

Association Between Serum Zinc Levels and Clinical Outcomes in Diabetic Patients Hospitalized With COVID-19: A Retrospective Study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with significant morbidity and mortality, particularly in patients with underlying conditions such as diabetes mellitus. Zinc is an essential trace element with important immunomodulatory and antiviral properties, and zinc deficiency has been suggested to worsen outcomes in viral respiratory infections. However, the relationship between serum zinc levels and clinical outcomes in diabetic patients with COVID-19 remains insufficiently explored.

Methods: This retrospective descriptive–analytical study was conducted on 158 diabetic patients hospitalized with confirmed COVID-19 at Shahid Sadoughi Hospital, Yazd, Iran. COVID-19 diagnosis was confirmed using RT-PCR and/or chest CT scan. Serum zinc levels were obtained from medical records, and patients were categorized into low zinc (<50 $\mu\text{g/dL}$) and normal zinc (50 – 70 $\mu\text{g/dL}$) groups. Clinical outcomes including ICU admission, intubation, length of hospital stay, and mortality were compared. Statistical analysis was performed using SPSS version 26.

Results: Patients with low serum zinc levels were significantly older than those with normal zinc levels ($p = 0.001$). ICU admission (26.3% vs. 12.8% , $p = 0.034$) and mortality (27.5% vs. 7.7% , $p = 0.001$) were significantly higher in the low zinc group. Low serum zinc was associated with increased odds of ICU admission ($\text{OR} = 2.42$) and death ($\text{OR} = 4.55$). No significant differences were observed in intubation rates or length of hospital stay.

Conclusion: Low serum zinc levels were associated with worse clinical outcomes, including higher ICU admission and mortality rates, in diabetic patients hospitalized with COVID-19. Assessment and correction of zinc deficiency may be beneficial in this high-risk population.

Introduction

In late December 2019, physicians in Wuhan, China, identified a cluster of patients presenting with pneumonia of unknown origin, which was later linked to exposure at a seafood and live animal market in the city (1). Following extensive investigations, the Chinese Centers for Disease Control and Prevention officially confirmed on January 9, 2020, that the causative agent was a novel coronavirus, initially named 2019-nCoV (2). One day later, the first genomic sequence of the virus was published online by Zhang and colleagues at Fudan University in Shanghai (3). By mid-January 2020, 62 cases had been reported within China and three additional cases were identified outside China, including two in Thailand and one in Japan. Due to the rapid increase in cases and global spread of the virus, the World Health Organization (WHO) declared the outbreak the sixth Public Health Emergency of International Concern on January 30, 2020, and officially named the disease Coronavirus Disease 2019 (COVID-19) on February 11, 2020. On the same day, the International Committee on Taxonomy of Viruses renamed the virus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) ((2),(4–6)).

The incubation period of COVID-19, defined as the time interval between viral exposure and onset of clinical symptoms, was initially reported to be approximately five days, with a range of four to seven days (7). However, different organizations have reported varying incubation periods; the WHO estimated a range of 2–10 days, the Chinese National Health Commission reported 10–14 days, and the United States Centers for Disease Control and Prevention reported a range of 2–14 days (8). Clinically, COVID-19 infection commonly presents with nonspecific symptoms such as malaise, fatigue, myalgia, fever, and dry cough. Gastrointestinal symptoms including nausea, vomiting, and diarrhea may precede fever in some patients. A minority of patients may experience headache, hemoptysis, or remain asymptomatic. In a study conducted in Wuhan involving 41 patients with confirmed COVID-19, fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%) were reported as the most prevalent clinical manifestations (9).

The global COVID-19 pandemic has prompted urgent investigation into pharmacological, traditional, complementary, and integrative medical (TCIM) approaches aimed at preventing infection, reducing disease severity, and improving recovery outcomes (3). Among the various supplements under investigation, zinc has received considerable attention. Zinc is an essential trace element with potent immunomodulatory and antiviral properties. Acting as a cofactor, signaling molecule, and structural component, zinc plays a critical role in numerous biological processes, including carbohydrate and lipid metabolism, as well as reproductive, cardiovascular, and nervous system function (4). Notably, zinc is vital for immune system regulation, influencing leukocyte and lymphocyte proliferation, differentiation, maturation, and function (5). Zinc also modulates inflammatory responses through intracellular signaling pathways (6) and is considered a key component of nutritional immunity (7). Alterations in zinc homeostasis significantly affect immune responses and may increase susceptibility to infectious and inflammatory diseases such as acquired immunodeficiency syndrome, measles, malaria, tuberculosis, and pneumonia (8). Previous studies have demonstrated an association between zinc status and the incidence of respiratory tract infections in both children and adults ((9),(10)).

Zinc deficiency is highly prevalent, particularly in developing countries, and is associated with an increased risk of infectious diseases such as pneumonia, diarrhea, and malaria (11). Recommended daily zinc intake ranges between 8 and 11 mg for adults, with therapeutic doses reported between 3 and 16 mg in clinical settings (12). Zinc supplementation has been shown to significantly reduce mortality in patients with severe pneumonia (13). Additionally, chloroquine derivatives have been identified as zinc ionophores that facilitate intracellular zinc uptake into lysosomes (11). The antiviral effects of zinc have been widely studied in various viral infections, including coronaviruses, hepatitis C virus, and human immunodeficiency virus (13). Proposed antiviral mechanisms include inhibition of viral RNA synthesis, topoisomerase activity, and viral replication (12). Despite these findings, the precise role of zinc in SARS-CoV-2 infection remains insufficiently explored. Currently, no definitive curative treatment for COVID-19 exists, and management relies on a multimodal approach involving corticosteroids, antiviral agents, and anticoagulant therapy. Although zinc supplementation is increasingly recommended in COVID-19 treatment protocols (11), it remains unclear whether hospitalized patients with COVID-19 truly exhibit zinc deficiency.

Given the global burden of COVID-19, its high daily mortality rate, the absence of definitive treatment, and the prolonged timeline required for widespread vaccination, investigating the potential benefits of low-cost and accessible interventions such as zinc supplementation is of critical importance. Even modest improvements in clinical outcomes may contribute significantly to patient survival. Therefore, this study aimed to evaluate the association between serum zinc levels and clinical outcomes in diabetic patients hospitalized with COVID-19 at Shahid Sadoughi Hospital in Yazd, Iran. Demonstrating a relationship between normal serum zinc levels and improved clinical outcomes could support the inclusion of zinc supplementation in the management of COVID-19 patients with zinc deficiency, particularly in high-risk populations such as individuals with diabetes mellitus.

Materials and Methods

Study Design

This study was a descriptive–analytical retrospective investigation conducted to assess the association between serum zinc levels and clinical outcomes in diabetic patients with COVID-19 who were hospitalized at Shahid Sadoughi Hospital in Yazd, Iran. The retrospective design enabled evaluation of patient outcomes using existing medical records without any intervention.

Participants

The study population consisted of hospitalized patients with confirmed COVID-19 and a concurrent diagnosis of diabetes mellitus whose serum zinc levels had been measured during hospitalization. The sample size was determined using the Cochran formula with a 95% confidence level, an estimated proportion of $p = 0.7$, and a margin of error of $d = 0.1$, resulting in a calculated sample size of 160 patients. A total of 158 eligible patients were ultimately included in the study. Inclusion criteria were confirmed COVID-19 infection, diagnosis of diabetes mellitus, and availability of serum zinc measurements. Exclusion criteria included discharge or death within the first 24 hours of admission, use of zinc supplements during the previous month, and presence of comorbid conditions other than diabetes mellitus.

COVID-19 Detection and Zinc Evaluation: COVID-19 infection was confirmed by an internal medicine or infectious disease specialist using reverse transcription polymerase chain reaction (RT-PCR) testing and/or chest computed tomography (CT) scan findings. Serum zinc levels were extracted from hospital laboratory records. Based on laboratory reference values, patients were classified into two groups: low serum zinc ($< 50 \mu\text{g/dL}$) and normal serum zinc ($50\text{--}70 \mu\text{g/dL}$). Data were retrospectively collected using a researcher-designed checklist that included demographic variables, serum zinc levels, and clinical outcomes such as length of hospital stay, ICU admission, need for intubation, and mortality.

Ethical Considerations: The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd (ethics code: IR.SSU.MEDICINE.REC.1402.276). Given the retrospective nature of the study and the lack of any therapeutic intervention, informed consent was not

required. All patient data were anonymized and treated as strictly confidential, and the information was used exclusively for research purposes.

Statistical Analysis

Statistical analyses were performed using SPSS software version 26. Qualitative variables were analyzed using the Chi-square test, while quantitative variables were compared using the independent samples t-test. Continuous data were reported as mean $\pm$ standard deviation, and categorical data were expressed as frequencies and percentages. A p-value of less than 0.05 was considered statistically significant.

Results

This retrospective study evaluated the association between serum zinc levels and clinical outcomes in hospitalized diabetic patients with COVID-19 at Shahid Sadoughi Hospital, Yazd. Patients were categorized into two groups based on serum zinc levels: low zinc ($< 50 \mu\text{g/dL}$) and normal zinc ($50\text{--}70 \mu\text{g/dL}$). Clinical outcomes including ICU admission, intubation, length of hospital stay, and mortality were compared between the two groups. A total of 158 patients were included in the study, of whom 78 (49.4%) were male and 80 (50.6%) were female. The mean age of the participants was 66.56 ± 12.4 years (range: 40–90 years). Overall, 31 patients (19.6%) were admitted to the intensive care unit (ICU), 14 patients (8.9%) required intubation, and 28 patients (17.7%) died during hospitalization. The mean serum zinc level was $48.52 \pm 11.32 \mu\text{g/dL}$, and the mean length of hospital stay was 6.85 ± 5.69 days (Table 1).

There was no significant difference in sex distribution between patients with low and normal serum zinc levels ($p = 0.63$). However, the mean age of patients with low zinc levels (72.27 ± 11.74 years) was significantly higher than that of patients with normal zinc levels (60.69 ± 10.17 years) ($p = 0.001$). The mean length of hospital stay was slightly longer in the low zinc group (7.13 ± 4.7 days) compared with the normal zinc group (6.56 ± 6.5 days), but this difference was not statistically significant ($p = 0.52$) (Table 1).

ICU admission was significantly more frequent among patients with low serum zinc levels (26.3%) compared with those with normal zinc levels (12.8%) ($p = 0.034$). Patients with low zinc levels had 2.42 times higher odds of ICU admission compared with patients with normal zinc levels ($\text{OR} = 2.42$). Although intubation was more common in the low zinc group (12.5%) than in the normal zinc group (5.1%), this difference was not statistically significant ($p = 0.103$). Mortality was significantly higher in patients with low serum zinc levels (27.5%) compared with those with normal zinc levels (7.7%) ($p = 0.001$). Patients with low zinc levels had a 4.55-fold increased risk of death compared with patients with normal zinc levels ($\text{OR} = 4.55$) (Table 1).

Table 1
Comparison of Clinical Variables by Serum Zinc Level

Variable	Low Zinc	Normal Zinc	P value
Sex (Male/Female)	38 (47.5%) / 42 (52.5%)	40 (51.3%) / 38 (48.7%)	0.63
Mean age (years)	72.27 ± 11.74	60.69 ± 10.17	0.001
Length of hospital stay (days)	7.13 ± 4.7	6.56 ± 6.5	0.52
ICU admission, n (%)	21 (26.3%)	10 (12.8%)	0.034
Intubation, n (%)	10 (12.5%)	4 (5.1%)	0.103
Mortality, n (%)	22 (27.5%)	6 (7.7%)	0.001

Discussion

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a major global health challenge, particularly among patients with underlying conditions such as diabetes mellitus, who experience higher rates of complications and mortality ((1), (2)). In the absence of a definitive antiviral treatment, increasing attention has been directed toward modifiable factors that may influence immune function and disease severity, including micronutrient status. Adequate balance of essential trace elements is critical for maintaining immune homeostasis, and deficiencies in micronutrients have been shown to impair immune responses, especially in individuals with metabolic disorders such as diabetes ((3),(4)).

The present study demonstrated that diabetic patients with COVID-19 and low serum zinc levels experienced significantly worse clinical outcomes compared with those with normal zinc levels. Specifically, ICU admission and mortality were significantly higher in patients with low zinc levels, while the frequency of intubation and length of hospital stay, although higher in the low-zinc group, did not reach statistical significance. These findings support previous evidence suggesting that zinc deficiency is associated with increased disease severity and adverse outcomes in COVID-19 ((5),(6)). Moreover, the observed older age in the low-zinc group is consistent with prior studies indicating that zinc deficiency is more prevalent among elderly patients and may partially explain their increased vulnerability to severe COVID-19 outcomes (7).

Zinc is a potent antioxidant and plays a crucial role in cellular defense mechanisms by serving as a cofactor for several antioxidant enzymes, including superoxide dismutase (SOD), and by stabilizing cellular membranes through inhibition of lipid peroxidation (8). Zinc deficiency leads to increased oxidative stress and inflammatory responses, which are known contributors to organ damage, particularly in cardiovascular tissues (9). Furthermore, zinc has an inverse relationship with inflammatory markers, and adequate zinc availability can suppress excessive inflammatory responses and free radical production (10). These mechanisms are particularly relevant in diabetic patients, as zinc plays an

essential role in insulin synthesis, storage, and secretion, and zinc deficiency has been linked to poor glycemic control and increased oxidative stress in this population (12).

The antiviral properties of zinc have been widely investigated in viral infections, including coronaviruses. Increased intracellular zinc concentrations have been shown to inhibit viral RNA-dependent RNA polymerase, thereby reducing viral replication (11). In vitro studies have demonstrated that zinc, particularly when combined with zinc ionophores such as pyrithione or chloroquine derivatives, can significantly suppress SARS-CoV replication (13). These antiviral mechanisms provide a biological rationale for the observed association between low serum zinc levels and worse clinical outcomes in COVID-19 patients.

Our findings are in agreement with the study by Jothimani et al., who reported that 57.4% of patients with COVID-19 were zinc deficient and that zinc deficiency was associated with higher rates of complications, acute respiratory distress syndrome, prolonged hospitalization, and mortality, with an odds ratio of 5.54 for adverse outcomes (10). Similarly, a study conducted in Spain showed that plasma zinc levels were significantly lower in patients who died compared with survivors, and that each unit increase in plasma zinc concentration at admission reduced in-hospital mortality by approximately 7% (11). Notably, plasma zinc levels below 50 µg/dL were associated with a 2.3-fold increased risk of death, a finding closely aligned with the results of the present study.

Additional studies further support these observations. Vogel et al. reported that serum zinc levels below 50 µg/dL at hospital admission were associated with worse clinical presentation, prolonged recovery, and increased mortality, particularly among patients with comorbidities such as diabetes mellitus (11). Yasui et al. also demonstrated that lower serum zinc levels were significantly associated with disease severity and the need for intubation, identifying zinc as an independent predictor of critical illness in COVID-19 (13). Moreover, Namdar et al. found that serum zinc levels were significantly lower in deceased COVID-19 patients compared with ICU-admitted and general ward patients, while vitamin B12 and vitamin D did not show a similar association, highlighting the specific importance of zinc (12).

Despite the strengths of this study, including a well-defined diabetic population and comprehensive outcome assessment, several limitations should be acknowledged. First, serum zinc measurement was not performed routinely in all hospitalized COVID-19 patients, which prolonged the data collection process and may have introduced selection bias. Second, the retrospective design limits causal inference and relies on the accuracy of medical records. Third, dietary intake, baseline nutritional status, and post-admission zinc supplementation were not assessed, which may have influenced serum zinc levels and outcomes. Future prospective, multicenter studies with standardized zinc assessment and supplementation protocols are needed to further clarify the role of zinc in COVID-19, particularly among high-risk populations such as patients with diabetes mellitus.

Conclusion

This study demonstrated that low serum zinc levels in diabetic patients hospitalized with COVID-19 were associated with significantly higher rates of ICU admission and mortality compared with patients who had normal zinc levels. Although intubation rates and length of hospital stay were higher in patients with zinc deficiency, these differences were not statistically significant. Given the immunomodulatory and antiviral properties of zinc, assessing serum zinc levels and considering supplementation in zinc-deficient diabetic patients may help improve clinical outcomes. Further prospective studies are required to confirm these findings and establish optimal zinc supplementation strategies.

Declarations

Author Contributions

- **Elham Doust Hosseini:** Contributed to data collection, data extraction, data analysis, literature review, and drafting of the manuscript.
- **Mohammad javad Mohammadifard:** Contributed to data collection, data extraction, data analysis, literature review, and drafting of the manuscript.
- **Mohammad Samet:** Contributed to study design, statistical consultation, data interpretation, and critical revision of the manuscript.
- **Fatemeh Al-Sadat Aghaei Meybodi:** Contributed to study conception and design, supervision of the study, data interpretation, manuscript editing, and final approval of the manuscript.

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate: This study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (Ethics Code: IR.SSU.MEDICINE.REC.1402.276). Due to the retrospective nature of the study, informed consent was waived. All procedures were conducted in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki and its later amendments.

Consent for Publication: Not applicable, as no individual identifiable data are included in this manuscript.

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Conflict of Interest: The authors declare that they have no conflicts of interest related to this study.

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Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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