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Coronavirus Pandemic

Hospitalizations and deaths of Brazilian children and adolescents with Severe Acute Respiratory Syndrome caused by COVID-19

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Abstract
Introduction: Since the onset of the pandemic, COVID-19 has affected the entire world population, however, data on child morbidity and mortality are scarce. This study aimed to analyze the profile of hospitalizations and factors associated with the deaths of Brazilian children and adolescents with Severe Acute Respiratory Syndrome caused by COVID-19.
Methodology: This cross-sectional study uses public domain data from the Influenza Epidemiological Surveillance System in 2021. The prevalence rates, lethality, and duration of hospitalization of children and adolescents with Severe Acute Respiratory Syndrome caused by COVID-19 were analyzed. Logistic regression and adjusted Odds Ratio were used. A $p < 0.05$ was considered significant.
Results: The prevalence of hospitalization among children and adolescents was 3.6%, and the case lethality rate was 4.0%. Higher lethality rates occurred among adolescents, natives, rural residents, those living in Brazil's northern and northeastern regions, and those who became critically ill and had comorbidities. Hospitalization time was longer for adolescents who became critically ill or had comorbidities. The highest chance of death was associated with: children under one year of age and adolescents, natives, and residents from the North, Northeast, and Southeast regions, who became critically ill and had comorbidities.
Conclusions: Despite lower hospitalization and death rates than adults, the prevalence, complications, and mortality from COVID-19 in the pediatric population are relevant. Knowledge of the profile of children and adolescents hospitalized due to COVID-19 and the factors associated with these deaths allows the guidance of response efforts directed to assist this vulnerable population.

Key words: COVID-19; Severe Acute Respiratory Syndrome; hospitalization; children; adolescents; pediatric.

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Introduction

The coronavirus disease 2019, or COVID-19, has spread rapidly worldwide, being classified by the World Health Organization (WHO) as a pandemic on March 11, 2020 [1,2]. Although it affects all age groups, the disease develops with more reserved outcomes in individuals aged over 60, and/or with underlying comorbidities [3]. In different countries, based on the analysis of the first epidemiological data, it was observed that children and adolescents were not the main transmission and disease agents [4,5]. Data from a systematic review, including 18 studies describing the clinical characteristics and management of children and adolescents with COVID-19, evidenced that the main route through which children were contaminated was their family members [6].

Regarding the disease's behavior, the pediatric population corresponds to the minority of symptomatic cases, presenting milder evolution of COVID-19, with reduced need for hospitalization and mortality compared to the adult population [7,8]. In this population, mild symptoms are prevalent when clinical manifestations occur, with a positive evolution, and recovery occurs in up to two weeks [6]. However, it cannot be ignored that asymptomatic or oligosymptomatic cases also impact the chain of infection transmission, and should be the target of preventive measures [9].

SARS-CoV-2 transmission occurs from an infected person to someone susceptible through droplets and aerosols produced by sneezing, coughing, speaking, and other actions that produce these particles [10]. Asymptomatic individuals are important disease carriers, as they can transmit the virus without being aware of their condition, especially when considering the gradual return to on-site activities and the greater flexibility regarding preventive measures [11]. Although efforts are being employed worldwide by the scientific community to understand the disease dynamics and establish forms of prevention, several aspects of COVID-19 still need to be evidenced, especially in the pediatric population [7,12,13].

Considering that the disease behavior is not equally manifested among the countries worldwide, and considering the heterogeneity of the Brazilian population and the challenges in access to, and the quality of the different health services, it is believed that the consequences of the COVID-19 pandemic on the health of children and adolescents in Brazil are still uncertain. In this context, it becomes relevant to evaluate the epidemiological context experienced in the national scenario, to identify those most susceptible to severe disease cases, such as Severe Acute Respiratory Syndrome (SARS), to subsidize the planning of future measures.

Therefore, the present study aims to analyze the profile of hospitalizations and factors associated with the deaths of Brazilian children and adolescents with SARS caused by COVID-19.

Methodology

This is a cross-sectional study related to the epidemiological surveillance of children and adolescent patients hospitalized for SARS caused by COVID-19 in 2021. The source of information was the non-nominal secondary database, without any identification of the individuals, from the Influenza Epidemiological Surveillance System (SIVEP-Gripe), referring to hospitalizations that occurred in 2021, available on the website: https://opendatasus.saude.gov.br and updated on February 7th, 2022.

The study population was composed of cases of children and adolescents hospitalized for SARS aged between zero and 18 years, and registered in the SIVEP-Gripe database between Epidemiological Weeks No. 1 to 52 of 2021, with a diagnosis of COVID-19 confirmed by laboratory criteria. Patients diagnosed only by clinical, clinical-epidemiological, or clinical-imaging criteria were excluded, as well as those with inconclusive results and those whose duration of hospitalization could not be calculated due to missing data.

A child was considered to be an individual aged between 0 (zero) and 11 years, and an adolescent was considered to be someone aged between 12 and 18 years. SARS was defined as the cases hospitalized for COVID-19 that presented at least one of the signs and symptoms, such as dyspnea, respiratory distress, low oxygen saturation (< 95%) on room air, and cyanosis. SARS-critical was characterized as the cases that required admission to the Intensive Care Unit (ICU) or needed invasive or non-invasive ventilatory support [14].

The variables of interest addressed in this study were the following: a) sociodemographic: age, sex, self-reported ethnicity, geographic area, and Brazilian region of residence; b) clinical: SARS-critical and presence of at least one comorbidity (chronic cardiovascular disease, chronic hematological disease; Down syndrome; chronic liver disease; asthma; diabetes mellitus; chronic neurological disease; chronic lung disease; immunodepression; chronic kidney disease, and obesity); c) outcomes: days of hospitalization, in-hospital lethality rates, and case evolution (survival or death).

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical program, version 23.0. Descriptive and inferential analysis was performed. The Kolmogorov-Smirnov test was used to assess variable normality. For the descriptive analysis, the absolute and relative frequency distributions, measures of central tendency, and variability measures were used, according to the normality test results.

The prevalence and lethality rates of the study population were calculated, and the profiles of the patients who either survived or who did not survive were compared in order to identify the differences between them. The in-hospital lethality rate was calculated by considering the total number of hospital deaths divided by the total number of hospitalized cases, multiplied by 100. The Mann-Whitney or Kruskal-Wallis non-parametric tests were used to compare the median length of hospitalization.

Multivariate analysis was performed using binary logistic regression with the Backward Stepwise method considering the number of independent variables obtained by the bivariate analysis, with a 95% confidence interval and $p < 0.05$. The association measure adopted was the Adjusted Odds Ratio (AOR). The Hosmer and Lemeshow test was used to adjust the model. A value of $p < 0.05$ was considered significant.

Since this is a study that includes only public domain data and does not identify the participants, no approval by the Ethics Committee on Research with Human Beings was required.

Results

In Brazil, in 2021, 1,048,575 individuals were hospitalized for SARS, and 389,299 cases were due to

COVID-19, confirmed by a positive RT-PCR test result. When defining only the age range of interest for the study, it was found that 14,116 (3.6%) corresponded to children and adolescents hospitalized for SARS caused by COVID-19, and, of these, 568 died, totaling a case lethality rate of 4.0%.

As shown in Table 1, higher lethality rates were observed among adolescents aged between 15 and 18 (9.8%), followed by the 12 to 14 age group (9.0%). Lethality was also higher among natives (21.7%), rural residents (10.9%), and in the northern (9.5%) and northeastern (9.4%) Brazilian regions. Patients who evolved to SARS-critical and who had at least one comorbidity had case lethality rates of 5.4% and 9.3%, respectively.

Regarding the comorbidities present in the study population and their respective lethality rates (Table 2), in descending order, chronic liver disease (25.6%), chronic cardiovascular disease (19.0%), Down's Syndrome (18.1%), obesity (17.6%), immunodepression (17.5%), chronic hematological and neurological disease (13.3%), chronic kidney disease (12.6%), chronic lung disease (9.3%), and diabetes (7.8%) stand out. The lower lethality rate in the presence of asthma (1.1%) is noteworthy.

The median length of hospitalization in the overall population was 5.0 (interquartile range: 3.0-9.0) days. Patients who died were hospitalized for more days (10.5 days; interquartile range 4.0-21.0) compared to survivors (5.0 days; interquartile range: 3.0-8.0), with a statistical significance of $p < 0.001$.

From this point of view, among the deaths, longer hospitalization times were observed for the 12 to 14 and 15 to 18 age groups, and also for the presence of SARS-critical and presence of at least one comorbidity (Table 3). Among survivors, the longest hospitalization times occurred in the 12 to 14 and 15 to 18 age strata, in the Asian and Native populations, in rural areas, and in the North and Northeast regions, in the presence of SARS-critical and at least one comorbidity.

When the length of hospitalization was analyzed according to the comorbidities, among the patients who died, only liver disease was associated with longer lengths. Among the survivors, those with cardiovascular, hepatic, neurological, renal, and immunodepression diseases were hospitalized for longer; however, asthma was associated with a shorter duration of hospitalization (Table 4).

Aiming to verify the factors associated with a higher death rate among children and adolescents hospitalized with SARS caused by COVID-19, bivariate and multivariate logistic regression was performed (Table 5).

Table 1. Absolute and relative frequencies of the total population, cases of deaths, and lethality, in children and adolescents hospitalized with SARS caused by COVID-19, according to sociodemographic data and clinical conditions. SIVEP-Gripe, 2021, Brazil (n = 14,116).

Variables	Total		Deaths		Lethality
	n	%	n	%	%
Total	14,116	100	568	100	4.0
Age group (years)					
< 1	6,103	43.2	229	40.3	3.7
1-4	4,436	31.4	91	16.0	2.1
5-11	1,772	12.6	75	13.2	4.2
12-14	576	4.1	52	9.2	9.0
15-18	1,229	8.7	121	21.3	9.8
Sex					
Female	6,385	45.3	275	48.4	4.3
Male	7,722	54.7	293	51.6	3.8
Self-declared ethnicity					
Caucasian	5,492	49.7	203	41.1	3.7
African	398	3.6	15	3.0	3.8
Asian	57	0.5	3	0.6	5.3
Mixed	5,048	45.7	260	52.6	5.2
Native	60	0.5	13	2.6	21.7
Geographic area of residence					
Urban	12,149	96.2	444	89.5	3.7
Rural	476	3.8	52	10.5	10.9
Macro region of the country					
North	545	3.9	52	9.2	9.5
Northeast	2,004	14.2	189	33.3	9.4
Midwest	1,670	11.8	49	8.6	2.9
Southeast	6,693	47.4	190	33.5	2.8
South	3,200	22.7	88	15.5	2.8
SARS-critical					
Yes	8,709	67.7	473	93.8	5.4
No	4,154	32.3	31	6.2	0.7
Presence of at least one comorbidity					
Yes	3,616	25.6	338	59.5	9.3
No	10,500	74.4	230	40.5	2.2

SARS: severe acute respiratory syndrome; SIVEP-Gripe: Influenza Epidemiological Surveillance Information System; n: absolute frequency; % relative frequency. Values refer to total valid responses, missing data not being considered. Source: SIVEP-Gripe data updated on February 7th, 2022.

Table 2. Absolute and relative frequencies of the total population, cases of deaths and lethality, in children and adolescents hospitalized with SARS caused by COVID-19, according to the presence of comorbidities. SIVEP-Gripe, 2021, Brazil (n = 14,116).

Comorbidities	Total		Deaths		Lethality
	n	%	n	%	%
Chronic cardiovascular disease					
Yes	373	17.3	71	33.3	19.0
No	1,789	82.7	142	66.7	79.3
Chronic hematological disease					
Yes	113	5.5	15	8.2	13.3
No	1,925	94.5	169	91.8	8.8
Down Syndrome					
Yes	188	9.1	34	17.3	18.1
No	1,880	90.9	163	82.7	8.7
Chronic liver disease					
Yes	43	2.2	11	5.9	25.6
No	1,954	97.8	175	94.1	9.0
Asthma					
Yes	854	36.5	9	4.9	1.1
No	1,485	63.5	176	95.1	11.9
Diabetes Mellitus					
Yes	128	6.2	10	5.3	7.8
No	1,928	93.8	177	94.7	9.2
Chronic neurological disease					
Yes	525	23.8	70	32.9	13.3
No	1,680	76.2	143	67.1	8.5
Chronic lung disease					
Yes	214	10.3	20	10.4	9.3
No	1,872	89.7	172	89.6	9.2
Immunodepression					
Yes	252	11.9	44	22.0	17.5
No	1,860	88.1	156	78.0	8.4
Chronic kidney disease					
Yes	111	5.4	14	7.5	12.6
No	1,928	94.6	173	92.5	9.0
Obesity					
Yes	199	9.7	35	18.4	17.6
No	1,860	90.3	155	81.6	8.3

SARS: severe acute respiratory syndrome; SIVEP-Gripe: Influenza Epidemiological Surveillance Information System; n: absolute frequency; % relative frequency. Values refer to total valid responses, missing data not being considered. Source: SIVEP-Gripe data updated on February 7th, 2022.

Table 3. Hospitalization time of children and adolescents with SARS caused by COVID-19, according to sociodemographic and clinical variables, for the outcomes of survival and death. SIVEP-Gripe, 2021, Brazil (n = 14,116).

Variables	Survivors			Deaths		
	Hospitalization days		*p* value	Hospitalization days		*p* value
	Median	Q1-Q3		Median	Q1-Q3	
Age group (years)			< 0.001[a] *			< 0.025[a] *
< 1	5.0	10.0-3.0		9.0	4.0-22.0	
1-4	4.0	7.0-2.0		11.0	6.0-20.0	
5-11	5.0	9.0-3.0		7.0	3.0-18.5	
12-14	7.0	14.0-3.0		12.0	5.0-22.0	
15-18	6.0	13.0-3.0		14.0	5.0-22.0	
Sex			0.239[b]			0.203[b]
Male	5.0	9.0-3.0		10.0	4.0-21.0	
Female	5.0	9.0-3.0		11.0	4.0-22.0	
Self-declared ethnicity			< 0.001[a] *			0.874[a]
Caucasian	5.0	3.0-8.0		11.0	4.0-22.0	
African	5.0	3.0-8.0		9.0	4.5-14.0	
Asian	6.0	3.0-14.0		8.0	5.5-21.5	
Mixed	5.0	3.0-9.0		10.0	4.0-21.0	
Native	6.0	4.0-12.0		15.0	4.0-24.5	
Geographic area of residence			< 0.021[b] *			0.810[b]
Urban	5.0	3.0-8.0		10.0	4.0-21.0	
Rural	5.0	3.0-11.0		8.0	3.5-28.0	
Macro region of the country			< 0.001[a] *			0.780[a]
North	6.00	3.0-12.0		9.0	4.0-22.0	
Northeast	6.00	3.0-13.0		10.0	4.5-22.5	
Midwest	4.00	2.0-8.0		7.0	3.0-21.0	
Southeast	5.00	3.0-8.0		11.0	4.0-20.0	
South	4.00	2.0-8.0		11.0	4.0-22.0	
SARS-critical			< 0.001[b] *			0.026[b] *
Yes	5.0	3.0-10.0		11.0	4.0-22.0	
No	4.0	2.0-7.0		7.0	2.0-11.0	
Presence of at least one comorbidity			< 0.001[b] *			< 0.001[b] *
Yes	6.0	3.0-12.0		14.0	6.0-26.0	
No	4.0	3.0-8.0		7.0	3.0-15.0	

SARS: severe acute respiratory syndrome; SIVEP-Gripe: Influenza Epidemiological Surveillance Information System; Q1: 1st quartile (25%); Q3: 3rd quartile (75%). Values refer to total valid responses, missing data not being considered. *Significant: $p < 0.05$, by Kruskal-Wallis[a] and Mann-Whitney[b] tests. Source: SIVEP-Gripe data updated on February 7th, 2022.

Table 4. Hospitalization time of children and adolescents with SARS caused by COVID-19, according to comorbidities and the outcomes of survival and death. SIVEP-Gripe, 2021, Brazil (n = 14,116).

Variables	Survivors			Deaths		
	Hospitalization days		*p* value	Hospitalization days		*p* value
	Median	Q1-Q3		Median	Q1-Q3	
Chronic cardiovascular disease			< 0.001*			0.095
Yes	9.0	4.0-17.0		17.0	7.0-32.5	
No	6.0	3.0-12.0		12.0	5.0-23.0	
Chronic hematological disease			0.128			0.580
Yes	6.5	4.0-14.5		11.0	7.0-19.0	
No	6.0	3.0-12.0		15.0	5.5-24.5	
Down Syndrome			0.265			0.216
Yes	7.0	3.0-15.0		18.0	7.0-34.0	
No	6.0	3.0-12.0		13.0	5.0-24.0	
Chronic liver disease			0.026*			0.032*
Yes	10.0	6.0-20.0		26.0	16.0-33.0	
No	6.0	3.0-12.0		14.0	5.0-23.5	
Asthma			< 0.001*			0.387
Yes	4.0	2.0-6.0		12.0	17.0-34.0	
No	8.0	4.0-15.0		5.0	12.5-24.0	
Diabetes Mellitus			0.630			0.211
Yes	7.0	4.0-10.0		7.0	9.0-10.0	
No	6.0	3.0-13.0		5.0	14.5-24.0	
Chronic neurological disease			< 0.001*			0.746
Yes	10.5	5.5-20.0		10.0	6.0-26.0	
No	6.0	3.0-11.0		15.0	5.0-24.5	
Chronic lung disease			0.810			0.364
Yes	7.0	3.0-13.5		16.5	6.0-32.0	
No	6.0	3.0-12.0		15.0	6.0-24.0	
Immunodepression			< 0.001*			0.445
Yes	8.00	5.0-20.0		11.0	5.0-22.0	
No	6.00	3.0-12.0		16.0	5.0-26.0	
Chronic kidney disease			0.001*			0.624
Yes	9.0	5.0-17.0		20.0	4.0-26.0	
No	6.0	3.0-12.0		12.0	5.0-24.0	
Obesity			0.317			0.563
Yes	7.0	4.0-10.0		15.0	6.0-21.5	
No	6.0	3.0-12.0		13.5	5.5-24.0	

SARS: severe acute respiratory syndrome; SIVEP-Gripe: Influenza Epidemiological Surveillance Information System; Q1: 1st quartile (25%); Q3: 3rd quartile (75%). Values refer to total valid responses, missing data not being considered. *Significant: $p < 0.05$, by Kruskal-Wallis[a] and Mann-Whitney[b] tests. Source: SIVEP-Gripe data updated on February 7th, 2022.

Table 5. Bivariate and multivariate logistic regression analysis for factors associated with deaths from SARS caused by COVID-19 in children and adolescents. SIVEP-Gripe, 2021, Brazil (n = 14,116).

Variables	Raw OR			Adjusted OR		
	OR	CI 95%	*p* value	AOR	CI 95%	*p* value
Age group (years)						
<1	1.871	1.462-2.394	< 0.001*	1.721	1.264-2.342	0.001*
1-4	1.000	-	-	1.000	-	-
5-11	2.124	1.556-2.901	< 0.001*	1.393	0.942-2.061	0.097
12-14	5.076	3.560-7.238	< 0.001*	3.448	2.218-5.359	< 0.001*
15-18	5.286	3.992-7.000	< 0.001*	3.447	2.419-4.913	< 0.001*
Sex						
Male	1.000	-	-	-	-	-
Female	1.138	0.961-1.346	0.133	-	-	-
Self-declared ethnicity						
Caucasian	1.000	-	-	1.000	-	-
African	1.082	0.633-1.849	0.774	0.714	0.374-1.360	0.305
Asian	1.496	0.462-4.844	0.501	1.487	0.404-5.477	0.551
Mixed	1.472	1.219-1.776	< 0.001*	0.779	0.593-1.024	0.073
Native	7.073	3.751-13.340	< 0.001*	3.235	1.358-7.705	0.008*
Geographic area of residence						
Urban	1.000	-	-	1.000	-	-
Rural	3.643	2.680-4.952	< 0.001*	1.488	0.968-2.287	0.070
Macro region of the country						
North	3.961	2.772-5.662	< 0.001*	3.921	2.430-6.327	< 0.001*
Northeast	4.614	3.554-5.989	< 0.001*	5.963	4.005-8.878	< 0.001*
Midwest	1.121	0.786-1.598	0.529	1.356	0.846-2.172	0.206
Southeast	1.084	0.839-1.401	0.537	1.428	1.040-1.960	0.028*
South	1.000	-	-	1.000	-	-
SARS-critical						
Yes	7.575	5.256-10.917	< 0.001*	7.494	4.939-11.372	< 0.001*
No	1.000	-	-	1.000	-	-
Presence of at least one comorbidity						
Yes	4.635	3.900-5.508	< 0.001*	3.572	2.836-4.500	< 0.001*
No	1.000	-	-	1.000	-	-

SARS: severe acute respiratory syndrome; SIVEP-Gripe: Influenza Epidemiological Surveillance Information System; OR: Odds Ratio; AOR: adjusted odds ratio. Quality of adjustment by Hosmer and Lemeshow test: $X^2 = 9.111$; $p = 0.333$. *Significance: $p < 0.05$. Source: SIVEP-Gripe data updated on February 7th, 2022.

In the final model, the following were associated with a higher death rate: Age groups under one year old (1.7 times) and 12 to 18 years old (3.4 times); Native ethnicity (3.2 times); Brazilian regions: North (3.9 times), Northeast (5.9 times), and Southeast (1.4 times); and clinical conditions: SARS-critical (7.5 times) and the presence of at least one comorbidity (3.6 times).

Discussion

Lethality rates

In this study, it was possible to observe that the pediatric age group comprised 3.6% of hospitalizations caused by COVID-19 in Brazil in 2021. The case lethality rate was 4.0% among hospitalized children and adolescents, and the highest rates were found in adolescents aged between 15 and 18 years (9.8%), followed by adolescents aged between 12 and 14 years (9.0%). These data are consistent with a study conducted in Iranian cities, where the case lethality rate was 4.3% among children and adolescents, with half of the deaths occurring in children over 5 [15].

Furthermore, in 2020, a study was conducted aiming to assess the impact of admission of pediatric patients with COVID-19 and eventual deaths in individuals aged between zero and 19 worldwide. This study showed that Brazil has one of the highest mortality rates from COVID-19 in pediatric patients, recording 23 deaths/million children, while in the United States, which has also been severely impacted by the disease, this figure was less than 2 deaths/million [16]. Furthermore, a higher lethality rate was observed among Native children and adolescents, pointing to the ethnic and social inequalities across the Brazilian regions. According to a Brazilian study, Native children and adolescents were approximately 3.3 times more likely to die than the Caucasian pediatric population [17].

The increased lethality rate in Native populations may be a result of historical barriers to health services, difficulty in accessing adequate sanitation, and the prevalence of infectious and chronic diseases among Native Brazilians. In addition, the high risk of contagion may be a reflection of limitations in access to safe drinking water, communication failures, and high numbers of trips to large cities and tourist attractions for Native communities [18,19].

The determinants of the Native population's health vulnerability in the context of the COVID-19 pandemic can be described in three interdependent dimensions: (1) Individual, which includes incorrect and/or insufficient knowledge regarding prevention and transmission of the novel coronavirus; (2) Social, which includes factors such as nutritional aggravations, high prevalence of chronic infectious-contagious diseases, and extended family nucleus; and (3) Programmatic, which includes, for instance, unavailability/insufficiency of healthcare and inputs, lack of basic sanitation, food insecurity, and difficulty in accessing health services [18]. Such factors ultimately contribute to the higher lethality rates for COVID-19 among the Native population, as observed in this study.

The present study also indicated that socioeconomic vulnerabilities may be related to the course of the disease and death, as a higher pediatric lethality rate was observed in residents of rural areas and the northern and northeastern regions of the country. Despite the high rates of social isolation in some states in the north and northeast regions, children living in these two regions are 3.4 times more likely to evolve to death than children living in other regions of Brazil [20]. Moreover, in less developed cities, the odds of death are 25% higher when compared to those with higher development indexes. Thus, in addition to sanitary conditions, the response to the pandemic should also consider social vulnerabilities regarding infrastructure, quality, and organization of the local health system [21]. Furthermore, the regionalized organization of health services may involve additional challenges in the pandemic context, especially if the distance to be traveled by patients to access the service is too great [22]. Added to this is the distribution of pediatric ICU beds per 10,000 pediatric inhabitants for each Brazilian region according to the 2016 Brazilian ICU Census, the lowest rates are in the northern and northeastern regions, corroborating a greater inequality of assistance and access to healthcare [23].

Another factor that contributed to the increased lethality in the pediatric population was the presence of at least one comorbidity and the development of SARS-critical during hospitalization. Although children are less susceptible to COVID-19, those with pre-existing comorbidities are more predisposed to the development of severe conditions [24]. Children and adolescents with comorbidities such as liver disease, obesity, diabetes, cardiovascular and renal disease, and immunosuppression have an increased prevalence of severe cases of COVID-19 and approximately a 10-fold greater risk of mortality compared to those without pre-existing health conditions [25–27]. A North American study with children and adolescents hospitalized for the disease associates a higher risk of severity with the presence of certain comorbidities, according to age group: among children aged under five, cardiac and congenital anomalies, with an emphasis on prematurity among those aged under one year; among adolescents aged between 12 and 18, type 1 diabetes, epilepsy and/or seizures, obesity, hypertension, and asthma [24].

The pathological mechanisms that link liver disease as a risk factor for increased lethality related to COVID-19 are not clear. Although most children have abnormal liver enzymes without signs of severity, those who already have some type of liver injury may progress to worsening of the condition due to some factors, such as the immunological damage caused by the inflammatory response to COVID-19; the toxicity of the virus due to its replication in hepatocytes; anoxia leading to ischemic hepatitis; drug-induced liver damage; and reactivation of pre-existing liver disease leading to worsening of cholestasis [28,29].

On the other hand, asthma carriers represented a lower lethality rate among people with comorbidities. Researchers have demonstrated that the excessive mucus production present in some asthma patients may be a protective factor, as mucus is the first barrier against infection, making it difficult for SARS-CoV-2 to reach the distal airways and enter alveolar type 2 cells, which are rich in ACE 2 receptors [30,31]. SARS-CoV-2 needs two proteins to enter host cells: First, the virus binds to the ACE 2 receptor, and then the transmembrane protein TMPRSS2 splits the Spike protein present in the viral envelope into two segments, enabling the virus to penetrate the host cell. In asthmatic patients, the cytokine storm caused by COVID-19 appears to be contained by the Th2 immune response, related to lower quantities of ACE 2 receptors in airway epithelial cells. Asthmatics also have a higher concentration of eosinophils, which is associated with a better COVID-19 prognosis [32]. In addition, inhaled corticosteroids, which are the first line in asthma treatment, evidently decrease the expression of ACE 2 receptors and TMPRSS2 proteins, reducing SARS-CoV-2 ability to bind to airway epithelial cells [32]. It is believed that collectively, all the described factors may be involved in the pathophysiology of COVID-19 in asthmatic patients and may explain why asthma acts as a protective factor.

Hospitalization time

Hospitalization time was longer in adolescents, in individuals who evolved to SARS-critical, and among those who had comorbidities. In addition, among survivors, the longest hospitalization time was among Asian and Native patients, those living in rural areas, and in the northern and northeastern regions of the country. In a multicenter study conducted in the United States, including 43,465 children and adolescents hospitalized with COVID-19, it was observed that 52% of the population was aged between 12 and 18 years, and in 28.7% of cases, comorbidities were present [24].

It is worth noting that during the predominance of the Omicron variant in the last two weeks of December 2021, the pediatric patient profile with the highest record of hospitalizations in the United States was that of children aged between zero and four years [33]. Still in the US, a cohort study concluded that approximately 5% of the more than 12,000 children observed were hospitalized, and of this total, 18% required intensive care [34].

In Brazil, where a large territorial extension and important social inequality exist, social vulnerabilities, concomitant infection rates, and the frailty of health services are factors that result in differences in infection, hospitalization, and mortality rates for COVID-19 throughout the territory [20,35,36]. The presence of comorbidities is more prevalent among the low-income population, which acts as a risk factor for more severe SARS-CoV-2 infections [35,36]. The factors described above suggest some explanations for the longer length of hospitalization in pediatric patients who resided in rural areas and in the northern and northeastern regions of Brazil.

Data in the literature demonstrate relationships between ethnic disparity and length of hospitalization for pediatric patients with COVID-19. A study conducted in the United States concluded that a higher rate of hospitalization was found among African American or Hispanic children under the age of five, and between 12 and 17. This population was four to five times more likely to be hospitalized compared to non-Hispanic Caucasian children [37]. Another study, which involved data from pediatric hospitalizations from hospitals in several countries, such as Italy, the United States, the United Kingdom, India, and Middle Eastern countries, evidenced that children of African descent were at a 15-fold increased risk of developing COVID-19-related Multisystemic Inflammatory Syndrome compared to children of Caucasian descent, thus requiring longer hospitalization times for care [38]. These findings suggest that ethnicity may therefore be a factor influencing the length of hospitalization and the course of SARS-CoV-2 infection in pediatric patients, also observed in this study's results. A Brazilian study shows that Blacks and mixed have a higher mortality rate compared to Whites, which is associated with social inequality and medical care. Thus, the fatality rate from COVID-19 tends to increase with the worsening of the socioeconomic condition [39].

It was evidenced in the present study that, among the pediatric patients who evolved to death, those with longer hospitalization times were those who developed SARS-critical and had at least one comorbidity, especially liver disease, cardiovascular, neurological, and renal diseases, as well as immunosuppression. Children with comorbidities such as obesity, diabetes, heart disease, chronic lung disease other than asthma, epileptic disorders, and immunosuppression have an increased prevalence of severe COVID-19 and may, therefore, require longer hospitalization for the management of more complex symptomatology [25].

On the other hand, patients with asthma have shorter hospitalization times among those with comorbidities, in addition to a lower chance of evolving to death. The cohort study with pediatric patients aged between zero and 21 years in the United States evidences asthma as a risk factor for hospitalization in children with COVID-19, but not for worse disease outcomes [40]. Asthma, then, does not seem to be associated with COVID-19 aggravation and seems to act as a protective factor against longer hospitalization times, severe cases, and subsequent deaths [26,31,41].

Factors associated with deaths

In the present study, the following were associated with a greater chance of death among children and adolescents: The age groups under one year and 12 to 18 years; the Native ethnicity; the North, Northeast, and Southeast Brazilian regions, in descending order; and the SARS-critical clinical conditions and having at least one comorbidity.

The higher mortality between 12 and 18 years old in the study can be explained by the fact that 45% of adolescents had at least one comorbidity, while its frequency was lower among children and children under one year (30% and 15%, respectively). The age groups observed are corroborated by other studies as factors associated with higher COVID-19 severity. A study carried out in the United States also found higher mortality among adolescents and its association with underlying clinical conditions [42]. In China, children under one year of age corresponded to 10.6% of severe and critical cases, the highest percentage among pediatric age groups. In the United States, a cohort study evidenced that age extremes, such as under three months and over 20 years old, are more prone to developing severe COVID-19 infection [43].

Furthermore, a study conducted in Rio Grande do Sul concluded that although children aged zero to nine years rarely evolve into severe forms of COVID-19, SARS-CoV-2 infection combined with any comorbidity worsens the prognosis regarding SARS and death outcomes [44]. A meta-analysis also demonstrates greater vulnerability for severe illness or death from COVID-19 among infants and adolescents, those with cardiac or neurological conditions, or obesity [45].

Moreover, ethnic disparities are shown to be important risk factors for the greater severity of the disease. A study conducted in six hospitals in the United States between July and August 2021 showed that the majority of pediatric patients hospitalized for COVID-19 were African American or Hispanic [37]. Researchers highlight that Native children and adolescents are up to 3.36 times more likely to die from the disease compared to the Caucasian pediatric population [17].

Also noteworthy is the presence of comorbidities contributing to a worse prognosis and mortality in the pediatric population. Approximately two-thirds of children and adolescents hospitalized for COVID-19 present with one or more underlying comorbidities, with about one-third of patients aged between 12 and 17 being obese. Compared to those who are not obese, obese patients required more complex and prolonged care [37,41]. Obesity is described as one of the most significant risk factors associated with mechanical ventilation in children aged two years and older. When associated with type 2 diabetes, obesity is increasingly related to the prediction of pediatric severe disease and mortality [43]. On the other hand, asthma seems to develop a protective role in COVID-19. Although this role is not yet well established, most studies point to a reduction in the death rate of up to 60% [31].

Another important factor is the socioeconomic vulnerability of the population. A Brazilian study conducted in Sergipe concludes that individuals living in poverty are more likely to live in crowded households, have less access to clean water for hand washing, as well as fewer opportunities for home office work and less access to health services; therefore, people in poverty are at a higher rate of infection and mortality from COVID-19 compared to populations living in better socioeconomic conditions [33,34,46].

Strengths and weaknesses of this study

Using a rich dataset covering children and adolescents nationwide, comprising 14,116 RT-PCR-confirmed COVID-19 hospitalizations over 12 months, or 52 epidemiological weeks, a profile of sociodemographic and clinical characteristics and the factors associated with mortality from the disease was evidenced.

Some limitations of the study should also be acknowledged. Firstly, the epidemiological information on pre-existing comorbidities presents low data filling completion, as this information is not mandatory. On this basis, the estimates from these variables should be interpreted with caution due to potential underreporting bias. Secondly, this study's data prevent analyzing the effects of the quality of in-hospital care from the perspective of physical infrastructure or human resources. And finally, the data only assess the hospitalized population, not allowing inferences about the COVID-19 cases that had no record of hospital admission.

Implications for clinical practice and health policies

Since the outbreak of the pandemic, concerns have been raised by health authorities about the collapse of healthcare systems and shortages of clinical hospital beds and intensive care units for patients with moderate and severe COVID-19. This study's findings suggest that regional differences exist in the survival of hospitalized pediatric patients nationwide, which may be due to geographic access to hospital beds and intensive care units.

From this research, it is noted that the pediatric population, despite corresponding to 3.6% of the hospitalized population for COVID-19 in Brazil in 2021, presented a lethality rate of 4.0%, which is relevant. In the present study, the following were associated with higher death rates among children and adolescents: The age groups under one year and 12 to 18 years; the Native ethnicity; the North, Northeast, and Southeast Brazilian regions, in descending order; and the SARS-critical clinical conditions and having at least one comorbidity.

It is worth noting that the data could not evaluate the effects of the new SARS-CoV2 variant, which caused a resurgence of cases and deaths in Brazil, nor the impact of vaccination against COVID-19, which started in January 2021.

Conclusions

By using a dataset that covers children and adolescents nationwide, comprising 14,116 hospitalizations for COVID-19 confirmed by RT-PCR over a period of 12 months, or 52 epidemiological weeks, a profile of sociodemographic and clinical characteristics and factors associated with mortality from the disease is obtained. The pediatric population, despite corresponding to 3.6% of the population hospitalized for COVID-19 in Brazil in 2021, presented a lethality rate of 4.0%, which is relevant. In the present study, the following were associated with a higher death rate among children and adolescents: The age groups under one year and 12 to 18 years; the Native ethnicity; the North, Northeast, and Southeast Brazilian regions, in descending order; and the SARS-critical clinical conditions and having at least one comorbidity.

Despite presenting lower rates of hospitalization and deaths than adults, the prevalence, complications, and mortality from COVID-19 in the pediatric population are relevant. Moreover, this study's findings expose the severity of the epidemic in the context of social inequality and the frailty of health services, especially in impoverished areas, where the impact of the pandemic on mortality is heightened. The study highlighted the impact of social inequalities on morbidity and mortality rates from COVID-19. Thus, knowledge of the impact of the disease on this population requires the adoption of public health strategies aimed at reducing social inequalities and access to health services. Thus, children and adolescents should not be neglected in the context of COVID-19 infection, and it is vital to develop studies that clarify the mechanisms that influence COVID-19 mortality. Finally, the knowledge of the profile of children and adolescents hospitalized for COVID-19 and the factors associated with the deaths allows the guidance of response efforts directed to assist this vulnerable population.

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Authors' Contributions

Maria Cristina B. Soares: Research conception and design; Data collection; Data analysis and interpretation; Methodology; Literature review; Article writing; Final approval of the version to be published. Igor R. Mendes: Research conception and design; Data collection; Interpretation of results; Final approval of the version to be published. Ana Peres C. Quintão: Research conception and design; Data collection; Interpretation of results; Final approval of the version to be published. Luana V. Toledo: Critical revision of the intellectual content of the manuscript and final approval of the version to be published. Ana Laura A. C. de Freitas: Literature review; final approval of the version to be published. Bruno D. Henriques: Critical revision of the intellectual content of the manuscript and final approval of the version to be published. Brunnella A. C. de

Freitas: Research conception and design; Data analysis and interpretation; Methodology; Writing - original draft; Final approval of the version to be published; Responsibility for all aspects of the work in ensuring the accuracy and integrity of any part of the work.

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