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BRIEF REPORT

Manifestations and clinical phenotypes are not specific enough to predict SARS-CoV-2 infection in symptomatic children

The massive number of infected individuals who have to be tested for SARS-CoV-2 has attracted the attention to novel diagnostic approaches, focusing on symptom-based screening.[1] Some countries have emerged national testing policies, but a large number of positive children do not report any of the included symptoms in those guidelines.[2]

This study aimed to analyse symptoms/signs associated with SARS-CoV-2 infection among symptomatic children screened for COVID-19 and define clinical phenotypes that could differentiate COVID-19 from other infections.

We performed a cross-sectional multicentre study, nested in a prospective, observational cohort, EPICO-AEP (Epidemiological Study of COVID-19 in Children of the Spanish Society of Paediatric).[3]

Eligible participants were children <18 years old with symptoms compatible with SARS-CoV-2 infection lasting ≤5 days (Table 1)[1] attended at 10 emergency departments in Spain, from 2 March to 15 June 2021 (third epidemic wave in Spain; >70% SARS-CoV-2 isolations identified as alpha variant). SARS-CoV-2 infection was diagnosed by reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab.

Patients were classified into two age groups (≤3 and >3 years). Standard statistical methods were used to summarise the data. Categorical variables were compared with χ^2 or Fisher's test and continuous variables with Kruskal–Wallis test.

Two-stage factor analysis, including exploratory and confirmatory analysis, was used to define clinical phenotypes (cluster of correlated symptoms/signs).[4] Factors including ≥2 symptoms with loadings ≥0.40 were selected based on habitual practice[4] and named as specific phenotypes. Once the symptom factor model was defined, factor scores were extracted, and the phenotypes associated with positive SARS-CoV-2 were evaluated using a univariable logistic regression. Correlations between clinical phenotypes were calculated using Pearson correlation test (*r*). Statistical analyses were performed by Factor v.4.0.3, R statistical v.4.0.5 and lavaan v.0.6-8 software packages.

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 consent from parents/guardians and by the consent of patients ≥12 years.

Overall, 1174 children were attended with symptoms compatible with COVID-19 and included in the study. The median age was 3.8 years (interquartile range: 1.7–9.0), and 518 (44.5%) were females (Table 1). Sixty-eight (5.8%) had a positive SARS-CoV-2 RT-PCR: 16/516 (3.1%) if ≤3 years and 52/657 (7.9%) if >3 years.

Children with COVID-19 had significantly less vomiting/nausea and diarrhoea, but more headache, myalgia and arthralgia (Table 1). Among children <3 years old, there were no significant differences according to SARS-CoV-2 result, except more vomiting in negative cases. Children >3 years old with SARS-CoV-2 infection showed a higher prevalence of fever, headache and myalgia, and lower abdominal pain, vomiting/nausea and diarrhoea than negative SARS-CoV-2 children.

The resulting factor model was composed of the following phenotypes: *Lower Respiratory* (dyspnoea, wheezing and chest indrawing), *Upper Respiratory* (runny nose and cough), *Gastrointestinal* (abdominal pain, vomiting/nausea and diarrhoea) and *Flu-like* (arthralgia, myalgia, fatigue, headache and sore throat).

Respiratory-related phenotypes (*Lower Respiratory* and *Upper Respiratory*) were correlated ($r = 0.62$), as well as *Flu-like* and *Gastrointestinal* phenotypes ($r = 0.32$). Only the *Flu-like* phenotype was associated with a positive SARS-CoV-2 result (Table 1). In younger children, no clinical phenotype was associated with the SARS-CoV-2 result, but in older children, the *Flu-like* phenotype was associated with positive SARS-CoV-2 (OR: 1.84 [95% CI: 1.09–3.11], $p = 0.023$) and the *Gastrointestinal* phenotype with negative SARS-CoV-2 (OR: 0.56 [95% CI: 0.34–0.91], $p = 0.020$).

Other studies comparing the clinical characteristics of children screened for SARS-CoV-2 infection also remarked the difficulties in defining a predictive profile of symptoms.[1] Some studies have identified some manifestations associated with SARS-CoV-2 infection, such as fever, headache or dysgeusia, but generally showing a low specificity.[5]

A previous study including children hospitalised with COVID-19 also classified patients according to phenotypes: discrete respiratory illness, systemic mucocutaneous-enteric illness and neurological phenotype.[2] The different groups compared with our study could be explained because they only included hospitalised patients.

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TABLE 1 Characteristics of children according to RT-PCR SARS-CoV-2 result

	Overall (*N* = 1174)	Negative result (*N* = 1106)	Positive result (*N* = 68)	OR [95% CI]	*p* Ratio	*p* Overall
Sex (female)	518/1165 (44.5%)	485/1098 (44.2%)	33/67 (49.3%)	1.23 [0.75; 2.02]	0.419	0.493
Age (years)	3.8 [1.7; 9.0]	3.7 [1.7; 8.7]	8.1 [3.2; 12.2]	1.11 [1.06; 1.17]	**<0.001**	**<0.001**
Groups of age						**0.001**
≤3 years	516/1174 (44.0%)	500/1106 (45.2%)	16/68 (23.5%)	Ref.	Ref.	
>3 years	657/1173 (56.0%)	605/1105 (54.8%)	52/68 (76.5%)	2.67 [1.54; 4.89]	**<0.001**	
Fever	760/1171 (64.9%)	712/1103 (64.6%)	48/68 (70.6%)	1.31 [0.78; 2.29]	0.315	0.378
Cough	547/1172 (46.7%)	520/1104 (47.1%)	27/68 (39.7%)	0.74 [0.44; 1.22]	0.239	0.289
Sore throat	286/1158 (24.7%)	263/1091 (24.1%)	23/67 (34.3%)	1.65 [0.96; 2.76]	0.069	0.082
Runny nose	603/1169 (51.6%)	568/1101 (51.6%)	35/68 (51.5%)	0.99 [0.61; 1.63]	0.984	1.000
Wheezing	101/1172 (8.6%)	100/1104 (9.1%)	1/68 (1.5%)	**0.17 [0.01; 0.78]**	**0.016**	0.052
Myalgia	84/1126 (7.5%)	70/1061 (6.6%)	14/65 (21.5%)	**3.91 [1.99; 7.25]**	**<0.001**	**<0.001**
Arthralgia	23/1124 (2.1%)	19/1060 (1.8%)	4/64 (6.3%)	**3.75 [1.03; 10.5]**	**0.045**	**0.037**
Fatigue	139/1147 (12.1%)	127/1081 (11.7%)	12/66 (18.2%)	1.68 [0.84; 3.14]	0.138	0.174
Dyspnoea	100/1166 (8.6%)	100/1099 (9.1%)	0/67 (0.0%)	–	–	**0.018**
Chest Indrawing	48/1164 (4.1%)	46/1096 (4.2%)	2/68 (2.9%)	0.74 [0.11; 2.48]	0.674	1.000
Headache	213/1128 (18.9%)	190/1065 (17.8%)	23/63 (36.5%)	**2.65 [1.53; 4.51]**	**0.001**	**<0.001**
Abdominal pain	259/1138 (22.8%)	251/1073 (23.4%)	8/65 (12.3%)	0.47 [0.20; 0.94]	**0.032**	0.055
Vomiting/nausea	318/1173 (27.1%)	310/1105 (28.1%)	8/68 (11.8%)	**0.35 [0.15; 0.70]**	**0.002**	**0.005**
Diarrhoea	225/1173 (19.2%)	223/1105 (20.2%)	2/68 (2.9%)	**0.13 [0.02; 0.41]**	**<0.001**	**0.001**
Conjunctivitis	18/1170 (1.5%)	18/1102 (1.6%)	0/68 (0.0%)	–	–	0.619
Oral inflammation	75/1173 (6.4%)	72/1105 (6.5%)	3/68 (4.4%)	0.69 [0.16; 1.94]	0.527	0.796
Rash	36/1173 (3.1%)	35/1105 (3.2%)	1/68 (1.5%)	0.52 [0.02; 2.44]	0.483	0.718
Dysgeusia or anosmia	23/940 (2.5%)	20/1086 (2.3%)	3/60 (5.0%)	2.36 [0.52; 7.20]	0.230	0.177
Days of symptoms	1.0 [1.0; 2.0]	1.0 [1.0; 2.0]	1.0 [1.0; 2.0]	0.91 [0.76; 1.09]	0.307	0.862
Days of fever	1.0 [0.0; 2.0]	1.0 [0.0; 2.0]	1.0 [1.0; 1.0]	0.96 [0.78; 1.18]	0.681	0.812
Clinical phenotypes						
Lower respiratory	−0.05 [−0.23; 0.32]	−0.05 [−0.23; 0.32]	−0.07 [−0.23; 0.31]	0.72 [0.44; 1.18]	0.192	–
Upper respiratory	−0.10 [−0.36; 0.42]	−0.10 [−0.37; 0.44]	−0.12 [−0.32; 0.35]	0.79 [0.45; 1.38]	0.407	–
Gastrointestinal	−0.14 [−0.39; 0.52]	−0.11 [−0.39; 0.58]	−0.14 [−0.38; 0.11]	0.70 [0.44; 1.10]	0.121	–
Flu-like	−0.12 [−0.22; 0.43]	−0.12 [−0.22; 0.43]	−0.09 [−0.19; 0.85]	2.24 [1.40; 3.59]	**0.001**	–

Note: For the prevalence of symptoms, fractions are shown as the number of cases having a symptom/number of patients evaluated for that symptom. For the clinical phenotypes, the mean scores are included. Significant *p*-values (<0.05) are shown in bold. Categorical variables are presented as frequencies (%) and continuous variables as medians (IQR). *p*-values and OR were calculated excluding cases with an unknown response.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio.

Due to the difficulty to differentiate clinically COVID-19 from other viral infections, efforts should be focused on developing and implementing less invasive microbiological tests with good performance, such as saliva or oral swab. Non-microbiological tests, such as lung ultrasound, could add additional diagnostic information.

This study has some limitations. It accounted for only one wave, including predominantly the alpha variant, and some relevant viruses, such as influenza, were not circulating, limiting the extrapolation of the data to latter waves with different variants and viruses circulating. Although SARS-CoV-2 was discarded, other viruses were not routinely tested, and negative SARS-CoV-2 cases were based on a single sample. Finally, the history of COVID-19 contact was not collected.

In conclusion, the screening for SARS-CoV-2 in children with symptoms compatible with COVID-19 is challenging. Although during the alpha variant wave some symptoms (headache, myalgia and arthralgia), or phenotypes (*Influenza-like* in older children) were more common, or some symptoms (notably diarrhoea) very uncommon among children with SARS-CoV-2 infection, they are not specific

enough to diagnose SARS-CoV-2 infection. Thus, clinicians should not rely only on their clinical judgement to diagnose SARS-CoV-2 in children and should use microbiological techniques to rule out COVID-19.

KEYWORDS

children, COVID-19, SARS-CoV-2

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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