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Frequency of Hypokalemia among Patients with Corona Virus Disease 2019 (COVID-19) and Correlation with The Disease Severity

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Abstract

Patients with COVID-19 experience multiple clinical conditions that may cause electrolyte imbalances. SARS-CoV-2 binds angiotensin I converting enzyme 2 (ACE2) of renin–angiotensin system (RAS) and causes prevalent hypokalemia. Hypokalemia is a concerning electrolyte disorder closely associated with severe complications. To evaluate frequency of hypokalemia in covid-19 patients and its correlation with disease severity and outcome. The current study was a retrospective cohort study conducted on 400 confirmed covid-19 patients above 18 years old admitted to Al Zahraa University Hospital during the period between November 2020 and March 2022.In the current study, all patients were divided according to serum potassium level and it revealed that there were 161 patients with normal potassium level (40.3%), 133 patients with mild hypokalemia (33.3%),75 patients with moderate hypokalemia (18.8%) and 31 patients with severe hypokalemia (7.8%). More ever we found that severity of disease was associated with severity of hypokalemia but there was no association between mortality and severity of hypokalemia. HTN was the commonest comorbidity (42.3%) and corticosteroid was a risk factor for hypokalemia development in our patients. Finally, hypokalemia was associated with long hospital stay and can be used as a predictor of severity of covid-19. Hypokalemia was a common electrolyte disturbance in covid-19 patients and most cases were of mild degree. Severity of hypokalemia was associated with disease severity but had no effect on mortality. Serum potassium level should be monitored in clinical practice of covid-19 cases.

Keywords: Corona virus, Covid-19, Hypokalemia, Angiotensin converting enzyme2 (hACE2) receptor.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic, was first detected in Wuhan (China) in late December 2019. The infection continued to spread rapidly and remains a serious threat to global health [1]. The lung is the principal target of the novel coronavirus, and atypical pneumonia is the most common clinical presentation. Multiple organs such as the heart, brain, liver and kidneys can be involved during this infection [2]. Systemic release of cytokines is thought to be the cause of organ dysfunction and, therefore, the major determinant of morbidity in these patients. Cytokines provoke a severe proinflammatory state leading to hypoxemia and sepsis requiring intensification of supportive therapy. [3]

Patients with COVID-19 can experience a long hospital stay. They usually undergo multiple treatments varying from delivering of ventilatory support to the administration of experimental agents for SARS-CoV-2 infection. In this setting, fever, hyperventilation, sweating, medication-related side effects and dietary changes may cause concerning electrolyte imbalances. Hypokalemia is a frequent lab abnormality. There is particular concern about this disorder as it may increase the susceptibility to potentially fatal arrhythmia in COVID-19 patients [4].

Possible causes of hypokalemia in the context of SARS-CoV2 infection may result from hyper-activation of the renin–angiotensin–aldosterone system (RAAS), gastrointestinal losses, anorexia secondary to concurrent illness and tubular damage caused by ischemia, nephrotoxic agents or the direct cytotoxic effect of SARS-CoV-2 causing diffuse tubular damage [5].

Hypokalemia results in cellular hyper polarity, increases resting potential, and hastens depolarization in cardiac cells and lung cells [6].

Severe hypokalemia (<2.5 mmol/L) can trigger ventricular arrhythmia and respiratory muscle dysfunction, both of which are life-threatening conditions in patients with severe COVID-19. This implies that hypokalemia should be seriously addressed in COVID-19 patients because these patients have a high prevalence of dysfunction in the heart, lungs, and other vital organs [7]. The aim of the current study was to evaluate frequency of hypokalemia in covid-19 patients and its correlation with disease severity and outcome of patients.

2. Patients and Methods

The current study is a retrospective cohort one conducted on 400 confirmed covid-19 patients (evidenced by positive PCR covid-19 real-time for all patients) above 18 years old admitted to Al Zahraa University Hospital during the period between November 2020 and March 2022.

Their sex distribution was (181 female & 219 male) and their age ranged from (18 to 91) years. They were divided according to serum potassium level into 4 groups:

Group 1: COVID-19 patients with normal potassium level (normokalemia) (3.5-5.5mmol\L).

Group 2: COVID-19 patients with mild hypokalemia (3-3.5 mmol\L).

Group 3: COVID-19 patients with moderate hypokalemia (2.5-3 mmol\L).

Group 4: COVID-19 patients with severe hypokalemia (below 2.5 mmol\L).

The study protocol was reviewed and approved by the ethical committee of the Faculty of Medicine for Girls, Al Azhar University.

2.1 Inclusion criteria

Patients above the age of 18 years old with Covid-19**.**

2.2 Exclusion criteria

Patients below 18 years old, patients who had another infectious disease, chronic liver disease, chronic kidney disease or received drugs causing hypokalemia.

2.3 Methods

All medical records of covid-19 patients admitted to hospital were reviewed as follow: review of medical history with special emphasize on age, sex and associated comorbidity, vital data of the patients, clinical manifestations recorded (fever, diarrhea and dry cough), oxygen saturation, mode of oxygenation, severity of disease (mild, moderate and severe) which was categorized according to diagnostic criteria of Egyptian Ministry Of Health guidelines [8], duration of hospital admission, treatment process (we focused on drugs that cause hypokalemia as corticosteroid) and outcome of the patients, discharged or died. Laboratory investigations include Complete blood count, Serum potassium, serum creatinine, serum albumin, CRP titre, serum ferritin, D-dimer & Arterial blood gases (ABG). Radiological data: CT chest to investigate cord staging of the patients.

2.4 Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean ± standard deviation and ranges. Also, qualitative variables were presented as numbers and percentages. Data were explored for normality using the Kolmogorov-Smirnov and Shapiro-Wilk Test. The significance of the test was determined based on *P* values: *P* value less than or equal to 0.05 was considered significant, while *P* value more than 0.05 was considered nonsignificant.

3. Results

As shown in Table .1. the demographic data of our study revealed that out of 400 COVID-19 patients, 181 (45%) were females and 219 (55%) were males. Their age ranged from 18 to 91 years, with mean ± SD (59.58±14.12). Out of 400 COVID-19 patients, 161 patients (40.3%) with normokalemia, 133 patients (33.3%) with mild hypokalemia, 75 patients (18.8%) with moderate hypokalemia and 31 patients (7.8%) with severe hypokalemia. As shown in Table .2. A comparison between demographic data among all patient groups revealed that there was no statistically significant difference identified as regard age (p-value=0.137) and gender (*p-value=0.08).* As shown in Table .3. A comparison between different laboratory data among all patient groups revealed that there was a statistically significant increase in platelet, serum ferritin and d-dimer with increased severity of hypokalemia (group IV). There was no statistically significant difference identified regarding WBCS, lymphocyte, CRP and serum albumin among the four patient groups. As shown in Table .4. arterial blood gas analysis among all patient groups, there was a statistically significant increase in respiratory alkalosis with an increase in severity of hypokalemia (group IV) (35.5%) with p-value <0.001 but there was no statistically significant difference identified regarding respiratory acidosis, metabolic alkalosis and metabolic acidosis. As shown in Table .5. and Figure .1 there was a statistically significant increase in severity of hypokalemia with increased days of hospital stay, with range 7-24 days, mean ± SD (16.06±3.86), p-value <0.001.(Table 5), (Fi. As shown in Figure .2. and Table .6. There was also a statistically significant increase in the severity of the disease with increased length of hospital stay with mean 11.45±4.79, p-value <0.001. As shown in Table .7. medications, there was a significant increase in severity of hypokalemia among patients who received corticosteroid treatment with a p-value of 0.009. As shown in Table .8. and Figure .3. disease severity, there was a highly statistically significant increase in severity of disease (83.9%) with increased severity of hypokalemia (group IV) with p-value <0.001. As shown in Table .9. Our statistical analysis revealed that there was no statistically significant difference identified between the severity of hypokalemia and the outcome of the patient with p-value = 0.127. As shown in Table .10. correlation between serum potassium with different parameters revealed that there was a statistically significant negative correlation between serum potassium level and serum creatinine, serum ferritin, D-dimer and length of hospital stay. There was a statistically significant positive correlation between serum potassium level and both Pco2 and o2 sat (which determine the severity of the disease). As shown in Table .11. and Figure .4. Receiver Operator Characteristics (ROC) curves were indices of K+ (mMol/L) as predictors of severity of COVID-19 in included patients. There was a significant predictor as denoted by the significantly large area under the curves (AUCs), which was used to define the best cut-off value of K+ (mMol/L) which was ≤3.1, with a sensitivity of 62.9% specificity of 72.4%, positive predictive value of 52.9%, negative predictive value of 79.8% with diagnostic area under the curve of 0.750 and accuracy 67.7%.

Table (1): Distribution of patients according to serum potassium level.

Hypokalemia Group	No.	%
Normokalemia (Group I)	161	40.3%
Mild Hypokalemia (Group II)	133	33.3%
Moderate Hypokalemia (Group III)	75	18.8%
Severe Hypokalemia (Group IV)	31	7.8%

Table (2): Comparison between patient groups regarding demographic data.

Demographic data	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	Test value	p-value
Age (years)						
Mean ± SD	60.68±14.21	59.35±13.82	59.85±13.98	54.10±14.65	*H:* 5.524	0.137
Range	25-91	18-86	25-83	26-81		
Sex						
Female	73 (45.3%)	69 (51.9%)	25 (33.3%)	14 (45.2%)	x^2: 6.659	0.084
Male	88 (54.7%)	64 (48.1%)	50 (66.7%)	17 (54.8%)		

Using: H-Kruskal Wallis test; Chi-square test p-value >0.05 NS

Table (3): Comparison between patient groups regarding laboratory data.

Laboratory data	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	Test value	p-value
WBCS (10^3/ul)						
Mean ± SD	10.48±4.14	9.79±3.58	9.56±4.24	10.29±3.82	*H:* 3.097	0.377
Range	2.5-33.8	2.9-18.1	2.8-16.6	4-16.3		
PLT (10^3/ul)						
Mean ± SD	221.72±89.93B	258.08±110.0A	229.51±93.67B	272.52±103.13A	*H:* 3.999	0.008*
Range	55-515	57-540	54-543	80-454		
Lymphocyte(10^3/ul)						
Mean ± SD	1.57±0.90	1.58±0.92	1.58±0.85	1.61±0.79	*H:* 0.357	0.949
Range	0.3-3.9	0.2-5.1	0.3-3.8	0.4-3.6		
S.Albumin (mg/dl)						
Mean ± SD	3.05±0.61	3.19±0.53	3.06±0.56	3.12±0.56	*F:* 1.633	0.181
Range	1.2-5.5	1.9-4.5	1.8-4.3	1.9-4		
S.ferrritin (ng/ml)						
Mean±SD	200.32±188.31B	213.68±185.11B	290.91±213.80A	329.39±231.71A	*H:* 18.049	<0.001**
Range	12-870	13-918	12-907	24-927		
D-dimer (µg/ml)						
Mean±SD	1.24±1.26BC	1.02±1.02C	1.54±1.31B	1.90±1.33A	*H:* 14.553	0.002*
Range	0.1-5	0.1-4.2	0.1-4.2	0.1-4.2		
CRP titre (mg/L)						
Mean±SD	60.45±50.52	65.47±55.31	62.83±50.89	83.48±82.12	*H:* 1.811	0.612
Range	3.5-300	6-372	12-266	6-310		

F: One-way Analysis of Variance test was performed & Multiple comparisons between groups through Post Hoc test, Tukey's test, H: Kruskal Wallis was performed & Multiple comparisons between groups through the Mann-Whitney test Means that do not share the same letter are significantly different at p-value (p<0.05), p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 Hs.

Table (4): Comparison between the four patient groups regarding arterial blood gas analysis result:

ABG	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	Test value	p-value
Respiratory acidosis	6 (3.7%)	6 (4.5%)	3 (4.0%)	1 (3.2%)	0.17	0.982
Metabolic acidosis	17 (10.5%)	9 (6.8%)	5 (6.7%)	2 (6.4%)	2.012	0.570
Respiratory alkalosis	7 (4.3%)	8 (6.0%)	13 (17.3%)	11 (35.5%)	35.68	<0.001**
Metabolic alkalosis	3 (1.9%)	2 (1.5%)	1 (1.33%)	0 (0.0%)	2.346	0.504

F: One-way Analysis of Variance test was performed & Multiple comparisons between groups through Post Hoc test: Tukey's test. H: Kruskal–Wallis was performed & Multiple comparisons between groups through the Mann-Whitney test, means that they do not share the same letter and are significantly different at p-value (p<0.05). p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS.

Table (5): Comparison between days of hospital stay among all patient groups.

Length of hospital stay **(days)**	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	F-test	p-value
Mean ± SD	4.77±0.87D	9.67±2.39C	14.01±3.36A	16.06±3.86A	389.628	<0.001**
Range	3-7	5-18	7-22	7-24		

F: One-way Analysis of Variance test was performed & Multiple comparisons between groups through Post Hoc test: Tukey's test, means that do not share the same letter are significantly different at p-value (p<0.05). **p-value <0.001 HS

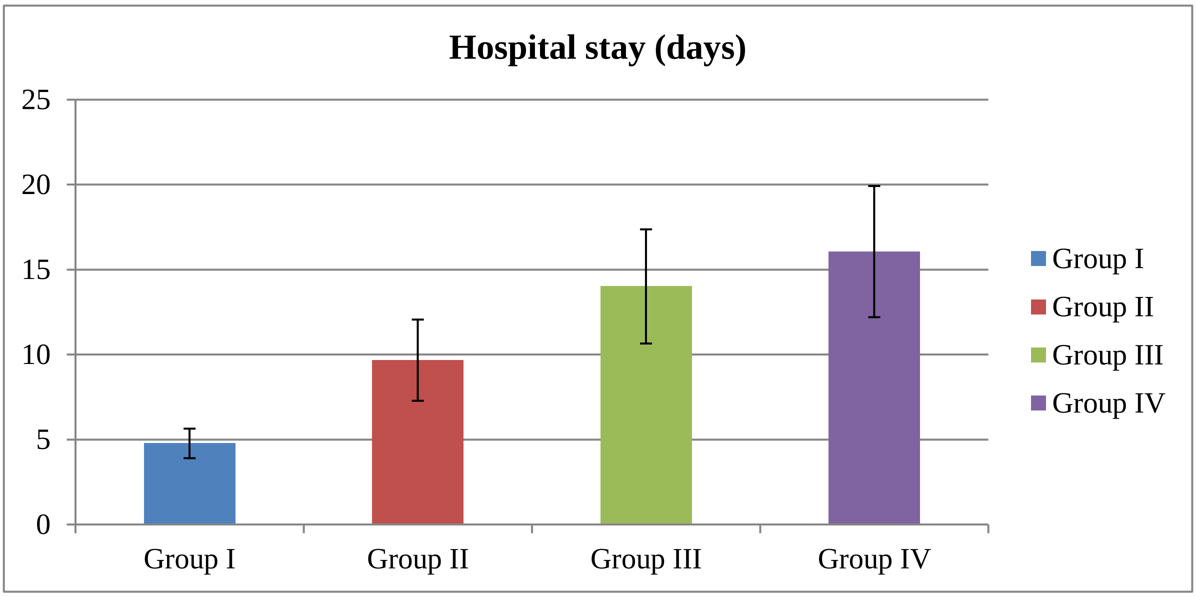

Figure 1: Days of hospital stay among the four patient groups.

Table (6): Comparison between the length of hospital stay with severity of disease

Length of hospital stay **(days).**	Mild (n=182)	Moderate (n=86)	Severe (n=132)	F-test	p-value
Mean ± SD	7.26±3.62B	8.95±4.63B	11.45±4.79A	36.963	<0.001**
Range	3-20	4-22	3-24		

F: One way Analysis of Variance test was performed & Multiple comparison between groups through Post Hoc test: Tukey’s test, **p-value <0.001 HS

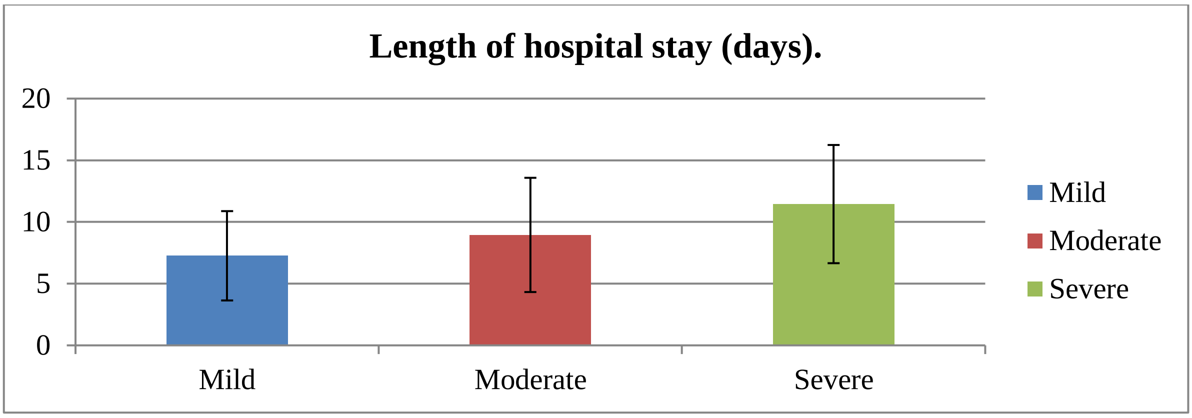

Figure (2): Length of hospital stay with severity of disease.

Table (7): Comparison between the four patient groups concerning the medications received.

Medication and Cortisone	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	Test value	p-value
Corticosteroid	108 (67.1%)	99 (74.4%)	60 (80%)	29 (93.5%)	11.580	0.009*
Supportive	33 (20.5%)	34 (25.6%)	27 (36.0%)	10 (32.3%)		
Insulin	54 (33.5%)	36 (27.1%)	19 (25.3%)	4 (12.9%)	7.076	0.070
B2 agonist	57 (35.4%)	39 (29.3%)	22 (29.3%)	7 (22.5%)	6.232 2.735	0.101 0.434

F: One-way Analysis of Variance test was performed & Chi-Square test p-value >0.05 NS

Table (8): Comparison between patient groups concerning disease severity.

Disease Severity of COVID-19	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	x^2	p-value
Mild	102 (63.4%)	69 (51.9%)	10 (13.3%)	1 (3.2%)	99.646	<0.001**
Moderate	35 (21.7%)	25 (18.8%)	22 (29.3%)	4 (12.9%)		
Severe	24 (14.9%)	39 (29.3%)	43 (57.3%)	26 (83.9%)		
Multiple comparisons	A	B	C	D		

Chi-Square test: **p-value <0.001 HS, Means that do not share the same letter are significantly different at p-value (p<0.05).

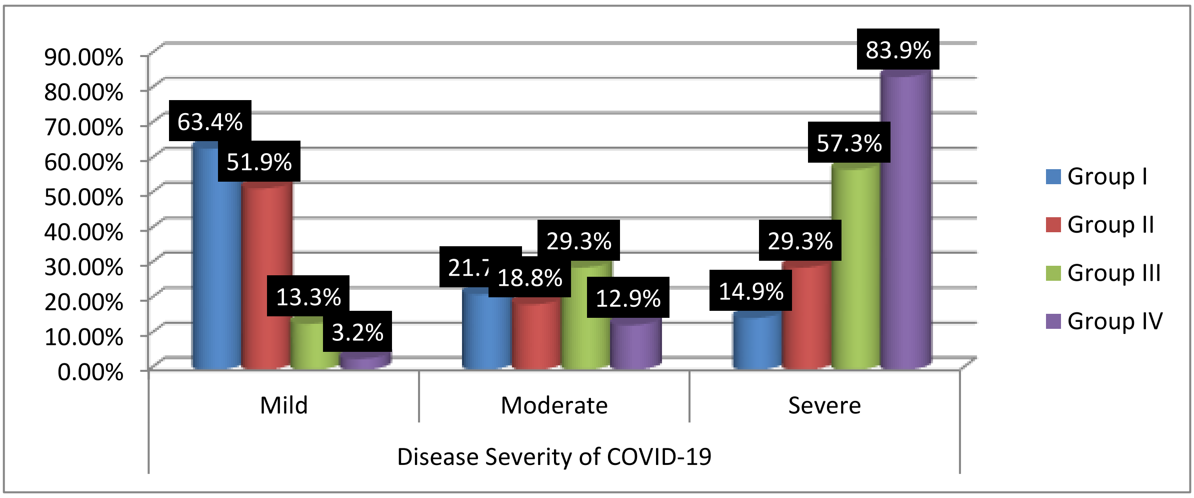

Figure (3): Comparison between patient groups concerning disease severity

Table (9): Comparison between patient groups concerning outcome.

Outcome	Group I (n=161)	Group II (n=133)	Group III (n=75)	Group IV (n=31)	x^2	p-value
Death	39 (24.2%)	51 (38.3%)	20 (26.7%)	14 (45.2%)	6.367	0.127
Discharge	122 (75.8%)	82 (61.7%)	55 (73.3%)	17 (54.8%)		

Chi-Square test; p-value >0.05 NS

Table 10: Correlation between serum K+ (mMol/L) with different parameters, using Pearson Correlation Coefficient among study group.

Parameters	K+ (mMol/L)	
	r-value	p-value
Age (years)	0.096	0.218
WBC (k/uL)	0.048	0.343
PLT (k/uL)	-0.080	0.111
LYMPH (k/uL)	-0.029	0.567
Creatinine (mg/dl)	-0.105	0.036*
S.Album (mg/dl)	-0.037	0.462
S.ferrritin (ng/ml)	-0.131	0.009*
D-dimer (µg/ml)	-0.099	0.049*
CRP titre (mg/L)	-0.085	0.090
PH	-0.044	0.382
PCO2 (mmHg)	0.214	<0.001**
HCO3 (Mmol/L)	-0.037	0.456
Hospital stays (days)	-0.764	<0.001**
So2% (disease severity)	0.331	<0.001**

Using: Pearson Correlation Coefficient, p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

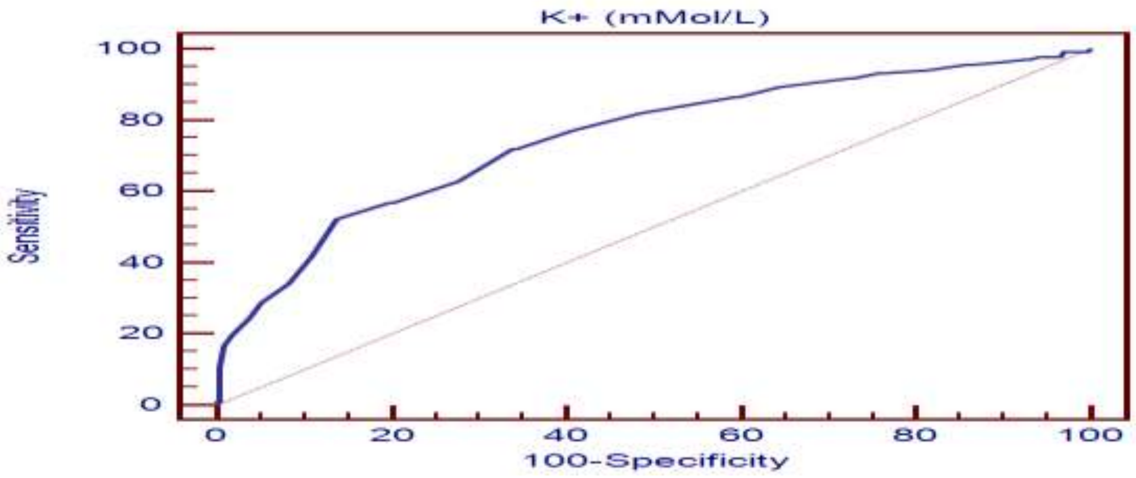

Figure (4): Receiver-operating characteristic (ROC) curve for prediction of disease severity of COVID-19 using K+ (mMol/L).

Table (11): Receiver-operating characteristic (ROC) curve analysis for prediction of disease severity of COVID-19 using K+ (mMol/L).

Cut-off	Sen.	Spe.	PPV	NPV	AUC [95% C.I.]
≤3.1	62.9%	72.4%	52.9%	79.8%	0.750 [0.704-0.792]

4. Discussion

The current study was carried out to evaluate the frequency of hypokalemia among patients with covid-19 and its correlation with severity of disease and outcome.

The current study is a retrospective cohort one conducted on 400 confirmed covid-19 patients (evidenced by positive PCR covid-19 real time for all patients); their sex distribution was (181 female & 219 male) and age ranged from (18 to 91) years. They were divided into 4 groups according to serum K level (normokalemia, mild, moderate and severe hypokalemia groups).

The results of our study revealed that distribution of male and female patients are nearly equal in hypokalemic and normokalemic groups.

There was no statistically significant difference between all groups according to distribution of gender.

Our findings agree with the study carried out by *Nasomsong et al. (2021*) [9] who divided the patients into 2 groups; normokalemia and hypokalemia and found that no statistical difference was identified regarding gender of patients between the two groups

Our findings agree also with the study carried out by *Yin et al. (2022*) [10] who found that no statistical difference was identified in gender of patients between hypokalemic and normokalemic groups.

Our findings disagree with *Pani et al. (2021*) [11] who estimated that female sex is a significant risk factor for hypokalemia in covid-19 patients and this study illustrate causes that interlink female sex with hypokalemia by experimental studies conducted in the 50s *(Sagild, 1956)* [12] and then confirmed in the 90s, *(Su et al., 2020)* [5] showed that women, especially aged ones, have less exchangeable body potassium than other subsets of the population. The women are, therefore, at high risk to develop hypokalemia because they have depleted deposits of potassium due to their different body composition, characterized by less amount of extracellular water compared to men.

In our study we found that, there was high prevelance of hypokalemia 60.0% among covid-19 patients and most of cases of mild degree. The degree of severity of hypokalemia was, mild, moderate and severe as follow 33.3%, 18.8% and 7.8% respectively.

The results of our study are matching with *Alfano et al. (2021*) [13] who reported that hypokalemia was detected in (41%) of patients and most of cases was of mild degree.

These findings were in agreement with the study done by *Chen et al. (2020)* [7], who demonstrated high prevelance of hypokalemia 62% in covid-19 patients and percentage of severity, mild 40%and severe 22%.

Also, these results come in agreement with *Yin et al. (2022*) [10] who reported that (48.15%) of patients with COVID-19 suffered from hypokalemia and the majority of patients (89.74%) patients experienced only a mild decrease in serum potassium level.

Also, our results showed that there was highly statistically significant increase in severity of disease with increase severity of hypokalemia and also serum K can be used as a predictor of severity of covid-19.

Severity of disease was assessed according to O2 saturation and the medical condition of the patients.

The study by *Moreno-Pérez et al. (2020*) [14] agreed with our result in that hypokalemia was a sensitive biomarker of severe progression of COVID-19.

The results of our study are also matching with *Lippi et al. (2020)* [15] who reported that there was significant relation between severity of disease and severity of hypokalemia. Our result also come in agreement with *Bhatangar et al (2021*) [16] who found that there was significant correlation between disease severity and severity of hypokalemia.

In our study**,** we found that serum ferritin and D-dimer (inflammatory markers) were more statistically significant higher in hypokalemic than normokalemic patients.

This agree with *Suresh et al. (2022*) [17] who found that Patients with hypokalemia (<3.5mmol/l) had significantly higher serum levels of ferritin and D-dimer.

This disagree with *Islam et al. (2020)* [18] who found in his study inflammatory markers in covid-19 patients (serum ferritin &D-dimer) has no significant relation with hypokalemia but this disagree in result may be related to the small sample size of this study than above mentioned studies [18].

In our study we found that, the length of hospital stay was within 3-24 days. There was positive significant relation between severity of disease and the length of hospital stay.

Our result agree with a study carried out by *Zhou et al. (2020*) [19] who demonstrated that Severity of covid-19 was associated with the length of hospital stay .

Our result also agree with *Gulten et al. (2021*) [20] who reported that patients with severe covid-19 had prolonged days of hospital stay relative to those with mild disease .

Also our result agree with *Birhanu et al. (2022)*[21] who demonstrated that patients who experienced severe form of covid-19 disease had significantly longer hospitalization stay than non-severe patients .

In our study also we found that; there was no statistically significant difference found between patients with and without hypokalemia regarding outcome (mortality) of the patients discharged or died and also no relation between severity of hypokalemia and outcome. Our result come in agreement with a study carried by *Kaya et al. (2021) [22].* who reported that there was no statistically significant relation between hypokalemia and outcome of patients.

This also come in agreement with *Tezcan et al. (2020)* [23]. Whose study was done to assess electrolyte abnormalities in covid-19 patients and its relation to poor prognosis and reported that hypokalemia has no effect on mortality.

The study by *Liu et al (2021)* [24]. reported that covid-19 patients with higher potassium level >5mm/l had significantly increase 30-day mortality compared to those with lower potassium level.

Our statistical analysis revealed that; the percentage of patients received corticosteroid treatment was statistically significant increase with increased severity of hypokalemia.

So in our study treatment by corticosteroid was considered a risk factor for development of hypokalemia in covid-19 patients.

Our result agrees with *Yang et al. (2020)* [25] who reported that corticosteroid treatment is a risk factor for hypokalemia in covid-19 patients and there was statistical increase in corticosteroid treatment among hypokalemic than normokalemic group with p-value=0.03. Our results also agree with *Dastenae et al. (2022).* Who found that there was high frequency of hypokalemia in covid-19 patients treated by corticosteroid so, corticosteroid treatment is a risk factor for hypokalemia in COVID-19 patients [26]. Our result disagrees with the study done by *wang et al (2020)* [27] who categorized covid-19 patients according to whether or not corticosteroid therapy was given and compared potassium level between 2 groups and revealed that there was no difference in serum potassium level between patients received corticosteroid treatment and patients not received. This mismatch between studies may be related to variation in number of people involved in the study, dose of corticosteroid received, presence of other factors that may predispose to hypokalemia as associated comorbidities and other drugs patients received that aggravate hypokalemia. In our study, PH of patients increased with increased severity of hypokalemia and there was a statistically significant increase in respiratory alkalosis (35.5%) with increase severity of hypokalemia. This agree with *Chen et al.2020* [7] who demonstrated that the prevalence of blood pH levels over 7.45, in patients with confirmed COVID-19, was statistically higher in severe hypokalemic patients, compared to those with normal potassium levels (29 vs. 6%, P < .05).

This also agrees with a study conducted by *Tsiberkin et al.2020* [28] who demonstrated that patients with hypokalemia had higher blood pH levels than those in the control group (7.46 vs. 7.35, P = 0.001).

This also agree with the study done by *Kaya et al. (2021)* [22]. who found that there was a statistically significant increase in blood PH level in hypokalemic patients than normokalemic and alkalosis was the only risk factor for hypokalemia in his study.

5. Conclusion

High prevalence of hypokalemia among covid-19 patients and most of cases were of mild degree. Hypokalemia was associated with disease severity and the length of hospital stay. Hypokalemia can be used as a predictor of the severity of COVID-19 disease. Corticosteroid was a risk factor for hypokalemia development in COVID-19 patients.

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