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Original Article

Inequalities and risk factors of COVID-19 patients with Down syndrome: a Brazilian cross-sectional, analytical-exploratory study

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ABSTRACT

Introduction: People with Down's syndrome, compose the group that has shown a significantly higher risk of severe illness or death from SARS-CoV-2 infection. This study analysed mortality risk in patients with Down syndrome infected by Sars-Cov-2 considering clinical and sociodemographic determinants.

Methods: For this purpose, we retrieved data from COVID-19 patients with and without Down syndrome admitted to the Brazilian hospitals with symptoms of SARS. The relationship between variables and deaths was assessed by univariate analysis, and the relative risks and confidence intervals were analyzed by Poisson regression with robust variance. Coefficients Pearson's and Spearman's were used to assess the relationship of Brazilian social indexes and rate of deaths.

Results: Out of 2597 COVID-19 patients with Down syndrome, 1105 (42.5%) died during hospitalization, and the mortality risk was 23.4% higher than patients without Down syndrome. The variables age >60 years, residence in the North region of Brazil, illiterate, and required ICU admission or mechanical ventilation were independently associated with higher mortality risk for patients with Down syndrome. The mortality rate also was negatively associated with Gross Domestic Product per capita and with literacy level and was positively associated with poverty level.

Conclusions: In the present study, we showed that school attainment/literacy correlated with the risk of mortality of Down syndrome patients infected by Sars-Cov-2 in the less favored Brazil regions. Our study suggests the need to develop education strategies and health promotion programs to mitigate the risk of mortality in COVID-19 patients with Down syndrome.

Keywords: *COVID-19; SARS-CoV-2; Down syndrome; illiteracy; Brazil; poverty*

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INTRODUCTION

Down syndrome, a genetic disorder characterized by trisomy of chromosome 21, is the commonest genetic cause for intellectual disability, with an incidence of 3.40 per 10,000 births (95% CI 3.41–5.99) in Brazil [1]. Recent findings have demonstrated that Brazilian individuals with Down syndrome under five years old, with low levels of schooling and being in a black ethnic group, are more likely to die [2].

Individuals with Down syndrome are more likely to have psychiatric and metabolic comorbidities such as obesity, diabetes, and thyroid dysfunction [3]. Still, they are not listed as "increased risk" groups of the main international health organizations (U.K. shielding list and the U.S. Centers for Disease Control). However, it is associated with pulmonary pathology and, given its prevalence, maybe a relevant risk factor for severe Coronavirus Disease 2019 (COVID-19) [4]. As other patients with intellectual and developmental disabilities [5], recent studies have shown that patients with Down syndrome had worse progression for COVID-19, including an increase in the level of

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unconsciousness [3], risk of death [6-11], and hospitalization rates [9-11] when compared with patients without Down syndrome.

Individuals with Down syndrome are more susceptible to have immune dysregulation, autoinflammatory conditions, and an exacerbated inflammatory response that may cause severe tissue damage [12] which has been associated with the triplication of chromosome 21 that leads to upregulation in its genes, including the *TMPRSS2* and *IFNAR1-2* genes [13]. The *TMPRSS2* gene encodes the TMPRSS2 protease, which further fusion the SARS-Cov-2 with the cellular membrane, and the *IFNAR1-2* genes, both interferon receptors (IFNRs), are involved in the inflammatory response by binding to interferon and the cytokines IL-10, IL-22, and IL-26 [4, 13].

In the present study, we investigated the profile of Brazilian patients with Down syndrome infected with SARS-CoV-2, aiming to estimate in-hospital mortality risk and identify associated factors. . This study also aimed to provide evidence to support local and government health programs to mitigate the worst outcomes in patients with Down syndrome infected by SARS-Cov-2.

METHODS

Study design and data source

In order to analyse the profile and outcomes in COVID-19 patients with Down syndrome, we used the Sistema de Informação de Vigilância Epidemiológica da Gripe (SIVEP-Gripe) public dataset (https://opendatasus.saude.gov.br/dataset/notificacoes-de-sindrome-gripal-leve-2020) that holds electronic health record data of patients admitted to the Brazilian hospitals with symptoms of a severe acute respiratory syndrome (SARS). Only hospitalized patients with positive RT-qPCR for SARS-CoV-2 and with known outcomes are considered as COVID-19 patients.

As shown in Figure S1, 2776,970 patients with symptoms of SARS were recorded from SIVEP-Gripe, from whom 1094,038 patients showed positive RT-qPCR for SARS-CoV-2. 2606 COVID-19 patients with Down syndrome were eligible for analysis after applying filters described in Figure S1. The first Down syndrome COVID-19 patient recorded was admitted on the 23rd of March 2020.

As control group, data from 2606 COVID-19 patients without Down syndrome in the same period were also collected randomly into age groups <01; 01 to 09; 10 to 19; 20 to 39; 40 to 59 and <60. The STROBE statement checklist (available at http://www.strobe-statement.org) was used to rate the degree of conformity.

This dataset had open-source data with no identifiers, and thus the need for patient consent was waived. Furthermore, in accordance with Resolution No. 510/2016, Article 2, of the Brazilian National Health Council (CNS), ethical approval by a Research Ethics Committee was not required, as the study utilized publicly available data that posed no risks to privacy or confidentiality.

Outcomes

The primary outcome measures were differences in in-hospital mortality risk in COVID-19 patients with Down syndrome considering clinical and sociodemographic variables of each patient. The selected variables collected were sex, race, age, zone of residence, schooling, symptoms, comorbidities, ICU admission, and the requirement of invasive or non-invasive mechanical ventilation. We also compared the mortality rates of COVID-19 patients with Down syndrome considering the social indexes for Federal District (Brasilia) and the 26 Brazilian states which are group in five regions [14].

Statistical

The data were exported and analysed using SPSS 19.0 software. Chi-square test or Fisher's exact test were used to perform the descriptive analysis on the mortality among demographic and clinical features dichotomous and to estimate the crude relative risk (RRs) and its 95% confidence level (CIs). Independent samples t-test or Mann Whitney were used for univariate comparisons of continuous data. The Poisson regression with robust variance model was used to analyse the RR and estimate their 95% CIs or adjusted prevalence ratios for secondary outcomes to each predictor. For the multivariable analysis, a generalized linear model (GLM) with Poisson distribution and log link function was used to estimate the association between exposure variables and in-hospital mortality. The model was adjusted for the following covariates: sex, race/ethnicity, educational level, geographic region of residence, age group, and the reference group classification (individuals with Down syndrome without COVID-19 or without a COVID-19 diagnosis). Robust standard errors were applied to account for potential overdispersion, and results are presented as adjusted RRs with 95% CIs. Shapiro-Wilk test was used to compare the distribution normality of indexes of each state of Brazil. Pearson's (r) or Spearman's (ρ) coefficients were used to analyse the relationship between the indexes and the rate of in-hospital deaths by discharge. All analyses were performed considering two-sided, and we considered significant p values <0.05. The complete dataset and the syntax used for the statistical analyses are available as supplementary material.

RESULTS

Demographic data of COVID-19 patients with Down syndrome

The descriptive profile and the associations between sociodemographic factors and in-hospital mortality are presented in Table 1. For COVID-19 patients with Down syndrome, no differences were observed between genders rates of discharged or dead (p=0.303). These patients living in rural areas had higher risk for in-hospital mortality than those living in urban areas (p=0.034).

Table 1: Demographics characteristics of Down syndrome patients with RT-qPCR positive for Sars-CoV-2 at hospital admission and in-hospital mortality risk (RRs) estimates from univariate analysis for each category.

Features	All cases n	Discharged n (%)	Deaths n (%)	p Value	RRs	Confidence intervals - CI 95%	
						Lower	Upper
Sex (n=2595)							
Female (ref)	1260	711 (56.4%)	549 (43.57%)				
Male	1335	780 (58.43%)	555 (41.57%)	0.303	0.954	0.873	1.043
Race (n=2164)							
White (ref)	1269	730 (57.53%)	539 (42.47%)				
Pardo	775	426 (54.97%)	349 (45.03%)	0.257	1.018	0.987	1.05
Black	96	47 (48.96%)	49 (51.04%)	0.097	1.06	0.99	1.136
Asian	19	10 (52.63%)	9 (47.37%)	-	-	-	-
Indigenous	5	2 (40.00%)	3 (60.00%)	-	-	-	-
Zona (n=2374)							
Urban (ref)	2255	1311 (58.14%)	944 (41.86%)				
Rural	109	53 (48.62%)	56 (51.38%)	0.034	1.227	1.016	1.483
Periurban	10	9 (90.00%)	1 (10.00%)	0.131	0.239	0.370	1.535
Brazilian regions (n=2597)							
Southeast (ref)	1354	808 (59.67%)	546 (40.32%)				
South	502	301 (59.96%)	201 (40.04%)	0.912	0.993	0.876	1.125
Northeast	395	176 (44.55%)	219 (55.44%)	<0.0001	1.375	1.232	1.534
Midwest	193	137 (70.98%)	56 (29.01%)	0.005	0.720	0.572	0.906
North	153	70 (45.75%)	83 (54.24%)	<0.0001	1.345	1.147	1.578
Schooling (n=936)							
Illiterate (ref)	250	112 (43.08%)	138 (56.92%)				
Low	383	223 (58.22%)	160 (41.78%)	0.004	0.787	0.668	0.928
High	293	189 (64.51%)	104 (35.49%)	<0.0001	0.669	0.552	0.810
Age. years (n=2597)							
Median (IQR)	1105	46.00 (15-77)	53.00 (21-83)			<0.0001*	
Age tiers. years (n=2597)							
<01	75	48 (64.00%)	27 (36.00%)	0.425	0.881	0.645	1.203
01 to 09	71	60 (84.51%)	11 (15.49%)	0.001	0.379	0.219	0.656
10 to 19	101	76 (75.25%)	25 (24.75%)	0.005	0.606	0.427	0.859
20 to 39	685	406 (59.27%)	279 (40.73%)	0.953	0.996	0.883	1.124
40 to 59 (ref)	866	512 (59.12%)	354 (40.88%)				
> 60	799	390 (48.81%)	409 (51.19%)	<0.0001	1.252	1.128	1.391

* Mean of differences

About race, most of COVID-19 patients with Down syndrome were White (n=1269; 48.69%), followed by Pardo (n=775; 29.74%), Black (n=96; 3.69%), Asian (n=19; 0.73%) and Indigenous (n=5; 0.19%) and no differences between race when considering the rates of death per discharged. The Asian and Indigenous groups were excluded of this analysis due to the small sample size (Table 1).

Due to inequalities in sociodemographic, education, and income between the five Brazilian regions [14], we considered each region separately to compare the outcomes (Table 1). Southeast, South, and Midwest are the regions with the best social indexes and represent 52.1%, 19.3%, and 15.2% of our sample of COVID-19 patients with Down syndrome. The Northeast and North regions showed poor social indexes and represented 7.4% and 5.9% of our analysed sample. In the univariate analyses, when compared with Southeast region (Table 1), the in-hospital mortality rates were similar than South

region while low rates of mortality was observed in the Midwest region. On the other hand, Northeast and North regions had higher mortality rates than Southeast region (Table 1).

Our analysis revealed a link between deaths and years of schooling in COVID-19 patients with Down syndrome (Table 1). Out of 936 cases with schooling registered, 250 (27.8%) were illiterate, 383 (40.9%) had low level of education (elementary school (years 1-5) plus middle school (years 6-9) and 293 (31.3%) had high-level education (high school and college education). The highest and most significant mortality rate was observed in illiterate patients when compared with patients with low or with high educational levels (Table 1).

Compared to patients in the 40- to 59-year age group, lower mortality risk was observed in the 1- to 9-year age group and in the 10- to 19-year age group. On the other hand, a mortality risk of 25.2% higher was found in patients aged 60 years and older (Table 1).

Clinical features and comorbidities of COVID-19 patients with Down syndrome

Chronic cardiovascular diseases (47.06%), diabetes (35,02%), obesity (21.0%), chronic neurologic disease (14.95%), asthma conditions (12.06%), chronic pulmonary disease (11.69%), and chronic liver disease (11.96%) were the most frequently reported comorbidities in COVID-19 patients with Down syndrome (Table 2). The risk of mortality in COVID-19 patients with Down syndrome was 16.7% increased among obese patients (p=0.015) and decreased by 18.2% for patients with chronic liver disease (p=0.029). Other comorbidities were similar between discharged or died patients (Table 2).

Table 2: Clinical characteristics of Down syndrome patients with RT-qPCR positive for Sars-CoV-2 included in the analysis at hospital admission and in-hospital mortality risk (RRs) estimates from univariate analysis for each category.

	Discharged n(%)	Deaths n(%)	p Value	RR	Confidence intervals - CI 95%	
					Lower	Upper
Reported comorbidities Chronic Cardiovascular Disease (n=2128)						
Yes	582 (27.3%)	420 (27.3%)				
No	666 (31.3%)	460 (21.6%)	0.619	1.026	0.927	1.135
Diabetes (n=2039)						
Yes	399 (19.6%)	315(15.4%)				
No	794(38.9%)	531(26.0%)	0.077	1.101	0.991	1.223
Obesity (n=1934)						
Yes	215 (11.1%)	191(9.9%)				
No	912 (47.2%)	616 (31.9%)	0.015	1.167	1.035	1.316
Chronic Neurological Disease (n=1946)						
Yes	165 (8.5%)	126(6.5%)	0.368	1.070	.926	1.235F
No	985(50.6%)	670(34.4%)				
Asthma (n=1914)						
Yes	143 (7.5%)	88 (4.6%)	0.39	0.928	0.78	1.104
No	992 (51.8%)	691 (36.1%)				
Chronic Pulmonary Disease (n=1933)						
Yes	131 (6.8%)	95 (4.9%)	0.655	1.038	0.882	1.223
No	1016 (52.6%)	691 (35.7%)				
Chronic Liver Disease (n=1927)						
Yes	151 (7.8%)	78 (4.0%)	0.029	0.818	0.677	0.988
No	991 (51.4%)	707 (36.7%)				

Continues...

Table 1: Continuation.

	Discharged n(%)	Deaths n(%)	p Value	RR	Confidence intervals - CI 95%	
					Lower	Upper
Chronic Hematological Disease (n=1929)						
Yes	141 (7.3%)	80 (4.1%)	0.139	0.875	0.728	1.051
No	1001 (51.9%)	707 (36.7%)				
Immunocompromised (n=1936)						
Yes	117 (6.0%)	76 (3.9%)	0.739	0.969	0.806	1.165
No	1035 (53.5%)	708 (36.6%)				
Chronic Kidney Disease (n=1926)						
Yes	110 (5.7%)	79 (4.1%)	0.783	1.025	0.859	1.225
No	1029 (53.4%)	708 (36.8%)				
Reported symptoms						
Dyspnea (n=2407)						
Yes	997 (41.4%)	888 (36.9%)	<0.001	1.673	1.447	1.934
No	375 (15.6%)	147 (6.1%)				
Oxygen saturation ≥95% (n=2408)						
Yes	988 (41.0%)	864 (35.9%)	<0.001	1.582	1.379	1.815
No	392 (16.3%)	164 (6.8%)				
Cough (n=2380)						
Yes	1054 (44.3%)	744 (31.3%)	0.268	0.941	0.845	1.047
No	326 (13.7%)	256 (10.8%)				
Fever (n= 2358)						
Yes	944 (40.0%)	656 (27.8%)	0.458	0.962	0.869	1.065
No	435 (18.4%)	323 (13.7%)				
Shortness of breath (n=2347)						
Yes	842 (35.9%)	785 (33.4%)	<0.001	1.565	1.387	1.765
No	498 (21.2%)	222 (9.5%)				
Sore throat (n=2126)						
Yes	309 (14.5%)	176 (8.3%)	0.019	0.859	0.754	0.979
No	948 (44.6%)	693 (32.6%)				
Vomiting (n=2107)						
Yes	193 (9.2%)	109 (5.2%)	0.076	0.87	0.741	1.02
No	1056 (50.1%)	749 (35.5%)				

Continues...

Table 1: Continuation.

	Discharged n(%)	Deaths n(%)	p Value	RR	Confidence intervals - CI 95%	
					Lower	Upper
Diarrhea (n=2098)						
Yes	262 (12.3%)	135 (6.4%)	<0.001	0.778	0.667	0.907
No	995 (46.8%)	732 (34.5%)				
Abdominal pain (n=1719)						
Yes	127 (7.4%)	54 (3.1%)	<0.001	0.707	0.561	0.891
No	889 (51.7%)	649 (37.8%)				
Fatigue (n=1768)						
Yes	312 (17.6%)	237 (13.4%)	0.296	1.065	0.947	1.198
No	725 (41.0%)	494 (27.9%)				
Loss of Smell (n=1700)						
Yes	126 (7.4%)	63 (3.4%)	0.023	0.794	0.644	0.98
No	877 (51.6%)	634 (37.3%)				
Loss of Taste (n=1698)						
Yes	118 (6.9%)	59 (3.5%)	0.032	0.8	0.644	0.993
No	887 (52.2%)	634 (37.3%)				
Hospital interventions						
Respiratory support (n= 2396)						
Absence or standard oxygen therapy	308 (12.9%)	74 (3.1%)				
Invasive	171 (7.1%)	550 (23.0%)	<0.001	3.938	3.196	4.851
Non-invasive	888 (37.1%)	405 (16.9%)	<0.001	1.618	1.299	2.016
ICU required (n=2455)						
Yes	459 (18.7%)	707 (28.8%)	<0.001	2.306	2.081	2.554
No	950 (38.7%)	339 (13.85)				

As shown in Table 2, in COVID-19 patients with Down syndrome, the most common symptoms were dyspnoea (78.3%), oxygen saturation ≥95% (76.9%), cough (75.5%), fever (67.9%), shortness of breath (69.3%). Less common symptoms were sore throat (22.8%), diarrhoea (18.0%), and vomiting (14.3%). In addition, some general symptoms such as myalgia (n=177) and headache (n=151) also were reported. In the univariate analyses, dyspnoea, oxygen saturation ≥95%, and breathing comfortably symptoms were associated with high mortality rates, while diarrhoea, sore throat, abdominal pain and loss of smell or taste were associated with high discharged rates (Table 2).

Hospital length of stay and hospital interventions of COVID-19 patients with Down syndrome

Out of 2396 COVID-19 patients with Down syndrome, a total of 1029 (43.0%) patients died, and the higher mortality risk was observed in patients that required non-invasive and invasive respiratory support when compared to absence or standard oxygen therapy (Table 2). Out of 1166 patients that required ICU admission, 707 (60.6%) patients died and showed a higher risk to die than patients who did not require ICU care (p<0.001).

Association between mortality risk in COVID-19 patients with Down syndrome and economic-social indicators for Brazilian regions

We also analysed the correlation between the rate of in-hospital deaths by discharge and the indexes of each state of Brazil [14] As shown in Figure 1, the in-hospital mortality rate was negatively associated with Gross Domestic Product (GDP) *per capita* (Figure 1A) and with literacy level (Figure 1B) while the poverty level (Figure 1C) was positively associated with the in-hospital mortality rate. We did not find evidence of significant correlation between mortality rate and follow indexes: food security (r=-0.2501; p=0.228), higher education (ρ=-0.3731; p=0.0662), life expectancy (r=-0.1756; p=0.4011), school dropout (ρ=0.1122; p=0.593), salary (ρ=-0.2501; p=0.228) and child mortality (r=0.0004; p=0.9842) (data not shown).

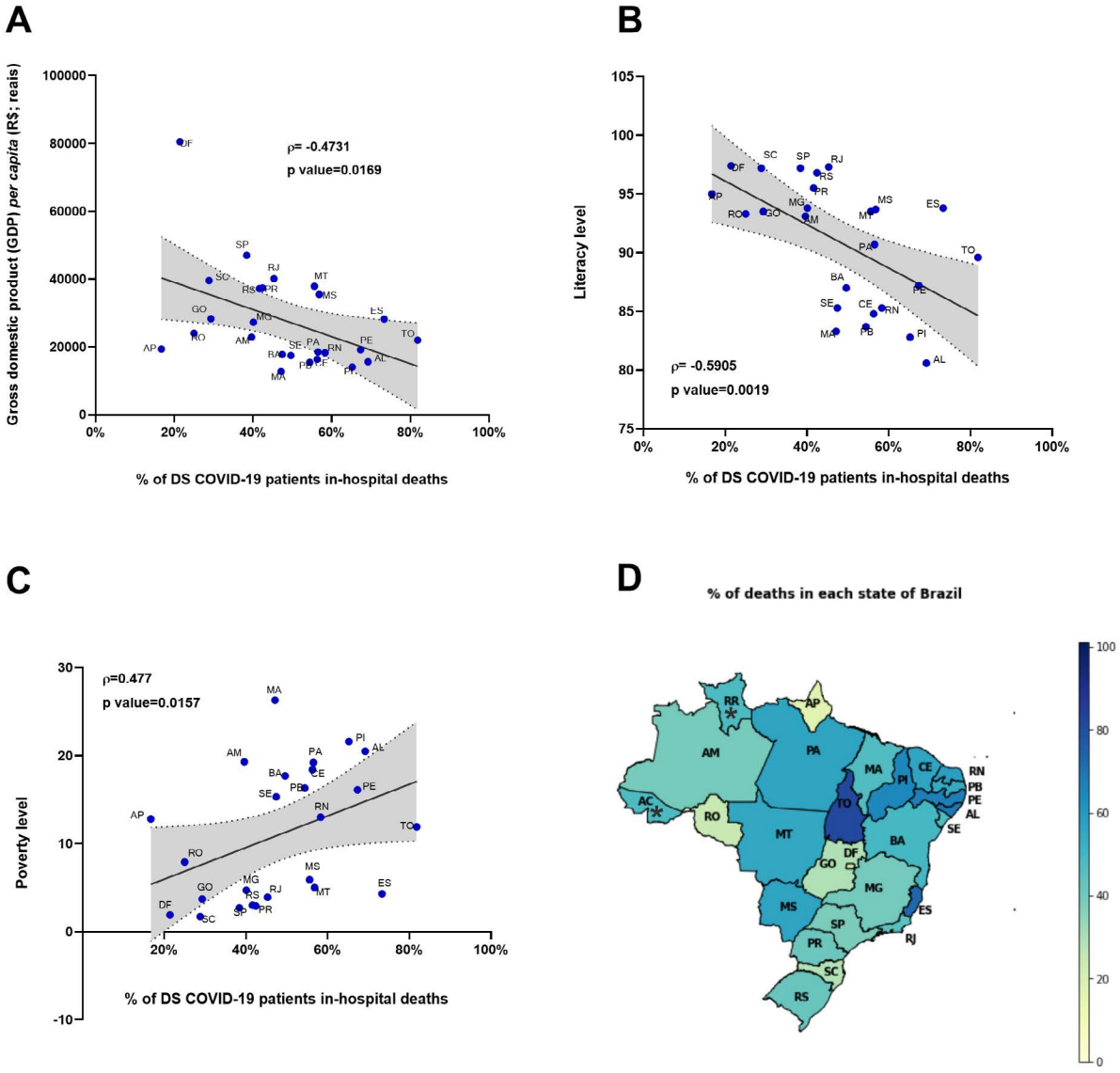

Figure 1: Spearman's correlation coefficient (ρ) between (A) Gross domestic product *per capita*, (B) literacy level and (C) poverity level with the percentage (%) of in-hospital mortality in Down syndrome patients with RT-qPCR positive for Sars-CoV-2 individualized by the rate of each state of Brazil (D) .* The mortality rate was not calculated for Acre (AC) and Roraima (RR) Brazilian states due to the absence of cases of in-hospital mortality or discharge.

Multivariate model for in-hospital mortality risk (RRs) for COVID-19 patients with Down syndrome

In the multivariate model, the robust Poisson regression was used to estimate the mortality risk ratios considering schooling level, age groups, macro regions of Brazil, ICU admission, and oxygen therapy variables. The relative mortality risk was increased at 56.7% for patients from the North Brazilian region 32.8% for patients who require ICU care, 31.6% for patients older than 60 years, and 95.1% and 279.3% for patients who use non-invasive or invasive mechanical ventilation, respectively. On the other hand, a decrease in the relative mortality risk was observed at 37.9% and 27.8% for patients with low and high schooling levels, respectively (Figure 2). When the variables diabetes and chronic liver disease were added in the multivariate model, both variables lose the significance observed in the univariate analysis, and do not impact the significance of the variables described above (data not shown).

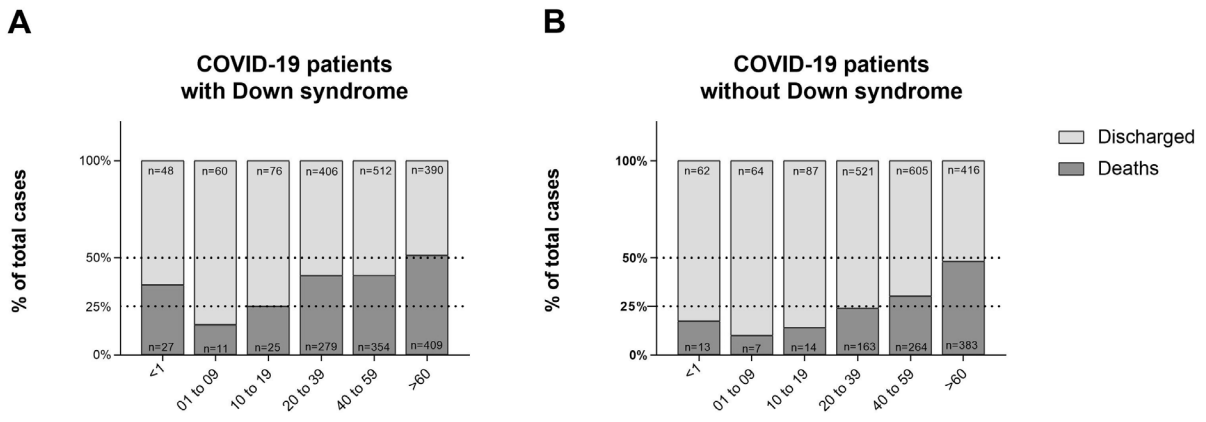

Figure 2: Multivariate model for in-hospital relative mortality risk (RRs) for COVID-19 patients with Down syndrome (circle) and random group without Down syndrome (square).

Comparison of COVID-19 patients with and without Down syndrome

As described in the Methods section, a control group was composed by COVID-19 patients without Down syndrome that was randomized by the same period and age groups that the COVID-19 patients with Down syndrome data were collected (Figure S1). The clinical and sociodemographic features and their associations with discharged and in-hospital mortality are presented in supplementary Tables S1 and S2. It is important to note that the objective of the group formed by COVID-19 patients without Down syndrome was to estimate how much being Down syndrome will impact the risk of mortality on COVID-19 disease considering the same seasonal period that we collected information from COVID-19 patients with Down syndrome. The risk of mortality and clinical characteristics of Brazilian patients that developed COVID-19 disease was recently published by our group and others [15].

In the COVID-19 patients without Down syndrome, differently that was observed in the COVID-19 patients with Down syndrome, we did not find an association between the risk relative of mortality with education levels low or high and with patients that reside in the North region of Brazil (Table S1).

Otherwise, similar to the Down syndrome COVID-19 group, a higher mortality risk was observed in patients that reside in the Northeast region, in patients with use of non-invasive mechanical ventilation older than 60 years and in patients requiring ICU care or invasive mechanical ventilation (Table 1 and Table S1). Likewise, in both COVID-19 groups-lower risk for mortality was shown for patients ranging 01 to 09 and 10 to 19 years compared to individuals who had 40-59 years.

When compared the reported symptoms, very similarity than COVID-19 patients with Down syndrome, the most frequent were dyspnoea (75.3%), cough (71.4%), oxygen saturation ≥95% (68.7%), shortness of breath (63.8%), and fever (61.7%) (Table S2). Likewise, in both groups were observed that reported symptoms dyspnoea, oxygen saturation ≥95%, and breathing comfortably symptoms were associated with high mortality rates, while diarrhoea, sore throat, abdominal pain and loss of smell or taste were associated with high discharged rates (Table 2 and Table S2). Due to this similarity, the symptoms were not included in the multivariate analysis.

About previous comorbidities, as expected of COVID-19 patients without Down syndrome [15], chronic cardiovascular diseases, diabetes, obesity, chronic pulmonary disease, and chronic liver disease were associated with higher mortality risk while asthma condition was associated with lower mortality risk (Table S2).

In the multivariate model, the same variables used in the COVID-19 patients with Down syndrome were included, and as shown in Figure 2, remained associated with higher mortality risk the necessity of ICU care (21.8%), use of invasive mechanical ventilation (24.8%) and age over than 60 years (10.2%). Across all age groups, the general mortality rates of COVID-19 patients with Down syndrome were 23.4% higher than COVID-19 patients without Down syndrome.

As shown in Figure 3, in the first year of life, the mortality rates of COVID-19 patients with Down syndrome nearly double compared with COVID-19 patients without Down syndrome (36.00 to 17.28%). Also, it is possible to observe that COVID-19 patients with Down syndrome had high mortality rates than those without Down syndrome in the 20 to 39 (40.7 vs 23.8%) and 40 to 59 (40.9 vs 30.3%) years. Lastly, the highest mortality rates in both groups were observed in patients older than 60 years (Figure 3).

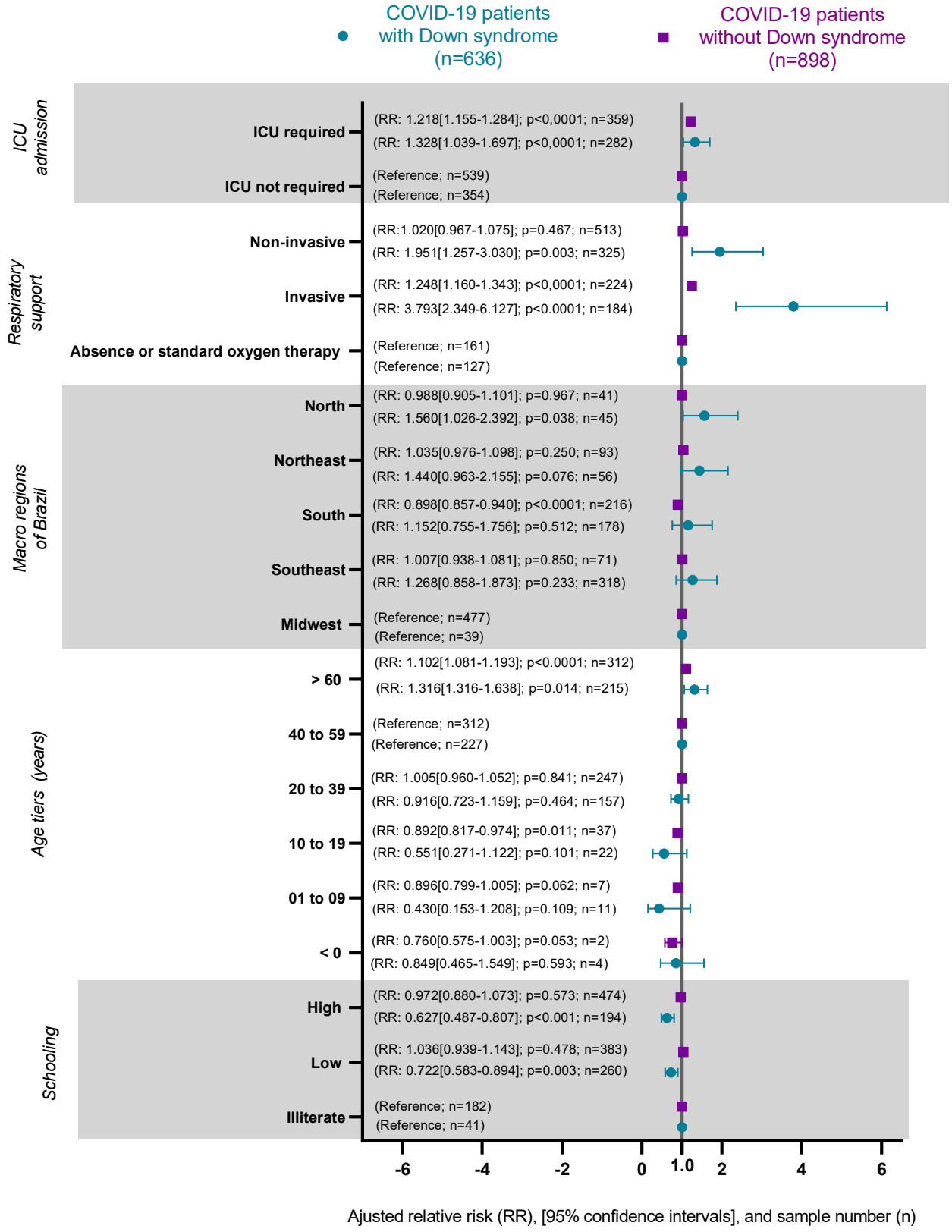

Figure 3: Comparison of in-hospital discharge and mortality stratified by age in COVID-19 patients with (A) Down syndrome and (B) random group without Down syndrome.

DISCUSSION

In the present study, our results showed the effects of clinical and sociodemographic features in mortality risk in hospitalized COVID-19 patients with Down syndrome from all regions of Brazil. The mortality risk was estimated using the Poisson regression, broadly suggested to directly estimate risk ratios for binary outcomes once this model considers the homogeneity of risk within the analysed variable [16].

Compared with the general Brazilian population, patients with Down syndrome have been more vulnerable to unfavourable clinical outcomes by infection with Sars-Cov-2 [15]. The estimates of increased in-hospital mortality risk reported for COVID-19 patients with Down syndrome in the literature vary in ranges of 2 to 3 times [3, 17], 6.5 times [9], ten times [6, 7] and even more than 20 times [8, 11] in comparison to different groups of patients. This disparity in these results could be due to the control groups used to compare the mortality rates with COVID-19 patients with Down syndrome, types of multivariable analysis, and their variables selected to estimate the relative mortality risks. However, all these studies reinforce that COVID-19 patients with Down syndrome had worse clinical outcomes, including younger mortality.

Our study demonstrated that in the first year of life, the mortality rate of COVID-19 patients with Down syndrome was about twice as compared to the COVID-19 patients without Down syndrome and that for young adults COVID-19 individuals with Down syndrome had a 17% higher mortality than COVID-19 individuals without Down syndrome (Figure 3). These results are in line with an online survey in the United Kingdom that demonstrates that although low, under-40 mortality rates were more significant than in the general population [3]. In addition, data from a study in Spain showed an odds ratio for mortality of adults with Down syndrome above 40 of 18.4% [10].

Differently from shown in general patients with COVID-19, our data suggests no disadvantage for male COVID-19 patients with Down syndrome for mortality risk once women and men presented similar mortality and discharged patterns (Table 1). A meta-analysis study showed that for the general population with COVID-19, the male gender is an independent risk factor for the worse progression of COVID-19 [18]. Moreover, a recent cohort study conducted with a sample of Brazilian Down syndrome patients showed that general mortality rates are not different among men and women [2].

Patients with Down syndrome who live in the North region of Brazil were pointed to have lower survival chances considering a period of 1996 to 2016 [2]. The authors suggested it could be a consequence of the low number of specialized health services for these patients in the North region. In addition, epidemiological studies showing the COVID-19 pandemic impacts of inequalities of Brazilian regions have been rising in the literature [19-21]. Our study reinforces these findings and brings important political implications. The association between education level and risk of in-hospital mortality revealed that improvements in education (low and high, respectively) could prevent about 27.1% and 32.5% of deaths in COVID-19 patients with Down syndrome compared to illiterate individuals, even adjusted by age tiers, gender, race, ICU admission and mechanical oxygen support required (Figure 1). Thus, the Brazilian regions states with poor social indexes are expected to present major negative impacts on educational levels and provide adequate health care services and strategies. As shown in Figure 1C, for COVID-19 patients with Down syndrome, there is a positive association between a higher mortality risk with poverty levels in Brazilian states. The results were reinforced by the association between risk of mortality and by GDP *per capita* (Figure 1A) and literacy level (Figure 1B) in Brazilian states.

This result highlights the importance of implementing educational programs and strategies for Down syndrome patients, particularly for individuals who live in poor conditions. Individuals with lower years of schooling will probably show poor lifestyles once higher educational levels, especially higher educational attainment, lead to a better understanding of health information processing ability [22]. In a multicentric study recently published by Hüls and cols., there are some suggestions to support caregivers and to provide good practices to mitigate risk factors and poor outcomes in Down syndrome patients during the pandemic time [17].

In Brazil, patients with Down syndrome, as others intellectual disabilities, were one of the priority groups for vaccination against COVID-19 in the Brazilian National Immunization Program. This is an important point to be note once recently studies have been shown that in adults with Down syndrome the antibody responses against SARS-CoV-2 were significantly decreased compared with those healthy individuals [23, 24].

The triplication of chromosome 21 that leads to the upregulation of the *TMPRSS2* gene may partly explain the higher susceptibility of people with Down syndrome to be infected by Sars-Cov-2. Besides *TMPRSS2*, the *IFNAR1-2* and *CCR2* genes have also been essential drivers in these complications [13, 25] and associated with exacerbation of inflammatory reactions caused by cytokine storms in immune and non-immune tissues and cells [4]. Moreover, due to the most common of multiorgan comorbidities, patients with Down syndrome need to have a follow-up visit to the hospital more frequently than patients without Down syndrome, which increases the risk of

infection by Sars-Cov-2. Additionally, Down syndrome individuals have higher rates of overweight [26], which was related to proinflammatory states and risk of poorer COVID-19 outcomes [27].

As expected, similar to general patients with COVID-19 [15], COVID-19 patients with Down syndrome that require more intensive supportive interventions as ICU admission and invasive or non-invasive support oxygen had a significantly higher risk of death (Table 2; Figure 1). On the other hand, conversely observed in the general Brazilian population that cardiovascular diseases, diabetes, and obesity were the most prevalent risk factors for mortality [15], the multivariate analysis revealed that these comorbidities were not an independent factor associated with mortality in COVID-19 patients with Down syndrome (data not shown). We believe these results could be attributed to the regular monitoring and treatment of common comorbidities in Down syndrome patients, such as obesity, diabetes, and cardiac diseases [3].

Our study presents some limitations. First, the analysed data in the present study were based on hospitalized COVID-19 patients Down syndrome patients. Thus, both clinical and administrative data showed in this study should not be extrapolated to the general COVID-19 patients with Down syndrome. Second, patient data missing or "not reported" are significantly high on the dataset and can reflect the rising number of notifications in the mandatory SIVEP-Gripe system of COVID-19 hospitalizations. Unfortunately, Brazilian hospitals do not share an integrated health system to streamline the process of these notifications and efforts to improve it are needed to help the health system of Brazilian hospitals.

In conclusion, we showed that besides symptoms and comorbidities to appear do not affect the mortality risk independently in COVID-19 patients with Down syndrome, and the school attainment/literacy seems to be correlated with mortality risk of patients with Down syndrome infected by Sars-Cov-2 in the less favoured Brazil regions. As an opportunity to improve the health equity education for patients with Down syndrome, governments and local social programs could support by using innovative medical technologies in regular programs adapted to the specific case of Down syndrome people to connect these communities to specialized centres. This mitigation strategy together with promotion of booster doses of the COVID-19 vaccine could improve the quality of life, decrease the mortality risk of infant and adult patients with Down syndrome and help public health cost containment.

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