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The Impacts of Clozapine Use on the Risk and Outcomes of COVID-19 Disease in Patients with Schizophrenia

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ABSTRACT

Introduction: Clozapine may affect the outcome of severe COVID-19 infection due to its anti-inflammatory and immunosuppressant effects. This study aimed to investigate whether the risk of COVID-19 changed in schizophrenic patients using clozapine and to compare patients using clozapine with other antipsychotics in terms of COVID-19 severity.

Methods: A total of 732 patients who were registered and followed up with a diagnosis of schizophrenia were included in the study. These patients' sociodemographic data, smoking status, medications, comorbidities, COVID-19 PCR results, and COVID-19 outcomes (inpatient care admission, intensive care unit admission, death) were retrospectively analyzed.

Results: Of the 732 patients included in our study, 177 were using clozapine. Ninety-six of 732 patients were diagnosed with COVID-19, and 34 of these were being treated with clozapine. We found that clozapine use was an independent risk factor for COVID-19 positivity (OR=1.81 95% CI=1.13–2.90), inpatient care admission (OR=3.01, 95% CI=1.12–8.06).

Conclusion: In our study, clozapine use was associated with an increased risk of COVID-19 positivity and inpatient care admission; however, it was not associated with ICU admission or death. Due to the frequent follow-up of patients using clozapine and the effects of clozapine on immunity, the frequency and/or identification of COVID-19 may be increased in these patients. Clozapine toxicity, granulocytopenia or agranulocytosis during the COVID-19 infection may have increased these patients' hospitalisation frequency.

Keywords: Clozapine, COVID-19, schizophrenia

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INTRODUCTION

Clozapine is the most effective medication for treatment-resistant schizophrenia and is the only effective treatment for many patients with schizophrenia (1). Side effects such as neutropenia, agranulocytosis, transient eosinophilia, cytokine release and fever may occur in patients using clozapine (2). The use of clozapine doubles the risk of pneumonia due to factors such as diabetes, weight gain, and especially aspiration pneumonia resulting from hypersalivation (3–4). Compared to other antipsychotic drugs, clozapine suppresses adaptive immunity and significantly reduces immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) levels (5).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a novel ribonucleic acid (RNA) virus from the same family as Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and was declared as the causative agent of the pneumonia epidemic in January 2020, which later caused a pandemic (6). The onset and prognosis of Coronavirus disease 2019 (COVID-19) vary considerably by age groups, and mortality risk increases with age (7). Mortality rates are increased in patients with diabetes, cardiovascular diseases and immunosuppression (8).

Many studies in the literature investigate the relationship between clozapine use and the risk of COVID-19 (9–12). In a study by Govind et al. (2020), which focused on clozapine use and the risk of COVID-19, it was found that clozapine use increased the risk of COVID-19 positivity by 1.76 times (9). Ohlis et al. (2021), in their study involving 8223 patients using antipsychotics, found that clozapine use did not affect the prognosis of COVID-19 (10). In a very recent study, Govind et al. (2022) followed 157 patients with schizophrenia spectrum disorder who were diagnosed with COVID-19 during 28 days of follow-up and they found no evidence that receiving clozapine treatment substantially increases the risk of these outcomes, compared to receiving any other types of antipsychotic treatment (11). Osimo et al. (2022), in their study with 13726 patients using antipsychotics, found that clozapine use increased the risk of COVID-19

Highlights

- **Hospitalization for COVID-19 has increased in clozapine using schizophrenia patients.**
- **Clozapine use is not associated with ICU admission in patients with schizophrenia.**
- **Clozapine use is not associated with death in patients with schizophrenia.**

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positivity by 1.99 times, but when only patients with schizophrenia were compared, clozapine use did not increase the risk of COVID-19 (12).

There are a few studies investigating the impacts of clozapine use on the risk and outcomes of COVID-19 disease in patients with schizophrenia. We aimed to investigate the rates of COVID-19 positivity, hospital admissions, intensive care unit (ICU) admissions and death in patients with schizophrenia who are currently using clozapine and compare them with schizophrenia patients who are using other antipsychotic drugs. We hypothesized that the use of clozapine had no effect on the outcome of COVID-19.

METHODS

Setting and Ethics Statement

This study was carried out by retrospectively analyzing patient files and the electronic records of Republic of Turkey's Ministry of Health Public Health Management System (HSYS). The research permission was obtained from the Rebuplic of Turkey's Ministry of Health COVID-19 Scientific Research Evaluation Commission with the date 27.02.2021 and the number T14412, for this study. The HSYS is an electronic health record system in which the test results of patients who underwent PCR testing during the pandemic, the medications given to patients diagnosed with COVID-19, and the clinical course of COVID-19 (hospitalization, ICU admission, death, etc.) were recorded (13). The Polymerase Chain Reaction (PCR) results of patients and the clinical course of patients diagnosed with COVID-19 were analyzed retrospectively by accessing HSYS. The records of comorbidities and medications of patients were obtained from patient files. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, dated March 15, 2021 with protocol number 2021/134.

Cohort

The study included 732 patients who were followed up in the Community Mental Health Center affiliated with our hospital, who regularly took medication and regularly attended clinical interviews every three months. Inclusion criteria were determined as 1) Diagnosis of schizophrenia according to ICD-10 and 2) Regular antipsychotic use between March 2019 and March 2021. Exclusion criteria were: 1) hospitalization for reasons other than COVID-19 (including psychiatric hospitalizations) between March 2020 and March 2021, 2) living in places with a high risk of COVID-19 transmission, such as nursing homes, and 3) the use of valproic acid, lithium or carbamazepine.

For the evaluation of COVID-19 outcomes, only patients whose diagnosis was confirmed by PCR positivity were included in the study. Patients whose Computed Tomography (CT) result was compatible with COVID-19 and whose PCR test was negative were not included in the study. The records of the patients who were hospitalized or admitted to the ICU with a diagnosis of COVID-19 or died due to COVID-19 were obtained from HSYS.

Patients who were regularly treated with clozapine for at least 12 months prior to the date of COVID-19 infection were defined as the exposed group. Those who received any antipsychotic or antipsychotic combination treatment other than clozapine during this period constituted the unexposed group.

Main Outcome Measures

The following results were the focus of our study: 1) COVID-19 PCR positivity, 2) COVID-19-related inpatient care admission, 3) COVID-19-related ICU admission, and 4) COVID-19-related death. These data were compiled using hospital records, patient files, and HSYS records.

Statistical Analysis

Data from the study were analyzed using Statistical Package for the Social Sciences (SPSS) 22.0. Firstly, descriptive analyses such as frequency distribution were performed. Chi-square analysis was used for the comparison of categorical variables and independent samples t-test was used for the comparison of continuous variables. Logistic regression analysis was performed to predict the effect of clozapine use on COVID-19. Except for the use of clozapine, the variables (age, sex, comorbid chronic diseases and smoking status) determined to be associated with COVID-19 in the literature were included in the regression model. Homer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-1 error level was used to infer statistical significance.

RESULTS

Our study included 177 patients using clozapine and 555 patients using non-clozapine antipsychotics. No significant difference was found between the patient groups using and not using clozapine in terms of sex, disease duration, employment and smoking status ($p>0.05$). However, it was found that clozapine recipients were significantly younger than non-recipients ($t=2.94$, $p<0.05$) (Table 1).

When the comorbid chronic diseases of the participants were examined, it was determined that diabetes mellitus was more common in the group using clozapine ($c^2=9.62$, $p=0.002$), but there was no significant difference between the two groups in terms of hypertension, cardiovascular disease, chronic lung disease and cancer. When evaluated in terms of any comorbidity, chronic diseases were more common among clozapine recipients ($c^2=6.48$, $p=0.011$) (Table 1).

When clozapine recipients and non-recipients were evaluated in terms of COVID-19-related parameters, higher COVID-19 positivity ($c^2=7.60$, $p=0.006$) and inpatient care admission ($c^2=4.13$, $p=0.042$) were determined in patients using clozapine compared to the group not using clozapine. However, no significant difference was found between the two groups in terms of intensive care admission or death (Table 2).

The effects of clozapine use on COVID-19 were evaluated with logistic regression analysis after removing the effect of age, sex, comorbidities and smoking status. Clozapine use was found to be an independent risk factor for COVID-19 positivity (OR=1.81 95% CI=1.13–2.90), inpatient care admission (OR=3.01, 95% CI=1.12–8.06) in the model including all patients. However, when only COVID-19 positive patients were included, it was found that the effect of clozapine use on inpatient care admission was not significant (Table 2).

DISCUSSION

We investigated the effect of clozapine use on COVID-19 risk and outcomes among patients with schizophrenia who received clozapine and those who were using any other antipsychotic than clozapine. Our results indicate that clozapine use in patients with schizophrenia was an independent risk factor for COVID-19 positivity and inpatient care admission due to COVID-19.

It was shown in the literature that the risk of COVID-19 positivity increases in patients with schizophrenia spectrum disorder using clozapine. However, in the study by Osimo et al. (2022), patients receiving clozapine were more likely to test positive for COVID-19 if a schizophrenia diagnosis was not taken into account (12). Unlike that study, our study also found that the risk of COVID-19 positivity increased in patients with

Table 1. Comparison of sociodemographic and clinical characteristics of groups with and without clozapine

		Clozapine (n=177)	Other antipsychotics (n=555)		
		n (%), Mean ± SD	n (%), Mean ± SD	t, c^2	p
Sex (female)		49 (27.7)	183 (33.0)	1.743	0.18
Age (years)		43.7±11.5	46.7±11.8	2.942	0.003
Duration of illness (years)		20.5±9.9	19.0±9.6	-1.811	0.071
Marital status	Single	134 (75.7)	361 (65.0)	8.027	0.018
	Married	23 (13.0)	122 (22.0)		
	Divorced/Widowed	20 (11.3)	72 (13.0)		
Employment	Unemployed	151 (85.3)	437 (78.7)	3.671	0.16
	Employed	8 (4.5)	37 (6.7)		
	Retired	18 (10.2)	81 (14.6)		
Education	Primary	81 (45.8)	325 (58.6)	9.126	0.010
	Secondary	70 (39.5)	162 (29.2)		
	Bachelor	26 (14.7)	68 (12.3)		
Smoking (yes)		96 (54.2)	314 (56.6)	0.298	0.58
Chronic diseases	Diabetes	56 (31.6)	113 (20.4)	9.613	0.002
	Hypertension	47 (26.6)	126 (22.7)	1.103	0.294
	Cardiovascular disease	11 (6.2)	33 (5.9)	0.017	0.89
	Chronic lung disease	11 (6.2)	29 (5.2)	0.254	0.61
	Cancer	0 (0.0)	5 (0.9)	1.606	0.20
	Overall	78 (44.1)	186 (33.5)	6.483	0.011
COVID-19 outcomes	COVID-19 (positive)	34 (19.2)	62 (11.2)	7.609	0.006
	Inpatient Care	8 (4.5)	10 (1.8)	4.133	0.042
	ICU admission	4 (2.3)	7 (1.3)	0.904	0.34
	Death	4 (2.3)	5 (0.9)	2.041	0.15

COVID-19: Coronavirus Disease 2019; ICU: Intensive Care Unit; SD: Standard Deviation

Table 2. Adjusted and unadjusted odds ratios from logistic regression models of COVID-19 related conditions, among patients with clozapine treatment as compared to treatment with other antipsychotics

COVID-19 Outcome	Sample			
	All Patients (n=732)		COVID-19 Positive (n=96)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
COVID-19 (positive)	1.892 (1.196–2.988)	1.818 (1.137–2.907)	–	–
Inpatient Care	2.580 (1.002–6.641)	3.014 (1.127–8.061)	1.600 (0.564–4.536)	1.764 (0.558–5.576)

*Adjusted for age, sex, comorbid chronic diseases (diabetes, hypertension, cardiovascular disease, chronic lung disease, cancer) and smoking status.
CI: Confidence Interval; COVID-19: Coronavirus Disease 2019; OR: Odds Ratio.

schizophrenia. We found that using clozapine increased inpatient care, but the use of clozapine was not found to affect ICU and death. In studies including patients with schizophrenia spectrum disorder, it has been shown that no significant relationship was found between clozapine use and the prognosis of COVID-19 (inpatient care, ICU admission, and death). Our study differs from other studies because it indicates increased inpatient care of clozapine users.

Secondary infections during COVID-19 have a negative effect on the prognosis of COVID-19 (14). It is known that clozapine increases the risk of pneumonia more than other antipsychotics because of agranulocytosis, granulocytopenia, sialorrhea and comorbid diseases (3–4). In patients using clozapine, secondary infections occurring during the COVID-19 process may have increased due to side effects, which may lead to an increase in the use of clozapine in hospitalizations due to COVID-19. Multiple studies have revealed that the white blood cell count in patients using clozapine is reduced during COVID-19 infection (15–16). These studies' limitations are that the sample groups are low and do not include a control group. In our study, there is no data on this, but granulocytopenia, agranulocytosis or secondary infections in patients using clozapine may be another factor affecting the increased frequency of hospitalization in these patients.

During the early stages of COVID-19 infection, pro-inflammatory cytokines such as Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), interferon- g and tumor necrosis factor-a prevent the infection (17). Although clozapine increases IL-1, IL-6 and C-reactive protein (CRP) levels initially, it is shown that clozapine inhibits the production of IL-6 and IL-8 in later stages of treatment (18). Due to the predominance of proinflammatory cytokines in clozapine users, the defence mechanism against COVID-19 infection may be impaired, and as a result, the risk of COVID-19 may increase.

More frequent follow-ups of patients using clozapine can make it easier to detect COVID-19 symptoms. However, more frequent follow-ups may increase exposure due to increased contact among these patients, which may confound the relationship between clozapine use and the risk of COVID-19. In a study by Osimo et al. (2022), it was found that more COVID-19 tests were performed in patients using clozapine (12). Our study has no data on the number of COVID-19 tests, but the increased number of COVID-19 tests in patients using clozapine may increase the COVID-19 positivity.

Infections may increase clozapine levels by inhibiting the Cytochrome P450 1A2 (CYP1A2) enzyme system and cause clozapine toxicity (19). In clozapine toxicity; often sedation and fluctuations in consciousness, fecal incontinence, hypersalivation, myoclonus, and epileptic seizures are observed (20). There are a few case reports of neurological symptoms with clozapine toxicity and hospitalization during COVID-19 infection (21–23). In some cases, these symptoms may be confused with the symptoms of COVID-19. Clozapine toxicity may also affect the increased frequency of hospitalization in patients using clozapine.

There are a few limitations of our study. In our study, we tried to minimize factors that would affect the possible relationship between COVID-19 and clozapine; however, we could not eliminate factors such as patients' cohabiting status and the number of people patients came into contact with. Metabolic syndrome is a risk factor for COVID-19 (24). Since we could not access the data required for the diagnosis of metabolic syndrome from patient files and electronic records, the distribution of metabolic syndrome in the group using clozapine and the group using non-clozapine antipsychotics is unknown. It is known that the risk of developing comorbidity with clozapine use is higher than other antipsychotics (25). In our study, patients using clozapine were found to have more comorbidities. Comorbidities increase the risk of COVID-19 and worsen the prognosis of COVID-19 (8). The increased risk of COVID-19 with clozapine use can be explained by the higher number of comorbidities in the patient group using clozapine.

The relationship between clozapine use and COVID-19 infection is complex and multifactorial. The risk of infection increases in patients using clozapine for reasons such as diabetes, alcohol and substance abuse, smoking, malnutrition, sedentary lifestyle, sialorrhea, agranulocytosis and clozapine-related antibody deficiency (26–27). The use of clozapine may increase the risk of COVID-19 infection due to these underlying characteristics. Although clozapine increases the risk of infection, it is notable that the patients' clozapine use has no higher intensive care admission or mortality arising out of COVID-19.

In other studies, it was found that clozapine increases the risk of COVID-19, but these studies have been investigated in schizophrenia spectrum disorder. Our study is specifically investigating patients using clozapine with a diagnosis of schizophrenia. Clozapine is the gold-standard treatment for treatment resistant schizophrenia; our data supports the view that its use during COVID-19 infections necessitates more careful monitorization, yet should not be restricted. Large-scale studies with larger patient groups are needed to understand the relationship between COVID-19 and clozapine better. As a result of these studies, the benefit-harm balance of clozapine use may change for clinicians, and treatment guidelines may be updated.

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, dated March 15, 2021 with protocol number 2021/134.

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