COVID-19 in Pediatric Intensive Care Units in Poland, PAPITCO-19 study (Polish Analysis in PICUs Trends of COVID-19)

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Article

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Abstract: Background: Children suffering from COVID-19 constitute about 10% of the entire population infected with the virus. In most of them, we observe asymptomatic or mild course; however, about 1% of affected children require a stay in the pediatric intensive care unit (PICU) due to the severe life-threatening course. The risk of respiratory failure, as in adults, is associated with the coexistence of concomitant diseases. The aim of our study was to analyze patients admitted to PICUs due to severe course of SARS-CoV-19 infection. Methods: A retrospective multi-center study, the analysis covered all children with a confirmed diagnosis of SARS-CoV-2 virus infection, who were admitted to PICUs, in the period from November 2020 to August 2021. We studied epidemiological and laboratory parameters, and the endpoint – survival or death. Results: The study analyzed 45 patients (0.075% of all children hospitalized in Poland due to COVID-19 at that time). Mortality calculated in the entire study group was 40% (n=18). Statistically significant differences between the compared groups (survived and died) concerned the parameters of the respiratory system, . Lung Injury Score and Pediatric Sequential Organ Failure Assessment A significant correlation between disease severity and the patient's prognosis was shown by the liver function parameter AST (p=0.028). Analyzing patients requiring mechanical ventilation and assuming survival as the primary outcome, a significantly higher oxygen index on the first day of hospitalization, lower pSOFA scores and lower AST levels (p: 0.007; 0.043; 0.020; 0.005; 0.039, respectively) were found. Conclusions: As in adults, children with comorbidities are most frequently at risk of severe SARS-CoV-2 infection. Increasing symptoms of respiratory failure, the need for mechanical ventilation and persistently high values of aspartate aminotransferase are indicators of poor prognosis.

Keywords: SARS-CoV-2; pandemic; children infection; respiratory failure

1. Introduction

In 2020, which was the first year of the COVID-19 pandemic, the population of pediatric patients accounted for 9.6 -13.6% of the total number of patients diagnosed with SARS-CoV-2 virus infection (1). Of this group, less than 1% re-quired intensive care (2). As in adults, the risk of death was associated with comorbidities, the most important of which were neurological diseases related to immobilization, chronic respiratory failure, and heart defects (3). At the end of April 2020, a new disease entity called the Pediatric Multisystem Inflammatory Syndrome temporally associated with

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SARS-CoV-2 (PIMS) appeared (4). Based on American data, it can be estimated that PIMS develops in about 1/1000 children infected with SARS-CoV-2 (5). PIMS is an acute and potentially serious generalized inflammatory syndrome that can lead to the development of complications. Unlike the severe course of COVID-19, PIMS usually affects children with an unremarkable medical history. Subsequent waves of the pandemic began to increasingly involve the youngest patients (2). By November 2021, as many as 17,000 children were hospitalized in Poland due to SARS-CoV-2 infection. Until then, we had recorded 91,000 deaths in adult patients and 29 deaths in children under the age of 14 (6). As in adults, the SARS-CoV-2 virus mainly affects the respiratory system; the infection manifests itself as fever and/or cough, and may cause acute respiratory failure. In some patients, we observed a fulminant course of infection, leading in some cases to treatment failure. Most studies have analyzed the entire population of children infected with the SARS-CoV-2 virus. Our study only included children diagnosed with COVID-19 who required treatment in Pediatric Intensive Care Units (PICUs) due to a life-threatening condition. The data come from all the leading pediatric centers in the country and reflect the actual clinical and epidemiological situation, which in the authors' opinion, proves its high practical usefulness.

2. Materials and Methods

Data Source

A retrospective multi-center study was conducted in 10 leading clinical Pediatric Intensive Care Units (centers with the number of patients are summarized in Table 1). In each of the departments, one person was appointed to be responsible for entering demographic, epidemiological, and clinical data into a common EXCEL database. The analysis covered all children with a confirmed diagnosis of SARS-CoV-2 virus infection, who were admitted to PICUs, in accordance with Polish admission criteria, in the period from November 2020 to August 2021.

Table 1. Number of patients from hospital participating in the study.

Hospital name, city	Number of patients
Upper Silesian Child Health Centre, Katowice	9
University Child Hospital, Lublin	9
University Hospital, Poznan	7
University Hospital Nr 1,Szczecin	4
University Child Hospital, Białystok	4
University Hospital, Rzeszów	3
Copernicus Hospital, Gdansk	2
University Clinical Centre of the Medical University of Warsaw	2
University Children's Hospital of Cracow	2
University Clinical Hospital in Wroclaw	2
Children's Memorial Health Institute, Warsaw	1

Reporting and Outcome

We analyzed 45 children admitted to the PICU with SARS-CoV-2 virus infection confirmed by PCR(without variant identification).. The analysis covered demographic, epidemiological, and laboratory data, including the following information: patient referral to PICU - referral from home, Hospital Emergency Department (ED), or Pediatric/Infectious Diseases Department; time elapsed from finding a positive result of SARS-CoV-2 to admission to the ward; comorbidities; congenital defects; results of laboratory tests; Pediatric Sequential Organ Failure Assessment (pSOFA) Score, variables: PaO_2:FiO_2, platelet count, bilirubin, mean arterial pressure by age group, or vasoactive

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infusion, Glasgow Come Score calculated using the pediatric scale; creatinine by age group; The lung injury score (LIS) based on four criteria, which are hypoxemia, respiratory compliance, chest radiographic findings, and the level of positive end-expiratory pressure [5] -each criterion receives a score from zero to four according to condition severity and those numbers are summed: 0 score - Indicates no lung injury,less than 2.5 score - indicates mild to moderate lung injury, more than 2.5 score - indicates presence of severe ARDS; treatment applied; need to support the respiratory system; oxygen demand; oxygenation index – the quotient of the partial pressure of oxygen in the arterial blood (PaO_2) and the oxygen content in the breathing mixture (FiO_2 - presented as a decimal fraction)

and the number of days of hospitalization. The collected data was analyzed to identify the predictors of COVID-19 survival in this group of patients. In addition, we performed a comparative analysis of mehanically ventilated patients divided into those who survived or died.

Statistical Analysis

Statistical analysis was performed using a standard software package (STATIS-TICA 13 software (STATSOFT; Statistica, Tulsa, OK, USA) and PQStat (PQStat Software (2022), PQStat v.1.8.4.162). For continuous variables mean values, standard deviations (SD), and median were estimated. For categorical variables, absolute numbers (n) and relative numbers (%) were assessed. The Shapiro-Wilk test was used to evaluate the normality of the distribution of quantitative data. In the case of abnormal distributions, the U Mann-Whitney test was used to compare continuous variables. The stochastic independence chi-square test with Yates's correction was used to compare categorical variables. The value of $p \leq 0.05$ was considered to be statistically significant. The odds ratio (OR) with a 95% confidence interval (CI) was calculated for the occurrence of death in children treated with mechanical ventilation compared to oxygen therapy; in patients with two or more comorbidities compared to children with a maximum of one concomitant disease and in children with pro-longed hospitalization (>10 days) in the ICU compared to patients with a stay shorter than 10 days.

3. Results

The study analyzed 45 patients (25 boys and 20 girls) treated at the PICU in the period from November 2020 to August 2021. This number is 0.075% of all children hospitalized in Poland due to COVID-19 at that time (6). The median age of patients was 2 years (IQR 11). Patients < 2 years of age accounted for 44% of the respondents, and children > 9 years of age accounted for 28.8%. The compared groups (survived and died) did not differ significantly in terms of sex, age, BMI (Body Mass Index), period (days) from diagnosis of infection to admission to the Intensive Care Unit, or comorbidities. Most children were referred from the Covid Ward (n=12; 26.6%), the Pediatric Department (n=12; 26.6%), or directly from home (n=9; 20%). Comorbidities were found in as many as 40 subjects (88.8%).The most common comorbidities were: neurological disorders (n=20), . immobilisation (n=13) and respiratory failure (n=12). 9 patients had a congenital heart diseases – ventricular septal defect (n=5), patent ductus arteriosus (n=1), pulmonary regurgitation (n=1), left heart hypoplasia (n=1), common arterial trunk (n=1)

The characteristics of the study groups are presented in Table 2. Of the 45 patients, only 7 (16%) did not require mechanical ventilation, while the remaining 38 (84%)children required intubation and mechanical ventilation, and mortality in this group was 44.7% (n=17). One child was treated with ECMO but did not survive. Mortality calculated in the entire study group was 40% (n=18). The most common cause of death was the occurrence of bacterial and fungal superinfections with the development of septic shock (n=10), cerebral edema as a result of CNS thrombovascular complications (n=5), and right heart failure (n=3).

Table 2. Characteristics of the study groups (survived vs died).

	Survived (n=27)	**Died (n=18)**	**p**
Sex Females			

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Males	n=9 n=18	n=11 n=7	0.125
Age [months] mean ± SD, median	73.15 ± 75.93; 30.5	71.82 ± 75.18; 26	0.654
BMI Underweight, n, % Normal, n, % Obesity, n, %	 13 (50.00%) 12 (46.15%) 1 (3.85%)	 7 (38.89%) 6 (33.34%) 5 (27.77%)	0.748
Time from positive test to hospitalization in the ICU [days] mean ± SD, median	2.24 ± 3.73; 1	5.06 ± 10.65; 1	0.608
Comorbidities 1. Neurological disorders, n, % 2. Immobilisation, n, % 3. Immunosuppressive drugs, n, % 4. Congenital heart diseases, n, % 5. Respiratory failure, n, % 6. None, n, %	 15 (55,55%) 10 (37,03%) 2 (7,4%) 3 (11,11%) 5 (18,5%) 5 (18,5%)	 5 (27,77%) 3 (16,66%) 2 (11,11%) 6 (33,33%) 7 (38,88%) -	0.227
Where the patient came from Covid-19 ward, n, % Emergency Room, n, % Home, n, % Pediatric Ward, n, % Other ICU, n, % Operating block, n, %	 6 (22.22%) 5 (18.53%) 5 (18.52%) 9 (33.33%) 1 (3.70%) 1 (3.70%)	 6 (33.33%) 2 (11.11%) 4 (22.22) 3 (16.67%) 2 (11.11%) 1 (5.56%)	0.691*
Oxygen therapy, n, %	7 (25,92%)	18 (100%)	**0.018***
Mechanical ventilation, n, %	20 (74,07%)	18 (100%)	
Circulatory failure	15 (57,69%)	12 (66,67%)	0,54
Hospitalization time [days] mean ± SD, median	16.56±13.60, 12	10.82±7.02, 11	0.330
Mortality, n, % study group		18 (40%)	

Legend: * statistical significance in U-Mann Whitney test.

Statistically significant differences between the compared groups (survived and died) concerned the parameters evaluating the efficiency of the respiratory system, i.e. $p0_2$ on admission, $SatO_2$ (arterial blood saturation) on admission, FiO_2 used on the first day, the oxygen index on the first and third day (figure 1), and LIS on the first day (p-values: 0.018, 0.018, 0.020, 0.003, 0.006, and 0.047, respectively). In addition, statistically significant differences in pSOFA (Pediatric Sequential Organ Failure Assessment) scores on the first, third, and fifth day of intensive therapy were found in the study groups (p=0.012, 0.007, and 0.001, respectively figure 2). A significant correlation between

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disease severity and the patient's prognosis was shown by the liver function parameter, i.e. AST (p=0.028, figure 3). The other assessed parameters did not differ significantly (Table 3). The applied treatment is presented in Table 4. Most of the children received steroid therapy and anticoagulant treatment. Immunoglobulins, convalescent plasma, and remdasivir were used less frequently. Tocilizumab was used in 3 patients. The average number of days of treatment in the ICU was 16 for patients discharged, and 10 for those who died. When analyzing patients requiring mechanical ventilation and assuming survival as the primary outcome, a significantly higher oxygen index on the first day of hospitalization, lower pSOFA scores on the first, third, and fifth day and lower AST levels (p: 0.007; 0.043; 0.020; 0.005; 0.039, respectively) were found. The time from positive test to ICU admission for mechanically ventilated patients who died was not statistically different from the time for ventilated survivors; p = 0.247 (for the dead: 5.24 days on average ± 10.59, median 1.0 vs. for "survivors": 1.63 ± 2.63, median 2.13).

Table 3. Selected laboratory and respiratory parameters in study groups (survived vs died).

Parameter (mean ± SD; median)	**Survived**	**Died**	**P in U-Mann Whitney test**
pH first measurement	7.33±0.13; 7.36	7.34±0.09; 7.31	0.763
pO2 first measurement [mmHg]	103.84±53.61; 84.4	72.75±49.49; 54.0	**0.018***
pCO2 first measurement [mmHg]	52.91±24.49; 47.0	51.68±21.85; 45.5	0.990
Arterial oxygen saturation first measurement	92.39±7.91; 95.0	78.43±20.92; 84.0	**0.018***
$Fi0_2$	0.65±0.30; 0.5	0.89±0.19; 1.0	**0.020***
Oxygen index- 1st day [mmHg]	207.73±137.32; 172.5	121.82±147.37; 57.6	**0.003***
Oxygen index- 3rd day [mmHg]	232.29±179.71; 180.0	145.07±142.96; 96.0	**0.006***
Oxygen index- 5th day [mmHg]	229.86±178.88; 158.5	143.87±135.10; 84.5	0.124
Lung injury score- 1st day	2.52±1.81; 2.0	2.73±1.35; 3.0	**0.047***
Lung injury score- 3rd day	2.62±1.44; 2.3	2.47±1.03; 3.0	0.939
Lung injury score- 5th day	2.23±1.29, 2.15	2.59±0.87; 3.0	0.873
pSOFA- 1st day	6.22±2.88; 5.5	9.38±3.12; 10.0	**0.012***
pSOFA- 3rd day	6.19±3.41; 5.0	10.50±3.10; 10.5	**0.007***
pSOFA- 5th day	5.78±3.15; 5.0	11.50±4.09; 12.0	**0.001***
WBC- 1st day [× 10^9 per L]	10.86±7.17; 9.69	10.81±10.10; 6.45	0.614
PLT- 1st day [× 10^9 per L]	202.82±113.68; 197.0	207.64±171.74; 142.0	0.832
HGB- 1st day [g/dL]	10.91±3.75; 9.8	10.94±1.51; 10.5	0.178
Procalcitonin- 1st day [ng/ml]	7.21±8.96; 2.34	6.64±17.33; 0.37	0.118
C-reactive protein- 1st day [mg/l]	58.85±106.87; 12.48	57.75±77.61; 17.4	0.365
D-dimer- 1st day [ng FEU/ml]	3573.71±4953.15; 1900.0	2813.75±3343.10; 1485.5	0.561
Creatynine- 1st day [mg/dl]	0.59±0.87; 0.26	0.47±0.32; 0.37	0.456

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Urea- 1st day [mg/dl]	48.70±54.35; 32.0	27.23±18.06; 24.0	0.217
Ferritine [µg/l]	2307.18±6288.94; 193.0	1112.53±1431.25; 430.75	0.433
LDH [U/l]	687.78±575.99; 434.5	817.23±678.26; 505.0	0.232
Troponin [pg/ml]	49.90±62.55; 24.6	950.94±2293.97; 204.0	0.089
IL-6 [pg/ml]	74.22±149.74; 18.085	95.12±124.83; 51.27	0.798
Lactate- 1st day [mmol/l]	3.03±4.23; 1.1	17.76±48.76; 3.26	0.070
AST- 1st day [IU/l]	83.04±132.24; 41.0	112.89±139.33; 66.5	**0.028***
ALT- 1st day [IU/l]	75.87±176.89; 25.0	118.22±281.05; 38.5	0.351

*statistical significance.

Table 4. Applied treatment in study groups (survived vs died).

Number (%)	Survived (n=27)	Died (n=18)	P in chi-square test
COVID-19 convalescent plasma	7(26.92%)	4 (23.53%)	0.803
Tocilizumab	2 (8%)	1 (5.88%)	0.793
Remdesivir	5 (19.23%)	6 (33,33%)	0.288
Steroid therapy	27 (100%)	16 (88,88%)	0.076
Anticoagulants	24 (92.30%)	13 (72,22%)	0.073
Immunoglobulins	7 (25,92%)	8 (44,44%)	0.196
Antispasmodics	11 (40,74%)	10 (55,55%)	0.329

The results are presented in Table 5. The risk of death was 13.5 times higher in the ventilated group but did not differ significantly (OR = 13.53; 95% CI 0.72 to 253.73; p=0.081).

Table 5. Characteristics of the ventilated patients (survived vs died).

Parameter [mean ± SD; median]	Ventilated patients who survived (N=21)	Ventilated patients who died (N=17)	P value
Time from positive test to hospitalization in the ICU [days]	**1,63 ± 2,63; 2,13**	**5,24 ± 10,59; 1,0**	**0,247**
Oxygen index in the 1st day [mmHg]	206.72 ± 147.89; 153.0	122.70 ± 151.86; 56.0	**0.007***
Oxygen index in the 3rd day [mmHg]	232.29 ± 179.71; 180.0	145.07 ± 142.96; 96.0	0.086
Oxygen index in the 5th day [mmHg]	229.86 ± 178.88; 158.5	143.87 ± 135.10; 84.5	0.124
Lung injury score in the 1st day	2.52 ± 1.81; 2.0	3.0 ± 1.35; 3.0	0.106
Lung injury score in the 3rd day	2.62 ± 1.44; 2.3	2.47 ± 1.03; 3.0	0.909

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Lung injury score in the 5th day	2.213±1.34,2.1	2.59 ± 0.87; 3.0	0,48
pSOFA in the 1st day	6.62 ± 2.78; 6.0	9.17 ± 3.16; 9.0	**0.043***
pSOFA in the 3rd day	6.47 ± 3.33; 5.0	10.33 ± 3.24; 10.0	**0.020***
pSOFA in the 5th day	6.0 ± 3.10; 5.0	11.22 ± 4.24; 11.0	**0.005***
WBC in the 1st day [× 10^9 per L]	10.86 ± 7.17; 9.69	18.22 ± 10.10; 6.45	0.868
PLT in the 1st day [× 10^9 per L]	202.82 ± 113.68; 197.0	162.0 ± 171.74; 142.0	0.985
HGB in the 1st day [g/dl]	10.91 ± 3.75; 9.8	10.2 ± 1.51; 10.5	0.126
Procalcitonin in the 1st day [ng/ml]	7.21 ± 8.96; 2.34	0.6 ± 17.33; 0.37	0.118
C-reactive protein in the 1st day [mg/l]	58.85 ± 106.87; 12.48	13.73 ± 77.61; 17.4	0.235
D-dimer in the 1st day [ng FEU/ml]	3573.71 ± 4953.15; 1900.0	429.0 ± 3343.09, 1485.5	0.897
Creatynine in the 1st day [mg/dl]	0.59 ± 0.87; 0.26	0.27 ± 0.32; 0.37	0.231
Urea in the 1st day [mg/dl]	48.70 ± 54.35; 32.0	8.0 ± 18.06; 24.0	0.362
Ferritine [µg/l]	1837.64 ± 5594.13; 152.65	1112.53 ± 1431.25; 430.75	0.650
LDH [U/l]	652.88 ± 526.68; 489.0	817.23 ± 678.26; 505.0	0.257
Troponin [pg/ml]	41.65 ± 59.86; 16.95	384.0 ± 2293.97; 205	0.130
NT proBNP [pg/ml]	10565.47 ± 15675.56; 2100.0	918.5 ± 441.94; 918.5	0.932
IL-6 [pg/ml]	74.22 ± 149.74; 18.08	7.54 ± 124.83; 51.27	0.798
Lactate [mmol/l]	2.95 ± 3.80; 1.7	17.76 ± 48.76; 3.26	0.092
AST in the 1st day [IU/l]	81.90± 135.85; 41.0	117.23± 142.36; 77.0	**0.039***
ALT in the 1st day [IU/l]	72.0 ± 166.48; 25.5	39.0 ± 281.05; 38.5	0.217

*statistical significance in U-Mann Whitney test.

4. Discussion

Children with severe SARS-CoV-2 virus infection and symptoms of impending respiratory and/or multiple organ failure require treatment in the Pediatric Intensive Care Unit. The key role in the mechanism of infection is played by the spike (S) protein, which is present on the surface of the virus and has an affinity for the ACE2 receptor protein (agiotensin-converting enzyme 2). The fusion of these two proteins allows viral particles to enter host cells.ACE2 is a receptor found on the mucosa of the upper and lower respiratory tract, enterocytes of the small intestine, in the kidneys, heart, testes, cholangiocytes and in the endothelium of blood vessels (27). There may be a cytokine storm

and rapid release of inflammatory mediators: e.g. pro-inflammatory cytokines (TNF alpha, IL-1, IL-6), anti-inflammatory cytokines (e.g. interleukin 10 and interleukin 1 receptor antagonists), and numerous oxygen free radicals and coagulation factors. Cytokines signal and stimulate cells of the immune system, including macrophages and T lymphocytes, to migrate towards the site of infection. Such a strong response of the immune system is observed in about 5% of patients (27). The consequence of these disorders is insufficient oxygenation of the blood and deteriorating respiratory function, which may lead to ARDS. The consequence of hypoxia and the development of a systemic inflammatory reaction can be multiple organ failure and shock. The need to use invasive ventilation with high pressure parameters may secondarily cause circulatory failure, which will make it even more difficult to maintain proper systemic homeostasis.

The consequences of these disorders include insufficient oxygenation of the blood and deteriorating respiratory function, which may lead to ARDS (Acute Respiratory Distress Syndrome) (7). In our study, the proportion of intubated children (84%) was higher than that reported in a similar study by Garcia-Salido *et al.*, where 61.1% of children required intubation (8), or by Shekerdemian et al., where only 38% of children required mechanical ventilation (9). Of the 45 patients, only 7 (16%) did not require mechanical ventilation (including 5 with high-flow oxygen therapy using Airwo; in 2 patients low-flow passive oxygen therapy via the nasal canula was sufficient), while the remaining 38 (84%) patients required intubation and invasive mechanical ventilation using the BiPAP, ASV, PCV mode (37 patients from the 1st day of admission, 1 patient after the unsatisfactory effect of high-flow oxygen therapy required intubation and invasive ventilation from the 2nd day of hospitalization in the ICU). Oxygen therapy is beneficial for patients with hypoxia to keep oxygen saturation above 94%. High-flow by nasal cannula, a face mask, or non-invasive ventilation (preferably using a continuous positive airway pressure helmet or full-face interface) or bilevel positive airway pressure machine is recommended.Endotracheal intubation should not be delayed if patients develop acute lung injury or ARDS (28). With the exception of 1 patient, all ventilated patients in our study required intubation and invasive ventilation from day 1 in the PICU. In the patients who died, the time of admission was not significantly different from those who survived and also required mechanical ventilation. Our study revealed some discrepancies in the criteria for admission to PICUs in Poland depending on the local situation. According to our latest up-to-date admission criteria, admitted patients are usually those diagnosed with a life-threatening condition, resulting mainly from acute respiratory and/or circulatory failure, as well as multiple organ failure syndrome, requiring the use of monitoring and treatment techniques, available only in PICU (14). Unfortunately, we still admit "too sick" patients to the ICU, despite available guidelines and recommendations (14, 24, 25). The pandemic is a particularly difficult time and the use of the so-called triage is associated with high stress regarding making a responsible decision (26) . The median age of our patients was 2 years. In the literature, severe course is most often described in two age groups – in children < 2 years of age (3, 22,34) and in adolescents – median 9 years (7, 28). Two multicenter studies in Europe showed that a higher prevalence of neonates required ICU admission than older patients (35,36). In our analysis, the interquartile range is extensive. Perhaps our group is younger due to the fact that in Poland, all disabled and handicapped children are born and they are often hospitalized in the first years of their lives.

Factors correlating with patient prognosis included statistically significant lower oxygen pressure at the time of admission to the ICU, which resulted in lower saturation values, the need for higher oxygen concentrations, a lower oxygen index, and a higher rate of lung damage). Oxygenation index (OI) is used to assess the respiratory capacity of the human body. OI < 200 mmHg in the presence of bilateral parenchymal changes in the lungs corresponding to non-cardiogenic pulmonary edema and the absence of symptoms of increased pressure in the left atrium meets the criteria for ARDS and is a poor prognosis factor.

Graft *et al.* reported on which children are at the most significant risk for severe complications from COVID-19 infection. Among the comorbid conditions, , diabetes, and obesity were predictors of severe COVID-19 in children. Of the 66 symptomatic patients, 55% required respiratory support, and 17% required critical care (10). The severe course of COVID-19 may manifest itself in the form of

shock, encephalopathy, myocardial damage, or renal failure, which may be caused by severe coagulopathies and/or a 'cytokine storm' (7, 9). Individual components evaluating multi-organ function in our study did not differ between the compared groups, although the total values according to the pSOFA scale were statistically higher in the group of children who did not survive. The SOFA score at admission is useful for predicting outcomes in the Pediatric Intensive Care Units (PICUs) and is more accurate than SIRS for definition of pediatric sepsis. Individual components evaluating multi-organ function in our study did not differ between the compared groups, although according to the pSOFA scale, the total values were statistically higher in the group of children who did not survive.Note the trend of higher markers of inflammation, tissue damage, and microcirculatory failure in non-survivors. Lactates, ferritin, LDH, and troponin were higher in this group of patients.

Circulatory failure and the need for vasoactive drugs in the study population were observed in almost 65% of patients, although in the available literature, myocardial damage and the need for vasoactive drugs were described more often in children with PIMS than with COVID-19 (10, 11, 12). Similarly, higher values of inflammatory markers such as CRP and procalcitonin were found more often in the group of children with PIMS than in COVID-positive patients (8, 13). Procalcitonin is a prohormone, a precursor of calcitonin, a hormone that plays a major role in calcium homeostasis. Elevated procalcitonin levels may be seen in sepsis and are particularly associated with septic shock and organ dysfunction requiring intervention. A majority of COVID-19 patients have procalcitonin levels in the normal range (29). Comparing all patients in terms of the criterion of survival, we did not observe a difference; however, the group of patients who survived and were invasively ventilated tended to have increased procalcitonin (29).

Another parameter, i.e. leukocytosis, showed normal values in most children with COVID (15), and it was elevated in only about 10% of patients (16). . NT-proBNP is a hormone released by the muscle cells of the heart ventricles when their tension increases, with increasing load(30). In ventilated patients who survived, it was slightly higher on day 1 than in patients who died, but we did not observe this trend for troponin. We observed a trend of a much higher value in all patients who died. It seems to be a marker of myocardial damage much more sensitive than NT-proBNP(30). IL-6 is one of the most prominent pro-inflammatory cytokines. Increased levels are recorded in COVID-19 patients, especially those with severe-to-critical disease. Evidence is accumulating on the relevance of IL-6 as a prognostic marker in COVID-19 (30). Interleukin-6 is one of the most important signaling molecules produced by cells of the immune system. It has been shown that IL-6 is a cytokine with dual activity, which means that on the one hand, it can have an anti-inflammatory effect by activating the classical signaling pathways. On the other hand, it induces a pro-inflammatory effect by activating the so-called trans-signaling pathways, thus activating the immune system. Perhaps for this reason, our results show a different trend – patients who survived had lower levels of IL-6, but those who died in the ventilated group had much higher levels of this marker.

The significantly higher laboratory indicator in the group of patients who died was aspartate aminotransferase. Aspartate aminotransferase was a laboratory marker significantly higher in the group of patients who died. Several studies have reported elevated AST, ALT, and LDH levels (17, 18) in children diagnosed with COVID-19 and treated in Pediatric Infectious Diseases Wards. Mania *et al.* suggested a poor correlation between the level of LDH (lactate dehydrogenase) and CK (creatine kinase) in children requiring intensive care, in comparison to children with a mild to moderate course of COVID-19 (17). The pathomechanism of liver damage in COVID-19 cases is complex and caused by many factors: hyperactive immune response and "cytokine storm", systemic inflammatory reaction, hypoxia, hypovolemia, acute respiratory failure, and septic shock(32,33). Disturbances in the intestinal microbiota (intestinal endotoxemia) are also considered. Drugs such as antivirals, antibiotics and paracetamol (used in high doses in these patients) may also be potentially hepatotoxic in the course of COVID-19. There are also hypotheses that liver damage in the course of SARS-CoV-2 results from the expression of the ACE2 receptor in cholangiocytes(31). AST levels can also rise in myocardial infarction and muscle damage, usually much more than ALT. Kidney damage can also cause an increase in AST. In the group of children who died, elevated AST levels on day 1 correlated

with the occurrence of statistically significant hypoxemia on admission, which could significantly contribute to myocardial and skeletal muscle damage and renal hypoxia.

In children treated for COVID-19 in PICU, it has not yet been possible to determine clear prognostic laboratory exponents, which may result from the limited number of studies and publications. Most likely, the correlation of elevated AST values in patients who died may be a predictor of liver damage coexisting with Covid-19, requiring further research (19). A more severe course of COVID-19 is more common in children with comorbidities and a positive genetic history (20, 21). The study group was dominated by underweight rather than obese children, which was most likely due to the child's poor condition and/or cachexia. Obesity is a risk factor for a severe course of COVID-19. One of the probable causes is the chronic inflammation associated with obesity, which interferes with the proper immune response and also affects the blood coagulation process.In addition, obesity is associated with functional impairment of the respiratory system.

The meta-analysis and systemic review based on 27 studies showed that obesity, diabetes, heart disease, chronic lung disease, seizures, and immunodeficiency are classified as risk factors for a severe course of COVID-19 infection (22). In our study group, only 5 children had no comorbidities and all of them survived. The others had comorbidities; the mortality rate in this group was as much as 40% and was assessed as higher compared to the reports of other researchers (6, 8). On the other hand, the mortality rate of children in the PICU compared to all children treated in hospitals due to COVID-19 in this period was 0.1% (28 deaths per 91,000 hospitalized patients), and it does not differ from the mortality rate of children due to the SARS-CoV-2 virus in the US (23).

Although we did not find a statistically significant difference in treatment, steroid and anticoagulant therapies were more frequently used in surviving children, which may have contributed to treatment outcomes.In the initial period of the pandemic, we did not have clear recommendations as to the therapy used. Today, recommendations for the use of steroid therapy and anticoagulant treatment in patients with severe COVID-19 are known.

The limitation of our study is the fact that our study group was strictly selected and consisted entirely of patients diagnosed with a very severe course of SARS-CoV-2 infection requiring intensive care and presented the actual condition of children critically ill due to SARS-CoV-2 infection. Further analysis of this issue is necessary.

5. Conclusions

As in adults, children with comorbidities are most frequently at risk of severe SARS-CoV-2 infection. Increasing symptoms of respiratory failure, the need for mechanical ventilation and persistently high values of aspartate aminotransferase are indicators of poor prognosis.

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References

1. Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus Disease 2019 in Children. Front Pediatr. 2021 May 28;9:668484. doi: 10.3389/fped.2021.668484
2. Leidman E, Duca LM, Omura JD, Proia K, Stephens JW, Sauber-Schatz EK. COVID-19 Trends Among Persons Aged 0-24 Years - United States, March 1-December 12, 2020. MMWR Morb Mortal Wkly Rep. 2021 Jan 22;70(3):88-94. doi: 10.15585/mmwr.mm7003e1. PMID: 33476314; PMCID: PMC7821770.
3. Graff K, Smith C, Silveira L, Jung S, Curran-Hays S, Jarjour J, Carpenter L, Pickard K, Mattiucci M, Fresia J, McFarland EJ, Dominguez SR, Abuogi L. Risk Factors for Severe COVID-19 in Children. Pediatr Infect Dis J. 2021 Apr 1;40(4):e137-e145. doi: 10.1097/INF.0000000000003043. PMID: 33538539.
4. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol. 2020 Aug;20(8):453-454. doi: 10.1038/s41577-020-0367-5. PMID: 32546853; PMCID: PMC7296515.

5. Clark B.C., Sanchez-de-Toledo J., Bautista-Rodriguez et al. Cardiac abnormalities seen in pediatric patients during the SARS-CoV2 pandemic: an international experience. J Am Heart Assoc 2020; 9 (21): e018007.
6. https://www.gov.pl/web/koronawirus/wykaz-zarazen-koronawirusem-sars-cov-2
7. Derespina KR, Kaushik S, Plichta A, Conway EE Jr, Bercow A, Choi J, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. J Pediatr. (2020) 226:55–63.e2. doi: 10.1016/j.jpeds.2020.07.039
8. García-Salido et al. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain. Crit Care. 2020 Nov 26;24(1):666. doi: 10.1186/s13054-020-03332-4. PMID: 33243303; PMCID: PMC7689392.
9. Shekerdemian LS et al.Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020 Sep 1;174(9):868-873. doi: 10.1001/jamapediatrics.2020.1948. PMID: 32392288; PMCID: PMC7489842.
10. Graff K, Smith C, Silveira L, et al. Risk factors for severe COVID-19 in children. Pediatr Infect Dis J 2021;40(4):e137-45.
11. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 disease severity risk factors for pediatric patients in Italy. Pediatrics. (2020) 146:e2020009399. doi: 10.1542/peds.2020-0 09399
12. Tang Y, Li W, Baskota M, Zhou Q, Fu Z, Luo Z, Shi Y, Chen Y, Liu E. Multisystem inflammatory syndrome in children during the coronavirus disease 2019 (COVID-19) pandemic: a systematic review of published case studies. Transl Pediatr. 2021 Jan;10(1):121-135. doi: 10.21037/tp-20-188. PMID: 33633944; PMCID: PMC7882293.
13. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr. 2021 Jul;180(7):2019-2034. doi: 10.1007/s00431-021-03993-5. Epub 2021 Feb 18. PMID: 33599835; PMCID: PMC7890544.
14. Krzych Ł, Bartkowska-Śniatkowska A, Knapik P, Zielińska M, Maciejewski D, Cettler M, Owczuk R, Kusza K. Guidelines of the Polish Society of Anaesthesiology and Intensive Therapy defining the rules of qualification and criteria for admitting patients to anaesthesiology and intensive care units. Anaesthesiol Intensive Ther. 2022;54(3):219-225. doi: 10.5114/ait.2022.118963. PMID: 36047288.
15. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: a systematic review. E Clin Med. (2020) 24:100433. doi: 10.1016/j.eclinm.2020.100433
16. Christophers B, Gallo Marin B, Oliva R, Powell WT, Savage TJ, Michelow IC. Trends in clinical presentation of children with COVID19: a systematic review of individual participant data. Pediatr Res. (2020). doi: 10.1038/s41390-020-01161-3
17. Mania A, Faltin K, Mazur-Melewska K, Małecki P, Jończyk-Potoczna K et al. M. Clinical Picture and Risk Factors of Severe Respiratory Symptoms in COVID-19 in Children. Viruses. 2021 Nov 25;13(12):2366. doi: 10.3390/v13122366. PMID: 34960635; PMCID: PMC8703640.
18. Henry BM, Benoit SW, de Oliveira MHS, Hsieh WC, Benoit J, Ballout RA, Plebani M, Lippi G. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): A pooled analysis and review. Clin Biochem. 2020 Jul;81:1-8. doi: 10.1016/j.clinbiochem.2020.05.012. Epub 2020 May 27. PMID: 32473151; PMCID: PMC7251358.
19. Marjot T, Webb GJ, Barritt AS 4th, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol*. 2021;18(5):348-364. doi:10.1038/s41575-021-00426-4
20. Oualha M., Bendavid M., Berteloot L., Corsia A., Lesage F., Vedrenne M., Salvador E., Grimaud M., Chareyre J., de Marcellus C., et al. Severe and fatal forms of COVID-19 in children. Arch. Pédiatrie. 2020;27:235–238. doi: 10.1016/j.arcped.2020.05.010.
21. Kompaniyets L., Agathis N.T., Nelson J.M., Preston L.E., Ko J.Y., Belay B., Pennington A.F., Danielson M.L., DeSisto C.L., Chevinsky J.R., et al. Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children. JAMA Netw. Open. 2021;4:e2111182. doi: 10.1001/jamanetworkopen.2021.11182
22. Choi JH, Choi SH, Yun KW. Risk Factors for Severe COVID-19 in Children: A Systematic Review and Meta-Analysis. J Korean Med Sci. 2022 Feb 7;37(5):e35. doi: 10.3346/jkms.2022.37.e35. PMID: 35132841; PMCID: PMC8822112
23. Delahoy MJ, Ujamaa D, Whitaker M, O'Halloran A, Anglin O et al. Hospitalizations Associated with COVID-19 Among Children and Adolescents - COVID-NET, 14 States, March 1, 2020-August 14, 2021. MMWR Morb Mortal Wkly Rep. 2021 Sep 10;70(36):1255-1260. doi: 10.15585/mmwr.mm7036e2. PMID: 34499627; PMCID: PMC8437052.
24. Bartkowska-Śniatkowska A, Byrska-Maciejasz E, Cettler M, Damps M, Jarosz K et al.Guidelines regarding ineffective maintenance of organ functions (futile therapy) in paediatric intensive care units. Anaesthesiol Intensive Ther. 2021;53(5):369-375. doi: 10.5114/ait.2021.111451. PMID: 35100794.

25. Damps M, Gajda M, Stołtny L, Kowalska M, Kucewicz-Czech E. Limiting futile therapy as part of end-of-life care in intensive care units. Anaesthesiol Intensive Ther. 2022;54(3):279-284. doi: 10.5114/ait.2022.119124. PMID: 36189906.
26. Kucewicz-Czech E, Damps M. Triage during the COVID-19 pandemic. Anaesthesiol Intensive Ther. 2020;52(4):312-315. doi: 10.5114/ait.2020.100564. PMID: 33165882.
27. Simon K, Rorat M, Janocha-Litwin J, Pazgan-Simon M. SARS-CoV-2 infection: etiopathogenesis, clinical picture, current therapeutic options – the author's observations. NOWOTWORY J Oncol 2021; 71: 38–41.
28. Adeyinka A, Bailey K, Pierre L, Kondamudi N. COVID 19 infection: Pediatric perspectives. J Am Coll Emerg Physicians Open. 2021 Jan 29;2(1):e12375. doi: 10.1002/emp2.12375. PMID: 33554209; PMCID: PMC7846069
29. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. Clin Chem Lab Med. 2020 Jun 25;58(7):1063-1069. doi: 10.1515/cclm-2020-0240. PMID: 32191623.
30. Potere N, Batticciotto A, Vecchié A, Porreca E, Cappelli A, Abbate A, Dentali F, Bonaventura A. The role of IL-6 and IL-6 blockade in COVID-19. Expert Rev Clin Immunol. 2021 Jun;17(6):601-618. doi: 10.1080/1744666X.2021.1919086. Epub 2021 May 27. PMID: 33874829.
31. Verdecchia P., Cavallini C., Spanevello A., Angeli F.: The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020. pii: S0953-6205(20)30151-5. doi: 10.1016/j.ejim.2020.04.037
32. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H et al.Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5. Epub 2020 Feb 24. Erratum in: Lancet Respir Med. 2020 Apr;8(4):e26. PMID: 32105632; PMCID: PMC7102538.
33. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX et al.China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013; PMCID: PMC7092819.
34. Kim L, Whitaker M, O'Halloran A, et al; COVID-NET Surveillance Team. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 States, March1-July 25, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1081–1088.
35. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020;4(9):653–661.
36. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020;370:m3249.