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Factors associated with high-dose antipsychotic prescriptions in outpatients with schizophrenia: An analysis of claims data from a Japanese prefecture

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Abstract

Background: Antipsychotics are commonly prescribed in high doses in combination with multiple psychotropic drugs. This study focused on the high-dose antipsychotic prescriptions in patients with schizophrenia, while aiming to identify their associations with patients' characteristics and concurrent psychotropic prescriptions.

Methods: This cross-sectional study used claims data from a prefecture in Japan, between October 2014 and March 2015, to investigate antipsychotic prescriptions in adult outpatients with schizophrenia. The objective variable was the presence/absence of a high-dose prescription. The explanatory variables included sex, age (category), presence of comorbid conditions, and the use of psychiatrist's therapy.

Results: After exclusion, a total of 13 471 patients with schizophrenia were analyzed. The frequency of high-dose prescriptions was higher in men, with chlorpromazine-equivalent values highest in the age ranges of 45-54 and 35-44 years for men and women, respectively. Patients aged below 65 years with cerebrovascular diseases showed a decrease in high-dose prescriptions. There was a high frequency of polypharmacy psychotropic drug use in combination with a high-dose antipsychotic prescription in patients aged below 65 years.

Conclusion: High-dose antipsychotics are often used in combination with several psychotropic agents in patients with schizophrenia. Our findings emphasize the need to evaluate the prescribing behavior of physicians to avoid high-dose antipsychotic prescriptions for improved patient care.

KEYWORDS

antidepressive agents, antipsychotic agents, hypnotics and sedatives, polypharmacy, schizophrenia

1 | INTRODUCTION

Antipsychotics are psychotropic drugs primarily used to treat schizophrenia and other psychotic disorders. In clinical practice, for treating schizophrenia, antipsychotics are typically prescribed in combination with mood stabilizers, antidepressants, and anxiolytics/hypnotics.[1,2] Anti-Parkinson's agents are often included in multiple drug regimens (polypharmacy), and prescribed for both the prevention and treatment of adverse reactions, such as extrapyramidal symptoms (EPS). However, a study reported that side effects including disorientation and hallucinations might occur.[3]

Patients with schizophrenia are often treated with second-generation antipsychotics, which often carry the risk of adverse reactions, such as EPS, metabolic syndrome, endocrine disorders, cardiovascular disorders, and osteoporosis.[4–6] Moreover, high-dose antipsychotic polypharmacy (APP) is reportedly associated with depressive disorders and even increased mortality rates.[7,8] In Japan, prescriptions of antipsychotics for treating schizophrenia mainly involve high-dose APP, alongside concurrent medications.[9] Although APP use in Japan is widespread compared with that in other East Asian countries,[10] there has been a slight decrease over the years, owing to the adoption of second-generation antipsychotic monotherapy.[11–13] Previous studies have chronicled the factors affecting antipsychotic prescription patterns and prevalence of polypharmacy in patients with schizophrenia.[14,15] However, studies examining the underlying factors associated with high-dose APP and co-prescriptions of other psychotropic medications in Japan since the growing use of second-generation monotherapy are lacking.

Although it is well established that antipsychotics have adverse reactions, the frequency of high-dose prescriptions has still not substantially decreased.[16] This is concerning, considering that the number of outpatients with schizophrenia is increasing.[17–19] To prevent the use of high-dose prescriptions, we must first understand the factors that have contributed to the current paradigm of high-dose prescriptions. Hence, it is pertinent to examine the factors in community-dwelling outpatients. This study focused on the high-dose antipsychotic prescriptions in outpatients with schizophrenia during their maintenance period using claims data from a single prefecture, while aiming to identify their associations between patients' characteristics and concurrent psychotropic prescriptions (antidepressants, anxiolytics/hypnotics, mood stabilizers, and anti-Parkinson's agents).

2 | METHODS

2.1 | Study design and participants

We conducted a cross-sectional study to evaluate adult outpatients with schizophrenia treated with antipsychotics.

2.2 | Data source

Claims data from both the National Health Insurance (Japan) (https://www.mhlw.go.jp/english/wp/wp-hw3/dl/2-001.pdf) and the Long Life Medical Care System (Japanese medical care system for the elderly adults aged 75 years or older), from a single prefecture between October 2014 and March 2015, were used for analysis. The data set was anonymized. Clinical data, including age at the start of the study (study start month − birth month), sex, coexisting diagnosis (diagnosis record), prescribed medicines (medicinal product codes), prescription days, dosages, and medical services were extracted. Previously published documents were used to define each psychotropic group.[20] We defined the following five drugs as mood stabilizers: sodium valproate, lithium carbonate, lamotrigine, carbamazepine, and topiramate.[21] Some antipsychotics, such as chlorpromazine and sulpiride, have multiple indications and were regarded as antipsychotics. The long-acting injectable medications that were approved in Japan at the time of data collection were as follows: haloperidol decanoate, fluphenazine decanoate, risperidone, and paliperidone palmitate.[22,23]

2.3 | Study population

We included a total of 22 100 patients aged 18 years and older with schizophrenia, as the registered diagnosis (ICD-10: F20). Patients whose main diagnosis was mood disorder (ICD-10: F30.x-39), dementia (ICD-10: F00.x-F07.x, F09), Alzheimer's disease (ICD-10: G30.x), or epilepsy (ICD-10: G40.x); patients who were prescribed anti-dementia drugs and medications for peripheral symptoms of dementia; and patients whose prescription data did not exist for long periods of time due to a change in residence or medical institution were excluded. Additionally, patients with a short prescription duration (<28 days) were also excluded, since it was presumed that their prescriptions were constantly subject to change.

2.4 | Drug utilization measures

The chlorpromazine-equivalent value (CPZ equivalent) per patient was used to calculate the daily antipsychotic dose per patient based on the chlorpromazine dose equivalents for antipsychotics.[24] If a patient had prescription data of multiple months, we used the mean value of CPZ equivalents calculated monthly.[25]

2.5 | Statistical analyses

The objective variable was the presence or absence of a high-dose antipsychotic prescription (binary data). Explanatory variables included sex, age (category), presence or absence of comorbidities, psychotropic drugs (antidepressants, anxiolytics/hypnotics, mood stabilizers, and anti-Parkinson's agents) prescribed concurrently, and psychiatrist's therapy. Psychiatrist's therapy is a form of medical fee remuneration obtained when a doctor in charge of psychiatry continues to give instructions or advice under a certain treatment plan. A chi-square test was conducted for the CPZ equivalent values, the

frequency of high-dose prescriptions and each explanatory variable, and those with a CPZ equivalent above 1000 mg/day of antipsychotics, which is considered as a high dose. [26,27]

Finally, multiple logistic regression analysis was conducted separately for patients aged 18-64 years (designated as adults) and for those aged 65 years and older (designated as older adults). The area under curve (C-index) was calculated. A threshold of $P < .05$ was considered significant.

All analyses were performed using IBM SPSS Statistics for Windows, version 23.0. (IBM Corp.).

2.6 | Ethical considerations

This study used anonymized data from an electronic data set; thus, it was not considered necessary to obtain consent from patients based on existing guidelines.[28] This study was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine, Japan (R0438).

3 | RESULTS

After exclusion, a total of 13 471 patients with schizophrenia qualified for the study, and the pertinent data were analyzed (Figure 1).

3.1 | Prescribing characteristics

In Table 1, the frequency distribution of the CPZ equivalent was disaggregated by age and patient comedications. The mean and median CPZ equivalents were 368.3 mg/day and 200 mg/day, respectively. A total of 2945 (21.9%) patients received ≥600 mg/day, which is the set medical dosage guideline[29,30] for patients with schizophrenia in the maintenance period. Meanwhile, 1139 (8.5%) patients received 1000 mg/day (high-dose prescriptions). The effective dose of antipsychotics for schizophrenia was assumed to be equal to the CPZ equivalent of 100 mg/day.[30,31] Moreover, 3599 (26.7%) patients received less than 100 mg/day.

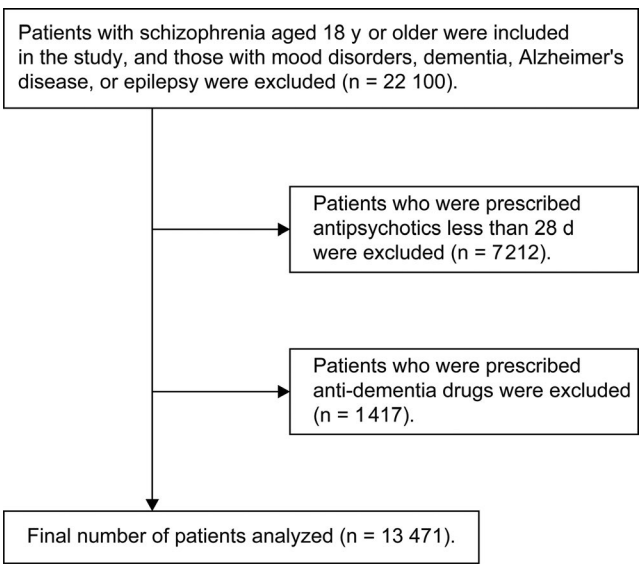

FIGURE 1 Flow chart of the study participants

3.2 | Relationship between each explanatory variable and CPZ equivalent

The characteristics of the patients classified by sex and age, presence or absence of comorbidities, presence or absence of each psychotropic prescription, CPZ equivalent, and percentage of high-dose prescriptions are shown in Table 2. The percentage of high-dose prescriptions was lower in patients with diabetes mellitus, cardiovascular, cerebrovascular, or kidney diseases than in those without any comorbidity. In this study, 7809 (58.0%) patients were prescribed with anxiolytics/hypnotics, 2634 (19.6%) were prescribed antidepressants, 2979 (22.1%) were prescribed mood stabilizers, and 4299 (31.9%) were prescribed anti-Parkinson's agents. Among the patients prescribed a CPZ equivalent of 1000 mg/day or more (a high-dose prescription), 837 (73.5%) were prescribed anxiolytics/hypnotics, 146 (12.8%) were prescribed antidepressants, 405 (35.6%) were prescribed mood stabilizers, and 706 (70.0%) were prescribed anti-Parkinson's agents.

3.3 | Relationship between sex, age, and high-dose prescriptions

The percentage of patients with high-dose prescriptions was higher in men. CPZ equivalents were highest in the groups aged 45-54 and 35-44 years in both men and women, respectively (Table 3).

3.4 | Factors associated with high-dose prescriptions

Owing to the observed differences in the number of high-dose antipsychotic prescriptions by age, a stratified analysis of high-dose prescription factors was conducted to compare patients aged below 65 years old with those aged over 65 years. A higher percentage of people aged 65 years and older was found in the low-dose group with a CPZ equivalent of less than 100 mg/day (Table 1). A multiple logistic regression analysis was conducted. In this analysis, the patients with CPZ equivalents of less than 100 mg/day were excluded to rule out the possibility of including patients with mood disorders or dementia from the medical fee data.

The adjusted odds ratio (OR) of a high-dose antipsychotic prescription was significantly higher in men aged 45-49 years (1.50; $P = .014$). For both men and women aged 60-64 years, the adjusted OR was lower (men: 0.54, $P = .006$; women: 0.51, $P = .002$). The

TABLE 1 Chlorpromazine-equivalent values by age and co-prescription

	0-100 mg	100-200 mg	200-300 mg	300-600 mg	600-1000 mg	≥1000 mg	Total
Age (y), n (%)	3608	2526	1679	2713	1806	1139	
18-34	273 (19.5)	240 (17.1)	198 (14.1)	324 (23.1)	229 (16.3)	139 (9.9)	1403
35-44	372 (13.3)	404 (14.4)	353 (12.6)	741 (26.4)	549 (19.6)	385 (13.7)	2804
45-54	314 (13.9)	346 (15.3)	264 (11.6)	561 (24.7)	436 (19.2)	346 (15.3)	2267
55-64	356 (18.2)	347 (17.7)	281 (14.3)	479 (24.5)	324 (16.5)	172 (8.8)	1959
65-74	677 (30.0)	497 (22.1)	347 (15.4)	431 (19.1)	217 (9.6)	84 (3.7)	2253
≥75	1616 (58.0)	692 (24.8)	236 (8.5)	177 (6.4)	51 (1.8)	13 (0.5)	2785
Comedications, n (%)							
Anxiolytics/hypnotics	1918 (24.6)	1399 (17.9)	910 (11.7)	1573 (20.1)	1172 (15.0)	837 (10.7)	7809
Antidepressants	881 (33.4)	564 (21.4)	320 (12.1)	446 (16.9)	277 (10.5)	146 (5.5)	2634
Mood stabilizers	657 (22.0)	483 (16.2)	333 (11.2)	597 (20.0)	504 (16.9)	405 (13.6)	2979
Anti-Parkinson's	587 (13.7)	581 (13.5)	502 (11.7)	1062 (24.7)	861 (20.0)	706 (16.4)	4299

adjusted OR for high-dose prescriptions was lower (0.55, $P = .007$) in patients with cerebrovascular disease. The adjusted OR was significantly higher for patients using psychotropics in combination with high-dose prescription (1.69 for anxiolytics/hypnotics and mood stabilizers, $P < .001$; 2.55 for anti-Parkinson's agents). The adjusted OR for the high-dose prescriptions was as low as 0.71 (95% CI: 0.60-0.85) in patients who received psychiatrist's therapy (Table 4).

In the logistic regression analysis for the patients aged 65 years or over, the adjusted OR for women aged 80 years and older was significantly lower (0.15, $P = .003$). The adjusted OR was significantly higher for psychotropics used in combination with a high-dose prescription (1.69, $P = .024$ for anxiolytics/hypnotics and 3.31, $P < .001$ for anti-Parkinson's agents); however, the adjusted OR was significantly lower at 0.45 (95% CI: 0.20-1.00, $P = .048$) for antidepressants (Table 5).

4 | DISCUSSION

This study focused on the high-dose antipsychotic prescriptions in outpatients with schizophrenia while aiming to identify their associations between patients' characteristics and concurrent psychotropic prescriptions.

4.1 | Mean Dose in CPZ equivalent

The mean value of CPZ equivalent obtained in this study (368.3 mg/day) was higher than the one reported in a large-scale survey of antipsychotic drugs in Japan (239 g/day) that targeted outpatient data (1272 people) from health insurance associatiations.[32] In the previous study, participants were workers aged 0-74 years and their families, and the medical fee information was extracted from approximately 330,000 beneficiaries from multiple health insurance associations. The age distributions in the present and the previous study (which included diseases other than schizophrenia) differed. These differences in the target populations may have contributed to the discrepancy in the mean dose.

4.2 | Relationship Between Sex, Age, and High-Dose Prescriptions

High-dose prescriptions by age were higher in men aged 45-49 years than in younger men (adjusted OR = 1.23). The adjusted OR was 0.54 in patients aged 60-64 years. A previous study revealed that middle-aged people were also prescribed higher doses, whereas older people were prescribed lower doses.[33]

While a previous study suggested that there was no difference between high-dose prescriptions in men and women,[27] our data revealed that high-dose prescriptions were significantly higher in men (10.4%) than in women (6.8%). This might be due to the differences in the time frame of the current study compared with that of the previous study. However, as our study population was not necessarily a representative sample of all Japanese individuals with schizophrenia, there may be inherent population-specific differences related to the high-dose antipsychotic prescriptions between the two genders.

With regard to sex differences by age, only men aged 45-54 years had a significantly higher percentage of high-dose prescriptions than women of the same age group.

4.3 | Relationship between high-dose antipsychotics and concurrent psychotropics

Patients aged less than 65 years were more likely to be prescribed mood stabilizers and anxiolytics/hypnotics with large doses of antipsychotics, which was consistent with the findings of the

TABLE 2 Demographic and clinical characteristics

	n (%) n = 13 471	High-dose prescription[a], n (%) n = 1139 (8.5%)	*P*-value
Sex, n (%)			
Male	6047 (44.9)	631 (10.4)	<.001
Female	7424 (55.1)	508 (6.8)	
Age (y), n (%)			
18-34	1403 (10.4)	139 (9.9)	<.001
35-44	2804 (20.8)	385 (13.7)	
45-54	2267 (16.8)	346 (15.3)	
55-64	1959 (14.5)	172 (8.8)	
65-74	2253 (16.7)	84 (3.7)	
≥75	2785 (20.7)	13 (0.5)	
Comorbidity, n (%)			
Cardiovascular diseases	2039 (15.1)	67 (3.3)	<.001
Cerebrovascular diseases	2001 (14.9)	35 (1.7)	<.001
Liver dysfunction	3152 (23.4)	247 (7.8)	.154
Diabetes mellitus	549 (4.1)	31 (5.6)	.016
Kidney diseases	334 (2.5)	8 (2.4)	<.001
No registered diseases	7842 (58.2)	812 (71.3)	<.001
Comedications			
Anxiolytics/hypnotics	7809 (58.0)	837 (10.7)	<.001
Antidepressants	2634 (19.6)	146 (5.5)	<.001
Mood stabilizers	2979 (22.1)	405 (13.6)	<.001
Anti-Parkinson's	4299 (31.9)	706 (16.4)	<.001
Department, n (%)			
Psychiatrist's therapy	9792 (72.7)	896 (9.2)	<.001

[a]Chlorpromazine-equivalent value ≥ 1000 mg.

TABLE 3 Sex/age classification and chlorpromazine-equivalent value

Age (y)	Sex	n	Mean (mg)	Median (mg)	1,000 mg or more (n)	*P*-value
18-34	Male	702	453.0	300.0	10.7% (75)	.330
	Female	701	384.3	226.7	9.1% (64)	
35-44	Male	1470	539.1	400.0	14.6% (214)	.181
	Female	1334	478.0	323.9	12.8% (171)	
45-54	Male	1238	569.5	400.0	17.9% (221)	<.001
	Female	1029	473.2	300.0	12.2% (125)	
55-64	Male	881	441.9	305.5	9.8% (86)	.165
	Female	1078	378.8	240.0	8.0% (86)	
65-74	Male	923	269.9	163.1	3.5% (32)	.585
	Female	1330	275.9	170.7	3.9% (52)	
≥75	Male	833	116.5	75.8	0.4% (3)	.590
	Female	1952	123.5	75.8	0.5% (10)	

previous studies.[14,34] The reason for the additional use of mood stabilizers lacks persuasive evidence.[35] However, mood stabilizers are typically prescribed in combination with antipsychotics for the purpose of sedation to treat symptoms such as hostility and aggression. In our study, antipsychotics were frequently used in combination with anxiolytics/hypnotics. This finding suggests

TABLE 4 Factors associated with high-dose antipsychotic prescriptions: multivariable analyses

	Odds ratio	95% CI	*P*-value
Males, age (y)			
18-34	Ref.		
35-39	1.23	0.87-1.73	.239
40-44	1.12	0.81-1.54	.505
45-49	1.50	1.08-2.06	.014
50-54	1.40	0.99-2.00	.055
55-59	1.05	0.71-1.56	.814
60-64	0.54	0.34-0.84	.006
Females, age (y)			
18-34	0.89	0.62-1.29	.538
35-39	1.13	0.79-1.63	.505
40-44	1.11	0.80-1.55	.534
45-49	0.98	0.68-1.41	.897
50-54	1.03	0.71-1.51	.867
55-59	0.95	0.64-1.42	.796
60-64	0.51	0.34-0.78	.002
Cardiovascular diseases	0.95	0.69-1.31	.762
Cerebrovascular diseases	0.55	0.36-0.85	.007
Liver dysfunction	0.90	0.76-1.06	.195
Diabetes mellitus	0.85	0.54-1.33	.468
Kidney diseases	1.03	0.44-2.41	.938
Anxiolytics/hypnotics	1.69	1.45-1.97	<.001
Antidepressants	0.63	0.52-0.77	<.001
Mood stabilizers	1.69	1.46-1.95	<.001
Anti-Parkinson's	2.55	2.22-2.94	<.001
Psychiatrist's therapy	0.71	0.60-0.85	<.001

AUC, area under the curve; CI, confidence interval.
Odds ratios are shown with their 95% CIs.
AUC = 0.701.

TABLE 5 Factors associated with high-dose antipsychotic prescriptions in older indivisuals: multivariable analyses

	Odds ratio	95% CI	*P*-value
Males, age (y)			
65-69	Ref.		
70-74	0.64	0.29-1.42	.268
75-79	0.15	0.02-1.16	.069
≥80	0.39	0.087-1.76	.220
Females, age (y)			
65-69	1.04	0.59-1.83	.893
70-74	0.90	0.48-1.70	.750
75-79	0.46	0.19-1.09	.078
≥80	0.15	0.044-0.53	.003
Cardiovascular diseases	1.06	0.60-1.88	.835
Cerebrovascular diseases	0.52	0.26-1.04	.063
Liver dysfunction	1.08	0.66-1.76	.756
Diabetes mellitus	0.97	0.43-2.19	.942
Kidney diseases	0.36	0.049-2.70	.323
Anxiolytics/hypnotics	1.69	1.07-2.66	.024
Antidepressants	0.45	0.20-1.00	.048
Mood stabilizers	1.20	0.68-2.10	.535
Anti-Parkinson's	3.31	2.12-5.18	<.001
Psychiatrist's therapy	1.02	0.61-1.71	.930

AUC, area under the curve; CI, confidence interval.
Odds ratios are shown with their 95% CIs.
AUC = 0.781.

that anxiolytics/hypnotics are often prescribed as treatment for insomnia, depression, and anxiety, which seems to be increasing in patients with schizophrenia.[36]

Prescriptions of antidepressants were low in all age groups. The reasons for the negative symptoms, such as amotivation, blunted affect, and asociality experienced by patients with schizophrenia in the chronic maintenance phase are unknown. Furthermore, the effectiveness of antidepressants in comorbid major depressive episodes remains unclear.[1] Although the use of a combination of antipsychotics and antidepressants to treat negative symptoms and comorbid major depressive episodes has been reported,[34] Asian clinicians do not prescribe antidepressants as frequently as those in other countries.[14]

Patients who were prescribed large amounts of antipsychotics had many concomitant prescriptions of anti-Parkinson's agents. This result was consistent with those of previous studies[14,37] and suggests that anti-Parkinson's agents are often used in combination with prophylactics to treat side effects such as EPS.

4.4 | Relationship between psychiatrist's therapy and high-dose prescriptions

The adjusted OR for the rate of high-dose prescriptions was as low as 0.71 (95% CI: 0.60-0.85) in patients aged <65 years who received psychiatrist's therapy. In addition, the medical fee can be claimed only by the mental health institution, except in special cases (such as a psychiatrist consulting in a private hospital). This nonpharmacologic intervention may be related to the reduced rate of high-dose prescriptions. The effects of psychiatrist's therapy on reducing antipsychotic high-dose prescriptions suggest the need for more holistic treatment plan for schizophrenia. In the future, studies assessing the diversity in interventions and prescription of antipsychotic drugs by physicians and institution-wide practices could help improve patient care.

4.5 | Limitations

This study has several limitations. First, this study employed a cross-sectional design; hence, changes in prescriptions (add-ons and discontinued agents) could not be assessed. Second, the proportions of middle-aged and elderly people among National Health Insurance beneficiaries are higher than those of Japanese population; thus, the average age may be skewed and affect the results. Therefore, in this study, age classification was introduced as a variable within our logistic regression analysis to assess the factors related to high-dose prescriptions. Third, during the maintenance period, there are often changes in drug prescriptions within a short span of time. Thus, we excluded patients who were prescribed drugs for less than 28 days.

In Japan, only a limited number of antipsychotics are approved as medications for delirium and various mood disorders. Thus, for such disorders, antipsychotics are sometimes prescribed with the diagnosis of "schizophrenia" to claim fees.[38] To account for this, we excluded patients who has main diagnosis codes of mood disorders, dementia, Alzheimer's disease, or epilepsy as well as schizophrenia from the analysis.

As we excluded patients who were prescribed drugs for less than 28 days, we likely excluded patients with acute delirium who were treated with antipsychotics, although we cannot rule out the possibility that additional non-schizophrenia use of antipsychotics was included.

The present study evaluated a large-scale claims data set. Our results showed that anxiolytics/hypnotics and anti-Parkinson's agents were often used in combination in patients with schizophrenia for whom antipsychotics were prescribed at high dosage. Antidepressants were used to a lesser extent in combination with high-dose antipsychotics in these patients.

Our study emphasizes the immediate need in Japan to evaluate the prescription tendencies of physicians and institutions to help avoid high-dose antipsychotic prescriptions to improve patient care. It is important for doctors and medical institutions prescribing high-dose drugs to be reviewed the contents of and prescription periods for combination treatment.

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CONFLICT OF INTEREST

The authors declare that they had no conflict of interest.

AUTHOR CONTRIBUTIONS

Dr Takahashi contributed to the design of the study, data extraction, statistical analysis, and writing of the manuscript. Dr Otsubo contributed to design of the study, data extraction, and writing of the manuscript. Dr Kunisawa contributed to the data extraction and statistical analysis. Dr Sasaki contributed to the writing of the manuscript. Dr Imanaka contributed to the design of the study, writing of the manuscript, and management of the overall study process. All authors approved the final version of the manuscript.

ETHICAL APPROVAL

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution, and it conforms to the provisions of the Declaration of Helsinki (Committee of Kyoto University Graduate School of Medicine, Japan, approval no. R0438).

DATA AVAILABLE STATEMENT

The data that support the findings of this study are proprietary data of the prefectural government and therefore are not publicly available. However, the data might be available from the prefectural government upon reasonable request.

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