INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

PAGE 288
2023 July; 29(3): 288 - 291
p-ISSN 0854-4263 e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

Analysis of the Relationship between Serum Magnesium Levels and Severity of COVID-19 Patients

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ABSTRACT

Magnesium (Mg) plays an important role in the homeostasis functions of the lungs and heart for humankind. However, there is limited information concerning the importance of such an electrolyte mineral to COVID-19 pathogenesis. The Mg level is not primarily considered for the analysis of infectious diseases in the laboratory. The purpose of this study was to analyze the relationship between Mg levels and COVID-19 patient severity at Dr. Wahidin Sudirohusodo Hospital, Makassar. This research was a retrospective study with a cross-sectional design. Samples were prepared from 186 patients. Serum Mg levels were measured using an ABX Pentra 400C analyzer and the patients diagnosed with COVID-19 were then classified into abnormal and normal magnesemia. Based on the severity of COVID-19, patients were then categorized into severe and non-severe. The obtained data were then statistically analyzed using the Kolmogorov-Smirnov test, Mann-Whitney test, Chi-Square, and odd ratio with a significant level of $p < 0.05$. The mean values of serum Mg levels of severe COVID-19 patients (2.53±2.03 mg/dL) were not significantly different compared to those of non-severe COVID-19 patients (2.12±0.83 mg/dL) with p=0.712. Patients with abnormal magnesemia had a 2.625 times higher risk of severe COVID-19 (95% CI = 1.499 – 4.757, p-value=0.001) compared to those with normal magnesemia. There was a significant relationship between serum Mg levels and the severity of COVID-19 patients at Dr. Wahidin Sudirohusodo Hospital. Patients with abnormal Mg levels had a 2.625 times higher risk of severe COVID-19. Magnesium concentration is an important parameter, which must be monitored in the laboratory analyses of COVID-19 patients.

Keywords: Magnesium, COVID-19, severity

INTRODUCTION

Magnesium (Mg) is the fourth most abundant mineral in the human body after calcium, sodium, and potassium, and is the second most abundant intracellular cation after potassium. As a micronutrient, magnesium is involved in many functions of the human organism, including immunity.[1] Magnesium is mainly found in cells, serving as a source of ATP and nucleic acids. Magnesium is a cofactor of more than 600 enzyme systems in the body that regulate a variety of physiological activities, including protein synthesis, muscle and nerve transmission, neuromuscular conduction, signal transduction, blood glucose management, and blood pressure regulation.[2]

Since the COVID-19 pandemic, many laboratory parameters have been used to support the improvement of the patient's condition, including measurement of Mg levels. Conditions associated with low Mg intake are important nutritional issues in the pathogenesis and prognosis of COVID-19. Obesity, a condition associated with low intake of Mg, appears to be a negative factor for increasing mortality and hospitalization in people with COVID-19.[3] Some studies have shown that Mg plays an important role in lung and heart function. In addition to obesity, other coexisting conditions such as hypertension, diabetes mellitus, and especially old age are associated with increased severity of COVID-19, due to an underlying chronic inflammatory state or a lower threshold for the development of organ dysfunction of the immune response.[4] All of these conditions, including old age and the chronic inflammatory state discussed above have been associated with low Mg status.[5]

Patients with severe manifestations of COVID-19 may require hospitalization in the Intensive Care Unit (ICU). Interestingly, up to 60% of critically ill patients in the ICU have been reported to experience some degree of Mg deficiency, even life-threatening effects, also due to the impact of causing hypokalemia and hypocalcemia.[6] However, there is limited information regarding the importance of Mg in COVID-19, perhaps because Mg is not routinely measured in databases and major studies.[7] In addition, serum concentrations representing only 1% of total body Mg do not accurately indicate

intracellular concentrations. In a scientific review, Wallace reported that appropriate constant monitoring of fully ionized Mg status may be an effective strategy to influence disease progression.[8]

Based on the background above, it is necessary to perform a study on the analysis of the relationship between serum Mg levels and the severity of COVID-19 patients at Dr. Wahidin Sudirohusodo Hospital, Makassar.

METHODS

This study was retrospective research using a cross-sectional study design. The research was carried out at the Medical Record and Information System Installation at Dr. Wahidin Sudirohusodo Hospital with the recommendation of ethics approval with No. UH21090618. The research was carried out for 6 months (February 2022–July 2022) beginning with screening COVID-19 patient data in medical records using code B34.2, involving patients who were treated and aged over 18 years and screening those who had serum Mg test results when diagnosed with COVID-19.

Subjects were patients with the main diagnosis of COVID-19 with positive PCR laboratory results and hospitalized based on the severity of disease (mild-moderate); patients with or without clinical symptoms of fever, cough, anorexia, fatigue, headache but had no signs of pneumonia; severe, and severe (severe-critical) who had clinical symptoms of severe pneumonia with a saturation <93% and the possibility of sepsis.[9] All research subjects in this study were categorized based on the results of medical records by clinicians and reassessments according to predetermined categories.

Serum Mg levels were measured using an ABX Pentra 400C analyzer and ABX Pentra Magnesium RTU reagent from France with the photometric test method using xylidyl blue. Serum Mg levels in the samples were interpreted as hypomagnesemia (<1.7 mg/dL), normomagnesemia (1.7-2.4 mg/dL), and hypermagnesemia (>2.4 mg/dL). Hypomagnesemia and hypermagnesemia were reported as abnormal results, while Mg levels within the range of normal values were reported as normomagnesaemia.[10]

The inclusion criteria for this study were COVID-19 patients who had laboratory results of serum Mg levels, whereas subjects aged less than 18 years old were excluded. The sample was determined by using a random sampling technique. Data on gender, age, comorbidities, Mg levels, and severity were processed using the Kolmogorov-Smirnov test. Differences in serum Mg levels based on severe and non-severe COVID-19 categories were analyzed using the Mann-Whitney test, whereas the relationship between Mg levels with the severity of COVID-19 was analyzed using the Chi-Square test with a significance result of $p<0.05$. The comparison between the risk of abnormal magnesemia and normal magnesemia to severe COVID-19 was analyzed using relative risk.

RESULTS AND DISCUSSIONS

The research subjects in this study consisted of a higher number (96) of males compared to females (90). The average age of the research subjects was 49

Table 1. Characteristics of research subjects

Characteristics	n (%)	Mean±SD	Min-Max	
Gender				
Male	96 (52%)			
Female	90 (48%)			
Age		49±16.55	18-90	
Comorbidity				
Hypertension	34 (35%)			
Diabetes mellitus	24 (25%)			
Kidney failure	15 (16%)			
Heart failure	10 (10%)			
Malignancy	13 (14%)			
Magnesium levels				
Hypomagnesemia (<1.7 mg/dL)	34 (18%)			
Normomagnesemia (1.7-2.4 mg/dL)	102 (54%)			
Hypermagnesemia (>2.4 mg/dL)	50 (38%)			
Severity of disease				
Non-severe	95 (48.9%)			
Severe	91 (51.1%)			
Serum Mg levels				
Non-severe COVID-19		2.53±2.03	0.33-15.00	*0.712
Severe COVID-19		2.12±0.83	0.28-4.42	

Kolmogorov Smirnov test; *Mann-Whitney test

years with the youngest age of 18 years old and the oldest age of 90 years old. Comorbidities reported in this study were hypertension found in 34 patients, diabetes mellitus found in 24 patients, kidney failure found in 15 patients, heart failure found in 10 patients, and malignancy found in 13 patients. Some patients had one or more comorbidities, whereas some patients did not have any comorbidities (Table 1).

The Chi-Square test was used to determine the relationship between serum Mg levels and the severity of COVID-19 patients (Table 2). There were 52 (27.9%) patients with abnormal magnesemia and 39 (21%) patients with normal magnesemia in the severe group. There were 32 (17.2%) patients with abnormal magnesemia and 63 (34.4%) patients with normal magnesemia in the non-severe group. The results of statistical tests showed a significant relationship between abnormal and normal magnesemia levels and the severity of COVID-19 patients (p-value =0.001).

Based on the measurement of Mg levels, hypomagnesemia was found in 18% of the subjects, normomagnesemia was found in 54% of the subjects, and hypermagnesemia was found in 38% of the subjects. These Mg levels were measured after the patient was diagnosed with COVID-19 with evidence of detected Sars-Cov-2 PCR results. There was no specific time for sampling; however, it was adjusted based on the initial screening by the clinician.

Based on the severity of the disease at the initial diagnosis of COVID-19, 95(48.9%) patients had non-severe disease, and 91(51.1%) patients had severe disease.

The relative risk test was used to determine how much the risk factor for abnormal serum Mg levels for severe exposure to the COVID-19 virus (Table 3). Patients with abnormal Mg levels were 1.619 times more likely to develop severe COVID-19 (95% CI =1.201-2.182, p-value =0.001).

Statistical analysis was used to analyze the relationship between Mg and the severity of COVID-19 patients. The severity of COVID-19 patients in this study group was distinguished into 2 categories; mild-moderate was classified as non-severe and severe-critical was classified as severe. There was no significant difference in mean serum Mg levels in severe and non-severe patients (p=0.712).[11]

The research subjects of this study consisted of 52% males of the total patients. This was possibly caused by a weakened immune response to infection in males and increased expression of the Angiotensin-Converting Enzyme-2 (ACE-2), which binds SARS-CoV-2, and the role of androgens in COVID-19.[12] Older patients predominated in this study group, similar to a study by Chen *et al.* It was justified because age is one of the main, perhaps even the most significant, risk factors for COVID-19.[13]

There was a significant relationship between abnormal magnesemia and the severity of COVID-19. Abnormal levels of magnesemia were found in 27.9% of subjects with severe COVID-19 and 17.2% of subjects with non-severe COVID-19 (p=0.001). The results of this study were in accordance with studies by Essabah *et al.*, which found that the prevalence of hypomagnesemia with severe COVID-19 was 12.2%, and in a study by Stefanno *et al.*, which explains that the prevalence was around 32-48%.[14,15] Deficiency of Mg was discussed as a risk factor for severe COVID-19 infection causing endothelial dysfunction, paroxysmal inflammation, and decreased immune response.[7]

Patients with abnormal Mg levels were 1.619 times more likely to develop severe COVID-19 (95% CI = 1.201-2.182, p-value =0.001). This was in line with the research of Sharma *et al.*, which found an increased risk of death in the care unit with age-adjusted logistic regression analysis and t association between

Table 2. Relationship between magnesium levels and severity of disease

	Severe (%)	Non-Severe (%)	Total	p-value
Abnormal magnesemia	52 (27.9%)	32 (17.2%)	84 (45. 1%)	0.001*
Normal magnesemia	39 (21%)	63 (33.9%)	102 (54.9%)	
Total	91(48.9%)	95(51.1%)	186	

Abbrev: *Chi-Square test

Table 3. Relative risk between Mg levels and severe COVID-19

Variable	Value	95% Confidence Interval		Significant p-value
		Lower Bound	Upper Bound	
Abnormal magnesemia	1.619	1.201	2.182	0.001*
Normal magnesemia	0.617	0.451	0.843	

Abbrev: *Mantel-Haenszel Odd Ratio

hypermagnesemia and death (p=0.007). His studies have shown that hypermagnesemia was a significant marker of disease severity and adverse outcome in COVID-19 infection.[16] In a study by Malynowska *et al.* odds ratio for hypermagnesemia also showed an increased probability of death.[17]

Optimal Mg status is required for the synthesis, transport, and activation of vitamin D. Magnesium modulates innate and adaptive immunity, as a composition of the gut microbiota, and is essential for Vitamin D activation and anti-inflammatory activity.[18] Magnesium plays a role in inhibiting the activity of the ACE-2 enzyme, which will increase TMPRSS2 promoter methylation, thereby inhibiting transcription and reducing enzyme expression. Magnesium can also inhibit furin activity; Mg deficiency can increase the infectivity of the virus. However, as the infection progresses, Mg deficiency can exacerbate the inflammatory response, which contributes to the occurrence of a cytokine storm involved in the pathogenesis of the severe clinical manifestations of COVID-19. Magnesium can alter the balance between the gut and host microbiota, thereby affecting the airway microbiota and immune response.[5]

This study found 21% normal magnesemia in patients who suffered from severe COVID-19 and 17.2% abnormal magnesemia in patients who suffered from non-severe COVID-19, indicating that there were several factors such as gender, age, and comorbidities in addition to Mg levels, which might affect the severity of COVID-19 patients. Comorbidities will affect a person's quality of life, thus affecting the severity of the disease when exposure occurs. Therefore, the unknown direct role of Mg in this study of COVID-19 remained a limitation in this study.

CONCLUSIONS AND SUGGESTIONS

There was no significant difference in serum Mg levels in severe and non-severe COVID-19 patients; however, there was a significant relationship between serum Mg levels and the severity of COVID-19 patients in Dr. Wahidin Sudirohusodo Hospital. Patients with abnormal Mg levels were 1.619 times more likely to develop severe COVID-19 when viral exposure occurs.

It was concluded that Mg concentration is a parameter, which must be monitored carefully in the COVID-19 patient. Further and more specific research was still needed to determine the role of serum Mg parameters in COVID-19 disease.

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