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ORIGINAL ARTICLE

Clinical spectrum of COVID-19 and risk factors associated with severity in Spanish children

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Abstract

We aimed to identify the spectrum of disease in children with COVID-19, and the risk factors for admission in paediatric intensive care units (PICUs). We conducted a multicentre, prospective study of children with SARS-CoV-2 infection in 76 Spanish hospitals. We included children with COVID-19 or multi-inflammatory syndrome (MIS-C) younger than 18 years old, attended during the first year of the pandemic. We enrolled 1200 children. A total of 666 (55.5%) were hospitalised, and 123 (18.4%) required admission to PICU. Most frequent major clinical syndromes in the cohort were mild syndrome (including upper respiratory tract infection and flu-like syndrome, skin or mucosae problems and asymptomatic), 44.8%; bronchopulmonary syndrome (including pneumonia, bronchitis and asthma flare), 18.5%; fever without a source, 16.2%; MIS-C, 10.6%; and gastrointestinal syndrome, 10%. In hospitalised children, the proportions were 28.5%, 25.7%, 16.5%, 19.1% and 10.2%, respectively. Risk factors associated with PICU admission were age in months (OR: 1.007; 95% CI 1.004 to 1.01), MIS-C (OR: 14.4, 95% CI 8.9 to 23.8), chronic cardiac disease (OR: 4.8, 95% CI 1.8 to 13), asthma or recurrent wheezing (OR: 2.5, 95% CI 1.2 to 5.2) and after excluding MIS-C patients, moderate/severe liver disease (OR: 8.6, 95% CI 1.6 to 47.6). However, asthmatic children were admitted into the PICU due to MIS-C or pneumonia, not due to asthma flare.

Conclusion: Hospitalised children with COVID-19 usually present as one of five major clinical phenotypes of decreasing severity. Risk factors for PICU include MIS-C, elevation of inflammation biomarkers, asthma, moderate or severe liver disease and cardiac disease.

What is Known:

- *All studies suggest that children are less susceptible to serious SARS-CoV-2 infection when compared to adults. Most studies describe symptoms at presentation. However, it remains unclear how these symptoms group together into clinically identifiable syndromes and the severity associated with them.*

What is New:

- *We have gathered the primary diagnoses into five major syndromes of decreasing severity: MIS-C, bronchopulmonary syndrome, gastrointestinal syndrome, fever without a source and mild syndrome. Classification of the children in one of the syndromes is unique and helps to assess the risk of critical illness and to define the spectrum of the disease instead of just describing symptoms and signs.*

Keywords COVID-19 · SARS-CoV-2 · Children · Clinical phenotypes · MIS-C · Severity

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Abbreviations

COVID-19	Coronavirus infectious disease
CRP	C-reactive protein
FWS	Fever without source

HFO	High-flow oxygen
IQR	Interquartile range
MIS-C	Multisystem inflammatory syndrome in children
RT-PCR	Real-time polymerase chain reaction
OR	Odds ratio
PICU	Paediatric intensive care unit
URTI	Upper respiratory tract infection

Introduction

Children under 18 years of age represented a minority hospitalised COVID-19 cases during the first year of the pandemic [1, 2]. Their symptoms are usually milder [3–5]. Symptoms at presentation have been described in some studies [6]; however, it remains unclear how these symptoms group together into clinically identifiable phenotypes.

Only 0.4% of severe cases are children [7]. Risk factors that lead to severe disease in children have been partly described, and include young age, obesity and underlying comorbidities, lymphopenia and elevation of other inflammatory biomarkers including high C-reactive protein (CRP) [8–10].

The present study aimed to define further the spectrum of COVID-19 in children and the risk factors for hospitalisation and admission in paediatric intensive care units (PICUs) during the first year of the pandemic in Spain.

Methods

Design

The Epidemiological Study of Coronavirus in Children (EPICO-AEP) is a multicentre cohort study conducted in Spain to assess the characteristics of children with COVID-19. In total, 76 hospitals collected data from the beginning of the epidemic in Spain (March 12th) until March 22nd, 2021. The study was approved by the Ethics Committee of Hospital 12 de Octubre, Madrid (code 20/101), and other participating hospitals. Participants were enrolled after signed or verbal consent from parents/guardians and by the consent of patients older than 12 years.

Eligible participants were children aged from 0 to 18 years who attended in any of the hospitals of the network from the first patient included in March 12th, 2020, to March 22nd, 2021, with a SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR), rapid antigen test or children fulfilling WHO criteria for multisystem inflammatory syndrome in children (MIS-C) [11]. Children hospitalised were enrolled during the whole year. Children attended in the emergency rooms and discharged without admission were recorded only until October 1st, 2020. Of the patients with MIS-C, 31 were described in a prior research report [12]. The protocol included follow-up until discharge.

Laboratory methods

Respiratory samples for SARS-CoV-2 RT-PCR were obtained from nasopharyngeal swabs and tracheal or bronchial aspirates, when available. Serum samples for SARS-CoV-2 serology were analysed in local clinical microbiology laboratories using commercial kits. The remaining haematological, biochemical and microbiological analyses were performed in the laboratories of each centre following routine validated methodology.

Definitions

Primary diagnoses related to COVID-19 were established according to data supplied by the attending physician. We categorised the diagnoses as the following: MIS-C, pneumonia, bronchitis, bronchiolitis, asthma flare or recurrent wheezing, flu-like syndrome, upper respiratory tract infection (URTI), fever without source (FWS), gastroenteritis, abdominal pain, skin or mucosae problems and asymptomatic. Diagnoses definitions are summarised in Supplementary Table 1. When more than one simultaneous diagnosis was present, a severity hierarchy was established to define the primary diagnosis, as follows: MIS-C > pneumonia > flu-like > gastroenteritis > bronchitis, bronchiolitis or asthma flare > URTI > fever without a source > abdominal pain > asymptomatic.

Admissions in PICUs did not follow uniform predefined criteria but as per clinical judgement.

For analysis purposes, diagnoses were categorised into five phenotypes: "MIS-C," "bronchopulmonary disease" (including pneumonia, bronchiolitis, bronchitis and asthma flare), "gastrointestinal disease" (including gastroenteritis and abdominal pain), "fever without a source" and "mild disease" (URTI, flu-like syndrome, skin or mucosae problems and asymptomatic patients).

Data management and statistical analyses

Researchers from each participating hospital collected pseudo-anonymised data using a standardised clinical research form on the electronic data capture system REDCap [13]. Data included main epidemiological, demographic, clinical and laboratory variables.

Continuous variables were categorised according to standard definitions [14]. To dichotomise the continuous

variables without a standardised categorisation, optimal cut-off points were assessed using generalised additive models implemented in the cutpointr R package [15–17].

We analysed baseline risk factors for hospitalisation and admission into a PICU due to COVID-19 or complications with binary logistic regression. The procedure backwards stepwise (likelihood ratio), as an exploratory test, was performed for those binary variables with a p-value < 0.2 in the univariable analysis. Statistical analyses were performed using SPSS.

Results

Features of the cohort

A total of 1200 children were enrolled of whom 666 (55.5%) were hospitalised. The remaining 534 (45.5%) children were discharged from the Emergency Departments after evaluation and care (Supplementary Fig. 1). Weekly admissions during the first year of the pandemic are shown in Supplementary Fig. 2.

The median age was 4.7 years (interquartile range [IQR], 9 months to 5.6 years) and 664/1199 (55.4%) were male. Close contact with a patient with confirmed COVID-19 was confirmed in 644/1182 (54.5%) participants. Baseline clinical information of the whole cohort is summarised in Tables 1 and 2.

Comorbidities were present in 330 patients (27.5%) (Supplementary Table 2). Symptoms at presentation are shown in Fig. 3. The most frequent primary diagnoses were URTI, 290/1200 (24.1%); fever without a source, 194/1200 (16.1%); pneumonia, 163/1200 (13.6%); MIS-C, 127/1200 (10.6%); flu-like syndrome, 126/1200 (10.5%); asymptomatic, 115/1200 (9.6%); gastroenteritis, 86/1200 (7.2%); bronchitis, 36/1200 (3%); abdominal pain, 34/1200 (2.8%); bronchiolitis, 12/1200 (1%); asthma flare, 11/1200 (0.9%); and skin or mucosae problems, 6/1200 (0.5%).

For a better and easier understanding, we grouped them into five major clinical phenotypes: 538/1200 (44.8%) presented with mild disease, 222/1200 (18.5%) bronchopulmonary disease, 192/1200 (16.2%) fever without a source, 128/1200(10.6%) MIS-C and 120/1200 (10%) gastrointestinal disease.

For the 666 hospitalised patients, the frequency of primary diagnosis is presented in Fig. 1. In summary, 189/666 (28.5%) had mild disease, 171/666 (25.7%) had bronchopulmonary disease, 127/666 (19.1%) had MIS-C, 110/666 (16.5%) had fever without a source and 68/666 (10.2%) had gastrointestinal disease.

The overlapping of diagnoses was not relevant: only 6% of children with respiratory disease had also gastrointestinal disease, and 20% of children with MIS-C had an X-ray compatible with pneumonia.

The patients with mild disease were admitted for different reasons, including significant prior serious comorbidity

Table 1 Summary characteristics of the total cohort globally and categorised by hospitalisation

Feature	Total		Not hospitalised		Hospitalised not PICU		PICU		p-value
	***N* = 1200**	**% of 1200**	***n* = 534**	**% of feature**	***n* = 543**	**% of feature**	***n* = 123**	**% of feature**	
Phenotypes									< 0.001
Mild	537	44.8	347	64.6	178	33.1	12	2.2	
Bronchopulmonary	222	18.5	51	23.0	143	64.4	28	12.6	
Fever without a source	194	16.2	84	43.3	108	55.7	2	1.0	
MIS-C (multisystem inflammatory syndrome)	127	10.6	0	0.0	51	40.2	76	59.8	
Gastrointestinal	120	10.0	52	43.3	63	52.5	5	4.2	
Sex									0.05
Male	665	55.4	280	42.1	306	46.0	79	11.9	
Close contact with COVID-19	644	53.7	309	48.0	280	43.5	55	8.5	0.013
Codetection	112	9.3	15	13.4	72	64.3	25	22.3	0.044
Virus-virus	33	2.8	8	24.2	16	48.5	9	27.3	
Virus-bacteria	78	6.5	7	9.0	55	70.5	16	20.5	
Respiratory support									< 0.001
Oxygen	182	15.2	6	3.3	89	48.9	87	47.8	
High-flow therapy	42	3.5		0.0	8	19.0	34	81.0	
Mechanical ventilation	32	2.7		0.0		0.0	32	100.0	
Complications	210		4	1.9	109	51.9	97	46.2	< 0.001

Table 2 Summary characteristics of the total cohort globally and categorised by hospitalisation (continuous variables)

	Total	**Not hospitalised**	**Hospitalised not PICU**	**PICU**	***p*-value**
	***N* = 1200**	***n* = 534**	***n* = 543**	***n* = 123**	
Age (months), Median [IQR]	58 [9–136]	63 [13–130]	36 [2–129.75]	120 [61–157] (excluding MIS-C): 101 [5–165]	< 0.001
	n = 1156	*n* = 497	*n* = 536	*n* = 123	
Weight percentile, Median [IQR]	50 [21–81]	53 [28–88]	41 [16.25–75]	53.5 [24–78]	< 0.001
	n = 979	*n* = 401	*n* = 476	*n* = 102	
Fever days Median [IQR]	3 [2–6]	3 [2–4]	4 [2–7]	7 [5–9]	< 0.001
	n = 777	*n* = 275	*n* = 400	*n* = 102	
Heart frequency Median [IQR]	124 [100–145]	110.5 [91–137]	130 [105–150]	126 [110–144]	< 0.001
	n = 874	*n* = 268	*n* = 487	*n* = 119	
Respiratory frequency, Median [IQR]	30 [22–40]	26 [20–35]	31 [24–41]	30 [22–44]	0.004
	n = 450	*n* = 89	*n* = 277	*n* = 84	
Oxygen saturation (%), Median [IQR]	98 [97–99]	98 [97–99]	98 [97–99]	98 [95–99]	0.073
	n = 872	*n* = 273	*n* = 482	*n* = 117	
Systolic blood pressure Median [IQR]	102 [91–114]	110 [96–119]	102 [92–111]	97 [85–115]	< 0.001
	n = 517	*n* = 87	*n* = 319	*n* = 111	
Diastolic blood pressure Median [IQR]	60 [52–69]	63 [56–70]	60 [52–69]	55 [47–67]	0.001
	n = 517	*n* = 87	*n* = 319	*n* = 111	
Haemoglobin (g/dL), Median [IQR]	12 [10–13]	12.5 [11–13]	12 [10–14]	11 [9–12]	0.123
	n = 86	*n* = 16	*n* = 55	*n* = 15	
Leucocytes (mm^3), Median [IQR]	7900 [5120–11,697.5]	7300 [50750–9842]	7870 [5135–11480]	9600 [5205–15795]	0.005
	n = 704	*n* = 118	*n* = 465	*n* = 121	
Lymphocytes (mm^3), Median [IQR]	1960 [992.5–3565]	2450 [1340–4000]	2150 [1115–3725]	800 [415–1852]	< 0.001
	n = 700	*n* = 115	*n* = 465	*n* = 120	
Neutrophils (mm^3), Median [IQR]	3640 [1800–7400]	3100 [1600–4900]	3451 [1747.5–7017.5]	6995 [2775–12,847.5]	< 0.001
	n = 701	*n* = 115	*n* = 466	*n* = 120	
Platelets (mm^3), Median [IQR]	255,500 [165000–379500]	267,000 [202750–363500]	270,000 [182000–389000]	180,000 [103000–311000]	< 0.001
	n = 730	*n* = 128	*n* = 479	*n* = 123	
AST (U/L), Median [IQR]	36 [25–55]	31 [22–48.5]	34 [25–50]	49 [32–82]	< 0.001
	n = 554	*n* = 88	*n* = 355	*n* = 111	
ALT (U/L), Median [IQR]	24 [15–45]	20 [15–29.5]	22 [15–39]	25 [43.5–87]	< 0.001
	n = 625	*n* = 105	*n* = 403	*n* = 117	
C-reactive protein (mg/L), Median [IQR]	43 [5–152.75]	3.5 [1–11.25]	18 [4.5–112]	195 [120.5–246.5]	< 0.001
	n = 180	*n* = 26	*n* = 109	*n* = 45	
Procalcitonin (ng/mL), Median [IQR]	9.5 [5–32.5]	5 [5–5]	6 [4.25–28.25]	16 [11–99]	0.246
	n = 16	*n* = 1	*n* = 8	*n* = 7	
Serum sodium (mEq/L), Median [IQR]	137 [135–139]	138 [136.5–140]	137 [135–139]	135 [133–139]	< 0.001
	n = 619	*n* = 97	*n* = 406	*n* = 116	
Lactate dehydrogenase (U/L), Median [IQR]	321 [250–417]	248 [203–312.5]	326.5 [258–416.25]	368 [287.25–507.5]	< 0.001
	n = 455	*n* = 65	*n* = 284	*n* = 106	
D-dimer (μg/L), Median [IQR]	1150 [448–3066.5]	350 [187–810]	926 [427–1965]	3078 [1631.5–5985]	< 0.001
	n = 361	*n* = 29	*n* = 235	*n* = 97	
IL-6 (pg/mL), Median [IQR]	99.5 [12.25–1328.75]		12 [6–65]	263.5 [64.5–611.5]	< 0.001
	n = 76	-	*n* = 34	*n* = 42	
Ferritin (ng/mL), Median [IQR]	282 [97–680]	77 [41.5–279]	208.5 [78.5–522.75]	552 [282.75–1312.5]	< 0.001
	n = 299	*n* = 21	*n* = 196	*n* = 82	
Urea (mg/dL), Median [IQR]	24 [17–32]	24.5 [16–32]	23 [17–30]	31 [21.5–49.5]	< 0.001
	n = 490	*n* = 66	*n* = 327	*n* = 97	
NT-proBNP (pg/mL), Median [IQR]	7994 [3676–17974]		4650.5 [1653.25–9066.5]	10,324 [4051–20404]	0.011
	n = 67	-	*n* = 24	*n* = 43	
Troponin I (ng/mL), Median [IQR]	320 [51–691]	-	78.5 [30–xx]	525 [72–702]	0.236
	n = 13		*n* = 2	*n* = 11	

PICU, paediatric intensive care unit; *IQR*, interquartile range; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *IL-6*, interleukin 6; *NT-proBNP*, N-terminal pro-B type natriuretic peptide

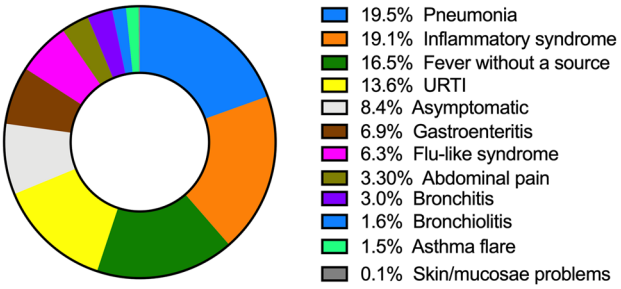

Fig. 1 Primary diagnoses of the 666 patients admitted with COVID-19

(18.8%), current concomitant autoimmune or thrombotic comorbidity (12.8%), current concomitant comorbidities not related with COVID-19 (11.3%), bacterial coinfections (8.5%), isolation (4.3%), other (3.2%) and unspecified reasons (40.9%) (see Supplementary Table 3).

A total of 206/666 (30.9%) hospitalised patients had complications. The most frequent complications were cardiological 75/666 (11.3%) and 59/666 (8.9%) shock. Cardiological complications included myocardial dysfunction 7.2%; valve dysfunction 2.6%; arrhythmia 2%; coronary abnormalities 1.8%; and aneurysms 0.5%. Other complications are outlined in Supplementary Table 4.

Coinfections were found in 97/666 (14.5%) patients, most often bacterial-viral infections (71/666; 10.6%).

Patients admitted to the PICU

A total of 123/666 (18.4%) hospitalised patients were admitted to a PICU, for a median of 5 (IQR 3) to 8 days (Table 1). The most frequent diagnoses were MIS-C 76/123 (61.8%) and pneumonia 27/123 (22%).

Nine (1.3% of hospitalised) patients died. Five of them had coinfections (3 bacterial due to *Enterococcus faecalis*, *Enterococcus faecium* and *Clostridium difficile*), and two viral (*Parainfluenzae* and type 1 herpes virus). All except one had serious comorbidities, which were malignancies ($n=3$), autoimmune chronic pulmonary disease, dilated myocardiopathy, STAT-3 immunodeficiency, severe congenital immunodeficiency and bronchopulmonary dysplasia. Three of them had haematopoietic stem cell transplantation. One patient without serious comorbidities had moderate overweight (body mass index, 24).

Four children needed extracorporeal membrane oxygenation support (ECMO), two of them died. A total of 57/123 (46.3%) children required inotropic support.

The risk of needing PICU admission was different across major clinical phenotypes. In the univariable analysis, only MIS-C had an increased risk of PICU (odds ratio [OR]: 32.5, 95% CI 20.5 to 51.5). Bronchopulmonary disease had an OR of 1.3 (95% CI 0.8 to 21.1), and the rest were protective: FWS (OR: 0.07, 95% CI 0.01 to 0.1), gastrointestinal disease (OR: 0.3, 95% CI 0.1 to 0.8) and mild disease (OR: 0.1, 95% CI 0.06 to 0.2) (Fig. 2).

In the univariable model, male sex (OR: 1.5, 95% CI 1.02 to 2.2), not having an identified close contact (OR: 1.6, 95% CI 1.1 to 2.5) and some specific comorbidities as chronic cardiac disease (OR: 2.5, 95% CI 1.07 to 5.9), asthma or recurrent wheezing (OR: 2.1, 95% CI 1.2 to 3.9) and moderate/severe liver disease (OR: 5.3, 95% CI 1.2 to 22.7) were predictors for PICU admission.

In the multivariable model, baseline risk factors associated with PICU admission were age in months (OR: 1.007; 95% CI 1.004 to 1.01), MIS-C (OR: 14.4, 95% CI 8.9 to 23.8), chronic cardiac disease (OR: 4.8, 95% CI 1.8 to 13) and asthma or recurrent wheezing (OR: 2.5, 95% CI 1.2 to 5.2). However, out of 18 children with pre-existing asthma or recurrent wheezing, none of them was admitted with asthma flare, but ten were admitted with MIS-C and eight with pneumonia. Excluding MIS-C, only age in months (OR: 1.005; 95% CI 1.001 to 1.009) and moderate/severe liver disease (OR: 8.6, 95% CI 1.6 to 47.6) remained significant.

Among those patients with blood tests performed (see Table 2), abnormalities were also associated with PICU admission; specifically leucocytosis > 15,000/mm^3 (OR: 2.4, 95% CI 1.5 to 3.9), neutrophilia > 10,000/mm^3 (OR: 4.3, 95% CI 2.8 to 6.8), lymphopenia < 1000/mm^3 (OR: 5.6, 95% CI 3.6 to 8.6), thrombopenia < 150,000/mm^3 (OR: 4.9, 95% CI 3.2 to 7.5), CRP > 20 mg/L (OR: 18.9, 95% CI 5.5 to 64), GPT > 37 U/L (OR: 4.2, 95% CI 2.8 to 6.5), LDH > 500 U/L (OR: 2.2, 95% CI 1.3 to 3.8), hyponatremia < 135 mmol/L (OR: 3.4, 95% CI 2.2 to 5.2), D-dimer > 500 ng/mL (OR: 4.4, 95% CI 2.1 to 8.9), IL-6 > 8.5 pg/mL (OR: 32.2, 95% CI 3.9 to 263), ferritin > 400 mg/dL (OR: 3.9, 95% CI 2.2 to 6.7).

MIS-C patients

A total of 127 (19.1% of hospitalised) children were diagnosed with MIS-C. The median age was 9.2 years (IQR 5.2 to 12.5). Of them, 35 (27.6%) fulfilled the criteria for Kawasaki disease, and 76/127 (59.8%) needed admission to a PICU.

A total of 54 children (42.5%) had positive SARS-CoV-2 RT-PCR in respiratory samples (nasopharyngeal swab or bronchial aspirate); IgM was positive in 32/99 (32%) and IgG in 96/105 tested (91%). All patients who were IgM positive were also IgG positive. Blood tests found in MIS-C revealed high-level inflammation and target-organ damage (Supplementary Table 5).

Cardiological complications (71/127, 56%) consisted of myocardial dysfunction 48/127 (37%), valvular dysfunction 17/127 (13%), pericardial effusion 12/127 (9.4%), arrhythmias 12/127 (9.4%) and coronary abnormalities 12/127

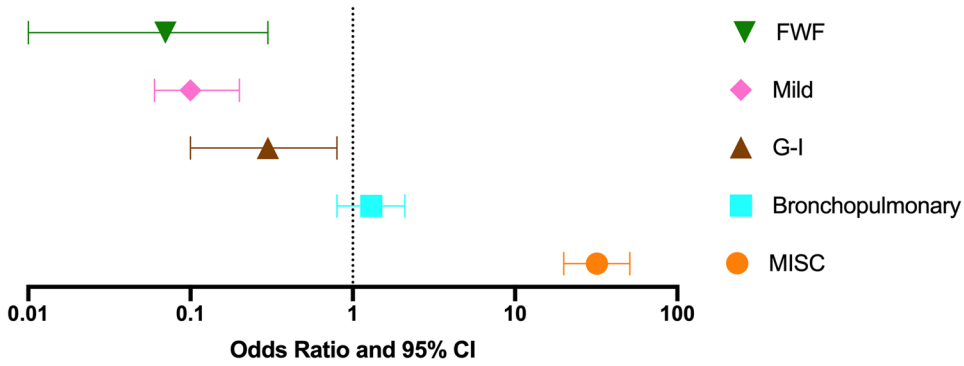

Fig. 2 Odds ratio and 95% confidence interval of PICU admission across major phenotypes. Horizontal axis is displayed as log (10) scale. FWF, fever without a source; G-I, gastrointestinal disease; MIS-C, multiinflammatory syndrome

(9.4%), of which 3/127 (2.3%) were aneurysms, and one of them a giant aneurysm in anterior descending artery (*Z*-score + 9). Other complications included renal failure 17/127 (13.3%), need of mechanical ventilation 16/127 (12.5%) and need of oxygen 58/127 (45.7%).

Three patients died: one patient with acute leukaemia and bone marrow transplant, one with overweight and one with malignant neoplasm.

Specific treatment was provided as follows: steroids only 22/126 (17.3%), intravenous immunoglobulin only 18/126 (14.2%), both 79/126 (62.2%) and none 7/126 (5.5%). Steroids used were mostly intravenous metil-prednisolone (119/126, 95%).

Median time of PICU admission was 5 days [3 to 7], and median time of admission was 9 days [6 to 12].

In the multivariable model, baseline features that in the model were associated with MIS-C were age in months (OR: 1.01, CI 95%: 1.007 to 1.01), male gender (OR: 1.7, CI 95%: 1.1 to 2.6) and immunosuppressive medication (OR: 6.4, 95% CI 2.2 to 18.5).

Discussion

In this study, we have identified the spectrum of COVID-19 in children attended in Spanish hospitals during the first year of pandemic. Initial features of COVID-19 are very unspecific, and patients may show a very wide spectrum of sign and symptoms, as shown in Fig. 3. We have identified twelve frequent diagnoses that can be grouped into five major clinical phenotypes for a more practical approach: MIS-C, bronchopulmonary disease, gastrointestinal disease, fever without a source (FWS) and mild disease. This classification better defines COVID-19 in children than previous definitions and can guide severity assessment.

We identified similar risk factors for critical disease as other studies [8, 18, 19]. We added some new factors, especially specific comorbidities. Interestingly, immunosuppression and neoplasia were not risk factors for PICU admission, although most deceased patients had serious immunosuppression or cancer. Most deceased patients were patients with severe comorbidities, and half of them had coinfections.

Age, asthma or recurrent wheezing and heart diseases are risk factors for PICU admission. Liver disease was in the limit of significance. Interestingly, asthmatic patients were not admitted to the PICU due to asthma flare, but due to pneumonia or MIS-C. These risk factors seem to influence predominantly patients with MIS-C, because after excluding patients with MIS-C of the analysis, only age and chronic liver disease remained as risk factors for PICU. Additionally, immunosuppressive treatments were risk factors for MIS-C. This may be considered for stepwise immunisation strategies in children, so those with significant pre-existing comorbidities get immunised first.

Other risk factors as IL-6, CRP, D-dimer and cytopaenia suggest immune dysregulation and severe inflammation in critical patients. CD4 and natural killer T-cell cytopaenia due to immune dysregulation have been described previously [20].

Immune dysregulation may also be involved in manifestations that are not clearly related to COVID-19 but have been found in this and other cohorts, such as diabetic debut, haemolytic anaemia or appendicitis. A significant increase in diabetic ketoacidosis in children was found during the COVID-19 pandemic [21]. A clinical picture consistent with appendicitis in children has been reported, as well as ileitis [22, 23]. In this study, some patients with appendicitis, diabetic debut and ileitis were also identified concomitantly or soon after SARS-CoV-2 infection.

Immune dysregulation is also involved in MIS-C. Some features of MIS-C, such as shock or cardiac disease, may be responsible for laboratory abnormalities such as high ALT or creatinine (Supplementary Table 5). However, specific mechanisms for kidney injury secondary to COVID-19 have been previously proposed [24].

The national seroprevalence study ENE-COVID [2] suggests that in December, 400,000 children were seropositive in Spain. Considering that our study included 10% of the 800 private and public hospitals of Spain, including

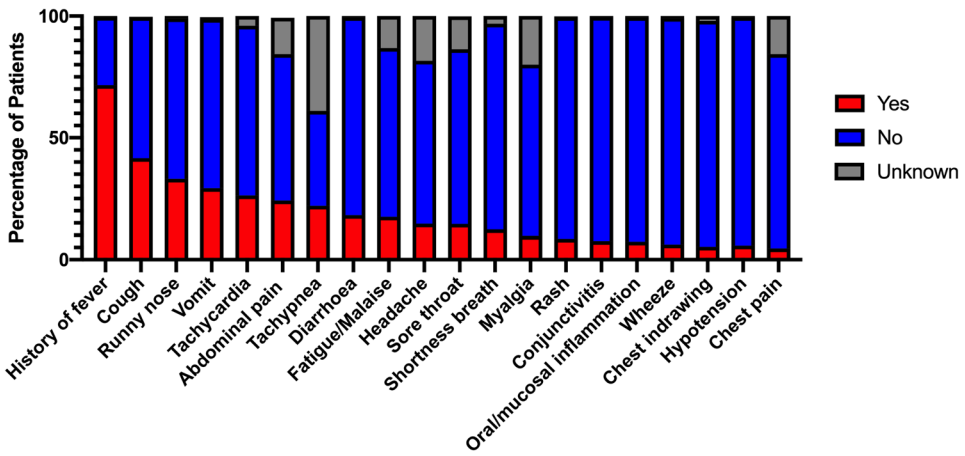

Fig. 3 Signs and symptoms at presentation of the 1200 enrolled patients. Those present in < 5% of patients are not displayed

most tertiary public hospitals, likely less than 1% of children with COVID-19 needed hospitalisation; and less than 0.05% needed intensive care.

This study included children attended in different hospitals. There is a risk of selection, case identification and reporting bias for hospitalisation and for PICU admission. Access to SARS-CoV-2 testing was not consistent during the enrolment, especially during the first wave. The diversity and broadness of the study are strengths, as they provide insight into the disease in a major clinical part of Spain through a prospective collection of data.

Although viral-bacterial coinfection was found in a significant proportion of hospitalised children, a full workup for coinfections was not done uniformly, and thus the role of coinfections is not completely clear. The study included few neonates because most neonates with COVID-19 in Spain were included in a different neonatal registry.

The ethnic origin was not recorded, so we cannot compare our study with other studies suggesting worse outcome in minorities. The categorisation and interpretation of this variable tend to be simplistic—for instance, Black versus others or Caucasians versus others, and the minority factor is often linked to economical and sociodemographic characteristics, which we did not collect [25, 26].

We believe that this classification is unique and helps to define the spectrum of the disease instead of just describing symptoms and signs. Understanding different clinical manifestations, and the heterogeneity of infection and post-infection manifestations, may help in diagnostic strategies.

Conclusions

The infrequent COVID-19 that requires hospitalisation in children presents as any of five major clinical phenotypes of decreasing severity: MIS-C, bronchopulmonary disease, gastrointestinal disease, mild disease and fever without a source. Risk factors for PICU include MIS-C, inflammation biomarkers and specific comorbidities as asthma, moderate or severe liver disease, and cardiac disease.

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Authors' contributions AT and CM conceptualised and designed the study. AT performed the statistical analysis. AT, CM, CG, AS and SV drafted the manuscript. All co-authors participated in the collection of data. All co-authors participated and were involved in the critical review of the final manuscript.

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Availability of data and material Available on reasonable request.

Declarations

Ethics approval The study was approved by the Ethics Committee of Hospital 12 de Octubre, Madrid (code 20/101), and other participating hospitals.

Consent to participate Participants were enrolled after signed or verbal consent from parents/guardians and by the consent of patients older than 12 years.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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