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## Serum trace elements levels and clinical outcomes among Iranian COVID-19 patients

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## ABSTRACT

**Objectives:** The relationship between immunity and trace elements levels is well known. We aimed to estimate the association of serum trace elements with severity and outcomes in the Coronavirus Disease-2019 (COVID-19) patients.

**Methods:** In this single-centered, prospective, observational study, we enrolled 114 patients admitted to severe intensive care units (ICUs) and corresponding 112 sex and aged-matched non-ICU ward patients. Demographic data, clinical characteristics, and outcomes were all collected. We analyzed serum levels of zinc (Zn), copper (Cu), selenium (Se), and manganese (Mn) in both severity groups.

**Results:** The serum levels of Cu, Se, and Mn in both groups were within the normal range while Zn serum levels were lower than normal values. Based on these findings, Zn, Cu, Se, and Mn serum levels were not associated with disease severity ( $P > 0.05$ ), while we found Zn serum levels were strongly associated with patient outcomes ( $P = 0.005$ ). Our results indicated lower Mn serum levels were associated with age more than 55 years ( $P = 0.006$ ). Our results were not in favor of a causal relationship between serum trace elements levels and disease severity.

**Conclusion:** We found Zn level to be a strong indicator for patients' outcomes that can be considered for monitoring patient prognosis. Nutritional measures or supplementation can help reduce poor outcomes caused by low Zn levels in Iranian COVID-19 patients.

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## Introduction

Human beings have experienced three major epidemics caused by coronaviruses including Severe Acute Respiratory Syndrome (SARS-2003), Middle East Respiratory Syndrome (MERS-2012), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV 2), which has infected more than 155 million, killing over 3.2 million people globally as of May 5, 2020 (Morfeld et al., 2021,

Organization, 2020). COVID-19 first appeared in December 2019 in Wuhan, China, and is now considered a public health emergency of international concern. SARS-CoV-2 genome consists of a positive-sense single-stranded RNA virus linked with a nucleoprotein inside a capsid containing matrix protein as well as a hemagglutinin-esterase (HE) protein found on some coronaviruses (Jiang et al., 2020, Khaerunnisa et al., 2020, Organization, 2020, Wu et al., 2020). The clinical manifestations of the disease usually include fever, headache, cough, gastrointestinal manifestations such as diarrhea, vomiting, and abdominal pain, and dyspnea. The acute coronavirus infectious disease is characterized by pneumonia, lymphocytopenia, exhaustion of lymphocytes, and cytokine storm syndrome in severe forms of COVID-19 that is manifested with increased plasma levels of cytokines (IL2, IL7, and IL10), granulocyte colony-stimulating factor (G-CSF), 10 kD interferon-gamma-induced protein (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory pro-

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tein 1- $\alpha$  (MIP1A), and interferon-alpha (TNF- $\alpha$ ) (Dietz and Santos-Burgoa, 2020, Kong et al., 2020, Wong et al., 2020).

Several micronutrients including vitamins and trace elements are required for the normal functioning of the immune system to protect the cells from oxidative stress (Lee et al., 2019). The major trace elements viz selenium (Se), zinc (Zn), copper (Cu), and manganese (Mn) holding immunomodulatory effects are components of antioxidant enzymes that can inhibit viral replication in the host cells and therefore have antiviral activity (Chaturvedi et al., 2004, Jayawardena et al., 2020). Unbalanced dietary habits may predispose individuals to viruses and other infections (Thurnham, 1997). Maintaining adequate micronutrient balance may boost the host's immune response and protect him/her against viral infections (Razzaque, 2020). Assessing trace elements levels in COVID-19 patients can provide a more robust and comprehensive approach for combating this devastating disease.

## Materials and Methods

### Patients

This prospective, cohort, observational study was conducted at Imam Reza hospital of Tabriz University of Medical Sciences, Tabriz, Iran. A total of 226 COVID-19 patients, confirmed by the nasopharyngeal swab tested with reverse transcription polymerase chain reaction (admitted from October 10 to December 10, 2020), were enrolled in the study. Pregnant patients and patients taking any form of dietary supplements/multivitamins or trace elements were excluded from the study. Patients were categorized into two groups: severe and non-severe patients based on the intensive care unit (ICU) and non-ICU ward hospitalization. Each severity group was individually matched for age and sex. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (Ref No: IR.TBZMED.REC.1399.711). All the procedures involving human samples conformed to the principles outlined in the Declaration of Helsinki. Participation was voluntary, and written informed consent was obtained from all patients or their legal guardians.

### Blood collection and trace elements measurement

Eight milliliters of blood were collected from each participant. After centrifugation for 10 min at 3000 g, 4 mL serum was obtained. Two mL of serum was used for determining Se and Mn concentrations, and the remaining 2 mL was used for Zn and Cu measurement. All necessary precautions were taken in the handling of the specimens collected as per standard laboratory guidelines considering COVID-19 complications. We measured serum Zn and Cu by Randox colorimetric assays (Randox Laboratories Ltd., Crumlin, UK). The reference range for serum Cu was 70–140  $\mu\text{g/dL}$ , and for Zn was 72.6–127  $\mu\text{g/dL}$  in men and 77.0–114  $\mu\text{g/dL}$  in women according to the kit instruction manual. Serum Se and Mn concentrations were determined by graphite furnace atomic absorption spectrophotometry (GFAAS), which is a type of atomic spectroscopic technique as described (Krawczyk-Coda, 2019). Serum levels ranging from 0.6 to 4.3  $\mu\text{g/L}$  were considered normal reference values for Mn (Flora, 2014). Regarding Se, normal reference values were considered to be 70 to 150  $\mu\text{g/L}$ , the most reference values given in the literature.

### Statistical analysis

Statistical analysis was performed using IBM SPSS version 21.0 (IBM SPSS Statistics, ARMONK, New York, USA). Data were expressed as mean  $\pm$  standard deviation (SD) for continuous variables or numbers, whereas categorical variables were described

as their respective percentages. The difference in serum trace elements levels between subgroups was analyzed using one-way analysis of variance (ANOVA) and unpaired t-tests. Moreover, Pearson's chi-squared test was used to analyze the significance of association between categorical variables. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

The demographic and clinical characteristics of the participants are presented in Table 1. The mean ages of patients in ICU and non-ICU ward groups were  $56 \pm 20.6$  and  $56.7 \pm 16.3$  years, respectively. Comparison of major symptoms between ICU and non-ICU ward patients showed no significance except for chest pain, fever, and lower chest wall indrawing ( $< 0.05$ ). Five patients in the non-ICU ward group had conjunctivitis. Moreover, none of the patients with COVID-19 showed skin rash or ulcers, lymphadenopathy, or hemorrhage. In comparison with non-ICU ward patients, the ICU cases had elevated heart rate ( $94.62 \pm 1.58$  vs.  $87.88 \pm 1.57$ ) with low oxygen saturation level ( $76.05 \pm 1.08$  vs.  $81.7 \pm 0.88$ ) that was significant ( $P < 0.05$ ). The difference between the two severity groups for the remaining cardiovascular parameters was not statistically significant. The ICU cases also showed a significantly higher frequency of obesity (9 (81.81%) vs. 2 (18.18%),  $P = 0.049$ ) and dementia (20 (76.92%) vs. 6 (23.07%),  $P = 0.005$ ). Other comorbidities among both severity groups were not significant. The serum levels of trace elements in patients are presented in Table 2. Cu and Zn levels were found to be  $95.74 \pm 1.25$  and  $67.87 \pm 1.12$   $\mu\text{g/dL}$ , respectively. Se and Mn levels were reported  $126.61 \pm 2.05$  and  $2.58 \pm 0.069$   $\mu\text{g/L}$ , respectively. Our findings indicated that in ICU patients compared to non-ICU ward patients, serum Zn levels ( $67.3 \pm 1.79$  vs.  $68.42 \pm 1.35$ ,  $P = 0.619$ ) and Cu levels ( $94.58 \pm 1.97$  vs.  $96.88 \pm 1.57$ ,  $P = 0.362$ ) were low though the difference was not significant. The serum values for Se and Mn in both groups were reported as  $130.19 \pm 3.19$  versus  $123.06 \pm 2.58$  ( $P = 0.084$ ) and  $2.68 \pm 0.11$  versus  $2.49 \pm 0.08$  ( $P = 0.167$ ), respectively, but the difference was not significant. According to our data, low Zn levels ( $69.66 \pm 1.34$  vs.  $62.43 \pm 1.81$ ,  $P = 0.005$ ) were found to be associated with death among COVID-19 patients (Table 3). Cu, Se, and Mn values were not associated with patient outcomes (Table 3). During this study, 170 (75.22%) patients were discharged from the hospital and 56 (24.78%) patients died. Of the 56 deaths, 27 (48.2%) were female and 29 (51.8%) were male. Regarding the association of trace elements with age variable, a significant difference was found in Mn levels of patients aged  $< 55$  and  $> 55$  years ( $2.80 \pm 1.11$  vs.  $2.38 \pm 0.90$ ,  $P = 0.006$ ). For the remaining, this association was not significant (Table 4). Cu and Se levels did not display any difference between males and females ( $P > 0.05$ ). Zn levels were significantly higher in men than women ( $71.36 \pm 18.83$  vs.  $64.31 \pm 13.80$ ,  $P = 0.002$ ) and Mn levels were significantly lower in men compared to women ( $2.44 \pm 0.96$  vs.  $2.72 \pm 1.07$ ,  $P = 0.047$ ) (Table 5).

## Discussion

The latest evidence on coronaviruses indicates that nutritional and metabolic derangements are associated with disease severity and susceptibility to infection (Jayawardena et al., 2020, Lv et al., 2020, Singer, 2021, Zeng et al., 2021). In this study, we measured serum trace elements status in severe and non-severe COVID-19 patients. Based on the findings, Zn, Cu, Se, and Mn levels were not associated with COVID-19 severity while Zn level was strongly associated with patient outcomes.

Zn is needed for the proliferation and function of NK cells, macrophages, neutrophils, T and B cells, production of cytokines, and inhibition of reactive oxygen species (Iddir et al., 2020, Rahman and Iddir, 2020). Due to its direct antiviral properties, Zn

**Table 1**  
Demographic and clinical characteristics of the patients with COVID-19

Parameter		All patients (n=226)	ICU group (n = 112)	Non-ICU group (n= 114)	P-value
Sex	Male	114	56 (50%)	58 (50.9)	0.895
	Female	112	56 (50%)	56 (49.2)	
Age (mean ± SD)		56.36 ± 18.54	56 ± 20.6	56.72 ± 16.3	0.34
Outcome	Deceased	56 (24.8%)	38 (33.9%)	18 (15.8%)	0.002
	Recovered	170 (75.2%)	74 (66.1%)	96 (84.2%)	
Initial symptoms	HR (beats per minute)	91.2 ± 1.12	94.62 ± 1.58	87.88 ± 1.57	0.003
	RR (breaths per minute)	21.81 ± 0.44	22.01 ± 0.52	21.57 ± 0.73	0.622
	Systolic BP (mmHg)	123.16 ± 1.35	124.33 ± 2.21	122.2 ± 1.64	0.439
	Diastolic BP (mmHg)	75.17 ± 0.9	74.5 ± 1.54	76.04 ± 1	0.405
	Oxygen saturation (spo2)	78.91 ± 0.71	76.05 ± 1.08	81.7 ± 0.88	0.000
	Fever	74	27 (37.5%)	45 (62.5%)	0.013
	Coughing	183	92 (51.39%)	87 (48.6%)	0.281
	Coughing with sputum production	17	5 (29.41%)	12 (70.58%)	0.084
	Coughing; bloody sputum/haemoptysis	10	6 (66.6%)	3 (33.3%)	0.295
	Sore throat	132	62 (48%)	67 (52%)	0.604
	Runny nose (Rhinorrhoea)	66	31 (47%)	35 (53%)	0.617
	Ear pain	25	16 (64%)	9 (36%)	0.126
	Wheezing	78	43 (56.57%)	33 (43.42%)	0.133
	Chest pain	144	78 (55.31%)	63 (44.68%)	0.026
	Myalgia	200	99 (50.25%)	98 (49.74%)	0.585
	Arthralgia	147	41 (27.89%)	106 (72.1%)	0.169
	Fatigue	187	94 (50.81%)	91 (49.18%)	0.423
	Dyspnea	216	110 (50.92%)	106 (49.07%)	0.605
	Lower chest wall indrawing	76	55 (74.32%)	19 (25.67%)	0
	Headache	121	60 (50.42%)	59 (49.57%)	0.784
	Abdominal pain	54	25 (46.29%)	29 (53.7%)	0.583
	Vomiting/Nausea	92	44 (48.35%)	47 (51.64%)	0.766
	Diarrhoea	15	6 (40%)	9 (60%)	0.444
	Conjunctivitis	5	0 (0%)	5 (100%)	0.025
	Skin rash	0	0	0	
	Skin ulcer	0	0	0	
	Lymphadenopathy	0	0	0	
	Bleeding/Haemorrhage	0	0	0	
Comorbidities	Chronic cardiac disease	46	26 (57.7%)	19 (42.2%)	0.218
	Obesity	11	9 (81.81%)	2 (18.18%)	0.049
	Chronic pulmonary disease	17	9 (56.25%)	7 (43.75%)	0.579
	Diabetes without complications	31	11 (35.48%)	20 (64.51%)	0.092
	Diabetes with complications	17	11 (68.75%)	5 (29.41%)	0.111
	Asthma	12	7 (63.63%)	4 (36.36%)	0.390
	Chronic kidney disease	55	38 (70.37%)	16 (29.62%)	0
	Rheumatic disorder	3	2 (66.66%)	1 (33.33%)	0.551
	Moderate or severe liver disease	4	3 (75%)	1 (25%)	0.556
	Mild liver disease	11	4 (36.36%)	7 (63.63%)	0.206
	Dementia	26	20 (76.92%)	6 (23.07%)	0.005
	Chronic neurological disorder	8	1 (12.5%)	7 (87.5%)	0.427
	Smoking	51	27 (52.94%)	24 (47.05%)	0.848
	Malignant neoplasm	6	2 (33.33%)	4 (66.66%)	0.420
	Chronic hematologic disease	6	2 (33.33%)	4 (66.66%)	0.420
Other relevant risk factor (Hypertension)	79	45 (56.96%)	34 (43.03%)	0.103	

Categorical data such as sex and outcome are represented as n (%). All other data are represented as mean ± SD.

**Table 2**  
Serum levels of Zn, Cu, Se, and Mn in patients with COVID-19 (severe and non-severe groups)

Elements	Normal range	Severity group			P-value
		All	ICU	Non-ICU	
Cu	70–140 µg/dL	95.74 ± 1.25	94.58 ± 1.97	96.88 ± 1.57	0.362
Zn	Men: 72.6–127 Women: 77.0–114 µg/dL	67.87 ± 1.12	67.3 ± 1.79	68.42 ± 1.35	0.619
Se	70 to 150 µg/L	126.61 ± 2.05	130.19 ± 3.19	123.06 ± 2.58	0.084
Mn	0.6 to 4.3 µg/L	2.58 ± 0.069	2.68 ± 0.11	2.49 ± 0.08	0.167

P-values are for comparison between ICU and non-ICU ward groups. Cu: copper, Zn: zinc, Se: selenium, Mn: manganese.

is beneficial for disease prevention. Development and maintenance of both innate and adaptive immune systems require proper intake of Zn; hence its deficiency causes dysfunction in lymphocyte maturation, impairment in cellular communication by cytokines, and weakness in innate immunity (Maare and Haase, 2016). Our findings showed Zn serum levels in both severity groups were less than the normal reference range and were strongly associated with patients' mortality, indicating a potential role for Zn in COVID-19 pathogenesis. In addition, we found gender differences in serum Zn levels among COVID-19 patients.

Se is an important component of some enzymes and works together with vitamin E to prohibit free radicals production (Jamaati et al., 2020). Se deficiency negatively impacts immune system function and increases viral replication and mutation rates (Harthill, 2011). Recently, lower Se levels have been reported to be associated with COVID-19 (Majeed et al., 2021) and also with the mortality risk of patients (Moghaddam and Heller, 2020). Our findings were not in agreement with those reports. We found a positive trend between Se levels and ICU patients. It seems that the critically ill patients possibly received Se supplement before

**Table 3**  
Serum trace elements levels by patients' outcomes (recovered vs. deceased)

Elements	Outcomes		P-value
	Recovered	Deceased	
Cu	95.12 ± 1.43	97.64 ± 2.63	0.389
Zn	69.66 ± 1.34	62.43 ± 1.81	0.005
Se	125.77 ± 2.41	129.15 ± 3.91	0.481
Mn	2.59 ± 0.07	2.57 ± 0.14	0.900

Cu: copper, Zn: zinc, Se: selenium, Mn: manganese.

**Table 4**  
Cu, Zn, Se, and Mn serum levels by age groups

Elements	Age (years)		P-value
	< 55 (n = 109)	≥ 55 (n = 117)	
Zn	68.7 ± 16.18	67.1 ± 17.51	0.36
Cu	96.01 ± 21.55	95.5 ± 16.215	0.67
Mn	2.8047 ± 1.11801	2.38 ± 90	0.006
Se	128.92 ± 34.01	124.48 ± 27.37	0.23

Zn: zinc, Cu: copper, Mn: manganese, Se: selenium.

**Table 5**  
Serum trace elements levels by sex

Elements	Age (years)		P-value
	Male (n = 114)	Female (n = 112)	
Zn	71.36 ± 18.83	64.31 ± 13.80	0.002
Cu	97.77 ± 17.47	93.69 ± 20.19	0.106
Mn	2.44 ± 96	2.72 ± 1.07	0.047
Se	128.40 ± 31.29	124.80 ± 30.23	0.382

Zn: zinc, Cu: copper, Mn: manganese, Se: selenium.

admission to ICU ward that were not recorded due to the recall bias.

Cu is an essential trace element that is needed for protecting DNA from oxidative stress (Karimi et al., 2015, Karimi et al., 2019, Uriu-Adams and Keen, 2005). Cu deficiency is associated with immune system dysfunction, enhanced rate of infections, and TNF- $\alpha$ -induced lung chronic inflammation (Bonham et al., 2002, Liu et al., 2016). Cu can also inhibit RNA replication in COVID-19 (Andreou et al., 2020). In the current study, the patients' Cu values fell within the normal range and were not associated with disease severity, patient outcome, sex, and age.

Mn plays an essential role in many cellular processes including enzymatic function (Kehl-Fie and Skaar, 2010). There is little information regarding Mn effect on immune development and COVID-19 pathogenesis. In a recently published study, liver dysfunction in severe COVID-19 was suspected to be associated with higher urinary Mn levels (Zeng et al., 2021). Our results indicated lower Mn levels were associated with age more than 55 years, indicating feeding this group with a low Mn diet and a possible susceptibility to disease.

## Conclusion

On the whole, our results were not in favor of a causal relationship between trace elements levels and disease severity. We identified Zn level as a strong indicator for patients' outcomes that can be considered for monitoring of patients' prognosis. Future studies on a larger population regarding trace elements levels at hospital admission time and after hospitalization would be valuable and helpful in the evaluation of the dynamic changes in patients with COVID-19. Finally, nutritional measures or supplementation may help reduce poor outcomes caused by this virus in Iranian patients.

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## Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (Ref No: IR.TBZMED.REC.1399.711).

## Availability of data and materials

All data are available via the corresponding author.

## Authors' contributions

A.K. and A.S.: Conceptualization and design of the study; A.K., O.B., Y.Y., M.M., A.M.K., and M.K.: Acquisition of data, analysis, and interpretation of data; O.B., Y.Y., and A.K.: Drafting the article; A.K. and A.S.: Critical revision of the article for important intellectual content.

## Conflicts of interest

The authors have no conflicts of interest to declare relevant to the content of this article.

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