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Original Article

# The Relationship Between Hypokalemia and Mortality in Hospitalized Patients With COVID-19 Pneumonia: A Prospective Study

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## Abstract

**Background:** COVID-19 infection presents a spectrum of clinical manifestations, from asymptomatic cases to severe respiratory complications such as viral pneumonia, respiratory failure, and systemic inflammatory responses leading to multiorgan failure and death. Prognostic factors influencing disease outcomes include demographic characteristics and clinical features, alongside laboratory parameters monitored during the course of illness. Hypokalemia has emerged as a significant marker in COVID-19 pneumonia, often associated with adverse clinical outcomes. It has been independently linked to the need for invasive mechanical ventilation. Moreover, it can precipitate cardiac dysrhythmias and exacerbate clinical severity. This study aims to contribute to the existing literature by exploring potential etiologies of hypokalemia and its implications for mortality rates among patients hospitalized with COVID-19 pneumonia.

**Methods:** A cohort of 300 patients aged>18 diagnosed with COVID-19 pneumonia were included in this study. Demographic data, symptoms, comorbidities, medications, duration of hospitalization, and blood potassium levels were recorded, and hypokalemia was defined as having at least three potassium values below 3.5 mmol/L within the first five days of hospitalization. The study investigated whether hypokalemia serves as a risk factor for mortality in COVID-19 patients.

**Results:** Among the 300 patients, 57 (19%) were identified with hypokalemia. Patients with hypokalemia were older compared to those without this *disturbance* ($P=0.012$). No significant correlation was found between hypokalemia and the presence of diabetes mellitus ($P=0.999$), hypertension ($P=0.193$), or cardiovascular disease ($P=0.781$). However, patients with hypokalemia had a higher usage rate of diuretics ($P=0.035$). The use of corticosteroids, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, insulin, beta-2 agonists, beta-blockers, antipsychotic drugs, and digoxin was similar between patients with and without hypokalemia ($P>0.05$). Hypokalemia was associated with a 4.79-fold increase in mortality ($P=0.003$), and each additional day of hospitalization increased mortality by 1.14 times ($P<0.001$).

**Conclusion:** Advanced age and diuretic usage could elevate the risk of hypokalemia in COVID-19 patients. Prolonged hospital stays and higher mortality rates among patients with hypokalemia suggest a need for the careful management of electrolyte imbalances.

**Keywords:** COVID-19, SARS-CoV-2, Mortality, Hypokalemia

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## Introduction

COVID-19 infection presents a spectrum of clinical manifestations, ranging from asymptomatic cases to severe pneumonia, respiratory distress, multiorgan dysfunction, sepsis, and even death (1,2). The prognosis of COVID-19 is influenced by various demographic and clinical factors, with laboratory parameters also playing a crucial role (3).

Hypokalemia, often associated with unfavorable outcomes, serves as an indicator of increased activity in the renin-angiotensin-aldosterone system among patients with COVID-19 pneumonia. In addition to reflecting disease progression, hypokalemia may independently elevate the risk of requiring invasive mechanical ventilation (4). Potassium, a vital intracellular electrolyte, holds pivotal roles in cardiovascular, musculoskeletal, gastrointestinal, respiratory, and neurological functions

(5,6). Hypokalemia can lead to dysrhythmias and precipitate serious clinical complications (7). Numerous studies indicate that hypokalemia alters the disease trajectory in COVID-19 patients (8). This study seeks to contribute to the existing literature by exploring potential causes of hypokalemia and its impact on mortality rates among individuals with COVID-19 pneumonia.

## Subjects and Methods

The study enrolled 300 patients aged 18 years and older, with a glomerular filtration rate of 60% or higher, who were admitted to Istanbul Medeniyet University Hospital with a diagnosis of COVID-19 pneumonia from March 2020 to September 2021.

All patients were provided with detailed information about the study and signed informed consent forms. The collected data were related to patients' age, gender, presence of comorbidities (e.g., diabetes mellitus, hypertension, and cardiovascular disease), and medications (i.e., diuretics, corticosteroids, insulin, beta 2 agonists, and angiotensin-converting enzyme [ACE] inhibitors/angiotensin receptor blockers [ARBs], beta-blockers, digoxin, and antipsychotic drugs). The other data included the presence of vomiting/diarrhea, hypomagnesemia, and hypokalemia, length of hospital stay, and discharge/death outcomes.

Patients' chronic diseases were documented by reviewing hospital records, while their regular medication usage was determined by examining hospital information management system records and Ministry of Health doctor's data bank records.

Hypomagnesemia was diagnosed if at least one of the measured magnesium values between the first and fifth days of hospitalization was below 1.6 mmol/L. Similarly, hypokalemia was defined as occurring if at least three out of five measured potassium values between the first and fifth days of hospitalization were below 3.5 mmol/L.

### *Statistical Analysis*

The data were analyzed using IBM SPSS Statistics 18 software (Copyright: SPSS Inc., 1989, 2010). The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Categorical variables were presented as frequencies (n) and percentages (%), while parametric continuous variables were expressed as means ± standard deviations (SD), and non-parametric variables were represented by median (minimum and maximum) values.

For the analysis of categorical variables, the Pearson chi-square, Fisher's exact, or Fisher-Freeman-Halton exact test was employed, with Yates and post hoc Bonferroni corrections applied where necessary. Considering that the assumptions for parametric tests were not met, the Mann-Whitney U test was utilized for comparing means between the two groups.

Univariate and multivariate logistic regression analyses were conducted to identify independent risk factors associated with dependent variables. Variables with *P* values less than 0.2 in the univariate analyses were included in the multivariate model. The results were reported as odds ratios (OR) with 95% confidence intervals.

Survival probabilities were estimated using the Kaplan-Meier method, and the log-rank test was performed to assess differences in survival probabilities between variable levels. A statistical significance level of 0.05 was considered for all analyses.

## Results

The study encompassed 300 patients, with a mean age of 59.54 ± 15.70 years. Among them, 101 (33.7%) had diabetes mellitus, 161 (53.7%) had hypertension, and 111 (37.0%) had cardiovascular disease. Additionally, 50 patients (16.7%) experienced vomiting/diarrhea, 51 (17.0%) had hypomagnesemia, and 57 (19.0%) had hypokalemia. Ultimately, 284 patients (94.7%) were discharged, while 16 (5.3%) succumbed during hospitalization. The mean hospital stay was 10.10 ± 6.10 days, ranging from 5 to 43 days. The relationship between the presence of hypokalemia and independent variables was investigated,

**Table 1.** The Relationship Between the Presence of Hypokalemia and Independent Variables

| | Hypokalemia | | |
|---|---|---|---|
| | **No (n = 243)** | **Yes (n = 57)** | ***P* Value** |
| Gender | | | |
| Female | 117 (48.1) | 33 (57.9) | 0.185 |
| Male | 126 (51.9) | 24 (42.1) | |
| Age (y) | 58 (20-96) | 67 (20-101) | 0.012 |
| Comorbidities | | | |
| DM | 82 (33.7) | 19 (33.3) | 0.999 |
| HTN | 126 (51.9) | 35 (61.4) | 0.193 |
| CVD | 89 (36.6) | 22 (38.6) | 0.781 |
| Drugs | | | |
| Diuretics | 79 (32.5) | 27 (47.4) | 0.035 |
| Corticosteroids | 53 (21.8) | 10 (17.5) | 0.595 |
| Insulin | 27 (11.1) | 8 (14.0) | 0.697 |
| Beta-2 agonists | 63 (25.9) | 14 (24.6) | 0.965 |
| ACE-Is/ARBs | 78 (32.1) | 23 (40.4) | 0.235 |
| Beta-blockers | 45 (18.5) | 8 (14.0) | 0.545 |
| Digoxin | 1 (0.4) | 0 (0.0) | 0.999 |
| Antipsychotics | 7 (2.9) | 2 (3.5) | 0.999 |
| Clinical and laboratory findings | | | |
| Vomiting/diarrhea | 37 (15.2) | 13 (22.8) | 0.236 |
| Hypomagnesemia | 38 (15.6) | 13 (22.8) | 0.271 |
| Patient Outcome | | | |
| Discharged | 235 (96.7) | 49 (86.0) | 0.003 |
| Death | 8 (3.3) | 8 (14.0) | |
| Day of hospitalization | 8 (5-38) | 11 (5-43) | < 0.001 |

*Note*. The results are expressed as the median (minimum-maximum) or n (% column). Mann-Whitney U test, Pearson Chi-square test, and Fisher's exact test. CVD: Cardiovascular disease; DM: Diabetes; HTN: Hypertension; ACE-Is: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blocker.

as detailed in Table 1.

The incidence of hypokalemia did not significantly differ between genders ($P=0.185$). Patients with hypokalemia had a significantly higher median age compared to those without this *disturbance* (67 vs. 58 years, $P=0.012$). Regarding comorbidities, no significant associations were found between diabetes mellitus ($P=0.999$), hypertension ($P=0.193$), cardiovascular disease ($P=0.781$), and hypokalemia. However, the use of diuretics was significantly associated with hypokalemia ($P=0.035$). Other medication usage and clinical findings did not exhibit significant differences between patients with and without hypokalemia ($P>0.05$).

Furthermore, there was no significant difference in the incidence of vomiting/diarrhea ($P=0.236$) or hypomagnesemia ($P=0.271$) between patients with and without hypokalemia. However, patients with hypokalemia had a significantly higher mortality rate (14.0% vs. 3.3%, $P=0.003$) and longer hospital stays (median 11 vs. 8 days, $P<0.001$) compared to those without hypokalemia.

Univariate and multivariate logistic regression analyses revealed that age (OR: 1.023, $P=0.019$), hospitalization days (OR: 1.112, $P<0.001$), and diuretic usage (OR: 1.868, $P=0.036$) were independent risk factors for hypokalemia. Additionally, hypokalemia significantly increased mortality (OR: 4.796, $P=0.003$), along with prolonged hospitalization (OR: 1.147, $P<0.001$). Multivariate analysis showed that hospitalization days were associated with both hypokalemia (OR: 1.108, $P<0.001$) and mortality (OR: 1.131, $P<0.001$), while the association between hypokalemia and mortality was not statistically significant (OR: 2.427, $P=0.153$, Tables 2 and 3).

## Discussion

The findings of this study demonstrated that hypokalemia is an independent risk factor associated with mortality and length of hospital stay. The homogeneous distribution in terms of gender, with the number of 150 female and 150 male patients, contributes to obtaining more objective results.

Due to the mean age of 59.54 ± 15.70 years, this study has a younger population compared to other studies (8,9), allowing us to independently evaluate the morbidity and mortality risk that increases with advanced age.

The frequency of hypokalemia in this study (19.0%) was similar to that of hypokalemia (15.8%) in the study performed by Mallow et al (10). It has been shown that hypokalemia is more common, especially in females aged

**Table 2.** Factors Affecting the Presence of Hypokalemia

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% GA )** | ***P* Value** | **OR (95% GA)** | ***P* Value** |
| Gender | | | | |
| Female | Reference | - | Reference | - |
| Male | 1.481 (0.827-2.652) | 0.187 | 1.838 (0.952-3.546) | 0.070 |
| Age (y) | 1.023 (1.004-1.043) | 0.019 | 1.017 (0.994-1.040) | 0.158 |
| Comorbidities | | | | |
| DM | 0.982 (0.533-1.810) | 0.953 | | |
| HTN | 1.477 (0.819-2.664) | 0.195 | 0.740 (0.297-1.844) | 0.518 |
| CVD | 1.088 (0.601-1.969) | 0.782 | | |
| Drugs | | | | |
| Diuretics | 1.868 (1.041-3.354) | 0.036 | 1.742 (0.719-4.219) | 0.219 |
| Corticosteroids | 0.763 (0.361-1.611) | 0.478 | | |
| Insulin | 1.306 (0.560-3.049) | 0.537 | | |
| Beta-2 agonists | 0.930 (0.477-1.814) | 0.930 | | |
| ACE-Is/ARBs | 1.431 (0.790-2.591) | 0.237 | | |
| Beta-blockers | 0.718 (0.318-1.622) | 0.426 | | |
| Digoxin | - | - | | |
| Antipsychotics | 1.226 (0.248-6.064) | 0.803 | | |
| Clinical and laboratory findings | | | | |
| Vomiting/diarrhea | 1.645 (0.808-3.349) | 0.170 | 2.296 (1.063-4.961) | 0.034 |
| Hypomagnesemia | 1.594 (0.784-3.239) | 0.197 | 1.022 (0.462-2.262) | 0.957 |
| Patient Outcome | | | | |
| Discharged | Reference | - | Reference | - |
| Death | 4.796 (1.717-13.396) | 0.003 | 2.657 (0.790-8.943) | 0.114 |
| Day of hospitalization | 1.112 (1.063-1.164) | <0.001 | 1.108 (1.054-1.164) | <0.001 |

*Note*. Variables with $P<0.2$ in univariate analysis were included in multivariate analysis (Nagelkerke R Square: 0.192. OR: Odds ratio; GA: CVD: Cardiovascular disease; DM: Diabetes; HTN: Hypertension; ACE-I: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blocker; CI: Confidence Interval.

**Table 3.** Factors Affecting Mortality

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | **OR (95% GA )** | ***P* Value** | **OR (95% GA)** | ***P* Value** |
| Gender | | | | |
| Female | 2.295 (0.777-6.774) | 0.133 | 2.420 (0.725-8.075) | 0.151 |
| Male | Reference | - | Reference | - |
| Age (year) | 1.035 (1.000-1.072) | 0.052 | 1.024 (0.977-1.072) | 0.322 |
| Comorbidities | | | | |
| DM | 0.890 (0.301-2.635) | 0.834 | | |
| HTN | 2.718 (0.856-8.630) | 0.090 | 0.740 (0.297-1.844) | 0.518 |
| CVD | 1.757 (0.640-4.822) | 0.274 | | |
| Drugs | | | | |
| Diuretics | 1.898 (0.691-5.211) | 0.214 | | |
| Corticosteroids | 1.771 (0.592-5.298) | 0.307 | | |
| Insulin | 1.817 (0.491-6.723) | 0.371 | | |
| Beta-2 agonists | 1.800 (0.632-5.129) | 0.271 | | |
| ACE-Is/ARBs | 1.194 (0.421-3.383) | 0.739 | | |
| Beta-blockers | 1.599 (0.495-5.165) | 0.433 | | |
| Digoxin | - | - | | |
| Antipsychotics | 2.300 (0.270-19.604) | 0.446 | | |
| Clinical and laboratory findings | | | | |
| Vomiting/diarrhea | - | - | | |
| Hypomagnesemia | 1.681 (0.520-5.438) | 0.386 | | |
| Hypokalemia | 4.796 (1.717-13.396) | 0.003 | 2.427 (0.719-8.198) | 0.153 |
| Day of hospitalization | 1.147 (1.083-1.214) | <0.001 | 1.131 (1.062-1.205) | <0.001 |

*Note*. Variables with $P<0.2$ in univariate analysis were included in multivariate analysis (Nagelkerke R Square: 0.284). OR: Odds ratio; GA: ; CVD: Cardiovascular disease; DM: Diabetes; HTN: Hypertension; ACE-I: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blocker.

65 and over (11). In this study, no significant difference was found between gender and the development of hypokalemia. This situation can be explained by the fact that our patients were predominantly in the young age range.

It is known that the use of diuretics is a risk factor for the development of hypokalemia by causing renal potassium loss (12). Rodenburg et al reported that the risk of hypokalemia increased 11 times in patients using diuretics, especially the thiazide group (13). In this study, following the literature, the use of diuretics in patients with COVID-19 has been observed to be associated with hypokalemia. Potassium loss through the gastrointestinal tract is one of the causes of hypokalemia (12), and as a result, the presence of vomiting/diarrhea was found to be a risk factor for the development of hypokalemia. Studies have also demonstrated that hypokalemia may develop with vomiting/diarrhea due to drug-induced (lopinavir/ritonavir) or cytopathic effects of the virus (8–14).

Although the effect of beta-blockers on increasing potassium levels is known (15), no correlation was detected between hypokalemia and beta-blocker use in our study. Likewise, no significant correlation was observed between the development of hypokalemia in COVID-19 patients with and without using ACE-Is/ARBs. In their study, Alfano et al reported no correlation between the use of ACE-Is/ARBs and hypokalemia (8). Although we expected hypokalemia to be found less frequently in these patients, we could not reach this result; this can be attributed to the fact that the drugs used in the treatment of COVID-19 (corticosteroids, beta-2 agonists, or lopinavir/ritonavir) mostly have a potassium level-lowering effect.

While the mortality rate was 3.3% in patients without hypokalemia, this rate was 14.0% in patients with hypokalemia, and a significant correlation was observed between the number of deaths and the presence of hypokalemia. In addition, it was determined that mortality increased 4.79 times in the presence of hypokalemia. Hospitalization periods were longer in patients with hypokalemia than in patients without hypokalemia. In another study, it was revealed that patients with hypokalemia have a higher sequential organ failure assessment score and have a longer hospitalization period (8).

This study had some limitations. It is known that potassium plays an important role in blood pressure regulation. Nonetheless, retrospective blood pressure values followed during the hospitalization period of the patients could not be reached in this study.

The arrhythmia effect of hypokalemia could not be evaluated in patients because retrospective *electrocardiogram* records could not be accessed. There were no data regarding the body mass index, smoking,

or blood lipid values, which could be used for evaluating the morbidity and mortality status of the patients more clearly.

## Conclusion

Advanced age and the use of diuretics emerged as risk factors for hypokalemia in COVID-19 patients. The presence of hypokalemia was correlated with longer hospital stays and a higher mortality rate, underscoring the importance of vigilance regarding electrolyte imbalances in patient management.

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### Authors' Contribution

**Conceptualization:** Aytekin Oguz.
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### Ethical Approval

The study received approval from the local ethics committee on September 8, 2021, with decision number 2021/0454. The study adhered to the principles outlined in the Declaration of Helsinki. All patients were informed about the study, and their participation was voluntary, with each patient providing written informed consent prior to their inclusion in the study.

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