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COVID-19 mortality in schizophrenia

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Les auteurs déclarent ne pas avoir de liens d'intérêts.

Abstract (limited 250)

Background. There is limited information describing the presenting characteristics and outcomes of patients with schizophrenia (SCZ) requiring hospitalization for coronavirus disease 2019 (COVID-19).

Aims. We aimed to compare the clinical characteristics and outcomes of COVID-19 SCZ patients with those of non-SCZ patients.

Method. This was a case-control study of COVID-19 patients admitted to 4 APHM/AMU acute care hospitals in Marseille, southern France. COVID-19 infection was confirmed by a positive result on polymerase chain reaction testing of a nasopharyngeal sample and/or on chest computed scan among patients requiring hospital admission. The primary outcome was in-hospital mortality. The secondary outcome was intensive care unit (ICU) admission.

Results. A total of 1092 patients were included. The overall in-hospital mortality rate was 9.0%. The SCZ patients had an increased mortality compared to the non-SCZ patients (26.7% vs. 8.7%, p=0.039), which was confirmed by the multivariable analysis after adjustment for age, sex, smoking status, obesity and comorbidity (adjusted odds ratio 4.36 [95% CI 1.09-17.44]; p=0.038). In contrast, the SCZ patients were not more frequently admitted to the ICU than the non-SCZ patients. Importantly, the SCZ patients were mostly institutionalized (63.6%, 100% of those who died), and they were more likely to have cancers and respiratory comorbidities.

Conclusions. This study suggests that SCZ is not overrepresented among COVID-19 hospitalized patients, but SCZ is associated with excess COVID-19 mortality, confirming the existence of health disparities described in other somatic diseases.

Key words: Schizophrenia; Psychiatry; COVID-19; observational study.

Research in context

Evidence before this study.

Schizophrenia (SCZ) patients are a population at particular risk of poor COVID-19 outcomes and it remains unclear if they are at increased risk of covid-19 infection. Among COVID-19 infection risk factors identified in schizophrenia, the presence of comorbidities, poor insight into somatic symptoms, stigma experience, delusions and cognitive impairment leading to a misperception of the risk related to the virus have been identified. Moreover schizophrenia patients are more frequently hard smokers with lower vitamin D levels and it is unclear how it may impact their chance of surviving to COVID-19. It has been already shown that they do not benefit from the same somatic care than patients without psychiatric disorders in their end-of-life of cancer for example. However it was unknown whether COVID-19 patients with SCZ benefit from the same care as non-SCZ patient.

Added value of this study.

This study is the first large cohort of sequentially hospitalized confirmed COVID-19 patients with and without SCZ. A total of 1092 patients were included in the analysis, with 15 patients with SCZ (frequency=1.37%, 95% confidence interval (CI) from 0.68 to 2.06). The SCZ patients were more likely to be smokers and to have cancers and respiratory comorbidities than the non-SCZ controls. They were mostly institutionalized (63.6%, 100% of those who died) and elderly.

The overall in-hospital mortality rate was 9.0%. SCZ patients had an increased mortality compared to non-SCZ patients (26.7% vs. 8.7%, p=0.039), which was confirmed by the multivariable analysis after adjustment for age, sex, smoking status, obesity and Charlson comorbidity index (adjusted odds ratio (aOR) 4.36 [95% CI 1.09-17.44]; p=0.038)

A total of 191 patients (17.5%) were admitted to the ICU. The SCZ patients were not more frequently admitted to the ICU than the patients without schizophrenia. None of the deceased SCZ patients were admitted to ICU vs. 28.7% (27/94) for patients without SCZ.

Implications of all the available evidence.

The mortality in SCZ patients was 3 times higher than that of the non-schizophrenia patients after adjustment for age, sex, smoking status, obesity and comorbidities confirming the existence of health disparities as already described in other somatic diseases. Contrary to what could have been expected, SCZ is not overrepresented among COVID-19 hospitalized patients compared to the prevalence of SCZ in the general population.

A delay in access to hospital care may be suggested by the higher respiratory rate at admission in patients with SCZ compared to patients without schizophrenia. None of the four non-survivor SCZ patients were admitted to the ICU, which would deserve to be better understood: advanced age and co-morbidities, cognitive impairment or death occurring before ICU admission.

Around three-quarters of the SCZ patients were institutionalized, and 100% of the SCZ patients who died were institutionalized. Contrary to what could have been expected, the SCZ patients were not younger than the non-SCZ patients, while their life expectancy is generally reduced compared to the general population. This result is in favor of a risk increase in institutionalized SCZ patients and against an increased risk of COVID-19 infection in the global SCZ population. Our results support a strategy of systematic detection in institutionalized SCZ patients.

Introduction

Only five months after the appearance of COVID-19, the disease caused by the coronavirus that appeared in China in December 2019, France has been bearing the full brunt of the health crisis that has been unleashed across the planet. On January 24th, 2020, the French Ministry of Health reported the first two cases in France; both were infected in China, where they had recently traveled. The first death due to the COVID-19 was registered on February 14th, 2020, in an older Chinese tourist. The next day, a religious demonstration brought 2,000 people together in the town of Mulhouse in East France, which was likely to be the starting point for serial contamination throughout the country, from Corsica to French Guiana, and from the Hautes-Alpes to Normandy and the Ile-de-France region. On April 4th, France reached an unprecedented milestone: 6,838 patients were hospitalized in intensive care unit (ICU), a record "in French medical history"(1).

Among all specific populations that may have a particularly poor COVID-19 outcome, patients with schizophrenia (SCZ) should be given particular attention. Since the Second World War, when SCZ patients died massively in asylums from malnutrition (the so-called "*extermination douce*" (gentle extermination)(2)), the somatic care of patients with SCZ has lagged behind that of other mentally healthy patients. We have recently found, in a national database study, that patients with schizophrenia received less high-intensity care than those without severe mental disorder(3), and it is unknown whether COVID-19 patients with SCZ benefit from the same care as non-SCZ patients. In summary, COVID-19 may strongly impact SCZ patients and the health and economic disparities they experience(4).

It also remains unknown whether SCZ is a risk factor for COVID-19 infection and/or COVID-19 mortality. Among COVID-19 risk factors, presence of comorbidities, poor insight into somatic symptoms, stigma experience, delusions and cognitive impairment leading to a misperception of the risk related to the virus have been identified(4). The prevalence of tobacco smoking is higher in patients with SZ than in the general population, with higher rates of heavy smokers and nicotine dependence(5), yet it remains unclear whether smoking is a protective factor or a risk factor for COVID-19 infection and mortality(6). Hypovitaminosis D has been identified in 27% of patients with SCZ vs. 21% of the general population(7), yet it remains unknown whether hypovitaminosis D may modify the risk for COVID-19 infection and/or mortality(8). SCZ

is also a risk factor for homelessness or institutionalization, which may mediate the risk for increased COVID-19 infection and/or mortality(9). In addition to these multiple risk factors for poor COVID-19 outcomes, active social withdrawal is one of the most frequent negative symptoms of SCZ that may protect noninstitutionalized patients from infection through spontaneous lock-down and social distancing.

The objective of the present study was to compare the presenting characteristics and outcomes of COVID-19 patients with SCZ with COVID-19 patients without SCZ.

Methodology

Setting

This study was conducted at Assistance Publique – Hôpitaux Marseille (APHM) – Aix-Marseille University (AMU), a quaternary, acute care hospital system in Marseille, southern France. APHM/AMU comprises four hospitals (La Timone, La Conception, Sainte-Marguerite, and North), 3,400 beds, and 2,000 physicians. Approximately 300,000 hospitalizations are recorded every year, involving approximately 200,000 patients. All consecutive patients who were sufficiently medically ill to require hospital admission with confirmed COVID-19 infection by positive result on polymerase chain reaction testing (PCR) of a nasopharyngeal sample and/or by chest computed scan (*i.e.*, extended bilateral ground-glass opacities and area of consolidation) were included. Eligible patients were admitted to any of 4 APHM/AMU acute care hospitals from February 27, 2020, to April 15, 2020. Clinical outcomes were monitored until May 4, 2020, the final date of follow-up. The APHM/AMU institutional review board (CADS) approved this work as minimal-risk research using data collected for routine clinical practice (CADS identifier: Q7APAN-M9GR8M-2020).

Data sources and collection

Data were obtained from the APHM/AMU clinical data warehouse. This warehouse contains all the clinical data available on all inpatient visits to one of the APHM/AMU facilities. No data were manually abstracted from the electronic medical record or charts. The data obtained

included patients' sociodemographic data, clinical data (*i.e.*, smoking status, overweight and obesity, symptoms, Charlson comorbidity index score(10) and main comorbidities), triage vital signs, initial laboratory test results, initial COVID-19 treatment, ICU admission, Simplified Acute Physiology Score II (SAPS II), length of ICU stay and ICU management (*i.e.*, mechanical ventilation, renal replacement therapy), palliative care, and outcomes (*i.e.*, length of hospital stay and in-hospital mortality). Clinical data, ICU admission and treatments, palliative care and outcomes were based on the 10th revision of the International Statistical Classification of Diseases (ICD10) and procedural codes were based on the classification commune des actes médicaux (CCAM) associated the French from the Programme de Medicalisation des Systèmes d'Information (PMSI) - French medico-administrative database based on diagnosis related-groups (DRGs). The Charlson comorbidity index predicts 10-year survival in patients with multiple comorbidities and was used as a measure of total comorbidity burden(10). The protocol recommended by a medical team from Marseilles for COVID-19 treatment was a combination of hydroxychloroquine (200 mg of oral hydroxychloroquine, three times daily for ten days) and azithromycin (500 mg on day 1 followed by 250 mg daily for the next four days)(11) thus explaining the important amount of this prescription in our study.

Definition of cases and controls

Cases were patients who had a diagnosis of SCZ according to specific ICD10 codes (i.e., F20*, F22*, or F25*). Controls were patients who did not have a diagnosis of mental illness according to specific ICD10 codes in the acute care database and who were not listed in the psychiatry databases.

Outcomes

The primary outcome was in-hospital mortality. The secondary outcome was ICU admission.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges. Categorical variables were summarized as counts and percentages. No imputation was made for missing data.

We used either the χ2 or Fisher's exact test and Student's t test or Mann-Whitney test to compare sociodemographic data, clinical data, triage vital signs, initial laboratory test results, initial COVID-19 treatment, ICU admission and treatments, palliative care, and outcomes between cases and controls. Then, multivariable logistic regression models were used to estimate the association between schizophrenia and the two endpoints. An initial multivariable regression model (model 1) included the main known prognostic factors: age, sex, smoking status, overweight and obesity, and Charlson comorbidity index. Two additional models were also performed, including prognosis factors previously listed and the two main COVID-19 treatments delivered in our institution (model 2: hydroxychloroquine and model 3: hydroxychloroquine-azithromycin combination). A significance threshold of p<0.05 was used. All analyses were performed in SAS (version 9.4).

Results

Characteristics of the patients

During the study period, a total of 1092 patients were included in the analysis (median age, 63 years [interquartile range [IQR], 51-76]; 46.7% female with no significant differences between SCZ and non-SCZ), with 15 SCZ patients (frequency=1.37%, 95% confidence interval (CI) from 0.68 to 2.06) and 1077 non-SCZ patients (98.63%) **(Figure 1, Table 1)**. The SCZ patients were more likely to be smokers (33.3%vs.11.1%, p=0.021) and to have cancers (20.0%vs. 5.5%, p=0.049) and respiratory comorbidities (26.7%vs.4.9%, p=0.006) than the non-SCZ controls. The SCZ patients had a higher level of creatinine kinase (213.5 IU/L vs. 98.0 IU/L, p=0.015) and a lower level of total bilirubin (4.5 μmol/L vs. 7.0 μmol/L, p=0.006) than the non-SCZ controls. A qualitative analysis of the 15 SCZ patients is presented in Supplementary Table S1. They were mostly institutionalized (63.6%, 100% of those who died) and elderly. The length of hospital stay was similar in the SCZ and non-SCZ patients (median [IQR] 10 days [7-15] vs. 7 [4-14] p=0.196).

In-hospital Mortality

The overall in-hospital mortality rate was 9.0%. The univariable analysis is presented in **Supplementary Table S2**. SCZ patients had an increased mortality compared to non-SCZ patients (26.7% vs. 8.7%, p=0.039) **(Table 2)**, which was confirmed by the multivariable analysis after adjustment for age, sex, smoking status, obesity and Charlson comorbidity index (model 1) (adjusted odds ratio (aOR) 4.36 [95% CI 1.09-17.44]; p=0.038) **(Table 3)**. The additional models (2 and 3) reported the same findings.

ICU admission

A total of 191 patients (17.5%) were admitted to the ICU (median SAPS II, 34.5 [IQR], 29-43; median SAPS II in the non-SCZ-patients, 35.0 [IQR], 29-43; and SAPS II in the two SCZ patients were 25 and 34 respectively). The univariable analysis is presented in **Supplementary Table S3**. The SCZ patients were not more frequently admitted to the ICU than the non-SCZ patients (13.3% vs. 17.6%, p=0.265; aOR 0.46 [95% CI 0.10-2.18]; p=0.330) (model 1) **(Table 3)**. The additional models (2 and 3) reported the same findings. None of the deceased SCZ patients were admitted to ICU vs. 28.7% (27/94) for non SCZ patients. The median length of ICU stay was 12.0 [IQR], 4.0-28.0, 13.0[IQR], (4.0-28.0) in the non-SCZ patients and the length of ICU stay for the 2 SCZ patients was 3 days and 5 days respectively.

Discussion

To our knowledge, this study is the first preliminary cohort of sequentially hospitalized confirmed COVID-19 patients with SCZ and non-SCZ. The mortality of the SCZ patients was 3 times higher than that of the non-SCZ patients after adjustment for age, sex, smoking status, obesity and comorbidities.

The first major finding of this study is that SCZ is not overrepresented among COVID-19 hospitalized patients compared to the prevalence of SCZ in the general population (between 0.5 and 1.5% in most countries)(12,13). Our data do not suggest that SCZ patients are more at risk of COVID-19 than the general population, contrary to what could have been expected(4). However, we cannot rule out the

possibility of a higher risk of COVID-19 in SCZ patients outside the hospital who have poor access to hospital care(14) and/or out-of-hospital deaths. Future studies should estimate the prevalence and management of COVID-19 for SCZ patients outside the hospital.

SCZ was associated with excess mortality after adjustment for age, sex, smoking status, obesity and comorbidity, underlining the existence of health disparities in COVID-19 as already described in other somatic diseases (3,15). Previous studies reported health care disparities in SCZ patients(16). A delay in access to hospital care may be suggested by the higher respiratory rate at admission in patients with SCZ patients compared to non-SCZ patients. Respiratory rate has been reported as an important indicator of serious illness(17). However, we have no precise information on the delay between the onset of infection and hospitalization. Further studies will need to explore access to hospital care in SCZ patients with COVID-19. In our study, we found no differences in the treatment protocol administered to SCZ patients compared to non-SCZ patients, and increased mortality remained significant after adjustment for treatment administration. We found no difference in access to the ICU. However, none of the SCZ patients who died were admitted to the ICU, which would deserve to be better understood: advanced age and co-morbidities, cognitive impairment or death occurring before ICU admission (for instance massive pulmonary embolism)(3). Factors consistently found in the literature to be associated with a decision to admit or refuse a patient to the ICU are bed availability, severity of illness, initial ward or team the patient was referred from, patient preference, do not resuscitate order status, age and functional status at baseline(18). Future studies (based on qualitative studies with ICU clinicians and national medico-administrative studies) should thus explore ICU admission in SCZ patients with COVID-19.

One major finding emerging from the qualitative analysis is that around two thirds of the SCZ patients were institutionalized, and 100% of the SCZ patients who died were institutionalized. We lack national data on the rate of elderly SCZ patients who are institutionalized, yet we can reasonably hypothesize that institutionalization is a risk factor for COVID-19 severe infection in elderly patients with SCZ. Hence preventive measures should target this population. Contrary to what could have been expected, the SCZ patients were not younger than the non-SCZ patients, while their life expectancy is generally reduced compared to the general population (19). This result is also in favor of a risk increase in

institutionalized SCZ patients and against an increased risk of COVID-19 infection in the global SCZ population. However, these results should be interpreted with caution, as we only identified 15 SCZ patients, and these results should be replicated in future wider databases. Our results support a strategy of systematic detection in institutionalized SCZ patients. This has already been done in a homeless shelter in Boston where 36% of the residents tested positive(20).

Limitations

This study had several limitations. First, the study population only included patients within the Marseilles metropolitan area, which may limit the generalizability of these results. Second, the sample size for the SCZ patients was limited (N=15). However, this first description of real-life data in patients with SCZ could be shared with other institutions and countries to achieve a larger sample and to provide a more complete picture of SCZ and COVID-19(21). Third, the data were collected from the electronic health record database. This precluded the level of detail that would have been possible with a manual medical record review. Additional limitations of our study include missing data for some variables and potential for inaccuracies in the electronic health records.

Strengths

This study is the first to explore the in-hospital mortality of SCZ patients due to COVID-19 infection. The results were adjusted for important confounding factors and suggest a remaining 3-fold increase in in-hospital mortality risk in SCZ patients.

Conclusion

This study suggests that SCZ may not be overrepresented among COVID-19 hospitalized patients compared to the prevalence of SCZ in the general population but that SCZ is associated with increased in-hospital mortality, confirming the existence of health disparities as already described in other somatic diseases. COVID-19 seemed to affect mostly institutionalized and elderly patients. These real-life health data should be shared with other health data producers to achieve a larger sample and to provide a more complete picture of SCZ and COVID-19.

Conflicts of interest. No conflicts to disclose.

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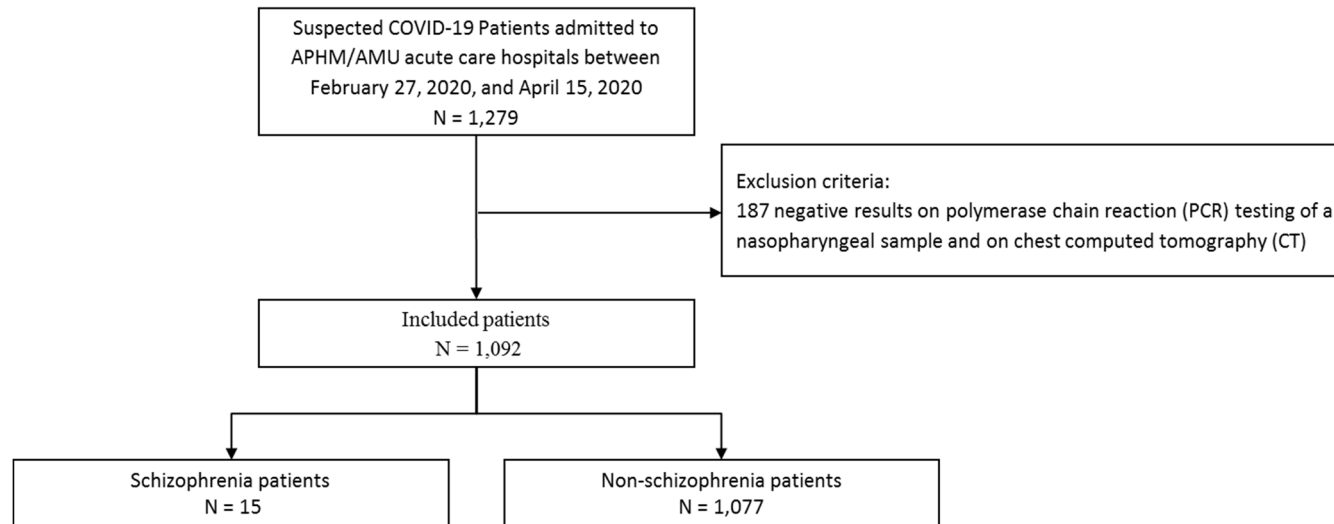
Figure 1. Flowchart.

Table 1. Baseline Characteristics of Patients Hospitalized With COVID-19 (n=1092).

Characteristics	Total	SCZ patients	Non-SCZ patients	p-value
	n=1092	n=15	n=1077	
	n(%)	n(%)	n(%)	
Socio-demographic data				
Age, median (IQR) — yr	62.5(51.0-76.0)	66.0(63.0-72.0)	62.0(51.0-76.0)	0.345
<18 yr	19(1.7)	0(0.0)	19(1.8)	0.714
18-65 yr	587(53.8)	7(46.7)	580(53.9)	
>65 yr	486(44.5)	8(53.3)	478(44.4)	
Male sex — no. (%)	593(54.3)	11(73.3)	582(54.0)	0.136
Clinical data				
Smoker	125(11.5)	5(33.3)	120(11.1)	**0.021**
Weight*				0.710
Normal weight	749(68.6)	10(66.7)	739(68.6)	
Overweight	128(11.7)	1(6.7)	127(11.8)	
Obesity	215(19.7)	4(26.7)	211(19.6)	
Symptoms				
Agueusia and/or anosmia	184(16.9)	2(13.3)	182(16.9)	0.999
Digestive symptoms (Diarrhea and/or nausea or vomiting)	250(22.9)	4(26.7)	246(22.8)	0.758
Respiratory symptoms (cough and/or pharyngitis and/or dyspnea and/or hemoptysis)	795(72.8)	11(73.3)	784(72.8)	0.999
General symptoms (asthenia and/or headache and/or myalgia/arthralgia)	532(48.7)	3(20.0)	529(49.1)	**0.025**
Comorbidities				

Charlson Comorbidity Index score				0.389
0	540(49.5)	8(53.3)	532(49.4)	
1-2	372(34.1)	3(20.0)	369(34.3)	
≥3	180(16.5)	4(26.7)	176(16.3)	
Cancer	62(5.7)	3(20.0)	59(5.5)	**0.049**
Hypertension	393(36.0)	0(0.0)	393(36.49)	**0.003**
Myocardial infarction	38(3.5)	1(6.7)	37(3.4)	0.412
Congestive Heart Failure	104(9.5)	2(13.3)	102(9.5)	0.647
Chronic renal disease	90(8.2)	1(6.7)	89(8.3)	0.999
Asthma	71(6.5)	1(6.7)	70(6.5)	0.999
Chronic pulmonary disease	57(5.2)	4(26.7)	53(4.9)	**0.006**
Liver disease	33(3.0)	0(0.0)	33(3.1)	0.999
Diabetes	260(23.4)	1(6.7)	259(24.1)	0.138
Vital signs				
Fever (≥38°C)	680(62.3)	10(66.7)	670(62.2)	0.723
Heart rate ≥100 beats/min	174(15.9)	3(20.0)	171(15.9)	0.719
Respiratory rate >24 cycles/min	229(21.0)	7(47.7)	222(20.6)	**0.022**
Initial laboratory findings, median (IQR)				
White-cell count (x10−9/L)	5.9(4.5-7.8)	6.2(4.9-10.0)	5.9(4.5-7.8)	0.270
Platelet count (x10−9/L)	205.0(159.0-255.0)	224.0(184.0-277.0)	204.5(159.0-255.0)	0.212
C-reactive protein (mg/L)	44.3(9.2-101.1)	52.0(9.5-168.0)	44.2(9.2-100.7)	0.378
Creatine kinase (U/L)	98.0(60.0-209.0)	213.5(134.5-340.0)	98.0(60.0-209.0)	**0.015**
Lactate dehydrogenase (U/L)	287.0(219.0-385.0)	324.0(255.0-469.0)	287.0(219.0-385.0)	0.355
Aspartate aminotransferase	37.0(27.0-55.0)	43.0(35.0-	37.0(27.0-	0.197

(U/L)		59.0)	55.0)	
Alanine aminotransferase (U/L)	27.0(19.0-41.0)	30.0(25.0-36.0)	27.0(19.0-41.0)	0.571
Total bilirubin (µmol/L)	7.0(5.0-10.0)	4.5(4.0-7.0)	7.0(5.0-10.0)	**0.006**
Creatinine (µmol/L)	77.0(62.8-98.0)	83.1(63.2-128.6)	77.0(62.8-98.0)	0.437
Sodium (mmol/L)	137.0(135.0-140.0)	138.0(135.0-140.0)	137.0(135.0-140.0)	0.642
Potassium (mmol/L)	4.0(3.7-4.3)	4.0(3.8-4.3)	4.0(3.7-4.3)	0.704
COVID-19 treatment initiated at admission				
Hydroxychloroquine	584(53.5)	5(33.3)	579(53.8)	0.115
Hydroxychloroquine-Azithromycin combination	399(36.5)	5(33.3)	394(36.6)	0.795
Antiviral agents	48(4.4)	0(0.0)	48(4.5)	0.999
Immunosuppressors	40(3.7)	0(0.0)	40(3.7)	0.999

*If Body Mass Index (BMI) is 18.5 to <25: normal weight; If BMI is 25.0 to <30: overweight; If BMI is 30.0 or higher: obesity.

Symptoms and comorbidities based on the 10th revision of the International Statistical Classification of Diseases from the Programme de Medicalisation des Systèmes d'Information (PMSI) - French medico-administrative database based on diagnosis related-groups (DRG).

p-value in bold: statistical significance.

Table2. Clinical outcomes and management of patients hospitalized with COVID-19 (n=1092).

	Total n=1092 n(%)	SCZ patients n=15 n(%)	Non-SCZ patients n=1077 n(%)	p-value
Outcomes and management				
In-hospital mortality	98(9.0)	4(26.7)	94(8.7)	**0.038**
ICU admission	191(17.5)	2(13.3)	189(17.6)	0.999
Recourse to mechanical ventilation	106(9.7)	1(6.7)	105(9.8)	0.999
Recourse to continuous renal-replacement therapy	21 (1.9)	0(0.0)	21 (2.0)	0.999
Palliative care	49(4.5)	1(6.7)	48(4.5)	0.500
Characteristics of stay				
Length of ICU stay, median (IQR)— no. of days	12.0(4.0-28.0)	-*	13.0(4.0-28.0)	-
Length of hospital stay, median (IQR)— no. of days	7.0(4.0-14.0)	10(7.0-15.0)	7.0(4.0-14.0)	0.196

Data based on the 10th revision of the International Statistical Classification of Diseases and common classification of medical acts from the Programme de Medicalisation des Systèmes d'Information (PMSI) - French medico-administrative database based on diagnosis related-groups (DRG).

ICU: Intensive care unit.

*Two SCZ patients were admitted to ICU with a length of ICU stay of 3 days and 5 days respectively.

p-value in bold: statistical significance.

Table 3. Associations between schizophrenia and in-hospital mortality and ICU admission (n=1092).

	In-hospital mortality		ICU admission	
	OR (95% CI)	p value	OR (95% CI)	p value
Without adjustment	3.80(1.19-12.20)	**0.025**	0.72(0.16-3.20)	0.671
With adjustment				
Model 1[a]	4.36(1.09-17.44)	**0.038**	0.46(0.10-2.18)	0.330
Model 2[b]	4.28(1.07-17.20)	**0.040**	0.53(0.11-2.61)	0.439
Model 3[c]	4.33(1.08-17.34)	**0.038**	0.46(0.10-2.23)	0.239

[a] Model 1: adjustment for 5 variables associated with COVID-19 outcome (age, sex, smoking status, obesity, Charlson comorbidity index)
[b] Model 2: adjustment for 6 variables associated with COVID-19 outcome (age, sex, smoking status, obesity, Charlson comorbidity index) and the initial COVID-19 treatment (hydroxychloroquine)
[c] Model 3: adjustment for 6 variables associated with COVID-19 outcome (age, sex, smoking status, obesity, Charlson comorbidity index) and the initial COVID-19 treatment (Hydroxychloroquine- Azithromycin combination)

OR (95% CI): Odds Ratios (95% confidence interval).

ICU: intensive care unit.

p-value in bold: statistical significance.