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ORIGINAL ARTICLE

Clinical characteristics and comorbidities of COVID-19 in unvaccinated patients with Down syndrome: first year report in Brazil

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Abstract

Patients with Down syndrome (DS) are more affected by the Coronavirus Disease (COVID)-19 pandemic when compared with other populations. Therefore, the primary aim of our study was to report the death (case fatality rate) from SARS-CoV-2 infection in Brazilian hospitalized patients with DS from 03 January 2020 to 04 April 2021. The secondary objectives were (i) to compare the features of patients with DS and positive for COVID-19 (G1) to those with DS and with a severe acute respiratory infection (SARI) from other etiological factors (G2) to tease apart the unique influence of COVID-19, and (ii) to compare the features of patients with DS and positive for COVID-19 to those without DS, but positive for COVID-19 (G3) to tease apart the unique influence of DS. We obtained the markers for demographic profile, clinical symptoms, comorbidities, and the clinical features for SARI evolution during hospitalization in the first year of the COVID-19 pandemic in Brazil from a Brazilian open-access database. The data were compared between (i) G1 [1619 (0.4%) patients] and G2 [1431 (0.4%) patients]; and between (ii) G1 and G3 [222,181 (64.8%) patients]. The case fatality rate was higher in patients with DS and COVID-19 (G1: 39.2%), followed by individuals from G2 (18.1%) and G3 (14.0%). Patients from G1, when compared to G2, were older (≥ 25 years of age), presented more clinical symptoms related to severe illness and comorbidities, needed intensive care unit (ICU) treatment and non-invasive mechanical ventilation (MV) more frequently, and presented a nearly two fold-increased chance of death (OR = 2.92 [95% CI 2.44–3.50]). Patients from G1, when compared to G3, were younger (< 24 years of age), more prone to nosocomial infection, presented an increased chance for clinical symptoms related to a more severe illness; frequently needed ICU treatment, and invasive and non-invasive MV, and raised almost a three fold-increased chance of death (OR = 3.96 [95% CI 3.60–4.41]). The high case fatality rate in G1 was associated with older age (≥ 25 years of age), presence of clinical symptoms, and comorbidities, such as obesity, related to a more severe clinical condition. Unvaccinated patients with DS affected by COVID-19 had a high case fatality rate, and these patients had a different profile for comorbidities, clinical symptoms, and treatment (such as the need for ICU and MV) when compared with other study populations.

Matheus Negri Boschiero, Camila Vantini Capasso Palamim, and Fernando Augusto Lima Marson have contributed equally to this study.

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Introduction

Several clinical features, such as obesity, cancer, and systemic arterial hypertension (SAH), among patients infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) were associated with the worst outcome. Thus, these features were associated with a high hospitalization rate, the need for mechanical ventilation, and critical illnesses that culminated in a higher mortality rate (Petrilli et al. 2020; Telle et al. 2021; Bhaskaran et al. 2021). However, among the health conditions that may favor a worse prognosis for SARS-CoV-2 infection, few studies have evaluated people with Down syndrome (DS) (Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021; Real de Asua et al. 2021).

Patients with DS and Coronavirus Disease (COVID)-19 presented a longer hospitalization time, worse severity, higher incidence of superinfections, and increased mortality rate, especially in those patients aged ≥ 40 years and with comorbidities such as kidney failure and diabetes mellitus (Villani et al. 2020; Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021; Real de Asua et al. 2021) when compared with other populations. Furthermore, patients with DS and COVID-19 were also younger, and more likely to have chronic lung diseases, autoimmune diseases, obesity, and dementia (Villani et al. 2020; Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021; Real de Asua et al. 2021). However, the actual effect of COVID-19 in patients with DS is not wholly elucidated yet since few studies addressed the subject, mainly based on case reports (Babamahmoodi et al. 2020; Malik and Kathuria 2021; Vazquez-Hernández et al. 2021; Newman et al. 2021; Vita et al. 2021; Alsahabi et al. 2021; El Kaouini et al. 2012; Malle et al. 2021a; Kuczborska et al. 2022).

The extra copy of chromosome 21, present in patients with DS, can alter their immune system by enhancing the expression of pro-inflammatory cytokines such as interleukin-6 (*IL-6*), tumor necrosis factor-alpha (*TNF*-alpha), interferon-alpha, beta receptor subunit 1 (*IFNAR-1*), and interferon-gamma receptor 2 (*IFNAR-2*). The immune response in some patients with DS can lead to a worse prognosis during SARS-CoV-2 infection. Patients with DS also have alteration in the endocytosis dynamics, which ultimately can facilitate virus infection, especially by the SARS-CoV-2 (Illouz et al. 2021; Altable and de la Serna 2021; Cataldo et al. 2008; Espinosa 2020; Inoue et al. 2007; Jiang et al. 2016; Kim et al. 2016; Botté and Potier 2020), once the chromosome 21 contains the gene responsible for the synthesis of the transmembrane serine protease 2 (TMPRSS-2) protein, which is essential for the SARS-CoV-2 membrane fusion (Hoffmann et al. 2020; Espinosa 2020; De Cauwer 2020; Illouz et al. 2021). Although it is biologically possible that the SARS-CoV-2 may affect patients with DS differently, observational studies are necessary to evaluate the real impact of COVID-19 in patients with DS in a world case scenario, enrolling a considerable population of patients with both conditions (DS and SARS-CoV-2 infection) simultaneously.

In this context, the primary aim of our study was to report the proportion of deaths (case fatality rate) from SARS-CoV-2 infection in Brazilian hospitalized patients with DS from January 2020 to April 2021. The secondary objectives were (i) to compare the demographic data, clinical symptoms, comorbidities, and patients' evolution during the hospitalization of Brazilian patients with DS and positive for COVID-19 [SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) positive] (G1) to those with DS and with the severe acute respiratory infection (SARI) from other etiological factors (SARS-CoV-2 RT-PCR negative) (G2) to tease apart the unique influence of COVID-19; and (ii) to compare the demographic data, clinical symptoms and patients' evolution during the hospitalization of patients with DS and positive for COVID-19 to those without DS but positive for COVID-19 disease (G3) (SARS-CoV-2 RT-PCR positive) to tease apart the unique influence of DS.

Materials and methods

This retrospective study performed an epidemiological analysis of hospitalized patients due to SARI, including the severe acute respiratory syndrome (SARS) due to the COVID-19, using demographic and clinical data available at OpenDataSUS (https://opendatasus.saude.gov.br/). The data was inputted in the OpenDataSUS by the Brazilian Ministry of Health according to the surveillance data of SARI and from the Information System platform for Epidemiological Surveillance of Influenza-Flu (SIVEP-Flu, in Portuguese *Sistema de Informação de Vigilância Epidemiológica da Gripe*) in one dataset. The SIVEP-Flu system has been in use since 2009 (having been implemented in response to the 2009 influenza H1N1 pandemic) and has since centralized the reporting of respiratory viruses and SARI for the Brazilian Ministry of Health (de Souza et al. 2020). This dataset has been used in several previous studies (Hillesheim et al. 2020; Baqui et al. 2020, 2021; de Souza et al. 2020; Kawa et al. 2021; Ranzani et al. 2021; Izbicki et al. 2021; Freitas et al. 2021; Boschiero et al. 2022; Zeiser et al. 2022; Sansone et al. 2022). The patients' characteristics were included in the individual registration form by the health professional who managed the patients. The Brazilian Ministry of Health described the SARI (hospitalized) patients as presenting at

least two (2) of the following clinical symptoms: fever (even if referred), chills, sore throat, headache, cough, runny nose, and olfactory or taste disorders in the presence of dyspnea/respiratory discomfort OR persistent pressure in the chest OR O_2 saturation below 95% in room air OR bluish discoloration of lips or face (https://opendatasus.saude.gov.br/).

The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021) and included the following information: (i) profiles of the viruses found in the patients included in the study; (ii) demographic profiles as sex, race, age (classified according to the main periods of human life (Dyussenbayev 2017), and place of residence; (iii) data for viruses infection such as living in an area that had a previous flu outbreak, respiratory hospital-acquired infection (nosocomial), and the use of an antiviral drug to treat Influenza virus infection; (iv) presence of comorbidities [cardiopathy, diabetes mellitus, SAH, respiratory disorders, obesity, and others]; (v) clinical symptoms related to SARI (fever, cough, loss of smell, loss of taste, myalgia and others); (vi) need for intensive care unit (ICU) and mechanical ventilation; and (vii) outcomes (clinically recovered or death) (https://opendatasus.saude.gov.br/). We described the racial background of the patients following the definitions set forth by the Brazilian Institute of Geography and Statistics (IBGE, in Portuguese *Instituto Brasileiro de Geografia e Estatística*), which acknowledges the following categories: White (Caucasian), Black (Afro-Brazilian), Asian, Indigenous peoples, and *Pardos* (individuals from multiracial background). The patients were grouped for age as (i) infant (< 1-year-old), (ii) child (1- to 12- years of age), (iii) youth (13- to 24- years of age), and (iv) mature (adults) (25- to 60- years of age) (Dyussenbayev 2017).

Importantly, in our study, none of the participants with DS were vaccinated against COVID-19. We carried out the study from 03 January 2020 to 04 April 2021, and the COVID-19 vaccination started in January 2021 in Brazil. However, the vaccination was done in phases, and in the first phase, only people over 60 years of age or institutionalized; institutionalized disabled people, Indigenous people living on Indigenous lands, and 34% of health workers who act, mainly in the front line to treat the patients with COVID-19 received the vaccines (Boschiero et al. 2021a). Individuals with DS were only included as a priority group in May 2021; that is, out of the range of our study according to the Brazilian Plan for COVID-19 vaccination (Vacinação contra a Covid-19 no Brasil).

We divided the patients into three groups: (Group 1; G1) patients with DS and SARS-CoV-2 RT-PCR-positive (COVID-19); (Group 2; G2) patients with DS who were diagnosed with a non-COVID-19 respiratory infection (SARI); and (Group 3; G3) non-DS (without comorbidities) patients with SARS-CoV-2 RT-PCR-positive (COVID-19) (Fig. 1). We categorized the G2 as non-COVID-19 based on the information described in a dataset that included the negative results for SARS-CoV-2 RT-PCR. In addition, we compared G1–G2 (to tease apart the unique influence of COVID-19) and G1–G3 (to tease apart the unique influence of DS).

Two authors (FALM and MNB) revised the epidemiological data from the patients' characteristics obtained in the dataset for better accuracy. After all, we used some synonyms to describe a symptom or comorbidity. Moreover, the authors classified symptoms and comorbidities previously described in the dataset as others in some cases. Also, we created new markers based on the number of patients that presented them [Supplementary Material (SM) Part I. List of clinical characteristics]. We performed all corrections on the dataset online using a video conference platform.

During the statistical analysis for G3, we first ensured that no patients had a diagnosis of DS. We also excluded any patients who had comorbidities that were associated with COVID-19 complications [presence of cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), hematologic disorder, hepatic disorder, asthma, diabetes mellitus, chronic neurological disease, chronic lung disease, immunosuppression disorder, renal disorder, obesity, cancer, SAH, thyroid disease, alcoholism, smoking, and other comorbidities without the identification in the dataset or with a low number of individuals to be part of an independent group of clinical marker]. The authors excluded the comorbidities to identify the patients' characteristics that enabled the differentiation of G1 patients from G3 patients without the impact of these comorbidities on the chance of death. In addition, we revised the data of all patients regarding demographic information, clinical symptoms, and hospitalization markers, checking each patient's data. We used the opportunity to manually include several clinical signs listed in the dataset as "other". Data inclusion and revision were carried out by two authors only as previously reported, and it was time-consuming, which also undermined the inclusion of comorbidities for G3. Also, we excluded pregnant women, patients living in other countries, patients without SARI definition, patients diagnosed with other diseases, and patients over 60 years of age from the G3.

Regarding the G1 and G2 groups, our data excluded patients over 60 years of age, pregnant women, patients with genetic disorders other than DS, and patients without a definition for SARI. The exclusion of patients aged over 60 years of age was based on (i) the high number of missing data for this age category; (ii) the low number of DS individuals in this age category, and this age category, by itself, is a risk factor for death; and, mainly, (iii) the presence of patients older than 60 years of age that were COVID-19 vaccinated during the period of study, which could bias our findings.

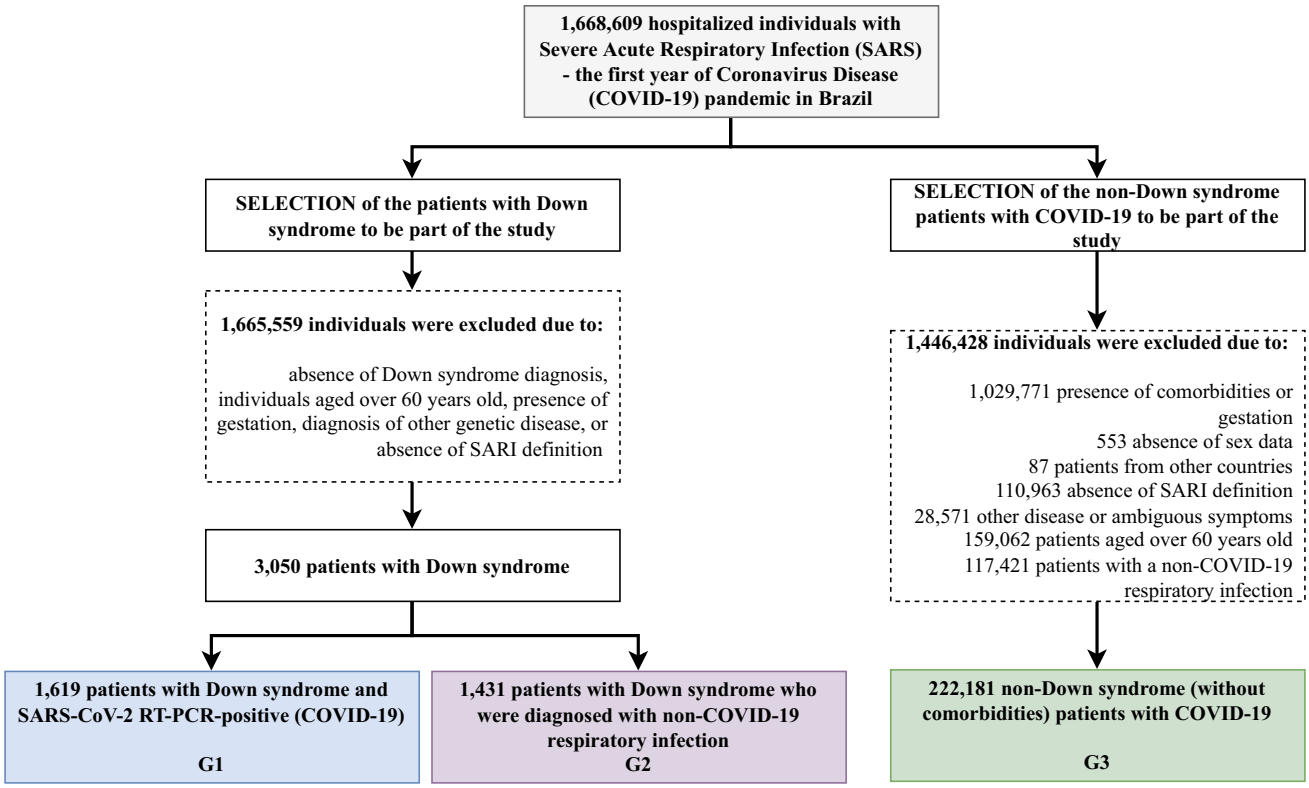

Fig. 1 Flux gram of severe acute respiratory infection (SARI) patients' selection to be part of the epidemiologic analysis presenting the inclusion and exclusion criteria and the distribution of the patients by groups. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The Brazilian Ministry of Health computed the data according to the surveillance data of SARI and from the Information System platform for Epidemiological Surveillance of Influenza-Flu (SIVEP-Flu). The SIVEP-Flu system has been in use since 2009 (having been implemented in response to the 2009 Influenza H1N1 pandemic) and has since centralized the reporting of respiratory viruses and SARI for the Brazilian Ministry of Health (de Souza et al. 2020). The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, real-time polymerase chain reaction

The inclusion and exclusion criteria, and the distribution of the patients in the groups, are summarized in Fig. 1.

We performed the statistical analysis using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Macintosh, Version 27.0). We employed the Chi-square test or Fisher Exact test to compare the proportion between the (i) G1 and G2 for demographic data, clinical symptoms, comorbidities, the need for mechanical ventilation support, and the need for ICU and outcomes; (ii) G1 and G3 for demographic data, clinical symptoms, the need for mechanical ventilation support and the need for ICU and outcomes; (iii) clinically recovered (hospital discharge) patients from G1 against patients with DS who died due to COVID-19 according to demographic data, clinical symptoms, comorbidities, the need for mechanical ventilation support and the need for ICU. We calculated the odds ratio (OR) and the 95% confidence interval (95%CI) to estimate the impact of each marker on the statistical analysis according to COVID-19 diagnosis or outcomes. We summarized the results in tables and figures. We built the figures using the GraphPad Prism version 8.0.0 for Mac, GraphPad Software, San Diego, California USA, www.graphpad.com.

In addition, we performed a multivariate analysis using the Logistic Regression Model with the Backward Stepwise method. The inclusion criteria for the regression model were significant associations (P-value ≤ 0.05) in the bivariate model. We performed three multivariate analyses using: (model 1) the demographic data and the clinical symptoms to differentiate the SARS patients from the G1 to those from G3; (model 2) the demographic data, the clinical symptoms, and the comorbidities to distinguish the patients with DS from the G1 to those from G2; and (iii) the demographic data, the clinical symptoms, the comorbidities and the follow-up of the patients during the hospitalization to differentiate the patients with DS and with COVID-19 who died to those who had clinically recovered (hospital discharge). We showed the Logistic Regression Model using the OR and the 95% CI. The researchers used goodness-of-fit tests to choose the best prediction model

with the fewest predictors, and we evaluated the data for the presence of multicollinearity.

The data used in our study were made publicly available. By being anonymized, it is a consent-free study since it does not present risks to the research participants and was exempt from ethical approval by an Ethics Committee.

Results

SARI patients' demographic and clinical characteristics

The original cohort accounted for 1,668,609 patients hospitalized due to SARI; however, 1,665,559 patients were excluded for not meeting the inclusion criteria to be in G1 ($n = 1619$ patients) or G2 ($n = 1431$ patients); and 1,446,428 patients were excluded for not meeting the inclusion criteria to be in G3 ($n = 222{,}181$ patients) (Fig. 1). Out of which 78,098 (34.7%) were female, 4022 (1.8%) were < 1-year-old, 6091 (2.7%) were between 1- and 12- years of age, 10,060 (4.5%) were between 13- and 24- years of age, and 205,058 (91.0%) were between 25- and 60- years of age (SM Part III. Tables 1 and 2). The G1 group accounted for 1619 (0.7%) patients, G2 for 1431 (0.6%) patients, and G3 for 222,181 (98.7%) patients (Fig. 1). The G1 group also accounted for 772 (47.7%) females, whereas G2 accounted for 665 (46.5%) females and G3 for 76,661 (34.5%) females. In all groups, most patients were classified between 25- and 60- years of age (SM Part III. Tables 1 and 2). When we compared all patient groups, the proportion of patients under one year of age was higher in the G2. In contrast, the patients described as G1 and G3 who presented SARS-CoV-2 infection were older.

The White race group was the most frequent of all groups (SM Part III. Table 3). The epidemiological week of the notification and the onset of symptoms of SARI by SARS-CoV-2 or other etiological agents in Brazil according to DS diagnosis are described in Fig. 2 and SM Fig. 1, respectively. We described the complete information regarding the SARI evolution in Tables 1 and 2 presented in SM Part II.

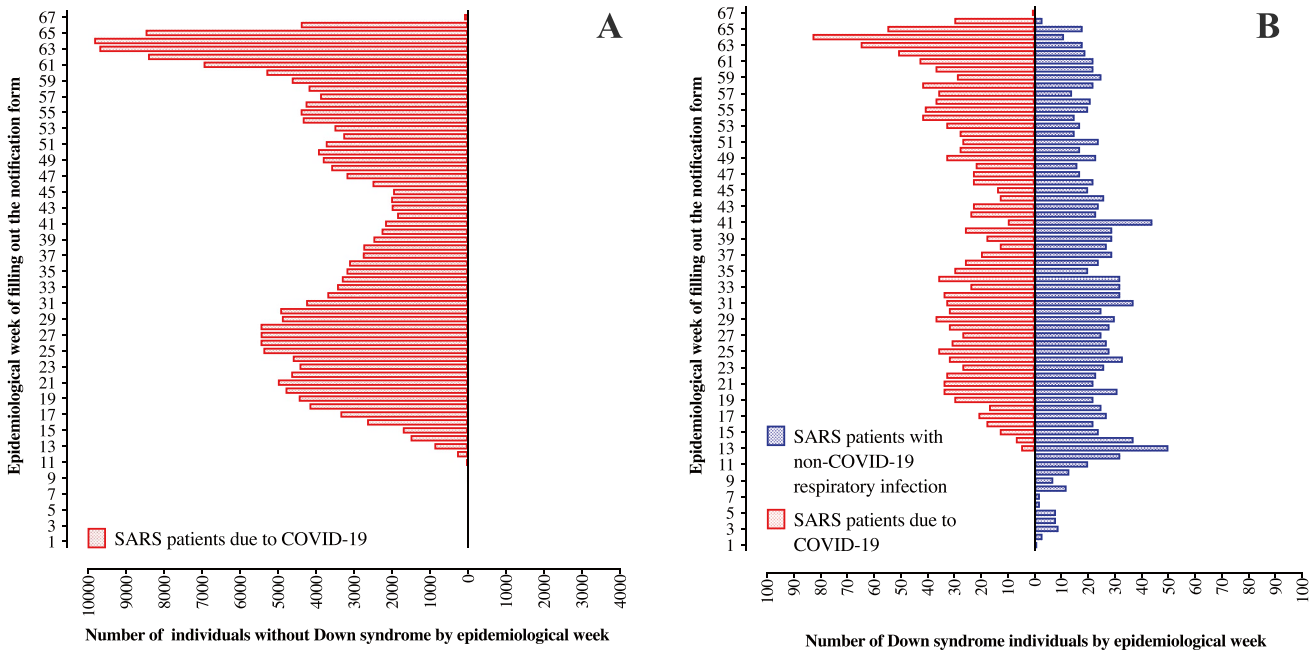

Fig. 2 Hospitalized severe acute respiratory infection (SARI) patients by the epidemiologic week of filling out the notification form. *SARS* severe acute respiratory syndrome, *RT-PCR* real-time polymerase chain reaction. **A** The number of hospitalized SARI patients with non-Down syndrome (DS) according to the Coronavirus Disease (COVID)-19 diagnosis. The red color shows (G3) non-DS (without comorbidities) patients with COVID-19. **B** The number of hospitalized SARI patients with DS according to the COVID-19 diagnosis. The blue color shows (G2) patients with DS and a non-COVID-19 respiratory infection; the red color shows (G1) patients with DS and SARS-CoV-2 RT-PCR-positive (COVID-19). Importantly, we deleted the patients with DS and other comorbidities [presence of cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), hematologic disorder, hepatic disorder, asthma, diabetes mellitus, chronic neurological disease, chronic lung disease, immunosuppression disorder, renal disorder, obesity, cancer, systemic arterial hypertension, thyroid disease, alcoholism, smoking, and other comorbidities without the identification in the dataset or with a low number of individuals to be part of an independent group of clinical marker] from G3. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021)

The most common symptoms in G1 patients were dyspnea (1,170; 78.7%), followed by cough (1116; 75.9%) and fever (1035; 70.4%), whereas the G2 patients' most common symptoms were respiratory distress (975; 74.6%), dyspnea (958; 72.4%), and fever (943; 70.7%). In G3 patients, the most common symptoms observed were cough (160,716; 82.0%), fever (148,246; 76.7%), and dyspnea (143,505; 75.4%). The most prevalent comorbidity in G1 patients was cardiopathy (481; 37.5%), followed by diabetes mellitus (336; 27.3%) and obesity (283; 23.5%). In G2 patients, the most prevalent comorbidities were cardiopathy (533; 45.6%), neuropsychiatric disorder (181; 16.5%), and diabetes mellitus (141; 12.9%).

The case fatality rate had higher frequency among the patients in G1 (541; 39.2%), followed by G2 (220; 18.0%) and G3 (25,571; 14%); the same profile occurred for the need for ICU—G1 [659; 44.7%], G2 [500; 38.4%], and G3 [44,444; 25.0%], and for the need of invasive mechanical ventilation—G1 [410; 28.2%], G2 [263; 20.3%], and G3 [19,226; 10.7%] (Fig. 3).

Profiles of the viruses found in the patients included in the epidemiologic analysis

We evaluated several other etiological agents that cause respiratory infection, and we found others that were more common than SARS-CoV-2, such as the Respiratory Syncytial Virus (RSV) and Rhinovirus. Other viruses (Adenovirus; Influenza A; Influenza B; Parainfluenza 1, 2, 3, and 4; and Metapneumovirus) that were also evaluated presented low prevalence when compared to those listed above. Furthermore, co-infections between SARS-CoV-2 and other viruses, such as Rhinovirus (146) and Parainfluenza 1 (12), were also observed, mainly in G3 patients. We described all the other etiological agents in SM Part II—Table 3.

Comparison between patients with COVID-19 and DS (G1) versus patients with non-COVID-19 SARI and DS (G2)

We presented the full description of the association between G1 and G2 regarding the patients' characteristics

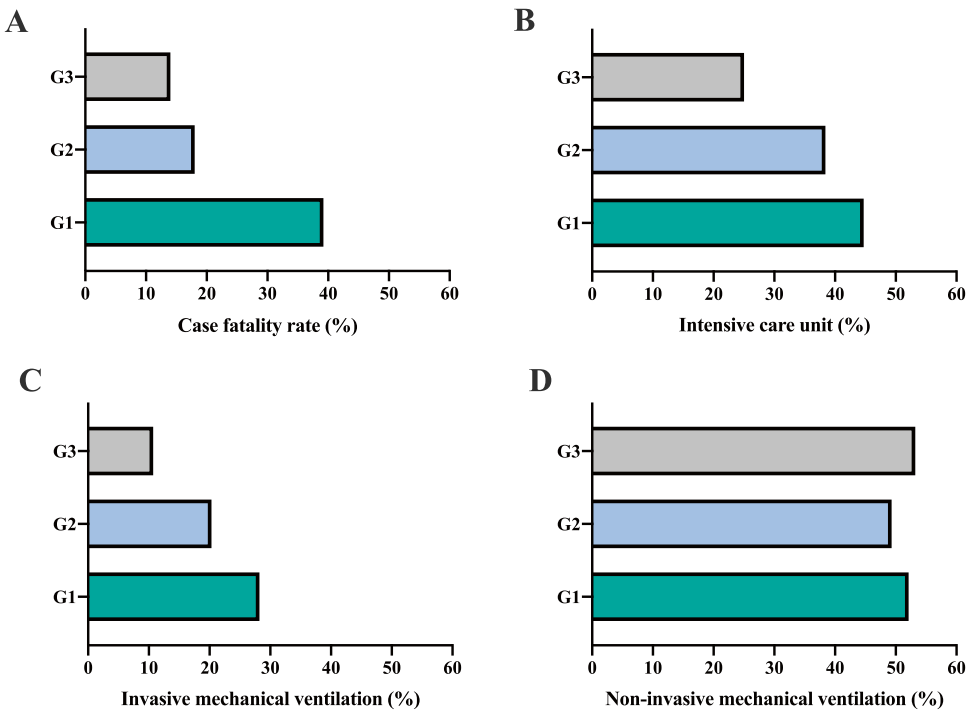

Fig. 3 Frequency of hospitalized severe acute respiratory infection (SARI) patients by case fatality rate (**A**), need for intensive care unit (**B**), the need for invasive mechanical ventilation support (**C**), and the need for non-invasive mechanical ventilation support (**D**). G1, patients with Down syndrome (DS) and SARS-CoV-2 RT-PCR-positive [Coronavirus Disease (COVID)-19]; G2, patients with DS and a non-COVID-19 respiratory infection; G3, non-DS (without comorbidities) patients with COVID-19. Importantly, we deleted the patients with DS and other comorbidities [presence of cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), hematologic disorder, hepatic disorder, asthma, diabetes mellitus, chronic neurological disease, chronic lung disease, immunosuppression disorder, renal disorder, obesity, cancer, systemic arterial hypertension, thyroid disease, alcoholism, smoking, and other comorbidities without the identification in the dataset or with a low number of individuals to be part of an independent group of clinical marker] from G3. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021). *RT-PCR* real-time polymerase chain reaction, % percentage

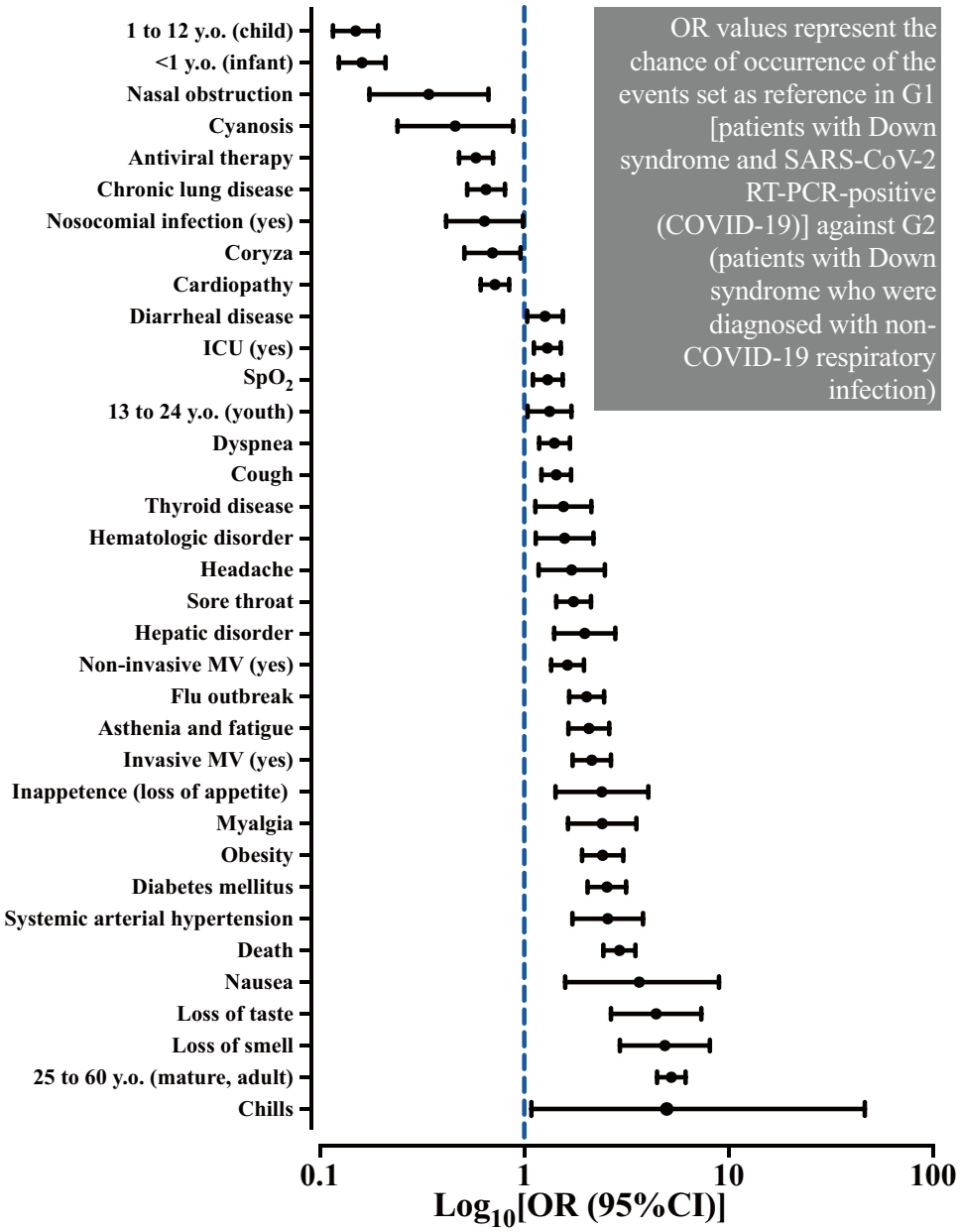

Fig. 4 Odds ratio (OR) values and the 95% confidence interval (95% CI) for the chance of occurrence of the events (patients' characteristics) using as a reference in G1 [patients with Down syndrome (DS) and SARS-CoV-2 RT-PCR-positive - Coronavirus Disease (COVID)-19] against G2 (patients with DS who were diagnosed with a non-COVID-19 respiratory infection). We compared the prevalence of patients with invasive and non-invasive methods for mechanical ventilation with the prevalence of patients who did not require mechanical ventilation. Also, we compared the prevalence of patients in each age category with the prevalence of patients in the other age categories. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021). *y.o.* years of age, SpO_2 peripheral arterial oxygen saturation, *MV* mechanical ventilation, *RT-PCR* real-time polymerase chain reaction, *ICU* intensive care unit. We presented only data with a significative *P*-value (≤ 0.05) in the bivariate model, and we used a $\log_{10}$ scale

in SM Part V (Tables 1–4) and the significant associations (*P*-value < 0.05) in Fig. 4.

Demographic characteristics

We observed several demographic differences between G1 and G2. For instance, most of the patients in G1 were older and aged between 13- and 24- years of age (OR = 1.33 [95%CI = 1.04–1.70]) and between 25- and 60- years of age (OR = 5.24 [95% CI 4.47–6.16]) when compared to patients in G2. Also, in G1, patients living in an area that had a previous flu outbreak were more common than in G2 (OR = 2.02 [95% CI 1.66–2.46]). In addition, patients in G1 presented a decreased risk of nosocomial infection (OR = 0.64 [95% CI 0.42–0.99]) when compared to patients in G2. We did not observe differences regarding sex and place of residence between patients in G1 and G2 (SM Part V. Table 1).

Clinical characteristics

Regarding clinical features, patients in G1 were more likely to present symptoms related to a more severe illness, such as cough (OR = 1.43 [95% CI 1.22–1.69]), dyspnea (OR = 1.41 [95% CI 1.18–1.67]) and low peripheral arterial oxygen saturation (SpO_2; < 95%) (OR = 1.30 [95% CI 1.10–1.54]) than patients in G2 (SM Part V. Table 2). We also observed that patients in G1 were more likely to have some comorbidities such as diabetes mellitus (OR = 2.54 [95% CI 2.04–3.15]) and obesity (OR = 2.42 [95% CI 1.92–3.05]). On the other hand, patients with comorbidities such as cardiopathy (OR = 0.72 [95% CI 0.61–0.84]) and chronic lung disease (OR = 0.65 [95% CI 0.56–0.81]) were less common in G1 when compared to patients in G2 (SM Part V. Table 3). Flu antiviral drugs were less common in patients in G1 than in those in G2 (OR = 0.58 [95% CI 0.48–0.70]) (SM Part V. Table 4).

Outcomes

Patients in G1 presented a greater probability to require ICU treatment (OR = 1.30 [95% CI 1.11–1.51]), invasive mechanical ventilation (OR = 2.14 [95% CI 1.72–2.66]), and noninvasive mechanical ventilation (OR = 1.63 [95% CI 1.35–1.96]), indicating a more severe illness in patients in G1 when compared to patients in G2. We also observed a nearly two fold-increased chance of death (case fatality rate) in patients in G1 when compared to patients in G2 (OR = 2.92 [95% CI 2.44–3.50]) (SM Part V. Table 4).

Multivariate analysis

Binary logistic regression was performed to determine whether the patients' characteristics differentiate SARI patients in the G1 and G2 groups. The model contained the selected characteristics that were significant in differentiating the SARI patients in G1 and G2 groups [Chi-square = 364.521; $df = 19$; P-value < 0.001]. The demographic data, clinical symptoms, and comorbidities that were predictive to be part of the G1 were (P-value < 0.05) living in an area that had a previous flu outbreak area [OR = 2.05 (95% CI 1.40–2.99)], loss of smell [OR = 4.21 (95% CI 1.74–10.17)], and presence of inappetence (loss of appetite) [OR = 4.14 (95% CI 1.32–12.98)]; on the other hand, patients who presented age < 1-year-old [OR = 0.10 (95% CI 0.05–0.19)], age between 1- and 12- years of age [OR = 0.15 (95% CI 0.08–0.26)], and the presence of chronic lung

Table 1 Multivariate analysis using the demographic data, the clinical symptoms, and the comorbidities to differentiate the patients with Down syndrome (DS) into the group of patients with SARS-CoV-2 RT-PCR-positive (COVID-19) (G1) from those patients with DS who were diagnosed with a non-COVID-19 respiratory infection (G2)

Patient characteristic[a]	*B*	SE	Wald	*df*	*P*-value	OR	95%CI for OR	
							Lower	Upper
Age groups								
< 1 y.o. (infant)	– 2.302	0.333	47.704	1	< 0.001	0.100	0.052	0.192
1 to 12 y.o. (child)	– 1.897	0.284	44.589	1	< 0.001	0.150	0.086	0.262
13–24 y.o. (youth)	– 0.322	0.244	1.737	1	0.187	0.725	0.449	1.170
25–60 y.o. (mature, adult)			83.027	3	< 0.001			
Living in a area that had a previous flu outbreak	0.720	0.193	13.865	1	< 0.001	2.054	1.406	2.999
Sore throat	0.352	0.200	3.110	1	0.078	1.422	0.962	2.103
Fatigue	0.330	0.193	2.921	1	0.087	1.391	0.953	2.032
Loss of smell	1.438	0.450	10.228	1	0.001	4.214	1.745	10.174
Inappetence (loss of appetite)	1.422	0.582	5.962	1	0.015	4.146	1.324	12.986
Diabetes mellitus	0.423	0.223	3.594	1	0.058	1.526	0.986	2.364
Chronic lung disease	– 0.786	0.234	11.296	1	0.001	0.456	0.288	0.721
Constant	0.264	0.125	4.486	1	0.034	1.302		

COVID-19 Coronavirus Disease, *y.o.* years of age, *SE* standard error, *df* degrees of freedom, *RT-PCR* real-time polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *OR* odds ratio, *95% CI* 95% confidence interval

[a]The model included the patients' characteristics with a significant P-value in the bivariate model. We used the following patients' characteristics: age, living in a area that had a previous flu outbreak, presence of nosocomial infection, clinical symptoms (cough, sore throat, dyspnea, peripheral arterial oxygen saturation < 95%, diarrhea, fatigue and asthenia, loss of smell, loss of taste, myalgia, headache, coryza, inappetence (loss of appetite), cyanosis, nasal obstruction, nausea, and chills), and comorbidities (cardiopathy, hematologic disorder, hepatic disorder, diabetes mellitus, chronic lung disease, obesity, systemic arterial hypertension, and thyroid disease). We evaluated the data for the presence of multicollinearity

We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021)

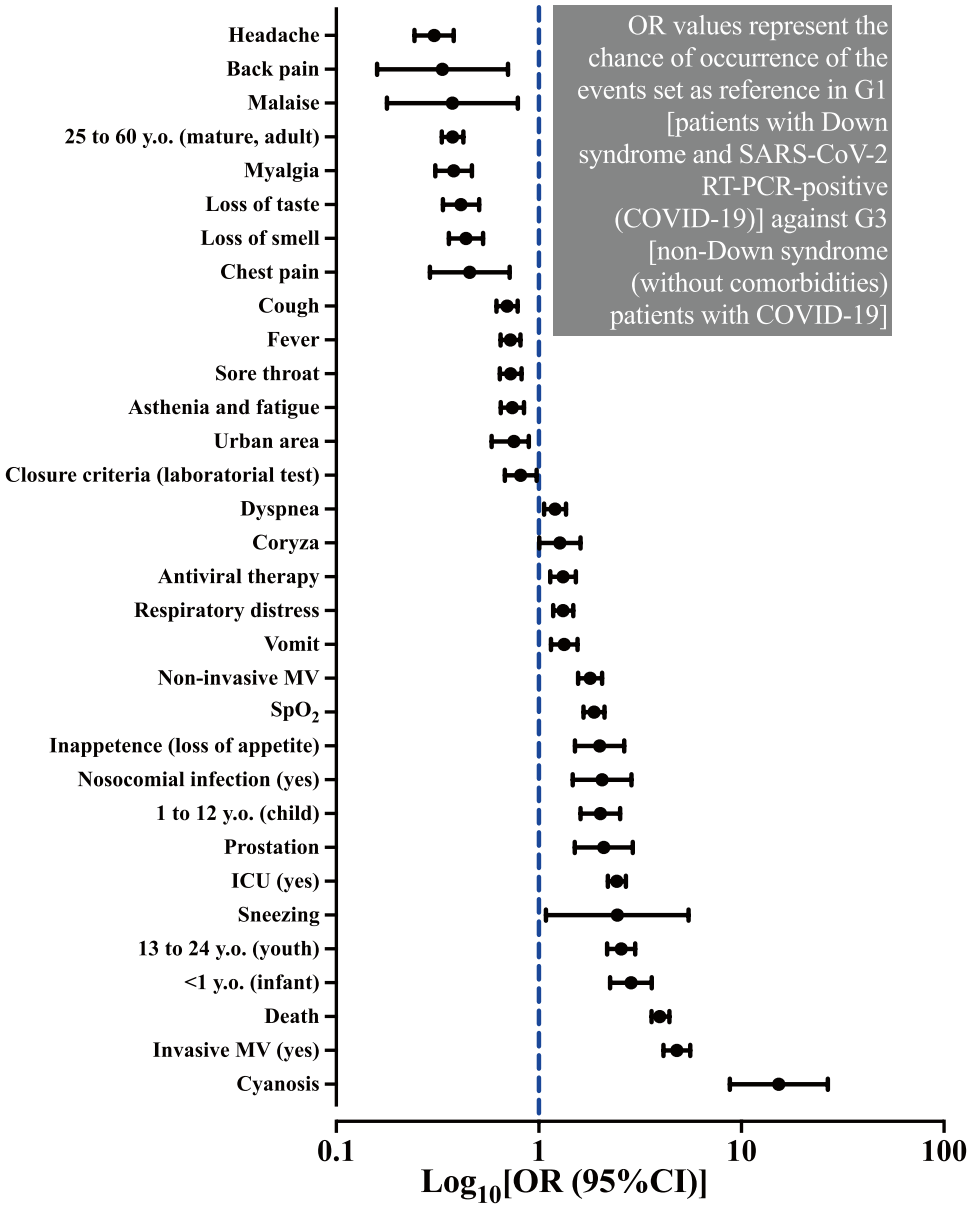

Fig. 5 Odds ratio (OR) values and the 95% confidence interval (95%CI) for the chance of the occurrence of the events (patients' characteristics) using as a reference in G1 [patients with Down syndrome (DS) and SARS-CoV-2 RT-PCR-positive - Coronavirus Disease (COVID)-19] against G3 [non-DS (without comorbidities) patients with COVID-19]. We compared the prevalence of patients with invasive and non-invasive methods for mechanical ventilation with the prevalence of patients who did not require mechanical ventilation. Also, we compared the prevalence of patients in each age category with the prevalence of patients in the other age categories. Importantly, we deleted the patients with DS and other comorbidities [presence of cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), hematologic disorder, hepatic disorder, asthma, diabetes mellitus, chronic neurological disease, chronic lung disease, immunosuppression disorder, renal disorder, obesity, cancer, systemic arterial hypertension, thyroid disease, alcoholism, smoking, and other comorbidities without the identification in the dataset or with a low number of individuals to be part of an independent group of clinical marker] from G3. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021). *y.o.* years of age, *RT-PCR* real-time polymerase chain reaction, SpO_2 peripheral arterial oxygen saturation, *MV* mechanical ventilation, *ICU* intensive care unit. We presented only data with a significative *P*-value (≤ 0.05) in the bivariate model, and we used a $\log_{10}$ scale

disease [OR = 0.45 (95% CI 0.28–0.72)] were less likely to be part of the G1 when compared to G2. We summarize the multivariate analysis findings in Table 1.

Comparison of patients with COVID-19 and DS (G1) and non-DS (without comorbidities) patients with COVID-19 (G3)

We presented the full description of the association between patients in G1 and G3 regarding the patients' characteristics in SM Part IV (Tables 1–3) and the significant associations (P-value < 0.05) in Fig. 5.

Demographic characteristics

The age groups classified as < 1-year-old (OR = 2.86 [95% CI 2.25–3.61]), between 1- and 12- years of age (OR = 2.01 [95% CI 1.61–2.52]), and between 13- and 24- years of age (OR = 2.55 [95% CI 2.17–2.99]) were more common in patients in G1 when compared to patients in G3. In brief, we observed nearly 3- and 2-times younger patients, < 1-year-old and 1- to 12- years of age, respectively, in G1 when compared to G3 (SM Part IV. Table 1). Nosocomial infection was also more prevalent in patients in G1 (OR = 2.05 [95% CI 1.47–2.87]) than in G3 patients. We did not observe differences in sex between patients in the G1 and G3 groups (SM Part IV. Table 1).

Clinical characteristics

We observed that patients in G1 presented an increased chance of symptoms related to a more severe illness, like respiratory distress (OR = 1.32 [95% CI 1.18–1.49]), low SpO_2 (< 95%) (OR = 1.87 [95% CI 1.66–2.11]), and dyspnea (OR = 1.20 [95% CI 1.06–1.36]) when compared to patients in G3. In contrast, symptoms like sore throat (OR = 0.73 [95% CI 0.64–0.82]) and loss of smell (OR = 0.44 [95% CI 0.36–0.53]) were not common in patients in G1 (SM Part IV. Tables 2). Most of the clinical symptoms measured or noted by physicians were more common in patients in G1 than those with self-reported symptoms, which suggests that patients with DS might have difficulty reporting specific symptoms.

Outcomes

Regarding medical support and outcomes, we observed that patients in G1 were more likely to use antiviral drugs to treat flu (OR = 1.32 [95% CI 1.14–1.52]), ICU treatment (OR = 2.43 [95% CI 2.19–2.69]), invasive mechanical ventilation (OR = 4.80 [95% CI 4.13–5.59]), and non-invasive mechanical ventilation (OR = 1.79 [95% CI 1.56–2.05]) when compared with patients in G3. We also observed almost a three fold-increased chance of death (case fatality rate) in patients in G1 than in patients in G3 (OR = 3.96 [95% CI 3.60–4.41]) (SM Part IV. Table 3).

Multivariate analysis

We performed binary logistic regression to determine whether the patients' characteristics could differentiate SARS patients in G1 and G3 groups. The model which containing the selected characteristics was significant in differentiating the SARS patients in G1 and G3 groups [Chi-square = 212.953; df = 10; P-value < 0.001]. The demographic data and clinical symptoms, which were predictive (P < 0.05) in this model to be part of the G1, were age < 1-year-old [OR = 1.93 (95% CI 1.24–3.02)], age between 13 and 24- years of age [OR = 3.11 (95% CI 2.39–4.07)], low SpO_2 (< 95%) [OR = 2.11 (95% CI 1.76–2.52)], vomit [OR = 1.31 (95% CI 1.03–1.66)], nosocomial infection [OR = 2.74 (95% CI 1.71–4.38)], coryza [OR = 2.20 (95% CI 1.57–3.08)], inappetence (loss of appetite) [OR = 1.91 (95% CI 1.26–2.87)], cyanosis [OR = 11.33 (95% CI 5.09–25.21)], and prostration [OR = 3.01 (95% CI 1.91–4.74)]. On the other hand, individuals presenting cough [OR = 0.78 (95% CI 0.65–0.93)], loss of taste [OR = 0.56 (95% CI 0.43–0.74)], myalgia [OR = 0.48 (95% CI 0.35–0.67)], headache [OR = 0.46 (95% CI 0.33–0.63)], chest pain [OR = 0.33 (95% CI 0.14–0.73)], and living in urban area [OR = 0.54 (95% CI 0.41–0.72)] were less likely to be part of the G1 when compared to G3. We summarize all the data in Table 2.

Characteristics associated with enhanced chance of death in patients with COVID-19 and DS (G1)

We presented the full description of the association between patients in G1 according to the outcome (death or hospital discharge) regarding the patients' characteristics in SM Part VI (Tables 1–4) and Fig. 6.

Demographic characteristics

We observed a high case fatality rate among patients in G1 aged between 25- and 60- years of age (OR = 1.62 [95% CI 1.21–2.16]); on the other hand, the patients aged between 1- and 12- years of age presented a decreased case fatality rate (OR = 0.28 [95% CI 0.14–0.54]) when compared to other patients age groups. We significantly associated no other sociodemographic characteristics with the case fatality rate in G1 (SM Part IV. Table 1).

Clinical characteristics

Regarding clinical symptoms, most of the patients who died in G1 presented clinical symptoms related to a more severe clinical condition such as dyspnea (OR = 1.83 [95% CI 1.37–2.45]), respiratory distress (OR = 1.90 [95% CI 1.46–2.47]), and low SpO_2 (< 95%) (OR = 1.85 [95%

Table 2 Multivariate analysis using the demographic data and the clinical symptoms to differentiate the severe acute respiratory syndrome (SARS) patients into the group of patients with Down syndrome (DS) and SARS-CoV-2 RT-PCR-positive (COVID-19) (G1) from those patients with non-DS (without comorbidities) with COVID-19 (G3)

Patient characteristic[a]	*B*	SE	Wald	*df*	*P*-value	OR	95%CI for OR	
							Lower	Upper
Age groups								
< 1 y.o. (infant)	0.661	0.227	8.467	1	0.004	1.937	1.241	3.023
1–12 y.o. (child)	0.391	0.213	3.388	1	0.066	1.479	0.975	2.243
13–24 y.o. (youth)	1.138	0.136	69.516	1	< 0.001	3.119	2.387	4.075
25–60 y.o. (mature, adult)			75.020	3	< 0.001			
Living in an urban area	– 0.600	0.144	17.367	1	< 0.001	0.549	0.414	0.728
Nosocomial infection	1.008	0.240	17.606	1	< 0.001	2.741	1.711	4.389
Fever	– 0.141	0.084	2.791	1	0.095	0.868	0.736	1.025
Cough	– 0.245	0.089	7.514	1	0.006	0.783	0.657	0.933
Peripheral arterial oxygen saturation < 95%	0.746	0.092	66.494	1	0.000	2.110	1.763	2.524
Vomit	0.271	0.123	4.856	1	0.028	1.311	1.030	1.667
Loss of taste	– 0.571	0.139	16.900	1	< 0.001	0.565	0.430	0.742
Myalgia	– 0.723	0.166	18.971	1	< 0.001	0.485	0.350	0.672
Headache	– 0.769	0.164	21.930	1	< 0.001	0.463	0.336	0.639
Coryza	0.789	0.172	21.047	1	< 0.001	2.201	1.571	3.083
Inappetence (loss of appetite)	0.645	0.209	9.483	1	0.002	1.905	1.264	2.872
Cyanosis	2.428	0.408	35.448	1	< 0.001	11.339	5.098	25.219
Prostration	1.103	0.232	22.681	1	< 0.001	3.014	1.914	4.745
Malaise	– 1.046	0.581	3.238	1	0.072	0.351	0.112	1.098
Chest pain	– 1.109	0.412	7.263	1	0.007	0.330	0.147	0.739
Back pain	– 1.048	0.580	3.261	1	0.071	0.351	0.112	1.094
Constant	– 4.343	0.172	634.993	1	< 0.001	0.013		

COVID-19 Coronavirus Disease, *y.o.* years of age, *SE* standard error, *df* degrees of freedom, *RT-PCR* real-time polymerase chain reaction, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *OR* odds ratio, *95% CI* 95% confidence interval

[*]We deleted the patients with DS and other comorbidities [presence of cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), hematologic disorder, hepatic disorder, asthma, diabetes mellitus, chronic neurological disease, chronic lung disease, immunosuppression disorder, renal disorder, obesity, cancer, systemic arterial hypertension, thyroid disease, alcoholism, smoking, and other comorbidities without the identification in the dataset or with a low number of individuals to be part of an independent group of clinical marker]

We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021)

[a.]The model included the patients' characteristics with a significant P-value in the bivariate model. We used the following patients' characteristics: age, place of residence, presence of nosocomial infection, and clinical symptoms (fever, cough, sore throat, dyspnea, respiratory distress, peripheral arterial oxygen saturation < 95%, vomit, fatigue and asthenia, loss of smell, loss of taste, myalgia, headache, coryza, inappetence (loss of appetite), cyanosis, prostration, malaise, sneezing, back pain, and chest pain). We evaluated the data for the presence of multicollinearity

CI 1.41–2.44]). We associated some of those symptoms with a high frequency of hospital discharge, such as diarrhea (OR = 0.54 [95% CI 0.39–0.74]) and abdominal pain (OR = 0.47 [95% CI 0.28–0.78]) (SM Part IV. Table 2). In addition, regarding comorbidities, we associated only obesity with a high case fatality rate (OR = 2.04 [95% CI 1.52–2.74]). In contrast, we associated other comorbidities such as asthma (OR = 0.59 [95% CI 0.37–0.93]), hepatopathy (OR = 0.53 [95% CI 0.32–0.88]), and hematologic disorder (OR = 0.56 [95% CI 0.34–0.93]) with a higher frequency in patients who had clinical recovery (SM Part IV. Table 3).

Outcomes

Patients who required ICU treatment (OR = 3.92 [95% CI 3.09–4.99]) or invasive (OR = 14.22 [95% CI 9.49–21.29]) and noninvasive (OR = 1.665 [95% CI 1.15–2.40])

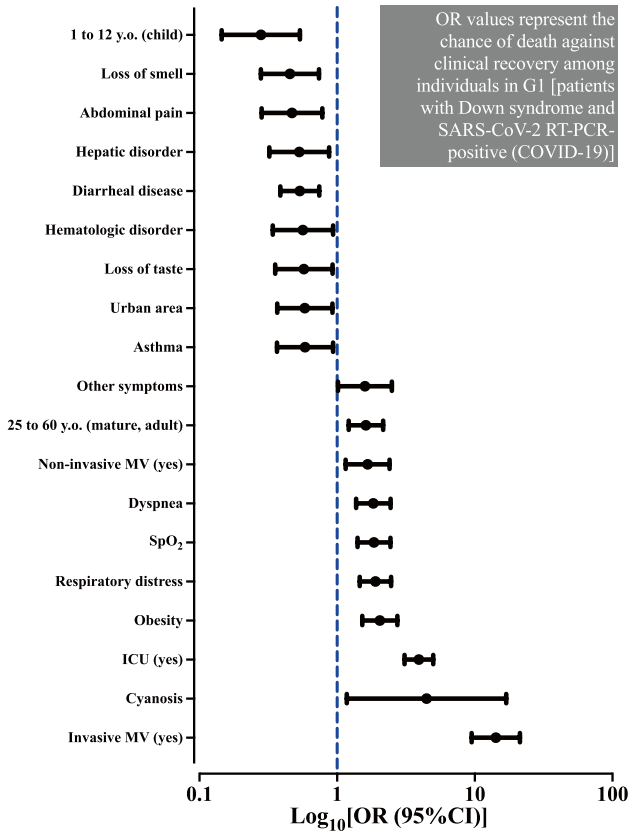

Fig. 6 Odds ratio (OR) values and the 95% confidence interval (95% CI) for the chance of death (case fatality rate) against clinical recovery among individuals in G1 [patients with Down syndrome and SARS-CoV-2 RT-PCR positive - Coronavirus Disease (COVID)-19]. We compared the prevalence of patients with invasive and non-invasive methods for mechanical ventilation with the prevalence of patients who did not require mechanical ventilation. Also, we compared the prevalence of patients in each age category with the prevalence of patients in the other age categories. We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021). *y.o.,* years of age, *RT-PCR* real-time polymerase chain reaction, SpO_2 peripheral arterial oxygen saturation, *MV* mechanical ventilation, *ICU* intensive care unit. We presented only data with a significative *P*-value (≤0.05) in the bivariate model, and we used a $\log_{10}$ scale

mechanical ventilation were more likely to die than to recover (SM Part IV. Table 4).

Multivariate analysis

We performed Binary logistic regression to determine whether the patients' characteristics in the G1 group could predict the chance of death (case fatality rate) in these patients. The model containing the selected characteristics was significant in predicting the case fatality rate in G1 [Chi-square = 152.549; *df* = 10; *P*-value < 0.001]. The demographic data and comorbidities associated with enhanced death ($P < 0.05$) in this model were the presence of obesity [OR = 1.74 (95% CI 1.03–2.92)]; need for ICU [OR = 1.64 (95% CI 1.03–2.60)]; and need for invasive mechanical ventilation [OR = 10.74 (95% CI 5.19–22.2)], whereas individuals living in an urban area [OR = 0.43 (95% CI 0.21–0.88)] and diagnosed with the hepatic disorder [OR = 0.39 (95% CI 0.16–0.96)] were more likely to recover. No clinical symptom was significant in the multivariate analysis. We summarize all the data in Table 3.

Discussion

Several patients' characteristics have been associated with worse outcomes in patients with COVID-19, such as obesity and older age (Petrilli et al. 2020; Telle et al. 2021; Bhaskaran et al. 2021). In addition, few studies have evaluated the impact of the SARS-CoV-2 infection on patients with DS, and most of them observed a high death rate or an increased number of COVID-19-positive patients who needed mechanical ventilation (Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021). To the best of our knowledge, our study is the only one that has evaluated a larger sample of patients with DS and COVID-19 (1619 patients: G1) to date. Also, we included two other different groups [G2: patients with DS who were diagnosed with non-COVID-19 respiratory infection—SARI; and G3: non-DS (without comorbidities) patients with COVID-19]. Most of the SARI patients in all groups were male (65.3%) and aged between 25- and 60-years-old (91.0%).

Since race can play an essential role as a risk factor for the SARS-CoV-2 infection, most of the patients in G1 and G3 were White. Reports showed that the burden on Black people is heavier since they are at higher risk of COVID-19 infection and death, mainly in Brazil (Golestaneh et al. 2020; Mackey et al. 2021; Martins-Filho et al. 2021). The race distribution might be explained by low access to the Public Health System for some racial groups (Silva et al. 2020), leading to underreporting of COVID-19 cases among *Pardos* and Black patients (Carvalho et al. 2021). White patients in Brazil can afford the services of private healthcare institutions, which have plenty of resources such as SARS-CoV-2 tests, enhancing their diagnosis capacity.

Our data demonstrated that the most prevalent symptoms in patients in the G1 and G2 groups were cough and fever, which follows a previous report (Guan et al. 2020). Moreover, we observed a high prevalence of dyspnea and respiratory distress in patients with DS, consistent with a more severe clinical condition (Guan et al. 2020). Our findings are similar to previous studies, demonstrating a more severe impact of COVID-19 and non-COVID-19 SARI in patients

Table 3 Multivariate analysis using the demographic data, the clinical symptoms, the comorbidities, and the follow-up of the patients during the hospitalization to differentiate the Down syndrome (DS) patients with SARS-CoV-2 RT-PCR-positive (COVID-19) who died from those who had clinical recovery

Patient characteristic	*B*	SE	Wald	*df*	*P*-value	OR	95%CI for OR	
							Lower	Upper
Living in an urban area	− 0.832	0.364	5.214	1	0.022	0.435	0.213	0.889
Diarrhea	− 0.577	0.302	3.649	1	0.056	0.562	0.311	1.015
Loss of smell	− 0.684	0.424	2.603	1	0.107	0.504	0.220	1.158
Cyanosis	1.777	1.159	2.353	1	0.125	5.913	0.610	57.286
Hepatic disorder*	− 0.929	0.457	4.128	1	0.042	0.395	0.161	0.968
Obesity	0.554	0.265	4.374	1	0.036	1.740	1.035	2.924
Need for intensive care unit	0.495	0.236	4.376	1	0.036	1.640	1.032	2.607
Mechanical ventilation								
Invasive mechanical ventilation	2.374	0.370	41.067	1	< 0.001	10.742	5.197	22.203
Non-invasive mechanical ventilation	0.288	0.315	0.834	1	0.361	1.333	0.719	2.472
No required			66.047	2	< 0.001			
Constant	− 0.829	0.439	3.566	1	0.059	0.437		

COVID-19 Coronavirus Disease, *y.o.* years of age, *RT-PCR* real-time polymerase chain reaction, *SE* standard error, *df* degrees of freedom, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *OR* odds ratio, *95% CI* 95% confidence interval

*All the patients who presented hepatic disorder aged between 13- to 24- years of age (4/88 patients) or between 25- to 60- years of age (84/88 patients), and this factor can contribute to the unexpected result

We obtained the data at OpenDataSUS (https://opendatasus.saude.gov.br/), and we enrolled only hospitalized patients in the dataset. The data obtained covered the first year of the COVID-19 pandemic in Brazil (from 03 January 2020 to 04 April 2021)

[a.]The model included the patients' characteristics with a significant *P*-value in the bivariate model. We used the following patients' characteristics: age, place of residence, clinical symptoms (dyspnea, respiratory distress, peripheral arterial oxygen saturation < 95%, diarrhea, abdominal pain, loss of smell, loss of taste, and cyanosis), comorbidities (hematologic disorder, hepatic disorder, asthma, obesity), and follow-up (need for intensive care unit and mechanical ventilation support). We evaluated the data for the presence of multicollinearity

with DS (Pérez-Padilla et al. 2010; De Toma and Dierssen 2021; Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021).

Several factors might be associated with a high infection rate by SARS-CoV-2 in patients with DS. For example, the *TMPRSS2*, which encodes a protein involved in the fusion between the virus and the cell, is located in chromosome 21; thus, overexpression of this gene due to the extra chromosome 21 in patients with DS might lead to an increased fusion rate between the virus and the cell membrane (Paoloni-Giacobino et al. 1997; De Cauwer 2020; Illouz et al. 2021). Patients with DS have several metabolic disorders, including endocytosis dysregulation. Dysregulation occurs due to increased expression of Synaptojanin-1, Intersectin-1, and Regulator of calcineurin 1. In addition, those patients have higher expression of pro-inflammatory cytokines, like IL-6, TNF-alpha, and interferon pathway, which could lead to an increased risk for the SARS-CoV-2 infection (Patel et al. 2015; Botté and Potier 2020; Altable and de la Serna 2021; Illouz et al. 2021).

Several studies have observed a higher infection chance for several viruses in patients with DS as well as greater severity, with a nearly 16-fold-increased hospitalization chance, an eight fold-increased intubation chance, and a 300-fold-increased chance of death from Influenza infection (Pérez-Padilla et al. 2010; Beckhaus and Castro-Rodriguez 2018; Mitra et al. 2018; Illouz et al. 2021). Most of the hospitalized patients in G1 were young, maybe due to the hospitalization criteria chosen by the health professionals assisting those patients. Also, we identified a higher chance of a COVID-19 diagnosis in places that had previous flu outbreaks. In this context, previous endemics might heighten sensitivity for future pandemics, leading such citizens to be more alert to a COVID-19 diagnosis.

Moreover, there are few heterogeneous studies on DS and COVID-19, and because of that, it is difficult to establish the exact risk factors linked to death or high infection rate in patients with DS (Babamahmoodi et al. 2020; Villani et al. 2020; Malik and Kathuria 2021; Vazquez-Hernández et al. 2021; Newman et al. 2021; Vita et al. 2021; Alsahabi et al. 2021; Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; El Kaouini et al. 2012; Emami et al. 2021; Real de Asua et al. 2021; Kuczborska et al. 2022). For instance, Illouz et al. (2021) observed that patients with DS and COVID-19 were younger and presented lower socioeconomic status; and, curiously, in a recent study, it

was demonstrated that the socioeconomic status evaluated by the Human Development Index was associated with a higher case fatality rate in Brazil (Palamim et al. 2022). Most of the patients with DS showed chronic lung disease or heart failure than non-DS COVID-19-positive patients (Illouz et al. 2021). For Malle et al. (2021a, b), patients with DS and with COVID-19 presented a higher prevalence of epilepsy, hypothyroidism, sepsis, and the need for invasive mechanical ventilation (Malle et al. 2021b). In the study put forward by Emami et al. (2021), patients with DS and with COVID-19 were more likely to require invasive mechanical ventilation and die (Emami et al. 2021). Clift et al. (2021) observed a high incidence of death and the need for hospitalization in patients with DS and positive for COVID-19 (Clift et al. 2021a). Asua et al. (2021) compared patients with DS and COVID-19 and patients with DS and non-COVID-19 pneumonia. Those authors observed higher in-hospital mortality in patients with COVID-19 and DS (Real de Asua et al. 2021). Finally, one of the most extensive trials reported that hospitalized patients with DS and positive COVID-19 were more likely to be of advanced age, male, obese, and have diabetes mellitus (Hüls et al. 2021). Importantly, in our study, several symptoms and clinical characteristics were more associated with death in G1, such as age between 25- and 60- years of age, dyspnea, respiratory distress, low SpO_2 (< 95%), and obesity, corroborating with the literature. Also, patients in G1 who needed ICU treatment and ventilatory support were more likely to die, which shows that our results are similar to the findings of previous studies (Hüls et al. 2021; Malle et al. 2021b; Illouz et al. 2021; Clift et al. 2021; Emami et al. 2021). Many other small studies, as case reports and case series, described patients with DS and COVID-19, and in most of the reports, they presented a high frequency of deleterious outcomes such as death, need for ICU, or need for invasive mechanical ventilation (Babamahmoodi et al. 2020; Villani et al. 2020; Kantar et al. 2020; Malik and Kathuria 2021; Vazquez-Hernández et al. 2021; Newman et al. 2021; Vita et al. 2021; Alsahabi et al. 2021; Kim-Hellmuth et al. 2021; El Kaouini et al. 2012; Malle et al. 2021a; Kuczborska et al. 2022). Furthermore, since our study is the most extensive study of this type until now, the chance for type II error is decreased due to the larger sample size. But we have some limitations, as described below.

Nevertheless, the toll of COVID-19 is not limited to patients with DS. In a recent report, learning disability seems to be a risk factor for enhanced hospitalization and death due to COVID-19. Severe learning disability was associated with an even higher risk of death (Turk et al. 2020; Landes et al. 2020; Williamson et al. 2021). Unfortunately, these patients with a learning disability, such as patients with DS, are also more likely to present several clinical and sociodemographic characteristics, including obesity, diabetes mellitus, epilepsy, and poverty, which can contribute to the enhanced risk of death by COVID-19 (Emerson et al. 2016; Kinnear et al. 2018; Williamson et al. 2020, 2021; Perera et al. 2020).

Many measures can be taken to attenuate the SARS-CoV-2 infection and its spread, such as hand hygiene, facial masks, social distancing, COVID-19 vaccination, and self-isolation (Reich and Elward 2022; Dey et al. 2022). However, due to the learning disability found in patients with DS, some of these measures might be challenging (Ortega et al. 2020). The lack of proper information associated with a learning disability might have made this group more vulnerable to COVID-19 (Courtenay and Perera 2020; Williamson et al. 2021). Nevertheless, it is noteworthy how patients with DS have unique behavioral and cognitive traits, such as constancy, commitment to habitual tasks, and tenacity; they also try to imitate and repeat several behaviors, almost as a ritual (Wishart 2007; Grieco et al. 2015; Ortega et al. 2020). These cognitive traits, allied to their behavior, might lead to a better understanding of protective measures, enhancing their willingness to stick to them in patients without severe learning disabilities (Ortega et al. 2020).

Our data demonstrated that some patients with DS and COVID-19 have a higher chance of death, perhaps by the genetic condition itself or because they are more likely to present several comorbidities that can also contribute to death. Public health measures aiming to prevent the disease, such as early containment and valuable advice for patients with DS, are relevant and necessary (Dard et al. 2020). In Brazil, to the best of our knowledge, three institutions (Down Syndrome Foundation, Pontifical Catholic University of Campinas, and Brazilian Cardiology Society) developed support materials to instruct patients with DS and their families in primary health care prevention, which was quite helpful (Russo et al. 2020). Families of patients with DS and individuals in contact with them must follow prevention measures (Cammarata-Scalisi et al. 2020). Also, we noticed that age was a risk factor for death only in the bivariate model. Maybe, the patients' distribution and the high number of clinical markers included in the multivariate analysis could mask the association between the risk for death and older age. Also, some reports did not find evidence of a higher chance of death according to age, mainly due to the severity and the presence of the DS phenotype. For example, patients with DS at an older age can present with a less severe spectrum of DS. Finally, as reported by Clift in a previous report: "*There was no evidence of interactions between DS and age, sex, or body mass index*" (Clift et al. 2021).

Although the Brazilian Ministry of Health has placed people with DS in a risk category for severe COVID-19 (as previous data proved greater vulnerability to respiratory infections, mainly due to the RSV and Influenza), they were

not considered a priority group to receive COVID-19 vaccination. The vaccination against COVID-19 began in Brazil in mid-January 2021 for health workers, institutionalized people (who reside in nursing homes) + 60 years of age, institutionalized people with disabilities, and the Indigenous peoples living in villages (Boschiero et al. 2021a). People with DS + 18 years of age were included as a priority group in the National Vaccination Plan in May 2021. However, several hindrances hampered the vaccination of patients with DS, such as the significant impact of COVID-19 in Brazil, and the poor management of the health crisis, including the low vaccination rate resulting from the delay in buying the vaccines (Boschiero et al. 2021a, b). Until November 2021, Brazil accounted for 157,394,902 (~ 75%) individuals vaccinated with the first dose and 123,671,574 (~ 59%) individuals vaccinated with two doses, placing Brazil behind countries such as Japan, Italy, Italy, the USA, and Germany (Ritchie et al. 2020). Unfortunately, the COVID-19 vaccination of patients with DS as a priority group started after the study period in Brazil.

Another important aspect regarding the patients with DS is a proper response to the COVID-19 vaccines since an inadequate immune response occurred for the hepatitis B, Influenza A/H1N1 and meningococcal vaccines (Kusters et al. 2011, 2012; Nisihara et al. 2014). Patients with DS have low lymphocyte count, impaired antibody response, cell-mediated immunodeficiency, and a constitutive Type I interferon pathway (Carsetti et al. 2015; MacLean et al. 2018; Huggard et al. 2018; Illouz et al. 2021). Those features could lead to an inadequate immune response to vaccines. Although no trial has evaluated the immune response of patients with DS for COVID-19 yet, this raises some questions about whether standard doses are sufficient to immunize those patients properly. The immune response of patients with DS to the vaccines should be better evaluated and, perhaps, to assess whether a booster vaccine dosage might be necessary for the patients' immunization, as it is already happening among the elderly and immunosuppressed in Brazilian patients.

Our study also may shed some light on the understanding of clinical and epidemiological characteristics of patients with DS and COVID-19, demonstrating how vulnerable they are. Future studies should also focus on how the SARS-CoV-2 vaccination could attenuate the burden of COVID-19 in patients with DS.

Study limitations

We used a public dataset and did not access the original data. Some epidemiological data were not attributed to the dataset for all patients, reducing the study power for some statistical analyses. There is evidence of COVID-19 underreporting in Brazil, and since we did not have access to the original data, we could not control for this study's bias. Some important markers were not included in the dataset correctly as the medicine types used during the follow-up and the length of stay in the hospital for patients with DS. Although this dataset is one of the largest in Brazil, we observed several data inconsistencies. For instance, many patients with DS were + 70 years of age, which is an infrequent event. The health professional calculated the body mass index and inputted classification into the dataset. Thus, we did not have access to the crude body mass index. Also, it was impossible to determine each disease from the disease spectrum regarding some patients' comorbidities, such as cardiopathy (which included the medical history of congenital heart disease, repaired or non-repaired), chronic neurologic disease, and chronic lung disease. The COVID-19 disease evolution presented a different outcome among the Brazilian regions due to the different impacts on the health system of each area. However, we could not perform a distinctive analysis due to the low number of patients with DS analyzed in each Brazilian state and the Federal District. Since the patients in the G3 group did not have DS or any comorbidities, comparisons with this group should be interpreted carefully. Also, the group of patients with non-COVID-19 SARI included individuals with the absence of a positive SARS-CoV-2 RT-PCR. However, it was not possible to affirm that all patients from G2 were negative for SARS-CoV-2 infection due to limitations in the diagnostic tests.

Highlights

- This study shows how patients with DS are affected by the COVID-19 pandemic in Brazil.
- Patients with DS and COVID-19 are more likely to die and need invasive mechanical ventilation or ICU treatment than patients with DS and non-COVID-19 respiratory infection and patients without DS and COVID-19.
- This study is one of the most extensive investigations that comprised and analyzed patients with DS and COVID-19.
- This study demonstrates that some characteristics such as obesity, dyspnea, respiratory distress, ICU treatment, and the need for invasive mechanical ventilation were risk factors for death in patients with DS and COVID-19.
- This study might encourage public health measures aimed at this vulnerable population, mainly the public ones.

Conclusions

Unvaccinated patients with DS and positive for COVID-19 were more affected by the disease than the general population, with an enhanced case fatality rate. In addition, patients with DS and COVID-19-positive demonstrated different characteristics, such as comorbidities and clinical symptoms, that might help physicians evaluate patients with a higher chance of death from the disease.

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Author contributions MNB and FALM performed data collection and corrected the data input. MNB, CVCP, MMO, and FALM performed the data interpretation, and FALM performed the statistical analyses. All the authors wrote and approved the manuscript and agreed with its submission to the Human Genetics journal.

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Availability of data and materials According to the severe acute respiratory infection surveillance, the Brazilian Ministry of Health inputted the data in the OpenDataSUS (https://opendatasus.saude.gov.br/) considering the Information System platform for Epidemiological Surveillance of Influenza (SIVEP-Flu).

Code availability Not required.

Declarations

Conflict of interest None.

Ethics approval The data used in our study are publicly available. It is a consent-free study for being anonymized since it does not present risks to the participants and is exempt from ethical approval by an Ethics Committee.

Consent to participate Not required.

Consent for publication The authors approved the manuscript and agreed with its submission.

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