COVID-19 Prognosis in Association with Antidepressant Use

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ABSTRACT

Introduction Various subtypes of severe acute respiratory syndrome coronavirus 2 and variations among immune systems in different ethnicities need to be considered to understand the outcomes of coronavirus disease 2019 (COVID-19). This study aimed to provide evidence for the association between the use of antidepressants and the severity of COVID-19.

Methods We used the National Health Information Data-COVID database. Patients with one or more prescriptions of any antidepressant were selected as the exposure group. Detailed analyses were performed to determine the type of medication associated with the prognosis.

Results The use of selective serotonin reuptake inhibitors (SSRIs) was associated with a lower risk of severe outcomes of COVID-19, whereas the use of tricyclic antidepressants (TCAs) increased the risk of poor prognosis of COVID-19. Detailed analyses showed that escitalopram was significantly associated with better clinical outcomes, and nortriptyline was linked to more severe COVID-19 outcomes.

Conclusion This study revealed an association between antidepressants and COVID-19 prognosis. SSRIs were significantly associated with a lower risk of severe outcomes, whereas TCAs were related to the poor prognosis of COVID-19.

Introduction

Since the emergence of coronavirus disease 2019 (COVID-19) at the end of 2019 and the declaration of the COVID-19 pandemic by the World Health Organization, more than 510 million infection, cases and 6.2 million fatalities have been reported confirmed as of May 2022 [1]. There are various subtypes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Variations in SARS-CoV-2 may be associated with an increase in cases and differences in clinical manifestations and vaccine efficacy [2]. Although approximately 9.7 billion vaccine doses have been administered, the disease remains a tremendous challenge. In addition to the vaccines, there are several ongoing trials for COVID-19 treatment, and potential candidates have been studied.

Various clinical manifestations of COVID-19 are reportedly caused by interactions between SARS-CoV-2 and the human immune system. Immune responses play essential roles in both SARS-CoV-2 clearance and disease progression. Liu et al. showed that high neutrophil proportions and neutrophil-to-lymphocyte ratios result in a poor prognosis of COVID-19 [3], and another study revealed that CD8 + T cell counts are decreased in COVID-19 patients [4].

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Neurotransmitters and neurochemicals can stimulate immune cell receptors, and several studies have shown associations between neurotransmitters and the immune response. For instance, the level of serotonin is reduced in inflammatory bowel disease patients [5], whereas elevated plasma glutamate levels are related to immune-mediated diseases, such as human immunodeficiency virus-associated dementia and some malignancies [6]. In this context, medications that affect neurotransmitter levels could be potential candidates for immune-related disease therapy.

Antidepressants are widely used not only for depression but also in medical conditions such as post-traumatic stress disorder, panic disorder, and obsessive-compulsive disorder. Their usage is also extended to off-label indications, including chronic pain and insomnia [7]. Although the mechanisms of action of different classes of antidepressants may vary, changes in neurotransmitter levels are a common result.

Since antidepressants can potentially treat immune-related diseases, several studies have focused on their function as anti-inflammatory mediators. A meta-analysis showed that antidepressants decrease the levels of inflammatory mediators, including interleukin (IL)-6 and IL-10 [8]. Several studies revealed that fluvoxamine decreases clinical deterioration in COVID-19 patients [9–11]. Studies have also shown that fluoxetine decreases severe symptoms of SARS-CoV-2 [12, 13] and even proposed this medication as an adjuvant therapeutic agent for COVID-19 [14]. An observational retrospective study in France proposed an association between antidepressants and COVID-19 severity [15]. Considering the non-negligible variations among the immune systems of different ethnicities [16] and the diversity of coronavirus subtypes across continents, this study aimed to provide evidence of the association between the use of antidepressants and the severity of COVID-19 in Asian patients.

Methods

Study design, data source, and ethical approval

We conducted a retrospective cohort study using a nationwide population cohort to investigate the relationship between antidepressant use prior to COVID-19 diagnosis and outcome severity. Four classes of antidepressants were included – selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and others. Antidepressants included in this analysis were as follows: SSRIs: fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, vortioxetine; SNRIs: venlafaxine, duloxetine, desvenlafaxine, milnacipran; TCAs: amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, amoxapine; others: trazodone, bupropion, mirtazapine, and tianeptine. We used the National Health Information Database (NHID)–COVID-19 provided by the National Health Insurance Sharing Service (NHISS) in cooperation with Korea Centers for Disease Control and Prevention. NHID-COVID provided information on patients diagnosed with COVID-19 between 1 January 2020 and 4 June 2020. Due to the Korean single-payer national health system, records of inpatient and outpatient visits covered by the system are kept in the NHIS database and include diagnostic codes, procedures, prescriptions, and demographic information. Codes for diagnosis, procedures and prescriptions are encrypted according to the International Classification of Diseases, 10th Revision (ICD-10), national procedure-coding system, and Anatomical Therapeutic Chemical classification. All codes used in this study are provided in Supplementary material Table 1. COVID-19 diagnosis confirmation date, treatment results, and the number of days in inpatient care were also given. The study protocol was approved by the Institutional Review Board of Chungbuk National University (CBNU-202007-HR-0122).

Selection of exposure and non-exposure groups

The confirmation date of COVID-19 diagnosis was set as the cohort entry date, and 180 days before the entry date was set as the exposure period. Patients with one or more prescriptions of any antidepressant(s) were selected as the exposure group. We ascertained exposure to antidepressants according to an intention-to-treat approach. Patients without antidepressant prescription were defined as the non-exposure group. To eliminate the effect of antidepressants after the COVID-19 diagnosis, we excluded patients if the antidepressant was started after cohort entry. Subjects with missing data were not included. After defining each group, we calculated the logit of the propensity score with logistic regression using covariates to clarify the effect of covariates on the patients. We used age, sex, and the logit of the propensity score to perform one-to-one matching of the exposure and non-exposure groups. The caliper used for the propensity score was 0.2. The detailed procedure for selecting the exposure and non-exposure groups is described in ▶ **Fig. 1**.

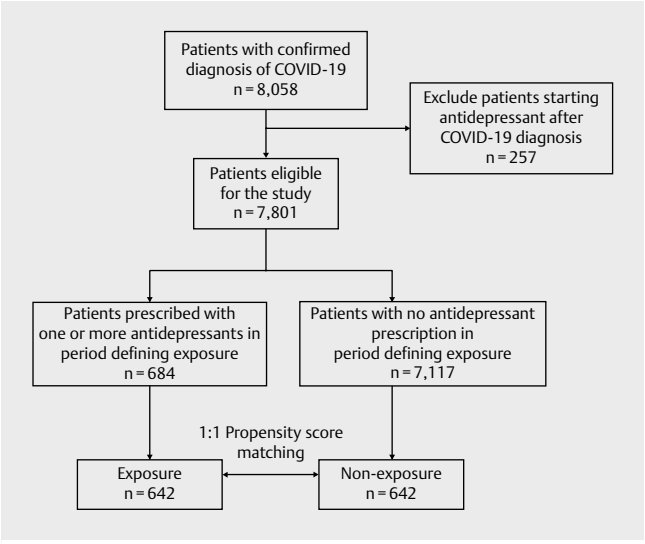
Severe outcomes

Severe outcomes defined in this study were composites of in-hospital death, intensive care unit admission, mechanical ventilation use, extracorporeal circulation, or cardiopulmonary resuscitation, which are defined by the national procedure-coding system. Follow-up started from the cohort entry date, and the end date was defined as each patient's first outcome to minimize any time-related biases, including immortal time bias [17]. Follow-up duration was calculated as the number of days between the cohort entry and the end dates.

Potential confounders in multivariable analysis

We assessed age and sex as the demographic factors known to affect COVID-19 severity. Age was stratified into 10-year bands. Comorbidities that could be associated with COVID-19 severity (diabetes mellitus types 1 and 2, hypertension, congestive heart failure, cerebrovascular disease, myocardial infarction, chronic obstructive pulmonary disease (COPD), asthma, renal disease, liver disease, cancer) were also included as confounders. In addition, disease states related to the indication of antidepressants (schizophrenia, mood disorder, anxiety) were included [7]. Patients diagnosed at least twice before the end date was defined as having comorbidities.

Detailed ICD-10 diagnostic codes were described in Supplementary material Table 2.



▶ **Fig. 1** A flowchart showing patient selection for this study.

Detailed analysis

We divided the exposure group into four sub-groups according to antidepressants (SSRI, SNRI, TCA, and others). In patients with multiple drug changes, the last prescription before cohort entry was selected. Subsequently, drug classes that showed statistically significant effects on the severity of COVID-19 were analyzed to determine the type of medication associated with the prognosis.

Sensitivity test

Since not much is known about the interval between antidepressant use and the decrease in inflammatory factors, we conducted a sensitivity test with various exposure periods: 30 days, 90 days, and 365 days before cohort entry.

Statistical analysis

Baseline characteristics were summarized for the exposure and non-exposure groups. Results were presented as numbers and percentages for categorical variables, and differences between groups were estimated according to chi-square tests. After matching for age, sex, and logit of the propensity score, the balance between the two groups was assessed by calculating the absolute standardized difference (aSD), and aSD of variables with 0.1 or more were considered significant imbalance. We checked the proportional hazard assumption by generating a Kaplan–Meier survival plot before conducting Cox proportional hazard regression analysis. The latter was conducted for each covariate to calculate the crude hazard ratio (cHR). Covariates showing statistically significant hazard ratios were entered into the multivariate model to estimate adjusted hazard ratios (aHRs). For the plotted Kaplan-Meier plots, we conducted log-rank tests to determine significant differences between groups. All statistical analyses were done using the SAS Enterprise Guide version 9.4 (SAS Institute Inc., Cary, NC, USA), and a 2-tailed confidence interval of 0.05 was considered to indicate statistical significance.

Results

Of 8,058 COVID-19 patients, 1,284 patients were included in our study. Among them, 684 patients were prescribed one or more antidepressants within the exposure period. After 1:1 propensity score matching, the exposure and non-exposure groups were selected (each n = 642; ▶ **Table 1**). The highest number of patients were in their 50 s (n = 143, 22.27 %), and there were no patients under 9 years of age. Mood disorder and anxiety showed statistically significant differences between the exposure and non-exposure groups ($p < 0.001$ and $p = 0.017$, respectively).

The risk of severe events of COVID-19 is presented in ▶ **Table 2**. There were 243 events with severe outcomes and 50 deaths. The severe outcomes of COVID-19 were more pronounced in patients over 50 than in those in their 20 s, with aHR values increasing with age (aHR 3.25, 7.05, 9.68, and 18.93 for the age groups of 50 s, 60 s, 70 s, and ≥ 80 s, respectively). Female patients had a 35 % lower risk than male patients ($p < 0.001$), and renal diseases or cancers were associated with a higher risk of poor prognosis by 57 % ($p = 0.048$) and 38 % ($p = 0.046$) respectively.

Further analysis was performed to investigate the influence of a specific class of antidepressants compared to non-users on severe outcomes of COVID-19. The use of SSRIs resulted in an approximately 34 % decrease in severe outcomes of COVID-19 (aHR: 0.66, CI: 0.46–0.96, $p = 0.030$). TCA users were 48 % more prone to severe COVID-19 outcomes (aHR: 1.48, CI: 1.08–2.02, $p = 0.014$). The use of SNRIs and other antidepressants did not show statistically significant associations with COVID-19 severity (▶ **Table 3**). The *p*-value of the log-rank test was less than 0.001, meaning that the three plots are significantly different. We generated Kaplan-Meier survival plots for each significant drug class and non-users to observe the effect over time (▶ **Fig. 2**). We further examined the link between each antidepressant and COVID-19 severity. Among SSRIs, escitalopram decreased the risk of COVID-19 severity by 38 % (aHR: 0.62, CI: 0.40–0.97, $p = 0.035$), while other SSRIs did not show statistical significance. Among TCAs, nortriptyline increased the probability of poor prognosis of COVID-19 by 62 % (aHR: 1.62, CI: 1.00–2.61, $p = 0.049$) (▶ **Table 4**).

Findings from sensitivity analyses were largely consistent: the use of SSRIs decreased the risk, whereas the use of TCAs increased the risk of COVID-19 severity. This was observed in Kaplan–Meier plots for each sensitivity test (30, 60, 180, and 365 days). In a log-rank test used to evaluate differences between groups, the *p*-values for each duration were < 0.001, 0.003, 0.012, and 0.015, respectively.

Discussion

The main finding of this study is that SSRI use is associated with a 34 % decrease in the risk of poor prognosis of COVID-19 (CI: 0.46–0.96, $p = 0.030$), whereas TCA use increased the risk of severe outcomes of COVID-19 by 48 % (CI: 1.08–2.02, $p = 0.014$). Among SSRIs, escitalopram was significantly associated with a 38 % reduction in severe outcomes of COVID-19 (CI: 0.40–0.97, 0.035). Among TCAs, nortriptyline was significantly associated with a 62 % higher risk of severity of the disease (CI: 1.00–2.61, 0.049).

▶ **Table 1** Baseline characteristics of COVID-19 patients in this study.

	Exposure (n = 642) (%)	Non-exposure (n = 642) (%)	*aSD*
Age (years)			< 0.01
0–9			
10–19	1 (0.16%)	1 (0.16%)	
20–29	69 (10.75%)	69 (10.75%)	
30–39	42 (6.54%)	42 (6.54%)	
40–49	71 (11.06%)	71 (11.06%)	
50–59	143 (22.27%)	143 (22.27%)	
60–69	127 (19.78%)	127 (19.78%)	
70–79	91 (14.18%)	91 (14.18%)	
80 +	98 (15.26%)	98 (15.26%)	
Sex			< 0.01
Male	252 (39.25%)	252 (39.25%)	
Female	390 (60.75%)	390 (60.75%)	
Schizophrenia			0.03
Yes	78 (12.15%)	68 (10.59%)	
No	564 (87.85%)	574 (89.41%)	
Mood disorder			0.01
Yes	452 (70.40%)	355 (55.30%)	
No	190 (29.60%)	287 (44.70%)	
Anxiety			0.02
Yes	391 (60.90%)	349 (54.36%)	
No	251 (39.10%)	293 (45.64%)	
Diabetes mellitus			0.02
Yes	259 (40.34%)	245 (38.16%)	
No	383 (59.66%)	397 (61.84%)	
Hypertension			< 0.01
Yes	305 (47.51%)	299 (46.57%	
No	337 (52.49%)	343 (53.43%)	
Congestive heart failure			0.06
Yes	82 (12.77%)	67 (10.44%)	
No	560 (87.23%)	575 (89.56%)	
Cerebrovascular disease			0.01
Yes	162 (25.23%)	158 (24.61%)	
No	480 (74.77%)	484 (75.39%)	
Myocardial infarction			0.04
Yes	23 (3.58%)	18 (2.80%)	
No	619 (96.42%)	624 (97.20%)	
Asthma			0.02
Yes	154 (23.99%)	162 (25.23%)	
No	488 (76.01%)	480 (74.77%)	
COPD			0.02
Yes	28 (4.36%)	30 (4.67%)	
No	614 (95.64%)	612 (95.33%)	
Renal disease			0.03
Yes	21 (3.27%)	17 (2.65%)	
No	621 (96.73%)	625 (97.35%)	
Liver disease			0.01
Yes	336 (52.34%)	333 (51.87%)	
No	306 (47.66%)	309 (48.13%)	
Cancer			0.05
Yes	60 (9.35%)	69 (10.75%)	
No	582 (90.65%)	573 (89.25%)	

Abbreviation: chronic obstructive pulmonary disease (COPD), absolute standardized mean difference (aSD). Absolute standardized mean differences were given to show balance of variables between exposure and non-exposure group at the baseline. aSD < 0.1 were considered well balanced.

▶ **Table 2** Risk factors affecting severe outcomes of the COVID-19 infection.

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Age (years)				
20–29	Ref		Ref	
30–39	0.40 (0.05–3.60)	0.415	0.38 (0.04–3.40)	0.7
40–49	2.15 (0.66–6.99)	0.202	2.00 (0.61–6.51)	0.252
50–59	3.86 (1.36–10.94)	0.011	3.25 (1.13–9.35)	0.029
60–69	9.59 (3.49–26.33)	<.001	7.045 (2.50–19.82)	<.001
70–79	14.13 (5.15–38.78)	<.001	9.68 (3.40–27.54)	<.001
80+	27.04 (9.98–73.26)	<.001	18.93 (6.70–53.52)	<.001
Sex				
Male	Ref		Ref	
Female	0.72 (0.57–0.91)	0.005	0.65 (0.51–0.83)	<.001
Non-exposure	Ref		Ref	
Exposure	1.08 (0.86–1.36)	0.513	1.04 (0.82–1.31)	0.771
Schizophrenia	0.98 (0.68–1.40)	0.897		
Mood disorder	1.46 (1.13–1.88)	0.003	1.19 (0.91–1.54)	0.207
Anxiety	1.24 (0.98–1.58)	0.071		
Diabetes mellitus	2.25 (1.79–2.84)	<.001	1.12 (0.87–1.45)	0.384
Hypertension	3.49 (2.69–4.52)	<.001	1.13 (0.83–1.53)	0.438
Congestive heart failure	2.98 (2.29–3.87)	<.001	1.29 (0.95–1.73)	0.100
Cerebrovascular disease	2.56 (2.03–3.22)	<.001	1.17 (0.91–1.50)	0.236
Myocardial infarction	2.80 (1.80–4.37)	<.001	1.17 (0.73–1.88)	0.507
Asthma	1.26 (0.98–1.62)	0.077		
COPD	2.62 (1.80–3.83)	<.001	0.92 (0.61–1.39)	0.685
Renal disease	3.07 (2.01–4.71)	<.001	1.57 (1.00–2.47)	0.048
Liver disease	1.52 (1.20–1.93)	<.001	0.94 (0.73–1.21)	0.614
Cancer	1.96 (1.44–2.66)	<.001	1.38 (1.01–1.89)	0.046

Abbreviation: chronic obstructive pulmonary disease (COPD); Cox regression hazard model was used to calculate crude and adjusted hazard ratios. Adjustments were made using variables showing statistical significance in the univariate analysis.

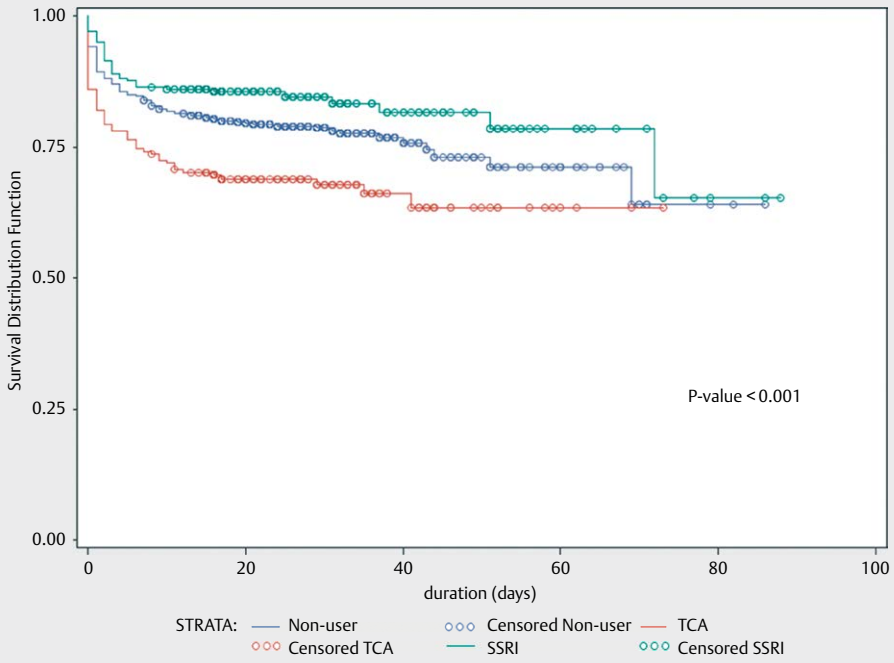
▶ **Table 3** Effects on severe outcome of COVID-19 by drug types of the antidepressants.

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
SSRI	0.72 (0.50–1.02)	0.067	0.66 (0.46–0.96)	0.030
TCA	1.58 (1.16–2.14)	0.004	1.48 (1.08–2.02)	0.014
SNRI	0.93 (0.50–1.72)	0.819	0.82 (0.44–1.53)	0.540
Other	1.16 (0.83–1.62)	0.385	1.14 (0.81–1.60)	0.453

Abbreviation: selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), serotonin-norepinephrine reuptake inhibitor (SNRI); Cox regression hazard model was used to calculate crude and adjusted hazard ratios (HR). Adjustments were made using variables showing statistical significance in the univariate analysis.

This study revealed that older age and sex (male) were associated with a poor prognosis of COVID-19. Older age is known as a risk factor for COVID-19 mortality: patients older than 75 have an approximately 13-fold higher mortality risk than those younger than 65 years [18]. Although the exact mechanism is unclear, aging was attributed to alterations in immune function and excessive production of inflammatory factors; thus, aging may increase pro-inflammatory responses [19]. The higher susceptibility of males to SARS-CoV2 is related to higher angiotensin I converting enzyme 2 (ACE2) levels in males than in females [20]. Consistent with the results from another study on patients with COVID-19 [21], our study showed that patients with renal disease or cancer had worse outcomes than those without such comorbidities. Since ACE2 acts as the main receptor for SARS-CoV2 and functions in various organs, including the kidney, multi-organ complications can be observed.

Neurotransmitters are known to influence innate and adaptive immune responses. Antidepressants are used to treat several conditions, including depression, generalized anxiety disorder, and neuropathic pain, by increasing the levels of neurotransmitters such as serotonin or norepinephrine. SSRIs inhibit 5-hydroxytryptamine (HT) reuptake and thus increase serotonin levels [22]. Another antidepressant group, TCA, works by inhibiting the reuptake of serotonin and norepinephrine and blocking the action of acetylcholine [23]. Glutamate identifies receptors such as metabo-



▶ **Fig. 2** The Kaplan-Meier plots of drug classes having a significant effect on the severe outcome of the COVID-19 compared to the non-users.

▶ **Table 4** Risk of each medication in SSRI and TCA groups.

	Unadjusted HR (95% CI)	*P*-value	Adjusted HR (95% CI)	*P*-value
Non-User	Ref		Ref	
SSRI				
Fluoxetine	0.79 (0.32–1.92)	0.595	1.17 (0.47–2.90)	0.738
Citalopram	–	–	–	–
Escitalopram	0.78 (0.51–1.18)	0.237	0.62 (0.40–0.97)	0.035
Fluvoxamine	1.03 (0.14–7.33)	0.980	1.03 (0.14–7.47)	0.976
Paroxetine	0.37 (0.09–1.49)	0.160	0.62 (0.15–2.51)	0.500
Sertraline	0.66 (0.24–1.78)	0.406	0.60 (0.22–1.65)	0.321
Vortioxetine	0.66 (0.09–4.73)	0.680	0.57 (0.08–4.16)	0.576
TCA				
Amitriptyline	1.52 (1.04–2.23)	0.033	1.41 (0.96–2.09)	0.082
Doxepin	1.44 (0.46–4.51)	0.974	2.05 (0.64–6.49)	0.225
Imipramine	1.29 (0.41–4.04)	0.664	1.08 (0.34–3.46)	0.893
Nortriptyline	1.76 (1.10–2.82)	0.018	1.62 (1.00–2.61)	0.049

Abbreviation: selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA); Cox regression hazard model was used to calculate crude and adjusted hazard ratios (HR). Adjustments were made using variables showing statistical significance in the univariate analysis. HR of citalopram was not calculated due to the small number of patients.

tropic glutamate receptor-1 and N-methyl-D-aspartate receptor on lymphocytes and targets dendritic cells and T lymphocytes [24]. Dopamine interacts with dopamine D2, D3, and D4 receptors and targets macrophages, natural killer cells, and B lymphocytes [25].

In this context, the alteration of neurotransmitter levels might affect COVID-19 pathophysiology. Moreover, ACE2 is associated with serotonin. A study postulated that ACE2 is significantly linked to dopa decarboxylase (DDC) [26]. DDC plays an essential role in dopamine and serotonin synthesis. Since ACE2 is coregulated with DDC, downregulation of ACE2 expression due to SARS-CoV2 may affect pathways relevant to dopamine and serotonin synthesis. Accordingly, Klempin et al. [27] revealed that ACE2-knockout mice have extremely low serotonin levels.

In this study, patients on SSRIs showed a better prognosis than those not taking the medication. A previous study also revealed that SSRIs are related to a less severe prognosis of COVID-19 [15],

while another proposed that SSRIs reduce the risk of coronary heart disease by ameliorating inflammation [28]. The role of serotonin in the immune system may help explain the association between SSRIs and COVID-19 severity; serotonin is recognized by receptors such as 5-HT1, 5-HT2, 5-HT3, and 5-HT7 on lymphocytes and targeted immune cells, including macrophage, dendritic cells, eosinophils, and T lymphocytes [29]. As stimulation of serotonin receptors results in the suppression of inflammatory responses, SSRIs might lead to anti-inflammatory effects [30, 31].

Consistent with a previous study [15], our results showed that SSRIs, especially escitalopram, were significantly associated with a reduced risk of intubation or death. It can be speculated that escitalopram has higher efficacy given its higher degree of selectivity to the receptors [32]. Hence, higher stimulation of receptors by escitalopram may lead to more anti-inflammatory outcomes than other SSRIs, including citalopram similar to escitalopram. On the other hand, we found that TCAs, especially nortriptyline, are linked to poor outcomes of COVID-19. The influence of ethnicity on antidepressant treatment is important; in comparison with Caucasians, patients with African ancestry show a lower response to antidepressant therapy [33]. In contrast, another study concluded that Asians show greater therapeutic responses than Caucasians and are significantly more likely to experience anticholinergic side effects [34]. Considering ethnicity-based differences in viral variants and responses to antidepressants, our study provides invaluable information demonstrating the association between antidepressants and COVID-19 prognosis in Asian patients and lays the basis for further research on the specific mechanisms and pathways that underlie the current results. Moreover, since this outcome cannot be mechanically explained, these findings need to be confirmed or reproduced in other studies.

TCAs are associated with an increased incidence of adverse coronary artery disease outcomes, and inflammatory factors are relevant to this association [28]. TCAs are related to acetylcholine, which identifies muscarinic and nicotinic receptors on lymphocytes and targeted macrophages, dendritic cells, and T lymphocytes [35]. Acetylcholine acts through the cholinergic anti-inflammatory pathway and directly affects pro-inflammatory cytokine production [36]. As TCAs block the action of acetylcholine, they might ultimately hinder anti-inflammatory effects, thus resulting in severe symptoms of COVID-19.

One of the limitations of our study is that laboratory test results, which may be associated with severity risk, were not available. Also, we could not adjust for possible social factors, including smoking and socioeconomic status. Data used in this study were based on diagnostic codes and prescription codes; hence, the accuracy of diagnoses and medication adherence could not be thoroughly verified. To minimize the influence of these limitations, we defined the selection of exposure and non-exposure groups based on one or more prescriptions of any antidepressant in a 180-day time window before the index date. We also performed sensitivity analyses and confirmed the results; hence, information bias may be low. Moreover, this study only included antidepressive medications; other concomitant medications, including somatic drugs such as hypertensive agents, were not included in the analysis. Further research is needed to investigate the effects of other medications. Nevertheless, to our knowledge, this is the first study to investigate the effects of antidepressants on COVID-19 prognosis in Asian patients. Therefore, these findings underline the need to further study the possible effects of antidepressant medication on the course of COVID-19 to increase the probability of an optimal outcome.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] WHO. (2022). WHO Coronavirus (COVID-19) Dashboard. Retrieved from https://covid19.who.int/

[2] Korber B, Fischer WM, Gnanakaran S et al. Tracking changes in SARS-CoV-2 spike: Evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020; 182: 812–827.e19

[3] Liu J, Li S, Liu J et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine 2020; 55: 102763

[4] Zhang W, Zhao Y, Zhang F et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol 2020; 214: 108393

[5] Coates MD, Mahoney CR, Linden DR et al. Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. Gastroenterology 2004; 126: 1657–1664

[6] Pacheco R, Gallart T, Lluis C et al. Role of glutamate on T-cell mediated immunity. J Neuroimmunol 2007; 185: 9–19

[7] Urits I, Peck J, Orhurhu MS et al. Off-label antidepressant use for treatment and management of chronic pain: Evolving understanding and comprehensive review. Curr Pain Headache Rep 2019; 23: 66

[8] Köhler CA, Freitas TH, Stubbs B et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: Systematic review and meta-analysis. Mol Neurobiol 2018; 55: 4195–4206

[9] Lenze EJ, Mattar C, Zorumski CF et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: A randomized clinical trial. JAMA 2020; 324: 2292–2300

[10] Reis G, Dos Santos Moreira-Silva EA, Silva DCM et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: The TOGETHER randomised, platform clinical trial. Lancet Glob Health 2022; 10: e42–e51

[11] Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum Infect Dis 2021; 8: ofab050

[12] Schloer S, Brunotte L, Goretzko J et al. Targeting the endolysosomal host-SARS-CoV-2 interface by clinically licensed functional inhibitors of acid sphingomyelinase (FIASMA) including the antidepressant fluoxetine. Emerg Microbes Infect 2020; 9: 2245–2255

[13] Zimniak M, Kirschner L, Hilpert H et al. The serotonin reuptake inhibitor Fluoxetine inhibits SARS-CoV-2 in human lung tissue. Sci Rep 2021; 11: 5890

[14] Pashaei Y. Drug repurposing of selective serotonin reuptake inhibitors: Could these drugs help fight COVID-19 and save lives? J Clin Neurosci 2021; 88: 163–172

[15] Hoertel N, Sánchez-Rico M, Vernet R et al. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: Results from an observational study [published online ahead of print, 2021 Feb 4]. Mol Psychiatry 2021. doi:10.1038/s41380-021-01021-4

[16] Marrelli D, Polom K, Roviello F. Ethnicity-related differences in tumor immunity: A new possible explanation for gastric cancer prognostic variability? Transl Gastroenterol Hepatol 2016; 1: 11

[17] Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008; 167: 492–499

[18] Ho FK, Petermann-Rocha F, Gray SR et al. Is older age associated with COVID-19 mortality in the absence of other risk factors? General population cohort study of 470,034 participants. PLoS One 2020; 15: e0241824

[19] Michaud M, Balardy L, Moulis G et al. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc 2013; 14: 877–882

[20] Patel SK, Velkoska E, Burrell LM. Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in? Clin Exp Pharmacol Physiol 2013; 40: 551–559

[21] Cai R, Zhang J, Zhu Y et al. Mortality in chronic kidney disease patients with COVID-19: A systematic review and meta-analysis. Int Urol Nephrol 2021; 53: 1623–1629

[22] Sangkuhl K, Klein TE, Altman RB. Selective serotonin reuptake inhibitors pathway. Pharmacogenet Genomics 2009; 19: 907–909

[23] Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol 2007; 151: 737–748

[24] Fallarino F, Volpi C, Fazio F et al. Metabotropic glutamate receptor-4 modulates adaptive immunity and restrains neuroinflammation. Nat Med 2010; 16: 897–902

[25] Talhada D, Rabenstein M, Ruscher K. The role of dopaminergic immune cell signalling in poststroke inflammation. Ther Adv Neurol Disord 2018; 11: 1756286418774225

[26] Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. J Med Virol 2020; 92: 1743–1744

[27] Klempin F, Mosienko V, Matthes S et al. Depletion of angiotensin-converting enzyme 2 reduces brain serotonin and impairs the running-induced neurogenic response. Cell Mol Life Sci 2018; 75: 3625–3634

[28] Mathews MJ, Mathews EH, Liebenberg L. The mechanisms by which antidepressants may reduce coronary heart disease risk. BMC Cardiovasc Disord 2015; 15: 82

[29] Herr N, Bode C, Duerschmied D. The Effects of Serotonin in immune cells. Front Cardiovasc Med 2017; 4: 48

[30] Dionisie V, Filip GA, Manea MC et al. The anti-inflammatory role of SSRI and SNRI in the treatment of depression: A review of human and rodent research studies. Inflammopharmacology 2021; 29: 75–90

[31] Gałecki P, Mossakowska-Wójcik J, Talarowska M. The anti-inflammatory mechanism of antidepressants - SSRIs, SNRIs. Prog Neuropsychopharmacol Biol Psychiatry 2018; 80: 291–294

[32] Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? Int Clin Psychopharmacol 2014; 29: 185–196

[33] Murphy E, Hou L, Maher BS et al. Race, genetic ancestry and response to antidepressant treatment for major depression. Neuropsychopharmacology 2013; 38: 2598–2606

[34] Matsuda KT, Cho MC, Lin KM et al. Clozapine dosage, serum levels, efficacy, and side-effect profiles: A comparison of Korean-American and Caucasian patients. Psychopharmacol Bull 1996; 32: 253–257

[35] Fujii T, Mashimo M, Moriwaki Y et al. Physiological functions of the cholinergic system in immune cells. J Pharmacol Sci 2017; 134: 1–21

[36] Borovikova LV, Ivanova S, Zhang M et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000; 405: 458–462