PREVALENCE OF HYPOKALEMIA IN COVID-19 AND ITS ASSOCIATION WITH CLINICAL AND COMMON LABORATORY PARAMETERS

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Abstract

Importance: Hypokalemia is a neglected common manifestation in COVID-19 patients admitted in hospital though it has serious consequences. Coronavirus may cause hypokalemia through disruptions of rennin-angiotensin system, gastrointestinal loss or other unknown mechanisms.

Objective: To investigate the prevalence of hypokalemia among patients with moderate to severe COVID-19 and its association with other clinical and laboratory parameters.

Design, Setting, and Participants: This was cross sectional observational study conducted at Dhaka medical College Hospital of Bangladesh from June, 2020, to August 2020. Participants were included who were positive for rt-PCR for COVID-19 according to the national guideline. The patients were classified as having severe hypokalemia (plasma potassium <3 mmol/L), hypokalemia (plasma potassium 3-3.5 mmol/L), and normokalemia (plasma potassium >3.5 mmol/L).

Results: Prevalence of hypokalemia among patients with COVID-19 was 20.2%, severe hypokalemia (2 patients [1.5%]) and hypokalemia (25 patients [18.7%]). One thirty four (134) patients with positive COVID-19 were included. The mean [SD] age of these 134 patients according to different potassium levels appear to be : 68 [2.83] years for severe hypokalemia , 51.93[11.68] years for hypokalemia and 50.73[14.7] years for normokalemia. Among them, 46 patients were females [34.32%]) and rest were males [65.68%]. Within the total sum of 134 patients, 107 were identified having normokalemia, [79.9%]. 25 patients [18. 7%] had hypokalemia and only two patients [1.5%] were found having normokalemia. Among 134 patients, three commonest symptoms were fever (132 patients [98.5%]), dry cough (123 patients (91.79%) and shortness of breath (122 patients [91.04%]), followed by less common symptoms like fatigue (89 patients [66.410%]), sore throat (60 patients [44.77%]), and diarrhea (44 patients, [32.83%]). Shortness of breath was associated with grades of hypokalemia (P=0.022). Only 26 patients (19.4%) manifested having vomiting/Nausea. The predominant comorbidities found among these 134 participants were Hypertension (68 patients [64.2%]), Diabetes (54 patients [52.9%]), Ischemic heart disease (37 patients [38.1%]) and Asthma (27 patients [31.0%]). The prevalence of comorbidities was not associated with Hypokalemia.

Conclusions Prevalence of hypokalemia among patients with COVID-19 is high (20.2%) and appropriate treatment is highly required.

Keywords: Potassium, Electrolyte imbalance, Corona, SARS-CoV-2, COVID-19, Dhaka, Bangladesh

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Introduction

Bangladesh is facing huge trouble to manage the current situation of worldwide COVID-19 pandemic from March of this year after the first diagnosis of (COVID-19) in the city Wuhan of China in December 2019.[1] The first three known cases were reported on 8 March 2020 by the country's epidemiology institute IEDCR.[2] On 18 March, Bangladesh reported its first coronavirus death. The patient was aged over 70 and had other morbidities.[3]

Although, it is a respiratory virus now it is considered a systemic diseases and can affect any organ. On the basis of affected organs, most common clinical features are fever, cough and dyspnea but other features such as myalgia, diarrhea; anosmia and hypogeusia are also common.[4] Among these, the most frequent and devastating manifestations is atypical pneumonia and ultimately a good proportion of patients develop respiratory distress syndrome (ARDS).[5–8]

Electrolytes imbalance, such as hypokalemia is another, much overlooked but troublesome manifestation of this virus.

Though hypokalemia is prevalent among patients with COVID-19, the exact mechanism for the development of hypokalemia is not clear, but several hypothesis have been proposed. Involvement of RAS is well accepted pathogenesis for hypokalemia in CoVID 19 but other important causes may be there, like gastrointestinal processes, such as diarrhea and vomiting, loss of appetite and poor diet.

Corona virus enters in human body through ACE2 which are attached to the cell membranes of cells in the lungs, arteries, heart, kidney, and intestines.[9,10] After invasion it enhances the degradation of ACE2. This low ACE2 leads to increased reabsorption of sodium and water, and excretion of potassium (K+).[11] Usually route of loss of potassium is either gastrointestinal or urinary loss.[11] It is expected that gastrointestinal loss contribute a major role creating hypokalemia in COVID as gastrointestinal symptoms are very common in COVID like vomiting and diarrhea but recent study shows gastrointestinal loss might not contribute much to hypokalemia. [12] Urinary K+ output in the hypokalemia group was more compared with the control group with normokalemia. Urinary loss of potassium consistent with the pathogenesis of SARS-CoV-2.[12]

Potassium is the most abundant cation in the intracellular fluid, and maintaining the proper distribution of potassium across the cell membrane is critical for normal cell function. To maintain the cellular polarity, resting potential, depolarization in cardiac cells and lung cells potassium have a critical role.[13] Minor change in serum can causes various type of arrhythmia like torsade de pointes, ventricular fibrillation as well as sudden death due to cardiac arrest. Human respiratory system also affected by hypokalemia and hypokalemia induced respiratory muscles paralysis have huge impact on pneumonia induced ARDS. So proper addressing of hypokalemia and its correction burning issues in clinical practice for patient's outcome. Moreover many ongoing trial drugs in SARS-CoV-2 patients can prolong the QTc interval (doxycycline, azithromycin and some drugs like methylprednisolone can causes remarkable hypokalemia which may worsen pre-existing electrolyte disturbance and cardiac involvement in SARS-CoV-2 .[14]

Normal potassium levels are between 3.5 and 5.0 mmol/L (3.5 and 5.0 mEq/L) with levels below 3.5 mmol/L defined as hypokalemia. It is classified as severe when levels are less than 2.5 mmol/L.[15] Hyperkalemia is a high level of potassium in the blood serum.

Because little is known about the prevalence of hypokalemia and its association with other clinical parametes for patients with COVID-19 in Bangladesh, present study was attempted.

Methods

The Objectives of this study were to see the prevalence of hypokalemia in hospitalized COVID-19 patients and to find out the association of clinical symptoms and biochemical parameters with hypokalemia. Methods: This cross-sectional study was conducted in COVID-19 dedicated hospital of DMCH2 in 2020 from 1st June to August in Dhaka, the capital of Bangladesh. It is one of the largest dedicated hospital COVID-19 patients.

This was a single center study and observational in nature. Informed consents were taken from all the patients during collection of primary data. Various vital signs, basic hematological data, parameters of liver and kidney functions, levels of oxygen saturation, and important electrolytes were recorded during admission.

We included patients with COVID-19 who were admitted in the Dhaka Medical College Hospital (DMCH), older than 18 years and were rtPCR positive for SARS-CoV-2 in nasal swab and throat swab.

We categorized the patients as having 4 levels of disease severity, as follows: mild cases involved mild clinical manifestations and no pneumonia; moderate cases involved respiratory symptoms and mild pneumonia; severe cases involved respiratory distress (e"30 breaths/min), oxygen saturation (d"93% at rest), and critically ill cases were those that met any of respiratory failure criteria and required mechanical ventilation, or those with shock or other organ failure that required intensive care unit care.

We classified the patients into 3 groups according to 3 levels of plasma K^+—severe hypokalemia (<3 mmol/L), hypokalemia (3-3.5 mmol/L), and normokalemia (>3.5 mmol/L).

Continuous variables were expressed as mean (± SD) and median (IQR). For comparing means, between two groups, students t test was employed and comparing means across more than two groups the nonparametric Kruskal-Wallis test was used. A two-tailed p value of less than 0·05 was considered statistically significant in case of all analyses. We performed statistical analysis using SPSS software (version 23.0, IBM, USA),

Results

In this study, 134 patients with positive COVID-19 were included. The mean [SD] age of these 134 patients according to different potassium levels appear to be : 68 [2.83] years for severe hypokalemia , 51.93[11.68] years for hypo-kalemia and 50.73[14.7] years for normo-kalemia. Among them, 46 patients were females [34.32%]) and rest were males [65.68% (Table 1). Within the total sum of 134 patient, 107 were identified having normokalemia, [79.9%].. 25 patients [18. 7%] had hypokalemia and only 2 patients [1.5%] were found having normokalemia.

Table I

Baseline characteristics (N=134)

	<3.00 mmol/L			3.00-3.5 mmol/L			>3.5-5.00 mmol/L		
	Mean (±SD)	Median (IQR)	n(%)	Mean (±SD)	Median (IQR)	n(%)	Mean (SD)	Median (IQR)	n(%)
Age (Years)	68(±2.83)	68(66-70)		51.39(±11.68)	53(42-59)		50.73(14.7)	50(40-60)	
Sex Male			1(0.8)			16(12)			70(52.6)
Female			1(0.8)			8(6)			37(27.8)

Table II

Distribution of potassium level (N·134)

		Frequency	Percent
Severe hypokalemia	<3.00 mmol/L	2	1.5
Hypokalemia	3.00-3.5 mmol/L	25	18.7
Normokalemia	>3.5-5.00 mmol/L	107	79.9
	Total	134	100.0

Table-III

Symptoms/complaints of the participants (N=134)

	Total patient	<3.00 mmol/L	3.00-3.5 mmol/L	>3.5-5.00 mmol/L	P
		n(%)	n(%)	n(%)	value
Fever	132 (98.5%)	2(0.02)	24(0.18)	106(0.803)	NA
Cough	123 (91.79%)	2(0.02)	24(0.18)	97(0.74)	0.348
Shortness of breath	122 (91.04%)	1(0.01)	24(0.18)	97(0.74)	0.022*
Fatigue	89 (66.41%)	1(0.01)	16(0.13)	72(0.57)	0.819
Sore throat	60 (44.77%)	1(0.01)	15(0.13)	44(0.38)	0.328
Headache	41 (30.59%)		7(0.07)	34(0.32)	0.390
Diarrhea	44 (32.83%)	1(0.01)	9(0.08)	34(0.29)	0.928
Nausea/ Vomiting	26 (19.4%)		3(0.03)	23(0.20)	0.351
Anosmia	39		6(0.05)	33(0.29)	0.471

Among 134 patients, 3 commonest symptoms were fever (132 patients [98.5%]), dry cough (123 patients (91.79%) and shortness of breath (122 patients [91.04%]), followed by less common symptoms like fatigue (89 patients [66.410%]), sore throat (60 patients [44.77%]), and diarrhea (44 patients, [32.83%]), (Table 3). Only 26 patients (19.4%) manifested having vomiting/Nausea.

The predominant comorbidities found among these 134 participants were Hypertension (68 patients [64.2%]), Diabetes (54 patients [52.9%]), Ischemic heart disease (37 patients [38.1%]) and Asthma (27 patients [31.0%]). The prevalence of comorbidities was not associated with Hypokalemia.

Table -IV

Comorbidities of the participants (N=134)

	Total		<3.00 mmol/L		3.00-3.5 mmol/L		>3.5-5.00 mmol/L	
	Count	%	Count	%	Count	%	Count	%
Hypertension	68	64.2%	1	0.9%	13	12.3%	54	50.9%
Diabetes mellitus	54	52.9%	2	2.0%	10	9.8%	42	41.2%
Ischemic heart disease	37	38.1%	1	1.0%	8	8.2%	28	28.9%
Asthma	27	31.0%	0	0.0%	5	5.7%	22	25.3%
COPD	18	24.7%	0	0.0%	4	5.5%	14	19.2%
CKD	11	14.9%	0	0.0%	1	1.4%	10	13.5%
Malignancy	1	1.5%	0	0.0%	0	0.0%	1	1.5%

Table-V

Physical findings of the participants (N=134)

	<3.00 mmol/L		3.00-3.5 mmol/L		>3.5-5.00 mmol/L		P1	P2	P3	Kruskal
	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)	Mean (SD)	Median (IQR)				wallis
Temperature	101	101	100	100	100.25	100				
(Fahrenheit)	(±1.41)	(100-102)	(±1.6)	(99-101)	(1.41)	(99-101)	0.424	0.458	0.585	0.510
Respiratory rate	1.5(±0.71)		1.5(1-2)	1.64(±0.5)	2(1-2)	1.67(0.47)	2(1-2)	0.719	0.618	0.840	0.868
(breaths/min)										
SPO_2 (%)	83.5	83.5	88	88.5	88.64	88				
	(±2.12)	(82-85)	(±5.28)	(86-91)	(6.89)	(85-94)	0.252	0.296	0.681	0.262

Table VI

Investigation findings of the participants (N=134)

	<3.00 mmol/L		3.00-3.5 mmol/L		>3.5-5.00 mmol/L		P1	P2	P3	Krukal Wallis
	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)	Mean (±SD)	Median (IQR)				
Hemoglobin (g/dL)	14.1 (±0.42)	14.1 (13.8-14.4)	12.35 (±1.69)	12.45 (11.2-13.04)	12.09 (2.01)	12.2 (10.95-13.35)	0.165	0.162	0.574	0.139
Total WBC (mm^3)	7.5 (±3.96)	7.5 (4.7-10.3)	10.4 (±4.13)	8.8 (8.2-12)	244.94 (1179.2)	9 (7.02-11.78)	0.351	0.777	0.354	0.673
Neutrophils (%)	70.45 (±6.01)	70.45 (66.2-74.7)	77.26 (±9.87)	79.5 (71.5-84.5)	77.41 (12.61)	81 (68-88)	0.352	0.439	0.956	0.475
Lymphocytes (%)	24.65 (±5.73)	24.65 (20.6-28.7)	18.39 (±8.54)	16.8 (13-23)	16.78 (10.19)	14 (9-24)	0.323	0.280	0.475	0.198
Platelets (mm^3)	252 (±89.1)	252 (189-315)	266.21 (±102.44)	231 (190-340)	272.86 (205)	235.5 (179-312.5)	0.853	0.887	0.891	0.803
ESR (mm, 1st min)	20(±.)	20(20-20)	43.6(±19.41)	42(30-62)	39.3(25.85)	32(20-52)	0.276	0.463	0.620	0.436
CRP	20 (±5.66)	20 (16-24)	29.95 (±26.14)	26 (17-33.5)	23.23 (21.43)	17 (6-29.5)	0.608	0.833	0.280	0.359
Ferritin	379.5 (±118.09)	379.5 (296-463)	634.78 (±625.53)	518.5 (316.5-657)	755.13 (870.54)	515 (310-965)	0.579	0.546	0.561	0.711
D dimer	1.01 (±0.69)	1.01 (0.52-1.5)	1.51 (±1.63)	1.02 (0.51-1.52)	1.41 (2.07)	0.96 (0.5-1.62)	0.678	0.787	0.841	0.736

Table-VII

Radiological findings

		<3.00 mmol/L N(%)	3.00-3.5 mmol/L N(%)	>3.5-5.00 mmol /L N(%)	P value
Chest X-ray	Bilateral infiltration	2(0.018)	21(0.19)	84(0.75)	0.509
	Clear		0(0)	5(0.045)	
CT chest	Groundglass opacity		7(0.226)	15(0.484)	0.231
	Consolidation			2(0.065)	
	Pulmonary infiltrate			6(0.194)	

P1, P2 and P3 are the P values derived from comparisons of mean levels of the row variables between 'severe hypokalemia and hypokalemia group', 'severe hypokalemia and 'normokalemia group', and 'hypokalemia and normokalemia group' respectively using student's t test. To determine the P value for comparisons among all 3 groups, non-parametric Kruskal-Wallis test was performed.

Discussion

In this study we found the prevalence of hypokalemia in COVID-19 positive patients was 20.2% consisting of 2 patients (1.5%) with severe hypokalemia and 25 patients (18.7%) with hypokalemia. It was seen the estimated prevalence of hypokalemia in our study was much lower than the previously performed studies[12,16], In first study prevalence of hypokalemia was noted 54% among the patients with COVID-19 where 95 out of 175 patients had plasma K$^+$ less than 3.5 mmol/L and only 10 patients had plasma K$^+$ greater than mmol/L,[12] Another retrospective analysis was conducted on 290 hospitalized patients with confirmed COVID-19 infection at the tertiary teaching hospital of Modena, Italy where hypokalemia (<3.5 mEq/L) was detected in 119 (41%) of patients.[16]

One reason behind the lower prevalence of hypokalemia in our study could be due to the smaller sample size than above mentioned studies. Another possibility could be patients' tendency in our country to take local medication like saline solution or ORS before appearing at hospital, that conservative treatment might have corrected the serum potassium level leading to lower prevalence. Also racial and dietary diversities could also intend this dissemblance.

The predominant comorbidities found among these 134 participants were Hypertension (68 patients [64.2%]), Diabetes (54 patients [52.9%]), Ischemic heart disease (37 patients [38.1%]) and Asthma (27 patients [31.0%]). The prevalence of comorbidities was not associated with Hypokalemia. These findings exhibited identical similarly to the findings of a meta-analysis by Gold et al.[17] Totally, 33 articles were included in the systematic review. Gold et al., in their meta-analysis incorporated 29,096 confirmed SARS-CoV-2 positive patients. Among the 29,096 patients included in the meta-analysis, 40.80% (95%CI: 35.49%, 46.11%) had comorbidities. Hypertension was more prevalent among severe cases [47.65% (95%CI: 35.04%, 60.26%)] Diabetes was more prevalent among fatal cases [24.89% (95%CI: 18.80%, 32.16%)] compared to total cases [9.65% (95%CI: 6.83%, 13.48%)] as well as respiratory diseases had also higher prevalence in fatal cases [10.89% (95%CI: 7.57%, 15.43%)] in comparison to total cases [3.65% (95%CI: 2.16%, 6.1%)].[17]

In our study, among 134 patients, three commonest symptoms were fever (132 patients [98.5%]), dry cough (123 patients (91.79%) and shortness of breath (122 patients [91.04%]) followed by fatigue (89 patients [66.410%]), sore throat (60 patients [44.77%]), and diarrhea (44 patients [32.83%]), (Table 3).The prevalence of vomiting was 19.4%. All findings were similar with recent study.

In another meta-analysis by Grant et al. to see prevalence of symptoms among COVID 19 patients, one forty eight (148) articles were included, which comprised 24,410 adults with confirmed COVID-19 from nine countries. The most prevalent symptoms were fever (78% [95% CI 75%-81%]; 138 studies, 21,701 patients; I2 94%), a cough (57% [95% CI 54%-60%]; 138 studies, 21,682 patients; I2 94%) and fatigue (31% [95% CI 27%-35%].[18]

The previous study also found that the degree of hypokalemia was associated with some clinical features that reflected the severity of the disease, including underlying conditions, high body temperature, and, notably, the elevated laboratory indices reflecting myocardial injuries, such as CK, CK–MB fraction, LDH, and abnormal ECG results. Our study only showed hypokalemia was associated with the shortness of breath and found no association of the degree of hypokalemia with other symptoms of COVID-19.

Because of the variations among laboratories and assays that may generate different reference values, to compare results is not always possible.

In the present study, prevalence of hypokalemia is 20.2%. only (27 of 134 patients).This prevalence of hypokalemia is important in clinical practice of COVID patients, because optimal concentrations of potassium is vital for proper functioning of patients' hearts. Previously it was mentioned potassium is the most abundant cation in the intracellular fluid, and maintaining the proper distribution of potassium across the cell membrane is critical for normal cell function.[13] Minor change in serum can causes various type of arrhythmia like torsade de pointes, ventricular fibrillation as well as sudden death due to cardiac arrest. So proper addressing the hypokalemia may have great impact on COVID-19 patients' outcomes.

This is why it is important to monitor and correct potassium level, if necessary, in COVID-19 cases.

Limitations
This study has some limitations. There are several risk factors associated with the severity of COVID-19. The confounding factors may affect the results. However, we believe our results will elucidate further on different aspects of management of COVID-19.

Conclusions

The prevalence of hypokalemia is high among COVID patients. Present study has identified the prevalence of hypokalemia and tried to show association with epidemiological features in patients with COVID-19. The correction of hypokalemia is essential in COVID-19 patients.

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