# Down syndrome *per se* is associated with increased risk for in-hospital mortality and morbidity in paediatrics with SARS-CoV-2 in Brazil

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**Author contributions**

Dr Char Leung conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Selle Arocha drafted the initial manuscript and reviewed and revised the manuscript for important intellectual content.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Abstract**

Down syndrome (DS) is the commonest chromosomal disorder. It is not clear if it is a risk factor for COVID-19 mortality and morbidity in paediatrics, those in low-to-middle income countries in particular. Data of paediatrics aged below 18 years with SARS-CoV-2 infection were gathered from a national registry in Brazil. A total of 14,684 hospitalised patients were included, including 261 patients with DS. After adjusted for sociodemographic and medical factors, paediatrics with DS had 1.8 times higher odds to die from COVID-19 (OR 1.82, 95% CI 1.22-2.68) and had 27% longer time to recovery (HR 0.73, 95% CI 0.61-0.86). PSM confirmed that patients with DS had a higher CFR and longer median time to recovery. Down syndrome per se was associated with increased risk for mortality and morbidity. The increased risk of death among people with DS may be due to social factors and biological factors such as immune responses.

## Introduction

First described by John Langdon Down in the 19th century, Down syndrome (DS) is a birth defect caused by a random error in cell division during fetal development. It is a rare disease yet the commonest chromosomal disorder, with an incidence of 14 *per* 10,000 live births globally and 4 per 10,000 in Brazil[1]. The prevalence rate of DS in Brazil is not known[2]. Nevertheless, the number of deaths in individuals with DS has increased in recent years with increased susceptibility observed in children[2]. Possible explanations include socioeconomic and regional difference in the quality of and access to healthcare, the North and Northeast region in particular[2,3]. Furthermore, while guidelines of healthcare for individuals with DS have been proposed by the Brazilian government, compliance remained poor[4].

Characterised by anatomical abnormalities and intellectual disabilities, individuals with DS are more prone to develop chronic diseases, including visual impairment (prevalence of 73%), thyroid disease (50%), congenital heart disease (25%), hypoacusis (27%), obesity (22%), osteoporosis (20%), and epilepsy (8%)[5]. Because of immune disturbances, they are also more susceptible to respiratory tract infections and acute respiratory distress syndrome (ARDS)[6]. Congenital heart defects and respiratory infections remain the most common causes of death[7] despite the improvement in treatment for DS over the past three decades[8]. In children with DS, up to 80% of all hospitalisations and admission to the paediatric ICU is due to lower respiratory tract infections and up to 29% of deaths are associated with pneumonia, influenza, and aspiration[9].

Children with DS may be at a higher risk of COVID-19-related mortality. First, respiratory failure is a major cause of death in patients with COVID-19. Second, comorbidities such as cardiovascular disease and obesity that are common in patients with DS have been identified as independently risk factors for COVID-19-related mortality[10]. Despite this, little attention is

paid to SARS-CoV-2 infection in children with DS. Relevant studies remain very rare and findings are limited. A case-control study by Emes and colleagues found low mortality rates in paediatric patients with SARS-CoV-2 in both high and low-to-medium countries, irrespective of the presence of DS, in contrast with higher mortality rates in adults with DS than those without DS[11]. In addition, the authors failed to find the association between paediatric DS and the risk of SARS-CoV-2 related mortality due to the limitation of the data. Against the background, the present work aims to fill this gap with a higher level of evidence by conducting a cohort study with propensity score matching that eliminates confounding stemming from comorbidities associated with DS. We used a nationwide database in Brazil to examine whether paediatric DS was associated with increased risk of COVID-19 related in-hospital mortality and morbidity.

## Methods

### Selection of study cohort

The study population was those registered in SIVEP-Gripe, a nationwide database managed by the Brazilian Government that has been studied and described elsewhere[2]. It was developed for the surveillance of severe acute respiratory syndrome (Síndrome Respiratória Aguda Grave, SRAG) related to influenza and other respiratory viruses since the influenza H1N1 pandemic in 2009. Patients diagnosed with one of the Compulsory Reporting Diseases (Doenças de Notificação Compulsória, DNC) and admitted to public or private hospitals were registered in SIVEP-Gripe. Upon the outbreak, COVID-19 has been declared a DNC and was incorporated in the surveillance network. SIVEP-Gripe is the primary source of information on COVID-19-related hospital admissions and deaths in Brazil. Basic demographic and medical data were systematically registered in a pre-determined form that was used for hospitalisation due to SRAG and verified by the medical practitioner at the point of care.

All data were gathered on the 26th November 2021 and all cases registered in SIVEP-Gripe that met all following criteria were included in the study, (i) PCR positive for SARS-CoV-2, (ii) recovered or died, (iii) aged <18 years, and (iv) the presence of Down syndrome. Patient died of causes other than SARS-CoV-2 infection were excluded.

Study definition

Patients meeting all selection criteria were categorized as DS or non-DS. That is, those with DS and without DS, according to the database.

Data source/measurement

Data of covariates were also gathered from SIVEP-Gripe, including sociodemographic factors and clinical characteristics (intervention, and signs and symptoms). These included age, sex, clinical endpoint (discharge or died), time to recover (time from admission to discharge), ethnicity (Caucasian, Asian, Hispanic/African, or indigenous), location (North, Northeast, Southeast, Center West, and South region), the need for ventilation, ICU admission, vaccination (against influenza and SARS-CoV-2), use of antivirals against influenza, signs and symptoms (including asymptomaticity), and comorbidities (chronic cardiovascular, hematologic, liver, renal and neurologic diseases, asthma, diabetes, immunocompromised, chronic pulmonary diseases, obesity, and respiratory viral infection other than SARS-CoV-2).

Sex and ethnicity were self-identified. Ethnicity was included to reflect the racial disparity in access to healthcare. Signs, symptoms, and comorbidities referred to those at symptom onset and at admission. They were included because they are predictors of in-hospital COVID-19 death[12]. Location referred to one of the five Regions in Brazil, namely North, Northeast, Southeast, Center West, and South. It was included to reduce the bias due to the geographical disparity in access to healthcare. Other clinical covariates were recorded during the clinical

course. Antivirals referred to those against influenza such as Oseltamivir and Zanamivir. Respiratory viral infections were confirmed using PCR tests and the viruses included influenza, respiratory syncytial virus, human parainfluenza virus, adenovirus, metapneumovirus, bocavirus, rhinovirus, enterovirus, and other coronaviruses that do not generally cause ARDS, namely NL63, OC43, 229E, and HKU1. They should not be ignored in high-risk individuals[13] and therefore are included in the analysis.

Complete data were not available for all variables. For any missing data on signs, symptoms, or comorbidities, the clinical condition is assumed to be absent, following the approach in a previous study that analysed the same database[14]. To reduce age-related selection bias, the age considered in this study was calculated as the difference between the date of birth and the date of symptom onset rather than the self-reported age. Cases without date of birth were considered missing data and were excluded.

### Definition of outcomes and comparison groups

The primary outcome was whether DS is associated with increased risk for in-hospital mortality, measured by odds ratios (OR) for mortality and the in-hospital case fatality rate, adjusted for demographic factors, pre-existing conditions other than DS, and intervention. The secondary outcome was whether DS is associated with increased risk for morbidity, measured by hazard ratios (HR) for recovery and median time to recovery, adjusted for demographic factors, pre-existing conditions other than DS, and intervention.

### Statistical analysis

For the primary outcome, the OR for mortality was calculated using a multivariable logistic regression model. The in-hospital case-fatality rate of patients with and without DS was statistically compared. Because patients with DS usually have a higher rate of comorbidities, confounding effects need to be eliminated. While multivariable logistic regression can

mitigate confounding, propensity score matching was used to further confirm the results. Binary logistic regression was used to generate propensity scores with each DS case matched to 3 non-DS cases. The selection of other variables followed that in computing the OR. However, to minimise over-matching bias, signs and symptoms were not included for matching because they might be mediators. As such, matching for other covariates should be sufficient to produce a balanced sample. Moreover, matching was performed without replacement and cases with missing data were excluded for matching. This assumption was assessed and discussed in the subsequent section. The predicted probabilities generated by the multivariable logistic regression model was used as scores for matching.

For the secondary outcome, the HR for time to recovery was calculated using a multivariable Cox regression model. Therefore, it also served as a subgroup analysis in which only recovered cases were considered. The median time to recovery of patients with and without DS was statistically compared. Similarly, propensity score matching was used to further confirm the results with the procedure described above. All variables but time to recovery were included in the logistic regression for producing the scares.

For the comparison of any descriptive statistics between the DS and non-DS cohort, Mann-Whitney tests or *t*-tests were used for continuous variables (i.e. age and time to recovery), depending on the normality condition. Fisher's exact tests (Chi-squared test is an approximate test) were used for dichotomous variables.

The forward variable selection procedure was adopted for all regression models, including the models for generating propensity scores, with a *p*-value of 10% as the threshold and the E-value for sensitivity analysis[15]. Briefly speaking, the E-value is the minimum strength of association that an unmeasured confounder would need to have with both the case and the control group to fully explain away a specific exposure-outcome association, conditional on

the covariates[15]. Because ICU admission and ventilation are mediators rather than confounders, they were removed from the regression analysis. The Southeast region where healthcare is generally more accessible in the country was chosen as the reference for the location variables. The Hispanic/African group was chosen as the reference for ethnicity as they are the largest ethnic group in the country. For the logistic regression model, the area under the receiver operating characteristic (ROC) curve was used to assess the goodness-of-fit. For the Cox regression model, the concordance index was used to assess the goodness-of-fit.

All calculations were performed using R Version 4.1.1. and packages "*MatchIt*" and "*survival*" were used. A *p*-value of 5% was considered significant.

### Ethics approval

Ethics approval is not required in Brazil and UK because the data are de-identified and publicly available.

## Results

A total of 2,812,965 cases were registered in the SIVEP-Gripe of which 1,162,755 (41.3%) were PCR positive for SARS-CoV-2 (Fig. 1). Among these patients, 17,018 (1.5%) aged below 18 years, 1,144,249 (98.4%) aged 18 or above, and 1,488 (0.1%) had age missing. Of those aged below 18 years, 261 (1.5%) and 16,757 (98.5) patients had and did not have DS, respectively. Among them, 78 (1.3%) died of causes other than SARS-CoV-2 infection and 2,256 (22.1%) had outcome missing. Consequently, a total of 14,684 cases (86.3%) with PCR diagnosis dated between 5$^{th}$ March 2020 and 22$^{nd}$ November 2021 met all selection criteria and were included in the study.

As shown in Table 1, 236 patients (1.6%) in the study cohort had DS. The sample was well balanced with no significant difference in the male proportion ($p$=0.237) and median age

($p$=0.670) between the two groups. The in-hospital case-fatality rate for those with and without DS was 23.7% and 8.2%, respectively, and the difference was highly significant ($p$<0.001). A longer median time to recover was observed in the DS group (8.5 days vs 5 days, $p$<0.001). Signs and symptoms that usually indicate a more severe clinical course of SARS-CoV-2 infection were more prominent in patients with DS. These include dyspnoea (59.8% vs 48.9%, $p$=0.001), low $SaO_2$ (58.9% vs 37.4%, $p$<0.001), and respiratory discomfort (59.8% vs 45.8%, $p$<0.001). Not surprisingly, patients with DS were more prone to chronic health conditions, most notably chronic cardiovascular disease (35.6% vs 3.5%, $p$<0.001) and immune disorder (6.78% vs 3.55%, $p$=0.013). Furthermore, patients with DS required more advanced healthcare as demonstrated by the higher rate of ICU admission (47.5% vs 27.0%, $p$<0.001) and ventilation (67.4% vs 44.5%, $p$<0.001).

As shown in Fig. 2, the multivariable logistic regression model suggested that patients with DS had a higher risk for in-hospital mortality (adjusted OR 1.82, 95% CI 1.22-2.68), after the adjusting for demographic and clinical factors, such as chronic cardiovascular diseases (adjusted OR 2.61; 95% CI 2.02-3.35), chronic neurological diseases (adjusted OR 2.41; 95% CI 1.93-2.98), chronic renal diseases (adjusted OR 1.99; 95% CI 1.29-3.01), chronic liver diseases (adjusted OR 4.15, 2.19-7.68), and obesity (adjusted OR 1.97; 95% CI 1.35-2.81). The adjusted OR for DS was smaller than the crude counterpart of 3.49 (95% CI 2.55-4.71) and the difference suggested the impact of confounding factors. Similarly, sizeable difference in the crude and adjusted ORs was observed for several comorbidities, suggesting an association between them.

The difference in the crude and adjusted ORs for location and ethnicity variables might not reflect the effect of confounding. This is because the adjusted ORs were calculated with a reference group, giving different interpretations. For example, the crude OR for North means that patients in the North region had two times the odds to death compared to those not in the

North region, whereas the adjusted OR means that patients in the North region had about 2.7 times the odds to death compared to those in the Southeast region (the reference group).

The area under the ROC was reported to be 0.80 (95% CI 0.79-0.81), indicative of excellent accuracy. Odds ratios related to COVID-19 mortality were usually around $2^{16}$, close to the computed E-values (Table S1), indicative of fair robustness of our results in terms of the influence of unmeasured confounders.

The difference in the case-fatality rate between the two cohorts after propensity score matching was shown in Table S2. Although matching was performed based on demographic and clinical variables, none of the sign and symptom variables were significantly different, in line with our assumption stated in the previous section and therefore did not need to be included to reduce over-matching bias. Furthermore, no significant difference was observed in demographic and clinical variables, indicative of efficient matching. Again, after the removal of confounding, the in-hospital case-fatality rate was 24.08% (46/191) and 16.93% (97/573) for patients with and without Down syndrome, respectively, and the difference was significant ($p$=0.032). Histograms showing estimated propensity scores indicate common support by DS status (Fig. S1).

For time to recovery, the Kaplan-Meier curves of DS and non-DS group were shown in Fig. 3. The log-rank test suggested a difference in the two survival curves ($p$<0.0001). It was clear that patients with DS had a lower probability of recovery during the first month of hospital admission. As shown in Fig. 4, patients with DS had 27% longer time to recovery (adjusted HR 0.73; 95% CI 0.61-0.86), after adjusted for demographic and clinical factors. Other comorbidities were also found to be significantly associated with longer time to recovery. Patients with chronic renal disease (adjust HR 0.66; 95% CI 0.54-0.79), chronic neurological disease (adjusted HR 0.58, 95% CI 0.53-0.64), chronic haematologic disease (adjusted HR

0.84; 95% CI 0.72-0.98) and chronic cardiovascular disease (adjusted HR 0.71; 95% CI 0.63-0.79) had 34%, 42%, 16%, and 29% longer time to recovery, respectively.

The concordance index was reported to be 0.61 (95% CI 0.61-0.62) meaning that the Cox regression model was adequate. Adjusted HRs related to time to recovery in COVID-19 patients were usually 1.2 and 1.7[17], smaller than most of the computed E-values (Table S3), indicative of fair robustness of our results.

The difference in the median time to recovery between the two cohorts after propensity score matching was shown in Table S4. The matched cohorts were well balanced with no significant difference in all measures. The median time to recovery was 9 and 6 days for patients with and without DS, respectively, and the difference was significant ($p$=0.005). Histograms showing estimated propensity scores indicate common support by DS status (Fig. S2).

**Discussion**

We found increased risk for in-hospital COVID-19 related mortality and morbidity in paediatric patients with DS, after adjusting for demographic and medical factors.

Apart from case reports/series, Emes et al[11] is so far the only large-scale study on COVID-19 in paediatric patients with DS. It is a case-control study with 328 cases selected from several countries and it may be prone to selection bias as all controls were selected from the US. The authors reported a mortality rate of 6.7% in children with DS in low-to-medium income countries, an estimate lower than that observed in our study cohort. This is partly attributed to the socioeconomic inequality and vulnerability in Brazil, despite efforts to ensure access to health services by people with disabilities[18]. Unfortunately, inequality in access to healthcare remains visible in the country. As shown in Fig. 2 and Fig. 4, paediatric patients with SARS-CoV-2 in the regions with a low socioeconomic profile such as North and Northeast had

about 3 to 4 times the odds to death and about 30% longer time to recovery, compared with those in the South region. Furthermore, inequality in access to heart surgery as a treatment for DS-related heart defects may also explain the higher in-hospital case-fatality rate observed in our study because chronic cardiovascular disease is found to be an independent risk factor for COVID-19-related in-hospital mortality. Even in southern Brazil, where healthcare is more accessible, only a quarter of patients with DS had undergone heart surgery[19]. Nevertheless, patients with DS who were submitted to heart surgery still have higher risk for COVID-19 related mortality. We found that DS *per se* is a mortality risk factor even after the adjustment for chronic cardiovascular disease.

Looking beyond Brazil, a number of factors specific to Latin America may explain why DS *per se* is a COVID-19 related risk factor for morbidity and mortality. First, quality healthcare may be out of reach for families having children with DS as they are often ostracized by the society due to the religiously motivated social perception of DS. For instance, medical practitioners in Ecuador rarely deal with the diagnosis of DS in a professional manner[20]. Even worse, this can lead to the lack of trust in the healthcare system, discouraging them from seeking professional help. Second, some families have no access to prenatal tests and healthcare for COVID-19 because of financial hardship rather than the geographical disparity in access to healthcare. Therefore, the increased risk for mortality resulting from the lack of healthcare is not reflected by the geographical variables in our study but associated with the DS status. This is not just an issue in Brazil because a sizeable population in Latin America have no access to any kind of health insurance[21]. Third, Latin America remains one of the least vaccinated areas in the world. Barely 30% of the population in region has been vaccinated. Accounting for only 8.4% of the world's population, Latin America contributed to 20% of the global confirmed cases of COVID-19 and 30% of the deaths.[22].

Increased risk of mortality and morbidity in patients with COVID-19 and DS intensifies the burden of DS that already has a greater impact on the society in Latin America than in most parts of the world due to the lack of resources. Prenatal diagnostic tests are not affordable to many people in Latin America. For example, the cost of non-invasive prenatal testing and amniocentesis accounted for 238% and 68% of the average monthly income in Brazil[23]. As of 2014, there was only one laboratory for genetic testing in Paraguay yet many samples were sent to Chile, Brazil, or Argentina for testing[24], further straining the resources in these countries.

There is no literature confirming the biological link between DS and COVID-19. Because cytokine release syndrome is a leading cause of COVID-19 related death, we speculated that the increased interleukin-6 (*IL-6*) production in children with DS[25] is responsible for the increased risk for mortality and that the elevated level of *IL-6* is a result of an altered immune response to viral infection in patients with DS, as in the case of influenza[26]. In addition, we also hypothesised that patients with DS may be more susceptible poor SARS-CoV-2 outcome because the *TMPRSS2* gene, a serine protease for SARS-CoV-2 spike protein priming for viral host cell entry, is located on *21q22.3*[27], a part of DS critical region.

A number of studies have reported patients with DS with SARS-CoV-2 infection although with a focus on the general population or adults. Nonetheless, they generally pointed to more severe COVID-19 in individuals with DS, in line with the present work. The first ever study was a case series reporting 5 patients (aged between 43y and 62y) with DS in Belgium[28]. While four of them had a severe clinical course, one was asymptomatic. In a dual-centre study on 7,246 COVID-19 patients including 12 with DS, levels of inflammation markers such as *C*-reactive protein and *IL-6* were not significantly different between those with ($n$=12) and without DS ($n$=60), albeit those with DS having more severe disease[29]. Nevertheless, the sample size is too small to refute the general belief that *IL-6* is prognostic

biomarker for COVID-19. In a study conducted in Sweden, COVID-19 patients with DS (*n*=85) had 1.8- and 4.3-times higher odds of COVID-19 diagnosis and ICU admission, respectively[30]. Based on a time-to-event analysis, a study on 8 million adults with SARS-CoV-2 infection reported a ten- and four-fold increased risk for COVID-19 related hospitalisation and death in patients with DS, respectively[31].

The major strength of our work is the effort in reducing confounding to enhance the robustness of the result. First, we included a variety of variables that was not considered elsewhere, for example intervention and respiratory viral infections. Location variables were included to account for the impact of the geographical disparity in access to healthcare. Second, comorbidities that are highly prevalent in patients with DS are also independent risk factors for COVID-19-related mortalities. Therefore, these comorbidities are strong confounders between DS and mortality, and between DS and time to recovery. While multivariable regression model was used to reduce confounding, propensity score matching was used to confirm the results. Finally, this is a cohort study with cases and controls gathered from the same target population, increasing the level of evidence.

Major limitations of this study include missing data that usually arises in nationwide registries. Although the use of a nationwide database implies large coverage of the population, inaccurate data are inevitable. Nevertheless, effort has been made to verify the data. Moreover, only hospitalised cases were considered, limiting the generalizability of our findings. Because pre-determined forms were used to standardise the nationwide reporting, there was no available information on management for DS. However, it is partly reflected in geographical variables that imply access to healthcare. Furthermore, there are no guidance and details on the diagnosis of most comorbidities, except for respiratory viral infections, which was confirmed with PCR tests. However, the data were registered and verified by

certified medical practitioners. Finally, the sample size for the DS group is small. DS is a rare disorder, and the present work only considered a subset (*i.e.* paediatrics).

To conclude, DS in children and adolescents *per se* is associated with increased risk of COVID-19 related in-hospital morbidity and mortality even after the adjustment for sociodemographic and clinical factors, such as chronic cardiovascular diseases that are common in DS. Social stratification and the lack of resources at the national level may play a role in intensifying the risk for COVID-19 related morbidity and mortality in paediatrics patients with DS.

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