

# Adherence to Antipsychotic Drugs by Medication Possession Ratio for Schizophrenia and Similar Psychotic Disorders in the Republic of Korea: A Retrospective Cohort Study

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**Objective:** Pharmacotherapy is considered as an essential element in the treatment of psychotic disorders including schizophrenia. Discontinuation of antipsychotic drugs increases medical use and economic burden. Therefore, maintenance of medication is essential to reduce the social burden caused by schizophrenia and schizophrenia similar psychosis (SSP), and hence, it is important to investigate the rate at which pharmacotherapy is maintained. Therefore, this study aimed to examine the current status of drug compliance using national health insurance data.

**Methods:** This was a retrospective cohort study, which analyzed data from the nationwide insurance claims database. A total of 343,134 patients who were newly diagnosed with schizophrenia and SSP during 2011–2015. The adherence to antipsychotic drugs was assessed by medication possession ratio (MPR) and the risk factors of poor adherence were defined as MPR < 40%.

**Results:** The average of the MPRs was 45.8%, and the proportion of patients with less than 40% of MPR was 50.8%. It was found that female patients, the experience of “general hospital outpatient,” “psychiatric hospital admission,” “general hospital admission,” and patients receiving “health insurance” showed high risk of having statistically significant low MPR (< 40%).

**Conclusion:** In this study, the drug adherence of schizophrenia and SSP patients currently under treatment, as estimated by MPR, was very low. However, it was also found that the MPR was high among patients receiving medical aid, with less medical expenses. Thus, it is possible to consider an institutional mechanism in which schizophrenia and SSP patients can be treated with less economic burden.

**KEY WORDS:** Psychotic disorders; Schizophrenia; Medication adherence; Medication possession ratio; Pharmacotherapy.

## INTRODUCTION

Psychotic disorders, including schizophrenia and schizophrenia similar psychosis (SSP), are among the most serious forms of mental illness with a high prevalence rate. Our previous study, which analyzed data from Korea’s Health Insurance Review and Assessment (HIRA) service, reported that the 12-month prevalence of SSP was 0.48–0.66%, and schizophrenia had a 12-month prevalence of 0.40–0.52% [1]. The annual incidence rate (IR) of SSP reached 118.8–148.7 per 100,000 person-year, and schizophrenia reported an IR of 77.6–88.5 per 100,000.

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In the treatment of schizophrenia and SSP, the administration of antipsychotics improves clinical symptoms, and in most cases pharmacotherapy, including antipsychotics, is considered as an essential element in treatment [2-6]. However, in patients with schizophrenia and SSP, it is likely that they will be passive in mental health management due to a lack of insight into their illness and a willingness to discontinue medication [7]. It is known that discontinuation of antipsychotic drugs increases medical use and economic burden, such as worsening of symptoms, recurrence, and hospitalization [8-10]. Furthermore, there have been reports that low medication adherence to antipsychotic drugs is associated with decreased functioning and increased relapse in schizophrenic patients [11-13].

Schizophrenia and SSP are typical disorders that place an economic burden on patients, their families, and the society as a whole. According to a report in 2005, direct medical expenses from schizophrenia in the Republic of Korea (hereafter, Korea) alone exceeded 400 million USD (US dollars), and considering socioeconomic costs including unemployment, exceeded 3,000 million USD [14].

Therefore, in order to properly respond to the issue of severe mental illness, it is necessary to understand the exact situation of drug adherence [15-17]. As mentioned above, maintenance of drug treatment is essential to reduce the social burden caused by schizophrenia and SSP, and hence, it is important to analyze not only the IR of the disorders, but also investigate the rate at which pharmacotherapy is maintained. However, due to the nature of mental illness, especially in psychotic disorders, it is not easy to analyze the exact situation because of the difficulties in conducting a complete survey and the diversity in the viewpoints of maintaining treatment [17-19]. Therefore, in this study, the current status of drug compliance was examined using National Health Insurance (NHI) data.

## METHODS

### Data Source

Since 1989, Korea implemented an obligatory universal coverage of medical insurance program, which includes 97% of the total population registered in the NHI, and the remaining 3% with the lowest socioeconomic sta-

tus are supported by the National Medical Aid (NMA). The NHI covers almost 97% of the total population, which was approximately 50 million in 2015 [1]. HIRA examines all the claims submitted to the NHI and NMA for reimbursement. The NHI claims database contains retrospective cohort data on basic information of the patients' sociodemographic characteristics and visits to medical institutions as well as precise information on their diagnoses, prescriptions or diagnostic procedures, and the characteristics of the medical clinics they visited [20]. The methods and structure of the HIRA database have been described elsewhere [21].

### Study Design and Participants

This was a retrospective cohort study. We estimated the antipsychotic drug adherence of SSP patients and investigated determinants of poor medication adherence using the NHI claims data from 2011 to 2015. We defined SSP patients as those who had visited medical institutions with the following diagnostic codes as primary diagnosis: schizophrenia, schizophreniform, acute/transient psychotic disorders, schizoaffective disorders, and other/unspecified nonorganic psychosis (International Classification of Diseases [ICD]-10 codes: F20, F23, F25, F28, and F29). Our SSP cohort consisted of 343,134 individuals who first visited with the abovementioned diagnoses. Among them, 326,917 patients were prescribed with antipsychotic drugs at least once during 2011–2015, and were included in this study; we studied the level of drug adherence and risk factors for suboptimal adherence. The study was approved by the Institutional Review Boards of the Seoul National University Hospital with IRB No of 1705-106-855.

### Statistical Analysis

SSP patients often change their choice of medical institutions for medication regardless of the size, type, or region of the institution. Therefore, we extracted prescriptions with the maximal days of antipsychotic drug prescribed for each individual and applied the characteristics such as hospital size or hospital visit type (psychiatry outpatient/admission, non-psychiatry outpatient/admission, or day hospital) from those prescriptions. These characteristics of the study population were also applied in the logistic regression model for determinants of suboptimal adherence. Medication adherence was measured by

medication possession ratio (MPR) and risk factors were identified by logistic regression analysis, where, an MPR of 40% or more was set as optimal medication adherence. Instead of proportion of days covered (PDC), MPR was used for calculating medication adherence considering that schizophrenia and SSP patients usually require consistent use of medication over a long period. Long-acting injectable antipsychotic drugs such as risperidone, extended-release preparations, or paliperidone palmitate were assumed as it was exposed as many days as the indicated days of use. For example, risperidone and paliperidone palmitate were calculated as 14 days and 28 days, respectively. At each episode of hospital admission or within each prescription, there were more than one use of the same product or same class of drugs. Considering the reality where usually different class of drugs are prescribed for extra in need of lack of the main medication effect, we applied the following rules: 1) when different classes of drugs were prescribed on different days within an admission or a prescription, we used the maximal day of any one kind of component as the exposure day of medication, and 2) when the same component drug was prescribed several times within an admission or a prescription, we summed all the prescribed days as the exposure day of medication. The final logistic regression model was verified as adequate with the concordance statistical estimate (c) of 0.64. The SAS Enterprise Guide, version 6.1 (SAS Institute, Cary, NC, USA) was used for all analyses.

## RESULTS

### Antipsychotic Drug Adherence

Between 2011 and 2015, a total of 343,134 patients were treated for a diagnosis of schizophrenia or SSP, and 326,917 patients were prescribed antipsychotics, the primary treatment for schizophrenia or SSP, more than once. The average of the MPRs for these patients was 45.8%, and the proportion of patients with an MPR less than 40% was 50.8% (Fig. 1). When the MPR section was analyzed as a 10% section, a value of 5–6% was observed, and a group of MPR 90% or more was analyzed as 21.6%.

The distribution was similar except for patients who were 65 years old, and the distribution of Seoul/metropolitan/other cities/other provinces was also explored. There were 81.4% patients covered under the health insurance

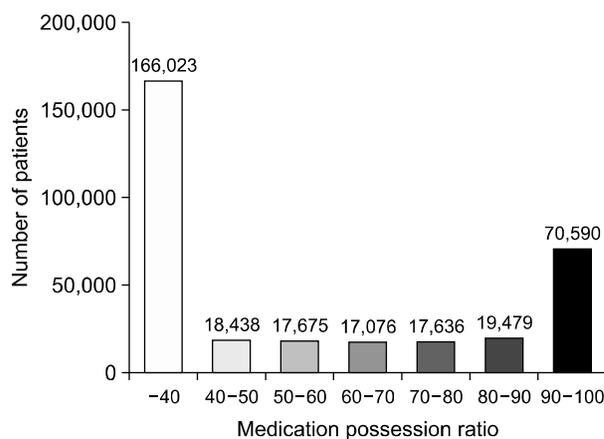


Fig. 1. Number of patients divided by adherence to antipsychotic drugs by medication possession ratio for schizophrenia and similar psychotic disorders in Republic of Korea.

and 18.6% patients under medical aid. It was observed that the higher the level of MPR, the higher was the proportion of medical aid patients (Table 1).

### Risk Factors for Suboptimal Adherence to Antipsychotic Drugs among Patients with Schizophrenia and SSP during 2011–2015

Determinants of suboptimal antipsychotic drug adherence were analyzed by comparing the  $\geq 40\%$  group with the remaining individuals using a multivariable logistic regression model (Table 2).

We found that female patients were associated with the risk of having statistically significant low MPR ( $< 40\%$ ) (odds ratio [OR]: 1.010, 95% confidence interval [CI]: 1.04–1.07,  $p < 0.0001$ ). Compared with the experience of “psychiatric hospital outpatient,” the experience of “psychiatric hospital admission” was associated with the risk of having statistically significant low MPR ( $< 40\%$ ) (OR: 1.55, 95% CI: 1.48–1.62,  $p < 0.0001$ ), and the experience of “general hospital admission” was associated with the risk of having statistically significant low MPR ( $< 40\%$ ) (OR: 6.68, 95% CI: 6.39–6.98,  $p < 0.0001$ ). Compared with “being treated in Seoul (the capital city),” “being treated in other metropolitan cities or other cities” was associated with the risk of having statistically significant low MPR ( $< 40\%$ ) (OR: 1.10, 95% CI: 1.08–1.13,  $p < 0.0001$ ; OR: 1.08, 95% CI: 1.06–1.11,  $p < 0.0001$ ). “Being treated in rural areas” was not associated with statistically significant low MPR. Finally, compared with “health insurance,” “medical aid” was associated

**Table 1.** Characteristics of newly diagnosed patients with schizophrenia and schizophrenia-similar disorders by antipsychotic drugs medication possession ratio (MPR) during 2011–2015 (n = 326,917)

Variable	MPR						
	< 5%	5–20%	20–40%	40–60%	60–80%	80–95%	95% ≤
Total	59,484 (18.2)	60,870 (18.6)	45,669 (14.0)	36,113 (11.0)	34,712 (10.6)	32,005 (9.8)	58,064 (17.8)
Sex							
Male	29,285 (49.2)	29,183 (47.9)	21,389 (46.8)	16,360 (45.3)	15,511 (44.7)	14,518 (45.4)	26,151 (45.0)
Female	30,199 (50.8)	31,687 (52.1)	24,280 (53.2)	19,753 (54.7)	19,201 (55.3)	17,487 (54.6)	31,913 (55.0)
Age group (yr)							
< 15	3 (0.0)	4 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
15–24	3,651 (6.1)	4,493 (7.4)	3,736 (8.2)	3,183 (8.8)	3,399 (9.8)	3,556 (11.1)	5,530 (9.5)
25–34	5,216 (8.8)	6,038 (9.9)	4,639 (10.2)	3,934 (10.9)	4,233 (12.2)	3,910 (12.2)	6,281 (10.8)
35–44	6,700 (11.3)	7,017 (11.5)	5,367 (11.8)	4,540 (12.6)	4,565 (13.2)	4,596 (14.4)	7,879 (13.6)
45–54	8,717 (14.7)	8,552 (14.0)	6,374 (14.0)	5,105 (14.1)	5,121 (14.8)	5,122 (16.0)	9,100 (15.7)
55–64	8,331 (14.0)	8,028 (13.2)	5,823 (12.8)	4,608 (12.8)	4,478 (12.9)	4,296 (13.4)	8,055 (13.9)
65 ≤	28,866 (45.2)	26,738 (43.9)	19,728 (43.2)	14,473 (40.8)	12,916 (37.2)	10,525 (32.9)	21,217 (36.5)
Type of medical institution							
Tertiary hospital	12,647 (21.3)	11,204 (18.4)	7,454 (16.3)	5,621 (15.6)	5,422 (15.6)	4,945 (15.5)	10,728 (18.5)
General hospital	18,214 (30.6)	16,418 (27.0)	11,213 (24.6)	8,382 (23.2)	7,808 (22.5)	6,651 (20.8)	14,427 (24.8)
Hospital	11,876 (20.0)	14,283 (23.5)	11,745 (25.7)	9,579 (26.5)	9,572 (27.6)	9,452 (29.5)	15,261 (26.3)
Clinic	14,887 (25.0)	16,613 (27.3)	13,413 (29.4)	11,068 (30.6)	10,610 (30.6)	9,816 (30.7)	15,896 (27.4)
Nursing hospital	1,845 (3.1)	2,317 (3.8)	1,797 (3.9)	1,431 (4.0)	1,269 (3.7)	1,101 (3.4)	1,705 (2.9)
Public clinic	15 (0.0)	35 (0.1)	47 (0.1)	32 (0.1)	31 (0.1)	40 (0.1)	47 (0.1)
Type of hospital visit							
Hospital outpatient	30,387 (51.1)	39,069 (64.2)	32,376 (70.9)	26,189 (72.5)	25,153 (72.5)	22,480 (70.2)	41,864 (72.1)
Hospital admission	25,637 (43.1)	16,098 (26.4)	7,434 (16.3)	4,558 (12.6)	3,661 (10.5)	3,190 (10.0)	3,942 (6.8)
Public clinic	3 (0.0)	17 (0.0)	16 (0.0)	15 (0.0)	19 (0.1)	17 (0.1)	24 (0.0)
Psychiatry outpatient	2,326 (3.9)	3,801 (6.2)	3,968 (8.7)	3,757 (10.4)	4,146 (11.9)	4,316 (13.5)	9,060 (15.6)
Psychiatry admission	1,129 (1.9)	1,880 (3.1)	1,868 (4.1)	1,584 (4.4)	1,718 (4.9)	1,976 (6.2)	3,135 (5.4)
Psychiatry ward	2 (0.0)	5 (0.0)	7 (0.0)	10 (0.0)	15 (0.0)	26 (0.1)	39 (0.1)
Total hospital days <sup>a</sup>	1,169 ± 2,800.0	4,261 ± 8,461.9	10,553 ± 19,041.0	18,103 ± 60,422.9	26,901 ± 47,127.0	37,986 ± 74,184.4	35,568 ± 83,237.0
Maximal hospital days	18 ± 16.4	20 ± 17.3	21 ± 17.3	21 ± 17.4	21 ± 17.7	21 ± 17.9	18 ± 16.1
Region of medical institution							
Seoul (capital city)	12,487 (21.0)	13,781 (22.6)	10,150 (22.2)	7,917 (21.9)	7,593 (21.9)	6,942 (21.7)	13,745 (23.7)
6 metropolitan cities	17,243 (29.0)	15,935 (26.2)	11,888 (26.0)	9,475 (26.2)	9,348 (26.9)	8,507 (26.6)	14,512 (25.0)
Other cities	14,874 (25.0)	15,383 (25.3)	11,549 (25.3)	9,228 (25.6)	8,847 (25.5)	7,994 (25.0)	14,405 (24.8)
Rural area	14,880 (25.0)	15,766 (25.9)	12,082 (26.5)	9,493 (26.3)	8,924 (25.7)	8,562 (26.8)	15,402 (26.5)
Type of medical coverage							
Health insurance	51,982 (87.4)	51,853 (85.2)	37,610 (82.4)	29,072 (80.5)	27,508 (79.2)	24,606 (76.9)	43,338 (74.6)
Medical aid	7,502 (12.6)	9,017 (14.8)	8,059 (17.6)	7,041 (19.5)	7,204 (20.8)	7,399 (23.1)	14,726 (25.4)

Values are presented as number (%) or mean ± standard deviation.

<sup>a</sup>Total hospital days with antipsychotic drugs prescription.

with the less risk of having statistically significant low MPR (< 40%) (OR: 0.92, 95% CI: 0.89–0.96,  $p < 0.0001$ ).

## DISCUSSION

The most important element in the treatment of schizophrenia or SSP is pharmacotherapy, and in most cases these disorders require lifelong drug therapy [11]. However, despite the high prevalence of these disorders, it is not easy to determine the extent to which patients maintain drug adherence. Therefore, as an alternative, this study

analyzed the MPR of the patients of schizophrenia or SSP as an important index in the treatment of schizophrenia and SSP. In the case of Korea, since, citizens are covered by NHI, it was possible to analyze representative data. Several previous studies have analyzed schizophrenia's MPR in different countries. One study was conducted only for Florida Medicaid recipients, and the other study was for the patients who were diagnosed as schizophrenia for the first time in Korea [7–22]. The present study was based on national data for five years to ensure representativeness, and is meaningful in that it is the first study to ana-

**Table 2.** Risk factors for suboptimal adherence to antipsychotic drugs among patients with schizophrenia and schizophrenia-similar disorders during 2011–2015 (n = 326,917)

Variable	Number (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) <sup>a</sup>	p value (for adjusted OR)
Sex				
Male	152,397 (46.6)	-	-	
Female	174,520 (53.4)	1.13 (1.11–1.14)	1.10 (1.04–1.07)	< 0.0001
Age group (yr)				
< 15	11 (0.0)	-	-	
15–24	27,548 (8.4)	0.17 (0.04–0.79)	0.17 (0.04–0.79)	0.02
25–34	34,251 (10.5)	0.20 (0.04–0.90)	0.19 (0.04–0.89)	0.04
35–44	40,664 (12.4)	0.20 (0.04–0.92)	0.20 (0.04–0.95)	0.04
45–54	48,091 (14.7)	0.22 (0.05–1.00)	0.22 (0.05–1.04)	0.06
55–64	43,619 (13.3)	0.23 (0.05–1.07)	0.22 (0.05–1.02)	0.05
65 ≤	132,733 (40.6)	0.28 (0.06–1.28)	0.24 (0.05–1.10)	0.07
Type of medical institution				
Tertiary hospital	85,021 (26.0)	-	-	
General hospital	83,113 (25.4)	1.05 (1.03–1.07)	1.01 (0.99–1.04)	0.3
Hospital	81,768 (25.0)	0.74 (0.72–0.75)	0.68 (0.66–0.70)	< 0.0001
Clinic	92,203 (28.2)	0.81 (0.79–0.83)	1.10 (1.08–1.13)	< 0.0001
Nursing hospital	11,465 (3.5)	0.92 (0.89–0.96)	0.77 (0.74–0.81)	< 0.0001
Public clinic	247 (0.1)	0.55 (0.43–0.71)	0.89 (0.63–1.25)	0.5
Type of hospital visit				
Hospital outpatient	217,518 (66.5)	1.86 (1.81–1.90)	1.69 (1.62–1.76)	< 0.0001
Hospital admission	64,520 (19.7)	6.75 (6.55–6.96)	6.68 (6.39–6.98)	< 0.0001
Public clinic	111 (0.0)	1.01 (0.68–1.51)	0.97 (0.57–1.64)	0.9
Psychiatry outpatient	31,374 (9.6)	-	-	
Psychiatry admission	13,290 (4.1)	1.22 (1.17–1.28)	1.55 (1.48–1.62)	< 0.0001
Psychiatry ward	104 (0.0)	0.33 (0.19–0.58)	0.40 (0.23–0.70)	0.001
Region of medical institution				
Seoul (capital city)	72,615 (22.2)	-	-	
6 metropolitan cities	86,908 (26.6)	1.07 (1.05–1.09)	1.10 (1.08–1.13)	< 0.0001
Other cities	82,285 (25.2)	1.03 (1.011–1.05)	1.08 (1.06–1.11)	< 0.0001
Rural area	85,109 (26.0)	1.00 (0.98–1.02)	1.02 (1.00–1.04)	0.1
Type of medical coverage				
Health insurance	265,969 (81.4)	-	-	
Medical aid	60,948 (18.6)	0.60 (0.58–0.61)	0.92 (0.89–0.96)	< 0.0001

OR, odds ratio; CI, confidence interval; -, not available.

<sup>a</sup>Adjusted for all the information in the table.

lyze drug adherence following previous studies of incidence and prevalence studies of schizophrenia and SSP patients [1].

This study is similar to the abovementioned Korean study, but it is very different from the study analyzing the results of Florida in the United States [22]. In this study, the overall MPR was 79%, and although there was a difference depending on the type of drug, the groups showing 80% to 100% of MPR were observed in 62% to 72% of the total patient group, and in those showing less than 50% MPR, the patient group was observed to be 8% to 15% depending on the type of drug, which showed a huge difference from the results of Korea. In addition, this

result was due to great resistance to medication. In Korea, traditionally, mental illness has been surrounded by stigma [23,24]. The fact that the duration of untreated psychosis in Korea is very long compared to other countries also bears out this fact [25,26].

As a result of the analysis of this study, the average value of MPR was only 45.8%, and 50.8% of patients receiving medication for schizophrenia and SSP were in the MPR group of less than 40%. Since, this study did not include patients who were not admitted to the hospital, were not prescribed antipsychotics, it can be concluded that the drug adherence of schizophrenia and SSP patients in Korea is very low.

In this study, in the comparative analysis of each MPR group by section, it was found that the higher the MPR group, the higher the proportion of medical aid patients. However, since it is known that patients with medical aid in Korea tend to have very much higher days of hospital admission, this needs to be considered in interpretation of this result. This is the same for the finding of this study where medical aid was not a risk factor for lower MPR but a factor for higher MPR. In addition, the percentage of hospitalization experiences at general hospitals or mental health clinics was reduced, and the average number of days of hospitalization by group was not significantly different around 20 days. This is in line with the analysis of the risk factor of low MPR. Compared to a case where outpatient treatment in a psychiatric hospital occupies the most part of treatment, the experience of hospitalization in a general hospital or a psychiatric hospital was highly correlated with the risk of low MPR (< 40%).

The major issue observed in this study was that the proportion of patients over 65 years of age was very high. Due to the medical characteristics of the Korea, diagnostic leniency required to use medications was considered to be attributed to off-label in Korea. Although there was a difference in the figures, the risk factor of low MPR was the same as that of general hospital, mental hospital admission, and outpatient treatment of general hospital. Compared to the capital city, Seoul, similarities were also associated with risk when receiving treatment in six metropolitan and other cities. However, the only difference was that the risk association between health insurance and medical aid patients was not statistically significant.

This study has some limitations. First, since, the study was based on medical insurance claim data, it was difficult to evaluate the contents of clinical conditions of each individual such as the reason of restarting medication or changing the regimen. Second, in this study, drug adherence was estimated with the MPR value, but in fact, possessing a drug may not necessarily mean consuming the drug; hence, this is a conceptual limitation of the study. Also, in HIRA data, in case of admitted patients, each episode of information of hospital use is classified in terms of admission. In other words, the medication prescribed on the day of discharge is also included. Therefore, in case of hospital admission, MPR might be over-evaluated. The overall adherence was critically low even though we used MPR for adherence calculation and added up all the pre-

scribed days. MPR is the sum of the days' supply for all fills of a given drug in a particular time period, divided by the number of days in the time period. Therefore, if an individual refills the medication before the former prescription ends, it can lead to overestimation of adherence. Third, in view of the concept that the drug should be consumed for a lifetime, it may be difficult to conclude that examining only the specific time period determined for this study (2011–2015) accurately reflects the exact drug adherence of a patient. Although rare, there might be some cured cases as well. However, this study is meaningful in that it is a study of citizens in one country, and in that it is the first study to investigate drug adherence of schizophrenia and SSP, which require lifelong drug treatment. Even though we did not apply a stricter method of calculation such as PDC, adherence to antipsychotic drugs of SSP patients was found to be low.

In this study, it can be seen that the drug adherence estimated by MPR of schizophrenia and SSP currently being treated is very low. Considering that the analysis shows that the MPR is high in medical aid patients with low medical expenses that they have to pay for themselves, it is possible to consider an institutional mechanism in which schizophrenia and SSP patients can be treated with less economic burden. In addition, it is considered that future research and continuous attention will be needed for patients who are not receiving adequate treatment.

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#### ■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

#### ■ Author Contributions

Conceptualization: Jin Yong Lee, Jee Hoon Sohn. Data curation: Jungmee Kim. Investigation: Sung Joon Cho.

Methodology: Jungmee Kim, Jin Yong Lee. Project administration: Jee Hoon Sohn. Supervision: Jin Yong Lee, Jee Hoon Sohn. Validation: Sung Joon Cho. Writing: Sung Joon Cho, Jungmee Kim, Jee Hoon Sohn, Jin Yong Lee.

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