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Non-communicable diseases, sociodemographic vulnerability and the risk of mortality in hospitalised children and adolescents with COVID-19 in Brazil: a cross-sectional observational study

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ABSTRACT

Objectives To analyse how previous comorbidities, ethnicity, regionality and socioeconomic development are associated with COVID-19 mortality in hospitalised children and adolescents.

Design Cross-sectional observational study using publicly available data from the Brazilian Ministry of Health.

Setting Nationwide.

Participants 5857 patients younger than 20 years old, all of them hospitalised with laboratory-confirmed COVID-19, from 1 January 2020 to 7 December 2020.

Main outcome measure We used multilevel mixed-effects generalised linear models to study in-hospital mortality, stratifying the analysis by age, region of the country, presence of non-communicable diseases, ethnicity and socioeconomic development.

Results Individually, most of the included comorbidities were risk factors for mortality. Notably, asthma was a protective factor (OR 0.4, 95% CI 0.24 to 0.67). Having more than one comorbidity increased almost tenfold the odds of death (OR 9.67, 95% CI 6.89 to 13.57). Compared with white children, Indigenous, Pardo (mixed) and East Asian had significantly higher odds of mortality (OR 5.83, 95% CI 2.43 to 14.02; OR 1.93, 95% CI 1.48 to 2.51; OR 2.98, 95% CI 1.02 to 8.71, respectively). We also found a regional influence (higher mortality in the North—OR 3.4, 95% CI 2.48 to 4.65) and a socioeconomic association (lower mortality among children from more socioeconomically developed municipalities—OR 0.26, 95% CI 0.17 to 0.38)

Conclusions Besides the association with comorbidities, we found ethnic, regional and socioeconomic factors shaping the mortality of children hospitalised with COVID-19 in Brazil. Our findings identify risk groups among children that should be prioritised for public health measures, such as vaccination.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the most comprehensive study in Brazil on risk factors for mortality of hospitalised children with COVID-19, covering both clinical and sociodemographic characteristics in a large population.

⇒ We included a large number of patients, representative of all of the country's regions, all of them with laboratory-confirmed COVID-19.

⇒ Our analysis relied on secondary data, with a high rate of missingness for ethnicity, but we have no evidence to believe in a differential missingness among ethnicities.

⇒ We did not have data on out-of-hospital mortality, which might be substantial especially in lower socioeconomic settings, possibly resulting in an underestimation of the pandemic effect in these settings.

⇒ We included hospitalised children only, therefore, our results might not be extrapolated for children with a less severe clinical presentation.

INTRODUCTION

The COVID-19 pandemic is the most significant health challenge of the century so far, with more than 160 million infected and 3.3 million deaths as of May 2021.[1] After a first wave that elicited radical containment measures around the world, during the last months of 2020, we have watched the numbers rise again, prompting countries to reinstate lockdowns and reinforce containment policies, with special focus on vaccination. Unfortunately, Brazil has lagged. The federal government has been widely criticised for questioning the seriousness of the disease or denying its gravity altogether,

delaying a timely response.[2 3] The country is currently struggling with its vaccination strategy, an effort hindered by partisan politics.

Children and adolescents are mostly spared by COVID-19, with few having severe symptoms and even fewer dying.[4] However, the description of the multisystem inflammatory syndrome in children reinforced that, although rare, severe clinical presentation and death is possible in the paediatric population.[5] Multiple studies have associated the presence of underlying comorbidities with severe clinical presentation and unfavourable outcomes in paediatric COVID-19 patients,[6–9] however, this association is less established than for adults. Additionally, it is well recognised that ethnic minorities and those with less favourable socioeconomic status (SES) suffer a disproportionate impact of the COVID-19 pandemic,[10 11] but few studies address this reality in children specifically.

In this study, we analyse a large dataset of COVID-19 hospitalised children and adolescents in Brazil to assess risk factors for mortality in this age group. We focused our attention on the association with non-communicable diseases (NCDs) and sociodemographic variables such as country region, socioeconomic development, ethnicity and age.

METHODS

Study design and population

This is a cross-sectional observational study using publicly available data from the Brazilian Ministry of Health. We analysed the SIVEP (Sistema de Informação da Vigilância Epidemiológica)-Gripe database,[12] which contains prospectively collected data from all patients with severe acute respiratory syndrome (SARS) across the country. In Brazil, the notification of SARS is mandatory, and all the registered cases are included in the dataset. The reporting form is standardised and usually filled in during hospitalisation. The studied data comprises all reported COVID-19 hospitalisations in Brazil, up to 7 December 2020 (online supplemental appendix p.1). We included all the patients younger than 20 years old, hospitalised with PCR-confirmed COVID-19 and with a known outcome.

Brazil is divided into 26 states and the Federal District, and grouped in 5 macroregions: North, Northeast, Central-west, Southeast and South. For analytical purposes, we chose to divide the country into two maximally contrasting regions: North (comprising the North and Northeast macroregions) and South (comprising the Central-west, Southeast and South macroregions). This division was based on economic, health and educational indexes, and is usual in sociodemographic and economic studies of the Brazilian population. Previous literature on COVID-19 in Brazil also divided the country in a similar way.[13]

The Brazilian Institute of Geography and Statistics divides the Brazilian population in five categories, based on self-reported skin colour: Branco (white), Amarelo (East Asian), Preto (black), Indígena (indigenous) and Pardo.[14] Pardo refers to mixed and diverse ethnic background, as a result of the intense ethnic mixing that characterises Brazilian people. In late 2020, 46.4% of Brazilians identified themselves as Pardo, 44% as white, 8.6% as black, and 1% as East Asian or indigenous.[15]

GeoSES is a Brazilian composite SES index that incorporates education, poverty, mobility, wealth, segregation, income and deprivation of resources and services, generating a score for each municipality ranging from −1 (less developed) to 1 (most developed) with good association with the Human Development Index (HDI).[16] We used the GeoSES of the patient's municipality as a proxy of SES, categorising by GeoSES terciles (high, middle, low) when necessary. It is important to note that in Brazil there is a considerable overlap between the regional, ethnic, and socioeconomic variables mentioned above (online supplemental appendix p.2–3).

To address NCDs, we retrieved data from the SIVEP-Gripe on previous comorbidities. The dataset comprises the following conditions: cardiovascular disease, haematological disease, hepatic disease, asthma, diabetes, neurological disease, pulmonary disease, immunosuppression, kidney disease, obesity, Down Syndrome and 'other comorbidities'. Therefore, most of the diseases are included in groups of diagnosis, rather than specific conditions.

The rate of missing data or data reported as 'unknown' varied among the variables. For comorbidities, we chose to assume missing data as absence of that comorbidity. More information on the handling of missingness can be found in online supplemental appendix p.4.

The outcome of interest was in-hospital mortality in children and adolescents with positive PCR for COVID-19.

Statistical analysis

Categorical variables were described using their absolute and relative frequency, and continuous variables using their mean and SD. Distribution according to outcome was initially analysed through the χ^2 test (categorical variables), the t-test (continuous variables normally distributed) or the Kruskal-Wallis rank test (continuous variables not normally distributed).

Multilevel mixed-effects generalised linear models (GLM) were built to calculate the OR and 95% CIs between exposure and outcome. Although survival analysis would be the best statistical choice, as it allows dealing with censored data, we had concerns over the reliability of time records in our data set, prompting us to choose GLM instead. We assumed the municipality where the subject resided and the health unit where hospitalisation occurred to be random effects. To study the association between sociodemographic factors together and mortality, we developed five explanatory models. Crude analysis, adjusting only for sex (model 1), was followed by adjustment for possible confounders (sex, age group, GeoSES, ethnicity and country region—model 2). To address the hypothesis of interaction between NCDs and

socioeconomic factors, we also build a model accounting for this possibility (model 3). Given the broad age range in paediatrics, the final models are equivalent to model 3, but present the results separately for those 10 years old or younger and older than 10 years old (models 4 and 5, respectively). We performed sensitivity analysis to determine the robustness of our findings by examining the extent to which results change by values of unmeasured variables—in this cases, unmeasured confounding—using the evalue module for STATA.[17] The data analysis was performed using STATA Statistical Software, V.14 (Stata 2015. Stata Statistical Software: Release 14. StataCorp).

Role of the funding source
This study received no funding.

Patient and public involvement
Since we conducted an epidemiological analysis of publicly available unidentified data, patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS
From 1 January 2020 to 7 December 2020, the SIVEP-Gripe database included 1 000 024 patients. We filtered it by age to only include patients less than 20 years old, finding a total of 79 498. Of that total, only 7706 had a positive PCR for SARS-CoV-2, and 758 of them were not hospitalised. Out of the 6948 remaining, the outcome was known for 5857, the final population included in our analysis (figure 1).

Concerning missingness, 1385 (23.6%) patients had no ethnicity recorded and 166 (2.8%) did not have GeoSES

data available. Sex was unknown for one patient (online supplemental appendix p.4).

Table 1 describes the sociodemographic and clinical features of the included patients. There was an even distribution among sexes, both in hospitalisation (51.4% male vs 48.6% female) and in death rates. The mortality for age follows a U-shaped curve, with a higher death rate among neonates and adolescents.

The North region accounted for 36% of the included patients, the same proportion of the population living in the region.[18] However, despite accounting for only one-third of the hospitalisations, this region concentrated 57% of the deaths. We found an overall mortality of 9.6% in the country, but it varied among regions, with a higher rate in the North. The overall mortality varied over time, with a higher rate in the early months of the pandemic—up to May 2020, for instance, it was 13.3%, declining consistently over the following months. We also found that although the distribution of cases among ethnicities roughly mirrors the population distribution, some ethnicities have a higher mortality than others, notably Indigenous and Pardo. Additionally, children who died lived in municipalities less socioeconomically developed than those who survived (GeoSES −0.23 vs −0.058, p<0.001).

In order to provide a clear picture of the disease distribution, we analysed the number of hospitalisations and mortality state by state (figure 2). São Paulo, the state with the largest population, leads with 1880 reported hospitalisations. However, proportionally to the total state population, São Paulo was only the fourth in the country, after Sergipe, Pernambuco and the Federal District. Roraima, the least populated state in Brazil, had the highest mortality rate (70.6%), a figure that needs to be interpreted with care due to the low number of cases reported in the state (only 18). The states with the highest mortality rates were mostly concentrated in the North.

Analysing NCDs prevalence, 39.6% of the children had at least one comorbidity, in the overall studied population and for both regions equally. The most frequently reported NCDs among hospitalised children with COVID-19 were asthma (7.8%), followed by immunosuppression (5.4%) and neurological conditions (5.1%). Multiple NCDs were reported by 10.4%. The overall mortality rate for children with NCDs was 15.8%, against 5.6% in healthy children. With the exception of asthma, all comorbidities increased the rate of death, especially kidney disease (29.2%) and cardiovascular disease (26.3%). Although we found a higher frequency of patients with one comorbidity in less developed settings, the frequency of patients with several comorbidities was fairly balanced among different socio-demographic realities (online supplemental appendix p.5).

Assessing the OR of mortality for all comorbidities and for cumulative comorbidities, we found that almost all categories significantly increased the odds of death. The exceptions were asthma, which appeared to be a protective factor (OR 0.42, 95% CI 0.24 to 0.67) in this population and hepatic diseases. Individually, cardiovascular disease
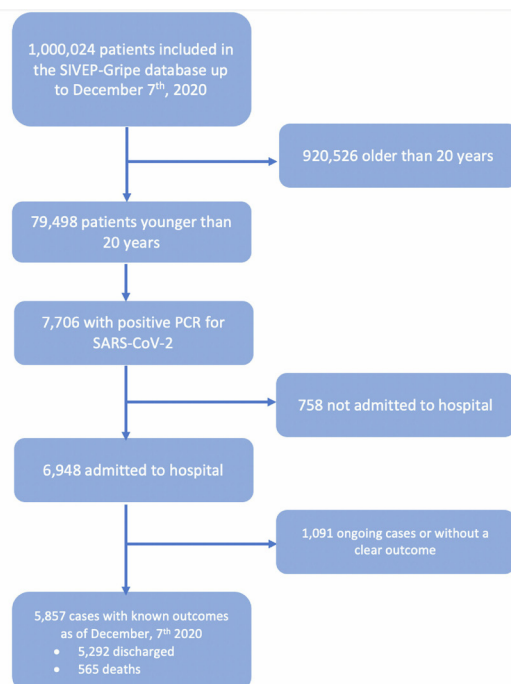

Figure 1 Flow chart of the patients included in this study.

Table 1 Sociodemographic description and preexisting non-communicable diseases for survivors and non-survivors among children and adolescents hospitalised with COVID-19

Characteristic	Categories	Survivors (N=5292)	Non-Survivors (N=565)
Region	North (N=2123)	1801 (84.8%)	322 (15.2%)
	South (N=3734)	3491 (93.5%)	243 (6.5%)
Age	0–28 days (N=362)	306 (84.5%)	56 (15.5%)
	29 days to 2 years (N=2122)	1939 (91.4%)	183 (8.6%)
	2–10 years (N=1433)	1340 (93.5%)	93 (6.5%)
	10–15 years (N=759)	667 (87.9%)	92 (12.2%)
	15–20 years (N=1181)	1040 (88.1%)	141 (11.9%)
Mean age by region (years)	North (N=2123)	6.6 (6.7)	7.0 (7.2)
	South (N=3734)	7.1 (6.9)	9.0 (7.4)
Sex	Male (N=3011)	2725 (90.5%)	286 (9.5%)
	Female (N=2845)	2566 (90.2%)	279 (9.8%)
Ethnicity	White (N=1833)	1704 (93%)	129 (7%)
	Pardo (N=2363)	2070 (87.6%)	293 (12.4%)
	Black (N=199)	182 (91.5%)	17 (8.5%)
	East Asian (N=36)	30 (83.3%)	6 (16.7%)
	Indigenous (N=41)	28 (68.3%)	13 (31.7%)
	Missing/unknown ethnicity (N=1385)	1278 (92.3%)	107 (7.7%)
NCDs	With any NCD (N=2318)	1952 (84.2%)	366 (15.8%)
	Without NCD (N=3539)	3340 (94.4%)	199 (5.6%)
	Cardiovascular disease (N=232)	171 (73.7%)	61 (26.3%)
	Asthma (N=455)	436 (95.8%)	19 (4.3%)
	Diabetes (N=150)	118 (76.7%)	32 (21.3%)
	Pulmonary disease (N=131)	111 (84.7%)	20 (15.3%)
	Obesity (N=88)	72 (81.8%)	16 (18.2%)
	Immunosuppression (N=317)	241 (76%)	76 (24%)
	Neurological disease (N=299)	243 (81.3%)	56 (18.7%)
	Renal disease (N=96)	68 (70.8%)	28 (29.2%)
	Liver disease (N=32)	25 (78.1%)	7 (21.9%)
	Hematologic disease (N=149)	123 (82.5%)	26 (17.5%)
GeoSES		−0.058 (0.31)	−0.23 (0.33)

Data are number (%) or mean (SD). GeoSES is a socioeconomic status index that ranges from −1 (less developed) to +1 (more developed). Missingness was found in both ethnic variables and GeoSES. One patient had no data on 'sex'.
NCD, non-communicable disease.

was the category that presented the strongest association with mortality (OR 4.98, 95% CI 3.31 to 7.49), followed by kidney disease (OR 4.79, 95% CI 2.67 to 8.6) and immunosuppression (OR 3.41, 95% CI 2.39 to 4.86). Having two or more comorbidities increased almost 10-fold the odds of death (OR 9.67, 95% CI 6.89 to 13.57) (figure 3). It is important to note that we excluded asthma when analysing multiple comorbidities.

Our next step was to study how regionality, socioeconomic and ethnic variables are associated with mortality. Figure 4 illustrates the association between each of those factors and COVID-19 mortality in hospitalised children. We found that Pardo (OR 1.93, 95% CI 1.48 to 2.51),

East Asian (OR 2.98, 95% CI 1.02 to 8.71) and Indigenous ethnicities (OR 5.83, 95% CI 2.43 to 14.02) have significantly increased mortality figures when compared with White. Analysing regions, children in the North region had more than three times the odds of death when compared with those in the South (OR 3.4, 95% CI 2.48 to 4.65). SES, estimated by the GeoSES index, also showed a significant correlation with mortality: children from cities in the middle third GeoSES group had a 50% lower odds of mortality when compared with those in the lowest third (OR 0.5, 95% CI 0.37 to 0.69). As for those in more developed cities, the odds reduction was almost 75% (OR 0.26, 95% CI 0.17 to 0.38).
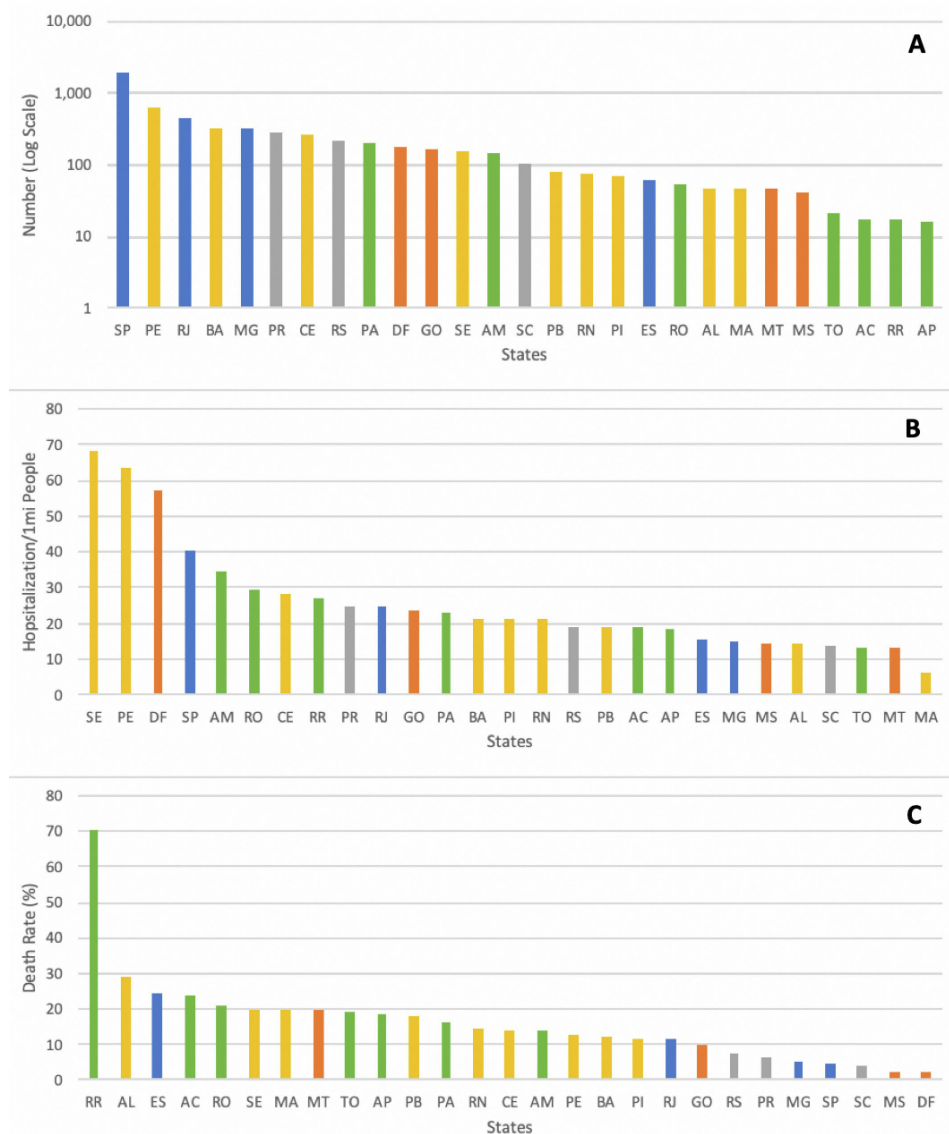
Figure 2 Distribution of COVID-19 paediatric hospitalisations in absolute numbers (A), proportional to population (B) and death rate (C) by state. N=5857. Bars are coloured by state macroregion: blue for Southeast; yellow for Northeast; grey for South; green for North; orange for Centre west. AC, Acre; AL, Alagoas; AM, Amazonas; AP, Amapá; BA, Bahia; CE, Ceará; DF, Distrito Federal; ES, Espírito Santo; GO, Goiás; MA, Maranhão; MG, Minas Gerais; MS, Mato Grosso do Sul; MT, Mato Grosso; PA, Pará; PB, Paraíba; PE, Pernambuco; PI, Piauí; PR, Paraná; RJ, Rio de Janeiro; RN, Rio Grande do Norte; RO, Rondônia; RR, Roraima; RS, Rio Grande do Sul; SC, Santa Catarina; SE, Sergipe; SP, São Paulo; TO, Tocantins.

To assess the association between all the aforementioned factors together and mortality, we analysed five explanatory models (table 2). Accounting for the relationship with mortality of having comorbidities (at least one, asthma excluded), adjusted only for sex, model 1 found an increase in the odds of death by almost five times (OR 4.81, 95% CI 3.82 to 6.06). Adjusting for sociodemographic variables (model 2), similar results were found . Considering the possibility of interaction between comorbidities and the sociodemographic factors (model 3), the association of comorbidities with mortality is lower, but all the factors keep significance. While the association with NCDs appears to be more relevant for adolescents (model 4), in children (model 5) the sociodemographic

factors are more important. Moreover, in adolescents, sex seems to be a relevant feature, with females having a 30% reduction in the risk of death, although the 95% CI included the unity (p=0.055).

We compared the rate of NCDs in the studied population to the rate among the deceased, for each sociodemographic category (figure 5). It is clearly noticeable that in the North region, in lower socioeconomic settings and among ethnic minorities, a higher proportion of healthy children died, even though the proportion of hospitalised children without comorbidities is fairly similar for all categories. This is also true for the younger than 10 years, as in adolescence more than 70% of the deaths were in children with at least one NCD. However, in the age
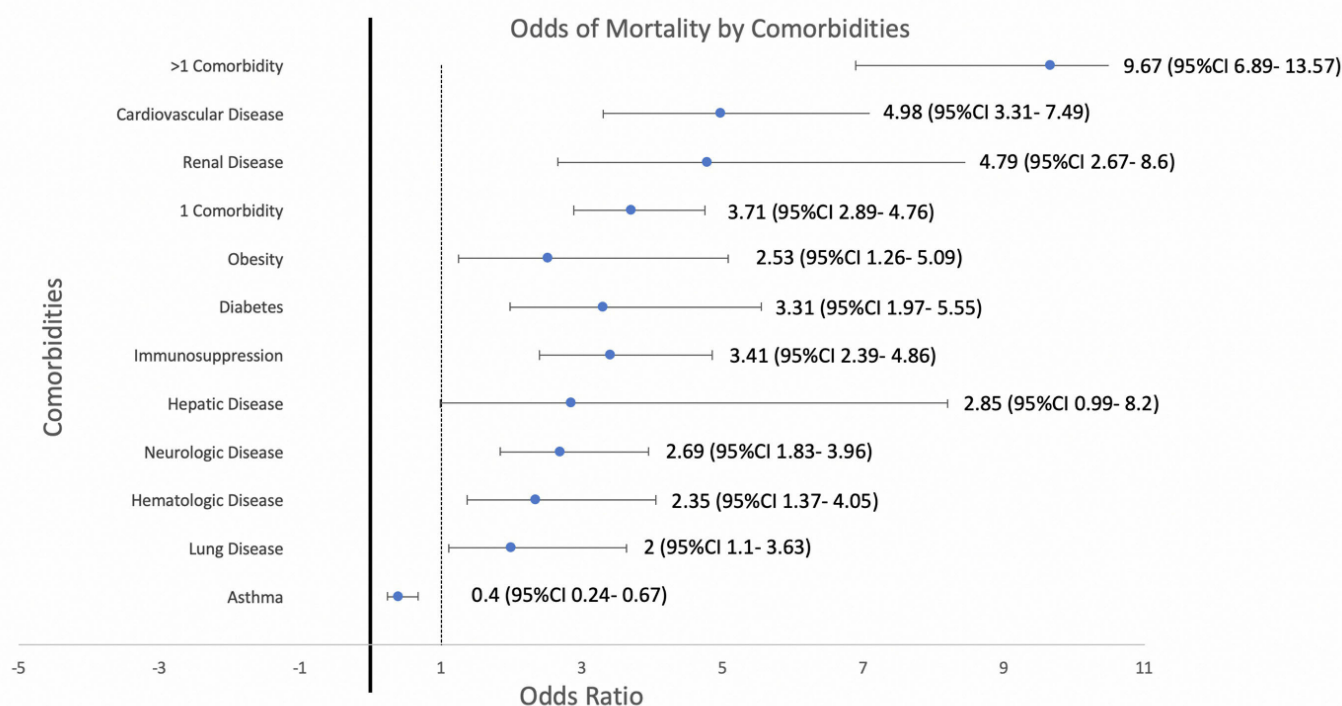
Figure 3 Risk of mortality for clinical features in multilevel mixed-effects generalised linear models, assuming municipalities and hospitals as random effects. Error bars represent 95% CIs, N=5857. For each individual condition, the reference group was patients without such condition. The groups '1 comorbidity' and '>1 comorbidities' includes all the aforementioned, Down syndrome and conditions disclosed as 'other comorbidities'. Both categories exclude asthma, as asthma seems to has a protective association. The reference group for them was patients without comorbidities.

categories, we see a larger gap in NCDs prevalence, with a higher rate among adolescents.

Finally, we performed sensitivity analysis for the primary outcomes in our study. For the North region, the observed relation with mortality could be explained away by an unmeasured confounder that was associated with both the exposure and the outcome by a risk ratio (RR) of at least 3.1. For indigenous and Pardo ethnicities, the RRs would need to be 4.3 and 3.3, respectively. For the protective association with high GeoSES municipalities, the RR would need to be 4.7.

DISCUSSION

This is, to our knowledge, the most comprehensive study on risk factors for mortality of hospitalised children with COVID-19 in Brazil, covering both clinical and sociodemographic characteristics in a large population. We found a higher risk of mortality in children and adolescents with NCDs, as well as among ethnic groups such as Indigenous and Pardo. We also found regional and socioeconomic disparities associated with mortality in this specific population, painting a broad picture of how these sociodemographic elements interact with NCDs to shape mortality in COVID-19 hospitalised children.

We found significant differences in mortality rate when splitting age in groups to consider previously described ages of potential risk, like neonates and older

adolescents.[19] The higher mortality in neonates might be related to the developing immune system, associated with an immature respiratory system, resulting in them being more prone to severe complications of lung infections. Adolescents, in turn, bear a higher burden of NCDs. Accordingly, in our explanatory models, having at least one NCD increased the risk of death over five times for adolescents, while for those younger than 10 years, the association with comorbidities was not significant.

The proportion of hospitalised children among the regions was consistent with the national population, evidencing a uniform distribution of the disease. As we studied data up to December, our results mirror a late stage of the pandemic's first wave in Brazil, with a widespread distribution of COVID-19. The state reporting the highest number of hospitalised children with COVID-19 was São Paulo. However, proportionally to population size, Sergipe, a small state in the Northeast macroregion, with 20 times less people than São Paulo, and significantly lower levels of socioeconomic development and health indicators, took the lead. These findings reinforce the idea that COVID-19 is disproportionally burdening more vulnerable populations, which can have catastrophic public health consequences. Two national serological household surveys also found inequalities in the prevalence of the disease, with a higher prevalence in poorer areas and among minorities.[20]
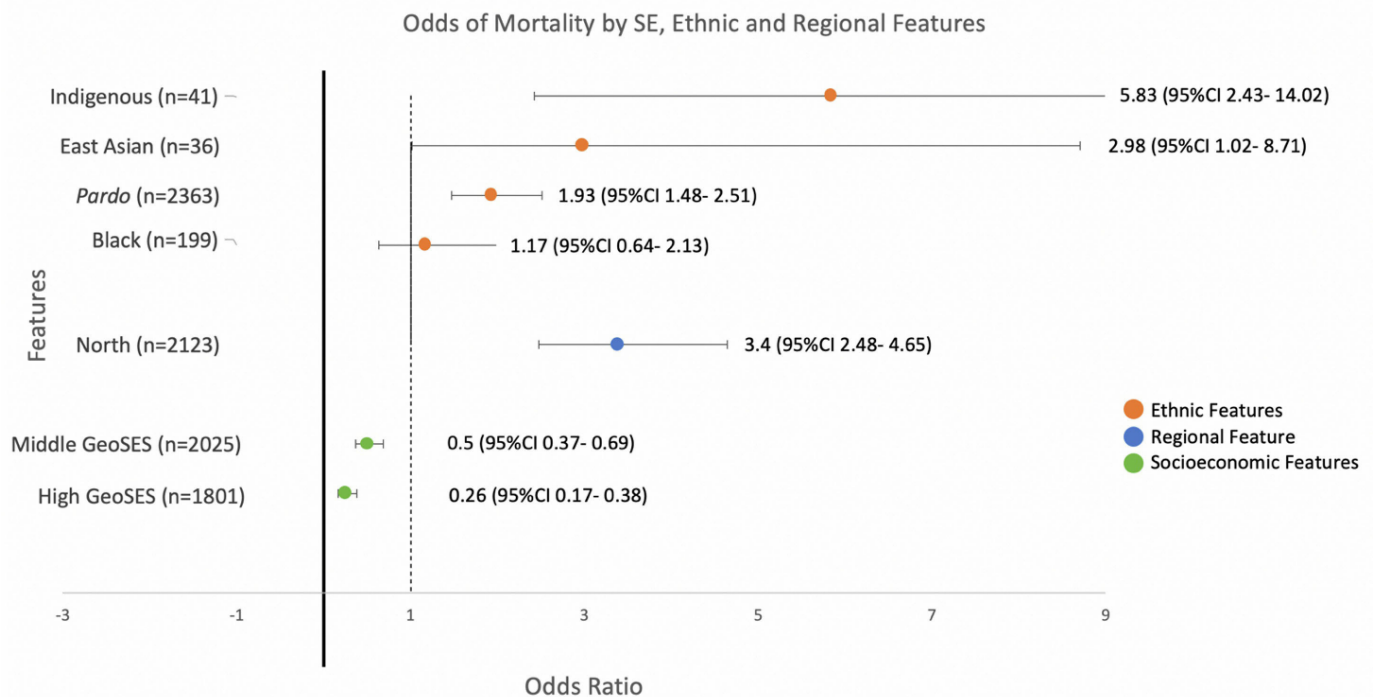
Figure 4 Risk of mortality for sociodemographic features in multilevel mixed-effects generalised linear models, assuming municipalities and hospitals as random effects. Error bars represent 95% CIs. N=4472 for ethnicity (1385 missing), 5857 for region and 5691 for socioeconomic development (166 missing). 'Pardo' means a wide range of mixed or diverse ethnic backgrounds. 'North' refers to both North and Northeast Brazilian macroregions. Socioeconomic development categorised by GeoSES terciles. Reference groups were 'white' for ethnicity, 'South' for region and low GeoSES tercile for socioeconomic development. SES, socioeconomic status.

We found a high prevalence of NCDs (39.6%) in hospitalised children with COVID-19, corroborating the findings of other studies.[6–9] Almost all the conditions studied individually posed as risk factors for mortality, however, it was their association that stood out. Due to the medical advances of the last decades, especially in newborn care and NCD treatments, we have seen a significant rise in the prevalence of children with multiple chronic conditions and medical complexity.[21] Our findings support the idea that this population is at a higher risk of mortality, and deserves special attention with respect to preventive measures, including vaccination.

Interestingly, asthma was a protective factor for mortality in our population, reducing the odds of death by 60%. This finding is in line with previous studies in adults that also found asthma patients to be at a lower risk of mortality.[22] Although the mechanisms mediating this phenomena are not yet clear, possible explanations include a lower expression of the ACE-2, the receptor used by COVID-19 for cell entry, or a protective effect of inhaled corticosteroids. Other possibilities might be related to reduced exposure, immunotolerance protection against severe inflammation due to chronic inflammation of the asthmatic lung, and mucus hypersecretion preventing the virus from penetrating the distal lung.[23] As we were interested in studying risk factors for mortality, we chose to exclude asthma as a comorbidity when analysing the relationship between NCDs and mortality. By doing

so, we reinforce the protective nature of the condition, and focus on the diseases that actually confer a higher risk and should justify a differential resource allocation for protection of children. The trade-off of this approach is an overestimation of the effect size of NCDs in mortality.

Other than multiple comorbidities, indigenous ethnicity was the most important risk factor for mortality in the population studied. Brazil is a country marked by discrimination and governmental negligence against Indigenous populations, reflecting on shortcomings in multiple socioeconomic and health indexes. Mortality for indigenous children and adolescents, for instance, is much higher than for non-indigenous.[24] This setting of structural disadvantage reflects on special vulnerability to diseases: in 2009, for example, the H1N1 influenza devastated indigenous tribes, with a mortality 4.5 times higher than the general Brazilian population.[25] The current Brazilian political scenario makes matters even worse: deforestation is on the rise, the National Indigenous Foundation was stripped of power, and illegal miners and loggers are infiltrating indigenous territories without governmental challenge.[26] Our data and previous literature[20 25] raise the alarm to a significantly higher risk of COVID-19 spreading and mortality among Indigenous, prompting quick and decisive governmental intervention.

Besides Indigenous, we identified Pardo and East Asian ethnicities as risk factors for mortality. In the early stages of the pandemic in Brazil, Baqui *et al* also found

Table 2 Explanatory models for the relationship between sociodemographic factors and mortality in hospitalised children with COVID-19 in Brazil

Models	OR	95% CI	P value
Model 1 (n=5856)			
Comorbidity	4.81	3.82 to 6.06	<0.001
Model 2 (n=4400)			
Comorbidity	4.71	3.63 to 6.11	<0.001
Model 3 (n=4400)			
Comorbidity	2.89	1.02 to 8.22	0.046
White	1.00	–	–
Pardo	2.13	1.29 to 3.54	0.003
Black	1.44	0.54 to 3.85	0.460
Asian	4.68	1.07 to 20.49	0.040
Indigenous	9.32	3.01 to 28.84	<0.001
South	1.00	–	–
North	1.76	1.08 to 2.86	0.023
Low GeoSES	1.00	–	–
Middle GeoSES	0.51	0.31 to 0.81	0.005
High GeoSES	0.34	0.17 to 0.69	0.002
Male	1.00	–	–
Female	0.99	0.79 to 1.25	0.959
Model 4 (n=2907)			
Comorbidity	2.85	0.87 to 9.34	0.083
White	1.00	–	–
Pardo	2.17	1.14 to 4.11	0.018
Black	2.13	0.63 to 7.17	0.220
Asian	5.79	0.92 to 36.30	0.061
Indigenous	15.78	4.18 to 59.54	<0.001
South	1.00	–	–
North	1.76	0.95 to 3.25	0.070
Low GeoSES	1.00	–	–
Middle GeoSES	0.58	0.30 to 1.12	0.105
High GeoSES	0.27	0.13 to 0.59	0.001
Male	1.00	–	–
Female	1.22	0.90 to 1.66	0.195
Model 5 (n=1493)			
Comorbidity	5.33	1.55 to 18.27	0.008
White	1.00	–	–
Pardo	2.22	0.94 to 5.20	0.067
Black	0.88	0.16 to 4.78	0.880
Asian	3.04	0.24 to 39.15	0.393
Indigenous	2.18	0.13 to 35.38	0.584
South	1.00	–	–
North	1.70	0.74 to 3.89	0.206
Low GeoSES	1.00	–	–
Middle GeoSES	0.49	0.23 to 1.06	0.071

Continued

Table 2 Continued

Models	OR	95% CI	P value
High GeoSES	0.35	0.12 to 0.97	0.043
Male	1.00	–	–
Female	0.68	0.46 to 1.00	0.055

Results of multilevel mixed-effects generalised linear models, with municipality and hospital as random effects. Model 1 considers exclusively the association of comorbidities (at least one, asthma excluded) with mortality, adjusted for sex. Model 2 includes adjustment for sociodemographic factors (ethnicity, region, age and GeoSES). Model 3 expands model 2, including the assessment of possible interactions between comorbidities and sociodemographic factors. Models 4 and 5 are equivalent to model 3, filtering for age group (up to 10 years old or older than 10 years old, respectively). The reference category for 'comorbidity' was patients without previous conditions.
SES, socioeconomic status.

Pardo ethnicity as a risk factor in adults, attributing it to a greater susceptibility of contracting COVID-19, reliance on public healthcare, and reduced access to intensive care.[13] It is reasonable to assume that Pardo children are subject to the same difficulties as adults, although the assessment of paediatric intensive care unit availability is compromised by the lack of official data on the subject. Additionally, Pardo and black children also have higher general mortality rates when compared with white,[24] mirroring generations of structural socioeconomic and health disadvantages. Surprisingly, in our study, black ethnicity was not associated with a higher mortality. The higher risk for East Asians is consistent with the findings of a recent meta-analysis including more than 18 million patients of all ages.[27]

The GeoSES index incorporates multiple social and economic dimensions, including variables often neglected like mobility and segregation.[16] It is, therefore, a more comprehensive proxy than the ones classically used, like the HDI. The analysis by GeoSES terciles clearly demonstrates the abyss separating different levels of privilege in Brazilian society. It is appalling to see children dying almost four times more in cities less socioeconomically developed. In the battle against COVID-19, these children are clearly being left behind.

We also found a regional association, with a higher mortality in Northern Brazil. Even in models incorporating all the sociodemographic factors together, the correlation stands, showing that there is a regional outcome discrepancy that is not explained by ethnicity or socioeconomic development alone. Baqui et al also found this regional association, attributing it to a difference in healthcare availability and variation in number of comorbidities.[13] Since the North region is less developed than the South, with worse health indexes, it is reasonable to assume that healthcare is also less available for children. However, we could not find a consistent difference in the prevalence of comorbidities among regions. This finding must be interpreted cautiously, as a lower availability of
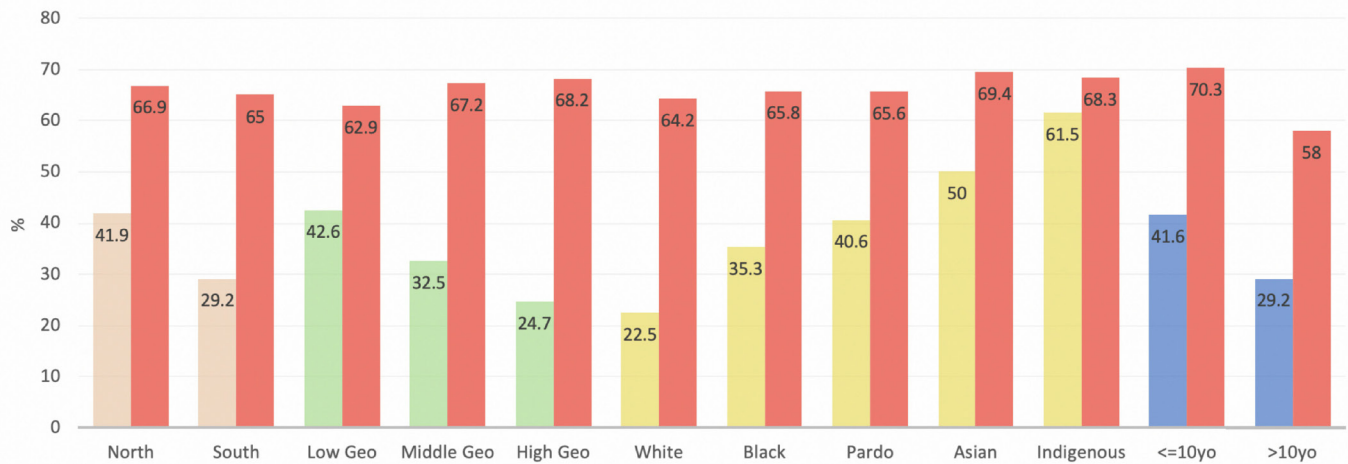
Figure 5 Frequency of children without NCDs for each sociodemographic category, both in the general hospitalised population and among the dead. Bars in red represent the general rate for each group, while the other bars represent the rate among the dead. 'Pardo' means a wide range of mixed or diverse ethnic backgrounds. 'North' refers to both North and Northeast Brazilian macroregions. Socioeconomic development categorised by GeoSES terciles. NCDs, non-communicable diseases; SES, socioeconomic status.

healthcare renders underdiagnosis more likely. We also expect that children in Northern Brazil have a worse control of their chronic conditions, contributing to poor outcomes.

While we found a fairly similar proportion of children without NCDs in both regions, among different ethnicities and in the GeoSES terciles, the rate among the deceased varies remarkably. There is a clear pattern of an excess of deaths in healthy children from less favourable socioeconomic settings and among minorities. While this might be related to underdiagnosis, it also raises an alarm for a possible failure of the Brazilian health system in protecting these populations.

To make sense of its interaction with NCDs and sociodemographic vulnerabilities, it has been proposed that COVID-19 be a part of a syndemic rather than a pandemic.[28] The syndemic theory is based on the synergism of two or more health conditions and the underlying socioeconomic inequality context, worsening their individual health outcomes .[29 30] We propose that there is a syndemic between COVID-19 and NCDs in Brazilian children, driven by large-scale socioeconomic forces that promote the concentration and interaction of these conditions. For a syndemic to occur, there must be two epidemics interacting. Our findings clearly show that the presence of NCDs worsens the outcomes of children with COVID-19, especially when multimorbidity is present.

We have evidence that the opposite is also true: COVID-19 can have an impact on people with NCDs, either increasing the risk of developing them or worsening their care. COVID-19, for instance, can impair glucose metabolism and complicate preexisting diabetes or even have a diabetogenic effect.[31] COVID-19 preventive strategies are based primarily on reducing social contact, which might lead to increased exposure to NCDs risk factors, like tobacco use and sedentarism. Furthermore, lockdowns have disrupted healthcare access for

patients living with chronic conditions, making disease management harder.[32]

Our data reinforce the previously described idea that COVID-19 is disproportionally burdening vulnerable populations, with a higher prevalence in states in the Northern region. Many factors might explain this higher transmissibility, like crowded living conditions and poor access to public health measures and healthcare.[20 27] Therefore, it is reasonable to conclude that the pandemic is clustering in vulnerable populations, driven by the major socioeconomic forces that are determinant to health. Literature shows that NCDs also cluster in these same populations that are more exposed to risk factors like unhealthy diets, physical inactivity and tobacco use. This is also true for children, with the exposure to these factors starting in the womb and continuing through life. The social determinants of health have a greater impact over children, since they are not able to advocate for themselves, and are socially and economically dependent on their caregivers.[33]

Approaching COVID-19 as part of a syndemic invites a broader vision that goes beyond biomedical solutions and encompasses the socioeconomic environment that promotes the disease cluster and interaction with NCDs.[28] Adequate treatment, preventive measures and vaccination are not enough: governmental intervention is necessary to address the challenge of changing disparities structurally rooted in Brazilian society. Fortunately, Brazil has precedent on this topic: the Bolsa Familia, a nationwide conditional cash transfer programme that covers over 15 million families, has been shown to significantly reduce childhood mortality.[34] This example illustrates how large governmental interventions tackling socioeconomic disparities can have a positive impact on children's health.

Our study had several limitations. Our analysis relied on secondary data, with case ascertainment bias being

a possibility. There was also a high rate of missingness for ethnicity, which could imbalance the results if the missingness was differential for some groups, but no evidence was found in literature to support this hypothesis. Interestingly, however, the mortality rate was significantly lower among patients without a reported ethnicity (7.7% vs 10.2%, p=0.006), despite being equally distributed among the North and South regions (p=0.15). These findings point to the presence of other explanatory factors, linked both to missingness and outcome. Ethnicity was defined on the basis of self-declared skin colour or appearance, rather than ancestry, and there is a significant overlap between the Pardo and Black categories. Considering this reality, some researchers approach these ethnicities as a single group, but we chose to keep them separate, observing the ethnicity reported by each subject. Unfortunately, there is no way to estimate how this overlap affected the effect size for these groups.

Under-reporting is also an issue, especially in less advantageous socioeconomic contexts, which might have underestimated the effect size in our models. Given this issue, differential misclassification for the presence of morbidity cannot be discarded. Analysing the patients who were excluded due to the lack of a clear outcome reported, we found that they are less likely to be white and more likely to live in less developed municipalities in the North region (online supplemental appendix p.6). These findings reinforce the hypothesis of under-representation of vulnerable populations, underestimating the effect size. As for the SES analysis, using municipality development as a proxy for SES can hide major discrepancies within each city, especially in large metropolises.

We were not able to fully address healthcare availability by ethnicity, SES and region, since our analysis was restricted to children only. Noticeably, the GeoSES index does not include a health component in its dimensions.[16] Therefore, the different levels of SES derived from the index do not cover health access or morbidity and mortality risks. We did not have data on out-of-hospital mortality, which might be substantial especially in lower socioeconomic settings, possibly resulting in an underestimation of the pandemic effect in these settings.

In conclusion, we have described how the presence of NCDs and sociodemographic vulnerabilities are associated with mortality in hospitalised children and adolescents with COVID-19 in Brazil. We have found a higher risk of death associated with most of the NCDs included, especially when more than one was present. Indigenous, Pardo and East Asian ethnicities, as well as the Northern region and lower socioeconomic development, were also risk factors for mortality. Putting these findings together, we proposed a syndemic approach for COVID-19 and NCDs in Brazilian children. Our findings are relevant for public health policy-makers, as the country is still planning its vaccination strategy and trying to find the best way to navigate the health challenges imposed by the COVID-19 pandemic.

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