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Acid-Base Disturbances in Pediatrics Infected With COVID-19, A Cross Sectional Study

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ABSTRACT

Background: Data on the pathophysiology and clinical spectrum of COVID-19 in children are few. The dominant respiratory outcome of COVID-19 is arterial hypoxaemia. Arterial Blood Gas (ABG) analysis helps detect early acid base balance alternations. Acid–base imbalance hasn't been outlined well in children with COVID-19.

Objective: The aim of the current study is to evaluate the blood gas levels as a reflection to the acid-base status among COVID19 children at admission and to detect the pattern of acid-base disorders.

Patients and methods: A total of 62 children with positive nasopharyngeal swabs were assessed for ABG at the time of admission in ElMatria Teaching Hospital from February 1, 2021 to the end of July 2021. **Results:** Among the study subjects, 53% were males and 47% were female. Most affected age group was <2 years. 53% presented by GIT manifestation (fever, nausea, vomiting, diarrhea), 37% presented by respiratory manifestation (fever, cough, dyspnea). Most common ABG finding was hypoxemia in 90.3% ($P<0.001$). PH (potential hydrogen**)** of about 50% was within the normal range, while 37.1% had acidosis and 12.9% had alkalosis ($P<0.001$). Base deficit was significantly found in 53.4% ($P=0.004$), while lactic acid was only elevated in 32.3% ($P=0.005$).

Conclusion: ABG should be evaluated in all COVID-19 patients at admission. Children may present with atypical COVID symptoms as diarrhea, and children may resist changes in acid-base balance.

Keywords: Coronavirus, ABG, Acidosis, Alkalosis, Cross sectional study, ElMatria Teaching Hospital.

INTRODUCTION

On March 2020, the Coronavirus disease of 2019 (COVID-19) was declared by the World Health Organization (WHO) as a pandemic (1). A worldwide regular attempt is needed to prevent the more unfold of the virus. During the COVID-19 outbreak, many studies have investigated laboratory biomarkers used to treat and determine the prognosis of COVID-19 patients, but none have investigated arterial blood gas and acid-base changes in infected children. Very few studies have done so. As COVID-19 becomes more severe, many patients require admission to the intensive care unit (ICU), resulting in frequent arterial blood gas (ABG) analysis. Various test results have been identified as risk predictors that may help in staging, monitoring, prognosis, and treatment of COVID-19 patients (2,3).

What is currently known is that children may have milder symptoms and require hospitalization less frequently than adults. Nonetheless, on May 14, 2020, the US Centers for Disease Control and Prevention (CDC) reported pediatric multisystem inflammatory syndrome (MIS-C) associated with COVID-19 (4,5). This statement is from a subset of pediatric patients who presented with multiple organ failure and severe inflammation and were diagnosed as SARS-CoV-2 positive.

One of the most major complications of COVID 19 is the arterial hypoxemia, thus affecting the lung compliance which could require mechanical ventilation (6,7). Acid base imbalance is a frequent association with patients who suffer from serious viral illnesses including COVID-19(8). Tropism of the virus for kidneys and lungs might hypothetically result in frequent acid–base changes due to kidney injury and pneumonia (9,10). To monitor acid base balance of COVID-19 patients, ABG should be carried out. Most cases of acid–base changes are mild and rarely symptomatic and may have a low tendency to affect organ homeostasis. Contrariwise, severe changes of acid–base balance can have severe multi-organ significances. The prevalence and impacts of acid–base disorders in COVID-19 patients have been poorly assessed until now (11).

As angiotensin-converting enzyme 2 (ACE2) is the entry pathway for SARS-CoV-2 (12), the renin-angiotensin system (RAS) is affected by COVID-19. When SARS-CoV-2 enters cells, it downregulates ACE2, upregulates RAS signaling, and produces angiotensin II and aldosterone. Both angiotensin II and aldosterone affect renal processing of hydrogen (H+) and bicarbonate (HCO3) and can cause acid-base disorders. (13). Reports on the clinical picture of COVID-19 in children are missing

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and the clinical patterns of children with COVID-19 remain uncertain.

The aim of this study was to describe the clinical, ABG finding of children with COVID-19 and the link between them.

PATIENTS AND METHODS

The study was conducted at ElMatria Teaching Hospital from February 1, 2021 to the end of July, 2021 (total 6 months). Children enrolled were those who were hospitalized and confirmed by PCR (polymerase chain reaction) to be infected with COVID-19.

Inclusion Criteria: Children who were confirmed to be COVID-19 positive and whose parents or guardians consented to participate in the study.

Exclusion criteria: Children who hadn't not tested positive for COVID-19 by PCR and whose consent to enroll in the study has not been obtained from their parents or guardians.

Study setting and subjects: A total of 62 children were assessed for ABG estimation at the time of admission. The pattern of their affection was observed

Sample size estimation: Sample size was calculated using the (G power software). As regarding the primary outcome (acid base disturbance) based on **Castro et al. (2020)** results that revealed 62 patients per group were appropriate sample size for the study. The power is 80% and α error probability = 0.05, effect size=0.18 [14].

Operational definitions:

1. Acidemia and alkalemia were defined according the reference ranges of PH for age and sex. Also, references for $PaCO_2$, PaO_2 and HCO_3 were reviewed for defining acidosis, alkalosis, hypoxemia and the base excess and deficit [15,16]. In children with multiple ABG analysis, we chose only the first analysis
2. Diagnosis of COVID-19 was carried out by nasal/oropharyngeal swabs in accordance with WHO guidelines in all children suspected to have COVID-19 infection. ABG analysis was needed to follow the respiratory gas exchange and acid–base status.

Nasopharyngeal swabs have been amassed in attention to the protection precautions and contamination manipulates tips and recommendations. Samples then have been loaded into the viral delivery encompassing tubes, and viral RNA become then extracted. Extracted nucleic acid become then combined with PCR primers. Samples have been then loaded into the Rotor gene thermal cycler from the carried out biosystems. After transcription become finished at 55°C for 10 mins, preliminary denaturation accompanied for 2 mins at 95°C, that become followed through forty-five cycles every of which become composed of a preliminary denaturation step at 95°C for ten seconds and annealing and extension step at 60°C for 60 seconds. Children were considered COVID 19 positive infection at what time a positive SARS-CoV-2 RT-PCR test was detected [17,18].

Ethics approval and consent to participate

The protocol of the current study was approved by GOTHI (General Organization of Teaching Hospitals and Institutes) Ethics Committee (approval number HM000140). Informed consent was obtained from each patient's parents or guardians prior to inclusion in the study. No penalties were imposed if parents refused to participate in the study. This study was conducted in accordance with the Declaration of Helsinki, taking into account the ethical principles of medical research involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 20 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean and standard deviation (SD). Independent samples t-test and ANOVA were used to compare between two or more independent groups of quantitative variables. P value ≤ 0.05 was considered significant.

RESULTS

During the study, children infected and confirmed with COVID-19, who were admitted at ElMatria Teaching Hospital, were evaluated for their demographic and clinical status. A total of 62 children were enrolled. Regards the demographic criteria; about 51% of studied children were categorized as <2 years old, about 24% of studied children were categorized as 2 - <6 years old, about 25% of studied children were categorized as 6-13 years old (**Figure 1A**). Male patients represented 53% (N= 33) of the study group. Female patients represented 47% (N= 29) of the study group Male to female ratio was 1.1:1 (**Figure 1B**).

Regarding the disease presentations 53% presented by GIT manifestation (fever, nausea, vomiting, diarrhea), 37% presented by respiratory manifestation (fever, cough, dyspnea), 10% presented by other manifestation (e.g. Myocarditis, Gilian Barre syndrome) (**Figure 1C**).

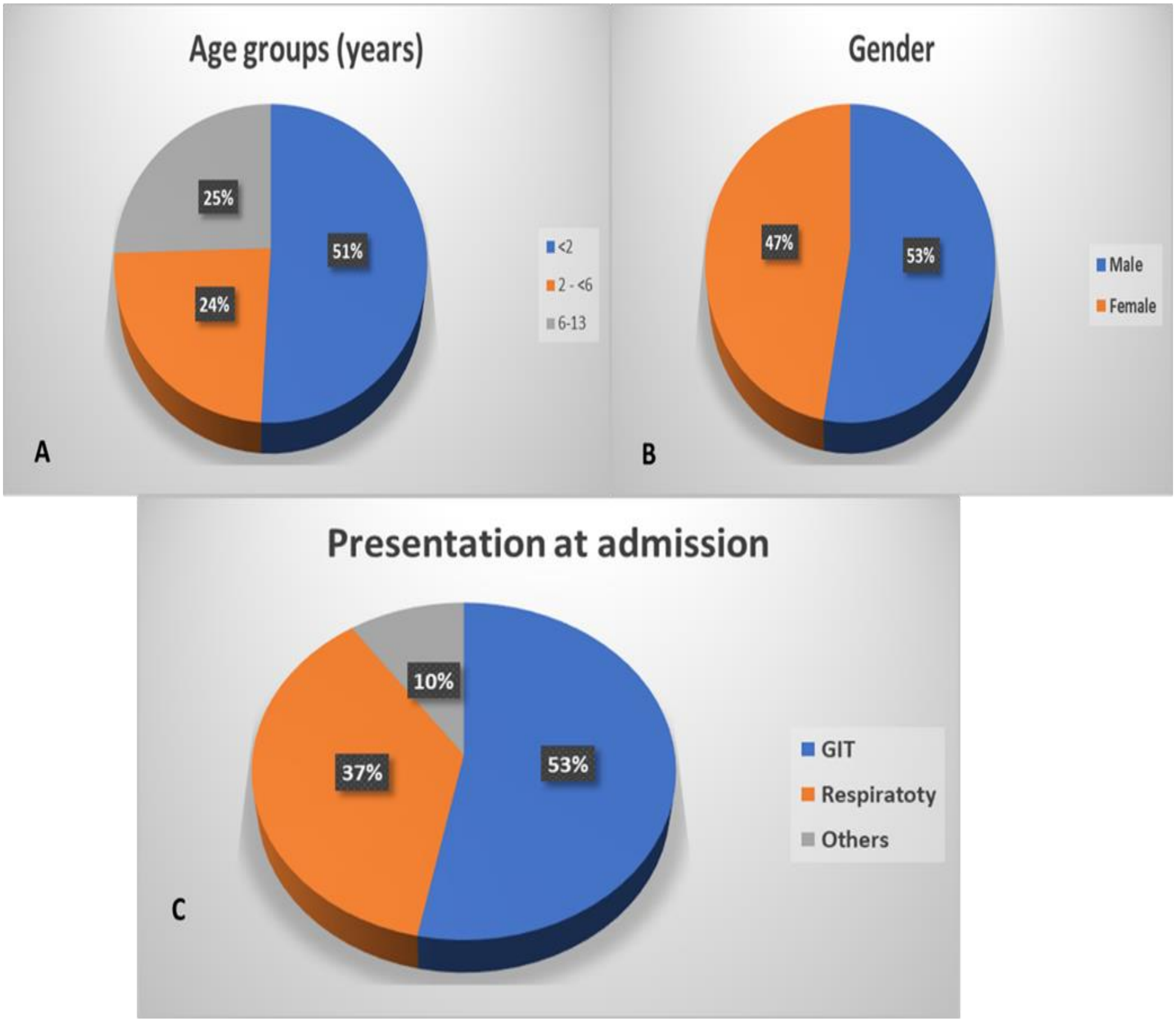

Figure 1A: Age groups among studied children, Figure 1B: Sex distribution among studied children, Figure 1C: Presentation at time of admission.

ABG analyses revealed that most patients (50%) were significantly with normal PH values while 37.1% were suffering of acidosis and 12.9% were suffering of alkalosis (P value= 0.001). No significant difference in PaCo2 levels among infected children (P value= 0.374) was present. On the other side, most of patients 90.3% were suffering from hypoxemia, while 6.2% showed normal PaO2, and only 3.2% had PaO2 >100 (P value <0.001). Amounts of acids and bases were assessed and revealed that 48.4 % had low HCO3, 35.5% had normal HCO3 and 16.1% had high HCO3 (P value= 0.007). On consequence and calculation of base excess and deficit, 53.2% had base deficit and 24.2% had base excess and 22.6% had normal amounts of bases (P value= 0.004). On contrary, 67.7% significantly had normal lactic acid levels and only 32.3% had high levels (P value= 0.005) (**Table 1**).

Table 1: ABG finding in the studied children.

Variable		Number (N= 62)	Percent (%)	95% CI*	P value
PH Level	Normal (7.35 – 7.45)	31	50	37 – 63	0.001
	Acidosis (<7.35)	23	37.1	25.2 – 50.3	
	Alkalosis (>7.45)	8	12.9	5.7 – 23.9	
PaCO2 (mmHg)	Normal (35 - 45)	21	33.9	22.3 – 47	0.374
	Low (<35)	25	40.3	28.1 – 53.6	
	High (>45)	16	25.8	15.5 – 38.5	
PaO2 (mmHg)	Normal (80 - 100)	4	6.5	1.8 – 15.7	<0.001
	Low (<80)	56	90.3	80.1 – 96.4	
	High (>100)	2	3.2	0.4 – 11.2	
HCO3 (mEq/L)	Normal (22 - 28)	22	35.5	23.7 – 48.7	0.007
	Low (<22)	30	48.4	35.5 – 61.4	
	High (>28)	10	16.1	80 – 27.7	
Lactic acid (mmol/L)	Normal (0.5 - 2.2)	42	67.7	54.7 – 79.1	0.005
	High (>2.2)	20	32.3	20.9 – 45.3	
Base excess or deficit (mEq/L)	Normal (-2 - +2)	14	22.6	12.9 – 35	0.004
	Base deficit (< -2)	33	53.2	40.1 – 66	
	Base excess (>2)	15	24.2	14.2 - 36.7	

DISCUSSION

The analysis of our data reported the spectrum of acid–base variations in children with COVID-19. GIT manifestation in the form of diarrhea is the main manifestation of this disease in our study followed by respiratory manifestations as pneumonia and some children were presented with atypical presentation like myocarditis and Guillain barre syndrome. These atypical presentations can disclose that COVID-19 presentation in pediatrics may differ from adult.

As mentioned above, diarrhea could be the presenting manifestation of COVID1-9 in children. This finding comes in line with a previous study which yielded that in a considerable number of patients, diarrhea was the presentation [(19)]. However, the percent of children who have it as a main symptom is larger in our study. This can be clarified by the widespread of diarrhea in our developing country [(20)].

Most patients with severe COVID-19 infection requiring hospitalization in the intensive care unit develop an atypical acute distress syndrome, often associated with preserved lung gas volumes [(21)].

This coincides with our findings as nearly almost patients (90.3%) were suffering from hypoxia in spite of insignificant variations in PaCO2 levels among infected children, this is referred to the specific phenomenon of “silent hypoxia” or “silent hypoxemia” [(22-24)]. The mechanisms included might be linked to focal lung injuries and the high pulmonary compliance [(25)].

Acid-base disorders are one of the most essential markers in the severity and pathogenesis of many diseases, such as COVID-19 infections [(26)]. Acidosis could arise due to a substantial rise in arterial carbon dioxide pressure (respiratory acidosis) or increase in various compounds such as lactic acid, arterial ketones, or as a consequence of kidney failure (metabolic acidosis); all of these factors can act concurrently in the rise of hydrogen protons and, accordingly, the decrease of blood and pH levels [(27,28)]. Previous studies have reported that lactate-induced metabolic acidosis in COVID-19 may be due to anaerobic glycolysis, which is favored as a result of hypoxemia. A product of the glycolytic pathway, pyruvate is not transported to mitochondria to follow the oxidation process. Instead, it is converted to lactate in the cytosol by the enzyme LDH (lactate dehydrogenase). Hypoxemia impairs tissue oxygenation and oxidative phosphorylation, so cells acquire ATP (adenosine triphosphate) via anaerobic glycolysis. As a result, lactate levels begin to rise significantly and metabolic acidosis increases [(29,30)].

However, lactic acid was only elevated in 32.2 % and 67.7% have normal lactic acid levels in our study, thus children might have different compensatory mechanisms rather than in adult that can resist the hypoxic effect of COVID-19, this issue was discussed in a previous study which revealed that; the principles of adaptation in children are different than in adults. Children have lower activity of anaerobic metabolism of carbohydrates than adults due to the lack of rate limiting enzyme phosphofructokinase, so lower levels of lactic acid are formed. In addition, the arteriovenous oxygen difference is greater in children; this contributes to the perfection of pattern of the adaptation regards the cardiorespiratory system. Local flow in peripheral circulation in working muscle is greater by 30% in children than in adults [31]. This could explain why in spite of ABG changes in studied patients are observed, only 37.1% developed acidosis while 50% were within normal PH.

In the current study, we found that most COVID-19 children (53%) were presented by GIT (gastrointestinal tract) manifestations in the form of diarrhea leading to loss of HCO3, thus about 48.4% have low HCO3 levels and about 53.2% have base deficit. This agreed with previous studies which reported that the SARS-CoV-2 virus can infect the intestines, inducing diarrhea that results in significant loss, hence increased incidence of acidosis occurrence ensues [32,33]. Although base deficit was present in a considerable number of children, not all of them were having acidosis. Indeed, base deficit is a weak and poor indicator of tissue acidosis. This finding is very close to a previous report [34].

Atypical manifestations of COVID-19 in children may predominate. This information was applied clinically in our study, as most of the children enrolled had a clinical picture of GIT involvement. The child's target site for COVID-19 infection may be the gastrointestinal tract. This preference can be explained by the higher expression of angiotensin-converting enzyme 2 (ACE2), the major receptor of the SARS-CoV-2 virus, in the intestinal tract. It has also been hypothesized that a number of previous reports have identified SARS-CoV-2 viral RNA in GIT, suggesting a role for the fecal-oral transmission route of COVID-19, signifying a role for the gastrointestinal manifestations in this study that could clarify the larger proportion [35].

Strength of the study

To our best knowledge, the current study is the first one that investigates ABG changes in children and correlates these changes with the clinical presentations.

CONCLUSION

Children have atypical COVID presentations more than adult since most of children in this study were presenting with GIT manifestation in the form of diarrhea. Furthermore, children have more capacity to resist changes in oxygen saturation to maintain acid base balance.

RECOMMENDATION

Health care workers should gain attention regarding the silent hypoxemia that is predominant in the infected children and can produce no changes neither in PH nor PCO2 values, thus masking of the current bad prognosis of children could ensue and delaying of the appropriate management could occur. Further studies are needed to link ABG results to the prognosis.

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