A multicenter study of confirmed COVID-19 cases: preliminary data of 2690 pediatric patients in Argentina during the first year of the pandemic

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ABSTRACT

Introduction. The current evidence indicates that the severity of the coronavirus disease 2019 (COVID-19) is lower in the pediatric population but local data are still limited. Objective: To characterize the clinical and epidemiological aspects of COVID-19 infection in patients younger than 18 years in Argentina.

Population and methods. Cross-sectional, observational, and analytical study of confirmed COVID-19 patients aged 0-18 years seen between March 2020 and March 2021 at 19 referral children's hospitals of Argentina. A multivariate analysis was done to identify predictors of severe cases.

Results. A total of 2690 COVID-19 cases were included: 77.7% lived in the Metropolitan Area of Buenos Aires; 50.1% were males; patients' median age was 5.6 years. Of them, 90% were seen during epidemiological weeks 20-47 of 2020; 60.4% had a history of contact with COVID-19 patients; and 96.6% in their family setting. Also, 51.4% had respiratory symptoms; 61.6%, general symptoms; 18.8%, gastrointestinal symptoms; 17.1%, neurological symptoms; 7.2%, other symptoms; and 21.5% were asymptomatic. In addition, 59.4% of patients were hospitalized and 7.4% had a severe or critical course. A total of 57 patients developed multisystem inflammatory syndrome. A history of asthma, bronchopulmonary dysplasia, congenital heart disease, moderate to severe malnutrition, obesity, chronic neurological disease and/or age younger than 6 months were independent predictors of severity. Living in a vulnerable neighborhood was a protective factor.

Conclusions. More than half of cases referred a history of contact with COVID-19 patients in the family setting. Hospitalization was not based on clinical criteria of severity. Severity was associated with the presence of certain comorbidities.

Key words: *coronavirus infections, COVID-19, child, multisystem inflammatory syndrome in children.*

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INTRODUCTION

Since the declaration of the world pandemic state on March 11th, 2020, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, has disseminated and generated a huge impact worldwide, not only in the health care setting but also in the financial and social context.[1] In Argentina, the first case was reported on March 3rd, 2020 and, by April 2021, more than 136 000 000 cases had been confirmed and 2 900 000 deaths had occurred in the world.[2]

According to initial data, children and adolescents may become infected but have a better prognosis compared to adults.[3,4] In general, they develop mild symptoms and usually recover 1 to 2 weeks after disease onset; 15-35% may be asymptomatic.[5]

In Argentina, until epidemiological week (EW) 11 of 2021, during the "first wave" of the pandemic, 9.4% of cases were recorded among individuals younger than 20 years, with a case fatality rate of 0.08%.[6]

Epidemiological surveillance of COVID-19 in the pediatric population showed specific characteristics since the beginning due to the limited information available and the higher impact among adults.[7]

In May 2020, the existence of a multisystem inflammatory syndrome associated with SARS-CoV-2 was reported in pediatric patients, which progressed to multiple organ failure in many cases.[8-10] Local information about COVID-19 characteristics in the pediatric population is still limited.[11,12]

The objectives of this study are to characterize COVID-19 infection in children and adolescents younger than 18 years in Argentina based on its clinical and epidemiological characteristics, assess the clinical characteristics of hospitalized patients with confirmed infection, and identify risk factors for severity.

POPULATION AND METHODS

Cross-sectional, multicenter, observational, and analytical study. All patients younger than 18 years with confirmed SARS-CoV-2 infection (according to the definition by the National Ministry of Health)[7] and seen at participating sites were included in a retrospective (March 1st-September 30th, 2020) and prospective manner (October 1st-October 31st, 2021). A total of 19 facilities located in the Autonomous City of Buenos Aires (CABA) and the provinces of Buenos Aires, Chaco, Córdoba, Mendoza, Santa Fe, and Tierra del Fuego participated.

Data collection

Data were collected by investigators at the participating sites. An *ad hoc* card was designed to collect epidemiological and clinical data. The following data were obtained: participating site, patient identification code, admission date, demographic data, hospitalization data (patients admitted to the unit and diagnosis upon admission), time elapsed from symptom onset, contact with a person with confirmed COVID-19 and/or acute upper respiratory infection (URI), presence of comorbidities (prematurity, chronic or recurrent respiratory disease, immunosuppression, malnutrition, congenital heart disease, neurological disease, liver disease, kidney disease, and metabolic disease), signs and symptoms, supplementary imaging and laboratory tests (if ordered by the treating physician), clinical course, and treatment administered.

Critical overcrowding was defined as per the National Statistics and Censuses Institute of Argentina (Instituto Nacional de Estadísticas y Censos, INDEC) as more than 3 inhabitants per room (leaving out the kitchen and bathroom) living together; and vulnerable or poor neighborhood was defined as per the National Registry of Poor Neighborhoods (Registro Nacional de Barrios Populares) as a neighborhood where at least 8 families lived in clusters or adjacent houses, more than half of the population lacked a property deed, and there was no regular access to 2 or more utilities.

COVID-19 severity was defined based on the clinical and radiological characteristics established by Dong et al.[13] Study coordination, data entry, and analysis were performed by the Department of Health Protection and Promotion of Hospital de Niños Ricardo Gutiérrez in the Autonomous City of Buenos Aires.

Etiologic diagnosis

Cases were confirmed using a reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 performed on nasopharyngeal aspirate or throat swab.

Diagnostic tests were accepted in addition to indirect immunofluorescence (IIF), including FilmArray and amplified PCR, to look for other viral etiologic agents that may have caused acute URI: respiratory syncytial virus (RSV), adenovirus (AV), influenza (IF) A and B, and parainfluenza (PIF) 1, 2, and 3.

For patients diagnosed with multisystem inflammatory syndrome in children (MIS-C) temporally related to COVID-19, a positive serology for SARS-CoV-2 was accepted as confirmation, according to the regulations of the Ministry of Health.

Statistical analysis

A general description was done estimating the mean and standard deviation or median and interquartile range (IQR) for numerical variables, depending on their distribution. Proportion and its corresponding 95% confidence interval (CI) were used for categorical variables. Continuous variables were analyzed using the t test or Wilcoxon's test. Categorical variables were analyzed using a χ^2 test with Yates' correction or Fisher's test.

The analysis of results of supplementary tests excluded patients diagnosed with MIS-C. A multiple logistic regression model was developed to identify predictor variables of severe disease. Cases classified as severe and critical according to Dong[13] were regarded as severe, whereas asymptomatic, mild or moderate cases were regarded as not severe. The STATA/SE software, version 13, was used for statistical analysis. The odds ratio (OR) with a 95% CI was used as a measure of association. The final model assessed calibration and discrimination; the former using the Hosmer-Lemeshow test estimated in deciles of risk and the latter using the Receiver Operating Characteristic (ROC) curve. Overall calibration with a $p > 0.05$ and a discrimination with an area under the ROC curve > 0.7 were considered adequate.

Ethical considerations

All cards were coded before analysis to warrant anonymity, in accordance with the Declaration of Helsinki and the Law of *Habeas Data* (Law no. 25326). This study was assessed and authorized by the research teaching and ethics committees of participating sites.

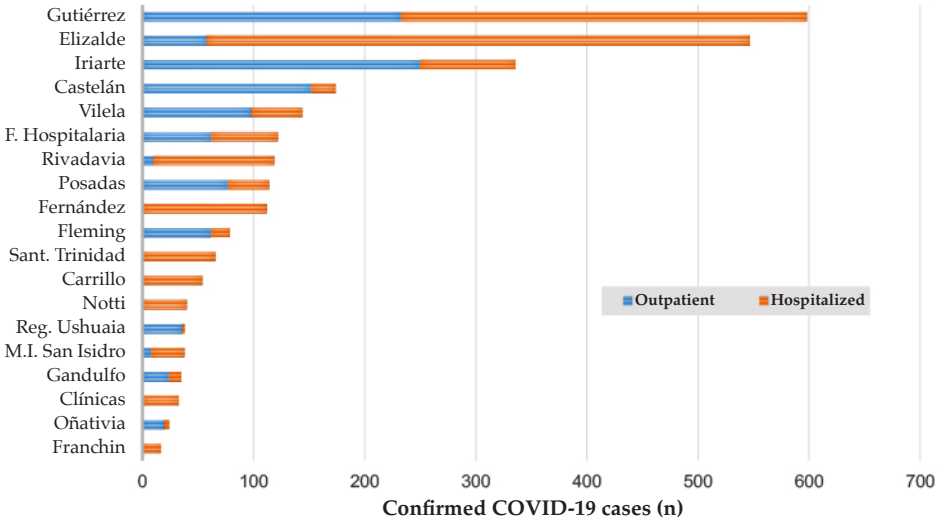
RESULTS

Between EW 12 of 2020 and EW 11 of 2021, a total of 2690 confirmed COVID-19 cases were included. Of them, 77.7% lived in the Metropolitan Area of Buenos Aires (AMBA)–CABA (40.5%) and province of Buenos Aires (37.2%)–, followed by the provinces of Chaco (6.5%), Mendoza (6.4%), Santa Fe (5.3%), Córdoba (2.5%), Tierra del Fuego (1.4%), Chubut (0.1%), and Misiones (0.1%) (*Figure 1*). Also, 90% of cases occurred between EW 20 and 47 (May 10th-November 21st), with a peak observed in EW 32 (August) (*Figure 2*).

Characteristics of confirmed cases

The median age of confirmed cases (n = 2690) was 5.6 years (IQR: 1.3-11.3 years); 21.2% were

FIGURE 1. *Distribution of outpatient and hospitalized COVID-19 cases by hospital (n = 2690)*



younger than 1 year; sex distribution was equal. In addition, 29.9% lived in poor neighborhoods and 28.7% in critical overcrowding conditions. A history of contact with individuals who had acute respiratory infection and/or COVID-19, confirmed by a laboratory test was reported in 60.4%, and no differences were observed among age groups. In 96.6% of these cases, contact with a confirmed COVID-19 case corresponded to a family member.

In addition, 59.4% (n = 1599) of patients were hospitalized (IQR = 28.5-98.5%), with a heterogeneous distribution among the different periods and jurisdictions. Hospitalization rates

FIGURE 2. *Distribution of COVID-19 cases by epidemiological week (n = 2690)*

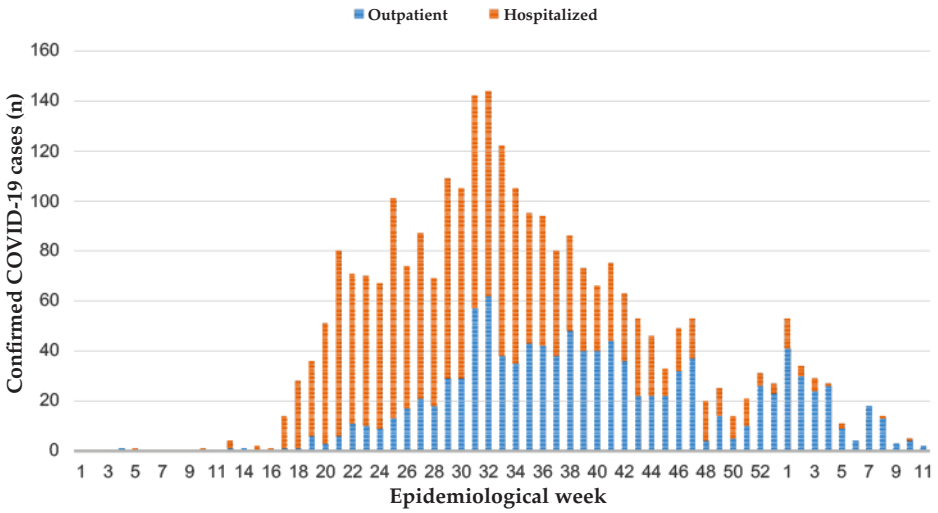
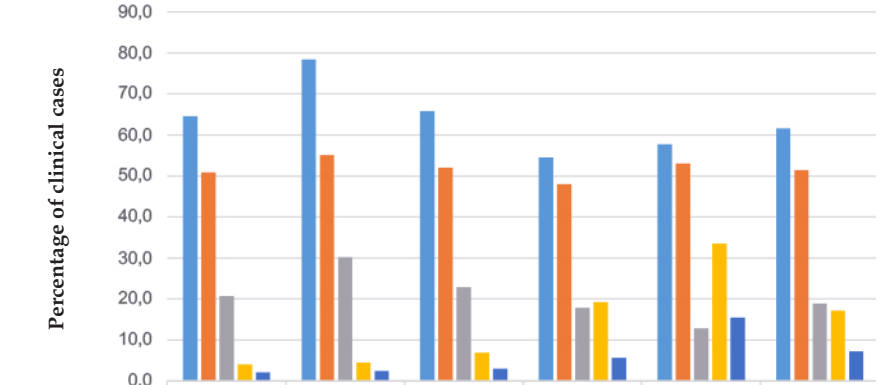


FIGURE 3. *Clinical presentation profile of confirmed COVID-19 cases by age group (n = 2690)*



	< 12 months	12-23 months	2-4 years	5-9 years	10-18 years	Total
General	64.6	78.4	65.8	54.5	57.8	61.69
Respiratory	50.9	55.1	52.0	48.0	53.0	51.4
Gastrointestinal	20.7	30.2	22.9	17.9	12.9	18.8
Neurological	4.0	4.5	6.9	19.2	33.5	17.1
Other	2.1	2.4	3.0	5.6	15.5	7.2

Note: Some cases had more than one presenting sign or symptom. Symptoms:

- General: fever, malaise, and myalgia.
- Respiratory: cough, odynophagia, rhinorrhea, and respiratory distress.
- Gastrointestinal: vomiting, nausea, diarrhea, and abdominal pain.
- Neurological: headache and seizures.
- Other: anosmia, dysgeusia, and non-specific rash.

were statistically different; infants younger than 1 year showed a higher hospitalization rate (29.6%). One or more comorbidities were observed in 23.4% of cases; respiratory disease was the most common one (52.5%). *Table 1* describes the clinical and epidemiological characteristics of the population and compares outpatients with hospitalized patients.

Also, 21.5% of patients were asymptomatic. The most common signs and symptoms included fever > 37.5 °C (69.4%), cough (35.9%), rhinorrhea (20.7%), and odynophagia (20.5%). *Figure 3* shows signs and symptoms, grouped and by age range; children aged 10 years or older showed a significantly higher percentage of neurological symptoms (headache) and anosmia, with or without dysgeusia.

TABLE 1. *Clinical and epidemiological characteristics and frequency of comorbidities of confirmed COVID-19 cases (total, outpatients and hospitalized patients; n = 2690)*

Characteristics of the population	**Total (n = 2690) % (n)**	**Outpatient (n = 1091) % (n)**	**Hospitalized (n = 1599) % (n)**	***p***
Age in years (median; interquartile range)	5.6 (1-11)	7.6 (3-13)	4.1 (1-10)	< 0.001
Age groups:				
< 12 months	21.2 (570)	8.8 (96)	29.6 (474)	
12-23 months	9.1 (245)	11.4 (124)	7.6 (121)	
2-4 years	16.1 (433)	16.9 (185)	15.5 (248)	< 0.001
5-9 years	22.5 (604)	25.0 (273)	20.7 (331)	
≥ 10 years	31.1 (838)	37.9 (413)	26.6 (425)	
Male sex	50.1 (1349)	50.3 (549)	50.0 (800)	0.913
Epidemiological week during symptom onset (week, week range)	32 (25-38)	35 (27-41)	30 (24-36)	< 0.001
Place of residence in AMBA	77.7 (2092)	68 (742)	84.4 (1350)	< 0.001
Place of residence in a poor neighborhood	29.9 (805)	19.2 (210)	37.2 (595)	< 0.001
Critical overcrowding	28.7 (774)	12.1 (132)	40.1 (642)	< 0.001
Contact with a COVID-19 patient	60.3 (1623)	50.2 (548)	67.2 (1075)	< 0.001
Contact with an ARI patient	24.3 (654)	17.6 (192)	28.9 (462)	< 0.001
Contact with a COVID-19 patient in the family setting	96.6 (1543)	97.9 (527)	95.4 (1016)	0.049
Comorbidities	23.4 (630)	12.1 (131)	31.2 (499)	< 0.001
Respiratory disease	(52.5)			
Asthma	6.5 (174)	5.3 (58)	7.2 (116)	0.053
Recurrent wheezing	4.8 (130)	3.1 (34)	6 (96)	< 0.001
Bronchopulmonary dysplasia	0.6 (18)	0.1 (1)	1.1 (17)	0.001
Perinatal respiratory distress	0.2 (6)	0 (0)	0.4 (6)	0.087
Cystic fibrosis	0.1 (3)	0.1 (1)	0.1 (2)	1
Metabolic disorder	(8.4)			
Obesity	1.3 (36)	0.2 (2)	2.1 (34)	< 0.001
Diabetes	0.6 (17)	0.5 (5)	0.7 (12)	0.489
Immunodeficiency	(3.2)			
Primary	0.6 (15)	0.2 (2)	0.81 (13)	0.034
Cancer	1.5 (40)	0.6 (7)	2.1 (33)	0.004
Acquired immunodeficiency	0.2 (6)	0 (0)	0.4 (6)	0.087
Transplant	0.04 (1)	0 (0)	0.06 (1)	1
Immunosuppressive therapy	0.9 (25)	0.4 (4)	1.3 (21)	0.012
Malnutrition	0.7 (18)	0.1 (1)	1.1 (17)	0.001
Chronic neurological disease	3.3 (88)	0.8 (9)	4.9 (79)	< 0.001
Congenital heart disease	1.3 (34)	0.2 (2)	2 (32)	< 0.001
Chronic kidney disease	1.1 (29)	0.3 (3)	1.6 (26)	< 0.001
Liver disease	0.3 (9)	0.2 (2)	0.4 (7)	0.326
Prematurity	1.7 (45)	0.4 (4)	2.6 (41)	< 0.001

AMBA: Metropolitan Area of Buenos Aires, ARI: acute respiratory infection, COVID-19: coronavirus disease 2019.

Initially, 5.6% of cases presented as acute lower respiratory infection (bronchiolitis: 2.5% and pneumonia: 3.1%) and 3.6%, as MIS-C.

Course and severity of hospitalized confirmed cases

The median length of stay among hospitalized confirmed cases (n = 1599) was 7 days (IQR: 3-9 days). A total of 57 patients diagnosed with MIS-C were recorded; their median age was 6.5 years. In this group, 61.4% received gamma globulin and 59.6%, corticosteroids; 52.6% required intensive care.

For the analysis of supplementary tests and course, patients with MIS-C were excluded due to its differential characteristics.

Among the 1542 hospitalized patients (excluding those with MIS-C), a chest X-ray was done in 30.9% (68.1% were normal; 14.6% had interstitial infiltrate; 7.3%, condensation; and 4.6%, air trapping) and a chest computed tomography scan was performed in 1.3% (10 were normal; 6 showed ground-glass lesions; 2, pleural effusion; and the rest, other infiltrates). Other respiratory viruses were looked for in 2.6% of cases (n = 41); virus co-infection was detected in 5: adenovirus, metapneumovirus, and rhinovirus.

Laboratory tests were done upon admission in 52.1% (n = 804) of cases; patients with a severe condition in the beginning had higher levels of leukocytes, neutrophils, erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, urea, and ferritin and a lower prothrombin time, with a statistically significant difference in relation to non-severe patients.

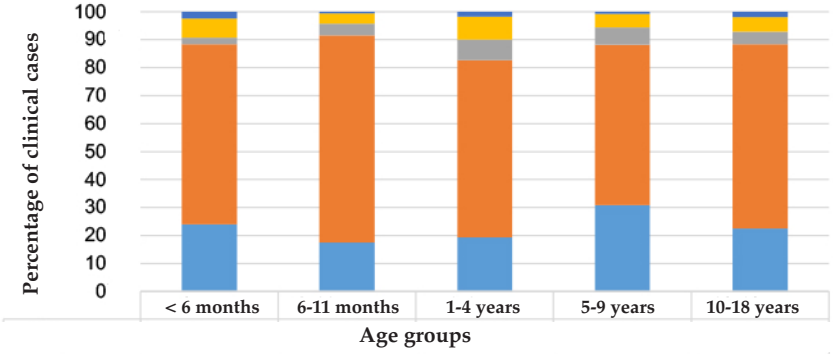
Figure 4 shows the distribution of patients by age group based on their final classification. In total, 7.4% (n = 114) of patients were classified as severe or critical: 84.2% required oxygen; 24.5%, intensive care; and 17.5%, mechanical ventilation. The multivariate analysis (*Table 2*) determined that the following were independent predictors of COVID-19 severity: history of asthma, bronchopulmonary dysplasia, congenital heart disease, moderate to severe malnutrition, obesity, chronic neurological disease, and age younger than 6 months. A history of living in a vulnerable neighborhood was an independent predictor with a protective effect.

Eight deaths were recorded (median age: 8.5 years, range: 0-16 years); all had comorbidities: chronic kidney disease (2), heart disease (2), and the rest, chronic lung disease, primary immunodeficiency disease, chronic liver disease, and debut of cancer.

DISCUSSION

To understand clinical and epidemiological management strategies in pediatrics it is essential to specify the differential characteristics of SARS-CoV-2 infection in this age group.[14] This study describes the clinical and epidemiological characteristics of patients with confirmed COVID-19 diagnosis seen at 19 referral children's

FIGURE 4. *Distribution of confirmed COVID-19 cases who were hospitalized based on final classification upon discharge, by age group (n = 1542)*



	< 6 months	6-11 months	1-4 years	5-9 years	10-18 years
Crítical	2.5	0.5	1.7	0.6	1.9
Severe	6.7	3.7	8.2	4.9	5.1
Moderate	2.5	4.2	7.4	6.2	4.6
Mild	64.3	74.1	63.5	57.5	65.8
Asymptomatic	24.0	17.5	19.3	30.8	22.6

hospitals in Argentina. The epidemic peak was observed 10 weeks before what has been described at a national level, probably because most cases were included by hospitals located in the AMBA, the first region chronically affected in the country.[15]

The differences observed in the percentage of hospitalization among the sites reflect the dynamics of pediatric case management strategies.[16] Initially, all pediatric patients were hospitalized (even if they had a mild condition); then, only infants younger than 1 year; and lastly, only those younger than 6 months, regardless of severity. The main objective of this strategy was to isolate the patient and its caregiver from the rest of their family. The limited information available about COVID-19 in pediatric patients was determining: according to this, children were considered "hyper-contagious" and the epidemiological characteristics of flu were taken as reference.[17] Based on these considerations, it may be said that pediatric hospitalization due to COVID-19 in 2020 was not necessarily associated with disease severity, as in the case of adults.[18,19] At this point, it is worth noting as a limitation of this study that some sites only included hospitalized cases and that epidemiological criteria for hospitalization varied among jurisdictions.

In this series, in general terms, children had a previous contact with confirmed COVID-19 cases in their family; in a variable percentage, such evidence has also been described in the bibliography.[15,20] One third of patients lived in poor neighborhoods in critical overcrowding conditions, which favored the transmission of SARS-CoV-2 via contact and droplets. In CABA, a prevalence study conducted in such neighborhoods showed a high rate of undetected infections (probably asymptomatic cases).[21]

The median age of patients was 5 years, similar to what has been described worldwide.[22] In the beginning of the pandemic, in a setting of limited access to diagnostic tests and considering that COVID-19 in adults displayed characteristics that were similar to those of flu, the situation was undertaken as the surveillance of respiratory viruses, considering the presence of fever and respiratory symptoms as mandatory for the definition of suspected case.

One in every 5 children was asymptomatic; this underscores the importance of making highly sensitive and specific molecular diagnostic tests in pediatrics and limiting the use of rapid antigen tests to symptomatic cases.[23] Other viruses were looked for in only 2% of cases: a current challenge will be to assess how other seasonal viruses behave in pediatrics outside the lockdown.[24]

Given the asymptomatic or oligosymptomatic presentation in pediatrics, it is worth noting the importance of refining the definition of case, prioritizing the epidemiological history of close contact, and considering the possibility of dissemination from an adult patient to cut the chain of transmission.[25]

In relation to the types of clinical presentation, as of 10 years old, the percentage of anosmia, dysgeusia, and headache is similar to that observed in adults.[26,27] In addition, 67% of cases were asymptomatic or mild, which is consistent with what has been published in pediatrics

TABLE 2. *Multivariate analysis of factors associated with a severe course of COVID-19 among hospitalized patients (n = 1542)*

Variable	OR	95% CI	*p*
Asthma	5.7	3.3-9.7	< 0.001
Bronchopulmonary dysplasia	6.3	2.0-20.0	0.001
Obesity	3.7	1.5-9.2	0.005
Heart disease	4.6	1.9-11.6	< 0.001
Neurological disease	2.2	1.1-4.7	0.032
Malnutrition	5.1	1.6-16.2	0.006
Place of residence in a vulnerable neighborhood	0.4	0.2-0.7	< 0.001
Prematurity	3.1	0.3-30.6	0.318
Diabetes	1.9	0.4-9.9	0.445
Age younger than 6 months	1.9	1.1-3.1	0.009
Chronic kidney disease	1.5	0.4-5.4	0.549
Cancer	2.3	0.7-7.1	0.127

Note: The model showed an adequate calibration when assessed using the Hosmer-Lemeshow test ($p = 0.328$) and an acceptable discrimination, according to the ROC curve, with an area under the curve of 0.729 (95% CI: 0.68-0.72).
OR: odds ratio; CI: confidence interval.

to date.[28,29] Besides, given the lesser severity, supplementary imaging tests were not requested per protocol but based on each participating site's standards and availability; most were normal.[30]

In 7% of cases, COVID-19 was severe, and the case fatality rate was 0.3% (all had comorbidities); the mortality rate was similar to what has been described at a national and international level.[31,32] The comorbidities that showed a significant association with progression to a severe condition included asthma, bronchopulmonary dysplasia, obesity, chronic neurological disease, heart disease, malnutrition, and age younger than 6 months.[33,34] A history of living in a vulnerable neighborhood was a protective factor. In view of the need to warrant isolation, patients in this population were hospitalized, mostly regardless of their age or the presence of comorbidities, until community isolation devices were available, in accordance with national regulations.[16]

Patients with severe conditions initially showed higher levels of leukocytes and neutrophils, unlike what has been reported in adults, since several publications have established an association between the presence of lymphopenia at disease onset and a more unfavorable course.[35] On the contrary, a history of living in a poor neighborhood was a strong protective factor, and this is consistent with the evidence that indicates that the case fatality rate due to COVID-19 was lower in this type of neighborhoods than in the general population.[36]

A challenge in pediatrics will be to assess also the specific characteristics of MIS-C and the long-term consequences of this disease.[37] This will be the topic of another publication by this group.

In Argentina, as in other countries, it was difficult to establish the characteristics of COVID-19 in pediatrics. In addition, the prolonged lockdown did not allow to detect other diseases, which prompted delayed consultations, and resulted in a reduction in pediatric controls and immunization coverage, among other aspects, which will be a challenge in the future.[38,39]

Children are susceptible to post-COVID-19 effects, including social isolation and, in many cases, an interruption in education. The introduction of COVID-19 vaccines in the pediatric population, based on ongoing scientific evidence, will allow to prevent this disease, especially among patients with underlying conditions, and to mitigate its long effects.[40]

CONCLUSIONS

Most SARS-CoV-2 infection cases in pediatrics are mild or asymptomatic. More than half of cases referred a history of contact with COVID-19 patients in the family setting. Hospitalization was not based on clinical criteria of severity. The place of residence in a vulnerable neighborhood was a protective factor against a severe course. COVID-19 severity was associated with the presence of certain comorbidities and age younger than 6 months. ■

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