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ORIGINAL ARTICLE

The association between schizophrenia and increased Covid-19 mortality in a cohort of over 2 million people in Brazil

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Objective: To determine clinical outcomes and mortality risk factors related to mental disorders in a cohort of hospitalized patients with Covid-19 in Brazil.
Methods: This retrospective cohort study used a Brazilian database called the Sistema de Vigilância Epidemiológica da Gripe (Influenza Epidemiological Surveillance System) to analyze patients aged ⩾ 18 years who were hospitalized with Covid-19 between 2020 and 2022. The exposure of interest was mental disorders (anxiety, depression, schizophrenia, and bipolar disorder) identified through self-report. The primary outcome was in-hospital mortality. Covariates included demographic and clinical characteristics. Descriptive statistics, *t*-tests, chi-square tests, and binary logistic regression were used to analyze the data.
Results: A cohort of 2,124,285 patients was included in the analysis, with 23,246 individuals (1.1%) self-reporting mental disorders, of which depression was the most prevalent (52.3%). The mortality rate of patients with mental disorders was 30.8%. Age, sex, region, dyspnea, low oxygen saturation, and comorbidities were associated with a higher mortality risk, as was schizophrenia (adjusted OR: 1.68; 95%CI 1.54-1.81).
Conclusions: Individuals with schizophrenia had a greater likelihood of Covid-19-related death than those without mental health conditions. These findings underscore the significant effect of serious mental disorders on Covid-19 mortality.

Keywords: Mental disorders; mental health; Covid-19; mortality; schizophrenia

Introduction

The Covid-19 pandemic and mental illness are two significant public health challenges that have profoundly affected individuals, families, and communities worldwide.[1] A complex relationship between mental illness and Covid-19 has been observed. First, the pandemic has significantly affected the mental health of the general population.[2-4] Studies have suggested that individuals with mental illness are more likely to be infected with Covid-19 than those without it.[5] Certain factors, such as limited access to health care services and the risk of undiagnosed chronic comorbidities, increase their vulnerability.[5] Additionally, some studies have shown that severe mental disorders, such as schizophrenia and bipolar disorder, are associated with a higher risk of severe Covid-19 outcomes.[6,7] For instance, a population-based study in Sweden during the first wave of the pandemic found that patients with severe mental illness were three times more likely to die from SARS-CoV-2 infection.[8] However, few studies have directly compared the burden of Covid-19 between severe mental disorders, such as schizophrenia and bipolar disorder, or common mood disorders, such as anxiety and depressive symptoms.

This population-based retrospective cohort study used a Brazilian national epidemiological surveillance system to compare the clinical outcomes and risk factors of Covid-19-related mortality among hospitalized adults with a broad spectrum of mental disorders.

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Methods

Study design and participants

We performed a retrospective cohort study of patients aged ⩾ 18 years who were admitted to Brazilian public and private hospitals between February 2020 and December 2022 with laboratory-confirmed Covid-19. The inclusion criteria were age ⩾ 18 years and positive quantitative reverse transcription real-time quantitative polymerase chain reaction test or antigen test results for SARS-CoV-2. Patients whose laboratory confirmation or test results were not available for analysis were excluded. A total of 2,124,285 hospitalized patients with positive test results for SARS-CoV-2 met the preliminary inclusion criteria (Figure 1).

Data source

We analyzed all hospitalized patients with laboratory-proven SARS-CoV-2 infection recorded in the Sistema de Vigilância Epidemiológica da Gripe (Influenza Epidemiological Surveillance System: SIVEP-Gripe) database between 2020 and 2022. This nationwide database was established by the Brazilian Ministry of Health to surveil severe acute respiratory syndrome in Brazil. Severe acute respiratory illness is a notifiable disease in Brazil, and it must be reported to health authorities within 24 hours of suspicion. Notification is compulsory, and the information is recorded in the SIVEP-Gripe database, which receives data from patients admitted to both public and private hospitals. This database of anonymized data and support material is publicly available at https://opendatasus.saude.gov.br/dataset.

Exposure of interest

The primary exposure of interest was the presence of mental disorders before admission. Individuals with mental disorders were identified by retrieving data from specific comorbidity fields in the database. The SIVEP-Gripe database provides fields for self-reporting several chronic medical conditions in binary (presence/absence) or text fields. After a thorough search, we created the variables "anxiety," "depression," "schizophrenia," and "bipolar disorder." Figure 1 shows a flowchart of the cases selected for analysis.

Covariates and definitions

The covariates in this study included demographic characteristics (age group, sex, race, and region) and clinical features (symptoms such as dyspnea and reduced oxygen saturation, number of associated comorbidities, year of hospitalization, and mental disorders). Comorbidities in the SIVEP-Gripe database included obesity, heart disease, pulmonary disease, asthma, renal diseases, hepatic disease, autoimmune disease, neurologic disease, hematologic disease, and diabetes. We created a categorical variable by grouping these comorbidities into four categories (none, one, two, and three or more comorbidities).

Outcome

The primary outcome was in-hospital mortality.

Statistical analysis

First, we conducted a descriptive analysis of all patients stratified according to the presence of mental disorders, with mean and SD for continuous variables and absolute and relative frequency for categorical variables. An independent samples *t*-test was used to compare means between groups, and the chi-square test was used to compare the proportions between groups. In the second

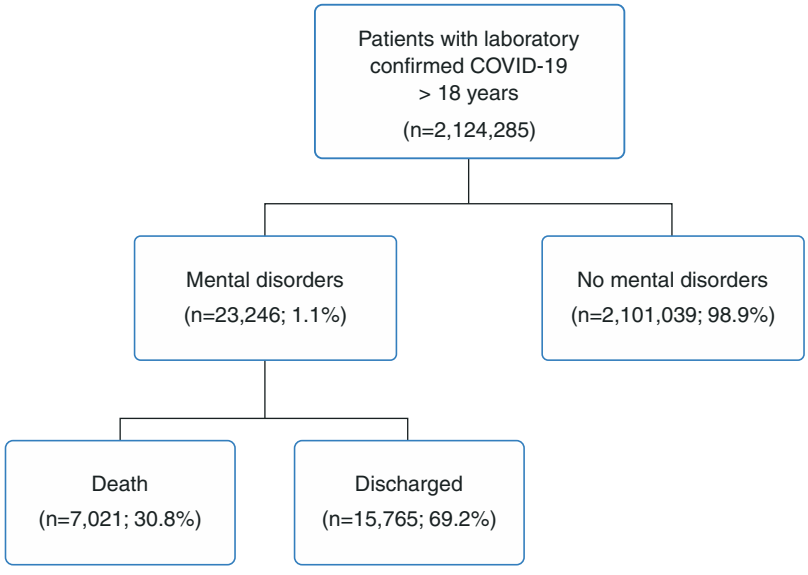


Figure 1 Flowchart of analyzed cases included in the study.

stage, we calculated the crude and adjusted odds ratios (OR and aOR, respectively) for in-hospital mortality for all patients using univariate and multivariate binary logistic regression. Variables with significant results in the univariate analysis were included in the multivariate model. The significance level was set at 5% ($p \leqslant 0.05$) for all tests. The model's goodness-of-fit was determined using the Hosmer-Lemeshow test and an omnibus test of model coefficients. Multicollinearity was assessed using the variance inflation factor and tolerance values. The models used in this study showed no multicollinearity among the variables and demonstrated appropriate fit. Statistical analyses were performed in IBM SPSS Statistics 27 (IBM, Armonk, NY, USA).

Ethics statement

Since the SIVEP-Gripe is a de-identified and open-access database that follows ethical principles for open data, ethical approval was not necessary. This study was based on the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational cohort studies.

Results

Table 1 describes the cohort's demographic and clinical characteristics, stratified according to the presence of mental disorders. A total of 2,124,285 patients were

Table 1 Characterization of patients with laboratory-confirmed Covid-19 stratified according to the presence of mental disorders (n = 2,124,285).

	Overall (%) 2,124,285 (100)	No mental disorders (%) 2,101,039 (98.9)	Mental disorders (%) 23,246 (1.1)	p-value
Age (years), mean (SD)	59.84 (17.43)	59.86 (17.44)	58.45 (15.96)	< 0.001
Age group (years)				
18.0-29.9	93,579 (4.4)	92,689 (4.4)	890 (3.8)	< 0.001
30.0-59.9	961,467 (45.3)	949,852 (45.2)	11,615 (50.0)	
60.0-79.9	770,274 (36.3)	761,833 (36.3)	8,441 (36.3)	
⩾ 80.0	298,965 (14.1)	296,665 (14.1)	2,300 (9.9)	
Sex (n=2,124,042)				
Female	954,799 (45.0)	940,176 (44.8)	14,623 (62.9)	< 0.001
Male	1,169,243 (55.0)	1,160,621 (55.2)	8,622 (37.1)	
Race (n=1,733,847)				
White	906,249 (52.3)	894,311 (52.1)	11,938 (64.1)	< 0.001
Non-White	827,598 (47.7)	850,909 (47.9)	6,689 (35.9)	
Region				
Southeast	1,049,801 (49.4)	1,039,461 (49.5)	10,340 (44.5)	< 0.001
South	362,590 (17.1)	356,154 (17.0)	6,436 (27.7)	
Midwest	215,464 (10.1)	213,021 (10.1)	2,443 (10.5)	
Northeast	356,644 (16.8)	353,068 (16.8)	3,576 (15.4)	
North	139,786 (6.6)	139,335 (6.6)	451 (1.9)	
Signs and symptoms				
Dyspnea	1,479,577 (69.7)	1,463,035 (69.6)	16.542 (71.2)	< 0.001
Oxygen saturation < 95% (n=1,759,083)	1,322,729 (75.2)	1,307,423 (75.2)	15,306 (77.6)	
Number of associated comorbidities				
None	1,040,959 (49.0)	1,030,697 (49.1)	10,262 (44.1)	< 0.001
1	630,273 (29.7)	622,412 (29.6)	7,861 (33.8)	
2	342,699 (16.1)	338,914 (16.1)	3,785 (16.3)	
⩾ 3	110,354 (5.2)	109,016 (5.2)	1,338 (5.8)	
Year of admission (n=2,115,110)				
2020	660,003 (31.2)	654,256 (31.3)	5,747 (24.9)	< 0.001
2021	1,231,153 (58.2)	1,216,605 (58.2)	14,548 (63.0)	
2022	223,954 (10.6)	221,145 (10.6)	2,809 (12.2)	
Mental disorders				
None	2,101,039 (98.9)	2,101,039 (100.0)	-	
Anxiety	5,617 (0.3)	-	5,617 (24.2)	< 0.001
Depression	12,157 (0.5)	-	12,157 (52.3)	< 0.001
Schizophrenia	3,534 (0.2)	-	3,534 (15.2)	< 0.001
Bipolar disorder	1,107 (0.1)	-	1,107 (4.8)	< 0.001
Deaths (n=2,080,899)				
Discharged	1,415,104 (68.0)	1,399,339 (68.0)	15,765 (69.2)	< 0.001
Yes	665,795 (32.0)	658,774 (32.0)	7,021 (30.8)	

Data presented as n (%), unless otherwise specified.

included in the cohort, with 23,246 (1.1%) self-reporting mental disorders. The mean age of included patients was 59.8 (SD, 17.4) years, slightly higher than that of patients with mental disorders (58.4 [SD, 15.9] years). Those with mental disorders were more often women (62.9%), White (64.1%), and from the southeastern (44.5%) and southern (27.7%) regions. These patients had a higher proportion of dyspnea and oxygen saturation $<$ 95% on admission, but a lower proportion of comorbidities than patients without mental disorders. Depression was the most frequent mental disorder (52.3%), followed by anxiety (24.2%). The overall hospital mortality rate among adults hospitalized with Covid-19 was 32%. Notably, the proportion of deaths was slightly higher among patients without (32%) than with (30.8%) mental disorders.

The unadjusted OR for mortality in all patients is shown in Table 2. The mortality risk was higher among non-White male patients aged $>$ 80 years who were admitted in 2021 from the northern and northeastern regions, with dyspnea and oxygen saturation $<$ 95% on admission and a greater number of comorbidities. Only patients with schizophrenia (OR: 1.50; 95%CI 1.40-1.60) had a higher mortality risk than without a mental disorder.

The binary logistic regression model of mortality risk factors for the entire cohort is shown in Figure 2. The mortality aOR increased with increasing age, being highest in individuals aged $>$ 80 years (aOR: 7.98; 95% CI 7.77-8.20), and it was nearly 20% higher in men (aOR: 1.18; 95%CI 1.16-1.19) than women. As with age, the mortality aOR increased with a greater number of comorbidities, more than doubling in those with three or more comorbidities (aOR: 2.40; 95%CI 2.37-2.44). The year in which hospitalized patients had the highest mortality risk was 2021 (aOR: 1.27; 95%CI 1.26-1.28). The only mental disorder significantly associated with increased mortality risk was schizophrenia (aOR: 1.68; 95%CI 1.54-1.82).

Table 2 Odds ratio (OR) of death in patients with laboratory-confirmed Covid-19 (n=2,124,285)

	Discharged (%) 1,415,104 (68.0)	Death (%) 665,795 (32.0)	OR (95%CI)	p-value
Age group (years)				
18.0-29.9	81,637 (89.6)	9,469 (10.4)	1.0	
30.0-59.9	746,585 (79.5)	192,823 (20.5)	2.22 (2.17-2.27)	$<$ 0.001
60.0-79.9	448,904 (59.4)	307,231 (40.6)	5.90 (5.77-6.03)	$<$ 0.001
$\geqslant$ 80.0	137,978 (46.9)	156,272 (53.1)	9.76 (9.54-9.98)	$<$ 0.001
Sex				
Female	641,148 (68.6)	294,007 (31.4)	1.0	
Male	773,797 (67.5)	371,723 (32.5)	1.04 (1.04-1.05)	$<$ 0.001
Race				
White	604,896 (67.7)	288,253 (32.3)	1.0	
Non-White	533,425 (65.9)	276,348 (34.1)	1.08 (1.08-1.09)	$<$ 0.001
Region				
Southeast	702,543 (68.2)	327,318 (31.8)	1.0	
South	252,027 (70.7)	104,658 (29.3)	0.89 (0.88-0.89)	$<$ 0.001
Central-West	154,514 (72.1)	59,788 (27.9)	0.83 (0.82-0.83)	$<$ 0.001
Northeast	218,096 (63.7)	124,384 (36.3)	1.22 (1.21-1.23)	$<$ 0.001
North	87,924 (63.9)	49,647 (36.1)	1.21 (1.19-1.22)	$<$ 0.001
Signs and symptoms				
Dyspnea	950,769 (65.5)	501,538 (34.5)	1.49 (1.48-1.50)	$<$ 0.001
Oxygen saturation $<$ 95%	833,310 (64.1)	465,997 (35.9)	2.03 (2.02-2.05)	$<$ 0.001
Number of associated comorbidities				
None	766,689 (75.5)	249,238 (24.5)	1.0	
1	399,116 (64.5)	219,736 (35.5)	1.69 (1.68-1.70)	$<$ 0.001
2	194,569 (57.7)	142,561 (42.3)	2.25 (2.23-2.27)	$<$ 0.001
$\geqslant$ 3	54,730 (50.2)	54,260 (49.8)	3.05 (3.01-3.08)	$<$ 0.001
Year of admission				
2020	449,810 (68.9)	202,900 (31.1)	1.0	
2021	807,269 (67.3)	392,539 (32.7)	1.07 (1.07-1.08)	$<$ 0.001
2022	152,783 (69.2)	68,033 (30.8)	0.98 (0.97-0.99)	$<$ 0.015
Mental disorders				
None	1,399,339 (68.0)	658,774 (32.0)	1.0	
Anxiety	4,290 (77.9)	1,214 (22.1)	0.60 (0.56-0.64)	$<$ 0,001
Depression	8,297 (69.5)	3,647 (30.5)	0.93 (0.90-0.97)	$<$ 0,001
Schizophrenia	2,034 (58.6)	1,437 (41.4)	1.50 (1.40-1.60)	$<$ 0.001
Bipolar disorder	789 (72.9)	293 (27.1)	0.79 (0.69-0.90)	$<$ 0.001

Data presented as n (%), unless otherwise specified.

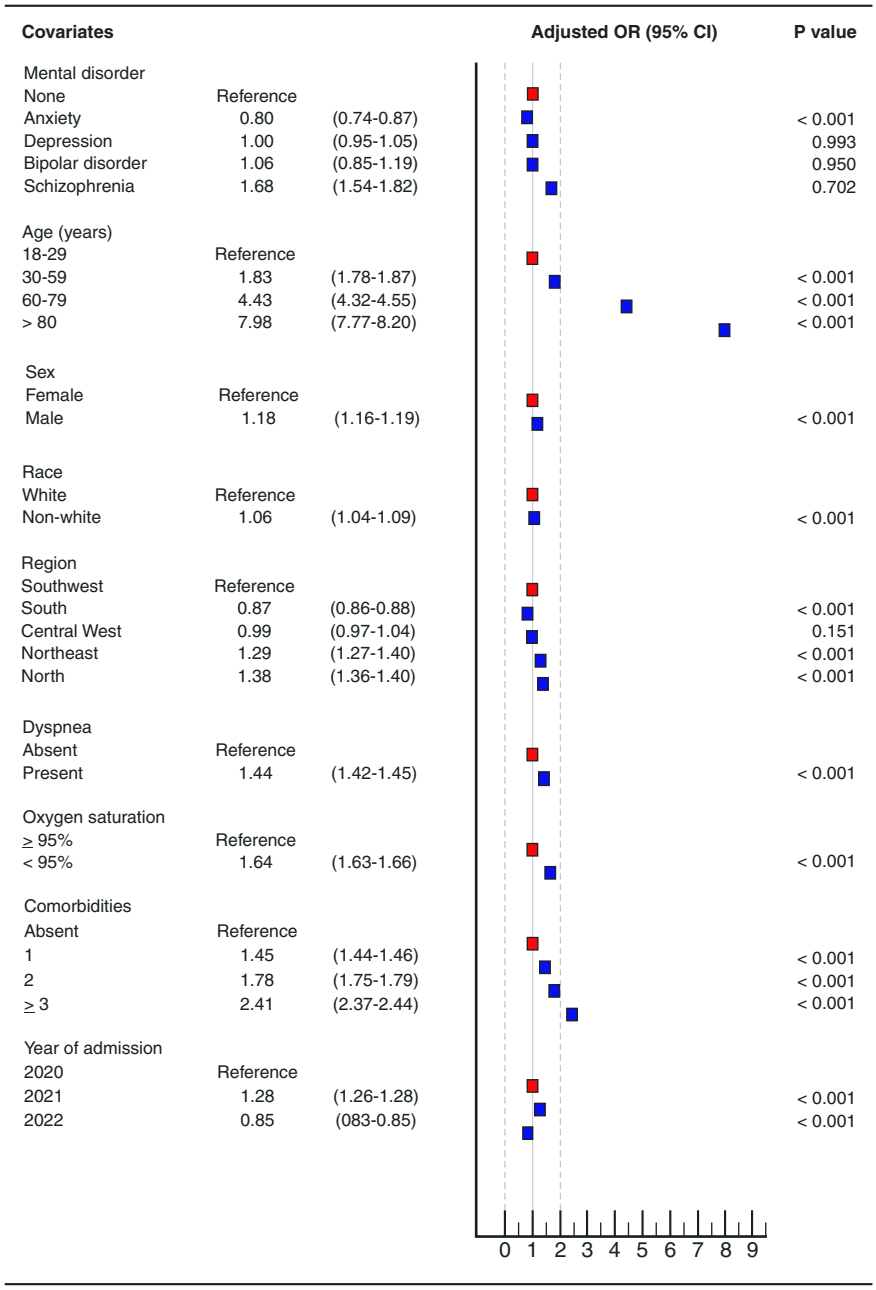


Figure 2 Adjusted odds of death for the entire cohort according to mental disorders and other clinical covariates. Red markers indicate the reference categories. OR = odds ratio.

Discussion

In this retrospective cohort study, we examined the outcomes of SARS-CoV-2 infection in a large Brazilian cohort of hospitalized patients with laboratory-confirmed Covid-19. The cohort consisted of 2,124,285 patients aged ⩾ 18 years. This study aimed to identify risk factors for mortality associated with mental disorders. Our findings indicate that patients with schizophrenia had a higher mortality risk than those without mental disorders, even after controlling for clinical and demographic factors in multivariate analysis.

Regarding demographic characteristics, mental disorders were more prevalent among Whites and women. The higher prevalence of mental disorders in these subgroups is supported in the literature, especially concerning women, whose social situations are often adverse, including gender inequality, sexism, and a double work burden.[9,10] Although White race is more frequently associated with mental disorders, the causal factors for this difference are not yet clear in the literature.[11]

According to our analysis, anxiety disorders, depression, and bipolar disorder were not risk factors for

mortality. While several studies[12,13] have indicated that anxiety is not associated with a higher mortality risk, a cohort study[14] that used the UK Biobank to assess Covid-19 outcomes in patients with mental disorders reported a mortality OR of 1.89 (95%CI 1.34-2.66) in individuals with anxiety disorder, highlighting the inconsistencies in current research on this topic. In contrast to our findings, depression and bipolar disorder have been identified as potential risk factors for mortality in certain Covid-19 cohorts, with OR ranging from 1.08 to 3.93 for depression[12,13,15] and from 1.82 to 2.10 for mood disorders.[12-14] Nevertheless, studies have consistently indicated that schizophrenia is the mental disorder most strongly linked to Covid-19-related death.[5-7,13,15,16]

In our study, individuals with schizophrenia had a higher risk of Covid-19-related mortality, indicated by an aOR of 1.68 (95%CI 1.54-1.82). Other studies on severe mental disorders as predictors of mortality in Covid-19 patients had comparable findings, with OR ranging from 1.80 to 4.09.[5-7,13,15,16]

A Swedish study of 103,999 patients found a higher risk of Covid-19-related mortality in those with psychotic disorders and bipolar disorder, with the OR being higher among older age groups,[6] which was similar to our result that mortality OR increased with age. As individuals age, their health vulnerability typically increases, including lower immune system capacity,[17] a higher likelihood of developing comorbidities, and higher mortality rates.[18] Consequently, older people are more susceptible to the negative effects of Covid-19, including a heightened risk of severe disease and mortality.[18,19]

The increased vulnerability to death in individuals with severe mental disorders, such as schizophrenia, is not exclusive to Covid-19. Pre-pandemic studies have shown that these individuals also have a higher mortality risk in other respiratory infections, such as influenza and pneumonia.[20,21] For instance, a cohort study that followed 6,097,834 individuals for 7 years, including 8,277 with schizophrenia, found mortality hazard ratios of 6.79 (95% CI 4.61-10.00) for women and 6.62 (95%CI 4.54-9.64) for men with schizophrenia who had influenza and pneumonia.[20]

A systematic review[22] on the association between benzodiazepine use and pneumonia found a pooled OR of 1.25 (95%CI 1.09-1.44) for pneumonia in users compared to non-users. Antipsychotic use increased the odds of 30-day (OR: 1.20, 95%CI 1.11-1.31) and 90-day mortality (OR: 1.19, 1.09-1.30) in patients hospitalized with pneumonia.[23] These medications, which are widely used to treat psychotic symptoms, may contribute to a greater risk of symptom severity and mortality in patients with severe mental disorders and Covid-19.

In addition to the potential effects of psychotropic drugs on the course of respiratory infections, it has been observed that the experimental medications used to treat Covid-19 (due to the situation's urgency and a lack of knowledge about the disease) can interact with psychotropic medications. The use of atazanavir, azithromycin, chloroquine/hydroxychloroquine, dipyridamole, famotidine, lopinavir/ritonavir in association with psychotropic drugs resulted effects such as QTc prolongation and neutropenia, showing that caution is required when treating Covid-19 patients with severe mental disorders.[24]

Our study has several limitations. The database contained self-report fields to identify health conditions, so the participants did not undergo a standardized diagnostic process. Self-reporting can result in under- or overestimation of the prevalence of mental disorders, although severe mental disorders such as schizophrenia may be more readily identified by the patients themselves. Nevertheless, Sordo Vieira et al.[25] reported high positive predictive values for self-reported diagnosis of depressive, panic, and hoarding disorders. Similarly, a Brazilian study[26] also found good accuracy in self-reported depression diagnosis. Another study limitation is that large administrative databases, such as the one used in this study, often involve certain inconsistencies, including the potential loss of important data during the form filling and input process.

To the best of our knowledge, this is the first Brazilian study to analyze Covid-19-related mortality among patients with mental disorders. Our results indicate that patients with severe mental disorders, such as schizophrenia, who contract Covid-19 have a higher mortality risk than the general population. Thus, special attention and care should be provided to patients with severe mental disorders, who already experience stigmatization and social exclusion, regarding the transmission and prognosis of respiratory infections.

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Disclosure

The authors report no conflicts of interest.

Author contributions

FESO: Conceptualization, Data curation, Methodology, Investigation, Formal analysis, Writing – original draft, Visualization, Writing – review & editing.
ST: Conceptualization, Data curation, Visualization, Writing – review & editing.
DRBM: Methodology, Formal analysis, Visualization, Writing – review & editing.
MCLO: Data curation, Conceptualization, Visualization, Writing – review & editing.
EAC: Data curation, Methodology, Formal analysis, Writing – review & editing.
HMJ: Conceptualization, Methodology, Writing – original draft, Visualization, Writing – review & editing.
EAO: Data curation, Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing.
All authors have read and approved of the final version to be published.

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