**Title**: Prevalence of hypokalemia and its correlation with hematological parameters and biomarkers of inflammation in adult COVID-19 patients in southeastern Iran, 2021-2022: a cross-sectional study

**Running title**: Hypokalemia and biomarkers in COVID-19

**Authors**:

Mahyar Rafiei1, Mehrdad Farrokhnia\*2

1. Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran

2. Infectious and Internal Medicine Department, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

**Corresponding Author (\*):** Mehrdad Farrokhnia

Address: Kerman University of Medical Sciences, Medical University Campus, Haft-Bagh Highway, Kerman, Iran

Postal Code: 7616913555

E-mail: [m.farokhniya@kmu.ac.ir](mailto:m.farokhniya@kmu.ac.ir)

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Abstract

**Background**

Since the COVID-19 outbreak, various studies have shown that hypokalemia is a common disorder, and it has been established that abnormalities in inflammatory biomarkers and complete blood count test (CBC) parameters are associated with the severity of the disease. So, this study investigates the association between hypokalemia and abnormalities in biomarkers of inflammation and CBC parameters, as well as the severity of COVID-19.

**Methods**

This single-centered cross-sectional study was conducted on 527 adult COVID-19 patients admitted to Afzalipour Hospital in Kerman, Iran, between March 2021 and March 2022. All patients had positive PCR tests, and their data was collected from electronic records. The relationship between hypokalemia and laboratory results, length of hospitalization, ICU admission, and mortality was analyzed by SPSS 27. **Results**

A total of 527 COVID-19 patients with an average age of 53.6 years and an average duration of hospitalization of 7.89 days were reviewed retrospectively. Most of the patients were hospitalized in the general wards (90.5%) and recovered (89.2%). In this study, the prevalence of hypokalemia was 12%, and there was no significant correlation with demographic data or laboratory findings, including ESR, CRP, LDH, lymphocyte, and platelet counts. There was also no association between hypokalemia and length of hospitalization, ICU admission, or mortality.

**Conclusion**

In total, it was found that 12% of COVID-19 patients had hypokalemia, and no significant association was found between hypokalemia and demographic data, laboratory findings, duration of hospital stay, ICU admission, or mortality.

**Keywords:** COVID-19; hypokalemia; complete blood count; biomarkers; inflammation; hematologic tests

**1 INTRODUCTION**

In December 2019, an outbreak of the novel beta coronavirus SARS-CoV-2 occurred in Wuhan City, Hubei Province, China, leading to the recognition of Coronavirus Disease 2019 (COVID-19).1 SARS-CoV-2, a single-stranded RNA virus, has caused over 772 million established cases and 6.9 million deaths worldwide.2, 3 Most COVID-19 cases have mild self-limiting manifestations (81%), but it can cause severe symptoms such as dyspnea, tachypnea, and hypoxia (14%), or critical respiratory symptoms (5%) that cause multiple organ failure and acute respiratory distress syndrome.4 Lung is the primary target of SARS-CoV-2, and atypical pneumonia is the most common clinical form, but other organs such as the heart, brain, liver, and kidneys can also be involved.5, 6 Systemic release of cytokines is thought to be a major reason for organ dysfunction and cause complications in these patients.7

Hypokalemia (serum potassium level less than 3.5 mmol/L)8 is a common electrolyte disorder seen in COVID-19 patients. A meta-analysis by Noori et al. reported that 24% of COVID-19 patients had hypokalemia.9 Few studies have examined the relationship between hypokalemia and the severity of the disease by analyzing the incidence of hypokalemia and elevated hospitalization length, ICU admission, or mortality, but their results were heterogenous.10-14 Chen et al. also examined the relation of hypokalemia with COVID-19 patients’ outcomes and inflammatory markers, which showed elevated levels of ESR and CRP in hypokalemic patients.15

Since the virus penetrates the host cells by binding the spike or S protein (S1) to ACE2 receptors,16 it is assumed that hypokalemia, which can increase vulnerability to arrhythmias, could occur due to virus binding to ACE2 and increased angiotensin 2, followed by an overactive renin-angiotensin-aldosterone system (RAAS) or other different causes such as digestive losses, anorexia due to the current disease, prolonged hospitalization, and tubular damage brought on by ischemia or nephrotoxic substances.17-20

SARS-CoV-2 also has a substantial impact on hematological systems, which can cause laboratory abnormalities including lymphopenia, thrombocytopenia, leukocytosis, and leukopenia, and also cause abnormalities in biomarkers of inflammation such as elevated levels of ESR, C-reactive protein (CRP), procalcitonin, D-dimer, and lactate dehydrogenase (LDH).21-24 It has been shown in various studies that abnormal laboratory findings such as elevated procalcitonin, serum ferritin, ESR, and CRP are among the inflammatory indicators that are strongly linked to the increased risk of COVID-19 intensification.25

As it was mentioned, while numerous studies have been conducted to find out the prevalence of hypokalemia and its correlation with the severity of the disease, few have examined the correlation between hypokalemia and CBC parameters, or inflammatory markers. Additionally, based on reviewed studies, no study with this sample size has investigated the correlation between the prevalence of hypokalemia on the first day of admission and biomarkers of inflammation, CBC parameters, length of hospitalization, ICU admission, and mortality.

Therefore, this study aimed to evaluate the relationship between hypokalemia and biomarkers of inflammation and the severity of the disease in order to assist in the management of the disease and the determination of the patient’s prognosis.

**2 METHODS**

**2.1 Study design**

In this single-centered cross-sectional study, the records of 527 adult COVID-19 patients admitted to the infectious ward or intensive care unit of Afzalipour Hospital in Kerman between March 21st, 2021, and March 20th, 2022, were the subject of the analysis. All of the patients included in the study had at least one positive SARS-Cov-2 RT-PCR test and were older than 18 years, and the records were gathered from the archive. The researcher entered patients’ demographic data, such as age, gender, length of hospital stays, and survival status, into the designated checklist. Additionally, laboratory results from the first 24 hours of the patient’s hospitalization, which include serum potassium, ferritin, ESR, CRP, LDH, lymphocyte count, and platelet counts from the CBC (complete blood count) test, have been imported into the checklist. In this study, hypokalemia is defined as serum potassium levels less than 3.5 mmol/L.8

**2.2 Inclusion and exclusion criteria**

The study included all patients older than 18 who were tested positive for SARS-Cov-2 by RT-PCR. Individuals whose serum potassium level was not assessed on their first day of admission were excluded from the research. Cases with inadequate laboratory results or insufficient information have been excluded from the study. After excluding problematic cases, a total of 527 patients entered the study, of whom ferritin of 93, CRP of 483, ESR of 481, LDH of 503, platelets of 525, and lymphocytes of 519 cases had been checked. All variables were analyzed except the level of ferritin due to significant missing data. Other missing data were replaced by imputation techniques.

**2.3 Outcome**

The primary outcome was finding the prevalence of hypokalemia in COVID-19 patients on their first day of admission. The secondary outcome was identifying the correlation between the incidence of hypokalemia and other laboratory abnormalities such as elevated levels of ESR, CRP, LDH, lymphopenia, and thrombocytopenia, and also investigating the association between the incidence of hypokalemia and increased risk of hospital stay, ICU transfer, and mortality.

**2.4 Statistical analysis**

For descriptive statistics, the frequency, relative frequency, and mean central index were employed. For columnar correlations involving all the required variables, the logistic regression test was employed, and the results were analyzed using SPSS software version 27.

**3. RESULTS**

This study was conducted on 527 COVID-19 patients from the ages of 18 to 96, with a mean age of 53.6 years (SD (standard deviation), 17.71) and a mean hospitalization duration of 7.89 days (SD, 7.84). Four hundred and seventy-seven patients which were 90.5% of all patients were admitted to the general wards and 50 patients which were 9.5% of all investigated patients were admitted to the ICU during their hospital stay. Four hundred and seventy patients which was 89.2% of all patients were eventually recovered, and 57 patients, which was 10.8% of all patients, expired. Two hundred and sixty-five patients which was 50.3% of all the patients were male and 262 patients which was 49.7% of all the patients were female. (Shown in Table 1)

The mean levels of laboratory findings in all of the COVID-19 patients are shown in Table 2.

Hypokalemia, which is evaluated on the first day of admission, was found in 63 patients which was 12% of all patients. (Shown in Table 3)

Among patients who had hypokalemia, 43 of the patients were female (68.3%) and 20 of them were males (31.7%). This difference was statistically significant (p-value = 0.002) based on a univariate logistic regression test. But among the patients who did not have hypokalemia, 219 (47.3%) of the patients were female and 244 (52.7%) of them were male. In both groups, patients with hypokalemia and patients without hypokalemia, most of the patients were admitted to general wards (92.1% of patients with hypokalemia, 90.3% of patients without hypokalemia), and most patients in each group were ultimately recovered (92.1% of patients with hypokalemia, 88.8% of patients without hypokalemia). The prevalence of hypokalemia did not significantly correlate with the risk of ICU admission or mortality. The mean days of hospitalization in COVID-19 patients with hypokalemia (7.07 days; SD, 7.00) were less than those without hypokalemia (8 days; SD, 7.95). This difference was not statistically significant (p-value = 0.37). The mean age of patients with hypokalemia was 48.92 years (SD, 15.77), which was less than the mean age of patients without hypokalemia, which was 54.23 years (SD, 17.87). This difference was found to be statistically significant (p-value = 0.02). (Shown in Table 4)

The mean levels of all laboratory findings other than CRP were lower in patients with hypokalemia than in patients without hypokalemia. The mean levels of laboratory findings in COVID-19 patients with or without hypokalemia had no statistically significant differences. (Shown in Table 5)

Based on a univariate logistic regression test, it was discovered that hypokalemia has a statistically significant association with the variables age and gender, but in multivariate logistic regression, there was no statistically meaningful association between hypokalemia and demographic or laboratory variables. (Shown in Table 6)

**4. DISCUSSION**

Considering the high prevalence of hypokalemia in COVID-19 patients in the literature9-15 and the studies conducted on laboratory findings, including CBC parameters and biomarkers of inflammation, which established the association of these biomarkers with the severity of the disease.23, 25, 26 This study aimed to find out the prevalence of hypokalemia and its association with CBC findings and inflammatory markers in adult patients with COVID-19 to determine the association of hypokalemia with the severity of the disease. In this study 527 patients with a mean age of 53.6 and a mean length of hospitalization of 7.89 days were reviewed retrospectively. Most patients were hospitalized in general wards, and most of them recovered.

The study’s results showed that 12% (63) of the patients had hypokalemia on the first day of their admission. The rate of hypokalemia was close to the studies conducted by Sarvazad et al.10 and Genovesi et al.14 which reported 9.1% and 9%, respectively. This prevalence rate of hypokalemia was considerably lower than the findings of most previous studies,9, 11-13, 15 which can be due to the measurement of blood potassium levels on the first day of hospitalization, as most studies examine the incidence of hypokalemia during hospitalization, not the first day of hospitalization. In this study there was no significant association between the prevalence of hypokalemia and increased ICU hospitalization risk, increased hospitalization duration, or increased mortality. There was heterogeneity in previous literature about the association between hypokalemia and the risk of ICU admission. This current study, as well as some of the previous studies,10, 11, 14 reported no significant association between hypokalemia and the risk of transferring to the ICU, which was against the findings of the Moreno et al. study.13 But the literature was consistent in terms of length of hospitalization and mortality, as in prior studies,12, 13 contrary to the current investigation, a significant association between hypokalemia and prolonged hospitalization was found. In the case of mortality, this study, just like previous studies, did not find any significant relationship between hypokalemia and mortality.11, 13, 14

These differences in results might be due to various reasons, such as differences in the timing of serum potassium measurements, which led to differences in the prevalence of hypokalemia, or differences in underlying diseases, laboratory errors, race, and virus variants.

Serum levels of CRP, ESR, LDH, platelet count, and lymphocyte count were studied in patients who had hypokalemia and patients who did not have hypokalemia. The results showed that the levels of all variables except CRP were lower in patients with hypokalemia than in the opposite group, but no significant correlation was reported between any of the variables and hypokalemia, and no association between hypokalemia and demographic variables or laboratory findings was seen. These results are against the findings of Chen et al., which found a significant association between higher levels of LDH and CRP and the existence of hypokalemia in COVID-19 patients.15 This difference also might be due to the different time of the potassium measurement, which caused a lower rate of hypokalemia in the present study.

In this study, serum potassium levels less than 3.5 mmol/L were considered as hypokalemia.8 Hypokalemia in the course of SARS-CoV-2 infection could be a result of the virus binding to ACE2 and causing a rise in angiotensin II17 and overactivation of the renin-angiotensin-aldosterone system (RAAS), gastrointestinal losses, secondary anorexia to the current disease, and tubular injury caused by ischemia or nephrotoxic substances. According to the recent hypothesis, the direct cytotoxic effect of SARS-CoV-2 may be linked to tubular damage, as the virus has been linked to damage caused by tubular emissions.18

Patients with COVID-19, on the other hand, may experience prolonged hospitalizations. They are usually undergoing several different treatments, including ventilating with a ventilator and various medications for SARS-CoV-2 infection, which can cause low serum potassium levels. In this treatment setting, fever, hyperventilation, sweating, drug-induced complications, and dietary changes may cause electrolytic imbalance. Hypokalemia can also cause fatal arrhythmias, resulting in various complications and an increased risk of death. However, these complications are associated with the severity of hypokalemia and usually occur in severe hypokalemia (values less than 2.5 mmol /L).19, 20

The limitations of the current study were its retrospective and single-center examination, defects in files and laboratory errors, the lack of examination of other factors affecting the severity of the disease, such as the history of underlying diseases and immunodeficiency, the lack of assessments of the trend of changes and the occurrence of hypokalemia in the hospitalization of patients with COVID-19, as well as its changes after the disease has improved in those who survived.

**5. CONCLUSION**

In total, the present study found that the prevalence of hypokalemia on the first day of hospitalization of patients with COVID-19 was 12%, and no statistically significant association between hypokalemia with demographic variables, laboratory findings, length of hospital stay, ICU admission, and mortality was found.

**CONFLICT OF INTEREST STATEMENT**

There are no conflicts of interest that the authors can disclose.

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**Table 1:** Determination of frequency of demographic characteristics in patients with COVID 19

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | **No. of patients** | | | **Percentage** |
| **Gender**  **Male** | | 265 | | | 50.3 | | |
| **Female** | | 262 | | | 49.7 | | |
| **Ward**  **General ward** | | 477 | | | 90.5 | | |
| **ICU** | | 50 | | | 9.5 | | |
| **Outcome**  **Recovered** | | 470 | | | 89.2 | | |
| **Expired** | | 57 | | | 10.8 | | |
|  | | **Mean** | | | **Standard deviation** | | |
| **Age (Years)** | | 53.6 | | | 17.71 | | |
| **Duration of hospitalization (Days)** | | 7.89 | | | 7.84 | | |

Abbreviation: ICU, intensive care unit

**Table 2:** Determination of laboratory findings in patients with COVID 19

|  |  |  |
| --- | --- | --- |
|  | **Mean** | **Standard deviation** |
| **ESR (mm/h)** | 47.87 | 28.12 |
| **CRP (mg/L)** | 46.71 | 9.39 |
| **LDH (U/L)** | 702.35 | 344.92 |
| **Platelet count (109/L)** | 190.72 | 89.93 |
| **Lymphocytes (109/L)** | 1.06 | 0.59 |

Abbreviation: ESR, estimated sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase

**Table 3:** Prevalence of Hypokalemia in Patients with COVID-19

|  |  |  |
| --- | --- | --- |
|  | **Prevalence** | **Percentage** |
| **With hypokalemia** | 63 | 12 |
| **Without hypokalemia** | 464 | 88 |

**Table 4:** Prevalence of Hypokalemia Based on Demographic Characteristics in Patients with COVID-19

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **With hypokalemia** | | | **Without hypokalemia** | | **P-value** |
| **Prevalence** | | **Percentage** | **Prevalence** | **Percentage** |
| **Gender**  **Male** | 20 | 31.7 | | 244 | 52.7 | 0.002 |
| **Female** | 43 | 68.3 | | 219 | 47.3 |
| **Ward**  **General ward** | 58 | 92.1 | | 417 | 90.3 | 0.64 |
| **ICU** | 5 | 7.9 | | 45 | 9.7 |
| **Outcome**  **Recovered** | 58 | 92.1 | | 411 | 88.8 | 0.43 |
| **Expired** | 5 | 7.9 | | 52 | 11.2 |
|  | **Mean** | **Standard deviation** | | **Mean** | **Standard deviation** | **P-value** |
| **Age** | 48.92 | 15.77 | | 54.23 | 17.87 | 0.02 |
| **Duration of hospitalization** | 7.07 | 7.00 | | 8 | 7.95 | 0.37 |

Based on independent t-test and chi-square test; Abbreviation: ICU, intensive care unit

**Table 5:** Determination of mean laboratory findings in patients with or without hypokalemia

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **With hypokalemia** | | **Without hypokalemia** | | **P-value** |
| **Mean** | **Standard deviation** | **Mean** | **Standard deviation** |
| **ESR (mm/h)** | 46.9 | 3.54 | 48 | 1.37 | 0.77 |
| **CRP (mg/L)** | 52.81 | 4.97 | 45.87 | 1.92 | 0.2 |
| **LDH (U/L)** | 670.18 | 37.46 | 706.8 | 16.74 | 0.43 |
| **Platelet count (109/L)** | 185.68 | 12.01 | 191.41 | 4.15 | 0.63 |
| **Lymphocytes (109/L)** | 0.94 | 0.04 | 1.08 | 0.02 | 0.09 |

Based on independent t-test; Abbreviation: ESR, estimated sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase

**Table 6:** Determination of the results of multivariate and univariate logistic regression in relation to hypokalemia with demographic variables and laboratory findings in patients with COVID-19

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Unadjusted** | | **Adjusted** | |
| **P-value** | **OR** | **P-value** | **OR** |
| **Age** | 0.02 | 1.01 | 0.20 | 0.97 |
| **Gender** | 0.00 | 0.41 | 0.27 | 0.35 |
| **Outcome** | 0.43 | 1.46 | 1.00 | 5157.00 |
| **Duration of hospitalization** | 0.37 | 1.01 | 0.37 | 0.92 |
| **Ward** | 0.64 | 1.25 | 1.00 | 3.02 |
| **ESR** | 0.77 | 1.001 | 0.32 | 1.01 |
| **CRP** | 0.21 | 0.99 | 0.19 | 0.98 |
| **LDH** | 0.43 | 1 | 0.24 | 1.002 |
| **Platelet count** | 0.63 | 1.001 | 0.97 | 1 |
| **Lymphocytes** | 0.09 | 1.59 | 0.78 | 1.25 |

Abbreviation: ESR, estimated sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase