



Mental disorders, psychopharmacological treatments, and mortality in 2150 COVID-19 Spanish inpatients

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Abstract

Objective: To determine how mental disorders and psychopharmacological treatments before and during COVID-19 hospital admissions are related to mortality.

Methods: Subjects included in the study were all adult patients with a diagnosis of COVID-19, confirmed clinically and by PCR, who were admitted to a tertiary university hospital in Badalona (Spain) between March 1 and November 17, 2020. Data were extracted anonymously from computerized clinical records.

Results: 2,150 subjects were included, 57% males, mean age 61 years. History of mental disorders was registered in 957 (45%). Throughout admission, *de novo* diagnosis of mood or anxiety, stress, or adjustment disorder was made in 12% of patients without previous history. Delirium was diagnosed in 10% of cases. 1011 patients (47%) received a psychotropic prescription during admission (36% benzodiazepines, 22% antidepressants, and 21% antipsychotics). Mortality rate was 17%. Delirium during admission and history of mood disorder were independently associated with higher mortality risk (hazard ratios, 1.39 and 1.52 respectively), while previous year's treatments with anxiolytics/hypnotics and antidepressants were independently associated with lower mortality risk (hazard ratios, 0.47 and 0.43, respectively).

Conclusion: Mental symptoms are very common in patients hospitalized for COVID-19 infection. Detecting, diagnosing, and treating them is key to determining the prognosis of the disease and functional recovery.

KEY WORDS

COVID-19, depressive disorder, delirium, psychopharmacology, mortality

Significant outcomes

- Mental disorders (depressive disorders, anxiety, stress and adjustment disorders, and delirium) are highly prevalent in COVID-19 inpatients.
- COVID-19 inpatients frequently receive psychopharmacological treatments (antidepressants, antipsychotics, and benzodiazepines) during admission.

- Both mental disorders and pharmacological treatments are independently associated with mortality, in different senses, and must therefore be considered in the management of the disease.

Limitations

- Study patients were those admitted to a tertiary hospital facility, so they may not be representative of the total COVID-19 patient population.
- Neither we were able to make a systematic mental status evaluation of patients because of the healthcare pressure and the protection and isolation needs of patients and professionals; therefore, diagnoses were clinically based, with no assessments of severity.
- The analyses were retrospective.

1 | INTRODUCTION

The disease caused by the infection with the new coronavirus SARS-CoV-2 (COVID-19) first appeared in Wuhan, China, and quickly spread throughout the world,¹ being declared a pandemic by the World Health Organization on March 11, 2020. As of February 12, 2021, there have been more than 107 million people infected and 2.3 million have died,^{2,3} and the numbers continue to rise. Past epidemics of respiratory viruses have been associated with high rates of psychiatric morbidity, and COVID-19 is not likely to be an exception.⁴ In fact, there is growing evidence of this association.⁵ However, much more attention has been paid so far to mental health problems in the general population, healthcare workers, or among COVID-19 survivors⁶ than in critically ill hospitalized patients. In the hospital setting, the workload assumed by liaison psychiatric units has been particularly important, posing challenges for proper clinical management of psychopathological conditions associated with COVID-19, especially anxiety and depressive disorders, insomnia, and delirium. These psychiatric complications need to be quickly and effectively treated, with different psychopharmacological options put on the table (anxiolytics, antidepressants, and antipsychotics). However, it is largely unknown what may be the effects of these drugs, and of the psychiatric disorders themselves, on the evolution and prognosis of infection.

1.1 | Aims of the study

In this observational study, we planned to assess the association of psychiatric morbidity and the use of psychotropic drugs with mortality in COVID-19 inpatients.

2 | MATERIAL AND METHODS

2.1 | Subjects

Study subjects were all adult patients with a positive result for the SARS-CoV-2 polymerase chain reaction (PCR) who were admitted to a tertiary university hospital in Badalona (Spain) throughout the period between March 1 and November 17, 2020. All procedures contributing to this work complied with the ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures were approved by Germans Trias i Pujol Hospital Research Ethics Committee. Informed consent was not collected as this was a retrospective study, and all data were extracted anonymously from computerized records.

2.2 | Data collection

The hospital's Information Systems Department anonymously extracted patients' computerized clinical data from several hospital-based and primary care-based platforms. Data included demographics; previous year medical, psychiatric, and medication history; and medical and pharmacological data during hospital admission. Psychiatric diagnoses were registered according to ICD-10 classification criteria. The presence of delirium was classified in a clinical basis, in compliance with the criteria of the Confusion Assessment Method (CAM) tool: acute onset, inattention, impaired consciousness, disorganized thinking, and fluctuating course.⁷ Death outcomes were also extracted from official databases, considering death for any cause, both during admission and after discharge, before December 17, 2020.

2.3 | Analyses

A binary logistic regression model was built to estimate multivariate associations with *de novo* diagnosis of mood or anxiety-stress-adjustment disorders during admission. The analysis was applied to the group of patients with no previous history of these disorders. Independent variables included in the analysis were sex; age; history of chronic medical conditions during the year prior to admission if present in more than 5% of the patients (dyslipidemia, obesity [$>30 \text{ kg/m}^2$], arterial hypertension, type 1 or 2 diabetes mellitus, ischemic heart disease, chronic renal failure, atrial fibrillation, malignancies [including lymphoproliferative], chronic obstructive pulmonary disease, sleep apnea/hypopnea syndrome, chronic heart failure, valvular disease, bronchial asthma, and cerebrovascular disease); history of psychiatric disorders during the year prior to admission (cognitive disorder and alcohol use disorder); medical complications during admission (bilateral viral pneumonia, acute respiratory failure, cardiac arrhythmias, acute kidney failure, and pulmonary embolism); treatments for COVID-19 during admission (antimalarial, glucocorticoids, antibiotics, antivirals, tocilizumab, and beta-interferon); ICU or semi-critical unit admission; and length of hospital stay.

A second binary regression logistic model was built to estimate multivariate associations with mortality. In addition to the above independent variables, the following were also included in the analysis: history of mood disorders, history of anxiety-stress-adjustment disorders, history of treatments with antidepressants and anxiolytics/hypnotics during the previous year, complications during admission with delirium or mood or anxiety-stress-adjustment disorders, and treatment during admission with antidepressants, benzodiazepines, or antipsychotics.

Finally, a multivariate Cox proportional hazard model of the survival analysis was used to assess the association of psychiatric disorders and psychotropic drugs with mortality, including all previous independent variables. A two-sided p value of <0.05 was considered significant for all analyses, which were performed using IBM SPSS Statistics 22.0.0 for Windows (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Population's characteristics

A total of 2150 COVID-19 adult inpatients were admitted to the hospital during the study period. 1,228 were male (57.1%), mean age 61.3 years (standard deviation [SD], 17.2). Table 1 shows the characteristics of the total sample as well as divided by sex. 308 patients (14.3%) required admission to an intensive care unit (ICU) for a mean of

17.0 days (SD, 19.1; highest, 112), and 457 (21.3%) to an ICU or semi-critical unit for a mean of 15.4 days (SD, 20.1; highest, 160).

3.2 | Psychiatric comorbidity

History of mental disorders during the year prior to admission was registered in 957 patients (44.5%): 649 patients (30.2%) had an anxiety-stress-adjustment disorder; 279 (13.0%) a mood disorder; 157 (7.3%) a cognitive disorder; 157 (7.3%) an alcohol use disorder; and 32 (1.5%) a psychotic disorder. Likewise, 298 patients (13.9%) had taken any psychotropic drug over the last year (174 [8.1%] benzodiazepines, 164 [7.6%] antidepressants, and 51 [2.4%] antipsychotics).

Throughout admission, 30 patients (1.4%) were diagnosed with a mood disorder and 527 (24.5%) with an anxiety-stress-adjustment disorder; 166 of them were *de novo* diagnosis (11.9% of the population without a previous history). Other 208 patients (9.7%) were diagnosed with delirium. A specific consultation with the psychiatry liaison unit was requested for 231 patients (10.7%).

Table S1 shows the binary logistic regression model of the *de novo* diagnosis of a mood or anxiety-stress-adjustment disorder. The following variables remained independently associated with a *de novo* diagnosis: lower prevalence of chronic pulmonary obstructive disease (Exp(B), 0.49; 95% CI, 0.25–0.95; $p = 0.04$), higher prevalence of previous atrial fibrillation (Exp(B), 5.60; 95% CI, 1.26–24.86; $p = 0.02$), treatment with glucocorticoids during admission (Exp(B), 1.96; 95% CI, 1.26–3.05; $p = 0.003$), admission to an ICU or semi-critical unit (Exp(B), 2.14; 95% CI, 1.34–3.41; $p = 0.001$), and longer length of hospital stay (Exp(B), 1.05; 95% CI, 1.04–1.06; $p < 0.001$) adjustment.

3.3 | Psychotropic drugs' prescriptions during admission

A total of 1011 patients (47.0%) received a psychotropic drug prescription during admission, and 767 of them were *de novo* prescriptions (41.4% of patients with no history of psychotropic treatments). Benzodiazepines were prescribed to 782 patients (36.4%), 668 of them *de novo* (32.8%), mainly lorazepam (536, 68.5%) and diazepam (267, 34.1%). Antidepressants were prescribed to 481 patients (22.4%), 370 of them *de novo* (18.1%), mainly mirtazapine (284, 59.0%) and SSRI (220, 45.7%). Finally, antipsychotics were prescribed to 452 patients (21.0%), 406 of them *de novo* (19.3%), mainly quetiapine (263, 58.2%) and haloperidol (231, 51.1%); 246 of these patients (54.4%) received antipsychotics in monotherapy.

TABLE 1 Characteristics of the total sample and divided by sex

	Total N = 2150	Females N = 922	Males N = 1228
Age (years), mean (SD) [†]	61.3 (17.2)	61.4 (18.9)	61.3 (15.8)
History of chronic medical conditions during the year prior to admission (>5% of patients)			
Any chronic medical condition, <i>n</i> (%)	1,703 (79.2)	731 (79.3)	972 (79.2)
Dyslipidemia, <i>n</i> (%)	1,023 (47.6)	431 (46.7)	592 (48.2)
Obesity (>30 kg/m ²), <i>n</i> (%)	939 (43.7)	462 (50.1)	477 (38.8)
Arterial hypertension, <i>n</i> (%)	894 (41.6)	385 (41.8)	509 (41.4)
Type 1 or 2 diabetes mellitus, <i>n</i> (%)	559 (26.0)	210 (22.8)	349 (28.4)
Ischemic heart disease, <i>n</i> (%)	360 (16.7)	121 (13.1)	239 (19.5)
Chronic renal failure, <i>n</i> (%)	326 (15.2)	96 (10.4)	230 (18.7)
Atrial fibrillation, <i>n</i> (%)	255 (11.9)	104 (11.3)	151 (12.3)
Malignancies, including lymphoproliferative, <i>n</i> (%)	233 (10.8)	82 (8.9)	151 (12.3)
Chronic obstructive pulmonary disease, <i>n</i> (%)	223 (10.4)	48 (5.2)	175 (14.3)
Sleep apnea/hypopnea syndrome, <i>n</i> (%)	202 (9.4)	62 (6.7)	140 (11.4)
Chronic heart failure, <i>n</i> (%)	164 (7.6)	77 (8.4)	87 (7.1)
Valvular disease, <i>n</i> (%)	163 (7.6)	72 (7.8)	91 (7.4)
Bronchial asthma, <i>n</i> (%)	154 (7.2)	97 (10.5)	57 (4.6)
Cerebrovascular disease, <i>n</i> (%)	148 (6.9)	61 (6.6)	87 (7.1)
Medical complications during admission (>5% of patients)			
Bilateral viral pneumonia, <i>n</i> (%)	1,822 (85.3)	725 (79.2)	1,097 (89.8)
Acute respiratory failure, <i>n</i> (%)	1,245 (58.3)	479 (52.3)	766 (62.7)
Cardiac arrhythmias, <i>n</i> (%)	234 (10.9)	96 (10.5)	138 (11.3)
Acute kidney failure, <i>n</i> (%)	125 (5.8)	32 (3.5)	93 (7.6)
Pulmonary embolism, <i>n</i> (%)	122 (5.7)	45 (4.9)	77 (6.3)
Treatments for COVID-19 during admission			
Antimalarial drugs (hydroxychloroquine or chloroquine), <i>n</i> (%)	1,069 (49.7)	440 (47.7)	629 (51.2)
Glucocorticoids, <i>n</i> (%)	1,015 (47.2)	368 (39.9)	647 (52.7)
Antibiotics, <i>n</i> (%)	864 (40.2)	337 (36.6)	527 (42.9)
Antivirals (darunavir, lopinavir/ritonavir, or remdesivir), <i>n</i> (%)	608 (28.3)	232 (25.2)	376 (30.6)
Tocilizumab, <i>n</i> (%)	256 (11.9)	75 (8.1)	181 (14.7)
Beta-interferon, <i>n</i> (%)	160 (7.4)	54 (5.9)	106 (8.6)
Mean length of hospital stay (days), mean (SD) [†]	14.0 (15.0)	12.2 (11.5)	15.4 (16.9)

[†]Standard deviation.

3.4 | Psychiatric comorbidity, psychotropic drugs, and mortality

Follow-up period for the assessment of vital status was closed on December 17, 2020, with a mean length of follow-up of 194.8 days (SD, 89.6; lowest 30; highest 299). During this period, a total of 369 patients died (17.2%). Table S2 shows the binary logistic regression model of death status. In addition to age (Exp(B), 1.08; 95% CI, 1.06–1.09; $p < 0.001$), history of malignancies (Exp(B), 2.06; 95% CI, 1.38–3.08; $p < 0.001$), chronic renal failure (Exp(B), 1.92; 95% CI, 1.23–2.99; $p = 0.004$), chronic heart failure (Exp(B), 1.70; 95% CI,

1.04–2.79; $p = 0.04$), or complications with acute respiratory failure (Exp(B), 9.73; 95% CI, 5.89–16.07; $p < 0.001$), also delirium (Exp(B), 1.83; 95% CI, 1.19–2.82; $p = 0.006$), treatment with antipsychotics during admission (Exp(B), 1.57; 95% CI, 1.10–2.22; $p = 0.01$), and history of mood disorder (Exp(B), 1.57; 95% CI, 1.03–2.40; $p = 0.04$) were independently associated with higher mortality rate, while history of treatment with antidepressants (Exp(B), 0.34; 95% CI, 0.17–0.67; $p = 0.002$) and anxiolytics/hypnotics (Exp(B), 0.33; 95% CI, 0.18–0.62; $p = 0.001$) was associated with lower mortality rate.

Table 2 shows the multivariate Cox regression for survival analysis. Previous associations remained unchanged

TABLE 2 Cox regression for survival analysis in COVID-19 inpatients

	HR ^a	95% CI ^b		P
		Low	High	
Sex (male)	1.095	0.848	1.413	0.49
Age	1.062	1.050	1.074	<0.001
History of chronic medical conditions during the year prior to admission				
Dyslipidemia	0.960	0.759	1.215	0.74
Obesity	0.867	0.690	1.091	0.22
Arterial hypertension	0.997	0.777	1.278	0.98
Type 1 or 2 diabetes mellitus	1.117	0.884	1.412	0.36
Ischemic heart disease	1.021	0.776	1.345	0.88
Chronic renal failure	1.404	1.039	1.899	0.03
Atrial fibrillation	1.117	0.513	2.435	0.78
Malignancies, including lymphoproliferative	1.514	1.149	1.994	0.003
Chronic obstructive pulmonary disease	1.257	0.955	1.654	0.10
Sleep apnea/hypopnea syndrome	1.166	0.852	1.596	0.34
Chronic heart failure	1.363	0.988	1.881	0.06
Valvular disease	1.159	0.836	1.606	0.38
Bronchial asthma	0.867	0.543	1.385	0.55
Cerebrovascular disease	0.959	0.677	1.357	0.81
Medical complications during admission				
Bilateral viral pneumonia	1.131	0.751	1.702	0.56
Acute respiratory failure	6.754	4.369	10.442	<0.001
Cardiac arrhythmias	0.858	0.388	1.895	0.71
Acute kidney failure	0.801	0.540	1.189	0.27
Pulmonary embolism	0.428	0.247	0.741	0.002
Treatments for COVID-19 during admission				
Antimalarial drugs (hydroxychloroquine or chloroquine)	0.843	0.649	1.096	0.20
Glucocorticoids	0.864	0.687	1.087	0.21
Antibiotics	1.187	0.934	1.508	0.16
Antivirals (darunavir, lopinavir/ritonavir, or remdesivir),	0.613	0.456	0.823	0.001
Tocilizumab	0.807	0.585	1.114	0.19
Beta-interferon	1.936	1.290	2.906	0.001
ICU ^c or semi-critical unit admission	2.459	1.826	3.311	<0.001
History of psychiatric disorders and treatments during the year prior to admission				
Cognitive disorder	1.105	0.766	1.594	0.59
Alcohol disorder	1.153	0.812	1.637	0.43
Mood disorder	1.521	1.125	2.056	0.006
Anxiety, stress, or adjustment disorder	0.826	0.618	1.103	0.20
Treatment with antidepressants	0.429	0.250	0.737	0.002
Treatment with anxiolytics/hypnotics	0.474	0.287	0.782	0.003
Psychiatric complications and treatments during admission				
Mood or anxiety, stress, or adjustment disorder	1.046	0.652	1.678	0.85
Delirium	1.392	1.044	1.857	0.02
Treatment with antidepressants	0.769	0.484	1.220	0.26
Treatment with benzodiazepines	0.820	0.649	1.037	0.10

(Continues)

TABLE 2 (Continued)

	HR ^a	95% CI ^b		P
		Low	High	
Treatment with antipsychotics	1.267	0.964	1.663	0.09

Follow-up period for mortality status assessment was closed on December 17, 2020, with a mean length of follow-up of 194.8 days (SD, 89.6; lowest 30; highest 299). During this period, a total of 369 patients died (17.2%).

^aHazard ratio.

^bConfidence interval.

^cIntensive care unit.

except that the use of antipsychotics during admission loses statistical significance as a variable independently associated with mortality. Figure 1 shows the cumulative mortality risk curve for all-cause mortality in relation to the presence of delirium, history of mood disorders, and previous treatment with antidepressants and anxiolytics/hypnotics.

4 | DISCUSSION

To our knowledge, this is one of the first reports about the association with mortality of mood disorders, anxiety-stress-adjustment disorders, and psychopharmacological treatments in a large cohort of COVID-19 hospitalized patients. Our study population had extensive medical comorbidity, with a 79% of subjects with a history of chronic medical disorders. These figures are higher to what some authors have found (23% by Zhou et al.,⁸ or 32% in the Chinese cohort by Conway et al.⁹), but not different from others, like 64% found by Zhang et al.¹⁰ or even 85% in the British cohort by Conway et al.⁹ Severity of COVID-19 itself was also high, with 14% of the patients requiring admission to an ICU and 17% of mortality.

COVID-19 inpatients are prone to develop mental health problems. However, we already found a high psychiatric morbidity before admission, with 45% suffering from a mental disorder during the previous year and 14% already on psychopharmacological treatments.

These data were clearly higher than those found in the general population in our setting, where the lifetime prevalence of mental disorders is between 19.5% and 21.3%,^{11,12} and the year-prevalence 8.4%.¹² In our opinion, these figures are in relation to the high prevalence of chronic medical conditions, all of them considered as risk factors for developing mental disorders. Moreover, patients with mental illnesses have a higher prevalence of chronic medical conditions, not only attributable to prescribed psychopharmacological treatments, but also to more sedentary lifestyles with a higher prevalence of smoking and other toxic habits. So, the high prevalence of chronic diseases in patients affected by COVID-19 could bidirectionally explain this association with mental illnesses.

Furthermore, 26% of the patients were diagnosed with a mood or an anxiety-stress-adjustment disorder during admission, 12% of the patients without previous psychiatric history. These data are in accordance with several other studies, such as 17% of affective disorders in a surveillance study in the UK,¹³ or 19% of anxiety and 13% of depressive symptoms in a study from Wuhan (China).¹⁴ Anxiety and depression morbidity can be related with psychosocial stressors such as social isolation, uncertainty about the future, grief for family or loved ones, stigma, traumatic memories of severe illness, or consequences in the work or academic environment.^{15,16} But also SARS-CoV-2 infection itself can have effects on the brain, either through direct viral infection or hypoxia,^{4,13,17,18} or by means of the immunological response.¹⁹ Furthermore, some drugs such as corticosteroids, interferon, or chloroquine may also promote psychiatric symptoms.²⁰⁻²² Indeed, in our population, *de novo* diagnosis during admission of mood or anxiety-stress-adjustment disorders was independently related to the use of glucocorticoids and to stress factors such as a longer length of stay or admission to ICU or semi-critical units. All these factors should be considered for the prevention or early treatment of this type of disorders.

Regarding delirium, it was diagnosed in a 10% of our sample. These figures are lower than those found in general in the hospital environment, which are between 14% and 24%, although they are highly variable depending on the type of setting.²³ They are also lower than those found in several COVID-19 studies. In a French series of 353 elderly patients with COVID-19, delirium was present in 27%, in two thirds of the cases in the hypokinetic form.²⁴ In another series of 322 hospitalized older COVID-19 patients in the UK, delirium was observed in 25%.²⁵ In a study on 707 patients over 50 years of age in Brazil, delirium figures were 33%.²⁶ Finally, delirium figures were as high as 84% in a population of 150 patients admitted to the ICU for an acute respiratory distress syndrome.²⁷ To our understanding, these differences can be explained by two main factors, in addition to differences in the severity of disease: (1) the age distribution in our study was wide, with only 44% of the patients over 65 years of age, while other studies focused on older populations; and (2) the diagnosis of delirium in our study was done through clinical records from physicians and nurses, so it was probably highly

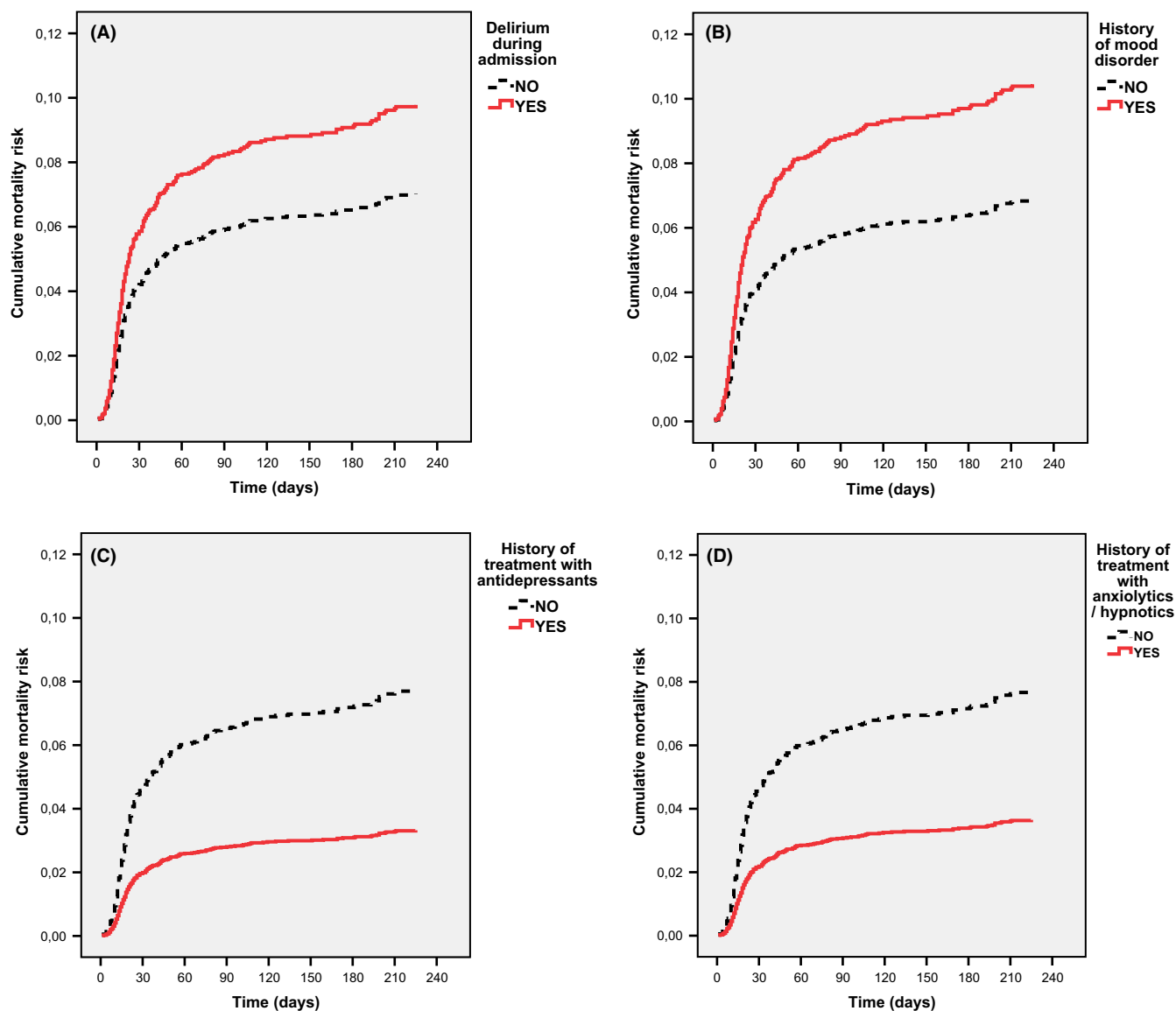


FIGURE 1 Cumulative mortality risk curve from the multivariate Cox regression for survival analysis. Delirium during admission: HR, 1.392; 95% CI, 1.044–1.857; $p = 0.02$. History of mood disorder: HR, 1.521; 95% CI, 1.125–2.056; $p = 0.006$. History of treatment with antidepressants: HR, 0.429; 95% CI, 0.250–0.737; $p = 0.002$. History of treatment with anxiolytics/hypnotics: HR, 0.474; 95% CI, 0.287–0.782; $p = 0.003$. Comparisons were adjusted for sex, age, history of medical and psychiatric disorders, and complications and treatments during admission if univariate association significance was <0.20 or they were clinically relevant. Follow-up period for mortality status assessment was closed on December 17, 2020, with a mean length of follow-up of 194.8 days (std dev, 89.6; lowest 30; highest 299). During this period, a total of 369 patients died (17.2%) [Colour figure can be viewed at wileyonlinelibrary.com]

	Baseline	30 days	60 days	90 days	120 days	150 days	180 days	210 days	240 days
Number at risk	2146	1740	1462	1320	1203	1134	1113	1044	586

specific, but possibly less sensitive, especially for the hypo-kinetic forms of delirium. Our results were, however, very similar to those obtained in a study on 852 patients in Italy, methodologically very similar to ours and with analogous limitations, where the authors found an 11% incidence of delirium.²⁸ These are particularly important data, as delirium is under-detected in clinical practice, with around 50% of cases

missed or diagnosed late,²⁹ especially the hypoactive subtypes. The occurrence of delirium in hospital settings is generally associated with several negative outcomes, both during hospital stay and after discharge. Hospitalized patients who experience delirium have longer hospital stays, higher numbers of hospital-acquired complications, and higher mortality rates. Cognitive impairment from delirium may persist

beyond hospital discharge, increasing the risks for subsequent diagnosis of dementia and functional deterioration. For this reason, we identify the need of standardized approaches to assess delirium in COVID-19 patients during hospitalization to improve management strategies, general outcomes of the infection, and time to recovery.

The high rates of psychiatric comorbidity resulted in high rates of prescription of psychotropic drugs, despite not knowing their effects on outcomes. Thus, 47% of the population was treated with some of them, and between 19% and 34% were *de novo* treatments. These results are similar to those found in a study on 247 hospitalized patients in which 16% of the survivors required new treatments with psychotropic drugs.³⁰

Based on these data, the importance of the epidemiological and therapeutic management of COVID-19-associated psychiatric comorbidity seems clear. But is it also relevant in terms of outcomes? We have used mortality as a clear and specific outcome.

Mortality in our population was 17%, similar to that of other centers,^{31,32} and it was independently associated with psychiatric factors already found in other non-COVID-19 populations. Thus, both the history of depressive disorders, but not anxiety, and the presence of delirium during admission were associated with an increase in mortality (HR 1.52, and 1.39 respectively). The association of depressive disorders with mortality is found in many chronic diseases,^{33,34} but not in acute illnesses like COVID-19. However, in this case, the pathophysiological etiology of this association ranges from psychological mechanisms that include affective and behavioral responses to social stressors and personal coping strategies, to neurobiological mechanisms such as inflammatory processes that explain a large part of depressive symptoms. As expected, the presence of delirium was also associated with increased mortality: 45% of the patients who presented delirium died compared to 14% of those who did not present it, figures only slightly lower than the 55%–57% of other studies.^{26,28}

Regarding medication, and as our group already found in patients with chronic heart failure,³⁵ the use of anxiolytics/hypnotics during the previous year was associated with a reduction in mortality (HR 0.47), as well as antidepressants (HR, 0.43). Obviously, these associations were found in a non-randomized sample, so they do not imply a cause-effect relationship. However, we can also hypothesize some of the potential mechanisms by which both benzodiazepines and antidepressants may be associated with a reduction in mortality. They can act by improving psychosocial risk factors well known to be relevant to prognosis for patients with medical conditions such as psychosocial stress and insomnia, but they may also have biological effects on several mechanisms involved in the pathophysiology of diseases, probably through effects on inflammation.

Mental symptoms are very common in patients hospitalized for COVID-19 infection. Detecting, diagnosing, and treating them is key to determining the prognosis of the

disease and functional recovery. There is a need to increase diagnostic strategies, especially in patients with delirium, to improve the overall results of the disease.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/acps.13304>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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