Factors Associated With Severe SARS-CoV-2 Infection

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abstract

BACKGROUND: Initial reports on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children suggested that very young age and comorbidities may increase risk of severe evolution, but these findings remained to be confirmed. We aimed to analyze the clinical spectrum of hospitalized pediatric SARS-CoV-2 infection and predictors of severe disease evolution.

METHODS: We conducted a French national prospective surveillance of children hospitalized with SARS-CoV-2 infection. We included all children with confirmed SARS-CoV-2 infection in 60 hospitals during February 15 to June 1, 2020. The main outcome was the proportion of children with severe disease, defined by hemodynamic or ventilatory (invasive or not) support requirement.

RESULTS: We included 397 hospitalized children with SARS-CoV-2 infection. We identified several clinical patterns, ranging from paucisymptomatic children, admitted for surveillance, to lower respiratory tract infection or multisystem inflammatory syndrome in children. Children <90 days old accounted for 37% of cases (145 of 397), but only 4 (3%) had severe disease. Excluding children with multisystem inflammatory syndrome in children (n = 29) and hospitalized for a diagnosis not related to SARS-CoV-2 (n = 62), 23 of 306 (11%) children had severe disease, including 6 deaths. Factors independently associated with severity were age ≥10 years (odds ratio [OR] = 3.4, 95% confidence interval: 1.1–10.3), hypoxemia (OR = 8.9 [2.6–29.7]), C-reactive protein level ≥80 mg/L (OR = 6.6 [1.4–27.5]).

CONCLUSIONS: In contrast with preliminary reports, young age was not an independent factor associated with severe SARS-CoV-2 infection, and children <90 days old were at the lowest risk of severe disease evolution. This may help physicians to better identify risk of severe disease progression in children.

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WHAT'S KNOWN ON THIS SUBJECT: Authors of preliminary reports on pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection suggested that very young age and comorbidities may increase the risk of severe evolution. The role of these conditions remains to be elucidated by additional studies.

WHAT THIS STUDY ADDS: We conducted a national hospital-based surveillance of SARS-CoV-2 infection from February to June 2020. By contrast with initial reports, children <90 days accounted for a large part of admitted children but were at the lowest risk of severe SARS-CoV-2 disease.

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Infection with the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease (COVID-19), emerged in late 2019 in China and has led to a major pandemic.[1] As of June 2020, it was responsible for >400 000 deaths worldwide.[2] France is among the most affected countries with 30 000 deaths reported to date.[2]

In epidemiological reports, children were underrepresented in severe cases, accounting for ~1% to 2% of hospitalized COVID-19.[3] This finding has been supported by researchers in several studies suggesting both a lower rate of infection in children than in adults[4,5] and a high proportion of benign forms among infected children.[6–8] However, severe disease evolution requiring intensive care can occur.[9,10] Furthermore, recently, severe pediatric inflammatory forms with hemodynamic failure have been described.[11–16] In this context, identifying these severe forms early among children infected by SARS-CoV-2 is critical.

Reports of SARS-CoV-2 infections in children suggested that children <1 year old and children with comorbidities may be at higher risk of severe disease evolution.[2,17] However, these studies were mainly focused on respiratory forms and did not cover the broad clinical spectrum of SARS-CoV-2 infections in children. Thus, factors associated with severe SARS-CoV-2 infection in children remain to be elucidated.

Because of the relative rarity of severe COVID-19 in children, an accurate description of the spectrum of severe COVID-19 in children requires wide-scale studies, with precise description of clinical features and outcomes, which are challenging to set up in the context of health care resources under high pressure. Thus, a few studies provided a description of these pediatric severe forms at a country level. Sparse information is available about factors associated with severe disease progression in children.[18] In France, we took advantage of a previously established national network of pediatric hospital surveilling bacterial meningitis for 20 years[19,20] to extend this system to children hospitalized with SARS-CoV-2 infection.

The aim with this national surveillance was to provide precise information on the clinical spectrum of hospitalized pediatric COVID-19, rate of severe forms, and predictors of severe disease progression.

METHODS

We conducted a national prospective surveillance of children hospitalized with SARS-CoV-2 infection. The study was approved by the Institut National de la Santé et de la Recherche Médicale ethics committee for evaluation, the institutional review board (IRB00003888), and was registered at ClinicalTrials.gov (NCT04336956).

Patients and Settings

We recruited 60 hospitals throughout France for this study, using the French pediatric bacterial meningitis network.[19,20] We included all pediatric patients with SARS-CoV-2 infection who were hospitalized in one of these centers from February 15 to June 1, 2020. Confirmed SARS-CoV-2 infection was defined by a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) result for SARS-CoV-2 on a nasopharyngeal swab and computed tomography (CT) scan–based cases were defined by characteristic chest CT scan lesions according to European Centre for Disease Prevention and Control and French National Health Agency case definition.[21] Radiologic evidence of lesions compatible with COVID-19 were unilateral or bilateral subpleural ground-glass opacities and consolidations, although other etiologies can cause ground-glass opacities on CT, including vaping and interstitial lung infections.[22,23] A CT scan was used to define the site of disease and/or in a few cases the presence of the infection. During the same period, Public Health France, the national French public health agency, counted all hospitalized pediatric SARS-CoV-2 infections cases in France, which allowed for estimating the completeness of our surveillance system. Similar to our surveillance system, the definition of cases counted by Public Health France included a positive RT-PCR result for SARS-CoV-2 or a characteristic chest CT scan lesions.[24]

For each patient, an electronic case report form was prospectively completed on a secure database, and the following data were recorded: demographic characteristics, comorbidities, initial symptoms and clinical signs, biological and microbiologic parameters, radiography findings, treatments, and course during hospitalization.

Outcome Measure

The main outcome was the proportion of severe disease evolution among all included children with a SARS-CoV-2 infection, defined by the need for either ventilatory or hemodynamic support during hospitalization, or death.[17] Ventilatory support was defined by use of noninvasive ventilation, including high-flow oxygen via nasal cannula, continuous positive airway pressure, and bilevel positive airway pressure or the use of invasive ventilation. We assessed demographic, clinical, and biological factors associated with severe disease progression in children at the acute phase of the SARS-CoV-2 infection. For biological factors, we considered explorations performed at admission. Hypoxemia was defined by oxygen saturation <95%.[25] Thrombocytopenia was defined by platelet count <150 g/L.

Secondary outcomes were rate of severe disease by clinical presentation, comorbidities, and age groups (<90 days, 90 days to <1 year, 1 to <5, 5 to <10, 10 to <15, and 15 to <18 years). Among comorbidities, obesity was defined by a BMI >25 and overweight by a weight >+2 SDs for age and sex on the basis of national weight curves and/or a BMI >25.[26]

Statistical Analysis

We described patient characteristics with numbers (percentages) for categorical variables and median (interquartile range [IQR]) for quantitative variables. We assessed the association between these characteristics and severe disease evolution by Fisher's exact test for categorical variables and the Mann–Whitney *U* test for quantitative variables. We then used a multivariate logistic regression model with the backward stepwise method to identify factors independently associated with disease severity, estimating odds ratios (ORs) and 95% confidence intervals (CIs). Variables significant at $P \leq .20$ on univariate analyses were included in the stepwise selection. Quantitative variables associated with severity were transformed into binary variables by using the receiver operating characteristic curve analysis. A 2-sided *P* value <.05 was considered statistically significant. All statistical analyses involved using R v3.6.1 (http://www.R-project.org).

RESULTS

Since February 15, 2020, 397 hospitalized children were included in the study: 385 had a positive RT-PCR nasopharyngeal test result for SARS-CoV-2, and 12 were CT scan based with radiologic evidence of lesions compatible with COVID-19; see flowchart (Supplemental Fig 3). On the basis of systematic mandatory reporting of any children hospitalized with SARS-CoV-2 infection via Public Health France (1032 cases over the same period), the completeness of our surveillance system was 38.5% (95% CI: 35.5–41.5).

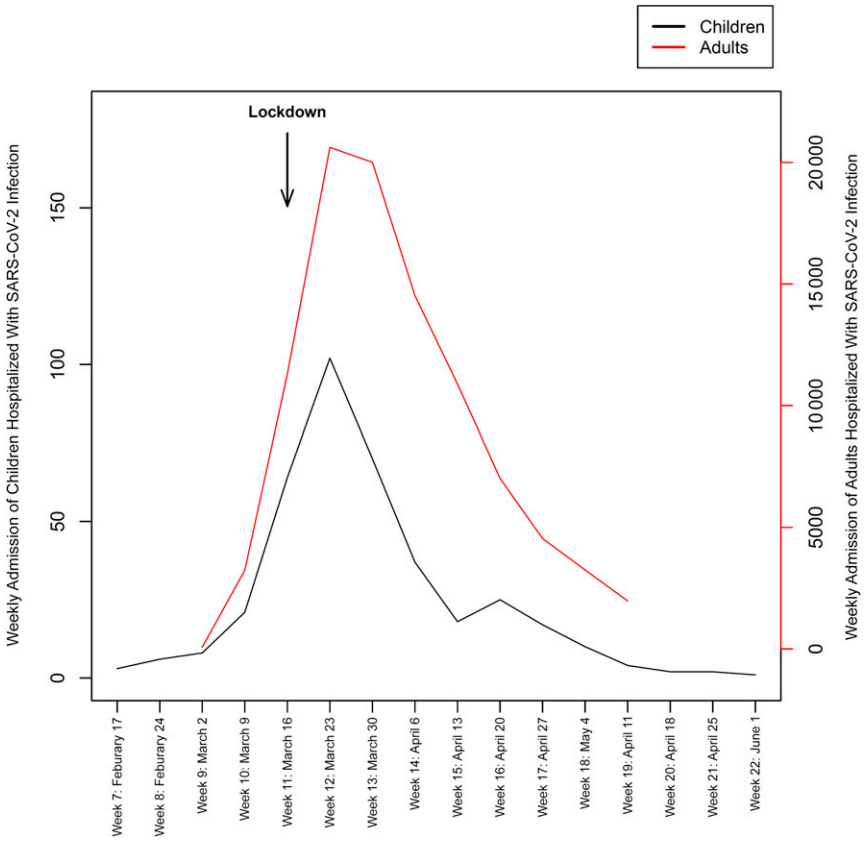

FIGURE 1
Evolution of weekly admission of children with SARS-CoV-2 infection, *N* = 397. The vertical arrow shows the national lockdown which started on March 17, 2020. Adult data are from Public Health France (*N* = 97 406).[38]

The weekly number of children admitted to hospital with SARS-CoV-2 infection peaked during March 23 to 30, 2020 (ie, 1 week after the national lockdown), and strongly decreased thereafter (Fig 1). This number mirrored the evolution of adults admitted with SARS-CoV-2 infection over the same period in France (http://www.santepubliquefrance.fr). The geographic distribution of cases is displayed in Supplemental Fig 4.

Patients Characteristics and Clinical Patterns

The clinical characteristics of children are in Table 1. The median age was 16 months (IQR, 51 days–134 months). Overall, 114 (29%) children had comorbidities, mainly chronic respiratory disease (such as asthma, cystic fibrosis, and bronchopulmonary dysplasia), immunosuppression or malignancy, neurologic disorders, and sickle cell disease (Table 1). The main symptoms were fever (*n* = 300 of 385, 78%), cough (*n* = 168 of 391, 43%), feeding difficulties (*n* = 152 of 385, 39%), shortness of breath or dyspnea (*n* = 119 of 390, 31%), and diarrhea (*n* = 93 of 392, 24%).

Among the 397 children included, levels of inflammatory parameters were low for most children (median C-reactive protein level [CRP], 5 mg/L [IQR, 2–36], procalcitonin level, 0.15 ng/mL [IQR, 0.1–0.37], neutrophil count, 3.8 g/L [IQR, 2.1–7.1]). A total of 80 of 301 (27%) cases showed

TABLE 1 General Characteristics of the Children Hospitalized With SARS-CoV-2 Infection in France, February 15 to June 1, 2020 (N = 397)

	Total N = 397
Age, median (IQR)	16 mo (51 d–134 mo)
<90 d, *n* (%)	145 (37)
90 d–<1 y, *n* (%)	48 (12)
1–<5 y, *n* (%)	46 (12)
5 y or older, *n* (%)	158 (40)
Male sex, *n* (%)	224/395 (57)
Prematurity if age <90 d, *n* (%)	20/133 (15)
Contact identification, *n*/*N* (%)	
Identified contact case	89/386 (23)
Suspected contact case	132/386 (34)
No contact case	165/386 (43)
Comorbidities, *n*/*N* (%)	114/397 (29)
Asthma, *n* (%)	25 (6)
Other chronic respiratory diseases, *n* (%)	14 (4)
Immunosuppression or malignancy, *n* (%)	27 (7)
Diabetes, *n* (%)	5 (1)
Cardiac diseases, *n* (%)	8 (2)
Sickle cell diseases, *n* (%)	22 (6)
Obesity, *n* (%)	12 (3)
Neurologic diseases, *n* (%)	24 (6)
Other congenital or malformation, *n* (%)	21 (5)
Clinical characteristics, *n*/*N* (%)	
Fever	300/385 (78)
Cough	168/391 (43)
Rhinitis	167/387 (43)
Shortness of breath or dyspnea	119/390 (31)
Diarrhea or vomiting	129/392 (33)
Feeding difficulties	152/385 (39)
Abdominal pain	60/244 (25)
Odynophagia	27/210 (13)
Anosmia	17/174 (10)
Ageusia	19/172 (11)
Myalgia	40/197 (20)
Headache	53/192 (28)
Wt (*z* score), mean (±SD),[a] *n*	0.16 (±3.1), 330
Height (*z* score), mean (±SD),[a] *n*	−0.66 (±1.6), 124
BMI, median (IQR), kg/m^2; *n*	16.4 (14.86326–19.05197); 137
Temperature °C; *n*	37.8 (37–38.4); 371
Biological parameters	
Initial CRP, mg/L, median (IQR); *n*	5 (2–36); 330
Maximal CRP, mg/L, median (IQR); *n*	7 (3–56); 330
Procalcitonin, ng/mL, median (IQR); *n*	0.145 (0.1–0.37); 166
Hemoglobin; *n*, g/dL, median (IQR)	11.5 (10.4–13.1); 323
Leukocytes, G/L, median (IQR); *n*	8.6 (5.86–12.18); 323
Neutrophils, G/L, median (IQR); *n*	3.76 (2.13–7.13); 302
Lymphocytes, G/L, median (IQR); *n*	2.4 (1.49–3.96); 301
Platelets, median (IQR); *n*	298 (210–385); 313
Chest radiograph, *n*/*N* (%)	203/381 (52)
Bilateral lesions, *n*	38
Alveolar condensation, *n*	52
Interstitial syndrome, *n*	32
Pleural effusion, *n*	9
Cardiomegaly, *n*	16
Hospital care, *n*/*N* (%)	
Hospital care ≥1,	180/397 (45)
Nasal oxygen	67/391 (17)
Bronchodilator	37/387 (10)
Enteral feeding tube	67/384 (17)
Intravenous hydration	108/371 (29)
Antibiotics, *n* (%)	167/391 (43)

lymphopenia and 28 of 313 (9%) showed thrombocytopenia.

Chest radiography findings were abnormal in 70 of 203 (34%) children, with bilateral interstitial infiltrate as the most-frequent lesion (Table 1).

A posteriori and on the basis of the final diagnosis recorded by the physicians and hospital treatments, we distinguished 4 different clinical patterns:

- Pattern 1: paucisymptomatic SARS-CoV-2 infection with no hospital treatment required, admitted for clinical surveillance (n = 148, 37%). Three of these paucisymptomatic children were admitted in February in a PICU to be isolated according to local guidelines, without any other criteria of intensive care requirement.
- Pattern 2: SARS-CoV-2 infection requiring hospital care (n = 158 cases, 40%), with 3 main forms of COVID-19 described: (1) lower respiratory tract infection (LRTI) (n = 95 of 158, 60%), (2) digestive form (n = 24 of 158, 15%), and (3) isolated fever (n = 28 of 158, 18%). We classified children according to the physicians' clinical assessment describing the severity of each organ involvement (oxygenotherapy requirement, intravenous rehydration, etc). Physicians also defined a primary diagnosis, which allowed for classification in the respiratory or digestive form. Other forms (n = 11 of 158, 7%) are detailed in Supplemental Table 5.
- Pattern 3: multisystem inflammatory syndrome in children (MIS-C) was defined by persistent fever, presence of laboratory markers of inflammation, manifestation of signs or symptoms of organ dysfunction, lacking an alternative diagnosis,[27] and, as for the other patients included in this cohort, a positive RT-PCR

TABLE 1 Continued

	Total *N* = 397
Corticosteroids, *n* (%)	17/389 (4)
Antiviral treatment, *n* (%)	7/390 (2)
Hydroxychloroquine, *n* (%)	2/387 (1)
Admission to PICU, *n* (%)	81/397 (20)
Length of hospital stay, d, median (IQR)	3 (2–7)
n	370
Length of stay in PICU, d, median (IQR)	5 (3–9)
n	68
Death, *n* (%)	6/396 (2)
Critical care in PICU, *n* (%)	43/81 (52)
Hemodynamic support, *n* (%)	21/76 (28)
Noninvasive ventilation support, *n* (%)	18/77 (23)
Invasive ventilation support, *n* (%)	17/74 (23)

[a] If age >30 d and sex was available. Categorical variables are described with numbers (percentages) and quantitative variables are described with median (IQR) or mean (±SD). For invasive and noninvasive ventilation, we reported the maximum ventilatory support required.

nasopharyngeal result for SARS-CoV-2 (MIS-C, *n* = 29, 7%).

- Pattern 4: hospitalization for another disease and COVID-19 was not the final diagnosis (*n* = 62 cases, 16%). Some of these were admitted children tested for COVID-19 as part of hospital-wide surveillance. The most frequent diagnoses were surgical pathology and urinary tract infection. Each diagnosis is detailed in Supplemental Table 6.

Both the clinical pattern of SARS-CoV-2 infection and the rate of severity were highly different depending on age group (Table 2, Fig 2). Children <90 days of age were the largest group, with 145 patients (37%) of our cohort. Their clinical pattern was specific because most them (59%, 85 of 145) were paucisymptomatic, no MIS-C were observed, and LRTI were diagnosed in 18 cases (12%). In this age group, fever was almost a constant finding (92%). Overall, 4 (3%) children <90 days had a severe disease. Among children <90 days old, 63 of 145 (43%) were <30 days old, among which severe disease was observed in 3 of 63 (5%) cases, including 2 LRTI and 1 other diagnosis: prematurity and *Escherichia coli* meningitis. In comparison, children between 3 and 12 months old were paucisymptomatic in only 33% (16 of 48) cases, as many as were diagnosed with LRTI (16 of 48). However, patients with severe diseases remained rare, with 3 of 48 cases (6%), and only 1 patient was diagnosed as MIS-C. LRTI was a major diagnosis in all age groups beyond 1 year with 20% to 36% of cases according to age group.

The number of patients with MIS-C increased in older children age between 1 and 5 years old, 5 to 10 years old, and 10 to 15 years old, with 7 of 46 cases (15%), 9 of 49 cases (18%), and 10 of 65 cases (15%), respectively, but decreased for children age between 15 and 18 years old (only 2 of 44 [5%] MIS-C cases). Antibiotics were the most-used treatment, with a percentage varying from 31% to 65% according to age group. Among children <90 days of age, 40% received antibiotics, despite most of them being paucisymptomatic.

The characteristics described by clinical patterns are provided in Supplemental Table 7, which clearly show a specific pattern for the 29 children diagnosed as MIS-C with high and persistent fever, higher inflammatory syndrome with a median CRP at 179 (105–270), high proportion of severe disease (52%), and a long delay between COVID-19 contact and hospitalization (34 days, IQR: 23–47).

Factors Associated With Severe Disease Excluding Patients with MIS-C

Factors associated with disease severity were assessed for pattern 1 and 2 children because pattern 3 (MIS-C) was not considered an acute SARS-CoV-2 infection and showed a specific profile, and outcomes from children in pattern 4 were not mainly related to SARS-CoV-2 infection. Overall, severe disease was detected in 23 of 306 children (11%, 95% CI: 8%–15%), including 20 patients requiring ventilatory support and 5 with hemodynamic support (Table 3). Numerous characteristics were associated with disease severity on univariate analysis (Table 3), but only 3 were independently associated on multivariate analysis: age ≥10 years (OR: 3.4, 95% CI: 1.1–10.3, *P* = .034), hypoxemia (OR: 8.9, 95% CI: 2.6–29.7, *P* = .0004), and CRP ≥80 mg/L (OR: 6.6, 95% CI: 1.4–27.5, *P* = .012).

Deaths

We recorded 6 deaths in our surveillance system, plus 1 patient positive for immunoglobulin G anti–SARS-CoV-2 antibody who was enrolled but not included in the main analysis because the case did not meet our inclusion criteria (negative on RT-PCR nasopharyngeal test) (Supplemental Fig 3). These 7 patients were the only deaths reported in children to Public Health France in the context of SARS-CoV-2 infection in France, and some were previously reported.[28] Among these 7 children, 3 had a comorbidity (immunodeficiency, leukemia, and encephalopathy). Most had a respiratory failure, with high levels of inflammatory parameters, and the imputability of SARS-CoV-2 infection in the death was high in 5 cases (Table 4).

TABLE 2 Characteristics and Evolution by Age Group

	<90 d (*n* = 145, 37%)	90 d–<1 y (*n* = 48, 12%)	1–<5 y (*n* = 46, 12%)	5–<10 y (*n* = 49, 12%)	10–<15 y (*n* = 65, 16%)	15–<18 y (*n* = 44, 11%)
Male sex, *n* (%)	93 (65)	29 (60)	28 (61)	25 (51)	33 (51)	16 (37)
Comorbidities, *n* (%)	12 (8)	9 (19)	20 (43)	17 (35)	32 (49)	24 (55)
Fever, *n*/*N* (%)	128/139 (92)	34/47 (72)	35/45 (78)	35/47 (74)	38/64 (59)	30/43 (70)
Cough, *n*/*N* (%)	44/142 (31)	27/46 (59)	16/46 (35)	25/49 (51)	28/64 (44)	28/44 (64)
Rhinitis, *n*/*N* (%)	86/143 (60)	31/45 (69)	18/46 (39)	11/47 (23)	10/63 (16)	11/43 (26)
Dyspnea, *n*/*N* (%)	31/141 (22)	22/48 (46)	13/46 (28)	20/49 (41)	17/62 (27)	16/44 (36)
Diarrhea, *n*/*N* (%)	30/142 (21)	14/48 (29)	7/46 (15)	14/49 (29)	20/64 (31)	8/43 (19)
Vomiting, *n*/*N* (%)	16/142 (11)	8/47 (17)	8/46 (17)	17/48 (35)	18/62 (29)	10/43 (23)
CRP, mg/L, median (IQR)	3 (1–5)	7 (4–23)	24 (4–83)	42 (10–207)	24 (2–105)	21 (3–135)
n	132	36	37	40	51	34
Procalcitonin, ng/mL, median (IQR)	0.1 (0.1–0.2)	0.1 (0.1–0.5)	0.3 (0.2–3.3)	3.9 (0.1–86)	6.9 (0.1–36)	1.1 (0.2–4.9)
n	102	15	13	16	9	11
Hemoglobin, g/dL, median (IQR)	11.3 (10.5–13.4)	11.3 (10.6–12.1)	10.9 (9.7–11.9)	11.9 (10.5–12.9)	12.5 (10.7–13.7)	12.7 (10.6–14.1)
n	129	33	37	39	49	36
Leukocytes, G/L, median (IQR)	7.5 (5.5–10.0)	9.9 (7.3–12.8)	10.6 (6.2–17.4)	10.5 (8.3–15.6)	8.4 (5.8–12.5)	7.3 (5.9–11.5)
n	128	33	37	39	51	35
Lymphocytes, G/L, median (IQR)	3.2 (2.0–4.8)	4.2 (3.0–5.5)	2.7 (1.7–4.0)	1.8 (0.9–2.6)	1.4 (1.0–2.3)	1.5 (1.2–2.4)
Neutrophils, G/L, median (IQR)	2.6 (1.6–3.7)	3.6 (1.5–5.9)	7.3(3.3–14.4)	7.5 (4.6–11.2)	5.6 (3.4–9.5)	4.8 (3.7–7.7)
Platelets, G/L, median (IQR)	328 (245–434)	349 (244–412)	266 (201–327)	273 (186–313)	248 (183–367)	246 (172–344)
Hospital care ≥1, *n*/*N* (%)	46/145 (32)	26/48 (54)	30/46 (65)	29/49 (59)	32/65 (49)	17/44 (39)
Nasal oxygen	9/145 (6)	9/48 (19)	9/46 (20)	14/49 (29)	15/65 (23)	11/44 (25)
Bronchodilator	2/145 (1)	7/48 (15)	8/46 (17)	9/49 (18)	7/65 (11)	4/44 (9)
Enteral feeding tube	22/145 (15)	10/48 (21)	10/46 (22)	9/49 (18)	9/65 (14)	7/44 (16)
Intravenous hydration	25/145 (17)	13/48 (27)	19/46 (41)	20/49 (41)	21/65 (32)	10/44 (23)
Antibiotics, *n*/*N* (%)	58/145 (40)	15/48 (31)	18/46 (39)	32/49 (65)	29/65 (45)	15/44 (34)
Corticosteroids, *n*/*N* (%)	0/145 (0)	1/48 (2)	4/46 (9)	5/49 (10)	4/65 (6)	3/44 (7)
PICU transfer,[a] *n* (%)	10 (7)	7 (15)	13 (28)	19 (39)	21 (32)	11 (25)
Severe disease, *n* (%)	4 (3)	3 (6)	6 (13)	13 (27)	12 (18)	6 (14)
Ventilatory support, *n* (%)	2 (1)	2 (4)	4 (9)	7 (14)	8 (12)	3 (7)
Hemodynamic support, *n* (%)	1 (1)	1 (2)	3 (7)	9 (18)	7 (11)	0 (0)
Deaths, *n* (%)	0 (0)	1 (2)	1 (2)	1 (2)	0 (0)	3 (7)
Length of hospital stay, d, median (IQR)	3 (2–4)	3 (2–7)	4 (2–7)	3.5 (2.5–6)	11 (7–17)	7 (3–20)

NA, not available.

[a] PICU transfer means that patients were admitted to PICU either from the emergency department or from a hospital department. Categorical variables are described with numbers (percentages), and quantitative variables with median (IQR). The cutoff used for normal CRP level was 10 mg/L. Severity was defined as need for either ventilatory or hemodynamic support during hospitalization, or death.

DISCUSSION

This national prospective study has allowed for analyzing the clinical spectrum of hospitalized SARS-CoV-2 infection in children, including acute infections and MIS-C, and assessing factors associated with severe clinical evolution. A total of 60 hospitals throughout France participated, which allowed us to obtain a completeness rate of 38.5%. The evolution of pediatric cases over time mirrored that of adult admission reported by Public Health France both temporally and geographically, which suggests that our network adequately captured the epidemiological pattern of hospitalized children with SARS-CoV-2 infections. The strong decrease in cases 2 weeks after the national lockdown highlighted the major impact of these unprecedented measures in reducing the burden of SARS-CoV-2 infection in children.

An important concern in the literature was the specific burden of SARS-CoV-2 infection in young children.[6,29,30] Authors of a report from China[6] described a higher rate of severe forms among children aged <1 year versus older children, and authors of another report from Italy suggest that infants aged <6 months seem significantly more susceptible to severe forms of the disease, leading to important concerns about this specific age group[6,29,30] and playing a role in recommending closure of most day care centers during lockdown in France. Our results shed particular light on this issue. On the one hand, children <90 days old were the leading group because they accounted for 37% of all children hospitalized, but on the other, 97% (141 of 145) of them had no severe disease and 68% were discharged from the hospital with little care. Fever was the most common symptom (92%, 128 of 139) in this age group, and 40% (58 of 145) received antibiotics. In another words, most of these children were hospitalized owing to risk of bacterial infection because they had fever without a clear source and were <90 days old.[31] The use of a rapid test at

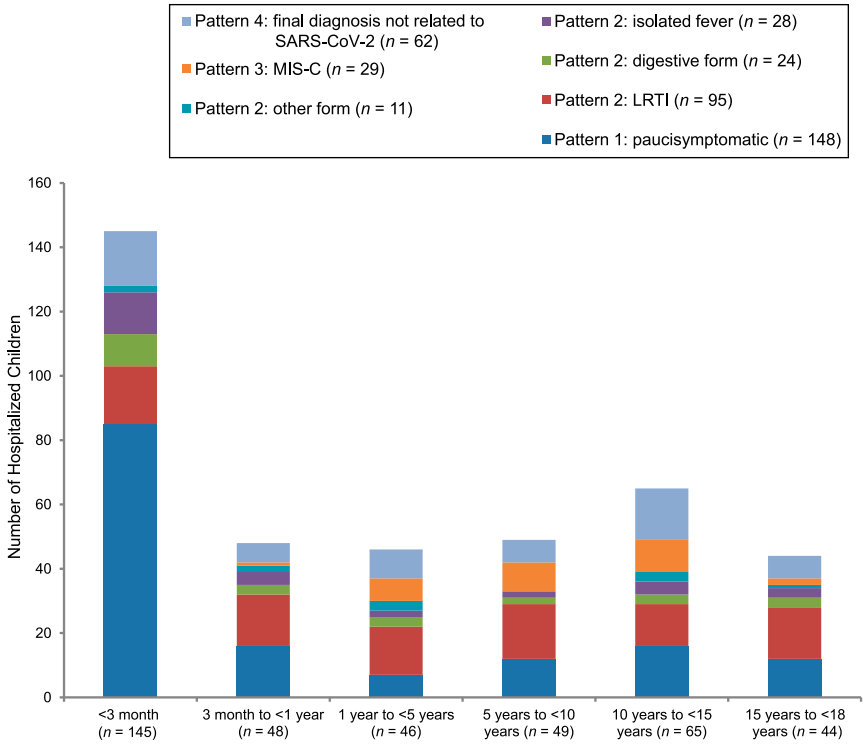

FIGURE 2

Clinical pattern by age group, *N* = 397. LRTI, low respiratory tract infection; MIS-C, pediatric inflammatory multisystem syndrome

the bedside to identify SARS-CoV-2 would be helpful to improve the care of these children in pediatric emergency departments.

In a recent study, Götzinger et al[32] also suggested that the likelihood of severe forms may be increased in children <1 month old. However, our findings suggest that the rate of severe forms was lowest in very young children and highest for children ≥10 years on both univariate and multivariate analysis. These findings agree with Zachariah et al,[17] who describe the disease course with COVID-19 in 14 children <1 year old, with no case of severe evolution.

The definition of severity should be considered in these comparisons. Although we defined severity as need for ventilatory or hemodynamic support, in line with Zachariah et al,[17] Dong et al,[6] who described the Chinese cohort, defined severe cases as respiratory symptoms, dyspnea, and hypoxemia,[6] and Götzinger et al[32] defined severe cases as admission to the PICU. In our cohort, several children <1 year old required transient nasal oxygenotherapy, and several were transferred to the PICU only for surveillance with regards to the very young age, depending on local practices. They evolved favorably in the large majority of cases, without ventilatory support, and have not been considered as severe cases. This information could be useful to guide reopening day care centers and recommend suitable mitigation measures, which are highly difficult to apply in these settings. According to the French Pediatric Society, the educational and social benefits provided by school far outweigh the risks of a possible COVID-19 contamination of children in school environments or in day care centers.[33]

We also identified several factors associated with severe disease evolution, including hypoxemia and CRP ≥80 mg/L. Few studies assessed factors associated with poor outcomes in pediatric COVID-19. The 2 main studies are a recent US monocentric cohort[17] and a multinational study.[32] Elevated levels of inflammatory parameters and respiratory symptoms were also found as a prognostic factor.[34]

This surveillance system allowed us to identify different clinical profiles of hospitalized children with SARS-CoV-2 infections, ranging from paucisymptomatic forms to MIS-C. The main clinical symptoms reported in our cohort agreed with the literature (fever in 70%–80%, cough in 40%–50%, dyspnea in 30%–40%).[7,17] Among this wide clinical spectrum, the proportion of severe forms was highly variable and greatest for LRTI (21%) and MIS-C (52%). This novel clinical entity has since been widely described in Italy,[11] France,[12,13] England,[15] and the United Sates,[14,16] reporting a high rate of PICU transfer (60%–75%) and hemodynamic support requirement (40%–50%).[11,12,15] Our findings confirm that MIS-C is among the most severe forms linked to SARS-CoV-2 infection in children. Our results are in line with previous studies suggesting that MIS-C happens not in the acute phase of the SARS-CoV-2 infection but as a postinfectious phenomenon despite our patients expressing a positive RT-PCR result.

Another issue of concern at the time of school reopening is children with comorbidities, including immunosuppression. Several comorbidities have been associated with poor outcomes in adults,[35] including chronic respiratory and cardiac diseases, but these remain unclear for children.[7,18,28,36,37] Comorbidities were frequent in our cohort (29%, *n* = 114), but these comorbidities were not independently associated with severe evolution and accounted for only 22 severe cases of hospitalization on

TABLE 3 Factors Associated With Severe Form of SARS-CoV-2 Infection

	Severe Forms (n = 23)	Nonsevere Form (n = 283)	Univariate Analysis		Multivariate Analysis	
	n/N (%)	n/N (%)	OR (95% CI)	P	OR (95% CI)	P
Age >10 y	12/23 (52)	56/283 (20)	4.4 (1.9–10.8)	<.0001	3.4 (1.1–10.3)	.034
Male sex	10/23 (43)	165/281 (59)	0.5 (0.2–1.3)	.16	—	—
Comorbidities	15/23 (65)	72/283 (25)	5.5 (2.3–14.2)	<.0001	2.9 (0.9–9.9)	.075[a]
Asthma	2/23 (9)	18/283 (6)	1.4 (0.2–5.3)	.66	—	—
Other chronic respiratory diseases	2/23 (9)	5/283 (2)	5.3 (0.7–26.3)	.055	—	—
Immunosuppression or malignancy	4/23 (17)	13/283 (5)	4.4 (1.1–13.8)	.017	—	—
Diabetes	0/23 (0)	4/283 (1)	0.0 (NA–10^53)	.99	—	—
Cardiac disease	1/23 (4)	6/283 (2)	2.1 (0.1–13.1)	.50	—	—
Obesity	1/23 (4)	5/283 (2)	2.5 (0.1–16.6)	.41	—	—
Neurologic disease	4/23 (17)	13/283 (5)	4.4 (1.1–13.8)	.017	—	—
Overweight	1/21 (5)	18/227 (8)	0.6 (0.0–3.1)	.61	—	—
Fever	18/22 (82)	215/275 (79)	1.3 (0.4–4.5)	.69	—	—
Cough	12/23 (52)	127/278 (46)	1.3 (0.6–3.1)	.55	—	—
Rhinitis	6/23 (26)	136/275 (49)	0.4 (0.1–0.9)	.037	—	—
Shortness of breath or dyspnea	12/22 (55)	55/270 (20)	4.7 (1.9–11.7)	.0007	—	—
Hypoxemia	8/19 (42)	17/271 (6)	10.9 (3.8–30.7)	.0001	8.9 (2.6–29.7)	.0004
Abdominal pain	1/16 (6)	25/160 (16)	0.6 (0.3–1.0)	.064	—	—
Diarrhea or vomiting	7/22 (32)	79/277 (29)	1.2 (0.4–2.9)	.74	—	—
Neurologic symptom	4/22 (18)	20/277 (7)	2.9 (0.8–8.6)	.08	—	—
CRP ≥80 mg/L	10/23 (43)	14/227 (6)	11.7 (4.3–31.7)	.0001	6.6 (1.4–27.5)	.012
Procalcitonin >2 ng/mL	5/13 (38)	6/118 (5)	11.7 (2.8–48.0)	.0005	—	—
Leukocytes >10 G/L	12/23 (52)	70/230 (30)	2.3 (1.0–5.6)	.055	—	—
Lymphocytes <1.5 G/L	8/20 (40)	39/212 (18)	3.0 (1.1–7.6)	.027	—	—
Neutrophils >10 G/L	7/20 (35)	15/212 (7)	7.1 (2.4–20.2)	.0003	—	—
Platelets <150 G/L	8/21 (38)	11/216 (5)	11.5 (3.9–33.7)	.0001	—	—

Association with severity was assessed for children with pattern 1 and 2 (n = 335) because outcomes from those with pattern 3 were not related to SARS-CoV-2 infection. Severity was defined as need for either ventilatory or hemodynamic support during hospitalization, or death. Variables significant at $P \leq .20$ on univariate analyses were included in the stepwise selection.—, variables not included in the final multivariate model.

[a] Multivariate analysis showed comorbidities due to the clinical relevance of this variable, even if not significant.

a national scale. These observations may also help policy makers allow for standard school activities for these populations and help physicians to reassure families in this process.

The main strength of our study was the use of a national surveillance system that captured a large part of hospitalized cases of SARS-CoV-2 infections with precise clinico-biological data in France, allowing us to define the rate of severe disease evolution by clinical pattern and factors associated with severe evolution. Our study also has several limitations. First, we decided to include only children with a positive RT-PCR nasopharyngeal result for SARS-CoV-2 or a CT scan revealing radiographic evidence of lesions compatible with COVID-19 and excluded children with positive serology alone. These criteria allowed us to enhance the imputability of SARS-CoV-2 infection in the clinical features observed but may have led to missing some patients with postinfectious disorders such as MIS-C, for which the RT-PCR nasopharyngeal test result may be negative.[11,13] Further studies including MIS-C with negative RT-PCR nasopharyngeal results for SARS-CoV-2 but positive serology are ongoing to appreciate this burden. Second, the clinical spectrum of included patients may depend on the SARS-CoV-2 testing strategy. At the early stage of the epidemic, only patients with respiratory symptoms were tested, and indications became broader when asymptomatic, digestive, and inflammatory forms had been described, which led some hospitals to adopt universal testing at admission.[17] Thus, the proportion of the different forms was likely be influenced by evolving local SARS-CoV-2 testing strategies, and the children in pattern 4 (positive for SARS-CoV-2 but hospitalized for another disease) may be overestimated. However, most of the PICUs throughout France followed the same testing policy, with wide indications for any child requiring PICU admission.

CONCLUSIONS

This national surveillance system allowed for describing the broad clinical spectrum of children hospitalized with acute SARS-CoV-2 infections and defining the risk of severe disease for each clinical form. Infants <3 months old were the main age group requiring hospitalization, but most of them expressed a mild form of COVID-19. The independent factors associated with increased risk of severe disease may help clinicians manage this infection in children.

TABLE 4 Characteristics of the 7 Children Who Died in a Context of SARS-CoV-2 Infection

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7[a]
Age	16 y	5 mo	5 y	16 y	4 y	17 y	9 y
Sex	Male	Male	Female	Female	Male	Female	Male
Comorbidity	No	Chronic granulomatous disease	No	No	Leukemia	Encephalopathy	No
Clinical presentation	Meningo-encephalitis	Respiratory failure	Septic shock	Respiratory failure	Respiratory failure	Respiratory failure	Vasoplegic shock
CRP, mg/L	249	169	293	147	1	235	277
procalcitonin, ng/mL	86	2.4	184	NA	NA	NA	22
Lymphocytes count, G/L	0.4	5.1	0.4	2.5	NA	1.2	1.0
Chest radiograph findings	NA	Alveolar and interstitial syndrome	Alveolar and interstitial syndrome, pleural effusion	Alveolar syndrome	Alveolar syndrome	Alveolar syndrome	Alveolar syndrome
Cause of death	Meningo-encephalitis	ARDS	Severe MRSA infection postvaricella	ARDS	ARDS	Pneumonia	Myocarditis
Imputability of SARS-CoV-2	Low	High but partial	Low	High	High but partial	High but partial	High

ARDS, acute respiratory distress syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available.

[a] Patient with negative SARS-CoV-2 RT-PCR result but positive SARS-CoV-2 immunoglobulin G were not included in our cohort.

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ABBREVIATIONS

CI: confidence interval
CRP: C-reactive protein level
CT: computed tomography
IQR: interquartile range
LRTI: lower respiratory tract infection
MIS-C: multisystem inflammatory syndrome in children
OR: odds ratio
RT-PCR: real-time reverse transcriptase polymerase chain reaction

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