López-Cuadrado, Teresa; Szmulewicz, Alejandro; Öngür, Dost; Martínez-Alés, Gonzalo. **Clinical characteristics and outcomes of people with severe mental disorders hospitalized due to COVID-19: A nationwide population-based study**. Gen Hosp Psychiatry. 2023 Sep-Oct:84:234-240.

https://doi.org/10.1016/j.genhosppsych.2023.08.004

Clinical Characteristics and Outcomes of People with Severe Mental Disorders Hospitalized due to COVID-19: A nationwide population-based study

Running title: COVID-19 hospitalization and severe mental illness

Teresa López-Cuadrado[1], Alejandro Szmulewicz[2], Dost Öngür[3], Gonzalo Martínez-Alés[2,4,5]

[1] Department of Chronic Diseases Epidemiology, National Center for Epidemiology, Carlos III Health Institute, Madrid, Spain.

[2] CAUSALab, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

[3] Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, MA, USA; Psychotic Disorders Division, McLean Hospital, Belmont, Massachusetts.

[4] Mental Health Network Biomedical Research Center (CIBERSAM), Madrid, Spain

[5] Hospital La Paz Institute for Health Research (IDIPaz), Madrid, Spain

Corresponding author:

Teresa López-Cuadrado, PhD. National Centre for Epidemiology. Instituto de Salud Carlos III

Monforte de Lemos 5, 28029 Madrid (Spain). Telephone: +34 918222693. Fax: +34 913877815

E-mail: teresalc@isciii.es

Word count (text): 2910

Tables: 3

Figures: 1

Supplement: 1 file (5 tables)

Acknowledgments

We would like to thank the Sub-Directorate General for Healthcare Information of the Spanish Ministry of Health for providing the data used in this study.

Author contributions

TLC and GMA conceptualised and designed the study. TLC performed the statistical analyses. TLC and GMA wrote the initial manuscript. All authors (TLC, AS, DO and GMA) contributed to the article and approved the final version

Funding Statement

This research was supported by the Instituto de Salud Carlos III (grant number PI19CIII/00037), the National Institutes of Mental Health (grant number P50MH115846), and an ASISA-Harvard Fellowship. Dr. Öngür received honoraria from Neumora Inc. and Guggenheim LLC for scientific presentations in the past 36 months. The funding source had no role in the design and conduct of the study, the analysis and interpretation of the data, or in the writing of the manuscript.

Availability of data and materials

The data come from anonymized registries. As a result of the confidentiality agreement signed with the Ministry of Health, the data from this study cannot be shared with third parties. The authors did not have special access privileges. Should any researcher wish to gain access to these data, they can do so by applying directly to the Ministry through the following link https://www.sanidad.gob.es/en/estadEstudios/estadisticas/estadisticas/estMinisterio/SolicitudCMBD.htm

Ethics approval and consent to participate

This study was approved by the Carlos III Institute of Health.

Abstract

Objetive:

Hospitalized COVID-19 patients with severe mental illness (SMI) have worse outcomes than counterparts without SMI. Barriers in access to acute care medical procedures among SMI patients may partially explain this phenomenon. Here, we examined differences in critical care admission and in-hospital mortality between hospitalized COVID-19 patients with and without SMI.

Methods:

This population-based study used Spain's nationwide electronic health records. Based on International Classification Diseases, Tenth Revision, ICD-10-CM codes, we identified all patients aged ≥15 years hospitalized due to COVID-19 between July 1st-December 31st, 2020, and compared patients with and without SMI in terms of (i) critical care admission and (ii) in-hospital mortality – overall and stratified by age. We used logistic regression models including sex, age, and comorbidity burden as measured by Charlson Comorbidity Index Score as covariates.

Results:

Of 118,691 hospital admissions due to COVID-19 of people aged ≥15 years, 1512 (1.3%) included a diagnosis of SMI. Compared to non-SMI patients, SMI patients had higher in-hospital mortality (OR,95%CI: 1.63,1.42-1.88) and were less frequently admitted to critical care (OR,95%CI: 0.70,0.58-0.85). Admission to critical care in SMI patients was lower than for non-SMI counterparts only among individuals aged ≥60 years. The magnitude of the difference in in-hospital mortality between SMI and non-SMI patients decreased as age increased.

Conclusions:

Individuals with SMI had reduced critical care admission and increased in-hospital mortality compared non-SMI counterparts, suggesting that differences in delivery of acute care medical procedures may partially explain higher risk of negative outcomes among COVID-19 patients with SMI.

Keywords: severe mental illness, hospital admissions, mortality, COVID-19

Introduction

People living with severe mental illness (SMI) (i.e., schizophrenia or bipolar disorder) have around 10-20 years shorter life expectancy than the general population [1] due to higher suicide rates [2] and mortality due to chronic medical conditions. The intersection of at least three factors seemingly underlies the association between SMI and higher prevalence [3] of and mortality due to chronic medical conditions [4]: First, current pharmacological agents commonly used in SMI (e.g., antipsychotic drugs) cause cardiological, metabolic, endocrinological and neurological side effects[5]. Second, some evidence indicates that the aging process may be accelerated in some forms of SMI (e.g., schizophrenia), driving early-onset aging-related metabolic and cognitive changes[6,7]. Third, social disadvantage and stigma reduce SMI patients' opportunities to remain healthy through different pathways, including higher prevalence of deleterious lifestyle habits (e.g., smoking, sedentary lifestyle [8–10]) and reduced access to medical care. Notably, recent evidence suggests that the gap in mortality due to chronic medical conditions between people with and without SMI is on the rise[11]. Reducing this gap is a major public health and clinical need.

There is also a growing body of evidence indicating that people living with SMI are at higher risk for adverse COVID-19-related outcomes than SMI-free counterparts – as suggested initially by a study during the initial pandemic outbreak in New York [12] and subsequently by population-based studies from Denmark [13] and South Korea[14].

The mechanisms underlying the apparent risk of worse clinical outcomes of COVID-19 patients with SMI remain mostly unexplored. One potential explanation is the presence of barriers in access to medical care among people living with SMI, an important actionable driver of the gap in chronic medical illness between people with and without SMI. There is substantial evidence that SMI patients systematically receive suboptimal care for chronic medical conditions, globally. For example, cardiovascular disorders are typically less frequently diagnosed and treated among individuals with schizophrenia than in the general population[15]. Likewise, individuals with SMI also have reduced access to life-saving, acute-care interventions, such as urgent surgery [16] or invasive cardiac procedures[17]. The role of potential differences in access to acute care medical procedures, such as invasive mechanical ventilation, in the association between SMI and adverse COVID-19-related outcomes and mortality, however, remains understudied. Only one population-based study examining COVID-19 inpatients from France between February-June 2020 assessed differences in ICU admission among patients with vs. without schizophrenia – suggesting reduced frequency of ICU admission among patients with schizophrenia[18].

The objective of this study is to enhance understanding of differences in acute healthcare delivery and in-hospital mortality among COVID-19 patients with and without SMI. Here, we used nationwide population-based data from the months following the initial COVID-19 pandemic outbreak in Spain to compare individuals with and without SMI in terms of admissions to critical care due to severe COVID-19 and in-hospital COVID-19 mortality.

Methods

Data source

We conducted a population-based study using Spain's nationwide hospital electronic health records (Conjunto Minimo Basico de Datos Hospitalarios – CMBD-H), an official database maintained by Spain's Ministry of Health. CMBD-H is a mandatory clinical-administrative database that includes data on all acute care hospital admissions and is thus considered nationally representative. For each hospitalization, the database features demographic and clinical information including length and cost of hospital stay and up to 20 diagnoses and 20 procedures. All information is coded in hospitals prior to discharge according to the International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM). As these data are de-identified, informed consent was not required, according to Spanish law.

Variables

We identified all patients aged ≥15 years hospitalized between July 1st and December 31st, 2020 who had a diagnosis of COVID-19 infection using the validated ICD-10-CM diagnosis code U07.1 and also presented an additional code identifying acute viral respiratory disease (i.e., viral pneumonia, acute lower respiratory tract infection, and acute respiratory distress). Table S1 summarizes the ICD-10-CM codes used to define acute viral respiratory disease. We did not include admissions before July 1st, 2020, to reduce the potential for selection bias due to formal and informal triaging of patients during the first few months of the pandemic – when Spain was a major COVID-19 hotspot and response to the initial pandemic outbreak overwhelmed Spain's health system[19]. We defined two comparison groups based on presence of SMI (i.e., diagnosis of any affective or non-affective disorder with psychotic features). Table S2 summarizes the ICD-10-CM codes used to define SMI.

Demographic variables included sex and age in years, categorized into groups (<60y, 60-69y, 70-79y, >80y). Clinical characteristics included comorbidity burden, measured using the Charlson Index Score in the version validated by Deyo and improved for ICD-10 [20] – calculated based on all secondary diagnoses and categorized into groups (0, 1-2, 3-4, >4 score); presence of specific comorbidities (e.g., diabetes, chronic obstructive pulmonary disease [COPD], or congestive heart failure); dichotomous variables indicating admission to critical care (i.e., admission to a general, coronary, burn, or post-surgical intensive care unit), presence of respiratory organ dysfunction, use of invasive mechanical ventilation, and in-hospital mortality; and length of stay in days as an indicator of hospital resource use.

Analyses

We first compared patients with and without SMI in terms of distribution of demographic and clinical characteristics. Between-group differences were tested using T-tests for continuous variables and Pearsons's Chi-Squared Test for categorical ones.

Next, we performed logistic regression models to study the associations (i) between SMI and in-hospital mortality and (ii) between SMI and critical care admission. Three sequential regression models were developed: a first crude (unadjusted) model; a second model adjusted by sex and age group; and a third model including sex, age group, and comorbidity burden as measured by Charlson Index Score group. In the final model, the interaction of severe mental illness and age-group was evaluated. We further conducted age group-stratified models, including sex, continuous age, and comorbidity burden as covariates. In addition, we conducted two sets of sensitivity analyses. First, we repeated all models after exclusion of patients hospitalized for ≤48 hours, to understand the potential role of early discharge/mortality on effect estimates. Second, we estimated the associations between SMI and in-hospital mortality/critical care admission using inverse probability weighting by a propensity score including sex, age, and all individual comorbidities instead of conditionally adjusted models, to understand the potential role of model misspecification and residual confounding on main findings. Results from regression models are expressed as Odds Ratios (ORs) with 95% confidence intervals (95% CIs). To examine differences in the distribution of time to in-hospital mortality between patients with and without SMI, we performed survival analyses using Kaplan–Meier estimates and log-rank tests. All procedures were performed with STATA 16 (StataCorp. LP, College Station, TX, USA).

Results

In Spain, between July-December 2020, there were 118,691 hospital admissions of people over 15 years of age due to COVID-19. A diagnosis of SMI was identified in 1512 cases (1.3%): 1,020 (67.5%) cases had non-affective psychosis (i.e., schizophrenia and schizophrenia-spectrum disorders) and 492 (32.5%) had bipolar disorder or major depressive disorder with psychotic features.

Table 1 summarizes the demographic and clinical characteristics of the study population, divided according to presence of SMI. Compared to the non-SMI group, patients with SMI were slightly older, had an overall higher burden of comorbidities – e.g., lower proportion of patients with no comorbidity (42.3% vs. 48.0% in the non-SMI group) and higher prevalence of specific comorbidities such as diabetes (26.7% vs. 23.8%) or dementia (10.4 vs. 6.1%). Of note, non-SMI patients had slightly higher burden of cardiovascular conditions, including congestive heart failure, acute myocardial infarction, and peripheral vascular disease. While the proportion of cases presenting with acute respiratory dysfunction was roughly similar between groups, the proportion of cases admitted to critical care was lower in people with than without SMI (7.5% vs 9.5%).

Table S3 compares SMI patients with non-affective psychotic disorders to SMI patients with affective psychosis. The affective psychosis patient group was slightly older on average (69.6 vs. 66.7 years) and included a higher proportion of females (58.1% vs. 43.9% in the non-affective psychosis group) and a lower burden or comorbidities (38.2% compared to 47.9%).

In-hospital mortality

Overall, approximately 14.4% of the study population died during hospital admission. In-hospital mortality was higher among patients with than without SMI (19.7% vs 14.3%). There was, however, no evident difference in mortality among patients with and without SMI admitted to critical care (32.5% vs 30.4%, p=0.626) – low statistical power did not allow for adjusted regression modelling comparing study groups in the population of critical patients. In models adjusted for sex, age group, and Charlson Index Score group, the in-hospital mortality OR (95% CI) for patients with vs. without SMI was 1.63 (1.42, 1.88). After model stratification by age group, we found an inverse relationship between increasing age and mortality: the increase in risk of in-hospital mortality among patients with SMI compared to non-SMI counterparts was higher in younger age groups. The largest increase in risk of death was found in the <60 y of age group, with in-hospital mortality OR (95% CI) for patients with vs. without SMI of 2.34 (1.50, 3.66) (Table 2). The main demographic and clinical characteristics of patients with and without SMI by age group shows in the table 3.

Figure 1 illustrates survival curves up to day 30 of admissions for individuals with and without SMI. There were no differences between groups in age strata <60y and ≥80y. Among individuals aged 60-69y and 70-79y, however, SMI patients had higher mortality during the earlier days of admission than non-SMI counterparts.

Admission to critical care

Almost 1 in 10 hospitalized cases were admitted to critical care. The percentage of ICU admissions was lower in patients with SMI (7.5% vs. 9.4%). The average stay in ICU is similar among patients with and without SMI (13.2 days vs 13.8 days). In models examining the association between SMI and critical care admission, after adjustment by sex, age group, and Charlson Index group, individuals with SMI had an OR (95% CI) of 0.70 (0.58, 0.85) of being admitted to critical care compared to non-SMI counterparts. Between-group differences in critical care admission varied across age groups. For individuals aged <60 critical care admission was roughly comparable among patients with and without SMI – prevalence of critical admission: 13.4% vs. 10.6%, respectively; adjusted OR (95% CI): 1.19 (0.89, 1.59). For individuals aged 60 years and older, critical care admission was systematically less frequent among patients with SMI, with adjusted ORs indicating around a 50% reduction in critical care admissions compared to non-SMI counterparts.

Sensitivity analyses excluding patients admitted ≤48 hours (Table S4) and using inverse probability weighting based on a propensity score including sex, age, and all individual comorbidities for confounding adjustment (Table S5) yielded similar results to the main findings.

Discussion

This nationwide population-based study, including all 118,691 clinical records of individuals aged over 15 years who were hospitalized due to COVID-19 in Spain between July and December 2020, examined differences in clinical characteristics and outcomes between patients with and without a previous diagnosis of SMI. Our main findings were that, after adjustment for sex, age, and medical comorbidities, (i) patients with SMI had around 60% higher in-hospital mortality than non-SMI counterparts [OR: 1.63, 95%CI (1.42, 1.88)] and (ii) admission to critical care was 30% less frequent among SMI than non-SMI patients [OR: 0.70, 95%CI (0.58, 0.85)]. These results extend existing evidence suggesting that individuals living with SMI are at an increased risk of adverse COVID-19 related outcomes and highlight the potential clinical relevance of barriers in access to critical care among acutely ill COVID-19 patients with SMI.

The finding of an increased mortality risk among SMI patients hospitalized due to COVID-19 is in keeping with an increasing body of evidence [21,22]. Two nationwide population-based studies using data from the initial pandemic outbreak in France, where hospitalized COVID-19 patients with non-affective psychotic disorders were found to have 30% higher mortality risk than patients without SMI [18], and 90% higher mortality risk than patients without any mental disorder [23]. Additionally, two South Korean population-based studies examined the association between SMI and COVID-19-related mortality during the initial months of the pandemic including all (hospitalized and non-hospitalized) COVID-19 cases. They reported COVID-19 patients with schizophrenia [24] or with any SMI [14] to have higher mortality risk than COVID-19 patients without any mental disorder, with ORs (95%CIs) of 2.25 (0.36, 14.03) and 2.27 (1.50, 3.41), respectively. Further, two large studies conducted in health systems in New York City (United States) [12] and Israel [25] reported higher mortality risk among COVID-19 patients with schizophrenia than among COVID-19 patients without any mental disorder, with ORs (95%CIs) of 2.67 (1.48, 4.80) and 3.27 (1.39, 7.68), respectively.

Several actionable factors may help explain excess COVID-19 mortality among SMI patients. As mentioned earlier, individuals living with SMI typically experience higher prevalence of chronic medical disorders associated with adverse COVID-19 outcomes[3,4,26]. Our estimates, however, indicate 60% increased mortality risk among hospitalized COVID-19 patients with SMI after adjustment for medical comorbidity. Individuals living with SMI also have higher prevalence of smoking [27] and typically face social disadvantage[28,29] and are overrepresented in low socioeconomic status social strata – both smoking [30] and socioeconomic adversity [31] are known risk factor for adverse COVID-19 outcomes. Also, there is debate regarding whether use of psychotropic medications may be associated with higher COVID-19 mortality [22,32]. These factors may partially underlie our findings. For instance, in line with previous research, we found larger estimates of increased mortality among hospitalized COVID-19 patients with SMI in the younger age group, with mortality OR, 95%CI of 2.34 (1.50, 3.66) compared to non-SMI counterparts, and differences in smoking prevalence between people with and without SMI are starker in younger ages and among more recently born cohorts [33]. Unfortunately, our data did not include reliable data on smoking, and this database does not systematically include socioeconomic status or use of specific medications – hence, some degree of unmeasured confounding may be present in our adjusted estimates. Importantly, results were similar in sensitivity analyses (i) limited to patients admitted for >48h, suggesting low probability of unmeasured confounding due to severity at hospital admission, and (ii) using an alternative approach to confounding control, suggesting robustness to modelling decisions.

There is also substantial evidence that a diagnosis of an SMI is typically associated with barriers in access to acute-care interventions driven by differences in healthcare delivery for patients with and without SMI, stigma, and discrimination towards SMI patients – conditioning treatment delays [16] and ultimately partially explaining the shortened life expectancy of individuals living with SMD [15,34]. Our finding that critical care admission was 30% lower among hospitalized COVID-19 patients with vs. without SMI are in keeping with the study by Fond et al., using a similar design from a comparable, universal-access healthcare national health system, where SMI patients had similarly decreased intensive care unit admission rate (23.7% vs 28.4%; adjusted OR=0.75 [95% CI, 0.62–0.91])[18]. Of note, we found no difference between SMI and non-SMI patients in critical care admission in the <60 years age group, also in line with results by Fond et al. [18] – suggesting that presence of an SMI diagnosis potentially only played a role in determining adequacy of critical admission in older patients. This finding does not lend itself to easy interpretation and adds to the ongoing debate surrounding use of critical care procedures for older patients, in general and during times of resource scarcity (e.g., during COVID-19 pandemic waves)[35].

The main strength of our study is that data come from a mandatory, nation-wide population-based electronic health records that can be considered nationally representative. In addition, results were similar across different modelling choices, suggesting robustness to potential model misspecifications. This study has limitations. First, as mentioned, we cannot rule out some degree of unmeasured confounding due to lack of information on socioeconomic and smoking status and use of specific medications. Second, as in any study based on clinical-administrative databases, data quality depends on clinical coding accuracy. However, we consider this possibility unlikely, as the CMBD-H database is subject to periodic quality audits[36]. Third, it seems plausible that some degree of selection bias due to restricting the study population to hospitalized COVID-19 patients may be present. Because Spain's tax-funded national health system provides universal healthcare at no cost to all individuals living in Spain, selection bias due to lack of access to hospital care is somewhat unlikely. Further, we excluded the initial months of the COVID-19 pandemic in order to reduce the potential for selection bias due to selective hospitalization of patients driven by the initial collapse of healthcare systems during the initial pandemic outbreak. By including only hospitalized patients, we likely underestimated the size effect of the difference COVID-19 mortality between people with and without SMI, as suggested by the larger differences found by population-based studies as well as studies based on data from non-representative large health systems including hospitalized and non-hospitalized patients [12,14,24,25].

Conclusions

We found that hospitalized COVID-19 patients with SMI had higher mortality and lower admission to critical care, compared to SMI-free counterparts and after adjustment for sex, age, and clinical characteristics. These results highlight the importance of prioritizing SMI individuals for preventative interventions (e.g., vaccination and boosters) to reduce risk of COVID-19 infection, as recommended by several high-income countries [37,38]. This is particularly relevant to low-income countries and countries experiencing shortages vaccine and booster delivery, especially during COVID-19 waves. In addition, our results underscore the potential for healthcare-system interventions to reduce barriers in access to critical care for people living with SMI, such as workshop-based interventions, skills-based interventions, and intensive social contact interventions that can reduce unconscious bias potentially impacting quality of care[39–41] – especially in older age groups.

Declaration of Competing Interest

The authors declare that they have no competing interests

Table 1. General characteristics of hospital admissions for COVID-19 in Spain, divided by presence of a preexisting diagnosis of severe mental illness during July and December 2020 (N=118,691)

	Total	**SMI**	**Non-SMI**	**P-value**
Number of admissions	118,691	1,512	117,179	
Sex, female	52,173 (44.0)	728 (48.1)	51,445 (43.9)	0.001
Age, mean (SD)	66.7±17.5	68.1±14.7	66.6±17.5	0.001
Age group				<0.001
<60y	40,788 (34.4)	396 (26.2)	40,392 (34.5)	
60-69y	21,472 (18.1)	355 (23.5)	21,117 (18.0)	
70-79y	22,395 (18.9)	395 (26.1)	22,000 (18.8)	
>80y	34,036 (28.7)	366 (24.2)	33,670 (28.7)	
Charlson Index				<0.001
0 points	56,864 (47.9)	640 (42.3)	56,224 (48.0)	
1-2 points	44,337 (37.3)	646 (42.7)	43,691 (37.3)	
3-4 points	12,309 (10.4)	174 (11.5)	12,135 (10.4)	
>4 points	5,181 (4.4)	52 (3.4)	5,129 (4.4)	
Main Charlson comorbidities				
Diabetes	28,289 (23.8)	404 (26.7)	27,885 (23.8)	0.008
COPD	16,160 (13.6)	211 (14.0)	15,949 (13.6)	0.698
Renal Disease	13,517 (11.4)	1778 (11.8)	13,339 (11.4)	0.636
Congestive Heart Failure	9,584 (8.1)	105 (6.9)	9,479 (8.1)	0.104
Dementia	7,269 (6.1)	157 (10.4)	7,112 (6.1)	<0.001
Hepatic Disease	5,449 (4.6)	78 (5.2)	5,371 (4.6)	0.288
Cancer	5,225 (4.4)	62 (4.1)	5,163 (4.4)	0.565
Stroke	4,104 (3.5)	63 (4.2)	4,041 (3.4)	0.129
Acute Myocardial Infarction	3,819 (3.2)	30 (2.0)	3,789 (3.2)	0.006
Peripheral Vascular Disease (PVD)	3,299 (2.8)	24 (1.6)	3,275 (2.8)	0.005
Acute respiratory dysfunction	43,467 (36.6)	583 (38.6)	42,884 (36.6)	0.116
Length of hospital stay, days				
Mean (SD)	10.1 (9.4)	11.9 (10.7)	10.1 (9.4)	
ICU admission	11,229 (9.5)	114 (7.5)	11,115 (9.5)	0.010
Invasive mechanical ventilation	6,817 (5.7)	72 (4.8)	6,745 (5.8)	0.099
Length of ICU stay, days				
Mean (SD)	10.15 (9.4)	11.91(10.7)	10.13 (9.4)	<0.001
In-hospital mortality	17,094 (14.4)	298 (19.7)	16,796 (14.3)	<0.001

Data presented as number of cases and (%).

Table 2. Association between SMI and in-hospital mortality, and admission to intensive care unit

	In-hospital mortality				**Critical care admission (n= 11,229)**			
	CFR% SMI	**CFR% Non-SMI**	**AOR (95% CI) SMI**	**P value for age-SMI interaction**	**Admissions% SMI**	**Admissions% Non-SMI**	**AOR (95% CI) SMI**	**P value for age-SMI interaction**
Model 1	19.7	14.3	1.47 (1.29, 1.67)		7.5	9.5	0.78 (0.64, 0.94)	
Model 2	19.7	14.3	1.60 (1.39, 1.83)		7.5	9.5	0.71 (0.59, 0.87)	
Model 3	19.7	14.3	1.63 (1.42, 1.88)		7.5	9.5	0.70 (0.58, 0.85)	
Model 3 stratified by age group								
<60y (with vs without SMI)*	5.8	2.0	2.34 (1.50, 3.66)	-----	13.4	10.6	1.19 (0.89, 1.59)	-----
60-69y (with vs without SMI)	14.9	7.7	2.13 (1.57, 2.89)	0.262	9.6	15.6	0.56 (0.39, 0.80)	0.001
70-79y (with vs without SMI)	25.3	16.2	1.92 (1.52, 2.43)	0.104	6.1	13.3	0.43 (0.29, 0.66)	<0.001
>=80y (with vs without SMI)	33.3	32.1	1.22 (0.98, 1.52)	<0.001	0.8	1.8	0.46 (0.16, 1.43)	0.090

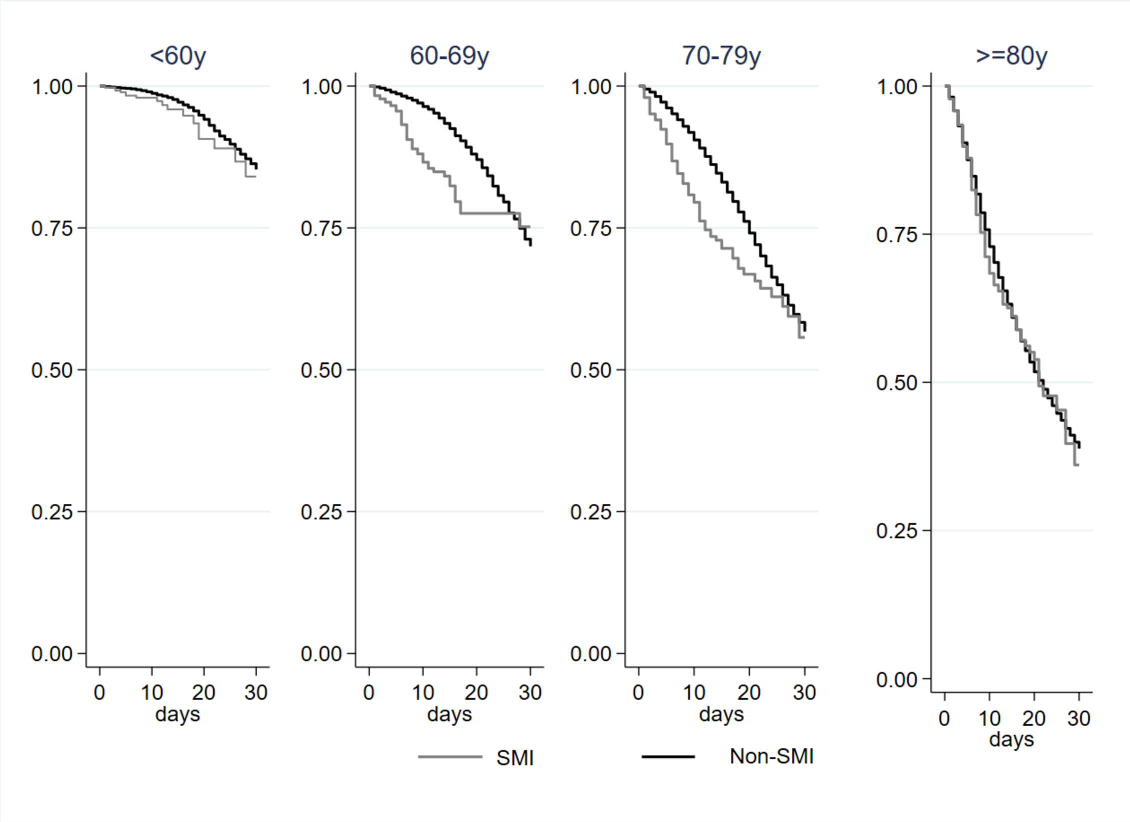
CFR, case fatality rate; AOR, adjusted odds ratio
Model 1. Unadjusted
Model 2. Adjusted by sex, age group
Model 3. Adjusted by sex, age group and Charlson Index
*adjusted by age

Table 3. General characteristics of hospital admissions for COVID, divided by age group and comparing SMI vs Non-SMI

	<60y N= 40,788			60-69y N=21,472			70-79y N= 22,395			>=80y N=34,036		
	SMI	**Non-SMI**	**P-value**	**SMI**	**Non-SMI**	**P-value**	**SMI**	**Non-SMI**	**P-value**	**SMI**	**Non-SMI**	**P-value**
Admissions	396	40,392		355	21,117		395	22,000		366	33,670	
Sex, female (%)	35.6	39.7	0.096	42.5	38.0	0.078	52.1	42.1	<0.001	62.8	53.8	0.001
Age, mean	48.6	46.7		64.6	64.3		74.7	74.5		85.5	86.8	
Charlson Index(%)			<0.001			0.001			0.234			0.116
0 points	61.9	72.8		42.0	51.3		35.4	34.6		29.0	24.9	
1-2 points	31.8	23.7		45.6	37.9		47.6	45.3		46.4	47.9	
3-4 points	3.5	2.2		9.9	6.9		13.2	13.9		20.0	19.9	
>4 points	2.8	1.3		2.5	3.8		3.8	6.2		4.6	7.2	
Main comorbidities												
Diabetes (%)	18.2	11.8	<0.001	29.3	26.0	0.161	31.6	33.8	0.376	28.1	30.3	0.380
COPD (%)	10.1	8.3	0.192	17.5	13.0	0.014	15.4	18.4	0.131	13.1	17.2	0.038
Renal Disease (%)	2.8	2.5	0.698	10.4	6.4	0.003	13.4	13.5	0.960	21.0	23.8	0.219
Congestive Heart Failure	1.3	0.9	0.487	4.2	3.4	0.393	8.1	8.5	0.754	14.5	19.3	0.019
Dementia (%)	0.5	0.1	0.029	2.5	0.8	<0.001	14.2	5.4	<0.001	24.6	17.0	<0.001
Hepatic Disease (%)	7.6	4.6	0.005	6.5	6.3	0.875	3.0	5.8	0.021	3.5	2.7	0.326
Cancer (%)	2.8	1.8	0.148	4.8	4.9	0.942	5.1	6.7	0.195	3.8	5.7	0.117
Stroke (%)	1.8	0.5	0.001	3.1	2.4	0.367	4.0	4.9	0.456	7.9	6.7	0.347
Acute Myocardial Infarction (%)	0.25	0.8	0.243	2.0	3.0	0.247	2.3	4.8	0.020	3.5	5.3	0.134
Respiratory dysfunction	36.6	30.8	0.013	43.9	40.9	0.241	40.5	41.0	0.829	33.3	37.9	0.072
ICU admission	13.4	10.6	0.070	9.6	15.6	0.002	6.1	13.3	<0.001	0.8	1.8	0.144
Intensive mechanical ventilation	9.6	5.5	<0.001	6.2	10.1	0.016	2.8	9.45	<0.001	0.3	0.9	0.205
Length of stay (days)	12.2	8.3	<0.001	12.7	11.1	0.005	12.2	11.9	0.574	10.5	10.5	0·941

Title of figure

Figure 1. Kaplan-Meier curves by age group



References

[1] Plana-Ripoll O, Pedersen CB, Agerbo E, Holtz Y, Erlangsen A, Canudas-Romo V, et al. A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. Lancet 2019;394:1827–35. https://doi.org/10.1016/S0140-6736(19)32316-5.

[2] Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry 2014;13:153–60. https://doi.org/10.1002/wps.20128.

[3] Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry Off J World Psychiatr Assoc WPA 2017;16:163–80. https://doi.org/10.1002/wps.20420.

[4] Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. BMJ 2013;346:f2539. https://doi.org/10.1136/bmj.f2539.

[5] Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry 2015;14:119–36. https://doi.org/10.1002/wps.20204.

[6] Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? Schizophr Bull 2008;34:1024–32. https://doi.org/10.1093/schbul/sbm140.

[7] Papanastasiou E, Gaughran F, Smith S. Schizophrenia as segmental progeria. J R Soc Med 2011;104:475–84. https://doi.org/10.1258/jrsm.2011.110051.

[8] Kelly DL, McMahon RP, Wehring HJ, Liu F, Mackowick KM, Boggs DL, et al. Cigarette smoking and mortality risk in people with schizophrenia. Schizophr Bull 2011;37:832–8. https://doi.org/10.1093/schbul/sbp152.

[9] Dixon L. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophr Res 1999;35 Suppl:S93-100. https://doi.org/10.1016/s0920-9964(98)00161-3.

[10] Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M, et al. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. World Psychiatry 2017;16:308–15. https://doi.org/10.1002/wps.20458.

[11] Tanskanen A, Tiihonen J, Taipale H. Mortality in schizophrenia: 30-year nationwide follow-up study. Acta Psychiatr Scand 2018;138:492–9. https://doi.org/10.1111/acps.12913.

[12] Nemani K, Li C, Olfson M, Blessing EM, Razavian N, Chen J, et al. Association of Psychiatric Disorders With Mortality Among Patients With COVID-19. JAMA Psychiatry 2021;78:380–6. https://doi.org/10.1001/jamapsychiatry.2020.4442.

[13] Barcella CA, Polcwiartek C, Mohr GH, Hodges G, Søndergaard K, Niels Bang C, et al. Severe mental illness is associated with increased mortality and severe course of COVID-19. Acta Psychiatr Scand 2021;144:82–91. https://doi.org/10.1111/acps.13309.

[14] Lee SW, Yang JM, Moon SY, Yoo IK, Ha EK, Kim SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. Lancet Psychiatry 2020;7:1025–31. https://doi.org/10.1016/S2215-0366(20)30421-1.

[15] Smith DJ, Langan J, McLean G, Guthrie B, Mercer SW. Schizophrenia is associated with excess multiple physical-health comorbidities but low levels of recorded cardiovascular disease in primary care: cross-sectional study. BMJ Open 2013;3. https://doi.org/10.1136/bmjopen-2013-002808.

[16] Nishihira Y, McGill RL, Kinjo M. Perforated appendicitis in patients with schizophrenia: a retrospective cohort study. BMJ Open 2017;7:e017150. https://doi.org/10.1136/bmjopen-2017-017150.
[17] Li Y, Glance LG, Lyness JM, Cram P, Cai X, Mukamel DB. Mental illness, access to hospitals with invasive cardiac services, and receipt of cardiac procedures by Medicare acute myocardial infarction patients. Health Serv Res 2013;48:1076–95. https://doi.org/10.1111/1475-6773.12010.
[18] Fond G, Pauly V, Leone M, Llorca P-M, Orleans V, Loundou A, et al. Disparities in Intensive Care Unit Admission and Mortality Among Patients With Schizophrenia and COVID-19: A National Cohort Study. Schizophr Bull 2021;47:624–34. https://doi.org/10.1093/schbul/sbaa158.
[19] Condes E, Arribas JR. Impact of COVID-19 on Madrid hospital system. Enfermedades Infecc Microbiol Clin Engl Ed 2021;39:256–7. https://doi.org/10.1016/j.eimc.2020.06.005.
[20] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J-C, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9. https://doi.org/10.1097/01.mlr.0000182534.19832.83.
[21] Toubasi AA, AbuAnzeh RB, Tawileh HBA, Aldebei RH, Alryalat SAS. A meta-analysis: The mortality and severity of COVID-19 among patients with mental disorders. Psychiatry Res 2021;299:113856. https://doi.org/10.1016/j.psychres.2021.113856.
[22] Vai B, Mazza MG, Delli Colli C, Foiselle M, Allen B, Benedetti F, et al. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. Lancet Psychiatry 2021;8:797–812. https://doi.org/10.1016/S2215-0366(21)00232-7.
[23] Descamps A, Frenkiel J, Zarca K, Laidi C, Godin O, Launay O, et al. Association between mental disorders and COVID-19 outcomes among inpatients in France: A retrospective nationwide population-based study. J Psychiatr Res 2022;155:194–201. https://doi.org/10.1016/j.jpsychires.2022.08.019.
[24] Jeon H-L, Kwon JS, Park S-H, Shin J-Y. Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: nationwide cohort study. Br J Psychiatry 2021;218:344–51. https://doi.org/10.1192/bjp.2020.251.
[25] Tzur Bitan D, Krieger I, Kridin K, Komantscher D, Scheinman Y, Weinstein O, et al. COVID-19 Prevalence and Mortality Among Schizophrenia Patients: A Large-Scale Retrospective Cohort Study. Schizophr Bull 2021;47:1211–7. https://doi.org/10.1093/schbul/sbab012.
[26] Melamed OC, Hahn MK, Agarwal SM, Taylor VH, Mulsant BH, Selby P. Physical health among people with serious mental illness in the face of COVID-19: Concerns and mitigation strategies. Gen Hosp Psychiatry 2020;66:30–3. https://doi.org/10.1016/j.genhosppsych.2020.06.013.
[27] Evans S, Banerjee S, Leese M, Huxley P. The impact of mental illness on quality of life: A comparison of severe mental illness, common mental disorder and healthy population samples. Qual Life Res 2007;16:17–29. https://doi.org/10.1007/s11136-006-9002-6.
[28] Bellos S, Skapinakis P, Rai D, Zitko P, Araya R, Lewis G, et al. Cross-cultural patterns of the association between varying levels of alcohol consumption and the common mental disorders of depression and anxiety: secondary analysis of the WHO Collaborative Study on Psychological Problems in General Health Care. Drug Alcohol Depend 2013;133:825–31. https://doi.org/10.1016/j.drugalcdep.2013.08.030.
[29] Cook BL, Wayne GF, Kafali EN, Liu Z, Shu C, Flores M. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. JAMA 2014;311:172–82. https://doi.org/10.1001/jama.2013.284985.
[30] Patanavanich R, Glantz SA. Smoking is associated with worse outcomes of COVID-19 particularly among younger adults: a systematic review and meta-analysis. BMC Public Health 2021;21:1554. https://doi.org/10.1186/s12889-021-11579-x.

[31] Mena GE, Martinez PP, Mahmud AS, Marquet PA, Buckee CO, Santillana M. Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile. Science 2021;372. https://doi.org/10.1126/science.abg5298.
[32] Boland X, Dratcu L. Antipsychotics and COVID-19: the debate goes on. Lancet Psychiatry 2021;8:1030. https://doi.org/10.1016/S2215-0366(21)00396-5.
[33] Dickerson F, Schroeder J, Katsafanas E, Khushalani S, Origoni AE, Savage C, et al. Cigarette Smoking by Patients With Serious Mental Illness, 1999-2016: An Increasing Disparity. Psychiatr Serv 2018;69:147–53. https://doi.org/10.1176/appi.ps.201700118.
[34] Jayatilleke N, Hayes RD, Chang C-K, Stewart R. Acute general hospital admissions in people with serious mental illness. Psychol Med 2018;48:2676–83. https://doi.org/10.1017/S0033291718000284.
[35] Haas LEM, de Lange DW, van Dijk D, van Delden JJM. Should we deny ICU admission to the elderly? Ethical considerations in times of COVID-19. Crit Care Lond Engl 2020;24:321. https://doi.org/10.1186/s13054-020-03050-x.
[36] Escuela Andaluza de Salud Pública. [CMBD Audit Manual. Andalusian Public Health System Hospitals] 2020. https://www.sspa.juntadeandalucia.es/servicioandaluzdesalud/sites/default/files/sincfiles/wsas-media-pdf_publicacion/2020/ManualauditoCMBD_hospSSPA.pdf.
[37] Siva N. Severe mental illness: reassessing COVID-19 vaccine priorities. Lancet 2021;397:657. https://doi.org/10.1016/S0140-6736(21)00429-3.
[38] De Picker LJ, Dias MC, Benros ME, Vai B, Branchi I, Benedetti F, et al. Severe mental illness and European COVID-19 vaccination strategies. Lancet Psychiatry 2021;8:356–9. https://doi.org/10.1016/S2215-0366(21)00046-8.
[39] Arboleda-Flórez J, Stuart H. From sin to science: fighting the stigmatization of mental illnesses. Can J Psychiatry Rev Can Psychiatr 2012;57:457–63. https://doi.org/10.1177/070674371205700803.
[40] Knaak S, Mantler E, Szeto A. Mental illness-related stigma in healthcare: Barriers to access and care and evidence-based solutions. Healthc Manage Forum 2017;30:111–6. https://doi.org/10.1177/0840470416679413.
[41] Nyblade L, Stockton MA, Giger K, Bond V, Ekstrand ML, Lean RM, et al. Stigma in health facilities: why it matters and how we can change it. BMC Med 2019;17:25. https://doi.org/10.1186/s12916-019-1256-2.