Observational Study

Symptom clusters helping the assessment of SARS-COV-2-infected children
Amiens cohort versus European data

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Abstract

Background: Since December 2019, the novel coronavirus (SARS-CoV-2) pandemic, caused >240 million cases and >5 million deaths. Given the current wider dissemination of pediatric cases, it is important to address questions regarding the clinical picture in children or if there are clinical patterns that may help us identify in an early stage what can be the prognosis and help clinicians with patient management. The study aimed to investigate in a French monocentric cohort and other European cohorts the presence of symptom clusterization and its possible connection to illness categories to help medical first-line screening and orientation in the pediatric emergency department (ED).

Methods: We conducted a retrospective cohort study describing clinical, laboratory, and radiological characteristics of SARS-CoV-2-infected children admitted to pediatric ED to assess the presence of symptom clustering. A scoping review of the literature was performed to further investigate symptom clusters.

Results: Of 1086 tested children, 48 tested positive to SARS-CoV-2. The clinical, laboratory, and radiological characteristics of our sample were fully described. Two distinct clusters of clinical phenotypes were identified as well as their potential association with illness categories in SARS-CoV-2-infected children. Comparison with similar European cohorts highlights how symptoms coming from the mucocutaneous-enteric, and the respiratory clusters are associated with a more severe clinical picture.

Conclusions: This study promotes the importance to identify early prognostic patterns to help clinicians in the decision process, especially in COVID-19 pediatric patients.

Abbreviations: CHU = Centre Hospitalier Universitaire, CPR = C-reactive protein, CT = computed tomography, CT-VL = cycle threshold viral load, ED = emergency departments, Hb = hemoglobin, IQR = interquartile ranges, MIS-C = multisystem inflammatory syndrome in children, NIH = National Institutes of Health, RBC = red blood cells, RDW = red blood cell distribution width, SARS-CoV-2 = coronavirus, STROBE = strengthening the reporting of observational studies in epidemiology, WBC = white blood cells, WHO = World Health Organization.

Keywords: COVID-19, cluster analysis, Europe, pediatrics, pediatric emergency medicine

1. Introduction

Since December 2019, the novel coronavirus (SARS-CoV-2) pandemic emerged, causing >240 million infections and >5 million deaths and these numbers are growing steadily.[1]

In the early stages of the epidemic, many children with SARS-CoV-2 were infected as part of family clusters,[2] and the mean incubation period is usually 2 days with a range of 2 to 10 days.

Transmission takes place through respiratory droplets or contact with symptomatic cases. Furthermore, SARS-CoV-2 has been detected in the stool of some patients especially in children, so fecal-oral transmission is potentially possible. Transmission from asymptomatic cases, especially children, seems to have also an important role. According to the experience of several countries affected by the pandemic, children might experience different symptoms than do adults and usually present milder

symptoms such as fever, dry cough, sore throat, runny nose, abdominal pain, nausea/vomiting, diarrhea, myalgia, asthenia, headache, and skin diseases.[3,4]

The data on laboratory markers in children also revealed lower lymphocytopenia (3%–3.5%) than adults (63%) in several studies. Also, children generally had lower increased C-reactive protein levels. Thus, the overall prognosis of the disease in children is relatively good.[5]

Even if, during this new epidemic wave due to the SARS-CoV-2 Delta variant, we observed a higher incidence in children than previous variants, pediatric SARS-CoV-2 cases continue to be less severe than cases in adults and the course of the disease in children is generally mild compared to adults, for reasons that are yet to be explained,[6] yet poses an organizational burden in the emergency departments (EDs) as well as the reorganization of pediatric services with the creation of Pediatric COVID Unit in some hospitals.

Nowadays, many questions remain open regarding clinical manifestations and prognosis in children. Given the current wider dissemination of pediatric cases, it is important to address questions regarding the clinical picture in children or if there are clinical patterns that may help us identify in an early stage what can be the prognosis and help clinicians with patient management.

Swann et al, in a comprehensive study with 651 pediatric cases admitted in over 130 hospitals, were able to identify a pattern of 3 clusters of symptoms which they identified as "systemic mucocutaneous-enteric" (with symptoms as headache, myalgia, sore throat, emesis, diarrhea, fatigue), "respiratory" (cough, fever, tachypnea, rhinorrhea, wheezing), and "neurological" (convulsion, seizures). Even if evidence for symptom clusterization has been described in an early phase of the epidemic, the literature has not investigated further on this issue especially in the pediatric population, except for the fact that the "mucocutaneous-enteric" cluster shares features with Multisystem Inflammatory Syndrome in Children (MIS-C).

In this work, we aimed to fully describe the clinical features of a cohort of children positive to SARS-CoV-2 infection admitted to the ED in a pediatric hospital in France, to investigate the presence of symptom clustering and to compare our findings with those reported by similar European pediatric cohorts.

2. Materials and Methods

We conducted a retrospective study on a children cohort in France, at the Centre Hospitalier Universitaire of Amiens (CHU) – Picardie, France. We checked the records of all patients admitted at the Pediatric ED of the CHU of Amiens-Picardie from March 20, 2020, to April 28, 2021, with COVID-19 suggestive symptoms or identified as contact of a SARS-CoV-2-positive case or admitted for other medical causes who received a nasopharyngeal swab for SARS-CoV-2 PCR screening. We included patients from 0 up to 17 years old which is the age range that has access to the PED. Patients >16 years old access the adult service. Newborns and patients with chronical disease have access to PED but in some cases may benefit of a special pathway with direct access to the hospital wards. Given the unprecedented nature of the pandemic and the small number of SARS-CoV-2-positive patients admitted to the Pediatric ED, we decided to include in the study all SARS-CoV-2-positive patients that accessed the Pediatric ED during the study period. For all positive patients, records on demographics, clinical symptoms at presentation, clinical outcomes (hospitalization and mortality) and available radiological imaging, laboratory values, and SARS-CoV-2 viral loads (VLs) from nasopharyngeal swab were collected by trained personnel in an anonymized format from the hospital digital records.

Hospitalization data were recorded as dichotomous for admission, continuous for days of hospitalization, categorical for reasons for hospitalization, and type of admission (levels are reported in Supplemental Digital Content 3, http://links.lww.

com/MD/G876). Clinical features were recorded as present/nonpresent and symptom clustering analysis was performed. The presence of MIS-C was assessed according to the WHO classification.[7] VL was collected as cycle threshold viral load (CT-VL) where the higher the value the lower the VL present in the sample. Laboratory data were analyzed both with full descriptive statistical analysis and considering out-of-range values according to the patient's age. Out-of-range values were defined according to Nelson Textbook of Pediatrics Reference intervals for laboratory tests.[8]

Patients were stratified into different illness categories (asymptomatic, mild illness, moderate illness, severe illness, critical illness) according to the American National Institutes of Health (NIH) Guidelines.[9] Age categories were grouped as 0 to 2 (infancy), from 2 to 12 (childhood), from 12 to 17 (early and middle adolescence) years old according to the American Academy of Pediatrics classification.[10] The sample size was determined by the number of positive patients that accessed the Pediatric ED of the CHU of Amiens-Picardie from March 20, 2020, to April 28, 2021.

Selection bias was minimized by the fact that all positive patients came from the same population and were included in the study. Loss at follow-up was not an issue due to the short period between enrollment and outcome. The risk of information bias was not considered to be a major issue since retrieving and ascertaining information on outcome, exposure, and selected clinical information was uniform, objective, and extracted by hospital digital records.

To further investigate symptom clusters that could help first-line screening in the ED, we performed a scoping review of the literature on the current evidence of major clinical characteristics in SARS-CoV-2-infected children (0–18 years old), with admission at the ED in the European region. A systematic literature search was performed in PubMed on May 25, 2021, supplemented by a hand search of references from relevant publications. Details on the research strategy and inclusion criteria are provided described Supplemental Digital Content 1 and 2, http://links.lww.com/MD/G876 .

2.1. Statistical methods

Unless otherwise stated, categorical variables were presented as absolute and relative frequency. Median and interquartile ranges (IQRs) were used to show continuous variables in the paper. Full descriptive statistical analysis including mean, median, minimum–maximum, standard deviation, and IQR for continuous variables may be found in Supplemental Digital Contents, http://links.lww.com/MD/G876.The ANOVA test or Kruskal–Wallis H test was used for the intergroup comparison of laboratory values in relation to the disease severity depending on the normality of the distribution.

For the analysis of symptom clustering, we used the Jaccard similarity coefficient (values between 0 and 1 where the higher the number, the higher is the co-occurrence) and presented as a hierarchically ordered heatmap. Clustering was obtained using the complete linkage agglomerative hierarchical clustering method. Estimation of the optimal number of clusters was performed using the Silhouette method (Supplemental Digital Content 8, http://links.lww.com/MD/G876). Missing data were dealt with complete-case data analysis.

We used Excel (Microsoft, Redmond, WA) for descriptive statistics and R [R Core Team version 4.1.1 (2021), Vienna, Austria][11] for plotting and advanced statistical analysis, with packages including tidyverse, ggplot2, ggrepel, dendextend, gplots, and UpSetR.

The study was approved by the CHU-Amiens, Haute Picardie ethics committee with the protocol number: PI2021_843_0052 and performed in the respect of the Helsinki declaration.

Informed consent to use recorded health data and publication was obtained from caregivers of all individual participants included in the study after the ethics committee approved the present study.

This cohort study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12]

3. Results

3.1. Participants and general characteristics

Of 1086 tested children admitted from March 20, 2020, to April 28, 2021, to the Pediatric ED of the CHU of Amiens-Picardie (France), 48 tested positive to SARS-CoV-2.

General characteristics of the study sample are resumed in Supplemental Digital Content 3, http://links.lww.com/MD/G876.

Regarding illness category at the presentation, 5 children were asymptomatic (10%), 32 presented mild illness (65%), 4 moderate illness (15%), 6 severe illness (8%), and only 1 had critical illness (2%), also presenting a condition of MIS-C. Thirty-three (69%) children were hospitalized, 29 children (88%) were admitted in ordinary care, 3 (9%) in subintensive care, and only 1 in intensive care. The median time of hospitalization was 3 days (IQR 2–6, range 1–25). All patients were discharged, and no deaths were reported.

3.2. Clinical findings

3.2.1. Amiens cohort. Clinical findings of our cohort stratified by illness presentation are reported in Table 1. Seven children required oxygen support (15%), while 1 MIS-C case needed intensive care support. Patients that needed respiratory support were either very young (<1 year) or older (≥8 years). Full clinical and radiological characteristics, as well as hospital management of these patients, are described in Supplemental Digital Content 4, http://links.lww.com/MD/G876 . The critical patient with clinical picture of MIS-C, presented fever, and an acute respiratory distress syndrome, needing mechanical ventilation due to a rapid respiratory failure, chest imaging positive for bilateral ground-glass opacities. The results of the clustering analysis of symptoms showed 2 distinct clusters of clinical phenotypes (Fig. 1). Symptoms that more frequently clustered were cough, rhinitis, fever, and dyspnea/

tachypnea (respiratory cluster) with a Jaccard similarity index (which defines co-occurrence of a pair of symptoms) varying from 0.22 to 0.59. This cluster was followed by a gastroenteric cluster (emesis, diarrhea, sore throat, and headache) showing a Jaccard similarity index ranging to 0.07 to 0.14. Neurologic symptoms (convulsion and anosmia/ageusia) formed a much looser association. Evidence of a minor overlap between a subcluster of "fever, cough, and dyspnea/tachypnea" and diarrhea was observed as well. Mucocutaneous-enteric and respiratory clusters were more frequent in severe forms, while neurological signs were more often present in less severe forms (Table 1).

3.3. Clinical findings

3.3.1. Scoping review results: European studies comparison. Our clinical findings were compared with those observed in the other European cohorts of children presenting in the ED[13–20] as resulted by our scoping review (Table 2).Similar prevalence of symptoms was observed in all cohorts. Fever was always the main symptom (43%–82%) except for Turkish cohort in which a different definition of fever wad adopted (>38.0°C compared to >37.5°C for other studies). Fever was often followed by cough (24%–51%). Dyspnea/tachypnea symptoms showed a prevalence around 10% (3%–23%), in all cohorts except for the English 1 (30%) which was characterized by a very high prevalence of critical cases and patients with MIS-C (almost 10 times higher in the English cohort). With regards to gastrointestinal symptoms, diarrhea symptoms varied from 7% to 36%, with the highest prevalence in the Spanish cohort, whilst emesis showed a steady prevalence around 10% except for the Turkish cohort (3%) and for the English and Spanish cohorts showing a prevalence of, respectively, 32% and 38%. However, in these 2 cohorts, nausea alongside with vomiting was considered. Headache was the most common neurological symptom (4%–18%). Anosmia and ageusia were reported only in 5 studies and varies between 2% and 13%.

3.4. Laboratory and radiological findings

3.4.1. Amiens cohort. Laboratory and diagnostic imaging were performed only on severer cases. Chest Computed Tomography showed pulmonary bilateral ground-glass opacities in 3 cases and pneumothorax in 1; chest X-rays of severe cases were less specific

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Table 1

Clinical characteristics of SARS-CoV-2 pediatric infected patients at ED admission stratified by illness categories of the Amiens cohort.

		Overall (n: 48)	Asymptomatic (n: 5)	Mild illness (n: 32)	Moderate illness (n: 4)	Severe illness (n: 6)	Critical illness (n: 1)
Fever	Respiratory cluster	33 (69)	—	23 (72)	4 (100)	5 (83)	1 (100)
Rhinitis		22 (46)	—	16 (50)	2 (50)	3 (50)	1 (100)
Cough		21 (44)	—	12 (38)	3 (75)	5 (83)	1 (100)
Dyspnea/ tachypnea		11 (23)	—	—	4 (100)	6 (100)	1 (100)
Diarrhea	Gastroenteric cluster	13 (27)	—	9 (28)	1 (25)	2 (33)	1 (100)
Emesis		5 (10)	—	4 (13)	—	—	1 (100)
Sore throat		2 (4)	—	—	2 (50)	—	—
Convulsion	Neurological cluster	4 (8)	—	4 (13)	—	—	—
Headache		6 (13)	—	5 (17)	1 (25)	—	—
Anosmia/ ageusia		2 (4)	—	1 (3)	—	1 (17)	—
Required oxygen support		7 (15)	—	—	—	6 (100)	1 (100)
Comorbidities*		16 (33)	2 (40)	10 (31)	1 (25)	2 (33)	1 (100)
MIS-C		1 (2)	—	—	—	—	1 (100)

ED = emergency department, MIS-C = multisystem inflammatory syndrome in children, SARS-CoV-2 = coronavirus.

*Comorbidities: asthma (n:3), asthma and bronchopulmonary dysplasia, renal atrophy, agenesis of corpus callosum, recurrent bronchiolitis, behavior disorders (n:2), West syndrome, Hirschsprung disease, Marfan syndrome, Hypertrophic cardiomyopathy, Preterm birth, recent tonsillectomy, recent 3% body burn.
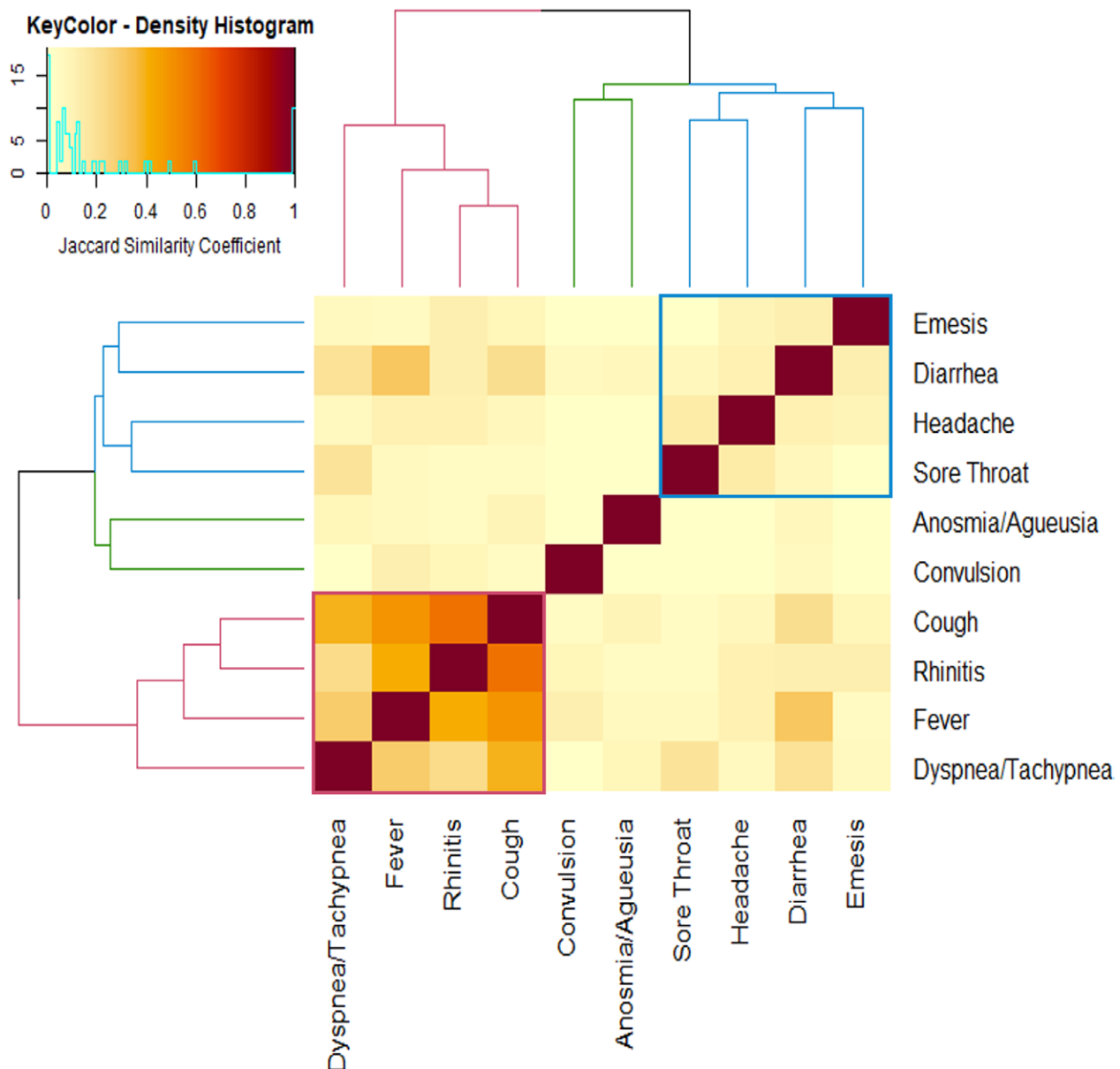
Figure 1. Dendrogram and heatmap describing symptom clustering in SARS-CoV-2-positive pediatric patients and representing symptom co-occurrence. Symptom co-occurrence was calculated using the Jaccard Similarity index where 0 (light yellow) represents when 2 symptoms never occur together and 1 (dark red) if they always appear together. Clustering was obtained using the complete linkage agglomerative hierarchical clustering method. The resulting 2 main symptom clusters (respiratory and gastroenteric clusters) are highlighted respectively by the red and blue squares. SARS-CoV-2 = coronavirus.

(for more detailed information: Supplemental Digital Content 4, http://links.lww.com/MD/G876). A summary of laboratory characteristics at pediatric ED presentation, stratified by illness categories may be found in Table 3, while for complete statistical analysis refer to Supplemental Digital Content 5, http://links.lww.com/MD/G876. No consistent derangements were observed in our cohort when considering the entire group. We did not find clinically and statistical relevant differences between laboratory exams in relation to the severity of the illness category. Yet, is possible to observe a decreasing trend in leukocytes (WBC), in red blood cells (RBCs) and hemoglobin (Hb), and an increasing trend in red blood cell distribution width (RDW) the more severe the illness category. The same trend is observable in WBC, RDW, and RBC if we consider hospitalization (Supplemental Digital Content 6, http://links.lww.com/MD/G876).

When considering the number of patients with laboratory abnormalities defined by age reference range, out-of-range values are more common in RBC, WBC, and C-reactive protein (CPR), respectively, in 50%, 39%, and 39% of cases.

3.5. Viral load

Values for VL were collected from 41 children: the median value was 23.39 (IQR 15.64–29.30), with a descending trend with the increase of illness category severity. Our data show a quadratic curvilinear association between age and CT-VL (Supplemental Digital Content 7, http://links.lww.com/MD/G876). Given the limits of our data that will be discussed in the limitation further in our article, it is not possible to infer further.

4. Discussion

The present study focused on early clinical aspects in a pediatric European population positive for SARS-CoV-2 presenting at

Table 2

Comparison between the clinical characteristics of SARS-CoV-2 pediatric infected patients at ED admission in Europe.

		Amiens cohort (n = 48)	Arslan et al[13] (n = 176)	Aykac et al[14] (n = 518)	Gunen Ozenen et al[15] (n = 251)	Lazzerini et al[16] (n = 159)	Parri et al[17] (n = 170)	Picão De Carvalho et al[18] (n = 103)	Storch-de-Gracia et al[19] (n = 39)	Swann et al[10] [n/tot (%)]‡‡
Country		France	Turkey	Turkey	Turkey	Italy	Italy	Portugal	Spain	United Kingdom
Fever	Respiratory cluster	33 (69)	51 (29)*	259 (50)	143 (57)	131 (82)	72 (48)	44 (43)	32 (82)*	403/577 (70)
Rhinitis		22 (46)	3 (2)†	—	11 (4)	32 (20)†	34 (20)	10 (10)†	14 (36)‡	77/479 (16)
Cough		21 (44)	79 (45)	177 (34)	60 (24)	58 (37)§	73 (43)	27 (26)	20 (51)	218/564 (39)§
Dyspnea/ tachypnea		11 (23)	6 (3)	29 (6)	20 (8)	12 (8)	17 (10)	8 (8)	9 (23)	158/536 (30)‖
Diarrhea	Gastroenteric cluster	13 (27)	13 (7)	49 (10)	9 (7)	18 (11)	19 (11)	13 (13)	14 (36)	90/522 (17)
Emesis		5 (10)	11 (6)¶	27 (5)	7 (3)	16 (10)	24 (14)	10 (10)¶	15 (38)¶	168/532 (32)¶
Sore throat		2 (4)	25/135 (19)	106 (21)	20 (8)	36 (23)	10 (6)	8 (8)#	4 (10)	50/418 (12)
Convulsion	Neurological cluster	4 (8)	—	—	—	2 (1)	—	—	—	—
Headache		6 (13)	—	66 (13)	11 (4)	13 (8)	8 (5)	19 (18)	7 (18)	55/398 (14)
Anosmia/ ageusia		2 (4)	15/118 (13)	34 (7)	5 (2)**	13 (8)	—	5 (5)††	—	—
Required oxygen support		7 (15)	—	—	9 (4)	4/45 (3)	13 (8)	1 (1)	22 (56)	124/651 (19)
Comorbidities		16 (33)	3 (2)	42 (8)	68 (27)	28 (18)	38 (22)	10 (10)	5 (13)	276/651 (42)
MIS-C		1 (2)	—	—	—	—	3 (2)	1 (1)	—	52/456 (11)

— = data not available, ED = emergency department, MIS-C = multisystem inflammatory syndrome in children, SARS-CoV-2 = coronavirus.

*Fever > 38°C.

†Rhinorrhea.

‡Nasal discharge.

§Cough + cough with sputum production.

‖Dyspnea + wheezing.

¶Vomiting and/or nausea.

#Odynophagia.

**Anosmia.

††Anosmia + dysgeusia.

‡‡Sample number changed depending on investigated item and is specified in the corresponding row (total).

the ED. Furthermore, it investigated the presence of symptom clusterization and its possible connection to illness categories to help medical orientation in the ED and compared findings with those observed by other European pediatric cohorts.

This cohort study confirms that only a small number of children admitted to the Pediatric ED resulted positive for SARS-CoV-2 (4%), and most of these cases (67%) fall within the mild illness classification according to the NIH scale; the prevalence of asymptomatic and severe cases was similar (around 10%), fewer moderate cases were observed and only one was critical. These data were in line with previous findings showing that children with SARS-CoV-2 often show less severe forms than adolescents or adults[14,21] with mild or no symptoms at all, and that it is common in a pediatric population to see symptoms that do not interest exclusively the respiratory system. The relevant (66%) number of hospitalizations observed is somehow justified by the precautionary attitude in a pediatric unit, and it is mainly due to surveillance (76%) than for real clinical requirements. This speaks to the necessity to identify early prognostic patterns to help clinicians in the decision process.

Our findings on symptom clustering were consistent with the those reported in an English cohort[20] even though our data tended to cluster around the "systemic mucocutaneous-enteric" and the "neurologic" with less strength than their analysis. This may be justified with our smaller sample size. In both cohorts, evidence of a minor overlap between a subcluster of "fever, cough, and dyspnea/tachypnea" and diarrhea was observed as well.

Furthermore, in our cohort, the more severe cases showed a common picture with a prevalence of symptoms belonging to respiratory and mucocutaneous-enteric clusters. This issue has been scarcely approached in literature[13,14,16,17,19] as, unfortunately, most authors did not stratify symptoms at presentation

by illness categories.. However, although Aykac et al[14] and Arslan et al[13] did not focus on this issue in their articles, their data seem to suggest that symptoms coming from the "systemic mucocutaneous-enteric," and the respiratory cluster occur in higher percentage in more severe cases, while loss of smell coming from the "neurological" cluster occurs more frequently in mild to moderate illness (except headache which is more represented in critical/severe cases). Furthermore, Swann et al[20] and Storch-de-Gracia et al[19] provide stratification by critical care admission and it is possible to observe that symptoms belonging to the "systemic mucocutaneous-enteric" cluster occur significantly more frequently in patients admitted to critical care.

This pattern is supported also by authors outside Europe, as Geva et al,[22] who show how mucocutaneous and gastroenteric clinical involvement is more common in patients with worse outcomes, while neurological involvement is equally represented in the entire cohort.

Although initial evidence of symptom clustering is present in the literature since the beginning of the pandemic,[20] this issue has not been thoroughly investigated up to now and many authors deem it important to further investigate this issue. Being able to identify symptom clustering and how they are related to disease severity and outcome may help implement a clinical bedside approach which may prove to be more useful than a radiological one in predicting child management and allowing a better resource allocation.[17,23]

Regarding VL values, the literature data show contrasting evidence on the VL association with disease severity[24–27] or age.[28–30] Studies in children are limited to a small population with conflicting results about the comparability of VL in children with COVID-19, despite well-defined cohorts of adult studies. Our findings support the existence of a descending trend with the

Table 3

Laboratory characteristics of SARS-CoV-2 pediatric infected patients at ED admission stratified by illness categories of the Amiens cohort.

		RBC	Hb	RDW	WBC	CPR	LDH	AST	ALT	ALP	CT-VL
Overall (n: 48)	n (%)	36 (75)	36 (75)	36 (75)	36 (75)	36 (75)	13 (27)	19 (40)	19 (40)	15 (31)	41 (85)
	Median (IQR)	4.41 (4.06–4.69)	12.30 (11.23–12.98)	12.80 (12.25–13.80)	9.15 (6.63–12.68)	1.10 (1.70–26.80)	307 (214–356.50)	37 (28–56)	29 (19–41)	234 (183–344)	25.48 (15.95–31.03)
	OfR, n (%)	18 (50)	7 (19)	4 (11)	14 (39)	14 (39)	0 (0)	3 (16)	2 (11)	4 (27)	
Asymptomatic (n: 5)	n (%)	2 (40)	2 (40)	2 (40)	2 (40)	2 (40)	1 (20)	1 (20)	1 (20)	1 (20)	5 (100)
	Median (IQR)	4.51 (NA)	13.20 (NA)	12.50 (NA)	10.15 (NA)	1.10 (NA)	150 (NA)	11 (NA)	21 (NA)	111 (NA)	29.30 (22.52–33.23)
	OfR, n (%)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Mild Illness (n: 32)	n (%)	24 (75)	24 (75)	24 (75)	24 (75)	24 (75)	8 (25)	12 (38)	12 (38)	10 (31)	28 (88)
	Median (IQR)	4.46 (4.07–4.70)	12.25 (11.30–12.90)	12.85 (12.25–13.80)	1057.675 pt0 (6.00–15.28)	7.90 (1.48–29.35)	310.50 (255–353.25)	38 (30.25–56.75)	30.50 (23.25–42.50)	293.50 (213.25–914.50)	23.71 (15.45–30.73)
	OfR, n (%)	14 (58)	3 (13)	2 (8)	10 (42)	10 (42)	0 (0)	1 (8)	1 (8)	2 (25)	
Moderate Illness (n: 4)	n (%)	3 (75)	3 (75)	3 (75)	3 (75)	3 (75)	1 (25)	1 (25)	1 (25)	1 (25)	2 (50)
	Median (IQR)	4.49 (4.27–4.71)	12.7 (12–13.30)	13 (12.70–13.20)	9.20 (6.60–9.40)	9.70 (0.49–128)	184 (NA)	15 (NA)	10 (NA)	79 (NA)	26.13 (NA)
	OfR, n (%)	0 (0)	1 (33)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	1 (100)	
Severe Illness (n: 6)	n (%)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	2 (33)	4 (67)	4 (67)	2 (33)	5 (83)
	Median (IQR)	3.90 (3.49–4.95)	11.80 (10.88–13.53)	13.40 (12.13–14.83)	8.20 (6.75–13.40)	3.05 (1.70–25.03)	337 (NA)	39 (26.25–68.25)	30.5 (15–98.50)	323.50 (NA)	19.64 (13.71–28.74)
	OfR, n (%)	4 (66)	2 (33)	1 (17)	3 (50)	2 (33)	0 (0)	2 (50)	1 (25)	0 (0)	
Critical Illness (n: 1)	n (%)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
	Median (IQR)	4.06	11.2	11.4	9.2	21	351	49	19	141	35.44
	OfR, n (%)	0 (0)	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	

ALP = alkaline phosphatase (U/L), ALT = alanine aminotransferase (U/L), AST = aspartate aminotransferase (U/L), CPR = C-reactive protein (mg/L), ED = emergency department, LDH = lactate dehydrogenase (U/L), OfR = out of range, NA = IQR not calculable, RBC = red blood cell count ($\times 10^6$/mm^3), Hb = hemoglobin (g/dL), RDW = red blood cell distribution width, SARS-CoV-2 = coronavirus, WBC = white blood cell count ($\times 10^3$/mm^3).

increase of illness category severity, however, once again, the small number of samples did not allow us to deep investigate this issue.

Our study has some methodological limitations. Primarily, given the generally low prevalence of serious outcomes in the pediatric population and the monocentric nature of this study, it suffers from a small sample size, even though all SARS-CoV-2-positive patients that accessed the Pediatric ED during the study period were enrolled in the study. However, the observed clinical symptoms and clusters were in line with findings of other European pediatric cohorts. Another limitation is that newborns and children with chronic diseases may have direct access to the clinical ward responsible for their follow-up, without passing through the pediatric ED which may result in an underestimation of the relationship between analyzed outcomes and comorbidities. These issues may limit generalizability of the study. This very specific population would require reference centers studies to further evaluate the impact of COVID-19.

Our study has some strengths as well. It was quite difficult to find other studies that comprehensively analyze SARS-CoV-2-infected children accessing the ED and address the issue from multiple angles (clinic, laboratory, radiographic imaging, and VL). Moreover, to the best of our knowledge, our study is one of the few studies that deeply evaluate the presence of symptom clustering and its potential association with illness categories in European pediatric populations. Other European pediatric cohort partially addressed this issue. However, heterogeneity in classification of illness categories as well as in data recorded (in terms of clinical, laboratory, radiological information), the different diagnostic and clinical approaches, or even the different organization of the various hospitals, within the pediatric cohorts analyzed in the European Region make difficult to compare findings. Systematic reviews[31,32] show how there is a need for a more standardized approach to data collection. This heterogeneity may be justified by the unprecedented nature of SARS-CoV-2 and COVID-19, yet a call for unification of basic variable collection and reporting is required.

5. Conclusion

We fully described the clinical symptoms of a cohort of children positive to SARS-CoV-2 infection admitted to the ED and identified the presence of symptom clusters and their potential association with illness categories severity. Mucocutaneous-enteric and the respiratory symptom clusters appeared, in fact, associated with a more severe clinical picture. Similar findings were observed in other European cohorts; however, further studies on this issue are needed.

Finally, this study highlights the importance to identify early prognostic patterns to help clinicians in the decision process, especially in COVID-19 pediatric patients.

Author contributions

All authors have participated in the study and consent to the publication of this manuscript. H.K.T. and L.P. share first co-authorship and have contributed equally to the present work. H.K.T., L.P., P.T., and C.K. authors contributed to the study's conception and design. Material preparation and data collection were performed by H.K.T., S.P., and J.R., and analysis was performed by L.P., M.M., and E.R. Scoping review was performed by M.M. and L.P. The first draft of the manuscript was written by L.P. and H.K.T., all authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgments

Correction

In figure 1, tachypnea was misspelled as tachipnea. This has been corrected.

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