



ORIGINAL ARTICLE

Risk factors for COVID-19-related mortality in hospitalized children and adolescents with diabetes mellitus: An observational retrospective cohort study

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Abstract

Background: Diabetes has been recognized as a major comorbidity for COVID-19 severity in adults. This study aimed to characterize the clinical outcomes and risk factors for COVID-19-related death in a large cohort of hospitalized pediatric patients with diabetes.

Methods: We performed an analysis of all pediatric patients with diabetes and COVID-19 registered in SIVEP-Gripe, a Brazilian nationwide surveillance database, between February 2020 and May 2021. The primary outcome was time to death, which was evaluated considering discharge as a competitive risk by using cumulative incidence function.

Results: Among 21,591 hospitalized pediatric patients with COVID-19, 379 (1.8%) had diabetes. Overall, children and adolescents with diabetes had a higher prevalence of ICU admission (46.6% vs. 26%), invasive ventilation (16.9% vs. 10.3%), and death (15% vs. 7.6%) (all $P < 0.0001$). Children with diabetes had twice the hazard of death compared with pediatric patients without diabetes (Hazard ratio [HR] = 2.0, 95% CI, 1.58–2.66). Among children with diabetes, four covariates were independently associated with the primary outcome, living in the poorest regions of the country (Northeast, HR, 2.17, 95% CI 1.18–4.01, and North, (HR 4.0, 95% CI 1.79–8.94), oxygen saturation < 95% at admission (HR 2.97, 95% CI 1.64–5.36), presence of kidney disorders (HR 3.39, 95% CI 1.42–8.09), and presence of obesity (HR 3.77, 95% CI 1.83–7.76).

Conclusion: Children and adolescents with diabetes had a higher risk of death compared with patients without diabetes. The higher risk of death was associated with clinical and socioeconomic factors.

KEYWORDS

children, COVID-19, diabetes, outcome, risk factors, SARS-CoV-2

1 | INTRODUCTION

The SARS-CoV-2 infection has been devastating worldwide particularly for older adults and those from vulnerable groups, including

racial and ethnic minority populations.^{1,2} Additionally, individuals with certain underlying medical conditions are also at increased risk of severe COVID-19.³ Recently, clinical and epidemiological studies have consistently identified diabetes as one of the major

comorbidities associated with COVID-19 severity and mortality among adults.^{4–8}

As most research on COVID-19 and diabetes has been done in adults, it is unclear whether this increased risk of a more severe course of COVID-19 is also present in the pediatric population. There is a paucity of data on the risk of death related to COVID-19 in pediatric patients with diabetes. The few studies reported are from high- or upper-middle income countries, often with a small sample size, which may limit the generalizability of findings. For example, in the first months of the pandemic, Cardona-Hernandez et al.⁹ collected data from large pediatric diabetes centers around the world and concluded that young individuals with diabetes (<25 years) were not at increased risk of hospitalization for COVID-19. On the other hand, in 2021, Elbarbay et al.¹⁰ conducted an international survey on the management of children with diabetes and COVID-19. In this survey, 44% of respondents reported increased episodes of diabetic ketoacidosis in newly diagnosed cases and 30% in established cases. However, there is still limited data on many aspects of how COVID-19 has affected children and adolescents with diabetes, especially in developing countries.¹¹

We recently described clinical outcomes and risk factors for death in children and adolescents hospitalized during the first and second waves of COVID-19 in Brazil.^{12,13} In both waves, we found an important and additive effect related to the presence of comorbidities in general. Based on data from the adult population, we hypothesized that COVID-19 in pediatric patients with diabetes would have a poorer outcome compared to COVID-19 in pediatric patients without diabetes. The aim of this study was to compare the risk of mortality in children with and without diabetes and to identify risk factors for mortality in a subsample of pediatric patients with diabetes, using the SIVEP-Gripe (Surveillance Information System for Influenza) dataset, a Brazilian nationwide registry of hospitalized COVID-19 cases.

2 | METHODS

2.1 | Study design

We performed a retrospective cohort study including all hospitalized pediatric cases recorded in the SIVEP-Gripe. Detailed information regarding this database, including reporting form and data dictionary, codes, and all de-identified data, are publicly available at <https://opendatasus.saude.gov.br/dataset/srag-2020> for data from 2020, and at <https://opendatasus.saude.gov.br/dataset/srag-2021-e-2022> for data from 2021–2022.

2.2 | Participants and case-defining

We included all consecutively registered patients, aged less than 20 years, with a positive quantitative RT-PCR (RT-qPCR) test result

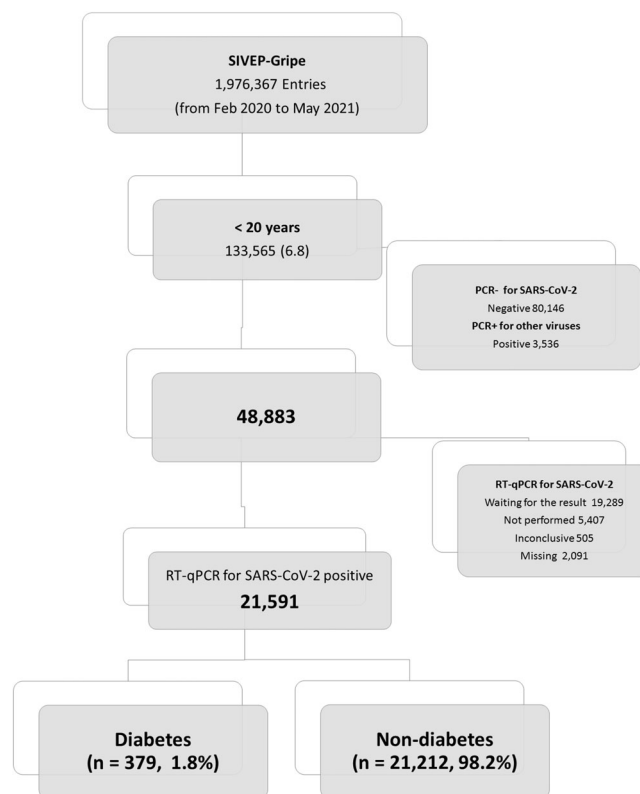


FIGURE 1 Flow diagram of cohort selection

for SARS-CoV-2 who had been admitted to the hospital. The RT-qPCR tests for SARS-CoV-2 were completed after hospital admission. For the present study, we integrated two datasets. We downloaded the first database on January 10, 2021 and the second database on May 29, 2021. For the purpose of analysis, we merged both datasets into a unique database and the cases were divided into two groups, (1) Wave 1 (44 epidemiological weeks from February 16, 2020 to December 31, 2020) and (2) Wave 2 (19 epidemiological weeks from January 1, 2021 to May 29, 2021). In addition, we updated on May 29, 2021, the outcomes of interest for pediatric patients admitted at Wave 1. The rationality in separate the sample into two waves was due to the emergence of the Gamma variant identified in January 2021 in the city Manaus, Brazil.¹⁴ This lineage became predominant in Brazil around February 2021 and was characterized by an increased transmissibility and with more severe spectrum of the disease both in adults and children.^{13,15}

We identified diabetes cases in the SIVEP-Gripe database by retrieving data from specific fields for comorbidities. In the database, information about comorbidities is provided in closed fields (yes/no) without any detailed information about the underlying condition. In addition to diabetes, the dataset provides data on the following comorbidities: asthma, obesity, and cardiovascular, lung, kidney, liver, autoimmune, neurologic, and hematologic diseases. The complete information about included and excluded cases are displayed in the flowchart (Figure 1).

2.3 | Covariates and definitions

Clinical, demographic, and epidemiological data recorded in SIVEP-Gripe are described elsewhere.¹² Briefly, demographic patient data included age, sex, ethnicity, and geographic regions of Brazil (North, Northeast, Central-West, Southeast, and South). The Brazilian Institute of Geography and Statistics (IBGE) classifies ethnicity in five categories: *Branco* (White), *Preto* (Black), *Pardo* (Brown), *Amarelo* (Asian), or *Indígena* (Indigenous).¹⁶ Clinical data included date of signs and/or symptoms onset, date of hospital admission, and findings at disease presentation (fever, cough, respiratory distress, gastrointestinal symptoms). Oxygen saturation obtained at admission was classified as a dichotomous variable in the SIVEP-Gripe database (cut-off point of <95%). In addition, the presence of comorbidities was assessed as risk factors for the event of the interest. For this analysis, we included separately three comorbidities: cardiovascular disease, kidneys disorders, and obesity. The remaining associated conditions were analyzed together. For this purpose, we created a categorical covariate “other_comorbidities.” This variable considered the sum of the other comorbidities included in the SIVEP-gripe. The other comorbidities included were asthma, pulmonary, hepatic, autoimmune disease, neurologic, and hematologic diseases. The variable “other_comorbidities” was categorized into three groups (none, 1, and 2 or more comorbidities).

The clinical course of the disease was reported in terms of respiratory support (none, noninvasive oxygen support, and invasive ventilation), admission to intensive care unit (ICU), hospital discharge, COVID-19-related death, and ongoing clinical situation. Severe spectrum of COVID-19 was defined by the admission to the intensive care unit (ICU), the need of mechanical ventilation, and disease-related death.

2.4 | Missing data management

Although several variables were mandatory in the SIVEP-Gripe registration form, others had the option “Ignored.” These variables presented a considerable amount of missing information. The following covariates had missing information: gender (0.08%), ethnicity (19.6%), oxygen saturation at admission (24.7%), ICU admission (8%), ventilatory support (5.5%), and primary outcome (0.8%). We use various strategies to partially overcome this problem. We describe these strategies in detail elsewhere.¹³ Briefly, in the first step, patients with missing information about the primary outcome were removed from the survival analyses. For those cases with missing data on a particular symptom or comorbidity, we assumed that the clinical condition was absent. Finally, we performed a multiple imputation using all predictors plus the cumulative incidence function for the primary outcome. Ten imputed data sets were generated using the multiple imputation chain equations (MICE) package from the R software (R Foundation for Statistical Computing, Vienna, Austria. Available on <https://cran.r-project.org/web/packages/mice/index.html>). We combined the results from analyses on each of the imputed values using Rubin's rules to

produce estimates and confidence intervals that incorporate the uncertainty of imputed values.^{17,18}

2.5 | Outcomes

The primary outcome was time until COVID-19-related death (in-hospital-mortality). The survival time was defined from the day of admission until the event (death or discharge). We also analyzed the need of health-care resources (ICU admission and respiratory support, defined as none, noninvasive, or invasive).

2.6 | Statistical analysis

The analysis was performed in three steps. First, we compared clinical, demographic and outcomes data in children and adolescents with and without diabetes. We used medians and interquartile ranges (IQRs) or means and standard deviations (SDs) to summarize continuous variables and calculated frequencies and proportions for categorical variables. We compared means and proportions using respectively the *F*-test and the chi-square test. Second, to assess the impact of diabetes on the survival of pediatric patients with COVID-19, we performed a survival analysis, using the cumulative incidence function (CIF)¹⁹ and the Fine-Gray subdistribution risk model²⁰ to estimate the incidence of outcomes over time in the presence of competing risks. A competing risk is an event whose occurrence precludes observation of the primary event of interest. In our study, as COVID-19-related death is the primary outcome, hospital discharge was analyzed as a concurrent event in the analysis. We performed both univariate and multivariate analyses of competitive risk survival, including age, sex, ethnicity, geographic macroregion, signs and symptoms at admission, oxygen saturation, obesity, and other comorbidities as covariates. Finally, the third step was performed on the subsample of pediatric patients with diabetes in order to identify risk factors for mortality in this group. For this step, we also performed a competitive risk survival analysis using the same methodology described in the second step. All statistical tests were two tailed, and statistical significance was defined as $P < 0.05$.

Ethical aspects.

We accessed data in SIVEP-Gripe, which are already deidentified and publicly available. Following ethically agreed principles on open data, this analysis did not require ethical approval in Brazil. We reported our findings following the guideline STROBE for observational cohort studies.²¹

3 | RESULTS

3.1 | Baseline demographic, clinical characteristics, and outcomes

The cohort comprised 21,591 cases, including 379 cases (1.8%) of diabetes. The demographic and clinical characteristics of the cohort

TABLE 1 Demographic, clinical characteristics, and outcomes of children and adolescents with laboratory-confirmed COVID-19 according to presence of diabetes ($n = 21,591$)

	Overall (%) 21,591 (100)	Nondiabetes (%) 21,212 (98.2)	Diabetes (%) 379 (1.8)	P
Age (years)				
Median (interquartile range)	4.7 (0.8–14.6)	4.5 (0.8–14.3)	14.7 (8.2–18.3)	<0.0001
Mean (SD)	7.4 (7.0)	7.3 (7.0)	12.5 (6.7)	<0.0001
Age group (years)				
0.0–9.9	13,856 (64.2)	13,750 (64.8)	106 (28.0)	<0.0001
10–19.9	7735 (35.8)	7462 (35.2)	273 (72.0)	
Gender ($n = 21,573$)				
Female	10,411 (48.3)	10,178 (48.0)	233 (61.5)	<0.0001
Male	11,162 (51.7)	11,016 (52.0)	146 (38.5)	
Wave				
First	11,574 (53.6)	11,366 (53.6)	208 (54.9)	0.64
Second	10,017 (46.4)	9846 (46.4)	171 (45.1)	
Region				
Southeast	8075 (37.4)	7892 (37.2)	183 (48.3)	<0.0001
South	2204 (10.2)	2160 (10.2)	44 (11.6)	
Central-West	2293 (10.6)	2259 (10.6)	34 (8.9)	
Northeast	5748 (26.6)	5651 (26.6)	97 (25.6)	
North	3271 (15.1)	3250 (15.3)	21 (5.5)	
Ethnicity				
White	8047 (37.2)	7866 (37.0)	181 (47.7)	<0.0001
Black/Brown	13,107 (60.7)	12,913 (60.9)	194 (51.2)	
Asian	181 (0.84)	179 (0.84)	2 (0.5)	
Indigenous	256 (1.2)	254 (1.2)	2 (0.5)	
Signs and symptoms at admission				
Fever	14,140 (65.5)	13,938 (65.7)	202 (53.3)	<0.001
Cough	12,971 (60.1)	12,773 (60.2)	198 (58.2)	0.002
Respiratory distress	9733 (45.1)	9540 (45.0)	193 (50.9)	0.022
Oxygen saturation < 95%	9580 (44.4)	9399 (44.3)	181 (47.8)	0.19
Dyspnea	10,470 (48.5)	10,227 (48.2)	243 (64.1)	<0.001
Odynophagia	3476 (16.5)	3512 (16.6)	78 (20.6)	0.041
Diarrhea	3094 (14.7)	3144 (14.8)	43 (11.3)	0.06
Vomit	3629 (16.8)	3537 (16.7)	92 (24.3)	<0.001
Abdominal pain	1454 (6.7)	1412 (6.7)	42 (11.1)	<0.001
Kidney disorders				
Yes	290 (1.3)	277 (1.3)	13 (3.4)	0.002
No	21,301 (98.7)	20,935 (98.7)	366 (96.6)	
Cardiovascular disorders				
Yes	698 (3.2)	647 (3.1)	51 (13.5)	<0.0001
No	20,893 (96.8)	20,565 (96.9)	328 (86.5)	
Obesity				
Yes	477 (2.2)	446 (2.1)	31 (8.2)	<0.0001
No	21,114 (97.8)	20,776 (97.9)	348 (91.8)	
Other morbidities				
None	17,243 (79.9)	16,920 (79.8)	323 (85.2)	0.002
1	3850 (17.8)	3807 (17.9)	43 (11.3)	

TABLE 1 (Continued)

	Overall (%) 21,591 (100)	Nondiabetes (%) 21,212 (98.2)	Diabetes (%) 379 (1.8)	P
≥2	498 (2.3)	485 (2.3)	13 (3.4)	
ICU admission (n = 19,867)				
Yes	5243 (26.4)	5076 (26.0)	167 (46.6)	<0.0001
No	14,624 (73.6)	14,433 (74.0)	191 (53.4)	
Ventilatory support (n = 20,396)				
Invasive	11,272 (55.3)	2069 (10.3)	61 (16.9)	<0.0001
Noninvasive	6994 (34.3)	6849 (34.2)	145 (40.3)	
None	2130 (10.4)	11,118 (55.5)	154 (42.8)	
Death				
Yes	1661 (7.7)	1604 (7.6)	57 (15.0)	<0.0001
No	19,930 (92.3)	19,608 (92.4)	322 (85.0)	

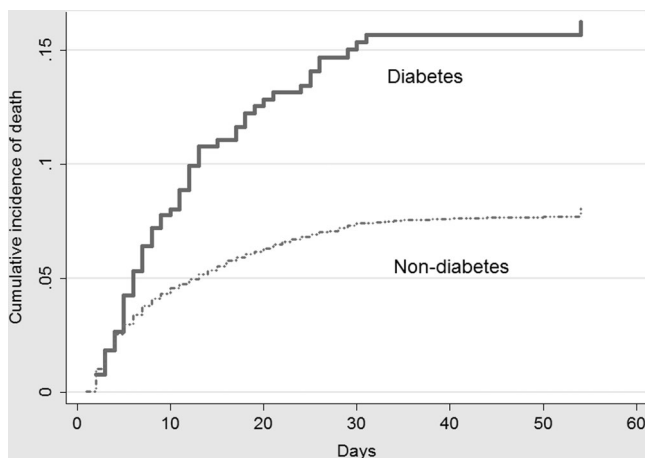


FIGURE 2 Cumulative incidence function of death according to the presence of diabetes (n = 21,591)

according to presence of diabetes are shown in Table 1. As expected, pediatric patients with diabetes were significantly older at presentation. Proportionally, children and adolescents with diabetes were more frequently of female gender, from the richest regions (South and Southeast) of the country and of White ethnicity compared with nondiabetic children. These patients also presented at baseline greater proportion of respiratory distress, dyspnea, and oxygen saturation < 95%. Cardiovascular disease, kidney disorders, and obesity were significantly more prevalent in children and adolescents with diabetes compared with those without. Pediatric patients with diabetes also had more associated comorbidities than those nondiabetics.

The clinical outcomes are also shown in Table 1. Overall, children and adolescents with diabetes had higher prevalence of the severe spectrum of COVID-19 compared with nondiabetic cohort, considering ICU admission (46.6% vs. 26%), use of invasive ventilation (16.9% vs. 10.3%), and death (15% vs. 7.6%) (all $P < 0.001$).

The CIF of death for patients with and without diabetes is shown in Figure 2. The estimated probability of fatal outcome for the first 10, 30, and 60 days of hospitalization for pediatric patients without diabetes was, respectively, 4.5%, 7.4%, 8%. For patients with diabetes, the respective figures were about 8%, 15%, and 18%. According to the Fine-Gray model, in the univariate analysis, children and adolescents with diabetes had twice hazard of death compared with pediatric patients without diabetes (HR = 2.0, 95% CI, 1.58–2.66, $P < 0.0001$). In the competing-risk multivariate survival analysis, adjusted by age, gender, region, ethnicity, respiratory symptoms, cardiovascular diseases, kidney disorders and obesity, children and adolescents with diabetes remained at higher risk of death compared with pediatric patients without diabetes (HR = 1.53, 95% CI, 1.17–2.03, $P = 0.002$).

3.2 | Risk factors of fatal outcome

Table 2 shows the competing-risk univariate analysis for the risk of death regarding the demographic characteristics and clinical features among the 379 children and adolescents with diabetes. Using the Fine and Gray model for the main outcome, geographic region, presence of respiratory symptoms at admission, oxygen saturation < 95% at admission, associated kidney disorders, and obesity were significantly associated with higher hazard of death. (Table 2).

After adjustment by the competing-risk multivariate regression analysis, four covariates remained significantly associated with the main outcome, living in the poorest regions of the country (Northeast, Hazard ratio [HR] 2.17, 95% CI 1.18–4.01, $P = 0.013$, and North, (HR 4.0, 95% CI 1.79–8.94, $P = 0.001$), oxygen saturation < 95% at admission (HR 2.97, 95% CI 1.64–5.36, $P < 0.0001$), presence of kidney disorders (HR 3.39, 95% CI 1.42–8.09, $P = 0.006$), and presence of obesity (HR 3.77, 95% CI 1.83–7.76, $P < 0.0001$).

TABLE 2 Univariate competing-risk survival analysis of children and adolescents with diabetes and COVID-19 ($n = 376$)

	Discharged (%)—283 (75.3)	Death (%)—57 (15.2)	Censored (%)—36 (9.6)	HR (95% CI)	P-value
Age (years)					
0.0 - 9.9	74 (70.5)	21 (20.0)	10 (9.5)	1.0	
10–19.9	209 (77.1)	36 (13.3)	26 (9.6)	0.62 (0.36; 1.06)	0.086
Gender					
Male	110 (75.9)	21 (14.5)	14 (9.7)	1.0	
Female	173 (74.9)	36 (15.6)	22 (9.5)	1.06 (0.62; 1.81)	0.22
Wave					
First	162 (78.6)	33 (16.0)	11 (5.3)	1.0	
Second	121 (71.2)	24 (14.1)	25 (14.7)	0.88 (0.52; 1.49)	0.64
Region					
Southeast	144 (79.5)	21 (11.6)	16 (8.8)	1.0	
South	33 (75.0)	6 (13.6)	5 (11.4)	1.17 (0.47; 2.88)	0.34
Central-West	29 (85.3)	3 (8.8)	2 (5.9)	0.77 (0.22; 2.64)	0.68
Northeast	64 (66.7)	20 (20.8)	12 (12.5)	1.94 (1.05; 3.57)	0.033
North	13 (61.9)	7 (33.3)	1 (4.8)	3.15 (1.38; 7.14)	0.006
Ethnicity					
White	137 (76.1)	24 (13.3)	19 (10.6)	1.0	
Non-White	146 (74.5)	33 (16.8)	17 (8.7)	1.26 (0.75; 2.14)	0.37
Signs and symptoms at admission					
Fever	156 (77.6)	30 (14.9)	15 (7.5)	0.95 (0.56, 1.59)	0.85
Cough	153 (77.3)	48 (13.1)	28 (9.6)	0.72 (0.43, 1.21)	0.22
Odynophagia	62 (80.5)	10 (13.0)	5 (6.5)	0.80 (0.41, 1.59)	0.54
Respiratory distress	132 (69.1)	38 (19.9)	21 (11.0)	2.07 (1.20, 3.58)	0.009
Dyspnea	170 (70.2)	46 (19.0)	26 (10.7)	2.44 (1.23, 4.73)	0.008
O ₂ saturation < 95%	120 (66.6)	41 (22.8)	19 (10.6)	2.99 (1.67, 5.32)	<0.0001
Diarrhea	36 (85.7)	5 (11.9)	1 (2.4)	0.72 (0.29, 1.79)	0.48
Vomit	75 (82.4)	9 (9.9)	7 (7.7)	0.55 (0.27, 1.11)	0.098
Abdominal pain	33 (80.5)	1 (2.4)	7 (17.1)	0.13 (0.01, 0.98)	0.05
Kidney disorders					
No	277 (97.9)	52 (91.2)	34 (94.5)	1.0	
Yes	6 (2.1)	5 (8.8)	2 (5.5)	3.05 (1.26, 7.39)	0.013
Cardiovascular disorders					
No	253 (89.4)	47 (82.4)	26 (72.2)	1.0	
Yes	30 (10.6)	10 (17.6)	10 (27.8)	1.56 (0.78, 3.11)	0.27
Obesity					
No	270 (78.3)	46 (13.3)	29 (8.4)	1.0	
Yes	13 (41.9)	11 (35.5)	7 (22.6)	3.41 (1.76, 6.61)	<0.0001
Other comorbidities					
0	242 (85.5)	45 (78.9)	33 (91.7)	1.0	
1	32 (11.3)	8 (14.0)	3 (8.3)	1.31 (0.63, 2.76)	0.11
≥2	9 (3.2)	4 (7.0)	0 (0.0)	2.46 (0.85, 7.06)	0.094

Note: Three missing information regarding outcome.

4 | DISCUSSION

In this retrospective cohort study, we describe the clinical presentation and outcomes of SARS-CoV-2 infection in 379 pediatric patients

with diabetes included in a cohort of hospitalized children and adolescents with proven SARS-CoV-2 infection in Brazil. First, our findings have shown that, overall, children and adolescents with diabetes had a higher risk of severe COVID-19 and about twice the hazard of death

compared with the nondiabetic cohort. Second, among diabetic pediatric patients, after adjustment by the competing risk survival analysis, four covariates were independently associated with fatal outcome: living in the poorest regions of Brazil (North and Northeast), an oxygen saturation < 95% at entry, and presence of associated obesity and kidney disorders.

The main outcome of interest in our study was COVID-19-related death. In our analysis, children with diabetes had an approximately 50% higher risk of fatal outcome compared to the general pediatric population, even after adjusting by the clinical and demographic characteristics. Few studies have addressed the association of diabetes with the severity of COVID-19 in children and adolescents. Of note, Demeterco-Berggren et al.²² reported a multicenter cross-sectional study of patients with type 1 diabetes and COVID-19 from 56 clinical centers in the United States. A total of 767 patients were analyzed, of which 415 (54%) were younger than 19 years. The analysis showed that older patients (>40 years) were at higher risk for COVID-19 severity, while children and younger adults had milder illness and no deaths were reported for this age group. Instead, our analysis revealed that hospitalized children and adolescents with diabetes from a developing country had a higher need for mechanical ventilation, ICU admission, and mortality rate compared to those without diabetes.

Our findings were similar to those previously reported for adult patients with diabetes. For example, several studies of adults with diabetes infected with SARS-CoV-2 have shown an increased prevalence of more severe COVID-19 outcomes, including death.^{23,24,25,26} Huang et al.²⁵ reported a meta-analysis of a total of 6452 patients from 30 studies in which adult patients with diabetes had an unfavorable outcome compared with the general population. The meta-analysis showed that diabetes was associated with a poor outcome, including disease progression (RR 3.31, 95%CI, 1.08, 10.14) and mortality (RR 2.12, 95%CI, 1.44–3.11). Another meta-analysis further demonstrated that adult patients with diabetes had more than twice the risk of ICU admission and more than triple the risk of death.²⁷ The population-based study by Barron et al.²⁸ showed that Type 1 and Type 2 diabetes were independently associated with a significantly increased odds of in-hospital death from COVID-19. Compared with adults without diabetes, the odds ratios of in-hospital death related to COVID-19 were 3.51 (95% CI 3.16–3.90) in individuals with Type 1 diabetes and 2.03 (1.97–3.90), 2.09 in those with Type 2 diabetes. It is noteworthy that these findings are quite similar to those found in our study. We emphasize that we did not find cohort studies with large samples of pediatric patients hospitalized with diabetes infected with SARS-CoV-2, highlighting the novelty and relevance of the present study.

Several mechanisms have been suggested as an underlying explanation for the more severe course of COVID 19 in patients with diabetes. While diabetes itself appears to be an independent risk factor, other important factors may contribute to an increased risk of COVID-19 severity and mortality in this group of patients, including older age, hypertension, cardiovascular disease, chronic kidney disease, obesity, a pro-inflammatory and hypercoagulable state, and glucose dysregulation.^{7,29} However, it is important to point out that most

mechanisms responsible for the higher mortality in adult patients with diabetes clearly are absent in pediatric population. Furthermore, it is unknown whether potential changes in immune response and increased cytokine storm propensity demonstrated in adults may also occur in pediatric patients with diabetes. Thus, further clinical studies in children with diabetes are clearly needed to assess the mechanisms involved in the poor outcome in pediatric age.

In the second step of our analysis, we evaluate risk factors of COVID-related death among children and adolescents with diabetes. After adjustment by the competing-risk survival analysis, patients from the poorest Brazilian geographic macro-regions (North and Northeast), those with low oxygen saturation at admission, and those with associated kidney diseases and obesity exhibited a higher hazard of death. The finding of an increased risk of in-hospital death in patients from the poorest Brazilian macroregions (North and Northeast) is similar to our previous studies about the entire cohort of hospitalized children and adolescents.^{12,13} In these studies, we provided evidence that the social factors were inextricably associated with clinical factors to determine the outcomes of COVID-19 in Brazil, especially for the most socioeconomically disadvantaged population.^{12,13} Brazil is a country of continental dimensions and is geopolitically divided into five macroregions: North, Northeast, Central-West, Southeast, and South. These macroregions have historical differences in social, economic, and health system infrastructure. In Brazil, despite the existence of an equitable universal public health system (SUS), there are disparities in the provision of health services, in health needs across different segments of the population, and in the access to healthcare.^{30,31} For example, Rocha et al.³² reported that among other social vulnerabilities, the figures of public ICU beds were significantly smaller in North and Northeast regions. In an analysis of the first 250,000 adults hospitalized with COVID-19, Ranzani et al.³³ clearly showed the regional inequality in the risk of dying during hospitalization. They reported an in-hospital mortality rate in nonelderly patients of 31% in the Northeast region compared to 15% in the South of the country. Another independent predictive factor of mortality in our cohort was an oxygen saturation lower than 95% at hospital admission. This finding is expected since the lung is one of the main target organs for SARS-CoV-2 infection and its damage results in greater risk of death for patients with COVID-19.³⁴ Therefore, early signs of lung involvement, such as reduced oxygen saturation on admission, likely indicate greater disease severity. It is noteworthy that two relevant comorbidities in the context of diabetes, kidney disorders and obesity, were independent risk factors for fatal outcome. Pre-existing chronic medical conditions were strongly related to the prognosis of COVID-19 in the general population, including children and adolescents.^{12,35,36} In adult cohorts, chronic kidney disease has been shown to be an independent risk factor for in-hospital death related to COVID-19 in the general population^{35,36} and recent studies have shown that this association is also present in patients with diabetes.^{5,37,38} Obesity has been widely associated with the severity and mortality of COVID-19.^{36,39,40} Since diabetes and obesity lead to pro-inflammatory, hypercoagulable and immune altered conditions, it would be expected an additional effect of obesity upon COVID-19

severity in diabetes patients. However, we must emphasize again that data on the role of obesity in the prognosis of children with diabetes and COVID-19 are limited in the pediatric population.²⁹ In addition, unfortunately the lack of detailed information on the clinical characteristics of the cohort in the SIVEP-Gripe database prevented us from further evaluating the relationship between these comorbidities and outcomes in children with diabetes.

The strength of this study relies on the size of the cohort, allowing the analysis of clinical characteristics, risk factors, and outcomes of hospitalized diabetic children and adolescents with proven SARS-CoV-2 infection. On the other hand, several limitations must be acknowledged in the current study. First, we should point out that our sample is comprised only for hospitalized patients with certainly a more severe spectrum of the disease. The major limitation of our study is the absence of fundamental information regarding both the patients' clinical characteristics prior to admission and data about in-hospital management in the SIVEP-Gripe database. Therefore, we were unable to include some important covariates in the analysis, such as data on diabetes type, treatment, and glycated hemoglobin A levels.⁵ The lack of information about the type of diabetes in our dataset precluded the assessment of whether this increased risk of a severe course of COVID-19 differs between types of diabetes in the pediatric population. In adults, for example, large cohort studies have shown an increased risk of COVID-19-related mortality, ICU admission, and hospitalization for Type 1 diabetes compared with Type 2 diabetes.^{28,41,42} It can be speculated, however, that our sample is possibly composed of the majority of Type 1 diabetes, since it was constituted by a young age group and with a relative low prevalence of other clinical characteristics of interest, such as obesity, hypertension, and kidney disorders.

Another relevant limitation is the lack of information on the level of care and clinical evolution during hospitalization. For example, in COVID-19, glycemic control also plays an important role in the severity of outcomes.²⁹ For example, Holman et al³⁷ demonstrated that adult patients with preadmission HbA1c \geq 86 mmol/mol (10.0%) compared with patients with HbA1c of 48–53 mmol/mol (6.5–7.0%) increased COVID-19-related mortality in both types of diabetes. Furthermore, glycemic control during hospital stay is an important prognostic factor for worse outcomes in hospitalized patients with COVID-19.^{26,43} Unfortunately, the SIVEP-Gripe database did not provide information on glycated hemoglobin A levels. Finally, missing data is another inherent issue due to the nature of a registry based on point-of-care case report forms. We used various strategies to try to partially overcome this limitation. For example, to clarify the fundamental point of the relationship between diabetes and its complications with the outcome, we have analyzed separately the relationship between fundamental covariates such as obesity and kidney disorders. Regarding, missing variables, we used the multiple imputation technique for relevant predictors.

In conclusion, in this analysis of a large nationwide database of hospitalized patients with proven COVID-19, we found that children and adolescents with diabetes had a more severe spectrum of the disease and a higher risk of death than patients without diabetes. Among

pediatric patients with diabetes and COVID-19, the higher hazard of death was associated with living in the poorest geographic regions of Brazil, low oxygen saturation at admission, and presence of obesity and kidney disease. Our findings suggest that the high mortality rates in children and adolescents with diabetes and COVID-19 in Brazil may be partially related to social and economic conditions and with the lack of appropriate support for these pediatric patients. Further prospective studies with large samples of pediatric patients with diabetes are necessary to investigate COVID-19 outcome, risk factors and potential mechanisms related to disease severity.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Ministerio da Saude at <https://opendatasus.saude.gov.br/dataset>

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