



Role of medical comorbidity in the association between psychiatric disorders and mortality among patients with COVID-19

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Abstract

We examined whether excess chronic medical comorbidity mediated excess COVID-19 inpatient mortality among people with mental disorders in the early phase of the pandemic, a question with important implications for public health and clinical decision-making. Using records of 2599 COVID-19 hospitalized patients, we conducted a formal causal mediation analysis to estimate the extent to which chronic comorbidity mediates the association between mental disorders and COVID-19 mortality. The Odds Ratio (95% CI) for Natural Indirect Effect and Controlled Direct Effect were 1.07(1.02, 1.14) and 1.40 (1.00, 1.95), respectively, suggesting that a large proportion of excess COVID-19 mortality among people with mental disorders may be explained by factors other than comorbidity.

Keywords COVID-19 · Mental disorders · Causal mediation analysis · Causal inference

Introduction

Substantial evidence indicates that mental disorders are associated with a higher risk of dying of COVID-19 [1–3]. Medical comorbidity might play a key role in this excess mortality risk: in comparison with the general population, people living with mental disorders (especially those

diagnosed with serious mental illness, such as schizophrenia, bipolar disorder, or major depressive disorder) have higher rates of many chronic medical comorbidities, including several risk factors for COVID-19 mortality, such as chronic obstructive pulmonary disease, diabetes mellitus, or chronic heart disease [4].

Notwithstanding, the extent to which the association between mental disorders and COVID-19 mortality is explained (i.e., mediated) by excess comorbidity burden remains unexplored. This question bears important public health and clinical implications. For instance, constraints in the supply and uptake of SARS-CoV-2 vaccines have now led health systems to prioritize vaccination of selected population groups. If excess COVID-19 mortality among people with mental disorders is driven by excess chronic medical comorbidity, then prioritization of vaccination of people with any chronic medical comorbidity may theoretically suffice to protect people with mental disorders. Otherwise, explicit prioritization of people with mental disorders for vaccination may be warranted, as recommended in several European countries [5, 6].

Here, we used electronic health records from a large teaching hospital in Madrid, Spain, to analyze the relationship between mental disorders and in-hospital mortality early in the pandemic. We further examined the extent to

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which the association between mental disorders and COVID-19 mortality was explained (i.e., mediated) by excess chronic medical comorbidity (Table 1).

Methods

Study sample

This cohort study used data from the electronic health records of La Paz University Hospital, a major teaching hospital in Madrid, Spain. We included all 2599 individuals aged ≥ 16 years who were hospitalized with a COVID-19 diagnosis for at least 24 h between March 16 and April 15, 2020, when vaccines against COVID-19 were unavailable. All data were entered by supervised last year medical students. Subjects were classified as having a mental disorder if, at hospital admission, their health records indicated an active diagnosis of a mental disorder (as per International Classification of Diseases, 10th edition [ICD-10], codes F01–F99). These comprised 346 patients: 156 (45%) had a diagnosis of major depressive disorder (ICD-10 codes F32–33), 88 (25%) had a diagnosis of anxiety or stress-related disorder (ICD-10 codes F40–F48), 69 (20%) had a diagnosis of schizophrenia–spectrum disorder (ICD-10 codes F20–29), 15 (4%) had a diagnosis of bipolar disorder (ICD-10 codes F30–31), and 22 (6%) had other mental health diagnoses.

We estimated patients' comorbidity burden by calculating their Charlson Comorbidity Index (CCI) [7] score using an online tool [8]. Additional covariates measured at admission included sociodemographic characteristics (age, sex, and foreign-born status), specific comorbidities, and COVID-19 severity (as per the World Health Organization's COVID-19 severity definition [9], CURB-65 severity scale [10], and initial requirements of oxygen therapy). We followed patients until death, discharge, or up to 30 days, whatever came first. To compute all-cause in-hospital mortality, discharged subjects were considered alive.

Data analysis

First, we compared hospitalized COVID-19 inpatients with and without mental disorders in terms of sociodemographic and clinical characteristics. Then, we estimated the association between having a mental disorder and CCI score, using multivariable linear regression models. Next, we estimated the association between having a mental disorder and all-cause mortality, using multivariable logistic regression models. To better understand the role of specific diagnoses, we also drew comparisons between patients with schizophrenia or bipolar disorder and the rest of the study sample. All models were adjusted by age, sex, and foreign-born status. Finally, we explored the extent to

which the association between having a mental disorder and all-cause mortality risk for COVID-19 inpatients was mediated by CCI score. Traditional mediation analyses based on mediator inclusion in multivariable models are not adequate for this research question, because they are vulnerable to mediator–outcome confounding and rely on the assumption of no exposure–mediator interaction [11]. Accordingly, we implemented a formal (i.e., counterfactual-based) causal mediation analysis, estimating controlled direct and natural indirect effects and bias-corrected bootstrap confidence intervals, controlling for confounding due to age, sex, and foreign-born status, and allowing for exposure–mediator interaction [11]. In a set of prespecified sensitivity analyses, we repeated all mediation analyses after stratification by age ($<$ vs. ≥ 75 years) and comorbidity burden (Charlson Comorbidity Index score 0–5 vs. 6–14).

Study procedures were approved by La Paz University Hospital's Institutional Review Board. Analyses were conducted using Stata v.15 for PC. Causal mediation analyses were performed using the *paramed* command.

Results

Supplementary Table 1 presents the sociodemographic and clinical characteristics of the 2599 study subjects, divided by presence of a mental disorder. People with mental disorders were older and had a greater comorbidity burden and worse COVID-19 severity indicators than mental disorder-free counterparts. They also had higher mortality risk (22.9% vs. 17.4%, $p = 0.01$). In age, sex, and foreign-born status-adjusted regressions, presence of a mental disorder was associated with higher comorbidity burden (Beta = 0.26, 95% Confidence Interval = 0.07, 0.45) and higher mortality risk (Odds Ratio = 1.48, 95% CI = 1.06, 2.05). Presence of schizophrenia or bipolar disorder, however, was neither associated with comorbidity burden (Beta = 0.03, 95% CI = -0.32, 0.37) nor with mortality risk (OR = 0.87; 95% CI = 0.41, 1.84) in similarly adjusted models.

Results from the causal mediation analysis indicate that comorbidity mediated the association between mental disorders and mortality only partially, with a large proportion of the association remaining unexplained by comorbidity: the Natural Indirect and Controlled Direct Effects indicated, respectively, 7% and 40% increased mortality risk. Sensitivity analyses after stratification by age and comorbidity burden yielded similar effect estimates with wider confidence intervals (data not shown) (Table 1).

Table 1 Results from the causal mediation analysis examining the role of medical comorbidity as a mediator in the association between having a mental disorder and mortality in a cohort of patientsaged ≥ 16 years who were hospitalized with a COVID-19 diagnosis for at least 24 h between March 16 and April 15, 2020, in La Paz University Hospital, Madrid

	OR	95% Confidence Interval
Total Effect of Mental Disorders on in-hospital mortality risk	1.49	1.06, 2.16
Controlled Direct Effect (not mediated through comorbidity)	1.40	1.00, 1.95
Natural Indirect Effect (mediated through comorbidity)	1.07	1.02, 1.14

Causal mediation model allowing for exposure–mediator interaction and adjusted for sex, age, and foreign-born status

Discussion

In a large cohort of hospitalized COVID-19 patients, we found that people whose records indicated an active diagnosis of a mental disorder had higher comorbidity burden and mortality risk than mental disorder-free counterparts. However, the association between mental disorders and mortality risk was only partially explained (i.e., mediated) by burden of medical comorbidity, after adjustment by age, sex, and foreign-born status.

Our main finding was that excess medical comorbidity was not a sufficient explanation for the association between mental disorders and excess in-hospital COVID-19 mortality. This is in keeping with long-standing links between mental disorders and worse clinical outcomes through a variety of pathways other than medical comorbidity, such as barriers in access to quality medical care for acute medical conditions [4, 12–14] or overall higher rates of social and economic adversity [15], and highlights the importance of enhancing social and economic support and access to care for people living with mental disorders to ameliorate the negative impact of the pandemic on their health outcomes. For example, these results should be an important but not the only argument in favor of prioritization of people living with mental disorders for SARS-CoV-2 vaccination, independently of chronic medical comorbidity, especially since there already is evidence that people with severe mental disorders are experiencing barriers in access to vaccination [16].

Contrary to previous research [1, 4], we did not find schizophrenia and bipolar disorder to be associated with a higher comorbidity burden or COVID-19-related mortality. This finding is puzzling and does not have an easy interpretation. Our estimates for these disorders lack precision due to an overall low number of patients with schizophrenia or bipolar disorder. The most plausible potential explanation, however, is that between March and April 2020, hospitalization requirements greatly exceeded hospital capacity in Madrid [17, 18], driving unprecedented triaging [19]. If people living with schizophrenia or bipolar disorder, who are routinely subject to barriers in access to care [20],

experienced more intense triaging than the general population, it seems plausible that those admitted to the hospital may be a selected, healthier sample of the population of people with schizophrenia or bipolar disorder infected with SARS-CoV-2 during the initial pandemic outbreak in Madrid. In fact, schizophrenia was more strongly associated with COVID-19-related mortality than other mental disorders in a study that was not limited to hospitalized patients [1] and, in our sample, individuals with schizophrenia or bipolar disorder were, on average, 5 years younger than the overall study sample.

Our study has several limitations. First, as mentioned earlier, we also cannot rule out certain degree of selection bias partially driving our results. Second, by measuring only in-hospital mortality, we most likely underestimated the overall mortality risk among hospitalized COVID-19 patients, probably biasing our effect estimates towards the null hypothesis. Third, while models were adjusted for foreign-born status, we did not have access to patients' socioeconomic status or race/ethnicity. These variables are typically associated with mental disorders and have been found to predict higher mortality risk due to COVID-19 [21]. Hence, there probably is some degree of residual confounding due to social disadvantage in our estimates. Fourth, data come from a single center, providing acute care to a specific catchment area. It is uncertain whether our effect estimates are transportable (e.g., valid) for other locations.

In conclusion, the excess mortality risk of people with mental disorders hospitalized due to COVID-19 is only partially explained by their comorbidity burden in causal mediation models adjusted by age, gender, and foreign-born status, and allowing for exposure–mediator interaction. Our finding highlights the importance of prioritizing efforts to ensure that people living with mental disorders access appropriate social and economic support and healthcare during the pandemic, regardless of age, gender, and burden of medical comorbidity.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00127-022-02271-5>.

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Data availability Data are available from the corresponding author under reasonable request.

Code availability Code is available from the corresponding author under reasonable request.

Declarations

Conflict of interest All authors declare no conflicts of interest related to this article.

Ethical approval Study procedures were approved by La Paz University Hospital's Institutional Review Board. All data were deidentified. Accordingly, need for informed consent was waived following Spanish rules.

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