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ORIGINAL ARTICLE

COVID-19 in a Subset of Hospitalized Children in Israel

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Background. Most pediatric coronavirus disease 2019 (COVID-19) is mild. We assessed nationally severe COVID-19, including pediatric inflammatory multisystem syndrome (PIMS), in hospitalized children.

Methods. An ongoing, prospective, national surveillance was conducted from March 2020 through March 2021, at 20 hospitals treating children <18 years across Israel (~75% of Israeli hospitals).

Results. Overall, 1007 cases (439 outpatients and 568 hospitalized) identified represent 0.35% of pediatric COVID-19 nationwide (n = 291 628). Of hospitalized cases, 464 (82%), 48 (8%), and 56 (10%) had mild, moderate/severe, and PIMS disease, respectively. The mean ± SD age was 5.6 ± 6.4 years. In mild, moderate/severe, and PIMS disease, 55%, 23%, and 4% of patients were <1 year old, respectively. Obesity was reported in 1%, 4%, and 13% of patients, respectively ($P < .001$). The most common symptom was fever in 67%, 60%, and 100%, respectively, whereas respiratory symptoms were documented in 33%, 41%, and 38% of patients, respectively. Lymphopenia was recorded in 25%, 60%, and 86% of cases, respectively. PIMS diagnosis was mainly serology-based (in 59%). Gastrointestinal symptoms, cardiovascular involvement, rash, and conjunctivitis were noted in 82%, 61%, 57%, and 34% of PIMS episodes, respectively. Elevated C-reactive protein (100%), ferritin, troponin, D-dimer, low albumin, and thrombocytopenia were common in PIMS. Echocardiography revealed pathological findings in 33% of patients. PIMS mainstay treatment included corticosteroids (77%) and intravenous immunoglobulin (53%). No mortality was recorded.

Conclusions. At a national level, pediatric COVID-19 is mild, even in hospitalized cases, with only a third presenting with respiratory involvement. PIMS is rare, but necessitates a high index of suspicion, and with suitable treatment prognosis is favorable.

Key words. children; coronavirus disease 2019 (COVID-19); multisystem inflammatory syndrome in children (MIS-C); pediatric inflammatory multisystem syndrome (PIMS); SARS-CoV-2.

In February 2020, the World Health Organization (WHO) designated a new strain of betacoronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) [1–4]. SARS-CoV-2 soon spread across the globe, with ~130 million people infected and more than 2 800 000 deaths, as of the end of March 2021 [1].

Epidemiological studies showed that childhood morbidity rates are low compared to their relative proportion in the population [2–7]. Children mainly acquire SARS-CoV-2 infection from their family members [2, 3].

Most pediatric patients have asymptomatic, mild, or moderate disease [5]. Moreover, the literature to date indicates that childhood morbidity tends to be milder compared to adults [2, 3, 8, 9]. COVID-19 can present with gastrointestinal symptoms only [5], and in young infants, it can manifest as nonspecific symptoms, such as fever and decreased appetite [10, 11].

Despite their relative rarity, severe cases, need of pediatric intensive care unit (PICU) admission, and mortality have also been reported in children [4, 12]. Since April 2020, a few

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studies have described a new febrile pediatric entity involving systemic hyper-inflammation, multi-organ involvement, abdominal pain, sometimes features reminiscent of Kawasaki-like disease, and cardiogenic shock with severe myocardial dysfunction, likely to be caused by a viral infection directly or as a postinfectious phenomenon, designated as pediatric inflammatory multisystem syndrome (PIMS) or multisystem inflammatory syndrome in children (MIS-C) [13–17].

In February 2020, the first COVID-19 patient was diagnosed in Israel. A short while thereafter, in March-May 2020, Israel took drastic social distancing and quarantine (lockdown) measures, which resulted in relatively low morbidity and mortality rates [18, 19]. These measures included closing nearly all flights to Israel in early March, closing schools and universities on March 12, followed by a national lockdown with strict social distancing policy starting March 19. These measures led to a decline in SARS-CoV-2 morbidity and as a result, part of these measures were discontinued in early May. In September 18, a second lockdown was declared, using the same measures as the first lockdown. It was relieved after a month, on October 18. A third lockdown was declared in late December 2020, and it was relieved in early February 2021. Notably, on December 19, 2020, Israel started an adult coronavirus vaccine, with rapid uptake, reaching 60% vaccination rate (2 doses) in adults by late March 2021.

This work aims to describe COVID-19 characteristics in hospitalized Israeli children nationwide, thus representing the most severe pediatric COVID-19 morbidity. This information is critical to enable better appreciation of the impact of various control measures and to prepare for another possible morbidity peaks.

METHODS

This ongoing, prospective surveillance, conducted at 20 hospitals treating children across Israel, was initiated on March 11, 2020. In the current report, we present data spanning between the study initiation date and March 17, 2020.

The Soroka University Medical Center served as the data coordinating center and obtained the hospital Ethics Committee approval with a waiver of informed consent for both local and collaborative data collection. Individual institutions contributing data obtained local ethics committee approval to collect and share de-identified data.

Setting and Study Population

We assessed COVID-19 morbidity in children <18 years treated in the in-hospital setting. We approached all medical centers treating inpatient children in Israel, and 20 out of 26 centers agreed to collaborate and submit weekly demographic and clinical data reports. We compared our number of hospitalizations to the number of pediatric hospitalizations reported by the Israeli Ministry of Health (IMOH) [19], and estimate that our surveillance allowed us a capture of ~60% of all childhood COVID-19 treated at pediatric emergency rooms (ER) or hospitalized.

The geographic distribution of the 20 medical centers reporting COVID-19 pediatric cases included all 6 Israel districts, allowing us to conduct a population-based study. Furthermore, these 20 hospitals included secondary- and tertiary-care hospitals in all areas of Israel.

Currently, the Jewish population accounts for ~80% of the total population in Israel (total population of ~9 000 000 people), with ~20% of the population being Arab Muslims [20, 21]. Notably, within the Jewish population, approximately 15% identify themselves as ultra-orthodox Jews, often living in closed communities [21, 22].

Case Definitions

COVID-19 was defined by a positive polymerase chain reaction (PCR) testing for SARS-CoV-2 of samples obtained from the oral cavity and/or the nasopharynx of a child. Additionally, we included PIMS cases with a positive serologic (or PCR) diagnosis of SARS-CoV-2 infection, performed as approved by the IMOH.

We defined 3 levels of disease severity: (1) mild disease: ranging from asymptomatic infection to symptoms such as fever and/or respiratory symptoms with no dyspnea. These children were hospitalized for various reasons, including social problems, observation, and ruling out serious bacterial infection; (2) moderate or severe disease: including fever, signs of respiratory distress with mild-moderate dyspnea, and children with hemodynamic instability requiring treatment but not defined as shock, for moderate severity, and for severe disease, PICU admission, respiratory failure requiring mechanical ventilation, acute respiratory distress syndrome, shock, and/or multi-organ failure; (3) PIMS: as defined by treating physicians and fulfilling PIMS diagnostic criteria, and included fever, elevated C-reactive protein (CRP) or other inflammatory marker, involvement of at least 2 organs/systems, evidence of SARS CO-V-2 infection or exposure to a COVID-19 patient, and exclusion of other plausible diagnosis (infectious and noninfectious) [23–25].

Data Collection

Data were collected and reported by a pediatric infectious diseases specialist in every medical center participating, using standardized questionnaires. Most patients (or their caregivers) were interviewed by the local study physician (often the treating physician) and, additionally, some data were obtained from the medical records.

The study questionnaires included: age, sex, ethnicity, nasopharyngeal/oral swabs for SARS-CoV-2 PCR obtainment date; recent contact with known COVID-19 patient; background illnesses, including heart disease, chronic lung disease and/or

asthma, developmental delay, diabetes, immune compromise, and malignancy; signs and symptoms, including fever, cough, rhinorrhea, respiratory distress, sore throat, weakness, diarrhea, abdominal pain, vomiting, headache, conjunctivitis, nausea, myalgia, rash, loss of smell/taste, chest pain, and irritability; disease outcome data, including hospitalization, disease severity, complications, PICU admission, and mortality; laboratory data, including complete blood count (CBC) parameters, CRP, troponin; nasal swabs for other viral pathogens (co-infection), blood, urine and cerebrospinal fluid cultures performance and results; imaging—chest radiography and computerized tomography (CT) performance and interpretation. Radiographic pneumonia diagnosis was based on the interpretation of the chest X-ray (plain films) by the treating physician.

For PIMS-reported cases, additional data included: method of viral diagnosis (serology, PCR, or both); the presence of all gastrointestinal, cardiovascular, neurologic, renal, and respiratory symptoms; blood levels of ferritin, albumin, D-dimer, and interleukin 6 (IL-6); echocardiography results; and treatment given, including corticosteroids, intravenous immunoglobulin (IV-IG), antibiotics, aspirin, low-molecular-weight heparin, plasmapheresis, remdesivir, and infliximab.

All reports included data regarding date of episode and disease severity. Unfortunately, demographic and clinical data were missing for 23% of mild hospitalized cases, and 47% of mild outpatients (data are full for hospitalized moderate/severe disease and PIMS episodes).

Statistical Analysis

Descriptive statistical univariate analyses were calculated using SPSS 24. Univariate analysis was performed using 2-tailed χ^2 test, Student *t* test, or Mann-Whitney *U* test to assess differences between mild disease, severe/moderate diseases, and PIMS episodes. The threshold of statistical significance was $P < .05$.

RESULTS

During the study period, 1007 children with SARS-CoV-2 infection, including 11 children with clinical diagnosis of PIMS (without SARS-CoV-2 infection confirmation) were identified in 20 hospitals. Of those 1007 children, 568 (56%) were hospitalized: 82% with mild disease, 8% with moderate/severe COVID-19 (non-PIMS), and 10% with PIMS. Four hundred and thirty-nine children (44%) were discharged from the pediatric ER and followed as outpatients (Figure 1).

The rates of reports are detailed in Figure 2.

Magnitude of COVID-19 Morbidity

Nationwide

According to the IMOH data, by March 17, 2021, overall 813 742 SARS-CoV-2–positive patients had been identified; among them, 291 628 (36%) were children [19]. Therefore, the 568 SARS-CoV-2–positive hospitalized children presented here represent 0.2% of the overall pediatric SARS-CoV-2 confirmed morbidity, and the 1007 SARS-CoV-2-positive children treated in pediatric ER or hospitalized represent 0.35% of the overall pediatric SARS-CoV-2 morbidity.

Demographic, Background Illness, and Outcome Characteristics of Pediatric COVID-19–Hospitalized Patients

The mean ± standard deviation (SD) age (years) of the overall study population was 5.6 ± 6.4, and the median age was 1.0 years. Overall, 208 (45%) were children <1 year old. Children with moderate/severe disease and PIMS were older than children with mild disease (Table 1). Overall, 54% of hospitalized patients were males, and 68% were Jewish. Forty-three percent of patients had known contact with a SARS-CoV-2–infected person. Gender distribution was similar in mild diseases and in PIMS, but higher rates of males were noted in moderate/severe disease. Ethnicity distribution was similar when comparing mild, moderate/severe, and PIMS patients.

Background illness was reported in 30% of patients, with prematurity, immunodeficiency, genetic, neurologic, and chronic lung disease most common in moderate/severe patients, and obesity significantly more common in PIMS patients.

Mechanical ventilation and PICU admission were more common in PIMS than in mild and moderate/severe diseases. No mortality was recorded among the entire study population.

The demographic, background illness, and outcome characteristics of pediatric COVID-19 outpatients (ER visits) are detailed in Table 1.

Clinical Characteristics of Pediatric COVID-19

Overall Hospitalized Study Population

The most common symptoms at presentation were fever (71%), cough (21%), and respiratory distress (15%). Notably, 7% of all patients were asymptomatic (hospitalized for various reasons, including social problems, trauma, and for observation) (Table 2).

Upper respiratory tract infection (URI) was reported in 22% of hospitalized patients, with higher rate in mild disease. In contrast, lower respiratory tract infection (LRI) signs and symptoms were reported in 13% of cases, with highest rate (35%) in moderate/severe disease.

Chest radiography was more commonly performed in PIMS and moderate/severe patients than in mild cases (52% and 48% vs 17%, $P < .001$). The rates of radiographic pneumonia were 4%, 25%, and 14% for mild, moderate/severe, and PIMS, respectively.

Other Symptoms

Rates of gastrointestinal symptoms, including diarrhea, vomiting, nausea, and abdominal pain, as well as rates of rash, conjunctivitis, irritability/apathy, myalgia, and weakness, were

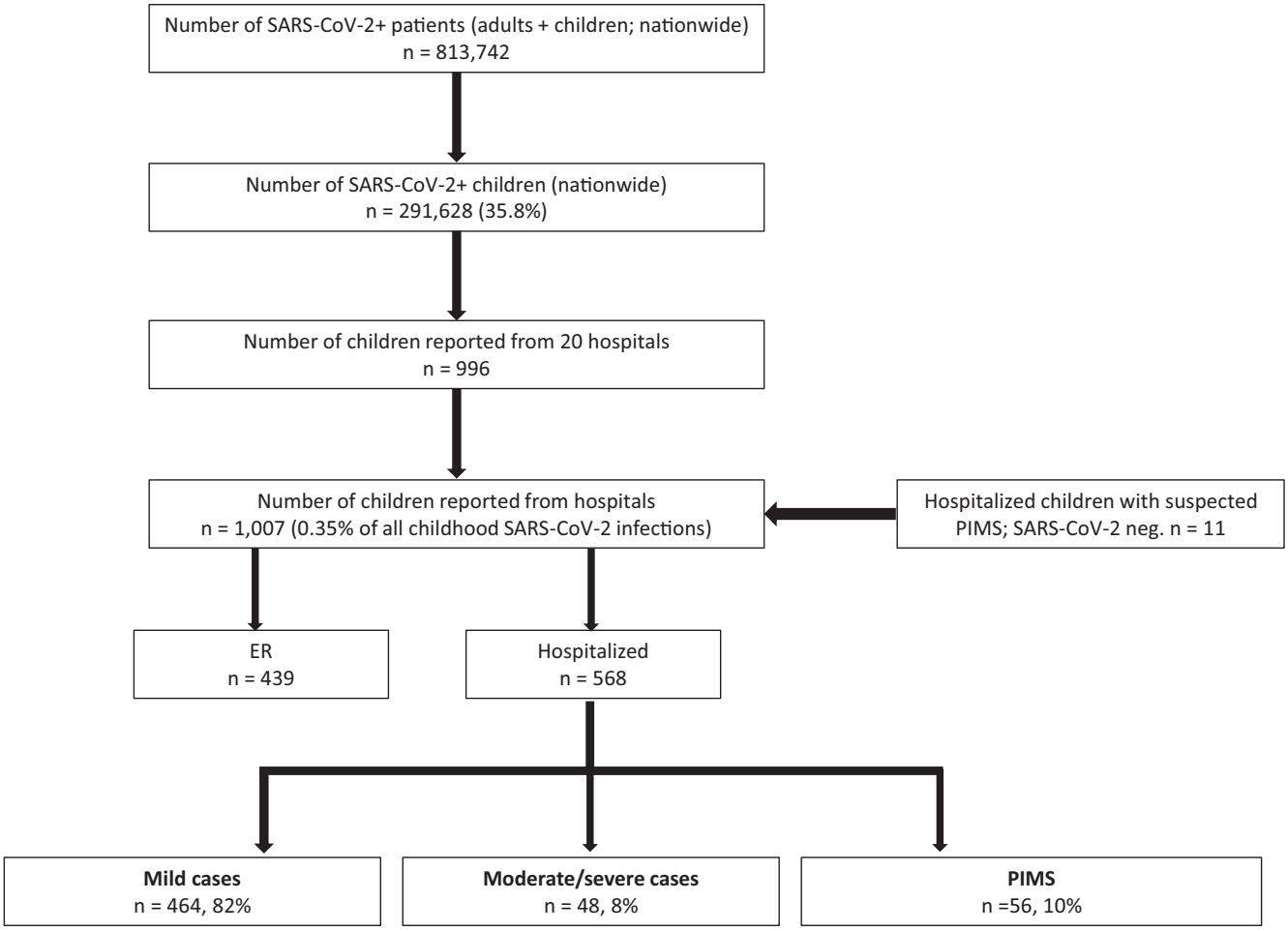


Figure 1. Study population: COVID-19 in children treated in 20 hospitals in Israel, March 11, 2020 through March 15, 2021.

higher in PIMS episodes than in other groups. In contrast, rates of loss of smell/taste were higher in moderate/severe episodes. The clinical characteristics of pediatric COVID-19 outpatients (ER visits) are detailed in Table 2.

Evidence for Bacterial or Viral (Non-SARS-CoV-2) Infection

Evidence for bacterial infection was recorded in 8% and 4% of mild and moderate/severe disease patients, respectively (none for PIMS, where "other infectious etiology" is an exclusion criterion).

Evidence for viral infection, other than SARS-CoV-2, included 8 episodes in the mild disease group and 5 episodes in the moderate/severe group.

Laboratory Characteristics

Lymphopenia, higher rate of neutrophils/lymphocytes >3.5, and thrombocytopenia were most common in PIMS. Elevated CRP and elevated troponin were mostly found in PIMS patients, while their rates were low in the other groups (Table 2).

PIMS

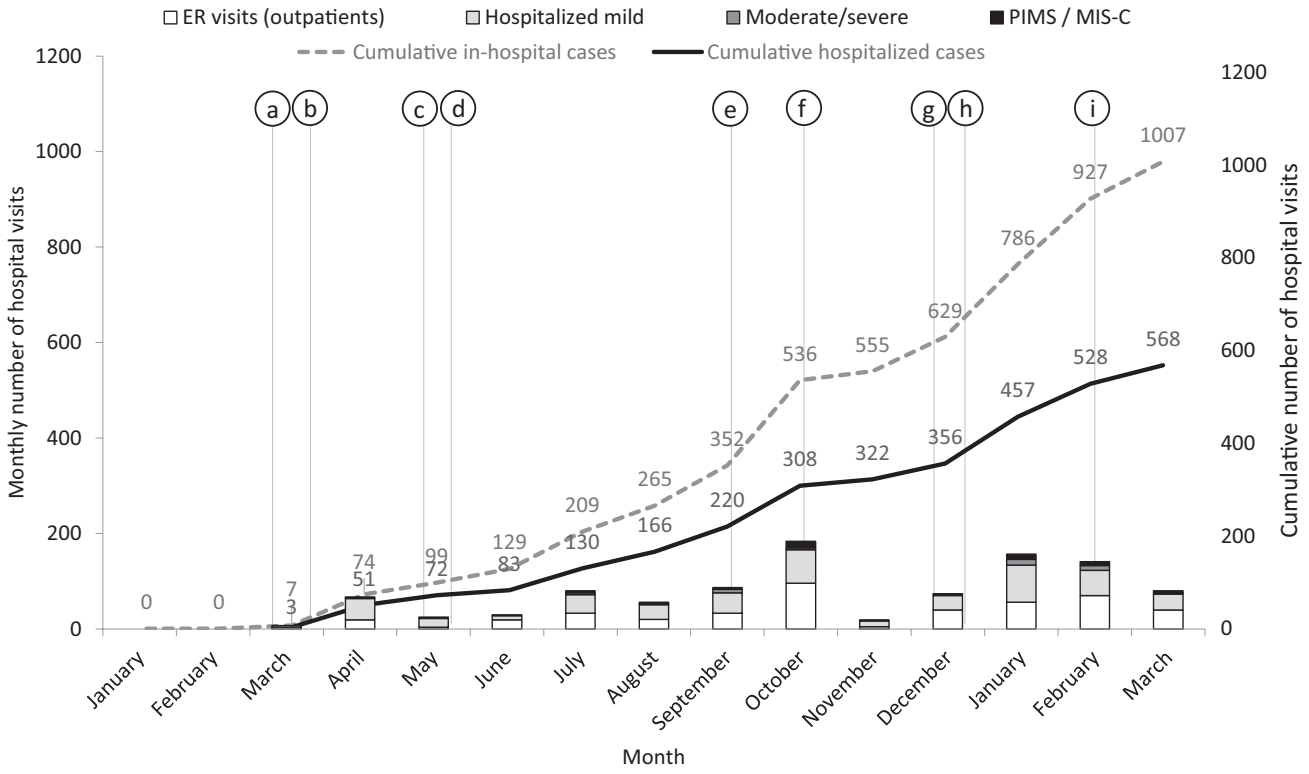
PIMS was diagnosed by serologic tests, indicating past infection, in 57% of cases. Nevertheless, 23% of PIMS were diagnosed only through positive SARS-CoV-2 PCR test, and in 11 cases (20%), diagnosis was clinical without a viral test support (based on clinical presentation criteria and exposure to COVID-19 patient) (Table 3).

Fever, gastrointestinal symptoms, cardiovascular involvement, and rash were noted in mot PIMS episodes. Respiratory presentation was recorded only in a minority of patients (39%). Lymphopenia and elevated CRP were observed in most of the cases, while thrombocytopenia was noted in 38% of patients. Other common laboratory findings included elevated levels of ferritin, troponin, and D-dimer, as well as low albumin levels.

Echocardiography was performed in 40 patients, with pathological findings identified in 32, including pericardial effusion (17 cases), coronary dilatation or hyperemia (10 cases), and reduced cardiac function/contraction (5 cases). The mainstay of treatment in PIMS included corticosteroids (82%) and IV-IG (57%).

DISCUSSION

We report nationwide the characteristics and clinical course of hospitalized children with COVID-19 treated in Israel between



a. 12 March, schools closed; b. 19 March, National lockdown; c. 3 May, school resume; d. 10 May, relief of lockdown; e. 18 Sep. 2nd lockdown; f. 18 Oct. pre-school return; g. 19 Dec. Corona vaccine campaign initiation; h. 27 Dec, 3rd lockdown; i. 11 Feb, school resume

Figure 2. Dynamics of COVID-19 in children in 20 hospitals in Israel, March 11, 2020 through March 15, 2021.

March 11 and March 17, 2021. The study population comprises most (but not all) of the pediatric cases treated in hospitals nationwide, allowing real appreciation of the presentation and prognosis of the most severe pediatric COVID-19 cases.

Our main findings include low disease rate (<1%) in terms of the proportion of children treated in hospitals of all children diagnosed with SARS-CoV-2 infection nationally. Furthermore, although the children in our study were all treated in hospitals, thus representing the most severe pediatric cases, >80% of the children had a mild disease, a third of the patients had no fever, and most patients presented without respiratory symptoms.

The finding of a low rate of respiratory symptoms among pediatric COVID-19 cases, and especially of LRI symptoms among mild, moderate/severe, and PIMS patients is somewhat surprising. Specifically, it stands in contrast to the findings in other studies reporting COVID-19 in adults, where LRI was a common presentation [26–28]. Nevertheless, our findings are similar to those found in a French study assessing severe childhood COVID-19 [25]. Therefore, these findings suggest that most SARS-CoV-2 infections in children are mild, and that among the most severe cases (ie, hospitalized patients), they can be divided generally into 3 groups. The first contains children with mild disease who are hospitalized for other, non-COVID-19 directly related, reasons. This is evident by the high proportion of young (often febrile) infants in this group, suggesting they were often hospitalized for a sepsis workup and exclusion of serious bacterial infections, rather than for direct COVID-19 symptoms. Furthermore, 9% of the patients in this group were asymptomatic. Notably, during the first outbreak peak (March through April), according to the IMOH policy, SARS-CoV-2–positive individuals had to be hospitalized, even if asymptomatic. During that period, 11 asymptomatic children were hospitalized. Therefore, the rate of asymptomatic patients in the overall pediatric population is probably higher. The second group of moderate/severe disease was characterized by high rates of non-COVID-19–related morbidity, including (among others) seizures in children with previous neurological conditions, appendicitis and duodenal rupture, exacerbation in diabetes mellitus, diagnosis of myelo/lymphoproliferative diseases, herpes encephalitis, bacterial infections, and hereditary spherocytosis. Thus, in the 2 groups of non-PIMS, the most severe cases of COVID-19 were often hospitalized for their comorbidity rather than for the direct impact of SARS-CoV-2 infection. The third group comprises patients with PIMS and represents a unique, rare, postinfectious phenomenon, which requires high level of suspicion from treating physicians for its

Table 1. Demographic, Background Illnesses, and Outcome Characteristics of Pediatric COVID-19–Hospitalized Patients

Characteristics	Mild—ER (Outpatients) n = 439 (Data, n = 233)	Overall Hospitalized n = 568 (Data, n = 460)	Mild Hospitalized n = 464 (Data, n = 356)	Moderate/Severe, Non-PIMSn = 48 (Data, n = 48)	PIMSn = 56 (Data, n = 56)	*P* Value[a,b,c]
Age						
Range	4 days–17.3 years	1 day–17.9 years	1 day–17.9 years	3 months–17 years	3 months–18 years	-
Mean ± SD (years)	7.6 ± 6.4	5.6 ± 6.4	4.6 ± 6.3	8.0 ± 6.5	9.8 ± 4.5	<.001[a], <.001[b], .12[c]
Median (years)	7.0	1.0	0.5	7.5	10.0	-
<1 year, n (%)	53 (23%)	208 (45%)	195 (55%)	11 (23%)	2 (4%)	<.001[a], <.001[b], .006[c]
Gender, n (%)						
Male	118 (51%)	249 (54%)	186 (52%)	35 (73%)	28 (50%)	.008[a], .78[b], .03[c]
Female	115 (49%)	211 (46%)	170 (48%)	13 (27%)	28 (50%)	
Ethnicity, n (%)						
Jewish	171 (73%)	314 (68%)	251 (71%)	28 (58%)	35 (63%)	.10[a], .27[b], .69[c]
Muslim	60 (26%)	135 (29%)	97 (27%)	18 (38%)	20 (36%)	.17[a], .20[b], 1.0[c]
Unknown/other	2 (1%)	11 (2%)	8 (2%)	2 (4%)	1 (2%)	.34[a], 1.0[b], .59[c]
Contacts, n (%)						
Contact with COVID-19 patient	135 (58%)	193 (42%)	159 (45%)	13 (27%)	21 (38%)	.03[a], .38[b], .30[c]
Travel abroad	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Background illnesses, n (%)						
Overall[d]	34 (15%)	139 (30%)	107 (30%)	21 (44%)	11 (20%)	.07[a], .12[b], .01[c]
Neurologic	8 (4%)	44 (10%)	37 (10%)	7 (15%)	0 (0%)	.46[a], .005[b], .004[c]
Congenital heart disease	1 (0.5%)	17 (4%)	13 (4%)	3 (6%)	1 (2%)	.42[a], .70[b], .30[c]
Genetic	3 (1%)	17 (4%)	10 (3%)	7 (15%)	0 (0%)	.002[a], .37[b], .04[c]
Chronic lung disease	7 (3%)	15 (3%)	11 (3%)	4 (8%)	0 (0%)	.09[a], .37[b], .04[c]
Obesity	2 (1%)	11 (2%)	2 (0.6%)	2 (4%)	7 (13%)	.07[a], <.001[b], .17[c]
Immunodeficiency	8 (4%)	12 (3%)	8 (3%)	4 (8%)	0% (0)	.04[a], .61[b], .04[c]
Renal failure	2 (1%)	8 (2%)	6 (2%)	1 (2%)	1 (2%)	.59[a], 1.0[b], 1.0[c]
Hematologic	1 (0.4%(	9 (2%)	6 (2%)	1 (2%)	2 (4%)	.59[a], .30[b], 1.0[c]
Prematurity	3 (1%)	12 (3%)	8 (3%)	4 (8%)	0 (0%)	.04[a], .61[b], .04[c]
Malignancy	1 (0.4%)	7 (2%)	5 (1%)	2 (4%)	0 (0%)	.20, 1.0[b], .21[c]
Diabetes	1 (0.4%)	4 (1%)	3 (1%)	1 (2%)	0 (0%)	.40[a], 1.0[b], .46[c]
Outcome						
Intensive care unit	0 (0%)	36 (6%)	0 (0%)	10 (21%)	26 (46%)	<.001[a], <.001[b], .007[c]
Mechanical ventilation	0 (0%)	15 (3%)	0 (0%)	5 (10%)	10 (18%)	<.001[a], <.001[b], .40[c]
Mortality	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0

Abbreviations: ER, emergency rooms; PIMS, pediatric inflammatory multisystem syndrome.
[a]Mild vs moderate/severe; [b]mild vs PIMS; [c]moderate/severe vs PIMS; [d]Overall background illnesses included all detailed diagnoses in the table (with a possibility of more than 1 background illness per child).

recognition [23, 25]. Of note, obesity was overrepresented in our series of children who had PIMS, as it was in other study findings [23] as well as in studies assessing obesity in severe COVID-19 in adults [28–30].

Laboratory findings are also inconsistent among hospitalized children with COVID-19, with lymphopenia, thrombocytopenia, highly elevated CRP, and elevated troponin being the most common findings in distinguishing mild, moderate/severe, and PIMS cases.

These findings suggest that it is almost impossible to assess the SARS-CoV-2 infection rate (ie, deciding upon a sampling policy) based only on clinical signs and symptoms. This presents a major challenge for infection control efforts and suggests that a low threshold for SARS-CoV-2 testing in the inpatient setting is required. Therefore, early SARS-CoV-2 detection and sampling policy on a population level should probably be based on a combination of signs and symptoms, known disease geographic clusters, and high-risk group screening.

Our findings reaffirm that children comprise a small fraction of severe COVID-19 cases, and that their symptoms are often mild. However, a few pediatric cases may progress to severe disease, and initial atypical presentations may delay the diagnosis of COVID-19, leading to unfavorable outcomes [8]. While severe diseases were uncommon in our study, some of their aspects are notable. First, all moderate/severe and PIMS cases were in children ≥3 months of age. This finding differs from early reports of severe COVID-19 where severity was associated with very young age [3, 4, 12]. Nevertheless, in recent reports describing hyper-inflammation, Kawasaki-like disease, MIS-C, and PIMS, most children were older than 5 years of age. [15, 23, 25] Second, PIMS patients often had gastrointestinal and myocardial involvement along with signs

Table 2. Clinical and Treatment Characteristics of Pediatric Mild Disease, Moderate/Severe COVID-19– and PIMS–Hospitalized Patients

Characteristics	Mild—ER (Outpatients) n = 439 (Data, n = 233)	Overall Hospitalized n = 568 (Data, n = 460)	Mild Hospitalized n = 464 (Data, n = 356)	Moderate/Severe, Non-PIMSn = 48 (Data, n = 48)	PIMS n = 56 (Data, n = 56)	*P* Value[a,b,c]
Clinical presentation, n (%)						
Fever	138 (59%)	325 (71%)	240 (67%)	29 (60%)	56 (100%)	.33[a], <.001[b], <.001[c]
Upper respiratory tract infection (URI)	69 (30%)	100 (22%)	88 (25%)	3 (6%)	9 (16%)	.003[a], .18[b], .14[c]
Lower respiratory tract infection (LRI)	6 (3%)	59 (13%)	30 (8%)	17 (35%)	12 (21%)	<.001[a],.007[b], .13[c]
Cough	64 (27%)	95 (21%)	73 (21%)	13 (27%)	9 (16%)	.35[a], .59[b], .23[c]
Respiratory distress	25 (11%)	71 (15%)	39 (11%)	16 (33%)	16 (29%)	<.001[a], .001[b], .67[c]
Runny nose	32 (14%)	48 (10%)	41 (12%)	4 (8%)	3)5%)	.63[a], .24[b], .70[c]
Sore throat	20 (9%)	26 (6%)	15 (4%)	1 (2%)	10 (18%)	.71[a], <.001[b], .01[c]
Chest pain	9 (4%)	19 (4%)	9 (3%)	2 (4%)	8 (14%)	.63[a], <.001[b], .10[c]
Diarrhea	19 (9%)	48 (10%)	26 (7%)	3 (6%)	19 (34%)	1.0[a], <.001[b], <.001[c]
Vomiting	26 (12%)	56 (12%)	26 (7%)	9 (19%)	21 (38%)	.02[a], <.001[b], .05[c]
Nausea	5 (2%)	23 (5%)	8 (2%)	3 (6%)	12 (21%)	.13[a], <.001[b], .05[c]
Abdominal pain	17 (8%)	55 (12%)	18 (5%)	8 (17%)	29 (52%	.007[a], <.001[b], <.001[c]
Rash	5 (2%)	44 (10%)	10 (3%)	2 (4%)	32 (57%)	.64[a], <.001[b], <.001[c]
Conjunctivitis	0 (0%)	22 (5%)	3 (1%)	0 (0%)	19 (34%)	1.0[a], <.001[b], <.001[c]
Seizures/encephalopathy	4 (2%)	13 (3%)	8 (2%)	2 (4%)	3 (5%)	.34[a], .18[b], 1.0[c]
Irritability/apathy	1 (0.4%)	25 (5%)	17 (5%)	0 (0%)	8 (14%)	.24[a], .01[b], .007[c]
Headache	18 (8%)	42 (9%)	20 (6%)	7 (15%)	15 (27%)	.03[a], <.001[b], .15[c]
Loss of smell/taste	6 (3%)	17 (4%)	5 (1%)	11 (23%)	1 (2%)	<.001[a], .59[b], .001[c]
Bell's palsy	3 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0[a], 1.0[b], 1.0[c]
Weakness	15 (6%)	54 (12%)	22 (6%)	10 (21%)	22 (39%)	.009[a], <.001[b], .06[c]
Dizziness	3 (1%)	12 (3%)	6 (2%)	1 (2%)	5 (9%)	1.0[a], .01[b], .21[c]
Myalgia	5 (2%)	17 (4%)	8 (2%)	3 (6%)	6 (11%)	.13[a], .006[b], .50[c]
Asymptomatic	31 (13%)	31 (7%)	31 (9%)	-	-	-
Chest radiography, n (%)						
Performed	22 (9%)	113 (25%)	61 (17%)	25 (52%)	27 (48%)	<.001[a], <.001[b], .84[c]
Pneumonia (per radiography)	3 (1%)	35 (8%)	15 (4%)	12 (25%)	8 (14%)	<.001[a], .007[b], .21[c]
Evidence for bacterial infection[d]	5 (2%)	30 (7%)	28 (8%)	2 (4%)	-	.56[a], –, –
Evidence for other viral infection[e]	0 (0%)	13 (3%)	8 (2%)	5 (10%)	-	.01[a], –, –
Treatment, n (%)						
Antibiotics given	9 (4%)	181 (39%)	131 (37%)	23 (48%)	27 (48%)	.16[a], .11[b], 1.0[c]
Laboratory						
Lymphocytes; mean ± SD	3.4 ± 2.4	3.3 ± 2.5	3.9 ± 2.5	2.1 ± 1.4	1.1 ± 1.0	<.001[a], <.001[b], <.001[c]
Lymphopenia (≤2000), n (%)	42% (30/71)	37% (147/398)	25% (75/302)	60% (24/40)	86% (48)	<.001[a], <.001[b], .008[c]
ANC/LYM ratio; mean ± SD	-	5.7 ± 6.4	1.7 ± 2.2	4.2 ± 3.5	17.3 ± 32.4	<.001[a], <.001[b], <.001[c]
ANC/LYM ratio ≥3.5, n (%)	-	87/371 (23%)	28/274 (10%)	17/48 (35%)	42/49 (86%)	<.001[a], <.001[b], <.001[c]
PLT; %mean ± SD	298 ± 111	306 ± 137	325 ± 128	269 ± 139	179 ± 136	.008[a], <.001[b], .008[c]
Thrombocytopenia, n (%)	2/67 (3%)	43 (9%)	12/300 (4%)	10/42 (24%)	21 (38%)	<.001[a], <.001[b], .19[c]
CRP (mg/dL); mean ± SD	1.6 ± 2.0	4.5 ± 7.6	1.8 ± 3.1	4.4 ± 4.8	19.2 ± 8.9	<.001,[a] <.001[b], <.001[c]
CRP >6 mg/dL	4/62 (6%)	89/376 (24%)	23/279 (8%)	24% (10/41)	100% (56)	.004[a], <.001[b], <.001[c]
Elevated troponin (>25, n (%)	-	15/68 (22%)	0/18 (0%)	2/151 (3%)	13/35 (37%)	.20[a], .002[b], .18[c]

Abbreviations: ANC/LYM, absolute neutrophil count/lymphocyte; CRP, C-reactive protein; ER, emergency rooms; PIMS, pediatric inflammatory multisystem syndrome; PLT, platelet; SD, standard deviation.

[a]Mild vs moderate/severe; [b]mild vs PIMS; [c]moderate/severe vs PIMS·[d]evidence for bacterial infection: 15 urinary tract infection episodes (10 with *Escherichia coli*, 3 with *Enterococcus* spp., 2 with *Klebsiella* spp.), 9 periodontal, parapharyngeal, and skin and soft tissue infections (2 in the moderate/severe group), 2 positive sputum cultures treated as pneumonia, 2 central line infections, and 2 *Salmonella gastroenteritis* cases; [e]evidence for viral infection, other than SARS-CoV-2: 8 episodes in the mild disease group (3 human metapneumovirus, 4 rhinovirus (3 as dual infections), 1 adenovirus, 1 enterovirus, 1 Epstein-Barr virus, 1 parainfluenza), and 5 episodes in the moderate/severe group (2 rhinovirus, 1 adenovirus, 1 herpes simplex virus encephalitis, 1 enterovirus meningitis).

of hyper-inflammation with a few respiratory symptoms. Laboratory findings upon hospital admission associated with PIMS presentation were lymphopenia, thrombocytopenia, neutrophilia, and elevated CRP, troponin, ferritin, and D-dimer levels. Third, all children recovered completely. These findings suggest that early recognition of severe COVID-19 is essential for an optimal outcome. Specifically, for PIMS, early recognition and treatment with IV-IG and steroids are probably associated with a more favorable clinical course [31]. Notably, antibiotics were used in more than a third of all cases (in each

Table 3. Clinical and Treatment Characteristics of PIMS Patients

Characteristics, n (%)	PIMS, n = 56
Diagnosis of SARS-CoV-2	
Serology only	26 (46%)
Serology + PCR	6 (11%)
PCR only	13 (23%)
No viral confirmation (contact with patient)	11 (20%)
Clinical presentation	
Fever	56 (100%)
Gastrointestinal symptoms	46 (82%)
Cardiovascular	34 (61%)
Rash	32 (57%)
Respiratory	22 (39%)
Conjunctivitis	19 (34%)
Acute kidney injury	11 (20%)
Neurologic	11 (20%)
Laboratory	
Lymphopenia <2000	48 (86%)
ANC/LYM ratio ≥3.5	42/49 (86%)
Thrombocytopenia	21 (38%)
CRP >6 mg/dL	56 (100%)
Elevated ferritin	32/35 (91%)
Elevated troponin (>25)	13/35 (37%)
Albumin <3.5	27/42 (64%)
D-dimer checked; elevated	38/47 (81%)
Elevated IL-6	3/8 (38%)
Echocardiography	
Pathologic/done	32/40 (57%)
Treatment	
Steroids	46 (82%)
IV-IG	32 (57%)
Steroids and IV-IG	28 (50%)
Antibiotics	27 (48%)
Aspirin	23 (41%)
Low-molecular-weight heparin	14 (25%)
Plasmapheresis	1 (2%)
Remdesivir	1 (2%)
Infliximab	1 (2%)

Abbreviations: ANC/LYM, absolute neutrophil count/lymphocyte; IL-6, interleukin 6; IV-IG, intravenous immunoglobulin; PCR, polymerase chain reaction; PIMS, pediatric inflammatory multisystem syndrome PLT, platelet; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

of the 3 groups), probably reflecting either high rate of febrile infant receiving antibiotic treatment until exclusion of serious bacterial infection, or older children with severe disease/PIMS, receiving antibiotics due to their "toxic" appearance.

One important implication of our study is that with increasing use of SARS-CoV-2 vaccines, currently targeting the adult population [32], future vaccination strategies should include a vaccine for children aiming at interruption of transmission, in contrast to the adult vaccines which aim is to prevent severe disease. It is also possible that with increased adult vaccination rates, a shift toward infection in young population, including children, will be noted with an increase in severe COVID-19 in children. Indeed, In Israel, where vaccine uptake among adults was the highest worldwide during December 2020 through March 2021, a campaign for vaccinating children ≥16 years old was initiated in February 2021, and the IMOH is considering future vaccination of younger children.

Our study has several limitations: First, although this is a nationwide surveillance, we were unable to retrieve data from several hospitals treating pediatric population in Israel. Additionally, some data were missing in certain cases.

In conclusion, pediatric SARS-CoV-2 infections in the in-hospital setting among Israeli children were characterized by a low disease rate, suggesting that most infected children have a mild disease, often without respiratory symptoms. Although uncommon, physicians should maintain a high index of suspicion for severe COVID-19 cases, including hyper-inflammation and myocardial involvement. Lymphopenia, thrombocytopenia, neutrophilia, and elevated CRP, troponin, ferritin, and D-dimer levels are more frequent in severe and especially PIMS cases.

Notes

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