JAMA Psychiatry | Original Investigation

Association of Psychiatric Disorders With Mortality Among Patients With COVID-19

Katlyn Nemani, MD; Chenxiang Li, PhD; Mark Olfson, MD, MPH; Esther M. Blessing, MD, PhD; Narges Razavian, PhD; Ji Chen, MS; Eva Petkova, PhD; Donald C. Goff, MD

IMPORTANCE To date, the association of psychiatric diagnoses with mortality in patients infected with coronavirus disease 2019 (COVID-19) has not been evaluated.

OBJECTIVE To assess whether a diagnosis of a schizophrenia spectrum disorder, mood disorder, or anxiety disorder is associated with mortality in patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study assessed 7348 consecutive adult patients for 45 days following laboratory-confirmed COVID-19 between March 3 and May 31, 2020, in a large academic medical system in New York. The final date of follow-up was July 15, 2020. Patients without available medical records before testing were excluded.

EXPOSURES Patients were categorized based on the following *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* diagnoses before their testing date: (1) schizophrenia spectrum disorders, (2) mood disorders, and (3) anxiety disorders. Patients with these diagnoses were compared with a reference group without psychiatric disorders.

MAIN OUTCOMES AND MEASURES Mortality, defined as death or discharge to hospice within 45 days following a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result.

RESULTS Of the 26 540 patients tested, 7348 tested positive for SARS-CoV-2 (mean [SD] age, 54 [18.6] years; 3891 [53.0%] women). Of eligible patients with positive test results, 75 patients (1.0%) had a history of a schizophrenia spectrum illness, 564 (7.7%) had a history of a mood disorder, and 360 (4.9%) had a history of an anxiety disorder. After adjusting for demographic and medical risk factors, a premorbid diagnosis of a schizophrenia spectrum disorder was significantly associated with mortality (odds ratio [OR], 2.67; 95% CI, 1.48-4.80). Diagnoses of mood disorders (OR, 1.14; 95% CI, 0.87-1.49) and anxiety disorders (OR, 0.96; 95% CI, 0.65-1.41) were not associated with mortality after adjustment. In comparison with other risk factors, a diagnosis of schizophrenia ranked behind only age in strength of an association with mortality.

CONCLUSIONS AND RELEVANCE In this cohort study of adults with SARS-CoV-2–positive test results in a large New York medical system, adults with a schizophrenia spectrum disorder diagnosis were associated with an increased risk for mortality, but those with mood and anxiety disorders were not associated with a risk of mortality. These results suggest that schizophrenia spectrum disorders may be a risk factor for mortality in patients with COVID-19.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2020.4442
Published online January 27, 2021.

Multimedia

Supplemental content

Author Affiliations: Department of Psychiatry, New York University Langone Medical Center, New York, New York (Nemani, Blessing, Goff); Nathan Kline Institute for Psychiatric Research, Orangeburg, New York (Nemani, Petkova, Goff); Department of Population Health, New York University Langone Medical Center, New York, New York (Li, Razavian, Chen, Petkova); Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Olfson).

Corresponding Author: Donald C. Goff, MD, Department of Psychiatry, New York University Langone Medical Center, One Park Avenue, New York, NY 10016 (donald.goff@nyulangone.org).

The coronavirus disease 2019 (COVID-19) pandemic has created unprecedented challenges to the health care system globally. Identification of risk factors associated with poor outcomes is important to guide clinical decision-making, target enhanced protective measures, and allocate limited resources. Risk factors identified to date include older age, male sex, cardiovascular disease, and diabetes.[1-5] Differences in outcomes by socioeconomic status and race have also received attention,[5-7] highlighting the potential for the pandemic to deepen existing health inequalities. However, evidence evaluating psychiatric diagnoses as potential risk factors for severe or fatal COVID-19 is limited.

The increased incidence of COVID-19 among individuals with mental disorders has been reported in at least 2 nationwide cohort studies in the US,[8,9] with depression and schizophrenia associated with the highest infection risk in one sample.[8] This association may be attributable to socioeconomic and environmental factors that contribute to exposure (eg, crowded housing, institutional settings, and lack of personal protective equipment). Because outcomes may differ by diagnosis, it is important to determine which infected patients are at increased risk of adverse outcomes. In a US cohort study of 1685 hospitalized patients with COVID-19, those with any psychiatric disorder had an increased risk of death, but specific diagnoses were not examined.[10] A Korean study found similar rates of adverse clinical events between patients with COVID-19 who had any mental illness and matched controls, but a higher risk of adverse clinical outcomes in individuals with severe mental illness.[11] To our knowledge, the risk of mortality by psychiatric diagnosis has yet to be evaluated.

The present study evaluated the association between psychiatric disorders and mortality among adults with COVID-19. Psychiatric disorders were grouped into schizophrenia spectrum disorders, mood disorders, and anxiety disorders. Based on previous studies of all-cause mortality,[12] we hypothesized that the risk of mortality would be increased in all 3 psychiatric diagnostic groups and would be highest for patients with schizophrenia spectrum disorders, intermediate for mood disorders, and lowest in patients with anxiety disorders compared with patients without psychiatric diagnoses.

Key Points

Question Is a diagnosis of schizophrenia spectrum, mood, or anxiety disorders associated with increased risk of mortality in patients with coronavirus disease 2019 (COVID-19)?

Findings In this cohort study of 7348 adults with laboratory-confirmed COVID-19 in a New York health system, a schizophrenia spectrum diagnosis was associated with an increased risk of death after adjusting for demographic and medical risk factors. Mood and anxiety disorders were not associated with increased risk of mortality.

Meaning A diagnosis of a schizophrenia spectrum disorder may be a risk factor for mortality in patients with COVID-19.

Methods

Study Design and Population

This retrospective cohort study was performed at the New York University (NYU) Langone Health System. The study was approved by the institutional review board of the NYU Grossman School of Medicine with a waiver of authorization for informed consent based on the determination that there was no more than minimal risk to patients in this observational study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

We identified consecutive adult patients, aged 18 years or older, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test results recorded between March 3 and May 31, 2020, in the NYU Langone Health electronic health record system. The health system includes more than 260 outpatient office sites and 4 acute care hospitals in Manhattan, Brooklyn, and Long Island, New York. Testing included real-time reverse transcriptase–polymerase chain reaction assays of nasopharyngeal, oropharyngeal, and sputum samples. The results were classified as positive if any test result was positive for SARS-CoV-2 RNA or negative if all test results were negative. Patients without medical records of encounters before March 3, 2020, were excluded. To preserve confidentiality, patients whose documented sex was not male or female were also excluded. Clinical outcomes were monitored for 45 days following the index testing date.

Data Collection and Definitions

For all identified patients with SARS-CoV-2 test results, we extracted psychiatric diagnostic codes from their electronic health records using billing/encounter diagnoses, external claim diagnoses, and inpatient hospital problems before their testing encounter. Patients were categorized in a hierarchical fashion into 3 mutually exclusive psychiatric diagnostic categories on the basis of *International Statistical Classification of Diseases, Tenth Revision*, codes documented before March 3, 2020, and before COVID-19 testing: (1) schizophrenia spectrum disorders, (2) mood disorders, and (3) anxiety disorders (eTable 1 in the Supplement provides *ICD-10* codes). Patients in each category were compared with a reference group of all remaining patients without psychiatric diagnoses documented before March 3, 2020. The reference group excluded patients with other primary psychiatric disorders (eTable 1 in the Supplement), but patients with organic mental disorders (*ICD-10* codes F00-F09), mental disorders due to substance use (*ICD-10* codes F10-F19), mental retardation (*ICD-10* codes F70-79), and disorders of psychological development (*ICD-10* codes F80-F89) were included in the reference group.

Because *ICD-10* codes for schizophrenia spectrum disorders include nonspecific diagnostic codes (F23, acute and transient psychotic disorders; F29, unspecified nonorganic psychosis), medical records review was performed for all SARS-CoV-2–positive patients with schizophrenia spectrum disorders for diagnostic validity. Review was performed blinded to outcome. Patients with psychosis secondary to a neurologic or medical condition were assigned to the reference group.

Table 1. Baseline Characteristics of Patients With Positive SARS-CoV-2 Test Results

Characteristic	No. (%)			
	Schizophrenia spectrum (n = 75)	Mood disorders (n = 564)	Anxiety disorders (n = 360)	Reference group (n = 6349)
Sex				
Male	42 (56.0)	225 (39.9)	143 (39.7)	3047 (48.0)
Female	33 (44.0)	339 (60.1)	217 (60.3)	3302 (52.0)
Age, y				
Mean (SD)	59.7 (15.0)	62.3 (18.7)	54.9 (19.3)	53.6 (18.4)
18-44	13 (17.3)	107 (19.0)	118 (32.8)	2212 (34.8)
45-54	9 (12.0)	64 (11.4)	61 (16.9)	1084 (17.1)
55-64	17 (22.7)	109 (19.3)	65 (18.1)	1201 (18.9)
65-74	27 (36.0)	126 (22.3)	46 (12.8)	890 (14.0)
≥75	9 (12.0)	158 (28.0)	70 (19.4)	962 (15.2)
Race				
White	47 (62.7)	326 (57.8)	220 (61.1)	2428 (38.2)
Black	17 (22.7)	73 (12.9)	44 (12.2)	1182 (18.6)
Asian	0	13 (2.3)	9 (2.5)	496 (7.8)
Other[a]	8 (10.7)	115 (20.4)	66 (18.3)	1489 (23.5)
Mixed	3 (4.0)	12 (2.1)	9 (2.5)	175 (2.8)
Unknown	0	25 (4.4)	12 (3.3)	579 (9.1)
Smoking status				
Current	20 (26.8)	43 (7.6)	38 (10.6)	270 (4.3)
Former	11 (14.7)	181 (32.1)	95 (26.4)	1046 (16.5)
Never	39 (52.0)	327 (58.0)	220 (61.1)	3997 (63.0)
Unknown	5 (6.7)	13 (2.3)	7 (1.9)	1036 (16.3)
Hypertension	58 (77.3)	388 (68.8)	190 (52.8)	2701 (42.5)
Heart failure	18 (24.0)	121 (21.5)	44 (12.2)	338 (5.3)
Myocardial infarction	32 (42.7)	210 (37.2)	89 (24.7)	839 (13.2)
Diabetes	28 (37.3)	232 (41.1)	91 (25.3)	1542 (24.3)
Chronic kidney disease	12 (16.0)	140 (24.8)	52 (14.4)	524 (8.3)
COPD	39 (52.0)	270 (47.9)	135 (37.5)	1321 (20.8)
Cancer	21 (28.0)	270 (47.9)	158 (43.9)	1396 (22.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] Other race included Guamanian or Chamorro, Native American, other Pacific Islander, Native Hawaiian, Samoan, or unspecified other race by patient report.

Patients with clear documentation indicating the absence of a schizophrenia spectrum diagnosis and the presence of an alternative psychiatric diagnosis were assigned to the appropriate diagnostic group.

The primary analysis included all patients with a psychiatric diagnosis of interest documented in any encounter before March 3, 2020. A secondary analysis was limited to patients with recently documented psychiatric diagnoses of interest recorded in an encounter between January 1, 2019, and March 3, 2020 (recent diagnoses). The same reference group of patients without psychiatric illness was used in both analyses.

The following patient-level characteristics were considered potentially related to both diagnostic category and COVID-19 outcome: age, sex, race, hypertension, diabetes, myocardial infarction, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, smoking status, and cancer. Race was determined by patient report (aggregated into Black, Asian, White, mixed, other, and unknown) and was included based on literature reporting differences in COVID-19–related mortality by race.[5-7] Medical comorbidities were extracted from encounters before March 3, 2020, and included diagnoses documented from the medical history, inpatient and outpatient problem list, billing/encounter and external claims, following previous reports.[2-4,13] Missing data for race and smoking status were assigned to unknown categories.

The outcome, mortality, was defined as death or discharge to hospice. Clinical outcomes were monitored for 45 days following testing and included data through July 15, 2020.

Statistical Analysis

The prevalence of psychiatric disorders among all patients tested for COVID-19 and among those who tested positive was first determined. Descriptive statistics were used to report the likelihood of a positive test result in each psychiatric diagnostic group compared with the reference group.

The 45-day mortality outcome was compared between each psychiatric diagnostic group and the reference group using odds ratios (ORs): odds (psychiatric group)/odds (reference group). Three types of ORs were estimated: (1) unadjusted; (2) demographically adjusted for sex, age (18-44, 45-54,

Table 2. Odds Ratios and Rates of 45-Day Case Fatality by Lifetime Psychiatric Diagnosis

SARS-CoV-2– Positive	Mortality or hospice, No. (%)	OR (95% CI)		
		Unadjusted	Demographically adjusted[a]	Fully adjusted[b]
All patients (n = 7348)	864 (11.8)	NA	NA	NA
Schizophrenia spectrum (n = 75)	20 (26.7)	2.93 (1.75, 4.92)	2.87 (1.62-5.08)	2.67 (1.48-4.80)
Mood disorders (n = 564)	104 (18.4)	1.82 (1.45, 2.29)	1.25 (0.98-1.61)	1.14 (0.87-1.49)
Anxiety disorders (n = 360)	39 (10.8)	0.98 (0.70, 1.38)	0.97 (0.67-1.41)	0.96 (0.65-1.40)
Reference[c] (n = 6349)	701 (11.0)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: NA, not applicable; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] The demographically adjusted OR included age, race, and sex.

[b] The fully adjusted model included demographic variables in addition to smoking status, hypertension, heart failure, myocardial infarction, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and cancer.

[c] The reference group excluded patients with any history of a schizophrenia spectrum, mood, or anxiety disorder diagnosis or other psychiatric diagnoses listed in eTable 1 of the Supplement.

Table 3. Multivariable-Adjusted Risk Model for 45-Day Case Fatality, With Lifetime Psychiatric Diagnoses[a]

Variable	OR (95% CI)
Age, y	
18-44	1 [Reference]
≥75	35.72 (22.99-55.52)
65-74	16.54 (10.60-25.82)
55-64	7.74 (4.95-12.10)
45-54	3.89 (2.40-6.30)
Schizophrenia spectrum disorder	2.67 (1.48-4.80)
Male sex	1.69 (1.43-2.00)
Heart failure	1.60 (1.24-2.06)
Other race vs White race[b]	1.47 (1.19-1.80)
White race vs Black race	1.41 (1.10-1.81)
Hypertension	1.38 (1.12-1.70)
Asian race vs White race	1.28 (0.94-1.75)
Diabetes	1.27 (1.07-1.51)
Never smoker vs current smoker	1.27 (0.84,1.93)
Chronic kidney disease	1.23 (0.98-1.55)
Mood disorder diagnosis	1.14 (0.87-1.49)
White race vs mixed race	1.08 (0.60-1.97)
Cancer	1.01 (0.85-1.22)
Former smoker vs never smoker	1.00 (0.93-1.22)
Myocardial infarction	1.00 (0.81-1.22)
Anxiety disorder	0.96 (0.65-1.41)
Chronic obstructive pulmonary disease	0.93 (0.77-1.12)

Abbreviation: OR, odds ratio.

[a] Excluding unknown race and unknown smoking history.

[b] Other race included Guamanian or Chamorro, Native American, other Pacific Islander, Native Hawaiian, Samoan, or unspecified other race by patient report.

55-64, 65-74, and ≥75 years, with 18-44 years serving as the reference group), and race (Asian, Black, White, mixed, and other); and (3) fully adjusted for the demographic factors plus hypertension, diabetes, myocardial infarction, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, smoking status, and cancer. Logistic regression models that included indicators for the psychiatric diagnostic categories (3 indicators with the control group as reference) were used to estimate ORs and the covariates were included to estimate the 3 types of ORs; 95% CIs were estimated based on those models. As a sensitivity analysis, for the fully adjusted ORs, a stepwise selection/elimination procedure was performed with candidate variable entry and exit criteria set to $P = .05$, with 2-tailed, unpaired testing. All analyses were conducted using SAS, version 9.3 (SAS Institute Inc).

Results

Patient Characteristics at Baseline

A total of 31 044 adult patients were tested for COVID-19 between March 3 and May 31, 2020. There were 2425 patients excluded owing to lack of diagnostic records before March 3, 2020; 2075 excluded owing to a primary psychiatric diagnosis that did not meet the criteria for schizophrenia spectrum, mood, or anxiety disorder categories (eTable 1 in the Supplement); and 4 patients excluded whose documented sex was not male or female. Of the remaining 26 540 patients tested, 7348 (27.7%) had a positive result (3891 [53.0%] women; 3457 [47.0%] men); mean (SD) age was 54 (18.6) years. Of eligible patients with positive test results, 75 patients (1.0%) had a history of a schizophrenia spectrum illness, 564 (7.7%) had a history of a mood disorder, and 360 (4.9%) had a history of an anxiety disorder. Baseline characteristics of the patients by group are reported in **Table 1**. The likelihood of a positive test among the diagnostic groups was 22.3% for the schizophrenia spectrum group, 25.4% for the mood disorder group, 24.1% for the anxiety disorder group, and 28.2% for the reference group. (eTable 2 in the Supplement).

45-Day Mortality

Overall, 864 patients (11.8%) died or were discharged to hospice within 45 days of a positive SARS-CoV-2 test result. A schizophrenia spectrum diagnosis was significantly associated with 45-day mortality after adjustment for age, sex, and race (OR, 2.87; 95% CI, 1.62-5.08) and after additional adjustment for medical risk factors (OR, 2.67; 95% CI, 1.48-4.80). After demographic adjustment, mood disorder diagnoses (OR, 1.25; 95% CI, 0.98-1.61) and anxiety disorder diagnoses (OR, 0.97; 95% CI, 0.67-1.41) were not significantly associated with mortality (**Table 2**). **Table 3** reports risk factors associated with COVID-19 mortality ordered by the magnitude of ORs from the fully adjusted logistic regression

Table 4. Odds and Rates of 45-Day Case Fatality by Recent Psychiatric Diagnosis

SARS-CoV-2–Positive	Mortality or hospice, No. (%)	OR (95% CI)		
		Unadjusted	Demographically adjusted[a]	Fully adjusted[b]
All patients (n = 7003)	822 (11.7)			
Schizophrenia spectrum (n = 46)	12 (26.1)	2.84 (1.47-5.52)	3.13 (1.50-6.54)	2.67 (1.26-5.69)
Mood disorders (n = 374)	80 (21.4)	2.19 (1.69-2.84)	1.52 (1.13-2.03)	1.27 (0.94-1.73)
Anxiety disorders (n = 234)	29 (12.4)	1.14 (0.77-1.70)	1.24 (0.80-1.93)	1.21 (0.77-1.90)
Reference[c] (n = 6349)	701 (11.0)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] The demographically adjusted OR included age, race, and sex.

[b] The fully adjusted model included demographic variables in addition to smoking status, hypertension, heart failure, myocardial infarction, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and cancer.

[c] The reference group excluded patients without any history of a schizophrenia spectrum, mood, or anxiety disorder diagnosis or other psychiatric diagnoses listed in eTable 1 of the Supplement.

model. Diagnoses of mood disorders (OR, 1.14; 95% CI, 0.87-1.49) and anxiety disorders (OR, 0.96; 95% CI, 0.65-1.41) were not associated with mortality after adjustment. Results from a sensitivity analysis with stepwise selection of variables yielded similar results (eTable 3 in the Supplement).

In the secondary analysis of patients with recently documented psychiatric diagnoses, a schizophrenia spectrum diagnosis was associated with 45-day mortality after adjustment for age, sex, and race (OR, 3.13; 95% CI, 1.50-6.54) and after additional adjustment for medical risk factors (OR, 2.67; 95% CI, 1.26-5.69). A mood disorder diagnosis was associated with mortality after adjustment for demographic variables (OR, 1.52; CI, 1.13-2.03), but the association was not significant after additional adjustment for medical risk factors (OR, 1.27; 95% CI, 0.94-1.73). Anxiety disorders were not associated with mortality after demographic (OR, 1.24; 95% CI, 0.80-1.93) or additional (OR, 1.21; 95% CI, 0.77-1.90) adjustment (**Table 4**). The relative ranking of ORs for 45-day mortality associated with psychiatric diagnoses compared with other risk factors is provided in **Table 5**. Results from a sensitivity analysis with stepwise selection of variables yielded similar results (eTable 4 in the Supplement).

Table 5. Multivariable-Adjusted Risk Model for 45-Day Case Fatality, With Recent Psychiatric Diagnoses[a]

Variable	OR (95% CI)
Age, y	
18-44	1 [Reference]
≥75	35.70 (22.73-56.07)
65-74	16.60 (10.53-26.17)
55-64	7.75 (4.91-12.24)
45-54	3.90 (2.39-6.38)
Schizophrenia spectrum disorder	2.67 (1.26-5.69)
Male sex	1.74 (1.46-2.06)
Heart failure	1.65 (1.27-2.14)
Other race vs White race[b]	1.49 (1.21-1.85)
Hypertension	1.43 (1.15-1.77)
White race vs Black race	1.35 (1.05-1.75)
Never smoker vs current smoker	1.31 (0.84-2.04)
Asian race vs White race	1.29 (0.94-1.78)
Diabetes	1.28 (1.07-1.53)
Mood disorder diagnosis	1.27 (0.94-1.73)
Chronic kidney disease	1.21 (0.96-1.53)
Anxiety disorder diagnosis	1.21 (0.77-1.90)
Never smoker vs former smoker	1.02 (0.84-1.25)
Cancer	1.01 (0.83-1.21)
Myocardial infarction	1.01 (0.81-1.24)
Mixed race vs White race	1.01 (0.56-1.83)
Obstructive lung disease	0.97 (0.80-1.18)

Abbreviation: OR, odds ratio.

[a] Excluding unknown race and unknown smoking history.

[b] Other race included Guamanian or Chamorro, Native American, other Pacific Islander, Native Hawaiian, Samoan, or unspecified other race by patient report.

Discussion

In this retrospective cohort study of 7348 patients with confirmed COVID-19, a schizophrenia spectrum diagnosis was associated with increased odds for 45-day mortality after controlling for age, sex, race, and known medical risk factors. Without adjustment, the odds for mortality in adults with mood disorders was increased compared with the reference group but was no longer statistically significant after adjustment for demographic characteristics and medical comorbidities. There was not a significant association between an anxiety disorder diagnosis and mortality.

Although previous observational studies in the US have reported an increased incidence of COVID-19 among patients with psychiatric disorders[8,9] and increased mortality risk in broadly defined cohorts of patients with any mental disorder,[8,10] to our knowledge, this is the first study to report the risk of mortality by psychiatric diagnostic group. The results of this analysis suggest that the risk of severe or fatal illness may differ by diagnosis. In a population that may be more susceptible to infection, determining which patients may be at highest risk for adverse outcomes is necessary to guide clinical decision-making, including the need for enhanced monitoring and targeted interventions.

The results should be interpreted with several caveats. During the study period, the pandemic was at its peak in New York City. Testing was largely restricted to symptomatic and high-risk people, as reflected in the high rate of positive test results (27.7%). The study population was limited to patients who had access to treatment within the NYU health care system and

received testing and evaluation. Mortality risk was increased in those with recent documentation of a mood disorder after demographic adjustment, suggesting that stage of illness (acute vs stable) may contribute to differential risk in patients with episodic psychiatric disorders.

The most notable finding from this study is the high risk of mortality associated with schizophrenia spectrum diagnoses, ranking second behind age in strength of an association among all demographic and medical risk factors examined in this sample. Individuals with schizophrenia spectrum disorders had 2.7 times the odds of dying after adjustment for known risk factors. A higher risk with schizophrenia spectrum diagnoses was expected based on previous studies of all-cause mortality, but the magnitude of the increase after adjusting for comorbid medical risk factors was unexpected. It is possible that unmeasured medical comorbidities contributed to this finding, although the risk remained significantly increased after adjustment for multiple established risk factors. Delays in treatment seeking or reduced access to care may have contributed to worse outcomes. However, the lower rate of positive test results in the schizophrenia spectrum group compared with the reference group argues against selection bias as an explanation for the higher odds of mortality observed.

Beyond systemic barriers to care and delayed treatment, adults with schizophrenia spectrum diagnoses may be more susceptible to COVID-19 mortality due to biological factors related to their psychiatric illness or treatment. The results of this analysis are consistent with those of a nationwide study from South Korea in which government-mandated testing and enhanced monitoring were provided to all citizens. The investigators reported a similar risk of infection but higher risk of severe clinical outcomes in patients with psychotic disorders.[11] Although the mechanism underlying this association is not clear, immune dysregulation in the setting of genetic or acquired risk factors is a possibility. Variation in the major histocompatibility complex is one of the most highly replicated findings in genome-wide association studies of schizophrenia susceptibility,[14-17] and previous research has shown deficits in cellular immunity resulting in dysfunctional T cell–mediated immune responses in patients with schizophrenia.[18,19] Genetic variability across major histocompatibility complex class I genes may contribute to differences in immune response to COVID-19,[20] and inappropriate T-cell responses have been implicated in the pathophysiologic characteristics of severe infection.[21-23] Perturbations in inflammatory cytokine signaling have been reported in association with schizophrenia,[24-26] which may increase COVID-19 severity and mortality.[27]

Strengths and Limitations

This study has several strengths. Comprehensive data were collected from a large number of consecutive patients with laboratory-confirmed COVID-19. Focusing on patients with confirmed infection eliminated variability associated with differing rates of infection, which may differ between patients with and without psychiatric diagnoses. The cohort included a demographically diverse population of patients from across several sites in a health care system. The prevalence of psychiatric diagnoses in patients tested for COVID-19 was consistent with what would be expected based on nationwide prevalence.[28] Allowing 45 days for follow-up ensured that most patients had reached a primary outcome by the end of the study. By limiting the extraction of psychiatric history to encounters before March 3, 2020, we were able to determine the risk of critical illness and mortality associated with premorbid psychiatric illness rather than psychological sequelae of the virus or psychosocial stressors associated with the pandemic.

The study also has several limitations. First, the accuracy of clinical psychiatric diagnoses could not be validated in all patients. Psychiatric disorders were grouped into broad categories to maximize the sample size; there may have been differences in risk associated with specific diagnoses within categories. Second, individuals with psychiatric disorders may be less likely to seek medical attention owing to amotivation, social isolation, or stigma, particularly when there are systemic barriers to accessing care. However, all patients in this study had received previous treatment within the NYU Langone Health Network and access to care was previously established. Third, the generalizability of these findings to other patient populations and health care systems is uncertain. This study took place in a severely challenged health system during a peak of the COVID-19 pandemic. In addition, psychotropic medications used at the time of the infection were not assessed and may have been associated with either harmful or protective effects.

Conclusions

In this cohort study of adults with SARS-CoV-2–positive test results in a large medical system in New York, adults with schizophrenia spectrum diagnoses were at significantly increased risk of mortality after controlling for demographic and medical risk factors. The risk of mortality was increased in patients with recent documentation of a mood disorder after adjustment for demographic variables, but the association did not remain significant after adjustment for medical risk factors. There was no significant association between a diagnosis of anxiety disorder and mortality. To our knowledge, this is the first study to evaluate specific psychiatric disorders as independent risk factors for mortality in patients with COVID-19. Further research is needed to determine whether specific psychiatric disorders are associated with an increased risk of fatal illness among patients with COVID-19 in other settings. Targeted interventions may be needed for patients with severe mental illness to prevent worsening health disparities.

ARTICLE INFORMATION

Accepted for Publication: November 23, 2020.

Published Online: January 27, 2021. doi:10.1001/jamapsychiatry.2020.4442

Author Contributions: Drs Namani and Goff had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Nemani, Olfson, Goff.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Nemani, Blessing, Goff.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Li, Razavian, Petkova. *Administrative, technical, or material support:* Goff. *Supervision:* Li, Goff.

Conflict of Interest Disclosures: Dr Goff reported receiving research support and travel reimbursement from Avanir Pharmaceuticals and Takeda. No other disclosures were reported.

REFERENCES

1. Grasselli G, Greco M, Zanella A, et al; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180(10):1345-1355. doi:10.1001/jamainternmed.2020.3539

2. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059. doi:10.1001/jama.2020.6775

3. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020;369:m1966. doi:10.1136/bmj.m1966

4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

5. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19 death in 17 million patients using OpenSAFELY. *Nature*. 2020;584(7821):430-436. doi:10.1038/s41586-020-2521-4

6. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. *N Engl J Med*. 2020;382(26):2534-2543. doi:10.1056/NEJMsa2011686

7. Millett GA, Jones AT, Benkeser D, et al. Assessing differential impacts of COVID-19 on black communities. *Ann Epidemiol*. 2020;47:37-44. doi:10.1016/j.annepidem.2020.05.003

8. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. [published online October 7, 2020]. *World Psychiatry*. 2020. doi:10.1002/wps.20806

9. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. Published online November 9, 2020. doi:10.1016/S2215-0366(20)30462-4

10. Li L, Li F, Fortunati F, Krystal JH. Association of a prior psychiatric diagnosis with mortality among hospitalized patients with coronavirus disease 2019 (COVID-19) infection. *JAMA Netw Open*. 2020;3(9):e2023282. doi:10.1001/jamanetworkopen.2020.23282

11. Lee SW, Yang JM, Moon SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *Lancet Psychiatry*. 2020;7(12):1025-1031. doi:10.1016/S2215-0366(20)30421-1

12. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry*. 2015;72(4):334-341. doi:10.1001/jamapsychiatry.2014.2502

13. Gupta S, Hayek SS, Wang W, et al; STOP-COVID Investigators. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med*. 2020;(July). doi:10.1001/jamainternmed.2020.3596

14. National Institute of Mental Health. Statistics. Updated January 2018. Accessed November 20, 2020. https://www.nimh.nih.gov/health/statistics/index.shtml

15. Mokhtari R, Lachman HM. The major histocompatibility complex (MHC) in schizophrenia: a review. *J Clin Cell Immunol*. 2016;7(6):479. doi:10.4172/2155-9899.1000479

16. Purcell SM, Wray NR, Stone JL, et al; International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*. 2009;460(7256):748-752. doi:10.1038/nature08185

17. Shi J, Levinson DF, Duan J, et al. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature*. 2009;460(7256):753-757. doi:10.1038/nature08192

18. Stefansson H, Ophoff RA, Steinberg S, et al; Genetic Risk and Outcome in Psychosis (GROUP). Common variants conferring risk of schizophrenia. *Nature*. 2009;460(7256):744-747. doi:10.1038/nature08186

19. Steiner J, Jacobs R, Panteli B, et al. Acute schizophrenia is accompanied by reduced T cell and increased B cell immunity. *Eur Arch Psychiatry Clin Neurosci*. 2010;260(7):509-518. doi:10.1007/s00406-010-0098-x

20. Müller N, Schwarz MJ. Immune system and schizophrenia. *Curr Immunol Rev*. 2010;6(3):213-220. doi:10.2174/157339510791823673

21. Nguyen A, David JK, Maden SK, et al. Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2. *J Virol*. 2020;94(13):e00510-20. doi:10.1128/JVI.00510-20

22. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol*. 2020;20(9):529-536. doi:10.1038/s41577-020-0402-6

23. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20(6):363-374. doi:10.1038/s41577-020-0311-8

24. Song JW, Zhang C, Fan X, et al. Immunological and inflammatory profiles in mild and severe cases of COVID-19. *Nat Commun*. 2020;11(1):3410. doi:10.1038/s41467-020-17240-2

25. Müller N. Inflammation in schizophrenia: pathogenetic aspects and therapeutic considerations. *Schizophr Bull*. 2018;44(5):973-982. doi:10.1093/schbul/sby024

26. Freudenreich O, Brockman MA, Henderson DC, et al. Analysis of peripheral immune activation in schizophrenia using quantitative reverse-transcription polymerase chain reaction (RT-PCR). *Psychiatry Res*. 2010;176(2-3):99-102. doi:10.1016/j.psychres.2008.11.007

27. Momtazmanesh S, Zare-Shahabadi A, Rezaei N. Cytokine alterations in schizophrenia: an updated review. *Front Psychiatry*. 2019;10:892. doi:10.3389/fpsyt.2019.00892

28. Del Valle DM, Kim-Schulze S, Huang H-H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26(10):1636-1643. doi:10.1038/s41591-020-1051-9