Relationship between antidepressants and severity of SARS-CoV-2 Omicron infection: a retrospective cohort study using real-world data

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Summary

Background Few studies have used real-world data to evaluate the impact of antidepressant use on the risk of developing severe outcomes after SARS-CoV-2 Omicron infection.

Methods This is a retrospective cohort study using propensity-score matching to examine the relationship between antidepressant use and COVID-19 severity. Inpatient and medication records of all adult COVID-19 patients in Hong Kong during the Omicron-predominated period were obtained. Severe clinical outcomes including intensive care unit admission and inpatient death after the first positive results of reverse transcription polymerase chain reaction as well as a composite outcome of both were studied. Cox proportional hazard models were applied to estimate the crude and adjusted hazard ratios (HR).

Findings Of 60,903 hospitalised COVID-19 patients admitted, 40,459 were included for matching, among which 3821 (9.4%) were prescribed antidepressants. The rates of intensive care unit admission, inpatient death, and the composite event were 3.9%, 25.5%, and 28.3% respectively in the unexposed group, 1.3%, 20.0%, and 21.1% respectively in the exposed group, with adjusted HR equal to 0.332 (95% CI, 0.245–0.449), 0.868 (95% CI, 0.800–0.942), and 0.786 (95% CI, 0.727–0.850) respectively. The result was generally consistent when stratified by selective serotonin reuptake inhibitors (SSRIs) and non-SSRIs. Antidepressants with functional inhibition of acid sphingomyelinase activity, specifically fluoxetine, were also negatively associated with the outcomes. The effect of antidepressants was more apparent in female and fully vaccinated COVID-19 patients.

Interpretation Antidepressant use was associated with a lower risk of severe COVID-19. The findings support the continuation of antidepressants in patients with COVID-19, and provide evidence for the treatment potential of antidepressants for severe COVID-19.

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Keywords: SSRI; Propensity-score matching; Real-world data; FIASMA

Introduction

Coronavirus disease (COVID-19) is a severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since early 2020, COVID-19 has become a global pandemic. In 2022, an uptrend in detection of the variant of concern, named

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Research in context

Evidence before this study

We searched PubMed for research articles published up to 26 August 2022 using the search terms "antidepressant" and "COVID-19". Three observational studies (one in the United States and the other two in France) reported a negative association between antidepressants and death among hospitalised COVID-19 patients during the early phase of the COVID-19 pandemic in 2020. Several randomised controlled trials and a cohort study examined specifically the effect of fluvoxamine, a selective serotonin reuptake inhibitor antidepressant, on either clinical deterioration or time-to-death and detected potential treatment effects of the medication if being given to the patients early after their infection. According to our observation, few studies have used real-world data to evaluate the impact of antidepressant use on the risk of developing severe outcomes after SARS-CoV-2 Omicron infection.

Added value of this study

Using the real-world data in Hong Kong, our study employed a matched retrospective cohort study to examine relationship between antidepressant use and COVID-19 severity caused by the Omicron variant. Our results suggested the use of antidepressants was associated with lower rates of intensive care unit admission, inpatient death, and the composite event of these two outcomes with the adjusted hazard ratios equal to 0.332 (95% CI, 0.245–0.449), 0.868 (95% CI, 0.800–0.942), and 0.786 (95% CI, 0.727–0.850) respectively. The result was generally consistent when stratified by selective serotonin reuptake inhibitors (SSRIs) and non-SSRIs. Antidepressants with functional inhibition of acid sphingomyelinase activity, specifically fluoxetine, were also negatively associated with the outcomes. The negative association was more apparent in female and fully vaccinated COVID-19 patients.

Implications of all the available evidence

Antidepressant use was associated with a lower risk of severe COVID-19 in the Omicron-predominated period. The findings support the continuation of antidepressants in patients with COVID-19, and provide evidence for the treatment potential of antidepressants for severe COVID-19.

Omicron was reported worldwide, even in many countries with high vaccination coverage. World Health Organization has recommended nirmatrelvir and ritonavir for treating mild and moderate COVID-19 patients who are at risk of hospital admission.[1] Nevertheless, nirmatrelvir and ritonavir are not applicable to all patients. Severe disparities in access to the drugs persisted, primarily affecting the socially vulnerable individuals.[2] In addition, since the treatment with nirmatrelvir and ritonavir should start within five days of symptom onset after the diagnosis of COVID-19,[3,4] patients beyond this course of disease are outside the target population. This also restricts their usage among people with limited access to health care and testing capacity. Moreover, medical contraindication of nirmatrelvir and ritonavir (e.g., co-administration with some drugs, severe kidney impairment, severe hepatic impairment, etc.) are prevalent among at-risk patients,[5,6] hindering the general use of the drugs. Hence, several generic medications have been widely investigated as a potential alternative for COVID-19 treatment.

Antidepressants are mainly used in treating psychiatric and other disorders, such as anxiety and depressive disorders. As the pathophysiologic process of COVID-19 is characterised by the cytokine storm in pulmonary tissues, the anti-inflammatory properties of antidepressants could lower the proinflammatory cytokines including interleukin-6 and tumour necrosis factor, and this would potentially improve the COVID-19 prognosis.[7] Supported by relevant observational studies,[8,9] several randomised controlled trials have suggested that fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, could reduce the risk of severity among patients with COVID-19.[10,11] Furthermore, encouraging clinical efficacy of fluvoxamine at a moderate to high dose for patients with COVID-19 has been showed by recent meta-analyses.[12,13] On top of SSRI, certain classes such as serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic, tetracyclic and α2-antagonist antidepressants, or any type of antidepressants with functional inhibition of acid sphingomyelinase (FIASMA) activity, may also be related to reduced risk of COVID-19 severity.[9,14–16]

To date, solid clinical evidence about the effect of antidepressants on reducing the severity of COVID-19 infection is still limited, especially due to the lack of real-world data for evaluation. In this study, we employed the official health data of the registry of infected cases, linking to their vaccination records, medical history, hospitalisation information, and death records in Hong Kong to examine the association between the concurrent use of antidepressants and COVID-19 severity during the Omicron-predominated period via a retrospective cohort investigation. We also assessed the effectiveness of several types of frequently prescribed antidepressants and evaluated the relationship by age, sex and COVID-19 vaccination status.

Methods

Study design

This is a retrospective cohort study using propensity score matching to examine the association between the exposure (i.e., antidepressant use) and the outcome (i.e., COVID-19 severity). For propensity score matching, we used the

nearest neighbour method without replacement, and the propensity score was estimated using logistic regression models. The matching ratio between exposed and unexposed groups was set at 1:4 for the intervention group treated by any antidepressant versus the control group, and at 1:15 for SSRIs or non-SSRIs treated group versus the control group.[8,17] The caliper was set at 0.2,[18] and the standardised mean difference (SMD) <0.1 was adopted as the criterion to assess the covariate balance between exposed and unexposed groups.[19,20] The propensity score matching was conducted using the R package *MatchIt* version 4.3.0. The *MatchIt* formula of the propensity score matching can be found in the Supplementary material.

Data source

Data of all hospitalised COVID-19 patients in Hong Kong who had their first positive reverse transcription-polymerase chain reaction (RT-PCR) results between January 1, 2022, and June 5, 2022, an Omicron-predominated period, were retrieved from the Hong Kong Hospital Authority, a statutory body to manage all public hospitals in Hong Kong. During the pandemic, all COVID-19 hospitalisations were followed up in the public hospital system. The database covered the inpatient and historical medication records of all the 41 public hospitals in Hong Kong. The vaccination records of the patients were obtained from the COVID-19 vaccination registry held by the Department of Health.

Study population

Inclusion criteria of the study population included (1) aged ≥18 years old; (2) having confirmed positive RT-PCR results; (3) having medication records and medical records indicating their severity outcomes (intensive care unit (ICU) admission and inpatient death). Patients who were prescribed antidepressants outside the defined time frame were excluded.

Exposure to antidepressant use

Three exposed groups including the COVID-19 patients exposed to any type of antidepressants, exposed only to SSRI antidepressants, and exposed only to non-SSRI antidepressants were studied in this investigation. Antidepressants prescribed to patients were identified through their Anatomical Therapeutic Chemical (ATC) classification codes. Twenty-one antidepressants were covered in the current datasets (i.e., N06AA02, N06AA04, N06AA06, N06AA09, N06AA10, N06AA16, N06AB03, N06AB04, N06AB05, N06AB06, N06AB10, N06AX03, N06AX05, N06AX11, N06AX12, N06AX16, N06AX17, N06AX21, N06AX22, N06AX23, N06AX26). The five initialized with N06AB and N06AX26 were SSRIs, and the others were non-SSRIs. Patients prescribed and administered antidepressants during the period from 10 days before to seven days after the first positive RT-PCR date were regarded as being exposed to antidepressants.[8] Those prescribed antidepressants outside this time frame were excluded to avoid potential late-prescription bias, while those who were never prescribed antidepressants were deemed as unexposed patients (Fig. 1).

Outcomes of COVID-19 severity

ICU admission and inpatient death after the first positive RT-PCR results during the present hospitalisation episode were used as a proxy for severe outcomes. A composite outcome of either ICU admission or inpatient death was also used. For those who did not experience the event, their event time was censored on the discharge date of their last hospitalisation during the study period. For those who did not experience the event and were not discharged yet, their event time was censored on June 12, 2022, seven days after the end date of data extraction. The event time was calculated as the number of days from the first positive RT-PCR date to the first occurrence of the specific events.

Confounding factors

The confounding factors used in the propensity score matching included age group (18–49, 50–59, 60–64, 65–69, 70–74, 75–79, and ≥80 years), sex, medical history, medication indication, benzodiazepines, vaccination status, use of anti-COVID-19 treatments, and the calendar week of the first positive RT-PCR date.

Medical history was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM), including hypertension (401.X-405.X), diabetes (250.X), coronary artery disease/ischemic heart disease (410.X-414.X), congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.X), arrhythmia (426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3), chronic obstructive pulmonary disease (496), asthma (493), malignancy (140.X-172.X, 174.X-208.X, 238.6), cerebrovascular disease (362.34, 430.X-438.X), peripheral vascular disease (093.0, 437.3, 440.X, 441.X, 443.1-443.9, 447.1, 557.1, 557.9, V43.4), chronic liver disease (070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.X, 571.X, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7), chronic kidney disease (585.X), obesity (278.0), and intellectual and developmental disability (317.X, 318.X, 319.X, 333.7, 343.X, 758.0). Medication indications for antidepressants were also identified using ICD-9 CM, including mood and anxiety disorders (296.X, 300.X, 309.X, 311.X), and other psychiatric disorders other than mood or anxiety disorders (290.X-295.X, 297.X-299.X, 301.X-308.X, 310.X, 312.X-316.X).[8] We examined the outpatient data and epidemiological investigation data to cross-check with the record of medical histories.

Benzodiazepines were matched and adjusted because they are frequently co-prescribed with antidepressants[21] and have been shown to be associated with COVID-19-related outcomes.[22] Benzodiazepines were

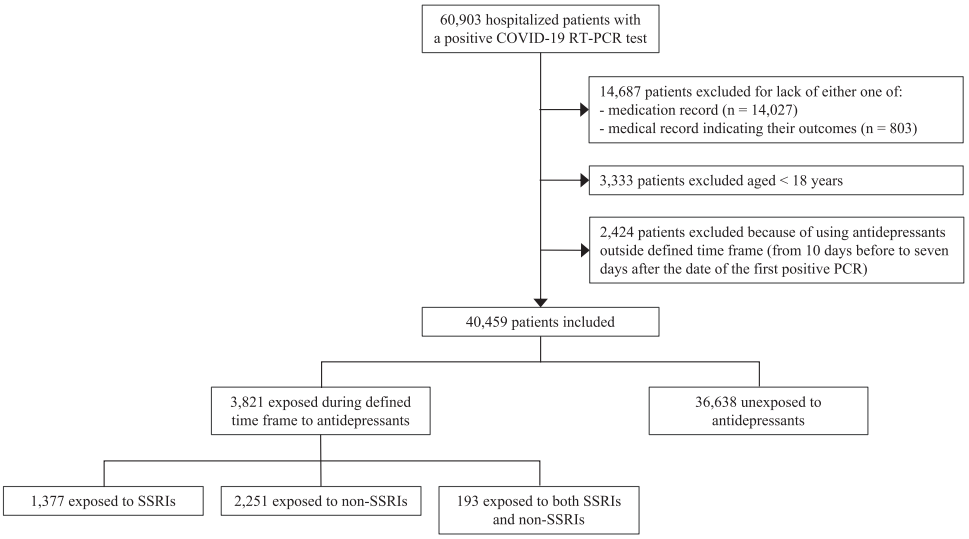

Fig. 1: **Procedure of including study participants.** SSRI: selective serotonin reuptake inhibitor.

identified through their ATC codes initialising with 'N03AE', 'N05BA', 'N05CD', and 'N05CF', including alprazolam, zopiclone, lorazepam, zolpidem, diazepam, midazolam, clonazepam, bromazepam, flunitrazepam, clobazam, chlordiazepoxide, triazolam, and nitrazepam. Patients are defined as being prescribed benzodiazepines if the prescription was delivered from 10 days before to seven days after the first positive RT-PCR date, the same time frame as antidepressants.

We grouped the vaccination status of the individuals into 0, 1, and ≥2 doses. Only those who had taken the respective doses of vaccine 14 days before the first positive RT-PCR date were regarded as being vaccinated with the dose, considering the latency between vaccine uptake and full development of immune responses. Anti-COVID-19 treatments included paxlovid, molnupiravir, dexamethasone, remdesivir, baricitinib, tocilizumab, and interferon beta-1b were recorded, among which the three most frequently prescribed medications, dexamethasone (n (%) = 13,977 (34.5%)), molnupiravir (n (%) = 5187 (12.8%)), and remdesivir (4536 (11.2%)) were separately matched, while the other anti-COVID-19 treatments were matched as a whole. The calendar week of the first positive RT-PCR date was matched to adjust the potential influence of virus variants and prevention and treatment measures on the association between antidepressant use and COVID-19 severity outcomes.

Statistical analysis

Descriptive statistics were presented for the exposed and unexposed groups. Cox proportional hazard models were used to examine the association between the antidepressant use and the time to experiencing severity outcomes of the patients. The proportional hazard assumption was checked using log–log Kaplan Meier survival estimates against time plots. The distributions of the time-to-event of the exposed and unexposed groups were visually presented using the adjusted survival curves. Weights were calculated during matching, and cluster-robust standard errors were determined with pair membership as the clustering variable. Crude and adjusted hazard ratios (HR) that adjusted for the confounding factors were respectively estimated and presented with their 95% confidence intervals (CIs). Additional analyses were conducted to explore the association between different antidepressant classes or specific antidepressants and severity outcomes. Antidepressant classes and specific antidepressants explored included fluoxetine, SSRIs other than fluoxetine,[8] SNRI, tricyclic, tetracyclic, and α2-antagonist antidepressants,[14] antidepressants proved in vitro to inhibit acid sphingomyelinase,[9] SSRIs with high to intermediate affinity agonist activity at sigma-1 receptor,[15,16,23] and SSRIs with low affinity agonist activity at the sigma-1 receptor.[16,23] Subgroup analyses were conducted by age, sex, and vaccination status. P-values were not adjusted for multiplicity in the subgroup analyses as an identification of which antidepressants related to the disease severity was beyond the primary objective of this study.

Sensitivity analyses

Four sensitivity analyses were carried out to assess the robustness of our study findings. First, the time frame of antidepressant use was redefined as within two days after the first positive RT-PCR date with reference to previous literature.[9,14] Second, we examined our results' robustness to the inclusion criteria on the time interval between hospital admission and RT-PCR diagnosis; specifically, we varied our inclusion criteria by considering patients with RT-PCR diagnosis 14, 7, and 3 days

before or after admission only. Third, analyses using the admission date as the start point of the event time were conducted among patients whose admission date was not more than seven days before or after the positive RT-PCR date. Fourth, to examine the influence of a potential immortal bias in the exposed group on the results, analyses comparing the effect of antidepressant use with that of an active comparator (i.e., paracetamol) were conducted.[9,24]

All analyses were conducted in R software version 4.1.1 (R Program for Statistical Computing). Detailed information about R packages used in the current study can be found in the Supplementary material.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Of 60,903 hospitalised COVID-19 patients, 40,459 were included for matching, with 3821 (9.4%) having antidepressants prescribed during the study period (Fig. 1). Of this exposed group, 1377 were exposed to SSRIs, 2251 were exposed to non-SSRIs, and 193 were exposed to both SSRIs and non-SSRIs. The matching yielded adequate balance, with SMDs for all covariates after matching being <0.1 (Fig. S1-S3). The distributions of covariates in the exposed and unexposed groups after matching were presented in Table 1. Most patients were ≥80 years old, accounting for 49.8%–62.5% within the groups. The majority of the individuals (76.5%–80.7%) were not vaccinated or vaccinated with only one dose. Hypertension was the most frequent medical history of all patients. The prevalence and association with COVID-19 severe outcomes of confounding factors in the matched antidepressant cohort, SSRI cohort, and non-SSRI cohort were shown respectively in Tables S1–S3.

In general, the rates of the severe events (i.e., ICU admission, death, and the composite outcome) were lower in the exposed groups compared with those in the unexposed groups (Table 2 and Figs. 2–4). Regarding the use of any antidepressants, the rates of ICU admission, inpatient death, and the composite event in the unexposed group were 3.9%, 25.5%, and 28.3%, respectively, while those in the exposed group were 1.3%, 20.0%, and 21.1%, with adjusted HRs equal to 0.332 (95% CI, 0.245–0.449), 0.868 (95% CI, 0.800–0.942), and 0.786 (95% CI, 0.727–0.850) respectively (Table 2 and Fig. 2).

The result was generally consistent when stratified by SSRIs and non-SSRIs (Table 2). Compared with the control group, the adjusted HRs of ICU admission, inpatient death, and the composite event in the exposed group of SSRIs were 0.260 (95% CI, 0.155–0.438), 0.872 (95% CI, 0.768–0.991), and 0.769 (95% CI, 0.680–0.871) respectively (Table 2 and Fig. 3). Similarly, that in the exposed group of non-SSRIs were 0.401 (95% CI, 0.277–0.581), 0.846 (95% CI, 0.767–0.934), and 0.790 (95% CI, 0.718–0.868) respectively (Table 2 and Fig. 4). The proportional hazard assumption of antidepressants, SSRIs and non-SSRIs was generally satisfied for each covariate (Fig. S4–S6).

Of different classes of antidepressants and specific single antidepressants, the protective effect of antidepressant use on severe COVID-19 outcomes was generally observed. In particular, exposure to tetracyclic antidepressants, antidepressants with acid sphingomyelinase inhibition function, and mirtazapine were significantly associated with a reduced risk of all the severity outcomes (tetracyclic antidepressants: ICU admission: adjusted HR = 0.365, 95% CI, 0.198–0.674; death: adjusted HR = 0.763, 95% CI: 0.647–0.899; composite event: adjusted HR = 0.715, 95% CI, 0.612–0.837; antidepressants with acid sphingomyelinase inhibition function: ICU admission: adjusted HR = 0.331, 95% CI, 0.234–0.466; death: adjusted HR = 0.885, 95% CI: 0.802–0.976; composite event: adjusted HR = 0.789, 95% CI, 0.718–0.866; mirtazapine: ICU admission: adjusted HR = 0.337, 95% CI, 0.179–0.636; death: adjusted HR = 0.764, 95% CI: 0.643–0.908; composite event: adjusted HR = 0.709, 95% CI, 0.602–0.836) (Table 3 and Fig. S7–S15).

In the subgroup analysis by age, the antidepressant effect did not differ apparently between patients aged <65 and ≥65 years. While in the subgroup analysis by sex, the effect of antidepressants was more apparent in female patients when compared with male patients (Table 4). The adjusted HRs of ICU admission, inpatient death, and the composite event in females were 0.288 (95% CI, 0.177–0.467), 0.869 (95% CI, 0.774–0.977), and 0.786 (95% CI, 0.703–0.879) respectively, whereas those in males were 0.365 (95% CI, 0.249–0.534), 0.872 (95% CI, 0.777–0.978), and 0.795 (95% CI, 0.712–0.886) respectively. In addition, the protective effect of antidepressants on death and the composite event was more apparent in patients fully vaccinated (i.e., ≥2 doses) (Table 4).

The results of the sensitivity analyses generally supported the robustness of our study findings (Table S4 and Figs. S16–S21). All sensitivity analyses yielded similar results to the primary analyses.

Discussion

In this study, we showed that the use of antidepressants, including SSRIs and non-SSRIs, was associated with a lower risk of severe outcomes of COVID-19 in the Omicron-predominated period. The findings generally echo with a similar retrospective cohort study using electronic health records to demonstrate a risk reduction

Characteristics	Unexposed to antidepressants (n = 11,080)	Exposed to antidepressants[a] (n = 3576)	Unexposed to SSRIs (n = 13,771)	Exposed to SSRIs[b] (n = 1368)	Unexposed to non-SSRIs (n = 17,709)	Exposed to non-SSRIs[c] (n = 2169)
Age, years (mean ± SD)	79 ± 15	79 ± 15	78 ± 16	76 ± 17	80 ± 14	81 ± 14
Age group, n (%)						
18-49	537 (4.8)	203 (5.7)	907 (6.6)	125 (9.1)	550 (3.1)	75 (3.5)
50-59	555 (5.0)	189 (5.3)	743 (5.4)	92 (6.7)	828 (4.7)	95 (4.4)
60-64	512 (4.6)	183 (5.1)	705 (5.1)	80 (5.8)	806 (4.6)	102 (4.7)
65-69	734 (6.6)	241 (6.7)	989 (7.2)	116 (8.5)	1183 (6.7)	135 (6.2)
70-74	972 (8.8)	314 (8.8)	1308 (9.5)	132 (9.6)	1496 (8.4)	179 (8.3)
75-79	1114 (10.1)	380 (10.6)	1442 (10.5)	142 (10.4)	1776 (10.0)	227 (10.5)
≥80	6656 (60.1)	2066 (57.8)	7677 (55.7)	681 (49.8)	11,070 (62.5)	1356 (62.5)
Sex, n (%)						
Female	5962 (53.8)	2048 (57.3)	7542 (54.8)	797 (58.3)	9440 (53.3)	1239 (57.1)
Male	5118 (46.2)	1528 (42.7)	6229 (45.2)	571 (41.7)	8269 (46.7)	930 (42.9)
Vaccination doses, n (%)						
0	6800 (61.4)	2125 (59.4)	8351 (60.6)	798 (58.3)	10,601 (59.9)	1315 (60.6)
1	2052 (18.5)	688 (19.2)	2460 (17.9)	249 (18.2)	3410 (19.3)	436 (20.1)
≥2	2228 (20.1)	763 (21.3)	2960 (21.5)	321 (23.5)	3698 (20.9)	418 (19.3)
Medical history, n (%)						
Hypertension	5279 (47.6)	1789 (50.0)	6267 (45.5)	642 (46.9)	8864 (50.1)	1136 (52.4)
Diabetes	2939 (26.5)	999 (27.9)	3387 (24.6)	344 (25.1)	5083 (28.7)	643 (29.6)
Cerebrovascular disease	2454 (22.1)	812 (22.7)	3151 (22.9)	309 (22.6)	3790 (21.4)	509 (23.5)
Arrhythmia	1536 (13.9)	513 (14.3)	1879 (13.6)	185 (13.5)	2624 (14.8)	334 (15.4)
Coronary artery disease	1389 (12.5)	466 (13.0)	1715 (12.5)	179 (13.1)	2288 (12.9)	293 (13.5)
Chronic kidney disease	1078 (9.7)	348 (9.7)	1264 (9.2)	125 (9.1)	1807 (10.2)	213 (9.8)
Congestive heart failure	1026 (9.3)	341 (9.5)	1250 (9.1)	126 (9.2)	1737 (9.8)	217 (10.0)
Chronic liver disease	659 (5.9)	219 (6.1)	787 (5.7)	81 (5.9)	1099 (6.2)	144 (6.6)
Malignancy	630 (5.7)	193 (5.4)	667 (4.8)	63 (4.6)	1192 (6.7)	131 (6.0)
Chronic obstructive pulmonary disease	441 (4.0)	140 (3.9)	490 (3.6)	48 (3.5)	766 (4.3)	95 (4.4)
Obesity	300 (2.7)	101 (2.8)	336 (2.4)	33 (2.4)	555 (3.1)	62 (2.9)
Asthma	216 (1.9)	79 (2.2)	262 (1.9)	27 (2.0)	388 (2.2)	53 (2.4)
Peripheral vascular disease	203 (1.8)	69 (1.9)	212 (1.5)	21 (1.5)	374 (2.1)	46 (2.1)
Intellectual and developmental disability	160 (1.4)	49 (1.4)	247 (1.8)	22 (1.6)	235 (1.3)	26 (1.2)
Mood and anxiety disorders	402 (3.6)	447 (12.5)	403 (2.9)	267 (19.5)	403 (2.3)	278 (12.8)
Other psychiatric disorders	3897 (35.2)	1404 (39.3)	4232 (30.7)	506 (37.0)	4441 (25.1)	894 (41.2)
Use of benzodiazepine	3481 (31.4)	1519 (42.5)	3690 (26.8)	561 (41.0)	3678 (20.8)	969 (44.7)
Use of anti-COVID-19 treatments, n (%)						
Dexamethasone	5009 (45.2)	1546 (43.2)	5816 (42.2)	531 (38.8)	7763 (43.8)	988 (45.6)
Molnupiravir	1899 (17.1)	642 (18.0)	2346 (17.0)	221 (16.2)	3146 (17.8)	415 (19.1)
Remdesivir	1365 (12.3)	426 (11.9)	1615 (11.7)	160 (11.7)	2133 (12.0)	256 (11.8)
Other anti-COVID-19 treatments[d]	1050 (9.5)	321 (9.0)	1267 (9.2)	122 (8.9)	1716 (9.7)	192 (8.9)

SSRI: selective serotonin reuptake inhibitor; SD: standard deviation. [a]Individuals exposed and unexposed to any antidepressants were matched using a 1:4 ratio. 245 individuals exposed to any antidepressants failed to be matched. [b]Individuals exposed and unexposed to SSRI antidepressants were matched using a 1:15 ratio. 9 individuals exposed to SSRI antidepressants failed to be matched. [c]Individuals exposed and unexposed to non-SSRI antidepressants were matched using a 1:15 ratio. 82 individuals exposed to non-SSRI antidepressants failed to be matched. [d]Other anti-COVID-19 treatments include paxlovid, baricitinib, tocilizumab, and interferon beta-1b.

Table 1: **Characteristics of exposed and non-exposed individuals after matching.**

in COVID-19 mortality when the patients were prescribed with SSRIs.[8] Provided that several SSRI (e.g., fluoxetine, fluvoxamine) and non-SSRI antidepressants act as FIASMA,[25] a recent study demonstrated antiviral and anti-inflammatory activities, and a modulation of ceramide system in the lung tissues of these functional inhibitors in a K18-hACE2 mouse model of SARS-CoV-2 infection.[26] Acid sphingomyelinase (ASM) catalyses

	Unexposed to antidepressants, n (%)	Exposed to antidepressants, n (%)	Crude HR (95% CI)	p	Adjusted HR (95% CI)[a]	p
Antidepressants						
ICU	435 (3.9)	46 (1.3)	0.334 (0.245, 0.454)	**<0.0001**	0.332 (0.245, 0.449)	**<0.0001**
Death	2827 (25.5)	716 (20.0)	0.835 (0.769, 0.906)	**<0.0001**	0.868 (0.800, 0.942)	**0.0007**
ICU or death	3141 (28.3)	756 (21.1)	0.764 (0.705, 0.826)	**<0.0001**	0.786 (0.727, 0.850)	**<0.0001**
SSRIs						
ICU	498 (3.6)	14 (1.0)	0.260 (0.152, 0.446)	**<0.0001**	0.260 (0.155, 0.438)	**<0.0001**
Death	3321 (24.1)	246 (18.0)	0.815 (0.716, 0.929)	**0.0022**	0.872 (0.768, 0.991)	**0.0360**
ICU or death	3677 (26.7)	258 (18.9)	0.731 (0.644, 0.830)	**<0.0001**	0.769 (0.680, 0.871)	**<0.0001**
Non-SSRIs						
ICU	564 (3.2)	30 (1.4)	0.390 (0.267, 0.570)	**<0.0001**	0.401 (0.277, 0.581)	**<0.0001**
Death	4375 (24.7)	451 (20.8)	0.847 (0.768, 0.935)	**0.0010**	0.846 (0.767, 0.934)	**0.0009**
ICU or death	4772 (26.9)	478 (22.0)	0.790 (0.718, 0.869)	**<0.0001**	0.790 (0.718, 0.868)	**<0.0001**

HR: hazard ratio; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor. [a]Adjusted for age group, sex, vaccination doses, comorbidity, psychiatric status, use of benzodiazepine, use of dexamethasone, use of molnupiravir, use of remdesivir, use of other anti-COVID-19 treatments, and week of first positive RT-PCR date.

Table 2: **Association between antidepressants and severity outcomes.**

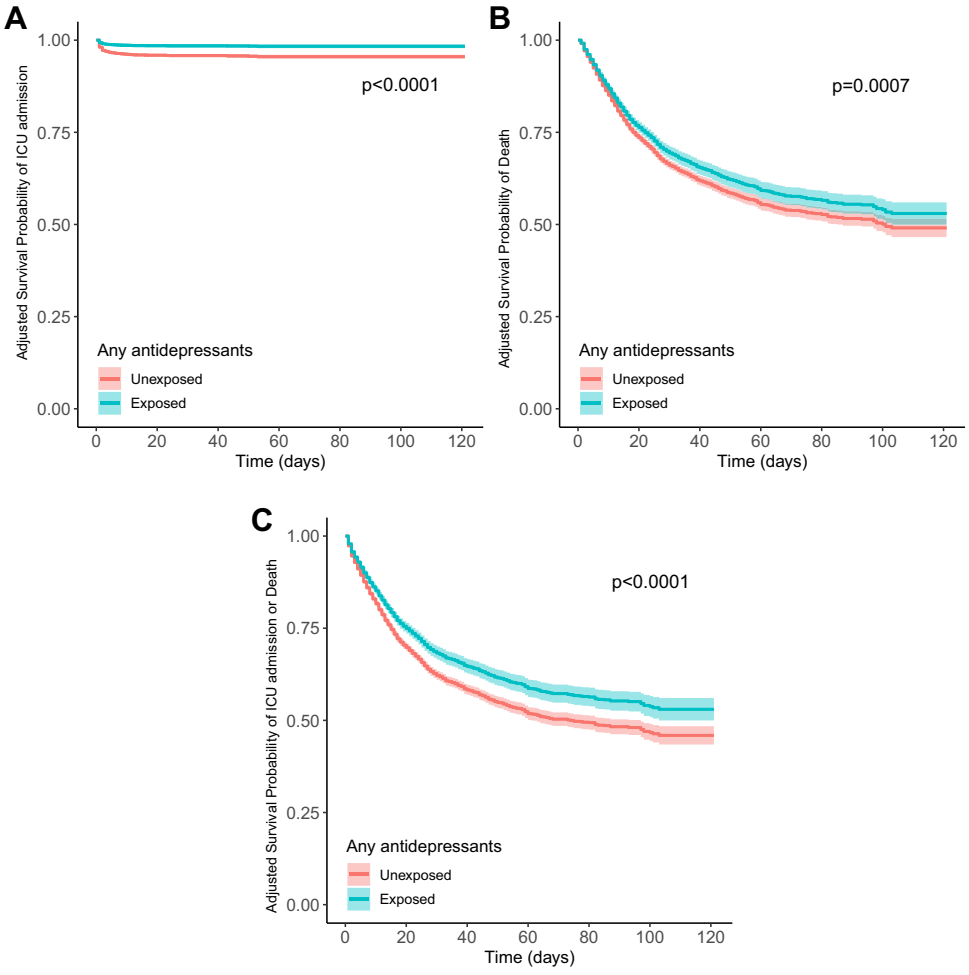

Fig. 2: **Survival distribution of time from the first positive RT-PCR results to a severity event for individuals exposed and unexposed to any antidepressants**. (A) ICU; (B) Death; (C) ICU or death. The survival probability was determined by using the conditional Cox proportional hazard model adjusted with the covariates. The shaded areas represent 95% confidence intervals.

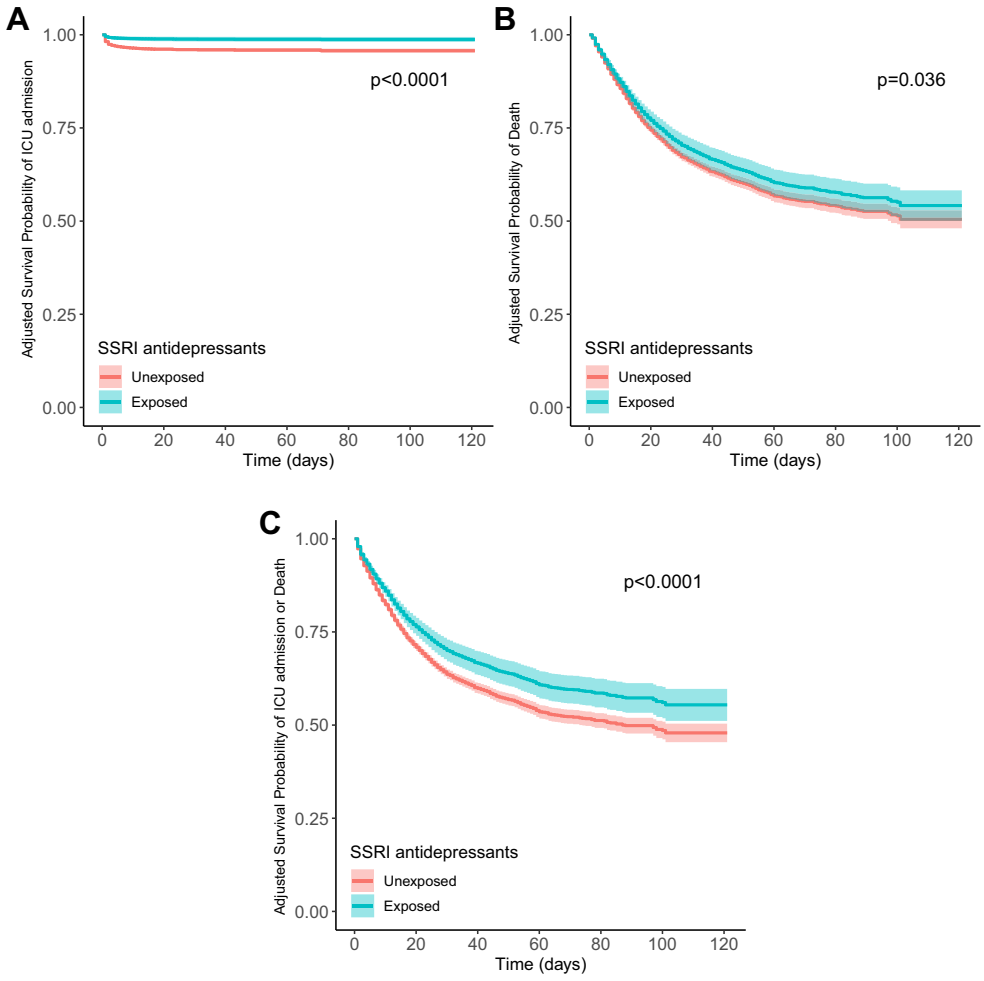

Fig. 3: **Survival distribution of time from the first positive RT-PCR results to a severity event for individuals exposed and unexposed to SSRI antidepressants**. (A) ICU; (B) Death; (C) ICU or death. The survival probability was determined by using the conditional Cox proportional hazard model adjusted with the covariates. The shaded areas represent 95% confidence intervals.

the conversion of sphingomyelin into the highly lipophilic ceramide, forming large gel-like platforms in the plasma membrane which SARS-CoV-2 uses for cell entry, thus FIASMA lowering the amount of ceramide or ceramide blockade could protect against infection with SARS-CoV-2.[27] In some observational studies, FIASMA reduced emergency department or hospital visits in outpatients with SARS-CoV-2, as well as the risk of intubation or death among inpatients with SARS-CoV-2.[16,23,28] Apart from the role of the FIASMA mechanism, the relationship could be explained by several mechanisms. The pathophysiologic process of COVID-19 is characterised by a cytokine storm in pulmonary tissues which may result in multi-organ failure and death. SARS-CoV-2 viral replication occurs in an intermediate compartment between the endoplasmic reticulum and the Golgi complex, resulting in increased endoplasmic reticulum (ER) stress and subsequently a cytokine storm.[15] The pathophysiologic process was supported by a case-control study showing that ER stress markers were identified in patients with SARS-CoV-2 infection.[29] The elevation of such cytokine storm induces acute respiratory distress syndrome and is thus positively related to the COVID-19 severity. Apart from that, in severe cases with excessive production of proinflammatory cytokines such as interleukin-6 and tumour necrosis factor, reduced negative feedback in the immune response was found, thus leading to a poorer prognosis.[7] As a strong proinflammatory cytokine, interleukin-6 has been identified as a biomarker highly correlated with COVID-19 mortality. A meta-analysis indicated that antidepressant medication treatments, particularly SSRI may reduce the level of serum interleukin-6 in patients with major depressive disorder.[30] A recent randomised controlled trial has demonstrated that the SSRIs and one of the more potent

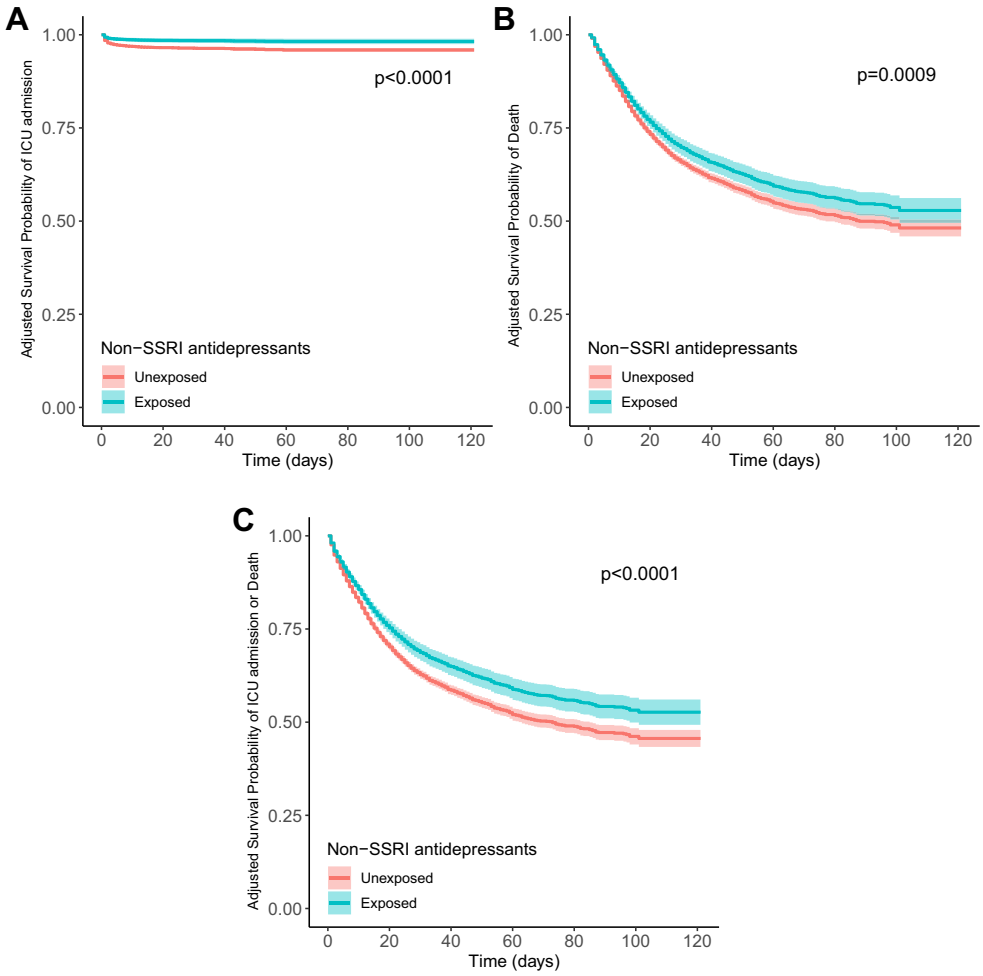

***Fig. 4:* Survival distribution of time from the first positive RT-PCR results to a severity event for individuals exposed and unexposed to non-SSRI antidepressants.** (A) ICU; (B) Death; (C) ICU or death. The survival probability was determined by using the conditional Cox proportional hazard model adjusted with the covariates. The shaded areas represent 95% confidence intervals.

adrenergic alpha-1 receptor agonists fluvoxamine was able to alleviate clinical deterioration and lessen disease severity in patients with mild COVID-19 illness.[10] Moreover, cytokine production is modulated by the sigma-1 receptor agonist which has been shown to restrict the endonuclease activity of an ER stress sensor inositol-requiring enzyme 1 (IRE1), also via other pathways, such as nuclear factor κ B, inflammasomes, Toll-like receptor 4, or peroxisome proliferator-activated receptor γ, thus leading to anti-inflammatory effects.[31,32] A study proposed that fluvoxamine can increase the nighttime plasma level of melatonin which exerts antioxidant and anti-inflammatory effects.[33]

In the subgroup analysis, we demonstrated that the antidepressant effect was more apparent in females infected with COVID-19, in line with another study showing female COVID-19 patients had a lower mortality rate than male patients.[34] In fact, a variation of antidepressant effect could be attributed to sex-based differences in pharmacokinetic profiles, physiological variables, and sex-specific conditions. Firstly, several studies indicated that females responded better to serotonergic antidepressants than males, possibly due to different pharmacokinetic profiles and hormonal status.[35] As antidepressants are lipophilic, they produce a greater drug distribution in women who have more adipose tissues than men. Women also have a relatively slower rate of gastric motility and emptying compared with men, further decreasing the clearance of antidepressants.[36] Secondly, the sex difference in response to antidepressants could be due to differential hormonal status. The female sex hormone estradiol increases the number of serotonin receptors in the brain by increasing the production of tryptophan hydroxylase, which is the rate-limiting step of serotonin synthesis from tryptophan. Estradiol also acts as an antagonist for the serotonin reuptake transporter

	Unexposed to antidepressants, n (%)	Exposed to antidepressants, n (%)	Crude HR (95% CI)	p	Adjusted HR (95% CI)[a]	p
Fluoxetine[b]						
ICU	130 (5.5)	3 (1.7)	0.296 (0.096, 0.916)	**0.035**	0.328 (0.116, 0.928)	**0.036**
Death	416 (17.7)	21 (12.0)	0.705 (0.464, 1.072)	0.10	0.778 (0.515, 1.176)	0.23
ICU or death	512 (21.8)	23 (13.1)	0.587 (0.393, 0.877)	**0.0093**	0.638 (0.439, 0.925)	**0.018**
SSRIs other than fluoxetine[c]						
ICU	451 (3.6)	11 (0.9)	0.248 (0.134, 0.456)	**<0.0001**	0.252 (0.138, 0.458)	**<0.0001**
Death	3092 (24.8)	226 (19.0)	0.846 (0.738, 0.969)	**0.016**	0.897 (0.784, 1.026)	0.11
ICU or death	3412 (27.3)	236 (19.9)	0.764 (0.670, 0.871)	**<0.0001**	0.799 (0.702, 0.908)	**0.0006**
SNRI antidepressants[d]						
ICU	130 (6.6)	4 (2.4)	0.328 (0.119, 0.905)	**0.031**	0.368 (0.139, 0.978)	**0.045**
Death	431 (22.0)	29 (17.5)	0.932 (0.661, 1.315)	0.69	0.975 (0.699, 1.362)	0.88
ICU or death	525 (26.8)	33 (19.9)	0.780 (0.561, 1.083)	0.14	0.793 (0.570, 1.103)	0.17
Tricyclic antidepressants[e]						
ICU	196 (5.3)	6 (2.3)	0.372 (0.163, 0.849)	**0.019**	0.389 (0.167, 0.903)	**0.028**
Death	676 (18.3)	43 (16.2)	0.892 (0.660, 1.205)	0.46	0.973 (0.728, 1.301)	0.85
ICU or death	815 (22.0)	48 (18.1)	0.764 (0.578, 1.012)	0.060	0.809 (0.618, 1.060)	0.12
Tetracyclic antidepressants[f]						
ICU	287 (3.5)	10 (1.3)	0.359 (0.190, 0.677)	**0.0016**	0.365 (0.198, 0.674)	**0.0013**
Death	2239 (27.1)	150 (19.4)	0.753 (0.639, 0.889)	**0.0008**	0.763 (0.647, 0.899)	**0.0012**
ICU or death	2438 (29.6)	159 (20.5)	0.704 (0.600, 0.826)	**<0.0001**	0.715 (0.612, 0.837)	**<0.0001**
α2-antagonist[g]						
ICU	287 (3.8)	9 (1.3)	0.337 (0.173, 0.657)	**0.0014**	0.337 (0.179, 0.636)	**0.0008**
Death	2037 (26.6)	138 (19.7)	0.773 (0.651, 0.918)	**0.0033**	0.764 (0.643, 0.908)	**0.0022**
ICU or death	2236 (29.2)	146 (20.8)	0.719 (0.609, 0.849)	**<0.0001**	0.709 (0.602, 0.836)	**<0.0001**
FIASMA antidepressants[h]						
ICU	699 (3.5)	34 (1.4)	0.331 (0.232, 0.472)	**<0.0001**	0.331 (0.234, 0.466)	**<0.0001**
Death	4561 (22.5)	449 (18.8)	0.854 (0.774, 0.943)	**0.0018**	0.885 (0.802, 0.976)	**0.014**
ICU or death	5076 (25.1)	478 (20.1)	0.770 (0.700, 0.847)	**<0.0001**	0.789 (0.718, 0.866)	**<0.0001**
SSRIs with high to intermediate affinity agonist activity at sigma-1 receptor[i]						
ICU	299 (4.4)	8 (1.5)	0.335 (0.165, 0.680)	**0.0025**	0.357 (0.183, 0.700)	**0.0027**
Death	1456 (21.3)	78 (14.8)	0.752 (0.606, 0.933)	**0.0095**	0.841 (0.681, 1.039)	0.11
ICU or death	1670 (24.5)	84 (15.9)	0.668 (0.543, 0.823)	**0.0002**	0.730 (0.596, 0.893)	**0.0022**
SSRIs with low affinity agonist activity at sigma-1 receptor[j]						
ICU	35 (6.0)	1 (2.2)	0.349 (0.049, 2.503)	0.30	0.405 (0.053, 3.108)	0.38
Death	116 (19.8)	8 (17.4)	0.910 (0.478, 1.731)	0.77	1.116 (0.606, 2.056)	0.72
ICU or death	139 (23.8)	9 (19.6)	0.823 (0.440, 1.542)	0.54	1.016 (0.593, 1.742)	0.95

HR: hazard ratio; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitors; FIASMA: functional inhibition of acid sphingomyelinase. [a]Adjusted for age group, sex, vaccination doses, comorbidity, psychiatric status, vaccination status, use of benzodiazepine, use of dexamethasone, use of molnupiravir, use of remdesivir, use of other anti-COVID-19 treatments, and week of first positive PCR date. [b]Individuals exposed and unexposed to fluoxetine were matched using a 1:15 ratio (175:2352). 1 individual exposed to fluoxetine failed to be matched. [c]Individuals exposed and unexposed to SSRIs other than fluoxetine were matched using a 1:15 ratio (1188:12,492). 11 individuals exposed to SSRIs other than fluoxetine failed to be matched. [d]Individuals exposed and unexposed to SNRI antidepressants were matched using a 1:15 ratio (166:1960). 5 individuals exposed to SNRI antidepressants failed to be matched. SNRI antidepressants prescribed in the current cohort included desvenlafaxine, duloxetine, venlafaxine, and milnacipran. [e]Individuals exposed and unexposed to tricyclic antidepressants were matched using a 1:15 ratio (265:3700). 4 individuals exposed to tricyclic antidepressants failed to be matched. Tricyclic antidepressants prescribed in the current cohort included amitriptyline, imipramine, nortriptyline, trimipramine, clomipramine, and dosulepin. [f]Individuals exposed and unexposed to tetracyclic antidepressants were matched using a 1:15 ratio (775:8248). 20 individuals exposed to tetracyclic antidepressants failed to be matched. Tetracyclic antidepressants prescribed in the current cohort included mianserin and mirtazapine. [g]Individuals exposed and unexposed to α2-antagonist antidepressants were matched using a 1:15 ratio (702:7646). 13 individuals exposed to α2-antagonist antidepressants failed to be matched. The only α2-antagonist antidepressant prescribed in the current cohort was mirtazapine. [h]Individuals exposed and unexposed to FIASMA antidepressants were matched using a 1:15 ratio (2382:20,258). 136 individuals exposed to FIASMA antidepressants failed to be matched. FIASMA antidepressants prescribed in the current cohort included amitriptyline, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, trimipramine, and venlafaxine. [i]Individuals exposed and unexposed to SSRIs with high to intermediate affinity agonist activity at sigma-1 receptor were matched using a 1:15 ratio (527:6820). 3 individuals exposed to SSRIs with high to intermediate affinity agonist activity at sigma-1 receptor failed to be matched. SSRIs with high to intermediate affinity agonist activity at sigma-1 receptor prescribed in the current cohort included fluoxetine, escitalopram, and citalopram. [j]Individuals exposed and unexposed to SSRIs with low affinity agonist activity at sigma-1 receptor were matched using a 1:15 ratio (46:585). 4 individuals exposed to SSRIs with low affinity agonist activity at sigma-1 receptor failed to be matched. SSRIs with low affinity agonist activity at sigma-1 receptor prescribed in the current cohort included paroxetine.

Table 3: **Association between different antidepressant classes or specific antidepressants and severity outcomes.**

	Unexposed to antidepressants, n (%)	Exposed to antidepressants, n (%)	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
Stratified by age[a]						
Aged <65 years (n = 2179)						
ICU	103 (6.4)	13 (2.3)	0.355 (0.197, 0.640)	**0.00057**	0.323 (0.187, 0.559)	**<0.0001**
Death	129 (8.0)	42 (7.3)	1.046 (0.730, 1.498)	0.81	0.925 (0.643, 1.33)	0.67
ICU or death	212 (13.2)	54 (9.4)	0.747 (0.550, 1.016)	0.063	0.666 (0.492, 0.902)	**0.0087**
Aged ≥65 years (n = 12,477)						
ICU	332 (3.5)	33 (1.1)	0.322 (0.225, 0.463)	**<0.0001**	0.340 (0.235, 0.490)	**<0.0001**
Death	2698 (28.5)	674 (22.5)	0.825 (0.758, 0.898)	**<0.0001**	0.850 (0.782, 0.925)	**0.00016**
ICU or death	2929 (30.9)	702 (23.4)	0.765 (0.705, 0.831)	**<0.0001**	0.787 (0.725, 0.854)	**<0.0001**
Stratified by sex[b]						
Male (n = 6646)						
ICU	265 (5.2)	27 (1.8)	0.367 (0.247, 0.545)	**<0.0001**	0.365 (0.249, 0.534)	**<0.0001**
Death	1462 (28.6)	347 (22.7)	0.809 (0.719, 0.909)	**0.00038**	0.872 (0.777, 0.978)	**0.020**
ICU or death	1638 (32.0)	370 (24.2)	0.745 (0.666, 0.832)	**<0.0001**	0.795 (0.712, 0.886)	**<0.0001**
Female (n = 8010)						
ICU	170 (2.9)	19 (0.9)	0.296 (0.183, 0.480)	**<0.0001**	0.288 (0.177, 0.467)	**<0.0001**
Death	1365 (22.9)	369 (18.0)	0.861 (0.767, 0.966)	**0.011**	0.869 (0.774, 0.977)	**0.018**
ICU or death	1503 (25.2)	386 (18.8)	0.782 (0.699, 0.875)	**<0.0001**	0.786 (0.703, 0.879)	**<0.0001**
Stratified by vaccination status[c]						
0 dose (n = 8925)						
ICU	180 (2.6)	20 (0.9)	0.352 (0.222, 0.560)	**<0.0001**	0.347 (0.219, 0.550)	**<0.0001**
Death	2088 (30.7)	503 (23.7)	0.829 (0.752, 0.913)	**0.00015**	0.862 (0.782, 0.949)	**0.0026**
ICU or death	2209 (32.5)	521 (24.5)	0.789 (0.718, 0.868)	**<0.0001**	0.813 (0.739, 0.893)	**<0.0001**
1 dose (n = 2740)						
ICU	109 (5.3)	10 (1.5)	0.271 (0.141, 0.521)	**<0.0001**	0.262 (0.133, 0.513)	**0.00010**
Death	441 (21.5)	138 (20.1)	0.995 (0.817, 1.211)	0.96	0.975 (0.799, 1.189)	0.80
ICU or death	520 (25.3)	147 (21.4)	0.845 (0.701, 1.020)	0.079	0.845 (0.704, 1.016)	0.073
≥2 doses (n = 2991)						
ICU	146 (6.6)	16 (2.1)	0.342 (0.203, 0.576)	**<0.0001**	0.374 (0.227, 0.616)	**0.00011**
Death	298 (13.4)	75 (9.8)	0.739 (0.570, 0.958)	**0.022**	0.703 (0.543, 0.911)	**0.0078**
ICU or death	412 (18.5)	88 (11.5)	0.608 (0.480, 0.768)	**<0.0001**	0.606 (0.480, 0.766)	**<0.0001**

HR: hazard ratio; CI: confidence interval. [a]Adjusted HR was calculated adjusted for sex, vaccination doses, comorbidity, psychiatric status, use of benzodiazepine, use of dexamethasone, use of molnupiravir, use of remdesivir, use of other anti-COVID-19 treatments, and week of first positive RT-PCR date. [b]Adjusted HR was calculated adjusted for age group, vaccination doses, comorbidity, psychiatric status, use of benzodiazepine, use of dexamethasone, use of molnupiravir, use of remdesivir, use of other anti-COVID-19 treatments, and week of first positive RT-PCR date. [c]Adjusted HR was calculated adjusted for age group, sex, comorbidity, psychiatric status, use of benzodiazepine, use of dexamethasone, use of molnupiravir, use of remdesivir, use of other anti-COVID-19 treatments, and week of first positive RT-PCR date.

Table 4: **Subgroup analysis of the association between antidepressants and severity outcomes by age, sex and vaccination status.**

(SERT) so that a higher concentration of synaptic serotonin could remain, leading to a potentially better response to antidepressants.[37] Nevertheless, the finding from this subgroup analysis warranted further studies to confirm in case of a potential spurious association.

Among the antidepressants, our results showed that mirtazapine, an α2-antagonist antidepressant prescribed in the current cohort, was significantly associated with COVID-19 severity. This finding is supported by an observational study illustrating beneficial effects of mirtazapine on reducing risk of intubation or death in hospitalised COVID-19 patients.[14] Unlike most other antidepressants, mirtazapine does not inhibit the reuptake of serotonin or noradrenergic. Mirtazapine has a dual mode of action, as it is a noradrenergic and specific serotonergic antidepressant. It works by inhibiting the central presynaptic α2-adrenergic receptors, causing an increased release of serotonin and norepinephrine, and blocking 5-HT_2 and 5-HT_3 receptors, and then 5-HT_1 receptors are activated with increased serotonin release.[38] Therefore, mirtazapine's dual mode of action explains its effectiveness as an antidepressant, which could be potentially related to its ability to alleviate death rates in COVID-19 patients.[39] In addition to its antidepressive mechanism, mirtazapine also acts as a potent antagonist of H1 histamine receptors,[40,41] thus may act as an alleviative of exaggerated lung inflammation. Nevertheless, the therapeutic effect of mirtazapine in preventing serious COVID-19 outcomes warranted further experimental investigations.

Antidepressant dosage may have a potential impact on the observed associations between different antidepressants and the severity outcome. In the outpatient setting, two randomised controlled trials found the use of fluvoxamine at a dose between 200 and 300 mg daily for 10–15 days could significantly reduce the risk of serious clinical outcome,[10,11] while a lower dose of fluvoxamine (i.e. 100 mg daily for 14 days) exhibited no significant benefit against placebo among overweight or obese non-hospitalised COVID-19 patients in another randomised controlled trial.[42] Several observational studies showed a use of less than 20 mg fluoxetine-equivalents per day was not associated with clinical deterioration, whereas dose-dependent associations were observed when daily prescription of fluoxetine-equivalents increased from 20 to 40 mg.[16,23] Due to a lack of relevant data, the current study did not account for the prescribed dosage. We acknowledge insignificant effects from several types of antidepressants in our study may be due to an insufficient dosage of the medications.

Of note, the rate of antidepressant exposure in this cohort consisting of COVID-19 patients (9.4%) was lower than that reported by a similar COVID-19 cohort in the United States (18.3%).[16] It was not surprising because their exposure was defined as at least one antidepressant documented in the home medication list at any encounter prior to the date of the first positive SARS-CoV-2 test, within a relatively wider time frame. Although the prevalence of antidepressant use in the general population in Hong Kong was unavailable, our estimate is within a range reported in different regions - the prevalence of antidepressant use was found to be 0.64% based on the national health insurance database of mainland China in 2017,[43] 7.2% from 27 European countries in 2010,[44] and 13.2% among American adults between 2015 and 2018,[45] respectively. The inconsistency between Hong Kong and other regions could be owing to a difference in healthcare systems and population characteristics.

Our study has several major limitations. First, while some studies used the disease onset date in defining the exposure to antidepressants, we instead used the disease confirmation date by RT-PCR due to missing information and potential recall bias of self-reported disease onset date through epidemiological investigation. Nevertheless, our sensitivity analysis has showed that the study findings were insensitive to different assumptions of exposure window. Second, as with many retrospective cohort studies employing a registry database, only limited information on covariates was available in this study using the centralised clinical data provided by the Hospital Authority of Hong Kong. The database stored the demographic characteristics of patients, data on hospital admissions, emergency department visits, diagnoses, prescription and drug dispensing, procedures, and laboratory tests, but the confounders such as total dosage administered and compliance with antidepressant treatment were not available and were thus unable to be controlled in this study. Third, the results of ICU admission should be interpreted with caution because ICU capacity was overwhelmed by the surge of cases during the study period.

In conclusion, we employed real-world data to demonstrate that antidepressants use, including SSRIs and non-SSRIs, was associated with a lower risk of severe COVID-19 in the Omicron-predominated period. Hence, our study offers an improved understanding of antidepressant use against COVID-19 severity. COVID-19 patients with psychiatric disorders are at higher risk of severe outcomes.[14,46] The findings of this study using real-world data support the continuation of antidepressants in patients with COVID-19. In addition, the protective effect of antidepressants for preventing severe COVID infections opens up the opportunity to explore new treatments for COVID-19 by repurposing the already existing medications. Experimental studies of the antidepressants' effectiveness in preventing severe COVID-19 in clinical settings are warranted.

Contributors

Study design and conceptualisation: HW, YW, KCC. Data collection and pre-processing: YW, CHKY, TYC, ZG, EKY. Data analysis and interpretation: HW, YW, XJ, CL, KCC. Writing - Original Draft: HW, YW, CTH, KMJ, ZW, KCC. Writing - Review and Editing: XJ, CL, EYML, CHKY, TYC, SZ, ZG, KL, EKY. All authors critically reviewed the manuscript, and gave final approval for publication.

Data sharing statement

The cases' surveillance data were extracted from electronic records in the system managed by the Hong Kong Hospital Authority. The vaccine history and contact tracing databases were extracted from the COVID-19 surveillance database provided by the Department of Health in Hong Kong. Restrictions apply to the availability of these data.

Ethics approval and consent to participate

This was an observational study based on identity-masked datasets provided by the Department of Health, The Government of the Hong Kong Special Administrative Region. Ethics approval was obtained from the Joint CUHK-NTEC Clinical Research Ethics Committee, The Chinese University of Hong Kong. As this study was a retrospective analysis using secondary data without any personal information, the requirement for obtaining informed consent was waived.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100716.

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