

SARS-COV-2 INFECTION IN CHILDREN AND YOUNG PEOPLE IN BULGARIA – A PROSPECTIVE, SINGLE-CENTER, COHORT STUDY

P. Velikov^{1,2}, N. Kapincheva^{1,2}, I. Trifonova³, V. Velez^{1,2}, M. Popov^{1,4}, I. Ivanov^{1,2}, R. Chipeva^{1,2}, T. Valkov^{1,2}, R. Yordanova^{1,2}, G. Dimitrov⁵, N. Korsun³, T. Tcherveniakova^{1,2}

¹Department of Infectious Diseases, Parasitology and Tropical Medicine, Medical University – Sofia, Bulgaria

²Infectious Disease Hospital “Prof. Ivan Kirov” – Sofia, Bulgaria

³National Laboratory “Influenza and ARD”, Department of Virology, National Centre of Infectious and Parasitic Diseases – Sofia, Bulgaria

⁴Multiprofile Hospital “Sv. Ivan Rilski” – Dupnitsa, Bulgaria

⁵Department of Medical Oncology, Medical University of Sofia, University Hospital “Tsaritsa Yoanna” – Sofia, Bulgaria

Abstract. Compared to other respiratory viruses, the proportion of hospitalizations due to SARS-CoV-2 among children is relatively low. While severe illness is not common among children and young individuals, a particular type of severe condition called multisystem inflammatory syndrome in children (MIS-C) has been reported. The aim of this prospective cohort study, which followed a group of individuals under the age of 19, was to examine the characteristics of patients who had contracted SARS-CoV-2, including their coexisting medical conditions, clinical symptoms, laboratory findings, and outcomes. The study also aimed to investigate the features of children who met the WHO case definition of MIS-C, as well as those who required intensive care. A total of 270 patients were included between March 2020 and December 2021. The eligible criteria were individuals between 0-18 with a confirmed SARS-CoV-2 infection at the Infectious Disease Hospital “Prof. Ivan Kirov” in Sofia, Bulgaria. Nearly 76% of the patients were ≤ 12 years old. In our study, at least one comorbidity was reported in 28.1% of the cases, with obesity being the most common one (8.9%). Less than 5% of children were transferred to an intensive care unit. We observed a statistically significant difference in the age groups, with children between 5 and 12 years old having a higher likelihood of requiring intensive care compared to other age groups. The median values of PaO₂ and SatO₂ were higher among patients admitted to the standard ward, while the values of granulocytes and C-reactive protein were higher among those transferred to the intensive care unit. Additionally, we identified 26 children who met the WHO case definition for MIS-C. Our study data supports the evidence of milder COVID-19 in children and young individuals as compared to adults. Older age groups were associated with higher incidence of both MIS-C and ICU admissions.

Key words: SARS-CoV-2, children, Bulgaria, MIS-C

Corresponding author: Dr. Petar Krasimirov Velikov, Infectious Disease Hospital “Prof. Ivan Kirov”, 17 Acad. Ivan Geshov blvd., 1606 Sofia, Bulgaria, tel.: +359896000721, e-mail: petar.kr.velikov@gmail.com

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INTRODUCTION

The proportion of hospitalizations related to SARS-CoV-2 infections among children and young individuals is only between 0.1% and 1.5% [1-3]. In contrast to other respiratory viruses, children seem to have a lower risk of infection than adults and the vast majority of reported cases in children are mild or asymptomatic with few recorded fatalities attributed to COVID-19 [2, 4-7]. Initial reports showed that only ~0.6% of children with COVID-19 were critically ill [6]. The occurrence of the severe disease has been estimated at 0.2% among children without comorbidities and at 5.1% when comorbidities are present [7].

A severe complication of COVID-19 has been reported in some children with SARS-CoV-2 infection [9, 10]. The condition was first described in May 2020 in UK, with evidence of a hyperinflammatory condition similar to Kawasaki disease [9]. These children presented with respiratory failure, cardiovascular insufficiency, or liver involvement [10-12]. The condition was termed multisystem inflammatory syndrome in children (MIS-C) and adolescents temporarily related to COVID-19. However, data comparing MIS-C due to COVID-19 in children in Bulgaria, as well as data on children requiring intensive care is scarce at most.

The purpose of our study was to describe the characteristics of children and young individuals under the age of 19 who were admitted to the hospital with a confirmed SARS-CoV-2 infection. We collected data prospectively on: comorbidities, clinical presentation, laboratory findings at admission, and outcomes of those who met the WHO case definition of MIS-C. Thereafter, we compared the cases with MIS-C patients diagnosed with COVID-19, as well as children who required intensive care compared to those who did not.

MATERIALS AND METHODS

Study design, setting, and patients

This study was conducted at the Infectious Disease Hospital “Prof. Ivan Kirov” in Sofia, Bulgaria and involved patients under 19 years of age who had a confirmed SARS-CoV-2 infection. Data was collected on 270 patients between March 8, 2020, and December 1, 2021, who tested positive for SARS-CoV-2 by polymerase chain reaction and/or serology tests. Patients were admitted to either the standard hospital ward or the pediatric intensive care unit (PICU) based on the clinical team’s discretion, and we also included patients who tested positive while already admitted for other clinical reasons. The primary objective was

to compare patients admitted and discharged from the standard ward to those eventually transferred to the intensive care ward, and our secondary objective was to compare patients meeting the WHO criteria for MIS-C with those diagnosed with COVID-19. Additionally, sequencing of nasopharyngeal samples collected throughout the study was conducted. Disease severity was determined based on the supplementary oxygen requirements.

Data sources and collection

Information regarding demographics, comorbidities, clinical presentation at admission, laboratory findings, treatments, and outcomes was gathered and recorded for each patient. The data was collected up to 28 days after discharge or transfer to an intensive care ward and was verified using the Bulgarian National Health Insurance Register. Prior to enrollment, written consent was obtained from the patient’s parent or guardian, and all information was anonymized to protect privacy.

Extraction and real-time PCR

Automated systems were used for nucleic acid extraction: ExiPrep DX viral DNA/RNA (Bioneer, Korea). Samples were tested with 96 wells, CFX96 Touch PCR Real-Time Detection System, Bio-Rad. A commercial GeneFinder™ COVID-19 Plus RealAmp kit (OSANG Healthcare Co., Ltd.) was used to conduct real-time PCR to detect SARS-CoV-2. The result of the real-time RT-PCR reaction was considered positive at Ct ≤ 38.

Sequencing

The Whole Genome Next Generation (INGS) method was used to perform sequencing analysis of 30 patient samples positive for SARS-CoV-2. Only patient samples with an appropriate Ct < 30 were selected. The sequencing analysis was carried out by the National Center for Infectious and Parasitic Diseases in Bulgaria. The ARTIC v3 method was used with tail amplicon reagents and an Illumina MiSeq v2 reagent kit with 500 cycles (Illumina). SARS-CoV-2 sequences were deposited in the GISAID databases.

Variables

The case report form was agnostic to the age of the patient and existing comorbidity variables were not tailored to the pediatric population. Other details on each variable can be found in the relevant table or figure.

Criteria for diagnosis of MIS-C

We applied the WHO case definition for MIS-C to identify children who met the criteria for the syndrome in this dataset [9].

Bias and missing data

This study was conducted in a single hospital that specializes in infectious diseases. Patients requiring intensive care were transferred to other hospitals as the hospital did not have its own intensive ward. Limited staff resources during high COVID-19 activity sometimes prevented the enrollment of patients, so the study could not report on all patients. The pandemic also disrupted routine care and research activities, which limited data collection and verification, especially during the peak of the outbreak. As a result, complete data was not available for all variables, and the denominators differ between analyses. The study was initially planned for one year but was extended by 8 months due to the insufficient number of enrolled patients.

Statistical analysis

Statistical analysis was performed by an independent statistician using IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows. SPSS Inc., Chicago, IL, USA) and MedCalc Version 19.6.3. Findings with $p < 0.05$ were considered statistically significant. The following methods were used: test of Kolmogorov-Smirnov and Shapiro-Wilk, independent samples t-test of Student, two-independent samples test of Mann-Whitney-U, Fisher's exact test, Fisher-Freeman-Halton exact test and test χ^2 .

RESULTS

From 8 March 2020 to 1 December 2021, a total of 270 patients with a confirmed SARS-CoV-2 infection were enrolled. All of the enrolled patients were

hospitalized at the Infectious Disease Hospital "Prof. Ivan Kirov" in Sofia, Bulgaria. All patients were either permanent or temporary residents of Bulgaria at the time of admission. The median age of the patients was 6.48 ± 6.04 years, with an age range from 20 days to 18 years. Of the enrolled patients, 145 (53.8%) were male and 125 (46.3%) were female. Of note, 206/270 (76%) were 12 years old or younger. All patients had a positive confirmatory PCR and/or serology test before enrollment. The highest enrollment periods were November 2020, March 2021, September, and October 2021, which corresponds to the overall data of hospitalized patients in Bulgaria at that time (Fig. 1).

Comorbidities

In 28.1% (76/270) of cases, at least one comorbidity was recorded. Obesity (8.9%, 24/270), asthma (6.7%, 18/270), neurological (3.3%, 9/270) and neurodegenerative disease (3.3%, 9/270) were the most common comorbidities (Table 1). Comorbidities that affected less than 2% of the cohort were grouped under "Others." These included respiratory (3, 1.1%), immune deficiency (4, 1.5%), hematologic (4, 1.5%) diseases, diabetes and other endocrine disorders (4, 1.5%), and genetic disorders (2, 0.7%).

Symptoms

The most common presenting symptoms and signs included: fever (228/270, 84.4%), pharyngitis (218/270, 80.7%), cough (187/270, 69.3%) and fatigue (170/270, 63%) (Fig. 2).

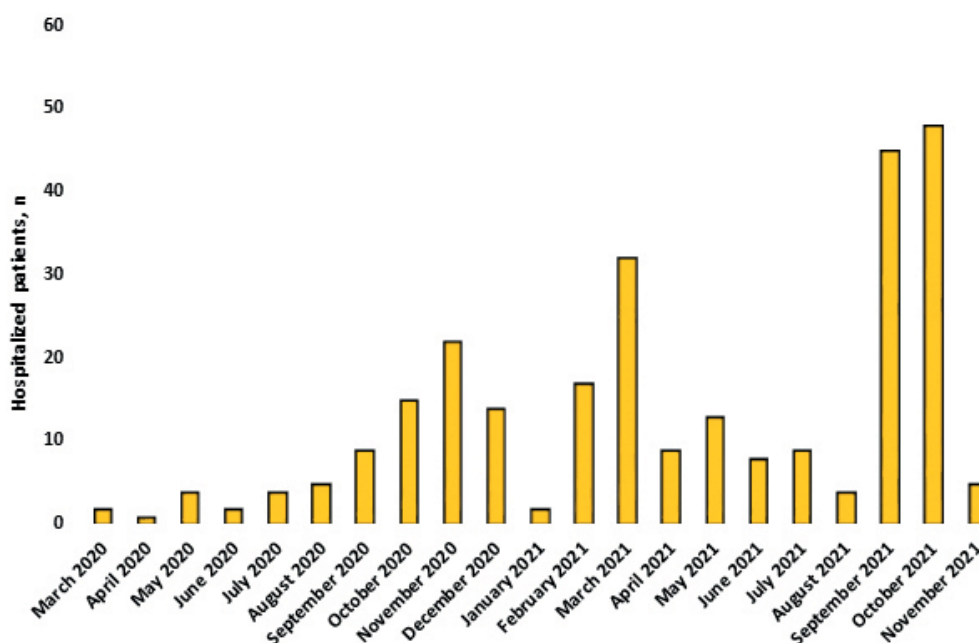


Fig. 1. Enrolled patients under 19 years with confirmed SARS-CoV-2 infection over time

Table 1. Demographic data for all patients under 19 years with laboratory confirmation of SARS-CoV-2 infection

Variable	Patients (n = 270, %)
Age group	
< 1 year	66 (24.4)
1-4 years	76 (28.1)
5-12 years	64 (23.7)
13-18 years	64 (23.7)
Gender	
Male	145 (53.7)
Female	125 (46.3)
PCR Positive	250 (92.6)
Anti-SARS-CoV-2 IgM/IgG Positive	24 (8.9)
SARS-CoV-2 Variant	
B.1.1.7 (Alpha)	17 (6.3)
B.1.617.2 (Delta)	12 (4.4)
AY.4.2	1 (0.4)
Unknown	240 (88.9)
Any comorbidity	
No	194 (71.9)
Yes	76 (28.1)
Obesity	
No	246 (91.1)
Yes	24 (8.9)
Asthma	
No	252 (93.3)
Yes	18 (6.7)
Neurological	
No	261 (96.7)
Yes	9 (3.3)
Neurodegenerative	
No	261 (96.7)
Yes	9 (3.3)
Low birth weight	
No	262 (97)
Yes	8 (3)
Rheumatological	
No	263 (97.4)
Yes	7 (2.6)
Cardiological	
No	263 (97.4)
Yes	7 (2.6)
Others	
No	253 (93.7)
Yes	17 (6.3)

Children requiring intensive care

In this study of 270 pediatric patients with confirmed SARS-CoV-2 infection, only a small percentage (4.8%) required transfer to an intensive care unit. Those who were treated in an intensive ward were more likely to have severe disease and cardiologic comorbidities, however the presence of any comorbidity as a whole did not reach statistical significance. Children between 5 and 12 years old were also found to have a higher chance of requiring intensive care. Patients in the intensive ward cohort also had a higher frequency of certain symptoms such as vomiting, abdominal pain, and rash, while those in the standard ward cohort had more frequent radiological findings in chest X-ray. Patients in the intensive ward were more likely to receive intravenous corticosteroids, anticoagulants, and supplementary oxygen.

Patients treated in a standard or intensive care ward did not differ significantly in terms of age and hospitalization duration; however, some blood tests indicated statistical significance at admission (Table 3). Median values of partial pressure of oxygen (PaO₂) and blood-oxygen saturation (SatO₂) were higher for patients admitted and treated in the standard ward, while the values of leukocytes, granulocytes, and C-reactive protein (CRP) at the time of admission were higher in those transferred to an intensive ward.

We performed a sub-group analysis for the cohorts excluding any children who met the criteria for MIS-C, however, due to the low number of participants in the new cohort, statistical significance was not reached and the results were not presented.

Analysis of the sequenced samples

A representative sample of 30 patient samples between the ages of 2 months and 18 years underwent sequencing analysis in this study, revealing two SARS-CoV-2 variants: alpha (56.6%) and delta (43.3%). B.1.1.7 was predominant from February to April 2021, while B.1.617.2 dominated from June to September 2021. One patient in September was also found to have a sublineage variant of delta AY.4.2. A statistically significant difference was found between the mean length of hospital stay for patients with the delta variant versus the alpha variant ($p < 0.001$). The average hospital stay was 6.47 ± 2.7 days for patients with B.1.1.7, compared to 3.15 ± 1.06 days for those with B.1.617.2 or AY.4.2. Patients with the delta variant had oxygen saturation levels close to normal at $94.5 \pm 2.8\%$, while those with the alpha variant had an average saturation level of $89 \pm 23.1\%$. However, there was no statistically significant difference in oxygen saturation rates between patients with the delta and alpha variants.

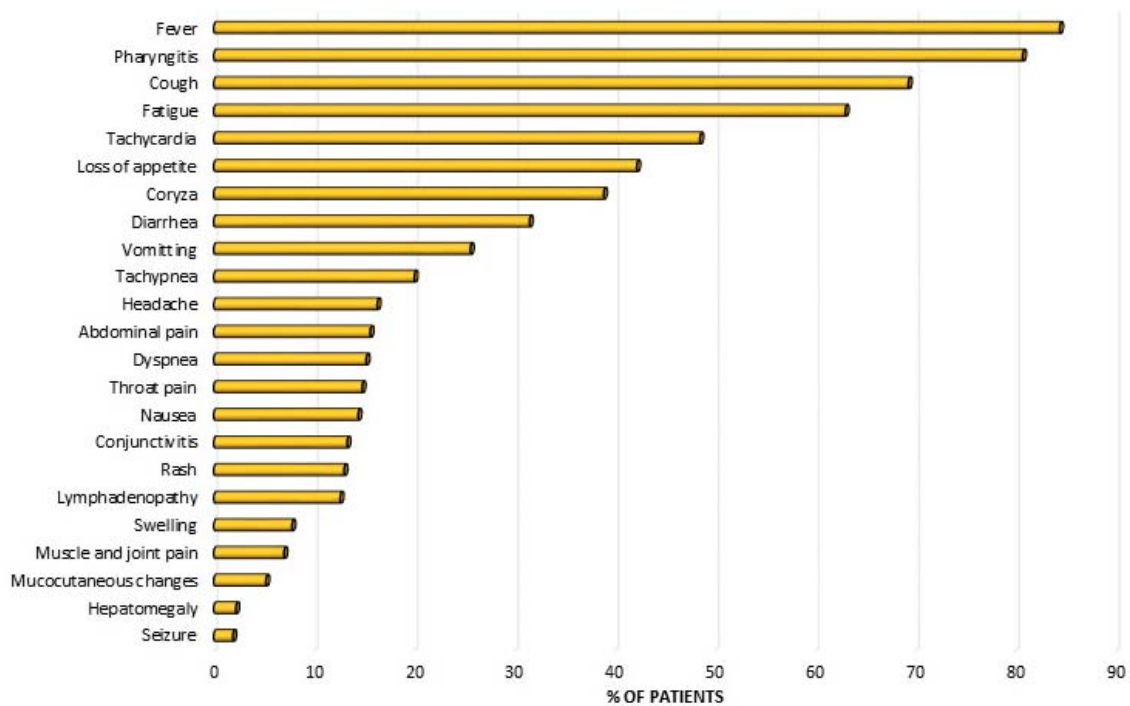


Fig. 2. Most common presenting symptoms and signs in children hospitalized with SARS-CoV-2 infection

Table 2. Comparative analysis of patients in standard ward versus those transferred to a pediatric intensive care unit according to gender, prior antibiotic treatment, disease severity, age group, comorbidities, symptoms, radiological findings in chest X-ray and applied treatment

Variable	Standard ward		Intensive ward		P
	n	%	n	%	
Gender					0.393
Male	136	52.9	9	69.2	
Female	121	47.1	4	30.8	
Antibiotic usage prior to admission	85	33.1	4	30.8	1.000
Disease severity					< 0.001
Severe disease	25	9.7	10	76.9	
Mild to moderate disease	232	90.3	3	23.1	
Age (years)					0.011
< 1	63	24.5	3	23.1	0.909
1-4	75	29.2	1	7.7	0.093
5-12	56	21.8	8	61.5	0.001
13-18	63	24.5	1	7.7	0.165
Comorbidity	Standard ward		Intensive ward		P
	n	%	n	%	
Presence of at least 1 condition	70	27.2	6	46.2	0.202
Cardiologic	4	1.6	3	23.1	0.003
Symptom	Standard ward		Intensive ward		P
	n	%	n	%	
Cough	182	70.8	5	38.5	0.026
Vomiting	62	24.1	7	53.8	0.024
Abdominal pain	35	13.6	7	53.8	0.001

Continuation of table 2

Rash	30	11.7	5	38.5	0.016
Swelling of extremities or eyelids	16	6.2	5	38.5	0.002
Mucocutaneous inflammatory signs	11	4.3	3	23.1	0.023
Conjunctivitis	29	11.3	7	53.8	< 0.001
Lymphadenopathy	27	10.5	7	53.8	< 0.001
Tachypnea	47	18.3	7	53.8	0.006
Radiological findings in chest X-ray	Standard ward		Intensive ward		P
	n	%	n	%	
Presence of any changes	142	55.3	3	23.1	0.042
Applied treatment	Standard ward		Intensive ward		P
	n	%	n	%	
Intravenous Corticosteroids (any)	34	13.2	10	76.9	< 0.001
Anticoagulant (any)	38	14.8	5	38.5	0.039
Supplementary oxygen	25	9.7	10	76.9	< 0.001

Table 3. Comparative analysis of patients treated in a standard ward versus those transferred to a pediatric intensive care unit according to age, hospitalization duration and laboratory investigations

Variable	Standard ward			Intensive ward			P
	n	$\bar{X}$	SD	n	$\bar{X}$	SD	
Age (years)	257	6.47	6.10	13	6.68	5.02	0.948
Hospitalization duration (days)	257	6.90	3.50	13	5.23	2.68	0.067
PaO ₂	245	69.50	12.05	12	56.88	15.51	0.001
SatO ₂	246	93.27	3.90	12	86.88	10.03	0.010
Leukocytes	257	7.24	4.04	13	10.40	5.31	0.011
Lymphocytes	257	2.65	1.87	13	2.12	2.01	0.128
Monocytes	257	0.61	0.44	13	0.83	0.83	0.755
Granulocytes	257	3.98	3.32	13	7.48	3.91	0.001
Hemoglobin	257	126.74	16.88	13	122.69	15.18	0.396
Thrombocytes	257	262.96	99.94	13	289.69	176.49	0.945
CRP	257	29.39	46.03	13	99.49	80.87	< 0.001

Outcome

One patient (0.4%) died during the hospitalization. This patient was a 16-year-old female who had a severe pre-existing comorbidity of post-infectious cardiomyopathy. Of the total number of patients, 4.8% (13/270) required transfer to the PICU, while the vast majority – 94.8% (256/270), were discharged after treatment in the standard ward. The children who were transferred to the PICU were closely monitored through the national health insurance system, and their survival was confirmed 28 days after transfer.

Children fulfilling the criteria for MIS-C

Of the 270 children included in the study, 26 (9.6%) met the World Health Organization (WHO) criteria for Multisystem Inflammatory Syndrome in Children (MIS-C). The first case was identified in mid-April 2020. Among the MIS-C patients, 25 out of 26 had positive serology for anti-SARS-CoV-2 IgM and/or IgG, and 10 out of 26 had a positive PCR test at admission.

Patients diagnosed with MIS-C or COVID-19 in the cohort had no significant differences in terms of gender and antibiotic treatment prior to hospitalization, but they

differed significantly in disease severity (Table 4). The MIS-C cohort had a larger percentage of patients with severe disease, while the COVID-19 cohort had mostly mild to moderate disease. The MIS-C diagnosis was significantly more relevant in the 5-12 years age group, while COVID-19 was diagnosed more often in the 13-18 years age group. MIS-C patients were significantly

more often obese, however other statistical differences were not noted in terms of comorbidities. MIS-C patients had more symptoms such as fever, vomiting, diarrhea, abdominal pain, and tachycardia, while cough was more frequent in patients with COVID-19. There were no statistically significant differences in radiological findings of the chest X-ray or specific changes between

Table 4. Comparative analysis of patients diagnosed with MIS-C and COVID-19 according to gender, prior antibiotic treatment, disease severity, age group, comorbidities, symptoms, radiological findings of chest X-ray and applied treatment

Variable	MIS-C		COVID-19		P
	n	%	n	%	
Gender					0.686
Male	15	57.7	130	53.3	
Female	11	42.3	114	46.7	
Antibiotic use prior to admission	8	30.8	81	33.2	1.000
Disease severity					< 0.001
Severe disease	14	53.8	21	8.6	
Mild to moderate disease	12	46.2	223	91.4	
Age (years)					< 0.001
< 1	3	11.5	63	25.8	0.107
1-4	5	19.2	71	29.1	0.287
5-12	16	61.5	48	19.7	< 0.001
13-18	2	7.7	62	25.4	0.044
Comorbidity					P
	n	%	n	%	
Presence of at least 1 condition	11	42.3	65	26.6	0.109
Obesity	8	30.8	16	6.6	0.001
Symptom					P
	n	%	n	%	
Fever	26	100.0	202	82.8	0.019
Cough	9	34.6	178	73.0	< 0.001
Vomiting	13	50.0	56	23.0	0.008
Diarrhea	13	50.0	72	29.5	0.044
Abdominal pain	10	38.5	32	13.1	0.002
Nausea	10	38.5	29	11.9	0.001
Rash	15	57.7	20	8.2	<0.001
Swelling of extremities or eyelids	11	42.3	10	4.1	< 0.001
Mucocutaneous inflammatory signs	9	34.6	5	2.0	< 0.001
Conjunctivitis	17	65.4	19	7.8	< 0.001
Lymphadenopathy	11	42.3	23	9.4	< 0.001
Tachycardia	21	80.8	110	45.1	0.001
Hepatomegaly	4	15.4	2	0.8	0.001
Radiological findings in chest X-ray					P
	n	%	n	%	
Presence of any changes	11	42.3	134	54.9	0.301
Applied treatment					P
	n	%	n	%	
Antibiotic (any)	20	76.9	128	52.5	0.022
Intravenous Corticosteroids (any)	14	53.8	30	12.3	< 0.001
Anticoagulant (any)	11	42.3	32	13.1	0.001
Supplementary oxygen	14	53.8	21	8.6	< 0.001

the two groups. MIS-C patients were more likely to be treated with antibiotics, corticosteroids, anticoagulants, and supplementary oxygen than COVID-19 patients.

The comparative analysis of patients diagnosed with MIS-C and COVID-19 (Table 5) indicated that there was a statistically insignificant difference between different age groups and hospitalization duration; however, there was statistical significance in laboratory investigations. The median values of partial pressure of oxygen, lymphocytes, and hemoglobin were higher in patients with COVID-19, while total leukocytes, granulocytes, and CRP were higher in patients with MIS-C.

DISCUSSION

The COVID-19 pandemic has not only caused worldwide economic damage, but has also exposed the existing gaps in the health systems of many countries, with hospital units exceeding capacity due to the number of patients in need of treatment. To better understand the situation during the initial phase of the pandemic, in-depth studies are necessary. Our study focused on the first 18 months of the pandemic, during which 270 cases of children and adolescents with COVID-19 and/or MIS-C were admitted to the "Prof. Ivan Kirov" Infectious Disease Hospital in Sofia. Another study found that the presence of comorbidities in children and adolescents increases the risk of severe COVID-19, ICU admission, and death. In our study, 28.1% (76/270) of children and adolescents had at least one comorbidity, however only the presence of a cardiologic comorbidity for increased risk of ICU admission and obesity for MIS-C were

relevant for our cohort. Other studies in larger age groups have reported a higher percentage of patients with comorbidities [9, 17].

Recent studies have suggested that the delta variant of SARS-CoV-2 may be associated with a more severe course of illness compared to the alpha variant [18]. Our study does not support this finding, as we observed lower measured saturation levels and longer hospital stays in children with the alpha variant compared to the delta variant. It is worth noting, however, that the number of patients infected with the delta variant in our study population was relatively low. Therefore, further research is needed to fully understand the impact of the delta variant on pediatric populations [19].

The most commonly reported presenting symptoms and signs were: fever, pharyngitis, cough and fatigue which corresponds to known information about SARS-CoV-2 infections [20].

In Bulgaria, the inappropriate use of antibiotics for viral infections is a significant concern [13, 26]. However, our study shows that the use of antibiotics before hospital admission does not appear to prevent clinical deterioration that can lead to PICU admission or the development of MIS-C.

Among the 270 children included in our study, a small percentage (4.8%, 13/270) required transfer to a pediatric intensive care unit (PICU). We observed that children between the ages of 5 and 12 years were more likely to require PICU care, but we did not observe any association with gender. Notably, the need for intensive care was lower in our study compared to

Table 5. Comparative analysis of patients with MIS-C and COVID-19 according to age, hospitalization duration and laboratory findings

Variable	MIS-C			COVID-19			P
	n	$\bar{X}$	SD	n	$\bar{X}$	SD	
Age (years)	26	6.75	4.47	244	6.45	6.19	0.387
Hospitalization duration (days)	26	6.31	3.32	244	6.88	3.50	0.383
PaO ₂	25	62.57	14.71	232	69.59	12.06	0.007
SatO ₂	25	90.22	7.92	233	93.27	3.93	0.063
Leukocytes	26	10.74	5.48	244	7.03	3.83	< 0.001
Lymphocytes	26	2.24	2.12	244	2.66	1.85	0.035
Monocytes	26	0.65	0.57	244	0.62	0.46	0.935
Granulocytes	26	7.86	4.18	244	3.75	3.10	< 0.001
Hemoglobin	26	117.62	12.14	244	127.50	16.96	0.002
Thrombocytes	26	253.50	158.47	244	265.40	97.47	0.145
CRP	26	119.18	90.02	244	23.55	32.97	< 0.001

previous studies [21]. It is worth noting that patients with severe disease at presentation are more likely to require intensive care immediately and therefore may not be admitted to our institution. Nonetheless, patients who required PICU care had severe disease more often compared to those treated only in a standard ward. Interestingly, radiological findings of chest X-ray were less frequent in patients requiring intensive care, which warrants further investigation as a potential predictor for severe disease. Our study confirmed laboratory findings at presentation that can serve as predictors for severe disease, including lower partial pressure of oxygen and blood-oxygen saturation, as well as the presence of leukocytosis with granulocytosis.

The incidence of all-cause mortality was remarkably low, at less than 1%, in our study population. The one patient who died was the case of a 16-year-old female patient with pre-existing cardiomyopathy who did not receive care in a PICU.

About 10% of children met the WHO criteria for MIS-C [10]. MIS-C cases were most common in the 5-12 year group, followed by the 1-5 year group, consistent with other studies that have also observed a higher prevalence of MIS-C in these age ranges. The first patient was identified in mid-April 2020 [22]. Moreover, our findings indicate that MIS-C cases were more likely to require admission to a pediatric intensive care unit, reflecting the more severe nature of the disease. At the time of admission, these patients presented with a range of symptoms that are typical of MIS-C, such as vomiting, diarrhea, abdominal pain, nausea, rash, swelling of extremities or eyelids, mucocutaneous inflammatory signs, conjunctivitis, and lymphadenopathy. Interestingly, we observed a higher incidence of tachycardia and hepatomegaly in our MIS-C patients, which is consistent with some previous studies [7, 12]. Our study found that patients with MIS-C were more likely to be treated with antibiotics despite the lack of laboratory data suggestive of a bacterial infection. This finding raises concerns about antibiotic misuse in Bulgaria. We also observed several laboratory findings that served as predictors for MIS-C, including lower partial pressure of oxygen, lymphocyte count, and hemoglobin levels at admission. In addition, patients with MIS-C were more likely to present with leukocytosis, granulocytosis, and higher CRP, which is consistent with previous reports [23-25].

This study does have limitations, including being conducted in a single center susceptible to selection bias and missing data due to incomplete investigations or the use of a standard case recording form. The incidence of MIS-C may also be underestimated due to

limitations of data in a single center, and the study does not include children who were not admitted to the hospital.

CONCLUSION

The study found that SARS-CoV-2 infections in children and adolescents are less severe than those in adults, and that admission to critical care and MIS-C was linked to older age. Antibiotic misuse for viral illnesses in Bulgarian children is a concerning issue. MIS-C patients are more likely to have mucocutaneous inflammatory signs and to be treated with corticosteroids and anticoagulants. The study calls for additional research into clinical and laboratory findings in children with COVID-19 and MIS-C, as well as long-term survival and the diagnosis of post-COVID-19 syndrome. However, the study's limitations, including selection bias and incomplete data, should be considered when interpreting the results.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Supplementary materials are available on OSF:
<https://osf.io/nj8m9>

Disclosure Summary: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

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Contributions and transparency

PV performed the concept and methodology planning, and initial analysis and wrote the original draft. PV and NK were involved in data collection and curation, and verifying the underlying data. PV and IT edited the manuscript. IT and NK performed all NPS testing. PV, NK, IT, RC, II, MP, TV, VV, RY, GD, NC and TT were involved in reviewing and finalizing the manuscript. All authors had full access to all data in the study and accept responsibility for the decision to submit the publication. The authors affirm that the manu-

script is an accurate, honest, and transparent account of the reported study, that important aspects have not been omitted, and that any discrepancies from the originally planned study have been explained.

Ethical considerations

The study was performed in accordance with the ethical standards of the institutional ethics committee, as well as with the Helsinki Declaration of the World Medical Association.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13):1239-1242. doi: 10.1001/jama.2020.2648.
2. European Centre for Disease Prevention and Control. Rapid risk assessment: Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. ECDC. 2020. Retrieved from <https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment>. [Last accessed January 25 2023]
3. American Academy of Pediatrics. Children and COVID-19: State data report. Version: 5/19/22 2022 26.05.2022. Retrieved from <https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/>. [Last accessed January 25 2023]
4. Yilmaz D, Ekemen Y, Karbuz A et al. Multisystem inflammatory syndrome in children associated with COVID-19 in 101 cases from Turkey (Turk-MISC study). *J Paediatr Child Health*. 2022;58(6):1069-1078. doi: 10.1111/jpc.15913.
5. Viner RM, Mytton OT, Bonell C. et al. Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis. *medRxiv*. 2020. <https://www.medrxiv.org/content/10.1101/2020.05.20.20108126v1>
6. Götzinger F, Santiago-García B, Noguera-Julián A et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661, doi: 10.1016/S2352-4642(20)30177-2.
7. Bhuiyan MU, Stiboy E, Hassan MZ et al. Epidemiology of COVID-19 infection in young children under five years: A systematic review and meta-analysis. *Vaccine*. 2021;39(4):667-77.
8. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020. 395:1607-8, doi:10.1016/S0140-6736(20)31094-1
9. 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 <http://dx.doi.org/10.1136/bmj.m3249>
10. World Health Organization. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020. Retrieved from <https://www.who.int/news-room/commentaries/detail/multisysteminflammatory-syndrome-in-children-and-adolescents-with-covid-19>. [Last accessed January 25 2023]
11. Yeh MJ, Bergersen L, Gauvreau K et al. COVID-19 international experience in paediatric patients with congenital heart disease. *Heart*. 2022 Dec 12. [heartjnl-2022-321208](https://doi.org/10.1136/heartjnl-2022-321208), doi: 10.1136/heartjnl-2022-321208.
12. Lazova S, Alexandrova T, Gorelyova-Stefanova N et al. Liver Involvement in Children with COVID-19 and Multisystem Inflammatory Syndrome: A Single-Center Bulgarian Observational Study. *Microorganisms*. 2021 Sep 15. 9(9):1958, doi: 10.3390/microorganisms9091958.
13. Machowska A, Stålsby Lundborg C. Drivers of Irrational Use of Antibiotics in Europe. *Int J Environ Res Public Health*. 2018; 23;16(1):27, doi: 10.3390/ijerph16010027,
14. Ministry of Healthcare of the Republic of Bulgaria. Public data on COVID-19 according to sex, age, date and regions. Retrieved from <https://data.egov.bg/data/view/492e8186-0d00-43fb-8f5e-f2b0b183b64f>. [Last accessed January 25 2023].
15. Lupu D, Tiganasu R. COVID-19 and the efficiency of health systems in Europe 2022. *Health Economics Review*, 12(1), 1-15.
16. Mahendradhata Y, Andayani NLP E, Hasri ET et al. The capacity of the Indonesian healthcare system to respond to COVID-19. *Frontiers in public health*, 2021;9, 649819.
17. Harwood R, Yan H, Da Camara NT et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: A systematic review and individual patient meta-analysis. *E Clin Med*, 2022;44, 101287.
18. Twohig KA, Nyberg T, Zaidi A et al. COVID-19 Genomics UK (COG-UK) consortium. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22(1):35-42. doi: 10.1016/S1473-3099(21)00475-8.
19. Loconsole D, Centrone F, Morcavallo C et al. Changing Features of COVID-19: Characteristics of Infections with the SARS-CoV-2 Delta (B.1.617.2) and Alpha (B.1.1.7) Variants in Southern Italy. *Vaccines (Basel)*. 2021;9(11):1354. doi: 10.3390/vaccines9111354
20. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. *J Prev Med Hyg*. 2020;61(3):E304-E312. doi: 10.15167/2421-4248/jpmh2020.61.3.1530.
21. López-Medina E, Camacho-Moreno G, Brizuela ME et al. Factors Associated With Hospitalization or Intensive Care Admission in Children With COVID-19 in Latin America. *Front Pediatr*. 2022 Apr 14;10:868297. doi: 10.3389/fped.2022.868297.
22. Payne AB, Gilani Z, Godfred-Cato S et al. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2. *JAMA Netw Open*. 2021 Jun 1;4(6):e2116420. doi: 10.1001/jamanetworkopen.2021.16420.
23. Riphagen S, Gomez X, Gonzalez-Martinez C et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-8. [https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)
24. Whittaker E, Bamford A, Kenny J et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-69. <https://doi.org/10.1001/jama.2020.10369>
25. Giacalone M, Scheier E, Shavit I. Multisystem inflammatory syndrome in children (MIS-C): a mini-review. *Int J Emerg Med*. 2021 Sep 10;14(1):50. doi: 10.1186/s12245-021-00373-6.
26. Zaykova K, Nikolova S, Pancheva R et al. A survey of knowledge, attitudes and use of antibiotics among Bulgarian population. *Biotechnology & Biotechnological Equipment*. 2022. 36:1, 933-941, DOI: 10.1080/13102818.2022.2145237