Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Exposure to psychotropic medications and COVID-19 course after hospital admission: Results from a prospective cohort study

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ABSTRACT

Objective: There is evidence of a bidirectional association between COVID-19 disease and psychiatric disorders. We aimed to assess whether exposure to psychotropic medications prior to hospitalization was associated with mortality or discharge within 30 days after hospital admission.

Methods: In this prospective study, we included all individuals with a laboratory-confirmed COVID-19 infection who were admitted to the Bologna University Hospital between 1st March 2020 and 31st January 2021. We collected data about pre-existing psychiatric disorders and the use of psychotropic medications at the admission. As univariate analyses, we estimated cumulative incidence functions for 30-day mortality and discharge stratifying by exposure to each of the psychotropic medication classes. Finally, we fitted Cox regression models to estimate cause-specific Hazard Ratios (HR) of 30-day mortality and discharge. Results were adjusted for socio-demographic (age, sex), clinically relevant variables (comorbidity, c-reactive protein levels, severity of disease at presentation, history of smoking, study period), and psychiatric variables (psychiatric disorder diagnosis, number of psychotropic medications).

Results: Out of a total of 1238 hospitalized patients, 316 were prescribed psychotropic medications at the time of admission. Among these, 45 (3.6%) were taking a first-generation antipsychotics (FGA) and 66 (5.3%) a second generation antipsychotic (SGA). Exposure to SGA was associated with increased rates of 30-day mortality (HR = 2.01, 95%CI = 1.02–3.97) and exposure to FGA was associated with decreased rates of 30-day discharge (HR = 0.55, 95%CI = 0.33–0.90).

Conclusion: Patients with COVID-19 infection exposed to FGA and SGA may have worse COVID-19 infection outcomes.

1. Introduction

Prior research conducted over 62,354 patients diagnosed with COVID-19 found an excess risk of 1.65 (95%CI = 1.59–1.71) of infection among individuals with a prior diagnosis of a psychiatric disorder [1]. Furthermore, pooled estimates from a recent meta-analysis of 23 studies showed that the presence of any psychiatric disorder was associated with a 2-fold increase in the odds of COVID-19 mortality (odds ratio [OR] = 2.00, 95%CI = 1.58.2.54) [2]. Taken together, these results suggest that psychiatric disorders may be independent risk factors for COVID-19 infection and for worse outcomes.

However, existing evidence suggests that this association could be at least partly confounded by other factors. In a recent study by Hoertel et al. [3], authors found that, accounting for age and sex, a psychiatric disorder diagnosis was associated with an OR of 1.71 (95%CI = 1.57–1.86) of death during hospitalization for COVID-19. Thes association reversed when further adjusting for the number of medical comorbidities (OR = 0.87, 95%CI = 0–76-0.96) [3]. Medical

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comorbidities are indeed more prevalent among individuals with psychiatric disorders [4,5] and are associated with COVID-19 mortality [6].

On the other hand, the excess of COVID-19 mortality observed in people with psychiatric disorders may be explained by exposure to psychotropic medications. Adverse effects of psychotropic medications could potentially worsen the course of COVID-19 infection through multiple mechanisms [7]. In a large study comprising 144,321 patients with COVID-19 [8], redemption of psychotropic medications within 90 days prior to infection was associated with a 2-fold increased risk of death (standardized risk ratio [RR] = 2.14, 95%CI = 1.77–2.51). Authors did not stratify analyses by specific medication class. Most of the evidence to date regards antipsychotics [2].

In this context, we aimed to assess whether exposure to psychotropic medications was associated with worse COVID-19 infection outcomes independently of underlying psychiatric disorder and of medical comorbidities. For this purpose, we conducted survival analysis on a retrospective cohort of patients hospitalized due to COVID-19 infection and estimated the effect of different categories of psychotropic medication on time to death or time to discharge from hospital within the first 30 days from the admission.

2. Materials and methods

2.1. Study design and setting

This is a prospective cohort study conducted at the Policlinico Sant'Orsola Malpighi, in Bologna, Italy, on patients with COVID-19. All patients were asked to participate to the study.

Participants were consecutive adults (≥18 years) with COVID-19, confirmed by PCR on nasopharyngeal swab, oropharynx, bronchoalveolar lavage, stool, or blood (rapid test was an acceptable alternative), who were admitted to the University Hospital Policlinco Sant'Orsola Malpighi between 1st March 2020 and 31st January 2021.

The present study was approved by the Local Ethic Committee (Study: "Predictors of ICU admission among patients with SARS-Cov-2 pneumonia"; Protocol Code: PREDI-CO; Internal code CE: EMI12-2021_283/2020/Oss/AOUBO evaluated on the 17th December 2020; Promoter: Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy). All patients provided verbal, not written, informed consent because of isolation precautions. All patients received standard of care treatment at the time of hospital admission according to the regional COVID-19 guidelines of Emilia Romagna [9] and updated data on treatment of COVID-19 [10].

2.2. Measures

Sociodemographic variables. We recorded age and sex for every participant.

Clinical assessment at hospital admission. The Body Mass Index (BMI) [11] was calculated for each participant. Chronic comorbidities were assessed using the Charlson Comorbidity Index (CCI) [12], which consists of 19 items, each corresponding to a different medical condition with a weighted score: myocardial infarction (1-point); congestive heart failure (1-point); peripheral vascular disease (1-point); cerebrovascular disease (1-point); dementia (1-point); chronic obstructive pulmonary disease (1-point); connective tissue disease (1-point); peptic ulcer disease (1-point); liver disease (mild: 1-point; moderate to severe: 3-points); diabetes (1-point); hemiplegia (2-points); moderate to severe chronic kidney disease (2-points); solid tumor (localized: 2-points; metastatic: 6-points); leukemia (2-points); malignant lymphoma (2-points; acquired immune deficiency syndrome (6-points). C-Reactive Protein (CRP) blood levels were obtained at hospital admission. The risk of multiorgan failure and mortality was assessed with a standardized Subsequent Organ Failure Assessment (SOFA) score [13]. We further recorder each patient's smoking habits.

Psychiatric assessment. At the admission, diagnoses of a mental disorder were recorded and grouped by International Classification of Diseases – 10th (ICD-10) revision as follows: Organic Disorders (OD) (ICD-10 F00-F09); Substance Use Disorders (SUD) (F10-F19); Schizophrenia Spectrum Disorders (SSD) (ICD-10 F20-F29); Mood Disorders (MD) (ICD-10 F30-F39); Neurotic Disorders (ND) (ICD-10 F40-F48); Personality Disorders (PD) (ICD-10 F60-F69); and Intellectual Disabilities (ID) (ICD-10 F70-F79). Diagnoses were retrieved from the clinical records. Patients did not receive any structured psychiatric assessment. A list of all regularly taken medications was obtained directly from the patient or a reliable family member or caregiver for each participant at admission, including first-generation antipsychotics (FGA), second-generation antipsychotics (SGA), antidepressants (AD), benzodiazepines (BDZ), mood stabilizers (MS), and z-drugs (ZD) (Supplemental Table 1).

A leakage study aimed to verify preexisting diagnoses of psychiatric disorders was performed using the electronic medical registry of the Department of Mental Health and Pathological Addiction of the Bologna Local Health Authority.

Outcome. The main outcomes were 30-day discharge and mortality following hospital admission. Time to event was calculated from hospitalization to death or discharge, whichever came first.

2.3. Missing data

Missing values were imputed via the "missRanger" package of R [14], which can handle both continuous and categorical missing variables using random forest models [15,16]. This method was found to offer good performance and the lowest imputation error when compared to other popular imputation techniques, such as multiple imputation by chained equations (MICE) and the nearest neighbour estimation [17]. In our study, the imputed values were closely aligned with the observed values for both continuous (normalized root mean squared error = 0.017) and categorical variables (proportion of falsely classified = 0.007).

2.4. Statistical analyses

Baseline sociodemographic, clinical, and psychiatric characteristics of participants were analyzed according to death during the hospitalization. Descriptive statistics (*t*-tests and χ^2) were conducted as appropriate to compare the different groups (survivors vs non-survivors).

Crude mortality rates were estimated for the total sample and stratified for gender and age bands. Mortality rates per 1000 person-days are reported along with 95% confidence intervals.

We used competing risk survival analysis to compare rates of 30-day death or discharge stratifying study participants by exposure to the different psychotropic medications prior to hospitalization taking into account the time-to-event. First, as univariate analyses, we estimated cumulative incidence functions (CIFs) and used Gray's test to compare equality of CIF curves across subgroups of interest (exposed vs non-exposed to the different classes of psychotropic medications) [18,19]. Then, we estimated cause-specific Hazard Ratios (HR) using Cox regression. The violation of the proportionality assumption was checked through Schoenfeld residuals evaluation [20] (*Supplemental Tables 2–3*). Separate models were fitted using either day-30 mortality or discharge as dependent variables and exposure to each class of psychotropic drugs (non-exposed = 0, exposed = 1) as independent variable. Only the psychotropic drugs that had a significant effect (as per Gray's test) on the CIF curves were added to the model. We further adjusted for age (continuous), sex (female = 0, male = 1), CCI, CRP levels, obesity (no = 0, yes = 1), history of smoking (no = 0, yes = 1), SOFA score, number of prescribed psychotropic drugs, having a baseline diagnosis of any psychiatric disorder (no = 0, yes = 1), and study period (first wave: March 2020–September 2020; second wave: October 2020–January 2021). Age, CCI, CRP, and SOFA score were categorized in quartiles for the regression analyses. The choice of covariates was made a priori based on

present literature and on consultation with experts. Variance Inflation Factors (VIF) were estimated to check for multicollinearity (*Supplemental Tables 4–5*). Survival analyses were performed using the "stcox" command of Stata 17, while the CIF curves were plotted using the ad-hoc R function "CumIncidence" provided by Scrucca et al. [19].

Sensitivity analyses were conducted on complete cases only for the main outcomes (*Supplemental Table 6*). To further test the robustness of our findings and control for hypothetical indication bias, we fitted additional Cox regression models including: a) all individual psychiatric disorders associated with both outcomes or with prescription of antipsychotics (*Supplemental Table 10*); and b) all individual psychiatric disorders and all individual antipsychotic drugs for which there were at least 5 outcome events (to avoid zero cells) (*Supplemental Table 13*). Univariate associations were detected analyzing Standardized Mean Differences (SMD).

Analyses were performed using RStudio R version 4.1.1 (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/) and Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Analyses were conducted following imputation of missing values.

The strengthening the reporting of observational studies in epidemiology (STROBE) checklist [21] is included in *Supplementary Materials*.

3. Results

3.1. Study population

A total of 2371 individuals were hospitalized in the study period (March 2020–January 2021) at the University Hospital Policlinico Sant'Orsola Malpighi of Bologna for COVID-19. 1246 patients were recruited for the present study (participation rate = 52.6%). Eight individuals were excluded because information on either date of hospital admission or date of death/discharge was missing. This resulted in a sample of 1238 patients. In the final sample, complete data were available for 1042 participants (84.2%). The proportion of missing covariate data was generally low, ranging from 1 (0.1%) on age to 127 (10.3%) on smoking history. The distribution of study covariates in the non-imputed sample along with the proportion of missing for each variable is shown in *Supplementary Materials*.

The final sample included 755 males (61.0%) and 483 females (39.0%), which were followed for an average time of 12.9 ± 8.8 days and a total 23,092 person-days at risk. Mean age was 68.1 ± 16.4 years, with females being significantly older (70.4 ± 17.0 years) than males (66.6 ± 15.8 years) at the admission (F = 2.62, $p < 0.001$).

In our sample, mortality rate was of 14.1 (95%CI = 12.5–16.0) per 1000 person-days; it was slightly greater for females (14.5, 95%CI = 11.9–17.7) than males (14.0, 95%CI = 12.0–16.2). The mortality rate increased along with age, ranging from 2.7 per 1000 person-days (95% CI = 1.1–6.5) in the 18–49 age group to 55.5 per 1000 person-days (95% CI = 42.6–72.3) among those aged 90 or more (Table 1).

3.2. Psychiatric assessment at the admission

At the admission, 320 (25.8%) out of 1238 patients had a diagnosis of a psychiatric disorder. The majority had a diagnosis of OD ($n = 154$, 12.4%) and MD ($n = 115$, 9.3%). Other diagnoses were ND ($n = 77$, 6.2%), SSD ($n = 13$, 1.1%), ID ($n = 17$, 1.4%), SUD ($n = 16$, 1.3%), and PD ($n = 10$, 0.8%).

Among individuals admitted, 316 (25.5%) were treated with a psychotropic medication: 182 (14.7%) were taking AD; 137 (11.1%) BDZ; 66 (5.3%) SGA; 50 (4.0%) MS; 45 (3.6%) FGA; and 15 (1.2%) ZD.

Among patients with a baseline diagnosis of a psychiatric disorder ($N = 320$), 261 (81.6%) were on a psychotropic drug and 59 (18.4%) were not taking any medication. Only a small proportion of patients ($N = 55$, 6.0%) without any psychiatric disorder was on a psychotropic drug at the admission.

Patients exposed to psychotropic drugs were more likely to be females ($N = 176$, 55.7% vs males $N = 140$, 44.3%; $\chi^2 = 49.63$; $p < 0.001$) and less likely to report obesity ($N = 41$, 13.0% vs non-obese $N = 275$, 87.9%; $\chi 2 = 7.09$; $p = 0.008$) compared with those non-exposed. They were older (76.9 ± 14.9 vs 65.0 ± 15.8; F = 3.08; $p < 0.001$), had a higher number of comorbidities (5.4 ± 2.7 vs 3.3 ± 2.6; F = 0.19; $p < 0.001$) and a worse clinical presentation as indicated by higher SOFA score (2.7 ± 1.7 vs 2.2 ± 1.6; F = 3.5; $p < 0.001$) (Table 2).

Table 1
Crude mortality rates by the end of the study period.

	All patients	Person-time (days)	No. deaths	Mortality rate per 1000 p-d (95%CI)
	N (%)	N	N	
Total	1238 (100%)	18,598	263	14.1 (12.5–16.0)
Sex				
Males	755 (61.0%)	11,966	167	14.0 (12.0–16.2)
Females	483 (39.0%)	6632	96	14.5 (11.9–17.7)
Age				
18–49	182 (14.7%)	1851	5	2.7 (1.1–6.5)
50–59	203 (16.4%)	2886	12	4.2 (2.4–7.3)
60–69	236 (19.1%)	4288	38	8.9 (6.4–12.2)
70–79	261 (21.1%)	4604	66	14.3 (11.3–18.2)
80–89	256 (20.7%)	3978	87	21.9 (17.7–27.0)
≥90	100 (8.1%)	991	55	55.5 (42.6–72.3)

p-d = person-days; 95%CI = 95% confidence interval.

Table 2
Comparison of patients non-exposed vs exposed to psychotropic drugs.

	Non-exposed	Exposed	Total	X^2/F (p)
	N (%)	N (%)	N (%)	
	Sociodemographic			
Sex				**49.63 (<0.001)[a]**
Males	615 (66.7%)	140 (44.3%)	755 (61.0%)	
Females	307 (33.3%)	176 (55.7%)	483 (39.0%)	
Age[c]	65.0 ± 15.8	76.9 ± 14.9	68.1 ± 16.4	**3.08 (<0.001)[b]**
	Co-morbidity			
Obesity				**7.09 (0.008)[a]**
No	741 (80.4%)	275 (87.0%)	1016 (82.1%)	
Yes	181 (19.6%)	41 (13.0%)	222 (17.9%)	
Charlson co-morbidity index[c]	3.3 ± 2.6	5.4 ± 2.7	3.8 ± 2.8	**0.19 (<0.001)[b]**
Smoking				1.82 (0.177)[a]
No	728 (79.0%)	238 (75.3%)	966 (78.0%)	
Yes	194 (21.0%)	78 (24.7%)	272 (22.0%)	
	Clinical presentation			
SOFA score[c]	2.2 ± 1.6	2.7 ± 1.7	2.3 ± 1.7	**3.5 (<0.001)[b]**
CRP[c]	8.0 ± 6.9	7.9 ± 7.2	8.1 ± 7.1	0.02 (0.856)[b]

[a]Pearson's chi-squared test; [b]t-test; [c]mean ± DS; SOFA = Sequential Organ Failure Assessment; CRP = c-reactive protein.

3.3. Comparison of survivors vs non-survivors

Out of 1238 patients admitted to COVID-19 wards, 263 (21.2%) died during the hospitalization. Of these, 167 were men (61.0%) and 96 were women (39.0%). In contrast, 588 men (60.3%) and 387 women (39.7%) survived, for a total of 975 patients (78.8%). The mean age of surviving patients was 65.1 ± 16.1 years, significantly lower than the one of deceased patients, which was 79.2 ± 12.0 years ($F = 36.43$, $p < 0.001$). The proportion of individuals with obesity was significantly higher among deceased patients ($n = 61$, 23.2%) than in survivors ($n = 161$, 16.5%) ($\chi^2 = 6.28$; $p = 0.012$). Smoking was significantly more prevalent among deceased patients ($n = 72$, 27.4%) than among survivors ($n = 200$, 20.5%) ($\chi^2 = 5.69$; $p = 0.017$).

The Charlson co-morbidity index was higher among deceased individuals (3.4 ± 2.7) compared with survivors (5.6 ± 2.4) ($F = 7.60$, $p = 0.006$).

About psychiatric comorbidities, deceased patients ($n = 71$, 27.0%) showed more frequently an organic-based cognitive impairment than survivors ($n = 83$, 8.5%) ($\chi^2 = 64.97$, $p < 0.001$). The presence of other psychiatric disorders, instead, did not vary significantly between the 2 groups.

Patients who died were more frequently taking FGA ($n = 24$, 9.1% vs $n = 21$, 2.2%; $\chi^2 = 17.08$, $p < 0.001$) or SGA ($n = 32$, 12.2% vs $n = 34$, 3.5%; $\chi^2 = 29.51$, $p < 0.001$) antipsychotics than survivors. Deceased patients ($n = 41$, 15.6%) were also more frequently on chronic BDZ therapy than non-deceased patients ($n = 96$, 9.8%) ($\chi^2 = 6.94$, $p = 0.008$).

Regarding the clinical presentation, the SOFA score of the deceased patients was significantly higher than the one of the survivors (3.7 ± 1.9 vs 1.9 ± 1.4; $F = 41.95$, $p < 0.001$); similarly, the blood levels of CRP was significantly higher in the deceased patients compared with survivors (11.6 ± 7.8 vs 7.0 ± 6.4; $F = 13.54$, $p < 0.001$) (Table 3).

3.4. Survival analysis

All psychotropic medications, except for MS and ZD, were associated with significantly increased probability of 30-day death as well as with decreased probability of 30-day discharge (Fig. 1). The strongest associations with mortality were found for antipsychotics, with patients exposed to FGA (exposed = 0.51 vs unexposed = 0.18; Gray's test = 36.2, $p < 0.001$) and to SGA (exposed = 0.47 vs unexposed = 0.18; $p < 0.001$; Gray's test = 36.2, $p < 0.001$) having higher probability of death. Regarding discharge rates, FGA (exposed = 0.40 vs unexposed = 0.70; $p < 0.001$; Gray's test = 9.43) and SGA (exposed = 0.42 vs unexposed = 0.71; $p < 0.001$; Gray's test = 20.25) were the class more strongly associated with reduced probability of recovery.

In multivariate analysis (Table 4), among psychotropic drugs, exposure to SGA was associated with a 2-fold increase in HR of 30-day mortality (HR = 2.01, 95%CI = 1.02–3.97; $p = 0.044$) while exposure to FGA was associated with decreased HR of 30-day discharge (HR = 0.55, 95%CI = 0.33–0.90; $p = 0.017$). The other psychotropic drugs were not associated with any outcome. Having a diagnosis of a psychiatric disorder did not increase HR of 30-day mortality nor affected 30-day discharge. Among covariates, scoring higher on SOFA and having higher levels of CRP at admission were significantly associated with all outcomes. Older age and obesity were associated with increased HR of 30-day mortality. Male sex was associated with decreased HR of 30-day discharge.

3.5. Sensitivity analyses

Multivariate Cox regression models were repeated on the complete-case sample ($N = 1042$). Results were similar to imputed analyses (*Supplemental Table 6*). In analyses adjusted for all individual psychiatric disorders associated with each outcome or with antipsychotics prescription, both SGA (HR = 2.10, 95%CI = 1.42–3.11; $p < 0.001$) FGA

Table 3
Comparison of survivors vs non-survivors.

	Survivor	Non-survivor	Total	X^2/F (p)
	N (%)	N (%)	N (%)	
	Sociodemographic			
Sex				0.89 (0.347)[a]
Males	588 (60.3%)	167 (63.5%)	755 (61.0%)	
Females	387 (39.7%)	96 (36.5%)	483 (39.0%)	
Age[c]	65.1 ± 16.1	79.2 ± 12.0	68.1 ± 16.4	**36.43 (<0.001)[b]**
	Co-morbidity			
Obesity				**6.28 (0.012)[a]**
No	814 (83.5%)	202 (76.8%)	1016 (82.1%)	
Yes	161 (16.5%)	61 (23.2%)	222 (17.9%)	
Charlson co-morbidity index[c]	3.4 ± 2.7	5.6 ± 2.4	3.8 ± 2.8	**7.60 (0.006)[b]**
Smoking				**5.69 (0.017)[a]**
No	775 (79.5%)	191 (72.6%)	966 (78.0%)	
Yes	200 (20.5%)	72 (27.4%)	272 (22.0%)	
	Psychiatric comorbidity			
Pre-existing diagnosis				
Organic Disorder				**64.97 (<0.001)[a]**
No	892 (91.5%)	192 (73.0%)	1084 (87.6%)	
Yes	83 (8.5%)	71 (27.0%)	154 (12.4%)	
Substance Use Disorder				2.18 (0.140)[a]
No	960 (98.5%)	262 (99.6%)	1222 (98.7%)	
Yes	15 (1.5%)	1 (0.4%)	16 (1.3%)	
Schizophrenia Spectrum Disorder				0.03 (0.871)[a]
No	965 (99.0%)	260 (98.9%)	1225 (98.9%)	
Yes	10 (1.0%)	3 (1.1%)	13 (1.1%)	
Mood Disorder				2.47 (0.116)[a]
No	891 (91.4%)	232 (88.2%)	1123 (90.7%)	
Yes	84 (8.6%)	31 (11.8%)	115 (9.3%)	
Neurotic Disorder				0.58 (0.447)[a]
No	917 (94.1%)	244 (92.8%)	1161 (93.8%)	
Yes	58 (5.9%)	19 (7.2%)	77 (6.2%)	
Personality Disorder				0.76 (0.383)[a]
No	966 (99.1%)	262 (99.6%)	1228 (99.2%)	
Yes	9 (0.9%)	1 (0.4%)	10 (0.8%)	
Intellectual Disability				0.69 (0.407)[a]
No	963 (98.8%)	258 (98.1%)	1221 (98.6%)	
Yes	12 (1.2%)	5 (1.9%)	17 (1.4%)	
Psychotropic treatment at admission				
Antidepressant				2.68 (0.102)[a]
No	840 (86.2%)	216 (82.1%)	1056 (85.3%)	
Yes	135 (13.8%)	47 (17.9%)	182 (14.7%)	

(*continued on next page*)

Table 3 (*continued*)

	Survivor	Non-survivor	Total	X^2/F (p)
First-generation Antipsychotic				**28.74 (<0.001)[a]**
No	954 (97.8%)	239 (90.9%)	1193 (96.4%)	
Yes	21 (2.2%)	24 (9.1%)	45 (3.6%)	
Second-generation Antipsychotic				**30.92 (<0.001)[a]**
No	941 (96.5%)	231 (87.8%)	1172 (94.7%)	
Yes	34 (3.5%)	32 (12.2%)	66 (5.3%)	
Benzodiazepine				**6.94 (0.008)[a]**
No	879 (90.2%)	222 (84.4%)	1101 (88.9%)	
Yes	96 (9.8%)	41 (15.6%)	137 (11.1%)	
Mood Stabilizer				0.70 (0.401)[a]
No	938 (96.2%)	250 (95.1%)	1188 (96.0%)	
Yes	37 (3.8%)	13 (4.9%)	50 (4.0%)	
Z-Drug				1.33 (0.249)[a]
No	965 (99.0%)	258 (98.1%)	1223 (98.8%)	
Yes	10 (1.0%)	5 (1.9%)	15 (1.2%)	
Clinical presentation				
SOFA score[c]	1.9 ± 1.4	3.7 ± 1.9	2.3 ± 1.7	**41.95 (<0.001)[b]**
CRP[c]	7.0 ± 6.4	11.6 ± 7.8	8.1 ± 7.1	**13.54 (<0.001)[b]**

[a]Pearson's chi-squared test; [b]t-test; [c]mean ± DS; SOFA = Sequential Organ Failure Assessment; CRP = c-reactive protein.

(HR = 0.68, 95%CI = 0.46–1.00; $p = 0.05$) exposure were still associated with worse outcomes (*Supplemental Table 10*). Regarding individual drugs, we found some evidence, though not robust, of an association between olanzapine (HR = 1.90, 95%CI = 0.97–3.70; $p = 0.06$) and quetiapine (HR = 1.57, 95%CI = 0.99–2.47; $p = 0.054$) and 30-day mortality (*Supplemental Table 13*).

4. Discussion

In univariate analyses, we found that COVID-19 patients with ongoing psychotropic treatment were at higher risk of 30-day death and decreased probability of 30-day recovery after hospitalization. However, in multivariate analysis, only APs among psychotropic drugs were associated with worse outcomes. Specifically, FGA were associated with decreased HR of 30-day discharge and SGA were associated with greater risk of 30-day death.

In our sample, overall mortality rate was of 14.1 (95%CI = 12.5–16.0) per 1000 person-days. Rates increased along with age, being as low as 2.7 per 1000 person-days (95%CI = 1.1–6.5) in the 18–49 age group and 55.5 per 1000 person-days (95%CI = 42.6–72.3) among those aged 90 or older. About 25% of the individuals admitted had a diagnosis of a psychiatric disorder, which in most cases was OD ($n = 154$, 12.4%) or MD ($n = 115$, 9.3%). A similar proportion of the sample was receiving a psychotropic treatment. The more commonly prescribed drugs were AD ($n = 182$, 14.7%) and BDZ ($n = 137$, 11.1%), while only a smaller proportion of patients were assuming FGA ($n = 45$, 3.6%) or SGA ($n = 66$, 5.3%).

4.1. Strengths and limitations

This a naturalistic, prospective cohort study and the major limitations belong to the study design. The group of patients included was heterogeneous regarding age, comorbidities, and psychiatric diagnoses. However, we adjusted for all the main confounders (age, gender, obesity, comorbidities, smoking, severity of clinical presentation, CRP levels) to test the association between exposure to psychotropic drugs and outcomes. Multiple imputation of missing values was undertaken to minimize loss of precision or selection biases and a sensitivity analysis on the complete-case sample was conducted to examine robustness of findings. We did not have information on the vaccination status of the recruited patients. However, considering that the vaccination campaign in Italy started on the 31st of December 2020 and that we stopped recruiting patients on the 31st of January 2021, it is unlikely that our results may have been biased by the vaccination status. We acknowledge that extending the period of recruitment may have allowed us to evaluate the effect of vaccines and to increase the statistical power of the study. Prior research suggests that psychotropic medications inhibiting the acid sphingomyelinase activity, such as fluvoxamine or chlorpromazine, may have dose-depending beneficial effects on COVID-19. Based on our results of a considerable association between antipsychotics and worse outcomes of COVID-19 infection, we performed sensitivity analyses to test the effect of individual antipsychotics while adjusting for psychiatric diagnoses (to account for indication bias). We found limited evidence of an association between olanzapine and quetiapine and 30-day mortality even though the threshold of significance ($p \leq 0.05$) was not reached. The failure to detect a significant association may be due to limited sample size, which prevented us from testing individual psychotropic compounds with different pharmacokinetic and pharmacodynamic profiles. Similarly, we could not investigate for the effect of different doses.

All data were entered in an anonymized electronic database. We conducted a leakage study using the informatic system of the local mental health service to maximize accuracy of data collection on psychiatric morbidity and prescriptions. Nevertheless, we could not test duration of exposure and adherence to treatment prior to the hospitalization. Furthermore, in this study, we only used baseline (i.e., at the time of the admission) information on psychotropic drugs which were regularly taken at home, thus not considering the possible effects of medication changes during the hospitalization.

Finally, our results were based on a single center experience and only severely ill patients (i.e., those requiring hospitalization) were included, limiting the degree of generalizability of our findings.

4.2. Comparison with previous literature

Several studies replicated the finding that patients with a mental disorder have greater mortality rates following COVID-19 infection compared with COVID-19 patients without mental disorders [22,23]. Interestingly, a recent large cross-sectional study showed the risk of death differed depending on the specific disorder, being the highest in patients with schizophrenia (OR = 3.74; 95%CI = 2.66–5.24), followed by those with mood disorders (OR = 2.76, 95%CI = 2.00–3.81) and anxiety disorders (OR = 2.39, 95%CI = 1.68–3.27) [23]. A recent meta-analysis [2] confirmed the finding that, among psychiatric disorders, psychotic and mood disorders present the most robust association with COVID-19 mortality, suggesting that these patients might carry an especially higher risk. Many factors could account for the increased mortality. Compared with the general population, individuals suffering with mental disorders are more likely to use tobacco [24,25] or other substances [26] and to have medical comorbidities [27] (e.g., metabolic syndrome or cardiovascular diseases), both associated with higher risk of severe COVID-19 illness. Furthermore, it has been recognized that inflammation is involved in the pathogenesis of both several mental disorders [28–30] and COVID-19 manifestations [31].

In our study, APs were associated with worse COVID-19 infection outcomes independently of the underlying psychiatric disorder (and of other potentially relevant confounders). This finding suggests that exposure to APs, could at least partly explain the association between

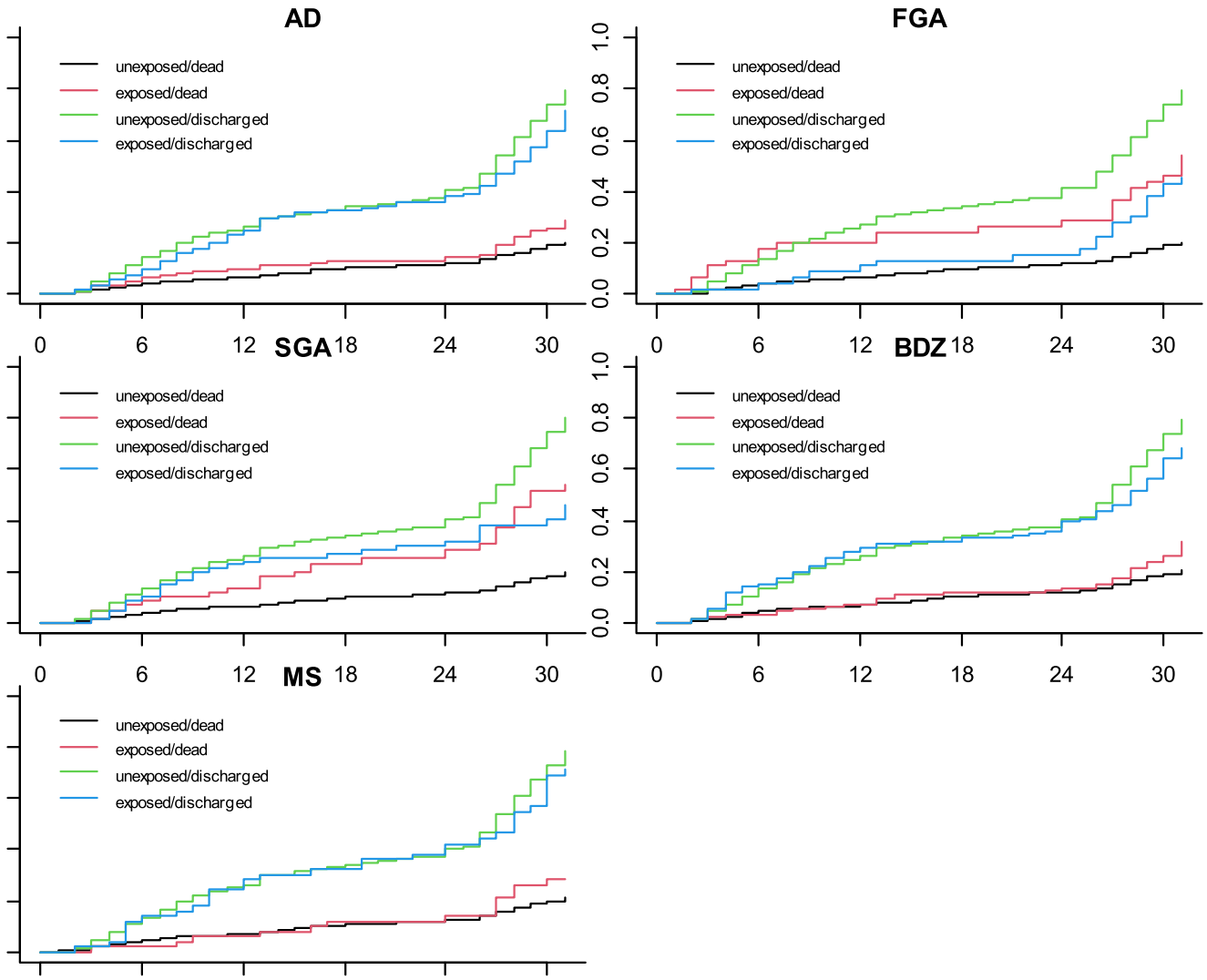

Fig. 1. Plot of Cumulative Incidence Functions for mortality and discharge by day 30.
AD = antidepressants; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics; BDZ = benzodiazepines; MS = mood stabilizers.

psychiatric disorders and COVID-19 mortality or worse prognosis. Several reasons could support this association, including: 1) pharmacokinetic and pharmacodynamic interactions with medical treatments for COVID-19 (especially risk of QTc prolongation) [32]; 2) increased risk of serious cardiovascular events [33] or respiratory distress [34], which could be even higher in presence of high dosages [35], combination of APs [36,37], and/or pre-existing pulmonary conditions [38]; 3) increased risk of pneumonia [39] or other infections [34] caused by AP-induced immunity abnormalities (e.g., neutropenia) [40,41] or reduction of airways clearance due to central sedation [42]; 4) increased risk of thromboembolism [33]. Nevertheless, prior studies on this subject have yielded conflicting evidence. In line with our results, a meta-analysis [2] of three studies [43–45] showed that pooled risk of mortality for those on AP was 2-times higher compared with those unexposed (adjusted OR = 2.43, 95%CI = 1.81–3.25). The estimates accounted for age in all three studies and for comorbidities in two of them. Conversely, a study conducted in New York [46] did not find evidence of an association between AP treatment and COVID-19 mortality (adjusted OR = 1.00, 95%CI = 0.48–2.08) within 60 days from diagnosis. However, Nemani et al. [46] limited their analyses to individuals affected by severe mental disorders (i.e., schizophrenia, schizoaffective disorder and bipolar disorder). In the case of severe mental disorders, AP treatment, by treating symptoms of the specific disorder or preventing relapses, may reduce rates of COVID-19 infection and mortality by indirectly increasing adherence to healthcare recommendations, as suggested by other studies in these population groups [47,48].

APs are licensed for psychotic and bipolar disorders, but their use off-label for other mental conditions (e.g., depression, dementia or obsessive-compulsive disorder) has increased over the years, especially since SGAs were introduced. In England, for instance, during the COVID-19 pandemic there was a substantial increase in the prescription of AP to people with dementia [49]. In our sample, APs were mostly prescribed to individuals with organic-based neurocognitive disorders, who are among the most vulnerable populations to the consequences of COVID-19 infection. Nevertheless, our analyses showed that exposure to AP was associated with greater chances of mortality independently of relevant confounders such as age or comorbidities (including dementia).

Finally, in multivariate analyses we did not find any evidence of an association between use of AD or BDZ and course of COVID-19 infection. There is common agreement that BDZ should be avoided in patients with COVID-19, especially in elderly patients with multiple comorbidities, due to risk of respiratory impairment [7]. On the other hand, there is evidence of a lower risk of death associated with several ADs [50,51].

Table 4
Cause-specific hazard ratios.

	Death (day 30)	Discharge (day 30)
	HR (95%CI)	HR (95%CI)
Age		
1st quartile	Ref	Ref
2nd quartile	1.94 (0.99–3.80)	0.91 (0.76–1.10)
3rd quartile	**3.34 (1.56–7.13)**	1.08 (0.83–1.41)
4th quartile	**3.37 (1.55–7.30)**	0.86 (0.63–1.16)
Sex (female)	0.96 (0.72–1.27)	**1.16 (1.01–1.32)**
Obesity	**1.42 (1.04–1.95)**	0.92 (0.77–1.10)
Charlson co-morbidity index		
1st quartile	Ref	Ref
2nd quartile	0.88 (0.44–1.77)	1.08 (0.85–1.37)
3rd quartile	1.32 (0.71–2.45)	0.90 (0.69–1.15)
4th quartile	1.41 (0.74–2.68)	0.82 (0.61–1.12)
Smoking	1.21 (0.91–1.61)	0.98 (0.93–1.15)
SOFA score		
1st quartile	Ref	Ref
2nd quartile	1.54 (0.89–2.66)	0.97 (0.83–1.13)
3rd quartile	**2.51 (1.58–3.99)**	0.92 (0.75–1.13)
4th quartile	**2.81 (1.78–4.44)**	**0.60 (0.46–0.77)**
CRP		
1st quartile	Ref	Ref
2nd quartile	1.24 (0.72–2.12)	**0.84 (0.72–1.00)**
3rd quartile	**2.51 (1.58–3.99)**	0.86 (0.72–1.02)
4th quartile	**2.81 (1.78–4.44)**	**0.64 (0.52–0.78)**
Antidepressant	0.85 (0.43–1.68)	0.88 (0.62–1.26)
First-generation antipsychotic	1.32 (0.63–2.75)	**0.55 (0.33–0.90)**
Second-generation antipsychotic	**2.01 (1.02–3.97)**	0.71 (0.43–1.27)
Benzodiazepine	1.03 (0.61–1.73)	0.78 (0.54–1.13)
N. of psychotropic drugs	1.03 (0.61–1.73)	1.20 (0.92–1.58)
Any psychiatric disorder	0.80 (0.53–1.20)	0.80 (0.63–1.01)
Study period		
First wave	Ref	Ref
Second wave	0.89 (0.68–1.15)	1.12 (0.99–1.28)

SOFA = Sequential Organ Failure Assessment; CRP = c-reactive protein. Hazard ratios in **bold** are statistically significant at 0.05 level.

5. Conclusion

This study adds evidence on the possible risks related to the prescription of AP in the context of the COVID-19 outbreak. Clinicians should be aware that some patients present a considerable degree of vulnerability and minimize off-label use of AP or adjust drugs posology to the lowest effective dosage and addressing comorbidities and unhealthy habits. This is especially relevant when treating frail patients, such as elder with a diagnosis of dementia.

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Declaration of Competing Interest

The authors have no competing interests to report.

Appendix A. Supplementary data

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