# Association between mental disorders and COVID-19 outcomes among inpatients in France: A retrospective nationwide population-based study

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## ARTICLE INFO

## ABSTRACT

*Background:* Mental disorders are at-risk of severe COVID-19 outcomes. There is limited and heterogeneous national data in hospital settings evaluating the risks associated with any pre-existing mental disorder, and susceptible subgroups. Our study aimed to investigate the association between pre-existing psychiatric disorders and outcomes of adults hospitalised for COVID-19.

*Method:* We used data obtained from the French national hospital database linked to the state-level psychiatric registry. The primary outcome was 30-days in-hospital mortality. Secondary outcomes were to compare the length of hospital stay, Intensive Care Unit (ICU) admission and ICU length. Propensity score matching analysis was used to control for COVID-19 confounding factors between patients with or without mental disorder and stratified by psychiatric subgroups.

*Results:* Among 97 302 adults hospitalised for COVID-19 from March to September 2020, 10 083 (10.3%) had a pre-existing mental disorder, mainly dementia (3581 [35.5%]), mood disorders (1298 [12.9%]), anxiety disorders (995 [9.9%]), psychoactive substance use disorders (960 [9.5%]), and psychotic disorders (866 [8.6%]). In propensity-matched analysis, 30-days in-hospital mortality was increased among those with at least one pre-existing mental disorder (hazard ratio (HR) 1.15, 95% CI 1.08–1.23), psychotic disorder (1.90, 1.24–2.90), and psychoactive substance disorders (1.53, 1.10–2.14). The odds of ICU admission were consistently decreased for patients with any pre-existing mental disorder (OR 0.83, 95% CI 0.76–0.92) and for those with dementia (0.64, 0.53–0.76).

*Conclusion:* Pre-existing mental disorders were independently associated with in-hospital mortality. These findings underscore the important need for adequate care and targeted interventions for at-risk individuals with severe mental illness.

## 1. Introduction

Since the first cases in December 2019 of the worldwide outbreak of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), populations with specific risk factors including old age, diabetes, obesity, and pre-existing cardiovascular or respiratory diseases have been largely described (Docherty et al., 2020; Richardson et al., 2020). To date, several studies have reported that patients with pre-existing mental disorders are at increased risk of morbidity and poor COVID-19 outcomes (Barcella et al., 2021; Lee et al., 2020; Yang et al., 2020). A large cohort study conducted among individuals with mental disorders in the United States reported significantly higher rates of

COVID-19 infection among patients with schizophrenia and depression (Wang et al., 2021). Another population-based study in Denmark examining potential risk factors for severe or fatal COVID-19 among a wide range of major chronic diseases suggested that a severe psychiatric disorder was associated with increased risk of hospitalisation and fatal COVID-19 disease (Reilev et al., 2020). Furthermore, pooled estimates from a meta-analysis demonstrated an increased risk of hospitalisation and mortality after SARS-CoV-2 infection among patients with mental disorders (Vai et al., 2021).

Several factors may contribute to adverse clinical outcomes among patients with severe mental illness. The extent to which pre-existing mental disorders are associated with poorer COVID-19 outcomes independently of somatic comorbidities has remained unclear. In addition, somatic comorbidities and socioeconomic deprivation are also more prevalent among people with pre-existing mental disorders and were also identified as important predictors of poor COVID-19 outcomes (Hughes et al., 2016; Lone et al., 2021). Because specific risks may differ depending of the underlying conditions and social determinants, additional evidence to estimate the risks and particular COVID-19 outcomes for each mental disorder is needed (Liu et al., 2021). Moreover, previous studies have largely focused on individual risk of SARS-CoV-2 infection and limited data on the care pathway with the hospital and the hospital outcomes is available.

In this nationwide retrospective exhaustive cohort study of patients hospitalised for COVID-19 in metropolitan France, we investigated the association of different psychiatric diagnoses with the primary endpoint of in-hospital mortality at 30 days and secondary endpoints of ICU admission, ICU length of stay and length of stay in hospital.

## 2. Methods

### 2.1. Study design and data collection

We did a retrospective cohort study using the French hospital database *Programme de médicalisation des systèmes d'information* (PMSI) in which records from the acute and psychiatric care are systematically collected. This national administrative health database collects exhaustively all discharge summaries for all inpatients admitted to public and private hospitals in France (Piroth et al., 2021). Based on the Diagnosis-related group (DRG) model, patients' abstracts from this coding system are anonymous, linked at the patient level and include both medical and administrative data. The PMSI indicates the dates of admission and discharge for all public or private hospital stays in France. Medical diagnoses are coded according to the ICD-10 classification and the main medical or surgical procedures are coded according to the Classification Commune des Actes Médicaux (CCAM). From the earlier stage of the COVID-19 pandemic, the state-level PMSI database was adapted to identify COVID-19 admissions, and hospitals were asked to perform accelerated data transmission for inpatients in a simplified manner, integrating at least in-hospital outcomes including the length of stay, intensive care unit admission and hospital deaths (Semenzato et al., 2021). All patients were followed up until the end of their hospital stay during the study period.

Covariates included baseline characteristics at admission and clinical comorbidities extracted for each patient from the PMSI databases. We used a set of potential and established risk factors for COVID-19: age, sex (female and male), diabetes mellitus (type one and two), dyslipidemia, BMI classes (<25, 25–30, and ≥30 kg/m2), smoking, heart diseases (ischemic disease, heart failure and arrhythmia), stroke (ischemic and hemorrhagic), chronic respiratory diseases, chronic liver diseases, chronic kidney diseases, cancer (solid tumour and haematological malignancy), immunodeficiency or organ transplant (Williamson et al., 2020). The Charlson and Elixhauser comorbidity indices were also computed (Charlson et al., 1987; Elixhauser et al., 1998). The details of the definitions, including ICD-10 codes used to capture these variables are displayed in the appendix. Patients hospitalised before March 2020

and adults<18 years were excluded from the analysis.

### 2.2. Study exposure and outcomes

For the whole COVID-19 cohort, we included all adults hospitalised from March to September 2020. Hospital stays for COVID-19 were identified with ICD-10 codes U07.10, U07.11, U07.12, U07.14, or U07.15. Inpatients with a pre-existing diagnostic of mental disorder were identified according to specific ICD-10 codes recorded both in the acute care and psychiatric PMSI databases in the 5-years before March 2020. Patients were then categorized into six mutually exclusive subtypes of psychiatric disorders: dementia disorders (F00–F09), substance use disorders (F10–19), psychotic disorders (F20–F29), mood disorders (F30–F39), anxiety disorders (F40–F48), and other psychiatric diagnosis, including eating disorders (F50), personality disorders (F60–69) and intellectual disabilities (F70–F79). We also conducted additional analyses for a subset of patients with a diagnosis of major depressive disorder (F32–F33) and bipolar disorder (F30–F31). The control group of patients without mental disorders excluded patients with these diagnoses.

The primary endpoint was 30-days in-hospital mortality. Secondary endpoints included length of hospital stay, ICU admission and ICU length of stay. Data were censored at September 30th, 2020 for death for patients still hospitalised for COVID-19 on September 30th 2020.

### 2.3. Statistical analysis

Characteristics of patients were expressed as frequencies and percentages for categorical variables, whereas continuous variables were reported as mean and standard deviation or median and interquartile range. To consider the potential confounding, we used propensity score matching to create COVID-19 cohorts of patients with or without any pre-existing mental disorder and then considering each psychiatric disorder separately (Austin, 2011). Propensity score was implemented using a one-to-one greedy nearest neighbor matching approach, with a caliper width of 0.1 SD of logit for the propensity score, without replacement. We calculated the propensity score using a logistic regression model. The full set of covariates previously described as well as mode of admission and hospital setting (university or non-university hospital) were considered as potential confounders and used for matching. Propensity-score matched models were fitted separately for the cohort of patients with at least one pre-existing mental disorder and for each psychiatric diagnosis cohorts. We calculated absolute standardized difference before and after applying propensity score methods to assess the balance of measured covariates (Austin, 2009). An absolute standardized difference of 10% or less was deemed to be an adequate balance.

For the primary outcome, we estimated the 30-day risk of in-hospital mortality for each group using a Cox proportional hazards model. In addition, to estimate the consistency of the effect sizes, a competing risk analysis was performed using a Fine–Gray regression model by treating discharge as a competing event (Lau et al., 2009). We checked the proportionality assumption for both models. Thirty-day mortality covered 95% of all in-hospital deaths observed over the study period. For the secondary outcomes, we used negative binomial models to examine the difference in length of hospital or ICU stay and binary logistic regression models to investigate ICU admission. Primary and secondary outcomes were compared separately between each psychiatric subgroup and the matched cohort of controls. As secondary analysis, we repeated the analysis among patients with two or more diagnoses of mental disorders. We also made comparisons using inverse probability weighting in a doubly robust approach to consider the potential bias in the overall cohort (Desai and Franklin, 2019). All analysis were performed as complete-cases analysis on the records and diagnoses reported in the national programs and no missing data strategies were conducted. A two-sided p < 0.05 was considered statistically significant.

All analyses were performed using version 4.0.3 of the R programming language (R Project for Statistical Computing; R Foundation).

### 2.3.1. Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### 2.3.2. Regulatory approval and ethical aspects

The PMSI (data from health care facilities) is a set of strictly anonymous databases, comprising all mandatory national health insurance hospital reimbursement data. AP-HP has a regulatory permanent access to the data from the PMSI.

## 3. Results

### 3.1. Study population

Overall, 97 452 adults hospitalised for COVID-19 (median age 67 IQR [51–81]) were included in this retrospective nationwide analysis, 51 758 (53.1%) were female, 27 786 (28.5%) were older than 80 years and 89 935 (92.3%) of COVID-19 admission to hospital were from home (Table 1, Fig. S1). Of these patients, 10 083 (10.3%) had a pre-existing mental disorder. The most prevalent pre-existing mental disorder was dementia (3581 [35.5%]) followed by mood disorders (1298 [12.9%]), anxiety disorders (995 [9.9%]), psychoactive substance use disorders (960 [9.5%]), and psychotic disorders (866 [8.6%], Table 2). Other psychiatric disorders (415 [4.1%]) including intellectual disabilities, eating and personality disorders are displayed in the appendix (Fig. S1). Patients in the mental disorders group were more likely to be female, with older age, with a higher prevalence of comorbidities (hypertension, chronic heart diseases, strokes, chronic kidney disease, and cancer) than those with no mental disorder. The Charlson and Elixhauser comorbidity indices were higher in the mental disorders group than in the control group.

On average, patients with dementia were older (median age 85 [80–89]) and half of them had at least one comorbidity (1808 [50.5%]). As expected, the Charlson and Elixhauser comorbidity indices were higher among the dementia group. The percentage of females was higher among patients with anxiety disorder (62.6%) and lower among patients with psychoactive substance use disorder (24.3%).

The overall in-hospital mortality at Day-30 was 15.7%. In-hospital death occurred in 2036 (20.2%) patients with mental disorders compared to 13 311 (15.2%) without mental disorders. In the whole unmatched COVID-19 cohort, 15 200 (15.6%) individuals were admitted to the ICU, 898 (8.9%) with any mental disorders compared with 14 302 (16.4%) without mental disorders. Patients with mental disorder had a shorter ICU length of stay than those without (median 7 IQR [3–13] versus 8 days [4–17]). The main baseline characteristics and in-hospital outcomes of severe psychiatric diagnoses before matching are summarised in Table 2. The median length of stay in hospital ranged from 7 (IQR 4–13) to 11 (IQR 6–17) days by cohorts and from 6 (IQR 3–12) to 9 (4–15); ; ; for the median ICU length of stay. After stratification by psychiatric subgroups, the proportion of patients admitted in ICU was lower in the dementia group with higher in-hospital mortality rates compared to other psychiatric diagnoses (5.9% and 31.6%, respectively). By contrast, ICU admission was higher among patients with substance use disorders and associated with lower in-hospital mortality rate (13.0% and 10.2%, respectively).

### 3.2. In-hospital outcomes of propensity-matched cohorts

Matching successfully achieved balance on the observed covariates for patients with at least one pre-existing mental disorder and for the different psychiatric diagnosis. Matched baseline characteristics and cofounding variables with absolute standardized differences before and after applying propensity score methods are provided in the appendix.

**Table 1**

Baseline characteristics and in-hospital outcomes of adults hospitalised for COVID-19 in the whole cohort and with or without any pre-existing mental disorder.

| | Overall | Any pre-existing mental disorder | Control group |
|---|---|---|---|
| Cohort | 97 452 | 10 083 | 87 369 |
| **Baseline characteristics** | | | |
| Age, median years (IQR) | 67 (51–81) | 75 (56–86) | 66 (51–81) |
| Age, years | | | |
| <50 | 21 845 (22.4) | 1901 (18.9%) | 19 944 (22.8%) |
| 50-59 | 14 349 (14.7) | 1038 (10.3%) | 13 311 (15.2%) |
| 60-69 | 16 362 (16.8) | 1238 (12.3%) | 15 124 (17.3%) |
| 70-79 | 17 110 (17.6) | 1611 (16.0%) | 15 499 (17.7%) |
| ≥80 | 27 786 (28.5) | 4295 (42.6%) | 23 491 (26.9%) |
| Sex | | | |
| Female | 45 694 (46.9%) | 5210 (51.7%) | 40 484 (46.3%) |
| Male | 51 758 (53.1%) | 4873 (48.3%) | 46 885 (53.7%) |
| Mode of admission | | | |
| From home | 89 935 (92.3%) | 8650 (85.8%) | 81 285 (93.0%) |
| Other (hospital setting) | 7517 (7.7%) | 1433 (14.2) | 6084 (7.0%) |
| Hospital setting | | | |
| University hospital | 30 696 (31.5%) | 3343 (33.2%) | 27 353 (31.3%) |
| Other public or private hospital | 66 756 (68.5%) | 6596 (66.8%) | 60 160 (68.7%) |
| Region | | | |
| Ile-de-France | 35 008 (35.9%) | 3652 (36.2%) | 31 356 (35.9%) |
| North East | 26 855 (27.6%) | 2901 (28.8%) | 23 954 (27.4%) |
| North West | 8773 (9.0%) | 915 (9.1%) | 7858 (9.0%) |
| South East | 20 396 (20.9%) | 2053 (20.4%) | 18 343 (21.0%) |
| South West | 6420 (6.6%) | 562 (5.6%) | 5858 (6.7%) |
| **Comorbidities** | | | |
| At least one comorbidity | 40 159 (41.2%) | 4461 (44.2%) | 35 698 (40.9%) |
| Charlson Comorbidity Index | | | |
| Mean (SD) | 0.57 (1.08) | 0.75 (1.28) | 0.54 (1.05) |
| 0 | 68 442 (70.2%) | 6366 (63.1%) | 62 076 (71.1%) |
| 1-2 | 22 199 (22.8%) | 2677 (26.5%) | 19 522 (22.3%) |
| ≥3 | 6811 (7.0%) | 1040 (10.3%) | 5771 (6.6%) |
| Elixhauser Comorbidity Index | | | |
| Mean (SD) | 1.40 (2.21) | 1.76 (2.51) | 1.36 (2.17) |
| 0 | 56 724 (58.2%) | 5295 (52.5%) | 51 429 (58.9%) |
| 1-4 | 30 355 (31.1%) | 3334 (33.1%) | 27 021 (30.9%) |
| ≥5 | 10 373 (10.6%) | 1454 (14.4%) | 8919 (10.2%) |
| Body Mass Index** | | | |
| ≥25 kg/m² | 7169 (7.4%) | 631 (6.3%) | 6538 (7.5%) |
| ≥30 kg/m² | 5968 (6.1%) | 523 (5.2%) | 5445 (6.2%) |
| Smoking status | 2460 (2.5%) | 406 (4.0%) | 2054 (2.4%) |
| Hypertension | 21 236 (21.8%) | 2326 (23.1%) | 18 910 (21.6%) |

*(continued on next page)*

**Table 1** (*continued*)

| | Overall | Any pre-existing mental disorder | Control group |
|---|---|---|---|
| Cohort | 97 452 | 10 083 | 87 369 |
| **Baseline characteristics** | | | |
| Diabetes | 11 606 (11.9%) | 1163 (11.5%) | 10 443 (12.0%) |
|   Type 1 | 783 (0.8%) | 95 (0.9%) | 688 (0.8%) |
|   Type 2 | 11 027 (11.3%) | 1095 (10.9%) | 9932 (11.4%) |
| Dyslipidaemia | 4446 (4.6%) | 453 (4.5%) | 3993 (4.6%) |
| Heart disease | | | |
|   Ischemic heart disease | 6832 (7.0%) | 802 (8.0%) | 6030 (6.9%) |
|   Heart failure | 5717 (5.9%) | 624 (6.2%) | 5093 (5.8%) |
|   Arrhythmias | 10 290 (10.6%) | 1177 (11.7%) | 9113 (10.4%) |
| Stroke (ischemic or hemorrhagic) | 2837 (2.9%) | 484 (4.8%) | 2353 (2.7%) |
| Peripheral vascular disease | 2735 (2.8%) | 331 (3.3%) | 2404 (2.8%) |
| Chronic respiratory disease | 21 015 (21.6%) | 2115 (21.0%) | 18 900 (21.6%) |
| Chronic kidney disease | 9252 (9.5%) | 1068 (10.6%) | 8184 (9.4%) |
| Chronic liver disease | 2037 (2.1%) | 266 (2.6%) | 1771 (2.0%) |
| Cancer (solid tumour and haematological malignancy) | 7395 (7.6%) | 924 (9.2%) | 6471 (7.4%) |
| Immunodeficiency or organ transplant | 1147 (1.2%) | 108 (1.1%) | 1039 (1.2%) |
| **In-hospital outcomes** | | | |
| Length of hospital stay, days | | | |
|   Median (IQR) | 9 (4–15); ; ; | 10 (5–16); ; ; | 8 (4–15); ; ; |
|   Mean (SD) | 10 (12) | 12 (11) | 11 (12) |
| Length of ICU stay, days | | | |
|   Median (IQR) | 8 (4–17); ; ; | 7 (3–13); ; ; | 8 (4–17); ; ; |
|   Mean (SD) | 13 (15) | 11 (13) | 13 (16) |
| ICU admission | 15 200 (15.6%) | 898 (8.9%) | 14 302 (16.4%) |
| In-hospital deaths | 15 347 (15.7%) | 2036 (20.2%) | 13 311 (15.2%) |

Data are n (%), unless otherwise indicated. Comorbidities classified according to the 10th revision of the International Classification of Diseases (ICD-10) from the French medico-administrative database (PMSI) - Diagnosis-Related Groups (DRG) based hospital system. Control group of inpatients without pre-existing mental disorder documented before March 2020. Body mass index classes: 18.5 to 25 (normal weight); 25 to 30 (overweight); ≥30.0 or higher (obesity). ICU = intensive care unit.

Results of the propensity-matched cohorts for the primary and secondary outcomes are shown in Table 3. Compared with adults without any mental disorder, 30-days in-hospital mortality was increased among those with at least one pre-existing mental disorder (hazard ratio (HR) 1.15, 95% CI 1.08–1.23). When stratifying in-hospital mortality risk by psychiatric disorder diagnosis, the most robust associations were found for psychotic (1.90, 1.24–2.90), psychoactive substance disorders (1.53, 1.10–2.14) and patients with other disorders (1.62, 1.10–2.38). Greater HR of COVID-19 mortality were reported among people with bipolar disorder (1.34, 1.08–1.71, appendix, Table S10). Increased in-hospital mortality risk for these psychiatric diagnoses was confirmed in the competing risk analysis including mood disorders (1.21, 1.02–1.44). No significant association was found for anxiety disorders (0.99, 0.74–1.33) and major depressive disorders (1.17, 0.97–1.40). For the secondary endpoints, length of hospital stay was consistently higher in people with at least one mental disorder or by psychiatric diagnosis in all analyses performed. Compared with adults without any mental illness, the odds

of ICU admission were significantly lower among those with at least one pre-existing mental disorder (odds ratio (OR) 0.83, 95% CI 0.76–0.92) with decreased ICU length of stay. In subgroup analyses, adults with dementia and those with other disorders – including intellectual disabilities, eating and personality disorders – had also lower odds of ICU admission than matched control subjects (0.64, 0.53–0.76) and 0.53 [0.37–0.73], respectively). We found no clear difference in ORs in the other psychiatric subgroups.

### 3.3. Sensitivity analysis

We did several sensitivity analyses to assess the robustness of our results. When using a different definition considering 1968 patients identified with two or more diagnoses of mental disorders (19.5% of patients with any pre-existing mental disorder, Fig. S1), results for the primary and secondary endpoints were mostly consistent with those from the main analysis (Table 4).

As alternative to our primary approach, the adjustment using inverse propensity score weighting analysis did not change the estimates (appendix, Table S8). The increased in-hospital mortality risk remains similar to that observed in the propensity score method, but the odds of ICU admission was consistently decreased in patients with at least one mental disorder and in the dementia subgroup than in those without mental disorders.

### 4. Discussion

Using a nationwide exhaustive retrospective cohort of 97 452 adults hospitalised for COVID-19 from the French national administrative hospital database, we reported stratified in-hospital outcomes by psychiatric diagnoses suggesting that patients with a pre-existing mental disorder may be at an increased risk of COVID-19-related death and prolonged length of stay in hospital, albeit modest, with the greater hazard ratio for psychotic disorders. When compared to patients without mental disorder, we also reported disparities in ICU admission and length of ICU stay, with lower rates among subgroups with dementia and those with other disorders including intellectual disabilities, eating and personality disorders.

The data presented in this study provide a comprehensive evaluation of at-risk comorbidities and in-hospital outcomes in COVID-19 patients who had a pre-existing mental disorder compared with propensity-matched cohorts of patients without mental disorder. Our results provide national estimates for susceptible subgroups of severe mental illness at risk of severe COVID-19 outcomes and support predictions from previous studies and meta-analysis reporting the presence of any mental disorder as a predictive factor independently associated with the risk of COVID-19-related in-hospital mortality (Vai et al., 2021; Toubasi et al., 2021; Fond et al., 2021a; Nemani et al., 2021). We also extend previous contributions by evaluating a wide range of in-hospital outcomes with matched cohorts of patients with similar underlying comorbidities except for mental condition.

A study conducted in 5-hospital system in the Northeast of the United States found that patients with a psychiatric diagnosis had 1.5 times the risk of dying after adjustment for pretreatment risk factors compared with those with no psychiatric comorbidity (Li et al., 2020). Similar patterns were identified in a vast cohort study from the French claims database, reporting that people with psychotic disorders and dementia were twice as likely to die in hospital, a risk in the lower range of current estimates (Semenzato et al., 2021; Atkins et al., 2020). Higher risk of severe or fatal COVID-19 outcomes by specific mental disorders were also detected in large series of hospitalised patients with schizophrenia or bipolar disorders with strong disparities according to the age and socioeconomic deprivation status (Fond et al., 2021b, 2021c; Fornaro et al., 2021). Furthermore, significant associations were also suggested in a matched cohort study in the UK reporting that patients with intellectual disabilities were at increased risk of dying from COVID-19 (RR

**Table 2**

Baseline characteristics and in-hospital outcomes of unmatched adults hospitalised for COVID-19 stratified by psychiatric diagnosis: dementia disorders, mood disorders, anxiety disorders, psychoactive substance use, psychotic disorders and other disorders.

| | Dementia | Mood disorders | Anxiety disorders | Psychoactive substance use | Psychotic disorders | Other disorders |
|---|---|---|---|---|---|---|
| Subcohort | 3581 | 1298 | 995 | 960 | 866 | 415 |
| **Baseline characteristics** | | | | | | |
| Age, median years (IQR) | 85 (80–89) | 68 (52–82) | 64 (43–85) | 55 (44–67) | 60 (46–71) | 55 (46–66) |
| Sex | | | | | | |
|   Female | 1983 (44.6%) | 793 (61.1%) | 623 (62.6%) | 232 (24.2%) | 440 (50.8%) | 67 (41.6%) |
|   Male | 1598 (55.4%) | 505 (38.9%) | 372 (37.4%) | 728 (75.8%) | 426 (49.2%) | 94 (58.4%) |
| Mode of admission | | | | | | |
|   From home | 2906 (81.2%) | 1159 (89.3%) | 891 (89.5%) | 864 (90.0%) | 775 (89.5%) | 136 (84.5%) |
|   Other (hospital setting) | 675 (18.8%) | 139 (10.7%) | 104 (10.5%) | 96 (10.0%) | 91 (10.5%) | 25 (15.5%) |
| Hospital setting | | | | | | |
|   University hospital | 1116 (31.2%) | 557 (33.1%) | 304 (30.6%) | 326 (34.0%) | 345 (39.8%) | 57 (35.4%) |
|   Other public or private hospital | 2465 (68.8%) | 1236 (66.9%) | 691 (69.4%) | 634 (66.0%) | 521 (60.2%) | 104 (64.6%) |
| **Comorbidities** | | | | | | |
| At least one comorbidity | 1808 (50.5%) | 547 (42.1%) | 409 (41.1%) | 378 (39.4%) | 344 (39.7%) | 70 (43.5%) |
| Charlson Comorbidity Index | | | | | | |
|   0 | 1849 (51.6%) | 887 (68.3%) | 701 (71%) | 670 (69.8%) | 623 (71.9%) | 122 (75.8%) |
|   1-2 | 1216 (34.0%) | 311 (24.0%) | 217 (21.8%) | 197 (20.5%) | 199 (23.0%) | 33 (20.5%) |
|   ≥3 | 516 (14.4%) | 100 (7.7%) | 77 (7.7%) | 93 (9.7%) | 44 (5.0%) | 6 (3.8%) |
| Elixhauser Comorbidity Index | | | | | | |
|   0 | 1678 (46.9%) | 708 (54.5%) | 549 (55.2%) | 565 (58.9%) | 472 (54.5%) | 84 (52.2%) |
|   1-4 | 1313 (36.7%) | 413 (31.8%) | 307 (30.9%) | 253 (26.4%) | 296 (34.2%) | 59 (36.6%) |
|   ≥5 | 590 (16.5%) | 177 (13.6%) | 139 (14.0%) | 142 (14.8%) | 98 (11.3%) | 18 (11.2%) |
| **In-hospital outcomes** | | | | | | |
| Length of hospital stay, days | | | | | | |
|   Median (IQR) | 11 (6–17); ; ; | 9 (4–15); ; ; | 9 (4–15); ; ; | 7 (4–13); ; | 10 (5–17); ; ; | 8 (3–14); ; ; |
|   Mean (SD) | 13 (10) | 12 (11) | 11 (11) | 10 (11) | 12 (11) | 10 (10) |
| Length of ICU stay, days | | | | | | |
|   Median (IQR) | 7 (3–13.5) | 7 (4–13); ; | 7 (2–15.5) | 6 (3–12); ; | 9 (4–15); ; ; | 5 (4–8) |
|   Mean (SD) | 10 (11) | 11 (13) | 13 (16) | 10 (12) | 12 (11) | 9 (10) |
| ICU admission | 213 (5.9%) | 129 (10.0%) | 87 (8.7%) | 125 (13%) | 107 (12.4%) | 39 (8.9%) |
| In-hospital deaths | 1133 (31.6%) | 204 (15.7%) | 106 (10.7%) | 98 (10.2%) | 119 (13.7%) | 81 (20.2%) |

Data are n (%), unless otherwise indicated. ICU = intensive care unit.

Other psychiatric disorders included eating disorders, personality disorders and intellectual disabilities.

**Table 3**

Primary and second COVID-19 endpoints among patients with pre-existing mental disorders compared with a matched cohort of patients with no psychiatric disorder.

| | Any pre-existing mental disorder | Dementia | Mood disorders | Anxiety disorders | Psychoactive substance use | Psychotic disorders | Other disorders |
|---|---|---|---|---|---|---|---|
| **Primary endpoint** | | | | | | | |
| In-hospital mortality within 30 days | | | | | | | |
| Cox regression model[a] | 1.15 (1.08–1.23) | 1.13 (1.04–1.23) | 1.19 (1.00–1.42) | 0.99 (0.74–1.33) | 1.53 (1.10–2.14) | 1.90 (1.24–2.90) | 1.62 (1.10–2.38) |
| Competing risk model[b] | 1.24 (1.16–1.32) | 1.30 (1.19–1.43) | 1.21 (1.02–1.44) | 1.12 (0.83–1.51) | 1.49 (1.08–2.06) | 2.01 (1.46–2.78) | 1.96 (1.35–2.85) |
| **Secondary endpoints** | | | | | | | |
| Length of hospital stay[c] | 1.24 (1.20–1.28) | 1.20 (1.15–1.26) | 1.25 (1.15–1.35) | 1.23 (1.09–1.38) | 1.18 (1.04–1.34) | 1.43 (1.26–1.63) | 1.27 (1.07–1.50) |
| Length of ICU stay[c] | 0.85 (0.78–0.94) | 0.60 (0.43–0.84) | 0.75 (0.51–1.09) | 1.07 (0.78–1.47) | 0.75 (0.58–0.97) | 0.79 (0.61–1.03) | 0.54 (0.25–1.13) |
| ICU admission[d] | | | | | | | |
| PS-matched model | 0.83 (0.76–0.92) | 0.64 (0.53–0.76) | 0.97 (0.79–1.20) | 1.08 (0.76–1.54) | 1.26 (0.95–1.67) | 1.12 (0.77–1.64) | 0.53 (0.37–0.73) |
| PS-matched model (multivariable adjustment) | 0.82 (0.74–0.90) | 0.62 (0.52–0.75) | 0.97 (0.78–1.22) | 1.01 (0.69–1.47) | 1.27 (0.95–1.72) | 1.24 (0.83–1.87) | 0.51 (0.36–0.71) |

Effect sizes are reported with their 95% CIs and were calculated for each matched psychiatric diagnosis separately with the group without pre-existing mental disorder as the reference group. Other psychiatric disorders included eating disorders, personality disorders and intellectual disabilities.

[a] Hazard ratios calculated using cox regression model.

[b] Fine and Gray model performed using a subdistribution hazard function taking into account the competing event of being discharged alive.

[c] Incidence rate ratios (IRR) calculated using negative binomial regression model.

[d] Odds ratios calculated using binary logistic regression model in the PS-matched samples. Multivariable adjustment included age, sex, smoking status, obesity, chronic respiratory disease, chronic kidney disease, chronic lung disease, hypertension, diabetes mellitus, dyslipidaemia, cardiovascular disease, cerebrovascular disease, cancer, immunodeficiency or organ transplant and hospital category. ICU = intensive care unit, PS = propensity score.

1.56, 95% CI 1.17–2.02) after hospital admission compared to the general population (Baksh et al., 2021).

The relative increase in mortality and decrease in ICU admission reported in our study strongly remind that patients with severe mental disorders might be at higher risk of poor COVID-19 outcomes than patients without mental disorders independently of their main risk factors for COVID-19. Additionally, the associations remained for adults with multiple pre-existing mental disorders in sensitivity analysis.

As we accounted for a wide range of at-risk comorbidities at baseline, this suggest that multiple factors may explain disparities reported

**Table 4**

Primary and second endpoints between patients with two or more pre-existing mental disorders compared with a matched cohort of patients with no psychiatric disorder.

| | Any pre-existing mental disorder | Dementia | Mood disorders | Anxiety disorders | Psychoactive substance use | Psychotic disorders | Other disorders |
|---|---|---|---|---|---|---|---|
| **Primary endpoint** | | | | | | | |
| In-hospital mortality within 30 days | | | | | | | |
| Cox regression model[a] | 1.29 (1.09–1.51) | 1.23 (1.00–1.53) | 1.37 (1.08–1.74) | 0.98 (0.74–1.31) | 1.17 (0.77–1.76) | 1.55 (1.11–2.17) | 1.63 (1.12–2.36) |
| Competing risk model[b] | 1.62 (1.37–1.91) | 1.50 (1.22–1.86) | 1.67 (1.31–2.12) | 1.28 (0.96–1.72) | 1.49 (1.08–2.06) | 1.88 (1.34–2.64) | 2.18 (1.50–3.16) |
| **Secondary endpoints** | | | | | | | |
| Length of hospital stay[c] | 1.28 (1.19–1.37) | 1.29 (1.17–1.42) | 1.24 (1.13–1.36) | 1.37 (1.22–1.54) | 1.25 (1.09–1.45) | 1.49 (1.30–1.70) | 1.29 (1.11–1.50) |
| Length of ICU stay | 0.71 (0.52–0.98) | 0.61 (0.44–0.87) | 0.88 (0.70–1.11) | 0.90 (0.67–1.21) | 1.02 (0.76–1.37) | 0.91 (0.70–1.19) | 0.62 (0.32–1.21) |
| ICU admission[d] | 0.76 (0.64–0.91) | 0.60 (0.41–0.85) | 0.86 (0.67–1.09) | 1.05 (0.77–1.42) | 0.89 (0.66–1.20) | 0.95 (0.70–1.29) | 0.57 (0.43–0.75) |

Effect sizes are reported with their 95% CIs and were calculated for each matched psychiatric diagnosis separately with the group without pre-existing mental disorder as the reference group. Other psychiatric disorders included eating disorders, personality disorders and intellectual disabilities.

[a] Hazard ratios calculated using cox regression model.

[b] Fine and Gray model performed using a subdistribution hazard function taking into account the competing event of being discharged alive.

[c] Incidence rate ratios (IRR) calculated using negative binomial regression model.

[d] Odds ratios calculated using binary logistic regression model in the PS-matched samples. Multivariable PS-matched models for ICU admission were not applied to avoid potential overfitting. ICU = intensive care unit, PS = propensity score.

among patients with mental disorders. A reduced access to primary and hospital care cannot be excluded to explain the difference in our primary and secondary endpoints. Previous studies found that medical behaviors differ between patients with or without mental disorders which may delay access to hospital or critical care and consequently explain the higher risk of death reported (Gervaix et al., 2019). Additional barriers due to care disruptions during the earlier stage of the COVID-19 pandemic may also increase these disparities in access to care along with the severity of patients at hospital admission (Busch et al., 2022). Dementia diagnosis has been identified as a significant risk factor for hospitalisation and death in COVID-19 patients (Semenzato et al., 2021; Williamson et al., 2020). Thus, severe mental disorders considered in the study sample are among the poorest prognosis factors for ICU admission. This is consistent with other findings reporting ICU admission as an important indicator in times of difficult access to healthcare resources (Anantham et al., 2020). Likewise, mental illness-related stigma may also have undesirable consequences for patients needing immediate therapeutic. Moreover, data from a European multicenter cohort study showed that the prevalence of frailty was associated with higher mortality and time to discharge among COVID-19 inpatients (Hewitt et al., 2020). In this respect, higher rates of frailty previously reported among patients with severe mental illness may also have detrimental impact on COVID-19 prognosis which is also a factor related with the decision-making process for ICU triage (Azoulay É et al., 2020; Pearson et al., 2022).

Although the mechanism underlying this association is not well understood, immune dysregulation including prolonged activation of stress responses have been reported, in particular among patients with schizophrenia which may increase COVID-19 severe outcomes (International Schizophrenia Consortium Purcell et al., 2009; Yuan et al., 2019). Anxiety disorders have also been associated with altered immune or inflammatory pathways, however no increased risk of mortality was found in our study (Nemani et al., 2021; Costello et al., 2019). Lastly, unmeasured conditions such as low socio-economic and lifestyle-related risk factors could contribute to these findings (Semenzato et al., 2021; Hamer et al., 2020).

Public health authorities in several countries have incorporated patients with severe mental illness in their national recommendations from the earlier stage of the COVID-19 vaccine roll-out and our results support evidence that individuals with severe mental illness need to be considered as priority groups for COVID-19 vaccination or booster dose on the basis of a pre-existing comorbidity (Kumar et al., 2021). Hence,

health-care practitioners should refer inpatients or outpatients with severe mental disorders on a priority basis to ensure these populations to be vaccinated at the same rate than other high-risk groups for COVID-19 (De Picker et al., 2021).

The strengths of this study include the detailed in-hospital baseline characteristics and clinical outcomes of adults hospitalised with COVID-19 using in a nationwide cohort study during the first wave of the pandemic. Moreover, the sample size allowed the use of propensity score matching to control for many covariates among psychiatric subgroups, with time-to-event and a wide range of sensitivity analyses. This study also has important limitations. As a retrospective study, we cannot exclude residual confounding or unmeasured confounding by factors not included in our analysis. Moreover, data on anti-COVID-19 treatments used in the first wave of the pandemic and psychotropics were not available in the PMSI database. We did not investigate the association of previous exposure to antipsychotic, anxiolytic or antidepressant drugs which have been shown to associated with an increased risk of death or severe COVID-19 events (Vai et al., 2021; Poblador-Plou et al., 2020). Pre-existing psychiatric status were identified using hospital database which did not allow to capture individuals with less severe forms treated outside the hospital and limited the interpretation of our results. Future studies should focus on ambulatory data to address this issue. As the PMSI database did not collect data on outpatient care utilization, delayed access to adequate care may in part explain the increase in severity. Although we used an administrative health database covering the entire reference population for hospitalised patients in France, available data including demographics and diagnoses (using codes from ICD-10) depend on the availability and the quality of the coding (Haute Autorité de santé (HAS), 2019). Finally, our results were obtained in the setting of the French health care system while differences may exist with other countries, including dynamic of COVID-19 infections, testing strategies, accessibility to care for patients with mental disorders or possible health care resources during the pandemic. Comparison with reliable in-hospital estimates from other countries will help to determine the influence of at-risk comorbidities, psychotropics or delayed treatment on the occurrence of severe COVID-19 outcomes among the psychiatric population and better allocate health care resources for at-risk subgroups for patients with severe mental disorders.

## 5. Conclusion

In this large analysis from a nationwide health administrative

database, we reported possible evidence of an association between a pre-existing mental disorder and poor in-hospital outcomes, independently of patient-level confounders that could be risk factors for COVID-19. These results indicate the important need for adequate care and targeted interventions, including prioritizing COVID-19 vaccination, for at-risk patients with severe mental disorders.

## Author contributions

A. Descamps, O. Launay, M. Leboyer and I. Durand-Zaleski conceptualized the original study. A. Descamps, J. Frenkiel, K. Zarca, and I. Durand-Zaleski developed the methodology. A. Descamps performed the analysis and wrote the original manuscript. M. Leboyer, C. Laidi, O. Godin, J. Frenkiel, K. Zarca, and O. Launay critically reviewed the manuscript and agreed to be accountable for all aspects of the work. I. Durand-Zaleski and M. Leboyer supervised the research. Data processing and analysis performed in this study were compliant to the Reference Methodology (MR-004) in health research from the French data protection authority (CNIL).

## Declaration of competing interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.08.019.

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