Original Research Article

Study of hypokalemia and correlation with severity of disease in patients with COVID-19 positive severe acute respiratory illness and COVID-19 negative severe acute respiratory illness

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ABSTRACT

Background: Although the coronavirus disease-2019 (COVID-19) pandemic is creating a major global health crisis, the risk factors for mortality and the detailed clinical course of disease has not yet established. Clinical spectrum of the disease varies from mild symptoms to ARDS. The main objective of this study was to determine hypokalemia and correlation of severity of disease with hypokalemia in patients with COVID-19 positive SARI (severe acute respiratory illness) and COVID-19 negative SARI patients.
Methods: The study was a cross-sectional study conducted on 265 SARI patients who were admitted in hospitals attached to BMCRI from April 2019 to December 2019. History was taken, general and systemic examination was done. Patients were categorized and selected patients with moderate and severe illness. RT-PCR for COVID-19 patients done using throat and nasal swab. Potassium levels were estimated and correlated with severity of illness in patients with COVID-19 positive and COVID-19 negative status.
Results: The study included 265 SARI patients, of which 135 were COVID-19 positive patients and 130 were COVID-19 negative. Patients categorized into moderate and severe SARI. Mean age of subjects with COVD-19 positive (severe) was higher, 58.70±15.598 followed by COVID-19 positive (moderate), 55.13±14.480. About 30% (N=90) belonged to severe SARI group, Chi square test showed statistical significant association with respect to age. In this study there was no statistically significant hypokalemia found between COVID-19 positive SARI patients (N=20, 14.81%) and COVID-19 negative SARI patients (N=17, 13.07%). However hypokalemia COVID-19 positive SARI patients 14.81% (N=20) and COVID-19 negative SARI patients 13.07% (N=17). And also there is no statistically significant hypokalemia between SARI severe and SARI moderate cases.
Conclusions: However in this study there is no statistically significant hypokalemia found between COVID-19 positive SARI patients and COVID-19 negative SARI patients. And also there is not statistically significant hypokalemia between SARI severe and SARI moderate cases. Hypokalemia is found in both in both COVID-19 positive SARI patients and COVID-19 negative SARI patients and relatively more in COVID-19 positive patients. Hypokalemia is one of the treatable condition and early detection and treatment reduces mortality.

Keywords: SARI, COVID-19, Hypokalemia

INTRODUCTION

Since December 2019, a life-threatening coronavirus was recognized as the etiological factor of a series of severe pneumonia cases. COVID-19 is contagious disease spread through air droplet and aerosol1. Spectrum of disease varies from mild influenza like illness to ARDS even may cause multiorgan dysfunction and death.[1] Increased death was associated with old age and patients with co-morbidities. COVID-19 virus invades human cells through binding angiotensin I converting enzyme 2 (ACE2) on the cell membrane. ACE2 is widely distributed in many types of human tissues, especially in the vital organs such as lungs liver, heart, kidney.[2]

ACE2 is the principal counter-regulatory mechanism for the main axis of the rennin-angiotensin system (RAS), which is important in the control of blood pressure and electrolyte balance.[3]

COVID-19 virus binds ACE2 and enhances the degradation of ACE2 and thus decreases the counter-act of ACE2 on RAS. The final effect is to increase reabsorption of sodium and water, and thereafter increase blood pressure and excretion of potassium (K+).

Besides, patients with COVID-19 often had gastro-intestinal symptoms such as vomiting and diarrhea. Collectively the impacts on RAS and gastrointestinal system by COVID-19 probably lead to disruptions of homeostasis of electrolytes and pH.[3]

Hypokalemia results in cellular hyperpolarity, increases resting potential and hastens depolarization in cardiac cells and lung cells and may cause arrhythmias and respiratory muscle paralysis. Hypokalemia is one of the life-threatening complication and should be monitored regularly to prevent mortality.[4]

Hypokalemia is one of the treatable condition and early detection and treatment reduces mortality.

Objective of our study was to correlate hypokalemia with severity of the disease in COVID-19 positive SARI and COVID-19 negative SARI patients.

METHODS

After obtaining institutional ethical committee clearance, cross-sectional study was conducted on 265 SARI patients who were admitted in hospitals attached to BMCRI from April 2019 to December 2019.

History was taken, general physical examination and a detailed systemic examination was done. Patients were categorized into mild, moderate and severe illness according to WHO clinical criteria. RT-PCR for COVID-19 patients done using throat and nasal swab. Potassium levels were done and correlated with severity of COVID-19 positive and negative SARI.[5]

WHO criteria for categorizing the patients

Mild disease

Symptomatic patients with ILI symptoms without evidence of viral pneumonia or hypoxia were categorized as mild.

Moderate disease

Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥90% on room air were categorized as moderate.

Severe disease

Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following like respiratory rate >30 breaths/min, severe respiratory distress or SpO2 <90% on room air was categorized as severe.

Objectives

The objectives were to study hypokalemia in SARI patients and to correlate hypokalemia with severity of disease in SARI COVID-19 positive patients and SARI COVID-19 negative patients.

Type design

The study design was a cross-sectional study. The study was conducted from a period of April 2019 to December 2019. The study was conducted at the hospital attached to BMCRI.

Inclusion criteria

In-patients who were diagnosed with SARI, of either sex with age more than 18 years and willing to give informed consent were included.

Exclusion criteria

Patients not willing to give informed consent, age less than 18 years and on diuretics and/or diuretics were excluded.

Ethical clearance was obtained from ethical committee.

Statistical method

Data was analyzed by descriptive statistics. Independent sample test was applied for quantitative variables between COVID-19 positive and COVID-19 negative subjects. Correlation between severity of COVID-19 infection and serum potassium levels was measured using Chi square test.

Statistical analysis

The statistical software used for data analysis were namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 and Microsoft word and excel have been used to generate tables and graphs.

RESULTS

In this study, mean age of subjects with COVID-19 positive (severe) was higher, 58.70±15.598 followed by COVID-19 positive (moderate), 55.13±14.480 (Table 1).

In this study, distribution of the subjects was based on age. Subjects was higher above 65 years, 80 (30.2%) followed by age group of 36 to 45 years, 51 (19.2%). Chi square test was applied to associate the age with severity. Chi square test showed statistical significant association with respect to age (χ2=35.15; p=0.002) (Table 2).

In this study distribution of the subjects based on gender. Males were higher, 174 (65.7%) as compared to females, 91 (34.3%). Chi square test was applied to associate the gender with severity. Chi square test showed no statistical significant association with respect to gender (χ2=3.16; p=0.78) (Table 3).

Table 1: Age distribution.

COVID-19	Severity	N	Minimum	Maximum	Mean	SD
Negative	Moderate	69	20	86	46.90	17.132
	Severe	61	19	91	52.56	15.988
Positive	Moderate	54	25	80	55.13	14.480
	Severe	81	24	96	58.70	15.598

Table 2: Distribution of age among the groups.

Age (in years)		Negative		Positive		Total
		Moderate	Severe	Moderate	Severe	
Less than 25	Count	9	4	1	1	15
	%	13.0	6.6	1.9	1.2	5.7
26 to 35	Count	9	5	5	7	26
	%	13.0	8.2	9.3	8.6	9.8
36 to 45	Count	22	12	8	9	51
	%	31.9	19.7	14.8	11.1	19.2
46 to 55	Count	7	13	13	11	44
	%	10.1	21.3	24.1	13.6	16.6
56 to 65	Count	9	10	9	21	49
	%	13.0	16.4	16.7	25.9	18.5
Above 65	Count	13	17	18	32	80
	%	18.8	27.9	33.3	39.5	30.2
Total	Count	69	61	54	81	265
	%	100.0	100.0	100.0	100.0	100.0
Chi square value=35.15						
P=0.002						

Table 3: Distribution of gender among the group.

Gender		Negative		Positive		Total
		Moderate	Severe	Moderate	Severe	
Female	Count	26	21	16	28	91
	%	37.7	34.4	29.6	34.6	34.3
Male	Count	43	40	38	53	174
	%	62.3	65.6	70.4	65.4	65.7
Total	Count	69	61	54	81	265
	%	100.0	100.0	100.0	100.0	100.0
Chi square value=3.16						
P=0.78						

Table 4: Distribution of subjects based on diabetes among the groups.

Diabetes		Negative		Positive		Total
		Moderate	Severe	Moderate	Severe	
Nil	Count	56	37	26	47	166
	%	81.2	60.7	48.1	58.0	62.6
Present	Count	13	24	28	34	99
	%	18.8	39.3	51.9	42.0	37.4
Total	Count	69	61	54	81	265
	%	100.0	100.0	100.0	100.0	100.0
Chi square value=15.79						
P=0.001*						

*significant.

Table 5: Distribution of subjects based on HTN among the groups.

HTN		Negative		Positive		Total
		Moderate	Severe	Moderate	Severe	
Nil	Count	47	30	38	48	163
	%	68.1	49.2	70.4	59.3	61.5
Present	Count	22	31	16	33	102
	%	31.9	50.8	29.6	40.7	38.5
Total	Count	69	61	54	81	265
	%	100.0	100.0	100.0	100.0	100.0
Chi square value=7.15						
P=0.067						

Table 6: Distribution of K+ levels.

COVID-19	Severity	N	Minimum	Maximum	Mean	SD
Negative	Moderate	69	2.9	7.6	4.349	0.8140
	Severe	61	2.7	6.4	4.390	0.8599
Positive	Moderate	54	3.2	6.6	4.246	0.6321
	Severe	81	2.8	39.0	4.652	3.9137

Table 7: Groups using independent t test.

Independent t test	COVID-19 negative versus COVID-19 positive	
	Mean difference	P value
Potassium level	0.12	0.66

Table 8: Comparison between moderate and severe sub groups using independent sample t test.

Comparison		Moderate versus severe	
		Mean difference	P value
COVID-19 negative	Potassium level	-0.04	0.78
COVID-19 positive	Potassium level	-0.4	0.45

In this study out of 265 (100%) subjects, 99 (37.4%) had diabetes, out of which 34 (42%) were COVID-19 positive (severe) followed by 28 (51.9%) were COVID-19 positive (moderate). Chi square test was applied to associate the diabetes with severity. Chi square test showed statistical significant association with respect to diabetes (χ^2=15.79; p=0.001) (Table 4).

In this study of 265 (100%) subjects, 102 (38.5%) had hypertension, out of which 33 (40.7%) were COVID-19 positive (severe) followed by 31 (50.8%) were COVID-19 negative (severe). Chi square test was applied to associate the hypertension with severity. Chi square test showed no statistical significant association with respect to hypertension (χ^2= 7.15; p=0.067) (Table 5).

In this study mean K+ levels was higher in COVID-19 positive (severe) subjects, 4.652±3.91 followed by COVID-19 positive (moderate) subjects, 4.24±0.632 (Table 6). And independent sample t test showed there is no statistical significant difference potassium levels p=0.66 between COVID-19 positive and negative subjects (Table 7). And also independent sample t test showed there is no statistical significant difference between serum potassium level between COVID-19 negative and COVID-19 positive subjects (Table 8).

DISCUSSION

In our study demographic characteristics of the study subjects studied showed that males were higher as compared to females which was similar to 51.5% of patients were male in study conducted by Liu et al.[10] Similar study was done by Mousavi-Nasab et al where 57.1% were males.[9]

Subjects taken were aged above 65 years, 80 (30.2%) followed by age group of 36 to 45 years, 51 (19.2%) with average age of 58.70±15. Similar study done by Liu et al showed average age was 62.1±14.6 years.[8]

We also studied distribution of diabetes and hypertension among the groups and out of 265 (100%) subjects, 99 (37.4%) had diabetes of which majority were severe COVID-19 positive. Association of diabetes with COVID-19 positive subjects was statistically significant.

102 patients had hypertension, which was more common with severe COVID-19 negative patients and then with severe COVID-19 positive patients, however association with hypertension was not statistically significant. Similar study done by Cheng et al showed that seventy-one patients (41%) had underlying diseases including hypertension (28 patients, 16%), diabetes (12 patients, 7%) and other conditions (31 patients, 18%).[6]

Potassium plays an important role in maintaining normal cell function. K+ is the main intracellular cation and almost all cells have the pump called Na±K±ATPase which pumps sodium out of the cell and K+ into the cell leading to a K+ gradient across the cell membrane. If potassium balance is disrupted (hypokalemia or hyperkalemia), this can also lead to disruption of heart electrical conduction, dysrhythmias and even sudden death.[4] The impact on RAS and gastrointestinal system by COVID-19 probably lead to disruptions of homeostasis of electrolytes and pH. Hypokalemia results in cellular hyperpolarity, increases resting potential and hastens depolarization in cardiac cells and may cause arrhythmias.[7] Previous studies have shown that significant changes in potassium are often associated with poor outcomes in many disease.

In this study there is no statistically significant hypokalemia found between COVID-19 positive SARI patients and COVID-19 negative SARI patients. And also there is no statistically significant hypokalemia between hypokalemia with SARI severe and SARI moderate cases. Similar study done by Liu et al showed patients with severe COVID-19 median baseline K+ level was 4.4.[10]

One more study done by Gelatino et al had mild severity of hypokalemia (90.7% had serum levels of K+ between 3.4 and 3 meq/l) and there is no associated mortality with hypokalemia in this group.[9] Unlike other study done by Chen et al hypokalemia was prevalent among the patients with COVID-19, among 54% (95 of 175) of patients had plasma K+ less than 3.5 mmol/l.[6]

Limitations

Association with mortality could not be established. As it was a cross sectional study, serial monitoring of potassium and correlation with the disease progression also could not be established. There were limited studies supporting hypokalemia in SARI patients.

CONCLUSION

However in this study there is not statistically significant hypokalemia found between COVID-19 positive SARI patients and COVID-19 negative SARI patients. And also there is not statistically significant hypokalemia between SARI severe and SARI moderate cases. Hypokalemia is found in both COVID-19 positive SARI patients and COVID-19 negative SARI patients and relatively higher in COVID-19 positive patients. Hence monitoring of serum potassium level is important in SARI patients and it is important to treat them to prevent mortality.

REFERENCES

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-20.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
3. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, Goor HV. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
4. Kardalas E, Paschou S, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. Endocr Connec. 2018;7(4):135-46.
5. WHO. Fact sheet: Clinical management of COVID-19 patients: living guidance, 2021. Available at:

https://app.magicapp.org/#/guideline/j1WBYn/section/j2xMZn. Accessed on 29 May 2021.

6. Chen D, Li X, Song Q, Hu C, Su F, Dai J, et al. Assessment of hypokalemia and clinical characteristics in patients with coronavirus disease 2019 in Wenzhou, China. JAMA Net Open. 2020;3(6):2011122.

7. Zacchia M, Abategiovanni ML, Stratigis S, Capasso G. Potassium: from physiology to clinical implications. Kid Dis. 2016;2(2):72-9.

8. Tongyoo S, Viarasilpa T, Permpikul C. Serum potassium levels and outcomes in critically ill patients in the medical intensive care unit. J Int Med Res. 2018;46(3):1254-62.

9. Alfano G, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, et al. Hypokalemia in patients with COVID-19. Clinic Experiment Nephrol. 2021;25(4):401-9.

10. Liu S, Zhang L, Weng H, Yang F, Jin H, Fan F, et al. Association between average plasma potassium levels and 30-day mortality during hospitalization in patients with COVID-19 in Wuhan, China. Int J Med Sci. 2021;18(3):736-43.

11. Moreno-Pérez O, Leon-Ramirez J, Fuertes-Kenneally L, Perdiguero M, Andres M, Garcia-Navarro M, et al. Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: a case series of 306 Mediterranean patients. Int J Infect Dis. 2020;100:449-54.

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