

## Poorer outcomes following COVID-19 infection for patients with depression: A cohort analysis in South Korea

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### ABSTRACT

**Introduction:** It remains unknown whether patients with pre-existing depressive conditions are at high risk of severe COVID-19. Therefore, this study aims to investigate the association between patients with pre-existing depressive conditions and severe COVID-19.

**Method:** This study is part of the Korea Disease Control and Prevention Agency-COVID19-National Health Insurance Service cohort study of an ongoing large-scale health screening survey of adults 18 years and older residing in South Korea. Pre-existing depression status was measured from 552,860 patients who participated in a biennial health screening from 2019 to 2020. Finally, 29,106 confirmed COVID-19 patients were enrolled and followed up to track any severe clinical events within 1 month of their diagnosis date. Adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using multivariate-adjusted logistic regression analysis.

**Results:** We identified 2868 COVID-19 patients with severe clinical events and 26,238 COVID-19 patients without severe clinical events. The moderate-to-severe depressive symptoms group showed an elevated odds of severe outcomes of COVID-19 (aOR, 1.46; 95% CI, 1.25–1.72), including those without vaccination (aOR, 1.32; 95% CI, 1.08–1.61) and those with complete vaccination (aOR, 1.76; 95% CI, 1.18–2.63). In addition, those who were diagnosed with depression along with depressive symptoms at the health screening revealed an increased risk of severe outcomes of COVID-19 (aOR, 2.22; 95% CI, 1.22–4.05).

**Conclusion:** Moderate-to-severe depressive symptoms were associated with higher odds of severe COVID-19 events in both no and complete vaccination groups. Participants with depressive symptoms may be at higher risk of severe outcomes of COVID-19.

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**Keywords:** cohort study, pre-existing depression, public mental health, severe COVID-19, social science, South Korea

### INTRODUCTION

In the early days of the pandemic, a major public health focus was to slow the spread of COVID-19. Therefore, the emphasis was on protecting the elderly, immunocompromised, and patients with respiratory and other underlying medical conditions. However, as COVID-19 continues to prolong, the concept of a new “normal” has emerged and is moving in a direction that focuses more on health risks to other vulnerable population groups, including individuals with severe mental illness.<sup>1</sup>

The COVID-19 pandemic disproportionately affects people with pre-existing mental health disorders.<sup>2</sup> They are a vulnerable group in consideration of both medical and socioeconomic aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, morbidity and mortality.<sup>3</sup> This increased risk is likely to be mediated by the risk factors for infectious diseases, including socioeconomic inequality, poverty, unemployment, social distancing, and physical inactivity.<sup>4</sup>

There is evidence that pre-existing health inequalities may be strongly reflected in the current COVID-19

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## CLINICAL IMPACT

### What is New

- To the authors' knowledge, this cohort study is one of the first to highlight the epidemiological need to screen a vulnerable group in Korea with pre-existing depressive symptoms.

### Clinical Implications

- This study supports the need to increase awareness of severe COVID-19 vulnerable groups and preventive management of people with moderate-to-severe depression.
- Our results could aid mental public health policymaking and guide efforts to improve preventive strategies against the risk of communicable diseases.

pandemic.<sup>5</sup> Patients with pre-existing mental disorders are at increased risk of contracting COVID-19 and are particularly vulnerable to the mental health threat of the pandemic.<sup>6-8</sup> Some longitudinal evidence suggests that the type of pre-existing mental health condition predicts different levels or changes in depressive and anxiety symptoms during a pandemic.<sup>9</sup> However, studies on the health risk effects according to pre-COVID-19 depressive symptoms or mental health conditions remain limited.

In the meantime, there have been previous studies on the risk that mental illness, such as severe depression, increases the risk of SARS-CoV-2 infection<sup>10</sup> and subsequent severe COVID-19.<sup>11</sup> However, it is still unclear how the epidemic and the prevalence of depression may affect SARS-CoV-2 infection, severe COVID-19, and mortality. Most previous studies were cross-sectional, targeting specific population groups affected by the COVID-19 pandemic, such as mental health service providers and their stakeholders<sup>2</sup> or people self-reporting a mood disorder,<sup>12</sup> who demonstrated the results of the primary survey. A few studies have explored the long-term effects of pre-existing depression on SARS-CoV-2 infection and severe COVID-19 in a large-scale population-based cohort. In the present study, we evaluated the association of pre-existing depressive status and severe clinical outcomes of COVID-19 in the Korea Disease Control and Prevention Agency-COVID19-National Health Insurance Service (K-COV-N) cohort, which represents up to 97% of all Korean citizens.<sup>13</sup>

## METHOD

### Data source

The current cohort study used data from the K-COV-N cohort. The National Health Insurance Service (NHIS) provides health insurance services to approximately 97% of the Korean population.<sup>13</sup> Health insurance claims—including medical health screening results, medical treatments, and medication prescriptions—have been collected by the NHIS. The Korea Disease Control and Prevention Agency (KDCA) operated as the Central Disease Control Headquarters for COVID-19 and collected data on COVID-19 and vaccinations. To promote academic research in analysing health damage caused by COVID-19 and to actively develop treatments for preventing infectious diseases, the NHIS and KDCA have linked the national health information with COVID-19-related records and thereby generated the K-COV-N cohort dataset. The eligibility dataset contains (1) demographic data, medical history, anthropometric measurements, and lifestyle questionnaires from the NHIS registered between 1 January 2009 and 31 December 2021; and (2) date of confirmation of COVID-19, date of death, area code of reporting institution, mode of transmission, dose of COVID-19 vaccines administered with the vaccination date, and type from the KDCA registered between 8 October 2020 and 31 December 2021. The dataset was matched by a confirmed COVID-19 case population with a 1:10 ratio using age and sex propensity scores. The COVID-19-related registers after 8 October 2020 were used due to the possibility of identifiability even though the personally identifiable data were strictly anonymised. Access to the dataset was allowed only after approval by the enquiry committee.

### Study population

A total of 2,882,789 participants who participated in health screenings from 2019 to 2020 were initially enrolled in the study. Among the participants who joined the health screenings, we excluded those who were not included for Patient Health Questionnaire-9 (PHQ-9) (n=2,329,929), diagnosed with COVID-19 before the follow-up period (n=17,228), and with missing information for other covariates (n=600). To investigate the association between the degree of depression severity and severe clinical events of COVID-19, we only included patients diagnosed with COVID-19 (n=44,706). A positive laboratory result by real-time RT-PCR assay was considered a confirmed case. Those who died within 1 month after COVID-19 infection before the severe clinical events (n=167) or were diagnosed with SARS-CoV-2 infection after

1 December 2021 due to a short follow-up period ( $n=15,433$ ) were additionally excluded. Finally, 29,106 confirmed COVID-19 patients were enrolled and followed up from the diagnosis date to any severe clinical events within 1 month (Fig. 1). The Institutional Review Board of CHA University Hospital approved the study (No.: CHAMC 2022-05-052), and informed consent was waived due to anonymous cohort data provided by the NHIS and KDCA.

### Exposure

The degree of depression severity was measured by PHQ-9. PHQ-9 is the most commonly used self-reported questionnaire formed with nine questions for screening depression in primary care.<sup>3</sup> The NHIS provides PHQ-9 to those aged 20, 30, 40, 50, 60 and 70 at the check-up year for screening depression. Participants were asked to answer each item by a score ranging from 0–3 (0=not at all; 1=several days; 2=more than half the days; 3=nearly every day). Then, we summed each score in total and categorised it into 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms

(scores of 5–9), and moderate-to-severe depressive symptoms (scores of 10–27). The accuracy of PHQ-9 in detecting depression<sup>4–5</sup> and its severity<sup>6</sup> has been validated through previous studies. The items in PHQ-9 are described elsewhere.<sup>7</sup>

### Outcome

Outcome was defined as any severe event that occurred within one month after the diagnosed date, including the requirement of oxygen supply with conventional oxygen therapy (COT), a high-flow nasal cannula, continuous positive airway pressure, admission to intensive care unit, the requirement of mechanical ventilation, extracorporeal membrane oxygenation, and death after severe clinical events of COVID-19. When the total number for each outcome was lower than 5, it was not described in the table.

We also categorised the study population by vaccination status to reduce bias. Vaccination status was classified by the completion of the primary series of any COVID-19 vaccines. The COVID-19 vaccines available in South Korea include BNT162b2 (Pfizer-

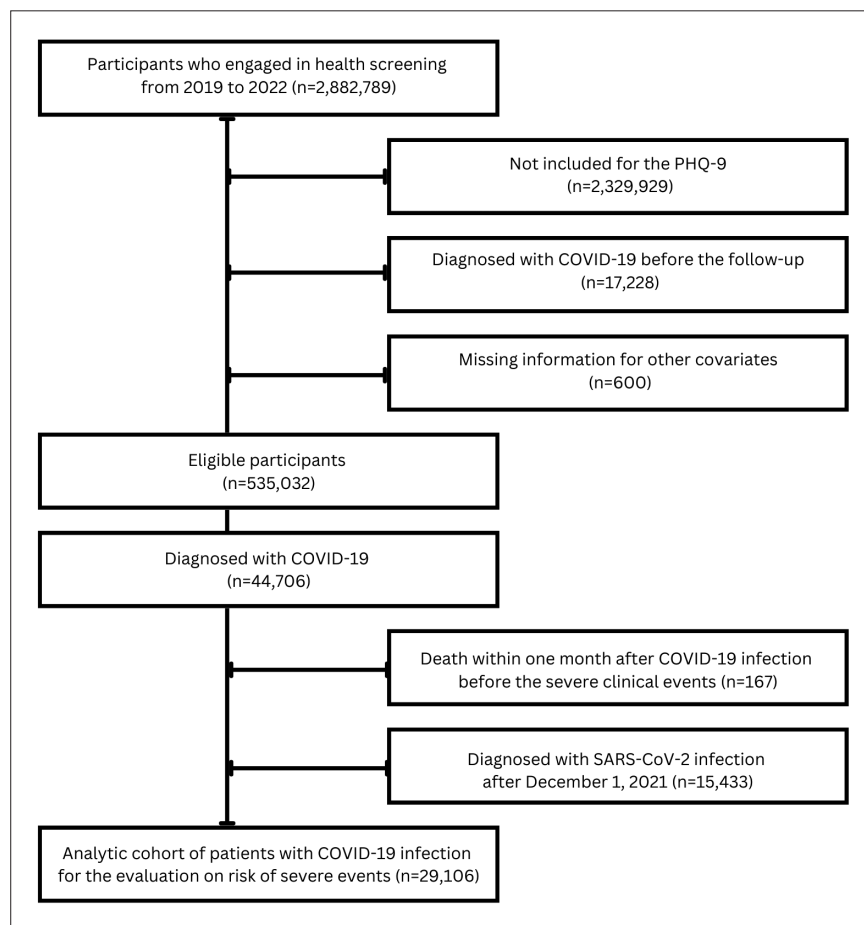


Fig. 1. Participant inclusion flowchart.

BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), NVX-CoV2373 (Novavax), and Ad26.COV2.S (Janssen/Johnson & Johnson) vaccines. We considered those with any heterologous COVID-19 vaccines as completion of the primary series if the number of doses was 2 or more. If the patient was diagnosed with COVID-19 within 14 days after vaccination, we did not count them as vaccinated due to the relatively short period for vaccine effectiveness.

### Covariates

For the adjustment, covariates were identified from the patient information before the start of follow-up. We included age, sex, household income, body mass index (BMI), smoking, alcohol consumption, moderate-to-vigorous physical activity (MVPA), history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and comorbidities. Household income was categorised as quartiles based on the insurance premium. Smoking was categorised as ever or never smoker, differentiating patients between those that smoked or did not smoke at least 100 cigarettes throughout their lifetime, respectively. Alcohol consumption was categorised by the current alcohol intake as drinker or non-drinker. MVPA was assessed by the duration of weekly MVPA using self-reported questionnaires. By multiplying the times per day (minutes per day) with the frequency per week (days per week) for moderate and vigorous physical activity, we categorised it into 4 levels: physically inactive; 1–74 min/week; 75–149 min/week; and  $\geq 150$  min/week. Underlying comorbidities were assessed by Charlson Comorbidity Index (CCI) score using claims data before the follow-up validated in the previous study.<sup>14</sup> Diagnosis of hypertension, diabetes mellitus, and dyslipidaemia was confirmed by the records of medical diagnosis from clinical physicians collected at the health screening. The history of organ transplantation was based on the Electronic Data Interchange codes of kidney, liver, heart, lung, pancreas, bone marrow, and small intestine during hospitalisation (Table S1). The history of autoimmune disorders was confirmed based on the ICD-10 codes from a previous study (Table S2).

### Statistical analysis

We analysed the association of the degree of depression severity with the odds of severe clinical COVID-19 events. From the diagnosis date of COVID-19, the patients were followed up for one month for any severe COVID-19 events. Continuous variables were presented

as mean  $\pm$  standard deviation (SD) and categorical variables as n (%). Event numbers for the outcomes were presented as n (%). Adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using multivariate logistic regression analysis. First, age and sex were adjusted for the multivariate regression. Next, covariates including age, sex, household income, BMI, smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, and CCI were adjusted. To reduce healthy vaccine bias, we categorised the patients by vaccination status depending on the completion of the primary series. To validate the degree of depression severity, we correlated every patient with the diagnosis of depression (ICD-10 codes of F32-F33) after the health screening. Individuals indicating an absence of depressive symptoms and without a diagnosis of depression were categorised as “devoid of depressive symptoms — authentic absence”. Similarly, those who reported moderate-to-severe depressive symptoms and were diagnosed with depression were considered as “moderate-to-severe depressive — genuine depression”. For the subgroup analyses, we stratified the patients with age ( $<65$ ,  $\geq 65$ ), sex (men, women), comorbidity (CCI; 0, 1,  $\geq 2$ ), hypertension (yes, no), diabetes mellitus (yes, no), and dyslipidaemia (yes, no) with the risk of severe COVID-19. *P* values of less than 0.05 were considered statistically significant in a two-sided manner. All data collection, mining, and statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

### RESULTS

The analytic cohort consisted of 29,106 adults aged 20 or more years who engaged in health screening from 2019 to 2020. Among them, 23,027 showed no depressive symptoms, 4404 showed mild depressive symptoms, and 1675 showed moderate-to-severe depressive symptoms. Compared with no depressive symptoms, those with moderate-to-severe depressive symptoms tended to be younger, women, physically inactive, have lower household income, have lower systolic blood pressure, have lower diastolic blood pressure, have lower CCI, and have no COVID-19 vaccination. Other descriptive characteristics are described in Table 1.

### Association of depression severity with the risk of severe COVID-19

There were 3,023 severe clinical COVID-19 events that occurred during the follow-up period. Table 2 shows the associations between depression severity with the risk of severe clinical COVID-19 events and stratified

Table 1. Descriptive characteristics of the study participants.

|                                               | No depressive symptoms<br>(n=23,027) | Mild depressive symptoms<br>(n=4404) | Moderate-to-severe depressive<br>symptoms (n=1675) |
|-----------------------------------------------|--------------------------------------|--------------------------------------|----------------------------------------------------|
| Age, years                                    | 49.2 ± 13.9                          | 44.8 ± 13.5                          | 44.3 ± 14.1                                        |
| Sex, n (%)                                    |                                      |                                      |                                                    |
| Men                                           | 11,903 (51.7)                        | 1914 (43.5)                          | 633 (37.8)                                         |
| Women                                         | 11,124 (48.3)                        | 2490 (56.5)                          | 1042 (62.2)                                        |
| Moderate-to-vigorous physical activity, n (%) |                                      |                                      |                                                    |
| Physically inactive                           | 6172 (26.8)                          | 1353 (30.7)                          | 574 (34.3)                                         |
| 1–74 min/week                                 | 5008 (21.8)                          | 1103 (25.1)                          | 345 (20.6)                                         |
| 75–149 min/week                               | 2966 (12.9)                          | 612 (13.9)                           | 217 (13.0)                                         |
| ≥150 min/week                                 | 8881 (38.6)                          | 1336 (30.3)                          | 539 (32.2)                                         |
| Household income, n (%)                       |                                      |                                      |                                                    |
| First quartile                                | 5073 (22.0)                          | 953 (21.6)                           | 437 (26.1)                                         |
| Second quartile                               | 5023 (21.8)                          | 996 (22.6)                           | 405 (24.2)                                         |
| Third quartile                                | 6057 (26.3)                          | 1237 (28.1)                          | 432 (25.8)                                         |
| Fourth quartile (highest)                     | 6874 (29.9)                          | 1218 (27.7)                          | 401 (23.9)                                         |
| Body mass index, kg/m <sup>2</sup>            | 24.6 ± 3.6                           | 24.5 ± 4.0                           | 24.4 ± 4.1                                         |
| Waist circumference, cm                       | 82.6 ± 10.2                          | 81.8 ± 17.8                          | 81.4 ± 11.0                                        |
| Systolic blood pressure, mmHg                 | 122.2 ± 14.8                         | 121.7 ± 14.4                         | 121.1 ± 14.1                                       |
| Diastolic blood pressure, mmHg                | 77.0 ± 10.4                          | 75.8 ± 10.6                          | 75.9 ± 10.3                                        |
| Triglyceride, mg/dL                           | 133.5 ± 108.5                        | 136.7 ± 123.7                        | 146.0 ± 126.8                                      |
| Cigarette smoking, n (%)                      |                                      |                                      |                                                    |
| Never smoker                                  | 15,049 (51.7)                        | 2805 (63.7)                          | 1016 (60.7)                                        |
| Ever smoker                                   | 7978 (34.7)                          | 1599 (36.3)                          | 659 (39.3)                                         |
| Alcohol consumption, n (%)                    |                                      |                                      |                                                    |
| Yes                                           | 15,044 (65.3)                        | 3263 (74.1)                          | 1217 (72.7)                                        |
| No                                            | 7983 (34.7)                          | 1141 (25.9)                          | 458 (27.3)                                         |
| Hypertension, n (%)                           | 4232 (18.4)                          | 636 (14.4)                           | 257 (15.3)                                         |
| Diabetes, n (%)                               | 1744 (7.6)                           | 283 (6.4)                            | 123 (7.3)                                          |
| Dyslipidaemia, n (%)                          | 1747 (7.6)                           | 313 (7.1)                            | 144 (8.6)                                          |
| Organ transplantation, n (%)                  | 6 (0.0)                              | 1 (0.0)                              | 0 (0.0)                                            |
| Autoimmune disease, n (%)                     | 3747 (16.3)                          | 785 (17.8)                           | 378 (22.6)                                         |
| Charlson comorbidity index, n (%)             |                                      |                                      |                                                    |
| 0                                             | 9495 (41.2)                          | 1837 (41.7)                          | 604 (36.1)                                         |
| 1                                             | 7828 (34.0)                          | 1490 (33.8)                          | 573 (34.2)                                         |
| ≥2                                            | 5704 (24.8)                          | 1077 (24.5)                          | 498 (29.7)                                         |
| COVID-19 vaccination, n (%)                   |                                      |                                      |                                                    |
| No                                            | 12,799 (55.6)                        | 2713 (61.6)                          | 1040 (62.1)                                        |
| Completion of primary series                  | 6436 (28.0)                          | 1020 (23.2)                          | 363 (21.7)                                         |

Continuous variables were presented as mean ± standard deviation and categorical variables as n (%). Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27).

Acronyms: COVID-19, coronavirus disease 2019; PHQ-9, Patient Health Questionnaire-9; NHIS, National Health Insurance Service.

the results with the vaccination status. Compared with those who showed no depressive symptoms, the moderate-to-severe depressive symptoms group showed an elevated risk (aOR, 1.46; 95% CI, 1.25–1.72). The risk was consistent when stratified with no vaccination (aOR, 1.33; 95% CI, 1.09–1.62) and completion of the primary series (aOR, 1.65; 95% CI, 1.11–2.47). There were 22,644 authentic absence and 160 genuine depression patients when correlated with the diagnosis of depression after testing for PHQ-9 (Table S3). When validated with the diagnosis of depression after the health screening test, the odds increased (aOR, 1.99; 95% CI, 1.12–3.53, Table 3). However, the odds showed no significance when stratified with the vaccination status. Those who were treated for COT showed statistically significant results when moderate-to-severe depressive symptoms were exhibited (aOR, 1.48; 95% CI, 1.26–1.74, Table S4). The risk was consistent for

COT when moderate-to-severe depressive symptoms were shown, stratified with no vaccination (aOR, 1.34; 95% CI, 1.10–1.63, Table S5) and completion of the primary series (aOR, 1.76; 95% CI, 1.19–2.65, Table S6). Other outcomes showed no significant results.

### Stratified analysis

A stratified analysis of the association of depression severity with the risk of severe clinical COVID-19 events is shown in Table S7. All patients were stratified by age, sex, hypertension, diabetes mellitus, dyslipidaemia, and CCI. Those with age <65 years (aOR, 1.34; 95% CI, 1.12–1.59), women (aOR, 1.55; 95% CI, 1.26–1.93), and history of dyslipidaemia (aOR, 1.81; 95% CI, 1.13–2.98) had an elevated risk when they had moderate-to-severe depressive symptoms. Conversely, the risk was also elevated with no comorbidities (aOR, 1.66; 95% CI, 1.21–2.28), no

Table 2. Association of depression severity with the risk of severe clinical COVID-19 events.

| Depressive symptoms <sup>a</sup>                  | Event      | Age, sex-adjusted OR<br>(95% CI) | Multivariable-adjusted OR<br>(95% CI) <sup>b</sup> |
|---------------------------------------------------|------------|----------------------------------|----------------------------------------------------|
| <b>Overall, 29106 (100%)</b>                      |            |                                  |                                                    |
| No                                                | 2282 (7.8) | 1.00 (Reference)                 | 1.00 (Reference)                                   |
| Mild                                              | 390 (1.3)  | 1.10 (0.98–1.23)                 | 1.08 (0.96–1.21)                                   |
| Moderate to severe                                | 196 (0.7)  | 1.53 (1.31–1.80) <sup>c</sup>    | 1.46 (1.25–1.72) <sup>c</sup>                      |
| <i>P</i> for trend                                |            | <.001                            | <.001                                              |
| <b>No vaccination, 16552 (56.9%)</b>              |            |                                  |                                                    |
| No                                                | 1620 (9.8) | 1.00 (Reference)                 | 1.00 (Reference)                                   |
| Mild                                              | 293 (1.8)  | 1.06 (0.93–1.22)                 | 1.05 (0.92–1.21)                                   |
| Moderate to severe                                | 137 (0.8)  | 1.38 (1.14–1.68) <sup>d</sup>    | 1.33 (1.09–1.62) <sup>d</sup>                      |
| <i>P</i> for trend                                |            | 0.004                            | 0.02                                               |
| <b>Completion of primary series, 7819 (26.9%)</b> |            |                                  |                                                    |
| No                                                | 382 (4.9)  | 1.00 (Reference)                 | 1.00 (Reference)                                   |
| Mild                                              | 54 (0.7)   | 1.15 (0.85–1.56)                 | 1.13 (0.84–1.45)                                   |
| Moderate to severe                                | 32 (0.4)   | 1.89 (1.28–2.81) <sup>d</sup>    | 1.65 (1.11–2.47) <sup>c</sup>                      |
| <i>P</i> for trend                                |            | 0.006                            | 0.04                                               |

The patients were categorised by vaccination status depending on the completion of the primary series. aOR was calculated using multivariate adjusted logistic regression and presented with 95% CI. Event number of severe COVID-19 was presented as n (%). <sup>a</sup>Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27).

<sup>b</sup>Adjusted for age, sex, household income, body mass index (BMI), smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and Charlson comorbidity index.

<sup>c</sup>*P*<0.05.

<sup>d</sup>*P*<0.01.

<sup>e</sup>*P*<0.001.

Acronyms: MVPA, moderate-to-vigorous physical activity; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

Table 3. Association of depression severity with the risk of severe clinical COVID-19 events correlated with the diagnosis of depression.

| Depressive symptoms – diagnosis <sup>a</sup>       | Event       | Multivariable-adjusted OR (95% CI) <sup>b</sup> |
|----------------------------------------------------|-------------|-------------------------------------------------|
| <b>Overall</b>                                     |             |                                                 |
| Devoid of depressive symptoms — authentic absence  | 2226 (9.8)  | 1.00 (Reference)                                |
| Moderate-to-severe depressive — genuine depression | 24 (0.1)    | 1.99 (1.12–3.53) <sup>c</sup>                   |
| <i>P</i> for trend                                 |             | 0.009                                           |
| <b>No vaccination</b>                              |             |                                                 |
| Devoid of depressive symptoms — authentic absence  | 1578 (12.4) | 1.00 (Reference)                                |
| Moderate-to-severe depressive — genuine depression | 17 (0.1)    | 1.82 (0.85–3.93)                                |
| <i>P</i> for trend                                 |             | 0.13                                            |
| <b>Completion of primary series</b>                |             |                                                 |
| Devoid of depressive symptoms — authentic absence  | 372 (4.9)   | 1.00 (Reference)                                |
| Moderate-to-severe depressive — genuine depression | 2 (0.0)     | 1.23 (0.15–9.95)                                |
| <i>P</i> for trend                                 |             | 0.85                                            |

The patients were categorised by vaccination status depending on the completion of the primary series. aOR was calculated using multivariate adjusted logistic regression and presented with 95% CI. Event number of severe COVID-19 was presented as n (%). <sup>a</sup>Degree of depression severity was measured by PHQ-9 at the NHIS health screening test from 2019 to 2020. By adding the scores of each 9 items, total score was calculated and categorised by 3 levels: no depressive symptoms (scores of 0–4), mild depressive symptoms (scores of 5–9), moderate-to-severe depressive symptoms (scores of 10–27). Every patient was correlated with the diagnosis of depression (ICD-10 code of F32–F33) after the health screening. Those who reported no depressive symptoms and were not diagnosed with depression were considered as devoid of depressive symptoms — authentic absence. Similarly, those who reported moderate-to-severe depressive symptoms and were diagnosed with depression were considered as moderate-to-severe depressive — genuine depression.

<sup>b</sup>Adjusted for age, sex, household income, body mass index (BMI), smoking, alcohol consumption, MVPA, history of hypertension, diabetes mellitus, dyslipidaemia, autoimmune disorder, history of organ transplantation, and Charlson comorbidity index.

<sup>c</sup>*P*<0.05.

<sup>d</sup>*P*<0.01.

<sup>e</sup>*P*<0.001.

Acronyms: MVPA, moderate-to-vigorous physical activity; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; International Classification of Diseases, 10th Revision, ICD-10.

hypertension (aOR, 1.58; 95% CI, 1.32–1.90), diabetes mellitus (aOR, 1.50; 95% CI, 1.26–1.79), and no dyslipidaemia (aOR, 1.43; 95% CI, 1.20–1.70). No significant interaction was found between subgroups.

## DISCUSSION

Pre-existing depressive status prior to the pandemic was associated with a higher odds of severe clinical COVID-19 events. Participants with moderate-to-severe depressive symptoms had a higher risk of severe COVID-19 events than those without pre-existing depressive symptoms. The results were consistent when stratified by the presence of vaccinations. In addition, moderate-to-severe depressive symptoms and diagnosis of depression had an over 2-fold risk of severe clinical events in patients with COVID-19. Further research is needed to determine whether depressive symptoms and depression may affect the long-term prognosis of COVID-19.

In previous studies, there was a bidirectional relationship between SARS-CoV-2 infection and mental

health disorders. First, there were papers reporting the prevalence of depression,<sup>15–16</sup> anxiety,<sup>17</sup> or insomnia during the corona epidemic,<sup>18</sup> or exacerbating existing mental disorders.<sup>17,19–20</sup> Meanwhile, there have been studies reporting that patients with pre-existing general or severe mental health disorders have a higher risk of COVID-19,<sup>7–8</sup> severe consequences of COVID-19, and mortality.<sup>10,19</sup> That is, due to several socioeconomic factors, the COVID-19 pandemic disproportionately affects people with pre-existing mental health disorders,<sup>10</sup> including depression, anxiety, and psychotic disorders. To date, several countries have characterised the mental health status of the general population with respect to COVID-19, but there is a lack of efforts evaluating pre-existing depressive conditions against severe COVID-19 in a large-scale population that involved individuals without severe depressive conditions or disabilities.<sup>12</sup>

There are several possible reasons that could explain the association between depressive symptoms and severe COVID-19. One possible mechanism includes the

immune system's vulnerability caused by the depressed mood state,<sup>25</sup> making individuals more susceptible to infections like COVID-19.<sup>26</sup> Similarly, there may be a connection between the occurrence of inflammatory diseases and the depressive symptoms, indicating that the increased cytokines may have an impact on the mood state.<sup>26</sup> Depression is often accompanied by comorbidities such as obesity, diabetes and cardiovascular disease, which are known risk factors for severe COVID-19.<sup>12</sup> Another possible explanation is that the stress may lead to dysregulation of the hypothalamic-pituitary-adrenal axis, resulting in increased inflammation and oxidative stress, both of which may facilitate the pathogenesis of severe COVID-19.<sup>27</sup> Our study is consistent with the results of a population-based cohort study in Catalonia, which revealed that pre-existing mental health disorders were associated with the severity of COVID-19.<sup>11</sup> Our analysis of the NHIS cohort expands the evidence supporting the association between pre-COVID depression symptoms and the heightened risk of severe COVID-19, utilising large population-level data.

Our study differs from previous studies in that ours is based on claims data from the NHIS that routinely collects data on clinical and socioeconomic characteristics, including lifestyle habits, such as smoking, drinking, physical activity, household income and comorbidities, which allowed the comprehensive and robust adjustments of potential confounding factors. The limitations of our study include the unavailability of repeated measurements on depressive status before and after COVID-19 because the Korea NHIS provides mandatory healthcare services and health screening examinations biennially. Another concern is the short duration of follow-up that limited the assessment of long-term outcomes of COVID-19. It highlights the need for further longitudinal studies to determine the long-term impact of mental health prior to the pandemic against COVID-19. Lastly, the limited number of patients with severe COVID-19 patients may be a weakness. Despite the above limitations, this study presents the first robust association of pre-existing depressive symptoms with severe clinical COVID-19 events.

Taken together, patients with moderate-to-severe depressive symptoms had higher odds of severe clinical COVID-19 events. It may be necessary to additionally consider individuals with severe mental illness as a vulnerable population against severe clinical COVID-19 events.

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### Competing interests

*The authors declare that they have no competing interests.*

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