## ORIGINAL RESEARCH

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# Electrolyte abnormalities in hospitalized COVID-19 patients at tertiary referral centers in Tehran: Hypermagnesemia as a marker of fatality: A retrospective cross-sectional study

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## Abstract

**Background and Aims:** To evaluate biochemical abnormalities and their association with the outcome of hospitalized coronavirus disease 2019 (COVID-19) patients at a tertiary referral center in Iran.

**Methods:** This retrospective study was conducted on COVID-19 patients who were admitted at tertiary referral centers in Tehran, Iran, from March 2021 to 2022. Demographic and biochemical laboratory data of the patients including blood sodium, potassium, calcium, and magnesium were collected from patient treatment sheets of severe COVID-19 patients admitted to a different ward of the hospital. A logistic regression model was fitted to identify the associated parameters with mortality.

**Results:** Four hundred and ninety-nine patients with COVID-19, including 287 males (57.5%), who had a mean age of $58.95 \pm 16.60$ years, were enrolled. Thirty-eight patients (7.62%) died during hospitalization. The factors we found to be independently associated with an increased risk of in-hospital death were having comorbidity (mortality of 94.7%, vs. 61% among those without comorbidity; odds ratio, 17.71; 95% confidence interval [CI], 3.81–82.37), hypermagnesemia (34.2%, vs. 26.2% among those with normal magnesium; odds ratio, 9.71; 95% CI, 2.958–31.91), and having a male gender (34.2%, vs. 26.2% among those were female; odds ratio, 9.71; 95% CI, 2.958–31.91)

**Conclusions:** Hypermagnesemia, having a male gender, and the existence of comorbidity in patients with COVID-19 is associated with an increase in mortality. Further studies on the pathogenic mechanisms and therapeutic implications need to be done.

**KEYWORDS**
coronavirus, electrolytes, magnesium, SARS-COV-2

# 1 | INTRODUCTION

Coronavirus (COVID-19) is not a localized respiratory infection; it is considered a systemic disease with a wide spectrum of manifestations varying with age, presence of co-morbidities, previous medical histories, etc.[1,2] On April 12, 2023, there have been 762,791,152 confirmed cases of COVID-19 in the world.[3]

Although clinical assessment of the patients is critical and indispensable in the management of COVID-19 patients, paraclinical data, including biomarkers and laboratory markers potentially can provide additional information with clinically significant on patient care.[4,5] Potentially laboratory data may play a crucial role in COVID-19 in several issues, including early suspicion of disease, confirmation, and classification of disease severity, identification of high-risk individuals and intensive care unit (ICU) admission criteria, rationalizing the trial therapy, assessing response to treatment, predicting the outcome and identification criteria for discharge of patients.[3,6,7]

This laboratory data in COVID-19 patients included a complex of immunological, inflammatory, coagulative cascades, and biochemical panels.[4,6] Since the availability and cost of each test are two important issues in choosing a marker, the best selection of one test and the best time of selection is one of the principles for high-value care for COVID-19. Currently, limited data is available on the prevalence and significance of serum electrolyte levels in COVID-19 patients.[5,8,9]

The current study aims to provide practical information to clinicians on the role of serum electrolyte levels on admission day and the relationships between these parameters and the clinical course of diseases in hospitalized COVID-19.

# 2 | MATERIAL AND METHODS

## 2.1 | Study design and participant selection

This retrospective analytical cross-sectional study was conducted on COVID-19 patients who were admitted at tertiary referral centers in Tehran, Iran, from March 2021 to 2022. The primary objective of the current study was to measure the serum level of selected electrolytes in hospitalized COVID-19 patients and to find out its association with diseases outcome. The study was conducted in agreement with the provisions of the Helsinki Declaration and its subsequent revisions. The study protocol was approved by the ethics code IR.SBMU.M-SP.REC.1400.687. No patient was interviewed during the study, and only retrospective data were used for analysis.

Data of patients with SARS-CoV-2 reverse transcriptase-polymerase chain reaction-positive aged 18 years and above who were admitted to different COVID-19 wards have enrolled in the study.

## 2.2 | Data collection

The medical file of each COVID-19 consisted of three parts: demographic characteristics, paraclinical data, and outcome data. Demographic data, including age, gender, any comorbid conditions, and biochemical laboratory data of the patients, including blood sodium, potassium, calcium, and magnesium at the admission day and outcome were collected from patient treatment sheets.

## 2.3 | Classification of electrolyte abnormalities

For this study, electrolyte abnormalities were categorized according to the blood level of each electrolyte.

## 2.4 | Statistical analysis

Data were analyzed using the SPSS version 21.0 Statistical package (SPSS Inc.). Quantitative and qualitative data were presented as mean ± standard deviation (SD), median (minimum–maximum), and frequency (percentage). Data preparation was done based on the study protocol. Descriptive statistics were applied to explore and describe the data. The normality of continuous data was evaluated using the Kolmogorov–Smirnov test. We used the independent sample t-test and chi-square (or Fisher's exact test) for comparison between alive and deceased patients. Mann–Whitney $U$ nonparametric tests were applied for biomarkers analysis between two groups. A binary logistic regression model was fitted to identify the associated parameters with mortality. Variables were selected primarily based on a theoretical conceptual framework predefined in the study proposal. Among the independent factors, which were the candidate to be entered into the multivariable modeling, those with a $p$-value of <0.3 were selected and entered into the statistical modeling procedure. A backward wald elimination technique was applied for modeling. Accordingly, the odds ratio (OR) and its 95% confidence interval (CI) were estimated for each factor associated with mortality. Type I error was predefined at 0.05.

# 3 | RESULTS

Four hundred and ninety-nine patients with COVID-19 were included in the study. The mean age of the patients was 58.95 ± 16.60 years, and there were 287 males (57.5%). The majority of cases had comorbidity (63.53%). Table 1 presents the serum level of electrolytes based on comorbidity status (Table 1).

As shown in Table 2, 38 patients had died of COVID-19 and 461 patients had fully recovered and been discharged (Table 2). Comorbidity was more predominant in deceased patients (94.7%) than in recovered patients (5.3%). The mean level of magnesium was 2.05 ± 0.5 mmol/L in the patients. Hypermagnesemia was more predominant in deceased patients (13, 34.2%) than in recovered patients (121, 26.2%) ($p$ = 0.002) (Table 2).

Table 3 shows logistic regression models. Male patients were 2.7 times more likely to mortality than females (OR = 2.745, 95% CI

**TABLE 1** Demographic and clinical characteristics of patients based on comorbidity status.

| | | Comorbidity status | | |
|---|---|---|---|---|
| | All (n = 499) | No (n = 182) | Yes (n = 317) | p-value |
| Age, years | | | | |
| Mean ± SD | 58.95 ± 16.60 | 61.22 ± 15.82 | 57.65 ± 16.92 | 0.02* |
| Median (min–max) | 60 (15–97) | 62.5 (19–97) | 57 (15–96) | |
| Gender, n (%) | | | | |
| Female | 212 (42.5) | 71 (39.0) | 141 (44.5) | 0.23** |
| Male | 287 (57.5) | 111 (61.0) | 176 (55.5) | |
| Sodium, mEq/L | | | | |
| Mean ± SD | 138.88 ± 14.45 | 140.4 ± 16.75 | 138.01 ± 12.89 | 0.25*** |
| Potassium, mEq/L | | | | |
| Mean ± SD | 4.14 ± 0.62 | 4.24 ± 0.5 | 4.08 ± 0.67 | 0.007*** |
| Calcium, mg/dl | | | | |
| Mean ± SD | 8.71 ± 1.62 | 8.54 ± 0.68 | 8.81 ± 1.36 | <0.001*** |
| Magnesium, mg/dL | | | | |
| Mean ± SD | 2.05 ± 0.5 | 2.0 ± 0.68 | 2.07 ± 0.32 | <0.001*** |

Abbreviation: SD, standard deviation.

*Result from Independent sample T-test.

**Result from Chi-squared.

***Result from Mann–Whitney U.

1.168–6.454) (Table 3). In addition, patients with comorbidity and hypermagnesemia had upper odds for mortality (Table 3).

# 4 | DISCUSSION

The result of the study demonstrated that hypermagnesemia, having a male gender, and the existence of comorbidity in patients with COVID-19 is associated with an increase in mortality.

The result of a previous study demonstrated multiple comorbidities and underlying conditions have been associated with severe illness.[10,11] So, although severe disease can occur in any individual, most with severe disease have at least one risk factor. In the study of Onder et al.[12] in Italy the mean number of pre-existing comorbidities was about three inpatients who died from COVID-19.

Recently, some researchers have suggested that alternation in serum magnesium levels in COVID-19 patients may be associated with the development of severe disease in COVID-19 patients and poor outcomes.[13–16] The results of the studies in this field are heterogeneous.[15–17] While some authors suggest that magnesium deficiency is associated with low-grade chronic inflammation and may exacerbate the course of COVID-19,[16] others state that hypermagnesemia among hospitalized COVID-19 patients is associated with an increased rate of mortality.[15]

Although the exact mechanism of the relationship between dysmagnesemia and COVID-19 outcome and possible mortality is unclear, it is the hypothesis that hypermagnesemia potentially represents increased cell turnover and higher severity of illness, which is frequently associated with more severe forms of diseases.[14]

A possible explanation for the high incidence of hypermagnesemia and poor outcomes in COVID-19 patients can be related to the common risk factor, including advanced age, diabetes, obesity, hypertension, arrhythmias, thrombosis, and cardiovascular events, between magnesium dysregulation and co-morbidities that related with mortalities.[17–20]

Another explanation can be related to the alternation of the level of cytokine, including higher levels of IL-6, IL-4, and IL-10.[21] It is hypothesized that the transcellular shift of magnesium from the intracellular to extracellular space in response to stress hormones is associated with vasopressor use[14–18] Although Lippi et al. reported the result of electrolyte imbalances in patients with severe COVID-19 in a meta-analysis.[22] The result of this meta-analysis demonstrated serum sodium level was significantly lower in patients with severe COVID-19, the result of our study is not congruent with existing literature.

Previous research showed that COVID-19 cases in men tended to be more severe than in women.[23] In agreement with the previous study, in our study, the male gender was statistically associated with poor outcomes because males were more susceptible to severe disease compared to females.

Our study had several limitations. The first limitation of our study is the evaluation of blood level of electrolyte only on admission day, so changes in the level of serum electrolytes in the course of admission was not considered in the interpretations of

**TABLE 2** Univariable analysis of the association between all parameters and mortality status.

| | Mortality | | OR | 95% CI | p-Value |
| --- | --- | --- | --- | --- | --- |
| | Deceased (n = 38) | Alive (n = 461) | | | |
| Age, years | | | | | |
| Mean ± SD | 59.84 ± 14.26 | 58.55 ± 16.80 | 0.99 | 0.97–1.02 | 0.73[a] |
| Median (min–max) | 63 (30–87) | 60 (15–97) | | | |
| Gender, n (%) | | | | | |
| Female (ref) | 18 (48.6) | 194 (42.5) | 1.898 | 0.91–3.91 | 0.08[b] |
| Male | 19 (51.4) | 262 (57.5) | | | |
| Comorbidity, n (%) | | | | | |
| Yes | 36 (94.7) | 281 (61) | 11.53 | 2.74–48.48 | **<0.001** |
| No (ref) | 2 (5.3) | 180 (39) | | | |
| Sodium, n (%) | | | | | |
| Hypo | 6 (15.8) | 31 (8.6) | 1.95 | 0.713–5.367 | 0.39 |
| Normal (ref) | 28 (73.7) | 301 (83.8) | - | - | |
| Hyper | 4 (10.5) | 27 (7.5) | 1.42 | 0.409–4.96 | |
| Potassium, n (%) | | | | | |
| Hypo | 7 (18.4) | 33 (7.2) | 2.38 | 0.93–6.10 | 0.19 |
| Normal (ref) | 30 (78.9) | 419 (90.9) | - | - | |
| Hyper | 1 (2.6) | 9 (2.0) | 1.498 | 0.18–12.21 | |
| Calcium, n (%) | | | | | |
| Hypo | 20 (52.6) | 155 (33.6) | 0.814 | 0.374–1.77 | 0.87 |
| Normal (ref) | 18 (47.4) | 299 (64.9) | - | - | |
| Hyper | 0 (0.0) | 7 (1.5) | 0.00 | 0 | |
| Magnesium, n (%) | | | | | |
| Hypo | 1 (2.6) | 28 (6.1) | 4.820 | 1.84–12.63 | **0.002** |
| Normal (ref) | 24 (63.2) | 312 (67.7) | - | - | |
| Hyper | 13 (34.2) | 121 (26.2) | 0.699 | 0.27–1.78 | |

*Note*: The reference for normal ranges of electrolytes: calcium: 8.6–10.3 mg/dL, sodium: 135–145 mEq/L, potassium: 3.5–4.5 mEq/L, magnesium level is 1.7–2.2 mg/dL.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

[a]Result from Independent sample T-test.

[b]Result from Chi-squared.

**TABLE 3** Logistic regression of related risk factors with mortality.

| Characteristic | B | SE | OR | 95% CI | p-Value |
| --- | --- | --- | --- | --- | --- |
| Gender, (male) | 1.010 | 0.436 | 2.745 | 1.168–6.454 | **0.02** |
| Comorbidity, (yes) | 2.874 | 0.784 | 17.713 | 3.809–82.368 | **<0.001** |
| MG, (Hyper) | 2.274 | 0.607 | 9.715 | 2.958–31.910 | **<0.001** |

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.

the results. Second, other biochemical abnormalities that potentially can be related to the changes in the abnormal serum electrolyte were not evaluated. Future studies are required to provide more details about a possible abnormality in the level of

serum electrolytes in COVID-19 patients and its relation with morbidity and mortality.

The importance of our study is the relatively proper sample size for evaluation of biochemical abnormalities, including serum sodium,

potassium, calcium, and magnesium level and their association with the outcome of hospitalized COVID-19 patients which only has been evaluated in limited studies.

## 5 | CONCLUSION

The results of our study demonstrated that hypermagnesemia in initial hospital admission is a marker of fatality in hospitalized COVID-19 patients. So, monitoring serum electrolytes levels at admission time and during hospitalization may be a useful predictor of the outcome of COVID-19 patients. Also, male gender and the existence of comorbidity in patients with COVID-19 are associated with an increase in mortality. Further studies on the pathogenic mechanisms and therapeutic implications need to be done.

## AUTHOR CONTRIBUTIONS

**Sayna Mardani**: Conceptualization; data curation; methodology; writing—review & editing. **Atousa Hakamifard**: Methodology; writing—original draft; writing—review & editing. **Kouros Aghazadeh Sarhangipour**: Conceptualization; writing—review & editing. **Masoud Mardani**: Conceptualization; data curation; methodology; supervision; writing—review & editing.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

All authors have read and approved the final version of the manuscript [CORRESPONDING AUTHOR or MANUSCRIPT GUARANTOR] had full access to all of the data in this study, and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

## ETHICS STATEMENT

The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethics code: IR.SBMU.MSP.REC.1400.687).

## TRANSPARENCY STATEMENT

The lead author Atousa Hakamifard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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