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Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study



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Summary

Background Evidence for the associations between mental illness and the likelihood of a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result and the clinical outcomes of COVID-19 is scarce. We aimed to investigate these associations with data from a national register in South Korea.

Methods A nationwide cohort study with propensity score matching was done in South Korea using data collected from the Health Insurance Review and Assessment Service of Korea. We defined mental illness as present if one of the relevant ICD-10 codes was recorded at least twice within 1 year for an outpatient or inpatient. Severe mental illness was considered as non-affective or affective disorders with psychotic features. We included all patients aged older than 20 years who were tested for SARS-CoV-2 through services facilitated by the Korea Centers for Disease Control and Prevention, the Health Insurance Review and Assessment Service of Korea, and the Ministry of Health and Welfare, South Korea. We investigated the primary outcome (SARS-CoV-2 test positivity) in the entire cohort and the secondary outcomes (severe clinical outcomes of COVID-19: death, admission to the intensive care unit, or invasive ventilation) among those who tested positive.

Findings Between Jan 1 and May 15, 2020, 216 418 people were tested for SARS-CoV-2, of whom 7160 (3.3%) tested positive. In the entire cohort with propensity score matching, 1391 (3.0%) of 47 058 patients without a mental illness tested positive for SARS-CoV-2, compared with 1383 (2.9%) of 48 058 with a mental illness (adjusted odds ratio [OR] 1.00, 95% CI 0.93–1.08). Among the patients who tested positive for SARS-CoV-2, after propensity score matching, 109 (8.3%) of 1320 patients without a mental illness had severe clinical outcomes of COVID-19 compared with 128 (9.7%) of 1320 with a mental illness (adjusted OR 1.27, 95% CI 1.01–1.66).

Interpretation Diagnosis of a mental illness was not associated with increased likelihood of testing positive for SARS-CoV-2. Patients with a severe mental illness had a slightly higher risk for severe clinical outcomes of COVID-19 than patients without a history of mental illness. Clinicians treating patients with COVID-19 should be aware of the risk associated with pre-existing mental illness.

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Introduction

COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since its emergence at the end of 2019.¹ Various risk factors for severe outcomes of COVID-19 have been elucidated.^{1,2} Risk factors are typically conditions that reduce general immunity and are associated with a history of chronic disease.^{1,2} These factors include being aged older than 65 years and having pre-existing conditions such as chronic obstructive pulmonary disease and asthma, hypertension, cardiovascular disease, chronic kidney disease, diabetes, obesity, malignancy, use of anti-inflammatory biological agents and transplantation, and chronic infection with HIV.^{2,3}

Mental illness adversely affects outcomes of various medical conditions.⁴ People with mental disorders are less likely to undergo screening for medical comorbidities,^{4,5}

and have a higher mortality and a poorer prognosis when they are diagnosed with a disease than the general population.⁵ Evidence concerning whether patients with a severe mental illness have different susceptibility to infection with SARS-CoV-2 or clinical outcomes after infection is scarce. Mental health disorders might increase the risk of infection in some individuals due to possible cognitive impairment as a result of the condition, a reduced awareness of risks, and fewer patients being accepted into psychiatric wards.⁶ Discrimination and stigma associated with mental illness might make it more difficult for individuals at risk to access health services at the appropriate time.⁷ Public health crises could cause recurrence or exacerbation of an existing mental health condition if individuals have a heightened stress response to the COVID-19 pandemic compared with the general public.⁸

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Research in context

Evidence before this study

Mental illness is known to be adversely associated with general medical conditions but evidence concerning whether patients with mental illness have different susceptibility to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or worse clinical outcomes is scarce. We searched PubMed and Google Scholar for studies published in English from database inception until May 25, 2020, describing mental illness and clinical outcomes of COVID-19 using the search terms "COVID-19" or "novel coronavirus" or "coronavirus disease" or "SARS-CoV-2" and "mental illness" or "mental health". We found no research articles that investigated the potential association between pre-existing mental illness and testing positive for SARS-CoV-2 or clinical outcomes of COVID-19.

Added value of this study

To our knowledge, this is the first nationwide study to investigate the association between mental illness and risk of

infection with SARS-CoV-2. We showed that a pre-existing diagnosis of a mental illness through use of ICD-10 criteria had no association with the risk of testing positive for SARS-CoV-2. Patients with non-affective or affective disorders with psychotic features had a slightly greater risk of severe clinical outcomes of COVID-19 than patients with other mental illnesses or without a mental illness.

Implications of all the available evidence

People with a diagnosis of a mental illness are not at increased risk of infection with SARS-CoV-2. When managing patients with COVID-19, clinicians should take their history of mental illness into account as this might influence the patient's clinical outcomes. Further research is necessary to support these findings and extend them to other populations.

We hypothesised that underlying mental illness might increase the risk of infection with SARS-CoV-2 or of severe outcomes after infection (ie, death, admission to the intensive care unit [ICU], and invasive ventilation). We aimed to investigate whether people with a pre-existing diagnosis of a mental illness had a higher risk of SARS-CoV-2 infection and if those infected had a greater number of adverse clinical outcomes than those without a history of mental illness.

Methods

Study design and participants

We did a large-scale cohort study using a South Korean national health insurance claims database. South Korea has a nationwide health system covering 98% of the population; medical conditions based on ICD codes in this database have been reported in previous studies.⁹ During the ongoing COVID-19 pandemic, the South Korean Government has provided complimentary and mandatory health services and insurance to all South Korean patients with COVID-19. We obtained data from National COVID-19 related registers, which included all patients who underwent laboratory SARS-CoV-2 tests in South Korea through services facilitated by the Korea Centers for Disease Control and Prevention (KCDC), the Health Insurance Review and Assessment Service of Korea, and the Ministry of Health and Welfare, South Korea, including COVID-19-related outcomes and death records.^{3,10,11} Other data were obtained from the Health Insurance Review and Assessment Service of Korea, including personal data records, outpatient and inpatient health-care records (ie, prescriptions, diagnoses, procedures, and health-care visits), and pharmaceutical visits.

The study population was defined as all individuals aged older than 20 years living in South Korea who underwent a SARS-CoV-2 test during the study period, by medical or KCDC referral (excluding self-referral; n=216 418). SARS-CoV-2 infection was confirmed by laboratory testing with real-time RT-PCR assays of nasal and pharyngeal swabs, which were authorised by the KCDC and in accordance with the guidelines established by WHO.¹¹

All patient-related data were anonymised to ensure confidentiality. The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003) and written informed consent was waived by the ethics committee, owing to the urgent need to collect data.

Procedures

We defined mental illness based on one of the following ICD-10 codes recorded at least twice within 1 year for an outpatient or inpatient during our observational period:^{3,12,13} non-affective psychotic disorders (F20–24 and F28–29); affective psychotic disorders (F25, F30–31, F32.3, F33.3); anxiety-related and stress-related disorders (F40–48); alcohol or drug misuse (F10–16, F18–19); mood disorders without psychotic symptoms (F32–34, F38–39, excluding F32.3 and F33.3); eating disorders (F50); and personality disorders (F60–63, F68–69). Severe mental illness was considered as non-affective or affective disorders with psychotic features, which are likely to be characterised by cognitive impairment and social isolation, which could result in not seeking care, poor adherence to treatment, and poor prognosis; and other mental illness was considered as mood disorders without psychotic symptoms, eating disorders, personality disorders, or anxiety and stress-related disorders.

For the National COVID-19-
related registers see
<https://hira-covid19.net/>

For the HIRA cohort see
<https://www.hira.or.kr/eng/>

	Patients tested for SARS-CoV-2		Patients who tested positive for SARS-CoV-2	
	No mental illness (n=164 540)	Any mental illness (n=51 878)	No mental illness (n=5717)	Any mental illness (n=1443)
Mean age, years (SD)	46.2 (18.3)	61.6 (19.2)	44.8 (17.9)	59.5 (17.2)
Gender				
Men	80 294 (48.8%)	22 170 (42.7%)	2297 (40.2%)	572 (39.6%)
Women	84 246 (51.2%)	29 708 (57.3%)	3420 (59.8%)	871 (60.4%)
Region of residence				
Rural	72 085 (43.8%)	22 465 (43.3%)	2789 (48.8%)	646 (44.8%)
Urban	92 455 (56.2%)	29 413 (56.7%)	2928 (51.2%)	797 (55.2%)
History of diabetes	21 048 (12.8%)	17 312 (33.4%)	556 (9.7%)	394 (27.3%)
History of cardiovascular disease	16 610 (10.1%)	16 218 (31.3%)	282 (4.9%)	223 (15.5%)
History of cerebrovascular disease	9343 (5.7%)	12 783 (24.6%)	219 (3.8%)	239 (16.6%)
History of COPD	9682 (5.9%)	8894 (17.1%)	186 (3.3%)	162 (11.2%)
History of asthma	19 135 (11.6%)	13 333 (25.7%)	483 (8.4%)	231 (16.0%)
History of hypertension	38 406 (23.3%)	27 832 (53.6%)	1015 (17.8%)	623 (43.2%)
History of chronic kidney disease	8701 (5.3%)	6632 (12.8%)	169 (3.0%)	84 (5.8%)
Charlson comorbidity index				
0	104 118 (63.3%)	13 100 (25.3%)	4175 (73.0%)	553 (38.3%)
1	17 882 (10.9%)	7843 (15.1%)	559 (9.8%)	246 (17.0%)
≥2	42 540 (25.9%)	30 935 (59.6%)	983 (17.2%)	644 (44.6%)

Data are n (%) unless specified. COPD=chronic obstructive pulmonary disease. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Table 1: Baseline characteristics

Outcomes

The primary outcome was SARS-CoV-2 test positivity among all individuals who underwent SARS-CoV-2 testing. The secondary outcome was severe clinical outcomes of COVID-19, which comprised death, admission to the intensive care unit, or invasive ventilation.

We obtained information on patient age, gender, and region of residence from the insurance eligibility data. Psychiatric hospitalisation was obtained from inpatient health-care records during the observation period. History of cardiovascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), hypertension, and chronic kidney disease was defined by at least two claims within 1 year using the appropriate ICD-10 code.¹¹ The Charlson comorbidity index score (using ICD-10 codes) was calculated, as reported previously.^{9,11} The region of residence was classified as urban (Seoul, Sejong City, Busan, Incheon, Daegu, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Gyeongsangbuk, Gyeongsangnam, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, and Jeju).^{11,14}

Statistical analysis

We compared SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 in a propensity score matched cohort. Propensity score matching was done to reduce potential confounding and to balance the baseline characteristics of the two groups, from the predicted probability of individuals with mental illness versus those

without mental illness using a logistic regression model with adjustment for age; gender; region of residence; history of diabetes, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index.

We matched both groups twice in a 1:1 ratio using a so-called greedy nearest-neighbour algorithm among all individuals who underwent SARS-CoV-2 testing and among patients who tested positive for SARS-CoV-2. Adequacy of matching was confirmed by comparing propensity score densities (appendix pp 16–18), and standardised mean differences (SMDs). This approach, assessed by SMDs, is calculated as the population mean difference between both groups, scaled by population SD; thus, this method is more meaningful than assessing *p* values from *t* tests.^{9,11}

Statistical analyses were performed in SAS, version 9.4 and R software, version 3.1.1. A two-sided *p*<0.05 was considered significant.

For the main analysis, the exposure was mental illness, the primary endpoint was a positive laboratory test result for SARS-CoV-2 among all individuals who underwent SARS-CoV-2 testing, and the secondary endpoint was severe clinical outcomes among patients with COVID-19. Additional analysis of severity of mental illness (no mental illness vs other mental illness vs severe mental illness) was done. Data were analysed using logistic regression models. Adjusted odds ratios (ORs) with 95% CIs for both groups in each matched cohort were estimated after adjusting for the following covariates:

See Online for appendix

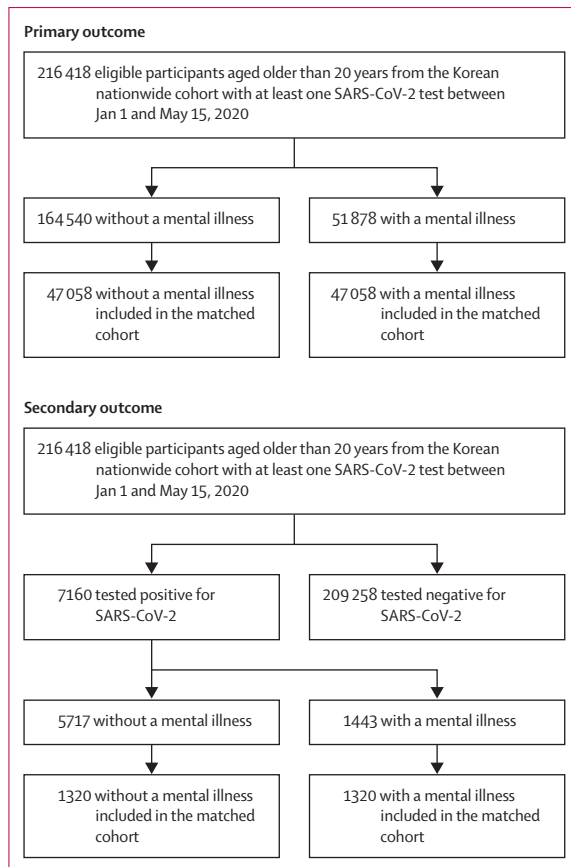


Figure 1: Study profile
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

age; gender; region of residence; history of diabetes, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index.

We repeated the main analysis of severity of mental illness (no mental illness vs other mental illness vs severe mental illness). We considered the additional analysis stratified by admission to the ICU, invasive ventilation, or death. We repeated the main analysis of psychiatric hospitalisation (no mental illness vs patients who have been admitted to a psychiatric ward during the observation period vs patients who never have been hospitalised in a psychiatric ward during the observation period). We redefined the matched cohort stratified by severity of mental illness (no mental illness vs severe mental illness). Finally, we repeated the main analysis using Firth’s bias-reduced logistic regression to reduce small sample bias.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	No mental illness (n=47 058)	Any mental illness (n=47 058)	SMD*
Mean age, years (SD)	60.2 (19.0)	60.2 (19.0)	0.024
Gender	0.024
Men	21 107 (44.9%)	20 555 (43.7%)	..
Women	25 951 (55.1%)	26 503 (56.3%)	..
Region of residence	0.008
Rural	19 731 (41.9%)	19 916 (42.3%)	..
Urban	27 327 (58.1%)	27 142 (57.7%)	..
History of diabetes	14 297 (30.4%)	13 991 (29.7%)	0.016
History of cardiovascular disease	12 542 (26.7%)	12 477 (26.5%)	0.004
History of cerebrovascular disease	8 314 (17.7%)	9 083 (19.3%)	0.047
History of COPD	6 634 (14.1%)	6 837 (14.5%)	0.013
History of asthma	10 530 (22.4%)	10 854 (23.1%)	0.018
History of hypertension	23 937 (50.9%)	23 272 (49.5%)	0.031
History of chronic kidney disease	5 458 (11.6%)	5 435 (11.5%)	0.002
Charlson comorbidity index	0.020
0	13 594 (28.9%)	13 093 (27.8%)	..
1	7 491 (15.9%)	7 753 (16.5%)	..
≥2	25 973 (55.2%)	26 212 (55.7%)	..
COVID-19	1 391 (3.0%)	1 383 (2.9%)	..
Minimally adjusted OR†	1 (ref)	0.99 (95% CI 0.92–1.07)	..
Fully adjusted OR‡	1 (ref)	1.00 (95% CI 0.93–1.08)	..

COPD=chronic obstructive pulmonary disease. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SMD=standardised mean difference. OR=odds ratio. *An SMD less than 0.1 indicates no major imbalance. All SMD values were less than 0.05 in the propensity score matched cohort. †Minimally adjusted for age and gender. ‡Fully adjusted for age; gender; region of residence; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index.

Table 2: Propensity score matched characteristics for the risk of those with a mental illness testing positive for SARS-CoV-2

Results

Between Jan 1 and May 15, 2020, 216 418 people were tested for SARS-CoV-2. We identified 164 540 individuals without a mental illness and 51 878 with a mental illness in the full unmatched cohort. We then matched 47 058 individuals without a mental illness and 47 058 with a mental illness in the propensity score matched cohort (table 1, figure 1, appendix pp 2–3, 16, 19).

Among the 7 160 patients who tested positive for SARS-CoV-2, we identified 5 717 participants without a mental illness and 1 443 with a mental illness in the full unmatched cohort. Subsequently, we matched 1 320 individuals without a mental illness and 1 320 with a mental illness in the propensity score matched cohort (table 1, figure 1, appendix pp 4–5, 17).

After propensity score matching among people who were tested for SARS-CoV-2, and among those who

tested positive, there were no major imbalances in the demographics and clinical characteristics between the group with a mental illness and the group with no mental illness (tables 2, 3). Among all people tested, 1391 (3.0%) people without a mental illness and 1383 (2.9%) of those with a mental illness tested positive for SARS-CoV-2 (figure 2; fully adjusted OR 1.00, 95% CI 0.93–1.08; minimally adjusted OR 0.99, 0.92–1.07). In subgroup analyses, 1023 (2.8%) of patients with other mental illnesses and 360 (3.3%) patients with a severe mental illness tested positive for SARS-CoV-2 (table 4; no mental illness vs other mental illness: fully adjusted OR 0.94, 95% CI 0.86–1.02; no mental illness vs severe mental illness: fully adjusted OR 1.10, 0.99–1.22).

Severe clinical outcomes of COVID-19 were observed in 109 (8.3%) patients without a mental illness, compared with 128 (9.7%) patients with a mental illness (figure 2; fully adjusted OR 1.27, 95% CI 1.01–1.66; minimally adjusted OR 1.28, 1.01–1.65). 71 (5.4%) patients without a mental illness died of COVID-19 compared with 89 (6.7%) with a mental illness (fully adjusted OR 1.38, 1.00–1.95; minimally adjusted OR 1.39, 1.01–1.95). In subgroup analyses, severe clinical outcomes of COVID-19 occurred in 78 (8.2%) patients with other mental illnesses and 50 (13.4%) with a severe mental illness (table 4; no mental illness vs other mental illness: fully adjusted OR 0.98, 95% CI 0.70–1.37; and no mental illness vs severe mental illness: 2.27, 1.50–3.41).

We also did a separate main analysis of each outcome (appendix pp 8–9). Of people who tested positive for SARS-CoV-2, 94 had a previous psychiatric hospitalisation and 1349 did not (appendix pp 10–11). The propensity score matched subgroup analysis showed that 12 (13.0%) patients who were hospitalised in a psychiatric ward during the observation period (Jan 1, 2017, to May 15, 2020) had severe clinical outcomes from COVID-19 compared with 109 (8.3%) of those without a mental illness (appendix p 12; fully adjusted OR 2.22, 95% CI 1.08–4.55). When we redefined the matched cohort stratified by severity of mental illness, patients with a severe mental illness had a higher risk of severe clinical outcomes of COVID-19 than patients with no history of mental illness (appendix pp 13–14, 18; fully adjusted OR 3.94, 95% CI 1.73–9.00). The results from Firth's bias-reduced logistic regression were consistent with our primary results for the risk of testing positive for SARS-CoV-2 and worse clinical outcomes of COVID-19 (appendix p 15).

Discussion

We showed that people with a previous diagnosis of a mental illness had the same risk for testing positive for SARS-CoV-2 as people with no history of mental illness in a nationwide cohort from South Korea. Patients with a mental illness had slightly worse clinical outcomes of COVID-19 but the numbers were small.

Respiratory diseases such as pneumonia are one of the major causes of death in patients with a severe mental

	No mental illness (n=1320)	Any mental illness (n=1320)	SMD*
Mean age, years (SD)	58.3 (16.6)	57.8 (16.8)	0.029
Gender			0.015
Men	511 (38.7%)	521 (39.5%)	..
Women	809 (61.3%)	799 (60.5%)	..
Region of residence			0.008
Rural	612 (46.4%)	607 (46.0%)	..
Urban	708 (53.6%)	713 (54.0%)	..
History of diabetes	314 (23.8%)	320 (24.2%)	0.012
History of cardiovascular disease	146 (11.1%)	169 (12.8%)	0.058
History of cerebrovascular disease	132 (10.0%)	162 (12.3%)	0.077
History of COPD	101 (7.7%)	105 (8.0%)	0.012
History of asthma	196 (14.8%)	185 (14.0%)	0.026
History of hypertension	492 (37.3%)	517 (39.2%)	0.043
History of chronic kidney disease	60 (4.5%)	73 (5.5%)	0.048
Charlson comorbidity index			0.025
0	603 (45.7%)	549 (41.6%)	..
1	208 (15.8%)	235 (17.8%)	..
≥2	509 (38.6%)	536 (40.6%)	..
Severe clinical outcomes of COVID-19†	109 (8.3%)	128 (9.7%)	..
Minimally adjusted OR‡	1 (ref)	1.28 (95% CI 1.01–1.65)§	..
Fully adjusted OR§	1 (ref)	1.27 (95% CI 1.01–1.66)§	..
Death	71 (5.4%)	89 (6.7%)	..
Minimally adjusted OR‡	1 (ref)	1.39 (95% CI 1.01–1.95)§	..
Fully adjusted OR§	1 (ref)	1.38 (95% CI 1.00–1.95)§	..

COPD=chronic obstructive pulmonary disease. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SMD=standardised mean difference. OR=odds ratio. *A SMD less than 0.1 indicates no major imbalance. All SMD values were less than 0.08 in the propensity score matched cohort. †Severe clinical outcomes of COVID-19 comprised admission to the intensive care unit, invasive ventilation, or death. ‡Minimally adjusted for age and gender. §Fully adjusted for age; gender; region of residence; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index. §Significant difference (p<0.05).

Table 3: Propensity score matched characteristics for the association of the severe clinical outcomes of COVID-19 with mental illness among all patients who were tested positive for SARS-CoV-2

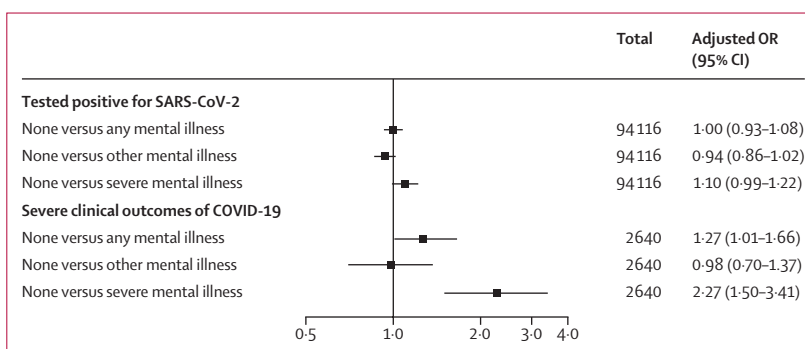


Figure 2: Propensity score matched association of mental illness with SARS-CoV-2
The severe clinical outcomes of COVID-19 comprised admission to the intensive care unit, invasive ventilation, or death. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. OR=odds ratio.

illness.⁶ A previous study with a large cohort (n=103 997) showed that chronic mental illness is an independent risk factor for mortality in patients with pneumonia.¹⁵ In addition, infectious pathogens (eg, toxoplasma,

	No mental illness	Other mental illness	Severe mental illness
Patients who were tested for SARS-CoV-2 (n=94 116)			
COVID-19			
Event number of total number	1391/47 058 (3.0%)	1023/36 257 (2.8%)	360/10 801 (3.3%)
Minimally adjusted OR*	1 (ref)	0.93 (0.85–1.01)	1.11 (0.99–1.23)
Fully adjusted OR†	1 (ref)	0.94 (0.86–1.02)	1.10 (0.99–1.22)
Patients who tested positive for SARS-CoV-2 (n=2640)			
Severe clinical outcomes of COVID-19‡			
Event number of total number	109/1320 (8.3%)	78/946 (8.2%)	50/374 (13.4%)
Minimally adjusted OR*	1 (ref)	1.05 (0.76–1.45)	1.90 (1.29–2.82)§
Fully adjusted OR†	1 (ref)	0.98 (0.70–1.37)	2.27 (1.50–3.41)§

Data are OR (95% CI) unless specified. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. OR=odds ratio. *Minimally adjusted for age and gender. †Fully adjusted for age; gender; region of residence; history of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index. ‡Severe clinical outcomes of COVID-19 comprised admission to the intensive care unit, invasive ventilation, or death. §Significant differences (p<0.05).

Table 4: Propensity score matched adjusted ORs for the risk of those with a mental illness testing positive for SARS-CoV-2 and the severe clinical outcomes of COVID-19 with mental illness

cytomegalovirus, Epstein-Barr virus) chronically induce or aggravate mental illness, including psychiatric disorders, cognitive disorders, personality disorders, and suicidal behaviour.¹⁶ These findings imply that mental illness is inherently associated with worse clinical pathophysiology rather than just affecting health screening or transmission of infection.

Mental illness itself is associated with high mortality¹⁷ and affects lifestyle, daily habits, socioeconomic status, and prognosis of comorbidity, which could affect the clinical outcomes of COVID-19. Social isolation, fear of infection, job loss, city lockdown, bereavements, and lack of a caregiver or family support could worsen a patient's underlying mental illness.^{18–20} Compared with people without depression, a patient with depression is about three times more likely not to follow treatment recommendations²¹ and depression is associated with a 1.8 times increased mortality from coronary heart disease.²² Concomitant mood disorder states progressively worsen health with a decreased life-time expectancy compared with depression alone, chronic disease alone, or comorbid chronic medical disease without depression.²³

A severe mental illness, including schizophrenia spectrum disorders, bipolar affective disorder, depression with psychosis, other psychotic illness, or first-episode psychosis,²⁴ results in serious functional impairment. Such disorders can cause abnormal thinking and perception, a loss of touch with reality, delusions, or hallucinations leading to cognitive impairment and social isolation, which could result in not seeking care, poor adherence to treatment, and difficulty in obtaining health care. Patients with a severe mental illness have a worse quality of life than people with disorders such as anxiety and depression.²⁵ We found that patients with a severe pre-existing mental illness were 2.3 times more likely to have severe COVID-19 outcomes than patients

with no history of mental illness or other mental illnesses. More severe COVID-19 outcomes also occurred in the inpatient treatment group compared with the outpatient treatment group. The effect of mental illness severity could be derived from one or a combination of factors such as a reduction in self-care and risk avoidance, isolation from society, and physical health conditions.^{23,26}

Our results suggest that for patients with COVID-19, their history of mental illness might influence clinical outcomes. Severe mental illness can be considered as a risk factor of severe COVID-19 illness that justifies additional attention and possibly treatment. For patients with a history of severe mental illness who are infected with SARS-CoV-2, psychiatric and psychological consultation is recommended to assist with his or her self-assertion and communication, the biggest difficulties for managing severe mental illness in the clinic.¹⁸ Patients with a severe mental illness showing acute respiratory symptoms should be prioritised for medical care. Active surveillance, monitoring, and support of people at risk for chronic stress disorders, depression, anxiety disorders, psychosis, substance use, and suicide should be put in place.¹⁸

Our study has several limitations. First, we defined mental illness on the basis of ICD codes in insurance claims data. However, claims-based definitions of mental illnesses are widely used, and these administrative data have high specificity with variable sensitivity for diagnoses and medical conditions.^{12,27} Second, our database does not include medications, which might affect the response to infection with SARS-CoV-2. By activating GABA_A receptors in immune cells, benzodiazepines increase susceptibility to infection and double the risk of secondary infections in patients who are critically ill.²⁸ Further study is needed to determine whether the severity of COVID-19 is associated with benzodiazepine use. Third, our analysis did not adjust for possible confounding factors such as obesity and cigarette smoking, although we included history of cardiovascular disease, diabetes, and respiratory disease, which are associated with these factors.²⁹ We could not match patient education level, socioeconomic status, and household income. Diagnosis and treatment of COVID-19 were provided free-of-charge by the South Korean Government; however, socioeconomic factors could still affect outcomes. Fourth, the COVID-19-related data provided by the government included only 3.5 years of the patient's psychiatric history, whereas a previous study found 7 years to be necessary to identify the incidence of schizophrenia in public health plan databases.³⁰

In conclusion, using a large, nationwide, propensity score matched cohort, we found no evidence of a relationship between SARS-CoV-2 test positivity and mental illness, but possible evidence of an association between mental illness and the severity of COVID-19 clinical outcomes. More research is needed to support our findings and to investigate further the relationship

between mental illness and COVID-19. Meanwhile, clinicians should record the history of mental illness in patients with COVID-19 and take it into consideration for prognosis and care.

Contributors

DKY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. SWL and DKY were responsible for study concept and design. HYK, JMY, SWL, and DKY were responsible for acquisition, analysis, or interpretation of data. HYK, JMY, and DKY were responsible for drafting of the manuscript. HYK, JMY, DKY, IKY, EKH, SYK, SC, S-HL, YMA, J-MK, and UMP were responsible for critical revision of the manuscript for important intellectual content. SWL, SYM, and DKY were responsible for statistical analysis. DKY was responsible for study supervision and was the guarantor for the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors approved the final version before submission.

Declaration of interests

We declare no competing interests.

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