Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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

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Objective To evaluate the severity and clinical outcomes of the SARS-CoV-2 gamma variant in children and adolescents hospitalized with COVID-19 in Brazil.

Study design In this observational retrospective cohort study, we performed an analysis of all 21 591 hospitalized patients aged <20 years with confirmed SARS-CoV-2 infection registered in a national database in Brazil. The cohort was divided into 2 groups according to the predominance of SARS-CoV-2 lineages (WAVE1, n = 11 574; WAVE2, n = 10 017). The characteristics of interest were age, sex, geographic region, ethnicity, clinical presentation, and comorbidities. The primary outcome was time to death, which was evaluated by competing-risks analysis, using cumulative incidence functions. A predictive Fine and Gray competing-risks model was developed based on the WAVE1 cohort with temporal validation in the WAVE2 cohort.

Results Compared with children and adolescents admitted during the first wave, those admitted during the second wave had significantly more hypoxemia (52.5% vs 41.1%; $P < .0001$) and intensive care unit admissions (28.3% vs 24.9%; $P < .0001$) and needed more noninvasive ventilatory support (37.3% vs 31.6%; $P < .0001$). In-hospital deaths and death rates were 896 (7.7%) in the first wave and 765 (7.6%) in the second wave ($P = .07$). The prediction model of death included age, ethnicity, region, respiratory symptoms, and comorbidities. In the validation set (WAVE2), the C statistic was 0.750 (95% CI, 0.741-0.758; $P < .0001$).

Conclusions This large national study found a more severe spectrum of risk for pediatric patients with COVID-19 caused by the gamma variant. However, there was no difference regarding the probability of death between the waves. *(J Pediatr 2022;244:178-85)*.

As of September 2021, more than 22 million cases of COVID-19 and more than 600 000 COVID-related deaths have been reported in Brazil. A new lineage of the SARS-CoV-2 virus (initially named P.1) was identified from genomic sequencing of samples from patients with COVID-19 in Manaus, Brazil in January 2021.[1] Concomitantly, Brazil experienced a severe second wave of causes related to a failure to mitigate the spread of this variant of concern.[2] The P.1, or gamma, lineage is characterized by the combination of K417T, E484K, and N501Y substitutions in spike protein[3] and this variant is an estimated 1.4-2.2 times more transmissible than the precursors.[4] The average daily prevalence of the gamma variant became predominant in Brazil in mid-February 2021 (https://outbreak.info/location-reports?loc=BRA).

Children usually present with an asymptomatic or mild course, with a much lower risk of severe COVID-19 than any other age group.[5,6] Nevertheless, a relatively low proportion of children might be at risk for severe disease and death.[7,8] We previously characterized the first 11 613 pediatric hospital admissions for COVID-19 in Brazil.[9] In the present study, we focused our analysis on children and adolescents (aged <20 years) admitted in the second wave, concomitantly with the expansion and dominance of the gamma variant, with the aim of comparing the clinical outcomes between distinct periods. In addition, we

AUC	Area under the receiver operating characteristic curve
CIF	Cumulative incidence function
ICU	Intensive care unit
SIVEP-Gripe	Influenza Epidemiological Surveillance Information System

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developed a clinical prediction model of COVID-19–related death in the pediatric population.

Methods

We performed a retrospective cohort study including all hospitalized pediatric cases recorded in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe).[10] Detailed information regarding this database, including the reporting form and data dictionary, codes, and all deidentified data, are publicly available at https://opendatasus.saude.gov.br/dataset/bd-srag-2020. Additional information regarding SIVEP-Gripe and the steps of the data retrieval are provided in **Appendix 1**.

We included all consecutively registered patients aged <20 years with a positive quantitative real-time polymerase chain reaction test result for SARS-CoV-2 who had been admitted to the hospital. Detailed information on included and excluded cases are displayed in flowcharts (**Figure 1**; available at www.jpeds.com). For the purpose of analysis, we integrated both datasets into a unique database and stratified the cases into 2 groups, WAVE1 (44 epidemiologic weeks from February 16, 2020, to December 31, 2020) and WAVE2 (19 epidemiologic weeks from January 1, 2021, to May 29, 2021). In addition, on May 29, 2021, we updated, the outcomes of interest for pediatric patients admitted at WAVE1.

Covariates and Definitions

The clinical, demographic, and epidemiologic data recorded in SIVEP-Gripe are presented elsewhere.[9] The clinical course of the disease was reported in terms of respiratory support (none, noninvasive oxygen support, or invasive ventilation), admission to an intensive care unit (ICU), discharge, death, and ongoing clinical situation. Detailed information regarding variables used in the study is provided in **Appendix 2** (available at www.jpeds.com).

Outcomes

The primary outcome was time until death (in-hospital mortality). Survival time was defined from the day of admission until the event (death or discharge).

Statistical Analyses

The sample comprised all pediatric patients (aged <20 years) with COVID-19 registered in the SIVEP-Gripe between epidemiologic weeks 8, 2020 to 19, 2021, divided into 2 groups (WAVE1 and WAVE2). Continuous variables are presented as median (IQR) or mean (SD), and categorical variables are recorded as frequency and proportion. Comparisons of medians and proportions were performed using the χ^2 test and Mann–Whitney *U* test, respectively. Mortality was evaluated by competing-risks analysis, using the cumulative incidence function (CIF).[11] Discharge was analyzed as a competing event in the competing-risks analysis. Complete data were not available for all variables, especially ethnicity, symptoms at presentation, and comorbidities. We carried out multiple imputation using all predictors plus the CIF for the primary outcome. This involved creating multiple copies of the data and imputing the missing values for each dataset with sensible values randomly selected from their predicted distribution. Ten imputed values were generated using the R MICE package (R Foundation for Statistical Computing. Available on https://cran.r-project.org/web/packages/mice/index.html). We combined the results from analyses of each of the imputed values using Rubin's rules to produce estimates and CIs that incorporate the uncertainty of imputed values.[12,13] For those cases with missing data on a given symptom or comorbidity, we assumed the clinical condition to be absent. Detailed information on the management of missing data is provided in **Appendix 2**.

Development of the Risk Prediction Model

We developed a clinical prediction model and a points-based risk scoring system following the guidelines provided by Austin et al for models in the presence of competing risks.[14] The development cohort was derived from the cases admitted in WAVE1. Detailed information on the development of the model is provided in **Appendix 3** (available at www.jpeds.com).

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 STROBE guidelines for observational cohort studies.[15]

Results

Epidemic Curve and Primary Outcome

A total of 21 591 patients aged <20 years with laboratory-confirmed SARS-CoV-2 infection were hospitalized during the pandemic period analyzed. The incident cases and deaths over time are shown in **Figure 2** (available at www.jpeds.com). In WAVE1, 11 574 patients (53.6%) were hospitalized, with an average of 263 cases per week, whereas in WAVE2, 10 017 patients (46.4%) were admitted, with an average of 527 cases per week. In-hospital deaths and death rates were 896 (7.7%) in the first wave and 765 (7.6%) in the second wave.

Clinical and Demographic Characteristics

The clinical and demographic characteristics of the cohort stratified according to the waves are shown in **Table I**. Compared with the first wave, hospitalized children in the second wave were younger, with a larger proportion of infants aged <2 years. There also were higher proportions of pediatric patients from the richest regions (South and Southeast) and of white ethnicity. Considering clinical presentation, patients hospitalized in the second wave had more respiratory symptoms, including cough, respiratory distress, and dyspnea. Overall, regarding preexistent conditions, children from the second wave were less affected by chronic conditions.

In relation to clinical outcomes, children admitted in the second wave had a significantly larger proportion of

Table I. Demographic and clinical characteristics of children with positive RT-qPCR COVID-19 stratified according to the period of admission

Covariates*	Overall (N = 21 591; 100%)	WAVE1, 2020 (N = 11 574; 100%)	WAVE2, 2021 (N = 10 017; 100%)	*P* value
Cases per wk, mean	304.0	263.0	556.5	<.0001
Age, y				
Median (IQR)	4.7 (8 mo-14.6 y)	5.2 (1.0-14.4)	4.0 (7 mo-14.7 y)	<.0001
Mean (SD)	7.4 (7.0)	7.5 (6.9)	7.3 (7.2)	
Age group (y), n (%)				
0-1.9	8012 (37.1)	4035 (34.9)	3977 (39.7)	<.0001
2-11.9	6854 (31.7)	3959 (34.2)	2895 (28.9)	
12-19.9	6725 (31.1)	3580 (30.9)	3145 (31.4)	
Sex, n (%) (N = 21 573)				
Male	10 411 (48.3)	5552 (48.0)	4859 (48.5)	<.0001
Female	11 162 (51.7)	6009 (52.0)	5153 (51.5)	
Region, n (%)				
Southeast	8075 (37.4)	4053 (35.0)	4022 (40.2)	<.0001
South	2204 (10.2)	959 (8.3)	1245 (12.4)	
Central-West	2293 (10.6)	1353 (11.7)	940 (9.4)	
Northeast	5748 (26.6)	3378 (29.2)	2370 (23.7)	
North	3271 (15.1)	1831 (15.8)	1440 (14.4)	
Ethinicity, n (%) (N = 17 360)				
White	6299 (36.3)	3177 (34.7)	3122 (38.0)	<.0001
Black/brown	10 706 (61.7)	5765 (63.0)	4941 (60.2)	
Asian	137 (0.8)	79 (0.9)	58 (0.7)	
Indigenous	218 (1.3)	127 (1.4)	91 (1.1)	
Signs/symptoms at presentation, n (%)				
Fever	14 140 (65.5)	7684 (66.40)	6456 (64.5)	.003
Cough	12 971 (60.1)	6752 (58.3)	6219 (62.1)	<.0001
Respiratory distress	9733 (45.1)	5081 (43.9)	4652 (46.4)	<.0001
O_2 saturation <95% (N = 16 264)	7523 (46.3)	3679 (41.1)	3844 (52.5)	<.0001
Dyspnea	10 470 (48.5)	5493 (47.5)	4977 (49.7)	.001
Odynophagia	3590 (16.6)	2066 (17.9)	1524 (15.2)	<.0001
Anosmia	748 (3.5)	339 (2.9)	409 (4.1)	<.0001
Ageusia	719 (3.3)	318 (2.7)	401 (4.0)	<.0001
Diarrhea	3187 (14.8)	1794 (15.5)	1393 (3.9)	.001
Vomiting	3629 (16.8)	1993 (17.2)	1636 (16.3)	.083
Abdominal pain	1454 (6.7)	668 (5.8)	786 (7.8)	<.0001
Number of comorbidities, n (%)				
None	16 445 (76.2)	8322 (71.9)	8123 (81.1)	<.0001
1	4309 (20.0)	2773 (24.0)	1536 (15.3)	
2	693 (3.2)	401 (3.5)	292 (2.9)	
>3	144 (0.7)	78 (0.7)	66 9 (0.7)	
Main comorbidities, n (%)				
Asthma	1415 (6.6)	865 (7.5)	550 (5.5)	<.0001
Pulmonary	415 (1.9)	247 (2.1)	168 (1.7)	.015
Neurologic	1257 (5.8)	705 (6.1)	552 (5.5)	.07
Malignancy	639 (3.0)	582 (5.0)	57 (0.6%)	<.0001
Cardiopathy	698 (3.2)	380 (3.3)	318 (3.2)	.671
Hematologic	501 (2.3)	269 (2.3)	232 (2.3)	1.00
Renal	284 (1.3)	174 (1.5)	110 (1.1)	.010
Diabetes	379 (1.8)	208 (1.8)	171 (1.7)	.640
Obesity	477 (2.2)	161 (1.4)	316 (3.2)	<.0001
Syndrome/chromosomal abnormality	442 (2.0)	222 (1.9)	220 (2.2)	.162
ICU admission, n (%) (N = 19 867)				
Yes	5243 (26.4)	2745 (24.9)	2498 (28.3)	<.0001
No	14 624 (73.6)	8292 (75.1)	6332 (71.7)	
Ventilatory support, n (%) (N = 20 392)				
Invasive	2130 (10.4)	1156 (10.8)	974 (10.1)	<.0001
Noninvasive	6990 (34.3)	3387 (31.6)	3603 (37.3)	
None	11 272 (55.3)	6190 (57.7)	5082 (52.6)	
Invasive ventilatory without ICU, n (%)				
No	21 185 (98.1)	11 361 (98.2)	9824 (98.1)	.65
Yes	406 (1.9)	213 (1.8)	193 (1.9)	
Outcomes, n (%)				
Discharge	17 867 (82.8)	10 015 (86.5)	7852 (78.4)	<.0001
Death	1661 (7.7)	896 (7.7)	765 (7.6)	
In-hospital	1888 (8.7)	517 (4.5)	1371 (13.7)	
Missing	175 (0.8)	146 (1.3)	29 (0.3)	
Death, n (%) (N = 21 416)				
No	19 775 (92.2)	10 532 (92.2)	9223 (92.3)	.627
Yes	1661 (7.8)	896 (7.8)	765 (7.7)	

*Data (n) in the first column represent the available data for those variables with missing values (sex, ethnicity, oxygen saturation, need for ICU, and ventilatory support).

hypoxemia (52.5% vs 41.1%), had more ICU admissions (28.3% vs 24.9%), and used more noninvasive ventilatory support (37.6% vs 31.6%). Of note, overall, 406 children who needed invasive ventilatory support were not admitted to an ICU (with similar rates in the 2 waves). Of these, 155 (38.2%) died, for a death rate approximately 5 times greater than that of the entire cohort.

The overall estimated CIFs for death and discharge for both waves are shown in **Figure 3** (available at www.jpeds.com). Competing-risk survival analysis found no significant difference in the risk of fatal outcome between the periods; however, at the time of this analysis, 517 children (4.5%) admitted during WAVE1 and 1371 (13.7%) admitted during WAVE2 were still hospitalized with an ongoing clinical condition. Moreover, among these still-hospitalized patients, 13% in WAVE1 and 21.9% in WAVE2 were receiving invasive ventilatory support at the time of analysis.

The estimated probability of a fatal outcome for children admitted in WAVE1 was 4.8% during the first 10 days of hospitalization, 6.7% during the first 20 days, and 8.1% at the end of follow-up. The respective probabilities for children admitted in WAVE2 were 4.4%, 7%, and 9.7% ($P = .07$). For hospital discharge, the respective probabilities were 54%, 78%, and 92% in WAVE1 and 54.5%, 79.5%, and 90% in WAVE2 ($P = .107$).

Development of the Model

The univariate competing-risk survival analysis for risk of death based on the clinical and demographic characteristics of our cohort is shown in **Table II** (available at www.jpeds.com). Using the Fine and Gray model to model mortality, the following variables were significantly associated with fatal outcome: age (infants and adolescents), regions (North and Northeast), ethnicity (black/brown and indigenous), and respiratory symptoms (respiratory distress, dyspnea, and oxygen saturation <95%). The presence of any comorbidity, number of comorbidities, and all the main preexisting medical conditions analyzed, except for asthma, increased the risk of death in univariable analysis.

After adjustment by the competing-risk multivariate survival analysis, based on the multiple imputation results, all covariates were retained as significant predictors of COVID-19–related death as shown in **Table III**. A risk weighting for each covariate was then derived from the estimated regression coefficients, which were multiplied by 10 and rounded to the nearest integer (**Table III**). A total risk score was calculated as the sum of these weightings for the variables. A risk score was calculated for each patient by adding up the obtained points. The risk score ranged from -1 for patients from the Central-West region without any risk factors to 57 points, with a median of 16 (IQR, 10-22), among children admitted in the WAVE1. Then the prognostic risk score was divided into 3 categories: low risk (<10 points), intermediate risk (between 10 and 29 points), and high risk (≥30 points).

Table III. Multivariate competing-risk survival analysis in children with positive RT-qPCR COVID-19 (WAVE, n = 11 428*)

Variables	Coefficient	HR (95% CI)	*P* value	Score
Age group (y)				
0-1.9	0.8705	2.388 (1.995-2.091)	<.001	9
2-11.9	-	1.0	-	0
12-19.9	0.8380	2.312 (1.934-2.764)	<.001	8
Region				
Southeast	-	1.0	-	0
South	0.0550	1.061 (0.806-1.397)	.672	1
Central-West	−0.1338	0.865 (0.637-1.174)	.351	−1
Northeast	0.7411	2.090 (1.743-2.507)	<.001	7
North	0.4594	1.560 (1.274-1.950)	<.001	5
Race				
White	-	1.0	-	0
Black/brown	0.0407	1.042 (0.863-1.257)	.671	1
Asian	0.5064	1.659 (0.825-3.337)	.155	4
Indigenous	1.0380	2.824 (1.825-4.368)	<.001	10
Respiratory symptoms				
No	-	1.0	-	0
1	0.3484	1.417 (1.094-1.834)	.008	3
2	0.5588	1.749 (1.407-2.173)	<.001	6
3	1.1079	3.028 (2.491-3.680)	<.001	11
Invasive ventilation without ICU				
No	-	1.0	-	0
Yes	1.726	5.622 (4.457-7.090)	<.001	17
Comorbidities				
None	-	1.0		0
1	0.8666	2.379 (2.048-2.764)	<.001	9
2	1.3551	3.878 (3.030-4.961)	<.001	14
≥3	1.4872	4.424 (2.819-6.944)	<.001	15

*Deaths, 896; censored, 517; 146 missing cases regarding primary outcome.

Prediction Model Performance in the Development Cohort

The C statistics of the risk score applied to the WAVE1 was 0.762 (95% CI, 0.746-0.779) (**Figure 4**, A). Of 11 428 patients in the WAVE1 group, 2646 (23.2%) were classified as low risk, 8022 (70.2%) were classified as intermediate risk, and 760 (6.7%) were classified as high risk for death. The death rates were 1.9% for the low-risk group, 7.5% for the intermediate-risk group, and 32.2% for the high-risk group ($P < .0001$). **Figure 5**, A shows the cumulative incidence of death curves for children in WAVE1 according to the risk score. The estimated probability of fatal outcome according to risk group for children admitted in WAVE1 was 1.7% for low risk, 6.2% for intermediate risk, and 28.2% for high risk (**Figure 5**, A).

Prediction Model Performance in the Validation Cohort

In the validation set (WAVE2), the performance as measured by the C statistic of the risk score was 0.750 (95% CI, 0.738-0.768) (**Figure 4**, B). Among patients in the WAVE2 group (9988 with data on primary outcome), 2227 (22.3%) were classified as low risk, 7220 (72.3%) as intermediate risk, and 541 (5.4%) as high risk group for death. The death rate in the 3 groups was 1.8%, 7.8%, and 30.1%, respectively ($P < .0001$). **Figure 5**, B shows the cumulative incidence of death curves for children in WAVE2 according to risk

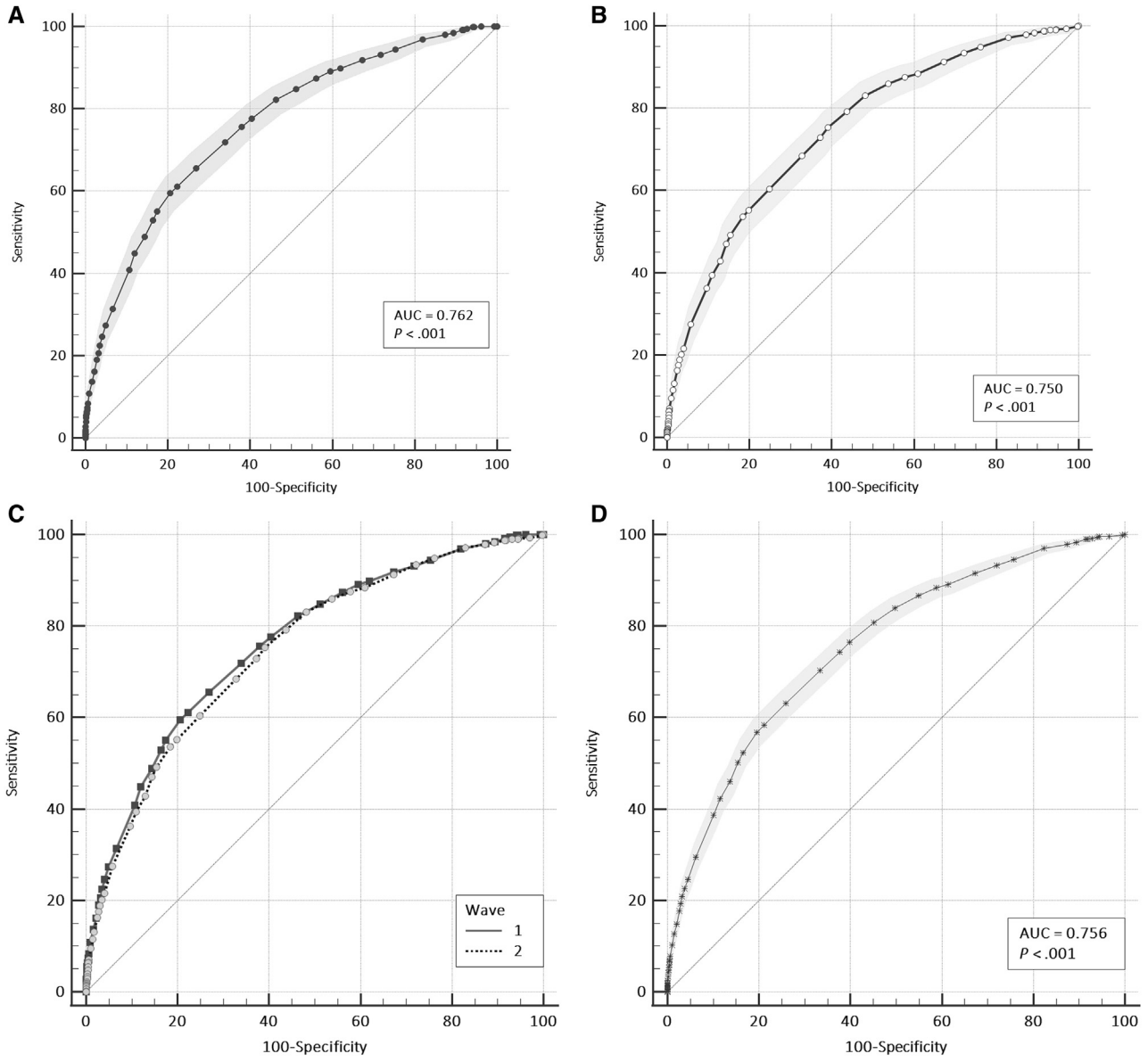

Figure 4. Receiver-operating characteristic curves estimated for evaluating the capacity of discrimination of the risk score to predict death. The shaded areas represent 95% CIs. **A,** Development cohort (n=11,428 patients, 896 events, c=0.762). **B,** Validation cohort (n= 9988 patients, 765 events, c=0.750). **C,** Comparison WAVE1 vs. WAVE2 (P = .32); **D**, Whole cohort (n = 21,416, events = 1661, c=0.756).

score. The estimated probability of fatal outcome during the first 20 days of hospitalization according to risk group for children admitted in WAVE2 was 1.7% in the low-risk group, 7.0% in the intermediate-risk group, and 27.5% in the high-risk group.

The performance of the prediction model was evaluated by the components of discrimination and calibration. There was no significant difference in the discrimination performance of the risk score between the original and validation sets as measured by the area under the receiver operating characteristic curve (AUC) (P = .31) (Figure 4, C). Model calibration was also assessed by competing-risk survival. Figure 5, C shows calibration CIF plots for the model of the risk score according to the risk groups. There was no difference between the predicted (WAVE1) and observed (WAVE2) curves in the low-, intermediate-, and high-risk groups, as evaluated by the Pepe and Mori test comparing the cumulative incidence of 2 groups of waves (low-risk group, χ^2 = 1.23, P = .24; intermediate-risk group, χ^2 = 0.104, P = .75; high-risk group, χ^2 = 1.49, P = .22).

Final Model Performance for the Whole Cohort

The AUC for the whole cohort (n = 21 445; deaths, n = 1661) was 0.756 (95% CI, 0.744-0.768; P < .0001) (Figure 4, D). The estimated probability of fatal outcome for the low-risk group was 1.3% during the first 10 days from hospitalization, 1.7% during the first 20 days, and 1.9% at the end of follow-up. The respective probabilities were

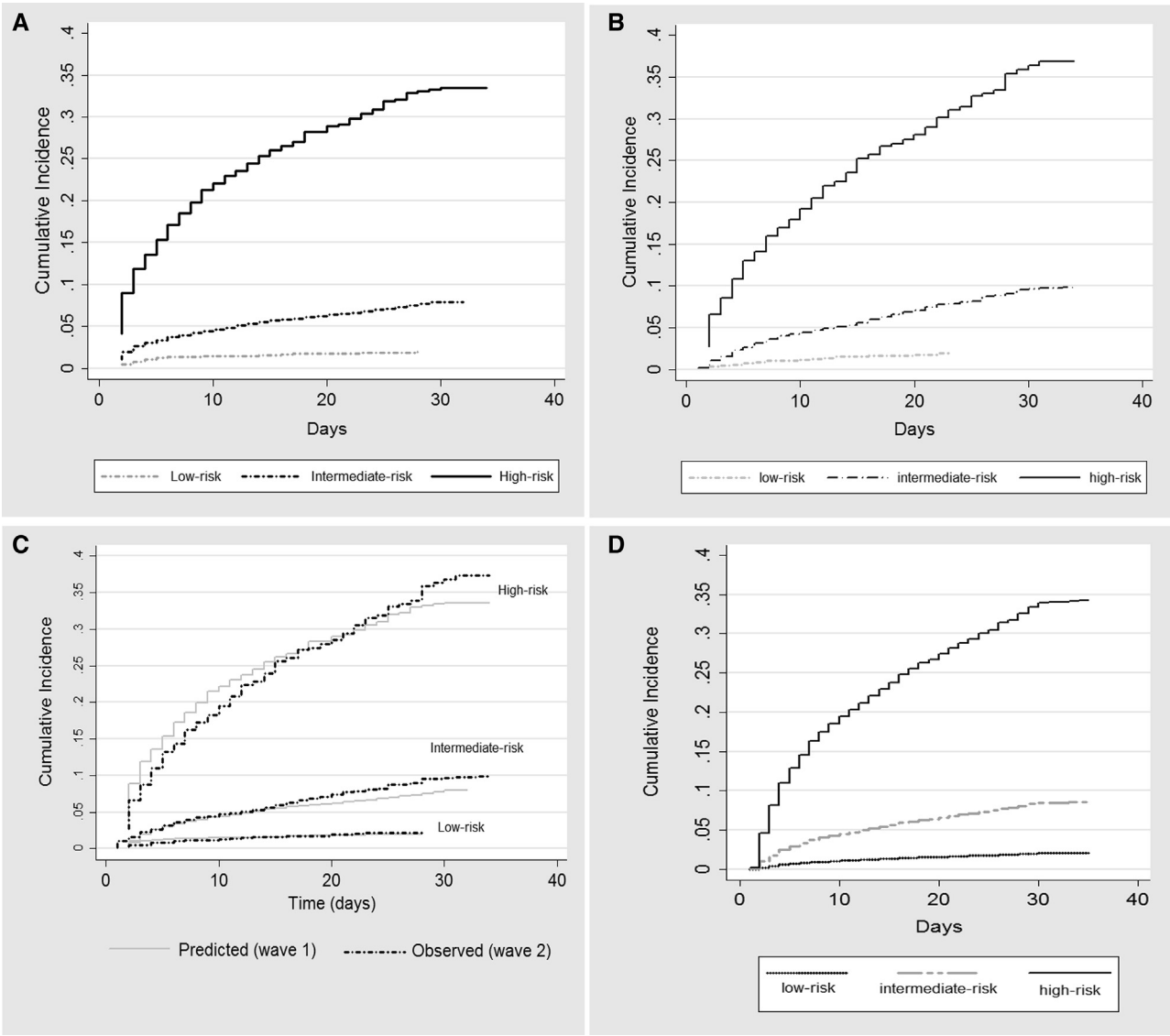

Figure 5. Cumulative incidence functions for mortality of children and adolescents with COVID-19 according to the risk score in the **A**, Development cohort (WAVE1); **B,** Validation set (WAVE2); **C,** Comparison WAVE1 vs. Wave 2; **D,** Whole cohort, Fine-Gray regression model.

4.4%, 6.5%, and 8.7% for the intermediate-risk group and 19.9%, 27.8%, and 34.4% for the high-risk group. On competing-risk survival analysis regression, compared with the low-risk group, the estimated risk of death was 4-fold higher (HR, 4.3; 95% CI, 3.4-5.0; $P < .0001$) in the intermediate-risk group and 20-fold higher (HR, 20.0; 95% CI, 15.9-25.2; $P < .0001$) in the high-risk group (**Figure 5**, D).

Discussion

In this large observational cohort study, we compared the dynamics of 2 distinct periods of the COVID-19 pandemic in Brazilian pediatric patients using a nationwide database of hospitalized cases. Our findings confirm the greater lethality of SARS-CoV-2 infection in pediatric age in Brazil compared with developed countries, with a death rate of ~7.5% in both waves. This figure is approximately 60-fold greater than the death rate of 0.12% (8 of 6338) in children and adolescents hospitalized in England.[16] In a previous analysis, we showed that this disparity in mortality rate was related mainly to socioeconomic and health care inequalities in Brazil.[9] In addition, our analysis has shown that in the second wave, the average number of cases and deaths per week doubled compared with first wave of the pandemic. Consequently, in absolute terms, there was roughly a similar number of cases and deaths in the 2 waves, even though the second wave included much fewer epidemiologic weeks. In addition, children and adolescents admitted in the second wave had significantly more hypoxemia and ICU admissions and needed more noninvasive ventilatory support. Nevertheless,

our analysis found no significant difference in case fatality rate between the waves.

Our data suggest that the gamma variant is more transmissible than its precursors and increases the burden of more severe cases, but without affecting the case fatality rate in hospitalized pediatric patients with COVID-19. Nevertheless, the comparison of death rates between the waves should be interpreted with caution owing to a substantial number of ongoing clinical situations in patients admitted during the second wave. In this regard, Bastos et al compared the 2 waves in the adult population in Brazil using the same database.[17] Based on data of roughly 1 200 000 COVID-19 hospitalizations, the authors showed that the second wave was associated with an increased burden of severe cases in adults. Of note, unlike in our study, they found an increase in in-hospital mortality, from 33.1% to 40.6%. For adult populations, this scenario of worse outcomes, possibly related with other variants of concern, also was reported in the second waves in the United Kingdom[18] and Africa.[19]

Using the pediatric patients admitted in the first wave as a developing cohort and those admitted in the second wave as a validation cohort, we developed a risk prediction model of a fatal outcome with good accuracy and excellent calibration. The risk model showed a moderately high AUC value of 0.756 (95% CI, 0.751-0.762). It means that the model ability to discriminate between patients who survived or died during the follow-up was approximately 75%. Moreover, based on the risk score, children were classified into low-risk, intermediate-risk, and high-risk groups, with an excellent agreement between the observed risk and the predicted risk grouped into these 3 categories.

Tthe prediction model showed that interweaving clinical, epidemiologic, and social factors were significantly associated with a higher hazard of death in pediatric age group. Regarding epidemiologic factors, age showed a "U" shape, with the infants and adolescents at increased risk of death. Accordingly, in a meta-analysis of 57 studies, Harwood et al reported similar findings.[20] Thet found that odds of poor outcomes were 1.6- to 2-fold higher in infants, and that teenagers had 1.4- to 2.2-fold higher odds of severe COVID-19.

Among clinical factors, the negative effect of the presence of any chronic condition was confirmed, as previously demonstrated in adult and pediatric cohorts.[5,9,21] The presence and number of respiratory symptoms exhibited a step gradient effect regarding the hazard of death. Concerning social factors, cases from the poorest regions of the country, with reduced access to ICU, and of vulnerable ethnicity had a significantly higher risk for poor outcomes.

In this context, we believe that our model not only highlights COVID-19 as an infectious disease, but also reinforces the syndemic nature of the pandemic. Syndemics, a concept proposed by Singer et al, is characterized by biological and social interactions that promote and enhance the negative effects of disease.[22] In this regard, our findings revealed the intricate role of biological, epidemiologic, and social factors for the outcomes of COVID-19.[23] Several studies have shown that such characteristics as ethnicity, poverty, and health access inequalities were strongly associated with the outcomes of COVID-19.[21,24-27] Saatci et al, using a large database in England, identified factors associated with severe COVID-19 in children, including young age, preexisting comorbidities, higher deprivation levels, and racial minorities.[28]

This large-scale study was used to develop and validate a clinical prediction model in pediatric patients with COVID-19. The major strength of this study is the use of recent data from thousands of pediatric patients with COVID-19, elucidating the roles of new SARS-CoV-2 variants at the current stage of the pandemic. The model exhibited good performance and excellent accuracy in predicting the hazard of death in children with COVID-19 in a developing country. Prediction models to estimate the risk of a poor outcome from COVID-19 can provide helpful assistance for clinical and public policy decision making.[29] In a systematic review, Wynants et al reviewed 145 models, 23 of which were for predicting mortality in adults with COVID-19.[30] However, a critical appraisal of these models showed a high risk of bias. Calibration and external validation, deemed essential before application can be considered, was rarely done or reported. We believe that our analysis, based on a robust dataset, allowed us to report a model with calibration and temporal validation, which strengthens our findings. In addition, the competing- risk survival analysis used in the development of the model avoided another potential bias, that is, when an individual may experience other types of events that prevent the event of interest from occurring.[31]

Our study has several limitations. In addition to the absence of a representative genomic surveillance in Brazil, various shortcomings of epidemiologic databases should be considered.[9] For instance, there is no link between the cases included in the dataset to the hospital records, and thus we had no access to relevant clinical data, such as laboratory/imaging results or treatment of the patients. It might be speculated that the performance of the model could have been improved had we had access to these data during hospital admission. Furthermore, SIVEP-Gripe contains a considerable amount of missing data. In an attempt to overcome this limitation, we used multiple imputation for relevant predictors.

Our present findings confirm the worse outcomes of COVID-19 in developing countries compared with developed countries. In addition, the results indicate that the second wave of COVID-19 in Brazil, probably related to the gamma variant, resulted in increased morbidity in pediatric patients but with no difference in death rate between the 2 waves. This difference in outcomes and epidemiologic profile presented by the gamma variant may indicate that new variants can lead to changes in the clinical and epidemiologic profile of COVID-19. Monitoring these aspects will be essential to define global public health responses to new variants that may arise.

In this study, we also developed and validated a risk score derived from a prediction model that predicted with accuracy the hazard of death in hospitalized pediatric patients from a

developing country. Currently, as the vaccination programs for adults have been moving forward in a heterogeneous pace worldwide, data on children might become the focus for the next steps to control the SARS-CoV-2 infection. In this context, our model may provide insight into elaborate future strategies to mitigate and prevent the consequences of the COVID-19 in the pediatric population. ■

All data from the SIVEP-Gripe were systematically collected by frontline healthcare workers. We are extremely grateful to the frontline clinical staff of the Brazilian Public Health System who collected these data in challenging circumstances for their invaluable contributions in these difficult times.

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Data Statement

Data sharing statement available at www.jpeds.com.

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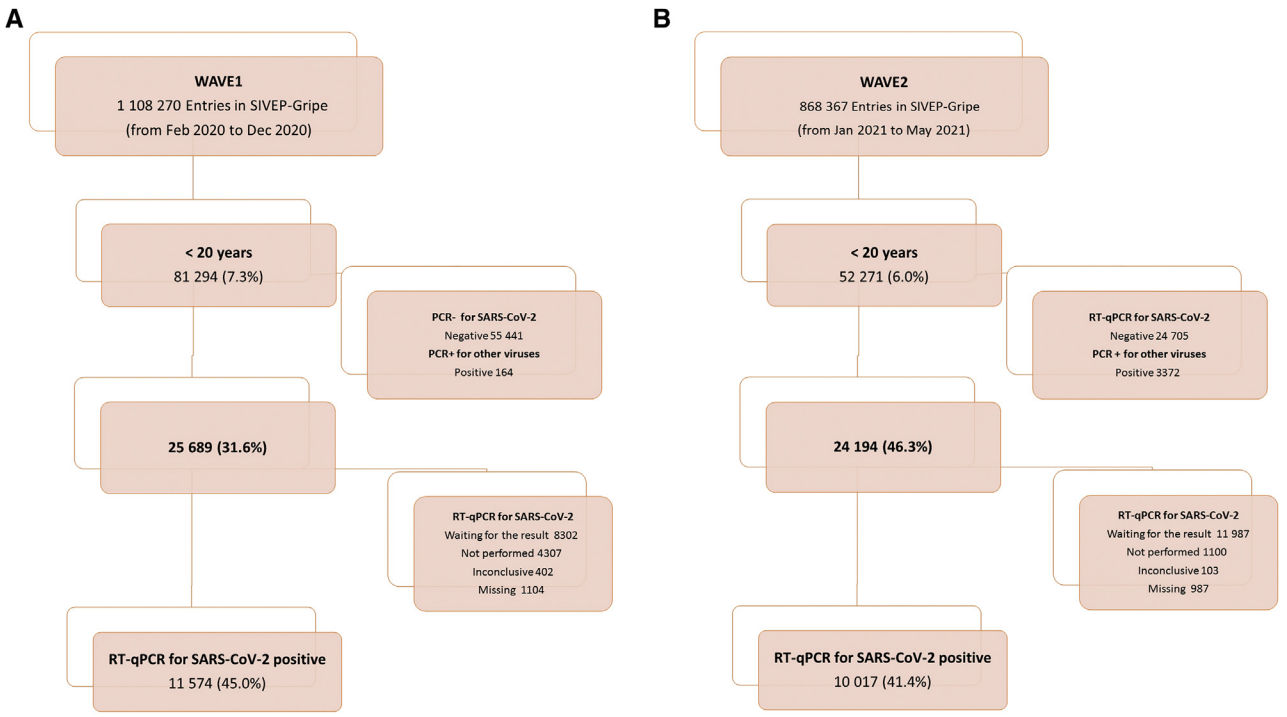

Figure 1. Flow diagram of the cohort selection: **A**, WAVE1; **B**, WAVE2.

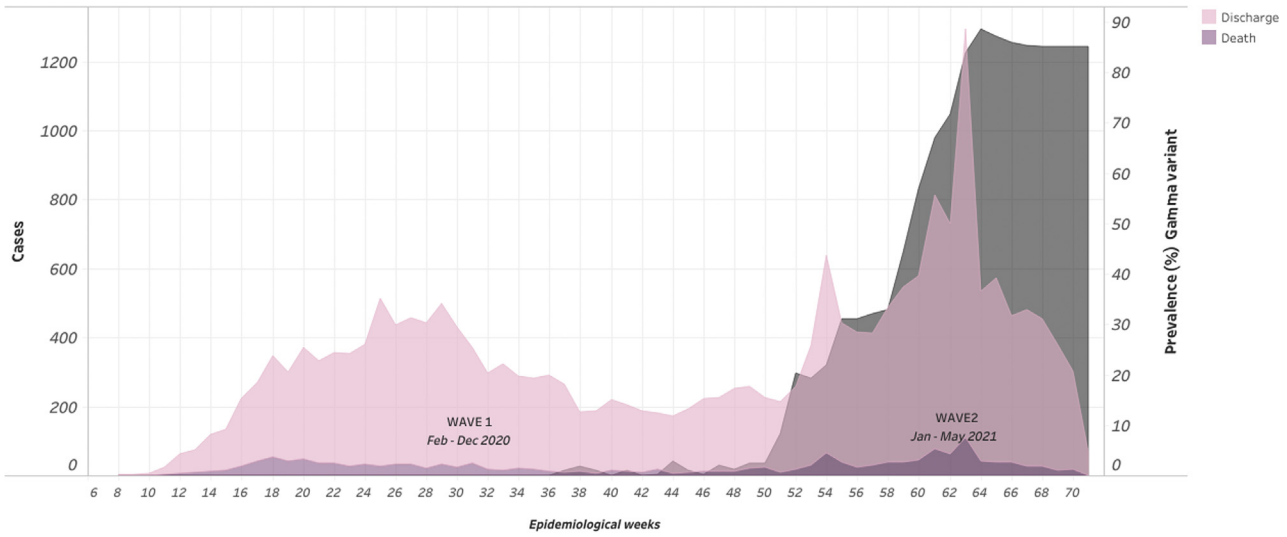

Figure 2. Temporal distribution of COVID-19 related hospital admissions and deaths in children and adolescents in Brazil, stratified by the distinct waves. The dark gray area corresponds to the prevalence of the gamma variant (secondary *y*-axis). In the graph, the figures from 52 to 70 in the x-axis correspond to the epidemiological weeks of 1-19 (January to May 2021). Data source: (1) Cases retrieved from SIVEP-Gripe https://opendatasus.saude.gov.br/dataset/bd-srag-2020; an open-source database of SARS provided by Brazilian Ministry of Health (Accessed on May 29, 2021). (2) Prevalence of Gamma strain retrieved from Outbreak.info (https://outbreak.info/location-reports?loc=BRA), an open-source database of COVID-19 resources and epidemiology data (Accessed on August 19, 2021).

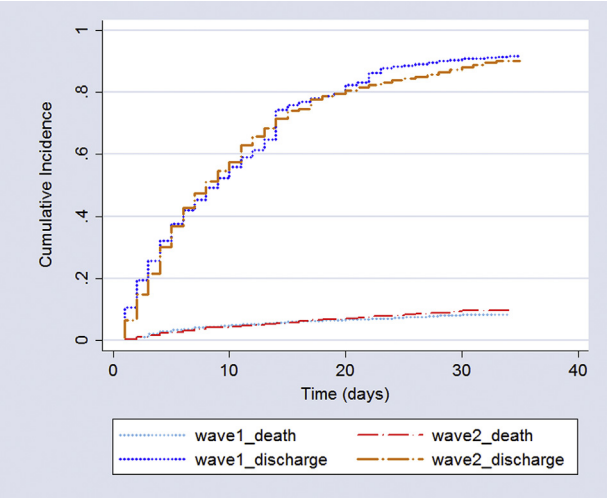

Figure 3. Cumulative incidence functions for mortality and discharge in children and adolescents with COVID-19 according to the waves.

Table II. Univariate survival analysis competitive risk according to the demographic and clinical characteristics of children with positive RT-qPCR COVID-19 (WAVE1, n = 11,428*)

Covariates†	Discharge (N = 10 015; 91.8%)	Death (N = 896; 8.2%)	HR (95% CI)	*P* value
Age group (y)				
0-1.9	3443 (34.4)	359 (40.1)	1.839 (1.546-2.187)	<.001
2-11.9	3548 (35.4)	197 (22.0)	1.0	
12-19.9	3024 (30.2)	340 (37.9)	1.953 (1.640-2.326)	<.001
Sex				
Female	4806 (48.0)	423 (47.3)	1.027 (0.901-1.171)	.681
Male	5202 (52.0)	472 (52.7)		
Sex (imputed)				
Female	5055 (48.0)	423 (47.2)	1.026 (0.900-1.170)	.692
Male	5467 (52.0)	472 (52.7)		
Region				
Southeast	3638 (36.3)	237 (26.5)	1.0	
South	878 (8.8)	64 (7.1)	1.122 (0.852-1.476)	.410
Central-West	1181 (11.8)	52 (5.8)	0.662 (0.490-0.893)	.007
Northeast	2745 (27.4)	381 (42.5)	2.021 (1.719-2.376)	<.001
North	1573 (15.7)	162 (18.1)	1.541 (1.262-1.881)	<.001
Race				
White	2844 (35.8)	215 (28.7)	1.0	
Black/brown	4930 (62.1)	500 (66.8)	1.308 (1.115-1.534)	.001
Asian	69 (0.9)	8 (1.1)	1.515 (0.752-3.050)	.244
Indigenous	100 (1.3)	26 (3.5)	3.272 (2.174-4.924)	<.001
Race (imputed)				
White	3832 (36.4)	262 (29.2)	1.0	
Black/brown	6488 (61.6)	598 (66.7)	1.338 (1.158-1.547)	<.001
Asian	90 (0.9)	8 (0.9)	1.276 (0.634-2.566)	.494
Indigenous	122 (1.2)	28 (3.1)	3.095 (2.097-4.567)	<.001
Signs and symptoms				
Fever	6743 (67.3)	566 (63.2)	0.850 (0.743-0.974)	.019
Cough	5988 (59.8)	414 (46.2)	0.599 (0.526-0.683)	<.001
Odynophagia	1839 (18.4)	109 (12.2)	0.628 (0.514-0.768)	<.001
Respiratory distress	4271 (42.6)	566 (63.2)	2.238 (1.954-2.562)	<.001
Anosmia	313 (3.1)	14 (1.6)	0.513 (0.302-0.869)	.013
Ageusia	294 (2.9)	13 (1.5)	0.508 (0.293-0.987)	.015
Diarrhea	1611 (16.1)	118 (13.2)	0.813 (0.670-1.08)	.037
Vomiting	1772 (17.7)	148 (16.5)	0.939 (0.787-1.120)	.487
Abdominal pain	596 (6.0)	48 (5.4)	0.908 (0.679-1.344)	.517
O_2 saturation <95%	3174 (38.6)	505 (69.8)	3.467 (2.451-4.062)	<.001
O_2 saturation <95% (imputed)	4041 (38.4)	581 (64.8)	2.810 (2.451-3.222)	<.001
Dyspnea	4628 (46.2)	584 (65.2)	2.117 (1.845-2.428)	<.001
Comorbidity (yes/no)	2637 (26.3)	452 (50.4)	2.663 (2.337-3.034)	<.001
Number of comorbidities				
None	7378 (73.7)	444 (49.6)	1.0	
1	2287 (22.8)	350 (39.1)	2.406 (2.092-2.766)	<.001
2	297 (3.0)	82 (9.2)	4.018 (3.191-5.058)	<.001
≥3	53 (0.5)	20 (2.2)	5.235 (3.395-8.073)	<.001
Main comorbidities				
Asthma	810 (8.1)	32 (3.6)	0.443 (0.312-0.613)	<.001
Pulmonary	192 (1.9)	32 (3.6)	1.728 (1.221-2.544)	.002
Neurology	537 (5.4)	126 (14.1)	2.621 (2.176-3.158)	<.001
Oncology	433 (4.3)	127 (14.2)	3.231 (2.693-3.876)	<.001
Cardiology	267 (2.7)	84 (9.4)	3.280 (2.630-4.092)	<.001
Hematology	225 (2.2)	33 (3.7)	1.627 (1.152-2.297)	.006
Renal	126 (1.3)	40 (4.5)	3.272 (2.398-4.464)	<.001
Diabetes	162 (1.6)	33 (3.7)	2.141 (1.523-3.008)	<.001
Obesity	132 (1.3)	23 (2.6)	1.883 (1.252-2.832)	.002
Syndrome	158 (0.9)	48 (2.7)	3.091 (2.322-4.116)	<.001

*Cases: 11 574; deaths, 896; censored, 517; 146 missing cases regarding primary outcome.
†Covariates with missing data: sex, 13; ethnicity, 2426; O_2 saturation, 2625 missing.