CLINICAL PRESENTATION OF COVID-19 IN PEDIATRIC AGE

By

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ABSTRACT

Introduction: *By March 2020, COVID-19 was declared a global pandemic by the World Health Organization (WHO), and at the time of writing there are more than 600 million confirmed cases and about 6 million deaths worldwide from COVID19 infection however, among 4.1 million COVID 19 deaths reported by MPIDR coverage database only 0.4 % of these deaths were children.*

Objectives and aim of study: *To Identify COVID 19 positive symptomatic cases within pediatric age group and studying variable clinical presentation and radiological findings and its impact on mortality.*

Patients and Methods: *This study included 50 cases under age of 18 years old with COVID-19 positive PCR from Minia University Hospital and Minia Health Insurance Hospital – Minia – Egypt from the 1st of January 2022 to 30th May 2022. We studied the different clinical presentation, radiological findings and laboratory investigations among those children and assessing the impact on mortality so we divide studied cases into 2 groups, improved and died group.*

Results: *Fever and upper respiratory tract symptoms are the most common clinical presentation while GIT symptoms are uncommon and associated with cases who have normal or very low suspicious in chest CT . 31 cases out of 50 (62%) improved while unfortunately 19 cases (38%) died.*

Conclusion: *Children are equally affected by COVID-19 infection as adults but symptoms and signs ranging from mild to moderate cases and less complicated than adults however, severe cases in our study were very critical and this reflected on percentage of died cases in our study (38%).*

Keywords: *COVID-19, pediatric age, SRAS-COV2.*

INTRODUCTION

A novel strain of coronavirus (referred to as SARS-CoV-2), which causes the sometimes severe respiratory infection COVID-19, was first identified in Wuhan city, China, toward the end of 2019 **(Zhu, Zhang et al. 2020)**.

International pediatric data suggest lower rates of severe coronavirus disease 2019 (COVID-19) in children and higher rates of asymptomatic infection **(Dong, Mo et al. 2020) (Lu, Zhang et al. 2020)**.

The first pediatric case was recorded in a 10-year-old kid from Shenzhen, China, whose family had visited Wuhan City **(Chan, Yuan et al. 2020)**.

Children tend to be less likely than adults to be impacted. Surveillance from various countries revealed that 1 to 5% of laboratory confirmed cases are children. Children under the age of 18 make up around 6% of laboratory-confirmed cases reported to the Centers for Disease Control and Prevention (CDC) in the United States **(Wu and McGoogan, 2020)**.

Italian data, published on March 18, 2020, reported that only 1.2% of 22512 Italian cases with COVID-19 were children **(Livingston and Bucher 2020)**.

COVID-19 symptoms are comparable in children and adults, although severe cases have been observed, COVID-19 infections in children are mild compared with that in adults . The weighted mean age of 7480 Children with laboratory-confirmed COVID-19 from Italy, China, and the United States was 7.6 years in a systematic analysis of observational data **(Stokes, Zambrano et al. 2020)**.

A different Chinese studies found that the majority of pediatric cases sustained either mild or moderate symptoms. Severely or critically affected cases were very rare **(Dong, Mo et al. 2020)**.

The symptoms are typical of acute respiratory infections included tachypnoea, tachycardia, fever, cough, sore throat, pharyngeal erythema, sneezing, rhinorrhea, myalgia, fatigue and wheezy chest. The less commonly presented symptoms and signs are diarrhea, vomiting, low oxygen saturations of less than 92% **(Dong, Mo et al. 2020) (Lu, Xiang et al. 2020)**.

Only a small percentage of children with COVID-19 need hospital admission, and only a few of them need PICU admission. Hospitalization rates have also been linked to children under the

age of one year, albeit hospitalization of newborns may not represent the severity of their disease **(Sun, Li et al. 2020)**.

The reference standard for diagnosing COVID-19 remains positive RT-PCR results. Due to possibility of false negative results, repeated testing that includes deep bronchial and fecal samples may be needed **(Li, Yao et al. 2020)**.

Chest computed tomography (CT) has become important in screening, diagnosis and follow up of patients with COVID-19 and it adds prognostic information. CT has shown high sensitivity rates even higher than polymerase chain reaction test **(Serrano, Alonso et al. 2020)**.

AIM OF THE WORK

To identify COVID 19 positive symptomatic cases within pediatric age group and studying variable clinical presentation and radiological findings and its impact on mortality.

PATIENTS AND METHODS

This prospective observational epidemiological study was conducted at Minia Health Insurance Hospitals and Minia University Hospital of Pediatrics, Minia, Egypt during the period from 1st of January 2022 to 30th May 2022.

Fifty children with Covid-19 positive real time PCR were included in this study by simple random method.

Ethical considerations of the study:

- This study was approved by the Institutional Review Board and Medical Ethics committee, Faculty of Medicine, Al-Azhar University (Assiut).
- The parents of all participants had signed written informed consent about study and they have been informed about their wright to withdraw from the study at any time.
- Data of the study are confidential.
- No conflict of interst regarding the study or publication.
- No financial support.

Inclusion criteria:

- Symptomatic male and female cases of COVID 19 positive PCR.
- Pediatric age group up to age of 18 years old.

Exclusion criteria:

- Cases of negative PCR for COVID 19 infection.
- Patients more than 18 years old.

All studied cases were being subjected to the following after confirmation to be positive PCR for COVID-19 infection:

- Full history taking including history of upper or lower respiratory tract infection history of associated medical problem and history of contact with infected cases.
- Complete general and local examination.
- Laboratory investigations including CBC, renal functions, liver functions, electrolytes and inflammatory markers (ferritin, D-dimer and LDH).
- Chest CT.

Statistical analysis:

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 25 and every used parametric test are listed below each table.

RESULTS

The study included 50 patients who justified inclusion criteria and divided into two groups according to prognosis to improved group including 31 cases (62%) and died group including 19 cases (38%). our detailed results will be demonstrated in the following tables.

Table (1): Demographic data of studied groups

Demographic data	Improved (n = 31)	Died (n = 19)	p value
Age:			
• Median	18m	18m	
• IQR	5m – 3.5y	4m – 10y	0.548
• Range	1m – 14y	2m - 13y	
Age groups:			
• Less than 5y	25 (80.6%)	12 (63.2%)	0.171
• 5y and above	6 (19.4%)	7 (36.8%)	
Sex:			
• Male N (%)	20 (64.5%)	11 (57.9%)	0.64
• Female N (%)	11 (35.5%)	8 (42.1%)	
Weight (kg):			
• Median	11	10	
• IQR	7 - 15	5.5 - 28	0.749
• Range	3.5 – 45	3.5 – 50	

Analyzed by Mann-Whitney U test and Chi square test or Fisher's exact test
*: Significant difference at P value < 0.05

Demographic data of both groups shown in **table 1** demonstrate that there was no significant difference when comparing both groups as regard demographic variables. We noticed that most of died cases were males (58%) and under the age of 5 years (63.2%).

Table (2): COVID manifestations in studied groups

Manifestations	Improved (n = 31)	Died (n = 19)	p value
Fever:			
• Mean ± SD	38.1 ± 0.71	39.1 ± 0.48	**<0.001***
• Range	37 – 40	38 – 40	
Fever grades:			
• **Normal (36.7 - 37.2)**	2 (6.5%)	0 (0%)	**0.033***
• **Low grade (37.3 - 37.8)**	8 (25.8%)	0 (0%)	
• **Moderate grade (37.9 - 39.4)**	19 (61.3%)	15 (78.9%)	
• **High grade (39.5 - 40.5)**	2 (6.5%)	4 (21.1%)	
Cough:			
• **Present**	24 (77.4%)	19 (100%)	**0.026***
• **Absent**	7 (22.6%)	0 (0%)	
Dyspnea:			
• **present**	25 (80.6%)	19 (100%)	**0.041***
• **Absent**	6 (19.4%)	0 (0%)	
Vomiting:			
• **present**	6 (19.4%)	6 (31.6%)	**0.326**
• **Absent**	25 (80.6%)	13 (68.4%)	
Diarrhea:			
• **Present**	5 (16.1%)	1 (5.3%)	**0.251**
• **Absent**	26 (83.9%)	18 (94.7%)	
Convulsion:			
• **Present**	1 (3.2%)	5 (26.3%)	**0.015***
• **Absent**	30 (96.8%)	14 (73.7%)	

Analyzed by independent t test and Chi square test or Fisher's exact test

*: Significant difference at P value < 0.05

As shown in **table 2**, there was a significant difference between improved and died groups in relation to fever (P value <0.001). moderate grade fever was the most frequent degrees range in both groups and 15 cases (78.9%) out of 19 died cases were with moderate grade fever. convulsion occurred in 5 (26.3%) cases out of 19 died cases with significant difference in compare to improved group (P value 0.015) . GIT symptoms were rare among studied groups so there is no significant difference between both groups.

Table (3): Laboratory investigations of studied groups

Laboratory investigations	Improved (n = 31)		Died (n = 19)		p value
	Median	Range	Median	Range	
Hb (g/dL)	12	8.9 - 16.1	8.8	7 - 12.2	<0.001*
TLC (cell/microL)	9000	4500 – 3300	12000	4000 – 2800	0.004*
PLT (cell/microL)	220.000	8500 – 497000	117,000	4500 – 238000	<0.001*
Lymphocytes %	25	7 – 50	12	8 – 55	0.031*
Neutrophils %	50	35 – 80	50	30 – 70	0.184
CRP (mg/dl)	12	3 – 90	48	4 – 138	0.003*
Urea (mg/dl)	27	18 – 157	40	24 – 120	0.002*
Creatinine(mg/dl)	.5	0.3 - 1.2	1	0.3 - 5.5	0.001*
D dimer	1	0.3 – 4	3	0.6 – 5	<0.001*
Ferritin (microgram/L)	145	80 – 836	220	100 – 777	<0.001*
Na (mEq/L)	142	133 – 160	150	130 – 158	0.027*
Ionized Ca (mmol/L)	1.1	0.8 - 1.28	.9	0.6 - 1.2	<0.001*
LDH (IU/L)	180	100 – 1366	300	140 – 500	0.001*

Analyzed by Mann-Whitney U test
*: Significant difference at P value < 0.05

Elevated serum D dimer found to be associated with higher mortality, median value of serum D dimer among died group was 3 with significant difference in compare to improved group (P value < 0.001). Also elevated serum ferritin level and serum LDH were associated with higher level of mortality with significant difference when compared to improved group p value is < 0.001 for both. in general, median value of CBC parameters of all studied were approximately within normal range but when comparing the improved group to died group CBC parameters will be significantly different and median values tend to be directed toward anemia, thrombocytopenia and leukocytosis in died group as shown in **table 3**.

Table (4): Degree of respiratory distress in studied groups

Degree of distress	Improved (n = 31)	Died (n = 19)	p value
I	7 (22.6%)	0 (0%)	<0.0001*
II	16 (51.6%)	0 (0%)	
III	8 (25.8%)	12 (63.2%)	
IV	0 (0%)	7 (36.8%)	

Analyzed by Chi square test or Fisher's exact test
*: Significant difference at P value < 0.05

There is a significant difference between improved and died group in relation to the different degrees of respiratory distress with P value <0.0001. All died cases were grade III (63.2%) and grade IV (36.8%) that indicates higher mortality with increased degree of respiratory distress as shown in **table 4**.

Table (5): CORADS score in studied groups

CORADS / prognosis	I 5(10%)	II 11(22%)	III 17(34%)	IV 12(24%)	V 5(10%)	p value
Improved	5 (100%)	11 (100%)	13 (76.5%)	2 (16.7%)	0 (0%)	<0.0001
Died	0 (0%)	0 (0%)	4 (23.5%)	10 (83.3%)	5 (100%)	

Analyzed by Chi square test or Fisher's exact test
*: Significant difference at P value < 0.05

According to COVID 19 Reporting and Data system , the most frequent grade in CT findings in studied groups were grade III in 17 cases (34%) followed by grade IV (24%). Grade V was only found in CT of 5 cases (10%) while 16 cases were CO-RADS I & II (normal or very low suspicious of COVID 19) despite being symptomatic and positive COVID-19 PCR. we noticed that all cases with CORADs V and 83.3% of those with CORADs IV were from died group that reflect a positive correlation between degree of CORADs and mortality meaning that the higher the CORADS the higher the mortality as shown in **table 5**.

Table (6): Correlation between CORADs score and different clinical presentation

CORADS / Symptoms	I 5 (10%)	II 11 (22%)	III 17 (34%)	IV 12 (24%)	V 5 (10%)	p value
Fever grades:						
➢ Normal (36.7 - 37.2)	0(0%)	2(18.2%)	0(0%)	0(0%)	0(0%)	
➢ Low grade (37.3 - 37.8)	1(20%)	3(27.3%)	4(23.5%)	0(0%)	0(0%)	**0.003***
➢ Moderate grade (37.9 - 39.4)	2(40%)	6(54.5%)	13(76.5%)	10(83.3%)	3(60%)	
➢ High grade (39.5 - 40.5)	2(40%)	0(0%)	0(0%)	2(16.7%)	2(40%)	
Cough	3(60%)	6(54.5%)	17 (100%)	12(100%)	5(100%)	**<0.0001***
Dyspnea	3(60%)	7(63.6%)	17 (100%)	12(100%)	5(100%)	**<0.0001***
Vomiting	0(0%)	5(45.5%)	3 (17.6%)	4(33.3%)	0(0%)	**0.229**
Diarrhea	0(0%)	5(45.5%)	1 (5.9%)	0(0%)	0(0%)	**0.009***
Convulsions	0(0%)	0(0%)	2 (11.8%)	3(25%)	1(20%)	**0.493**

Analyzed by Chi square test or Fisher's exact test
*: Significant difference at P value < 0.05

For all cases, there was a significant difference between different grades of CO-RADS in relation to fever, cough, dyspnea and diarrhea with P value (0.003), (0.0001), (0.0001) and (0.009) subsequently as shown in **table 6**.

Table (7): Comorbidities of studied groups

Comorbidities	Improved (n = 31)	Died (n = 19)	p value
No	24 (77.4%)	11 (57.9%)	
chronic renal failure	0 (0%)	2 (10.5%)	
CNS infection	1 (3.2%)	1 (5.3%)	
pleural effusion	1 (3.2%)	1 (5.3%)	
Congenital heart diseases	5 (16.1%)	0 (0%)	0.089
congenital biliary atresia	0 (0%)	1 (5.3%)	
diabetic ketoacidosis	0 (0%)	1 (5.3%)	
intracranial hemorrhage	0 (0%)	1 (5.3%)	
cerebral palsy	0 (0%)	1 (5.3%)	

Analyzed by Chi square test or Fisher's exact test
*: Significant difference at P value < 0.05

Our study showed that there was no significant difference between improved and died groups as regard associated comorbidities with P value 0.089 as shown in **table 7**.

DISCUSSION

Regarding the clinical data of the our study, the age of all patients ranged from 1month to 14 years with 18 months as the median age and IQR (5months: 5 years). Age group less than 5 years old was the more frequent (74%) than those of 5years or more (26%).

Knowing that the median age of died group in our study is 18 month and age group below 5 years was 63.2% within the died group, there is no significant difference as regard age when comparing died and improved group with P value 0.054. In contrast to our study, **Zachariah et al., 2020** reported that the median age of died group was 14 year with significant difference in comparing with the mildely diseased cases P value 0.001.

As regard sex distribution among our study, male patients were more common 31 (62%) while female patients were 19 (38%). Study by **Polónyiová et al., 2021** found that 54.8% were males and 45.2% were females, and also agree with **Lenicek Krleza et al., 2021** who found that 52.7% male and 47.8% females.

As regard clinical manifestations of studied cases fever was the most common sign in 96% of cases specifically the moderate grade fever (37.9: 39.4C) which found in 68% of cases while high grade fever (39.5 and more) was found in only 6 cases (12%). Dyspnea was found in 2nd degree after fever in 88% of cases. Cough was the most common symptoms in 44 cases (86%). While GIT symptoms like vomiting and diarrhea were less frequent and were found in 24% and 6% of cases subsequently. finally CNS symptoms like convulsion was found in 6 cases (12%). While in a study including 50 patients by **Zachariah et al., 2020** he found that fever was in 80% of cases, dyspnea in 34% of cases while GIT symptoms in only 14% of cases but **Hsieh et al., 2022** reported that fever was in 54% of 78 studied cases and dyspnea was in 28% of cases while GIT symptoms was only in 15% of cases.

In our study, mortality was associated with presence of some symptoms and signs including fever (p value <0.001), cough (p value 0.026) and dyspnea with (p value 0.041). Grunting (respiratory distress grade III) was in 63.2% of died case and while cyanosis (respiratory distress grade IV) was in 36.8% that indicates positive correlation between degree of respiratory distress and mortality. This data is coordinated with that which

reported by **Dewi, Kaswandani et al., 2021** which found that fever, cough and dyspnea were the most common presentation among 20 died cases out of 50 cases with positive COVID 19 PCR.

Regarding CBC data of our study, the median value of hemoglobin level, WBCs count and platelets count were significantly different when comparing both improved and died group with P value 0.001, 0.03 and 0.001 subsequently. CBC parameters median values within died group were shifted to anemia, leukocytosis and thrombocytopenia and this is quietly coordinated with results of **Jiehao et al., 2020** who found that COVID-19 is associated with leukocytosis and thrombocytopenia.

Regarding inflammatory biomarkers, our study revealed that there were increase in most biomarkers within the died group that indicates its association with high mortality. For example, CRP was elevated in 72% of cases with significant difference between died and improved groups with p value 0.003. While LDH was elevated in 62% with significant difference between died and improved group p value 0.001. These results are in agreement with **Alhazzani et al., 2020** who found that 60.7% of patients with elevated CRP and 41% of patients with elevated LDH.

There was a positive correlation between CT chest findings based on CO-RADs score and clinical presentation like fever, cough, dyspnea and diarrhea with P value 0.003, 0.0001, 0.0001 and 0.009 subsequently and insignificant to rest of symptoms and signs. Also there was a significant difference between improved and died group in relation to different stage of CO-RADs with P value 0.003. All 5 cases (100%) with CO-RADS V died also 10 cases (88%) out of 12 with CO-RADS IV which indicates that the higher the CO-RADS the higher the mortality. This result is in agreement **Hu, Zhan et al., 2020** who concluded that Chest CT findings were worsening in patients who died of COVID19, with moderate positive correlations between CT findings and laboratory findings related to poor prognosis and death. Also, **Naik et al., 2022** concluded a positive correlation of CO-RADS classification on HRCT thorax and inflammatory markers with COVID-19 related mortality. This indicates the strong relation between severity of symptoms and corresponding pulmonary affection in CT according to CO-RADS.

Out of studied 50 cases, we found that 15 cases (30%) were associated with comorbidities. the most common was congenital heart diseases 5 cases representing 10% of all studied cases and 42.1% of died cases however, there is no significant difference in mortality in relation to associated comorbidities when compared to improved cases with P value 0.089. In contrast, **Sharif et al., 2021** decided that increasing comorbidities with other factors were associated with more severe symptoms, high fatality rates and prolonged hospital stay in patients with COVID-19.

CONCLUSION

- Children at any age are susceptible to COVID-19 virus infection.
- Both sexes are susceptible to COVID-19 virus infection with predominance of male sex.
- Fever is the most common clinical presentation in the affected cases with respiratory symptoms predominance than gastrointestinal symptoms.
- The higher the degree of pulmonary affection in CT chest the higher the severity of clinical presentation and mortality (positive correlation).
- Elevated inflammatory markers is associated with high mortality rate (positive correlation).
- Presence of chronic co-morbidities aggravates the clinical presentation but found to be not associated with increasing mortality (insignificant difference in compare to improved cases).

RECOMMENDATIONS

- Educating the community about the dangers of the COVID-19 infection and urging them to isolate themselves away from their kids when they feel any symptoms of COVID infection.
- Informing children especially those at school age and their teachers about precautionary measures, wear personal protective equipment (PPE) and social distancing to decrease the risk of virus transmission between them.
- Urging adults to get vaccinated to reduce cases of infection and thus reduce the risk of infection in children.
- Further studies to evaluate of possible vaccination of children less than 5 years to decrease risk of infection.
- Further studies to assess risk factors for development of complications and mortalities

in children infected with COVID-19.

- Further studies to research possible treatments to avoid occurrence of complications and mortality.

LIMITATIONS OF STUDY

- PCR is not a routine investigation in some of hospitals that lead to missing a lot of cases could be added to the study.
- Parents denial about history of contact with infected persons with COVID-19 making difficulties in suspicious of mildly diseased children.

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