CLINICS

ORIGINAL ARTICLE

Differences among Severe Cases of Sars-CoV-2, Influenza, and Other Respiratory Viral Infections in Pediatric Patients: Symptoms, Outcomes and Preexisting Comorbidities

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OBJECTIVES: Previous studies focusing on pediatric patients hospitalized with severe coronavirus disease 2019 (COVID-19) have been limited to small case series. We aimed to evaluate the characteristics of a large population of pediatric patients with severe COVID-19 and compare them with patients with severe cases of influenza and other respiratory viruses (ORV).

METHODS: We performed a cross-sectional study of Brazilian data from the National Epidemiological Surveillance Information System, gathered from January 1st to July 14th, 2020. The sample included 4,784 patients (2,570 with confirmed COVID-19, 659 with influenza, 1,555 with ORV). Outcome measures included clinical features, preexisting comorbidities, pediatric intensive care unit admissions, need for ventilatory support, and death.

RESULTS: Compared with the influenza and ORV groups, the COVID-19 group had a higher proportion of newborns and adolescents, as well as lower frequencies of fever, cough, dyspnea, respiratory distress, and desaturation. Although use of invasive ventilatory support was similar among groups, death rate was highest for COVID-19 (15.2% *vs.* 4.5% *vs.* 3.2%, $p<0.001$), with death risk more than three times the other groups (adjusted OR=3.7 [95% CI 2.5-5.6]). The presence of two or more comorbidities further increased this risk (OR=4.8 [95% CI 3.5-6.6]). Preexisting comorbidities were reported in 986 patients with severe COVID-19 (38%). Mortality rate among COVID-19 patients was significantly higher for almost all comorbidities reported.

CONCLUSION: Severe COVID-19 had a higher mortality rate than other viral respiratory illnesses, despite the lower frequency of fever, cough, dyspnea, respiratory distress, and desaturation. Death risk was strongly associated with preexisting comorbidities.

KEYWORDS: Pediatrics; Epidemiology; COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by a new agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in Wuhan, China, and then spread globally. On March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic health emergency (1).

Early studies on Chinese patients reported high morbidity and mortality, especially among elderly patients with comorbidities (2,3). The clinical spectrum of COVID-19 ranges from asymptomatic to severe respiratory insufficiency and death. Approximately 15% of adult Chinese COVID-19 patients developed severe outcomes, and 6% of them required admission to the intensive care unit, mechanical ventilation, or died (2).

Pediatric COVID-19 has been reported in Chinese, Italian, Spanish, and US populations, with a frequency ranging from 1.7% to 2% in population-based studies (4,5,7-10). The vast majority of children and adolescents with COVID-19 are asymptomatic or present with mild or moderate manifestations (4,5,9,11,12). The broad clinical spectrum in pediatric populations includes fever (41-56%), cough (44-54%), dyspnea (11-13%), diarrhea (9-13%), and vomiting (10-11%) (5-9). In a large nationwide case series in China, severe symptoms were reported in 5.8% of pediatric COVID-19 patients (10). Oxygen desaturation ranged from 1.0% to 2.3% (5-6) in hospital cohorts, and an overall mortality rate of 0.1 to 0.6% was reported in children and adolescents with this infectious disease in both hospital and population-based studies

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(5,6,8,10). However, studies focusing specifically on the clinical features and outcomes of hospitalized children and adolescents with severe COVID-19, especially with regard to preexisting comorbidities, have so far been limited to small case series of patients admitted to the pediatric intensive care unit (PICU) or general wards in the USA and Canada (13-15).

Along with Asia, Europe, and the USA, Latin America is currently an epicenter of COVID-19. On February 26th, COVID-19 was reported for the first time in Brazil, rapidly achieving community transmission. On July 26th, the Brazilian Ministry of Health reported 2,394,513 confirmed COVID-19 cases, the second highest number of cases worldwide (16). However, in spite of this, no previous study has reported the features of COVID-19 in children and adolescents in a Latin American country. To our knowledge, no large analysis focusing on the incidence, outcomes, and preexisting comorbidities of severe acute respiratory illness (SARI) among pediatric COVID-19 patients has yet been carried out, nor has there been a study comparing this severe infectious disease with influenza and other common respiratory viral infections. Therefore, the objective of the present study was to evaluate pediatric patients with severe COVID-19, particularly focusing on cumulative preexisting comorbidities and outcomes. We also compared the features of pediatric COVID-19 with those of influenza and illnesses caused by other common respiratory viruses.

MATERIAL AND METHODS

This study was conducted in accordance with the ethical standards of our institutional ethics committee (CAPPesq – CAE 33118820.0.0000.0068).

This is a cross-sectional study of data routinely collected by Brazilian health authorities and made accessible to the public through the National Epidemiological Surveillance Information System. In Brazil, it is compulsory to report all cases of SARI by filling out a data form. Our definition of pediatric SARI was based on modified WHO guidelines and encompassed all cases of flulike symptoms that required hospitalization, including fever, cough, sore throat, and signs of respiratory impairment (difficulty breathing, dyspnea, or desaturation) (17-19). All SARI patients included in the study had symptoms severe enough to require admission to the general ward or PICU of a Brazilian hospital.

Patients were considered eligible for the study if they were less than 20 years old and had a viral infection confirmed by laboratory tests. Ongoing cases were excluded, as either the clinical symptomatology or the outcome might change after the end of data collection.

We found 4,784 closed cases of SARI patients with confirmed viral etiology reported from January 1st up to July 14th, 2020. "Closed cases" were defined as those with reported final outcomes (death or cure). We divided the patients into three groups according to the viral agent: SARS-CoV-2 (N=2,570), influenza (N=659), and other respiratory viruses (ORV; N=1,555). Patients were assigned to the ORV group if an immunofluorescence assay or polymerase chain reaction (PCR) test returned a positive result for respiratory syncytial virus (RSV), adenovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, metapneumovirus, bocavirus, or rhinovirus. The most frequent viral agents in the ORV group were RSV (35.5%), rhinovirus (22.5%), metapneumovirus (14.5%), and adenovirus (10%). SARS-CoV-2 infection was confirmed by real-time reverse-transcription PCR (RT-PCR), while influenza was confirmed by either positive PCR or positive immunofluorescence assay.

All variable fields in database entries were assessed for missing data. Entries in the SARI database have data fields that are "mandatory" (absence of data makes it impossible to include the record in the system), "essential" (although not mandatory, the data are necessary for the investigation of the case or the calculation of an epidemiological or operational indicator), "internal" (not appearing on the form and automatically filled in by the system), and "optional" (filled in only if necessary). Because of this, there is great variability in the completeness of the information in the system. If more than 20% of entries were missing data for a variable, the lack of data was considered to have an important impact.

SARI data forms are filled out during hospital admission, when the patient is assessed for comorbidities. As the most likely reason for not reporting a clinical feature (*e.g.*, chronic cardiovascular disease) was its absence, we considered the pattern of empty data fields to be nonrandom, rendering it impossible to apply multiple imputation. Instead, we assumed that if information on a specific clinical feature was not reported, this implied its absence, and only entries stating "information not known" would correspond to missing data. A similar approach has been adopted in previously published studies (19). The SARI database included entries for the following categories of preexisting pediatric comorbidities: Down syndrome, diabetes mellitus, immunodepression, chronic cardiovascular diseases, chronic hepatic diseases, chronic neurological conditions, chronic kidney diseases, chronic hematologic diseases, asthma, and chronic pneumopathies. There was no mention of a specific diagnosis in most of the entries.

We compared the frequencies of all demographic and clinical variables among patients in the three viral agent groups, testing for significant differences using the chi-square test. We also performed crude and adjusted logistic regression to determine the odds of negative clinical outcomes among the ORV and SARS-CoV-2 groups as compared with the influenza group, which was considered the baseline. We tested the association between preexisting comorbidity and the outcomes of death, PICU admission, invasive ventilatory support, and noninvasive ventilatory support using Fisher's exact test. Finally, we calculated the number of reported comorbidities for each patient and determined how this affected the risk of death in the three viral agent groups, again with the influenza group as baseline. We set the probability of rejecting the null hypothesis at 5%. Data analysis was performed using Stata statistical software (release 14; StataCorp LP, College Station, TX, USA).

All procedures were reviewed and approved by the Research Ethics Committee of the FMUSP Academic Medical Center (Hospital das Clínicas, School of Medicine, University of São Paulo, Brazil).

RESULTS

As of July 14th, 2020, 165,051 SARI patients with laboratory-confirmed SARS-CoV-2 (both closed and open cases) had been reported in Brazil, of whom 161,748 (98%) were adults and 3,303 (2%) were under 20 years of age. The Brazilian states reporting the highest number of pediatric SARI cases caused by SARS-CoV-2 were São Paulo (N=1,117, 33.8% of the total), Pernambuco (N=349, 10.8%),

Rio de Janeiro (N=316, 9.6%), Mato Grosso (N=312, 9.4%), and Amazonas (N=133, 4.0%).

Table 1 shows the distribution of demographic and clinical characteristics and outcomes according to viral agent. Chi-square tests were used to obtain p values for the significance of the differences among the three groups. The proportion of males was lower in the SARS-CoV-2 group than in the influenza and ORV groups (52.0% *vs.* 54.6% *vs.* 57.0%, p=0.01), while the proportion of newborns and adolescents was higher in the SARS-CoV-2 group than in the other groups ($p<0.001$). The frequencies at presentation of fever, cough, dyspnea, respiratory distress, and oxygen desaturation were lower in COVID-19 patients than in the influenza and ORV groups ($p<0.001$), while the frequency of diarrhea was higher ($p<0.001$). Invasive ventilatory support rates were similar among groups, but COVID-19 patients had a lower rate of noninvasive ventilatory support use, especially when compared to the ORV group. However, the death rate was higher in the SARS-CoV-2 group than in the influenza and ORV groups (15.1% *vs.* 4.8% *vs.* 3.6%, $p<0.001$) (Table 1).

Table 2 compares the risk of PICU admission, ventilatory support, and death among the three groups using both crude and adjusted odds ratios, with influenza patients as the reference. While the adjusted model found no significant differences in PICU admission risk, it found that the ORV group had greater odds of needing invasive or noninvasive ventilatory support. The risk of death was comparable between the influenza and ORV group, but the SARS-CoV-2 group had more than three times the risk compared to the other two groups (adjusted OR=3.74 [CI 2.5-5.6], $p<0.001$) (Table 2).

A greater number of comorbidities significantly increased the risk of death for all groups. For patients in the SARS-CoV-2 group, the risk of death was almost five times higher when two or more comorbidities were present than in patients without preexisting conditions (OR=4.81 [95% CI 3.48-6.63]), and the same was true for influenza (OR 5.73 [95% CI 2.04-16.11]) (Table 3).

Preexisting comorbidities were reported in 986 infants, children, and adolescents with severe COVID-19 (38% of the total). We analyzed the death rate among patients with each type of preexisting pediatric comorbidity. With the exception of asthma and chronic hematologic diseases, all underlying diseases were significantly associated with a higher death rate. However, the frequency of death was significantly lower in severe COVID-19 patients with asthma than in those without this respiratory condition (5.6% *vs.* 15.8%, p=0.001) (Table 4).

Chronic cardiovascular diseases, Down syndrome, chronic hepatic diseases, neurological conditions, chronic pneumopathies, and immunodepression were all associated with a significantly higher chance of needing invasive ventilatory support (Table 4).

DISCUSSION

To our knowledge, this is the largest study evaluating pediatric patients with severe COVID-19, and also the first to compare this emerging infectious disease with other respiratory viral infections. COVID-19 patients showed higher mortality in spite of lower frequency of fever, cough, dyspnea, oxygen desaturation, and respiratory distress at admission compared with other viral agents. Death risk in these patients was strongly associated with cumulative preexisting comorbidities. Almost all underlying diseases increased the risk of death; a notable exception was asthma.

One of the major strengths of the present study was the inclusion of a large number of patients affected by different

Table 1 - Demographic and clinical details of pediatric patients with severe acute respiratory infection according to viral agent.

	SARS-CoV-2 (N=2,570)		ORV (N=1,555)		Influenza (N=659)		
Variable	N	%	N	%	N	%	*p**
Male sex	1,340	52.0	886	57	360	54.6	0.010
Age							
<30 days	161	6.3	45	2.9	9	1.4	<0.001
30 days to 2.00 years	934	36.3	1,176	75.6	278	42.2	
2.01-10.00 years	544	21.2	268	17.2	271	41.1	
10.01-15.00 years	391	15.2	37	2.4	64	9.7	
15.01-19.99 years	540	21.0	29	1.9	37	5.6	
Nonwhite ethnicity	1,100	59.7	553	49.9	307	61.0	<0.001
Fever	1,820	76.9	1,364	89.3	634	96.6	<0.001
Cough	1,544	68.0	1,425	92.8	603	92.6	<0.001
Dyspnea	1,227	56.3	1,143	76.8	418	66.0	<0.001
Respiratory distress	1,166	54.7	1,283	85.5	508	79.6	<0.001
Oxygen saturation <95%	806	39.4	999	68.2	300	48.5	<0.001
Diarrhea	360	18.3	143	10.1	84	14.1	<0.001
Vomiting	375	19.1	246	17.3	97	16.4	0.198
PICU	644	31.0	539	35.7	188	31.0	0.008
Ventilatory support							
Invasive	298	13.7	206	14.1	70	12.1	<0.001
Noninvasive	637	29.3	784	53.6	197	34.1	<0.001
None	1,242	57	470	32.2	311	53.8	<0.001
Death	353	15.2	49	3.3	27	4.5	<0.001

Data represent closed cases entered into the National Epidemiological Surveillance Information System between January 1st and July 14th, 2020. Ethnicity was determined on the basis of self-declared skin color.

*Chi-square test.

PICU=pediatric intensive care unit; ORV=other respiratory virus (respiratory syncytial virus, adenovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, metapneumovirus, bocavirus, rhinovirus).

Table 2 - Risk of negative outcomes according to viral agent in pediatric patients with severe acute respiratory illness.

	Crude model			Adjusted model*		
Outcomes	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
PICU						
Influenza	1.00			1.00		
ORV	1.23	1.00-1.50	0.04	1.15	0.94-1.42	0.16
SARS-CoV-2	1.00	0.82-1.21	0.98	1.03	0.85-1.25	0.76
Invasive VS						
Influenza	1.00			1.00		
ORV	1.94	1.43-2.65	<0.001	1.81	1.33-2.47	<0.001
SARS-CoV-2	1.10	0.80-1.42	0.66	1.11	0.83-1.49	0.47
Noninvasive VS						
Influenza	1.00			1.00		
ORV	2.63	2.12-3.25	<0.001	2.41	1.95-3.00	<0.001
SARS-CoV-2	0.81	0.66-0.99	0.04	0.85	0.69-1.04	0.116
Death						
Influenza	1.00			1.00		
ORV	0.71	0.44-1.15	0.163	0.72	0.45-1.17	0.186
SARS-CoV-2	3.78	2.53-5.66	<0.001	3.74	2.50-5.60	<0.001

Data represent closed cases entered into the National Epidemiological Surveillance Information System between January 1st and July 14th, 2020.
*Adjusted for sex and age.
PICU=pediatric intensive care unit; ORV=other respiratory virus (respiratory syncytial virus, adenovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, metapneumovirus, bocavirus, rhinovirus); OR=odds ratio; 95% CI=95% confidence interval; VS=ventilatory support.

Table 3 - Relationship between number of comorbidities and risk of death according to viral agent in pediatric patients with severe acute respiratory infection.

	Frequency		Crude model			Adjusted model*		
Number of comorbidities	**N**	**%**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Influenza								
0	477	72.4	1.00			1.00		
1	143	21.7	2.16	0.87-5.34	0.09	2.12	0.86-5.26	0.103
⩾2	39	5.9	5.84	2.09-16.38	0.001	5.73	2.04-16.11	0.001
Other respiratory virus								
0	876	69.3	1.00			1.00		
1	300	23.7	2.47	1.33-4.56	0.004	2.51	1.35-4.69	0.004
⩾2	88	6.9	2.65	1.06-6.64	0.038	2.71	1.06-6.96	0.037
SARS-CoV-2								
0	1584	61.6	1.00			1.00		
1	707	27.5	3.01	2.32-3.91	<0.001	3.03	2.34-3.94	<0.001
⩾2	279	10.9	4.76	3.45-6.56	<0.001	4.81	3.48-6.63	<0.001

Data represent closed cases entered into the National Epidemiological Surveillance Information System between January 1st and July 14th, 2020. Absence of information on a comorbidity was assumed to indicate absence of comorbidity.
*Adjusted for sex and age.
ORV=other respiratory virus (respiratory syncytial virus, adenovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, parainfluenza 4, metapneumovirus, bocavirus, rhinovirus); OR=odds ratio; 95% CI=95% confidence interval.

viral agents. All COVID-19 patients in our study had their diagnosis confirmed by RT-PCR, the gold standard molecular assay for SARS-CoV-2 infection (20). Laboratory confirmation was also required for the other viral agent. By restricting the analysis to patients with a lab-confirmed diagnosis, our study may provide a more reliable picture of severe COVID-19 in infants, children, and adolescents. Brazil is a continent-sized country, making it a challenge to collect representative data. In the present study, we used a nationwide database with reported cases from all states, improving our ability to obtain data truly representative of the Brazilian population.

We considered all COVID-19 patients with SARI to be severe cases, as they required hospital admission and presented respiratory insufficiency criteria. These criteria were also used by previous COVID-19 studies to define critical and severe illness (10,14,21).

Our results agreed with previous studies showing a lower incidence of severe COVID-19 in children and adolescents than in adults. Regarding the clinical presentation of pediatric COVID-19, our analysis supported other reports showing a high frequency of fever and cough and a low frequency of gastrointestinal manifestations at disease onset (5,6,10,13). Children and adolescents with COVID-19 rarely develop severe disease that leads to respiratory failure requiring mechanical ventilation (9-10).

Another relevant point is that a considerable percentage of our pediatric patients with severe COVID-19 did not present with fever or cough. In contrast, over 90% of pediatric influenza patients presented both symptoms in early disease. Therefore, these symptoms may help pediatricians differentiate between these two conditions.

Notably, a higher mortality rate (15.2%) was observed in pediatric patients with severe COVID-19 than in the other

Table 4 - Relationship between preexisting comorbidities and negative outcomes in severe acute respiratory infection caused by SARS-CoV-2 (N=986).

	Death			Invasive ventilatory support		
Preexisting comorbidity	**N**	**%**	***p****	**N**	**%**	***p****
Chronic cardiovascular diseases						
No	313	14.0	<0.001	276	18.5	<0.001
Yes	40	45.4		22	44.9	
Chronic hematologic diseases						
No	340	15.0	0.2	290	19.4	0.96
Yes	13	21.0		8	19.0	
Down syndrome						
No	344	15.0	0.008	290	19.0	0.01
Yes	9	33.3		8	44.4	
Chronic hepatic diseases						
No	347	15.0	0.021	293	19.2	0.03
Yes	6	35.3		5	45.4	
Asthma						
No	345	15.8	0.001	281	19.3	0.92
Yes	8	5.6		17	19.8	
Diabetes mellitus						
No	326	14.4	<0.001	288	19.1	0.05
Yes	27	44.2		10	33.3	
Chronic neurologic conditions						
No	327	14.8	0.01	256	17.4	<0.001
Yes	26	23.8		42	58.3	
Chronic pneumopathies						
No	338	14.9	0.002	285	18.8	<0.001
Yes	15	31.2		13	58.5	
Immunodepression						
No	314	14.4	<0.001	270	18.8	0.03
Yes	39	26.9		28	27.4	
Chronic kidney diseases						
No	343	15.0	0.034	290	19.1	0.13
Yes	10	27.8		8	30.8	

Data represent closed cases entered into the National Epidemiological Surveillance Information System between January 1st and July 14th, 2020.
*Fisher's exact test.

virus groups. This level of mortality is novel in the literature, with previous studies reporting death rates lower than 5%. In a retrospective study of 46 children with COVID-19 admitted to a tertiary-care medical center in New York, Chao et al. reported only one death (2.1%), a child with metastatic cancer whose life-sustaining therapy was withdrawn (13). Shekerdemian et al. retrospectively studied 48 patients admitted to the PICU in 46 North American centers, reporting two deaths (4.2%), both of critically ill children who required mechanical ventilation and had preexisting comorbidities. The high death rate reported in our study might be related to the fact that, despite the government's efforts to increase hospital capacity, the high number of cases in the country has strained the Brazilian health system, often leading to inadequate health support in a country that already suffers from an inequitable distribution of health professionals and PICU bed capacity, reflecting deep socioeconomic disparities. Indeed, in a cross-sectional observational study using the same SARI databank, Baqui et al. reported socioeconomic and health access inequalities as the genesis of different mortality rates among Brazil's ethnicities and regions (19).

Furthermore, the prevalence of chronic pediatric diseases has been increasing in recent years, resulting in considerable morbidity and mortality, including a higher risk of severe COVID-19 infection (22-24). Indeed, in our study, more than one-third of pediatric COVID-19 patients with SARI had at least one preexisting comorbidity. With the exception of asthma and chronic hematologic diseases, all underlying diseases were significantly associated with a higher mortality in patients with severe COVID-19, as well as a greater chance of needing invasive ventilatory support. Shekerdemian et al. reported at least one previous comorbidity in 85% of pediatric patients with severe COVID-19 hospitalized in the PICU, with immunosuppression/cancer being particularly common (14). On the other hand, studies with pediatric COVID-19 patients seldom list asthma as a comorbidity, suggesting that it may not be an aggravating factor for COVID-19 (25). Interestingly, our data showed a lower death rate in the asthma group compared with patients without the disease.

Our study has certain limitations. Our national surveillance databank had a high rate of missing data, especially regarding preexisting pediatric comorbidities, and had no data on laboratory and imaging abnormalities and their possible impact on COVID-19 outcomes. Even when statistically significant, results regarding comorbidities must be considered with caution, as we chose to assume that lack of reported data meant absence of comorbidity. Although a similar approach can be found in previously published studies, it is not possible to ascertain if this method reflects reality. Additionally, as the comorbidity section of the surveillance form is usually filled in when the patient is admitted, the odds that some fields will be missing data are not correlated with outcomes. This may introduce a nondifferential systematic error; however, the error's main effect is likely to be reduction of the effect size rather than generation of false associations. Another limitation of our

study is the division of viral agents into only three groups, including one group representing nine different viruses that may be associated with diverse clinical features and outcomes. Finally, the databank we used did not include enough data for us to evaluate multisystem inflammatory syndrome in our patients (26).

We must emphasize that the clinical presentation and outcomes described in this study concern only a subset of pediatric COVID-19 patients: hospitalized children and adolescents with severe symptoms. Therefore, our results cannot be generalized to all children with COVID-19. Large population studies are needed to evaluate the broad impact of COVID-19 on children's health.

CONCLUSIONS

In conclusion, a higher mortality rate was observed in patients with severe COVID-19 compared with other viral diseases, despite the lower frequency of fever, cough, dyspnea, oxygen desaturation, and respiratory distress. Death risk in COVID-19 patients was strongly associated with cumulative preexisting pediatric comorbidities.

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AUTHOR CONTRIBUTIONS

Sousa BL, Ferraro AA and Silva CA conceptualized and designed the study, carried out the analysis, drafted the initial manuscript reviewed and revised the manuscript. de Carvalho WB and Carneiro-Sampaio M conceptualized the study,critically reviewed and revised the manuscript.

REFERENCES

1. World Health Organization (WHO). WHO Director-General's opening remarks at the media briefing on COVID-19: 11 March 2020. Published March 11, 2020.[Accessed June 12, 2020]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. https://doi.org/10.1056/NEJMoa2002032
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72-314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42. https://doi.org/10.1001/jama.2020.2648
5. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663-5. https://doi.org/10.1056/NEJMc2005073
6. Parri N, Lenge M, Buonsenso D; Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in Pediatric Emergency Departments in Italy. N Engl J Med. 2020;383(2):187-90. https://doi.org/10.1056/NEJMc2007617
7. Tagarro A, Epalza C, Santos M, Sanz-Santaeufemia FJ, Otheo E, Moraleda C, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatr. 2020:e201346.
8. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6. https://doi.org/10.15585/mmwr.mm6914e4
9. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020;174(9):882-9. https://doi.org/10.1001/jamapediatrics.2020.1467
10. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145(6):e20200702. https://doi.org/10.1542/peds.2020-0702
11. Silva CA, Queiroz LB, Fonseca CB, Silva LEVD, Lourenço B, Marques HHS. Spotlight for healthy adolescents and adolescents with preexisting chronic diseases during the COVID-19 pandemic. Clinics. 2020;75:e1931. https://doi.org/10.6061/clinics/2020/e1931
12. Palmeira P, Barbuto JAM, Silva CAA, Carneiro-Sampaio M. Why is SARS-CoV-2 infection milder among children? Clinics. 2020;75:e1947. https://doi.org/10.6061/clinics/2020/e1947
13. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. J Pediatr. 2020;223:14-19.e2. https://doi.org/10.1016/j.jpeds.2020.05.006
14. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020;174(9):868-73. https://doi.org/10.1001/jamapediatrics.2020.1948
15. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatr. 2020;174(10):e202430. https://doi.org/10.1001/jamapediatrics.2020.2430
16. Brazilian Ministry of Health. Painel de casos de doença pelo coronavírus 2019 (COVID-19) no Brasil pelo Ministério da Saúde, 2nd version. [Accessed July 26, 2020]. Available from: https://covid.saude.gov.br
17. Sistema de Informação de Vigilância Epidemiológica da Gripe, Secretaria de Vigilância em Saúde, Ministério da Saúde. Ficha de Registro Individual - Casos de Síndrome Respiratória Aguda Grave Hospitalizados. [Accessed May 29, 2020]. Available from: http://www.vs.saude.ms.gov.br/wp-content/uploads/2019/11/Ficha-SIVEP_GRIPE-SRAG_Hospital.pdf
18. Bastos LS, Niquini RP, Lana RM, Villela DAM, Cruz OG, Coelho FC, et al. COVID-19 and hospitalizations for SARI in Brazil: a comparison up to the 12th epidemiological week of 2020. Cad Saude Publica. 2020;36(4):e00070120. https://doi.org/10.1590/0102-311x00070120
19. Baqui P, Bica I, Marra V, Ercole A, van der Schaar M. Ethnic and regional variations in hospital mortality from COVID-19 in Brazil: a cross-sectional observational study. Lancet Glob Health. 2020;8(8):e1018-26. https://doi.org/10.1016/S2214-109X(20)30285-0
20. Mustafa NM, A Selim L. Characterisation of COVID-19 Pandemic in Paediatric Age Group: A Systematic Review and Meta-Analysis. J Clin Virol. 2020;128:104395. https://doi.org/10.1016/j.jcv.2020.104395
21. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020;16(3):223-31. https://doi.org/10.1007/s12519-020-00343-7
22. Alveno RA, Miranda CV, Passone CG, Waetge AR, Hojo ES, Farhat SCL, et al. Pediatric chronic patients at outpatient clinics: a study in a Latin American University Hospital. J Pediatr. 2018;94(5):539-45. https://doi.org/10.1016/j.jped.2017.07.014
23. Passone CGB, Grisi SJ, Farhat SC, Manna TD, Pastorino AC, Alveno RA, et al. Complexity of Pediatric Chronic Disease: Cross-Sectional Study with 16,237 Patients Followed by Multiple Medical Specialties. Rev Paul Pediatr. 2019;38:e2018101. https://doi.org/10.1590/1984-0462/2020/38/2018101
24. Ramos GF, Ribeiro VP, Mercadante MP, Ribeiro MP, Delgado AF, Farhat SCL, et al. Mortality in adolescents and young adults with chronic diseases during 16 years: a study in a Latin American tertiary hospital. J Pediatr. 2019;95(6):667-73. https://doi.org/10.1016/j.jped.2018.06.006
25. Shaker MS, Oppenheimer J, Grayson M, Stukus D, Hartog N, Hsieh EWY, et al. COVID-19: Pandemic Contingency Planning for the Allergy and Immunology Clinic. J Allergy Clin Immunol Pract. 2020;8(5):1477-88.e5. https://doi.org/10.1016/j.jaip.2020.03.012
26. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383(4):334-46. https://doi.org/10.1056/NEJMoa2021680