

Risk of COVID-19 Infection and of Severe Complications Among People With Epilepsy

A Nationwide Cohort Study

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Abstract

Background and Objectives

The goal of this work was to evaluate whether patients with epilepsy were more susceptible to coronavirus disease 2019 (COVID-19) infection and at greater risk of severe complications when infected with COVID-19 compared with patients without epilepsy.

Methods

We included participants who underwent at least 1 severe acute respiratory syndrome coronavirus 2 real-time reverse-transcription PCR test between January 1 and June 4, 2020, from the Korean nationwide COVID-19 dataset. Epilepsy was defined according to the presence of diagnostic code in health claims data before the COVID-19 diagnosis. To investigate the association between epilepsy and the susceptibility for or severe complications of COVID-19, a 1:6 ratio propensity score matching (PSM) and logistic regression analysis were performed. Severe complications with COVID-19 infection were defined as a composite of the incidence of mechanical ventilation, intensive care unit admission, and death within 2 months after COVID-19 diagnosis.

Results

Among 212,678 study participants who underwent a COVID-19 test, 3,919 (1.8%) had a history of epilepsy. After PSM, there was no significant difference in COVID-19 PCR positivity according to epilepsy history (odds ratio [OR] 0.86, 95% CI 0.67–1.11). Of the 7,713 individuals with confirmed COVID-19 infection, 72 (0.9%) had a history of epilepsy. Among the patients with COVID-19, severe complications occurred in 444 (5.8%) individuals. After PSM, the presence of epilepsy was associated with the occurrence of severe complications after COVID-19 infection (OR 2.05, 95% CI 1.04–4.04). Mortality after COVID-19 infection did not differ according to the presence of epilepsy history (OR 1.55, 95% CI 0.65–3.70).

Discussion

The presence of epilepsy was not associated with increased susceptibility to COVID-19 infection or mortality related to the infection. However, there was an increased risk of severe complications with COVID-19 in patients with epilepsy; therefore, careful management and monitoring may be necessary.

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Glossary

COVID-19 = coronavirus disease 2019; **ICD-10** = International Statistical Classification of Diseases and Related Health Problems, 10th revision; **ICU** = intensive care unit; **NHIS** = National Health Insurance Service; **OR** = odds ratio; **PSM** = propensity score matching; **RT-PCR** = reverse-transcription PCR; **SMD** = standardized mean difference.

The global pandemic of coronavirus disease 2019 (COVID-19) is the biggest health threat of the 21st century. As of July 30, 2021, there were >196 million global cases of COVID-19 infection and >4 million deaths related to COVID-19.¹ The prognosis of most patients infected with COVID-19 is not bad; however, a significant proportion experience critical complications. A nonnegligible number of patients with COVID-19 require mechanical ventilation or hospitalization in an intensive care unit (ICU), and some patients eventually die. In particular, individuals with underlying medical conditions are more vulnerable to COVID-19.²⁻⁴

Epilepsy is a frequent and serious neurologic disease that affects 70 million people worldwide.⁵ It is a brain disorder characterized by an enduring predisposition leading to epileptic seizures.⁶ The socioeconomic burden of epilepsy is significant, and patients often face discrimination and social stigma.⁷ Mortality in patients with epilepsy is higher than in the general population, which may be due to comorbid conditions such as head trauma or stroke.⁸ Furthermore, infectious diseases such as pneumonia are associated with poor prognosis and mortality in patients with epilepsy. Patients with epilepsy are 3 times more likely to develop pneumonia and have a higher chance of mortality from pneumonia.^{9,10} Recently, research on the association between COVID-19 infection and epilepsy has been proposed.^{11,12} However, studies on epilepsy and COVID-19 remain limited.

In this study, we investigated whether patients with epilepsy were more susceptible to COVID-19 infection than those without epilepsy using a nationwide population-based cohort. In addition, we investigated whether the risk of severe complications with COVID-19 such as mechanical ventilation, admission to ICU, and mortality increased in patients with epilepsy.

Methods

Study Design and Participants

We performed a retrospective observational study using a nationwide COVID-19 dataset in South Korea. South Korea has a single-payer national health insurance system called by the National Health Insurance Service (NHIS). Because the NHIS pays costs according to the health claims and billing records of health care providers, the NHIS created a health care database that includes information on demographics, hospital visit, diagnosis, medical procedures, prescriptions, and mortality of the whole Korean population.^{13,14} Diagnoses at each hospital visits were recorded with ICD-10 codes. In the face of the COVID-19 pandemic, the Korea Disease Control and Prevention Agency and NHIS released a nationwide dataset

of patients who underwent a COVID-19 test for academic research.¹⁵ The nationwide COVID-19 dataset included participants living in South Korea who underwent at least 1 real-time reverse-transcription PCR (RT-PCR) assays of nasal and pharyngeal swabs for COVID-19 from January 1 to June 4, 2020. The real-time RT-PCR assay kit followed the World Health Organization guideline and was validated by the Korea Centers for Disease Control and Prevention.¹⁶

Using the health claims data in the nationwide COVID-19 dataset, we defined patients with epilepsy as those who met both of the following criteria: (1) a diagnostic code for epilepsy or seizure (epilepsy [ICD-10 code G40], status epilepticus [ICD-10 code G41], Landau-Kleffner syndrome [ICD-10 code F803], and convulsion [R56]) with insurance claims before a COVID-19 RT-PCR test and (2) prescription of antiepileptic drugs.¹⁷ Antiepileptic drugs included carbamazepine, clobazam, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, vigabatrin, valproate, zonisamide, and tiagabine.¹⁸

This study was approved by the Institutional Review Board of our institution (Seoul Hospital Ewha Womans University College of Medicine 2020-10-021). Due to the retrospective analysis of this fully anonymized dataset, the requirement for informed consent was waived.

Study Outcomes

In current study, we investigated whether patients with epilepsy were more susceptible to COVID-19 infection than those without epilepsy in study participants who underwent COVID-19 test and whether patients with epilepsy more frequently died or had severe complication of COVID-19 infection than those without epilepsy in patients diagnosed with COVID-19. Severe complication of COVID-19 infection was defined as a composite of the incidence of mechanical ventilation, admission to the ICU, or mortality within the 2 months after a positive COVID-19 diagnosis. Mechanical ventilation was identified by claim codes of mechanical ventilation (M5850, M5857, M5858, and M5860).¹⁹ Admission to the ICU was defined as the presence of the procedure codes for intensive care (AH110, AH150, AH180–AH185, AH190–AH195, AH210, AH250, AH280–AH289, AH28A, AH290–AH299, AH380–AH389, AH38A, AH390–AH399, AH501, AJ001–AJ011, AJ020–AJ021, AJ031, AJ100–AJ390, AJ2A0, AJ3A0, AJ500–AJ590, V5100, V5200, V5210–V5220, V5500–V5520). Mortality and timing of death were provided by NHIS and have been validated previously.^{20,21}

Covariates

We acquired information on sex, age at COVID-19 diagnosis, and household income level (tertiles). In our COVID-19 dataset, age is presented as an interval (10 years) for privacy reasons. Therefore, it was divided by the median value and dichotomized on the basis of 60 years of age. In addition, we obtained information on comorbid conditions such as hypertension, diabetes, stroke, heart failure, atrial fibrillation, coronary artery disease, asthma, chronic kidney disease, and malignancy. These were defined with the related health claims codes before the COVID-19 test.²² A detailed definition of these comorbid conditions is given in eMethods, links.lww.com/WNL/B874.

Data Availability

The dataset used in the analysis of the present study is available from the National Health Insurance Sharing Service.²³ Access to the data source is available after submitting a complete application form, a research proposal, and an approval document for research purposes from an institutional review board and receiving approval from the inquiry committee of research support in NHIS.

Statistical Analysis

We performed a comparative analysis of COVID-19 susceptibility and severe complications of COVID-19 in the unmatched cohort and the matched cohort using propensity score matching (PSM). PSM was performed with the greedy nearest-neighbor algorithm to compare the populations with and without epilepsy to balance the baselines of both groups and reduce potential confounding factors. To investigate the association of epilepsy with COVID-19 test positivity and severe complications of COVID-19, a 1:6 PSM ratio was performed among all individuals who received a COVID-19 PCR test and COVID-19–positive patients. The propensity score was calculated from sex, age, household income, and comorbid conditions. As for whether PSM was appropriate, standardized mean differences (SMDs) were used. If the SMDs were <0.1 in absolute value, PSM was considered appropriate. In the matched cohort after PSM, we performed univariate logistic regression analysis to calculate the odds ratio (OR) and 95% CI of the study outcome. If there are variables with potential imbalance after PSM (SMD > 0.1), we additionally performed multivariate logistic regression analysis adjusted for the variables to remove residual confounding bias.²⁴ For secondary analysis, further analysis was performed for each severe complication outcome such as mechanical ventilation, ICU care, and death. Statistical analyses were executed with R software, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 version (SAS Inc, Cary, NC). Two-sided values of $p < 0.05$ were considered significant.

Results

Baseline Characteristics of Participants

The nationwide COVID-19 dataset in South Korea consisted of 212,678 participants >20 years of age with at least 1 severe

acute respiratory syndrome coronavirus 2 test between January 1 and June 4, 2020 (Figure 1). Of these, 208,759 individuals without epilepsy and 3,919 (1.8%) individuals with epilepsy were identified in the unmatched cohort. Among 212,678 individuals who underwent the COVID-19 RT-PCR test, 7,713 (3.6%) were positive for COVID-19.

Susceptibility to COVID-19 Infection

To test for susceptibility to COVID-19 infection according to epilepsy, we applied 1:6 ratio PSM to 208,759 individuals without epilepsy and individuals 3,919 with epilepsy, who were appropriately matched (Figure 1 and Table 1). After PSM, COVID-19 PCR positivity did not show a significant difference according to epilepsy (OR 0.86 [95% CI 0.67–1.11]) (Table 2).

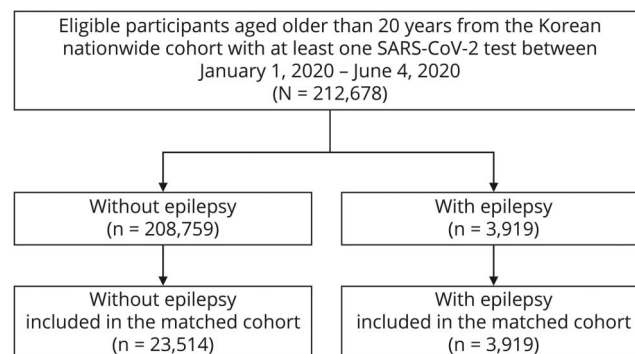
COVID-19 Prognosis by Epilepsy

In a COVID-19 dataset, there were 7,713 (3.6%) patients with positivity for COVID-19. Of these, 72 (0.9%) had epilepsy in the unmatched cohort. Next, we applied PSM for 432 individuals without epilepsy and 72 individuals with epilepsy (Figure 2 and Table 3), who were appropriately matched except household income, hypertension, and malignancy.

Severe complications of COVID-19 occurred in 444 of 7,713 (5.8%) individuals infected with COVID-19, including 171 (2.2%) cases of mechanical ventilation, 265 (3.4%) cases of ICU admission, and 224 (2.9%) cases of death (Table 4 and eTable 1, links.lww.com/WNL/B874). In the unmatched cohort, severe complications and mortality after COVID-19 were noted more frequently in individuals with epilepsy ($p < 0.001$ for severe complications and $p = 0.001$ for mortality).

After PSM, the development of severe complications of COVID-19 was more frequent in individuals with epilepsy than in those without (OR 2.05 [95% CI 1.04–4.04]). However, there was no significant difference in mortality according to the presence of epilepsy (OR 1.55 [95% CI 0.65–3.70]). In a

Figure 1 Flowchart of a Nationwide Cohort Study of COVID-19 and Epilepsy Between January 1 and June 4, 2020



COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 1 Baseline Characteristics of Participants Who Underwent COVID-19 Testing With and Without Epilepsy Before and After PSM

Variable	Before PSM		After PSM		SMD ^a
	Without epilepsy	With epilepsy	Without epilepsy	With epilepsy	
No.	208,759	3,919	23,514	3,919	
Sex, male, n (%)	98,105 (46.99)	1,933 (49.32)	11,673 (49.64)	1,933 (49.32)	0.0046
Age, n (%)					0.0304
<60 y	139,715 (66.93)	1,714 (43.74)	9,944 (42.29)	1,714 (43.74)	
≥60 y	69,044 (33.07)	2,205 (56.26)	13,570 (57.71)	2,205 (56.26)	
Household income, n (%)					-0.0090
T1, lowest	70,372 (33.71)	1,861 (47.49)	11,091 (47.17)	1,861 (47.49)	
T2	69,999 (33.53)	954 (24.34)	5,717 (24.31)	954 (24.34)	
T3, highest	68,388 (32.76)	1,104 (28.17)	6,706 (28.52)	1,104 (28.17)	
Medical history, n (%)					
Hypertension	63,429 (30.38)	2,146 (54.76)	13,051 (55.50)	2,146 (54.76)	0.0188
Diabetes	27,974 (13.4)	1,017 (25.95)	6,130 (26.07)	1,017 (25.95)	0.0017
Stroke	10,740 (5.14)	915 (23.35)	5,372 (22.85)	915 (23.35)	-0.0127
Heart failure	15,435 (7.39)	671 (17.12)	4,102 (17.44)	671 (17.12)	-0.0023
Atrial fibrillation	7,082 (3.39)	332 (8.47)	1,950 (8.29)	332 (8.47)	-0.0176
Coronary artery disease	14,119 (6.76)	535 (13.65)	3,067 (13.04)	535 (13.65)	-0.0161
Asthma	14,181 (6.79)	459 (11.71)	2,701 (11.49)	459 (11.71)	-0.0077
Chronic kidney disease	18,806 (9.01)	723 (18.45)	4,357 (18.53)	723 (18.45)	-0.0009
Malignancy	29,698 (14.23)	910 (23.22)	5,632 (23.95)	910 (23.22)	0.0150

Abbreviations: COVID-19 = coronavirus disease 2019; PSM = propensity score matching; SMD = standardized mean difference; T = tertile.
^a A standardized difference in matched cohort.

secondary outcome analysis for individual complications after COVID-19 diagnosis with the PSM cohort (eTable 1, links.lww.com/WNL/B874), presence of epilepsy was associated with mechanical ventilation (OR 3.22 [95% CI 1.25–8.27] and ICU admission (OR 3.51 [95% CI 1.56–7.89]). Additional adjustment for household income, hypertension, and malignancy, not balanced in the PSM, did not affect the significance of epilepsy on severe complications of COVID-19 (eTable 2).

Discussion

In this study, we investigated whether patients with epilepsy were more susceptible to COVID-19 infection compared with those without epilepsy and whether severe complications were more likely to occur when such patients were infected with COVID-19. The key findings of this study are that individuals with epilepsy did not have greater COVID-19 susceptibility; however, patients with COVID-19 with epilepsy were at higher risk for severe complications than patients with COVID-19 without epilepsy.

There are insufficient information and mixed conclusions about the susceptibility of patients with epilepsy to COVID-19 infection.²⁵ A study conducted in Iran on patients in health care facilities found that patients with epilepsy were not more susceptible to COVID-19 infection compared with those without epilepsy.²⁶ In contrast, a study of hospitalized patients in Spain showed that patients with active epilepsy had a higher incidence of COVID-19.²⁷ It was hypothesized that comorbidity accompanying patients with epilepsy increased COVID-19 susceptibility. These 2 studies represented slightly different population due to different inclusion criteria. The latter study included patients with active epilepsy confirmed with detailed clinical information on epilepsy, while the Iranian study defined patients with epilepsy according to self-declaration. These criteria might include patients with resolved epilepsy and patients with epilepsy mimic. These different inclusion criteria may have influenced the results in these 2 studies. Patients with epilepsy in the Spanish study were on antiepileptic drugs and had mostly focal epilepsy. Our study also targeted patients who had received antiepileptic drugs, but the status of epilepsy is unknown due to a lack of the information in this cohort based on health

Table 2 Proportion of COVID-19–Infected Patients in Participants Who Underwent COVID-19 Test With and Without Epilepsy Before and After PSM

Variable	Before PSM		OR [95% CI]	p Value	After PSM		OR (95% CI)	p Value
	Without epilepsy (n = 208,759), n (%)	With epilepsy (n = 3,919), n (%)			Without epilepsy (n = 23,514), n (%)	With epilepsy (n = 3,919), n (%)		
COVID-19				<0.001				0.248
Negative	201,118 (96.34)	3,847 (98.16)	Referent		23,015 (97.88)	3,847 (98.16)	Referent	
Positive	7,641 (3.66)	72 (1.84)	0.49 (0.39–0.62)		499 (2.12)	72 (1.84)	0.86 (0.67–1.11)	

Abbreviations: COVID-19 = coronavirus disease 2019; OR = odds ratio; PSM = propensity score matching. OR and p value were derived from univariate logistic regression for positivity in COVID-19 test.

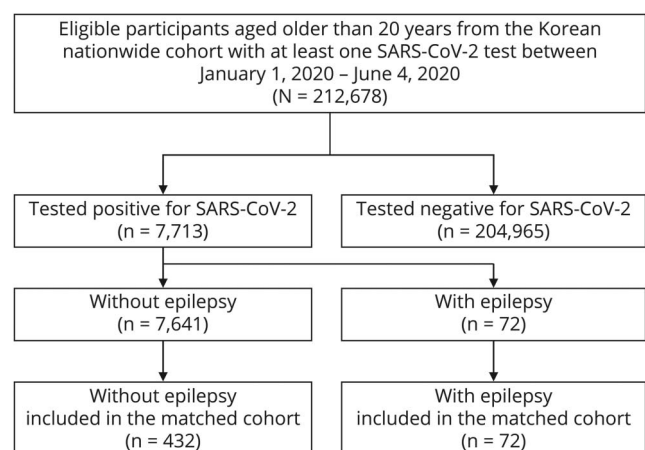
claims data. This point should be taken into account in the interpretation of the results of this study. In our study, control for known major comorbid conditions via PSM may have had an effect on the result. Nonetheless, these results are consistent with previous speculations that epilepsy alone might not be a risk factor for increased COVID-19 infection.²⁸ Furthermore, the initial COVID-19 spread is associated with health care facilities; therefore, patients with epilepsy living in nursing facilities are more likely to be exposed. In addition, visiting a hospital to fill a prescription may increase the likelihood of COVID-19 exposure. Conversely, social stigma may have reduced exposure to infection by reducing going outside.⁷ On the basis of these discussion points, a recent study demonstrated that the presence of mental illness is not associated with COVID-19 susceptibility.¹⁵

Our study suggested that a history of epilepsy might influence clinical outcomes in patients with COVID-19. Contrary to the susceptibility to COVID-19, severe complications occurred more frequently when patients with epilepsy were infected with COVID-19. To date, studies of the effect of epilepsy on the outcome of patients with COVID-19 are not sufficient. Therefore, the causes of more serious complications in patients with epilepsy who are infected with COVID-19 are yet to be elucidated. One possibility is an association with epilepsy comorbid conditions. Many patients with epilepsy have ≥ 1 other medical problems.⁵ Although our study adjusted for some comorbid conditions using PSM, unknown comorbid conditions may contribute to worsening symptoms when patients become infected with COVID-19.^{10,27,29} Moreover, COVID-19 infection and treatment may be a factor that worsens the prognosis in patients with epilepsy. Furthermore, antiepileptic drug administration may interact with COVID-19 treatment, reducing efficacy.^{30,31} In addition, although a detailed mechanism has not been elucidated, the occurrence of status epilepticus may increase in patients due to increased systemic inflammation from COVID-19 infection.³² When complications related to epilepsy occur, there is a possibility that the appropriate treatment could not be achieved in a timely manner due to limited medical

resources. Last, the COVID-19 pandemic has affected the health care system, which may have affected the use of medical facilities by patients with epilepsy.³³

Our study has some limitations. First, it had a retrospective cohort design; therefore, a causal relationship could not be proved. Second, it is difficult to generalize our results for overall ethnicity because our dataset consisted of the Korean general population alone. In addition, because different results could be derived depending on the time of the COVID-19 pandemic and the country where the study was conducted, attention should be paid to the generalization of this study. With a concentrated outbreak of COVID-19, a shortage of medical resources would affect the quality of treatment and prognosis of the patients. Third, detailed information on the severity or characteristics of epilepsy could not be acquired because our dataset does not have detailed information on epilepsy such as EEG data, etiology of epilepsy, genetic information, duration of disease, and neuroimaging data. Last,

Figure 2 Flowchart Depicting Patient Selection for the Analysis of COVID-19 Prognosis According to Epilepsy



SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 3 Baseline Characteristics of Patients With COVID-19 With and Without Epilepsy Before and After PSM

Variable	Before PSM		After PSM		SMD ^a
	Without epilepsy	With epilepsy	Without epilepsy	With epilepsy	
No.	7,641	72	432	72	
Sex, male, n (%)	3,009 (39.38)	39 (54.17)	220 (50.93)	39 (54.17)	-0.0657
Age, n (%)					0.0049
<60 y	5,455 (71.39)	37 (51.39)	221 (51.16)	37 (51.39)	
≥60 y	2,186 (28.61)	35 (48.61)	211 (48.84)	35 (48.61)	
Household income, n (%)					0.1439
T1, lowest	3,305 (43.25)	42 (58.33)	270 (62.5)	42 (58.33)	
T2	2,187 (28.62)	13 (18.06)	94 (21.76)	13 (18.06)	
T3, highest	2,149 (28.12)	17 (23.61)	68 (15.74)	17 (23.61)	
Medical history, n (%)					
Hypertension	1,699 (22.24)	29 (40.28)	198 (45.83)	29 (40.28)	0.1222
Diabetes	756 (9.89)	12 (16.67)	72 (16.67)	12 (16.67)	<0.0001
Stroke	284 (3.72)	14 (19.44)	72 (16.67)	14 (19.44)	-0.0720
Heart failure	318 (4.16)	10 (13.89)	63 (14.58)	9 (12.50)	0.0723
Atrial fibrillation	126 (1.65)	2 (2.78)	15 (3.47)	2 (2.78)	0.0472
Coronary artery disease	303 (3.97)	6 (8.33)	44 (10.19)	6 (8.33)	0.0774
Asthma	337 (4.41)	7 (9.72)	47 (10.88)	7 (9.72)	0.0454
Chronic kidney disease	433 (5.67)	4 (5.56)	21 (4.86)	4 (5.56)	-0.0302
Malignancy	493 (6.45)	4 (5.56)	36 (8.33)	4 (5.56)	0.1170

Abbreviations: COVID-19 = coronavirus disease 2019; PSM = propensity score matching; SMD = standardized mean difference; T = tertile.
^a A standardized difference in matched cohort.

this study was conducted on patients in the early stages of the COVID-19 pandemic. Therefore, application may be limited to patients with various mutations, especially the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants, which are currently the dominant species. However, our study is meaningful because it confirmed the correlation between the prevalence of epilepsy in the COVID-19–infected population and the outcome of COVID-19 in the general population.

Our study demonstrated that the presence of epilepsy was not associated with increased susceptibility to COVID-19 infection. Among COVID-19–infected patients, mortality after COVID-19 infection did not differ among patients with and without epilepsy. However, the presence of epilepsy was associated with an increased risk of severe complications with COVID-19. Therefore, careful monitoring and intensive management are necessary for this population at high risk.

Table 4 Severe Complications in Patients With COVID-19 With and Without Epilepsy Before and After PSM

Outcomes	Before PSM				After PSM			
	Without epilepsy (n = 7,641), n (%)	With epilepsy (n = 72), n (%)	OR (95% CI)	p Value	Without epilepsy (n = 432), n (%)	With epilepsy (n = 72), n (%)	OR (95% CI)	p Value
Severe complications in COVID-19 ^a	431 (5.64)	13 (18.06)	3.69 [2.01–6.77]	<0.001	42 (9.72)	13 (18.06)	2.05 [1.04–4.04]	0.039
Death	217 (2.84)	7 (9.72)	3.69 [1.67–8.13]	0.001	28 (6.48)	7 (9.72)	1.55 [0.65–3.70]	0.320

Abbreviations: COVID-19 = coronavirus disease 2019; OR = odds ratio; PSM = propensity score matching.
 OR and p value are derived from univariate logistic regression analysis.

^a Composite of mechanical ventilation, admission to intensive care unit, or death within 2 months after COVID-19 diagnosis.

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Disclosure

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Jee Hyun Kim, MD, PhD	Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Korea	Design and conceptualized study; drafted the manuscript; critical revision of the manuscript for important intellectual content
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Jinkwon Kim, MD, PhD	Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Korea	Design and conceptualized study; acquisition of data; analyzed and interpreted the data; drafted the manuscript; critical revision of the manuscript for important intellectual content; study supervision
Tae-jin Song, MD, PhD	Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, Korea	Design and conceptualized study; acquisition of data; interpreted the data; drafted the manuscript; critical revision of the manuscript for important intellectual content; study supervision

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