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Original Article

# The Association of Serum Zinc, Copper and Selenium Levels on Mortality, Need for Mechanical Ventilation and Duration of ICU Stay in Critically Ill Patients with COVID-19: A Cross-Sectional Study

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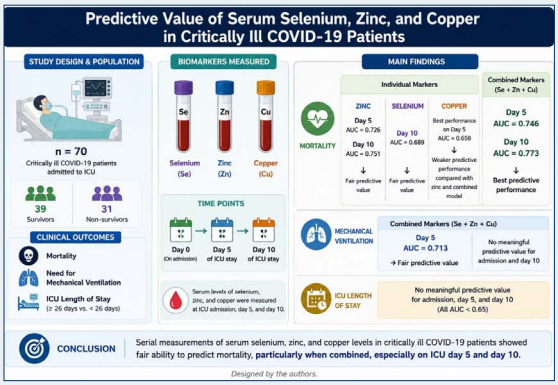
## Abstract

**Introduction:** The objective of the study was to evaluate the effect of serum zinc (Zn), copper (Cu), and selenium (Se) levels on outcomes of patients with Coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU).




**Methods:** This cross-sectional study was conducted on COVID-19 patients. Serum concentrations of Zn, Cu, and Se on admission, on the 5, th and 10th days in the ICU were measured in all subjects, and their association with patients' outcomes were evaluated. The area under curve (AUC) of the receiver operating characteristic (ROC) curve and adjusted binary logistic regression analysis were used to explore the association between Zn, Cu, and Se levels on mortality as the primary outcome.

**Results:** Seventy patients, including 33 (47.1%) men and 37 (52.9%) women, were enrolled. Lower serum levels of Zn (85.93 ± 14.20 vs. 92.55 ± 8.25, $P = 0.017$) and Se (97.29 ± 11.74 vs.104.74 ± 9.17, $P = 0.004$) were observed in the non-survivors group compared to survivors of COVID-19. In adjusted analysis, higher Zn levels were associated with lower odds of mortality on 5th (OR:0.909, 95%CI:0.839-0.985, $P = 0.020$) and 10th (OR:0.911, 95%CI:0.85-0.975, $P = 0.007$) day of ICU and increased with higher levels of Cu on 5th day of ICU (OR:2.852, 95%CI:1.487-7.666, $P = 0.034$).

**Conclusion:** This study suggests a fair predictive value of Zn and a poor predictive value of Se and Cu, as well as a fair predictive value of their cumulative effect on mortality. However, these micronutrients did not predict the need for mechanical ventilation and ICU Length of stay. Except for the combination of serum Se, Zn, and Cu on the 5th day of ICU, which had fair predictive value for mechanical ventilation.

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## Introduction

Following the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Wuhan, China between late 2019 and February 2022, more than 388 million cases of coronavirus disease 2019 (COVID-19) have been reported globally, and more than 5.7 million people have died as a result.[1-3] In addition, the emergence of new variants of SARS-CoV-2 with altered traits effecting the virus characteristics, such as transmissible and virulent, has made it even more difficult to try to end the pandemic.[4,5] Even though over half of the world's population has received recommended vaccines, vaccination alone was not sufficient enough to stop the disease from spreading further,[6] and it remains important to study the underlying mechanism of the COVID-19 pathogen.[7] Growing evidence suggests that host immune dysregulation is a major contributor to disease progression and adverse outcomes in COVID-19.[8,9] Excessive immune activation following viral replication may trigger an exaggerated inflammatory response characterized by increased cytokine production.[10,11] This may result in coagulopathy, thromboembolic consequences, acute inflammation, and hyperimmune response.[12]

The immune system needs enough micronutrients to perform its essential monitoring and defensive functions.[13] Research indicates that a micronutrient deficit may weakens the body's defenses against COVID-19 and accelerates the development of serious illness.[14] Serum Zinc (Zn), Copper (Cu), and Selenium (Se) levels are suggested as potential predictors of poor outcomes in critically ill patients. Essential metals, also known as biometals, are micronutrients that have signaling, catalytic, cofactor, and structural functions in the functioning of organisms. Zn, Cu, and Se are essential elements that regulate immune system function, including antiviral immunity and inflammatory response.[15-18] Zn contributes to multiple immune and metabolic pathways and is involved in maintaining normal antiviral defense mechanisms. In association with COVID-19, Inadequate Zn status may impair both innate and adaptive immune mechanisms, thereby increasing susceptibility to severe viral infections,[19-22] lymphopenia,[23] and activation of Nuclear factor kappa B (NF-κB) pathway that produces interleukin 6 (IL-6) and other cytokines involved in "cytokine storm".[24-26] Furthermore, studies have indicated that Zn can directly combat viruses by hindering the replication of SARS-CoV in laboratory settings.[27] Cu participates in several biological processes including antioxidant defense, cellular metabolism, and immune regulation.[17,28] Cu can have an active antioxidant response during inflammation, same as Zn. Because Cu deficiency reduces T-cell proliferation, it can cause immunosuppression and neutropenia.[29] Cu can also potentially have antiviral properties by stimulating autophagy.[30] Twenty-five different selenoproteins play a role in maintaining redox balance, managing stress in the endoplasmic reticulum, and regulating inflammatory responses.[31] In general, Se can be a minor determinant of viral severity.[32] Similar to Zn, Se is recognized for its inhibitory effects on NF-κB. Research suggests that it may reduce apoptosis triggered by NF-κB activation and potentially contribute to cytokine storms observed in severe cases of COVID-19.[33] Se deficiency causes oxidative stress in the host, which not only disrupts the host's immune system but also rapidly mutates benign RNA viruses into pathogens.[34] Studies conducted in laboratory settings indicated that Se supplementation can hinder the reproduction of the circovirus.[35]

Although several studies have explored the association between trace elements and COVID-19 outcomes, their findings remain inconsistent.[28,29,36,37] Thus, we conducted this study to evaluate the association of serum Zn, Cu, and Se levels in COVID-19 patients admitted to the intensive care units (ICU)s.

## Materials and Methods

### *Study design and ethics statement*

This single-center, cross-sectional study was conducted on COVID-19 patients admitted to the ICU of Emam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran. This medical facility in Ardabil Province serves as both an educational and healthcare institution, providing 551 beds (340 active beds) for the treatment of various adult health issues. The protocol study was reviewed and approved by the Research Council of Ardabil University of Medical Sciences under the ethics code IR.ARUMS.REC.1399.056 in accordance with the Declaration of Helsinki of the World Medical Association.[38] In addition, the study was conducted and reported in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[39]

### *Study population*

This research recruited adult patients with severe COVID-19 who were hospitalized to ICUs. The study did not include patients who were pregnant or who were using any kind of nutritional supplements, multivitamins, or trace elements. An infectious disease specialist used the Iranian National Committee on COVID-19's recommendations and the World Health Organization's (WHO) interim guidelines to identify the subjects. Positive results from a chest computed tomography (CT) and real-time polymerase chain reaction (RT-PCR) of the respiratory tract samples were used to diagnose COVID-19.

### *Data collection and outcomes*

This study gathered data on the demographic and clinical characteristics such as comorbidities, severity of illness based on Acute Physiology and Chronic Health Evaluation (APACHE) IV, and laboratory data including hemoglobin, white blood cells (WBCs) and platelet; as well as comorbidities including hypertension, chronic kidney disease, malignancies, lung diseases, ischemic heart disease, neurological comorbidities, and diabetes mellitus. APACHE score is used for in-patient mortality prediction based on physiological and laboratory variables. This score

utilizes multivariate linear regression to predict hospital mortality and ICU length of stay (LOS). Vandenbrande et al. aimed that APACHE IV in critically ill COVID-19 patients presents the best scoring system for discrimination and calibration.[40] The primary outcome was mortality rate and the secondary outcomes were undergoing mechanical ventilation (MV) and LOS.

***Measurement the Serum levels of Zn, Cu, and Se"***

Fasting blood samples (3 cc) were collected from all patients at the time of ICU admission, on the 5th day, and on the 10th day of ICU stay and were centrifuged within 30 min of collection. The serum samples were stored at -20°C. All specimens were handled with appropriate care, following standard laboratory protocols that accounted for potential COVID-19 complications. Serum Zn and Cu levels were measured using Randox colorimetric assays (Randox Laboratories Ltd., Crumlin, UK). According to the kit's instructions, the established reference ranges were 70-140 μg/dL for serum Cu, and for serum Zn, they were 72.6-127 μg/dL for men and 77.0-114 μg/dL for women. Serum Se concentrations were quantified using graphite furnace atomic absorption spectrophotometry (GFAAS).[41] Regarding Se, normal reference values were considered to be 70 to 150 μg/L.

***Statistical analysis***

The Shapiro-Wilk test was performed to assess the data's normal distribution. For continuous variables, normally distributed data are expressed as mean and standard deviation (SD), and for categorical traits, as percentage (%). However, the median and Interquartile Range (IQR) are used to represent data that are not normally distributed. The t-test or Chi-square (Fisher's exact test) for continuous and categorical variables, respectively, were used to compare clinical factors and demographic traits between the non-survivor and survivor groups. Two-way analysis of variance with repeated measurements (RMANOVA), adjusted, and non-adjusted models were used to evaluate changes in blood levels of Se, Zn, and Cu according to time trends (on admission, fifth day, and tenth day of ICU). Age, gender, comorbidities, and APACHE IV score were among the baseline data that were taken into consideration while creating the adjusted RMANOVA model. Binary logistic regression, both unadjusted and adjusted (adjusting for age, gender, comorbidities, and APACHE IV), was used to determine the predictive effect of Se, Zn, and Cu on outcomes (mortality, MV, and ICU length of stay). The results were presented as odds ratios (OR) with 95% confidence intervals (CI). For Cu, Zn, and Se, the receiver operating characteristic (ROC) the curve was created at various points in time. Area under curve (AUC) between (0.9–1.0), (0.8–0.9), (0.7–0.8), and (0.6–0.7) was regarded as outstanding, good, fair, and bad, respectively, according to the general recommendation for the discriminative power of a test based on ROC. SPSS (ver. 21) was used for statistical analysis (IBM Corp. Released 2012).

## Results

***Patient's characteristics***

Demographic and clinical characteristics of participants according to survivor and non-survivor groups are presented in Table 1. A total of 70 patients with COVID-19 were enrolled, including 33 men (47.1%) and 37 women (52.9%). COVID-19 survivors and non-survivors showed similar baseline characteristics, except for significantly higher age (61.71 ± 14.66 vs. 58.33 ± 14.46, $P = 0.009$) and APACHE IV scores (31.61 ± 8.61 vs. 27.85 ± 5.90, $P = 0.034$) in non-survivors compared with survivors.3.2.

***Time trends of micronutrients changes***

Time trend changes of Se, Zn, and Cu levels on admission, 5th day, and 10th day of ICU between survival and non-survival groups are presented in Table 2. Comparison of the mean serum levels of Se on admission, 5th day, and 10th day of ICU in the non-survival group showed a significant decrease (106.7 ± 13.60 to 97.29 ± 11.74, $P < 0.001$). However, no significant change in Se levels was observed in the survival group at the three times intervals (104.1 ± 10.85 to 104.74 ± 9.17, $P = 0.426$). The mean level of serum Se on the 10th day of ICU in non-survival group was significantly lower than the survivor group (97.29 ± 11.74 vs.104.74 ± 9.17, $P = 0.004$) (Figure 1A). The results of the ANOVA repeated measure on Se showed a significant time and group interaction in adjusted analyses according to age, gender, comorbidities, and APACHE IV score ($P < 0.001$) (Supplementary File, Figure S1).

Comparison of the mean serum levels of Zn three times on admission, 5th day and 10th day of ICU showed a significant reduction in the non-survivor group (90.28 ± 6.53 to 85.82 ± 7.61, $P = 0.002$). However, in three different periods, no significant changes in selenium levels were observed in the surviving group (91.88 ± 9.31 vs. 92.82 ± 8.76, $P = 0.156$). According to the results, the mean level of Zn on the 5th day (85.93 ± 14.20 vs. 92.55 ± 8.25, $P = 0.017$) and 10th day (85.82 ± 7.61 vs. 92.82 ± 8.76, $P < 0.001$) of ICU in the patients of the non-survival group was remarkably lower than the survival group (Figure 1B). The results of the Analysis of variance (ANOVA) repeated measure on Zn showed a significant time and group interaction in adjusted and unadjusted analyses between two groups ($P < 0.001$) (Supplementary File, Figure S2).

Comparison of the mean serum levels of Cu at three times on admission, 5th day, and 10th day of ICU showed a significant reduction in both survival (1.15 ± 0.22 to 0.964 ± 0.121, $P < 0.001$) and non-survivor (1.21 ± 0.32 to 0.977 ± 0.163, $P < 0.001$) groups. The mean level of serum Cu on the 5th day (1.07 ± 0.140 vs. 1.01 ± 0.106, $P = 0.0125$) of ICU in the patients of the non-survive group was remarkably higher than the survival group (Figure 1C). The results of ANOVA repeated measure on Cu showed no significant time and group interaction in both adjusted ($P = 0.556$) and unadjusted ($P = 0.486$) analyses between the two groups (Supplementary File, Figure S3).

**Table 1.** Demographic and clinical characteristics of participants according to survivor and non-survivor groups

| Variables | | Total Participants (n=70) | Survivors (n=39) | Non-survivors (n=31) | *P*-value |
|---|---|---|---|---|---|
| Age (years) | Mean±SD (range) | 62.49±15.19 (27-93) | 58.33±14.46 (27-38) | 61.71±14.66 (41-93) | **0.009*** |
| | Median (IQR) | 64 (50.75-72.25) | 59 (25-32) | 70 (57-80) | |
| Gender | Male (%) | 33 (47.1) | 18 (46.2) | 15 (48.4) | 0.853 |
| | Female (%) | 37 (52.9) | 21 (53.8) | 16 (51.6) | |
| Comorbidities | Yes (%) | 49 (70) | 29 (74.4) | 20 (64.5) | 0.372 |
| | No (%) | 21 (30) | 10 (25.6) | 11 (35.5) | |
| Type of | HTN (%) | 25 (35.7) | 17 (43.6) | 8 (25.8) | 0.123 |
| comorbidities | CKD (%) | 6 (8.6) | 2 (5.1) | 4 (12.9) | 0.395 |
| | Cancer (%) | 2 (2.9) | 0 | 2 (6.5) | 0.193 |
| | Lung disease (%) | 3 (4.3) | 3 (7.7) | 0 | 0.249 |
| | IHD (%) | 19 (27.1) | 11 (28.2) | 8 (25.8) | 0.823 |
| | Neurologic (%) | 2 (2.9) | 2 (5.1) | 0 | 0.499 |
| | DM (%) | 20 (28.6) | 14 (35.9) | 6 (19.4) | 0.128 |
| APACHE IV | Mean±SD (range) | 29.51±7.41 (15-60) | 27.85±5.901 (15-40) | 31.61±8.605 (16-60) | **0.034*** |
| | Median (IQR) | 30 (25-34) | 28 (25-32) | 30 (27-35) | |
| Hb | Mean±SD (range) | 13.09±2.32 (7.4-20) | 12.89±2.311 (8.4-20) | 13.34±2.35 (7.4-19) | 0.423 |
| | Median (IQR) | 13.2 (11.55-14.7) | 13.2 (11-13.9) | 13.2 (11.9-15) | |
| Platelet | Mean±SD (range) | 191014.3±82440.7 (53000-525000) | 200666.6±85439.5 (81000-525000) | 178870.9±78178.3 (53000-395000) | 0.275 |
| | Median (IQR) | 173500 (236000-130000) | 187000 (151000-263000) | 169000 (117000-233000) | |
| WBC | Mean±SD (range) | 8477.14±3593.92 (3000-18000) | 8025.64±3375.3 (3000-17000) | 9045.16±3831.3 (3300-18000) | 0.241 |
| | Median (IQR) | 7950 (5575-10425) | 7500 (5500-9900) | 8400 (6200-10600) | |
| ICU LOS | Mean±SD (range) | 27.43±9.95 (15-62) | 25.95±10.48 (15-62) | 29.29±9.07 (15-55) | 0.165 |
| | Median (IQR) | 26 (20-32.5) | 23 (18-30) | 28 (22-35) | |
| MV | Yes (%) | 61 (78.1) | 32 (82.1) | 29 (93.5) | 0.153 |
| | No (%) | 9 (12.9) | 7 (17.9) | 2 (6.5) | |

Abbreviations; Chronic kidney disease (CKD), Ischemic heart disease (IHD), Hypertension (HTN), Diabetes mellitus (DM), Hemoglobin (Hb), White Blood Cells (WBCs), length of stay (LOS), Mechanical ventilation (MV), Acute Physiology and Chronic Health Evaluation IV (APACHE IV), * $P<0.05$ considered as significant

**Table 2.** Time trend changes of Selenium, Zinc, and Copper, on admission, 5th day, and 10th day of ICU stay according to survivor and non-survivor groups

| Groups | Time trends | | | *P*-value [a] | Time interaction | | Time * group interaction | |
|---|---|---|---|---|---|---|---|---|
| | On admission | 5th day | 10th day | | Unadjusted (*P*-value) [b] | Adjusted (*P*-value) [c] | Unadjusted (*P*-value) [d] | Adjusted (*P*-value) [e] |
| Selenium (Se) | | | | | | | | |
| Survivors | 104.1±10.85 | 102.9±9.67 | 104.74±9.17 | 0.426 | **<0.001*** | 0.461 | 0.635 | **<0.001*** |
| Non-survivors | 106.7±13.60 | 104.2±8.76 | 97.29±11.74 | **<0.001*** | | | | |
| *P*-value [f] | 0.357 | 0.579 | **0.004*** | | | | | |
| Zinc (Zn) (µg/L) | | | | | | | | |
| Survivors | 91.88±9.31 | 92.55±8.25 | 92.82±8.76 | 0.156 | 0.080 | **0.008*** | **0.014*** | **0.036*** |
| Non-survivors | 90.28±6.53 | 85.93±14.20 | 85.82±7.61 | **0.002*** | | | | |
| *P*-value [f] | 0.419 | **0.017*** | **0.001*** | | | | | |
| Copper (Cu) | | | | | | | | |
| Survivors | 1.15±0.22 | 1.01±0.106 | 0.964±0.121 | **<0.001*** | **<0.001*** | 0.872 | 0.486 | 0.556 |
| Non-survivors | 1.21±0.32 | 1.07±0.140 | 0.977±0.163 | **<0.001*** | | | | |
| *P*-value [f] | 0.361 | **0.025*** | 0.704 | | | | | |

* $P<0.05$ considered as significant, [a] *P*-value based on paired t-test within the group, [b] Unadjusted *P*-value based on time interaction in repeated measures ANOVA, [c] Adjusted *P*-value (adjusting for age, gender, comorbidities and APACHE IV) based on time interaction in repeated measures ANOVA, [d] Unadjusted *P*-value based on time*group interaction in repeated measures ANOVA, [e] Adjusted *P*-value (adjusting for age, gender, comorbidities and APACHE IV) based on time*group interaction in repeated measures ANOVA, [f] *P*-value based on t-test between groups

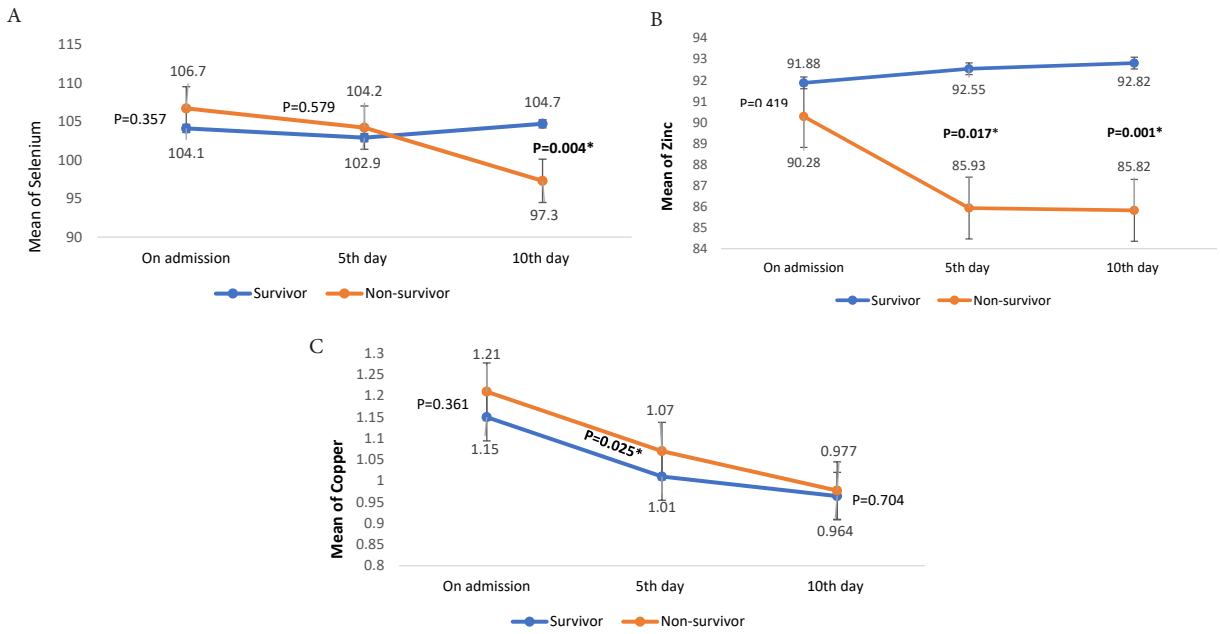


**Figure 1.** Time trend changes of (A) Selenium, (B) Zinc, and (C) Copper, on admission, the 5th day, and the 10th day of ICU

### *Logistic regression analysis*

Unadjusted and adjusted binary logistic regression analysis to compare the predictive effect of Se, Zn, and Cu on outcomes including mortality, needed MV, and ICU length of stay are presented in Table 3. According to the unadjusted analysis, minimal evidence of reduction of odds ratio (OR) for mortality was obtained from higher levels of Se on 10$^{th}$ day of ICU (OR: 0.929, 95%CI: 0.88-0.981, $P=0.008$), Zn on 5$^{th}$ day of ICU (OR: 0.921, 95%CI: 0.858-0.987, $P=0.020$) and Zn on 10$^{th}$ day of ICU (OR: 0.904, 95%CI: 0.847-0.964, $P=0.002$). However, the OR of mortality was remarkably increased with higher levels of Cu on the 5$^{th}$ day of ICU (OR: 1.283, 95%CI: 1.498-8.22, $P=0.032$). In adjusted analysis, OR of mortality was decreased with higher levels of Zn on 5$^{th}$ (OR: 0.909, 95%CI: 0.839-0.985, $P=0.020$) and 10$^{th}$ (OR: 0.911, 95%CI: 0.85-0.975, $P=0.007$) day of ICU and increased with higher levels of Cu on 5$^{th}$ day of ICU (OR: 2.852, 95%CI: 1.487-7.666, $P=0.034$). Whereas, no predictive effect of Se, Zn, and Cu was observed on MV and LOS ICU at different measurement times. Except the OR of ICU LOS was significantly increased with the level of Se on the 10$^{th}$ day of ICU in both unadjusted (OR: 1.058, 95%CI: 1.00-1.12, $P=0.049$) and adjusted (OR: 1.081, 95%CI: 1.014-1.153, $P=0.017$) analysis.

### *ROC curve results of micronutrients for predicting outcomes*

Table 4 shows the predictive value of Se, Zn, and Cu for outcomes with cutoff points in different measurement times. According to the results, Se, Zn, and Cu had fair predictive values for mortality with AUC between 0.658 and 0.751. Best performing predictive value for mortality was related to the level of Zn on 10$^{th}$ day of ICU (AUC: 0.751, 95% CI: 0.633-0.846, $P<0.0001$), and the best cut-off value (≤ 88) had a value sensitivity 67.74%, specificity 82.05%, (LR+) 3.77, (LR-) 0.39, PPV 75%, NPV 76.2%, and 0.497% of Yuden index. Lower performing predictive value for mortality was related to the level of Zn on 5$^{th}$ day of ICU (AUC: 0.658, 95% CI: 0.534-0.767, $P<0.017$), and the best cut-off value (> 1.02) had a value sensitivity 61.29%, specificity 69.23%, (LR+) 1.99, (LR-) 0.56, PPV 61.3%, NPV 69.2%, and 0.305% of Yuden index. However, the micronutrients had no significant predictive value for MV and ICU LOS with AUCs from 0.515 to 0.687 and 0.509 to 0.623, respectively. ROC curves of Se, Zn, and Cu to predict mortality, needed MV, and ICU LOS, on admission, the 5$^{th}$ day, and the 10$^{th}$ day of ICU are available in the Supplementary File, Figure S4).

### *Cumulative effect of micronutrients*

To have a cumulative effect of micronutrients, a new marker in a prediction regression model was introduced in three different time intervals to predict the outcomes of COVID-19 (Table 5). Combined markers on the 5$^{th}$ day and 10$^{th}$ day of ICU had significant fair predictive value for mortality with AUCs (0.746, 95%CI: 0.628-0.843, $P<0.0001$) and (0.773, 95%CI: 0.658-0.865, $P<0.001$), respectively. According to a comparison of the AUCs using the Delongi test, the cumulative effect of micronutrients on the 5$^{th}$ day of ICU was comparable as a predictor of mortality with Se on the 5$^{th}$ day of ICU (AUC: 0.746 vs. 0.552, $P=0.0248$). In terms of the cumulative effect of micronutrients on the 10$^{th}$ day of ICU to predict mortality, it was comparable with Cu on the 10$^{th}$ day of ICU (AUC: 0.773 vs. 0.541, $P=0.0102$). However, there was no remarkable difference between the AUCs of the combined marker and Se on the 10$^{th}$ day of ICU (AUC: 0.773 vs. 0.689, $P=0.140$), Zn on the 5$^{th}$ day of ICU (AUC: 0.746 vs. 0.726, $P=0.626$) and Zn on 10$^{th}$ day of ICU (AUC: 0.773 vs. 0.751, $P=0.581$) for predicting mortality. In terms of the cumulative effect of micronutrients on the 5$^{th}$ day of

**Table 3.** Unadjusted and adjusted binary logistic regression analysis to compare the predictive effect of Selenium, Zinc, and Copper on mortality, need for mechanical ventilation, and duration of ICU stay

| Variables | Unadjusted | | Adjusted | |
|---|---|---|---|---|
| | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| Mortality vs. survival | | | | |
| Selenium on admission | 1.019 (0.979-1.06) | 0.353 | 1.035 (0.989-1.083) | 0.137 |
| Selenium on 5$^{th}$ day | 1.015 (0.964-1.068) | 0.574 | 1.042 (0.98-1.107) | 0.187 |
| Selenium on 10$^{th}$ day | 0.929 (0.88-0.981) | **0.008*** | 0.944 (0.889-1.001) | 0.055 |
| Zinc on admission | 0.976 (0.92-1.035) | 0.414 | 0.972 (0.909-1.038) | 0.398 |
| Zinc on 5$^{th}$ day | 0.921 (0.858-0.987) | **0.020*** | 0.909 (0.839-0.985) | **0.020*** |
| Zinc on 10$^{th}$ day | 0.904 (0.847-0.964) | **0.002*** | 0.911 (0.85-0.975) | **0.007*** |
| Cu on admission | 2.293 (0.389-4.502) | 0.359 | 2.269 (0.355-4.496) | 0.386 |
| Cu on 5$^{th}$ day | 1.283 (1.498-8.22) | **0.032*** | 2.852 (1.487-7.666) | **0.034*** |
| Cu on 10$^{th}$ day | 1.949 (0.066-7.48) | 0.699 | 2.393 (0.054-9.192) | 0.651 |
| Need for MV vs. no need for MV | | | | |
| Selenium on admission | 1.022 (0.962-1.086) | 0.482 | 1.081 (0.973-1.201) | 0.147 |
| Selenium on 5$^{th}$ day | 1.042 (0.953-1.138) | 0.366 | 1.144 (0.982-1.334) | 0.084 |
| Selenium on 10$^{th}$ day | 1.006 (0.944-1.073) | 0.844 | 1.067 (0.946-1.205) | 0.289 |
| Zinc on admission | 0.956 (0.873-1.047) | 0.333 | 0.915 (0.801-1.045) | 0.189 |
| Zinc on 5$^{th}$ day | 0.921 (0.822-1.032) | 0.158 | 0.894 (0.765-1.046) | 0.162 |
| Zinc on 10$^{th}$ day | 0.925 (0.843-1.014) | 0.097 | 0.872 (0.749-1.016) | 0.078 |
| Cu on admission | 0.806 (0.064-1.096) | 0.867 | 0.718 (0.017-2.657) | 0.861 |
| Cu on 5$^{th}$ day | 0.215 (0.001-4.315) | 0.573 | 0.681 (0.021-6.671) | 0.944 |
| Cu on 10$^{th}$ day | 2.859 (0.018-4.227) | 0.683 | 3.124 (0.067-8.982) | 0.189 |
| ICU length of stay (≥26 days vs. <26 days) | | | | |
| Selenium on admission | 1.033 (0.991-1.077) | 0.126 | 1.047 (1-1.095) | 0.051 |
| Selenium on 5$^{th}$ day | 1.058 (1.00-1.12) | **0.049*** | 1.081 (1.014-1.153) | **0.017*** |
| Selenium on 10$^{th}$ day | 1.019 (0.975-1.064) | 0.411 | 1.042 (0.99-1.096) | 0.114 |
| Zinc on admission | 1.017 (0.96-1.078) | 0.563 | 1.017 (0.957-1.081) | 0.583 |
| Zinc on 5$^{th}$ day | 0.999 (0.959-1.04) | 0.951 | 1.01 (0.964-1.059) | 0.668 |
| Zinc on 10$^{th}$ day | 1.006 (0.954-1.06) | 0.832 | 1.017 (0.961-1.076) | 0.569 |
| Cu on admission | 1.718 (0.296-3.973) | 0.546 | 1.595 (0.27-3.412) | 0.606 |
| Cu on 5$^{th}$ day | 1.072 (0.026-4.998) | 0.971 | 0.555 (0.011-7.453) | 0.768 |
| Cu on 10$^{th}$ day | 0.145 (0.004-4.723) | 0.278 | 0.08 (0.002-3.508) | 0.19 |

Adjusting for age, gender, comorbidities, and APACHE IV *$P<0.05$ considered as significant, Abbreviations: Odds ratio (OR), Confidence Interval (CI)

ICU for predicting MV, results showed the increase in AUC (AUC: 0.713, 95%CI: 0.593-0.815, $P=0.032$) to compare AUCs for each micronutrient. However, these differences were not remarkably ($P>0.05$). Comparison ROC curves of Se, Zn, and Cu with combined markers to predict mortality, MV, and ICU LOS, on admission, 5$^{th}$ day, and 10$^{th}$ day of ICU are presented in Figure 2.

## Discussion

In this single-center, cross-sectional study, we assessed serum levels of Zn, Cu, and Se in patients with severe COVID-19 and compared the predictive ability of these micronutrients on outcomes such as mortality, MV, and ICU LOS. In addition, to evaluate and compare the cumulative effect of micronutrients, the combination of Se, Zn, and Cu in three different time intervals was used as a new marker in the predictive regression to predict the consequences of COVID-19. Lower serum levels of Zn and Se were observed in the non-survival group compared to survivors of COVID-19, which may indicate the association of the micronutrients with virus control and mortality. However, in adjusted regression analysis, results showed little evidence of association between micronutrients and COVID-19 outcomes. We found fair predictive value of Zn (5$^{th}$ and 10$^{th}$ day of ICU) and poor predictive value of Se (10$^{th}$ day of ICU) and Cu (5$^{th}$ day of ICU), as well as fair predictive value of their cumulative effect (5$^{th}$ and 10$^{th}$ day) for mortality. However, these micronutrients were not predicted to be needed for MV and ICU LOS. Except the combined serum Se, Zn, and Cu on the 5$^{th}$ day of ICU had a fair predictive value for MV with AUC (0.713).

Considering to antiviral, immunomodulatory, and anti-inflammatory functions of Zn, Cu, and Se, there has been a great deal of interest in their potential use in the management of the disease since the beginning of the COVID-19 pandemic.[29,36,37,42] Numerous investigations

**Table 4.** ROC curve results of Selenium, Zinc, and Copper on admission, 5th day, and 10th day of ICU to predict mortality, need for mechanical ventilation, and duration of ICU stay

| | Variables | AUC (95% CI) | *P*-value | SN | SP | LR+ | LR- | PPV | NPV | Youden Index | Cut-point |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Selenium on admission | 0.586 (0.462-0.703) | 0.224 | 54.84 | 66.67 | 1.65 | 0.68 | 56.7 | 65.0 | 0.2151 | >105 |
| | Selenium on 5th day | 0.552 (0.428-0.671) | 0.460 | 64.52 | 51.28 | 1.32 | 0.69 | 51.3 | 64.5 | 0.1580 | >99 |
| | Selenium on 10th day | 0.689 (0.567-0.794) | **0.005*** | 41.94 | 100.0 | 16.35 | 0.58 | 100.0 | 68.4 | 0.4194 | ≤91 |
| | Zinc on admission | 0.593 (0.469-0.709) | 0.183 | 80.65 | 48.72 | 1.57 | 0.40 | 55.6 | 76.0 | 0.2936 | ≤93.9 |
| Mortality | Zinc on 5th day | 0.726 (0.606-0.826) | **0.0004*** | 77.42 | 69.23 | 2.52 | 0.33 | 66.7 | 79.4 | 0.4665 | ≤90 |
| | Zinc on 10th day | 0.751 (0.633-0.846) | **<0.0001*** | 67.74 | 82.05 | 3.77 | 0.39 | 75.0 | 76.2 | 0.4979 | ≤88 |
| | Cu on admission | 0.560 (0.437-0.679) | 0.408 | 51.61 | 71.79 | 1.83 | 0.67 | 59.3 | 65.1 | 0.2341 | >1.2 |
| | Cu on 5th day | 0.658 (0.534-0.767) | **0.017*** | 61.29 | 69.23 | 1.99 | 0.56 | 61.3 | 69.2 | 0.3052 | >1.02 |
| | Cu on 10th day | 0.541 (0.418-0.661) | 0.574 | 35.48 | 84.62 | 2.31 | 0.76 | 64.7 | 62.3 | 0.2010 | >1.02 |
| | Selenium on admission | 0.546 (0.422-0.665) | 0.621 | 29.51 | 100.0 | 2.80 | 0.77 | 95.0 | 16.1 | 0.2951 | >111 |
| | Selenium on 5th day | 0.584 (0.460-0.701) | 0.403 | 16.39 | 100.0 | 2.07 | 0.87 | 93.3 | 14.6 | 0.1639 | >112 |
| | Selenium on 10th day | 0.515 (0.393-0.637) | 0.851 | 44.26 | 77.78 | 1.99 | 0.72 | 93.1 | 17.1 | 0.2204 | >102 |
| | Zinc on admission | 0.598 (0.474-0.714) | 0.456 | 96.72 | 33.33 | 1.45 | 0.098 | 90.8 | 60.0 | 0.3005 | ≤100 |
| MV | Zinc on 5th day | 0.687 (0.565-0.792) | 0.074 | 44.26 | 88.89 | 3.98 | 0.63 | 96.4 | 19.1 | 0.3315 | ≤89.03 |
| | Zinc on 10th day | 0.674 (0.551-0.781) | 0.102 | 62.30 | 77.78 | 2.80 | 0.48 | 95.0 | 23.3 | 0.4007 | ≤91 |
| | Cu on admission | 0.529 (0.406-0.650) | 0.743 | 26.23 | 100.0 | 2.36 | 0.74 | 100.0 | 16.7 | 0.2623 | ≤0.95 |
| | Cu on 5th day | 0.551 (0.427-0.670) | 0.611 | 26.23 | 88.89 | 2.36 | 0.83 | 94.1 | 15.1 | 0.1512 | ≤0.97 |
| | Cu on 10th day | 0.536 (0.412-0.656) | 0.728 | 24.59 | 88.89 | 2.21 | 0.85 | 93.7 | 14.8 | 0.1348 | >1.03 |
| | Selenium on admission | 0.604 (0.480-0.719) | 0.124 | 24.32 | 93.94 | 4.01 | 0.81 | 81.8 | 52.5 | 0.1826 | >118 |
| | Selenium on 5th day | 0.623 (0.499-0.736) | 0.067 | 48.65 | 75.76 | 2.01 | 0.68 | 74.4 | 50.4 | 0.2441 | >103 |
| | Selenium on 10th day | 0.569 (0.445-0.687) | 0.321 | 35.14 | 81.82 | 1.93 | 0.79 | 73.7 | 46.5 | 0.1695 | >109 |
| | Zinc on admission | 0.532 (0.408-0.652) | 0.655 | 37.84 | 75.76 | 1.56 | 0.82 | 63.7 | 52.0 | 0.1360 | >95.2 |
| ICU LOS | Zinc on 5th day | 0.550 (0.426-0.669) | 0.473 | 45.95 | 66.67 | 1.38 | 0.81 | 60.8 | 52.3 | 0.1261 | >94 |
| | Zinc on 10th day | 0.514 (0.392-0.636) | 0.837 | 18.92 | 90.91 | 2.08 | 0.89 | 70.0 | 50.0 | 0.0982 | >98 |
| | Cu on admission | 0.539 (0.416-0.659) | 0.576 | 62.16 | 54.55 | 1.37 | 0.69 | 60.6 | 56.2 | 0.1671 | >1.1 |
| | Cu on 5th day | 0.509 (0.386-0.630) | 0.901 | 13.51 | 93.94 | 2.23 | 0.92 | 71.5 | 49.2 | 0.0745 | ≤0.88 |
| | Cu on 10th day | 0.554 (0.431-0.673) | 0.433 | 51.35 | 63.64 | 1.41 | 0.76 | 61.3 | 53.8 | 0.1499 | ≤0.93 |

Abbreviations; ROC: Receiver operating characteristic; LOS: Length of stay, MV: Mechanical ventilation, CI: Confidence interval, SN: Sensitivity; SP: Specificity; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio; PPV: Positive Predictive value; NPV: Negative Predictive value; AUC: Area under curve, *$P<0.05$ considered as significant

found a negative correlation between COVID-19 severity and mortality and blood levels of Zn and Se.[43,44] Skalny et al,[37] reported that serum Se levels inversely associated with lung damage in COVID-19. According to Jothimani et al, a considerable proportion of COVID-19 patients had Zn deficiency in comparison to healthy controls..[44] Moreover, 13% lower Se levels in Indian COVID-19 patients compared to healthy controls is reported.[45] A large population-based study in China reported that the Se concentration in hair is associated with a higher COVID-19 cure rate.[46] A study by Heller et al,[43] demonstrated that the combination of serum SELENOP, Zn, and age is a reliable predictor of COVID-19 survival. In contrast, evidence showed that the increase in serum Cu was associated with the intensity of COVID-19,[28, 37] which confirms the findings of this study that showed a higher mean level of Cu on the 5th day of ICU in the non-survivor group than in the survivor group.

In line with the present study, some studies found little evidence of the effect of Zn, Se, or Cu levels for preventing infection, and disease progression.[29] Zn, Cu, and Se levels were not linked to COVID-19 severity, but Zn levels were highly linked to patient outcomes, according to a prospective study by Bagher Pour et al. that evaluated blood trace element status in both severe and non-severe COVID-19 patients.[47] An observational study by Razeghi Jahromi et al,[42] reported that the correlation between Se and Zn with COVID-19 severity lost its significance after adjusting for confounding factors such as age, urea, and C-reactive protein. It can be concluded that the effect of confounding variables on the effect of Se, Zn, and Cu levels in predicting the severity of COVID-19 and its associated consequences is very high. Therefore, this can be one of the reasons for the difference between the results of the studies which can related to the study population, research setting, and severity of diseases.

**limitations of the study**

The small sample size of this study as a single-center observational study was the main limitation which indicates the need for future studies on this topic. Furthermore, due to the cross-sectional design of our study, examination of changes over time was not possible, and the long length of

**Table 5.** Cumulative effect of Selenium, Zinc, and Copper on admission, 5th day, and 10th day of ICU to predicting mortality, need for mechanical ventilation, and duration of ICU stay

| Markers | AUC (95% CI) | *P*-value | SN | SP | LR+ | LR- | PPV | NPV | Youden index | Cut-point |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality (Yes vs. No) | | | | | | | | | | |
| On admission | 0.594 (0.470-0.710) | 0.172 | 38.71 | 79.49 | 1.89 | 0.77 | 60.0 | 62.0 | 0.1820 | >0.47648 |
| 5th day | 0.746 (0.628-0.843) | **<0.0001*** | 96.77 | 56.41 | 2.22 | 0.057 | 63.8 | 95.6 | 0.5318 | >0.33927 |
| 10th day | 0.773 (0.658-0.865) | **<0.0001*** | 61.29 | 84.62 | 3.98 | 0.46 | 76.0 | 73.3 | 0.4591 | >0.50992 |
| MV (Yes vs. No) | | | | | | | | | | |
| On admission | 0.632 (0.508-0.744) | 0.231 | 62.30 | 66.67 | 1.87 | 0.57 | 92.7 | 20.7 | 0.2896 | >0.87828 |
| 5th day | 0.713 (0.593-0.815) | **0.032*** | 57.38 | 88.89 | 5.16 | 0.48 | 97.2 | 23.5 | 0.4627 | >0.89618 |
| 10th day | 0.694 (0.572-0.799) | 0.065 | 68.85 | 77.78 | 3.10 | 0.40 | 95.5 | 26.9 | 0.4663 | >0.86083 |
| ICU length of stay (≥26 days vs. <26 days) | | | | | | | | | | |
| On admission | 0.609 (0.485-0.724) | 0.109 | 75.68 | 48.48 | 1.47 | 0.50 | 62.3 | 64.0 | 0.2416 | >0.48028 |
| 5th day | 0.627 (0.503-0.740) | 0.059 | 51.35 | 75.76 | 2.12 | 0.64 | 70.4 | 58.1 | 0.2711 | >0.52286 |
| 10th day | 0.595 (0.471-0.711) | 0.164 | 51.35 | 72.73 | 1.88 | 0.67 | 67.9 | 57.1 | 0.2408 | >0.55276 |

Abbreviations; LOS: Length of stay, MV: Mechanical ventilation, CI: Confidence interval, SN: Sensitivity; SP: Specificity; LR+: Positive Likelihood Ratio; LR-: Negative Likelihood Ratio; PPV: Positive Predictive value; NPV: Negative Predictive value, AUC: Area under curve; *$P<0.05$ considered as significant

patients' follow-up should be considered in future studies.

## Conclusion

Our findings revealed a fair predictive value of Zn, a poor predictive value of Se and Cu, and a fair predictive value of their cumulative effect on mortality. However, these micronutrients were not predicted to be needed for MV and ICU LOS. On the fifth day of stay in the ICU, the combined serum levels of Se, Zn, and Cu were found to have a fair predictive value for MV.

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**Competing Interests**

The authors have no conflicts of interest to disclose related to this study.

**Consent for Publication**

Not applicable.

**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Ethical Approval**

The protocol study was reviewed and approved by the Research Council of Ardabil University of Medical Sciences under the ethics code IR.ARUMS.REC.1399.056 in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent was obtained from all subjects and/or their legal guardian(s).

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**Supplementary Files**

Supplementary file 1 contains Figures S1-S4.

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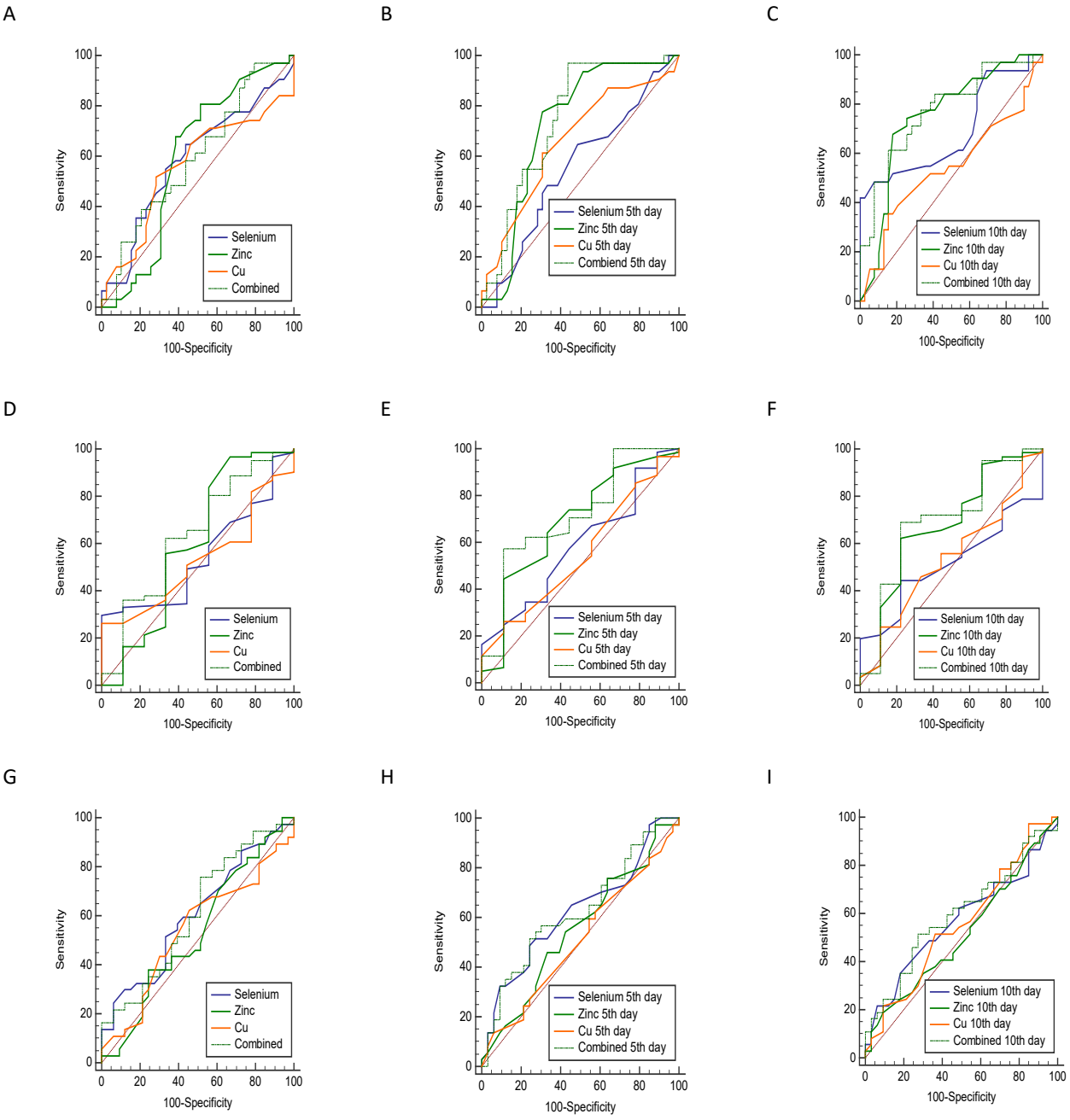


**Figure 2.** Comparison of ROC curves for serum selenium, zinc, copper, and their combined marker for predicting mortality, mechanical ventilation, and ICU length of stay on admission, the 5th day, and the 10th day of ICU stay.


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