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ORIGINAL ARTICLE

Pneumonia, gastrointestinal symptoms, comorbidities, and coinfections as factors related to a lengthier hospital stay in children with COVID-19—analysis of a paediatric part of Polish register SARSTer

Anna Mania[a]*, Maria Pokorska-Śpiewak[b]*, Magdalena Figlerowicz[a], Małgorzata Pawłowska[c], Katarzyna Mazur-Melewska[a], Kamil Faltin[a], Ewa Talarek[b], Konrad Zawadka[b], Anna Dobrzeniecka[b], Przemysław Ciechanowski[d], Joanna Łasecka-Zadrożna[d], Józef Rudnicki[d], Barbara Hasiec[e], Martyna Stani[e], Paulina Frańczak-Chmura[e], Izabela Zaleska[f], Leszek Szenborn[f], Paulina Horecka[g], Artur Sulik[g], Barbara Szczepańska[h], Ilona Pałyga-Bysiecka[h], Izabela Kucharek[i,j], Adam Sybilski[i,j], Małgorzata Sobolewska-Pilarczyk[c], Urszula Dryja[k], Ewa Majda-Stanisławska[k], Sławomira Niedźwiecka[l], Ernest Kuchar[m], Bolesław Kalicki[n], Anna Gorczyca[o] and Magdalena Marczyńska[b]

[a]Department of Infectious Diseases and Child Neurology, Poznan University of Medical Sciences, Poznan, Poland; [b]Department of Children's Infectious Diseases, Medical University of Warsaw, Warsaw, Poland; [c]Department of Infectious Diseases and Hepatology, Faculty of Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [d]Department of Paediatrics and Infectious Diseases, Regional Hospital in Szczecin, Szczecin, Poland; [e]Department of Children's Infectious Diseases, Provincial Jan Boży Hospital in Lublin, Lublin, Poland; [f]Department of Paediatrics and Infectious Diseases, Wroclaw Medical University, Wroclaw, Poland; [g]Department of Pediatric Infectious Diseases, Medical University of Bialystok, Bialystok, Poland; [h]Collegium Medicum Jan Kochanowski University, Kielce, Poland; [i]2nd Department of Paediatrics, Centre of Postgraduate Medical Education, Warsaw, Poland; [j]Department of Paediatrics and Neonatology with Allergology Center, Central Clinical Hospital of the Ministry of the Interior, Warsaw, Poland; [k]Department of Paediatric Infectious Diseases, Medical University of Lodz, Lodz, Poland; [l]Department of Paediatric Infectious Diseases, Pomeranian Center of Infectious Diseases and Tuberculosis in Gdańsk, Gdańsk, Poland; [m]Department of Paediatrics with Clinical Assessment Unit, Medical University of Warsaw, Warsaw, Poland; [n]Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Warsaw, Poland; [o]The Ward of Pediatric Infectious Diseases and Hepatology, The John Paul II Hospital in Krakow, Krakow, Poland

ABSTRACT

Background: Although COVID-19 is associated with a mild course in children, a certain proportion requires admission to hospital due to SARS-CoV-2 infection and coexisting diseases. The prospective multicenter study aimed to analyze clinical factors influencing the length of the hospital stay (LoHS) in children with COVID-19.

Methods: The study included 1283 children from 14 paediatric infectious diseases departments with diagnosed SARS-CoV-2 infection. Children were assessed in respective centres regarding indications for admission to hospital and clinical condition. History data, clinical findings, laboratory parameters, treatment, and outcome, were collected in the paediatric SARSTer register. The group of children with a hospital stays longer than seven days was compared to the remaining patients. Parameters with a statistically significant difference were included in further logistic regression analysis.

Results: One thousand one hundred and ten children were admitted to the hospital, 763 children were hospitalized >24 h and 173 children >7 days. 268 children had comorbidities. Two hundred and eleven children had an additional diagnosis with coinfections present in 135 children (11%). Factors increasing the risk of higher LoHS included pneumonia [odds ratio—OR 3.028; 95% confidence interval—CI (1.878–4.884)], gastrointestinal symptoms [OR = 1.556; 95%CI (1.049–2.322)], or rash [OR = 2.318; 95%CI (1.216–4.418)] in initial clinical findings. Comorbidities [OR = 2.433; 95%CI (1.662–3.563)], an additional diagnosis [OR = 2.594; 95%CI (1.679–4.007)] and the necessity of the empirical antibiotic treatment [OR = 2.834; 95%CI (2.834–6.713)] were further factors related to higher LoHS.

Conclusions: The clinical course of COVID-19 was mild to moderate in most children. Factors increasing the risk of higher LoHS included pneumonia, gastrointestinal symptoms, comorbidities, an additional diagnosis, and the empirical antibiotic treatment.

*These authors contributed equally to this work.

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CONTACT
Anna Mania
amania@ump.edu.pl
Department of Infectious Diseases and Child Neurology, Poznań University of Medical Sciences, ul. Szpitalna 27/33, Poznań, 60-572, Poland

Introduction

Children account for a relatively small proportion o patients with coronavirus disease 2019 (COVID-19). The number of cases reported in children is significantly lower than in adults [1]. Children are also less likely to experience severe disease. Most of the patients do not require admission to the hospital [2,3]. Nevertheless, in the circumstances of the severe acute respiratory coronavirus type 2 (SARS-CoV-2) pandemic with a large number of infected individuals, more paediatric cases are reported [4,5]. Therefore, a certain proportion of SARS-CoV-2 infected children may develop more significant clinical course and related consequences [6].

Several hypotheses explain the milder clinical course and less severe outcomes of COVID-19 in children. Frequent respiratory tract infections, mucosal competition of pathogens, non-specific protections of other vaccinations, and lower expression of angiotensin-converting enzyme 2 (ACE-2), known as SARS-CoV-2 receptor on the surface of respiratory epithelium being some of them [7]. COVID-19 usually manifests as respiratory illness, especially in adults. Typical symptoms include fever, cough, dyspnoea, and fatigue [8]. However, gastrointestinal symptoms including abdominal pain, diarrhoea, and vomiting are reported frequently in paediatric patients, which may be explained by the relatively high expression of ACE-2 molecules on the surface of gastrointestinal epithelium in children [9].

Until 31 December 2020, 80,316,555 cases of COVID-19 were diagnosed worldwide and 1,294,878 in Poland with the number of deaths 1,770,695 and 28,554, respectively. According to the available data from the first two months of the COVID-19 pandemic, children constituted 6.68% of cases in Poland [10].

Most individuals recover spontaneously from the infection. Nevertheless, some, especially older patients, may develop acute respiratory illness and multiorgan failure, associated with high fatality cases despite aggressive treatment in intensive care units. The mortality rate among children is low. A small proportion of children develops severe symptoms [11,12]. However, it is necessary to identify potential factors associated with the severe clinical course that may require a more intensive approach in this group of patients.

This study aims to evaluate history data, clinical and laboratory findings, and treatment of children with COVID-19 concerning the duration of hospital stay.

Materials and methods

We present data from the first two waves of infections in the cohort of Polish paediatric patients from 1 March 2020 until 31 December 2020. This prospective multicenter study based on the paediatric part of a Polish SARSTer register (SARSTer-PED) included 1283 patients (age range 5 days–18 years; median 6 years) from 14 paediatric infectious diseases departments. In Poland, from 1 March 2020 to 31 August 2020, all SARS-CoV-2 infected children were evaluated in the paediatric infectious diseases departments. Starting from 1 September 2020, children were referred by general practitioners according to their clinical status. The first wave was observed between 1 March and 31 August 2020. The period starting from 1 September to 31 December 2020 was considered the 2nd wave.

History data, including potential SARS-CoV-2 exposure, were taken, and physical examination was performed in all patients. The decision regarding hospital admission was based on the general condition and the patient's vital signs, including oxygen saturation <95%, temperature >38 °C, the severity of physical findings, coexisting diseases, and response to ambulatory treatment. The patient admitted to the hospital underwent further testing involving complete blood count (CBC), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), clinical chemistry parameters, fibrinogen level, international normalized ratio (INR), D-dimer, electrolytes levels, urinalysis, when clinically appropriate. The parameters were evaluated using standard laboratory analyzers. Imaging studies were performed according to clinical indications. Blood culture was assessed in all febrile patients, urine culture, and pharyngeal swab according to clinical findings. Children were also evaluated for coinfections when clinically indicated, including respiratory syncytial virus and influenza virus type A and B using real-time polymerase chain reaction tests (RT-PCR; Cobas InfluenzaA/B&RSV, Cobas; Xpert Xpress FLU/RSV, Cepheid), PCR panel for additional respiratory pathogens comprising adenovirus, rhinovirus, bocavirus, parainfluenza virus, coronavirus, Epstein-Barr virus (EBV), *Mycoplasma pneumoniae*, *Staphylococuss aureus*, and *Streptococcus pneumoniae*. Stool tests for rotaviruses/adenoviruses were performed, and serological tests for parvovirus B19, EBV, *M. pneumoniae*, if clinically appropriate. SARS-CoV-2 infection was confirmed by CE IVD RT-PCR tests (various analyzers) from the nasopharyngeal swab. Until 2 September 2020, children were repeatedly tested by RT-PCR if clinically indicated to document negativity. Starting from 3 September, the isolation period depended on clinical findings (3 days after the resolution of symptoms, not <10 days). Therefore, control RT-PCR testing was not performed. After validation and approval of the second generation antigen testing for SARS-CoV-2 infection (30 October 2020), this method was also used to confirm the diagnosis of COVID-19 in symptomatic patients. The most widely used antigen test was COVID-19 Ag Rapid Test Device (Abbott, Jena, Germany), sensitivity 98.1% (95% CI: 93.2–99.8%), specificity 99.8% (95%CI: 98.6–100.0%). According to state sanitary regulations, positive tests were considered sufficient to confirm SARS-CoV-2 infection, while all negative results were evaluated with the RT-PCR method.

Based on the assumption that more severe clinical conditions on admission and more severe clinical findings result in a lengthier hospital stay, children were divided into two groups regarding the length of their hospital stay (LoHS): 0–7 *vs.* >7 days.

Continuous data were presented as the median and interquartile range (IQR). For frequency of categorical data, number and the percentage were given. The Chi-square test was used for the analysis of categorical data. Continuous data were compared using the Mann–Whitney test. p-Values <.05 were considered statistically significant. Further analysis was performed using logistic regression. Parameters with a statistically significant difference were included in the univariate analysis. Parameters significant in the univariate analysis were included in the multivariate analysis. Thus, parameters without significance were excluded from the model until only significant parameters remained. The results were presented as odds ratio (OR) and 95% confidence interval (95%CI). Results with CI not including 1.0 were considered statistically significant.

The study was approved by the Ethical Committee of the University of Medical Sciences in Poznan (No 2865/20).

Results

The study includes 1283 children [median age 6, IQR (1;13)], 650 boys, and 633 girls. The distribution of cases is shown in Figure 1. The baseline characteristics of the study group are presented in Table 1. From the group of 1283 children, 1110 (86%) were admitted to the

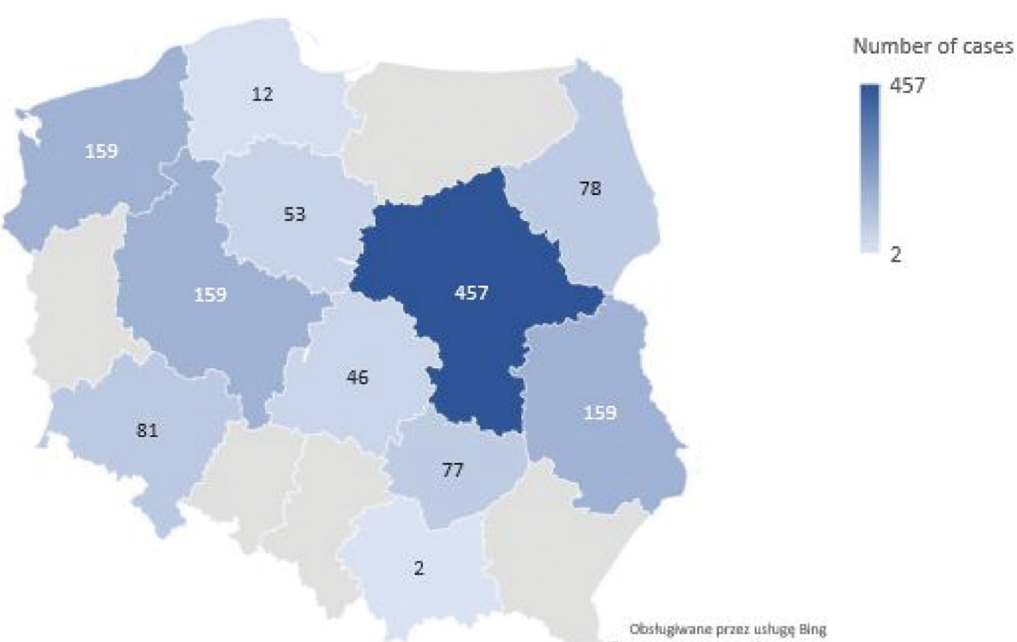

Figure 1. The number of cases and regions of Poland covered by the SARSTer-PED register.

Table 1. Baseline characteristics of the study group ($N = 1283$).

Feature	Number
Age	
Range	5 days–18 years
Median (IQR) (years)	6 (1; 13)
Gender	
Male/female	650 (50%)/633 (50%)
Household contact with an infected family member	
Yes	705 (55%)
Other confirmed contact	
Yes	48 (4%)
Confirmed COVID-19 in a family member (data available for 606 patients)	
Before the diagnosis established in the child	260 (43%)
Diagnosis in the child established simultaneously	281 (46%)
After the diagnosis established in the child	65 (11%)
Duration to negative PCR testing for SARS-CoV-2 infection (data available for 286 patients)	
Days, median (IQR)	14 (11; 21)
Hospitalization	
Yes	1010 (86%)
Lasting 1-day	347 (27%)
Lasting > 24 h; ≤ 7 days	590 (46%)
Lasting > 7 days	173 (13%)
Duration (days), Median (IQR)	5 (3; 8)
Duration of any symptoms before admission	
Days; median (IQR)	2 (1; 4)
Duration of fever before admission	
Days; median (IQR)	1 (0;3)
International travel	
(During 14 days before the onset of the disease)	43 (3)
Comorbidities including:	
Present	268 (21%)
Asthma	26 (2%)
Cardiovascular diseases	22 (2%)
Immunodeficiency	19 (1%)
Obesity	8 (<1%)
Neoplastic diseases	6 (<1%)
Diabetes	5 (<1%)
Hypertension	4 (<1%)

Data are presented as number (%) unless otherwise indicated.

Table 2. Additional diagnoses in patients with COVID-19, $n = 211$.

Diagnosis	Number of cases (%)
Infections	135 (64%)
Urinary tract infection	29 (14%)
Gastrointestinal infection (rota, adeno, and noro)	25 (12%)
Otitis media	18 (9%)
Viral respiratory tract infections (other than COVID-19)	11 (5%)
Bacterial pneumonia	8 (4%)
Sepsis	8 (4%)
Bacterial pharyngitis	8 (4%)
Other bacterial infections	6 (3%)
Stomatitis	6 (3%)
Infectious mononucleosis	5 (2%)
Bacterial skin infections	3 (1%)
Bacterial gastrointestinal infections	3 (1%)
Herpes virus	3 (1%)
Varicella	2 (1%)
Surgical conditions	21 (10%)
Appendicitis	5 (2%)
Abscesses	4 (2%)
Head injury	3 (1%)
Burns	3 (1%)
Bone fractures	3 (1%)
Intussusception	3 (1%)
Other causes of admission	55 (26%)
Epilepsy and seizure episodes	5 (2%)
PIMS-TS	5 (2%)
Thrombocytopenia	3 (1%)
Reactive arthritis	2 (2%)
Anaemia	2 (2%)
Other singular conditions	38 (18%)

PIMS-TS: paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

hospital. LoHS was 1 day in 347 (27%), over 24 h to 7 days in 590 (46%), and over 7 days in 173 children (13%). Children with comorbidities accounted for 268 cases, including asthma—26 (2%), cardiovascular diseases—22 (2%), immune deficiencies—19 (1%) children, as presented in Table 1. Despite having COVID-19, the group of 211 children was admitted to the hospital, with the additional diagnosis being the cause of the hospital stay. The most common conditions included different infections other than COVID-19 from several foci (coinfections—135 children, 11% of the whole study cohort): urinary tract infections (UTI) (29 children, 14% of children with additional diagnoses), gastrointestinal coinfections with rota-, adeno- or noroviruses (25 children, 12% of children with other diagnoses), otitis media (18 children, 9% of children with additional diagnoses). Other viral infections of the respiratory tract were developed by 11 patients (0.85% of the whole study group)—with two cases of influenza and singular cases of infections with other viruses: adeno-, rhino-, boca-, RSV, parainfluenza. Eight children presented bacterial infections of the respiratory tract with pneumonia (0.63% of the whole study cohort—seven cases of *S. pneumoniae* and 1 *M. pneumoniae*). Instances of sepsis comprised *S. pneumoniae*: four children, *Escherichia coli*: two children, *Klebsiella oxytoca*—one child. Seventy-five children (35%) were diagnosed with a bacterial coinfection. Twenty-one children were hospitalized due to conditions that required surgical intervention. The additional diagnoses are presented in Table 2.

Comparison between groups concerning LoHS (>7 *vs.* 0–7 days) revealed significantly younger age ($p = .001$), less frequent household contacts ($p = .001$), more frequent comorbidities ($p < .0001$; OR = 2.73 95%CI (1.968; 3.905) in univariate logistic regression) present in the group with higher LoHS. Lengthier hospital admissions occurred more frequently during the 2nd wave of the COVID-19 pandemic (Table 3).

Clinical symptoms

Children with COVID-19 that required LoHS > 7 days presented a longer duration of fever (medians 2 *vs.* 1; $p < .0001$), more frequent gastrointestinal symptoms (abdominal pain, vomiting, diarrhoea, or any of them)—36 *vs.* 21% ($p < .0001$), COVID-19 related pneumonia (32 *vs.* 9%; $p < .0001$), weakness (36 *vs.* 22%; $p < .0001$), rash (12 *vs.* 5%; $p = .0001$), dyspnoea (10 *vs.* 5%; $p = .01$) and seizures (55 *vs.* 1%; $p = .0005$). Another diagnosis as a

Table 3. Comparison of clinical presentation of COVID-19 in children according to the duration of hospitalization.

Clinical factor	Patients hospitalized for >7 days $N=173$	Patients hospitalized for 0–7 days $N=1110$	p	OR (95%CI)
Age (months) Median (IQR)	52.0 (5.7–153.0)	78.5 (18.0–156.0)	**.001**	**0.987 (0.976; 0.989)**
Sex (male/female)	90 (52%)/83 (48%)	560 (50%)/550 (50%)	.70	–
Household contact with an infected family member	77 (45%)	639 (58%)	**.001**	**0.591 (0.428; 0.816)**
Confirmed other contact	2 (1%)	45 (4%)	.05	–
International travel during 14 days before the onset of symptoms	7 (4%)	36 (3%)	.58	–
Comorbidities	66 (38%)	202 (18%)	**<.0001**	**2.773 (1.968; 3.905)**
Wave of COVID-19 (1st/2nd)	41 (24%)/132 (76%)	424 (38%)/685 (62%)	**.0002**	**1.988 (1.379; 2.894)**
Clinical presentation				
Asymptomatic course of COVID-19	34 (20%)	508 (46%)	.16	–
Duration of fever (days) Median (IQR)	2 (0; 4)	1 (0; 2)	**<.0001**	**1.857 (1.108; 1.269)**
Fever	89 (51%)	508 (46%)	.16	–
Cough	54 (31%)	363 (33%)	.61	–
Rhinitis	38 (22%)	301 (27%)	.15	–
Weakness	63 (36%)	242 (22%)	**<.0001**	**2.073 (1.473; 2.917)**
Pneumonia related to COVID-19	55 (32%)	101 (9%)	**<.0001**	**4.656 (3.185; 6.808)**
Gastrointestinal symptoms	62 (36%)	233 (21%)	**<.0001**	**2.101 (1.492; 2.962)**
Diarrhoea	41 (24%)	150 (14%)	**.0005**	**1.988 (1.345; 2.937)**
Vomiting	23 (13%)	88 (8%)	**.01**	**1.781 (1.091; 2.907)**
Abdominal pain	23 (13%)	95 (9%)	**.04**	**1.638 (1.007; 2.665)**
Headache	14 (8%)	127 (11%)	.19	–
Sore throat	10 (6%)	104 (9%)	.12	–
Anosmia	5 (3%)	99 (9%)	**.006**	**0.304 (0.122; 0.757)**
Loss of appetite	18 (10%)	75 (7%)	.08	–
Muscle pain	12 (7%)	84 (8%)	.76	–
Dyspnoea	17 (10%)	59 (5%)	**.01**	**1.941 (1.103; 3.416)**
Rash	20 (12%)	50 (5%)	**.0001**	**2.771 (1.606; 4.782)**
Chest pain	6 (3%)	41 (4%)	.88	–
Conjunctivitis	6 (3%)	19 (2%)	.12	–
Seizures	9 (5%)	15 (1%)	**.0005**	**4.006 (1.725; 9.303)**
Another diagnosis accompanying COVID-19	72 (42%)	139 (13%)	**<.0001**	**4.980 (3.507; 7.072)**
Laboratory testing				
White blood cell count (G/l) Median (IQR)	9.2 (5.7; 13.1)	7.4 (5.4; 10.8)	**.001**	**1.07 (1.03; 1.10)**
Lymphocytes (%) Median (IQR)	38.8 (23.95–58.0)	45.0 (31.9; 61.0)	**.02**	**0.99 (0.98; 0.99)**
Neutrophils (%) Median (IQR)	43.0 (20.0–60.0)	40 (24.0; 53.0)	.28	–
Red blood cell count (T/l) Median (IQR)	4.52 (3.98; 4.85)	4.65 (4.33; 4.95)	**.0003**	**0.550 (0.414; 0.732)**
Hemoglobin g/dl Median (IQR)	12.4 (11.0; 13.7)	12.8 (11.8; 13.9)	**.02**	**0.897 (0.814; 0.988)**
Platelets (G/l) Median (IQR)	291 (228; 374.5)	290 (233.5; 358)	.088	–
CRP (mg/L) Median (IQR)	3.5 (0.6; 23.3)	1.0 (1.0; 6.0)	**.002**	**1.014 (1.009; 1.019)**
PCT (ng/L) Median (IQR)	0.1 (0.04; 0.4)	0.05 (0.05; 0.09)	**<.0001**	**1.012 (1.001; 1.023)**
Interleukin-6 (pg/mL) Median (IQR)	10.8 (3.7; 63.8)	0.5 (0.5; 4.04)	**<.0001**	**1.011 (1.005; 1.017)**
D-Dimer (ng/mL) Median (IQR)	484 (289; 1035)	296 (200; 485)	**<.0001**	0.999 (0.997; 1.002)
Fibrinogen (g/l) Median (IQR)	3.21 (2.23–4.75)	2.88 (2.36; 3.40)	**.031**	**1.386 (1.174; 1.636)**
ALT (IU/L) Median (IQR)	19 (12; 35)	17 (13; 25)	**.027**	**1.006 (1.002; 1.011)**
AST (IU/L) Median (IQR)	31.5 (23; 46)	33 (25; 44)	.76	–
Bilirubina (mg/dl) Median (IQR)	1.11 (0.4; 7.82)	4.1 (0.5; 8.0)	.25	–
GGTP (IU/l) Median (IQR)	36.0 (11.0; 69.0)	14.0 (12.0–19.0)	**.019**	1.005 (0.999; 1.011)
Urea (mmol/l) Median (IQR)	3.82 (2.83; 5.79)	3.97 (3.01–5.10)	**.019**	0.973 (0.871; 1.088)
Creatinine (umol/l) Median (IQR)	30.94 (22.54; 55.25)	36.24 (25.63–50.39)	.28	–
Na (mmol/) Median (IQR)	138 (137; 141)	139 (138; 141)	**.007**	**0.911 (0.859; 0.965)**
K (mmol/l) Median (IQR)	4.5 (4.0; 4.96)	4.41 (4.10; 4.77)	.28	–
LDH (U/l) Median (IQR)	318 (244; 461)	259 (204; 332)	**<.0001**	**1.004 (1.002; 1.005)**

(*continued*)

Table 3. Continued.

Clinical factor	Patients hospitalized for >7 days N = 173	Patients hospitalized for 0–7 days N = 1110	p	OR (95%CI)
Treatment				
Azithromycin	33 (19)	170 (15)	.2	–
Empirical antibiotic	101 (58)	118 (11)	**<.0001**	**8.392 (5.937; 11.857)**
Oxygen therapy	11 (4)	14 (1)	**<.0001**	**5.316 (2.372; 11.910)**
Intensive care unit	3 (2)	0	**<.0001**	–

Data are presented as number (%), unless otherwise indicated.
The significance of chi-square test or Mann-Whitney test are given in the 4th column (p), OR and 95%CI are calculated for $p < 0.05$.

Table 4. Multivariate analysis of risk factors influencing prolonged hospital stay.

	OR	95% CI
GI symptoms	1.556	1.049–2.322
Rash	2.318	1.216–4.418
COVID-19-related pneumonia	3.028	1.878–4.884
Comorbidities	2.433	1.662–3.563
Another diagnosis	2.594	1.679–4.007
Empirical antibiotic	4.361	2.834–6.713

OR: odds ratio; 95%CI: confidence interval; GI symptoms: gastrointestinal symptoms.

cause for hospital admission was also associated with lengthier hospital admission—42 *vs.* 13%; $p < .0001$. These parameters showed significant differences in univariate logistic regression, as presented in Table 3. Thus, in the multivariate logistic regression, GI symptoms, COVID-19 related pneumonia, and rash were associated with an increased risk of LoHS > 7 days (Table 4).

Laboratory parameters

Although with slight statistically significant differences between evaluated groups, most laboratory parameters medians were within reference values in both compared groups. Children with a LoHS > 7 days developed statistically higher median CRP ($p = .002$), IL-6 ($p < .0001$), fibrinogen ($p = .031$), and LDH levels ($p < .0001$). These parameters showed significant differences in the univariate analysis. However, none of them was proven significant in the multivariate logistic regression (Tables 3, 4).

Treatment

Children with LoHS > 7 days obtained empirical antibiotic treatment (58 *vs.* 11%; $p < .0001$) and oxygen therapy (4 *vs.* 1%; $p < .0001$) more frequently. Only children from this group required management in the intensive care unit (3 children—0.23% of the study cohort). All children that required admission to ICU had comorbidities.

Table 5. Treatment of COVID-19.

Treatment	Number of treated patients (%)
Antipyretics	347 (27%)
Paracetamol	172 (13%)
Ibuprofen	33 (3%)
Paracetamol and ibuprofen	142 (11%)
Azithromycin	203 (16%)
Clarithromycin	2 (<1%)
Empirical antibiotic	252 (20%)
Arechine	4 (<1%)
Remdesivir	1 (<1%)
Lopinavir/ritonavir	1 (<1%)
Immunoglobulins	3 (<1%)
Convalescent plasma	4 (<1%)
Oxygen therapy	22 (2%)
Mechanical ventilation	0 (0)
Treatment in the intensive care unit	3 (<1%)

According to the subsequent guidelines, various treatment methods were used, which were presented in Table 5. The most widely used medications were antipyretics (paracetamol and ibuprofen)—27% of children. Antibiotics were used in 252 patients (20%), convalescent plasma in four children (<1%), and remdesivir in one child (<1%). The outcome of COVID-19 was favourable in all reported cases. No deaths were observed in the study cohort.

Logistic regression multivariate analysis revealed that risk factors associated with a LoHS > 7 days included GI symptoms, COVID-19 related pneumonia, comorbidities, additional diagnosis on admission, and the need for empirical antibiotic treatment. The results of the multivariate logistic regression analysis are presented in Table 4.

Discussion

As reported in epidemiological studies, COVID-19 in children is considered a relatively mild disease [12,13]. Therefore, the majority of children do not require admission to the hospital. In our study, 1110 were hospitalized (86% of the whole study group), and 763 children stayed longer than 24 h. This tendency was prominent, especially in the first months of the COVID-19 pandemic in Poland, when all children were referred to the infectious diseases departments for evaluation. Compared to the first wave, lengthier hospital stays were more frequent during the 2nd wave of COVID-19 pandemics when a higher infection rate was observed. Therefore patients in better clinical condition were assessed in the primary healthcare settings and not referred to hospitals.

However, certain conditions in children may be associated with a high risk of severe course of the disease, including malignancies, immune deficiencies, chronic pulmonary and heart diseases, genetic and neurological disorders [14]. In our cohort, comorbidities were present in 268 (21%) and were associated with an increased risk of lengthier hospital stay. Available reports stress the high fatality rate in obese adults [15]. In our cohort, no deaths were observed, and obesity was present in eight children only. In our patients, the most frequently noted comorbidities included asthma and cardiovascular diseases.

Children with COVID-19 from our cohort presented respiratory or gastrointestinal tract symptoms, weakness, rash, and seizures more often in a group with LoHS $>$ 7 days. The logistic regression analysis assessed GI symptoms, COVID-related pneumonia, and rash as the risk factors of lengthier hospital stay. Respiratory tract involvement is a typical clinical manifestation in children and adults, while GI symptoms are reported more frequently in the paediatric population [16]. Skin lesions in the course of COVID-19 are often described. Urticarial, polymorphic, and vesicular exanthems were noted in the course of COVID-19. Thus, the most typical skin manifestations associated with COVID-19 are acral ischaemic chilblain-like lesions present mainly on the toes and feet [17].

Analysis of the laboratory parameters revealed differences between the groups, with higher inflammatory indexes in children with LoHS $>$ 7 days. None of the parameters was proven significant in the logistic regression analysis. Typically described laboratory abnormalities in children with COVID-19 include lymphopenia, elevated CRP, PCT, and LDH [18]. Abnormalities in coagulation parameters like elevated fibrinogen and D-dimer are also frequently mentioned [19].

The prevalence of bacterial coinfection was estimated at 7% in patients with COVID-19 and 14% in ICU patients. In available reports, bacterial infections affected 35% of patients despite the site with the most commonly reported pathogen—*M. pneumoniae*. Viral coinfections account for 3% of cases, with RSV and influenza as the most frequent pathogens [20,21]. In our study cohort, bacterial coinfections of the respiratory tract accounted for 0.63% of cases, while viral coinfections of the respiratory tract were noted in 0.85% of the participants. More common coinfections were observed regarding UTI (bacterial—mostly *E. coli*) and GI tract (adeno-, rota-, and noroviruses but also bacterial infections). Only one case of proven *M. pneumoniae* infection and two cases of influenza were reported in our study cohort. Children with additional diagnoses other than coinfection usually required surgical interventions. The additional diagnosis was a risk factor for a more extended hospital stay. Five children with paediatric inflammatory response syndrome temporally related to SARS-CoV-2 (PIMS-TS) were registered in the study due to the positive results of the RT-PCR test for SARS-CoV-2 RNA in nasopharyngeal swabs. Most children with PIMS-TS were reported to a different register and involved in another research [22].

Over a year of the COVID-19 pandemic treatment approach has been modified according to the ongoing observations and studies. Remdesivir was proven effective in shortening the recovery in hospitalized adults with COVID-19 related respiratory tract infection [23]. The drug is recommended in hospitalized patients (12 years and older) with COVID-19 related pneumonia with hypoxia in the initial phase of the disease. Several attempts of the treatment with convalescent plasma were described previously with a varied outcome [24,25]. The management of our cohort was carried according to then-current guidelines [26]. Four children received convalescent plasma, and one was treated with remdesivir. Azithromycin was commonly used in both groups of children, especially during the first wave of pandemics. Although this substance shows *in vitro* activity against SARS-CoV-2 and has immunomodulatory properties, the evidence is unsatisfactory and requires further studies [27]. The use of antibiotics in our study cohort was more extensive than the frequency of the coexisting diagnosis of bacterial infection (252 therapies *vs.* 75 diagnoses). The empirical antibiotic treatment was usually implemented based on a child's more severe clinical condition and elevated inflammatory indexes as traditional markers to support such decision. Since elevated inflammatory indexes are observed in the course of COVID-19 in children even without bacterial coinfection, the decision concerning the requirement for empiric antibacterial is challenging. In most cases, the antibiotic treatment was continued when clinical improvement was observed, and inflammatory indexes decreased even without positive bacterial cultures.

These patients were frequently hospitalized for a period >7 days. Therefore the use of empirical antibiotic therapy was proven a risk factor of lengthier hospital stay. The wide use of antibiotic treatment in patients with COVID-19 not always associated with bacterial coinfections or superinfections was described by other authors reaching 78–93% of hospitalized patients [28]. Therefore, the counselling concerning more reasonable antibiotic use in COVID-19 to reduce antimicrobial prescribing requires strong consideration.

Severe clinical course requiring admission to the ICU is relatively rare, however possible in children. In our study, only three children were hospitalized in the ICU (0.23%), all of them having comorbidities. Data from available reports vary from 1.8 to 6.8%. Moreover, it is not always clear if COVID-19 or comorbidities caused the ICU admission. At the same time, the necessity for ICU admission depends on the comorbidities and complex medical backgrounds of evaluated children [29]. COVID-19 may exacerbate the coexisting chronic disease or be an additional factor for the severe clinical course in a patient. Therefore, the influence of comorbidities and SARS-CoV-2 infection on the clinical outcome may be combined. In our study, the need for oxygen therapy was also observed more frequently in patients with LoHS > 7 days. However, oxygen therapy was not proven significant in the multivariate logistic regression.

Pointing the study's shortcomings, we have to stress that it was performed in hospital settings and was based on a prospectively filled register. Data came from multiple centres. Therefore, not all the details were available. Participation in the survey was voluntary. Not all the care centres designated for care on COVID-19 paediatric patients in Poland participated in the protocol. Thus, not all cases of hospitalized children with COVID-19 were included in the study. Nevertheless, the group is significant, and the percentage of children from specific centres is similar to the overall prevalence in the country.

In conclusion, based on our findings, the clinical course of COVID-19 was mild to moderate in most children. Coinfections were present in 11% of children. Factors increasing the risk of the lengthier hospital stay included pneumonia, gastrointestinal symptoms, or rash in initial clinical evaluation. Other factors were comorbidities, an additional diagnosis other than COVID-19 on admission, and the necessity of the empirical antibiotic treatment.

Disclosure statement

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ORCID

Anna Mania http://orcid.org/0000-0003-0141-2560
Maria Pokorska-Śpiewak http://orcid.org/0000-0001-7783-6904
Magdalena Figlerowicz http://orcid.org/0000-0003-4731-0658
Małgorzata Pawłowska http://orcid.org/0000-0002-6044-0425
Katarzyna Mazur-Melewska http://orcid.org/0000-0003-2695-4649
Kamil Faltin http://orcid.org/0000-0002-5200-7285
Ewa Talarek http://orcid.org/0000-0002-3466-0782
Izabela Zaleska http://orcid.org/0000-0002-3762-3901
Leszek Szenborn http://orcid.org/0000-0001-6574-8229
Artur Sulik http://orcid.org/0000-0002-8391-4793
Barbara Szczepańska http://orcid.org/0000-0002-3334-039X
Ilona Pałyga-Bysiecka http://orcid.org/0000-0002-5781-0886
Adam Sybilski http://orcid.org/0000-0003-2389-277X
Ewa Majda-Stanisławska http://orcid.org/0000-0002-7178-5293
Ernest Kuchar http://orcid.org/0000-0002-7883-2427
Bolesław Kalicki http://orcid.org/0000-0003-1606-5100
Anna Gorczyca http://orcid.org/0000-0002-5087-270X
Magdalena Marczyńska http://orcid.org/0000-0001-5731-6346

References

[1] Murillo-Zamora E, Aguilar-Sollano F, Delgado-Enciso I, et al. Predictors of laboratory-positive COVID-19 in children and teenagers. Public Health. 2020;189:153–157. Dec
[2] Ladhani SN, Amin-Chowdhury Z, Davies HG, et al. COVID-19 in children: analysis of the first pandemic peak in England. Arch Dis Child. 2020;105(12):1180–1185.
[3] Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr. 2020;174(9):882–889.
[4] Pereira MFB, Litvinov N, Farhat SCL, et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. Clinics. 2020;75:e2209.
[5] García-Salido A, de Carlos Vicente JC, Belda Hofheinz S, 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;24(1):666.
[6] Mania A, Mazur-Melewska K, Lubarski K, et al. Wide spectrum of clinical picture of COVID-19 in children – from mild to severe disease. J Infect Public Health. 2021;14(3):374–379.
[7] Borrelli M, Corcione A, Castellano F, et al. Coronavirus disease 2019 in children. Front Pediatr. 2021;9:668484.
[8] Nathan N, Prevost B, Sileo C, et al. The wide spectrum of COVID-19 clinical presentation in children. JCM. 2020;9(9):2950.

[9] Mitsuyama K, Tsuruta K, Takedatsu H, et al. Clinical features and pathogenic mechanisms of gastrointestinal injury in COVID-19. JCM. 2020;9(11):3630.
[10] gov.pl. Koronawirus: informacje i zalecenia. Raport zakażeń koronawirusem (SARS-CoV-2). [cited 2021 Jul 21]. Available from: https://www.gov.pl/web/koronawirus/wykaz-zarazen-koronawirusem-sars-cov-2
[11] Jackowska T, Wrotek A, Jankowski M, et al. Significant COVID-19 burden in polish children. Arch Med Sci. 2020 [cited 2021 Jul 29]. Available from: https://www.archivesofmedicalscience.com/Significant-COVID-19-burden-in-Polish-children,125661,0,2.html
[12] Mehta NS, Mytton OT, Mullins EWS, et al. SARS-CoV-2 (COVID-19): what do we know about children? A systematic review. Clin Infect Dis. 2020;71(9):2469–2479.
[13] Badal S, Thapa Bajgain K, Badal S, et al. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: a systematic review and meta-analysis. J Clin Virol. 2021;135:104715.
[14] Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702.
[15] Oualha M, Bendavid M, Berteloot L, et al. Severe and fatal forms of COVID-19 in children. Arch Pediatr. 2020;27(5):235–238.
[16] Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: deleterious impact on infected patients. J Infect Public Health. 2020;13(12):1833–1839.
[17] Andina D, Belloni-Fortina A, Bodemer C, et al. Skin manifestations of COVID-19 in children: part 1. Clin Exp Dermatol. 2021;46(3):444–450.
[18] Henry BM, Benoit SW, de Oliveira MHS, et al. Laboratory abnormalities in children with mild and severe coronavirus disease 2019 (COVID-19): a pooled analysis and review. Clin Biochem. 2020;81:1–8.
[19] Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93(2):1057–1069.
[20] Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27(1):83–88.
[21] Lansbury L, Lim B, Baskaran V, et al. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266–275.
[22] Okarska-Napierała M, Ludwikowska K, Szenborn L, et al. Pediatric inflammatory multisystem syndrome (PIMS) did occur in Poland during months with low COVID-19 prevalence, preliminary results of a nationwide register. JCM. 2020;9(11):3386.
[23] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 — final report. N Engl J Med. 2020;383(19):1813–1826.
[24] Figlerowicz M, Mania A, Lubarski K, et al. First case of convalescent plasma transfusion in a child with COVID-19-associated severe aplastic anemia. Transfus Apher Sci. 2020;59(5):102866.
[25] Małecki P, Faltin K, Mania A, et al. Effects and safety of convalescent plasma administration in a group of polish pediatric patients with COVID-19: a case series. Life. 2021;11(3):247.
[26] Marczyńska M, Pokorska-Śpiewak M, Talarek E, et al. Management of a child with Covid-19. Przegląd Pediatr. 2020;49:7.
[27] Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, et al. Azithromycin in the treatment of COVID-19: a review. Expert Rev anti Infect Ther. 2021;19(2):147–163.
[28] Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71:2459–2468.
[29] Pathak EB, Salemi JL, Sobers N, et al. COVID-19 in children in the United States: intensive care admissions, estimated total infected, and projected numbers of severe pediatric cases in 2020. J Public Health Manag Pract. 2020;26(4):325–333.