Outcomes of SARS-CoV-2 and Seasonal Viruses Among Children Hospitalized in Brazil

Cristiane S. Dias, MD, PhD,[a] Lilian M. Diniz, MD, PhD,[a] Maria Christina L. Oliveira, MD, PhD,[a] Ana Cristina Simões e Silva, MD, PhD,[a] Enrico A. Colosimo, PhD,[b] Robert H. Mak, MD, PhD,[c] Clara C. Pinhati, MD,[a] Stella C. Galante, MD,[a] Isadora Y. Veloso, MD,[a] Hercílio Martelli-Júnior, PhD,[d] Eduardo A. Oliveira, MD, PhD[a]

abstract

BACKGROUND AND OBJECTIVES: Understanding how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts with other respiratory viruses is crucial for developing effective public health strategies in the postpandemic era. This study aimed to compare the outcomes of SARS-CoV-2 and seasonal viruses in children and adolescents hospitalized with severe acute respiratory infection (SARI).

METHODS: This population-based, retrospective cohort study included children and adolescents hospitalized with SARI from February 2020 to February 2023 in Brazil. The main exposure of interest was viral etiology. The primary outcome was in-hospital mortality. Competing risk analysis was used to account for time dependency and competing events.

RESULTS: A total of 235 829 patients had available results of the viral tests, with SARS-CoV-2 predominance. According to the competing-risk survival analysis, the estimated probability of a fatal outcome at 30 days of hospitalization according to the viral strain was 6.5%, 3.4%, 2.9%, 2.3%, 2.1%, and 1.8%, for SARS-CoV-2, coinfection, adenovirus, influenza, other viruses, and respiratory syncytial virus, respectively. Individuals with a positive test for SARS-CoV-2 had hazard of death 3 times higher than subjects with a negative test (hazard ratio, 3.3; 95% confidence interval, 3.1–3.5). After adjustment by the competing-risk multivariable analysis, admission in Northeast and North regions, oxygen saturation <95%, and the presence of comorbidities were risk factors for death in all viral strains.

CONCLUSIONS: SARS-CoV-2 infection had the highest hazard of in-hospital mortality in this pediatric cohort hospitalized with SARI. Regardless of viral etiology, the presence of underlying medical conditions was a risk factor for death.

WHAT'S KNOWN ON THIS SUBJECT: The coronavirus disease 2019 pandemic and the implementation of mitigation measures have affected circulation of seasonal respiratory viruses. Little is known about the comparative outcomes of severe acute respiratory syndrome coronavirus 2 and common respiratory viruses in children.

WHAT THIS STUDY ADDS: Among children hospitalized with acute respiratory infection, severe acute respiratory syndrome coronavirus 2 infection presented the highest risk of in-hospital mortality compared with seasonal viruses. The presence of underlying medical conditions was a risk factor for death for all viruses.

To cite: Dias CS, Diniz LM, Oliveira MCL, et al. Outcomes of SARS-CoV-2 and Seasonal Viruses Among Children Hospitalized in Brazil. *Pediatrics.* 2024;153(2):e2023064326

[a]*Department of Pediatrics, Health Sciences Postgraduate Program, School of Medicine, and* [b]*Department of Statistics, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil;* [c]*Department of Pediatrics, Rady Children's Hospital, University of California, San Diego; and* [d]*Health Science/Primary Care Postgraduate Program, State University of Montes Claros (Unimontes), Montes Claros, Minas Gerais, Brazil*

Drs Oliveira and Dias conceptualized and designed the study, coordinated and supervised data collection, and drafted the initial manuscript; Dr Colosimo conceptualized and designed the study, performed the statistical analysis; Drs Diniz, Oliveira, Simões e Silva, Mak, Pinhati, Galante, Veloso, and Martelli-Junior designed the data collection instruments, collected data, and conducted the initial analyses; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2023-064326

Accepted for publication Nov 21, 2023

Acute respiratory infection in children is a significant global health problem, with heterogeneous clinical manifestations and pathogens involved, including respiratory syncytial virus (RSV) and influenza.[1] The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020 has had an evident impact on the epidemiology of acute respiratory infections worldwide, underscoring the importance of data that directly compare the burden of SARS-CoV-2 infection and other viral etiologies.[2] Previous studies, mainly in adults, have shown that coronavirus disease 2019 (COVID-19) is associated with a higher risk of death and utilization of health care resources than other viruses.[3,4] Understanding how SARS-CoV-2 interacts with other respiratory viruses and how it affects children and adolescents is important in the postpandemic era. In this context, a comprehensive assessment of the outcomes caused by emergent and seasonal viruses is pivotal to setting preventive measures, including vaccination strategies.[5]

In this retrospective cohort study, we used the Brazilian national epidemiologic surveillance system to compare clinical outcomes of SARS-CoV-2 and seasonal virus infections and risk factors of death among children and adolescents hospitalized with severe acute respiratory infection (SARI).

METHODS

Study Design and Participants

We analyzed all cases hospitalized with SARI recorded in the Influenza Epidemiologic Surveillance Information System (SIVEP-Gripe). SIVEP-Gripe is a nationwide database established by the Ministry of Health to keep surveillance of SARI in Brazil.[6] To be registered in the SIVEP-Gripe database, patients must present with a flu-like syndrome and at least 1 of the following criteria: Dyspnea, respiratory distress, oxygen saturation <95% in room air, and cyanosis. For pediatric cases, child-specific symptoms (intercostal retractions, nasal dilation, dehydration, and lack of appetite) are also considered for inclusion in the database. SARI is a notifiable disease in Brazil, and it must be reported to the health authorities within 24 hours of suspicion. The notification is compulsory, and the information is recorded in the SIVEP-Gripe database, which receives data from patients admitted to both public and private hospitals. Upon admission, cases were tested for SARS-CoV-2 and other common seasonal respiratory viral etiologies using reverse transcriptase-polymerase chain reaction or antigen testing. Detailed information regarding the SIVEP-Gripe database, including report form, data dictionary, codes, and all deidentified data, are publicly available at https://opendatasus.saude.gov.br/dataset. Additional information regarding this data set, including the steps of the data retrieving and management, is provided in detail in Supplemental Information 1. The inclusion criterion was pediatric patients (aged <18 years old) registered in the database between February 2020 to February 2023. The information about included and excluded cases is displayed in Fig 1.

Covariables and Definitions

SIVEP-Gripe provides clinical and demographic data, including age, sex, ethnicity, country regions, date of symptom onset, date of admission, signs and or symptoms at admission, oxygen saturation, and comorbidities. For analysis, age was categorized into 3 groups (aged <2 years, 2–11 years, and 12–17 years). Additional information regarding data preparation, definitions of covariates, and missing management are detailed in Supplemental Information 2.

Exposure of Interest

The primary exposure of interest was the virus strain identified by the laboratory tests at admission.

Outcomes

The primary outcome was in-hospital mortality. The clinical course was reported regarding respiratory support (none, noninvasive oxygen support, and invasive ventilation), admission to the ICU, and death.

Statistical Analysis

The analysis was conducted in 3 consecutive stages. First, we used summary statistics to describe the clinical and demographic characteristics of the population included in the analysis. For this stage, descriptive data are presented as means (and SDs), medians (and interquartile ranges), counts, and proportions. We used the F test and the χ^2 test for comparisons between groups when appropriate. In the second step, we evaluated the effect of viral etiology on the survival of children and adolescents with SARI. For this step, we carried out a competing-risk survival analysis, using the cumulative incidence function (CIF)[7] and the Fine-Gray model[8] to estimate the cumulative incidence of the primary outcome over time. In this analysis, in-hospital mortality was the primary outcome, and hospital discharge was considered a competing event. Finally, we conducted a multivariable competing-risk survival analysis for each viral strain to identify independent risk factors of death. All models were adjusted by sex, ethnicity, year of admission, region of hospitalization, oxygen saturation at admission, and comorbidities. The results are expressed as adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were 2-tailed, and statistical significance was set at $P < .05$. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

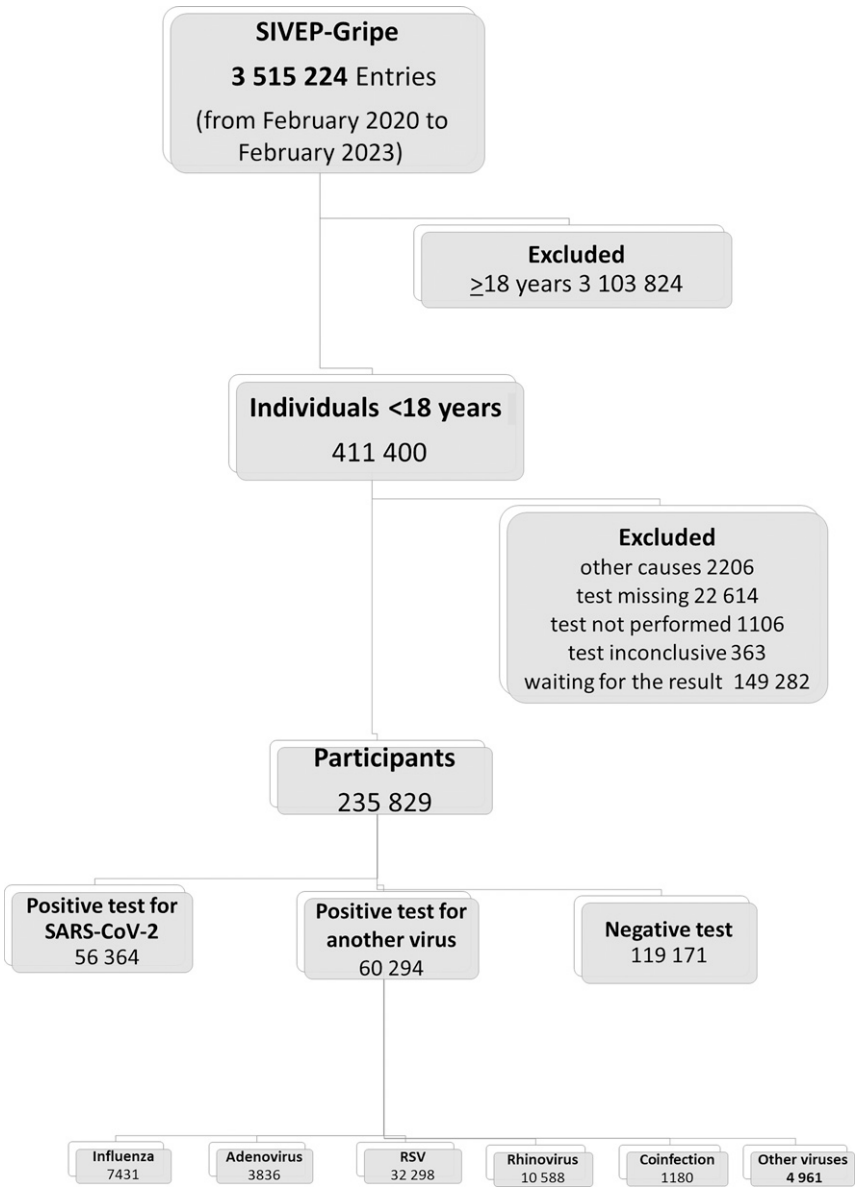

FIGURE 1
Flow diagram of cohort selection.

Ethical Aspects

We accessed data in SIVEP-Gripe, which are already deidentified and publicly available. The study was approved by the Federal University of Minas Gerais institutional review board (Research Ethics Committee, reference number 6.127.414).

RESULTS

Participants

Between February 16, 2020, and February 21, 2023, 3 515 224 cases of SARI were reported in the SIVEP-Gripe. Among them, 411 400 patients (11.7%) were <18 years of age at admission. A total of 175 707 cases were excluded. Therefore, the final sample consisted of 235 829 hospitalized pediatric patients (Fig 1). We performed a sensitivity analysis for those cases without information on viral etiology tests (described in detail in Supplemental Information 3).

The demographic and clinical characteristics of the 235 829 pediatric patients hospitalized with SARI according to viral etiology are shown in Table 1. The overall mean age at admission was 3.8 years (SD 4.5). Regarding viral etiology, there was a higher proportion of positive cases for SARS-CoV-2 in adolescents, whereas RSV cases predominate in infants. Regarding clinical outcomes, 54 962 (25.6%) patients were admitted to the ICU, 105 401 (50.63%) required noninvasive oxygen support, 18 472 (8.9%)

TABLE 1 Demographic Features, Clinical Characteristics, and Outcomes of Children and Adolescents According to the Laboratory-Confirmed Viral Etiology

	Overall (%)	Test Negative	SARS-CoV-2	RSV (%)	Rhinovirus (%)	Influenza (%)	Adenovirus (%)	Coinfection (%)[a]	Other Viruses (%)[b]	*P*
	235 829 (100)	**119 171 (31.0)**	**56 364 (14.6)**	**32 298 (8.4)**	**10 588 (2.7)**	**7431 (1.9)**	**3836 (1.0)**	**1180 (0.3)**	**4961 (1.3)**	
Age (y)										
Median (IQR)	1.9 (0.5–5.4)	2.4 (0.7–5.7)	2.8 (0.6–9.3)	0.4 (0.2–1.2)	2.4 (0.8–5.2)	4.0 (1.3–8.6)	1.8 (0.9–3.3)	0.6 (0.3–2.0)	1.3 (0.5–2.8)	<.001
Mean (SD)	3.8 (4.5)	3.9 (4.2)	5.3 (5.7)	1.0 (1.7)	3.5 (3.5)	5.4 (4.8)	2.6 (2.5)	2.0 (3.4)	2.2 (2.8)	<.001
Age group (y)										
<2	118 698 (50.3)	53 430 (44.8)	24 715 (43.8)	27 351 (84.7)	4677 (44.2)	2468 (33.2)	2041 (53.2)	874 (74.1)	3142 (63.3)	<.001
2–11	96 955 (41.1)	57 551 (48.3)	21 314 (37.8)	4805 (14.9)	5549 (52.4)	4013 (54.0)	1746 (45.5)	262 (22.2)	1715 (34.6)	
12–17	20 176 (8.6)	8190 (6.9)	10 335 (18.3)	142 (0.4)	362 (3.4)	950 (12.8)	49 (1.3)	44 (3.7)	104 (2.1)	
Gender (n = 235 729)										
Female	106 486 (45.2)	53 876 (45.2)	25 837 (45.9)	14 493 (44.9)	4551 (43.0)	3279 (44.1)	1623 (42.3)	516 (43.7)	2311 (46.6)	<.001
Male	129 243 (54.8)	65 242 (54.8)	30 493 (54.1)	17 798 (55.1)	6032 (57.0)	4 151 (55.9)	2213 (57.7)	664 (56.3)	2650 (53.4)	
Admission y										
2020	46 768 (19.8)	28 010 (23.5)	14 768 (26.2)	1255 (3.9)	1198 (11.3)	798 (10.7)	260 (6.8)	54 (4.6)	425 (8.6)	<.001
2021	77 905 (33.0)	37 991 (31.9)	19 537 (34.7)	12 686 (39.3)	3047 (28.8)	2279 (30.7)	533 (13.9)	330 (28.0)	1 502 (30.3)	
2022	104 975 (44.5)	50 106 (42.0)	21 132 (37.5)	16 882 (52.3)	6015 (56.8)	4191 (56.4)	2965 (77.3)	759 (64.3)	2925 (59.0)	
2023	6181 (2.6)	3046 (2.6)	927 (1.6)	1475 (4.6)	328 (3.1)	163 (2.2)	78 (2.0)	37 (3.1)	109 (2.2)	
Region										
Southeast	115 185 (48.8)	65 809 (55.2)	23 945 (42.5)	16 379 (50.7)	1178 (16.8)	3663 (49.3)	1034 (27.0)	613 (51.9)	1964 (39.6)	<.001
South	45 972 (19.5)	20 305 (17.0)	7529 (13.4)	8779 (27.2)	4657 (44.0)	1192 (16.0)	1785 (46.5)	257 (21.8)	1468 (29.6)	
Central-West	22 581 (9.6)	8741 (7.3)	5638 (10.0)	3736 (11.6)	2180 (20.6)	821 (11.0)	501 (13.1)	126 (10.7)	838 (16.9)	
Northeast	38 492 (16.3)	19 497 (16.4)	12 464 (22.1)	2622 (8.1)	1631 (15.4)	1513 (20.4)	253 (6.6)	154 (13.1)	358 (7.2)	
North	13 599 (5.8)	4819 (4.0)	6788 (12.0)	782 (2.4)	342 (3.2)	242 (3.3)	263 (6.9)	30 (2.5)	333 (6.7)	
Ethnicity (n = 188 105)										
White	88 409 (47.0)	43 998 (46.3)	18 808 (41.2)	14 230 (56.4)	4276 (51.3)	2928 (49.0)	1728 (56.5)	481 (51.4)	1960 (50.4)	<.001
Brown	90 597 (48.2)	46 300 (48.7)	24 389 (53.5)	9939 (39.4)	3790 (45.4)	2757 (46.2)	1233 (40.3)	408 (43.6)	1781 (45.8)	
Black	6665 (3.5)	3721 (3.9)	1517 (3.3)	815 (3.2)	183 (2.2)	211 (3.5)	67 (2.2)	37 (4.0)	114 (2.9)	
Asian American	1152 (0.6)	583 (0.6)	336 (0.7)	124 (0.5)	43 (0.5)	31 (0.5)	8 (0.3)	7 (0.7)	20 (0.5)	
Indigenous	1282 (0.7)	497 (0.5)	546 (1.2)	106 (0.4)	50 (0.6)	44 (0.7)	25 (0.8)	2 (0.2)	12 (0.3)	
Signs and symptoms at baseline										
Fever	154 063 (65.3)	74 962 (62.9)	38 269 (67.9)	20 846 (64.5)	6252 (59.0)	6120 (82.4)	3118 (81.3)	852 (72.2)	3644 (73.5)	<.001
Cough	179 352 (76.1)	91 010 (76.4)	36 324 (64.4)	28 910 (89.5)	8685 (82.0)	6003 (80.8)	3160 (82.4)	1014 (85.9)	4246 (85.6)	<.001
Respiratory distress	132 905 (56.4)	69 135 (58.0)	25 252 (44.8)	22 305 (69.1)	6693 (63.2)	3529 (47.5)	2085 (54.4)	752 (63.7)	3154 (63.6)	<.001
Dyspnea	132 783 (56.3)	69 949 (58.7)	26 381 (46.8)	20 874 (64.6)	6611 (62.4)	3294 (44.3)	1931 (50.3)	701 (59.4)	3042 (61.3)	<.001
Oxygen saturation <95% (n = 194 863)	112 218 (57.6)	59 525 (57.7)	20 343 (48.2)	18 917 (69.1)	5624 (65.6)	2806 (48.9)	1703 (56.6)	641 (65.0)	2659 (70.0)	<.001
Odynophagia	25 218 (10.7)	12 623 (10.6)	8004 (14.2)	1453 (4.5)	973 (9.2)	1267 (17.1)	432 (11.3)	79 (6.7)	387 (7.8)	<.001
Diarrhea	23 995 (10.2)	11 892 (10.0)	7259 (12.9)	2455 (7.6)	724 (6.8)	655 (8.8)	479 (12.5)	118 (10.0)	413 (8.3)	<.001
Vomit	38 716 (16.4)	20 479 (17.2)	9671 (17.2)	4161 (12.9)	1491 (14.1)	1337 (18.0)	702 (18.3)	187 (15.8)	688 (13.9)	<.001
Abdominal pain	13 582 (5.8)	7364 (6.2)	4139 (7.3)	650 (2.0)	557 (5.3)	455 (6.1)	205 (5.3)	37 (3.1)	175 (3.5)	<.001
Number of comorbidities										
None	203 544 (86.3)	102 395 (85.9)	46 345 (82.2)	30 389 (94.1)	9217 (87.1)	6429 (86.5)	3409 (88.9)	1064 (90.2)	4296 (86.6)	<.001
1	26 468 (11.2)	13 843 (11.6)	8006 (14.2)	1584 (4.9)	1167 (11.0)	862 (11.6)	359 (9.4)	91 (7.7)	556 (11.2)	
2	4842 (2.1)	2440 (2.0)	1649 (2.9)	288 (0.9)	162 (1.5)	124 (1.7)	58 (1.5)	23 (1.9)	98 (2.0)	
≥3	975 (0.4)	493 (0.4)	364 (0.6)	37 (0.1)	42 (0.4)	16 (0.2)	10 (0.3)	2 (0.2)	11 (0.2)	
ICU admission (n = 215 060)										
No	160 098 (74.4)	83 987 (76.8)	35 512 (72.2)	21 165 (69.2)	7431 (74.3)	4886 (75.8)	2852 (78.0)	718 (64.0)	3547 (75.0)	<.001
Yes	54 962 (25.6)	25 357 (23.2)	13 642 (27.8)	9438 (30.8)	2575 (25.7)	1562 (24.2)	805 (22.0)	403 (36.0)	1180 (25.0)	

TABLE 1 Continued

	Overall (%)	Test Negative	SARS-CoV-2	RSV (%)	Rhinovirus (%)	Influenza (%)	Adenovirus (%)	Coinfection (%)[a]	Other Viruses (%)[b]	*P*
	235 829 (100)	**119 171 (31.0)**	**56 364 (14.6)**	**32 298 (8.4)**	**10 588 (2.7)**	**7431 (1.9)**	**3836 (1.0)**	**1180 (0.3)**	**4961 (1.3)**	
Oxygen support (n = 208 239)										
None	84 366 (40.5)	42 041 (40.1)	24 528 (50.7)	7709 (25.8)	3306 (34.3)	3110 (49.5)	1637 (46.6)	338 (31.3)	1697 (37.1)	
Noninvasive	105 401 (50.6)	54 081 (51.5)	18 889 (39.1)	19 439 (65.1)	5626 (58.3)	2701 (43.0)	1581 (45.0)	614 (56.9)	2 470 (54.1)	<.001
Invasive	18 472 (8.9)	8794 (8.4)	4943 (10.2)	2734 (9.1)	712 (74)	468 (7.5)	293 (8.3)	127 (11.8)	401 (8.8)	
In-hospital mortality rate (n = 234 337)										
No	227 259 (97.0)	115 729 (97.7)	52 379 (93.9)	31 847 (98.8)	10 366 (98.2)	7232 (97.8)	3716 (97.1)	1138 (96.9)	4852 (97.9)	
Yes	7078 (3.0)	2726 (2.3)	3377 (6.1)	371 (1.2)	193 (1.8)	161 (2.2)	110 (2.9)	37 (3.1)	103 (2.1)	<.001

Data (n) in the first column represent the available data for those variables with missing values (gender, ethnicity, oxygen saturation, ICU admission, ventilatory support, and death). IQR, interquartile range.

[a] Coinfection: SARS-CoV-2/RSV, 874; SARS-CoV-2/influenza, 176; and SARS-CoV-2/adenovirus, 150.

[b] Other virus: Meta, 2154; parainfluenza, 1872; and boca, 1373 (some cases with >1 virus identified).

required invasive ventilation and 7078 (3.0%) individuals had a fatal outcome. Interestingly, although RSV positive cases had proportionally lower oxygen saturation at entry and required more ICU admission and oxygen support, the in-hospital mortality rate was higher for SARS-CoV-2 positive cases (Table 1).

Epidemic Curve

Figure 2 shows the cases hospitalized with SARI over time in patients <18 years of age with laboratory-confirmed viral etiology, stratified by age group and year of hospitalization. The first laboratory-confirmed SARS-CoV-2 infection was reported in Brazil on February 16, 2020. Figure 2 shows that SARS-CoV-2 infection became prevalent in all age groups around the 14th epidemiologic week of 2020 and maintained a prevalence >80% throughout 2020. During the second year of the pandemic, SARS-CoV-2 infection was still prevalent in children, but RSV became dominant in infants around the 10th epidemiologic week. During the third year of the pandemic, with the emergence of the omicron variant, SARS-CoV-2 infection became predominant again, regardless of age, until around the ninth epidemiologic week, when RSV returned to predominate in infants (Fig 2).

Risk Factors of Fatal Outcome

According to the competing-risk survival analysis, the overall estimated probability of death of the entire cohort was 3.2%. Figure 3 illustrates the CIF according to viral etiology. The estimated probability of a fatal outcome at 30 days of hospitalization according to the viral strain was 6.5%, 3.4%, 2.9%, 2.3%, 2.1%, and 1.8%, for SARS-CoV-2, coinfection, adenovirus, influenza, other viruses, and RSV, respectively. For those cases with a negative test at admission, the probability of death was estimated as 2.4% (Fig 3).

In the competing-risk univariate analysis, children with a positive test for SARS-CoV-2 had a hazard of death 3 times higher compared with individuals with a negative test (HR, 3.3; 95% CI, 3.1–3.5). Cases with coinfection (HR, 1.7; 95% CI, 1.2–2.4) and a positive test for adenovirus (HR, 1.4; 95% CI, 1.2–1.7) also had a significantly increased death hazard compared with the reference category. On the other hand, cases with a positive test for RSV (HR, 0.57; 95% CI, 0.51–0.65) and rhinovirus (HR, 0.79; 95% CI, 0.69–0.94) had a relatively reduced hazard of death during hospital stay (Fig 4).

Figure 5 shows the multivariable competing risk analysis models of death risk factors for each of the main viral strains (Fig 5A–D). For RSV-positive cases, the following covariates were associated with fatal outcome, age (12–17 years), Indigenous ethnicity, admission in Northeast or North regions, oxygen saturation <95% at admission, and presence of comorbidities (Fig 5A). For influenza-positive cases, age (12–17 years), admission in Northeast or North regions, oxygen saturation <95%, and presence of comorbidities (Fig 5B). For adenovirus cases, covariates associated with the primary outcome were Indigenous ethnicity, admission in Northeast or North regions, oxygen saturation <95%, and presence of comorbidities (Fig 5C). For SARS-CoV-2–positive cases, age (<2 years and 12–17 years), Indigenous ethnicity, admission in Northeast or North regions, oxygen saturation <95%, and presence of comorbidities were risk factors of death. Of note, admission after 2021 was increasingly protective against death for cases positive for SARS-CoV-2 (Fig 5D).

DISCUSSION

In this population-based study conducted over the 3 years of the COVID-19 pandemic in Brazil, we analyzed a nationwide database of hospitalized children and adolescents with

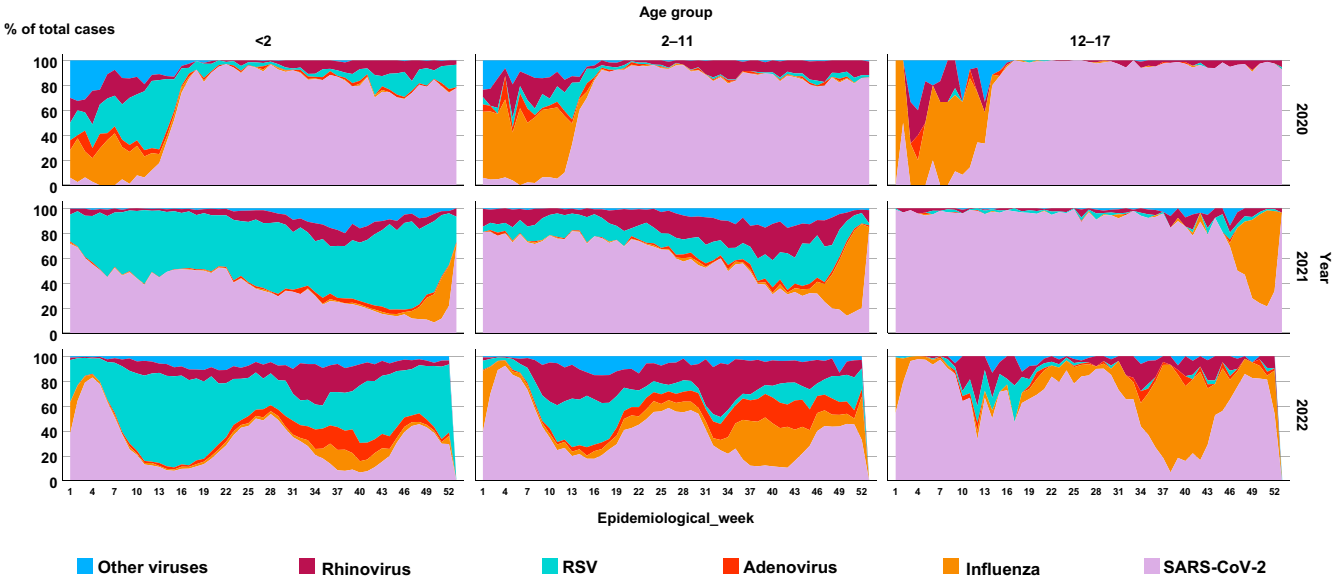

FIGURE 2

Incident cases of SARI in children and adolescents according to the viral etiology, age, and year of admission during the 3 years of the COVID-19 pandemic in Brazil.

SARI and confirmed viral etiology. To our knowledge, this report is the first large-scale study assessing competing risks of death in children and adolescents with SARI associated with SARS-CoV-2 and other seasonal respiratory viruses. After accounting for competing events and confounding factors, patients infected with SARS-CoV-2 had the highest risk of death compared with those with a negative test. Positive tests for adenovirus, influenza, and coinfections were also associated with an increased risk of death. Other risk factors for death included hospitalization in the poorest regions of Brazil, low oxygen saturation at admission, and presence of comorbidities.

The COVID-19 pandemic has dramatically affected the epidemiology of acute respiratory infections. The measures taken to mitigate the pandemic have affected the spread of respiratory viruses, like RSV, influenza, and parainfluenza, leading to a decrease in infections and hospitalizations.[9–13] During the analyzed period from 2020 to 2023, we observed an apparent alternating trend in dominance between SARS-CoV-2 and RSV in infants, whereas for adolescents, SARS-CoV-2 was the leading cause of hospitalization. Some studies have reported an RSV surge when physical distancing measures were eased, and schools reopened, resulting in a shift in the peak season and increased infections in older children.[14–17] Interestingly, in our cohort, a positive test for RSV was associated with an overall comparatively lower risk of death in our cohort. However, we must emphasize that RSV was related to 327 deaths in Brazil in the period analyzed, and RSV-associated morbidity and mortality is a substantial health care burden worldwide.[18–21]

Additionally, staggered COVID-19 vaccination campaigns may have affected the circulation and transmission of the SARS-CoV-2.[5,22] Interestingly, we observed that hospitalization after the second year of the pandemic conferred a significant protection against death, which may be related to a range of factors, including a steep learning curve regarding COVID-19 and the vaccine programs. In this regard, our previous studies have shown that, despite limited protection against SARS-CoV-2 infection, the vaccine schedules conferred significant protection against hospitalization and death.[23–25]

Our analysis showed that, among all viral etiologies, SARS-CoV-2 had the highest hazard of death among children and adolescents hospitalized with SARI. Compared with subjects with a negative test at admission, positive cases for SARS-CoV-2 had a crude HR of 3.3 (95% CI 3.1–3.5). Importantly, we also found in the competing-risk survival analysis that not only SARS-CoV-2 infection but also adenovirus, influenza, and cases with coinfection had a significant hazard of death. Notably, in the United States, an epidemiologic analysis of all infectious and respiratory diseases from 2019 to 2022 revealed that COVID-19 ranked the first cause of death in children and adolescents, followed by influenza and pneumonia.[26] In a French nationwide, population-based study, Piroth and colleagues[3] showed an overall in-hospital mortality higher in patients with COVID-19 than in those with influenza (16.9% vs 5.8%). Of note, in adolescents, the in-hospital mortality was 10 times higher for COVID-19 than for influenza.[3] In adults, Ludwig et al[27] found an overall in-hospital mortality more than twofold higher in COVID-19 versus influenza (14% vs 6%) in

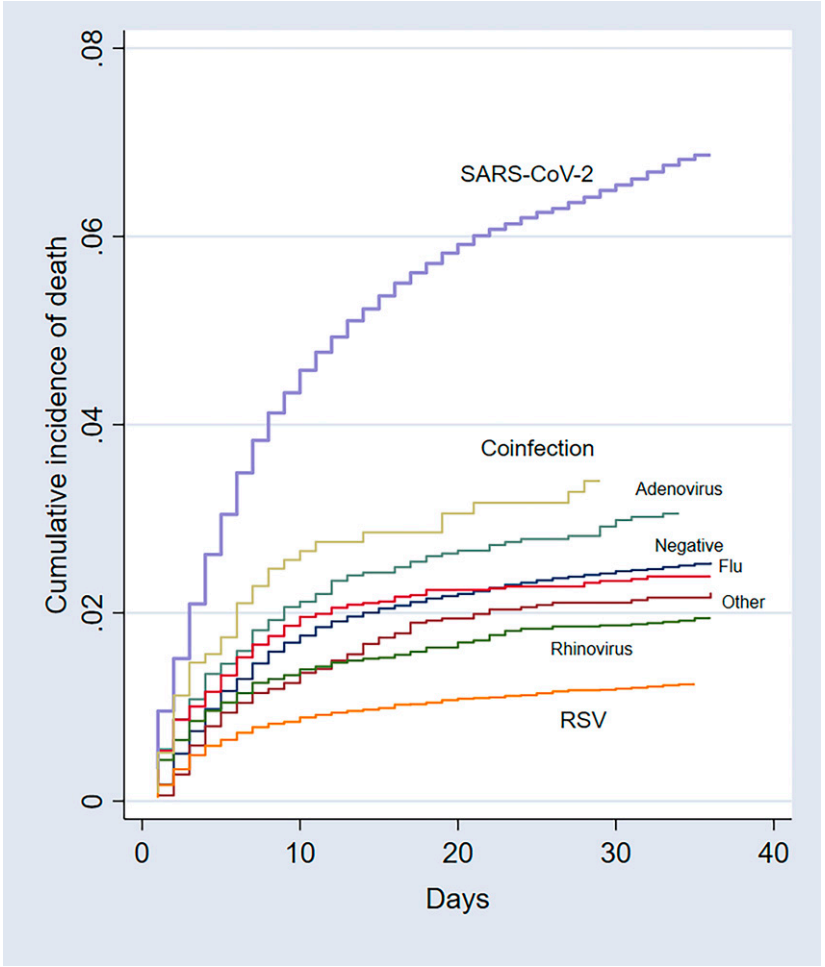

FIGURE 3
Cumulative incidence of death in children and adolescents with SARI according to viral strain.

Germany. Using a similar methodology to our study, Portmann and colleagues[4] reported that the adjusted HR for in-hospital death for the SARS-CoV-2 omicron variant versus influenza was 1.54 (95% CI 1.18–2.01) in a cohort of hospitalized patients in Switzerland. Interestingly, regarding coinfection, Agathis et al[28] reported that respiratory virus codetections increased disease severity among children <5 years of age hospitalized with SARS-CoV-2 infection.

Covariates		HR (95% CI)	P
Virus strain			
Negative test	Reference		
RSV	.58	(.51–.65)	<.001
Rhinovirus	.79	(.69–.94)	.007
Other viruses	1.07	(.87–1.32)	.512
Influenza	1.18	(.99–1.39)	.052
Adenovirus	1.42	(1.16–1.75)	.001
Coinfection	1.75	(1.25–2.45)	.001
SARS-CoV-2	3.32	(3.13–3.50)	<.001

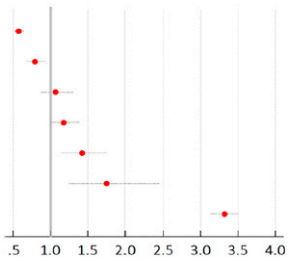

FIGURE 4
Unadjusted hazard of death in children and adolescents with SARI according to the viral strain. Reference category: Negative test at baseline.

A

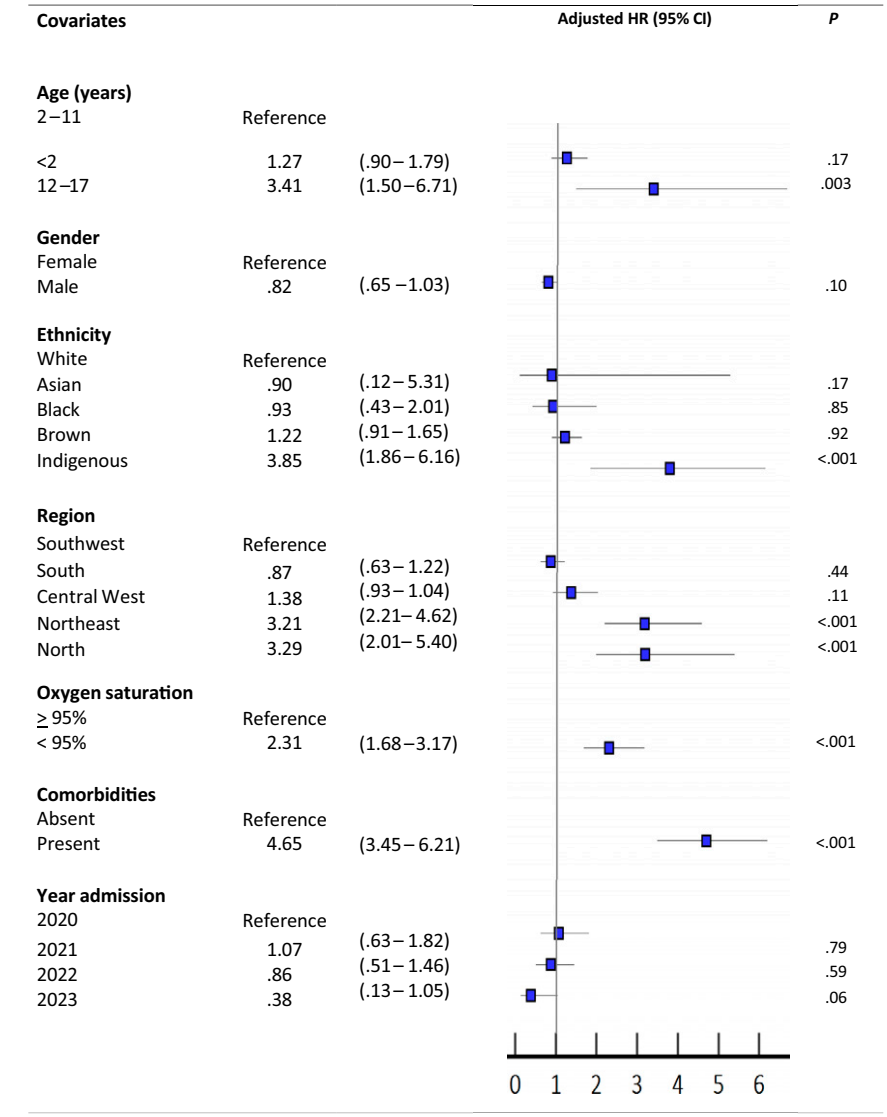

FIGURE 5

Adjusted hazard of death in children and adolescents with SARI according to the viral strain. (A) RSV, (B) adenovirus, (C) influenza, and (D) SARS-CoV-2. Reference category: Negative test at baseline.

In the second step of our analysis, we evaluated risk factors of in-hospital mortality among pediatric patients with SARI according to the viral etiology. As expected, the factors related to death varied among the virus strains. However, of particular interest, in the competing-risk multivariable analysis, the following 3 covariates were significantly associated with death in all models: Presence of oxygen saturation <95% at admission, hospitalization in the poorest regions of the country (Northeast and North), and presence of comorbidities. Our analysis confirmed previous findings regarding factors associated with in-hospital mortality in children with SARI. The presence of any chronic medical condition was identified as a risk factor, consistent with several previous COVID-19 pediatric studies.[29–38] Comorbidities have been shown to increase the severity of clinical outcomes and the risk of ICU admission, extended hospitalization, and mortality in pediatric influenza cases, as well.[39] The importance of hypoxemia as a predictor of mortality in children with acute lower respiratory infections has been demonstrated in a meta-analysis conducted before the COVID-19 pandemic.[40] Furthermore, our data revealed that children and adolescents hospitalized in less-developed regions of Brazil had a higher hazard of death compared with those in the wealthiest region. Health disparities, including factors like race, poverty, and access to health care,

B

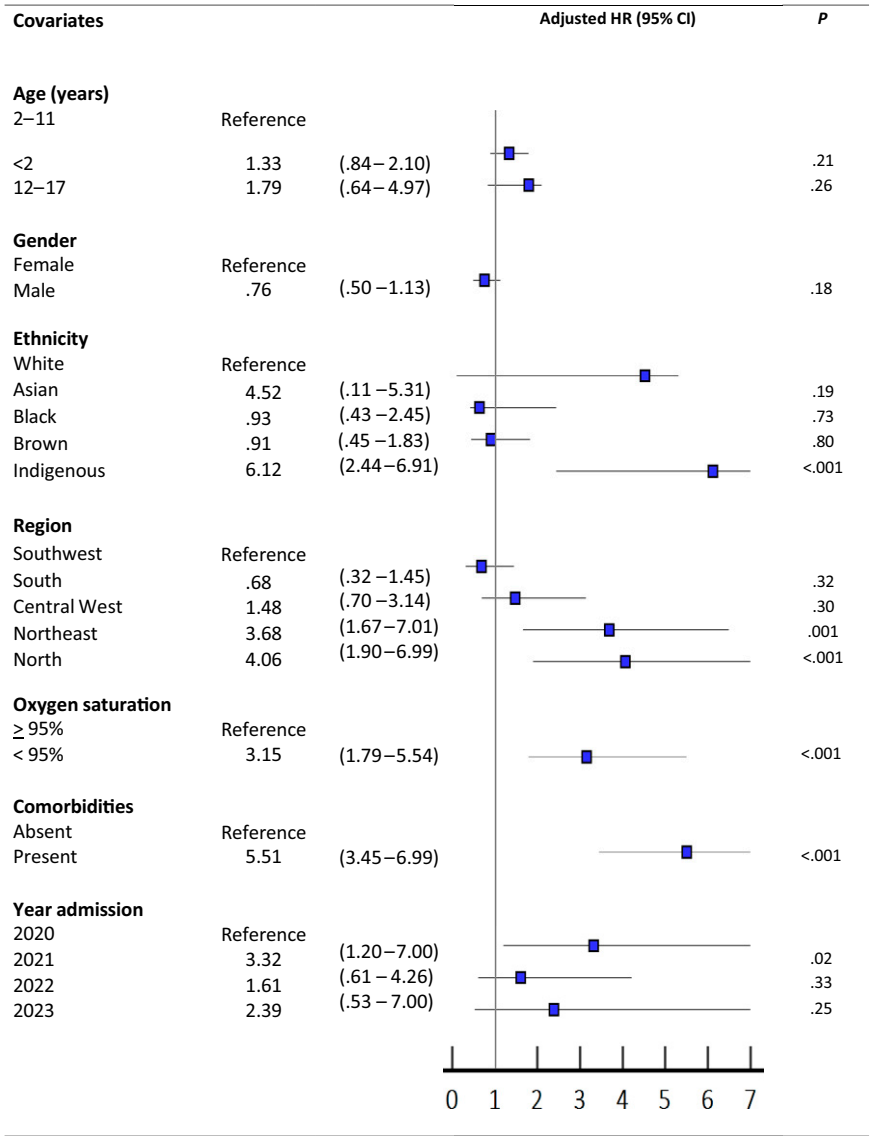

FIGURE 5
Continued

have been strongly associated with COVID-19 outcomes in several studies.[41,42] Brazil is a middle-income country with significant disparities in the social determinants of health, including differences in access to and quality of public health services, as a low coverage of ICU in North and Northeast regions.[43,44]

Some aspects of our results deserve further discussion. As previously mentioned, our findings highlight that some risk factors for death are shared among all strains of the virus. However, it should be noted that age was associated with the primary outcome in almost all models, except the adenovirus model. We previously reported that age as a risk factor for COVID-19–related death was "U" shaped, with infants and adolescents at higher risk for a worse outcome.[30,33,45] In the present analysis, we found that adolescents were at higher risk of death than the reference group (aged 2–11 years) in all virus models, except those who tested positive for adenovirus. Unexpectedly, infants (aged <2 years) were at an increased risk of death only in cases positive for SARS-CoV-2, but not for seasonal viruses. Similarly, indigenous ethnicity was also strongly associated with death in all models, except the flu model. Our previous studies also showed that indigenous ethnicity was a risk factor for COVID-19–related death. Therefore, we cannot rule out the possibility that the relatively small sample size of seasonal viruses may have hampered the analysis, increasing the likelihood of false-negative results in some of these

C

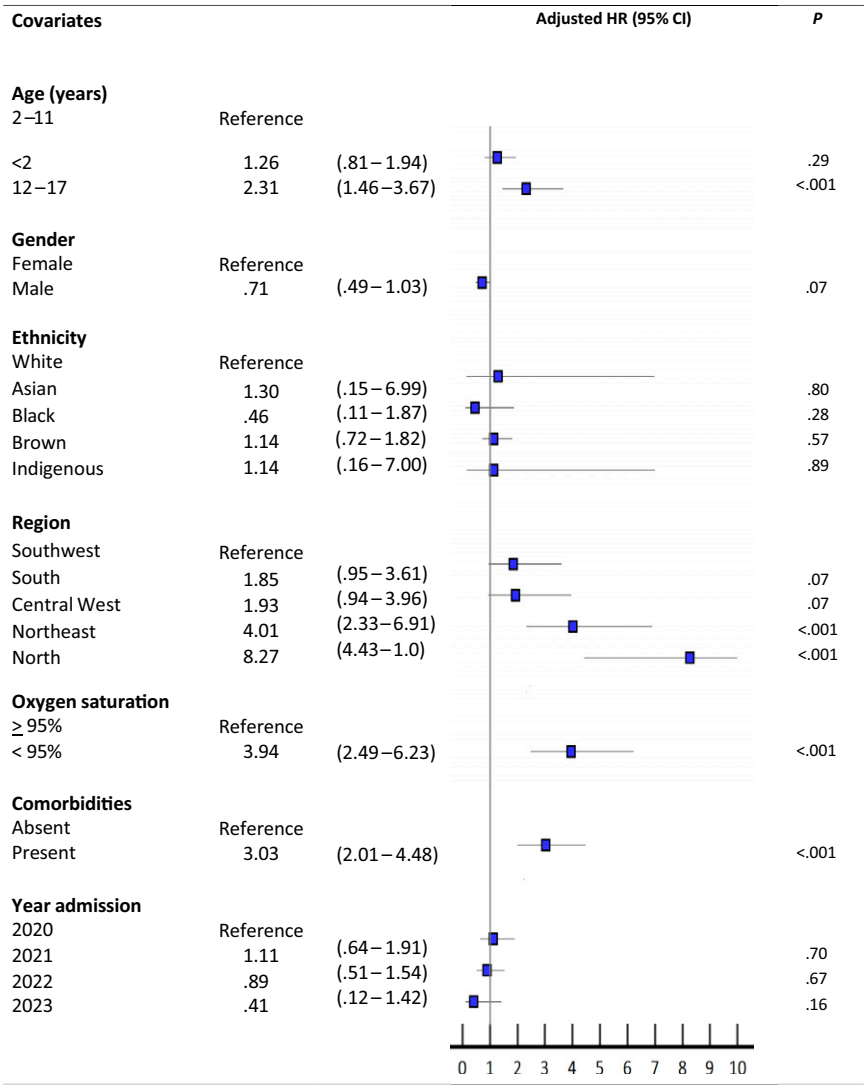

FIGURE 5
Continued

models. However, despite these issues possibly related to study power, we must emphasize that our results highlight more susceptible subgroups of pediatric patients, whose characteristics may need to be considered in future epidemics, regardless of viral etiology.

The strength of this study is its large cohort size, which allowed comparisons of clinical characteristics, outcomes, and risk factors for death in children and adolescents with SARI caused by SARS-CoV-2 and other respiratory viral infections. However, our study has several limitations. First, a major limitation is the lack of essential information on viral etiology tests for many patients, most labeled in the database as "awaiting test results." To address this issue, a sensitivity analysis was performed for patients with an unknown viral etiology. In this analysis, there was no discernible pattern in the clinical outcomes in cases with unknown viral etiology, except for cases labeled as inconclusive, with a mortality rate similar to the cases with positive SARS-CoV-2 test results. Secondly, another relevant issue concerns the heterogeneity of testing for other viruses in Brazil during the pandemic period. The testing strategies varied widely between Brazilian regions, depending on test availability. During periods of high demand, the viral testing panel provided by the Ministry of Health focused on the most prevalent viruses; namely, SARS-CoV-2, influenza, and RSV. Therefore, the true prevalence of other viruses such as adenovirus may have been underestimated in our cohort. Although all models were controlled for region and year of admission, we cannot rule out the possibility that this may have introduced bias into the analysis. For example,

D

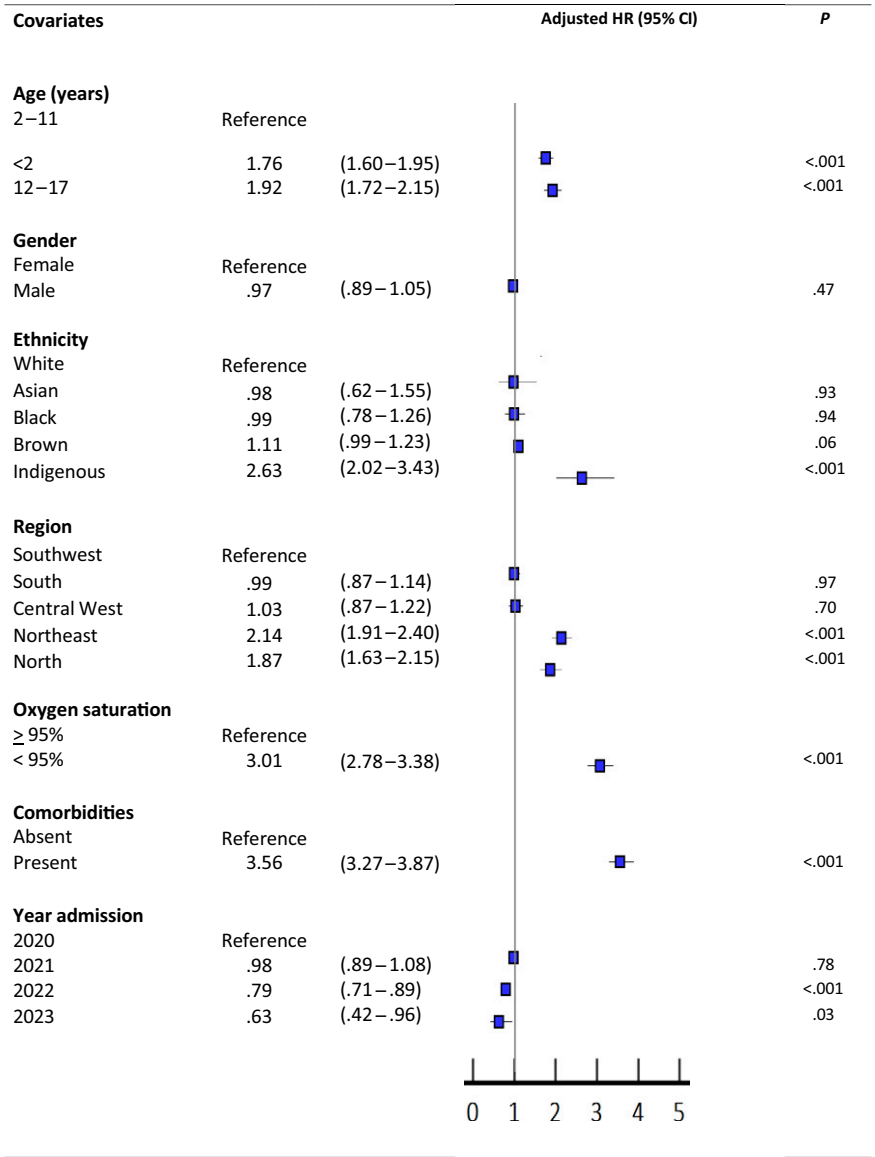

FIGURE 5
Continued

some patients with severe clinical conditions or immunosuppressive diseases may have been investigated in more detail for the presence of adenovirus, and this characteristic may have influenced survival analysis. Third, information on vaccination status was not included in the analysis because of the heterogeneity of vaccination campaigns among different age groups. This decision was made because many pediatric cases were not vaccinated, because vaccine schedules were not available for children and adolescents in 2020 and most of 2021. Finally, we must consider that, despite the size of the cohort included in the analysis, the study setting may limit the generalizability to other populations. Consistent with our previous analyses of successive COVID-19 pandemic waves in Brazil,[30,33,45] the mortality rate (6.1%) from SARS-CoV-2 infection in children was much higher than that in developed countries, which reported an overall mortality rate of <1% in hospitalized patients.[46] We found that these findings are mainly related to the lack of access to health care in regions of the country with poor socioeconomic conditions, especially in vulnerable ethnic groups such as indigenous individuals. In this sense, we believe that these peculiar aspects of a middle-income country like Brazil may hinder the generalization of our findings to a certain extent. Therefore, further comparative studies on the outcomes of

SARS-CoV-2 and seasonal viruses in diverse scenarios are required.

CONCLUSIONS

In this analysis based on a national multicenter registry that obtained information on various clinical aspects of children and adolescents hospitalized with SARI of laboratory-confirmed viral etiology, we found that SARS-CoV-2 infection had the highest mortality rate among virus strains. Our analysis showed heterogeneous viral circulation among different age groups during the 3 years of the pandemic in Brazil. Risk factors for death varied between different strains of the virus. However, an increased risk of death was uniformly associated with comorbidities, hospitalization in the poorest regions of Brazil, and low oxygen saturation at admission. Presumably, SARS-CoV-2 will eventually become an endemic seasonal pathogen, but little is known about how SARS-CoV-2 will behave in this new environment in terms of equilibrium dynamics with seasonal viruses. In this context, our findings highlight the importance of monitoring and understanding viral epidemiology in the post–COVID-19 era to establish timely preventive measures to lessen the severity of upcoming seasonal outbreaks of respiratory viruses.

ACKNOWLEDGMENTS

We thank all frontline health care workers for their impressive efforts to tackle the COVID-19 pandemic in Brazil. All data from the SIVEP-Gripe were systematically collected by these frontline health care workers.

ABBREVIATIONS

CI: confidence interval
CIF: cumulative incidence function
COVID-19: coronavirus disease 2019
HR: hazard ratio
RSV: respiratory syncytial virus
SARI: severe acute respiratory infection
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Address correspondence to Eduardo A. Oliveira, MD, PhD, Department of Pediatrics, Health Sciences Postgraduate Program, School of Medicine, Federal University of Minas Gerais, R. Engenheiro Amaro Lanari 389/501, Belo Horizonte, 30310, Minas Gerais, Brazil. E-mail: eduolive812@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FUNDING: Supported by the National Council for Scientific and Technological Development (CNPq) and Research Support Foundation of Minas Gerais (FAPEMIG). The funders had no role in the design or conduct of this study.

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated they have no conflicts of interest relevant to this article to disclose.

REFERENCES

1. Wald ER, Schmit KM, Gusland DY. A pediatric infectious disease perspective on COVID-19. *Clin Infect Dis*. 2021;72(9):1660–1666
2. Wells J, Young JJ, Harvey C, et al. Real-time surveillance of severe acute respiratory infections in Scottish hospitals: an electronic register-based approach, 2017–2022. *Public Health*. 2022;213:5–11
3. Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med*. 2021;9(3):251–259
4. Portmann L, de Kraker MEA, Fröhlich G, et al. CH-SUR study group. Hospital outcomes of community-acquired SARS-CoV-2 omicron variant infection compared with influenza infection in Switzerland. *JAMA Netw Open*. 2023;6(2):e2255599
5. Chiotos K, Fitzgerald JC. COVID-19 in children-learning from the past, planning for the future. [Published online ahead of print July 31, 2023] *JAMA Pediatr*. 2023. 10.1001/jamapediatrics.2023.2354
6. Bastos LS, Niquini RP, Lana RM, et al. COVID-19 and hospitalizations for SARI in Brazil: a comparison up to the 12th epidemiological week of 2020. *Cad Saude Publica*. 2020;36(4):e00070120
7. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multistate models. *Stat Med*. 2007;26(11):2389–2430
8. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509
9. Abo YN, Clifford V, Lee LY, et al. COVID-19 public health measures and respiratory viruses in children in Melbourne. *J Paediatr Child Health*. 2021;57(12):1886–1892
10. Ciofi Degli Atti M, Rizzo C, D'Amore C, et al. Acute respiratory infection emergency access in a tertiary care children hospital in Italy, prior and after the SARS-CoV-2 emergence. *Influenza Other Respir Viruses*. 2023;17(3):e13102
11. Sachs N, Goldberg L, Levinsky Y, et al. The effect of the COVID-19 pandemic on pediatric respiratory hospitalizations. *Isr Med Assoc J*. 2023;25(3):171–176
12. Maglione M, Pascarella A, Botti C, et al. Changing epidemiology of acute viral respiratory infections in hospitalized children: the post-lockdown effect. *Children (Basel)*. 2022;9(8):1242

13. Yeoh DK, Foley DA, Minney-Smith CA, et al. Impact of coronavirus disease 2019 public health measures on detections of influenza and respiratory syncytial virus in children during the 2020 Australian winter. *Clin Infect Dis*. 2021;72(12):2199–2202

14. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. *Pediatrics*. 2021;148(3):e2021052089

15. Foley DA, Yeoh DK, Minney-Smith CA, et al. The interseasonal resurgence of respiratory syncytial virus in Australian children following the reduction of coronavirus disease 2019-related public health measures. *Clin Infect Dis*. 2021;73(9):e2829–e2830

16. Rao S, Armistead I, Messacar K, et al. Shifting epidemiology and severity of respiratory syncytial virus in children during the COVID-19 pandemic. *JAMA Pediatr*. 2023;177(7):730–732

17. Rao S, Armistead I, Tyler A, Lensing M, Dominguez SR, Alden NB. Respiratory syncytial virus, influenza, and coronavirus disease 2019 hospitalizations in children in Colorado during the 2021–2022 respiratory virus season. *J Pediatr*. 2023;260:113491

18. Cohen C, Zar HJ. Deaths from RSV in young infants-the hidden community burden. *Lancet Glob Health*. 2022;10(2):e169–e170

19. Shi T, McAllister DA, O'Brien KL, et al. RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet*. 2017;390(10098):946–958

20. Wildenbeest JG, Billard MN, Zuurbier RP, et al. RESCEU Investigators. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. *Lancet Respir Med*. 2023;11(4):341–353

21. Li Y, Johnson EK, Shi T, et al. National burden estimates of hospitalizations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study. *Lancet Respir Med*. 2021;9(2):175–185

22. Klein NP, Demarco M, Fleming-Dutra KE, et al. Effectiveness of BNT162b2 COVID-19 vaccination in children and adolescents. *Pediatrics*. 2023;151(5):e2022060894

23. Oliveira EA, Oliveira MCL, Colosimo EA, et al. Vaccine effectiveness against SARS-CoV-2 variants in adolescents from 15 to 90 days after second dose: a population-based test-negative case-control study. *J Pediatr*. 2023;253:189–196.e2

24. Oliveira EA, Oliveira MCL, Silva ACSE, et al. Effectiveness of BNT162b2 and CoronaVac vaccines against omicron in children aged 5 to 11 years. *World J Pediatr*. 2023;19(10):949–960

25. Oliveira EA, Oliveira MCL, Simões E Silva AC, et al. Association of prior COVID-19 vaccination With SARS-CoV-2 infection and death in children and young persons during the omicron variant period in Brazil. *JAMA Pediatr*. 2023;177(10):1100–1102

26. Flaxman S, Whittaker C, Semenova E, et al. Assessment of COVID-19 as the underlying cause of death among children and young people aged 0 to 19 years in the United States. *JAMA Netw Open*. 2023;6(1):e2253590

27. Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. *Int J Infect Dis*. 2021;103:316–322

28. Agathis NT, Patel K, Milucky J, et al. CDC COVID-NET Surveillance Team. Codetections of other respiratory viruses among children hospitalized with COVID-19. *Pediatrics*. 2023;151(2):e2022059037

29. Götzinger F, Santiago-García B, Noguera-Julián A, et al. ptbnet COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicenter cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653–661

30. Oliveira EA, Colosimo EA, Simões E Silva AC, et al. Clinical characteristics and risk factors for death among hospitalized children and adolescents with COVID-19 in Brazil: an analysis of a nationwide database. *Lancet Child Adolesc Health*. 2021;5(8):559–568

31. Campbell JI, Dubois MM, Savage TJ, et al. Pediatric COVID-19 US Registry. Comorbidities associated with hospitalization and progression among adolescents with symptomatic coronavirus disease 2019. *J Pediatr*. 2022;245:102–110.e2

32. Graff K, Smith C, Silveira L, et al. Risk factors for severe COVID-19 in children. *Pediatr Infect Dis J*. 2021;40(4):e137–e145

33. Oliveira EA, Simões E Silva AC, Oliveira MCL, et al. Comparison of the first and second waves of the coronavirus disease 2019 pandemic in children and adolescents in a middle-income country: clinical impact associated with severe acute respiratory syndrome coronavirus 2 gamma lineage. *J Pediatr*. 2022;244:178–185.e3

34. Tsankov BK, Allaire JM, Irvine MA, et al. Severe COVID-19 infection and pediatric comorbidities: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;103:246–256

35. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open*. 2021;4(6):e2111182

36. Oliveira EA, Mak RH, Colosimo EA, et al. Risk factors for COVID-19–related mortality in hospitalized children and adolescents with diabetes mellitus: An observational retrospective cohort study. *Pediatr Diabetes*. 2022;23(6):763–772

37. Ward JL, Harwood R, Kenny S, et al. Pediatric hospitalizations and ICU admissions due to covid-19 and pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 in England. *JAMA Pediatr*. 2023;177(9):947–955

38. Woodruff RC, Campbell AP, Taylor CA, et al. Risk factors for severe COVID-19 in children. *Pediatrics*. 2022;149(1):e2021053418

39. Norman DA, Cheng AC, Macartney KK, et al. Influenza hospitalizations in Australian children 2010–2019: the impact of medical comorbidities on outcomes, vaccine coverage, and effectiveness. *Influenza Other Respir Viruses*. 2022;16(2):316–327

40. Lazzerini M, Sonego M, Pellegrin MC. Hypoxemia as a mortality risk factor in acute lower respiratory infections in children in low and middle-income countries: systematic review and meta-analysis. *PLoS One*. 2015;10(9):e0136166

41. Mathur R, Rentsch CT, Morton CE, et al. OpenSAFELY Collaborative. Ethnic differences in SARS-CoV-2 infection and COVID-19–related hospitalization, ICU admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. *Lancet*. 2021;397(10286):1711–1724

42. Saatci D, Ranger TA, Garriga C, et al. Association between race and COVID-19 outcomes among 2.6 million children in England. *JAMA Pediatr*. 2021;175(9):928–938

43. Castro MC, Massuda A, Almeida G, et al. Brazil's unified health system: the first 30 years and prospects for the future. *Lancet*. 2019;394(10195):345–356

44. Rocha R, Atun R, Massuda A, et al. Effect of socioeconomic inequalities and vulnerabilities on health-system preparedness and response to COVID-19 in Brazil: a comprehensive analysis. *Lancet Glob Health*. 2021;9(6):e782–e792

45. Oliveira EA, Oliveira MCL, Simoes e Silva AC, et al. Clinical outcomes of omicron variant (B.1.1.529) infection in children and adolescents hospitalized with COVID-19 in Brazil with observational data on the efficacy of the vaccines in adolescents. *Pediatr Infect Dis J*. 2023;42(3):218–225

46. Swann OV, Holden KA, Turtle L, et al. ISARIC4C Investigators. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective, multicenter, observational cohort study. *BMJ*. 2020;370:m3249