Association of Benzodiazepines With SARS-CoV-2 Infection and Clinical Outcomes: a Nationwide Cohort Study

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Abstract

The evidence for the impact of benzodiazepine (BZD) use on infection or clinical outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is limited. We evaluated the association of BZD use with SARS-CoV-2 infection and the clinical outcomes of coronavirus disease 2019 (COVID-19) using a nationwide COVID-19 database from South Korea. This nationwide cohort study was performed using the COVID-19 database from the Health Insurance Review and Assessment Service of Korea, and SARS-CoV-2 positivity was investigated according to BZD use. SARS-CoV-2-positive adult patients were assessed in three groups, those who needed hospitalization, those with severe symptoms requiring intensive care, and those who died. A multivariate logistic regression model was used for all the analyses. After adjusting for potential confounding factors, there was no association between BZD use and SARS-CoV-2 positivity. SARS-CoV-2-positive patients with BZD use showed an increased risk of need for hospitalization from COVID-19 compared to those without BZD use (odds ratio [OR]: 1.33, 95% confidence interval [CI]: 1.07–1.65). In addition, there was a higher risk for long-term users (OR: 2.64, 95% CI: 1.08–6.47). Chronic BZD use contributed to a higher risk of the need for hospitalization among COVID-19 patients, whereas BZD use did not increase the risk of SARS-CoV-2 test positivity, severe outcomes, or mortality.

Introduction

The coronavirus disease (COVID-19) pandemic is causing a global crisis. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with consequences ranging from asymptomatic disease to death.¹ However, 14% of SARS-CoV-2-positive patients show severe disease, and 5% show critical health conditions;² the risk of mortality (0.1%) associated with COVID-19 is much higher than that associated with seasonal influenza.³ Various risk factors such as age $\geq$ 65 years, chronic obstructive pulmonary disease (COPD), asthma, hypertension, cardiovascular disease, chronic kidney disease, diabetes, obesity, malignancy, immunosuppressant use and transplantation, and chronic human immunodeficiency virus (HIV) infection have been identified.³

Benzodiazepines (BZD) and BZD receptor agonists have been known to increase the risk of pneumonia and death due to pneumonia.^{4,5} There is also concern about the risk of respiratory depression by BZD use in people with pre-existing respiratory problems, although reports have been conflicting; an increased risk of respiratory exacerbations was reported for patients with COPD,⁶ while associations of BZD use with hospital admission or impaired blood gases were not significant in COPD patients.⁷ A few recent studies on the characteristics of severe COVID-19 cases^{8–10} have focused on the use of BZD. However, the results have been inconsistent.

Given the high prevalence (2.6–23.7%) of BZD use,^{11–16} investigating the impact of BZD use on infection or clinical outcomes of SARS-CoV-2 is beneficial for public health. Here, we assessed the association of BZD use with SARS-CoV-2 positivity and clinical outcomes in three groups of patients, those in need of hospital admission, those with severe symptoms requiring intensive care, and those who died, using a nationwide cohort data from South Korea.

Methods

Study design and population

In this study, National Health Information Database (NHID)-COVID data provided by the National Health Insurance Service (NHIS) were used; data pertaining to the period from 2015 to 2020 were obtained. The dataset included data from patients with COVID-19 who tested positive from January 1 to May 30, 2020. Control groups included general controls and subjects who showed negative SARS-CoV-2 test results.

There are two different study population in this study. Study population 1 is to examine the association between benzodiazepine use and SARS-CoV-2 test positivity, and study population 2 is to investigate the association between benzodiazepine use and clinical outcomes in SARS-CoV-2-positive patients. The initial population for the year 2020 included a total of 351,377 subjects. These were categorized into 8,070 patients with SARS-CoV-2, and 343,307 controls. After excluding those with missing values, 328,373 subjects remained. They were divided into two different groups according to whether BZD was used or not: 52,151 subjects used BZD and 276,222 subjects did not use BZD. Using the 1:1 propensity score matching (PSM) method, 52,151 participants each from the case group and the control group were selected as the final study subjects (out of a total of 104,302 subjects). In addition, a total of 7,596 patients with COVID-19 were divided into two groups according to whether BZD used or not: 1,074 subjects used BZD and 6,522 subjects did not use BZD (Fig. 1). All methods were performed in accordance with the relevant guidelines and regulations.

Measures

Outcome variables

In this study, we set SARS-Cov-2 test positivity and clinical outcomes as the outcome variables. The clinical outcomes for SARS-CoV-2-positive patients consisted of three variables: hospital admission, severe symptoms requiring intensive care or invasive ventilation, and mortality. Patients who died before receiving hospital care were also included in the first group, as it was assumed that they needed hospital admission.

Variables of interest

The study subjects were divided into two groups according to BZD use. Use of BZD was defined based on claim history in 2019, one year before the outbreak of COVID-19 in 2020.

BZD categories were based on the following main ingredient codes: clobazam (135702ATB), clonazepam (136401ATB), chlorthalidone (131201ATB, 131202ATB, 255800ATB), diazepam (142930BIJ), flunitrazepam (160601ATB), flurazepam (161801ATB), ethyl loflazepate (156201ATB, 156202ATB),

alprazolam (105501ATB, 105502ATB, 105504ATB, 105505ATB, 105507ATB), bromazepam (118501ATB), clonazepam (137302ATB), etizolam (156501ATB, 156502ATB, 156503ATB), lorazepam (185501ATB, 185504ATB), tofisopam (241201ATB), and triazolam (243501ATB, 243502ATB). In addition, chronic BZD use was categorized based on a 90-day usage period and a 180-day usage period within a year.^{16,17}

Covariates

In this study, we adjusted for variables that could directly or indirectly affect outcomes, including basic independent variables such as sex, age, and residential area. The residential areas were grouped based on the major regions and the metropolitan areas where the incidence of COVID-19 was high in Korea at that time (Seoul, Gyeonggi-do, Daegu, and Gyeongbuk); the rest of the regions were combined into a single group. Type of insurance coverage was classified into three different groups: workplace, local, and medical benefits. Participants' clinical baseline characteristics were also considered as covariates. The Charlson Comorbidity Index (CCI) was used to confirm the patients' comorbidity status in 2019, which was the year prior to the COVID-19 outbreak. Based on CCI data, the severity of comorbidity was categorized as 0, 1, or 2+. Additionally, we reviewed the disease records for the period from 2015 to 2018 for diabetes, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, and chronic kidney disease, which could be associated with worse clinical outcomes and BZD use.

Statistical analysis

We investigated the results after 1:1 PSM; in this method, the case and control participants who have a similar propensity score values are matched.¹⁸ We matched case and control groups by including age, sex, and CCI variables as parameters in the propensity score model. The association between BZD use and SARS-CoV-2 positivity was examined in a total of five models. Model 1 was a crude model for the association between BZD use and SARS-CoV-2 positivity; model 2 was a minimally adjusted model adjusted for age and sex; model 3 was the fully adjusted model, which was adjusted for age, sex, residential area, type of insurance coverage, CCI, and disease history (diabetes, cardiovascular disease, cerebrovascular disease, COPD, asthma, hypertension, and chronic kidney disease); model 4 was the fully adjusted model for the association between the chronic use of BZD for 90 days and SARS-CoV-2 positivity; and model 5 was the fully adjusted model for the association between the chronic use of BZD for 180 days and SARS-CoV-2 positivity. Among patients who tested positive for SARS-CoV-2, Pearson's chi-square tests were used to compare the sociodemographic and clinical characteristics with respect to BZD use and chronic BZD use. To examine the association of BZD use and the chronic BZD use with the risk of SARS-CoV-2 positivity and clinical outcomes, we used multivariable logistic regression models after adjusting for sex, age, residential area, CCI, and disease history.

All the statistical analyses were performed using SAS statistical software version 9.4 (Statistical Analysis System Institute, Cary, NC, USA).

Results

The characteristics of the study participants are shown in Table 1. A total of 328,373 individuals were divided into two groups as follows: those who did not use BZD (n = 276,222) and those who used BZD (n = 52,151). The two groups were matched by propensity scoring, and 52,151 propensity-matched pairs were defined (eTable 1). Of the total subjects, 145,758 (44.4%) were men and 182,615 (55.6%) were women. A majority of the participants (84.1%) was aged 20–39 years; 31.1% were in the 40–59 age group. Comorbidities were recorded in 193,945 (59.1%) individuals, while no comorbidities were observed in 134,428 (40.9%) individuals.

Table 2 shows the association between BZD use and the risk of SARS-CoV-2 positivity; we identified these associations before and after adjusting for potential confounders. After PSM, there was no association between BZD use and the risk of SARS-CoV-2 positivity (model 1: odds ratio [OR]: 1.01, 95% confidence interval [CI]: 0.93 – 1.10, model 2: OR: 1.01, 95% CI: 0.93 – 1.10, model 3: OR: 1.09, 95% CI: 1.00 – 1.20). Moreover, model 4 and 5 showed that there were no associations between chronic BZD use and the risk of SARS-CoV-2 positivity (model 4: OR: 0.94, CI: 0.81 – 1.10, model 5: OR: 0.99, CI: 0.83 – 1.18).

Table 3 shows the distribution of the study population who tested positive for SARS-CoV-2. Of 7,596 individuals, 1,074 (14.1%) used BZD and 6,522 (85.9%) did not use BZD. Of the BZD use group, 59 (5.5%) individuals died, 111 (10.3%) needed intensive care or invasive ventilation, and 939 (87.4%) were in need of hospitalization.

Figure 2 shows the association between BZD use and the clinical outcomes of COVID-19 among patients who tested positive for SARS-CoV-2. After adjusting for potential confounding variables, the risk of need for hospitalization due to COVID-19 was higher in those with BZD use than in those without BZD use (OR: 1.33, 95% CI: 1.07 – 1.65). In addition, the risk of need for hospitalization was higher in COVID-19 patients who used BZD for more than 180 days than in those who did not use BZD (OR: 2.64, 95% CI: 1.08 – 6.47).

Discussion

Using a nationwide cohort database from South Korea, in this study, we showed that the chronic use of BZD contributed to an increase in the risk of the need for hospitalization among COVID-19 patients. However, BZD use did not significantly influence the risk of SARS-CoV-2 positivity, severe outcomes, or mortality.

In animal studies, BZD increased mortality due to a variety of bacterial infections^{19–22} and bacterial superinfections related to influenza.¹⁹ In human subjects, controversy persists regarding a causal connection between BZD use and infections.²³ The association between BZD use and the increased need for hospitalization in this study may be in line with previous studies which showed increased susceptibility to superinfections in influenza-infected animals²⁴ and humans.⁵ The underlying mechanism may be related to the effects of BZD on the immune system; BZD amplifies the effect of the gamma-aminobutyric acid receptor in immune cells, which may lead to an immune-suppressant profile.²⁴ Regarding the long term use of BZD, chronic consumption of BZD was related to the appearance of modified lymphocyte subsets.^{25,26} However, relatively few cases of severe COVID-19 and inaccessible variables in our data, such as the dosage of BZD, may require replication of pharmacoepidemiologic research on the relationship between BZD and COVID-19.

Recent studies on the association between mental illness and COVID-19 outcomes have shown a higher risk for severe COVID-19 outcomes in patients with a mental illness, though the analyses did not include adjustment for BZD use.^{27,28} Since BZD is frequently prescribed for anxiety symptoms and sleep disturbances, our findings suggest that BZD use should be considered in further studies on the relationship between mental illness and COVID-19 outcomes. Likewise, adjusting for mental illness in future studies in the association between BZD and COVID-19 outcomes would uncover the risk of BZD use regardless of psychiatric diagnoses. However, it is interesting to note that 87.7% of BZD prescriptions were related to non-psychiatric diagnoses in a nationwide cohort study from South Korea.¹⁶

Due to limited medical resources, especially with reference to negative pressure beds, policies on the priority for hospitalization among COVID-19 patients have been amended. For example, South Korea has introduced a residential treatment center to isolate asymptomatic patients or patients who do not need hospital care. Therefore, patients with moderate-to-severe symptoms may be hospitalized first.²⁹ In this regard, the results of this nationwide cohort study may be applied to efficiently set strategies for managing COVID-19 patients, based the finding that patients with chronic BZD use need to be monitored frequently due to a high risk of need for hospitalization; however, the strategies should also consider our finding that BZD use does not imply increased severity of clinical outcomes related to COVID-19.

Some limitations of this study should be acknowledged. Although a validation study showed the overall agreement of diagnosis at 82.0%,³⁰ outcomes were identified by diagnostic and procedural codes, and possible misclassifications cannot be ruled out. Moreover, data about the indication and BZD dose, as well as the hospitalization period were unavailable, which precluded a full assessment. The use of nationwide longitudinal data strengthens the causal relationship established in our study, and the generalizability of our findings. However, we could not include all the COVID-19 patients up to the present, and thus may have missed analyzing new clinical outcomes that may have resulted due to various mutations in SARS-CoV-2.

In summary, BZD use was not associated with the risk of SARS-CoV-2 positivity, severe outcomes, or mortality. However, BZD use, especially for more than 180 days, conferred a higher risk of need for hospitalization among COVID-19 patients. Health professionals and public health authorities need to be alert about patients with long-term use of BZD, and these patients need to be closely monitored even if they currently do not need hospital care.

Declarations

Ethics approval and consent to participate

The data were anonymized before they were obtained; thus, informed consent was not required. The Yonsei University Institutional Review Board approved this study (Approval number: 4-2020-1240).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the National Health Insurance Service in South Korea but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Health Insurance Service in South Korea.

Competing interests

There are no conflicts of interest to declare.

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Authors' contributions

H.Y.P. and J.K. designed the study and drafted the manuscript. H.Y.P. is responsible for study concept and design. J.K. took responsibility for acquisition, analysis, or interpretation of data. H.Y.P., J.K., S.K.A., and E.C.P. contributed to the discussion and reviewed and edited the manuscript. S.K.A. and E.C.P. are the guarantors of this work and as such, had full access to all study data. S.K.A. and E.C.P. assume responsibility for the integrity of the data and the accuracy of the data analysis.

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Not applicable

References

1. Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J. & Prescott, H. C. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *Jama* **324**, 782-793 (2020).

2. Wu, Z. & McGoogan, J. M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama* **323**, 1239-1242 (2020).
3. Jordan, R. E., Adab, P. & Cheng, K. (British Medical Journal Publishing Group, 2020).
4. Obiora, E., Hubbard, R., Sanders, R. D. & Myles, P. R. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax* **68**, 163-170 (2013).
5. Nakafero, G., Sanders, R. D., Nguyen-Van-Tam, J. S. & Myles, P. R. The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data. *Pharmacoepidemiology and Drug Safety* **25**, 1263-1273, doi:<https://doi.org/10.1002/pds.4028> (2016).
6. Vozoris, N. T. *et al.* Benzodiazepine use among older adults with chronic obstructive pulmonary disease. *Drugs & aging* **30**, 183-192 (2013).
7. Ekström, M. P., Bornefalk-Hermansson, A., Abernethy, A. P. & Currow, D. C. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *Bmj* **348** (2014).
8. Genet, B. *et al.* COVID-19 In-Hospital Mortality and Use of Renin-Angiotensin System Blockers in Geriatrics Patients. *Journal of the American Medical Directors Association* **21**, 1539-1545, doi:10.1016/j.jamda.2020.09.004 (2020).
9. Poblador-Plou, B. *et al.* Baseline Chronic Comorbidity and Mortality in Laboratory-Confirmed COVID-19 Cases: Results from the PRECOVID Study in Spain. *International journal of environmental research and public health* **17**, 5171, doi:10.3390/ijerph17145171 (2020).
10. Reilev, M. *et al.* Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *International journal of epidemiology* **49**, 1468-1481 (2020).
11. Mellinger, G. D., Balter, M. B. & Uhlenhuth, E. H. Insomnia and its treatment: prevalence and correlates. *Archives of general psychiatry* **42**, 225-232 (1985).
12. Ohayon, M. M., Caulet, M., Priest, R. G. & Guilleminault, C. Psychotropic medication consumption patterns in the UK general population. *Journal of clinical epidemiology* **51**, 273-283 (1998).
13. Chong, Y., Fryar, C. D. & Gu, Q. *Prescription sleep aid use among adults: United States, 2005-2010*. (US Department of Health and Human Services, Centers for Disease Control and ..., 2013).
14. Olfson, M., King, M. & Schoenbaum, M. Benzodiazepine use in the United States. *JAMA psychiatry* **72**, 136-142 (2015).
15. Cunningham, C. M., Hanley, G. E. & Morgan, S. Patterns in the use of benzodiazepines in British Columbia: examining the impact of increasing research and guideline cautions against long-term use. *Health policy* **97**, 122-129 (2010).
16. Oh, S.-H. *et al.* In-depth investigation for prescribing trends of benzodiazepines in South Korea. *Int J Clin Pharmacol Ther* **52**, 460-470 (2014).
17. Bushnell, G. A., Stürmer, T., Gaynes, B. N., Pate, V. & Miller, M. Simultaneous Antidepressant and Benzodiazepine New Use and Subsequent Long-term Benzodiazepine Use in Adults With Depression, United States, 2001-2014. *JAMA Psychiatry* **74**, 747-755, doi:10.1001/jamapsychiatry.2017.1273 (2017).
18. Rosenbaum, P. R. & Rubin, D. B. The central role of the propensity score in observational studies for causal effects. *Biometrika* **70**, 41-55, doi:10.1093/biomet/70.1.41 (1983).
19. Sanders, R. D. *et al.* Benzodiazepine augmented γ -amino-butyric acid signaling increases mortality from pneumonia in mice. *Critical care medicine* **41**, 1627 (2013).
20. Laschi, A., Descotes, J., Tachon, P. & Evreux, J. Adverse influence of diazepam upon resistance to *Klebsiella pneumoniae* infection in mice. *Toxicology letters* **16**, 281-284 (1983).
21. Domingues-Junior, M., Pinheiro, S., Guerra, J. & Palermo-Neto, J. Effects of treatment with amphetamine and diazepam on *Mycobacterium bovis*-induced infection in hamsters. *Immunopharmacology and immunotoxicology* **22**, 555-574 (2000).
22. Galdiero, F. *et al.* Effects of benzodiazepines on immunodeficiency and resistance in mice. *Life sciences* **57**, 2413-2423 (1995).
23. Brandt, J. & Leong, C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs in R&D* **17**, 493-507 (2017).
24. Sanders, R. D. *et al.* Immune cell expression of GABAA receptors and the effects of diazepam on influenza infection. *Journal of neuroimmunology* **282**, 97-103 (2015).
25. Lechin, F. *et al.* Peripheral blood immunological parameters in long-term benzodiazepine users. *Clinical neuropharmacology* **17**, 63-72, doi:10.1097/00002826-199402000-00007 (1994).
26. Cosentino, M. *et al.* Assessment of lymphocyte subsets and neutrophil leukocyte function in chronic psychiatric patients on long-term drug therapy. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **20**, 1117-1129, doi:[https://doi.org/10.1016/S0278-5846\(96\)00100-5](https://doi.org/10.1016/S0278-5846(96)00100-5) (1996).
27. Jeon, H. L., Kwon, J. S., Park, S. H. & Shin, J. Y. Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: nationwide cohort study. *The British journal of psychiatry : the journal of mental science*, 1-8, doi:10.1192/bjp.2020.251 (2021).
28. Lee, S. W. *et al.* Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *The lancet. Psychiatry* **7**, 1025-1031, doi:10.1016/s2215-0366(20)30421-1 (2020).
29. Ladner, D., Katsumasa, H. & Kyuri, K. The Republic of Korea's first 70 days of responding to the COVID-19 outbreak. *Global Delivery Initiative, Case Study* **13** (2020).
30. Park, E. *et al.* Assessment of level of agreement in disease codes between health insurance claims data and medical records. *Wonju: Health Insurance Review and Assessment service* (2018).

Tables

Table 1. General characteristics of the study population

Variables	Overall participants	
	N	%
Total	328,373	100·0
Benzodiazepine use		
No	276,222	84·1
Yes	52,151	15·9
Age		
20-39	121,707	37·1
40-59	102,102	31·1
60-79	77,042	23·5
80+	27,522	8·4
Sex		
Male	145,758	44·4
Female	182,615	55·6
Residential Area		
Seoul	54,069	16·5
Gyeonggi-do	101,327	30·9
Daegu	57,779	17·6
Gyeongbuk	27,271	8·3
Others	87,927	26·8
Type of Insurance Coverage		
NHI (community)	79,799	24·3
NHI (workplace)	232,470	70·8
Medical aid	16,104	4·9
CCI		
0	134,428	40·9
1	154,646	47·1
2+	39,299	12·0
History of Diabetes		
No	266,827	81·3
Yes	61,546	18·7
History of Cardiovascular Disease		
No	300,582	91·5
Yes	27,791	8·5
History of Cerebrovascular Disease		
No	301,142	91·7
Yes	27,231	8·3
History of COPD		
No	316,520	96·4
Yes	11,853	3·6
History of Asthma		
No	271,097	82·6
Yes	57,276	17·4
History of Hypertension		

No	241,649	73·6
Yes	86,724	26·4
History of Chronic Kidney Disease		
No	320,270	97·5
Yes	8,103	2·5
<i>NHI: National health insurance, CCI: Charlson Comorbidity Index, COPD: chronic obstructive pulmonary disease</i>		
<i>All individual characteristics were surveyed as of 2020, and the last survey was recorded until the end of May 2020.</i>		

Table 2. The results of the analysis of the association between benzodiazepine use and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positivity after 1:1 propensity score matching

Variables	SARS-CoV-2 test positivity																			
	Model 1				Model 2				Model 3				Model 4				Model 5			
	OR	95% CI			OR	95% CI			OR	95% CI			OR	95% CI			OR	95% CI		
Benzodiazepine use																				
No	1.00	-			1.00	-			1.00	-			1.00	-			1.00	-		
Yes	1.01	0.93	-	1.10	1.01	0.93	-	1.10	1.09	1.00	-	1.20	0.94	0.81	-	1.10	0.99	0.83	-	
Age																				
20-39	-				1.00	-			1.00	-			1.00	-			1.00	-		
40-59	-				0.91	0.82	-	1.01	0.69	0.62	-	0.77	0.69	0.62	-	0.77	0.69	0.62	-	
60-79	-				0.39	0.35	-	0.44	0.31	0.27	-	0.35	0.31	0.27	-	0.35	0.31	0.27	-	
80+	-				0.47	0.41	-	0.55	0.47	0.39	-	0.56	0.47	0.39	-	0.56	0.47	0.39	-	
Sex																				
Male	-				1.00	-			1.00	-			1.00	-			1.00	-		
Female	-				1.36	1.23	-	1.49	1.24	1.13	-	1.36	1.24	1.13	-	1.36	1.24	1.14	-	
Residential Area																				
Seoul	-				-				1.00	-			1.00	-			1.00	-		
Gyeonggi-do	-				-				5.37	4.48	-	6.44	5.34	4.45	-	6.40	5.34	4.46	-	
Daegu	-				-				0.84	0.65	-	1.08	0.84	0.65	-	1.08	0.84	0.65	-	
Gyeongbuk	-				-				3.99	3.24	-	4.91	3.98	3.23	-	4.90	3.98	3.24	-	
Others	-				-				0.83	0.66	-	1.04	0.83	0.66	-	1.04	0.83	0.66	-	
Type of Insurance Coverage																				
NHI (community)	-				-				1.00	-			1.00	-			1.00	-		
NHI (workplace)	-				-				0.84	0.76	-	0.93	0.84	0.76	-	0.93	0.84	0.76	-	
Medical aid	-				-				1.55	1.31	-	1.83	1.57	1.33	-	1.86	1.56	1.32	-	
CCI																				
0	-				-				1.00	-			1.00	-			1.00	-		
1	-				-				1.08	0.97	-	1.20	1.07	0.96	-	1.20	1.08	0.96	-	
2+	-				-				1.08	0.93	-	1.26	1.07	0.92	-	1.25	1.07	0.92	-	
History of Diabetes																				
No	-				-				1.00	-			1.00	-			1.00	-		
Yes	-				-				1.04	0.92	-	1.17	1.04	0.93	-	1.17	1.04	0.92	-	
History of Cardiovascular Disease																				
No	-				-				1.00	-			1.00	-			1.00	-		
Yes	-				-				0.97	0.82	-	1.14	0.98	0.83	-	1.15	0.97	0.83	-	
History of Cerebrovascular Disease																				
No	-				-				1.00	-			1.00	-			1.00	-		
Yes	-				-				0.98	0.85	-	1.14	0.99	0.85	-	1.16	0.99	0.85	-	
History of COPD																				
No	-				-				1.00	-			1.00	-			1.00	-		

Yes	-	-	0·87	0·68	-	1·11	0·87	0·68	-	1·11	0·87	0·68	-
History of Asthma													
No	-	-	1·00		-		1·00		-		1·00		-
Yes	-	-	0·94	0·84	-	1·05	0·95	0·85	-	1·06	0·95	0·85	-
History of Hypertension													
No	-	-	1·00		-		1·00		-		1·00		-
Yes	-	-	1·03	0·92	-	1·16	1·04	0·92	-	1·17	1·03	0·92	-
History of Chronic Kidney Disease													
No	-	-	1·00		-		1·00		-		1·00		-
Yes	-	-	0·72	0·51	-	1·02	0·71	0·50	-	1·01	0·71	0·50	-
<i>NHI: National health insurance, CCI: Charlson Comorbidity Index, COPD: chronic obstructive pulmonary disease</i>													
<i>Model 1: crude model; Model 2: minimally adjusted; Model 3: fully adjusted; Model 4: chronic use of BZD for 90 days; Model 5: chronic use of BZD for 180 da</i>													

Table 3. General characteristics of the patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Variables	Total		Hospital admission [†]		Severe outcome [‡]		Mortality	
	N	%	N	Row %	N	Row %	N	Row %
Total	7,596	100·0	6,019	79·2	464	6·1	233	3·1
Benzodiazepine use								
No	6,522	85·9	5,080	77·9	353	5·4	174	2·7
Yes	1,074	14·1	939	87·4	111	10·3	59	5·5
Age								
20-39	2,839	37·4	1,975	69·6	58	2·0	1	0·0
40-59	2,563	33·7	2,026	79·0	99	3·9	16	0·6
60-79	1,795	23·6	1,622	90·4	216	12·0	100	5·6
80+	399	5·3	396	99·2	91	22·8	116	29·1
Sex								
Male	2,992	39·4	2,464	82·4	250	8·4	131	4·4
Female	4,604	60·6	3,555	77·2	214	4·6	102	2·2
Residential Area								
Seoul	501	6·6	493	98·4	20	4·0	3	0·6
Gyeonggi-do	4,971	65·4	3,521	70·8	234	4·7	150	3·0
Daegu	422	5·6	415	98·3	41	9·7	14	3·3
Gyeongbuk	921	12·1	837	90·9	101	11·0	50	5·4
Others	781	10·3	753	96·4	68	8·7	16	2·0
Type of Insurance Coverage								
NHI (community)	2,048	27·0	1,606	78·4	115	5·6	66	3·2
NHI (workplace)	4,898	64·5	3,855	78·7	293	6·0	125	2·6
Medical aid	650	8·6	558	85·8	56	8·6	42	6·5
CCI								
0	3,559	46·9	2,584	72·6	108	3·0	22	0·6
1	3,291	43·3	2,749	83·5	249	7·6	116	3·5
2+	746	9·8	686	92·0	107	14·3	95	12·7
History of Diabetes								
No	6,409	84·4	4,917	76·7	291	4·5	108	1·7
Yes	1,187	15·6	1,102	92·8	173	14·6	125	10·5
History of Cardiovascular Disease								
No	7,192	94·7	5,635	78·4	407	5·7	183	2·5
Yes	404	5·3	384	95·0	57	14·1	50	12·4
History of Cerebrovascular Disease								
No	7,117	93·7	5,554	78·0	395	5·6	162	2·3
Yes	479	6·3	465	97·1	69	14·4	71	14·8
History of COPD								
No	7,456	98·2	5,887	79·0	435	5·8	200	2·7
Yes	140	1·8	132	94·3	29	20·7	33	23·6
History of Asthma								
No	6,541	86·1	5,137	78·5	366	5·6	172	2·6
Yes	1,055	13·9	882	83·6	98	9·3	61	5·8
History of Hypertension								

No	6,016	79.2	4,545	75.5	249	4.1	67	1.1
Yes	1,580	20.8	1,474	93.3	215	13.6	166	10.5
History of Chronic Kidney Disease								
No	7,528	99.1	5,953	79.1	447	5.9	213	2.8
Yes	68	0.9	66	97.1	17	25.0	20	29.4
<i>NHI: National health insurance, CCI: Charlson Comorbidity Index, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit</i>								
[†] Hospital admission comprised admission, admission to the intensive care unit, invasive ventilation, or mortality.								
[‡] Severe outcome comprised admission to the intensive care unit or invasive ventilation.								

Figures

Figure 1

Flowchart showing the selection of the study population. NHID-COVID: National Health Information Database-Coronavirus disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 2

The results of the analysis of the association between benzodiazepine use and clinical outcomes. BZD: benzodiazepine.

Supplementary Files

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