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Effect of magnesium on severity and mortality of COVID−19 patients: A systematic review

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ABSTRACT

Unbalanced magnesium levels in the body, like other minerals, are a factor that is important in the severity and mortality of COVID-19. This study was designed to investigate the relationship between serum magnesium levels and clinical outcomes in COVID-19 patients. In this systematic review, a comprehensive search was performed in PubMed, Scopus, and Web of Science databases until September 2021 by using the keywords COVID-19, severe acute respiratory syndrome coronavirus 2, coronavirus disease, SARS-COV-infection 2, SARS-COV-2, COVID 19, and magnesium. End-Note X7 software was used to manage the studies. Articles that evaluated effect of magnesium on COVID-19 were included in the analysis. After reviewing several articles, 12 studies were finally included in the ultimate analysis. The studies show that hypomagnesemia and hypermagnesemia are both factors that increase mortality in patients with COVID-19, even in one study, hypomagnesemia is the cause of doubling the deaths in COVID-19 patients. Some studies have also found a negative correlation between magnesium deficiency and infection severity, while some others have reported no correlation between magnesium level and disease severity. According to the important role of magnesium in the body and its involvement in many physiological reactions, as well as differences in physical and physiological conditions of COVID-19 patients, in addition to the need for studies with larger sample sizes, monitoring and maintaining normal serum magnesium levels during the disease seems necessary as a therapeutic target, especially in patients admitted to the intensive care unit.

KEYWORDS: Magnesium; Severity; Mortality; COVID-19; Systematic review

1. Introduction

The coronavirus is part of a viral family that is common in animals around the world, and few of them affect humans. In the last two decades, only two species (SARS and MERS) have caused two large-scale epidemics[1]. However, a series of viral pneumonia cases with symptoms including fever, shortness of breath, cough, fatigue, and pneumonia have been reported. The disease was named by the World Health Organization coronavirus 2019 (COVID-19) and was finally declared a public health and pandemic challenge on March 11, 2020, due to its widespread in most countries[2] and up to the 15th of August 2022, there were 587 396 589 definitive cases and 6 428 661 mortalities[3].

Simultaneously with the onset of the pandemic, various researches were initiated to identify differential diagnostic methods and effective treatments of the disease[1]. Magnesium was also studied as the fourth mineral element in the human body that reduces the severity of infectious and inflammatory diseases of the lungs and strengthens the immune system[4], which could be considered a treatment method in patients with COVID-19[1].

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In the human body, magnesium has a cofactor role in more than 300 enzyme systems, that regulate various biochemical reactions[5]. Normal magnesium concentrations range from 0.75 to 0.95 mmol/L[6] and serum levels less than 1.7-1.8 mg/dL (0.75 mmol/L) are defined as hypomagnesaemia[7]. Association of low magnesium levels with several chronic and inflammatory diseases such as Alzheimer's disease, asthma, attention deficit hyperactivity disorder, insulin resistance, type 2 diabetes, hypertension, cardiovascular disease (such as stroke), migraine headaches, and osteoporosis have been confirmed[8]. The relationship between the severity and mortality of COVID-19 and serum magnesium levels has been reported in studies to be different so that both magnesium deficiency and increased magnesium level are considered effective in the disease severity and mortality. Due to the limitations of published studies in this field, a comprehensive study is necessary for better decision-making by clinical specialists. Therefore, the present study investigated the relevance between the severity and mortality of COVID-19 and serum magnesium levels.

2. Methods

2.1. Search strategy

This systematic review was conducted following the PRISMA Checklist. A comprehensive search was performed in three databases including PubMed/MEDLINE, Scopus, and Web of Science, using the following keywords COVID-19, COVID 19 pandemic, coronavirus disease 2019, SARS-CoV-2, COVID-19 virus infections, SARS coronavirus 2 infection, COVID 19, and magnesium from 2020 to September 2021. AND, OR, and Mesh term operators were also used to improve the search result.

2.2. Inclusion and exclusion criteria

Included articles in this review were all observational and interventional studies that investigated the impact of magnesium on COVID-19 and were published in the English language. Excluded articles were review studies, case reports, letters to editors, commentaries, and reports.

2.3. Study selection and data collection

All extract articles were entered into Endnote X7 software to remove duplicates. The remained studies were selected according to title and abstract, respectively. Then, their full text was reviewed for eligibility. Articles that investigated the effect of magnesium on COVID-19 were included in the analysis.

The prepared checklist was used to extract the data and information such as surname of the first author, year of publication, country of study, type of study, sample size, and the main findings extracted from each study.

2.4. Quality assessment

"Adapted Newcastle-Ottawa Quality Assessment Scales" checklist was used to assess the quality of the articles in this review[9]. This tool consists of three separate parts: selection, comparison, and conclusion. Studies were scored based on overall scores and divided into 3 categories: good, moderate, and poor.

2.5. Data analysis

According to the goals of this study, included articles were divided into 8 groups: magnesium and mortality in COVID-19[10-12], magnesium and hypokalemia in COVID-19[13], magnesium and markers of disease severity in COVID-19[14-19], magnesium and need for mechanical ventilation in COVID-19[12], magnesium and need for vasopressors in COVID-19[12], magnesium and acute kidney injury (AKI) in COVID-19[12], magnesium and stay in Intensive Care Unit (ICU) in COVID-19[17] and level of magnesium in COVID-19 patients[12-18,20,21].

3. Results

From 408 articles that were retrieved as the search result in the databases based on the intended keywords, after deleting duplicates (131 articles) and non-related articles according to the title and abstract (261 articles), 16 articles remained. Then, by a review of the remaining articles, 3 other articles were excluded due to combined intervention (1 article), a letter to the editor (1 article), and a conference paper (1 article). Afterward, the full text of the articles reviewed, 1 article was deleted due to lack of access to the full text, and finally, 12 articles remained for analysis in this systematic review (Figure 1).

Based on the result of quality assessment checklist, 9 articles were of good quality and three articles were of moderate quality. Table 1 shows the summarized results.

3.1. Magnesium and mortality in COVID-19

In one retrospective study in Iran, the prognostic factors associated with mortality in patients with COVID-19 were investigated. The results showed that increased odds of in-hospital mortality were associated with decreased level of magnesium (OR=0.032, P<0.001) on admission[10]. In another retrospective study in COVID-19 hospitalized patients in Iran, magnesium serum level with an average rank of 46.83 was one of the least important predictors of mortality in COVID-19 patients[11]. A retrospective study in hospitalized COVID-19 patients in New York found an association between hypomagnesemia (>2.4 mg/dL) and increased mortality. This study showed that hypomagnesemia patients had twice mortality rate compared with patients with normal serum magnesium levels[12].

3.2. Magnesium and hypokalemia in COVID–19

In a retrospective study performed on non-ICU admitted COVID-19 patients in Modena, the serum magnesium level was not a predictive factor of hypokalemia (P=0.05)[13].

3.3. Magnesium and markers of disease severity in COVID–19

In one study in Ankara, the magnesium level of pregnant women in the first trimester, was associated with white blood cell (P<0.001, r= −0.435), neutrophil (P=0.002, r= −0.366), lymphocyte (P=0.002, r= −0.378), erythrocyte sedimentation rate (P=0.001, r=0.384), hematocrit (P=0.02, r= −0.276) and creatinine (P=0.04, r= −0.250). In the third trimester, magnesium level was associated with lymphocyte (P=0.04, r= −0.254), C-reactive protein (P=0.03, r=0.271), ferritin (P=0.03, r= −0.272) and creatinine (P=0.01, r=0.306) levels. These results showed no correlation between disease severity and magnesium level[14]. A cross-sectional study on ICU-admitted COVID-19 patients in Iran revealed an independent and inverse correlation between magnesium levels with a higher score of severity. The lower level of magnesium was significantly and independently correlated with higher APACHE scores and higher lung damage (P=0.028 and P=0.045, respectively)[15]. One study in pediatric COVID-19 patients in Iran revealed that magnesium can be considered a predictor of SARS-CoV-2 RNAaemia with an AUC level of 0.808. This study revealed that most of the patients with SARS-CoV-2 RNAaemia (67%) had a severe form of COVID-19 and one-third of these patients died[16]. In a prospective cohort study in hospitalized patients with COVID-19 in France, there was a significant and negative association between magnesium deficiency and infection severity (P<0.001). After exclusion of sex ratio, the infection severity (OR=0.46, P=0.04, and OR=0.39, P=0.01) was the strongest predictor of magnesium deficiency for critical and moderate COVID-19, respectively. Also, the number of hypomagnesemia cases (<0.75 mmol/L) was significantly more in moderate COVID-19 patients than in critical form (P<0.001), while hypomagnesemia (≥0.95 mmol/L) was significantly increased in severity (P=0.040)[17]. In a cohort study in COVID-19 patients, magnesium levels did not correlate with SpO_2, fever, lung involvement, CT grade, or C-reactive protein levels[18]. In a cohort of COVID-19 patients in China, severe cases revealed significantly lower whole blood levels of magnesium compared with non-severe cases (P=0.002). However, the plasma magnesium level didn't show a difference between the two groups (P=0.068). The hemoglobin and red blood cell were positively correlated with magnesium (CC=0.37 and 0.33)[19].

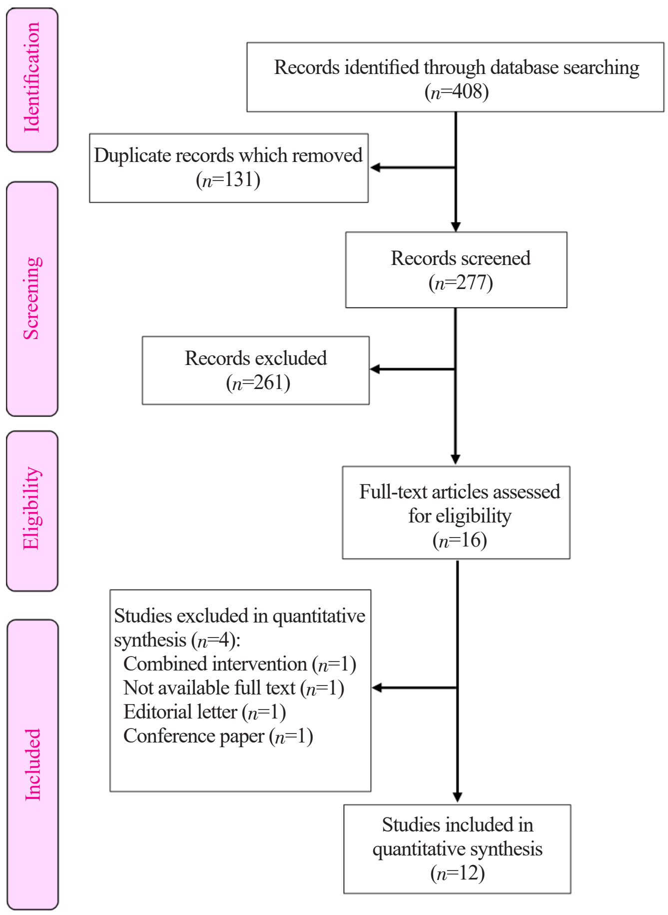

Figure 1. The study flowchart.

Table 1. Characteristics of articles included.

Authors and year	Location	Study type	Sample size	Quality assessment	Main outcomes
Alamdari *et al*. (2020)[10]	Iran	Retrospective	396 survived 63 non-survived	Good	- On admission, older age COVID-19 patients with increases in BMI, CRP, and creatinine along with lymphopenia and hypomagnesemia are at higher risk of mortality.
Alfano *et al*. (2021)[13]	Italy	Retrospective	119 with hypokalemia 171 no hypokalemia	Good	- On admission, hypokalemic patients had lower serum calcium and magnesium in comparison to normokalaemic patients.
Anuk *et al*. (2021)[14]	Turkey	-	100 healthy 100 COVID-positive pregnant women	Moderate	- In the first and third trimesters, pregnant women had higher serum magnesium levels in the COVID-19 arm in comparison to the control arm. - In the third trimester, higher serum magnesium led to reductions in WBC, neutrophils, and lymphocytes, and an increase in CRP. - No correlation between disease severity and magnesium level.
Beigmohammadi *et al*. (2021)[15]	Iran	Cross-sectional	60 patients admitted to ICU	Good	- COVID-19 patients had lower serum levels of magnesium. - There was a significant and independent association between lower magnesium levels with higher APACHE scores and higher lung damage.
Ouyang *et al*. (2020)[21]	China	-	82 survivors 25 non-survivors	Good	- In the last tests, magnesium level was significantly increased in non-survivors compared to survivors (P<0.001).
Pourakbari *et al*. (2021)[16]	Iran	-	96 pediatric patients	Moderate	- Magnesium level was significantly different between the negative and positive SARS-CoV-2 RNAaemia groups. - Magnesium can consider a predictor of SARS-CoV-2 RNAaemia with AUC levels of 0.808.
Quilliot *et al*. (2020)[17]	France	Prospective cohort	Moderate: 43 Severe: 108 Critical: 149	Good	- Moderate form of COVID-19 had significantly low serum magnesium, while a critical form of COVID-19 had significantly high serum magnesium. - Magnesium deficiency had significantly and negatively associations with severity of infection, sex ratio, oxygen therapy, stay in ICU, and positive nephropathy. - Female sex and nephropathy were the strongest predictors of magnesium deficiency and after exclusion of sex ratio, infection severity in critical and moderate COVID-19.
Skalny *et al*. (2021)[18]	Russia	Cohort	Mild: 50 Moderate: 50 Severe: 50 Healthy: 44	Good	- Between patients and controls, no significant difference was seen in level of magnesium. - Magnesium levels did not correlate with SpO_2, fever, lung involvement, CT grade, or CRP levels.
Zeng *et al*. (2021)[19]	China	Retrospective	Non-severe: 202 Severe: 104	Good	- Whole blood magnesium was lower in the severe group compared with the non-severe group. - The hemoglobin and RBC were positively correlated with magnesium (CC=0.37 and 0.33).
Sarvazad *et al*. (2020)[20]	Iran	Cross-sectional	24 ICU 34 Outpatients	Good	- Normal level of serum magnesium was higher in the outpatient group than in the ICU group.
Shanbehzadeh *et al*. (2021)[11]	Iran	Retrospective	1 353 hospitalized	Moderate	- Magnesium with an average rank of 46.83 showed the lowest importance for predicting mortality in patients with COVID-19.
Stevens *et al*. (2021)[12]	USA	Retrospective	1 685 hospitalized	Good	Hypomagnesemia patients (>2.4 mg/dL): - Had double mortality rate compared with patients with the normal level of magnesium. - Had more respiratory failure needing mechanical ventilation compared with normal magnesium level patients (28% *vs*. 21%, P=0.01) - Had more shock needing pressors (35% *vs*. 27%, P<0.01). - Had more incidence of AKI (65% *vs*. 50%, P<0.001), and severe AKI to need (RRT) (18% *vs*. 5%, P<0.001). - Seen more commonly with increases in age, male sex, AKI needing RRT, hyperkalemia, and higher CPK.

AKI: Acute kidney injury; BMI: Body mass index; CPK: Creatine phosphokinase: CRP: C-reactive protein; ICU: Intensive care unit; RBC: Red blood cell; RRT: Renal replacement therapy; USA: United States of America; WBC: White blood cell.

3.4. Magnesium and need for mechanical ventilation in COVID–19

A retrospective study in hospitalized patients with COVID-19 in New York found that hypomagnesemia patients had more respiratory failure needing mechanical ventilation compared with normal magnesium level patients (28% *vs.* 21%, P=0.01)[12].

3.5. Magnesium and need for vasopressors in COVID–19

One retrospective study in hospitalized COVID-19 patients in New York found that hypomagnesemia patients had more shock requiring pressors (35% *vs.* 27%, P<0.01)[12].

3.6. Magnesium and acute kidney injury (AKI) in COVID–19

A retrospective study in patients hospitalized with COVID-19 in New York found that hypomagnesemia patients had more incidence of AKI (65% *vs.* 50%, P<0.001), and severe AKI to need renal replacement therapy (18% *vs.* 5%, P<0.001)[12].

3.7. Magnesium and stay in ICU in COVID–19

In a prospective cohort study in hospitalized COVID-19 patients in France, there was a significant and negative association between magnesium deficiency and stay in ICU (P=0.028)[17].

3.8. Level of magnesium in COVID–19 patients

In one study in Ankara, pregnant women with COVID-19 in the first and third trimesters had higher serum magnesium levels compared with healthy pregnant women, respectively [(1.557±0.211) mg/dL *vs.* (1.848±0.335) mg/dL, P<0.001 and (1.947±0.657) mg/dL *vs.* (2.767±0.394) mg/dL, P<0.001][14].

In a retrospective study performed on non-ICU admitted COVID-19 patients in Modena, magnesium level on admission was statistically significantly lower in hypokalemic compared with normokalaemic patients (P=0.028)[13]. A cross-sectional study on ICU-admitted COVID-19 patients in Iran reported low serum levels of magnesium in COVID-19 patients[15].

One study in pediatric COVID-19 patients in Iran showed that SARS-CoV-2 RNAanemia patients had a significantly lower level of magnesium[16]. In a prospective cohort study in hospitalized COVID-19 patients in France, the serum magnesium level was statistically significantly lower in females compared with males [(0.73±0.12) mmol/L *vs.* (0.80±0.13) mmol/L)], while the sex ratio M/F was higher in severe and critical form of COVID-19 (P<0.001). Also, the risk of magnesium deficiency was significantly and negatively correlated with a sex ratio (M/F, P<0.001), oxygen therapy (P<0.001), and positive nephropathy (P=0.026). Also, female gender (OR=2.67, P<0.001) and nephropathy (OR=2.12, P=0.032) were the strongest predictors of magnesium deficiency[17].

In a cohort study in COVID-19 patients, no significant difference was seen in serum magnesium levels between patients and control groups[18]. In a cross-sectional study performed in Iran in COVID-19 patients without underlying disease, the outpatient group had higher normal magnesium levels (1.8-2.2 mg/dL) compared with the ICU group. Also, hypomagnesemia (>2.6 mg/dL) in the ICU group was significantly higher compared to the outpatient group (P=0.04)[20].

In the last laboratory test findings of inpatients with COVID-19 in China, the magnesium level was significantly increased in non-survivors in comparison to survivors (1.02 mmol/L *vs.* 0.90 mmol/L, P<0.001)[21]. A retrospective study in hospitalized COVID-19 patients in New York concluded that hypomagnesemia was seen more commonly with increases in age, male sex, AKI needing renal replacement therapy, hyperkalemia, and higher creatine phosphokinase[12].

4. Discussion

This systematic review aimed to investigate changes in the severity and consequences of COVID-19 with serum magnesium levels and revealed that there is a relationship between severity of COVID-19, including the need for oxygen therapy, shock requiring pressors, stay in ICU and mortality and serum magnesium levels.

Magnesium is playing a role in a wide range of vital functions in human physiology. In addition to the immune system, magnesium is required for all enzymatic reactions requiring adenosine triphosphate and kinases, neuromuscular excitability, cell permeability, regulation of ion channels, mitochondrial function, cell proliferation, apoptosis, *etc*[22].

Hypomagnesemia is defined as Mg<1.7 mg/dL (0.7 mmol/L) in blood serum. Important signs and symptoms are seen when serum Mg is less than 1.2 mg/dL (0.5 mmol/L)[23]. Hypermagnesemia is identified as serum Mg greater than 2.6 mg/dL (1.1 mmol/L), which presented with important signs and symptoms when serum Mg is greater than 4.8 mg/dL or 2 mmol/L[23].

The results of multiple studies revealed that hypomagnesemia[10] and hypermagnesemia[12] both can increase the risk of mortality in patients with COVID-19. Although serum magnesium levels have been reported to be higher in patients who died of COVID-19[21], it does not affect predicting the prognosis of the disease[11].

Various studies have examined serum levels in patients with COVID-19. Numbers of studies have shown that patients with COVID-19 have low levels of magnesium[15,16]. However, a cohort study by Skalny *et al*. did not show the difference in magnesium levels in patients with COVID-19 and the control[18]. Alfano *et al*. reported that magnesium serum levels at admission were significantly lower in hypokalemic patients than in normal patients[13], which is in line with the generally accepted logic that magnesium deficiency is often associated with hypokalemia. Magnesium deficiency simultaneously aggravates hypokalemia and makes it resistant to potassium therapy[24]. Various investigations which revealed a relationship between serum magnesium levels and disease severity in patients with COVID-19 have reported different results. Some have found it to be ineffective[14,18], some have linked magnesium deficiency to increased disease severity[15,19] and one study found a relationship between magnesium deficiency and moderate disease severity[17]. While other investigations were reported severe hypomagnesemia and hypermagnesemia in COVID-19 patients which have severe disease and hospitalized in the ICU[17], some have reported that despite the same serum magnesium level in patients at admission, this value varies during the hospitalization period in patients with severe and moderate disease[19,21]. One study also found that hypermagnesemia was associated with an increased need for oxygen therapy and shock therapy, and increased the risk of renal failure in COVID-19 patients[12]. While in a cohort study, Tan *et al*. showed that 150 mg of oral magnesium along with other supplements was effective in reducing the disease severity and the need for oxygen therapy and hospitalization in the ICU[25].

It is ambiguous how hypomagnesemia and hypermagnesemia affect the prognosis of COVID-19, only one study investigated the cause of hypomagnesemia in COVID-19 patients. This study reported that sex ratio, oxygen therapy, ICU admission period, and nephropathy were among the risk factors for hypomagnesemia in these patients, and female sex (OR=2.67, P<0.001) and nephropathy (OR=2.12, P=0.032) had the strongest association[17]. However, there is growing evidence that magnesium deficiency causes a variety of diseases including the respiratory system, reproductive system, nervous system, gastrointestinal tract, and cardiovascular system disorders and nephropathy, diabetes, and cancer[4]. On the other hand, Stevens *et al*. reported that hypermagnesemia in patients with increasing age, male gender, and acute nephropathy are more likely to have hyperkalemia and higher creatine phosphokinase and require renal replacement therapy[12]. Also, because COVID-19, which is characterized by respiratory symptoms with varying degrees of damage to other organs and tissues[26], normal serum magnesium levels maintenance is important.

5. Conclusion

According to the important role of magnesium in the body and its involvement in many physiological reactions, as well as differences in the physical and physiological conditions of patients, conducting studies with a small sample size would not be helpful for clinicians. However, according to these results, it can be concluded that the measurement of serum magnesium should be considered at the time of admission of patients. Also, if there are any side effects of reducing or increasing magnesium during treatment, the necessary monitoring during treatment to maintain magnesium at a normal level, especially in patients admitted to the ICU, should be considered.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

H.S., R.A. and A.M. conceived of the presented idea and developed the theory and performed the computations. R.A. and A.M. verified the analytical methods. H.S. investigated and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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