













Retrospective cohort of children and adolescents hospitalized by COVID-19 in Brazil from the beginning of the pandemic to August 1st, 2020

Coorte retrospectiva de crianças e adolescentes hospitalizados por COVID-19 no Brasil do início da pandemia a 1º de agosto de 2020

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ABSTRACT: *Objectives:* To characterize the study population, estimating the in-hospital lethality rate by state and analysing associated factors with COVID-19-related deaths. *Methods:* A retrospective cohort study was carried out of hospitalised children and adolescents diagnosed with COVID-19, confirmed by RT-PCR, whose outcome was death by COVID-19 or recovery, from 2020 March 1 to August 1. The data source was the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe in Brazilian acronym), where patients with Severe Acute Respiratory Syndrome (SARS) are notified. Children were defined as those between the ages of 0 and 11, and adolescents those between 12 and 18. A bi and multivariate analysis were performed using Poisson Regression with robust variance, with adjusted Relative Risk as the final association measure. *Results:* A total of 4,930 cases were analysed; 2,553 (51.8%) were males, 2,335 (47.4%) were brown-skinned. The Federative Unit of Roraima presented the highest in-hospital case-fatality rate, with 68.8% (11 / 16). Multivariate analysis showed that belonging to the age group adolescent (RR = 1.59; 95%CI 1.12 – 2.25; p = 0.009), SARS-critical patient (RR = 4.56; 95%CI 2, 77 – 7.51; p < 0.001) and presenting immunological disorders (RR = 2.24; 95%CI 1.58 – 3.17; p < 0.001) as comorbidities were statistically associated factors with death by COVID-19. *Conclusion:* It was observed that adolescents, SARS-critical patients, and presence of immunological disorders were important factors associated with death. Active surveillance and differentiated care are recommended for patients with chronic diseases and special immunological conditions.

Keywords: Child. Adolescent. Hospitalization. Coronavirus infections. Severe acute respiratory syndrome.

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RESUMO: *Objetivos:* Caracterizar a população do estudo, estimar a taxa de letalidade intra-hospitalar por estado e analisar fatores associados aos óbitos por COVID-19. *Métodos:* Foi realizado estudo de coorte retrospectiva de crianças e adolescentes hospitalizados com diagnóstico de COVID-19 confirmado por transcrição reversa seguida de reação em cadeia da polimerase (RT-PCR), tendo como desfecho óbito por COVID-19 ou recuperação, entre 1º de março e 1º de agosto de 2020. A fonte de dados foi o Sistema de Informação de Vigilância Epidemiológica da Gripe (SIVEP-Gripe), ao qual são notificados pacientes internados com Síndrome Respiratória Aguda Grave (SRAG). Consideraram-se crianças os pacientes com idade entre 0 e 11 anos completos e adolescentes aqueles com idade entre 12 e 18 anos completos. Realizou-se análise bi e multivariável por meio de Regressão de Poisson com variância robusta, utilizando-se como medida de associação final o Risco Relativo ajustado (RRa). *Resultados:* Dos 4.930 casos analisados, 2.553 (51,8%) eram do sexo masculino. A raça/cor autodeclarada parda foi a mais frequente, com 2.335 (47,4%). A unidade federativa de Roraima apresentou a maior taxa de letalidade intra-hospitalar, com 68,8% (n = 11/16). A análise multivariada mostrou que pertencer ao grupo etário adolescente (RR = 1,59; IC95% 1,12 – 2,25; p = 0,009), ter sido classificado como SRAG-crítico (RR = 4,56; IC95% 2,77 – 7,51; p < 0,001) e apresentar imunopatia (RR = 2,24; IC95% 1,58 – 3,17; p < 0,001) como comorbidade configuraram-se como fatores associados ao óbito pela COVID-19. *Conclusão:* Observou-se que ser adolescente, ter classificação de SRAG-crítico e imunopatia como comorbidade foram importantes fatores associados ao óbito. Recomenda-se vigilância ativa e cuidados diferenciados a portadores de doenças crônicas e condições imunológicas especiais.

Palavras-chave: Criança. Adolescente. Hospitalização. Infecções por coronavírus. Síndrome respiratória aguda grave.

INTRODUCTION

In December 2019, the world was put on alert, when a new type of coronavirus (later called SARS-CoV-2) was discovered to affect the respiratory tract of humans, causing from asymptomatic infections to the most severe manifestations, with acute respiratory syndromes that can cause death. The first cases, originated in Wuhan, China, spread rapidly across Chinese territory, reaching the entire Asian continent, and expanding to the European and American continents in less than three months¹⁻³, until January 30, 2020, when the World Health Organization (WHO) stated that the spread of COVID-19 cases around the world constituted a Public Health Emergency of International Importance (PHEI)².

Virus transmission occurs through contact with respiratory droplets generated by infected people. The manifestations differ from organism to organism, depending on the immune system, the pre-existing conditions, the age, and the amount of virus with which one was exposed⁴.

Children and adolescents seem to have been less affected by the COVID-19 pandemic since the infection occurs in a milder way in them⁵. More than a month after the start of cases, on January 20, 2020, China notified the first case in a child. Studies conducted in China, European countries, and the United States of America estimate that 1 to 5% of confirmed cases of COVID-19 occur in the population subgroup of children and adolescents^{5,6}. Still,

the first major report from the Chinese Center for Disease Control and Prevention showed that of the 44,672 confirmed cases, only one death occurred among children and adolescents⁷. In Brazil, the notification of the first case in this age group was on March 4, about a week after the notice of the arrival of the virus in the country⁸.

Until epidemiological week (EW) 31, which ended on August 1, 2020, 17,580,163 cases of the disease have been confirmed worldwide. At the time, Brazil already accumulated 2,707,877 cases⁹.

Among the issues that seek to explain the relatively small number of children and adolescents affected by COVID-19 is the fact that these people present the ongoing development of the cellular and humoral immune system, the possible protection from previous infections by the respiratory syncytial virus, and the immaturity of receptors called angiotensin 2 (ACE-2) converting enzymes in childhood¹⁰. In addition, the control measures proposed by the governments, which include the closure of educational institutions and the consequent greater social isolation, stand out¹¹.

An aspect of interest relates to the role of children and adolescents as reservoirs of SARS-CoV-2 and in the dynamics of disease transmission¹²⁻¹⁶. The adoption of preventive measures such as respiratory etiquette, hand washing, social distancing, among others, is not well understood by this age group and, for children under two years old, pediatricians do not recommend mask use, since there is a risk of suffocation^{17,18}.

At the end of April 2020, doctors in the United Kingdom issued an alert on the occurrence of clinical manifestations temporarily related to COVID-19 infection in children and adolescents, called Pediatric Multisystem Inflammatory Syndrome¹⁹.

Given these peculiarities related to these age groups, and the importance of understanding the impact of the new coronavirus in the community, there is a need to generate evidence on hospital admissions of children and adolescents by the COVID-19 Brazil, to contribute to the conduct of actions to protect and promote the health of the public, as well as to inform decision-making.

In this sense, this article aims to analyze children and adolescents hospitalized for COVID-19 in Brazil, with the specific objectives of:

- characterize the study population in time, person and place;
- estimate the in-hospital mortality rate per federal unit (FU);
- analyze factors associated with COVID-19 deaths in this population subgroup.

METHODS

A retrospective cohort study of hospitalized children and adolescents was conducted, with a diagnosis of COVID-19 confirmed in the molecular biology test (reverse transcription followed by polymerase chain reaction — Real-Time PCR) and with detectable result for SARS-CoV-2, having death by COVID-19 or recovery as the outcome.

Secondary, non-nominal data were used from the epidemiological Influenza Surveillance Information System (SIVEP-Gripe in its Portuguese acronym), in the public domain, made

available on the Ministry of Health's (MS) website and accessed on September 14, 2020, including reported cases with a date of onset of signs and symptoms between March 1 and August 1, 2020 (EW 10 to 31).

The data analyzed comprised the 27 FU of the country, with an estimated population of 211.7 million people in 2020. Children under 19 represent 31.2%, with 66.1 million children and adolescents²⁰.

The individual aged between 0 (zero) and 11 full years was considered as a child and the adolescent was considered as one belonging to the age group of 12 to 18 full years²¹.

The following case definitions were used:

- Severe Acute Respiratory Syndrome (SARS): case of COVID - 19 with the presence of at least one of the following signs and symptoms: dyspnea, respiratory distress, low O₂ saturation (<95%) in ambient air and cyanosis²².
- Critical-SARS: case of SARS that required hospitalization in an intensive care unit (ICU) or required ventilatory support, invasive or non-invasive.

The definition of SARS was based on that described in the chapter on Surveillance of Severe Acute Respiratory Syndromes of the Epidemiological Surveillance Guide²², and the definition of critical-SARS developed for this study was adapted from Chung's *et al.* classifications²³ in order to analyze the level of severity and the risk factor for death.

The variables of interest approached in this study were: epidemiologic week of the onset of symptoms, changes in (deaths, and recovered), date of development, and FU of residence, and hospital stay; sex (male, female, and unspecified); age in years; self-reported color-race (white, black, yellow, brown, and indigenous); signs and symptoms, comorbidity, chest X-Ray results (normal, interstitial infiltrates, consolidation, joint, and other), hospitalization in the ICU; ventilatory support (invasive and non-invasive); and the use of the antiviral medication. For the analysis of death-associated factors, secondary variables were created and added based on the main ones, namely: age in years/age group (child and adolescent); race/color (black/brown and white)^{24,25}; SARS and critical-SARS.

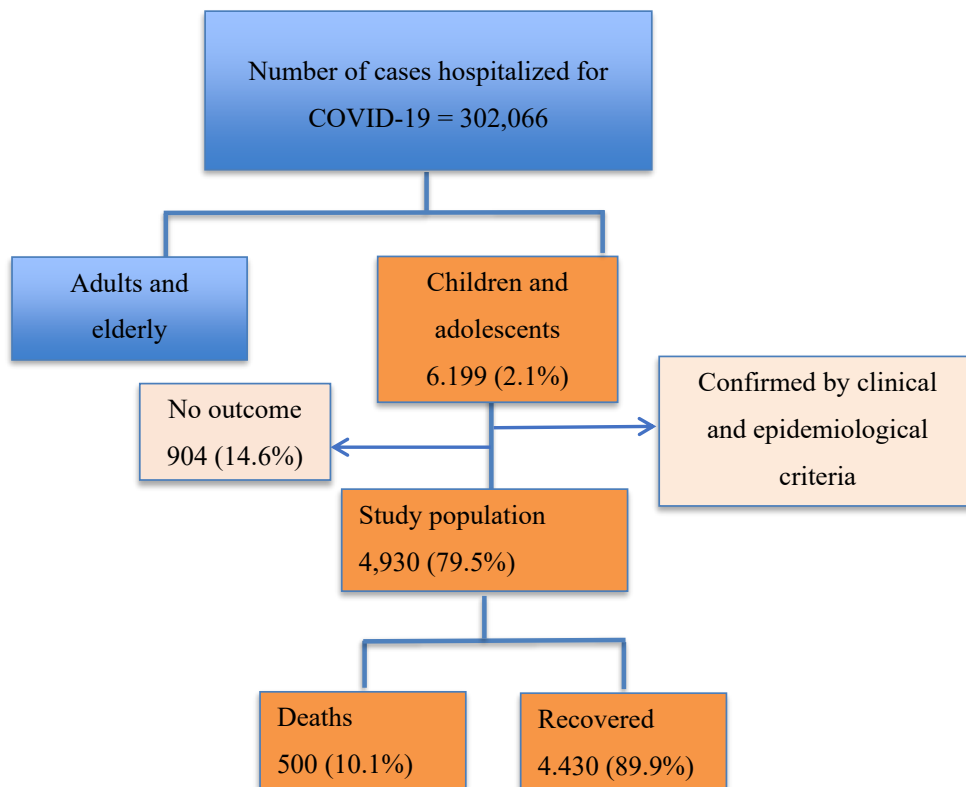
For the descriptive analysis, measures of absolute and relative frequency, central tendency and dispersion were calculated. The in-hospital mortality rate was calculated considering the total number of hospital deaths divided by the total number of hospitalized cases, multiplied by 100. For the bivariate analysis, Fisher's Exact Test was applied, as an association measure the gross Relative Risk (RR) with confidence interval (CI) 95% and $p < 0.05$, and in the comparison between medians, the Mann-Whitney U test was used.

In order to remove possible confounding factors, multivariate statistical analysis was performed using Poisson regression with robust variance, considering the number of independent variables obtained by bivariate analysis ($p < 0.20$). Thus, the option was a regression of the type *backward stepwise*. The association measure adopted was the adjusted relative risk (adjusted RR), respecting the absence of multicollinearity (correlation between two or more independent variables) in the model. The likelihood-ratio test was considered for choosing the best model.

For data processing and analysis, the following programs were used: Epi Info™ 7.2, Stata/SE 13.1, QGIS 2.18 “Las Palmas” and Microsoft Excel 2016.

RESULTS

In the period between March 1 and August 1, 2020, corresponding to EW 10 to 31, 302,066 hospitalized cases for COVID-19 were reported, of which 295,867 (97.9%) were adults and elderly and 6,199 (2.1%) were children and adolescents. Of these, 365 (5.9%) were diagnosed according to clinical and epidemiological criteria and 904 (14.6%) had no record of the outcome. As shown in Figure 1, in the study period, 4,930 (79.5%) cases with outcome (death or recovery) constituted the study population, of which 500 (10.1%) evolved to death and 4,430 (89.9%) were classified as recovered. Among the deaths, 323 (64.6%) were children (zero to 11 full years).

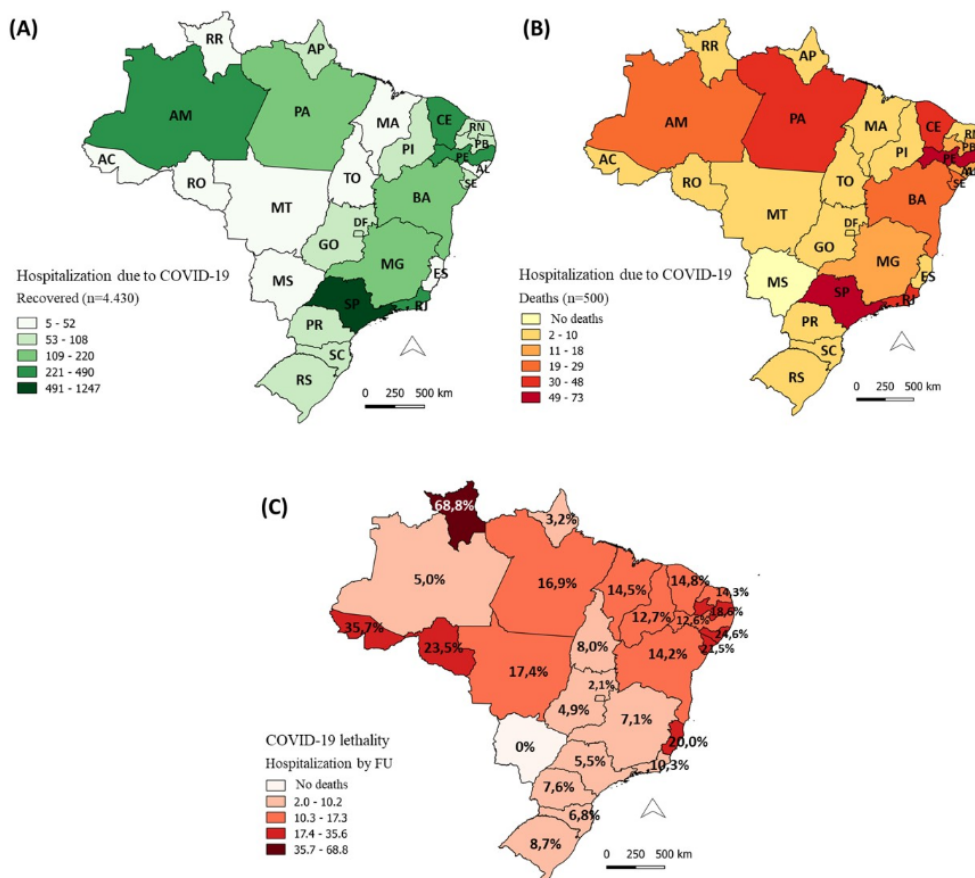


Source: Sivep-Gripe data updated until September 14, 2020.

Figure 1. Distribution flowchart of hospitalized cases for COVID-19, from March 1 to August 1, Brazil, 2020.

Regarding the distribution of cases over the period, it was observed that 1,554 (31.5%) of hospitalizations occurred between EW 10 to 20 (March 1 to May 16, 2020), with an average of three deaths/day, and 3,376 (68.5%) between EW 21 to 31 (May 17 to August 1, 2020), with an average of four deaths/day (data not presented in table).

Considering the distribution of cases according to the FU of residence, São Paulo had the highest frequency of hospitalized patients, with 1,320 (26.8%), of which 1,247 (94.5%) recovered and 73 (4.5%) evolved to death. Subsequently the Amazon with 517 (10.5%) hospitalized patients, of which 491 (95,0%) recovered and 26 (5%) died (Figures 2A and 2B and Supplementary Material).



Source: Sivep-Gripe data updated until September 14, 2020.

Figure 2. (A) Recovered cases of children and adolescents hospitalized by COVID-19 second federative unit of residence, March 1 to August 1, Brazil, 2020; (B) Deaths of children and adolescents hospitalized by COVID-19 second Federative unit of residence, March 1 to August 1, Brazil, 2020; (C) Intra-hospital mortality rates per federative unit of hospitalization, March 1 to August 1, Brazil, 2020.

Regarding the highest in-hospital mortality rates per FU of hospitalization, Roraima presented 68.8% (n = 11 / 16), Acre 35.7% (n = 5 / 14) and Alagoas 24.6% (n = 17 / 69) (Figure 2C).

Of the total of 4,930 cases, 3,610 were children (73.2%) and 1,320 (26.8%) adolescents. Males represented 2,553 (51.8%).

The mean age of children and adolescents was 6.2 years (SD = 6.4). The mean of those who progressed to death was 6.8 years (SD = 7.1) and for those recovered, it was 6.1 years (SD = 6.4) (Table 1).

The highest fatality rates occurred in the age groups of 15 to 18 years, with 13.6%, from 12 to 14 years, with 13.1%, and of children under one year old, with 12.6% (Table 1).

Among those under one year old, 171 (4.7%) had symptoms on the same day of birth, of which 33 (19.3%) developed to death. Among the latter, 18 (54.5%) were hospitalized in the ICU, with a median of zero day (Q1–Q3: 0 – 0) between the date of onset of signs and

Table 1. Characterization of hospitalized cases of COVID-19 in children and adolescents, according to sex, age group, ethnicity/skin color, and evolution (n = 4,930) from March 1 to August 1, Brazil, 2020

Characteristics	Deaths (n = 500)		Recovered (n = 4,430)	
	n	%	n	%
Sex				
Male	266	10.4	2,287	89.6
Female	234	9.8	2,142	90.2
Indeterminate	0	0.0	1	100.0
Age group (years)				
<1	190	12.6	1,318	87.4
1 - 4	67	6.0	1,048	94.0
5 - 11	66	6.7	921	93.3
12 - 14	54	13.1	359	86.9
15 - 18	123	13.6	784	86.4
Self-declared ethnicity/skin color				
White	98	7.9	1,139	92.1
Black	14	10.4	121	89.6
Asian	2	8.0	23	92.0
Pardo	250	10.7	2,085	89.3
Indigenous	19	22.1	67	77.9
No information	117	10.5	995	89.5
Age (years)	Media		Standard Deviation	
All cases	6.2		6.4	
Deaths	6.8		7.1	
Recovered	6.1		6.4	

Source: Sivep-Gripe data updated until September 14, 2020.

symptoms and hospitalization. The median between the date of onset of signs and symptoms and the date of diagnosis by RT-PCR was six days (Q1-Q3: 3 – 9) (data not shown in Table).

Of the 4,930 cases, 2,335 (47.4%) self-reported race-color as Brown, of which 250 (10.7%) died. The race/ color white comes next, with 1,237 (25.1%) cases, of which 98 (7.9%) were death (Table 1).

A total of 1,219 (24.7%) cases were admitted to the ICU. Of these, 300 (24.6%) progressed to death and 919 (75.4%) recovered. As for the imaging tests of the cases admitted to the ICU, 667 (54.7%) had chest X-ray records, resulting in interstitial infiltrate present in 68 (22.7%) deaths and 187 (20.3%) recovered. Regarding ventilatory support during ICU hospitalization, of 822 cases (67.4%) that received this resource, 442 (53.8%) needed the invasive type, of which 220 (49.8%) developed to death and 222 (50.2%) recovered (data not presented in Table).

Of the 4,930 cases, 3,180 (64.5%) met the definition of SARS, of which 1,857 (37.7%) met the definition of critical-SARS.

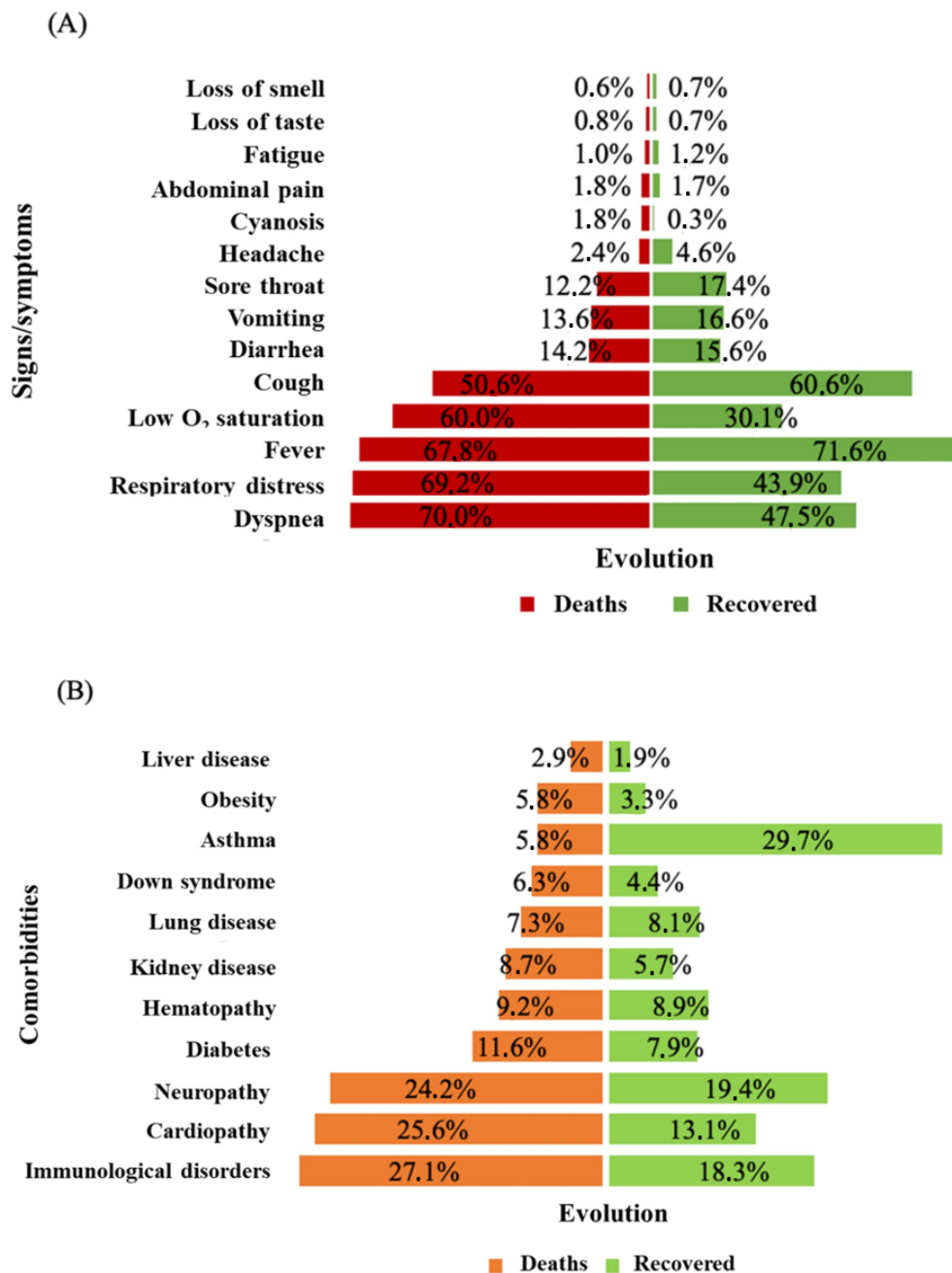
The most frequent signs and symptoms among the 500 cases of SARS that evolved into death were dyspnea with 350 (70%), respiratory distress with 346 (69.2%), fever with 339 (67.8%) and low oxygen saturation with 300 (60%) (Figure 3A). Among the 207 deaths with comorbidities, the most frequent were immunopathology with 56 (27.1%), heart disease with 53 (25.6%) and neuropathy with 50 (24.2%) (Figure 3B).

The median time between onset of symptoms and hospitalization was three days for both deaths and recoveries (Q1–Q3: from 0 to 6, and from 1 to 6, respectively; $p = 0.006$); The median period of time between the check-in and for the change, for those who have died, it was six days (Q1–Q3: 2 – 14), and the recovered five days (Q1–Q3: 3 – 11) with $p = 0.971$; and, in between, the hospital stay in the ICU, and the evolution to death was five days (Q1–Q3: 2 – 14, 2 – 11, respectively; $p = 0.591$).

In the bivariate analysis, it was found that they had a higher risk of progressing to death in all the cases that were presented to the following factors: being in the age group of adolescents (RR = OR 1.49; 95% CI 1.26 – 1.78; $p < 0.001$); - be of the race/ color, self-reported black/mixed-brown race (RR = 1.34; 95%CI 1.08 – cop \$ 1.68; $p < 0.008$); it has been ranked as critical-SARS (RR = 4.13; 95%CI 3.43 – 3.96; $p < 0.001$); have heart disease (RR = WITH 2.07; 95%CI 1.58 – 2.72; $p < 0.001$), immunopathology (RR = 1.74; 95%CI 1.32 – 2.30; $p < 0.001$), diabetes (RR= 1.57; 95%CI 1.08 – 2.30; $p = 0.032$), and neuropathy (RR = 1.47; 95%CI 1.09 – to 1.97; $p = 0.013$). Asthma was configured as a risk reduction factor for death (RR = 0.25; 95%CI 0.10 – 0.62; $p = 0.003$ (Table 2).

The other variables that are related to the signs and symptoms of respiratory disease were tested in a bivariate analysis, that is, low oxygen saturation (RR = 4.12; 95%CI 3,33 – 5,09; $p < 0.001$), respiratory distress (RR = 3.23; 95%CI 2.57 – 4.06; $p < 0.001$), dyspnea (RR = 3; 95%CI 2.39 – 3.78; $p < 0.001$), and cyanosis (RR = 2.89; 95%CI 1.66 – 5.05; $p = 0.003$) (data not shown in table). These variables were grouped in the set of the critical-SARS variable to compose the best regression model.

Multivariate analysis showed that these associated factors with COVID-19 death remained: belonging to the adolescent age group (RR = 1.59; 95%CI 1.12 – 2.25; $p = 0.009$), having



Source: Sivep-Gripe data updated until September 14, 2020.

Figure 3. (A) Signs and symptoms of cases hospitalized by COVID-19 in children and adolescents according to evolution, March 1 to August 1, Brazil, 2020 (n = 4,930); (B) Comorbidities of cases hospitalized by COVID-19 in children and adolescents according to evolution, March 1 to August 1, Brazil, 2020 (n = 1,214).

Table 2. Bivariate and multivariate analysis of factors associated with the risk of developing to death from COVID-19 in children and adolescents, March 1 to August 1, Brazil, 2020 ($R^2 = 0.1381$).

Variables	Gross RR			Adjusted RR		
	RR	95%CI	p-value	aRR	95%CI	p-value
Age group/adolescent	1.49	1.26 – 1.78	< 0.001	1.59	1.12 – 2.25	0.009
Ethnicity/skin color Black/pardo	1.34	1.08 – 1.68	0.008	-	-	-
Cough	0.81	0.67 – 0.98	0.035	0.78	0.55 – 1.10	0.162
Headache	0.37	0.27 – 0.81	0.003	0.38	0.09 – 1.49	0.167
Sore throat	0.79	0.60 – 1.03	0.084	-	-	-
Critical SARS	4.13	3.43 – 4.97	< 0.001	4.56	2.77 – 7.51	< 0.001
Cardiopathy	2.07	1.58 – 2.72	< 0.001	1.49	0.94 – 2.37	0.086
Neuropathy	1.47	1.09 – 1.97	0.013	1.45	0.92 – 2.27	0.107
Immunopathy	1.74	1.32 – 2.30	< 0.001	2.24	1.58 – 3.17	< 0.001
Diabetes	1.57	1.08 – 2.30	0.032	-	-	-
Kidney disease	1.64	1.07 – 2.51	0.044	-	-	-
Asthma	0.22	0.12 – 0.39	< 0.001	0.25	0.10 – 0.62	0.003
Obesity	1.81	1.09 – 3.00	0.035	-	-	-
Down syndrome	1.57	0.95 – 2.58	0.124	-	-	-
Antiviral use	1.16	0.93 – 1.45	0.180	-	-	-

RS: relative risk; 95%CI: 95% confidence interval; aRR: adjusted relative risk.
Source: Sivep-Gripe data updated until September 14, 2020.

been classified as SARS-critical (RR = 4.56; 95%CI 2.77 – 7.51; $p < 0.001$) and having immunopathology (RR = 2.24; 95%CI 1.58 – 3.17; $p < 0.001$). Asthma remained a factor associated with reduced risk of death (RR = 2.24; 95%CI 1.58 – 3.17; $p < 0.001$) (Table 2).

DISCUSSION

The present study characterized the cases of COVID-19 that occurred in children and adolescents in Brazil who were hospitalized and reported in Sivep-Gripe. More than two-thirds of the cases were recorded in children under five years old and more than half of the cases occurred in male children and adolescents.

Although the population most susceptible to the new coronavirus is mainly composed of elderly people with low immunity²⁶, it should be noted that respiratory viruses are a common cause of respiratory tract infection in children, being considered an important reason for hospitalizations²⁷.

At the beginning of the pandemic, the discussion began on the role of children and adolescents as reservoirs of SARS-CoV-2 and in the dynamics of disease transmission¹²⁻¹⁶.

It is important to emphasize that these scenarios have changed with the new clinical presentations of the disease in children. This is because some of them evolved into Pediatric Multisystem Inflammatory Syndrome, with severe clinical manifestations and similar picture to those observed in children and adolescents with Kawasaki disease, incomplete Kawasaki disease, and/or toxic shock syndrome²⁸, which were not objects of this study.

A considerable number of children was found presenting signs and symptoms less than 24 hours after birth, and almost a fifth of these children evolved to death, most having been admitted to the ICU on the same day they were born — although there is still missing information on the serological condition of their mothers during pregnancy. Even so, the suspicion of vertical transmission is raised, corroborating Alzamora *et al.*, who reported cases of infection in newborns with RT - PCR positive between 16 and 30 hours after birth, pointing to this possibility²⁹.

The self-declared ethnicity/skin color *parda* represents half of those who evolved to death, being the predominant ethnicity/skin color in the Brazilian population of low income, right next to the black²⁵, which indicates the importance of social inequalities in the evolution of the disease. The study by Silva Filho *et al.* suggests that the lack of home infrastructure leads to a higher risk of contagion and spread of respiratory infections³⁰. Souza also showed that mortality from respiratory diseases increased worryingly in all Brazilian regions³¹. Given the considered levels of social inequality in the country, a disproportionate effect of COVID-19 among the most vulnerable is likely.

As to the signs and symptoms presented, most of those who died presented dyspnea, respiratory distress, fever, low oxygen saturation, and cough. As for comorbidities, there was a predominance of immunopathologies, followed by unspecified heart diseases and neuropathies.

A study conducted in Iran with 30 children hospitalized with COVID-19 found similar results regarding clinical manifestations and comorbidities. There were reports of leukemia among the comorbidities present in some children who evolved to death, with fever, dyspnea, and cough being the most frequently presented signs and symptoms³².

Almost a third of those hospitalized needed ICU care. However, more than a third of those who needed ventilatory support received it invasively. Among the changes observed on the chest X-ray of these patients, more than two-thirds of those who presented interstitial infiltrate died.

The Roraima FU showed the highest in-hospital mortality rate in the analyzed period. This rate may be overestimated, since this FU and Acre State together have the lowest hospitalization records, which may suggest underreporting of hospitalized cases. It should be recalled that, for this study, only cases with outcome (death or recovery) were considered.

Multivariate analysis of factors associated with COVID-19 death showed that adolescents had a higher risk of developing death compared to children. Some hypotheses may explain this peculiarity, including that children have lower expression of ACE-2, and immature ACE-2 receptors in childhood may hinder cell invasion. The other would be the existence of some protection due to previous infections by the respiratory syncytial virus^{10,33}.

Those who progressed to the critical stage of the disease (SARS-critical) presented almost five times more risk of evolving to death. Cough and headache were not directly associated factors, but were determinants for increased risk when present, independently adjusting the regression model analyzed with other variables.

Among the comorbidities, immunopathology was an important factor associated with COVID-19 death in hospitalized children and adolescents. In this study, although most of those who evolved to death had heart disease and/or neuropathy as a underlying disease, these comorbidities did not remain as factors directly associated to death, but were important for increased risk, independently adjusting the regression model analyzed with other variables.

Considering that COVID-19 predominantly affects the respiratory tract and that respiratory virus infections are frequent causes of complication of asthma, there is concern that COVID-19 has a more severe presentation in asthmatic patients. Thus, several institutions linked to health considered asthma patients as a likely risk group for COVID-19^{34,35}. In this study, asthma was observed as a risk reduction factor for COVID-19 death in bivariate and multivariate analysis. Those who have this underlying disease could possibly be controlled at the time they were infected with SARS-CoV-2 or received differentiated care during hospitalization. It may also be that they were under corticosteroid treatment before becoming infected with SARS-CoV-2, which may positively influence the evolution of COVID-19³⁶.

The results herein represent the population of children and adolescents hospitalized for COVID-19 and notified in the Sivep-Gripe throughout the national territory. Among the limitations, it was not possible to analyze the variables chest-in drawing and vacillation of nasal wing, which are important signs of severity in children, because they are variables that do not exist in the database, and these data were optionally recorded as other signs. Even though, many signs and symptoms may be underestimated due to the high occurrence of incompleteness, resulting from the lack of updating of the database, according to the patient's evolution.

Children and adolescents, in addition to being seen as an age group with an important role in the dynamics of transmission¹²⁻¹⁶, also present vulnerability factors for aggravation. Therefore, there is still much to be discovered about SARS-CoV-2 infection in children and adolescents. However, the findings of this study bring attention to reflect on the most vulnerable subgroups and immunological conditions related to severity and death.

Children and adolescents vulnerable to the severity and death from COVID-19 must be included in public health policies as a risk group. In addition, it is necessary, during the on-going pandemic, to maintain active surveillance for children and adolescents, especially those with chronic diseases, particularly immunopathologies, cardiopathies, and neuropathies, which are part of a group of great importance and of greater risk for the severity and death from COVID-19. In addition, detailed investigation of children diagnosed with COVID-19 who have started signs and symptoms less than 24 hours after birth must be carried out to show a possible vertical transmission.

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Page 6, 2nd paragraph:

Where it reads:

Considering the distribution of cases according to the FU of residence, Sao Paulo had the highest frequency of hospitalized patients, with 1,320 (26.8%), of which 1,247 (94.5%) recovered and 73 (4.5%) evolved to death. Subsequently the Amazon with 517 (10,5%) hospitalized patients, of which 491 (95,0%) recovered and 26 (5%) died (Figures 2A and 2B and Supplementary Material).

It should read:

Considering the distribution of cases according to the FU of residence, Sao Paulo had the highest frequency of hospitalized patients, with 1.320 (26.8%), of which 1.247 (94.5%) recovered and 73 (4.5%) evolved to death. Subsequently the Amazon with 517 (10.5%) hospitalized patients, of which 491 (95.0%) recovered and 26 (5.0%) died (Figures 2A and 2B and Supplementary Material).

Page 8, 7th paragraph:

Where it reads:

In the bivariate analysis, it was found that they had a higher risk of progressing to death in all the cases that were presented to the following factors: being in the age group of adolescents (RR = OR 1.49; 95% CI 1.26 – 1,78; $p < 0.001$); - be of the race/color, self-reported black/mixed-brown race (RR = 1.34; 95%CI 1.08 – cop \$ 1.68; $p < 0.008$); it has been ranked as critical-SARS (RR = 4.13; 95%CI 3.43 – 3.96; $p < 0.001$); have heart disease (RR = WITH 2.07; 95%CI 1.58 – 2.72; $p < 0.001$), immunopathology (RR = 1.74; 95%CI 1.32 – 2.30; $p < 0.001$), diabetes (RR= 1.57; 95%CI 1.08 – 2.30; $p = 0.032$), and neuropathy (RR = 1.47; 95%CI 1.09 – to 1.97; $p = 0.013$). Asthma was configured as a risk reduction factor for death (RR = 0.25; 95%CI 0.10 – 0.62; $p = 0.003$ (Table 2).

The other variables that are related to the signs and symptoms of respiratory disease were tested in a bivariate analysis, that is, low oxygen saturation (RR = 4.12; 95%CI 3,33 – 5,09; $p < 0.001$), respiratory distress (RR = 3.23; 95%CI 2.57 – 4.06; $p < 0.001$), dyspnea (RR = 3; 95%CI 2.39 – 3.78; $p < 0.001$), and cyanosis (RR = 2.89; 95%CI 1.66 – 5.05; $p = 0.003$) (data not shown in table). These variables were grouped in the set of the critical-SARS variable to compose the best regression model.

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In the bivariate analysis, it was found that they had a higher risk of progressing to death in all the cases that were presented to the following factors: being in the age group of adolescents (RR = 1.49; 95%CI 1.26 – 1.78; $p < 0.001$); be of the race/color, self-reported black/mixed-brown race (RR = 1.34; 95%CI 1.08 – 1.68; $p = 0.008$); it has been ranked as critical-SARS (RR = 4.13; 95%CI 3.43 – 4.97; $p < 0.001$); have heart disease (RR = 2.07; 95%CI 1.58 – 2.72; $p < 0.001$), immunopathology (RR = 1.74; 95%CI 1.32 – 2.30; $p < 0.001$), diabetes (RR = 1.57; 95%CI 1.08 – 2.30; $p = 0.032$), and neuropathy (RR = 1.47; 95%CI 1.09 – 1.97; $p = 0.013$). Asthma was configured as a risk reduction factor for death (RR = 0.22; 95%CI 0.12 – 0.39; $p < 0.001$) (Table 2).

The other variables that are related to the signs and symptoms of respiratory disease were tested in a bivariate analysis, that is, low oxygen saturation (RR = 4.12; 95%CI 3.33 – 5.09; $p < 0.001$), respiratory distress (RR = 3.23; 95%CI 2.57 – 4.06; $p < 0.001$), dyspnea (RR = 3.0; 95%CI 2.39 – 3.78; $p < 0.001$), and cyanosis (RR = 2.89; 95%CI 1.66 – 5.05; $p = 0.003$) (data not shown in table). These variables were grouped in the set of the critical-SARS variable to compose the best regression model.

Pages 8 and 10, 9th paragraph:**Where it reads:**

Multivariate analysis showed that these associated factors with COVID-19 death remained: belonging to the adolescent age group (RR = 1.59; 95% CI 1.12 – 2.25; $p = 0.009$), having been classified as SARS-critical (RR = 4.56; 95% CI 2.77 – 7.51; $p < 0.001$) and having immunopathology (RR = 2.24; 95%CI 1.58 – 3.17; $p < 0.001$). Asthma remained a factor associated with reduced risk of death (RR = 2.24; 95%CI 1.58 – 3.17; $p < 0.001$) (Table 2).

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Multivariate analysis showed that these associated factors with COVID-19 death remained: belonging to the adolescent age group (aRR = 1.59; 95%CI 1.12 – 2.25; $p = 0.009$), having been classified as SARS-critical (aRR = 4.56; 95%CI 2.77 – 7.51; $p < 0.001$) and having immunopathology (aRR = 2.24; 95%CI 1.58 – 3.17; $p < 0.001$). Asthma remained a factor associated with reduced risk of death (aRR = 0.25; 95%CI 0.10 – 0.62; $p = 0.003$) (Table 2).

