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ORIGINAL PAPER

Severe and critical COVID-19 in children: a simple single-center, cross-sectional study

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ABSTRACT

The aim of the study: Description of the severe and critical clinical course of COVID-19 in children.
Material and methods: There is descriptive, single-centered, cross sectional study with recruited of 16 children of severe and critical COVID-19 aged from 1 month till 17 years with hypoxic respiratory failure (8) and multisystem inflammatory syndrome in children (8). The study included of detailed information in period from the manifestation of the disease and hospitalization, the main clinical manifestations at admission to PICU, length of stay, comorbidity and outcomes.
Results: Severe course and complications of SARS-CoV-2 infection among 16 children for the one year cross period were reported. Comorbid conditions were noted in 62.5% children. The two deceased children had only anemia, which was not diagnosed before admission. The underlying conditions were: mental retardation, epilepsy, severe obesity, congenital brain malformations, cerebral palsy, congenital heart diseases, anemic, bronchopulmonary dysplasia, adrenoleukodystrophy, Down syndrome and subinfections such as acute herpetic encephalitis, salmonellosis, chronic hepatitis B. Four children have died due to acute respiratory failure (3) and pulmonary thrombosis (1). Indicators of activity of inflammation and coagulopathy did not differ in them from children who survived.
Conclusions: Different comorbid states are associated with severe COVID-19 in children, but the data on specific conditions is limited. Knowledge of comorbid conditions in children that increase the risk of severe or critical course of COVID-19 allows to define the optimum measures of epidemiological control in such children and to modulate the therapy from the onset of the infectious disease. Children without underlying medical conditions may develop severe and critical COVID-19 and require additional supervision or medical attention. More clinical research should be done on pediatric population with critical and severe SARS-CoV-2 infection in other countries.

KEY WORDS:
children, comorbidity, critical and severe COVID-19.

INTRODUCTION

Medical community continues to accumulate knowledge about new coronavirus disease (COVID-19) and understanding of it is evolving [1-3]. The infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as a rule, is milder in children compared with adults [4]. Earlier it was stated that children did not belong to a risk group for mortality and severe disease due to SARS-CoV-2. Despite the fact that children of all ages

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appear susceptible to SARS-CoV-2 infection with no significant gender difference, both neonates and infants are vulnerable to infection [5]. Nevertheless, more and more publications appear, in particular systematic reviews indicating that coronavirus infection leads to loss of children. Severe and critical course of COVID-19 determined by the existing of the acute respiratory distress syndrome, multisystem inflammatory syndrome in children (MIS-C), toxic shock syndrome, thrombosis and comorbidities [6-8]. According to Zhou *et al*., severe course of COVID in children is defined as: early respiratory symptoms (fever and cough) and may be accompanied by gastrointestinal symptoms (diarrhea), that progresses around 1 week, and dyspnea occurs, with central cyanosis, oxygen saturation (SpO_2) is < 92%, with other hypoxia manifestations. The critical course of COVID-19 is defined as: children can quickly progress to acute respiratory distress syndrome or respiratory failure and may also have shock, encephalopathy, heart failure, coagulopathy, and acute kidney injury [9].

Despite the fact that the main clinical symptoms are still being identified and most comorbid conditions are indicated, the data on them is still heterogeneous [10, 11]. Yet most researchers claim that there is limited data regarding the demographics and clinical features of SARS-CoV-2 infection in children and we need a better understanding of the global impact of COVID-19 on the pediatric population [12].

AIM OF THE STUDY

Description of severe and critically ill children with COVID-19 hospitalized in Pediatrics Intensive Care Unit (PICU) of Regional Children's Infectious Diseases Hospital since August 2020 for a period of one year.

MATERIAL AND METHODS

STUDY DESIGN AND SETTING

A descriptive, single-center, cross-sectional study was conducted. We analyzed the hospitalized children with severe and critical course of COVID-19 staying in PICU for a period of one year from August 2020 till August 2021. The diagnosis of clinical syndromes associated with SARS-CoV-2 was based on the WHO recommendations [13, 14]. MIS-C was diagnosed on the criteria**:** age 0 to 19 years; fever for ≥ 3 days; clinical signs of multisystem involvement at least 2 (rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs, hypotension or shock, cardiac dysfunction, evidence of coagulopathy, acute gastrointestinal symptoms), elevated markers of inflammation, evidence of SARS-CoV-2 infection, no other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes [13]. Syndrome of severe hypoxic respiratory failure was determined in ventilated children with the oxygenation index using SpO_2 according to the WHO recommendations and depending on the type of invasive ventilation (oxygenation index ≥ 12.3) and non-invasive ventilation (SpO_2:FiO_2 ≤ 264) [14]**.**

ETHICAL APPROVAL

This study was approved by the Ethics Committee (The protocol № 5, 2020), which was conducted with the involvement of underage patients and did not contain measures that could harm their health. The parents were informed about the methods and scope of the study and gave their consent to participation of their children in this study.

SAMPLING

149 children with COVID-19 were hospitalized in the PICU during the cross period. The focus of our study (sampling) based on the analyses of 8 children with MIS-C and 8 children with acute respiratory failure who needed in mechanical ventilation. The age of the children ranged from 1 month to 17 years.

INCLUSION CRITERIA

0-18 years old children with severe and critical COVID-19 with MIS-C and acute respiratory failure need in mechanical ventilation.

EXCLUSION CRITERIA

Multisystem inflammatory syndrome and hypoxemia of the other different etiology and those who did not agree to participate in the study.

DATA COLLECTION

The study included a detailed scrutiny of medical history and analysis of medical documents to determine the period from manifestation of the disease till hospitalization, the main clinical signs at admission to PICU, clinical course, and length of stay, comorbidity and outcomes.

STATISTICAL ANALYSIS

Statistical analysis was performed with MedCalc program, version 14.8 – © 1993-2014 MedCalc Software (Acacialaan 22 B – 8400 Ostend, Belgium). Descriptive analysis was performed, relative risk (RR) and 95% confidence interval (CI) was determined. For comparison of two independent groups the Mann-Whitney (MW) test was used, for comparison of proportions the Fisher's test was carried out. The difference in parameters was considered statistically significant at $p < 0.05$ and if CI excluded "1".

RESULTS

393 severe and critically ill children due to different diseases and conditions were admitted to the PICU of our center for the period from August 2020 to August 2021. Among them there were 145 (36.8%, 95% CI: 0.32-0.42) children with COVID-19, and 248 (63.1%, 95% CI: 0.58-0.68) with other diseases and conditions. A total of 16 from 145 admissions due to COVID-19 were categorized as MIS-C (5.5%) and severe acute respiratory failure (5.5%) in our center (11.0%), and comparison with MIS and hypoxic respiratory failure due to other different origin was 2.8% (RR = 3.9, 95% CI: 1.6-9.2). 16 children with MIS-C and acute respiratory failure admitted to PICU range by gender – 11 (69%) males and 5 (31%) females, $p = 0.0398$, and the median age was 9 (min. 1 month; max. 17 years old) years (Table 1).

8 (50%) of patients got infected by household contacts, others got infected through other unknown ways. The distribution of children by age in the group was equal. Despite the fact that the median values of the children`s ages with acute respiratory failure and MIS-C were different, there were no significant differences in the of children`s age variation between MIS-C and acute respiratory failure, 12,5 [3,5; 15] years and 6 [1 mo; 17] years respectively, $p = 0.1303$.

Development of severe disease symptoms requiring hospitalization and intensive therapy in children in this study ranged from 1 to 9 days of the disease manifestations, and this period lasted for less than 7 days in 75% of children ($p = 0.0083$). There were no significant differences in period from manifestation till hospitalization in children with acute respiratory failure and MIS-C, $p = 0.4418$.

The diagnosis was made on the 2nd day in PICU and then confirmed routinely by polymerase chain reaction (PCR) from nasal swabs in 6/16 children. In cases where the PCR was negative, the determination of elevation of immunoglobulin (IgM and IgG) was in 3/16 and 10/16 respectively.

Clinical presentation of severe and critical COVID-19 at admission to PICU was different (Table 2).

81% of children had fever with median of 39.5°C and 6 (46%) of them had body temperature over than 40°C. There was significant decrease of SpO2 ≤ 93% in 8 children with acute respiratory failure, $p = 0.0281$. Different behavioral and neurologic symptoms were observed in 13 children (81.2%, 95% CI: 0.62-1.0) and 3 of them were mentally destroyed, emotional problems were revealed in 2 children, 1 child had high level of irritability, 1 child demonstrated moderate coma and 2 children had convulsions. Significantly comorbidities were prevalent in pediatric cohort with acute respiratory failure – 10 (62.5%, 95% CI 0.39-0.87) and there were children with one or more comorbidities: mental retardation 5/10, epilepsy (Dravet syndrome, Ohtahara syndrome) 3/10, severe obesity 3/10, congenital brain malformations 1/10, cerebral palsy 2/10, congenital heart diseases (CHD) 2/10, anemia 2/10, bronchopulmonary dysplasia (BPD) 1/10, adrenoleukodystrophy 1/10, Down syndrome 1/10, hypersensitive allergic reaction 1/10, and co-infections such as acute herpetic encephalitis 1/10, salmonellosis 1/10, chronic hepatitis B 2/10.

On admission, all children required respiratory support. Oxygen via non-rebreathe mask was required for 8 (50%, 95% CI: 0.26-0.75) children with MIS-C, non-invasive ventilation (continuous positive airway pressure) for 2 (12.5%, 95% CI: 0.03-0.29) children and mechanical ventilation via endotracheal tube for 6 (37.5%, 95% CI: 0.14-0.62) children with acute respiratory failure.

All children were treated with antibiotics, glucocorticoids, heparin and physiological solution. Antiviral therapy (Remdesivir) was administrated in 1 child. Intravenous immunoglobulin G was applied in 8/16 children with MIS-C, and tocilizumab in 1 child.

TABLE 1. Demographic Data of Children Treated in PICU for COVID-19

Data	*n* (%)	95% CI
Age, years		
< 1 years	2 (13)	-
1-6 years	4 (25)	0.04; 0.46
7-10 years	1 (6)	-
11-17 years	9 (56)	0.32; 0.80
Male	11 (69)	0.46; 0.92
Rural area citizens	4 (25)	0.04; 0.46
Day from disease onset, Me [min; max]	5 [1; 9]	3.7; 6.2
< 7 days	12 (75)	0.54; 0.96
> 7 days	4 (25)	0.04; 0.46

TABLE 2. Clinical presentation of COVID-19 in children at admission to PICU

Presentations	*n* (%)	95% CI
Behavioral and neurologic	13 (81)	0.62; 1.0
Fever, > 38°C	13 (81)	0.62; 1.0
Decreased urine output	12 (75)	0.54; 0.96
Respiratory	10 (62)	0.38; 0.86
Gastrointestinal	10 (62)	0.38; 0.86
Cardiovascular (circulatory)	2 (13)	-
Skin	2 (13)	-
Edema	7 (44)	0.20; 0.68
Ophthalmologic	9 (56)	0.32; 0.80
Pain (throat, headache, stomachache)	8 (50)	0.26; 0.75
SpO_2, %	93 [48; 99]	84; 98
MIS-C	97 [79; 99]	94; 99
hypoxic respiratory failure	82 [48; 94]	71; 94

Clinical course of MIS-C associated with COVID-19 in children in our center was characterized by severe pneumonia in 7/16 (43.7%, 95% CI: 0.20-0.68) and Kawasaki-like syndrome in 1/16 (6.3% 95% CI: –0.06-0.18). Clinical trajectory of severe and critical COVID-19 was characterized by complications and poor outcomes in 4 children with acute respiratory failure (Table 3).

Critical condition of children on admission to PICU was noted significantly more often than severe one ($p = 0.0398$). All children had respiratory, circulatory, coagulative and cerebral disorders. The overall case fatality rate of COVID-19 in this cross-sectional study was 2.8% up to the time of the report (RR = 0.97, 95% CI: 0.3-3.3). Detailed data of the baseline characteristics of the dead children are listed in Table 4.

The dead children were aged 1 year and below, 6 and 11 years, without gender difference. During hospitalization, 3/4 had severe cerebral impairment and all children needed respiratory support via invasive mechanical ventilation, 2/4 children had bradycardia. Only in one child who had meningeal irritation, leukocytosis with neutrophilia, and a shift to the young forms we suspected bacterial co-infections. This child had the highest procalcitonin level compare of other children. There were no significant differences in the laboratory parameters of acute inflammation and coagulopathy upon admission to the PICU in disease survivors and those who died of it: CRP 96 [min. – 2; max. – 384] mg/l, and 96 [min. – 2; max. – 192] (MW test, $p = 0.8512$) mg/l; procalcitonin 3.28 [min. 0.025; max. – 49.39] ng/ml and 0.59

TABLE 3. Clinical course of COVID-19 in children treated in PICU

Characteristic	Abs. (%)	95% CI
Severe illness	5 (31)	0.08; 0.54
Critical illness	11 (69)	0.46; 0.92
Organ system failure, among them: Respiratory Circulatory Renal Cerebral Adrenal Coagulopathy Hepatic and GIT	11 (69) 11 (100) 10 (91) 6 (55) 8 (73) 1 (9) 10 (91) 2 (18)	0.46; 0.92 0.93; 1.05 0.74; 1.08 0.26; 0.84 0.47; 0.99 -
Shock/hypotension/vasoactive support	11 (69)	0.46; 0.92
Pneumothorax and pneumonediastinum	1 (6)	-
Heart thrombosis (atrium and pulmonary artery)	2 (13)	-
Length of stay in PICU total, Me [min., max.]	8 [3, 19]	4.93; 11.1
Length of stay in PICU died, Me [min., max.]	13 [3, 19]	9.32; 16.7
Length of stay in PICU discharged, Me [min., max.]	7 [4, 14]	4.54; 9.46
Death	4 (40)	0.16; 0.64

TABLE 4. Demographic, clinic, laboratory date and medications of children with poor outcomes from COVID-19

N	Age, years	Sex	SpO_2*	PICU (days)	Comor-bidity	Medications	CRP*	D-dimer*	Procalcitonin*
P1	6	f	79	9	Anemic	Antibiotics, dexamethasone, enoxaparine, aspirine, dobutamine, epinephrin	192	1000	16.3
P2	11	m	98	19	Anemic	Antibiotics, dexamethasone, enoxaparine, aspirine, dobutamine, epinephrine, anxiolytic	96	3000	0.024
P3	1	m	48	17	BPD. CHD. Mental retardation	Antibiotics, dexamethasone, methylpredisolone enoxaparine, diuretics	96	1043	0.9
P4	<1	f	60	3	Down syndrome	Antibiotics, dexamethasone, enoxaparine, aspirine, dopamine, epinephrine	0	1647	0.029

** on admission*

[min. – 0.024; max. – 16.30] ng/ml (MW test, $p = 0.5394$); D-dimer 2324 [min. 1043; max. – 3000] ng/ml and 2064 [min. – 652; max. – 6126] ng/ml (MW test, $p = 0.8391$), respectively. The causes of death in 3 children were severe respiratory failure due to diffuse bilateral lung opacities and pulmonary thrombosis in 1 child with Down syndrome. In addition to the specified treatment, which all children with COVID-19 received at the PICU, the deceased children were also prescribed drugs supporting hemodynamics (inotropes, vasopressors), antiplatelet agents, and diuretics (Table 4).

DISCUSSION

In this descriptive single-center cross-sectional study, we report the characteristics and clinical course of severe and critically ill children with COVID-19 treated in PICU within a period of one year. For detail analysis we choose of the cohort of 16 children aged from 1 month to 17 years who had acute respiratory failure and needed in mechanical ventilation ($n = 8$) and with MIS-C ($n = 8$). We emphasized the period from the first manifestations of the disease to hospitalization and from the main clinical manifestations on admission to PICU to outcomes including length of stay and comorbidity. We intended to provide pediatric community with the information concerning presentation and outcomes of COVID-19 in children with severe and critical course of the disease. The majority of children treated in PICU with severe and critical COVID-19 during our study were males. And among the dead children there was an equal distribution of males and females.

Our research confirms the published result that half of children were presented as family cluster cases, which at the present time no longer raises any questions regarding the epidemiology of this virus [15].

Different clinics and centers show different information on the quota of children with MIS-C and severe acute respiratory failure, severe and critical course of COVID-19. Apparently, this is due to the peculiarity of population, the time of information`s collection, various epidemiological state, capacity of health care systems and etc.

Yonker *et al*. reported that among 192 children admitted to urgent care clinics at Massachusetts General Hospital 26% were with acute SARS-CoV-2 infection; and 9% with MIS-C [16]. Other authors indicated that among 117 children 7.7% were severe illness, and 12.8% critical illness, and 12.0% MIC-S [17]. In systematic review of complete data of 1475 children were 2% children with severe, and 0.7% children with critical disease, and 0.08% of mortality [18]. We identified critical and severe COVID-19 in 5.5% of children requiring mechanical ventilation due to acute respiratory failure and 5.5% of children with MIS-C. The overall case fatality rate of COVID-19 in this cross-sectional study was 2.8% up to the time of the report (RR = 0.97, 95% CI: 0.3-3.3).

The next special issue for discussion is symptoms of COVID-19 at admission to PICU. In a multicenter study of a case series of 1,116 patients under 21 years of age hospitalized with MIS-C or acute severe COVID-19, it was noted that the clinical signs of acute severe COVID-19 and MIS-C may be similar, but still have different patterns of clinical presentation of organ damage. However, both conditions cause severe illness [19]. So in our center the diagnosis was based on the WHO criteria for acute respiratory failure and MIS-C, but it still took time.

It has been established by the series of descriptive cases that high inflammatory markers at admission or during hospitalization (CRP, procalcitonin, interleukin 6, ferritin, D-dimer) associated with severe disease in children [20, 21]. This was no exception in our cases observations. Moreover, we have shown that there were no significant differences in the CRP, D-dimer and procalcitonin upon admission to the PICU in disease survivors and those who died of it.

Continuing the discussion we found different published data both for comorbid conditions in children as predictors of severe and critical COVID-19, and for the prognostic characteristics of MIS-C. Levi Hoste *et al.* in the description of epidemiological, clinical and prognostic characteristics of 953 MIS-C cases with average age of 8 years, 25.3% of children were obese, while other comorbidities were rare [22].

At the same time, according to Webb and Osburn, 55% of incidental and 47% of potentially symptomatic patients had at least one identified comorbid state and there was a significant relationship between obesity, asthma and severe disease [23].

Another study examining underlying medical conditions associated with severe COVID-19 in a large population of children found that asthma (10.2%), neurodevelopmental disorders (3.9%), anxiety and fear-related disorders (3.2%), depressive disorders (2.8%), obesity (2.5%) increased the risk. The strongest risk factors for hospitalization were type 1 diabetes mellitus, cardiac and circulatory congenital anomalies and prematurity [24].

In a systematic review, with the inclusion of 2914 pediatric patients with COVID-19 and the age range from 1 day to 17 years, 79% were reported to have no comorbidities, and among 21% of those with comorbidities, the most common were asthma, immunosuppression, and cardiovascular disease [25].

The 2021 Centers for Disease Control and Prevention reports on underlying medical conditions associated with high risk for severe COVID-19 clearly identify those conditions, but they characterize both adults and children. The risk factors associated with a severe course of the disease are divided into established and possible. Moreover, they are all based on data of at least 1 meta-analysis or

systematic review or on observational studies. The risk factors are: cancer, cerebrovascular disease, chronic kidney disease, chronic obstructive pulmonary disease and other lung diseases (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension), diabetes mellitus type 1 and type 2, Down syndrome, heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies), HIV, neurologic conditions, including dementia, obesity and overweight, pregnancy, current and former smoking, sickle cell disease, solid organ or blood stem cell transplantation, substance use disorders, use of corticosteroids or other immunosuppressive medications, cystic fibrosis, thalassemia, asthma, hypertension, immune deficiencies, liver disease [25]. A similar one-year cross-sectional study of COVID-19 in Italian Pediatric Emergency Departments demonstrated that 22% children from 170 had comorbidities. We have demonstrated a higher rate of comorbidities 62.5%. But the samples were different because in Italian cohort of 170 children severe and critical COVID-19 was diagnosed in 2 patients and there were no any poor outcomes [26].

Considering our 4 patients who died from COVID-19 it is obvious that BPD in combination with mental retardation and Down syndrome were the underling factors that led to poor outcome in 2 of them. The rest of the children had moderate anemia of unknown origin during hospitalization. We suggested that anemia could have been a comorbid condition and suspected relation with severe COVID-19 and poor outcomes.

Published study have associated anemia with significant mortality in hospitalized patients due to COVD-19 in adults [27]. There is limited number of studies with controversial findings regarding the association between anemia at admission and COVID-19 outcomes, especially in children. If we consider anemia as a likely symptom of a severe COVID-19, then there is an explanation for this process. Inflammation profoundly affects erythropoiesis through different mechanisms, partly sustained by abnormal iron metabolism mediated by interleukin IL-6 overproduction and partly due to other pro-inflammatory cytokines, such as interferon-γ, IL-1, IL-33 and tumor necrosis factor α [28]. The question of the mechanisms of the development of anemia, or its influence as a comorbid state on the course of COVID-19 in children, requires further study. About Down syndrome, changes in the immune system response associated with trisomy 21 are cause severe course and poor outcomes of many viral infections, including COVID-19, which took place in our observation [29].

Finally, we declare that acute encephalitis, salmonellosis and chronic hepatitis B are possible risk factors for the severe course of COVID-19, but without lethal outcomes. These three observational cases most likely relate to the third phenotype of COVID manifestation envisaged by World Federation of the Society of Anesthesiologists in which the phenotypes of COVID-19 are distinguished: cardio-vascular shock, characterized by severe vasoplegia; hypoxic respiratory failure; accidental detection of SARs-CoV-2 upon admission (an alternative pathology requiring admission to the pediatric intensive care unit) [30].

There were some inherent limitations associated with this study; firstly, sample size. Our model was based on prospective single-center cross-sectional study and was limited by the time and number of patients. Secondly, there were very few prior researches and gaps in the studies relevant to anemia and COVID-19 in children. Thirdly, our study was limited by the period in PICU without follow-up children who had a critical and severe course of COVID-19 and survived. Fourthly, we were unable to assess the impact of diseases such as encephalitis, chronic hepatitis B and salmonellosis on the course of COVID in children, which may undermine the effectiveness of the study. Further large-scale studies of our and other populations of children with severe and critical COVID-19 are required in order to determine the strength of the effect on the course of comorbid conditions and other risk factors. This is especially important for health care providers and stakeholders to develop plans for the prevention of severe covid-19 in this category of children.

CONCLUSIONS

Different comorbid states are associated with severe COVID-19 in children, but the data on specific conditions is limited. Knowledge of comorbid conditions in children that increase the risk of severe or critical course of COVID-19 allows to define the optimum measures of epidemiological control in such children and to modulate the therapy from the onset of the infectious disease. Children without underlying medical conditions may develop severe and critical COVID-19 and require additional supervision or medical attention. More clinical research should be done on pediatric population with critical and severe SARS-CoV-2 infection in other countries.

DISCLOSURE

The authors declare no conflict of interest.

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