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Special Issue Article

Risk of Mortality in Elderly Coronavirus Disease 2019 Patients With Mental Health Disorders: A Nationwide Retrospective Study in South Korea

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ABSTRACT

Objective: *This study aimed to investigate the different clinical characteristics among elderly coronavirus disease 2019 (COVID-19) patients with and without mental disorders in South Korea and determine if these characteristics have an association with underlying mental disorders causing mortality.* ***Method:*** *A population-based comparative cohort study was conducted using the national claims database. Individuals aged ≥65 years with confirmed COVID-19 between January 1, 2020 and April 10, 2020 were assessed. The endpoints for evaluating mortality for all participants were death, 21 days after diagnosis, or April 10, 2020. The risk of mortality associated with mental disorders was estimated using Cox hazards regression.* ***Results:*** *We identified 814 elderly COVID-19 patients (255 [31.3%] with mental disorder and 559 [68.7%] with nonmental disorder). Individuals with mental disorders were found more likely to be older, taking antithrombotic agents, and had diabetes, hypertension, chronic*

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obstructive lung disease, and urinary tract infections than those without mental disorders. After propensity score stratification, our study included 781 patients in each group (236 [30.2%] with mental disorder and 545 [69.8%] with nonmental disorder). The mental disorder group showed higher mortality rates than the nonmental disorder group (12.7% [30/236] versus 6.8% [37/545]). However, compared to patients without mental disorders, the hazard ratio (HR) for mortality in elderly COVID-19 patients with mental disorders was not statistically significant (HR: 1.57, 95%CI: 0.95−2.56). ***Conclusion:*** *Although the association between mental disorders in elderly individuals and mortality in COVID-19 is unclear, this study suggests that elderly patients with comorbid conditions and those taking psychiatric medications might be at a higher risk of COVID-19.* (Am J Geriatr Psychiatry 2020; 28:1308−1316)

INTRODUCTION

The recent outbreak of coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization.[1] As of September 13, 2020, a total of 28,637,952 cases of laboratory-confirmed COVID-19 have been reported worldwide, of which 917,417 patients have died.[2] According to emerging data, COVID-19 is particularly dangerous for elderly individuals,[3] who account for the majority of deaths.[4] Mental health disorders could potentially worsen the outcomes. Although there is a significant prevalence of mental health disorders in elderly individuals, especially dementia, no studies have investigated the association between mental health disorders and COVID-19 in this patient population.

Rapid transmission of COVID-19 could exacerbate the risk of mental health problems and existing psychiatric symptoms, thereby compromising daily functioning.[5] Problems, particularly related to mental health in elderly individuals have been reported in the context of the COVID-19 pandemic.[6] Elderly with dementia or cognitive decline have been reported to become more stressed, angry, anxious, agitated, and withdrawn during the COVID-19 outbreak.[7] Moreover, COVID-19 further exacerbates the vulnerability of individuals with dementia.[8] Retrospective studies during the 2003 severe acute respiratory syndrome epidemic demonstrated that suicide rates in elderly individuals had surged during that time.[9] It is, therefore, important to recognize the distinctive impact of COVID-19 on mental health of elderly population.[10]

In South Korea, the number of elderly people has been steadily increasing, and mental health problems have become common in elderly individuals, with the prevalence of major depressive disorder being estimated at 5.37%.[11] More than 100 countries outside of China, reported COVID-19 cases and out of these, South Korea was one of the first ones.[12] However, only a few studies have reported the mental health of elderly individuals to be directly impacted by the COVID-19 outbreak.

In the current study, we explored the differences in clinical characteristics between elderly COVID-19 patients with and without mental disorders in South Korea. We also investigated how these characteristics were associated with underlying mental disorders leading to mortality in such patients.

METHODS

Data Source

We used the data provided by the Health Insurance Review and Assessment Service, a South Korean government-affiliated agency that reviews the accuracy of national health insurance claims.[13] This database contained demographic information of the patients and the healthcare service information such as diagnoses, prescription medications, procedures, and devices. The Health Insurance Review and Assessment Service data were encoded using the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) version 5[14] in combination with a de-identification procedure. The OMOP CDM is maintained by the Observational

Health Data Sciences and Informatics network and provides tools to facilitate data analysis. The advantage of using the OMOP CDM is that the framework for observational analysis enables rapid analysis, and common analysis codes, along with standardized data, can be applied across multiple center databases without sharing patient-level data.[15,16] This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB-MED-EXP-20-077), and the requirement for informed consent was waived.

Study Design

The source population consisted of individuals aged ≥65 years with lab-confirmed COVID-19 between January 1, 2020 and April 10, 2020, with the date of diagnosis used as the index date. We excluded patients who were not continuously observed in the database at least 1 year prior to their index date. Patients were classified into two groups: a mental disorder and a nonmental disorder group, depending on whether they received a psychiatric illness diagnosis within 6 months before the index date. Furthermore, an additional analysis was conducted to compare the risk of mortality between the dementia group and the nonmental disorder group (see Supplementary Material for cohort definitions). Patients were followed up until death, 21 days after the index date, or April 10, 2020.

Statistical Analysis

We present baseline demographic and clinical characteristics (medical history, medication use, symptoms, and risk scores) as number (%) for categorical variables and mean (SD) for continuous variables. Differences between the mental disorder and the nonmental disorder group were compared using independent two-sample *t*-tests (for continuous variables) and $\chi 2$ tests (for categorical variables). To minimize group differences in baseline characteristics, we developed a propensity score model for both cohorts with regularized regression. Propensity scores were estimated for the following strategies: 1) without propensity scores and 2) with minimum propensity scores (age, sex, and index month). We determined equipoise using a preference score definition based on patients with a propensity score distribution between 0.25 and 0.75.[17] Cox proportional hazard models were used to assess and compare the adjusted and unadjusted hazard ratios (HR) between the mental disorder and non-mental disorder groups. HR were presented at 95% confidence intervals (CI) and p values. All p values less than 0.05 were considered statistically significant. All analyses were performed using the open-source Observational Health Data Sciences and Informatics Cohort Method and survival R package.[18]

RESULTS

Demographic and Clinical Characteristics

A total of 814 participants were included in the study: 255 patients with and 559 patients without mental disorders, respectively. The demographic and clinical characteristics of the patients are shown in Table 1. The mental disorder group more likely included older females with diabetes, hypertension, chronic obstructive lung disease, urinary tract infections, and osteoarthritis (Table 1). There was no significant difference between the two groups in their history of neoplasms, but the mental disorder group was more likely to have a history of antithrombotic agent use and medication for acidity related disorders (Table 1). The mental disorder group used antidepressants (31.0%), anxiolytics (31.8%), and antipsychotics (15.7%) significantly more than the non-mental disorder group. Almost half of the patients in the mental disorder group had dementia (51.8%), organic mental disorder (54.5%), depression (45.9%), or anxiety disorder (41.2%). In addition, the mental disorder group was more likely to have symptoms of fever, nausea, and vomiting (Table 1). In risk scores, Charlson comorbidity index, CHA_2DS_2-VASc score, and Diabetes Complications Severity Index were significantly higher in the mental disorder group than in the nonmental disorder group (7.4 versus 5.2, $t = 7.78$, df = 466.78, p <0.001; 4.9 versus 3.8, $t = 8.39$, df = 499.76, p <0.001; and 4.4 versus 3.2, $t = 6.96$, df = 476.65, p <0.001; respectively; Table 1). After propensity score stratification for age and sex, our study lost 33 patients (19 with mental disorder and 14 with nonmental disorder) and finally included 781 patients in each group (236 [30.2%] with mental disorder and 545 [69.8%] with nonmental disorder). Table 2 presents the baseline characteristics for the stratification of

TABLE 1. Baseline Characteristics of Both Groups

Characteristic	Nonmental Disorder % or Mean (SD) (n = 559)	Mental Disorder % or Mean (SD) (n = 255)	$\chi^2_{(df)}/t_{(df)}$[a]	p Value
Age	73.7 (6.7)	77.2 (7.5)	$6.48_{(448)}$	**<0.0001**
Age group			$45.07_{(7)}$	**<0.0001**
65–69	32.9	18.9		
70–74	24.8	18.1		
75–79	22.3	24.1		
80–84	12.7	19.6		
85–89	4.7	14.1		
90–94	2.5	4.1		
95–99	0.2	0.7		
100–104	0	0.4		
Sex: female	48	57.3	$5.49_{(1)}$	**0.0192**
Medical history: General				
Chronic liver disease	6.1	7.5	$0.34_{(1)}$	0.5613
Chronic obstructive lung disease	6.6	11.8	$5.48_{(1)}$	**0.0193**
Diabetes mellitus	29.3	41.2	$10.56_{(1)}$	**0.0012**
Gastroesophageal reflux disease	29.5	34.9	$2.12_{(1)}$	0.1453
Gastrointestinal hemorrhage	2.3	2.7	$0.01_{(1)}$	0.9088
Human immunodeficiency virus infection	0.4	0	$0.04_{(1)}$	0.8468
Hyperlipidemia	53.7	61.2	$3.71_{(1)}$	0.0541
Hypertensive disorder	56.7	72.5	$17.93_{(1)}$	**<0.0001**
Lesion of liver	4.1	5.5	$0.48_{(1)}$	0.4886
Osteoarthritis	16.6	23.9	$5.59_{(1)}$	**0.018**
Pneumonia	32	36.1	$1.12_{(1)}$	0.2896
Psoriasis	0.4	0.8	$0.07_{(1)}$	0.7896
Renal impairment	15.4	14.9	$0.01_{(1)}$	0.9421
Rheumatoid arthritis	2.3	4.3	$1.77_{(1)}$	0.1829
Ulcerative colitis	0.2	0.4	$0.00_{(1)}$	1.0000
Urinary tract infectious disease	6.3	11.4	$5.63_{(1)}$	**0.0177**
Viral hepatitis C	1.3	1.6	$0.00_{(1)}$	0.9718
Visual system disorder	42	41.2	$0.02_{(1)}$	0.8769
Medical history: Psychiatric illness				
Acute stress disorder		0.8		
Anxiety disorder		41.2		
Bipolar disorder		14.5		
Dementia		51.8		
Depressive disorder		45.9		
Insomnia		19.2		
Organic mental disorder		54.5		
Panic disorder		9.4		
Psychoactive substance dependence		0.8		
Psychoactive substance use disorder		1.6		
Psychoactive substance-induced organic mental disorder		1.2		
Psychosomatic factor in physical condition		1.6		
Psychotic disorder		12.5		
Schizophrenia		8.2		
Medical history: Neoplasms				
Hematologic neoplasm	1.6	1.2	$0.03_{(1)}$	0.8709
Malignant lymphoma	1.1	1.2	$0.00_{(1)}$	1.0000
Malignant neoplasm of anorectum	19	17.3	$0.24_{(1)}$	0.6274
Malignant neoplastic disease	0.7	0.8	$0.00_{(1)}$	1.0000
Malignant tumor of breast	1.4	3.1	$1.83_{(1)}$	0.1757
Malignant tumor of colon	1.6	2.0	$0.00_{(1)}$	0.9471
Malignant tumor of lung	1.6	1.6	$0.00_{(1)}$	1.0000
Malignant tumor of urinary bladder	3.9	2.4	$0.89_{(1)}$	0.3463

(*continued*)

TABLE 1. (*continued*)

Characteristic	Nonmental Disorder % or Mean (SD) (n = 559)	Mental Disorder % or Mean (SD) (n = 255)	$\chi^2_{(df)}/t_{(df)}$[a]	p Value
Medication use: General				
Agents acting on the renin-angiotensin system	31.1	36.1	$1.73_{(1)}$	0.1880
Antibacterials for systemic use	68.9	68.2	$0.01_{(1)}$	0.9200
Antiinflammatory and antirheumatic products	47.9	49.4	$0.10_{(1)}$	0.7540
Antineoplastic agents	2.1	2.0	$0.00_{(1)}$	1.0000
Antipsoriatics	1.4	2.0	$0.07_{(1)}$	0.7966
Antithrombotic agents	41	51.0	$6.72_{(1)}$	**0.0095**
Beta blocking agents	13.4	16.9	$1.41_{(1)}$	0.2349
Calcium channel blockers	30.1	36.9	$3.41_{(1)}$	0.0646
Diuretics	19.7	25.9	$3.62_{(1)}$	0.0571
Drugs for acid related disorders	57.8	71.0	$12.38_{(1)}$	**<0.0001**
Drugs for obstructive airway diseases	20.9	22.4	$0.13_{(1)}$	0.7136
Drugs used in diabetes	24.2	23.9	$0.00_{(1)}$	1.0000
Immunosuppressants	2.5	2.7	$0.00_{(1)}$	1.0000
Lipid modifying agents	37	43.5	$2.84_{(1)}$	0.0919
Opioids	61.2	62.4	$0.06_{(1)}$	0.8094
Medication use: Psychiatry				
Antidepressants	3.9	31.0	$115.38_{(1)}$	**<0.0001**
Antipsychotics	1.8	15.7	$56.28_{(1)}$	**<0.0001**
Psychostimulants, agents used for ADHD and nootropics	7.0	7.8	$0.09_{(1)}$	0.7669
Anxiolytics	12.5	31.8	$41.65_{(1)}$	**<0.0001**
Symptoms				
Nausea and vomiting	22.5	38.0	$20.38_{(1)}$	**<0.0001**
Fever	34.7	43.1	$4.97_{(1)}$	**0.0258**
Cough	37.9	42.7	$1.51_{(1)}$	0.2195
Muscle pain	70.3	70.2	$0.00_{(1)}$	1.0000
Risk scores				
CCI	5.2 (3.4)	7.4 (3.7)	$7.78_{(466.78)}$	**<0.0001**
CHA_2DS_2-VASc	3.8 (1.6)	4.9 (1.6)	$8.39_{(499.76)}$	**<0.0001**
DCSI	3.2 (2.1)	4.4 (2.2)	$6.96_{(476.65)}$	**<0.0001**

Notes: **Bold type** indicates statistical significance. CCI: Charlson comorbidity index; DCSI: Diabetes Complication Severity Index.
[a] χ^2 tests & *t*-tests were performed.

TABLE 2. Comparison of Baseline Demographics Before and After Propensity Score Stratification in Both Groups

	Before Stratification				After Stratification			
Characteristic	Mental Disorder % (n = 255)	Nonmental Disorder % (n = 559)	$\chi^2_{(df)}$	p Value[a]	Mental Disorder % (n = 236)	Nonmental Disorder % (n = 545)	$\chi^2_{(df)}$	p Value[a]
Age group			$45.07_{(7)}$	**<0.0001**			$5.90_{(7)}$	0.5509
65–69	18.9	32.9			30.0	30.7		
70–74	18.1	24.8			19.2	19		
75–79	24.1	22.3			21.4	25.4		
80–84	19.6	12.7			19.5	18.4		
85–89	14.1	4.7			4.5	3		
90–94	4.1	2.5			3.9	3.4		
95–99	0.7	0.2			1.0	0.2		
100–104	0.4	0			0.5	0		
Sex: female	57.4	48	$5.49_{(1)}$	**0.0192**	51.7	53.9	$0.21_{(1)}$	0.6498

Bold type indicates statistical significance.
[a] χ^2 tests was performed.

TABLE 3. Numbers of Patients, Death Counts, Incidence Rates (per 1,000 Person-Years), and Hazard Ratios for Both Groups

Analysis	Groups	Subjects	PY	Number of Deaths	IR	Wald χ^2	HR (95%CI)	p Value
Without PS adjustment	Nonmental disorder	559	17	42	2,343.49	2.29	1.00 (reference)	0.1761
	Mental disorder	255	9	35	3,879.74		1.38 (0.86−2.21)	
PS stratification	Nonmental disorder	545	17	37	2,115.57	2.92	1.00 (reference)	0.0733
	Mental disorder	236	8	30	3,631.92		1.57 (0.95−2.56)	

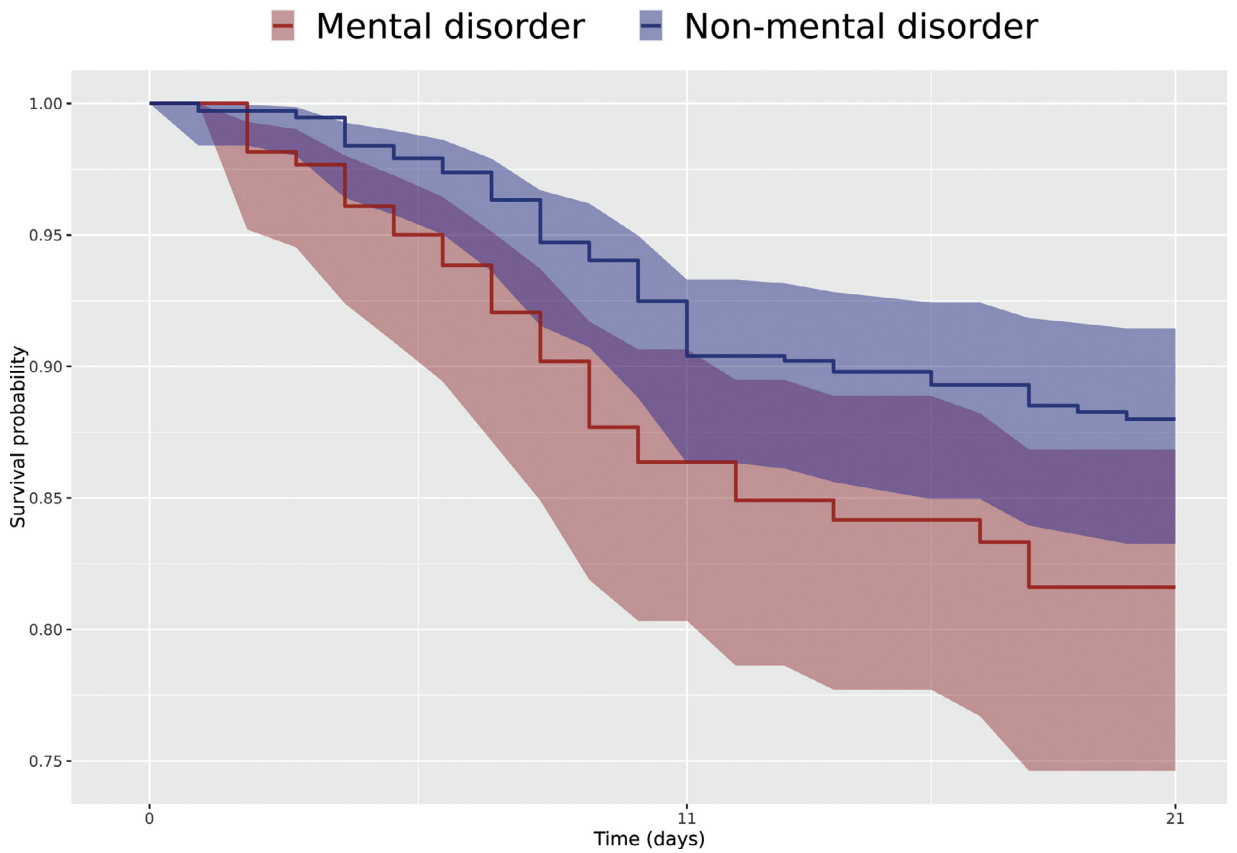
Notes: Degrees of freedom for Wald χ^2 analyses presented in the table = 1. PY: person-years; IR: incidence ratio (per 1,000 PY); HR: hazard ratio; CI: confidence interval; PS: propensity score.

propensity scores for the two groups, with prestratification differences in age and sex, but no statistically significant differences after stratification.

Risk of Mortality

Table 3 summarizes the number of patients, the number of postindex outcomes, person-years, incidence ratio, and HRs observed within 2 groups of interest. The prestratification HR of mortality for the mental disorder group was not statistically significant (HR: 1.38, 95%CI: 0.86−2.21, p = 0.1761). After propensity stratification for age and sex, the poststratification HR of mortality was also not statistically significant (HR: 1.57, 95%CI: 0.95−2.56, p = 0.0733) (Table 3 and Fig. 1).

FIGURE 1. Kaplan-Meier plot for time-to-event comparison of mortality between individuals with and without mental disorders.



CONCLUSION

To our knowledge, this study is one of the earliest reports providing evidence of the impact of COVID-19 on elderly patients with mental disorders. Our nationwide retrospective analysis shows that elderly COVID-19 patients with mental disorders in South Korea did not have a significantly higher risk of mortality than those without mental disorders and that the risk remained insignificant after adjusting for age and sex. However, co-morbid conditions including diabetes, hypertension, chronic obstructive lung disease, and urinary tract infections, which are known to be associated with mortality in patients with COVID-19 were not adjusted for in our analysis.[19,20] Also, the use of antithrombotic agents might be not only associated with co-morbid conditions that increase mortality, but also with the reduced risk of morbidity effect in COVID-19.[21] The use of antithrombotic agents with these conflicting effects was not adjusted for in our analysis. Considering this, it remains unclear whether mental disorders are associated with mortality in COVID-19.

The mental disorder group showed higher mortality rates than the nonmental disorder group, 12.7% (30 of 236) versus 6.8% (37 of 545). These findings are consistent with those of previous studies on influenza outbreaks in psychogeriatric wards. A mortality rate of 25 % has been reported for elderly patients.[22] Similarly, during the first COVID-19 outbreak in South Korea, patients with mental disorders were found to have a 7% mortality rate, higher than the 1% mortality rate observed in the general population.[23] However, these studies were observational rather than comparative, and no adjustments were made for various confounding factors.

In the current study, the mental disorder group was significantly older than the group without mental disorders. Increasing death rates from COVID-19 have been associated with older age in a multivariable regression model.[24] The current study also found that individuals in the mental disorder group were more likely to have diabetes, hypertension, chronic obstructive lung disease, and urinary tract infections and the use of antithrombotic agents than the nonmental disorder group. Risk scores, including the Charlson comorbidity index, CHA_2DS_2-VASc score, and Diabetes Complications Severity Index were significantly higher in the mental disorder group. Previous research has found that the presence of co-morbidities is a risk factor for poor outcomes in patients with severe acute respiratory syndrome.[25] Benzodiazepine use, which was recorded for 31.8% of individuals in the mental disorder group of our study, has been associated with increased influenza-related mortality.[26] In addition, the mental disorder group had higher incidences of fever symptoms, nausea, and vomiting. Comparing characteristics between both groups thus suggests that the mental disorder group had more risk factors for COVID-19.

Our findings do not show a clear association between mental disorders in elderly individuals and mortality due to COVID-19. However, the mental disorder group itself showed a higher risk of COVID-19 than the non-mental disorder group. These findings are consistent with the fact that elderly individuals and those with underlying mental disorders and physical illnesses are more vulnerable to COVID-19 than the general population.[27] Also, due to the nature of mental disorders, COVID-19 patients with such co-morbid disorders can face barriers in accessing timely health services, which may make treatment less effective.[28] Considering that almost half of the patients in our mental disorder group had dementia and organic mental disorders, patients with cognitive decline may also fail to adhere to infection prevention measures, and their reduced activity due to negative symptoms or fear of infection can further impair their physical health and immunity.[27] Actually, Brown et al. suggested increased mortality and morbidity in patients with Alzheimer's disease and related dementias.[8]

Strengths and Limitations

This study has several strengths. First, to the best of our knowledge, this is one of the earliest reports on mortality risk due to COVID-19 in elderly patients with mental disorders. Second, the population-based cohort design based on a nationwide database of individuals' comprehensive medical histories enhances the validity of our findings. This study has, however, some limitations. First, there might be concerns about data quality due to the common limitations of observational database research. Second, although we were able to adjust for age and sex, two important factors affecting death, we did not adjust for

confounders such as hypertension and diabetes, which differed between the two cohorts. Also, we did not control for the effect of medications such as antipsychotics, which could increase the risk of metabolic syndrome. Finally, because of the limitations of the national health insurance claims data, laboratory test results were not included in this study.

In conclusion, elderly patients with mental disorders might have a higher risk when infected with COVID-19, due to their age, co-morbid conditions, and psychiatric medications. Our findings, therefore, suggest that more attention might be paid to elderly COVID-19 patients with comorbid conditions and psychiatric medications, regardless of whether they have mental disorders. Further investigations are needed to clarify the associations between mental disorders in elderly individuals and mortality due to COVID-19.

AUTHORS CONTRIBUTION

Research conception & design: Lee DY, Cho J, Son SJ, Hong CH, Rho HW; Data acquisition: Cho J, Park RW, Kim CS; Data analysis and interpretation: You SC, Lee EY; Statistical analysis: Park BH, Son SJ; Drafting of the manuscript: Lee DY, Cho J; Critical revision of the manuscript: Son SJ, Park BH, Aizenstein H, Andreescu C, Karim H.

DISCLOSURE

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2020.09.016.

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