Specific adverse outcomes associated with selective serotonin reuptake inhibitors use in COVID-19 patients might be potentiated by remdesivir use

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Title: Specific adverse outcomes associated with selective serotonin reuptake inhibitors use in COVID-19 patients might be potentiated by remdesivir use

Running title: Remdesivir and SSRI associated adverse outcomes

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Author contribution:

IP, PB and ML designed the study and collected data. ML performed statistical analyses. IP and ML drafted and critically revised the manuscript. IP, PB, IK, MOH and ML interpreted data, critically revised the manuscript for important intellectual content, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Abstract:

Background: Due to non-consistent reports in the literature, there are uncertainties about the potential benefits and harms of selective-serotonin-reuptake-inhibitors (SSRI) in patients with Coronavirus-disease-2019 (COVID-19).

Aim: To investigate associations of SSRIs with clinical characteristics and unwanted outcomes among real-life severe and critical COVID-19 patients and their relationship with remdesivir use.
Methods: This retrospective cohort study evaluated a total of 1558 COVID-19 patients of the white race treated in a tertiary center institution, among them 779 patients treated with remdesivir and 779 1:1 case-matched patients.

Results: A total of 78 (5%) patients were exposed to SSRIs during hospitalization, similarly distributed among patients treated with remdesivir and matched patients (5.1% and 4.9%). No significant associations of SSRI use with age, sex, comorbidity burden, and COVID-19 severity were present in either of the two cohorts ($P<0.05$ for all analyses). In multivariate analyses adjusted for clinically meaningful variables, SSRI use was significantly associated with higher mortality among remdesivir (adjusted-odds-ratio (aOR) 2.0, P=0.049) and matched patients (aOR 2.22, P=0.044), and with higher risk for mechanical-ventilation (aOR 2.57, P=0.006), venous-thromboembolism (aOR 3.69, P=0.007) and bacteremia (aOR 2.22, P=0.049) among remdesivir treated patients.

Conclusions: Adverse outcomes associated with SSRI use in COVID-19 patients might be potentiated by remdesivir use, and clinically significant interactions between these two drug classes might exist. Although our findings raise important considerations for clinical practice, they are limited by retrospective nature of the study, lack of ethnic diversity and the potential for unmeasured confounding factors. Future studies exploring underlying biological mechanisms are needed.

Keywords: depression; SARS-CoV-2; SSRI; remdesivir

Introduction

Although vaccines proved to be effective in controlling the Coronavirus disease 2019 (COVID-19) pandemic, hesitancy, waning effect and the emergence of new SARS-COV-2 variants still pose the need for effective and inexpensive alternative treatments, especially in low-income countries (Uraki et al., 2023; Bagić et al., 2022; Kolarić et al., 2021; Lancet Commission on COVID-19 Vaccines and Therapeutics Task Force Members, 2021). The idea of repurposing already regulatory-approved drugs to battle COVID-19 was appealing from the beginning of the COVID-19 pandemic. Among others, selective serotonin reuptake inhibitors (SSRI) were one of the candidates (Smith et al., 2022). It has been proposed that SSRIs directly or mediated by serotonin stimulate σ-1 receptors in the endoplasmic reticulum and interact with acid sphingomyelinase which in turn reduces SARS-CoV-2 replication and attenuates inflammation (Hashimoto, 2021; Gouda and Mégarbane, 2022). However, these findings could not be clearly verified in randomized controlled trials (RCTs) as well as in observational studies (Deng et al., 2023; Vatvani et al., 2023).

Remdesivir (RDV) is the first antiviral drug developed and approved for the treatment of severe COVID-19. It has been found to reduce recovery time and the need for mechanical ventilation (MV) (Beigel et al., 2020). Although initial research failed to reach positive survival benefit, latter large RCTs in line with retrospective cohort studies imply that remdesivir has a positive impact against mortality and progression to MV, notably if introduced during low oxygen demand (Ali et al., 2022; WHO Solidarity Trial Consortium, 2022; Lucijanić et al., 2022; Garibaldi et al., 2022). Its use is recommended by several guidelines in both severe and non-severe COVID-19 patients (National Institutes of Health, 2023; NICE, 2023; World Health Organization, 2022).

There are uncertainties about the potential benefits and harms of SSRI use in patients with COVID-19. Preclinical studies found a synergistic interaction of RDV and an SSRI on SARS-CoV-2 inhibition (Schloer et al., 2021). To the best of our knowledge, there are no published data on concurrent usage of SSRIs and remdesivir and their possible synergistic effect. Therefore, we aimed to investigate associations of SSRIs with clinical characteristics and outcomes among real-life severe and critical COVID-19 patients and their relationship with remdesivir use.

Methods

We have retrospectively evaluated a cohort of 1558 COVID-19 patients, who were hospitalized and treated in a tertiary referral institution University hospital Dubrava in the period from March 2020 to June 2021. All patients were adults of the white race and were tested positive for SARS-CoV-2 infection by either the polymerase chain reaction (PCR) or the antigen test. Patients were selected from a larger cohort of 5959 consecutive COVID-19 patients treated in the same institution whose medical records were recorded as a part of a hospital Registry project. Among them, patients treated with remdesivir were identified and subsequently 1:1 case-matched to patients non-treated with remdesivir, based on age, sex, Charlson comorbidity index (CCI), COVID-19 severity on admission, and maximal oxygen supplementation requirement during hospitalization, resulting in two comparable cohorts of patients (exposed and non-exposed to remdesivir). Upon evaluation of written and electronic medical records for SSRI use, those with missing or unreliable data were excluded together with their respective pair from the other group, resulting in two final cohorts each comprising of 779 patients.

Patients were treated according to the contemporary national and the World Health Organization guidelines (World Health Organization, 2020). The majority of patients were treated with corticosteroids and low molecular weight heparins (LMWH). Remdesivir was given to patients

requiring oxygen supplementation up to the fifteenth day from the first onset of symptoms, per contemporary recommendations (World Health Organization, 2020). SSRI use was considered present if patients received the drug from the SSRI class at any time during hospitalization. No special SSRI selection criteria were applied. SSRI type, dosage and duration were recorded. COVID-19 severity on admission was determined using the WHO recommendations (World Health Organization, 2020). Comorbidities were recorded as individual entities and as a cumulative comorbidity burden assessed by CCI (Charlson et al., 1987). The functional status of patients was determined using the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al., 1982). During hospitalization unwanted outcomes of in-hospital mortality, mechanical ventilation (MV), venous thromboembolism (VTE), arterial thrombosis, major bleeding, and bacteriemia were considered. Thromboses had to be proven by objective imaging and/or laboratory methods and were considered only if properly evaluated and documented in the medical records. Major bleeding was defined by the International Society on Thrombosis and Haemostasis criteria (Schulman et al., 2005). Bacteriemia was considered if positive blood cultures were obtained. In addition, duration of hospital stay and post-discharge mortality were assessed.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the University hospital Dubrava Review board (Nm. 2021/1410-01).

Statistical methods

Due to the non-normal distribution of numerical variables, assessed by the Kolmogorov-Smirnov test, they were presented as the median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and were compared using the chi-squared test. Logistic regression was used to perform multivariate analyses and to assess the odds of unwanted clinical outcomes associated with SSRI

use. Models were created using the backward approach. When interpreting obtained findings, P values <0.05 were considered statistically significant. All analyses were done using the MedCalc statistical software, version 22.007 (MedCalc Software Ltd, Ostend, Belgium).

Results

Overview of patient cohorts

We analyzed a total of 1558 severe or critical COVID-19 patients, 779 treated with remdesivir and 779 matched paired patients. Patients treated with remdesivir and matched patients were of comparable age (median 66 and 66 years, respectively), sex (38% and 38% females, respectively), CCI (median 3 and 3, respectively) and COVID-19 severity at admission (18% and 16.7% critical patients, respectively), as well as regarding maximal required oxygen flow during hospitalization (median 14 and 14 L/min, respectively), as expected per matching criteria (P > 0.05 for all analyses).

SSRI exposure and its clinical associations

A total of 78 (5%) patients were exposed to SSRIs during hospitalization which was similar among patients treated with remdesivir and matched patients (5.1% and 4.9%, respectively, P = 0.816). Most frequently used SSRI was escitalopram (13 and 17 patients, respectively), followed by fluvoxamine (15 and 10 patients, respectively), sertraline (8 and 5 patients, respectively), paroxetine (3 and 6 patients, respectively), and citalopram (1 and 0 patients, respectively), without significant differences regarding SSRI subtype between patients treated with remdesivir and matched patients (P = 0.383). The median duration of SSRI use was 8 days, IQR (6-12.5) and it did not significantly differ between remdesivir exposed and matched patients (median 9 vs 8 days,

P = 0.178). Median SSRI doses were 10 mg for escitalopram, 300 mg for fluvoxamine, 50 mg for sertraline, 20 mg for paroxetine, and 20 mg for citalopram, and with the exception of escitalopram that had somewhat higher doses in remdesivir exposed patients (median ↑10 vs 10 mg, P = 0.035), they did not significantly differ between remdesivir exposed and matched patients (P > 0.05 for all analyses).

Clinical characteristics of patients treated with remdesivir stratified according to SSRI exposure are shown in Table 1. Among patients treated with remdesivir, SSRI-exposed patients in comparison to SSRI non-exposed patients had significantly lower platelet count (median 193 vs 222 $x10^9$/L, respectively, P = 0.026), and were otherwise of similar age, sex, COVID-19 severity and associated inflammatory response, and similar comorbidity profile (P > 0.05 for all analyses).

Clinical characteristics of matched (non-treated with remdesivir) patients stratified according to SSRI exposure are shown in Table 2. Among matched patients, SSRI-exposed patients in comparison to SSRI non-exposed patients had a significantly higher frequency of dementia (21.1% vs 9.3%, respectively, P = 0.018), and were otherwise of similar age, sex, COVID-19 severity and associated inflammatory response, and a similar profile of other comorbidities (P>0.05 for all analyses).

SSRI exposure and clinical outcomes among patients treated with remdesivir and matched patients

In an overall cohort, SSRI use was significantly associated with higher mortality and higher risk for MV (P < 0.05 for all analyses), without significant associations with VTE, arterial thrombosis, major bleeding, and bacteriemia (P > 0.05 for all analyses).

Among patients treated with remdesivir, SSRI use was significantly associated with higher risks for MV, VTE, and bacteriemia (P < 0.05 for all analyses), as shown in Figure 1A. Among matched

(non-treated with remdesivir) patients there were no significant associations present with SSRI use (P > 0.05 for all analyses) as shown in Figure 1B. However, mortality risk associated with SSRI use was non-significantly higher in both subgroups of patients (treated and non-treated with remdesivir).

We further explored associations of SSRI use with unwanted clinical outcomes in a series of multivariate logistic regression models adjusted for clinically meaningful parameters. Results for significant associations are presented in Table 3. In multivariate analyses, among both remdesivir-treated and non-treated patients SSRI was significantly associated with higher mortality (adjusted OR (aOR) 2.0, 95% CI (1.0-4.02), P = 0.049 among patients treated with remdesivir and aOR 2.22, 95% CI (1.02-4.83), P = 0.044 among matched patients, respectively). After multivariate adjustments, among patients treated with remdesivir, SSRI use remained significantly associated with higher risk for MV (aOR 2.57, 95% CI (1.31-5.05), P = 0.006), VTE (aOR 3.69, 95% CI (1.68-5.69), P = 0.007) and bacteremia (aOR 2.22, 95% CI (1.0-4.93), P = 0.049).

Additional considerations

Considering the length of hospitalization, there were no significant differences regarding SSRI use during hospitalization, neither in the whole cohort (median 12 vs 11 days, P = 0.306), nor in remdesivir exposed (median 13 vs 12 days, P=0.131) and non-exposed patients (median 11 vs 11 days, P = 0.985).

Considering post-discharge mortality, there were no significant differences between SSRI-exposed and non-exposed patients, neither in the whole cohort (P=0.309), nor in remdesivir exposed (P = 0.607) and non-exposed patients (P = 0.364).

Considering potential differences in clinical outcomes between σ-1 receptor agonists (escitalopram, fluvoxamine, citalopram) versus other SSRIs, there were no significant differences

present regarding any of evaluated clinical outcomes, neither in the whole cohort, nor among remdesivir exposed and matched patients ($P > 0.05$ for all analyses).

Discussion

As our findings suggest, SSRI use in COVID-19 might not be safe and adverse outcomes associated with SSRI use might be potentiated by remdesivir. The mechanisms behind these associations are unknown at the moment. There are several points we would like to emphasize.

Current findings raise important considerations for clinical practice in the treatment of COVID-19. They call for potential avoidance of this drug combination, increased monitoring of patients exposed to both SSRIs and remdesivir, additional consideration of measures aimed at mitigation of VTE and bacterial superinfections, as well as higher intensity of antithrombotic and antibacterial prophylaxis in patients exposed to both remdesivir and SSRIs, especially in situations when these are considered due to other risk factors as well. It should be noted that our findings originate from retrospective cohort study and despite all the analytical efforts taken into account when approaching the clinical question of concomitant remdesivir and SSRI use, we could not fully account for the potential impact of unmeasured confounding factors. Thus, these findings should be considered as exploratory, currently providing low level of evidence. However, they are first published findings highlighting these important clinical associations and should prompt further research in independent datasets and related clinical contexts, hopefully exposing underlying biological mechanisms.

The prognostic significance of SSRIs in the treatment of COVID-19 remains undisclosed. Several SSRIs have been proposed to have beneficial effects on COVID-19 by various mechanisms. However, fluvoxamine stood out as the most probable and investigated member of the class (Oskotsky et al., 2021; Visos-Varela et al., 2023; Vatvani et al., 2023; Hashimoto, 2021). There

are conflicting results regarding its use and clinical outcomes in observational studies in various clinical settings (Visos-Varela et al., 2023; Wang et al., 2023; Stauning et al., 2023; Osores et al., 2023). Furthermore, several RCTs carried out in outpatient setting measured mortality as an outcome, yet only one study reported clinical events. Others reported emergency room visits, hospitalization risk, oxygen requirement, mechanical ventilation, and various composite outcomes (Deng et al., 2023; Reis et al., 2022; Bramante et al., 2022). While early trials TOGETHER and STOP COVID showed a favorable impact on clinical outcomes, several other studies oppose it (Bramante et al., 2022; Reis et al., 2022; McCarthy et al., 2023). It has been suggested that potential benefits of SSRIs, notably fluvoxamine, regarding SARS-CoV-2 infection may be dose-dependent (Hashimoto, 2023) and low doses (typically used as the initial doses for psychiatric disorders) may not provide potential clinical benefits reported with medium or high doses (Deng et al., 2023). However, a recently published large RCT found no improvement in time to sustained recovery as a primary outcome with the use of fluvoxamine 100 mg twice a day, while a secondary outcome of fewer healthcare use events in the fluvoxamine group did not reach a meaningful difference (Stewart et al., 2023). To date, prominent healthcare organizations do not recommend SSRIs use for this indication due to lack of evidence (National Institutes of Health, 2023; NICE, 2023). SSRIs are well known for their inhibitive action on platelet aggregation. SSRIs deplete serotonin storage in platelets and aggregation is induced by adenosine diphosphate (ADP) and collagen (Halperin and Reber, 2007; Dietrich-Muszalska and Wachowicz, 2017). An association between antidepressants use and increased risk of VTE was observed in UK women. While in this study all classes of antidepressants including SSRIs were independently related to VTE (Parkin et al., 2017), this finding regarding SSRI use was not confirmed by another study in the Asian population (Wu et al., 2013). It is not clear whether depression itself or SSRIs are accountable for this effect.

SSRIs have been reported to inhibit interleukin 6 (IL-6) inflammatory signal cascade known to cause severe disease and might prevent end organ damage in COVID-19 infection (Foletto et al., 2022). On the other hand, membrane-bound histidine sensor kinase CpxA acts as a serotonin receptor on enterohemorrhagic bacteria such as *E. coli* and *Citrobacter rodentium*. Increased serotonin levels inhibit the expression of virulence genes resulting in decreased *C. rodentium* loads. Inversely, genetic or pharmacological lowering of serotonin levels increases pathogenesis and decreases host survival. Many other gastrointestinal pathogens also carry CPxA receptor and might exert a similar effect (Kumar et al., 2020). However, increased serotonin levels stimulated the production of bacterial virulence factors and increased biofilm formation in *Pseudomonas aeruginosa* (Knecht et al., 2016). By modulating serotonin disposition SSRIs might predispose patients to certain types of bacterial infections.

Remdesivir is a prodrug that inhibits viral RNA synthesis. Its metabolite GS-443902 acts as an analog of adenosine triphosphate (ATP) (Humeniuk et al., 2021). As adenosine is used to cease supraventricular tachycardia structural similarity of RDV metabolite may explain its reported side-effects bradycardia, hypotension and QTc interval prolongation (Touafchia et al., 2021; Bistrovic and Lucijanic, 2021; Bistrovic et al., 2022). Adenosine can cause vasodilatation particularly affecting the microvessels and inhibiting platelet aggregation thus protecting patients from arterial thrombotic incidents. On the other hand, adenosine diphosphate metabolite potentiates serotonin-mediated platelet aggregation. Adenosine may also hamper immune response mediated by T cell and reduce inflammation which might suggest rationale for predisposition to observed bacteriemia in remdesivir users (Layland et al., 2014; Vijayan et al., 2017; Lucijanic et al., 2023; Lucijanic et al., 2022; Galan et al., 2009). It has been shown that a hypoxemic setting in inflammatory bowel disease stimulates serotonin synthesis and release and is potentiated by adenosine agonist (Dammen et al., 2013). Although a connection between SSRI and remdesivir pharmacodynamics

remains elusive and current mechanisms unknown, our study suggests that these two drug classes might have a higher incidence of adverse events when used together.

The main limitations of our study are retrospective study design and single center experience. We could not assess potential differences associated with specific SSRI subtypes due to small sample sizes associated with individual SSRIs and the consequent loss of statistical power for these analyses. We were also unable to investigate specific dosing regimens and duration of SSRIs use as predictive factors for occurrence of unwanted outcomes with concomitant exposure to remdesivir. Due to the registry-level dataset, no meaningful patient-level clinical messages could be extracted for further evaluation. The study only included adult patients of the white race which may limit the generalizability of the findings to other racial groups and healthcare settings. Being a retrospective study, there may be inherent biases (such as selection bias and information bias) present. While the analyses were adjusted for several clinically meaningful variables, the potential impact of unmeasured confounders (lifestyle factors, severity of psychiatric conditions requiring SSRIs, etc.) cannot be excluded.

Nevertheless, our findings put forward important novel observations of potential remdesivir and SSRI interactions present in real-life COVID-19 patients experiencing severe or critical form of the disease. They need to be further evaluated in independent cohorts of patients with the goals of validation of current findings, as well as recognition of mechanisms underlying these associations. Future studies should aim to establish a clearer cause-and-effect relationship between SSRI use and clinical outcomes in COVID-19 patients. Prospective studies or randomized control trials would provide a stronger level of evidence, and they should include a more diverse patient population in terms of race and healthcare settings to improve the external validity of the study.

Conclusion

Adverse outcomes associated with SSRI use in COVID-19 patients might be potentiated by remdesivir use and clinically significant interactions between these two drug classes might exist. Among patients treated with remdesivir and SSRI, higher risks of MV, VTE, and bacteriemia were observed. Similar was not present in non-remdesivir control patients. Although exact mechanisms for these observations cannot be disclosed, we may speculate that both serotonin and adenosine signaling pathways, which play important roles in the homeostasis of multiple organ systems, and their disbalance may be underlying these observations. Although our findings raise important considerations for clinical practice, they are limited by retrospective nature of the study, lack of ethnic diversity and the potential for unmeasured confounding factors. Future studies evaluating specific SSRI dosages, other specific therapies, other ethnic contexts and exploring the biological mechanisms behind observed associations are needed.

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Table 1: Associations of clinical characteristics with SSRI use among remdesivir exposed patients

Remdesivir exposed	**SSRI use**	**No SSRI**	**P value**
Nm of patients	40	739	-
Age (years), median and IQR	66 (56-70.5)	66 (56-74)	0.468
Sex			0.547
Female	17 (42.5%)	279 (37.8%)	
Male	23 (57.5%)	460 (62.2%)	
COVID-19 severity			0.443
Mild	-	6 (0.8%)	
Moderate	-	7 (0.9%)	
Severe	36 (90%)	590 (79.8%)	
Critical	4 (10%)	136 (18.4%)	
Duration of symptoms (days), median and IQR	7 (4-9)	7 (4-9)	0.947
Oxygen supplementation requirement at admission (L/min)	6 (3-12)	6 (4-15)	0.761
ECOG functional status	2 (1.5-3)	2 (1-3)	0.354
CCI, median and IQR	3 (2-5)	3 (2-4)	0.398
Arterial hypertension	26 (65%)	459 (62.1%)	0.713
Diabetes mellitus	10 (25%)	231 (31.3%)	0.405

Hyperlipoproteinemia	8 (20%)	156 (21.1%)	0.867
Obesity	15 (37.5%)	305 (41.3%)	0.637
Active smoking	-	44 (6%)	0.112
Chronic heart failure	2 (5%)	55 (7.4%)	0.563
Atrial fibrillation	2 (5%)	80 (10.8%)	0.243
Chronic kidney disease	1 (2.5%)	37 (5%)	0.474
Chronic obstructive lung disease	1 (2.5%)	38 (5.1%)	0.458
Asthma	2 (5%)	32 (4.3%)	0.840
Active malignancy	1 (2.5%)	50 (6.8%)	0.288
Dementia	3 (7.5%)	48 (6.5%)	0.803
CRP (mg/L), median and IQR	83.9 (38-176)	101 (56-156)	0.418
IL-6 (pg/mL), median and IQR	30.3 (16.2-50.8)	38 (14.4-78.3)	0.675
Ferritin (µg/L), median and IQR	685 (369-1956)	961 (561-1584)	0.280
D-dimers (mg/L FEU), median and IQR	0.73 (0.53-2.29)	1 (0.59-1.82)	0.312
eGFR (ml/min/1.73 m^2)	87.4 (67.7-99.1)	87.7 (70.3-100.6)	0.839
WBC (x10^9/L), median and IQR	6.7 (4.9-8.8)	7.6 (5.4-10.3)	0.179

Absolute neutrophils ($x10^9$/L), median and IQR	5.03 (3.66-6.96)	6 (4.2-8.7)	0.055
Absolute lymphocytes ($x10^9$/L), median and IQR	0.79 (0.55-1.23)	0.74 (0.52-1.02)	0.356
Platelets ($x10^9$/L), median and IQR	193 (156-249)	222 (171-289)	0.026 *
Hemoglobin (g/L), median and IQR	130.5 (120-141.5)	132 (120-143)	0.878
RDW (%), median and IQR	13.6 (13.1-14.4)	13.8 (13.3-14.5)	0.399

* statistically significant difference at level $P<0.05$. Abbreviations: WHO=the World health organization, IQR=interquartile range, COVID-19=Coronavirus disease 2019, ECOG=the Eastern cooperative oncology group functional status scale, CCI=Charlson comorbidity index, CRP=C reactive protein, IL-6=interleukin 6, FEU=fibrinogen equivalent units, eGFR=estimated glomerular filtration rate calculated using the CKD-EPI formula, WBC=white blood cell count, MPV=mean platelet volume, RDW=red blood cell distribution width.

Table 2: Associations of clinical characteristics with SSRI use among remdesivir non-exposed patients

Remdesivir non-exposed	**SSRI use**	**No SSRI**	**P value**
Nm of patients	38	741	-
Age (years), median and IQR	66.5 (55-72)	66 (58-74)	0.594
Sex			0.593
Female	16 (42.1%)	280 (37.8%)	
Male	22 (57.9%)	461 (62.2%)	
COVID-19 severity			0.718
Mild	-	6 (0.8%)	
Moderate	-	7 (0.9%)	
Severe	32 (84.2%)	604 (81.5%)	
Critical	6 /15.8%)	124 (15.8%)	
Duration of symptoms (days), median and IQR	8.5 (3-11)	7 (3-10)	0.167
Oxygen supplementation requirement at admission (L/min)	6 (2-15)	8 (4-15)	0.334
ECOG functional status	2 (1-3)	2 (1-3)	0.954
CCI, median and IQR	3 (2-5)	3 (2-4)	0.482
Arterial hypertension	28 (73.7%)	453 (61.1%)	0.121

Diabetes mellitus	13 (34.2%)	200 (27%)	0.330
Hyperlipoproteinemia	10 (26.3%)	163 (22%)	0.533
Obesity	11 (28.9%)	269 (36.3%)	0.357
Active smoking	2 (5.3%)	50 (6.7%)	0.721
Chronic heart failure	4 (10.5%)	74 (10%)	0.914
Atrial fibrillation	5 (13.2%)	89 (12%)	0.832
Chronic kidney disease	4 (10.5%)	56 (7.6%)	0.504
Chronic obstructive lung disease	4 (10.5%)	42 (5.7%)	0.216
Asthma	1 (2.6%)	27 (3.6%)	0.744
Active malignancy	-	43 (5.8%)	0.127
Dementia	8 (21.1%)	69 (9.3%)	0.018 *
CRP (mg/L), median and IQR	77.4 (33.7-126.2)	95.6 (44.3-164.2)	0.108
IL-6 (pg/mL), median and IQR	71.3 (45-151)	45.6 (17.2-106.4)	0.239
Ferritin (µg/L), median and IQR	898 (532-1322)	910 (465-1590)	0.941
D-dimers (mg/L FEU), median and IQR	1.11 (0.57-3.42)	1.26 (0.71-2.97)	0.490
eGFR (ml/min/1.73 m^2)	79 (61-101)	81 (60-96)	0.574
WBC (x10^9/L), median and IQR	9.6 (6.8-13.5)	8.1 (5.8-11.5)	0.112

Absolute neutrophils ($x10^9$/L), median and IQR	8.1 (5.1-10.6)	6.5 (4.3-9.7)	0.073
Absolute lymphocytes ($x10^9$/L), median and IQR	0.68 (0.4-0.96)	0.8 (0.55-1.14)	0.110
Platelets ($x10^9$/L), median and IQR	217 (165-310)	227 (164-297)	0.951
Hemoglobin (g/L), median and IQR	132 (121-140)	132 (118-143)	0.870
RDW (%), median and IQR	13.5 (13.1-15.1)	13.7 (13.2-14.7)	0.394

* statistically significant difference at level $P<0.05$. Abbreviations: WHO=the World health organization, IQR=interquartile range, COVID-19=Coronavirus disease 2019, ECOG=the Eastern cooperative oncology group functional status scale, CCI=Charlson comorbidity index, CRP=C reactive protein, IL-6=interleukin 6, FEU=fibrinogen equivalent units, eGFR=estimated glomerular filtration rate calculated using the CKD-EPI formula, WBC=white blood cell count, MPV=mean platelet volume, RDW=red blood cell distribution width.

Table 3: Multivariate logistic regression models investigating associations of SSRI with unwanted clinical outcomes.

	Remdesivir exposed, mortality	Remdesivir exposed, MV	Remdesivir exposed, VTE	Remdesivir exposed, bacteriemia	No remdesivir, mortality
SSRI use	OR 2.0 (1.0-4.02) P=0.049 *	OR 2.57 (1.31-5.05) P=0.006 *	OR 3.69 (1.68-5.69) P=0.007 *	OR 2.22 (1.0-4.93) P=0.049 *	OR 2.22 (1.02-4.83) P=0.044 *
Age (years)	OR 1.03 (1.0-1.05) P=0.005 *	-	-	-	OR 1.04 (1.02-1.06) P<0.001 *
Male sex	OR 1.4 (0.98-2.01) P=0.061	OR 1.6 (1.12-2.29) P=0.009 *	-	OR 2.02 (1.21-3.34) P=0.007 *	-
ECOG scale	OR 1.54 (1.32-1.82) P<0.001 *	OR 1.58 (1.35-1.85) P<0.001 *	-	OR 1.23 (1.02-1.49) P=0.033 *	OR 1.52 (1.31-1.77) P<0.001 *
Critical COVID-19	OR 2.99 (1.95-4.59) P<0.001 *	OR 3.72 (2.48-5.59) P<0.001 *	OR 3.09 (1.68-5.68) P<0.001 *	OR 1.58 (0.95-2.66) P=0.081	OR 2.67 (1.68-4.22) P<0.001 *
CCI	OR 1.15 (1.04-1.28) P=0.006 *	OR 1.07 (0.99-1.16) P=0.077	-	-	OR 1.19 (1.06-1.33) P=0.002 *
Dementia	-	-	-	-	-

Platelets ($x10^9$/L)	-	-	OR 1.0 (1.0-1.01) P=0.001*	OR 0.99 (0.99-1.0) P=0.089	OR 0.99 (0.99-0.99) P<0.001 *

*statistically significant at level P<0.05. OR with their respective 95% confidence intervals are shown (in brackets). Abbreviations: MV=mechanical ventilation, VTE=venous thromboembolism, SSRI= selective serotonin reuptake inhibitors, OR=odds ratio, ECOG=Eastern Cooperative Oncology Group functional status scale, COVID-19=Coronavirus disease 2019, CCI=Charlson comorbidity index.

Figure 1: A) Clinical outcomes (mortality, mechanical ventilation – MV, venous thromboembolism – VTE, arterial thrombosis – Art. thr., major bleeding – major bleed and bacteriemia) associated with SSRI use in patients concomitantly exposed to remdesivir and **B)** non-exposed to remdesivir. * sign depicts statistically significant associations.