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Original Article

Frequency of Hypokalemia, Clinical Implications and Risk Factors in Patients of COVID-19

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Abstract

Objective: To determine the frequency of hypokalemia among COVID-19 patients and assess its impact on the patients management.
Study type, settings & duration: It was a cross-sectional study conducted at Mayo Hospital, Lahore from July 2020 to January 2021.
Methodology: A total of 212 SARS-COV-2 positive patients who had developed severe disease were enrolled. Based on the level of potassium, the patients were classified as mild, moderate and severe hypokalemia cases. Data was collected using a structured questionnaire including demography, clinical presentations and medication including use of anticoagulant and steroids.
Results: Of the total 210, 46 (21.9%) patients had hypokalemia and among them 23 (11%) showed mild, 17 (8.1%) moderate and 6 (2.9%) severe hypokalemia. Out of 210, 17 (23.9%) patients were treated with hydrocortisone, 11 (17.4%) with methylprednisolone and 18 (23.3%) with dexamethasone and no significant difference was seen in development of hypokalemia (p =0.630). Similarly, 39 (21.4%) patients were given enoxaparin and 7 (24.1%) were given heparin, but no significant association was found between the type of anticoagulant being given and hypokalemia (p =0.754). No significant difference was observed with respect to gender in the development of hypokalemia (p =0.782).
Conclusion: This study showed that hypokalemia was a significant clinical manifestation among SARS-COV-2 patients. Further it was noted that treatment regime used for COVID-19 management and gender of the patients are not a risk factor for developing the hypokalemia.
Key words: Severe COVID-19, hypokalemia, steroids, anticoagulant.

Introduction

COVID-19 is the third highly pathogenic human coronavirus disease (after severe acute respiratory syndrome and Middle East Respiratory Syndrome) which is highly contagious and posed the severest threat to global health in this century.[1] The ongoing pandemic of COVID-19 infected more than 130 million humans and cost over 2.84 million lives.[2] The disease manifests itself as respiratory-related illness including fever, cough, sore throat, difficulty in breathing, body aches, vomiting, nausea and diarrhea. Most of the patients reported to be asymptomatic or having mild disease but a few, including mostly older people with co-morbid conditions, had severe disease.[3] It mainly affects the lungs, however multi-organ involvement (heart, liver and kidney) was also reported.[4,5]

SARS-CoV-2 binds with angiotensin I converting enzyme 2 (ACE2) found in many vital organs (heart, liver, kidneys and lungs).[6,7] Since ACE2 is principal regulator of rennin-angiotensin system (RAS), it is responsible for control of blood pressure in addition to maintaining electrolyte balance.[8] After binding of the virus with ACE2, it increases degradation of ACE2 which in turn results in increased urinary loss of potassium.[9] In severe cases of COVID-19, hypoxia leading to hyperventilation (Alkalosis), diarrhea, decreased appetite, fever, perspiration and medicines affecting potassium metabolism (steroids, diuretics, insulin)

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Authors Contribution

SZ, UM &, MMA conceptualized the project. SA, AK & SH did the data collection. SZ & SA also did the literature search. SZ, SA & AK performed the statistical analysis. Drafting, revision & writing of manuscript were done by IR & MANS.

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all might contribute to decrease in potassium level leading to hypokalemia (decreased potassium in the serum). These are the few possible mechanisms responsible for hypokalemia in COVID-19 patients.

Hypokalemia fastens depolarization by elevating resting potential of membrane in the heart and lung cells that can lead to arrhythmias and muscular dysfunction of respiratory muscles in COVID-19.[10,11] Thus, it is a life-threatening condition and can affect outcome because organ dysfunction by COVID-19 also involve in heart and lungs. There is a lack of literature regarding the exact mechanism and the prevalence of hypokalemia in COVID-19 patients. To the best of our knowledge, no study has been reported from our country. We aim to know the prevalence of hypokalemia, clinical implications and causes in COVID-19 patients.

Methodology

This was a cross-sectional study conducted at Department of Internal Medicine, Mayo Hospital, Lahore for a duration of 6 months from July 15, 2020 to January 14, 2021. All the COVID-19 PCR positive patients >16 years who were admitted to Mayo Hospital during the study period were enrolled. Patients with previous history of end stage renal disease (ESRD) were excluded. A structured questionnaire was developed to collect information including socio-demographic factors (age, gender), laboratory findings, comorbidities and treatment regime.

Patients were classified into 3 groups including mild disease (with clinical symptoms and no lung involvement), moderate disease (with clinical symptoms and involvement of lungs to some extent but having saturation above 90%) and severe disease (with worsened clinical symptoms, lung involvement to much greater extent, having saturation below 90% and requiring high flow oxygen) respectively. Patients suffering from severe COVID-19 were included. Hypokalemia was defined as serum potassium <3.5 mmol/L and was further classified as mild (serum potassium 3.1-3.4 mmol/L), moderate (potassium 2.5-3.0 mmol/L) and severe (a serum potassium of <2.5 mmol/L).

Data was entered, cleaned and analyzed using SPSS 23. Over all frequencies were calculated and categorical variables like age, type of steroid use and type of anticoagulation used were compared using *Chi*-square. The significant level of this study was set at α=0.05. The Shapiro-wilik test was used to check the normality of data.

The ethical approval was obtained from the Institutional Review Board of King Edward Medical University, Lahore through reference no. 672/RC/KEMU.

Results

Out of 210 patients, 154 (73.3%) were males and 56 (26.7%) were females. Mean age was (56.18±13.01) years. Of those, 181 were being given Enoxaparin while 29 were being treated with Heparin. Steroids given included hydrocortisone to 71 patients, methylprednisolone to 62 patients and dexamethasone to 77 patients. The difference of variables in hypokalemic and non-hypokalemic patients are provided in Table-1.

Table 1: Clinical data of the male and female patients.

	Not-hypokalmeic		*Hypokalemic*	
	Median	*IQR*	*Median*	*IQR*
Quantity of Oxygen (Liter)	11	9	10	11
Oxygen Saturation (%)	93	5	92	8
Serum Creatinine	1.1	0.5	1.1	0.3
Srum Ferritin Level	1456	932.5	1018	824
D-Dimers Level	0.8	1.6	0.45	0.9
Serum Potassium Level	4.3	0.8	3.05	0.6

Of the total, 46 patients (21.9%) had hypokalemia and among them, 23 patients (11%) showed mild hypokalemia, 17 patients (8.0%) showed moderate hypokalemia while 6 patients (2.8%) had severe hypokalemia (Figure). Significant differences were observed in age groups and serum ferritin level (Table-2 & 3).

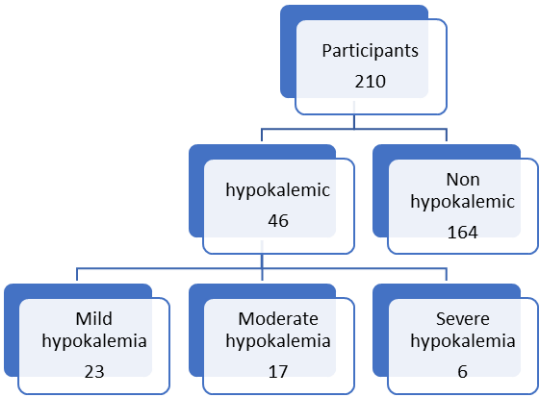

Figure: Flow chart depicting the hypokalemic patients.

Among patients, 17 (23.9%) patients were treated with hydrocortisone, 11 (17.4%) with methylprednisolone and 18 (23.3%) with dexamethasone developed hypokalemia. However, no significant association could be found (*p* =0.630). Similarly, 39 (21.43%) patients were given enoxaparin and 7 (24.1%) were given Heparin

Table 2: Multivariate analysis of hypokalemia with various factors.

	B	*S.E.*	*Wald*	*df*	*Sig.*	*Exp (B)*
Age	-0.027	0.013	4.178	1	0.041*	0.974
Gender	-0.067	0.383	0.031	1	0.861	0.935
Quantity of Oxygen (Liter)	-0.014	0.008	3.217	1	0.073	0.986
Oxygen Saturation (%)	0.015	0.011	1.909	1	0.167	1.016
Serum Creatinine	-0.006	0.387	0	1	0.988	0.994
Serum Ferritin Level	-0.001	0	4.932	1	0.026*	0.999
D-Dimers Level	-0.074	0.053	1.911	1	0.167	0.929

Table 3: Association of hypokalemia with type of steroid and anticoagulant used.

Variables		*Gender*				χ^2	*p*
		Male		*Female*			
		N	*%*	*N*	*%*		
Type of Steroids	Hydrocortisone	51	32.9	20	35.7	0.6252	0.710
	Methylprednisolone	45	29.0	18	32.1		
	Dexamethsone	59	38.1	18	32.1		
Type of Anti-coagulation	Enoxaparin	129	83.2	53	94.6	4.5231	0.032
	Heparin	26	16.8	3	5.4		
Degree of hypokalemia	No Hypokalemia	121	78.6	43	76.8	1.085	0.781
	Mild Hypokalemia 3.1-3.5	18	11.7	5	8.9		
	Modearte Hypokalemia 2.50-3.0	11	7.1	6	10.7		
	Severe Hypokalemia less than 2.5	4	2.6	2	3.6		
Presence or absence of hypokalemia	Yes	33	21.4	13	23.2	0.0765	0.782
	No	121	78.6	43	76.8		

Table 4: Association of hypokalemia with type of steroid and anticoagulant used.

Variables		*Hypokalemia*		χ^2	*p*
		Yes	*No*		
Type of Steroid	Hydrocortisone	17	54	0.8981	0.630
	Methylprednisolone	11	51		
	Dexamethasone	18	59		
Type of Anticoagulation	Enoxaparin	39	142	0.0980	0.754
	Heparin	7	22		
Outcome	Alive	35	121	0.09	0.752
	Dead	11	43		

developed hypokalemia, but no significant association was found between the type of anticoagulant being given and Hypokalemia (*p* =0.754) (Table-3). Of the total, 25.4% patients were died however there was no significant association found between outcome as death and hypokalemia (*p* =0.752) (Table 4).

Discussion

Coronavirus, (COVID-19) has created havoc across the world, subjecting millions of people to death. Most patients complain only of mild breathing difficulties however patients with underlying co-morbid conditions can develop life-threatening illness. So, the clinical presentation varies from patient to patient and depends on various factors.[12] Although hypokalemia is seen as a significant finding in patients infected with SARS-COV-2, however not much research done on this finding.[13] Therefore, this study was designed to find out the prevalence of hypokalemia and associated factors in SARS-COV-2 infected patients.

The mean age of the patients was 56 years, which agrees with many studies indicating that the elderly population was more likely to get infected with SARS-COV2.[14,15] In this study, 22% were with hypokalemia which is contrasting with a retrospective analysis carried out in Modena, Italy reporting 42% hypokalemia.[16] Another study indicated 30.7% as hypokalemia,[17] while the study carried out in 2019 at Wenzhou, China reported 55% patients having hypokalemia.[18] Several different reasons can be attributed to these contrasting results in comparison to our study. SARS-COV 2 has different strains, and the geographical distribution is different that affects the severity of the disease.[19] Racial distribution of the disease and the set up in which the study was carried out might also contribute to these

differences where many of the factors contributing to hypokalemia like insensible losses might vary. Even though the literature shows contrasting results, it does show a significant association of hypokalemia with SARS-COV2.

The hypokalemic patients can be subdivided into mild, moderate and severe categories with the prevalence of 11.0%, 8.1% and 2.9% respectively. Similar findings were reported from Wenzhou China[20] as 55% (18/33) of these patients had mild hypokalemia. However, a study carried out in China showed 90.7% of the cases to show mild hypokalemia and a relatively much stronger association with COVID-19.[16,17] The hypokalemia is a sensitive biomarker to assess the severity of the disease.[21]

Despite several mechanisms being proposed for low potassium levels, no clear explanation has been given that can convincingly describe the link between COVID-19 and hypokalemia.

Two parameters analyzed including the treatment regime and gender and did not find any link between development of hypokalemia. Decrease degradation of ACE by the virus is one of the proposed mechanisms.[9,21] Other mechanisms include renal, gastrointestinal or skin losses of potassium, decrease uptake, respiratory alkalosis and increased elimination of potassium by the drugs.[6-8]

The study findings showed no association of hypokalemia with any gender which is contradicting with other studies.[15,16] Among the drugs, an effort was made to find out the relationship between steroids and anticoagulant use with low potassium levels. Among steroids, hydrocortisone, methylprednisolone, and dexamethasone were used but no relationship was found between the type of the steroid and potassium levels as the *p*-value was greater than 0.05 which contrasted with other studies.[16] To our surprise, use of steroids was not found to be significantly linked with decreased potassium levels. This was an overwhelming finding since steroids are generally considered to lower potassium levels. We also got similar results with anticoagulant use. Enoxaparin and heparin were used as anticoagulants and neither of these showed significant co-relation with hypokalemia.

Different laboratory parameters were also measured. Creatinine levels were normal while ferritin and D-dimers were significantly elevated in majority of the patients corresponding with other studies.[22,23]

Hypokalemic patients are prone to severe cardiac and pulmonary complications. Disturbance in the heart rhythm can predispose to life taking arrhythmia. Similarly respiratory muscle dysfunction can lead to respiratory arrest and death.[10,11] Therefore, efforts must be made to prevent the development of hypokalemia in patients infected with SARS-COV-2 so that the life-threatening complications resulting from it can be prevented. The outcome in terms of mortality was more in hypokalemic patients but statistically insignificant difference was found among the participants as compared to previous study.[24]

In short, the current study showed that hypokalemia is another important clinical manifestation among SARS-COV-2 patients. Moreover, the treatment regime used for COVID-19 management did not has any role in development of the hypokalemia. Similarly, both male and female patients are at equal risk for developing hypokalemia.

Our study had some limitations. The study was single centered, small sample size, case control and cohort matching were not done. Patients of different severity were considered, so many confounders contributing to the severe form of the disease may also affect the study results. Further it was not clear whether the patient already had a history of hypokalemia or not. Therefore, if the study population could be stratified to limit the effect of the confounders and the sample is large, we can gather further valid data on the topic. Hypokalemia is an important laboratory finding in the treatment of SARS-COV2 infected patients. The drug used and gender are not the risk factor for hypokalemia.

Conflict of interest: None declared.

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