

Schizophrenia and PCR-proved cases of COVID-19: A preliminary case-control study

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ABSTRACT

Objectives: The coronavirus infection (COVID-19) significantly impacts populations worldwide, including individuals with schizophrenia. This study meant to investigate whether COVID-19 patients with schizophrenia have the same disease severity and outcome as those without schizophrenia. **Methods:** This case-control, retrospective study included 108 adult patients who attended a tertiary care hospital with a polymerase chain reaction (PCR)-confirmed diagnosis of COVID-19. The study cohort was divided into the patient group (n=54) with confirmed schizophrenia diagnosis and the matched control group. The patients' medical data were retrieved from archived hospital e-medical records from 1 January to 26 February 2021. A logistic regression study was made to identify the risk of concomitant comorbidities. **Results:** Females accounted for 25.9% of the study population. Approximately 75% of the participants were aged ≥ 50 (50–69) years. None of the study participants were admitted to the ICU. Patients with schizophrenia had more comorbidities (68.5%) than COVID-19 patients without schizophrenia (35.2%). Nevertheless, patients with schizophrenia were less likely to have a concomitant cerebrovascular disease (OR = 0.48, 95% CI = 0.39–0.58, $p < 0.001$), epilepsy (OR = 0.48, 95% CI = 0.39–0.59, $p < 0.001$), or bronchial asthma (OR = 0.49, 95% CI = 0.40–0.59, $p < 0.001$). There were no reported cases of mortality in either study group. **Conclusions:** Although COVID-19 patients with schizophrenia had multiple comorbidities, they did not necessarily present a severe course or detrimental outcome compared to COVID-19 patients without schizophrenia. Further studies are required to confirm the findings of this study.

Keywords: COVID-19; disease outcome; disease severity; SARS-CoV-2; schizophrenia

1. INTRODUCTION

The newly emerged coronavirus disease (COVID-19) pandemic has a remarkable impact on the population worldwide and is predicted to have a tremendous burden on all patients, including those with schizophrenia (Al-Saud et al., 2020; Kozloff et al., 2020). The estimated prevalence of schizophrenia among non-institutionalized persons is 0.3% to 0.75% worldwide, with a lifetime-related morbidity rate of approximately 0.5%–1.0%

in different populations (Moreno-Küstner et al., 2018). In Saudi Arabia, it is a common psychiatric diagnoses among inpatients (55.8%) and outpatients (28.9%) in psychiatric settings (Alosaimi et al., 2017). Accumulating evidence indicates that several factors increase the risk of patients with schizophrenia to be infected with the serious intense respiratory disorder coronavirus (SARS-CoV-2) that is associated with poor outcomes, including: (1) features of the diseases itself as cognitive impairment, disorganized behavior, and poor insight impair adherence to infection control measurements (Maguire et al., 2019); (2) their sociodemographic characteristics, such as living in crowded housing where mental health-supportive houses with rooms in which social distancing are impractical (Morgan et al., 2017); (3) comorbid substance use, a highly prevalent disorder in these patients, adds more complexity to decision making (Hunt et al., 2018 7); (4) over-presentation in COVID-19 outbreak vulnerable populations (for example, prisoners and homeless individuals) (Kinner et al., 2020; Tsai and Wilson, 2020), (5) associated comorbidities which are common in this type of patients than the general population, such as cardiovascular diseases, chronic respiratory disorders, and diabetes (Correll et al., 2018; Zareifopoulos et al., 2018), increase the COVID-19-related mortality rate (Guan et al., 2020); (6) the antipsychotic medications prescribed to schizophrenia patients (some shared with COVID-19 treatment as clozapine) increase the risk of mortality associated with pneumonia due to potential sedation, hypersalivation, and impaired swallowing which are worsened by the body's immune response (De Leon et al., 2020); and (7) disparities getting to health care systems which partially related to the effects of stigma on help-seeking (Thorncroft et al., 2016), or limited resources (Emanuel et al., 2020).

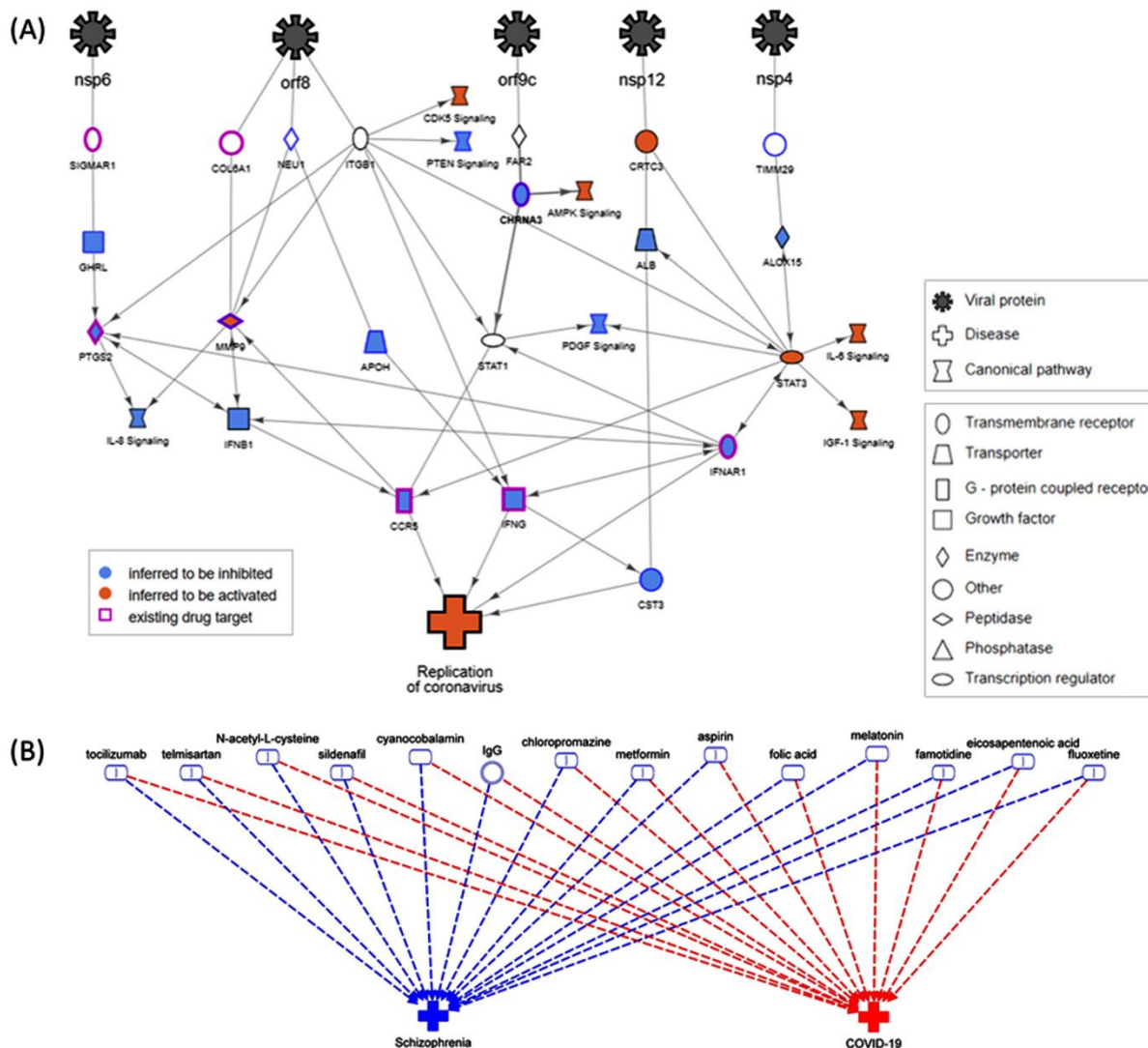


Figure 1 Connecting the dots between COVID-19 and schizophrenia. (A) Deregulated molecules and pathways during coronavirus replication. Coronavirus biological networks were explored in Ingenuity Pathway Analysis which is constructed using the evidence from the biomedical literature to predict gene and drug effects on selected biological processes, diseases, and pathways. Viral proteins promote several signaling pathways which are closely related to the pathogenesis of schizophrenia. (B) Schizophrenia and COVID-19 shared drug targets. Similar drugs could target both diseases.

Recent evidence indicates that the COVID-19 pandemic may impact mental health in the general population and, more specifically, in patients with schizophrenia (Yao et al., 2020). Furthermore, SARS-CoV-2 can exacerbate symptoms and signs of schizophrenia through immune-associated mechanisms (Severance et al., 2011). Aberrant immune and inflammatory responses are thought to be significant players in the pathogenesis of schizophrenia (Miller and Goldsmith, 2019). Human proteins interact with coronaviruses to promote viral replication. Some of these proteins are considered master regulators of multiple metabolic and signaling pathways involved in the pathogenesis of schizophrenia (Engmann et al., 2011). These include activation of AMP-activated protein kinase, interleukin-6 (IL-6), insulin-like growth factor 1 (IGF-1), and cyclin-dependent kinase 5 (CDK5) signaling pathways.

The induction of epigenetic modification by IL-6 has been proposed as a component within the pathology of schizophrenia through repression of the glutamate decarboxylase 67, which in turn influences the gamma-aminobutyric acid levels and impairs neural oscillations (Kundakovic et al., 2009; Gandal et al., 2012). IGF-1, a trophic mediator controlled by growth hormone and related with the development, proliferation and growth of neural cells, was suggested to be connected with the pathophysiology of chronic schizophrenia and other disorders treated with antipsychotic drugs (Okamoto et al., 2021). Furthermore, dysfunctional signaling of the CDK5 activator disturbs synaptic protein expression and cognition in schizophrenia (Engmann et al., 2011) and neurodegenerative diseases (Cortés et al., 2019).

As studies related to COVID-19 with schizophrenia in the author's region are scarce, more data are required to explore whether COVID-19 patients with schizophrenia have the same disease severity and outcome compared with those without schizophrenia (Figure 1).

2. METHODS

Study participants

This case-control retrospective study included 108 patients with a polymerase chain reaction (PCR)-proven diagnosis of COVID-19. The study cohort was divided into two groups, with the patient group composed of 54 patients with a confirmed schizophrenia diagnosis and the control group composed of matched individuals without schizophrenia. The COVID-19 laboratory diagnosis was based on real-time PCR technology (Logix Smart COVID-19 test, Co-Diagnostics, Inc., USA). It tests for the presence of ribonucleic acid (RNA) of SARS-CoV-2, including running the appropriate negative and positive controls and applying all the quality measurements recommended by the manufacturer. The researcher collected the medical data of COVID-19 patients from archived hospital e-medical records from 1 January to 26 February 2021. These data were related to the patients' sociodemographic data (age class: 30–39, 40–49, 50–59, 60–69, and 70–80 years; and gender), baseline clinical data (overweight or obese: yes or no; main comorbidities: yes or no; and type of comorbidity), laboratory data (kidney function tests: serum creatinine levels and blood urea nitrogen (BUN); liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, and total bilirubin; and serum electrolyte levels: sodium and potassium), and outcome data related to seriously care unit admission and mortality. Patients with severe mental disorders other than schizophrenia, such as bipolar disorders and recurrent major depression, were excluded. Informed patient consent was waived as the data were obtained from medical records without meeting the patients. The information assembled was anonymized and kept entirely secret. The study was conducted concurring to the standards of the Announcement of Helsinki and its afterward corrections.

Statistical analysis

BM Social Sciences Statistical Package (SPSS) Statistics intended for Windows version 27.0 (Armonk, NY: IBM Corp.), and GraphPad Prism for Windows, version 9.0 (San Diego, California USA, "www.graphpad.com"), were used for statistical analysis. A two-sided chi-square test was used for categorical data, while the Mann-Whitney U test was used for quantitative variables. Logistic regression analysis was performed to identify the risk of concomitant comorbid conditions. Data are reported as odds ratios (ORs) and 95% confidence intervals (95% CIs). Statistical significance was set at $p < 0.05$.

3. RESULTS

Baseline characteristics of the study population

A total of 108 patients were included in this study. 54 COVID-19 schizophrenia patients were compared to age-matched and gender-matched COVID-19 controls without psychiatric comorbidities. Females accounted for 25.9% of the study population. Approximately 41% of the study population had 50–59 years, while 34% had an age range of 60–69 years (Figure 2, Table 1).

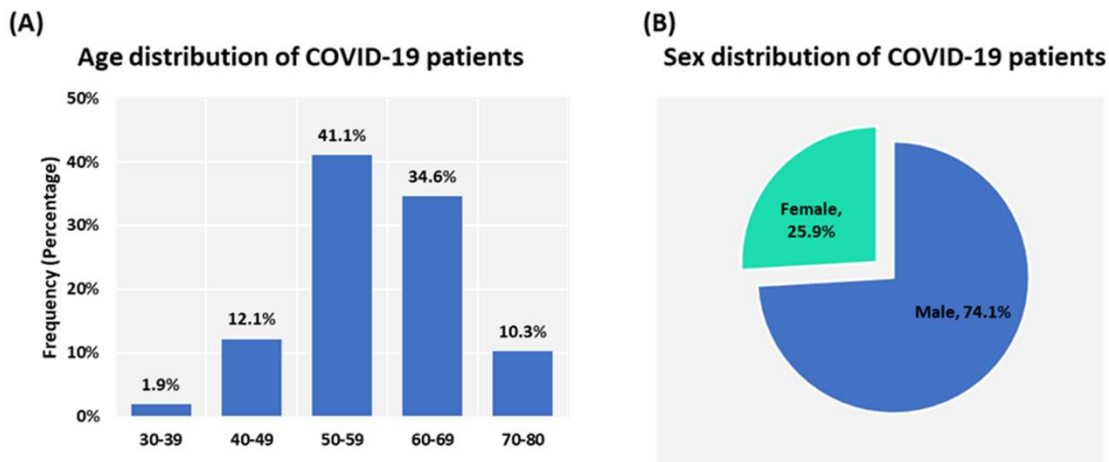


Figure 2 Demographic characteristics of the study population

Table 1 clinical characteristic of COVID-19 cohorts

Characteristics	Levels	Total	Controls	Schizophrenia	P-value
Age in years	30-39	2 (1.9)	1 (1.9)	1 (1.9)	0.78
	40-49	13 (12.1)	7 (13.2)	6 (11.1)	
	50-59	44 (41.1)	19 (35.8)	25 (46.3)	
	60-69	37 (34.6)	19 (35.8)	18 (33.3)	
	70-80	11 (10.3)	7 (13.2)	4 (7.4)	
Sex	Male	80 (74.1)	37 (68.5)	43 (79.6)	0.27
	Female	28 (25.9)	17 (31.5)	11 (20.4)	
Weight in Kg	Median (IQR)	73 (61-82)	79 (66.3-88)	68 (54-81)	0.002
Any comorbidity	Not present	52 (48.1)	35 (64.8)	17 (31.5)	0.001
	Present	56 (51.9)	19 (35.2)	37 (68.5)	
Type of comorbidity	HTN	18 (16.7)	9 (16.7)	9 (16.7)	0.95
	DM	13 (12)	7 (13)	6 (11.1)	0.77
	CKD	4 (3.7)	2 (3.7)	2 (3.7)	0.99
	CVD	4 (3.7)	4 (7.4)	0 (0)	0.12
	Asthma	2 (1.9)	2 (3.7)	0 (0)	0.50
	Hypothyroidism	15 (13.9)	5 (9.3)	10 (18.5)	0.27
	Epilepsy	3 (2.8)	0 (0)	3 (5.6)	0.24
	IHD	10 (9.3)	3 (5.6)	7 (13)	0.32

Data are presented as frequency (percentage) or median (interquartile range; IQR). Two-sided Chi-square or Mann-Whitney U tests were used. Statistical significance was set at $P < 0.05$. Abbreviations; HTN: hypertension, DM: diabetes Mellitus, CKD: chronic kidney diseases, CVD: cerebrovascular diseases, IHD: ischemic heart diseases.

Comorbidities associated with COVID-19 patients

None of the participants in the study were admitted to the ICU (Table 1). COVID-19 patients with schizophrenia had more comorbidities (68.5%) than COVID-19 patients without schizophrenia (35.2%). Hypothyroidism (18.5 vs. 9.3%), epilepsy (5.6 vs. 0.0%), and ischemic heart disease (13 vs. 5.6%) were more prevalent in patients with schizophrenia than in the controls. While, cerebrovascular diseases (7.4 vs. 0.0%) and asthma (3.7 vs. 0.0%) are the predominant comorbidities within the control bunch compared to schizophrenia patients (Table 1). These results were confirmed by univariate regression analysis for the presence of comorbidities in COVID-19 patients, as shown in (Figure 3). Psychiatric patients were less likely to have concomitant cerebrovascular disease (OR = 0.48, 95% CI = 0.39–0.58, $p < 0.001$), epilepsy (OR = 0.48, 95% CI = 0.39–0.59, $p < 0.001$), or bronchial asthma (OR = 0.49, 95% CI = 0.40–0.59, $p < 0.001$).

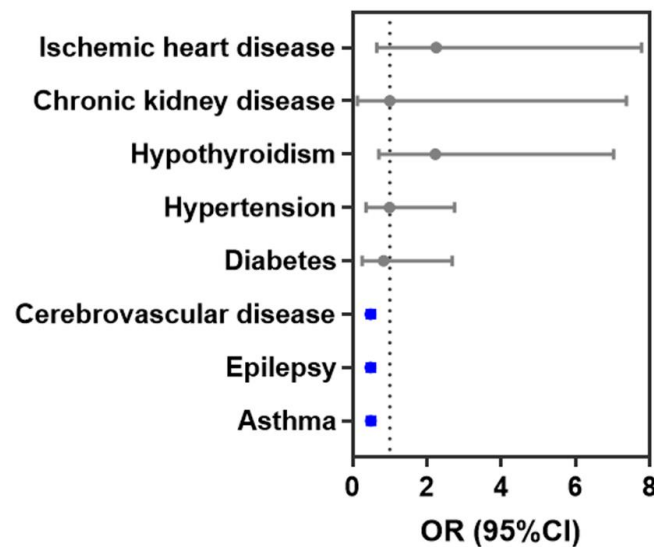


Figure 3 Univariate regression analysis for the presence of comorbidities in COVID-19 patients. Logistic regression analysis was employed, and data are reported as odds ratio (OR) and 95% confidence interval (95%CI).

Laboratory parameters of the study population

In the total study population, the mean values of the laboratory parameters were obtained. Serum creatinine level was 49 mmol/L (16.5–75 mmol/L), while the BUN level was 3 mmol/L (1.1–6 mmol/L). ALT level was 51.5 U/L (25.3–88.3 U/L), while AST level was 26 U/L (18–48.5 U/L). Serum albumin was 4.3 g/dL (3.5–5.6 g/dL). Meanwhile, the total bilirubin level was 6 (5–9.6), and the direct bilirubin level was 2 mmol/L (2–3 mmol/L). The serum sodium level was 137 mmol/L (135–140 mmol/L), whereas the serum potassium level was 4 mmol/L (3.8–4.2 mmol/L). Significantly higher levels of serum creatinine ($p < 0.001$), blood urea nitrogen ($p < 0.001$), and ALT ($p < 0.001$) were observed in patients with schizophrenia (Figure 4).

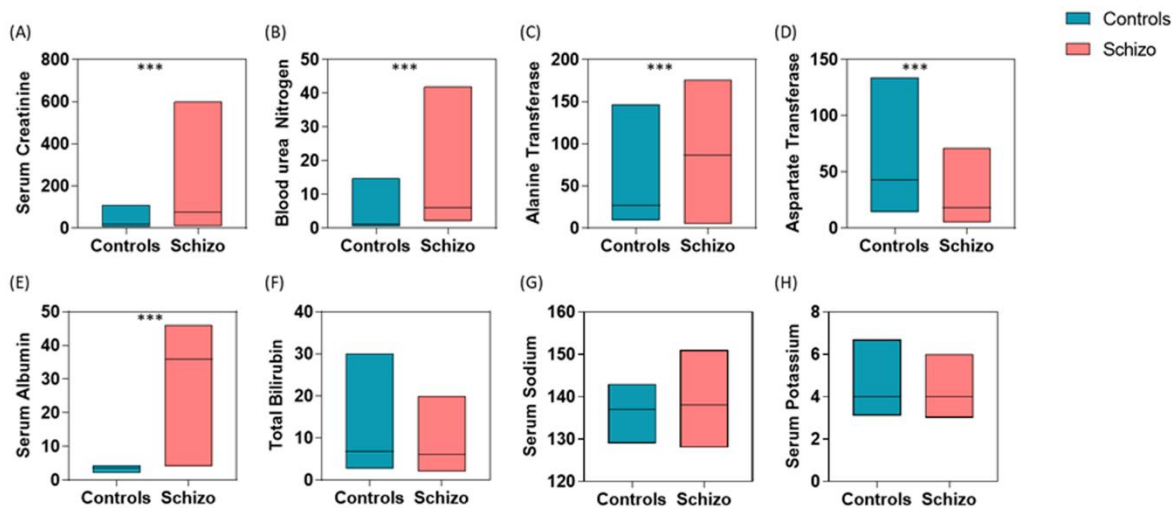


Figure 4 Biochemical Characteristics of COVID-19 patients. Nonparametric test (Mann-Whitney U test) was performed. Statistical importance was fixed at $p < 0.05$. (***) $p < 0.001$.

4. DISCUSSION

In this hospital-based study, female participants accounted for only 25.9% of the study population, in line with many regional and international studies which indicate that COVID-19 is more prevalent among males than females (Alyami et al., 2020; Bwire, 2020). Several reasons for this gender-related difference have been proposed, including genetic and environmental factors (Bwire, 2020). The expression of angiotensin-converting enzyme-2, which is the receptor for coronavirus in host cells, is higher in males than females and has been implicated as the main genetic factor contributing to this difference. This was supported by single-cell RNA-

sequencing analysis (Zhao et al., 2020). Furthermore, gender-based immunological differences are induced by sex hormones, the X chromosome (Ghazeeri et al., 2011), and gender-related behaviors (lifestyle) (Bwire, 2020). Besides the COVID-19-related influence, the probability of males with schizophrenia was reported to be slightly higher than that of females, with an approximate rate ratio of 1.4:1 (McGrath et al., 2004).

Interestingly, none of the study contributors were admitted to the ICU. This could be explained by: (1) the implementation of effective healthcare systems and therapeutic protocols by the Saudi government for COVID-19 patients, which decreases the probability of life-threatening complications; (2) the international travel lockdown and household quarantine; and (3) the increased adherence of citizens to personal protective measures (Alyami et al., 2020). Earlier studies showed that COVID-19-related hospital mortality occurs more frequently in individuals aged >65 years in China, while it was more frequent among those >70 years old in the USA (Acter et al., 2020; Xie et al., 2020). Hence, the decreased frequency of admission in this study may be because 75% of the present study populations are 50–69 years old.

An unexpected finding of this study is that schizophrenia patients infected with SARS-CoV-2 did not necessarily present with a severe course or detrimental outcome compared to COVID-19 patients without schizophrenia (controls). Although a latest Korean study found that schizophrenia is related with a higher risk of extreme COVID-19 infection. The authors of another previous study found that schizophrenia patient have multiple severe comorbidities that been known as risk factors for severe COVID-19 (Ji et al., 2020). Also, Fond et al., (2021) stated that differences in health care between hospitalized COVID-19 schizophrenia patients and patients without a diagnosis of mental defect in their national cohort study on French individuals with COVID-19 could impact the disease severity. Patients with schizophrenia have been reported to have a strong serological response to coronaviruses, including SARS-CoV-2 (017), as it has been proposed that exposure to several pathogens in the pre- and post-natal time of patients with schizophrenia could play a role in disease etiology (Kneeland and Fatemi, 2013), leading to increased protection against SARS-CoV-2 and less severe presentation of the disease.

Furthermore, susceptibility genes related to schizophrenia have been associated in the pathogen's virulence and life cycle (Wilcox and Quadri, 2014). These genes, including the netrin G1 gene, which is located on chromosome 1p and codes for a pre-protein that guides axon growth during neuronal development, share sequence homology with SARS-CoV-2 genes (Lehrer and Rheinstein, 2020), and their interactions with the immune system and viral pathogens might make patients more resistant to COVID-19 or have less severe presentations (Ekinci and Ekinci, 2021). Another speculation is that increased ACE activity in patients with schizophrenia (Gadelha et al., 2015) may participate in the protection and less severe presentation of COVID-19 patients with schizophrenia. The high ACE activity is associated with increased angiotensin 2 production, which subsequently produces a high pH milieu (Cure and Cumhur Cure, 2020) that reduces SARS-Co-2 virulence and load in patients with schizophrenia (Ekinci and Ekinci, 2021).

Although schizophrenia patients in the current study had more prevalent multiple comorbidities (68.5%) such as hypothyroidism, epilepsy, and ischemic heart diseases than the controls (35.2%), this seems to have no measurable impact on disease outcome. Nevertheless, the present observation was in line with the previous literature that confirms that: (1) there is a higher proportion of hypothyroidism among patients with schizophrenia (Radhakrishnan et al., 2013; Sharif et al., 2018); (2) epilepsy could be more prevalent in patients with schizophrenia, partly due to the presence of shared genetic elements implicated in the neurodevelopment of both disorders (Casella et al., 2009); and (3) cardiovascular diseases were found to be the major disease associated with schizophrenia, as there are common risk factors in patients with schizophrenia, which are more susceptible to cardiovascular diseases, including metabolic syndrome, sedentary behavior, tobacco smoking, impacts of antipsychotics, long-chain omega-3, lack of fatty acid and genetics links between cerebrovascular diseases and schizophrenia (Casella et al., 2009; Hennekens et al., 2005).

Regarding laboratory investigations, the current patients with schizophrenia showed higher serum levels of kidney function test parameters, particularly serum creatinine and blood urea nitrogen and liver enzyme ALT, than the controls. These findings are in line with previous results from a population-based retrospective cohort study that suggested that schizophrenia is associated with a 25% rise in the risk of developing chronic kidney disease within a 3-year follow-up period (Tzeng et al., 2005), as well as another study, which revealed that liver disease is more prevalent in patients with schizophrenia than in the normal population (Fuller et al., 2011). Chronic use of antipsychotic drugs could also contribute to liver injury, including subclinical cases and elevated serum ALT levels to varying degrees (Lv and Yi, 2018).

5. CONCLUSION

Although this study explored the difference in the results of COVID-19 patients with and without schizophrenia, some limitations should be considered, including the following: (1) the sample size was limited; (2) the observed frequencies may be influenced by hospital-based patient selection; and (3) some data, such as smoking and treatment received, were not sufficiently coded in the hospital databases. However, the worldwide absolute mortality data suggest that COVID-19 infection may have different impacts across countries due to multiple factors like climate, facility organization, and COVID-19 public management strategies. The present findings should be replicated in larger multicenter cohorts, including hospitalized and non-hospitalized patients, to understand the true relationship between COVID-19 and schizophrenia and confirm the present results.

Author Contribution

Saleh A. Alghamdi did all the works alone.

Ethical approval

The study was approved by the Medical Ethics Committee of the Ministry of Health (ethical approval number: No. 389).

Funding

This study has not received any external funding.

Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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