

Article

Clinical and Evolutionary Features of SARS Cov-2 Infection (COVID-19) in Children, A Romanian Perspective

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Abstract

Background: Given the potential for additional development to clarify a better knowledge of the overall impact of COVID-19 on the pediatric population, the clinical symptoms of SARS-CoV-2 infection in children and adolescents are still being explored. Morbidity in children is characterized by a variable clinical course. Our study's goal was to compare clinical aspects of 230 pediatric patients who tested positive for SARS-CoV-2 and were hospitalized between April 2020 and March 2022.

Methods: In a retrospective analysis, we compared two groups hospitalized in the infectious diseases clinical ward IX at the National Institute for Infectious Diseases "Prof. Dr. Matei Balș," Bucharest, Romania. The first group of 88 patients was admitted between (April–December 2020) and their clinical manifestations were compared with the second group of 142 children followed between July 2021 and March 2022.

Results: Of 230 children, the median age was 4.5 (interquartile range 0.6-17) years, 53.9% were male. 88 (36.21%) patients (first group) were admitted during the second wave in Romania, mostly aged < 5 years old, and experienced digestive manifestations like fever ($p=0.001$), and diarrhoea ($p=0.004$). The second group experienced different clinical signs when compared with the first group, with higher temperature and increased respiratory symptoms analogous to those of acute respiratory viral infections. The proportion in the second group increased, and 64.5% had symptoms for a median interval of 5 days; age (0-4 -years old) and length of stay were both proportionally inversely ($p<0.01$) and with correlation with hospital admission ($p = 0.04$). We report two Paediatric Inflammatory Multisystem Syndrome (PIMS) in the second group, with favourable evolution under treatment. Comorbidities were risk factors for complications appear ($p < 0.001$) in both groups. All paediatric cases admitted to our clinic evolved favourably and no death was recorded.

Conclusions: In the first group children experienced digestive symptoms, whereas the second group experienced mild and moderate respiratory symptoms. We confirmed risk factors for severe cases as manifestations across the age spectrum, 0-4 (digestive symptoms) and 5-12 years old (for respiratory symptoms), associated comorbidities, fever, and male gender. The potential effects of COVID-19 infection in children older than 5 years should encourage caregivers to vaccinate and improve the prognosis among pediatric patients at risk.

Keywords: SARS-CoV-2; COVID-19; children; clinical features; comorbidities; male gender

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been rapidly spreading since December 2019, becoming the worst epidemic of the twenty-first century [1-8]. Clinical evidence indicates that this disease primarily affects adult populations, bypassing most youngsters who, from the start, have only had modest symptoms [9-12]. Nevertheless, many features of SARS-CoV-2 infection in children and adolescents remain uncertain [13].

This study aims to describe and compare clinical features of children hospitalized for COVID-19 at the infectious diseases clinical ward IX at the National Institute for Infectious Diseases "Prof. Dr. Matei Bals," Bucharest, Romania. This information could contribute to a wide understanding of this disease in pediatric practice.

Compared to the adult population, a smaller number of children were admitted to the clinic related to COVID-19 infection [14]. Data from around the nation and the world showed that just 2 to 3 per cent of affected kids needed to be hospitalized [15]. According to evidence, up to 50% of children with coronavirus infection may not show any symptoms and hence go undiagnosed [16, 17]. Children's COVID-19-related mortality makes up about 2% of all deaths [18]. Children are less likely to get severe disease symptoms if they test positive for SARS-CoV-2, according to both scientific and empirical data that has a certain degree of accuracy. Angiotensin-converting enzyme number 2 (ACE-2) expression levels, prior endothelium damage, and innate immunity are the major three elements that a recent study is proposing to correlate to explain this tendency. As an age-related condition, higher levels of ACE-2 expression in children's alveolar epithelium have been linked to protection from the beginning of acute respiratory distress that may occur after sepsis or other non-coronavirus respiratory infections, among other illnesses and conditions [19-21].

A knowledge gap exists concerning children's low sensitivity to COVID-19 and the emergence of mild disease in the pediatric population. Fever, coughing, nausea, vomiting, diarrhea, skin rashes, anosmia, fatigue, headaches, muscle stiffness, shivers, and nasal congestion are common manifestations. Pediatric comorbidities, such as diabetes, asthma, heart congenital disorders, central nervous system diseases, and metabolic diseases, raise the probability of admission to an intensive care unit, but it is typically still low for children compared to adults [22].

Genetic studies have demonstrated that SARS-CoV-2 is a zoonotic single-stranded RNA virus (viral zoonosis-snakes, bats) and through an intermediate host, it acquires human cell receptors [23-25]. The pandemic evolved in successive waves (6 so far) without a specific season but with a predominant specific strain for each of them (strains β , γ , μ , δ , omicron). The coronaviruses HCoV-NL63, HCoV-OC43, HCoV-229E, and HCoV-HKU1 are the four most prevalent ones. According to a Chinese study, hospitalized children with acute respiratory tract infections had a 4.3 per cent positive rate for these four HCoV infections. Common human coronaviruses with its 4 serotypes: 229E, NL63, OC43 and HKU1, cause in immunocompetent individuals light or moderate infections of the upper respiratory tract, clinically manifested by fever, altered general state, rhinorrhoea, odynophagia, cough, headache). In immunocompromised persons and those of extreme ages, coronaviruses can determine lower respiratory tract infections such as pneumonia or bronchitis. Most people get infected with one or several of these viruses at some point in their lives thus the adult population presents serotype protective neutralizing antibodies. Transmission of the infection is predominantly airborne but also through direct contact with contaminated objects or surfaces. While coronaviruses have suffered genetic mutations as a consequence of successive passage from one host to another (mammal, human) this resulted in new coronaviruses with different pathogenesis and increased virulence in humans that cause more and more severe forms of diseases [26-30].

Based on the clinical characteristics, laboratory results, and chest radiograph imaging, including asymptomatic infection, the severity of COVID-19 was classified as mild, moderate, severe, or critical. The following severity score was used for the diagnostic standards in our study groups. (See Table 1). [31]

ASYMPTOMATIC:	All the following must be present No signs or symptoms AND negative chest X-ray (CXR) AND the absence of criteria for other cases
MILD:	Any of the following (AND absence of criteria for more severe cases) 1. Symptoms of upper respiratory tract infection 2. AND the absence of pneumonia at CXR

MODERATE:	All the following (AND absence of criteria for more severe cases) 1. Cough AND sick appearing or pneumonia at CXR Severe: Any of the following (AND absence of criteria as for critical case) 3. Oxygen saturation less than 92% 4. OR difficult breathing or other signs of severe respiratory distress (apnea, gasping, head nodding) 5. OR need for any respiratory support
CRITICAL:	Any of the following 1. Patient in the intensive care unit 2. OR intubated 3. OR multiorgan failure 4. OR shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, acute kidney injury

Table 1. Disease severity score described by Parri, adapted by Dong et al. [31-33].

In Romania, the first cases of infection with the new coronavirus were registered in March 2020. The diagnosis was made based on the patient's direct exposure to SARS-CoV-2, clinical symptoms such as cough, fever, and breathing difficulties without a known cause, and confirmation through RT-PCR testing. COVID-19 has various clinical forms, from asymptomatic to severe ones, some with evolution to multiple organ failure and death. Severe clinical forms are frequently met in patients with comorbidities (cardiovascular diseases, diabetes, renal impairment, obesity, tumours). In children with SARS-CoV-2, the infection is usually asymptomatic, or mild but more severe clinical cases have been observed especially in patients with associated risk factors (obesity, type 1 or 2 diabetes, cardiovascular diseases, chronic pulmonary diseases, including asthma, chronic renal diseases, including dialysis, chronic liver diseases, immunosuppression, human deficiencies, HIV/AIDS, prolonged usage of immunosuppressors) [34,35].

One life-threatening complication is Multisystem Inflammatory Syndrome associated with COVID-19 (MIS-C or PIMS-TS) that can occur in SARS-CoV-2 infection in children and adolescents, especially during the recovery time [36].

The diagnostic is established based on the assessment of the presence of the inflammatory syndrome (certified by laboratory investigations) associated with multiple-organ failure (renal, cardiac, haematological, respiratory, gastrointestinal, dermatological, neurological). These cases featured in Literature during the first pandemic waves when severe forms of diseases in children were also registered, with an incidence rate of approximately 1 to 5000 cases of COVID-19 [37,38]. The first cases were documented in USA and Italy, both in previously healthy children as well as in those with comorbidities [39-44].

Material and method

The authors have undertaken a clinical retrospective study on COVID-19 paediatric cases admitted to National Institute for Infectious Diseases „Prof. Dr. Matei Bals”, Bucharest, Romania between April 2020-March 2022. The following parameters were monitored: age, gender, clinical signs, evolution, complications, and comorbidities. Data were collected from medical records, and all the children included in our study had laboratory-confirmed SARS-CoV-2. Nasopharyngeal swabs were taken from all patients who addressed an acute illness at the National Institute for Infectious Diseases, Bucharest, Romania within 24 hours of admission and tested using a reverse transcription-polymerase chain reaction (RT-PCR) kit (Thermo Scientific).

Patients aged less than 18 years on the date of hospital admission were enrolled on the study group. For this report, we included a total of 230 patients who resemble the peak distribution waves at admission as follows: the first group of 88 patients, which corresponds to the year 2020 (between April and December 2020), and the second group of 142 patients which were admitted between July 2021 and March 2022. (See fig.1). Among 243 pediatric patients, 13 of

them who were hospitalized between January and June 2021 were not included in the research group as we used to compare the larger groups of the pandemic waves. When values were regularly distributed, we presented continuous variables as mean (SD: standard deviation) and median (IQR: interquartile range) otherwise. Categorical variables were presented as frequencies and percentages. When comparing groups, categorical data were compared using the Chi-square or Fisher's exact test, continuous data were compared by applying the Mann – Whitney test and two-way ANOVA was used to explore the main factors influencing comorbidities. Significant statistical differences resulted in $p < 0.05$. Statistical analyses were performed using GraphPad Prism 9.4.0 (GraphPad, CA, USA).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the ethics committees of our National Institute. Informed consent was obtained from all subjects involved in the study.

Results

During the study period, a number of 230 paediatric COVID-19 infections were recorded at National Institute for Infectious Diseases „Prof. Dr. Matei Bals”, Bucharest, Romania. All cases of SARS-CoV-2 in children evolved favourably, without deaths through the study, but two cases (from the second group) presented Multiple Organ System Failure with favourable evolution under treatment. Figure 1 evidences the distribution in waves of admissions, with a peak registered between January and March 2022. The gradual increase in the number of cases was the consequence of a highly contagious strain selection.

Distribution of admitted cases of COVID-19

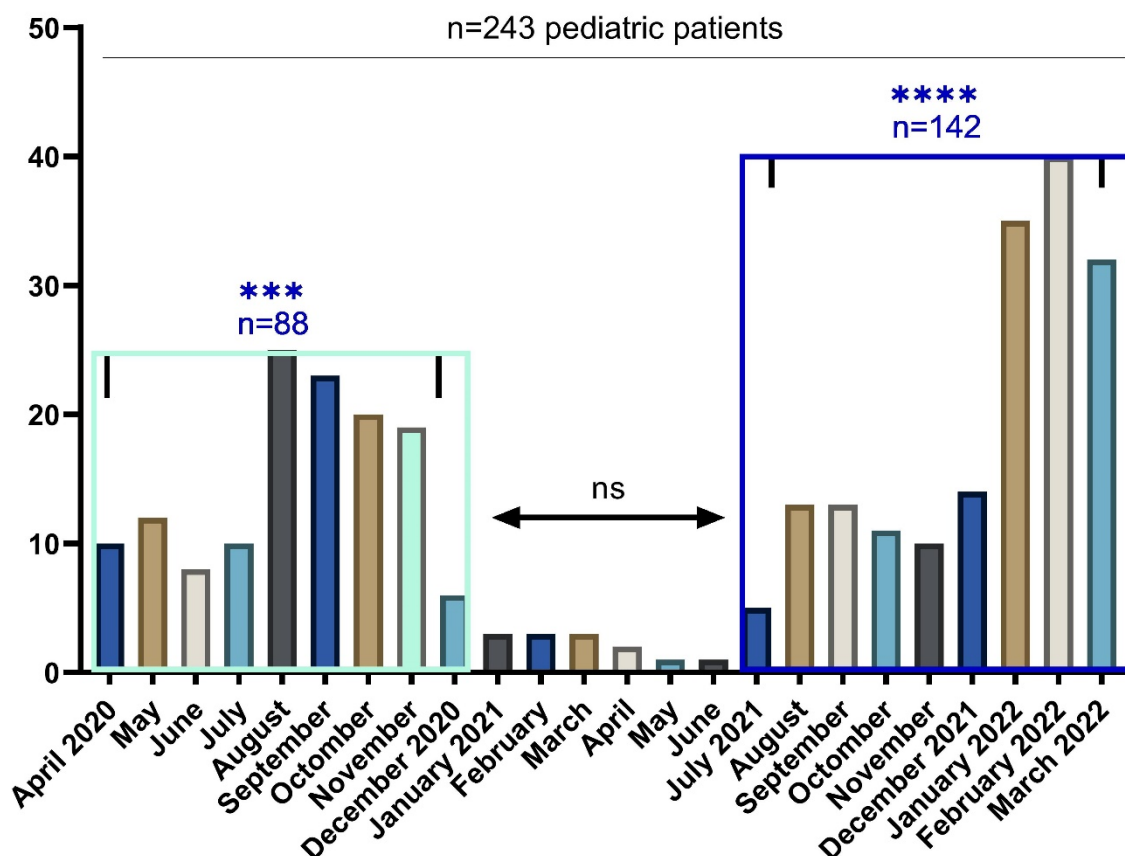


Fig. 1- Distribution of admitted cases of COVID-19

The analysis of SARS CoV-2 associated deaths showed that in our ward the rate of mortality was zero in children while in adult patients it reached 2,05% (29/1.412) reported to the number of adult patients hospitalized in the same

period at our hospital. In terms of demographic characteristics, there were more males in both arms, 55% in the first group and 53.5% in the second group, ($p=0.05$) and the mean value for age in the first group was lower compared to those admitted in the second group (0.8 years (IQR: 0.6, 7.9 years) vs. 1.5 years (IQR: 1.5, 12.8 years); $p < 0.001$, $z = -4.260$, $r = 0.1$. (see Table 2).

The median length for hospitalization for the first group was 1 day shorter than the second group, 4 days (IQR 2-5 days) vs 5 days (IQR 3-7 days), though with statistical significance of $p=0.04$. The hospitalization rate was higher among children with co-morbidities, ($p<0.01$ for both groups).

Characteristics	First group	Second group	p-value
n (%)	88 (38.26)	142 (61.74)	
Male gender (%)	49 (55)	76 (53.5)	0.05
Age			
0–4	34 (38.64)	38(26.76)	0.001
5–12	34 (38.64)	74 (52.11)	0.02
13–18	20 (22.72)	30 (21.13)	0.65
Fever, n (%)	73 (83)	116 (81.9)	0.001
Shortness of breath /Respiratory distress, n (%)	55 (62)	89 (62.68)	0.02
Sore throat	55 (62%)	97 (68%)	0.05
diarrhoea	42 (47.73)	54 (38)	0.04

Table 2: Identification of risk factors for both groups

In what concerns the onset clinical picture of SARS CoV-2 in children it has been observed to be polymorphous and particularised based on the child's age. Thus, in small children (under the age of 1, both groups) digestive symptomatology predominated (lack of appetite, diarrhoea, ($p=0.04$), acute dehydration syndrome (without statistical significance) accompanied by fever (was documented in almost all patients-82.2%);(see Table 2).

In pre-school children, symptomatology is polymorphous with the occurrence of upper respiratory tract infections (62.6%) and fever (81.9%). In school-aged children and adolescents the clinical picture of upper respiratory tract infections such as fever, rhinorrhea, odynophagia, dysphagia, cough and sore throat ($p=0.005$). Rarely have we encountered systemic type manifestations in children (sweats, exanthema, arthralgias, headaches) such as agenesia and anosmia that are specific to the adult patient (Fig. 2).

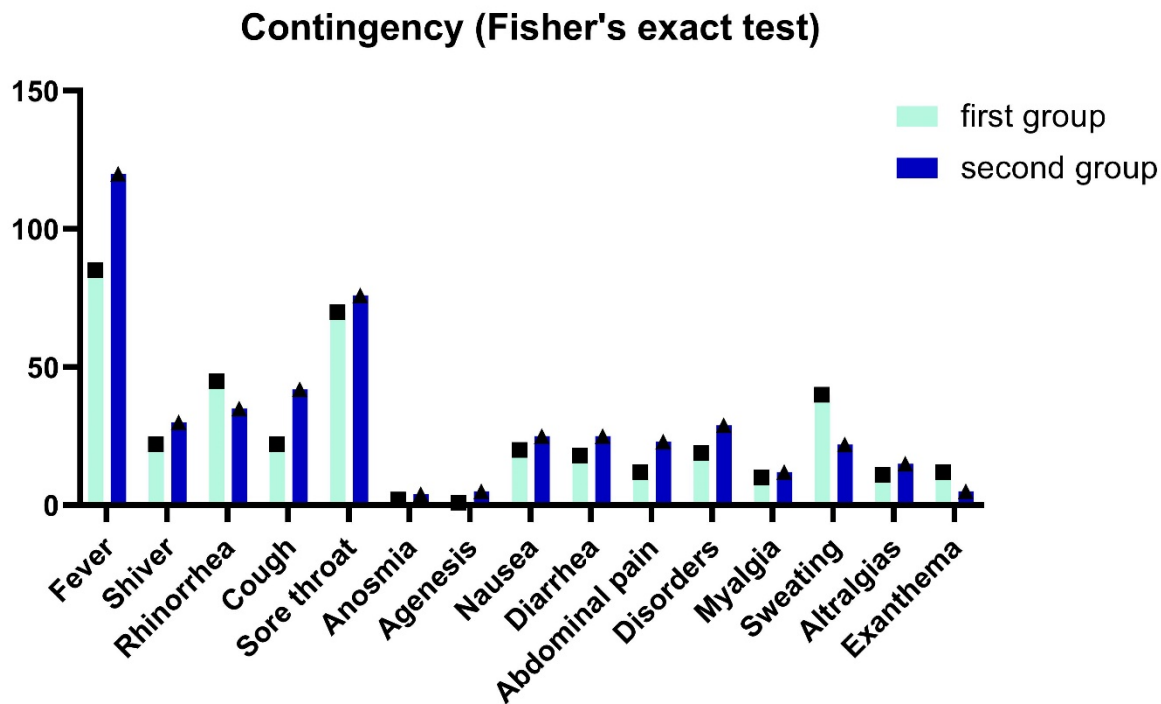


Fig. 2 - COVID-19 Clinical features in children between the two groups. P-value <0.0001)

Clinical symptoms in both study groups associate fever with cough and sore throat (62% vs 68%, $p=0.05$), and for the digestive tract, up to 47.73% vs 38% of cases may develop diarrhoea ($p=0.04$) with abdominal pain. Other less frequent clinical features are respiratory symptoms associated with gastrointestinal symptoms, (18.3 vs 17.9%);(See fig. 3).

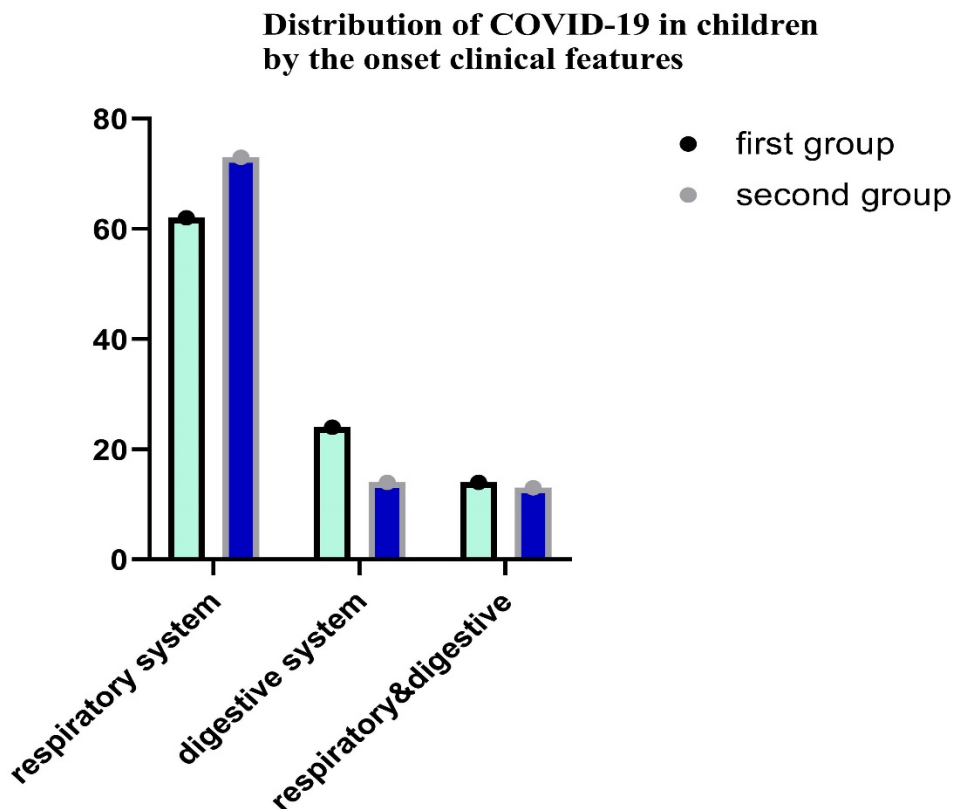


Fig. 3 - Distribution of COVID-19 in children by the onset clinical features

From the analysis of the cases studied, it was observed that SARS-CoV-2 infection in children predominated in the age groups 0-4 years (38.64% vs 26.76%), and 5-12 years (38.64% vs 52.11%). There were significant differences between age groups 0-4-years-old, ($p=0.001$), and 5-12-years-old ($p=0.02$);(See Fig. 4).

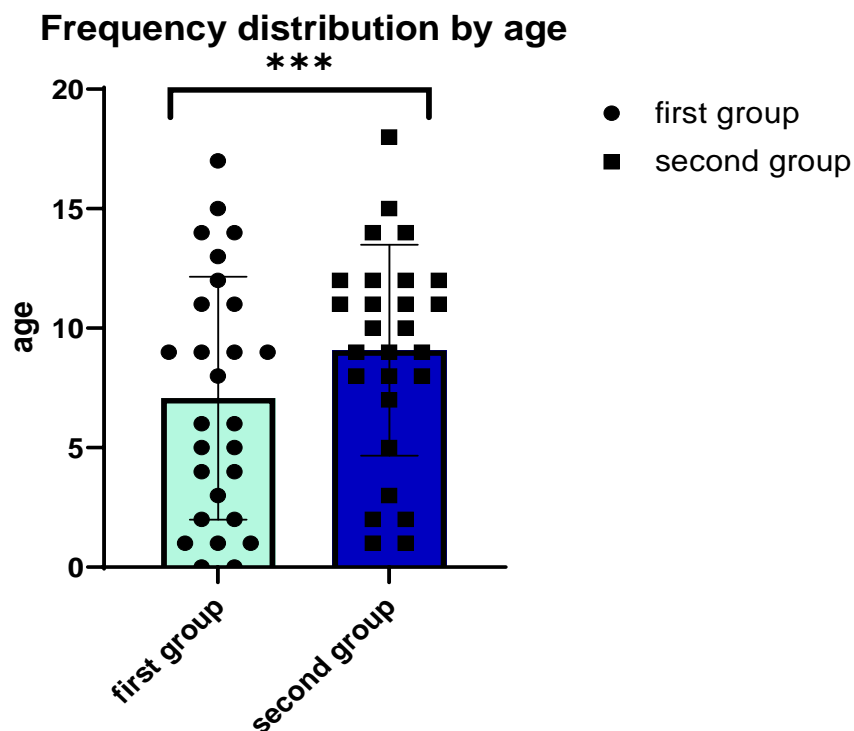


Fig.4- Distribution of COVID-19 cases in children by age

A percentage of 10.29% of the patients from the first group and 12.45% of the second group, presented various comorbidities at the time of hospitalization (obesity, chronic haematological, metabolic, neurological, autoimmune, and oncological diseases). Figure 5 shows that, among the associated comorbidities of COVID-19 in children, the best represented were obesity for both groups, haematological diseases and oncological pathology.

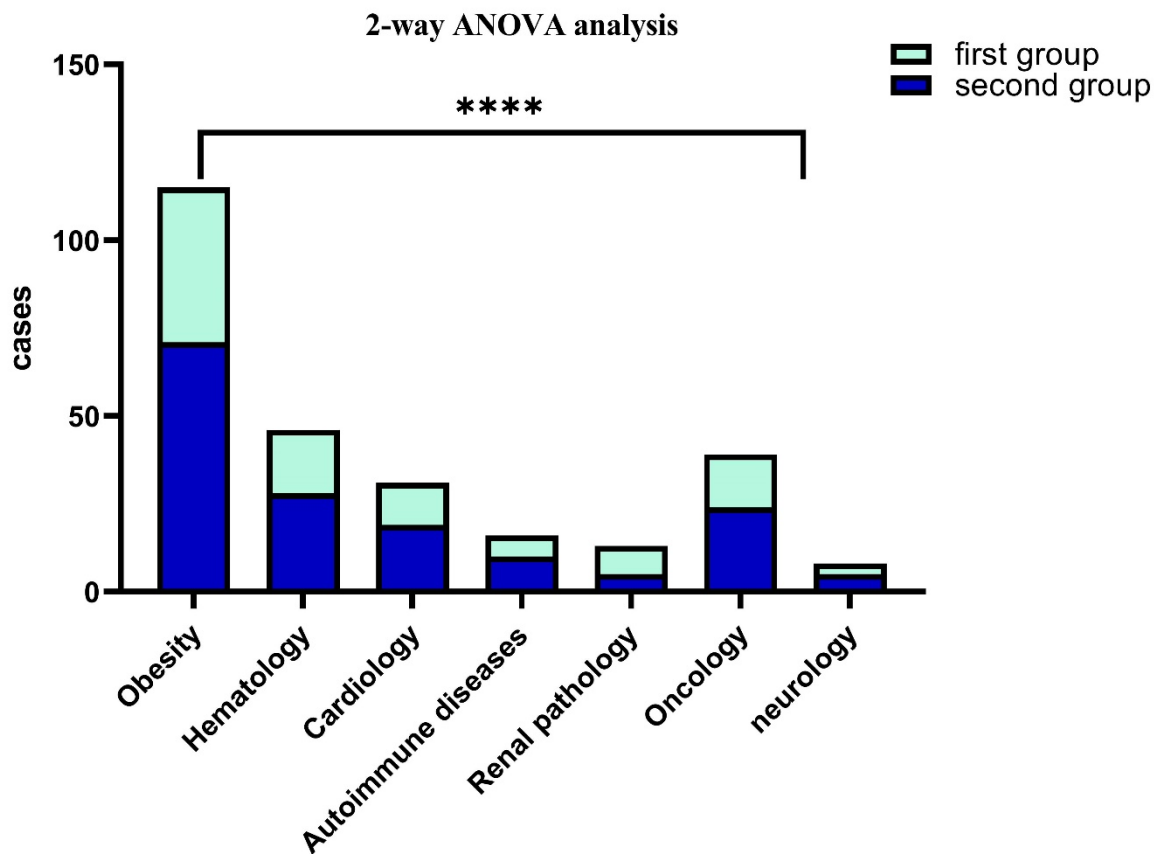


Fig. 5 – Results of 2-way ANOVA to compare the main effects of the associated COVID-19 comorbidities in children in both groups.

From the standpoint of clinical forms of COVID-19, it was found that most cases in children were mild and moderate the severity of the disease is not correlated with age, but it is associated with the presence of comorbidities ($p=0.0001$). We haven't registered critical forms of COVID-19 in children but in two situations it was complicated by PIMS in the second group (1.46%).

The duration of hospitalization for pediatric patients with obesity was longer than other comorbidities, (median =4 days [IQR=12.0-5.0 days]. ($p<0.001$). BMI percentiles were calculated using BMI (kg/m^2), age, and gender. Those children with BMI percentiles ≥ 95 th percentile were considered to have obesity.

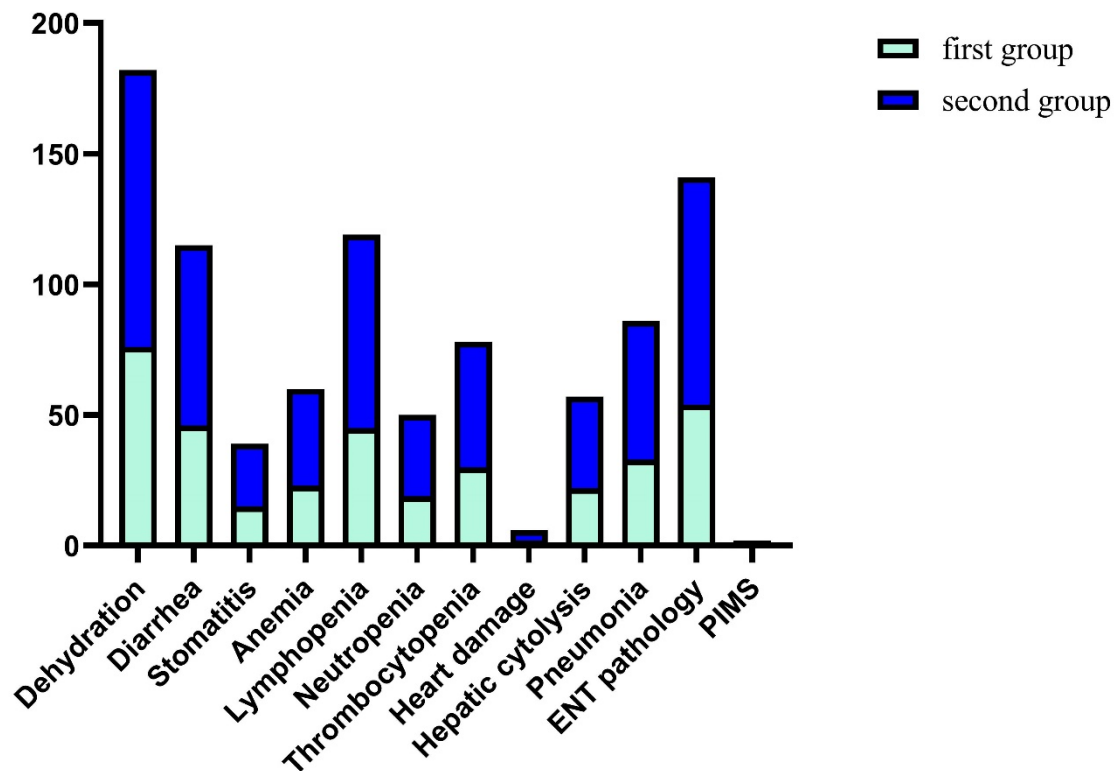


Fig.6- Complications of SARS CoV-2 infection in children

The histogram from figure 6 shows the main complications associated with SARS-CoV-2 infection in children. It is observed that the best represented are the digestive ones (acute diarrheal disease - 41.9%, acute dehydration syndrome - 75.5%, stomatitis - 17.2% and hepatic cytolysis syndrome - 27.9%) as well as the haematological (anaemia - 26.3%, lymphopenia - 34.5%, neutropenia - 22.2% and thrombocytopenia - 34.5%). We also recorded a significant percentage of cases with acute interstitial pneumonia (37.3%) and ENT involvement - 60.9% (pharyngitis, laryngitis, otitis, anosmia). Cardiac impairment (myocarditis, pericarditis, heart rhythm disorders) was present in 2.4% of cases and only 2 children presented with PIMS, with a favourable evolution under the established treatment.

According to the severity classification described by Parri, adapted by Dong et al, (see Table 1), we reported 51% vs 44.6% mild forms, 59% vs 65.4% moderate forms, and 0 critical forms.

Discussion

In this retrospective study, we compared the clinical features of hospitalized pediatric patients who tested positive for COVID-19, during two waves. Our analysis has shown that in the second group, the average number of cases was increased compared with the first wave analyzed, with older age, a predilection for upper respiratory symptoms, and higher temperature as distinct clinical characteristics. The second group experienced an increase in the number of hospitalization and duration. The first group experienced digestive symptoms, affecting the case severity in hospitalized patients with COVID-19 in age 0-4 years old. Among clinical courses in both groups, the negative prediction was the presence of fever, male gender, chronic condition and comorbidities. The disease's progression varied in our research population, from moderate to mild forms, and no critical to severe patterns were found in each group. The differences in clinical features may indicate that a new variant of COVID-19 can lead to changes in the clinical profile of pediatric patients, especially for categories aged >5 years old.

Assessing the admitted cases and correlating them with other studies, we concluded that slightly more frequent respiratory symptoms children presented respiratory symptomatology in the second group, where the older category was observed.

We found a lower percentage of associated clinical manifestations for both digestive and respiratory pathology, as we discovered that in the first group, patients with gastrointestinal pathology had considerably lower ages compared to those in second group by examining the median ages for which they were admitted. Characteristics which significantly influenced COVID-19 infection while the presence of a clinical picture characteristic for upper respiratory tract infections (sore throat, nasal obstruction, rhinorrhoea, cough, odynophagia, dysphagia, dysphonia) sometimes accompanied by difficulty in breathing) was the clinical manifestations of both groups in the 5-12-years old age category.

The main symptom was fever, which was followed by cough, rhinitis, and digestive issues. This is different from other reports, where fever and digestive disturbance were less common (36-56%). The reduced size of our study may be a contributing factor in the disparity between the other findings [45].

SARS-CoV-2 infection in children is more frequent in ages under 5 as vaccinations are absent in this age in first group. Paediatric COVID-19 cases presented a large picture of complications, the recurring ones being the digestive ones, ENT and haematological ones. A low percentage of children presented cardiac complications and two had PIMS with favourable evolution.

Hospital stays were a little bit longer in the second group, which was likely due to complications and comorbidities, especially for obesity pathology, which is similar to those reported in other studies [46,47]. Obesity comorbid problems have been related to many COVID-19 outcomes. Patients with oncological disorders were also more likely to have increased severity of COVID-19. According to literature and past study, diabetes and heart disease are the two most important risk factors for mortality in patients who have COVID-19, but in our study were less frequent.

The main limitation of our study is its monocentric nature and the small number of cases included. However, the importance of our reporters is the specificity of clinical features in the pediatric population compared with previous studies described before and from the Romanian perspective.

Conclusions

Although the number of cases of COVID-19 in children wasn't very large (230 paediatric cases), there was an increased number of hospitalized children between 5-12 years old in the second group with predominancy of respiratory manifestations, so we can report the evolution of clinical symptoms has emerged in this category. The progression of clinical symptoms and hospitalizations in the older group draws attention to the necessity of vaccination in this category.

The introduction, on a large scale, of COVID-19 vaccination in all age groups represents one of the most effective methods of specific prophylaxis along with non-specific methods (hand washing, physical distancing, protection mask).

Subsequent studies, based on acquired clinical experience, will establish the particularities of SARS CoV-2 infection in children, useful for identifying the most successful methods of diagnosis and treatment of COVID-19.

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