Original Article

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ISSN: 1735-0344 *Tanaffos 2023; 22(2): 236-247*

TANAFFOS

Relationship between Plasma Levels of Zinc and Magnesium with the Treatment Process and Mortality Risk in COVID-19 Patients

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Received: 10 July 2022

Accepted: 20 January 2023

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Background: The COVID-19 pandemic is considered a major health problem all over the world which has caused extensive and worldwide mortality and morbidities along with vast economic and political impact. Limitations of our knowledge and controversies in treatment modalities make the control and management of this disease more difficult. The status of electrolytes especially Mg and Zn in plasma and its correlation with the clinical situation and criteria for recovery has been investigated in various studies. Limited data in Iran mandate the design of a trial for evaluating our critically ill patients. We designed this study to investigate the correlation between plasma levels of Mg and Zn and the outcome including patients' need for assisted/ controlled ventilation, time required for weaning, length of ICU stay, and probable cause of death.

Materials and Methods: 413 patients with severe respiratory signs of COVID-19 disease who were admitted to the ICUs of 3 medical centers of Shahid Beheshti University of Medical Sciences were evaluated for plasma levels of Mg and Zn. Supplemental therapy was introduced when needed and was followed until discharge from ICU or death. All recorded data were analyzed by statistical methods and results were compared with similar studies.

Results: 20.6% and 35.1% of all participants had low serum levels of Mg and Zn, respectively. 11 patients (2.7%) died through the treatment period. 56.9% and 61.0% of participants received Mg and Zn supplements, respectively.

Conclusion: According to our results, serum Mg and Zn levels did not show a significant correlation with the risk of death due to severe COVID-19 disease, prolonged assisted ventilation, or duration of ICU stay. There was no significant association between Mg and Zn supplementation with the risk of death due to severe COVID-19; however, it showed an inverse relationship with the time required for assisted ventilation and the duration of ICU stay. It seems that Mg and Zn supplementation can be useful in preventing or managing some of the morbidities among COVID-19 patients.

Keywords: COVID-19; ICU; Mortality; Magnesium; Zinc

INTRODUCTION

During the past 2 years, the COVID-19 pandemic affected many countries nearly all around the world. Many people are infected by a new generation, the so-called SARS-Cov-2 corona virus. Due to our limited knowledge about this disease and its pathogenicity, there are many problems for managing and controlling it. One of the main features of COVID-19 disease especially in severe cases is the progressive respiratory problems that may lead to respiratory insufficiency or even death. Many aspects of the disease as well as the role of many interventions in its prevention or control are still unknown. One of the main challenging items in this regard is the role of some minerals and electrolytes on the respiratory profile.

SARS-CoV-19 virus can attach to converting angiotensin II enzyme (ACE II) which is expressed in many tissues and organs such as lungs, arteries, and intestines (1). In severe cases, it can stimulate the immune system and cause progressive inflammation and cytokine storm (2). About 20% of all infected patients need ICU admission (3) while about 80% of them will need ventilatory support with a mortality rate of 30-90% (4). Thus, prompt detection of disease and on-time control of the pathway of disease can prevent such a disaster.

Recent studies indicate that an individual's Zn profile can influence their susceptibility to anti-viral immunity. Zinc-deficient people are more susceptible to viral infections (5). Zn ++ cations can inhibit coronavirus replication by inhibiting RNA polymerase (6). On the other hand, Zn can reduce the virus entry into the host cell by downregulation of the ACE-2 enzyme (7). Clinically, zinc deficiency is defined as plasma zinc level lower than 70 mg/100ml (10.7 mmol/L) (8). Several studies showed that normal levels of Zn correlate with survival and zinc supplementation should be considered for patients with essential zinc deficiency (9). Yasui et al showed that there is a meaningful decrease in plasma zinc levels among severe cases of COVID-19 (8). However, some studies suggest that a decrease in plasma zinc level can have a supportive effect due to lower zinc availability for bacteria and limiting cytokine response (10). Also, it has been reported that an in vitro increase in Zn plasma levels inhibits macrophage activation, phagocytosis, and O_2 consumption (11). Also, Zn redistribution from plasma to the liver, thymus, and bone marrow can have a supportive effect against invading pathogens (12).

Magnesium is essential in basic biochemical reactions through cell membranes (13,14), protein, and nucleic acid metabolism (15). Mg has also an anti-inflammatory effect (16). In a study conducted in Morocco, hypomagnesemia had a direct effect on ICU stay in severe COVID-19 patients (17). A study in Kermanshah, Iran, showed that hypomagnesemia is more common among ICU admitted COVID-19 patients (18). Another study in France also showed that there is an inverse relation between ICU stay and plasma levels of Magnesium (19). In another study, it was shown that both low and high plasma levels of Mg correlate with higher mortality rates (20). Despite insufficient data, several studies showed that both low and high levels of plasma Mg levels correlate with the profile of many illnesses, despite controversies (21-24). In many medical centers, supplemental therapy by adding Mg products is very popular, but its effect on the course of COVID-19 disease is still unclear (25-31). In some studies, a positive effect (27, 29-31), and in others no correlation between Mg plasma levels and the course of the disease are reported (25,26,28). Several studies have shown that there are some changes in concentrations of minerals and electrolytes, especially Zn and Mg, during COVID-19 disease (32-37).

Many physiologic findings insist on the importance of Zn plasma levels in the clinical course of pulmonary and coronary diseases (38 - 44). Several studies investigated the effect of some minerals and vitamins on the condition of patients with acute and critical respiratory problems (30,45-49).

Due to the high incidence and prevalence of COVID-19 disease as well as its high rate of mortality and morbidity, it seems logical to find an exact response to these questions, especially when the former studies have generally controversial results.

Due to the high incidence and prevalence of COVID-19 disease and the lack of sufficient data about the probable correlation between some nutritional elements and the severity of COVID-19 as well as the proper response to therapy, we designed a study to evaluate the role of normal and abnormal values of plasma Zn and Mg in mortality rate of COVID-19 patients and some very important morbidities such as duration of ICU admission and assisted ventilation.

Despite several studies about the role of Mg and Zn deficiency on ventilatory parameters and the duration of ventilation, due to rather insufficient data and controversial results, we were encouraged to design and conduct a prospective descriptive study to evaluate and assess the role of Mg and Zn supplementation on the course of respiratory problems, need for assisted ventilation, and weaning course in addition to their probable role in preventing death in patients with severe COVID-19 disease.

Given the above findings and still more unknowns, we hypothesized that normal levels of plasma Mg and Zn can reduce the mortality rate from COVID-19 disease and its respiratory morbidities in ICU admitted cases..

MATERIALS AND METHODS

We designed a prospective descriptive-analytical study. This study was a multi-center study and was done in intensive care units of 3 tertiary medical centers of Shahid Beheshti University of Medical Sciences, Tehran, Iran. All adult patients (above 18 years old) which admitted to the COVID-19 intensive care units were included in the study. Inclusion criteria were all adult patients admitted to COVID-19 ICU, confirmed severe COVID-19 disease, availability of data about plasma levels of Zn and Mg at the admission, and signed informed consent by the patient or her/his relatives. Exclusion criteria were unacceptance by the patient, unavailability of Zn and Mg profile at admission time, and early death for a reason other than COVID-19 disease.

During five months, all severe cases of COVID-19 patients who were admitted to ICUs of three tertiary hospitals of Shahid Beheshti University of Medical Sciences were included in this study. No case selection and no interventional approaches in treating protocols made by researchers. All patients were admitted to the ICU with Zn and Mg plasma level measurements and during the ICU stay, these profiles were repeated every day. Plasma levels of Mg and Zn were followed by the research team. Patients were divided into three groups with normal, low, or high plasma levels. No intervention was made by the research team, but all data about medications, treating protocols, weight, height, body mass index, assisted ventilation status, duration and modes for assisted ventilation, duration of ICU and hospital stay, status at discharge, and the probable or exact cause of death as well as nutritional and/or supplemental therapy were recorded in a 3 pages questionnaire. There were 3 approaches for data recording; patient and/or family interview, physical examination of the patient, and clinical/para-clinical data recording.

Due to insufficient data about differences between mean and standard deviations in the relationship between Zn and Mg profile and duration of ICU stay and assisted ventilation, we designed a pilot study at first. In this pilot study, 68 patients among these 3 ICUs were selected randomly and derived data were summarized and used for the main study.

The main study included data from 413 patients: 85 had low plasma Mg levels compared to 328 with normal levels, and 145 had low Zn levels compared to 268 with normal levels. Statistical analysis of data was done using SPSS version 20 software.

RESULTS

In this study 413 patients were selected in COVID-19 ICUs in 3 tertiary medical centers of Shahid Beheshti University of Medical Sciences, Tehran, Iran. From a total number of 413 cases (52.5 % female and 4705% male), 20.6% and 35.1% had lower plasma levels of Mg and Zn, respectively. During hospital stay, 11 cases died (2.7%). The mean ± standard deviation for all age groups was 49.0±16.7 years. Among all cases, 180 cases (43.6%) had a history of co-existing disease, mainly hypertension (32%), diabetes (22.5%), coronary artery disease (15%), and renal dysfunction (3.6%). During ICU stay, antibiotics and antacids were prescribed for 34.6% and 11.9 %, respectively. There were only 5 cases of malnutrition at the time of ICU admission. In 67.3% of all cases, enteral feeding began during the first week using a nasogastric tube.

During ICU stay, 56.9% and 61.0% of all cases received supplemental Mg and Zn, respectively. In this regard, 94.1% and 95.9% of cases with low plasma concentrations of Mg and Zn as well as 47.3% and 42.2% of cases with normal plasma levels of Mg and Zn received supplemental therapy, respectively.

From a demographic point of view, there were some differences in time and duration of ICU admission, duration of assisted ventilation, and need for supplemental therapy between 3 medical centers (P<0.05). There was also a significant difference between these 3 medical centers in terms of normal and/or low plasma levels for Mg and Zn, body mass index duration of ICU stay, and need for supplementation by Mg and Zn (P<0.05).

The effect of possible confounders including age, sex, body mass index levels, nutritional status, antibiotic and antiacid drug use, food intake method, treatment centers, comorbidities, and magnesium or zinc supplementation were adjusted in regression models.

The β and 95% CI for the times needs for auxiliary ventilation and the hospitalization days were 0.68 (-0.77, 2.13), P = 0.358 and 0.49 (-0.89, 1.89), P = 0.488 for patients with low compared to normal Mg group, respectively. Also, for patients in the low compared to normal Zn group, the β, and 95% CI for the times needed for ventilation and the hospitalization days were 0.38 (-0.91, 1.68), P = 0.561 and 0.94 (-0.28, 2.18), P = 0.133, respectively (Table 1).

The OR (95%CI) of death incidence, more than 2 weeks need of assisted ventilation, and hospitalization for patients with low Mg compared to the normal group were 3.24 (0.36 – 28.82), P=0.292, 1.16 (0.63 – 2.12), p-0.619, and 1.09 (0.59 – 1.99), P=0.775 in the final adjusted model. For patients with low Zn vs normal group, the OR (95%CI) of death incidence, more than 2 weeks need of assisted ventilation, and hospitalization were 2.49 (0.28 – 21.76), P=0.409, 1.11 (0.63 – 1.95), P=0.703, and 1.53 (0.86 – 2.70), P=0.141, respectively (Table 2).

We also conducted additional analysis to assess the association between Mg and Zn supplementation with mentioned outcomes. Among all study populations, patients who consumed Mg supplementation compared with those who received no Mg supplement showed no association with death incidence (OR (95%CI): 0.31 (0.04 – 2.26, P=0.253)). However, lower risk of more than 2 weeks need of ventilation (OR (95%CI): 0.29 (0.18 – 0.48, P<0.001)), and hospitalization (OR (95%CI): 0.30 (0.19 – 0.49, P<0.001)) was observed (Table 3).

Table 1. Beta coefficients and 95% confidence interval between serum zinc and magnesium levels with the number of days requiring ventilation and hospitalization in study participants

Description	Non-standard beta coefficient (95% confidence interval)	P-value
Low magnesium levels versus normal levels		
Number of days required ventilation		
Model 0	-1.35(-2.77, 0.06)	0.061
model 1*	-1.27(-2.69, 0.14)	0.079
model 2†	-1.23(-2.66, 0.19)	0.089
model 3‡	0.68(-0.77, 2.13)	0.358
Number of hospitalization days		
model 0	-1.61(-2.98, -0.25)	0.020
model 1*	-1.47(-2.82, -0.11)	0.034
model 2†	-1.26(-2.62, 0.09)	0.068
model 3‡	0.49(-0.89, 1.89)	0.488
Low levels of zinc versus normal levels		
Number of days required ventilation		
Model 0	-2.34(-3.51, -1.18)	<0.001
model 1*	-2.32(-3.49, -1.16)	<0.001
model 2†	-2.16(-3.43, -0.99)	<0.001
model 3 ¶	0.38(-0.91, 1.68)	0.561
Number of hospitalization days		
Model 0	-2.06(-3.18, -0.93)	<0.001
model 1*	-2.01(-3.13, -0.89)	<0.001
model 2†	-1.70(-2.83, -0.57)	<0.001
model 3 ¶	0.94(-0.28, 2.18)	0.133

A negative beta coefficient indicates an inverse relationship and a positive beta coefficient indicates a direct relationship between low levels of magnesium and zinc with the number of days required for hospitalization and ventilation. If the reported confidence interval for beta coefficients is zero, it is not statistically significant, and if it is not zero, the relationship is statistically significant.

* Adjusted for age and gender

† Adjusted for Model 1 plus body mass index levels, nutritional status, antibiotic use, antacids, diet, treatment centers and comorbidities,

‡ Adjusted for Model 2 plus magnesium supplementation,

¶ Adjusted for Model 2 in addition to zinc supplementation

Table 2. Odds ratio and 95% confidence interval between serum zinc and magnesium levels with the risk of death from COVID-19 and the need for more than 2 weeks of assisted ventilation and hospitalization in the study participants

Description	Odds ratio (95% confidence interval)	P-value
Low magnesium levels versus normal levels		
Risk of death and mortality		
Model 0	1.85(0.46-7.34)	0.381
model 1*	2.00(0.50-8.00)	0.327
model 2†	1.69(0.28-9.94)	0.560
model 3‡	3.24(0.36-28.82)	0.292
Requires artificial ventilation for more than two weeks		
model 0	0.65(0.38-1.11)	0.112
model 1*	0.65(0.38-1.11)	0.116
model 2†	0.64(0.37-1.11)	0.119
model 3‡	1.16(0.63-2.12)	0.619
Need to be hospitalized for more than two weeks		
Model 0	0.56(0.33-0.95)	0.034
model 1*	0.58(0.34-0.98)	0.046
model 2†	0.61(0.35-1.07)	0.086
model 3‡	1.09(0.59-1.99)	0.775
Low levels of zinc versus normal levels		
Number of hospitalization days		
Model 0	0.86(0.21-3.38)	0.830
model 1*	0.88(0.22-3.50)	0.864
model 2†	1.28(0.22-7.29)	0.775
model 3‡	2.94(0.28-21.76)	0.409
Requires artificial ventilation for more than two weeks		
Model 0	0.47(0.30-0.73)	
model 1*	0.47(0.30-0.74)	0.001
model 2†	0.47(0.30-0.75)	0.002
model 3‡	1.11(0.63-1.95)	0.703
Need to be hospitalized for more than two weeks		
Model 0	0.53(0.34-0.82)	0.005
model 1*	0.54(0.34-0.84)	0.006
model 2†	0.59(0.37-0.93)	0.024
model 3‡	1.53 (0.86-2.70)	0.141

* Adjusted for age and gender

† Adjusted for Model 1 plus body mass index levels, nutritional status, antibiotic use, antacids, food intake, treatment centers and comorbidities

‡ Adjusted for Model 2 plus magnesium supplementation

¶ Adjusted for Model 2 plus zinc supplementation

For patients who consumed Zn supplementation compared with those who received no Zn supplement, the OR (95%CI) of death incidence, more than 2 weeks need of assisted ventilation, and hospitalization were 0.32 (0.04 – 2.29), P=0.259, 0.20 (0.11 – 0.35), P<0.001, and 0.17 (0.10 – 0.31), P<0.001, respectively (Table 4).

Table 3. Odds ratio and 95% confidence interval between magnesium supplementation and risk of death due to COVID-19 and the need for more than 2 weeks of assisted ventilation or hospitalization in the study participants

Description	People with normal magnesium status (n=328)		The whole population (n=413)	
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Risk of death and mortality				
Model 0	0.34(0.08-2.36)	0.346	0.79(0.22-2.80)	0.726
model 1*	0.33(0.06-1.85)	0.210	0.71(0.19-2.57)	0.607
model 2†	0.28(0.03-2.13)	0.221	0.31(0.04-2.26)	0.253
Need to be hospitalized for more than two weeks				
Model 0	0.30(0.18-0.48)	<0.001	0.34(0.22-0.53)	<0.001
model 1*	0.28(0.17-0.45)	<0.001	0.33(0.22-0.51)	<0.001
model 2†	0.26(0.15-0.43)	<0.001	0.29(0.18-0.48)	<0.001
Need to be hospitalized for more than two weeks				
Model 0	0.30(0.18-0.48)	<0.001	0.34(0.22-0.53)	<0.001
model 1*	0.25(0.15-0.42)	<0.001	0.32(0.21-0.49)	<0.001
model 2†	0.24(0.14-0.41)	<0.001	0.30(0.19-0.49)	<0.001

* Adjusted for age and gender

†Adjusted for Model 1 plus body mass index levels, nutritional status, antibiotic use, antacids, food intake, treatment centers and comorbidities, and magnesium levels (in whole population analysis)

Table 4. Odds ratio and 95% confidence interval between zinc supplementation and risk of death due to COVID-19 and the need for more than 2 weeks of assisted ventilation or hospitalization in the study participants

Description	People with normal zinc status (n=268)		The whole population (n=413)	
	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Risk of death and mortality				
Model 0	0.55(0.10-2.89)	0.482	0.67(0.19-2.37)	0.541
model 1*	0.39(0.06-2.22)	0.291	0.60(0.16-2.18)	0.442
model 2†	0.23(0.03-2.23)	0.234	0.32(0.04-2.29)	0.259
Need to be hospitalized for more than two weeks				
Model 0	0.25(0.15-0.43)	<0.001	0.26(0.17-0.40)	<0.001
model 1*	0.22(0.12-0.39)	<0.001	0.25(016-0.39)	<0.001
model 2†	0.18(0.09-0.33)	<0.001	0.20(0.11-0.35)	<0.001
Need to be hospitalized for more than two weeks				
Model 0	0.21(0.12-0.36)	<0.001	0.26(0.16-0.40)	<0.001
model 1*	0.16(0.09-0.29)	<0.001	0.23(0.15-0.37)	<0.001
model 2†	0.11(0.06-0.23)	<0.001	0.17(0.10-0.31)	<0.001

* Adjusted for age and gender

† Adjusted for Model 1 plus body mass index levels, nutritional status, antibiotic use, antacids, diet, treatment centers and comorbidities, and zinc levels (for whole population analysis)

DISCUSSION

This study aimed to evaluate the correlation between plasma levels of Mg and Zn with duration of ICU stay, respiratory care, and probable death from severe COVID-19 disease.

We could not confirm any statistically meaningful correlation between plasma concentrations of Mg and Zn and death from severe COVID-19 disease. This study could not prove a valid statistical relationship between plasma levels of Mg and Zn with mortality from COVID-19 disease.

Several studies showed that there are some changes in concentrations of minerals and electrolytes during COVID-19 disease (1,49).

Hypomagnesemia is a common and noticeable abnormality among patients undergoing intensive care (45). In our study, 20.6% of cases had low plasma levels for Mg. A study from Iran confirmed a 32% incidence of hypomagnesemia among COVID-19 patients. Subsequently, severe hypomagnesemia was higher in patients with severe COVID-19 (18). Haraj et al. reported a 12.2 % incidence of hypomagnesemia (17). In another study from France, the incidence of low Mg levels was 48% with 13% diagnosed as hypomagnesemia (19). In a study from Wuhan, the incidence was reported as 21.6 % with a greater reduction in Mg level among critically ill patients (50).

In our study, there is no direct statistically meaningful correlation between hypomagnesemia and factors such as duration of ICU stay, need for assisted ventilation, or death from disease. This finding is challenging. In a study from Iran, hypomagnesemia correlated with an increasing mortality rate from COVID-19 (51). Another study suggests a higher mortality rate in diabetic patients with hypomagnesemia (52). Gunay et al. found that low plasma Mg levels do not predict mortality rate (53) but another study suggested premature death of old COVID-19 patients with low Mg plasma levels (54). Quilliot et al. reported a decrease in the severity of the infection and the need for O_2 among low plasma Mg cases (19). A clinical trial from China concluded that hypomagnesemia can increase enzyme activity and inflammatory response resulting in death (50). Low plasma levels of vitamin D, zinc, and magnesium caused a higher APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) score and therefore more critical situations (55).

Our study showed a direct relationship between Mg supplementation in both normal and low-level Mg circumstances with decreasing ICU stay as well as the need for prolonged assisted ventilation. Similarly, Ostojic et al. showed a better blood O_2 saturation after the administration of a dietetic formula containing Mg (31). Moreover, combination of vitamin B12, vitamin D, and Mg caused a decrease in ventilator support and critical care cases (30). Many factors such as sample size, place of research, substandard care, or over-standard care can vigorously affect the results of any trials (56).

Mg is an important mineral in our body. It has anti-inflammatory and vasodilator effects and has an important role in immune response (57). Low Mg level results in smooth muscle contraction which is important in vessels and respiratory function (58). Minimal Mg deficiency can cause cardiovascular symptoms and moderate to high deficiency results in hypokalemia and cardiac events (59). In a recent study, hypomagnesemia is detected in about 30% of cases by a prolongation of QT Interval (60). This finding may be important as a cause for sudden cardiac arrest (61, 62). ATP regeneration after a cytokine storm needs Mg and hypomagnesemia can cause this problem more significantly (63). Hypomagnesemia in patients with COVID-19 may cause "blocking effects of calcium channels" which is caused by magnesium ions and ultimately leads to a more severe inflammatory response in COVID-19 patients (64). Many hypomagnesemic patients may benefit from Mg supplements (65-67). This is also true in our study because both cases with normal and low Mg levels can experience better conditions after receiving supplemental Mg.

It is unclear whether COVID-19 can cause a reduction in plasma Zn levels (68). Zeng et al showed low Zn levels in severe cases of COVID-19 (37). In our study, 35.1% of cases showed a decrease in plasma Zn level. This reduction can be beneficial (10). In general, it seems that zinc requirement in COVID-19 patients increases. Albumin is the carrier of Zn in plasma and it was shown that hypoalbuminemia has a direct relationship with the severity of COVID-19 (69). Zinc has a positive effect in stabilizing DNA and proteins as well as antioxidant function. Many studies showed that even minimal reductions in zinc content resulted in abnormal immune responses (70). On the other hand, Zn supplementation can prevent sectional diarrhea and pneumonia (71).

In our study, serum Zn concentration did not have any statistically meaningful correlation with mortality due to severe disease, ICU stay, or need for prolonged assisted ventilation. Other studies had different results. Ali et al. reported that there is no correlation between plasma Zn level and mortality from COVID-19 (72). However, a study in India had a different result (73). In a study in Spain, there was an inverse correlation between plasma Zn and duration of hospital stay (47). On the other hand, Tomasa-Irriguible et al. showed low plasma Zn concentration correlated with longer ICU stay and intubation in COVID-19 patients (74). Skalny et al. proved that plasma Zn level has a positive correlation with arterial O_2 saturation and a negative correlation with fever, lung injury, and higher plasma CRP (75). Talha et al. found that low plasma Zn level correlates with a doubled risk for hypoxemia and the need for supplemental O_2 (76). In another study, they found no relation between plasma Zn level and the severity of COVID-19 (77). In our study, Zn supplement was administered for 95% of cases, although no positive effect of zinc supplementation was detected. Another study reported a positive effect of Zn supplement for the prevention and treatment of common cold viruses (78). However, a recent cohort study did not show any relation between Zn supplement and improvement of COVID-19 disease (26).

On the other hand, in some studies, there was a positive effect of zinc supplementation on subsiding inflammation, increasing lymphocytes, and reducing clinical signs and symptoms (27,29). Also, in a study in France, it was proposed that the Zn supplement can cause faster recovery from COVID-19 (79). Some studies indicated that supplement therapy in combination with medications can cause a better and faster result (80). An important point of view is that high Zn plasma levels can affect the immune system and lead to B and T cell intoxication resulting in a very negative effect (81). Thus, many researchers believe that randomized RCTs are mandatory to evaluate the effectiveness of the Zn supplement on the immune system.

CONCLUSION

The present study did not find any significant relationship between serum magnesium levels and the risk of death due to COVID-19, auxiliary ventilation time, and length of hospital stay. Although different statistical models were used, it was found that lower levels of zinc at the time of admission and during the first week of hospitalization were significantly associated with a decrease in the need for assisted ventilation and a shorter hospitalization time. However, after adjusting for the effect of zinc adjuvant supplementation, no statistically significant relationship was observed between lower than normal zinc levels with a decrease in the time required for auxiliary ventilation and hospitalization time. Also, the findings of the present study did not show a significant relationship between serum zinc levels and the risk of mortality due to COVID-19. Another part of the findings of the present study indicates a statistically significant relationship between receiving magnesium and zinc supplementation with reducing the time required for adjuvant ventilation and hospitalization time in all participants, regardless of serum magnesium and zinc status at the beginning of admission and the first week of hospitalization, and also in people with normal plasma magnesium and zinc levels.

We had limitations for conducting this trial. It was impossible to use FFQ (Food Frequency Questionnaire) or

MNA (Mini Nutrition Assessment) questionnaires due to the unconsciousness of many patients. Likewise, unavailability of proper patient bed scales in ICUs as well as unconscious patients' weight measurement forced us to try alternative ways for this aim.

We propose conducting clinical trials through multi-center studies with larger sample sizes to overcome the limitations of our study. Finally introducing a unique protocol based on all scientific data can be beneficial for controlling morbidities and probable mortality from COVID-19 disease.

Acknowledgements

We appreciate assistance from all our colleagues in ICUs who collaborated with us in conducting this research.

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