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The association between serum levels of micronutrients and the severity of disease in patients with COVID-19

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Objectives: This study aimed to compare the serum level of micronutrients with normal amounts, and assess their association with the severity of disease and inflammatory cytokines in patients with coronavirus disease 2019 (COVID-19).
Methods: The present cross-sectional study included 60 patients admitted to the intensive care unit with COVID-19. We recorded data on demographic characteristics, anthropometric information, and medical history. Serum levels of inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, interferon-gamma, tumor necrosis factor-alpha, interleukin-6), vitamins (A, B_9, B_{12}, C, D, E), and minerals (magnesium, zinc, iron) were measured. A radiologist assessed the severity of lung involvement according to patient computed tomography scans. The severity of illness was evaluated with the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score, oxygen saturation, and body temperature. Independent associations among the serum levels of micronutrients with the severity of COVID-19 were measured.
Results: Median patient age was 53.50 years (interquartile range, 12.75 years). Except for vitamin A and zinc, serum levels of other micronutrients were lower than the minimum normal. Patients with APACHE score ≥25 had a higher body mass index ($P = 0.044$), body temperature ($P = 0.003$), erythrocyte sedimentation rate ($P = 0.008$), C-reactive protein ($P = 0.003$), and lower oxygen saturation ($P = 0.005$), serum levels of vitamin D ($P = < 0.001$), and zinc ($P = < 0.001$) compared with patients with APACHE score <25. We found that lower serum levels of vitamin D, magnesium, and zinc were significantly and independently associated with higher APACHE scores (P = 0.001, 0.028, and < 0.001, respectively) and higher lung involvement (P = 0.002, 0.045, and < 0.001, respectively).
Conclusions: Lower serum levels of vitamin D, zinc, and magnesium were involved in severe COVID-19.

Introduction

Coronavirus disease of 2019 (COVID-19) is a recently discovered virus with a high rate of transmission and various clinical manifestations from asymptomatic contamination to severe disease that requires admission to the intensive care unit (ICU) [1]. The severity of COVID-19 can be related to not only viral load but also regulated immune responses in patients. The rapid replication of the virus due to improper and unregulated function of the immune system results in a destructive inflammatory response, characterized by increased serum levels of inflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor, and erythrocyte sedimentation rate (ESR) [2–4]. The data available to date have shown that unregulated responses of the immune system could be responsible for multiorgan failure, which is the leading cause of death in severely ill patients [5,6].

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Micronutrients, including vitamins and minerals, have been reported to play a vital role in the regulation and integrity of the immune system [7,8]. The epigenetic aspects of the mechanisms controlling the immune system responses and inflammatory processes, such as methylation and modification of DNA, and its proteins depend on the sufficient storage of some vitamins and minerals [7–9]. Thus, low levels of micronutrients may influence the severity of infectious diseases, such as COVID-19 [9–11]. Due to the high mortality rate in critically ill patients with COVID-19, one of the challenges facing researchers is to identify the mechanisms involved in virulence and severity of illness in patients with COVID-19 [9–12]. Therefore, considering the crucial role of micronutrients in the regulation of immune responses, this study assessed the serum levels of micronutrients and their relationship with the severity of COVID-19.

Methods

Study design, participants, personal history, and physical examination

This cross-sectional study included middle-aged and older patients with polymerase chain reaction-confirmed COVID-19 who were admitted to the ICU of Imam Khomeini Hospital (Tehran, Iran) between March and June 2020. The study protocol was developed per the Strengthening the Reporting of Observational Studies in Epidemiology Statement [13], and was approved by the ethics committee of the Tehran University of Medical Sciences. Patients who had undergone chemotherapy in the previous 3 mo, those with immunosuppressed diseases (e.g., human immunodeficiency virus), and those who had taken vitamin or mineral supplements within 3 mo before enrollment, were excluded from the study. Data on demographic characteristics and previous underlying diseases were collected. A physical examination was performed to measure weight, height, vital signs, and oxygen saturation. Body mass index (BMI) was calculated. All patients were informed of the purpose and method of the study, and written informed consent was obtained.

The inclusion criteria were age >20 y, both sexes, definitive diagnosis of COVID-19, and agreement to cooperate in the study. The exclusion criteria were patients who had undergone chemotherapy in the previous 3 mo, those with immunosuppressed diseases (e.g., human immunodeficiency virus), and those who had taken vitamin or mineral supplements within 3 mo before enrollment.

Laboratory measurements

All included patients provided blood samples from the antecubital vein for laboratory measurement at the time of admission. Complete blood cell counts and differential counts were determined via a standardized automatic cell counter. CRP was measured using the enzyme-linked immunosorbent assay method. ESR was measured using an automated erythrocyte sedimentation rate analyzer. Serum levels of IL-6, tumor necrosis factor-alpha, and interferon-gamma were measured using an enzyme-linked immunosorbent assay. We measured blood concentrations of vitamins A, B9, B 12, C, E, and D by high-performance liquid chromatography. Minerals, including magnesium, zinc, and iron were measured using a coupled plasma mass spectrometer.

Methods of disease severity assessment

An intensivist physician through www.mdcalc.com measured the Acute Physiology and Chronic Health Evaluation (APACHE), which is a commonly used severity-scoring system, for patients at the time of admission. An APACHE score of ≥25 was considered the high score for mortality [14]. A lung computed tomography (CT) scan was performed and analyzed for the existence of ground-glass opacity or consolidation patterns by a radiologist. Involvement of each lobe was scored as follows: No involvement (score 0), 1% to 25% involvement (score 1), 26% to 49% involvement (score 2), 50% to 75% involvement (score 3), and 76% to 100% involvement (score 4).

Subsequently, individual lobar scores were summed to obtain the overall severity score of the lungs in each patient. The severity of lung involvement in each patient was classified on the basis of overall severity score as follows: No involvement (score 0), minimal involvement (score range, 1–5), mild involvement (score range, 6–10), moderate involvement (score range, 11–15), severe involvement (score range, ≥16) [15,16].

Statistical analysis

Data analyses were performed with IBM SPSS Statistics software, version 17. The normality of variables was assessed with the Kolmogorov–Smirnov test. The results are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Continuous data with normal distribution were compared using the independent *t* test, and data without a normal distribution were compared using the Mann–Whitney U test. Categorical variables were compared using a χ^2 test.

The correlation between serum level of micronutrients and severity of disease was analyzed in different models. A multivariate linear regression analysis was performed to identify an independent association of serum level of micronutrients with APACHE score and CT involvement severity. $P < 0.05$ was considered for statistical significance.

Results

Comparison of demographic data, clinical characteristics, and inflammatory markers between two groups according to APACHE score

Table 1 summarizes the demographic data, clinical characteristics, and inflammatory markers of patients grouped according to APACHE score. In total, 60 patients were enrolled and categorized into two groups at the time of the analysis: APACHE score ≥25 (n = 20) and APACHE score <25 (n = 40).

The median age of patients was 53.50 years (IQR, 12.75 years). Age and sex distributions were comparable between the study groups. Mean BMI and temperature were significantly higher in the group with APACHE score ≥25 compared with the other group (*P* = 0.044 and 0.003, respectively). Oxygen saturation with or without respiratory aid was significantly lower in the group with APACHE score ≥25 compared with the other group (*P* = 0.005 and < 0.001, respectively). The group with APACHE score ≥25 used more invasive respiratory aids compared with the other group and vice versa (*P* = 0.001). There was no significant difference in the frequency of previous underlying diseases between the study groups.

Among the inflammatory markers, serum levels of ESR and CRP were significantly higher in the group with APACHE score ≥25 compared with the other group (*P* = 0.008 and 0.003, respectively). Other inflammatory markers, including IL-6, tumor necrosis factor-alpha, and interferon-gamma showed no significant differences between the study groups. Regarding lung CT involvement, the group with APACHE score ≥25 had a higher severity score and higher prevalence rate of severe involvement compared with the group with APACHE score <25 (*P* < 0.001).

Comparison of serum level of micronutrients between two groups according to APACHE score

Table 2 summarizes the data on serum levels of vitamins and minerals between the two groups. The serum levels of vitamin D and zinc were significantly lower in the group with APACHE score ≥25 compared with the group with APACHE score <25 (*P* < 0.001).

Association of micronutrients with APACHE score and computed tomography involvement severity

Table 3 illustrates the association between serum levels of micronutrients and severity of disease according to APACHE and lung involvement scores. In the multivariate model, serum levels of vitamin D, zinc, and magnesium had an independent and inverse association with APACHE and lung involvement scores after adjustment for confounders.

Table 1
Comparison of demographic and baseline characteristics between groups

Variables	Total	APACHE score <25 (n = 40)	APACHE score ≥25 (n = 20)	P-value
Age, y	53.50 (12.75)	50.00 (16.5)	56.00 (8.50)	0.141
Sex, n				
Male	39	24	15	0.390
Female	21	16	5	
***Body mass index, kg/m^2**	25.90 (2.70)	25.40 (2.58)	26.89 (2.73)	0.044
Temperature,°C	37.53 (0.55)	37.38 (0.46)	37.82 (0.61)	0.003
Respiratory aids, n				
Mask with reserve	16	13	3	0.001
Simple mask	11	10	1	
Nasal aid	5	5	0	
CPAP	5	4	1	
Noninvasive ventilation	2	2	0	
Invasive ventilation	21	6	15	
Underlying disease, n				
Diabetes mellitus	5	5	0	0.057
Asthma	12	5	7	
Thyroid diseases	6	6	0	
Malignancy	19	13	6	
Diabetes mellitus and hypertension	18	11	7	
Oxygen saturation				
With aid	96.00 (2)	96.00 (2.5)	95.00 (2)	0.005
Without aid	89.00 (4.75)	90.00 (3)	87.00 (3)	< 0.001
WBC count, × 109/L	6.95 (7.00)	6.70 (7.98)	7.05 (7.22)	0.931
Neutrophil count, × 109/L	80.20 (11.40)	80.65 (9.22)	79.90 (22.90)	0.456
Lymphocyte count, × 109/L	12.35 (11.00)	12.40 (10.60)	12.25 (15.88)	0.925
Erythrocyte sedimentation rate, mm/hr	63.50 (46)	54.00 (55.25)	85.50 (50)	0.008
***C-reactive protein, mg/L**	87.50 (115.25)	82.50 (87.25)	118.50 (124.75)	0.003
Interleukin-6, pg/mL	189.65 (191.85)	177.70 (164.57)	229.2 (233.97)	0.272
Tumor necrosis factor-alpha, pg/mL	207.7 (211.67)	207.6 (174.04)	248.2 (292.10)	0.410
Interferon-gamma, pg/mL	118.15 (122.50)	82.80 (108.00)	141.7 (237.10)	0.293
CT involvement score	13.00 (9.00)	9.50 (6.00)	18 (3.00)	< 0.001
CT involvement severity, n				
No involvement	0	0	0	< 0.001
Minimal	9	9	0	
Mild	17	17	0	
Moderate	27	14	13	
Severe	7	0	7	

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; CPAP, continuous positive airway pressure; CT, computed tomography; WBC, white blood cell count
*Normally distributed variables

Table 2
Comparison of serum levels of micronutrients between groups

Variables	Total	APACHE scor e <25	APACHE score ≥25	P-value
Vitamin A, mcmol/L	0.25 (0.40)	0.30 (0.37)	0.20 (0.39)	0.841
Vitamin B9, mcg/L	8.20 (8.37)	9.10 (8.87)	6.05 (7.75)	0.147
Vitamin B12, pg/mL	374.3 (541.05)	429.40 (564.3)	260.75 (546.25)	0.117
Vitamin C, mg/dL	0.40 (0.60)	0.40 (0.50)	0.25 (0.27)	0.063
Vitamin D, ng/mL	28.95 (13.39)	33.38 (13.26)	20.08 (8.49)	< 0.001
Vitamin E, mcg/mL	7.45 (6.65)	7.75 (7.22)	7.30 (6)	0.406
Magnesium, mg/dL	1.90 (0.40)	2 (0.85)	1.80 (0.10)	0.060
Zinc, mcg/dL	70.00 (44.5)	80.00 (32.75)	50.50 (18)	< 0.001
Iron, mcg/dL	48.00 (36.75)	52.00 (38.75)	38.00 (27)	0.249

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation

Comparison of serum level of micronutrients with minimum of serum reference values

This study showed that the mean or median of serum levels of micronutrients was significantly lower than the expected minimum serum levels, except for zinc and vitamin A (Table 4).

Discussion

We evaluated and compared the serum levels of micronutrients to the minimum normal range, and demonstrated that, except for vitamin A and zinc, serum levels of other micronutrients were significantly lower than normal in patients with COVID-19 who were admitted to the ICU. Furthermore, we assessed the association between these micronutrients and the severity of disease, and our results showed that lower serum levels of vitamin D, zinc, and magnesium were significantly and inversely correlated with a higher severity score, independent of confounding factors. A crucial challenge for researchers and experts is to identify the predictive factors involved in the higher severity of COVID-19 in terms of determining therapeutic goals to improve survival, especially in critically ill patients.

Critical ill patients experience several metabolic changes that increase the provision of nutrients to the vital tissues and the

Table 3
Multivariate linear regression analysis to identify the independent association of serum level of micronutrients with APACHE score and severity of CT involvement

Micronutrients	APACHE score		CT involvement severity score	
	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value
Vitamin A, mcmol/L	3.673 (−1.553 to 8.899)	0.164	1.742 (−2.025 to 5,509)	0.357
Vitamin B9, mcg/L	0.150 (−0.072 to 0.373)	0.181	0.073 (−0.088 to 0.233)	0.367
Vitamin B12, pg/mL	0.004 (0.000–0.008)	0.056	0.002 (−0.004 to 0.005)	0.096
Vitamin C. mg/dL	1.481 (−1.975 to 4.937)	0.394	0.933 (−1.535 to 3.401)	0.451
Vitamin D, ng/mL	−0.157 (−0.251 to −0.063)	0.001	−0.111 (−0.178 to −0.044)	0.002
Vitamin E, mcg/mL	0.004 (−0.040 to 0.049)	0.849	0.012 (−0.237 to 262)	0.921
Mg, mg/dL	−2.578 (−4.868 to −0.287)	0.028	−1.688 (−3.334 to −0.042)	0.045
Zinc, mcg/dL	−0.096 (−0.147 to −0.045)	< 0.001	−0.082 (−0.119 to −0.046)	< 0.001
Iron, mcg/dL	0.021 (−0.040 to 0.083)	0.491	0.001 (−0.043 to 0.045)	0.971
Body mass index, kg/m^2	0.123 (−0.264 to 0.511)	0.526	0.072 (−0.212 to 0.355)	0.355

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; CI, confidence interval; CT, computed tomography
*Adjusted for body mass index, temperature, respiratory aids, oxygen saturation, erythrocyte sedimentation rate, C-reactive protein, vitamin D (except for vitamin D model), zinc (except for zinc model), and micronutrients, including Vitamin C, D, zinc, magnesium (only for body mass index model)

Table 4
Comparison of serum levels of micronutrients to the minimum level of normal range

Variables	Total	Normal range	*P*-value*
Vitamin A, mcmol/L	0.25 (0.40)	0.3–0.8	0.203
Vitamin B9, mcg/L	8.20 (8.37)	3–17	< 0.001
Vitamin B12, pg/mL	374.3 (541.05)	160–950	< 0.001
Vitamin C, mg/dL	0.40 (0.60)	0.6–2	0.003
Vitamin D, ng/mL	28.95 (13.39)	> 20	< 0.001†
Vitamin E, mcg/mL	7.45 (6.65)	5–18	< 0.001
Magnesium, mg/dL	1.90 (0.40)	1.7–2.2	< 0.001
Zinc, mcg/dL	70.00 (44.5)	70–120	1.00
Iron, mcg/dL	48.00 (36.75)	60–70	< 0.003

*Sign test
†One sample *t* test

chances of survival, such as the release of pituitary hormones, stimulation of the sympathetic nervous system, and antioxidant depletion [17,18]. Micronutrients, classified as vitamins or minerals, have an essential role in intermediaries in metabolism, wound healing, immune function, antioxidant activity, cellular differentiation and proliferation, antioxidant activity, and blood coagulation. Micronutrient needs are elevated during acute illness because of increased demands and losses [19].

Various factors, including advancing age [20–22], increasing inflammatory markers (e.g., CRP) [21,23], and comorbidities (e.g., diabetes mellitus and cardiovascular disease) [21,22], have been shown to be related to higher severity and mortality rate for COVID-19.

The role of nutritional status in the modulation of immune system function has been previously elucidated and affects outcomes in infectious diseases [24]. A few numbers of studies focused on the role of micronutrient deficiencies in the prognosis of patients with COVID-19. The result of a systematic review and meta-analysis showed that vitamin D deficiency, especially in elderly subjects, is associated with higher severity of disease and mortality among patients with COVID-19 [25]. This result has been hypothesized to be related to the higher inflammatory response in vitamin D-deficient patients, which confronts the patient with severe disease [26].

Our results reinforced this hypothesis, but found that the serum level of vitamin D was not lower than the normal lower serum levels of vitamin D and are independently associated with higher severity of COVID-19 according to APACHE and lung CT involvement scores. Vitamin C deficiency is another nutritional status that has received little attention as a potential cause of disease severity. A pilot study by Arvinte et al. [27] found that vitamin C deficiency, besides advancing age, is a potential predictor of mortality among ICU-admitted patients with COVID-19. Also, the beneficial effects of vitamin C administration on critically ill patients have been previously elucidated, probably due to its potential immunomodulatory and antiinflammatory effects [28]. However, levels of vitamin C were lower than normal in our patients, and the results did not show an independent association between lower serum level of vitamin C and higher severity scores.

Although the regulatory effects of vitamin A, different types of vitamin B, and vitamin E on the immune system have been proven [7,29], no study specifically has focused on the association between the levels of these vitamins and the prognosis of patients with COVID-19. We evaluated the serum levels of these vitamins, and found no significant values in predicting disease severity.

The immunomodulatory effects of minerals in infectious disease have been shown in several studies [7,29]; however, few studies have focused on patients with COVID-19. Several studies found that zinc deficiency in patients with COVID-19 is associated with a higher rate of complications, hospitalizations, and mortality compared with patients with a sufficient level of zinc [30–33]. We also showed that zinc deficiency is independently correlated with higher severity of COVID-19 based on both APACHE and CT involvement scores. Studies on deficiencies of other minerals in patients with COVID-19 are scarce. We showed an independent and inverse association of serum magnesium levels with a higher severity score, but no association was found between iron deficiency and severity of COVID-19.

Several potential limitations in this study should be considered. First, this is a single-center study with a small number of cases, which limits further analysis with more controlling confounders. Second, given the cross-sectional design of our study, the causality of the association cannot be detected. On the other hand, some conditions, such as the use of vasoactive drugs, hypermetabolism of critically ill patients, and need for mechanical ventilation that increases required micronutrients, are other limitations of the study.

Overall, our results reinforce the evidence that serum levels of vitamin D, zinc, and magnesium are independently associated with the severity of COVID-19. Randomized clinical trials are recommended to identify the effectiveness of micronutrient supplements on improving the prognosis of severe cases of patients with COVID-19. Evidence has reported that intake of some nutrients may require an increase in particular conditions, such as infection, compare with regular conditions [34–36]. In this way, some evidence found that supplementation may modify the severity of immune response and inflammatory process, and improve the survival of infectious diseases [7,37,38], although due to insufficient studies, no definite conclusion can be made in this regard.

Conclusions

Low serum levels of some micronutrients, such as B9, B12, vitamins C and D, magnesium, and iron, were observed in patients with COVID-19. Furthermore, lower levels of vitamin D, zinc, and magnesium were correlated with more severe disease. We recommend identifying and addressing the deficiency of micronutrients that could be involved in immune system responses to prevent severe COVID-19 disease.

CRediT author statement

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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