

# Demographic and Clinical Factors Related to Severe COVID-19 Infection and Mortality in Patients With Schizophrenia

Okan Ekinçi, MD and Aslı Erkan Ekinçi, MD

**Abstract:** We aimed to explore the prevalence and determinants of severe COVID-19 disease and mortality in patients with schizophrenia in this study. We conducted a retrospective observational study of 1620 patients with schizophrenia. Of the 1620 patients, 52 (3.2%) tested positive for SARS-CoV-19. Among SARS-CoV-2–positive patients, 40 patients were hospitalized, and 17 patients required intensive care unit admission due to COVID-19 (76.9% and 32.7%, respectively). Severe COVID-19 disease was noted in 17 patients (32.7%) requiring intubation. In the logistic regression analysis, antipsychotic dose, and comorbidity score were independently associated with a greater risk of severe COVID-19 disease in patients with schizophrenia. Our study suggests that factors such as age, sex, comorbidities, and a daily antipsychotic dose may have effects on the poor outcome of SARS-CoV-2 disease in schizophrenia patients. In addition, the current findings propose that mortality may be associated with an older age, comorbidity score, and a longer duration of psychiatric disease among the SARS-CoV-2–positive patients with schizophrenia. However, the findings of our study should be verified in prospective and larger sample studies.

**Key Words:** Schizophrenia, COVID-19, severe, mortality

(*J Nerv Ment Dis* 2022;210: 257–263)

According to the World Health Organization, coronavirus disease (COVID-19) has affected approximately 180,000,000 people worldwide and has resulted in approximately 4,000,000 deaths (World Health Organization, 2021a). This infectious disease may be asymptomatic but may also cause death, especially in older patients and patients with other medical comorbidities. Recently, new variants of the virus have become more infectious, but the lethality of the disease has not changed (Sakurai et al., 2020; Zhang et al., 2020). Many factors have been suggested to be related to the mortality and the poor prognosis of COVID-19. Obesity, male sex, and comorbidities, including chronic pulmonary disease (CPD), diabetes mellitus, hypertension, and older age, have been reported to be the main determinants of the mortality and poor prognosis in patients with COVID-19 (Nanda et al., 2021). However, factors that predispose patients to high mortality rates and severe outcomes related to COVID-19 are poorly understood, especially in special patient populations such as patients with schizophrenia.

Schizophrenia is a debilitating and chronic mental disorder that has a prevalence of approximately 1%. Recently, it has been suggested that patients with schizophrenia may be considered a high-risk population for COVID-19 because these patients have some clinical and demographic features that may make them more predisposed to infectious diseases (Fond et al., 2021a; Kozloff et al., 2020; Taquet et al., 2021). Patients with schizophrenia have high rates of comorbidities, such as

hypertension, diabetes mellitus, and CPD, which are important predisposing factors for severe COVID-19 infection (Carney et al., 2006). Therefore, these factors are likely related to the mortality and poor prognosis in patients with schizophrenia who are infected by SARS-CoV-2. On the other hand, the limited access to medical care, poor hygiene, a poor insight into somatic symptoms, stigmatization, and a higher smoking rate may make these patients predisposed to a higher mortality and more severe COVID-19 disease (Kozloff et al., 2020). Beyond these factors, patients with schizophrenia may be more susceptible to severe COVID-19 disease and a higher mortality due to psychiatric drug treatment (Nemani et al., 2021a).

To our knowledge, few studies have examined the prevalence and prognosis of COVID-19 in patients with schizophrenia. Fond et al. (2021b) carried out a case-control study of patients, which included hospitalized COVID-19 patients. They found that schizophrenia was associated with an increase in mortality after adjusting for age, sex, smoking status, obesity, and comorbidities, which are well-known risk factors for mortality in COVID-19. However, the study had a sample which was composed of only inpatients with COVID-19 (Fond et al., 2021b). Another study reported a relationship between schizophrenia and an increased COVID-19 mortality compared with controls, which was not associated with sociodemographic and medical factors. This study had a large sample size and included both inpatients and outpatients with schizophrenia (Tzur Bitan et al., 2021). Nemani et al. (2021a) reported that patients with schizophrenia spectrum diagnoses were at significantly increased risk of mortality after controlling for demographic and medical risk factors. Subsequently, a follow-up study by Nemani et al. (2021b) did not find an association between antipsychotic use and mortality. In the context of the relationship between antipsychotic use and COVID-19, a recent study reported that receiving clozapine treatment was associated with increased risk of COVID-19 infection, compared with receiving any other type of antipsychotic treatment. However, this study did not evaluate the relationship between mortality and antipsychotic use (Govind et al., 2021).

The relationships among schizophrenia, the determinant factors of severe COVID-19, and mortality remain to be examined. We aimed to explore the prevalence of COVID-19 in patients with schizophrenia and to investigate possible risk factors for severe COVID-19 infection and mortality in terms of antipsychotic drug use as well as the clinical and demographic features among patients with schizophrenia. We hypothesized that patients with schizophrenia would have higher SARS-CoV-2–positive rates, as well as higher rates of severe infection and mortality, and that some demographic and clinical features and antipsychotic drug use would be related to severe COVID-19 infection and mortality in patients with schizophrenia.

## METHODS

This was a retrospective observational study. The study sample was composed of patients with schizophrenia admitted to our psychiatry outpatient and inpatient clinics and the Community Mental Health Centre (CMHC) at the Uşak Education and Research Hospital in Uşak, Turkey, from September 2019 to March 2020. The Uşak Education and Research Hospital is a tertiary hospital located in Uşak that has a population of approximately 400,000. This hospital is the only hospital in the Uşak province that provides psychiatric care, so it is possible to say that it is a hospital that obtains the majority of the data related to

Psychiatry Department, Uşak University Medical Faculty, Uşak, Turkey.  
Send reprint requests to Okan Ekinçi, MD, Kemaloz Mah. Atatürk Bulvarı, Uşak Üniv. 1 Eylül kampüsü, Uşak Üniversitesi Tıp Fakültesi, Psikiyatri AD, 64100 Uşak, Türkiye. E-mail: drokanekinci@yahoo.com.  
Okan Ekinçi ORCID ID: <https://orcid.org/0000-0001-8059-9022>.  
Aslı Erkan Ekinçi ORCID ID: <https://orcid.org/0000-0001-6331-9412>.  
Ethical Requirement statement: The study was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the Ethics Commission of Uşak University (decision number: 07-04-2021/14).  
Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.  
ISSN: 0022-3018/22/21004-0257  
DOI: 10.1097/NMD.0000000000001500

the treatment and follow-up of most psychiatric patients living in this city. Therefore, a good generalizability of the data is expected.

The study was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the Ethics Commission of Uşak University (decision number: 07-04-2021/14). We included individuals who met the following inclusion criteria: having one of the *ICD-10* codes for schizophrenia (code F20); taking regular antipsychotic medication between September 1, 2019, and March 10, 2020; and having no comorbidities related to mental retardation, epilepsy, brain injuries, or cognitive disorders. This date was selected because it was before March 11, 2020, the date of the first diagnosed case of COVID-19 in Turkey; therefore, the risk of reverse causation was ruled out.

Initially, we reviewed the charts of 1902 patients with schizophrenia, 72 of them were excluded from the study due to not being prescribed antipsychotic medications. Subsequently, the charts of 1830 patients with schizophrenia who had a regular follow-up at the outpatient and inpatient clinics and were receiving any type of antipsychotic treatment during the chosen period for the study were reviewed for the inclusion and exclusion to the present study. We excluded 150 patients because of comorbidities, including mental retardation, brain injury, and/or epilepsy, and 60 patients were excluded due to lack of required information for the analysis. During the time, of all patients admitted to the psychiatry outpatient and inpatient clinics and the CMHC, 1620 patients met the inclusion criteria of individuals with an *ICD-10* diagnosis of schizophrenia (F20) who were on antipsychotic medication.

Clinical (duration of disease, age at illness onset, suicidality, drug status, comorbid mental disease) and demographic variables (age, sex, smoking, socioeconomic class, occupation, place of residence) were collected through a review of the digital outpatient charts, inpatient files, and nurse observation charts. The number of hospitalizations refers to admissions for psychiatric illnesses during the chosen period for the study. Length of stay at psychiatry services refers to the cumulative days of hospitalization in a psychiatry inpatient clinic within the specified time.

Patients were also retrospectively followed from March 11, 2020, until the end of the observation period (May 4, 2021) for COVID-19 status and disease course. We carefully reviewed the patient's digital medical records, detailed discharge summaries, intensive care unit (ICU) clinician notes, and mortality forms to obtain information on the COVID-19 status and disease course. Testing included real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays of nasopharyngeal and/or oropharyngeal 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. The results of COVID-19 RT-PCR testing were also obtained from the e-Nabız (Turkish Health Record System). The main outcomes of the confirmed COVID-19 cases through positive RT-PCR results were as follows: 1) only outpatient care; 2) hospitalization; 3) ICU admission (mechanical ventilation required *vs.* nonrequired patients); and 4) death. A COVID-19 infection was defined as "severe" if the patient required mechanical ventilation.

The study also used a retrospective, cross-sectional study of patient records to obtain the following variables, which were being evaluated as risk factors for a poor COVID-19 prognosis: smoking, body mass index (BMI), and comorbid medical diseases such as diabetes, hypertension, CPD, and cardiovascular disease. The Charlson Comorbidity Index (CCI) was used as a measure of the total comorbidity burden (Bannay et al., 2016). One of the authors (O.E.) reviewed charts to assess the COVID-19 status and the demographic and clinical characteristics of the patients. The other investigator (A.E.) assessed only the status of antipsychotic drug use in the patients to prevent bias. The antipsychotic drugs prescribed were divided into three categories as follows: 1) first-generation antipsychotics (FGAs); 2) second-generation antipsychotics (SGAs); and 3) the combination of SGA and FGA drugs. We obtained information about antipsychotics taken by the patients from their electronic follow-up charts and confirmed these drugs and their daily dosages by the E-Reçete system (Turkish Drug Prescription and Record System).

The last antipsychotic drugs taken and the last dosage taken by the patients before the date of the COVID-19 diagnosis were recorded and used in the analysis. The daily doses of all antipsychotic drugs were converted to a chlorpromazine equivalent (CPZE) dose (expressed as milligrams of chlorpromazine) (Atkins et al., 1997; Woods, 2003). If a patient was taking more than one antipsychotic from the same group (SGA or FGA), they were classified in that group, whereas if they were taking more than one antipsychotic from a different group, they were classified as combined use (SGA + FGA). The total daily dose was calculated by summing of CPZE doses of all antipsychotics taken by the patients, regardless of the type of AP.

## Statistical Analysis

SPSS 23.0 (SPSS Inc) statistical package program was used to analyze the variables. Descriptive variables are presented as frequencies and percentages, and continuous data are presented as the mean  $\pm$  standard deviation. The Shapiro-Wilk test for normality was used to check the distribution of the continuous data. Pearson's chi-square test or Fisher's exact test was performed to compare differences for the categorical variables between the patients who were COVID positive and those who were COVID negative. *T*-test was used to compare the differences in the continuous variables between the groups (patients who were COVID positive *vs.* those who were negative, patients with severe COVID-19 *vs.* those with nonsevere, and deceased *vs.* nondeceased patients). A Pearson or a Spearman correlation analysis was used to explore the associations among the length of stay in the ICU, length of stay at the COVID-19 inpatient clinic, and the numeric variables. Logistic regression analysis was used to assess the effects of the clinical and demographic factors and the antipsychotic drug type and dosage on the presence of severe COVID-19 disease and SARS-CoV-2 seropositivity as dependent variables. We did not perform a logistic regression analysis to assess the effects of clinical and demographic variables on mortality due to the small sample size of deceased patients in the present study. The results from the regression are reported as odds ratios with 95% confidence intervals.

We used the Bonferroni correction to control the type 1 error for multiple comparisons in univariate analyses. We divided  $p = 0.05$  by the number of comparisons ( $n = 8$ ) to get the Bonferroni critical value,  $p < 0.00625$  to be significant (Simes, 1986). For all demographic data and clinical characteristics, each variable that showed and/or reached statistical significance with  $p < 0.00625$  between the groups in the univariate analysis was entered into the logistic regression model for analysis. In addition, we detected multicollinearity by using a metric known as the variance inflation factor (VIF), which measures the correlation and strength of correlation between the predictor variables in a regression model. None of the VIF values for the predictor variables in our regression analyses are greater than 4, which indicates that multicollinearity will not be a problem in the regression model (Pan and Jackson, 2008).

## RESULTS

A total of 1620 patients with schizophrenia were included in the analyses. The mean age of the patients was  $46.47 \pm 10.75$  years, and males accounted for 59.1% of the cohort. Of the 1620 patients, 52 (3.2%) were SARS-CoV-2 positive. The rate of FGA + SGA use was higher in the SARS-CoV-2-positive patients, whereas SGAs were the most commonly used antipsychotics in both the SARS-CoV-2-positive and SARS-CoV-2-negative patients. Table 1 presents the sociodemographic and clinical characteristics of the study participants based on the SARS-CoV-2 serological status (Table 1). A logistic regression analysis showed that CPZE dose of AP, CCI scores, being married, and smoking were independently associated with a greater risk of SARS-CoV-2 seropositivity in patients with schizophrenia. Because one outcome measure was tested against 12 hypothesized predictors, a Bonferroni-adjusted significance level of 0.00416 (0.05/12) was

**TABLE 1.** Sociodemographic and Clinical Features of Patients With Schizophrenia According to SARS-CoV-2 Status

	SARS-CoV-2 Status				Statistic	p
	Negative (n = 1568)		Positive (n = 52)			
	Mean	SD	Mean	SD		
Age	46.69	10.65	39.59	11.46	$t = 4.71, df = 1618$	<0.001
No. hospitalizations	1.40	1.54	2.88	2.50	$t = -6.63, df = 53.95$	<0.001
Duration of disease	18.51	7.70	13.61	8.89	$t = 4.48, df = 1618$	<0.001
BMI	25.47	2.19	26.75	2.25	$t = -4.11, df = 1618$	<0.001
Age at illness onset	28.18	6.62	25.98	4.58	$t = 2.38, df = 1618$	0.017
No. psychiatric admission	4.05	1.72	6.05	3.07	$t = -7.97, df = 1618$	<0.001
Charlson Comorbidity Index	0.42	0.94	0.7308	1.10463	$t = -2.31, df = 1618$	0.021
CPZE dose of antipsychotic	349.6269	199.97520	592.30	270.32	$t = -6.41, df = 52.86$	<0.001
	n (%)		n (%)			
Sex						
Female	629 (40.1%)		25 (48.1%)		$\chi^2 = 1.324, df = 1$	0.254
Male	939 (59.9%)		27 (51.9%)			
Type of Antipsychotic						
FGA	162 (10.3%)		4 (7.7%)		$\chi^2 = 38.49, df = 2$	<0.001
SGA	1240 (79.1%)		28 (53.8%)			
Combined (FGA + SGA)	166 (10.6%)		20 (38.5%)			
Education level						
No education	348 (22.2%)		3 (5.8%)		$\chi^2 = 9.87, df = 2$	0.07
First level	983 (62.7%)		43 (82.7%)			
High level	237 (15.1%)		6 (11.5%)			
Working status						
No work	984 (62.8%)		42 (80.8%)		$\chi^2 = 12.74, df = 3$	0.0065
Officer	237 (15.1%)		6 (11.5%)			
Worker	77 (4.9%)		4 (7.7%)			
Housewife	270 (17.2%)		0 (0.0%)			
Marriage status						
Single	924 (58.9%)		48 (92.3%)		$\chi^2 = 23.36, df = 1$	<0.001
Married	644 (41.1%)		4 (7.7%)			
Smoking						
No	433 (27.6%)		26 (50.0%)		$\chi^2 = 12.42, df = 1$	0.001
Yes	1135 (72.4%)		26 (50.0%)			
Suicide						
No	1344 (85.7%)		33 (63.5%)		$\chi^2 = 19.54, df = 1$	0.007
Yes	224 (14.3%)		19 (36.5%)			
Place of residence						
Rural	444 (28.3%)		42 (80.8%)		$\chi^2 = 65.94, df = 1$	<0.001
Urban	1124 (71.7%)		10 (19.2%)			

calculated to account for the increased possibility of type I error in the logistic regression analysis (Table 2).

Among the SARS-CoV-2-positive patients, 40 patients were hospitalized, and 17 patients required ICU admission due to COVID-19 (76.9% and 32.7%, respectively). All patients that were admitted to the ICU required mechanical ventilation. Therefore, severe COVID-19 disease was noted in 17 patients (32.7%) requiring intubation. Death occurred in 7 patients (13.5%). Table 3 presents the clinical characteristics of the study participants based on positive SARS-CoV-2 test results (Table 3).

Patients with severe COVID-19 and schizophrenia had a significantly higher BMI, CCI score, and CPZE antipsychotic dose than those with nonsevere COVID-19 ( $27.42 \pm 2.09$  vs.  $25.35 \pm 1.93$ ,  $t = -3.43$ ,  $p = 0.001$ ;  $1.29 \pm 1.68$  vs.  $0.45 \pm 0.50$ ,  $t = -2.719$ ,  $p = 0.002$ ; and  $697.14 \pm 229.43$  vs.  $376.47 \pm 218.03$ ,  $t = -4.803$ ,

$p < 0.001$ , respectively). Patients with severe COVID-19 and schizophrenia were older than those with nonsevere COVID-19; when compared with patients with nonsevere COVID-19, the patients with severe COVID-19 were also predominantly male and had a higher rate of FGA use. A logistic regression analysis showed that age, male sex, CPZE antipsychotic dose, and CCI scores were independently associated with a greater risk of severe COVID-19 disease in patients with schizophrenia. Because one outcome measure was tested against six hypothesized predictors, a Bonferroni-adjusted significance level of 0.00833 (0.05/6) was calculated to account for the increased possibility of type I error in the logistic regression analysis (Table 4).

Seventeen Pearson correlation tests among length of stay in the ICU, length of stay in COVID-19 inpatient clinic, and other variables were performed and tested against a Bonferroni-adjusted  $p$  level of 0.00294 (0.05/17). In this analysis, we found that length of stay in the

**TABLE 2.** Predictors of COVID-19 Seropositivity Among Patients With Schizophrenia

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Type of antipsychotic								
FGA use (reference category)			1.428	2	0.490			
SGA use	0.262	0.528	0.246	1	0.620	1.299	0.462	3.657
Combined (FGA + SGA) use	0.353	0.375	0.883	1	0.347	1.423	0.682	2.970
Sex	-0.365	0.405	0.812	1	0.368	0.695	0.314	1.535
BMI	0.048	0.103	0.213	1	0.644	1.049	0.856	1.285
Age	-0.040	0.017	5.542	1	0.019	0.961	0.929	0.993
Comorbidity index	0.824	0.192	18.492	1	0.000 <sup>a</sup>	2.280	1.566	3.320
CPZE dose of AP	0.005	0.001	45.663	1	0.000 <sup>a</sup>	1.005	1.004	1.007
Place of residence	0.547	0.302	3.279	1	0.070	1.728	0.956	3.125
Marriage status	2.173	0.568	14.617	1	0.000 <sup>a</sup>	1.114	1.037	1.347
Smoking	-1.206	0.321	14.108	1	0.000 <sup>a</sup>	0.299	0.160	0.562
No. psychiatric hospitalizations	0.149	0.086	2.995	1	0.084	1.161	0.980	1.375
No. psychiatric outpatient admissions	0.189	0.083	5.198	1	0.023	1.209	1.027	1.422
Duration of psychiatric disease	-0.003	0.056	0.003	1	0.955	0.997	0.894	1.112

<sup>a</sup>Significant after Bonferroni correction ( $p < 0.00416$ ).

ICU due to COVID-19 was positively and significantly related to age and significantly and negatively related to BMI, number of psychiatric admissions, length of stay for psychiatry services, CPZE dose of AP, and number of psychiatric hospitalizations. Table 5 presents the correlation coefficients among length of stay in the ICU, length of stay in the inpatient clinic, and clinical variables among patients with schizophrenia and COVID-19 (Table 5).

When the demographic variables and mortality among the study population were considered, the data showed that all of the deceased patients were male. The mean age of the deceased patients was significantly higher than that of the nondeceased patients ( $57.71 \pm 2.41$  vs.  $36.77 \pm 9.55$ ,  $t = -5.72$ ,  $df = 50$ ,  $p < 0.001$ ). Deceased patients were predominantly living in urban areas (57.1%). There was no significant difference between the deceased and nondeceased patients in terms of type and daily dose of antipsychotic drug use ( $\chi^2 = 2.25$ ,  $df = 2$ ,  $p = 0.341$  and  $t = -0.378$ ,  $df = 50$ ,  $p = 0.71$ , respectively). The deceased patients had a significantly higher duration of psychiatric disease than the recovered patients ( $35.7143 \pm 1.60357$  vs.  $24.4667 \pm 2.56373$ ,  $t = -2.86$ ,  $df = 50$ ,  $p = 0.006$ ). On the other hand, the deceased patients had higher CCI scores than the nondeceased participants ( $3.14 \pm 0.89$  vs.  $0.35 \pm 0.48$ ,  $t = -12.45$ ,  $df = 50$ ,  $p < 0.001$ ). Among the deceased patients, the most prevalent comorbid diseases were diabetes mellitus, CPD, and hypertension (85.7%, 85.7%, and 42.9%, respectively).

**DISCUSSION**

This retrospective study reported the prevalence of COVID-19 infection and identified the demographic and clinical variables related to severe COVID-19 and mortality due to COVID-19 in patients with schizophrenia. The prevalence of COVID-19 was 3.3% among the studied patients with schizophrenia. In particular, comorbidity score, and daily antipsychotic dose were significant determinants of severe COVID-19 disease, whereas mortality was associated with an older age, comorbidity score, and a longer duration of psychiatric disease among the SARS-CoV-2-positive patients with schizophrenia.

According to the WHO data, the positivity rate of SARS-CoV-2 in the general population in Turkey is currently approximately 6% (World Health Organization, 2021b). In our study, we found a SARS-CoV-2 positivity rate (3.3%) that was less than the frequency in the general population,

which is contrary to our initial hypothesis. In some previous studies, it has been reported that SARS-CoV-2 positivity is low in schizophrenia patients, contrary to what is expected for schizophrenia, which is similar to the current findings. It has been suggested that this low frequency may be related to these patients' social isolation because these patients tend to stay away from close contact with family members (Fond et al., 2021b; Tzur Bitan et al., 2021). On the other hand, there may be other factors that protect this group of patients from SARS-CoV-2 transmission. Our study found that SARS-CoV-2-positive patients used combined antipsychotics (SGA + FGA) with a higher frequency, were

**TABLE 3.** Clinical Features of SARS-CoV-2 Positive Patients With Schizophrenia

		n (%)
Hospitalization requirement		40 (76.9%)
Intensive care unit requirement		17 (32.7%)
COVID-19 symptoms	Anosmia	17 (32.7%)
	Respiratory symptoms	52 (100%)
	GIS symptoms	29 (55.8%)
	General symptoms	42 (80.8%)
Mortality rate		7 (13.5%)
Length of stay at COVID-19 service (n = 40), d	Mean ± SD	8.57 ± 6.28
Length of stay at ICU (n = 17), d	Mean ± SD	16.36 ± 11.17
Comorbid diseases	Congestive heart failure	1 (1.9%)
	Cerebrovascular disease	2 (3.8)
	Hemiplegia	1 (1.9%)
	CPD	12 (23.1%)
	Connective tissue disease	2 (3.8%)
	Peptic ulcer	1 (1.9%)
	Mild liver disease	2 (3.8%)
	Diabetes mellitus	16 (30.8%)
	Hypertension	13 (25%)

**TABLE 4.** Predictors of Severe COVID-19 Among Patients With Schizophrenia

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Sex	4.511	2.138	4.452	1	0.035	9.105	1.378	60.14
Age	0.090	0.043	4.350	1	0.037	1.094	1.005	1.190
Type of antipsychotic								
FGA use (reference category)			3.348	2	0.187			
SGA use	-0.602	1.855	0.105	1	0.746	0.548	0.014	2.077
FGA + SGA use	2.983	1.698	3.085	1	0.079	1.974	0.708	5.558
BMI	-0.233	0.260	0.800	1	0.371	0.792	0.476	1.319
Comorbidity index	0.318	0.092	11.957	1	0.001 <sup>a</sup>	1.375	1.148	1.647
CPZE dose of AP	0.012	0.004	10.416	1	0.001 <sup>a</sup>	1.989	1.982	1.995

<sup>a</sup>Significant after Bonferroni correction ( $p < 0.00833$ ).

exposed to higher daily antipsychotic doses, and more frequently lived in the rural area. An earlier study also reported that patients with schizophrenia taking clozapine more frequently contracted SARS-CoV-2 than those using other antipsychotics (Govind et al., 2021). Therefore, whether such factors play a protective or predisposing role during the transmission of the virus is a matter that needs to be further investigated among schizophrenia patients.

The COVID-19-infected patients of schizophrenia were younger than those who were not infected, but once they were infected, older age was related to worse outcomes. This finding may be related to the increased social isolation in older patients with schizophrenia. Social isolation may cause a lower infection rate by reducing the risk of exposure to SARS-CoV-2 in these patients. Specific groups at greater risk of social isolation include older people who are socially excluded and patients with a severe mental disorder. The COVID-19 pandemic is also increasing the number of older adults who are socially isolated (Plagg et al., 2020; Stain et al., 2012; Wu, 2020). Another predictor of SARS-CoV-2 positivity among individuals with schizophrenia was being married in the current study. Single patients may have been less likely infected because family members are considered to be one of the main routes of COVID-19 transmission (Liu et al., 2020; Rajmil, 2020).

We found an inverse relationship between smoking and SARS-CoV-2 infection. A number of studies have found a low rate of smoking among COVID-19 patients, leading researchers to conclude that smoking may be a protective factor against SARS-CoV-2 infection (Guan et al., 2020; Miyara et al., 2020). However, this interesting finding may be related to the use of hospital data, which has been suggested not to be suitable for determining the risk of SARS-CoV-2 infection among smokers due to its cross-sectional nature (*i.e.*, determining risk factor and disease at the same time) (van Westen-Lagerweij et al., 2021).

As expected, the course of the disease was more serious in patients with schizophrenia, and the death rate was also higher in the current study than that in the general population. This finding is also supported by earlier studies (Fond et al., 2021b; Tzur Bitan et al., 2021). In previous studies, it has been reported that having a diagnosis of schizophrenia itself is associated with death related to COVID-19, even after adjusting for confounding factors (Fond et al., 2021a; Nemani et al., 2021a; Tzur Bitan et al., 2021). We found in our study here that age, male sex, and the presence of comorbid diseases were associated with severe SARS-CoV-2 disease, and these are factors that are reported to be associated with a poor prognosis for COVID-19 in all patients, with and without a psychiatric disorder (Ji et al., 2020; Nasiri et al., 2020; Yang et al., 2020). Advanced age and male sex in psychiatric disorders have also been associated with mortality and intensive care hospitalization in COVID-19 patients (Wang et al., 2021). There are few publications on the fact that the presence of comorbid medical diseases in

schizophrenia worsens the course of COVID-19 (Fond et al., 2021b; Lee et al., 2020; Nemani et al., 2021a; Wang et al., 2021). In our study, it was also found that the rates of comorbid medical diseases, especially diabetes mellitus, CPD, and hypertension, were higher in patients with severe COVID-19 and schizophrenia than in nonsevere patients.

Another remarkable finding of our study was the relationship between the doses of antipsychotic drugs used by patients and the severity of COVID-19. The antipsychotic drug type (FGA, SGA, or FGA + SGA) used by the patients was not associated with the severe COVID-19 disease. On the other hand, neither the antipsychotic type nor the dose was associated with mortality due to COVID-19 in our study. This finding is consistent with the follow-up study by Nemani et al. (2021b). However, patients with schizophrenia who died due to COVID-19 had a significantly higher duration of psychiatric disease compared with the nondeceased patients. This finding may reflect the decreased immunity secondary to increased inflammation and cortisol levels in patients with schizophrenia with a longer duration of psychiatric disease (Dahan et al., 2018; Ritsner et al., 2004; Szymona et al., 2017). However, it is important to note that the univariate analyses of factors associated with COVID-19 mortality may not have had adequate power to detect any associations given the low number of deaths related to COVID-19 in the present study. Therefore, these analyses are very preliminary and also likely lacking generalizability.

To our knowledge, there is only one study that examined the association of an infection of SARS-CoV-2 with antipsychotic drugs in

**TABLE 5.** Correlation Coefficients Between Length of Stay at ICU and COVID-19 Inpatient Clinics and Clinical and Demographic Variables

	Length of Stay COVID-19 Inpatient Clinic	Length of Stay at COVID-19 ICU
Age	0.547 <sup>a</sup>	0.542 <sup>a</sup>
No. psychiatric hospitalizations	-0.487 <sup>a</sup>	-0.726 <sup>a</sup>
Duration of psychiatric disease	0.434 <sup>a</sup>	0.328*
BMI	-0.397 <sup>a</sup>	-0.465 <sup>a</sup>
No. psychiatric admissions	-0.458 <sup>a</sup>	-0.497 <sup>a</sup>
Length of stay at psychiatry services	-0.489 <sup>a</sup>	-0.580 <sup>a</sup>
Charlson Comorbidity Index	0.333*	0.339*
CPZE dose of AP	-0.336*	-0.548 <sup>a</sup>

\* $p < 0.05$ .

<sup>a</sup>Significant after Bonferroni correction ( $p < 0.00294$ ).

patients with schizophrenia. In this study, it was reported that patients taking clozapine had an increased risk of contracting COVID-19 compared with patients using other antipsychotics (Govind et al., 2021). In our study, we found that the daily dose of antipsychotic drugs was associated with severe COVID-19, regardless of the type of antipsychotic taken by the patient. It is reported that both FGA and SGA drugs can lead to immune dysfunction, a predisposition to thromboembolic events, and pneumonia in patients with schizophrenia (Papola et al., 2019; Zhang et al., 2011). Antipsychotics may cause a severe SARS-CoV-2 infection through immune dysfunction, further increasing the tendency to pneumonia and embolism when antipsychotic drugs are given in high doses, and there potentially could be direct drug to drug interactions. However, high doses of APs might just be a surrogate indicator of clinical severity, and the positive correlation between CPZE doses of APs and the worse outcome might not only be a direct result of a pharmacological agent to the physical condition in the present study. We should also acknowledge that our sample size of individuals with schizophrenia and COVID-19 is limited and that, as a result, our analyses are exploratory/preliminary at best.

We found negative relationships among the length of stay at ICU, length of stay at COVID-19 clinic, and CPZE doses of AP. However, we could not find any differences at CPZE doses of AP between deceased and nondeceased patients possibly due to low sample size and statistical power. On the other hand, the lack of data on whether the patients' antipsychotics were continued during the stay at COVID-19 inpatient clinic or ICU makes it difficult to explain these findings. It seems necessary to investigate both whether the dosages and type of APs are associated with severe COVID-19 disease and death and to investigate the mechanism of such a relationship, if any, with prospective and large-sample studies.

We found a negative relationship among the length of stay at ICU, the number of psychiatric admissions, length of stay at psychiatry services, and the number of psychiatric hospitalizations. There are several alternative explanations for these findings, most notably the fact that patients with schizophrenia who are frequently admitted to psychiatry clinics and have long periods of hospitalization in psychiatric services are likely to come into greater contact with health services than other patients. Therefore, these patients are more likely to be tested if they develop symptoms. This may lead to early detection and intervention, which has been suggested to improve the outcome in patients with COVID-19 (Goyal et al., 2020).

Our study did not find any relationship between the severity of COVID-19 and BMI. Obesity is a strong risk factor for susceptibility, transmission, and severity of COVID-19 (Sattar et al., 2020; Stefan et al., 2021). Moreover, we found a negative relationship between the length of stay at ICU and BMI in patients with COVID-19 and schizophrenia. As mentioned earlier, it is possible to comment on this contradictory finding that patients with higher BMI may have died shortly after being transferred from the COVID-19 inpatient clinic to ICU. On the other hand, BMI measurements for some patients were not recent due to a lack of reliable data and the retrospective nature of the study. This limitation may reduce the validity of our findings regarding the relationship between BMI and COVID-19 severity in patients with schizophrenia.

It cannot be ignored that our work has some limitations. First, the most important limitation is that the study is retrospective and analyzed only limited data that can be accessed. Further, the fact that the sample is from a single center and small in size reduces the generalizability of the results. In addition, another important limitation is that we had no information about the severity of psychopathology during COVID-19 infection. Last, the small number of deceased patients decreased statistical power and prevented us from characterizing determinant factors associated with mortality in patients with schizophrenia.

## CONCLUSIONS

Despite these limitations, our study indicates that COVID-19 has a severe outcome and results in more frequent deaths in patients with

schizophrenia. Our findings suggest that factors such as age, sex, comorbidities, and the daily antipsychotic dose may have an effect on the severe course of COVID-19 in schizophrenia patients. We did not observe an association between antipsychotic use and mortality in patients with schizophrenia. However, the findings of our study should be verified in prospective studies and studies with larger sample sizes.

## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

- Atkins M, Burgess A, Bottomley C, Riccio M (1997) Chlorpromazine equivalents: A consensus of opinion for both clinical and research applications. *Psychiatr Bull.* 21:224–226.
- Bannay A, Chaignot C, Blotière PO, Basson M, Weill A, Ricordeau P, Alla F (2016) The best use of the Charlson Comorbidity Index with electronic health care database to predict mortality. *Med Care.* 54:188–194.
- Carney CP, Jones L, Woolson RF (2006) Medical comorbidity in women and men with schizophrenia: A population-based controlled study. *J Gen Intern Med.* 21:1133–1137.
- Dahan S, Bragazzi NL, Yogev A, Bar-Gad M, Barak V, Amital H, Amital D (2018) The relationship between serum cytokine levels and degree of psychosis in patients with schizophrenia. *Psychiatry Res.* 268:467–472.
- Fond G, Pauly V, Leone M, Llorca PM, Orleans V, Loundou A, Lancon C, Auquier P, Baumstarck K, Boyer L (2021a) Disparities in intensive care unit admission and mortality among patients with schizophrenia and COVID-19: A National Cohort Study. *Schizophr Bull.* 47:624–634.
- Fond G, Pauly V, Orleans V, Antonini F, Fabre C, Sanz M, Klay S, Jimeno MT, Leone M, Lancon C, Auquier P, Boyer L (2021b) Increased in-hospital mortality from COVID-19 in patients with schizophrenia. *Encephale.* 47:89–95.
- Govind R, Fonseca de Freitas D, Pritchard M, Hayes RD, MacCabe JH (2021) Clozapine treatment and risk of COVID-19 infection: Retrospective cohort study. *Br J Psychiatry.* 219:368–374.
- Goyal DK, Mansab F, Iqbal A, Bhatti S (2020) Early intervention likely improves mortality in COVID-19 infection. *Clin Med (Lond).* 20:248–250.
- Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ, Li L, Chen PY, Sang L, Wang W, Li JF, Li CC, Ou LM, Cheng B, Xiong S, Ni ZY, Xiang J, Hu Y, Liu L, Shan H, Lei CL, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Cheng LL, Ye F, Li SY, Zheng JP, Zhang NF, Zhong NS, He JX. China Medical Treatment Expert Group for COVID-19 (2020) Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. *Eur Respir J.* 55:2000547.
- Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, Na Y, Choi H, Gong SY, Choi YH, Ko KP, Im JS, Jung J (2020) Effect of underlying comorbidities on the infection and severity of COVID-19 in Korea: A nationwide case-control study. *J Korean Med Sci.* 35:e237.
- Kozloff N, Mulsant BH, Stergiopoulos V, Voineskos AN (2020) The COVID-19 global pandemic: Implications for people with schizophrenia and related disorders. *Schizophr Bull.* 46:752–757.
- Lee SW, Yang JM, Moon SY, Yoo IK, Ha EK, Kim SY, Park UM, Choi S, Lee SH, Ahn YM, Kim JM, Koh HY, Yon DK (2020) Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: A nationwide cohort study. *Lancet Psychiatry.* 7:1025–1031.
- Liu T, Gong D, Xiao J, Hu J, He G, Rong Z, Ma W (2020) Cluster infections play important roles in the rapid evolution of COVID-19 transmission: A systematic review. *Int J Infect Dis.* 99:374–380.
- Miyara M, Tubach F, Pourcher V, Morélot-Panzini C, Pernet J, Haroche J, Lebbah S, Morawiec E, Gorochoff G, Caumes E, Hausfater P, Combes A, Similowski T, Amoura Z (2020) Low rate of daily active tobacco smoking in patients with symptomatic COVID-19. Available at: <https://www.qeios.com/read/WPP19W.4>. Accessed June 25, 2021.
- Nanda S, Chacin Suarez AS, Toussaint L, Vincent A, Fischer KM, Hurt R, Schroeder DR, Medina Inojosa JR, O'Horo JC, DeJesus RS, Abu Lebdeh HS, Mundi MS,

- Iftikhar S, Croghan IT (2021) Body mass index, multi-morbidity, and COVID-19 risk factors as predictors of severe COVID-19 outcomes. *J Prim Care Community Health*. 12:21501327211018559.
- Nasiri MJ, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, Jamshidi P, Murthi M, Mirsaedi M (2020) COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic review and meta-analysis. *Front Med*. 7:459.
- Nemani K, Conderino S, Marx J, Thorpe LE, Goff DC (2021b) Association between antipsychotic use and COVID-19 mortality among people with serious mental illness. *JAMA Psychiatry*. 78:1391–1393.
- Nemani K, Li C, Olsson M, Blessing EM, Razavian N, Chen J, Petkova E, Goff DC (2021a) Association of psychiatric disorders with mortality among patients with COVID-19. *JAMA Psychiat*. 78:380–386.
- Pan Y, Jackson RT (2008) Ethnic difference in the relationship between acute inflammation and serum ferritin in US adult males. *Epidemiol Infect*. 136:421–431.
- Papola D, Ostuzzi G, Gastaldon C, Morgano GP, Dragioti E, Carvalho AF, Fusar-Poli P, Correll CU, Solmi M, Barbui C (2019) Antipsychotic use and risk of life-threatening medical events: Umbrella review of observational studies. *Acta Psychiatr Scand*. 140:227–243.
- Plagg B, Engl A, Piccoliori G, Eisendle K (2020) Prolonged social isolation of the elderly during COVID-19: Between benefit and damage. *Arch Gerontol Geriatr*. 89:104086.
- Rajmil L (2020) Role of children in the transmission of the COVID-19 pandemic: A rapid scoping review. *BMJ Paediatr Open*. 4:e000722.
- Ritsner M, Maayan R, Gibel A, Strous RD, Modai I, Weizman A (2004) Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. *Eur Neuropsychopharmacol*. 14:267–273.
- Sakurai A, Sasaki T, Kato S, Hayashi M, Tsuzuki SI, Ishihara T, Iwata M, Morise Z, Doi Y (2020) Natural history of asymptomatic SARS-CoV-2 infection. *N Engl J Med*. 383:885–886.
- Sattar N, McInnes IB, McMurray JJV (2020) Obesity is a risk factor for severe COVID-19 infection: Multiple potential mechanisms. *Circulation*. 142:4–6.
- Simes RJ (1986) An improved Bonferroni procedure for multiple tests of significance. *Biometrika*. 73:751–754.
- Stain HJ, Galletly CA, Clark S, Wilson J, Killen EA, Anthes L, Campbell LE, Hanlon MC, Harvey C (2012) Understanding the social costs of psychosis: The experience of adults affected by psychosis identified within the second Australian National Survey of psychosis. *Aust N Z J Psychiatry*. 46:879–889.
- Stefan N, Birkenfeld AL, Schulze MB (2021) Global pandemics interconnected—obesity, impaired metabolic health and COVID-19. *Nat Rev Endocrinol*. 17:135–149.
- Szymona K, Zdzisińska B, Karakula-Juchnowicz H, Kocki T, Kandefer-Szerszeń M, Flis M, Rosa W, Urbańska EM (2017) Correlations of Kynurenic acid, 3-Hydroxykynurenine, sIL-2R, IFN- $\alpha$ , and IL-4 with clinical symptoms during acute relapse of schizophrenia. *Neurotox Res*. 32:17–26.
- Taquet M, Luciano S, Geddes JR, Harrison PJ (2021) Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 8:130–140.
- Tzur Bitan D, Krieger I, Kridin K, Komantscher D, Scheinman Y, Weinstein O, Cohen AD, Cicurel AA, Feingold D (2021) COVID-19 prevalence and mortality among schizophrenia patients: A large-scale retrospective cohort study. *Schizophr Bull*. 47:1211–1217.
- van Westen-Lagerweij NA, Meijer E, Meeuwse EG, Chavannes NH, Willemsen MC, Croes EA (2021) Are smokers protected against SARS-CoV-2 infection (COVID-19)? The origins of the myth. *NPJ Prim Care Respir Med*. 31:10.
- Wang Q, Xu R, Volkow ND (2021) Increased risk of COVID-19 infection and mortality in people with mental disorders: Analysis from electronic health records in the United States. *World Psychiatry*. 20:124–130.
- Woods SW (2003) Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 64:663–667.
- World Health Organization (2021a) Coronavirus disease (COVID-19) situation reports. Available at: [www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports](http://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). Accessed June 26, 2021.
- World Health Organization (2021b) Coronavirus disease (COVID-19) situation reports. Available at: <https://covid19.who.int/region/euro/country/tr>. Accessed June 26, 2021.
- Wu B (2020) Social isolation and loneliness among older adults in the context of COVID-19: A global challenge. *Glob Health Res Policy*. 5:27.
- Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y (2020) Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int J Infect Dis*. 94:91–95.
- Zhang R, Dong L, Shao F, Tan X, Ying K (2011) Antipsychotics and venous thromboembolism risk: A meta-analysis. *Pharmacopsychiatry*. 44:183–188.
- Zhang X, Tan Y, Ling Y, Lu G, Liu F, Yi Z, Jia X, Wu M, Shi B, Xu S, Chen J, Wang W, Chen B, Jiang L, Yu S, Lu J, Wang J, Xu M, Yuan Z, Zhang Q, Zhang X, Zhao G, Wang S, Chen S, Lu H (2020) Viral and host factors related to the clinical outcome of COVID-19. *Nature*. 583:437–440.