Descriptive Analysis Of Electrolyte Imbalance In Relation To Severity Of Illness In COVID-19 Pediatric Patients Admitted In A Tertiary Care Hospital In Rawalpindi, Pakistan

Rai Muhammad Asghar[1], Mudassar Sharif[2], Khalid Saheel[3], Asad Shabbir[4], Abid Hussain[5], Muhammad Hussain[6]

Abstract

Objectives: To determine the frequency of electrolyte imbalance in pediatric COVID-19 patients and their impact on the severity of disease and outcome.

Methods: A retrospective observational study was done from January 2021 to July 2021 on 61 children admitted in Benazir Bhutto Hospital Rawalpindi, a tertiary care teaching hospital affiliated with Rawalpindi Medical University (RMU) Pakistan. The age of the patients ranged from infants to 12 years. All the children who were PCR positive or those whose HRCT was suggestive of COVID-19 were included in the study.

Results: During the study period of 7 months, 61 confirmed COVID-19 patients were admitted. 37(60.7%) were males and 24 (39.3%) were females. The age of the patients ranged from infants to 12 years with a mean age of 27.25 months. Out of 61 admitted cases, 28 children (45.9%) had moderate & 33(54.1%) patients had severe disease. 46(75%) patients were discharged while 15(25%) patients expired. A number of electrolyte abnormalities were observed. A total of 30 patients (49.2%) were hyponatremic &13 patients (21.3%) were hypernatremic. Hypokalemia was observed in 34(55.7%) & hyperkalemia was found in 2 patients (3.3%), hypochloremia was observed in 13(21.3%) while hyperchloremia was present in 3(4.9%) patients. Hypocalcemia was found in 9(14.7%) patients. 11(18%) patients with Hyponatremia and 6(9.8%) patients with hypernatremia expired. The potassium abnormalities were also associated with significant mortality.14(22.9%) patients with hypokalemia and 2(3.2%) with hyperkalemia expired. Hypocalcemia was found in 9(4.9%) patients who expired.

Conclusions: Hypokalemia and hyponatremia were frequent electrolyte disorders in children with COVID-19. These electrolyte abnormalities were associated significantly with severity of disease and a higher risk of death in children with COVID-19

Keywords: COVID-19, Electrolytes, Hypokalemia, Hyperkalemia, Hyponatremia, Hypernatremia, Hypocalcemia

[1] Dean of Paediatrics, Pediatric Department, Rawalpindi Medical University; [2,3] Associate Professor Pediatric Department, Rawalpindi Medical University; [4] Assistant Professor, Pediatric Department, Rawalpindi Medical University; [5] Senior Medical Officer, Pediatric department, Rawalpindi Medical University; [6] Consultant Pediatrician, Pediatric Department, Benazir Bhutto Hospital, Rawalpindi.

Correspondence: Dr. Abid Hussain, Senior Medical Officer, Pediatric department, Rawalpindi Medical University. **Email:** researchcellpaeds@gmail.com

1. Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first discovered in Wuhan, China in January 2020[1]. Since then, the virus has affected multiple countries and was declared as global pandemic on 11th March 2020, by WHO.

The common symptoms include cough, fever and pharyngitis[2]. However, certain serious complications are seen in pediatric patients with COVID-19 including myocarditis, pediatric inflammatory multisystem syndrome (PIMS), acute respiratory distress syndrome (ARDS), meningoencephalitis, acute kidney injury, disseminated intravascular coagulation and shock[3].

Over the time, many biochemical abnormalities have been studied in the pathogenesis of severe disease. Electrolyte imbalance has also been described in COVID-19. The possible explanation of this finding is the impact of virus on gastrointestinal system[4], renal system[5] and renin-angiotensin-aldosterone axis, as ACE2 is a known receptor for SARS-CoV-2 spike complex[6], hence disturbing fluid and electrolyte homeostasis. Hyponatremia, hypokalemia and hypocalcemia are associated with severe COVID-19[7].

Kidneys play an important role in maintenance of normal volume and osmolality of body fluids, acid-base balance, normal electrolyte concentrations along with toxin excretion. Kidneys are primary source of prorenin and angiotensin converting enzyme (ACE). Another important organ involved in electrolyte and volume homeostasis for regulating the transport of ions is the intestinal epithelium. The epithelial cells normally absorb large volumes of fluid and ions daily, but diarrhea or vomiting could result in water and electrolyte loss. Furthermore, in some cases with Covid-19 infection, the syndrome of inappropriate antidiuretic hormone

secretion (SIADH) has been reported, leading to disturbances in fluid and electrolytes[8].

COVID-19 disease may present with predominant gastrointestinal symptoms like diarrhea, which can cause hyponatremia[9]. Coronavirus enters the cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptors[10]. Due to the high level of these receptors in kidney cells, the kidneys are not immune to coronavirus invasion. The kidneys involvement with pathogens can disrupt a wide range of body mechanisms and cause many problems such as fluid and electrolyte imbalances. A large single-center study in China revealed renal involvement in 75.4% (251 of 333) of COVID-19 patients, with majority having proteinuria, hematuria or acute kidney injury[5]. The most common renal complication in COVID-19 hospitalized patients is electrolyte disorder[11,12].

Electrolyte imbalance has previously been linked to increased risk of mortality in infectious diseases. Hypokalemia is known to exacerbate acute respiratory distress syndrome (ARDS) and acute cardiac injury, which are common complications in COVID-19, especially in patients with underlying lung or heart disease[13]. Similarly, hyponatremia can lead to cerebral edema, rhabdomyolysis, seizures and coma. Chloride imbalance is also linked to acute kidney injury, increased morbidity and mortality[14].

Currently, there is a very limited data on electrolyte imbalance in children with COVID-19. The aim of this study was to explore frequency of electrolyte imbalance in hospitalized pediatric patients and its correlation with disease severity and outcomes.

2. Materials & Methods

This was a retrospective, observational study conducted on children admitted with moderate to severe COVID-19. Study period was from January 2021 to July 2021, after ethical approval from Institutional Review Board of RMU. Diagnosis of COVID-19 was done according to WHO Guidelines and required at least one positive nasopharyngeal RT-PCR or Radiological findings (on Chest Xray or HRCT) consistent with COVID-19. 61 children with ages of 1 to 16 years were included after fulfilling diagnostic criteria. Patients with pre-existing medical conditions including chronic kidney disease, tubulopathy or any previously diagnosed renal disease, syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus, septicemia and those on diuretic therapy for any other disease were excluded. Disease was further classified into mild, moderate and severe categories in accordance with WHO guidelines. A mild disease is a confirmed case

with non-specific upper respiratory tract infection and no radiological sign of pneumonia, a moderate disease is a confirmed case with fever and cough, difficulty breathing without any danger signs, having the radiological evidence of pneumonia requiring hospitalization with or without need of oxygen support and severe disease is a confirmed case having at least one danger sign together with radiological evidence of pneumonia and or sepsis, septic shock, respiratory failure/ARDS, multiple organ dysfunction. Danger signs include severe dehydration, lethargy, irritability, decreasing conscious level, central cyanosis, chest in drawings, tachypnea, convulsions, signs of shock, myocarditis or SpO2 less than 92%.

Only patients with moderate to severe disease were admitted and included in this study. Treatment included Oxygen, steroids, anti-viral drugs and antibiotics on individual case basis. Records were reviewed and data on demographics, presenting complaints, disease severity, laboratory parameters (blood counts, serum electrolyte, liver and renal function tests) and treatment received (non-invasive/invasive mechanical ventilation, antibiotics, anti-viral drugs, steroids and diuretics) was collected.

3. Results

During the study period of 6 months, 61 confirmed COVID-19 patients were admitted. 37(60.7%) were males and 24 (39.3%) were females. The age of the patients ranged from infants to 12 years with a mean age of 27.25 months. Out of 61 admitted cases, 28 children (45.9%) had moderate & 33(54.0%) had severe disease. 46(75%) patients were discharged while 15(25%) patients expired.

Table 1: Demographic Features

Gender	Frequency (n=)	Percentage
Male	37	60.7
Female	24	39.3
Age		
Less than 1 year	33	54.1
1-4 years	13	21.3
5-8 years	10	16.4
9-12 years	5	8.2
Disease frequency		
Mild	0	0.0
Moderate	28	45.9
Severe	33	54.1
Total:	61	100
Outcome		
discharged	46	75.5%
Expired	15	24.5%

All Patients were assessed for electrolyte abnormalities and association of these electrolyte abnormalities with the severity of disease and outcome. A total of 30 patients (49.2%) were hyponatremic &13 patients (21.3%) were hypernatremia. Hypokalemia was observed in 34(55.7%) & hyperkalemia in 2 patients (3.3%) and hypochloremia was observed in 13(21.3%) while hyperchloremia was present in 3(4.9%) patients.

Table 2: Electrolyte abnormalities in the study population

Electrolyte Imbalance	Number (n=)	%
With a normal Sodium level	18	29.
Hypernatremia	13	21.3
Hypo natremia	30	49.2
With a Normal potassium level	20	32.8
Hyperkalemia	2	3.3
Hypokalemia	34	55.7
With a Normal chloride level	45	73.8
Hyperchloremia	3	4.9
Hypochloremia	13	21.3

Table 3: Association of electrolyte abnormalities with severity of disease

Parameter	Variable	moderate N=	%	severe N=	%
Na	<135	14	22.9	16	26.2
	135-145	10	16.4	8	13.1
	>145	4	6.5	9	14.7
K	<3.5	12	19.6	22	36
	3.5-4.5	14	22.9	6	9.8
	>5	0	0	2	3.27
Cl	<95	7	11.4	6	9.8
	95-108	21	34.4	24	39
	>108	0	0	3	4.9
calcium	<8.5	14	22.9	15	24.6
	8.5-10.7	14	22.9	18	29.5
	>10.7	0	0	0	0

11(18%) patients with Hyponatremia and 6 (9.8%) patients with hypernatremia expired. The potassium abnormalities were also associated with significant mortality. 14(22.9%) patients with hypokalemia and 2 (3.2%) with hyperkalemia expired. Hypochloremia was found in 4(6.5%) patients, hyperchloremia in 2(3.2%) patients and Hypocalcemia in 9(14.7%) patients who expired.

Table 4: Association of electrolyte abnormalities without come

Parameter	Variable	Discharged N=	%	expired N=	%
Na	<135	19	31.0	11	18
	135-145	16	26.2	2	3.27
	>145	7	11.4	6	9.8
K	<3.5	25	40.9	14	22.9
	3.5-4.5	17	27.86	3	4.9
	>5	0	0	2	3.2
Cl	<95	10	16.4	4	6.5
	95-108	32	52.4	13	21.3
	>108	0	0	2	3.2
Calcium	<8.5	20	2.78	9	14.7
	8.5-10.7	22	36	10	16.4
	>10.7	0	0	0	0

4. Discussion

We evaluated the electrolyte imbalance in paediatric COVID-19 patients and its impact on severity of disease and outcome. Majority of our patients were male i.e. 60.7%. This finding is similar to a study conducted on pediatric patients in China where more boys were affected[15]. 54.1% of our hospitalized patients were infants, which is in accordance with a study suggesting higher rates of hospitalization in infants as compared to older children and adults.[16]

Regarding electrolyte imbalance, 49.1% of patients with moderate to severe disease had hyponatremia and 2.3% had increased sodium levels. This is comparable to a study where 57% patients suffered from low sodium levels, and this decreased level of sodium increased the odds of mechanical ventilation but was not associated with death.[13] 11(18%) of our patients with hyponatremia died. Earlier reports have also suggested increased frequency of hyponatremia with COVID-19 illness and was found to be an independent risk factor for severe outcomes including mechanical ventilation and death[17,18]. A meta-analysis revealed incidence of hyponatremia in 24% of patients, with poor outcome in 20%[19]. Mortality in our patients with hypernatremia was high (9.8%). Another study also documented a high frequency of hyponatremia but more in-hospital deaths due to hypernatremia[21]. A longer stay in hospital and a higher risk of death due to hypernatremia is also reported by another study[13].

Hypokalemia was found to be the most common electrolyte imbalance in our study where total of 34 (55.7%) patients were affected. Among these, 19.6% belonged to moderate severity group while36% had severe disease. A previous study has also described

hypokalemia as a common abnormality in hospitalized COVID-19 patients with prevalence of 41% [21].

The most frequent electrolyte disorders in our study were hypokalemia (55.7%) followed by hyponatremia (49.2%), hypernatremia (21%) and hypochloremia (21%). Another study has quoted almost similar findings of electrolyte imbalance where hyponatremia was the most frequent electrolyte abnormality 146 (35.8%), 39 (9.5%) had hypocalcemia, hypokalemia and hypochloremia were found in 28 (6.8) patients while seven (1.7%) of the patients had hyperkalemia[22]. Regarding severity of disease, hypokalemia was most commonly related with severe disease (36%) followed by hyponatremia (26.2%).

Mortality in hypokalemic patients was found to be 22.9%. 3.3% of our patients had hyperkalemia but it was associated with 100% mortality. Liu et al. has quoted that compared with potassium levels of 4.0 to 4.5 mmol/L, the adjusted hazard for 30-day mortality during hospitalization was 4.14 (95% CI: 1.29–13.29; p = 0.017) for >5 mmol/L and 1.99 (95% CI: 0.54–7.35; p = 0.300) for <4 mmol/L[23].

Higher mortality rate observed in our study can be attributed to severity of disease in our patients as we included only those belonging to moderate and severe disease, where many needed ventilatory support for disease management. Other factors may include voids in healthcare infrastructure, limited access to essential medical products and budgetary constraints in Pakistan[24].

5. Conclusion

Hypokalemia and hyponatremia were common electrolyte disorders in children with COVID-19. Electrolytes need to be assessed in all COVID-19 patients and monitored during hospital admission. These electrolyte abnormalities were significantly associated with severity of disease and a higher risk of death in children with COVID-19. Early recognition and treatment of electrolyte imbalance can help in reducing disease severity and associated mortality. There is limited data available on electrolyte imbalance in pediatric patients with COVID-19 and further studies are needed.

CONFLICTS OF INTEREST- None

Financial support: None to report.
Potential competing interests: None to report

References

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270-3.
2. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. Pediatr Infect Dis J. 2020 Jun;39(6):469.
3. Ciuca IM. COVID-19 in children: an ample review. Risk Management and Healthcare Policy. 2020;13:661.
4. Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K, Schnoll-Sussman F et al. SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant. World J Gastroenterol. 2020 Apr 14;26(14):1546.
5. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol. 2020 Jun 1;31(6):1157-65.
6. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 2020 Feb 24;6(1):1-4.
7. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020 May;57(3):262-5.
8. Mabillard H, Sayer JA. Electrolyte disturbances in SARS-CoV-2 infection. F1000 Res. 2020 Jun;9:587
9. Taheri M, Bahrami A, Habibi P, Nouri F. A review on the serum electrolytes and trace elements role in the pathophysiology of COVID-19. Biol Trace Elem Res. 2021 Jul;199(7):2475-81.
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270-3.
11. Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. Ann Med. 2020 Oct 2;52(7):345-53.
12. Bonanad C, Díez-Villanueva P, García-Blas S, Martínez-Sellés M. Main challenges of electrolyte imbalance in older patients with COVID-19 and risk of QT prolongation. Rev Esp De Cardiol (Engl Ed.). 2021 Feb;74(2):199.
13. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem. 2020 May;57(3):262-5.
14. KalikkotThekkeveedu R, Ramarao S, Dankhara N, Alur P. Hypochloremia secondary to diuretics in preterm infants: should clinicians pay close attention?. Glob Pediatr Health. 2021 Feb;8:2333794X21991014.

15. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020 Jun 1;145(6).
16. Covid CD, Team R, Covid CD, Team R, COVID C, Team R, et al. Coronavirus disease 2019 in children—United States, february 12–april 2, 2020. Morb Mortal Wkly Rep. 2020 Apr 10;69(14):422
17. De Carvalho H, Letellier T, Karakachoff M, Desvaux G, Caillon H, Papuchon E,et al. Hyponatremia is associated with poor outcome in COVID-19. J Nephrol. 2021 Aug;34(4):991-8.
18. Gheorghe G, Ilie M, Bungau S, Stoian AM, Bacalbasa N, Diaconu CC. Is there a relationship between COVID-19 and hyponatremia?Medicina. 2021 Jan;57(1):55.
19. Akbar MR, Pranata R, Wibowo A, Sihite TA, Martha JW. The prognostic value of hyponatremia for predicting poor outcome in patients with COVID-19: a systematic review and meta-analysis. Front Med. 2021 Jun 14;8:805.
20. Hirsch JS, Uppal NN, Sharma P, Khanin Y, Shah HH, Malieckal DA, Bellucci A et al. Prevalence and outcomes of hyponatremia and hypernatremia in patients hospitalized with COVID-19. Nephrol Dial Transplant. 2021 Jun;36(6):1135-8.
21. Alfano G, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, et al. Hypokalemia in Patients with COVID-19. Clin Exp Nephrol. 2021 Apr;25(4):401-9.
22. Tezcan ME, Gokce GD, Sen N, Kaymak NZ, Ozer RS. Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized coronavirus disease 2019 patients. NMNI. 2020 Sep 1;37:100753.
23. Liu S, Zhang L, Weng H. 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: 736- 743.
24. Atif M, Malik I. Why is Pakistan vulnerable to COVID-19 associated morbidity and mortality? A scoping review. The Int J Health Plan Manag. 2020 Sep;35(5):1041-54.