

Variation of clinical patterns of COVID-19 disease in children in the first year of pandemic

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ABSTRACT

Introduction. SARS-CoV-2 infection has put humanity to the test since December 2019, quickly becoming a global public health problem. There is a significant difference between the pediatric population versus the adult population in terms of infection rate, modes of transmission, clinical manifestations. The study aimed to identify some patterns of clinical presentation of SARS-CoV-2 infection in the pediatric population in "Dr. Victor Gomoiu" Children's Clinical Hospital in 2020, also following any possible variations between the first two waves of the pandemic.

Materials and methods. The study was based on the descriptive observational analysis of two groups of SARS-CoV-2 positive patients, corresponding to the two pandemic waves. Patients were classified into some clinical patterns, using the definition of suspected / confirmed case established by the National Institute of Public Health (INSP) and transmitted through the National Center for Surveillance and Control of Communicable Diseases (CNSCBT), as well as the recommendations of the international guidelines and protocols.

Results. There are found to be present some mild clinical forms of the disease secondary to SARS-CoV-2 virus infection, most children showing digestive symptoms. Starting with August (Group 2) there is a significant increase in the number of cases, as well as the appearance of a larger number of cases that associated respiratory symptoms.

Conclusions. The study is showing the low impact of the SARS-CoV-2 virus infection in the pediatric population, compared to adults, especially in the first wave of the pandemic, the children having been considered "the hidden victims" of the pandemic, rather than its face. It is considered necessary the long-term monitoring of SARS-CoV-2 infected children, as the remote consciousness of the infection having been incompletely elucidated. Analyzing the epidemiological data obtained in the study, we are concluding the need for some sustained global efforts to define, more clearly, the variations in the patterns of the presentation of SARS-CoV-2 infection in children, in the context of the evolution of the pandemic.

Keywords: pandemic, SARS-CoV-2 infection, child

INTRODUCTION

One year since the World Health Organization declared the COVID-19 pandemic (March 11, 2020) there are still countless questions that have not been answered about SARS-CoV-2 infection and especially about its impact on the pediatric population [1].

Belonging to a well-known family (Coronaviridae, genus Betacoronavirus), the SARS-CoV-2 virus has put humanity to the test since December 2019.

The devastating effects of other pandemics that have occurred over time are well known worldwide. However, at a time when scientific research and medical advances are showing spectacular results, the whole of humanity has been surprised by the magnitude of the COVID-19 pandemic in a relatively short amount of time [2,3].

At the time of writing, WHO had reported 141,057,106 confirmed cases worldwide (in Europe 49,364,480) and 3,015,043 deaths [1].

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Originally called the New Coronavirus, the SARS-CoV-2 virus has rapidly spread, being difficult to manage globally and quickly, becoming a global public health problem, leading to an international mobilization, probably, unprecedented in the recent human history [2,3].

Romania faced the first confirmed positive case of SARS-CoV-2 virus infection on February 26, 2020, and about a month after that, the first secondary deaths of this infection appeared. The epidemiological situation imposed, starting with March 16, 2020, the establishment of the state of emergency on the Romanian territory, involving special measures both from a sanitary and socio-economic point of view. Subsequently, from May 14, 2020, the state of emergency was replaced by a series of other measures, and 1 year after the first case confirmed in the country, there is still a struggle to try to limit the spread and especially the impact of the COVID-19 Pandemic in the population. At the time of writing, 1,029,304 cases and 26,232 deaths secondary to SARS-CoV-2 infection were confirmed in Romania [4,5].

From the analysis of international and national epidemiological data, since the first months of the pandemic, there is a significant difference between the pediatric population versus the adult population, in terms of infection rate, methods of transmission, clinical manifestations. In the first months of the pandemic, the incidence of the new coronavirus infection among children was reported at about 3%, so that now, it reaches 6.44% of a total number of 65,000 infected children (April 12, 2021) [6]. Reports from the US Centers for Disease Control (CDC) on the rate of SARS-CoV-2 infection in children have shown an upward trend. Thus, if at the beginning of April 2020, the incidence of infection with the new coronavirus in children was only 2.6%, one year later (April 8, 2021) the figures reached 13.5%, given that about 3,542,692 infected children were reported [7].

Following the evolution of the pandemic, there is a change in the pattern of involvement of the pediatric population, which, although it remains less affected compared to adults, faces new facets of infection with the evolution of the second and third wave [8,9].

OBJECTIVE

We proposed to identify possible variations from one wave to another of the COVID-19 pandemic, regarding the way of clinical presentation of hospitalized children with the diagnosis of SARS-CoV-2 infection in “Dr. Victor Gomoiu” Children’s Clinical Hospital in 2020. The objective derives from the fact

that, starting with August, Romania crossed a second wave of the pandemic, with the significant increase of the number of cases in the general population. In the context of this epidemiological phenomenon, the aim was to establish some possible particular clinical patterns in children confirmed with SARS-CoV-2 infection in the 2 temporal stages (pandemic waves).

MATERIAL AND METHOD

A descriptive observational study was performed, which included pediatric patients (0-18 years) confirmed with SARS-CoV-2 infection by RT-PCR testing of nasopharyngeal exudate. The study took place between March 31, 2020 and December 31, 2020 at “Dr. Victor Gomoiu” Children’s Clinical Hospital, Bucharest. Following the evolutionary trend of SARS-Cov-2 infection at national level, we considered it necessary to divide the analyzed period into two-time phases corresponding to the first two waves of the pandemic. Thus, we divided the patients included in the study into two groups corresponding to the two-time stages considered: group 1 (included hospitalized patients confirmed positive for SARS-CoV-2 infection between March 31, 2020 and July 30, 2020), respectively group 2 (patients hospitalized confirmed positive SARS-CoV-2 from the beginning of second wave until the end of 2020: August 01, 2020 and December 31, 2020).

The first patient confirmed COVID-19 positive by RT-PCR test of nasopharyngeal exudate was hospitalized on March 31, 2020. According to the hospital’s internal protocol, patients who met hospitalization criteria were subjected to epidemiological triage, and were subsequently isolated in the buffer zones within the pediatric clinical departments where nasopharyngeal swab specimens were collected for SARS-CoV-2 detection by RT-PCR [10].

The inclusion criteria in the two groups were: age of patients: 0-18 years; hospitalization in “Dr. Victor Gomoiu” Children’s Clinical Hospital in one of the two temporal stages analyzed (Group 1: March 31 and July 30, 2020; Group 2: August 01 and December 31, 2020); positive RT-PCR testing of nasopharyngeal exudate.

The evaluation and classification of cases in clinical patterns was performed using the definition of suspected/confirmed case, established by the National Institute of Public Health (INSP) and transmitted through the National Center for Surveillance and Control of Communicable Diseases (CNSCBT), as well as recommendations international guidelines and protocols.

In assessing the severity of clinical forms of the disease, we took into account the following criteria:

- Asymptomatic infection: absence of clinical signs and symptoms suggestive of SARS-CoV-2 infection, positive SARS-Cov-2 detection by RT-PCR of nasopharyngeal exudate;
- Mild infection: either respiratory symptoms suggestive of upper respiratory tract infection, with or without fever, fatigue, impaired general condition, odynophagia, myalgia, or digestive symptoms (loss of appetite, nausea, vomiting, abdominal pain, diarrhea) in afebrile or associating fever/respiratory manifestations;
- Moderate infection: symptoms suggestive of pneumonia (fever, subsequent productive dry cough, wheezing, altered pulmonary stethacoustics) but without the presence of hypoxemia; characteristic radiological changes (cardiopulmonary radiography/pulmonary CT); even in the absence of suggestive clinical manifestations;
- Severe infection: respiratory/digestive symptoms with rapid evolution to worsening and the appearance of acute respiratory failure, hypoxemia requiring the administration of oxygen therapy;
- Critical form: clinical picture suggestive of respiratory distress requiring care in ICU, shock, encephalopathy, heart damage, multi-systemic organ damage [11,12].

The study consisted in analyzing the parameters extracted from the observation sheets of patients included in the two groups, namely: demographic data, medical history, epidemiological context (notion of contact), symptoms present at hospitalization, evolution in dynamics. The processing of the obtained data was done with the help of the Microsoft Excel program.

RESULTS

During the analyzed period (March 31, 2020 and December 31, 2020), 4146 patients were hospitalized, of which 103 patients were confirmed with SARS-CoV-2 infection by RT-PCR testing. The incidence of confirmed cases of infection with the new coronavirus during the study period was 2.48%.

Taking into account the two pandemic waves, the patients included in the study were divided into 2 groups: group 1 (the analyzed time period was March 31 and July 30, 2020), which includes 13 patients (12.6%), and in group 2 (period of time analyzed was August 01 and December 31, 2020), which includes 90 patients (87.4%), as can be seen in Figure 1.

In order to establish the clinical features of the patients included in the study, the reasons for hospitalization (signs and symptoms) were analyzed.

Fever associated with respiratory symptoms (respiratory picture is considered a classic form of presentation in adults), was present in 30 patients included in group 2 (33.3%), while in patients included in group 1, this symptom was present only in one patient (7.6%) in association with digestive manifestations.

Overall evaluating the 103 patients included in the study, we observed the following clinical ways of presentation: 46 patients (44.7%) had digestive symptoms, 39 patients (37.9%) had respiratory symptoms, while 18 patients (17.4%) were asymptomatic. It should be noted that patients confirmed with SARS-CoV-2 infection, but without clinical manifestations of acute disease, were hospitalized for the evaluation of other chronic pathologies (surgical, ENT, neurological etc.). At the same time, according to the internal protocol, all patients who were hospitalized were tested by RT-PCR.

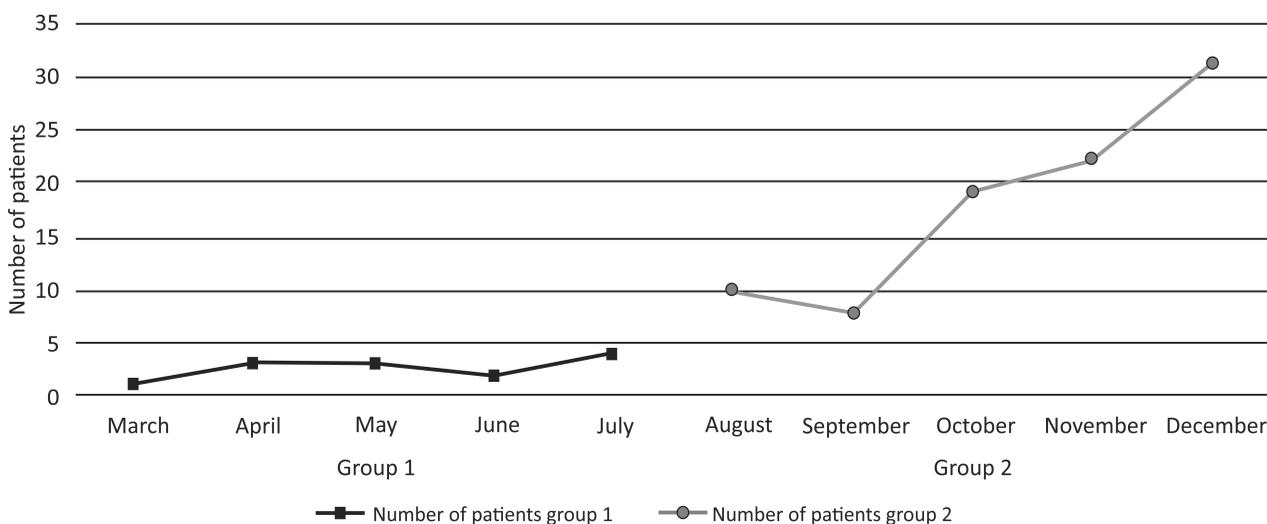


FIGURE 1. Distribution of the number of patients in groups over time

Evaluating the ways of patients' clinical presentation included in the two groups, we identified the existence of some clinical patterns. These are found in the two temporal clusters in different proportions, as it can be seen in Figures 2A and 2B, and defined as:

- Digestive symptomatology: abdominal pain, nausea, vomiting, diarrhea, dysphagia, reduced appetite
- Respiratory symptomatology: nasal obstruction, rhinorrhea, cough, shortness of breath, wheezing, odynophagia, altered pulmonary stethacoustics
- Asymptomatic: absence of clinical signs and symptoms suggestive of SARS-CoV-2

It was evaluated the existence of correlations between the way of presentation and the presentation moment, related to the time elapsed since the beginning of the pandemic. Considering that Romania has entered the 2nd pandemic wave since August (time that coincides with the relaxation of measures taken

to limit the spread of infection, but also with the reopening of most tourism units and later, schools), we noticed a significant increase in the number of children infected with the SARS-CoV-2 virus in the second group compared to the first group.

Following the time distribution of pediatric cases, a biphasic distribution is observed. Thus, in the first temporal stage, considered the first pandemic wave (Group 1), it is found that pediatric patients presented mild clinical forms of the disease, secondary to SARS-CoV-2 virus infection. Most children had digestive manifestations (8 patients, 61.5% of patients in group 1 had digestive manifestations).

However, starting with August (group 2) there is a significant increase in the number of cases, as well as the appearance of a larger number of cases that have associated respiratory symptoms.

Among the reasons for presenting to the emergency room, the fever is the main cause of symptoms, being found in 7 of the patients admitted in the first

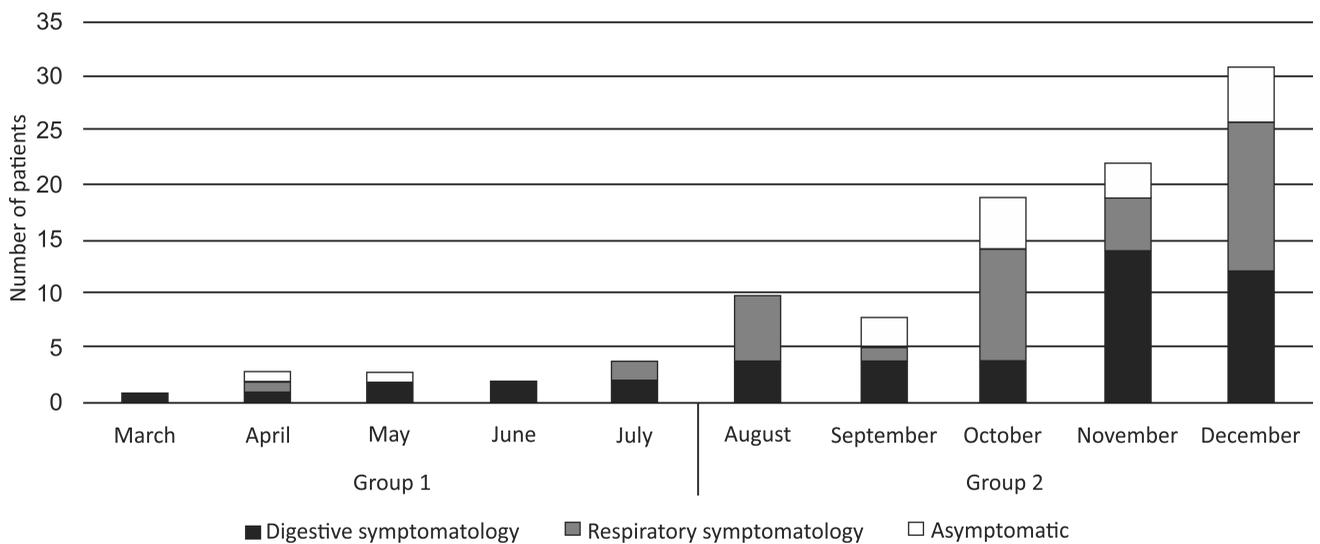


FIGURE 2A. The ways of clinical presentation related to the two temporal phases

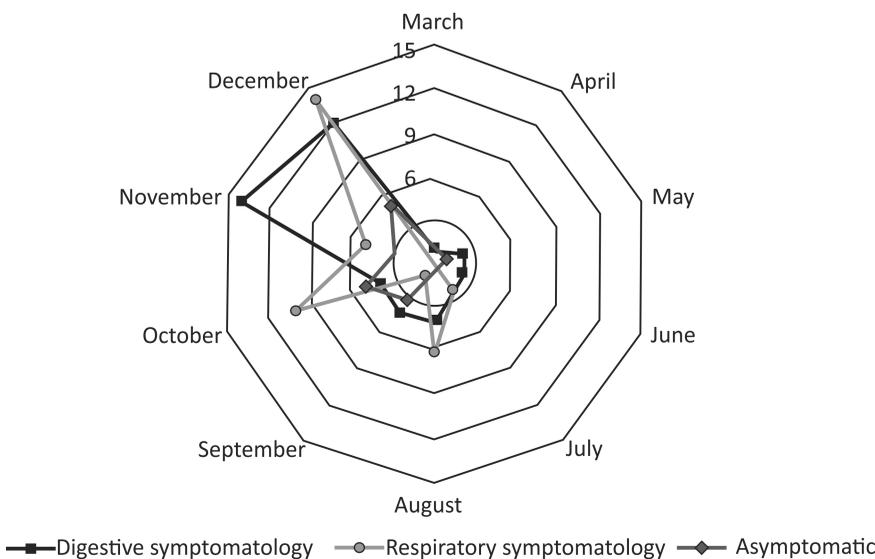


FIGURE 2B. The ways of clinical presentation related to the two temporal phases

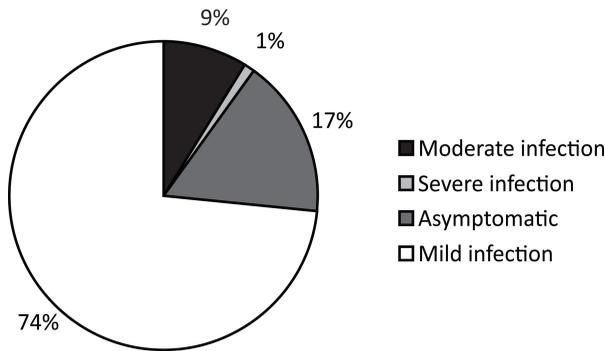


FIGURE 4. Classification of clinical forms according to severity

.Analyzing the data of the patients diagnosed with moderate forms of the disease, we found the following: 1 patient, aged 3 months, had a clinical picture of acute bronchiolitis, 7 patients were diagnosed with acute pneumonia, and one patient was operated for acute abdominal surgery.

Evaluating the incidence of SARS-CoV-2 infection according to gender in the studied patients, a slight predominance of males is observed in both groups (group 1: 7 boys –53.8%; group 2: 59 boys – 65.5%).

However, a statistically significant temporal correlation cannot be established, related to the gender distribution of the patients evaluated in the two mentioned temporal phases, as it can be seen in Figure 5 (p = 0.410).

The distribution by age groups has showed a difference in the structure of the two groups. Thus, it is found that group 1 includes a higher number of cases in patients < 5 years of age, a special category being represented by infants aged < 6 months (30.4% of patients in this group). Although in group 2 there is a significant impairment in the age group 0-6 months (38% of patients in this group), what attracts our attention is the significant increase in the number of

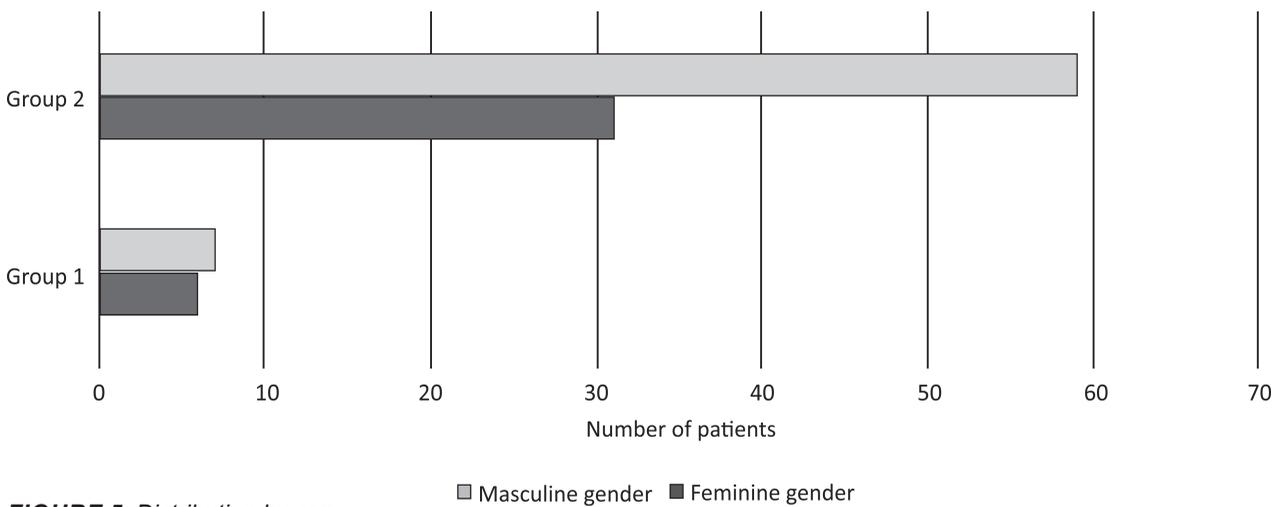


FIGURE 5. Distribution by sex

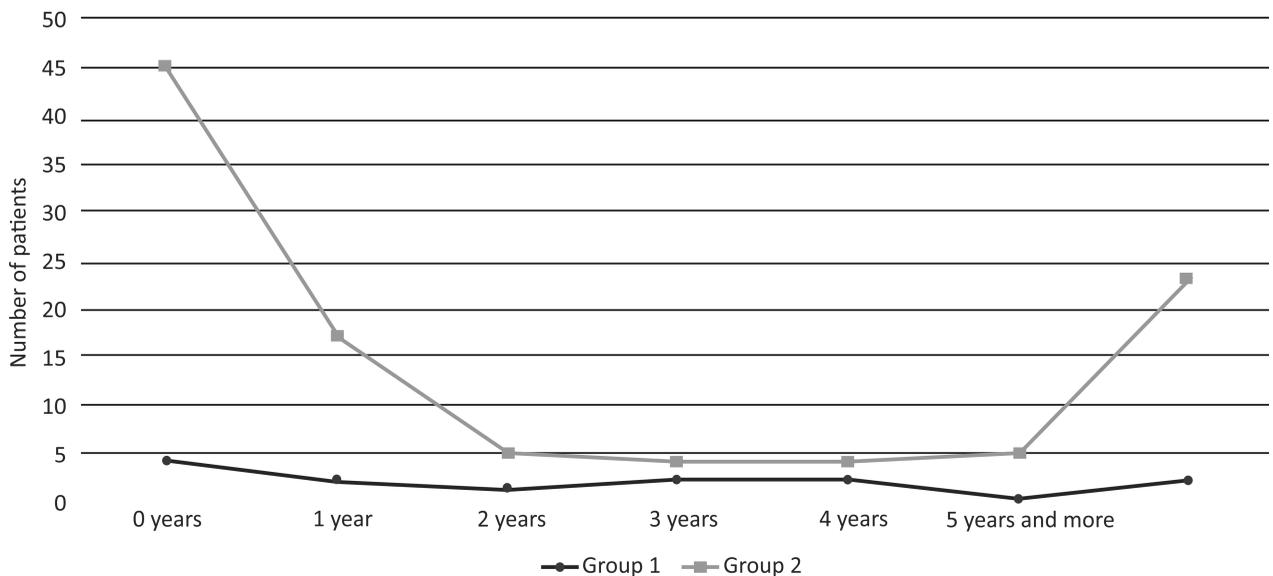


FIGURE 6. Distribution by age

cases in the age group over 5 years, represented by schoolchildren and adolescents, as shown in Figure 6.

DISCUSSIONS

Analyzing the 103 patients confirmed SARS-CoV-2 positive by RT-PCR, we have observed a relatively low incidence compared to the adult population, of only 2.48% in the first months of the pandemic, which could be explained by a possible underdiagnosis of the cases or a possible predominant asymptomatic infection in children. This observation is consistent with data from the literature. However, the impact that SARS-CoV-2 infection may have on the pediatric population should not be overlooked, as children are considered “hidden victims of the pandemic”, rather than the face [18]. Subsequently, however, there is a significant increase in the incidence, this upward trend having been in line with the situation described in the literature [2,18,24].

The relaxation of the prevention measures, the reopening of educational units (nurseries, kindergartens, etc.) starting with August, but especially, the increase in the number of people who travelled for tourism during this period, could explain the significant increase in the number of confirmed cases of SARS-CoV-2 infection. This phenomenon is found both in the studied group and in the literature [1,5].

Assessing the clinical symptoms presented at the hospitalization by the patients included in the study, we have identified the presence of the digestive manifestations (abdominal pain, vomiting, diarrhea, dysphagia, loss of appetite) in 44.7% of patients, respiratory manifestations (nasal obstruction, rhinorrhea, cough, respiratory difficulties, odynophagia) in 37.9%, and asymptomatic in 17.4% of cases. Comparing the two pandemic waves, we have observed a biphasic distribution of the cases as follows: in the first temporal cluster, the digestive symptoms have predominated, later, with increasing incidence of SARS-CoV-2 infection in the pediatric population and the evolution to second pandemic wave respiratory symptoms have predominated. These data confirm already published data, thus allowing the outline of possible clinical patterns of SARS-CoV-2 infection in children [19,20,22,23].

Similarly, to the data published so far, the results of the study conducted in our clinic have attested to the predominance of the mild forms in the pediatric population infected with SARS-CoV-2 (73.78%) compared to the moderate forms (8.73%) which are more characteristic of adults [5, 14,21,25,26].

Analyzing the gender distribution of the patients included in the study, we have observed the predominant impairment of the male patients, independent of

the time cluster analyzed, data having been consistent with the cohorts described in the literature [2,5,15].

In the published multicenter studies, targeting the pediatric population infected with SARS-CoV-2, it has been observed a generalized impairment of the age group, but with the predominant involvement of patients <1 year of age. Analyzing the data of the patients included in the study, we have observed the same predominant trend of infant impairment in both waves of the COVID-19 pandemic, pointing out that there are age-related features that cause these patients to be vulnerable (immature immune system, greater susceptibility to infections, etc.) [2,17,18]. Also, we have to acknowledge that there is an increase in the number of cases in the age category represented by schoolchildren and adolescents, explained by the opening of schools.

CONCLUSIONS

The study shows that in the first months after the onset of the pandemic, children are infected with the new coronavirus in a small percentage compared to adults.

Regarding the direct damage, following the study, we noticed that, with the evolution of the pandemic, the incidence of infection among children is increasing, along with the increased incidence found in adults. The data obtained are showing a significant increase in the number of cases of infection in children with the onset of wave 2 (August 2020).

As it has been demonstrated in other studies to date, we have observed that SARS-CoV-2 infection in children, causes asymptomatic (most common) or mild to moderate forms of the disease. Severe forms are extremely rare in children, especially if we refer to the first wave of the pandemic. We have noticed that the presence of digestive manifestations as the dominant clinical picture, was a characteristic of the first temporal period analyzed. With the advance towards the autumn-winter months, the respiratory manifestations appeared, which became predominant. The presence of fever is also an important clinical feature of SARS Cov-2 infection in children.

Assessing the age of the patients included in the study, we pointed out that, in the second temporal period, there is an increase in the number of cases in children over 5 years of age. This observation will require further studies, especially as some published literature data are drawing attention to the long-term consequences of the SARS-CoV-2 infection, especially in school-age children and/or adolescents (occurrence of multisystemic inflammatory syndrome)

post COVID-19, pulmonary, cardiac complications etc.).

Analyzing the epidemiological data obtained in the study, we conclude the need for sustained global efforts, to more clearly define the variations of patterns of presentation of SARS-CoV-2 infection in children, in the context of the evolution of the pandemic.

The remote follow-up of these infected children is necessary, because, although they are apparently less severely affected compared to adults, the remote consequences of SARS-CoV-2 infection are still unknown.

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REFERENCES

- World Health Organisation. Available at: <https://www.who.int/ith/diseases/sars/en>.
- Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020 Feb 10;41(2):145-151.
- UNICEF. COVID-19 and children. <https://data.unicef.org/topic/covid-19-and-children>.
- Institutul National de Sanatate Publica. Infectia cu noul coronavirus SARS-CoV-2 - situatia la nivel global actualizata zilnic. Available at: <http://www.cnscbt.ro>.
- Spatariu L, Buzoianu E, Chindriş S, Pleşca D. A clinical and epidemiological characteristics in children confirmed with SARS-CoV-2 infection in a non-COVID-19 Pediatric clinical hospital from Romania in the first 6 months of the pandemic. *Lo Zibaldone del terzo Millenn Graf Nappa*. 2020:235-245.
- Bialek S, Gierke R, Hughes M, McNamara LA, Pilišvili T, Skoff T. Coronavirus disease 2019 in children: Current status - Morbidity and Mortality Weekly Report. *CDC COVID-19 Response Team*. 2020;69(14):422-426.
- Centers for Disease Control and Prevention. COVID-19. Available at: <https://www.cdc.gov/coronavirus/2019-nCoV/index.html>.
- Sun D, Zhu F, Wang C, et al. Children Infected With SARS-CoV-2 From Family Clusters. *Front Pediatr*. 2020;8(June):2-9.
- Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med*. 2020;382(17):1663-1665.
- Davitoiu AM, Chindris S, Iancu M, Tincu I, Spataru L, Pleşca DA. Managementul paraclinic al infecției cu SARS-CoV-2 la pacientul pediatric. *Rom J Pediatr*. 2020;69(3):215-220.
- Zhou B, Yuan Y, Wang S, et al. Risk profiles of severe illness in children with COVID-19: a meta-analysis of individual patients. *Pediatr Res*. 2021;(November 2020):1-6.
- Wu H, Zhu H, Yuan C, et al. Clinical and Immune Features of Hospitalized Pediatric Patients With Coronavirus Disease 2019 (COVID-19) in Wuhan, China. *JAMA Netw Open*. 2020;3(6):e2010895.
- Baj J, Karakula-Juchnowicz H, Teresiński G, et al. COVID-19: Specific and Non-Specific Clinical Manifestations and Symptoms: The Current State of Knowledge. *J Clin Med*. 2020;9(6):1753.
- García-Salido A. Three Hypotheses About Children COVID19. *Pediatr Infect Dis J*. 2020;39(7):e157-e157.
- Brizuela M, Lenzi J, Ulloa-Gutiérrez R, et al. Influence of sex on disease severity in children with COVID-19 and Multisystem Inflammatory Syndrome in Latin America. *medRxiv*. 2021:2021.02.07.21251212.
- She J, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. *J Med Virol*. 2020;92(7):747-754.
- Zimmermann P, Curtis N. Coronavirus Infections in Children Including COVID-19. *Pediatr Infect Dis J*. 2020;39(5):355-368.
- Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109(6):1088-1095.
- Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission. *Gastroenterology*. 2020; 158(6):1518-1519.
- Donà D, Minotti C, Costenaro P, Da Dalt L, Giaquinto C. Fecal-Oral Transmission of SARS-CoV-2 In Children. *Pediatr Infect Dis J*. 2020; 39(7):e133-e134.
- Mazza A, Di Giorgio A, Martelli L, Pelliccia C, Pinotti MA, Quadri V, Verdoni L, Decio A, Ruggeri M, D'Antiga L. Patterns of Presentation of SARS-CoV-2 Infection in Children. Experience at the Italian Epicentre of the Pandemic. *Front Pediatr*. 2021 Jan 28;9:629040.
- Chang T-H, Wu J-L, Chang L-Y. Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J Formos Med Assoc*. 2020;119(5):982-989.
- Paret M, Lighter J, Pellett Madan R, Raabe VN, Shust GF, Ratner AJ. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Febrile Infants Without Respiratory Distress. *Clin Infect Dis*. 2020;71(16):2243-2245.
- Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020;323(14):1335.
- Xu H, Liu E, Xie J, et al. A follow-up study of children infected with SARS-CoV-2 from western China. *Ann Transl Med*. 2020; 8(10):623-623.
- Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, Leung JW, Belay ED. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. *J Pediatr*. 2020 Aug 5; 226:45-54.e1.