion

Hypomagnesemia might increase symptoms and may be associated with mortality in COVID-19 by affecting enzyme activity and activating the inflammatory response. Thus, magnesium might play a key role in the pathogenesis of COVID-19. Serum magnesium could also be a potential marker of the severity of COVID-19. Monitoring the level and supplementation of magnesium should be one of the key points in treatment.

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