ORIGINAL ARTICLE

The Impact of Selective Serotonin Reuptake Inhibitor Use on the Clinical Outcomes of Hospitalized COVID-19 Patients

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Abstract

Background: Coronavirus has impacted people and healthcare systems globally. Despite the positive impact of vaccinations in curbing transmission, the emergence of new variants remains a concern. Thus, it is crucial to explore therapeutic interventions that can mitigate the severity of Coronavirus disease 2019 (COVID-19). Considering the probable anti-inflammatory properties of selective serotonin reuptake inhibitors (SSRIs), recent findings suggested that the acute administration of SSRIs in COVID-positive individuals may have alleviated symptom severity. This retrospective observational study aimed to assess the impact of SSRI use on the outcome of hospitalized COVID-positive patients.

Methods: In this retrospective observational study, a comprehensive analysis of electronic health records of 9815 patients diagnosed with COVID-19 in Shahid Faghihi hospital, Shiraz, Iran, from July 2020 to March 2021 was conducted, capturing demographic and clinical data. Employing R software, we used a logistic regression model, with mortality as the primary outcome and SSRI usage as the variable of interest.

Results: A total of 167 patients received medications of the SSRI family during the course of hospital admission. Following adjustment for age, gender, and race, the analysis revealed no statistically significant difference in mortality odds between COVID-19-positive patients on SSRIs and those not receiving SSRI treatment.

Conclusion: This study confirms the value of leveraging extensive clinical databases to identify potentially beneficial drugs for managing COVID-19. Given the burden of pandemics caused by novel pathogens, rigorous evaluation of the safety and efficacy of repurposed medications is paramount.

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Introduction

The COVID-19 pandemic originated in Wuhan, China, in December 2019, initially presenting as a case of pneumonia with an unknown cause.[1] Recognizing its global impact, the World Health Organization (WHO) declared it a pandemic on March 11, 2020. In March 2022, over 486 million COVID-19 cases and 6 million deaths were reported.[2] The pandemic has led to an unprecedented worldwide effort in the form of numerous

studies and research designed to develop effective, preventive, and therapeutic interventions.[1] The low price and wide availability of some drugs in the market made them socially and medically attractive either for the intention of preventing the infection, alleviating the severity, or improving patient outcome during and after the process of the disease.[2-4] Numerous clinical studies have been published since then. However, the effectiveness of some of these compounds has not yet been confirmed after careful clinical studies.[4] The common use of neuropsychiatric drugs in the general population and the probable anti-inflammatory effects of some antidepressant classes of medications have led to the investigation of the possible effects of this category of drugs on the recovery process of patients with COVID-19. One of the most popular and widely accessible antidepressant classes for the treatment of depression and anxiety is the selective serotonin reuptake inhibitors (SSRIs).[5, 6] The key role of inflammation in the progression and severity of the infection leading to morbidity and mortality of COVID-19 is well established.[7-9] Cytokine storm has been identified as a life-threatening factor responsible for severe pulmonary and systemic complications of COVID-19.[10, 11] SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been found to exhibit anti-inflammatory effects in several in vitro studies.[12, 13] Several mechanisms have been proposed for their anti-inflammatory effects; altering key inflammatory pathways including the signal transducer and activator of transcription 3 (STAT3) and nuclear factor (NF)-kB pathways that can, in turn, reduce the expression of downstream proinflammatory cytokines such as interleukin-6 and tumor necrosis factor (TNF)-α, both of which are involved in the cytokine storm, can be explained.[6] The probable anti-inflammatory effects of SSRIs have been highlighted in different clinical settings; inhibition of TNF-alfa and nitric oxide production in microglial cells,[14] probable anti-inflammatory effects in preventing Alzheimer's disease,[15] and their anti-inflammatory effects in dermatologic disorders[16] along with the contribution of their anti-inflammatory properties to their anti-depressant and anxiolytic[17, 18] effects are of the many examples of their beneficial suppression of the immune system reactions in different clinical settings. Also, Fluoxetine and other SSRIs have been shown to have a direct antiviral effect.[19] The COVID-19 virus has been shown to activate the ceramide system, which facilitates virus entry into cells. SSRIs can alter the sphingomyelin/ceramide system and reduce ceramide levels, and this alteration can prevent the replication of COVID-19.[20, 21] Depression and anxiety have also been identified as risk factors associated with the severity of COVID-19 infection.[6, 22] Therefore, considering the possibility of a dual anti-inflammatory-antiviral effect and also their antidepressant/anxiolytic properties, these medications have been proposed as possible therapeutic options for COVID-19 patients.[6, 21, 23, 24] Several studies have investigated the role of SSRI/SNRI antidepressants on patient outcomes following clarification of the involved mechanisms of infection. Reduction in the rate of hospital admissions and mortality as well as severity of infection in hospitalized patients, along with assistance in treating mild to moderate outpatient infection, are of the findings of previous studies on the use of SSRIs in COVID-19 infection.[25, 26] In a recently published study, positive impacts of SSRIs on the outcome and prognosis of COVID-19 infection were highlighted possibly by inducing a reduction in IL-6 levels.[27] However, controversy exists between reported data in different population groups with slightly different settings.[4] Due to the variability in reported data to date, in this study, we decided to investigate the relationship between antidepressant medications and the outcome of COVID-19 in hospitalized patients.

Methods

This study was designed as a retrospective observational study. To investigate the impact of SSRIs/SNRIs on the outcome of patients with COVID-19, we reviewed the electronic medical records of 9815 patients with laboratory-confirmed COVID-19 infection from July 2020 to March 2021. Data were collected from the major COVID-19 referral hospital in the south of Iran during the COVID-19 pandemic. All demographic and medical data of patients older than 18 years of age with PCR-confirmed COVID-19 infection, including age, sex, admission to the ward or intensive care unit (ICU), length of hospital stay, medications on admission, including SSRIs/SNRIs, and patient outcome in terms of survival or death, were investigated and recorded. Inclusion criteria were as follows: adult patients aged 18 years and above, patients who had been hospitalized with a confirmed COVID-19 diagnosis, and those who were concurrently receiving treatment with an antidepressant medication, including an SSRI or an SNRI, during their admission. Patients under the age of 18 years, who lacked a documented COVID-19 diagnosis, and those not prescribed an SSRI antidepressant medication upon admission or before being admitted were not included in this study. Comorbidities among the study participants were evaluated using the Charlson Comorbidity Index (CCI), a widely recognized tool for predicting mortality by classifying comorbid conditions. Each patient's comorbidities were identified based on predefined lists of ICD-10 codes, which were then utilized to calculate the CCI score. The CCI categorizes patients into three groups based on their score: 0 (no comorbidities), 1-2 (mild comorbidities), and ≥3 (severe comorbidities). This stratification allowed for a comprehensive assessment of the potential impact of comorbid conditions on patient outcomes, particularly in the context of COVID-19 severity and mortality.[28] The severity of the infection was not considered an inclusion or exclusion criterion, and all patients admitted to the hospital due to a confirmed

COVID-19 infection were included, including those with moderate to severe disease that were admitted to the ward or patients with severe disease that were admitted to the intensive care unit (ICU). The statistical analyses of the data were conducted using the SPSS 25.0 software package (SPSS, Chicago, IL, USA). A logistic regression analysis was performed to evaluate the effect of the different collected factors on the outcome of the study population. An adjusted logistic regression model was executed to control for factors such as age, gender, and length of hospital stay. All statistical tests were considered significant at a threshold of P value≤0.05.

Ethical Consideration

The study was approved by the ethics committee of Shiraz University of Medical Sciences with the reference code of IR.SUMS.REC.1399.1007.

Results

In this retrospective study on hospitalized COVID-19 patients, among the 9815 patients evaluated, only a small number (167 patients) received SSRIs during their admission. Of these, 34 (20%), 43 (25.7%), 55 (32.9%), and 35 (20.9%) patients were given fluoxetine, citalopram, sertraline, and escitalopram, respectively, making them the primary study group. No patient received an SNRI during admission. A control group, which consisted of 422 COVID-19 patients who did not meet the SSRI inclusion criteria, was used with comparable baseline characteristics to allow for clear outcome comparisons.

Table 1 provides demographic details of our study population. Gender distribution showed a slightly higher predominance of male patients in both groups, consisting of 52.7% of SSRI-users and 55.5% of non-SSRI-users; also, the difference between the two groups was not statistically significant (P=0.512). The age distribution across groups was comparable, though patients on SSRIs had a slightly higher proportion in the >70 age group (30.5% vs. 25.6% in the control; P=0.209). Marital status differed more noticeably: a significantly higher proportion of SSRI users were single (15%) compared to non-users (12.3%), while a markedly larger proportion of non-SSRI users were married (84.6% vs. 76% in SSRI users), indicating potential social differences in the population receiving SSRIs.

The Charlson Comorbidity Index scores, reflecting comorbidity burden, showed slightly higher percentages of individuals in the control group with fewer comorbidities. Specifically, 71.9% of SSRI users had a Charlson index of 0 compared to 77.7% of non-SSRI users; however, this difference was not statistically significant (Table 1).

Outcome

The primary outcome of this study was in-hospital mortality among COVID-19 patients, comparing those who were administered SSRIs during hospitalization with those who did not. In the SSRI group (n=167), a total of 15 patients (9 %) experienced mortality compared to the control group (n=422), in which 42 patients (9.9%) died. This difference reflects no significant difference in mortality rate among groups.

Table 2 presents the results of a univariate logistic regression analysis which aimed at understanding the potential influence of several variables on the outcome of mortality.

Univariate logistic regression analysis indicates that, in the context of this study, none of the examined variables (Age, Gender, Marital status, Length of Hospitalization, and SSRI usage) demonstrated a statistically significant impact on mortality outcomes. However, a slightly elevated probability of mortality was observed among SSRI users, with an Odds ratio of 1.27, suggesting a potentially higher risk of mortality compared to non-users.

Table 1: Demographic and Clinical Characteristics of the Study Population

Demographic/Clinical Characteristic	Patients on SSRIs (n=167)	Patients Not on SSRIs (n=422)	P value
Gender			
Female (%)	79 (47.3)	188 (44.5)	0.512
Male (%)	88 (52.7)	234 (55.5)	
Age Group			
>70 (%)	51 (30.5)	108 (25.6)	0.209
50-69 (%)	67 (40.1)	175 (41.5)	0.754
30-49 (%)	36 (21.6)	122 (28.9)	0.063
18-29 (%)	12 (7.2)	17 (4.0)	0.118
Marital Status			
Single (%)	25 (15.0)	52 (12.3)	0.394
Married (%)	127 (76.0)	357 (84.6)	0.017
Charlson Comorbidity Index			
0 (%)	120 (71.9)	328 (77.7)	0.158
1-2 (%)	35 (21.0)	72 (17.1)	0.301
≥3 (%)	12 (7.2)	22 (5.2)	0.357

SSRI: Selective Serotonin Reuptake Inhibitors

Table 2: Effect of different factors, including age, gender, marital status, length of hospitalization and SSRI use, on the patient outcome (survival). (Uni-variate logistic regression analysis)

Variable	P value	OR	Confidence Interval 95%
Age	0.89	0.99	0.99 - 1.01
Gender	0.10	0.71	0.47 - 1.07
Marital Status	0.42	1.31	0.68 - 2.51
Length of Hospitalization	0.36	1.01	0.98 - 1.05
SSRI Use	0.29	1.27	0.85 – 1.98

OR: Odds Ratio; SSRI: Selective Serotonin Reuptake Inhibitor

Table 3: Effect of different factors, including age, gender, marital status, length of hospitalization, and SSRI use, on patient outcome (survival). (multivariate logistic regression analysis)

Variable	P value	OR	Confidence Interval 95%
Age	0.85	0.99	0.99 - 1.01
Gender	0.16	1.36	0.88 - 2.09
Marital Status	0.34	1.38	0.71 - 2.69
Length of Hospitalization	0.37	1.01	0.98 - 1.05
SSRI Use	0.41	1.21	0.76 – 1.94

OR: Odds Ratio; SSRI: Selective Serotonin Reuptake Inhibitor

Additionally, female patients showed a 1.4-fold increased risk of mortality compared to male patients, though this risk did not reach statistical significance.

Table 3 displays the results of a multivariate logistic regression analysis, which aimed to evaluate the combined impact of these variables on mortality outcomes. Similar to the univariate analysis, none of the variables—including Age, Gender, Marital Status, SSRI Use, or Length of Hospitalization—demonstrated strong statistical significance in predicting mortality when considered collectively. These findings suggest that, while some variables showed trends toward increased mortality risk, they were not statistically robust predictors in this study population.

Discussion

In this retrospective observational study, we found that antidepressant usage was not significantly and substantially linked with a decreased risk of mortality or reduction in the length of hospitalization encompassing a sizable sample of patients hospitalized with COVID-19. Researchers in various countries have studied how SSRIs affect COVID-19 patients' outcomes. Based on the systematic review and meta-analysis conducted by Firouzabadi and her colleagues, it was determined that SSRI/SNRIs could potentially have a positive impact on decreasing mortality among COVID-19 patients. Furthermore, the study suggested that fluvoxamine might be more effective than fluoxetine in this regard. The favorable safety profile and cost-effectiveness of SSRI/SNRIs for short-term usage also provide additional benefit to recommend these medications as potentially helpful interventions for preventing mortality associated with COVID-19.[29] In the clinical trial conducted by Eric J. Lenze and his colleagues, which comprised 152 adult outpatients with confirmed COVID-19, the effect of fluvoxamine on clinical deterioration was evaluated. In this preliminary study, adult outpatients with symptomatic COVID-19 infection treated with fluvoxamine had a lower chance of clinical worsening over 15 days compared to patients on placebo. However, the authors noted that determining clinical effectiveness would require larger randomized trials with more precise outcome assessments.[30] Another placebo-controlled, randomized, trial involving eligible Brazilians with a recognized risk factor for severe illness also benefited from SSRI therapy during active infection. Randomly, patients were given fluvoxamine (100 mg twice daily for 10 days) or a placebo (1:1). Reduction in the need for hospitalization was evident in the fluvoxamine-treated patients.[31] A retrospective multicenter study examined the relationship between SSRI antidepressant use and a lower risk of intubation or death in hospitalized patients with coronavirus disease in 2019. This study reported a lower risk of intubation or death in patients receiving SSRIs (fluoxetine, escitalopram) and SNRIs (venlafaxine).[32] Several other studies have reported similar findings that reflect the positive role of SSRIs in preventing the severe disease in COVID-19 infection. However, there are other studies in which the effectiveness of SSRIs has not been proven. In a study conducted by Rauchman *et al.* involving 9,044 COVID-19 patients across six hospitals, researchers analyzed electronic medical records. They used a logistic regression model to assess mortality as the outcome and SSRI (Selective Serotonin Reuptake Inhibitor) status as the exposure. Notably, patients on SSRIs continued using their medications during their hospitalization. The study found that there was no significant difference in the likelihood of death between COVID-positive patients who were on chronic SSRIs and those who were not, even after adjusting for age, gender, and race.[4] In an open-label, prospective cohort trial conducted in April and May 2021, 51 ICU

COVID-19 patients admitted to the University Hospital Dubrava and University Hospital Centre Zagreb, Croatia, were treated with fluvoxamine 100 mg three times daily for 15 days in addition to standard therapy. These patients were matched for age, gender, vaccination against COVID-19, disease severity, and comorbidities with 51 ICU controls. The results showed that there were no statistically significant differences between the two groups in terms of the number of days on ventilator support or the duration of ICU and total hospital stay. However, the overall mortality rate was lower in the fluvoxamine group (58.8%) compared to the control group (76.5%), with a hazard ratio (HR) of 0.58 and a 95% confidence interval (CI) of 0.36–0.94 (P=0.027).[33] In line with our study results, severe infection could not be prevented by the use of fluvoxamine in another randomized controlled trial. Fluvoxamine did not show positive effects in preventing hypoxemia, hospital admission, length of hospital stay, or death.[34] The rate of vaccination, patients' comorbid diseases, severity of disease on admission, risk of patients for deterioration of the disease, pharmacogenetic differences in different populations, and availability of resources and healthcare facilities are among the many different factors that could influence patient survival in a pandemic situation such as the COVID-19 outbreak. As mentioned in the discussion, several studies in different study populations and different study settings have been conducted on the efficacy of SSRI/SNRI class of medication and their role in preventing disease severity in COVID-19 patients, yet conclusive results in defining their exact role are yet to be discovered. Furthermore, the ideal fluvoxamine therapy plan and the impact of fluvoxamine on the efficacy of other medications, such as monoclonal antibodies and budesonide, are still unknown, and further research is required in this aspect.[35]

This study has some limitations; being a single-center study limits the generalizability of its data. The retrospective nature of the study along with the poor documentation at our medical centers limits the number of patients with complete data that could be included in research studies. Also, missing demographic and past medical data, and lack of availability and documentation of concomitant medications administered to every patient must be considered as a limiting factor as well. These missing factors might have played a role as a confounding factor and might have contributed to patient outcome; also, its missing data are not negligible in this study.

Conclusion

This study did not show any significant association between SSRI use and COVID-19 mortality in hospitalized COVID-19 Iranian patients in the South of Iran.

Authors' Contribution

Laleh Mahmoudi, Mohammad Javad Fallahi, Ramin Niknam and Dena Firouzabadi designed, implemented and supervised the research. Laleh Mahmoudi, Dena Firouzabadi and Navid Esmaeilzadeh Shahri gathered, analyzed and interpreted the data. Laleh Mahmoudi, Mohammad Javad Fallahi, Ramin Niknam, and Dena Firouzabadi Navid Esmaeilzadeh Shahri, and Mohammad Abbasinazari helped with the preparation of the manuscript draft. Laleh Mahmoudi, Mohammad Javad Fallahi, Ramin Niknam, and Dena Firouzabadi Navid Esmaeilzadeh Shahri, and Mohammad Abbasinazari revised the manuscript and contributed to the preparation of the final version of the manuscript.

Conflict of Interest

None declared.

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