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ORIGINAL ARTICLE

Comorbidity patterns and mortality among hospitalized patients with psychiatric disorders and COVID-19

Marina **Sánchez-Rico**,[1,2] Katayoun **Rezaei**,[1] Alfonso **Delgado-Álvarez**,[2] Frédéric **Limosin**,[1,3,4] Nicolas **Hoertel**,[1,3,4] Jesús M. **Alvarado**[2]

[1]*Département Médico-Universitaire de Psychiatrie et Addictologie, Assistance Publique-Hôpitaux de Paris, Hôpital Corentin-Celton, Issy-les-Moulineaux, France.* [2]*Departamento de Psicobiología y Ciencias del Comportamiento, Facultad de Psicología, Universidad Complutense de Madrid, Campus de Somosaguas, Pozuelo de Alarcon, Spain.* [3]*Institut National de la Santé et de la Recherche Médicale 1266, Institut de Psychiatrie et Neurosciences de Paris, Paris, France.* [4]*Faculté de Santé, Unité de Formation et de Recherche de Médecine, Université Paris Cité, Paris, France.*

Objectives: To examine the association between psychiatric and non-psychiatric comorbidity and 28-day mortality among patients with psychiatric disorders and COVID-19.
Methods: Multicenter observational retrospective cohort study of adult patients with psychiatric disorders hospitalized with laboratory-confirmed COVID-19 at 36 Greater Paris university hospitals (January 2020-May 2021) (n=3,768). First, we searched for different subgroups of patients according to their psychiatric and non-psychiatric comorbidities through cluster analysis. Next, we compared 28-day all-cause mortality rates across the identified clusters, while taking into account sex, age, and the number of medical conditions.
Results: We found five clusters of patients with distinct psychiatric and non-psychiatric comorbidity patterns. Twenty-eight-day mortality in the cluster of patients with mood disorders was significantly lower than in other clusters. There were no significant differences in mortality across other clusters.
Conclusion: All psychiatric and non-psychiatric conditions may be associated with increased mortality in patients with psychiatric disorders and COVID-19. The lower risk of death among patients with mood disorders might be in line with the potential beneficial effect of certain antidepressants in COVID-19, but requires further research. These findings may help identify at-risk patients with psychiatric disorders who should benefit from vaccine booster prioritization and other prevention measures.

Keywords: COVID-19; psychiatric disorders; comorbidity; mortality; clustering; mood disorders

Introduction

After the unprecedented worldwide infectious-disease crisis created by the global spread of the novel coronavirus (SARS-CoV-2) and its variants,[1] the causative agents of COVID-19, several studies[2-9] have suggested that psychiatric disorders, including schizophrenia spectrum disorders,[5,6,8,9] mood disorders,[2,8,9] anxiety disorders,[5] intellectual and developmental disabilities,[3] substance-induced psychiatric disorders,[8] and dementia,[10] were associated with higher COVID-19-related mortality.

Studying risk factors of COVID-19-related mortality in people with psychiatric disorders is of utmost importance to prevent and treat these medical risk factors in this vulnerable population and to reduce health disparities.[5,11,12] Prior work supports that comorbid medical illnesses are more frequent among people with psychiatric disorders than in the general population[13] and are associated with increased all-cause mortality[11] and COVID-19-related mortality.[14] However, it remains poorly known whether specific psychiatric or non-psychiatric disorders, or specific combinations thereof, or the total number of disorders (whatever they are), predict the risk of COVID-19-related death among patients with psychiatric disorders.[12,15]

In this report, we used data from the Assistance Publique-Hôpitaux de Paris (AP-HP) Health Data Warehouse,[16-23] which includes data on all patients with laboratory-confirmed COVID-19 who had been consecutively admitted to any of the 36 AP-HP university hospitals in Greater Paris, to examine the association of psychiatric and non-psychiatric comorbidities with 28-day all-cause mortality among inpatients with psychiatric disorders and COVID-19. We took advantage of two unsupervised machine learning techniques, uniform manifold approximation and projection (UMAP)[24] and hierarchical cluster analysis, to identify different subgroups of patients, and

Correspondence: Marina Sánchez-Rico, 4 Parv. Corentin Celton, 92130 Issy-les-Moulineaux, France.
E-mail: marinals@ucm.es
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used multivariable logistic regression models to compare mortality rates while adjusting for sex, age, and the total number of psychiatric and non-psychiatric disorders.

Methods

Setting and cohort assembly

We conducted a multicenter observational retrospective cohort study at 36 AP-HP university hospitals from the beginning of the epidemic in France, i.e., January 24, 2020, until May 1, 2021.[16-23] We included all adults (aged 18 years and older) who had been admitted to one of these centers for laboratory-confirmed COVID-19, as ascertained by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) analysis of nasopharyngeal or oropharyngeal swab specimens.

Data sources

The AP-HP Health Data Warehouse contains all available clinical data on all inpatient visits for COVID-19 to the 36 Greater Paris university hospitals.[16-23] The data included patient demographic characteristics, vital signs, laboratory test and RT-PCR test results, medication administration data, current medical diagnoses, and death certificates.

ICD-10 diagnosis codes

Patient information regarding recorded diagnoses at the time of hospitalization was obtained through electronic health records and based on ICD-10 codes, including infectious and parasitic diseases (A00-B99), neoplasms and diseases of the blood (C00-D89), endocrine disorders (E00-E89), mental disorders (F01-F99), diseases of the nervous system (G00-G99), eye-ear-nose-throat disorders (H00-H95), cardiovascular disorders (I00-I99), respiratory disorders (J00-J99), digestive disorders (K00-K95), dermatological disorders (L00-L99), diseases of the musculoskeletal system (M00-M99), and diseases of the genitourinary system (N00-N99). Diagnoses were grouped at a two-digit level (e.g., intestinal infectious diseases [A0], mood disorders [F3], hypertensive diseases [I1]), for a total of 138 potential two-digit diagnoses. To avoid ''empty variables,'' we only kept diagnoses with a frequency of at least 0.5% in the full sample. Of the 138 two-digit diagnoses included in the sample, 96 (69.6%) had a frequency of at least 0.5% and were included in the analyses.

Patient characteristics

From the same electronic health records, we extracted information on patient characteristics at the time of hospitalization. These variables included: sex; age, which was categorized into four classes as previously recommended[16-18,21,23] (18-50, 51-70, 71-80, and 81+ years); and the number of second-digit ICD-10 diagnosis for each participant. To further explore the severity of each patient's condition based on their current comorbidities, we additionally computed the Elixhauser Comorbidity Index, based on the Swiss weights modification.[25]

Study baseline and outcome

Study baseline was defined as the date of hospital admission with COVID-19. The outcome was 28-day all-cause mortality from study baseline. Patients who were discharged from the hospital before day 28 or died after day 28 were considered to be alive.

Ongoing use of psychotropic medication

Data on psychotropic medication use was also recorded. These medications included antidepressants (amitriptyline, amoxapine, citalopram, clomipramine, duloxetine, escitalopram, fluvoxamine, fluoxetine, mianserine, mirtazapine, paroxetine, sertraline, tianeptine, venlafaxine, and vortioxetine), antipsychotics (amisulpride, aripiprazole, chlorpromazine, clozapine, cyamemazine, flupentixol, haloperidol, levomepromazine, loxapine, olanzapine, quetiapine, paliperidone, penfluridol, propericiazine, risperidone, tiapride, and zuclopenthixol), benzodiazepines or Z-drugs (alprazolam, bromazepam, clobazam, clonazepam, clorazepate, diazepam, lorazepam, nitrazepam, oxazepam, prazepam, nordazepam, midazolam, lormetazepam, zolpidem, and zopiclone), mood stabilizers (carbamazepine, divalproex, gabapentin, oxcarbazepine, lamotrigine, lithium, phenobarbital, pregabalin, and valpromide), and functional inhibitors of acid sphingomyelinase activity (FIASMA)[19] (amitriptyline, aripiprazole, chlorpromazine, clomipramine, duloxetine, escitalopram, flupentixol, fluvoxamine, fluoxetine, paroxetine, and sertraline).[20]

Medication use was defined as having an ongoing prescription of each medication at hospital admission (i.e., one prescription at hospital admission and at least one prior prescription of the same active pharmaceutical ingredient dating from the preceding 6 months).

Statistical procedure

Comorbidity clusters

In order to identify subgroups of patients according to their psychiatric and non-psychiatric comorbidities, we performed a hierarchical cluster analysis among two-digit ICD-10 diagnosis codes. To minimize potential consistency and computational issues due to the large number of diagnoses,[26] we transformed the binary matrix of diagnoses into a two-dimensional projection using UMAP.[24] In order to select the most suitable classification, we performed a statistical procedure based on the combination of study conditions for UMAP (4×2) and the clustering algorithm (4×16). The conditions manipulated in UMAP included the number of neighbors (15, 50, 100, and 200) and the minimum embedding distance (0.1 and 0.5). The Manhattan equation for distance was used for UMAP and did not vary, as previously recommended.[24] The clustering algorithm was performed using Euclidean distance[27] and included the following manipulated conditions: linkage function (average, ward, complete, centroid)

and number of clusters (5 to 20). In total, we ran 512 ($4 \times 2 \times 4 \times 16$) models according to different configurations, and selected the best one based on the average silhouette coefficient (SC).[28]

Associations with mortality

We calculated frequencies of all diagnoses forming each cluster at both levels of ICD-10 grouping diagnoses. We also studied the distribution of patient characteristics within each cluster. To compare the association between each cluster and 28-day mortality, we used logistic regression models. To reduce the effects of confounding, the main analysis was a multivariable logistic regression model adjusted for age, sex, and the number of medical (psychiatric and non-psychiatric) conditions based on two-digit ICD-10 diagnosis codes. We obtained adjusted odds ratios (AOR) and 95%CIs for the association of each cluster with 28-day mortality for all analyses.

As a sensitivity analysis, we reproduced the main analysis using the Elixhauser Comorbidity Index[25] instead of the number of medical (psychiatric and non-psychiatric) conditions based on two-digit ICD-10 diagnosis codes.

We performed additional analyses and used chi-square tests to compare the prevalence of psychotropic medication groups (antidepressants, antipsychotics, benzodiazepines or Z-drugs, mood stabilizer medications, and FIASMA psychotropic medications) across clusters.

For all associations, we performed residual analyses to assess the fit of the data to the model, checked assumptions, and examined the potential influence of outliers. Because we did not have a single hypothesis in this study and our analyses were exploratory, statistical significance in the main analysis was set *a priori* at a two-sided p-value < 0.05. To reduce the risk of type I error due to multiple testing, we applied Bonferroni correction in the additional analyses, including pairwise comparisons of psychotropic medications across clusters. All analyses were conducted in R software version 4.1.3 (R Project for Statistical Computing).

Ethics statement

This observational study using routinely collected data received approval from the institutional review board of the AP-HP Health Data Warehouse (decision CSE-20-20_COVID19, IRB00011591, April 8, 2020). The institution's initiatives ensure patient information and consent regarding the different approved studies through a transparency portal, in accordance with European Regulation on data protection, and is authorized by the French National Commission on Information Technology and civil Liberties (Commission nationale de l'informatique et des libertés, CNIL; request for authorization no. 1980120).

Results

Characteristics of the cohort

Of the 51,265 adult patients hospitalized with COVID-19, as ascertained by a positive RT-PCR test, 2,176 (4.2%) were excluded because of missing data. Of the remaining 49,089 patients, 3,768 (7.7%) had at least one ICD-10 diagnosis of mental, behavioral, and neurodevelopmental disorder (F01-F99) (Figure 1). Twenty-eight-day-mortality occurred in 842 (22.3%) patients. Sex, age, and number

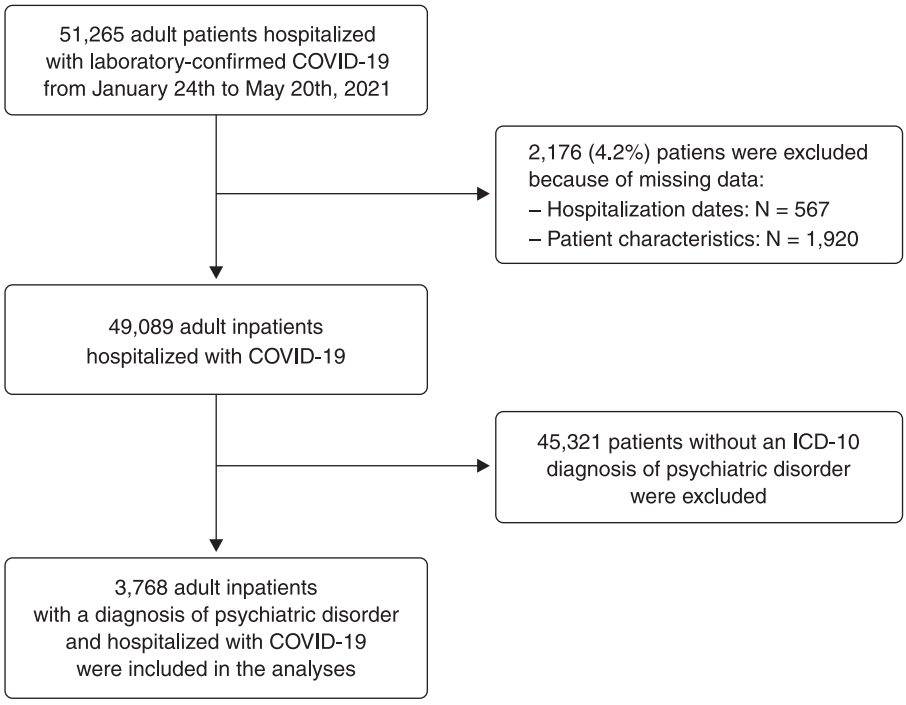

Figure 1 Study cohort. COVID-19 = coronavirus disease 2019.

of medical conditions were significantly associated with 28-day mortality (Tables S1 and S2, available as online-only supplementary material).

Model selection and clusters

The model with the highest average SC (ASC) (= 0.81) was a two-dimensional UMAP projection, with 100 neighbors and a minimum embedding distance of 0.1, using the centroid linkage function for the clustering, and five clusters as cutoff. All five clusters showed great consistency, with an ASC of at least 0.75 for all cases (Figure 2, Table S3).

The distribution of diagnoses by cluster is presented in Figure 3. The main psychiatric diagnosis in cluster 1 (n=585; ASC = 0.82) was anxiety disorder (F40-F48) (68% of individuals from this cluster), and the main non-psychiatric medical condition was influenza or pneumonia (J09-J18). In cluster 2 (n=1,999; ASC = 0.82), 98.6% of patients presented with illness-induced psychiatric disorders (F01-F09), and almost half of them had malnutrition (E40-E46, 47%), influenza or pneumonia (J09-J18, 46.7%), or hypertensive diseases (I10-I16, 46.2%). Cluster 3 (n=694; ASC = 0.75) comprised 98.6% of patients with substance-induced psychiatric disorders (F10-F19); 63.8% of them were diagnosed with influenza or pneumonia (J09-J18), and 47.7% with other diseases of the pleura and post-procedural disorders of respiratory system (J90-J99). Almost all individuals from cluster 4 (n=405; ASC = 0.81) had mood disorders (F30-F39, 99%), and half of them (49.9%) also had a diagnosis of influenza or pneumonia (J09-J18). Cluster 5 (n=85; ASC = 0.92) was the smallest and most compact cluster, with 44.7% of patients presenting with a diagnosis of intellectual disability and 54.9% with a diagnosis of influenza or pneumonia (J09-J18).

The distributions of patient characteristics by cluster are shown in Table S4. Clusters 2 and 4 included a higher rate of older women with a greater number of medical conditions, while cluster 3 mainly comprised younger men with a greater number of medical conditions. Clusters 1 and 5 did not show a statistically different proportion of men and women, and mainly included younger patients.

Associations between clusters and mortality

Death occurred in 19% (111/585) of patients in cluster 1, 27.8% (556/1,999) in cluster 2, 15.9% (110/694) in cluster 3, 13.1% (53/405) in cluster 4, and 14.1% (12/85) in cluster 5. In the main analysis adjusting for sex, age, and number of comorbidities, patients from cluster 4 had a significantly reduced 28-day mortality when compared with those from cluster 1 (AOR = 0.53, 95%CI 0.37-0.77, p = 0.001), cluster 2 (AOR = 0.62; 95%CI 0.45-0.85; p = 0.003), cluster 3 (AOR = 0.67; 95%CI 0.45-0.97; p = 0.036), and cluster 5 (AOR = 0.45; 95%CI 0.22-0.94; p = 0.027). There were no significant differences in mortality across other clusters. Results were similar in the sensitivity analysis using the Elixhauser Comorbidity Index instead of the number of comorbidities (Table 1).

Prevalence of psychotropic medications by cluster

Antipsychotic use was more prevalent among patients in cluster 1 (21.7%), but this prevalence was only significantly different when compared with patients in clusters 2 (13.1%) and 3 (5.5%). The use of benzodiazepines or Z-drugs was relatively similar across all clusters, except in cluster 3 (2.9%), in which the prevalence was significantly lower than in other clusters. Mood stabilizers were significantly more prevalent in cluster 4 (15.1%) than in clusters 1 (8.2%), 2 (6.5%), and 3 (4.9%). Antidepressant

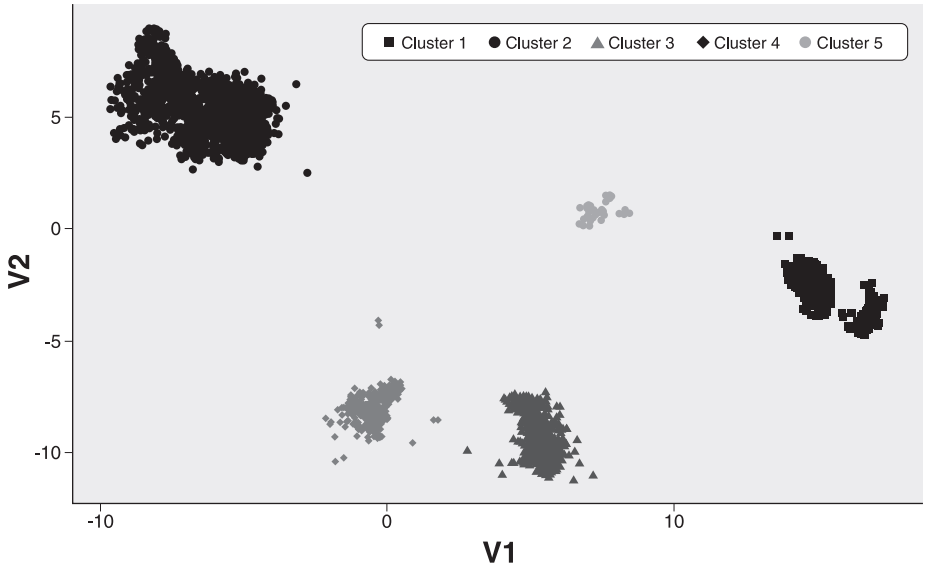

Figure 2 Uniform manifold approximation and projection (UMAP) two-dimensional space projection by cluster in the selected model.

Table 1 Association between clusters and 28-day mortality among patients with psychiatric disorders hospitalized with COVID-19 (n=3,768)

Cluster	Number of events/number of patients (%)	Multivariable logistic regression model adjusted for sex, age, and number of comorbidities - OR (95%CI)				
		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
1	111/585 (19.0)	Ref.	1.16 (0.9-1.5; 0.245)	1.25 (0.92-1.71; 0.159)	1.88 (1.30-2.74; 0.001)†	0.84 (0.44-1.72; 0.607)
2	556/ 999 (27.8)	0.86 (0.67-1.11; 0.245)	Ref.	1.08 (0.82-1.41; 0.593)	1.62 (1.18-2.24; 0.003)†	0.72 (0.38-1.46; 0.332)
3	110/694 (15.9)	0.80 (0.58-1.09; 0.159)	0.93 (0.71-1.22; 0.593)	Ref.	1.50 (1.03-2.20; 0.036)†	0.67 (0.35-1.37; 0.245)
4	53/405 (13.1)	0.53 (0.37-0.77; 0.001)†	0.62 (0.45-0.85; 0.003)†	0.67 (0.45-0.97; 0.036)†	Ref.	0.45 (0.22-0.94; 0.027)†
5	12/85 (14.1)	1.20 (0.58-2.30; 0.607)	1.39 (0.68-2.63; 0.332)	1.50 (0.73-2.87; 0.245)	2.25 (1.06-4.48; 0.027)†	Ref.
		Multivariable logistic regression model adjusted for sex, age, and Elixhauser Comorbidity Index - AOR (95%CI)				
1	111/585 (19.0)	Ref.	1.16 (0.90-1.50; 0.244)	1.19 (0.87-1.63; 0.266)	1.85 (1.28-2.69; 0.001)†	0.93 (0.49-1.91; 0.835)
2	556/1,999 (27.8)	0.86 (0.67-1.11; 0.244)	Ref.	1.03 (0.78-1.35; 0.856)	1.59 (1.16-2.21; 0.004)†	0.80 (0.43-1.62; 0.509)
3	110/694 (15.9)	0.84 (0.61-1.14; 0.266)	0.98 (0.74-1.28; 0.856)	Ref.	1.55 (1.07-2.27; 0.023)†	0.78 (0.41-1.60; 0.470)
4	53/405 (13.1)	0.54 (0.37-0.78; 0.001)†	0.63 (0.45-0.86; 0.004)†	0.64 (0.44-0.94; 0.023)†	Ref.	0.50 (0.25-1.06; 0.058)
5	12/85 (14.1)	1.07 (0.52-2.05; 0.835)	1.25 (0.62-2.35; 0.509)	1.28 (0.63-2.44; 0.470)	1.99 (0.94-3.94; 0.058)	Ref.

AOR = adjusted odds ratio; COVID-19 = coronavirus disease 2019; OR = odds ratio.
† Two-sided p-value < 0.05.

Figure 3 Distribution of ICD-10 two-digit diagnoses within each cluster. B90-B99, other infectious diseases; E08-E16, diabetes mellitus or other disorders of glucose regulation; E40-E46, malnutrition; E50-E64, other nutritional deficiencies; E65-E68, overweight, obesity, and other hyperalimentation; E70-E89, postprocedural endocrine and metabolic complications and disorders; F01-F09, illness-induced psychiatric disorders; F10-F19, substance-induced psychiatric disorders; F20-F29, psychotic disorders; F30-F39, mood disorders; F40-F48, anxiety disorders; F60-F69, disorders of adult personality and behavior; F70-F79, intellectual disabilities; F80-F89, pervasive and specific developmental disorders; G30-G37, other degenerative diseases of the central nervous system and demyelinating diseases of the central nervous system; G40-G47, episodic and paroxysmal disorders; I10-I16, hypertensive diseases; I20-I28, ischemic and pulmonary heart diseases; I40-I49, other forms of heart disease; J09-J18, influenza and pneumonia; J40-J47, chronic lower respiratory diseases; J80-J86, other respiratory diseases principally affecting the interstitium and suppurative and necrotic conditions of lower respiratory tract; J90-J99, other diseases of the pleura and intraoperative and postprocedural disorders of respiratory system; N10-N19, renal tubulo-interstitial diseases, acute kidney failure, and chronic kidney disease.

use was significantly more prevalent in cluster 4 (27.9%) than in all other clusters (cluster 1, 14.7%; cluster 2, 19.2%; cluster 3, 7.2%; cluster 5, 8.2%). Similarly, the use of FIASMA psychotropic medications was significantly more prevalent in cluster 4 (19%) than in all other clusters

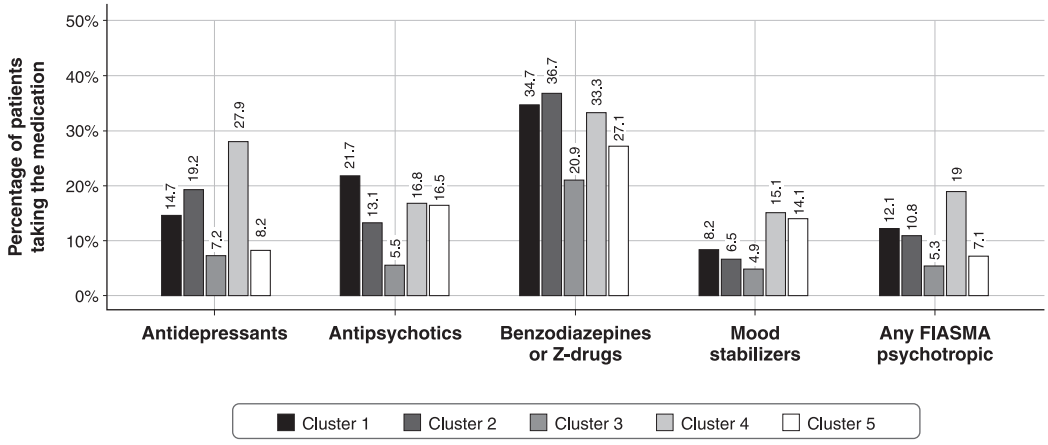

Figure 4 Prevalence of psychotropic medications by cluster. FIASMA = functional inhibitors of acid sphingomyelinase activity.

(cluster 1, 12.1%; cluster 2, 10.8%; cluster 3, 5.3%; cluster 5, 7.1%) (Figure 4, Table S5).

Discussion

In this multicenter observational retrospective cohort study of 3,768 adult patients with psychiatric disorders hospitalized with laboratory-confirmed COVID-19, we identified five distinct clusters of patients based on their medical psychiatric and non-psychiatric comorbidities. Following adjustment for sex, age, and number of medical conditions, there were no significant differences in mortality across clusters, except for cluster 4, in which almost all patients had a diagnosis of mood disorder and for which mortality rate was significantly lower than in other clusters.

Twenty-eight-day mortality did not significantly differ across most clusters. This result supports that all psychiatric and non-psychiatric conditions could be associated with increased mortality in patients with psychiatric disorders and COVID-19, as previously suggested.[12,15] It also suggests that the relationship of medical psychiatric and non-psychiatric disorders with mortality may be better explained by the number and the severity of these disorders rather than by specific individual psychiatric or non-psychiatric disorders or specific combinations of disorders. More broadly, this finding is in line with the central role of comorbidity in a cumulative way in the relationships between psychiatric disorders and medical and social adverse outcomes.[12,29-33]

A notable exception was cluster 4, in which almost all patients had a diagnosis of mood disorder and for which mortality was significantly lower than in all other clusters. Patients from cluster 4 were significantly more likely to take antidepressants and FIASMA psychotropic medications than in all other clusters, while the prevalence of other psychotropic medication families did not significantly differ as compared to other clusters. This finding is in line with the potential beneficial effect of certain antidepressants in COVID-19, specifically antidepressants with high FIASMA activity, as suggested by prior work, including preclinical data,[34-36] observational studies,[19-21,37] and clinical trials,[38-40] but needs to be confirmed in additional research.

Our study has several limitations. First, an inherent bias in observational studies is unmeasured confounding. Second, inflation of type I error might have occurred in this study due to multiple testing. Therefore, the present results should be considered in light of this limitation and need to be confirmed by other studies. Third, there is potential underreporting of psychiatric disorders, medical illnesses, and ongoing medications in our sample in the context of overwhelmed hospital units during the peak incidence of COVID-19. Fourth, the precise date of the diagnoses of psychiatric disorders during the visit (e.g., at hospital admission or at the end of the visit) was not available. Fifth, diagnoses of psychiatric disorders were based on ICD-10 diagnosis codes made by the practitioners in charge of the patients during the hospitalization for COVID-19 and were not ascertained by psychiatrists. Finally, despite the multicenter design, our results relied on a cohort study of hospitalized patients with COVID-19 in Paris and may not be generalizable to outpatients or to other countries.

Our results suggest that all psychiatric and non-psychiatric conditions may be associated with increased mortality in patients with psychiatric disorders and COVID-19. The potentially lower risk of death among patients with mood disorders might be in line with the potential beneficial effect of certain antidepressants in COVID-19, but this requires replication. These findings may help identify at-risk patients with psychiatric disorders who should benefit from vaccine booster prioritization and other prevention measures.

Disclosure

MSR, FL, and NH are inventors on a patent application related to methods of treating COVID-19, filed by Assistance Publique-Hôpitaux de Paris in France. The other authors report no conflicts of interest.

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