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ORIGINAL RESEARCH ARTICLE

Association of Antipsychotic Drugs with the Risk of Recurrent Venous Thromboembolism: A Retrospective Study of Data from a Japanese Inpatient Database

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Abstract

Background Approximately a decade has passed since the addition of venous thromboembolism to the list of significant adverse reactions of antipsychotic drugs. However, only a few studies have investigated the relationship between antipsychotic use and venous thromboembolism in the Japanese population.

Purpose We aimed to evaluate the risk of recurrent venous thromboembolism in users of antipsychotic drugs and update the evidence on venous thromboembolism in the Japanese population.

Methods A cross-sectional retrospective analysis of data from a large Japanese claims database, managed by Medical Data Vision Co. Ltd., was conducted. Adult patients who experienced venous thromboembolism between October 2014 and September 2018 in acute care hospitals were identified. The risk of recurrent venous thromboembolism was evaluated with logistic regression using demographic variables. The data of patients using antipsychotic drugs within specific therapeutic classes were also evaluated.

Results We included 8960 patients (mean age, 69 years; 59.2% female). Recurrent venous thromboembolism was observed in 686 patients (7.7%). The risk of recurrent venous thromboembolism was significantly higher in younger patients [< 65 years: reference; 65–74 years: odds ratio (OR) 0.81, 95% confidence interval (CI) 0.66–0.99, $p = 0.04$; ≥ 75 years: OR 0.77, 95% CI 0.64–0.94, $p = 0.01$], those with history of surgery (OR 1.39, 95% CI 1.18–1.65, $p = 0.01$), and anticoagulant users (OR 2.25, 95% CI 1.46–3.48, $p = 0.01$) and was significantly lower in the presence of comorbidities (OR 0.68, 95% CI 0.58–0.81, $p < 0.01$) and fractures (OR 0.49, 95% CI 0.26–0.94, $p = 0.03$). Long-term antipsychotic drug prescriptions (> 14 days) were associated with a higher risk of venous thromboembolism than short-term prescriptions (≤ 14 days) (OR 1.56, 95% CI 1.04–2.34, $p = 0.03$).

Conclusions In patients with a history of venous thromboembolism, particular attention should be paid to recurrence in younger patients. If antipsychotic drugs are prescribed for > 14 days to patients with a history of venous thromboembolism, they should be administered carefully, guided by reported findings. Further evaluations using different databases or populations are required to generalize the findings of this study.

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Key Points

We updated the evidence regarding patients with venous thromboembolism treated with antipsychotic drugs in Japan.

The risk of recurrent venous thromboembolism was significantly higher in younger patients.

Among users of antipsychotic drugs, prescriptions exceeding 14 days were associated with an increased risk of recurrent venous thromboembolism.

1 Introduction

Venous thromboembolism (VTE), a blood clot that forms in a vein, can be classified as deep vein thrombosis (DVT) or pulmonary embolism (PE). It is the third most common cause of vascular death after myocardial infarction and stroke, with annual incidence of 1–2 cases per 1000 people [1]. VTE is the leading cause of morbidity and mortality worldwide, whereas PE is an independent predictor of reduction in survival rate [2, 3]. The risk of VTE recurrence varies with time from onset, with the highest risk being within the initial 6–12 months [4], and it is known to persist over time [5–7].

VTE can be caused by various factors such as blood flow stagnation, vascular endothelial disorder, and blood hypercoagulation [8]. A trigger can be the presence of any temporary or discontinued factor, including surgery, trauma, immobilization, pregnancy, oral contraceptive use, and hormone replacement therapy, within 3 months before diagnosis of the condition.

Several drugs have been associated with occurrence of VTE. The use of antipsychotic (AP) drugs is associated with VTE onset. Observational studies on the relationship between APs and VTE have mainly been conducted countries other than Japan, and several systematic reviews have been published in recent years [9–11]. Although no conclusions have been made about which type of AP drug may induce VTE or whether typical or atypical type of AP may induce VTE, these studies have suggested that a high risk of VTE is associated with AP administration. In the revised version of "Precautions for Use" of APs published in March 2010 by Japan's Ministry of Health, Labor and Welfare Safety Division, Pharmaceutical and Food Safety Bureau, VTE was added as an important adverse reaction. The package inserts of APs in Japan caution users about the onset of VTE. In some cases, wherein APs are used in the postoperative recovery period or in long-term care, they may lead to unintentional oversedation as an adverse reaction, leading to provoked VTE [12, 13].

However, only a few studies from Japan have been included in several systematic reviews that have been conducted in recent years [9–11]. Moreover, these studies were conducted before 2013 and have become obsolete, and only a few observational studies included in these reviews set VTE recurrence as the outcome [14–16]. According to therapeutic guidelines, once a patient develops VTE, recurrence control may be necessary [8, 17, 18]. Although it is useful to identify the risk factors for VTE recurrence, there is insufficient information on this topic. As approximately a decade has passed since the addition of venous thromboembolism to the list of significant adverse reactions of APs, it is necessary to confirm the relationship between AP use and VTE.

Therefore, to generate new evidence, we aimed to explore the risk of recurrent VTE associated with AP use on the basis of the findings obtained to date and results of the analysis of data from a large-scale acute treatment phase patient database.

2 Materials and Methods

2.1 Study Design and Data Source

This study was a cross-sectional study and was performed retrospectively using anonymized data from the health claims and Diagnosis Procedure Combination (DPC) database of 469 acute care hospitals, which covers approximately 27% of acute care hospitals across Japan and is managed by the Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). DPC is a patient classification method developed in Japan for inpatients in the acute phase of illness. This database contains both inpatient and outpatient administrative data from various hospitals. As of 15 November 2022, approximately 40 million patients had been registered in this database and are made up of demographic characteristics, including age and sex distributions. Thus, the data do not include any information that could be used to identify individuals or hospitals. The diagnosis for each patient was established using the International Classification of Diseases, 10th revision (ICD-10) codes [19].

2.2 Patient Selection

We extracted data from the MDV database between 1 October 2014 and 30 September 2018. Patients aged ≥ 18 years were selected according to the following inclusion criteria for the acute phase of VTE: a primary diagnosis of PE (ICD-10 code I26) and DVT (ICD-10 codes I80 and I82) [20] at admission. The index hospitalization date for VTE

was defined as the date of admission for VTE, as indicated by the ICD-10 diagnostic code. We excluded patients with obstetric VTE indicated by the codes O22, O87, and O88, as specified in a previous study [20]. We also excluded patients whose weight or height values were absent or abnormal [weight (kg): weight < 10 or > 150; height (cm): 100 ≤ height ≤ 200; body mass index (BMI, kg/m^2): > 100] and those with an abnormal smoking index. Patients who were not covered by the DPC system were excluded.

2.3 Variables

We selected the following variables to investigate the association of VTE recurrence with the representative characteristics of patients. The patients' clinical and demographic characteristics were extracted within the baseline period that corresponds to the duration of hospitalization due to initial VTE or on the index hospitalization date and were included as covariates: age (< 65, 65–74, and ≥ 75 years), sex, BMI (< 18.5, 18.5–24.5, and ≥ 25), smoking history, Charlson Comorbidity Index (CCI) (0 and ≥ 1) [21, 22], history of fractures or surgery, use of concomitant medications (such as high-risk drugs such as those in hormone replacement therapy and oral contraceptive therapy) [8, 17, 18], anticoagulants, APs [9–11]), history of or current psychiatric diagnosis, and cumulative duration of AP prescription (≤ 14 days and > 14 days).

Recurrent VTE was defined if patients were readmitted the second time with primary diagnosis of VTE. Each patient's information regarding AP use and recurrent VTE were used until 1.5 years from the index hospitalization date for VTE. According to the Japanese medical system, patients were categorized on the basis of their age as follows: late elderly (≥ 75 years), elderly (≥ 65 years to < 75 years), and non-elderly (< 65 years). Smoking history was derived from the smoking index (presence/absence). The individual components of the CCI were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcerative disease, mild liver disease, diabetes without complications, diabetes with complications, hemiplegia, moderate or severe renal disease, malignancy, moderate or severe liver disease, metastatic solid tumor, and acquired immune deficiency syndrome. Each disease score for calculating CCI was assigned to the coding algorithm and scored [21, 22]. In addition to basic patient information, the variable was selected to adjust for confounding factors. The factors that might contribute to the onset of VTE are selected from previous research [9–11] and the guidelines for diagnosis, prevention, and treatment of VTE [8, 17, 18]. The use of AP was classified as phenothiazine, butyrophenone, benzamide, serotonin-dopamine antagonist (SDA), serotonin-dopamine antagonist (MARTA), and dopamine partial agonist (DPA), and presence of multiple AP use or no AP use. The cumulative number of days of AP prescription was calculated from the initial occurrence of VTE to 1.5 years after the onset of VTE. For patients with multiple APs, the cumulative AP prescription days was calculated as the mean of the administration period of each AP [23].

Detailed information regarding data coding is provided in the Supplementary Information 1, Online Resources 1–6.

2.4 Informed Consent and Patient Details

The study protocol was approved by the Ethics Review Board of our university (approval number: human medical-2020-013), which waived the need for informed consent because of the study design, which involved a secondary analysis of a claims database and did not directly involve the participants (in designing the research question, selecting the outcome measures, and interpreting and writing the results of this study). The participants had the opportunity to opt out, which was announced on the study website.

2.5 Statistical Methods

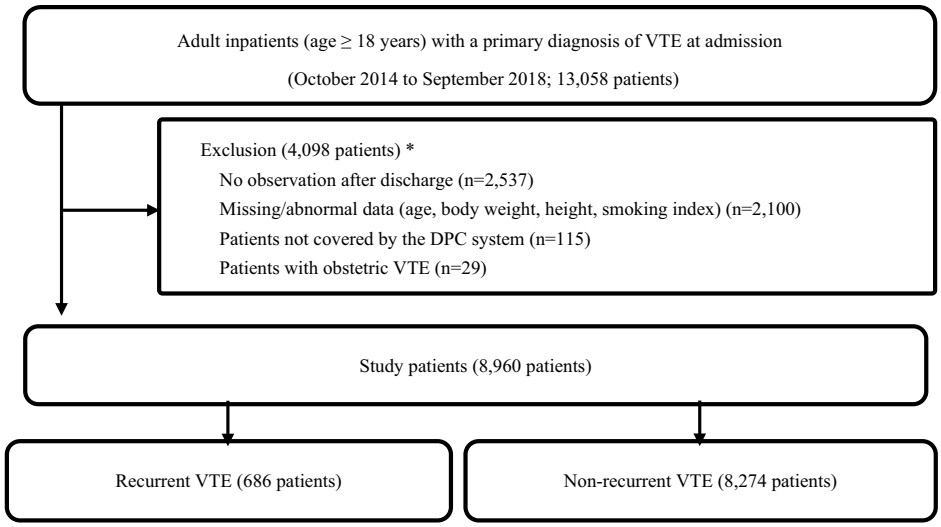
Patient background and characteristics are summarized as mean and standard deviation or proportion depending on variable distribution. Regarding patient background, categorical variables were compared using the chi-squared test and continuous variables using the Wilcoxon rank-sum test. The multivariable logistic regression model was applied to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) after checking the multicollinearity of variables on the basis of whether the variance inflation factors were < 10.0, and a p-value of < 0.05 indicated statistical significance. All statistical analyses were performed using JMP Pro version 15.2.1 (SAS Institute, Cary, North Carolina, USA).

3 Results

Between October 2014 and September 2018, 13,058 patients with primary diagnoses were identified. Among them, we excluded 4098 patients who met the exclusion criteria. Finally, 8960 patients were included. Consequently, there were 686 patients in the recurrent VTE group (7.7%) and 8274 patients in the non-recurrent VTE group (92.3%) (Fig. 1).

The patients in the recurrent VTE group were younger and had higher frequency of smoking habits, surgeries, anticoagulant therapy use, and long-term AP administration (> 14 days) than those in the non-recurrent VTE group. In contrast, the former group had fewer comorbidities and fractures (Table 1).

Fig. 1 Patient selection



*Some patients were duplicated.

DPC, Diagnosis Procedure Combination; VTE, venous thromboembolism

Table 1 Demographic and clinical characteristics at baseline of patients included in the Medical Data Vision database, 2014–2018

	Recurrent VTE ($N = 686$, 7.7%)	Non-recurrent VTE ($N = 8274$, 92.3%)	*p*-value
Age, mean (SD)	65.9 (16.4)	69.0 (15.5)	< 0.01*
Age (%), years			< 0.01*
< 65	272 (39.7 %)	2629 (31.8 %)	
65–75	165 (24.1 %)	2097 (25.3 %)	
≥ 75	249 (36.3 %)	3548 (42.9 %)	
Female (%)	390 (56.9 %)	4919 (59.5 %)	0.18
BMI (%)			0.08
< 18.5	64 (9.33 %)	734 (8.87 %)	
18.5–25	361 (52.6 %)	4712 (57.0 %)	
≥ 25	261 (38.1 %)	2828 (34.2 %)	
Smoking history (%)	217 (31.6 %)	2301 (27.8 %)	0.03*
CCI score (≥ 1) (%)	415 (60.5 %)	5701 (68.9 %)	< 0.01*
Fracture (%)	10 (1.46 %)	262 (3.17 %)	0.01*
Surgery (%)	239 (34.8 %)	2357 (28.5 %)	0.01*
High-risk drug use (%)	14 (2.04 %)	159 (1.92 %)	0.83
Anticoagulant use (%)	664 (96.8 %)	7708 (93.2 %)	0.01*
Antipsychotic drug use (%)			0.26
Phenothiazine	22 (3.21 %)	282 (3.41 %)	
Butyrophenone	18 (2.62 %)	240 (2.90 %)	
Benzamide	4 (0.58 %)	25 (0.30 %)	
SDA	20 (2.92 %)	233 (2.82 %)	
MARTA	15 (2.19 %)	185 (2.24 %)	
DPA	5 (0.73 %)	19 (0.23 %)	
Multiple APs	49 (7.14 %)	509 (6.15 %)	
None	553 (80.6 %)	6781 (82.0 %)	
Psychiatric disease (%)	155 (22.6 %)	1673 (20.2 %)	0.14
AP prescription (> 14 days) (%)	72 (10.5 %)	627 (7.58 %)	0.01*

AP antipsychotic, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *DPA* dopamine partial agonist, *MARTA* multi-acting receptor-targeted antipsychotics, *SD* standard deviation, *SDA* serotonin-dopamine antagonist, *VTE* venous thromboembolism

*$p < 0.05$

The risk of recurrent VTE was significantly higher in younger patients (< 65 years: reference) (65–74 years: OR 0.81, 95% CI 0.66–0.99, $p = 0.04$, ≥ 75 years: OR 0.77, 95% CI 0.64–0.94, $p = 0.01$), those with a history of surgery (OR 1.39, 95% CI 1.18–1.65, $p = 0.01$), and anticoagulant users (OR 2.25, 95% CI 1.46–3.48, $p = 0.01$), and was significantly lower in the presence of comorbidities (OR 0.68, 95% CI 0.58–0.81, $p < 0.01$) and fractures (OR 0.49, 95% CI 0.26–0.94, $p = 0.03$). Long-term prescriptions (> 14 days) were associated with a higher risk of VTE than short-term prescriptions (≤ 14 days) (OR 1.56, 95% CI 1.04–2.34, $p = 0.03$) (Table 2).

Table 2 Multivariable logistic regression for VTE recurrence

	OR	95% CI	*p*-value
Age (%), years			
< 65	Ref		
65–75	0.81	0.66–0.99	0.04*
≥ 75	0.77	0.64–0.94	0.01*
Female (%)	0.98	0.82–1.18	0.85
BMI (%), kg/m^2			
< 18.5	Ref		
18.5–25	0.82	0.62–1.09	0.18
≥ 25	0.95	0.71–1.27	0.73
Smoking history (%)	1.12	0.93–1.37	0.23
CCI score (≥ 1) (%)	0.68	0.58–0.81	< 0.01*
Fracture (%)	0.49	0.26–0.94	0.03*
Surgery (%)	1.39	1.18–1.65	0.01*
High-risk drug use (%)	1.15	0.66–2.02	0.62
Anticoagulant use (%)	2.25	1.46–3.48	0.01*
Antipsychotic use (%)			
None	Ref		
Phenothiazine	0.75	0.46–1.22	0.25
Butyrophenone	0.91	0.56–1.50	0.72
Benzamide	1.79	0.60–5.38	0.30
SDA	0.92	0.56–1.52	0.75
MARTA	0.71	0.39–1.30	0.27
DPA	2.23	0.80–6.24	0.13
Multiple APs	0.81	0.52–1.26	0.35
Psychiatric disease (%)	1.12	0.90–1.40	0.30
AP prescription (> 14 days) (%)	1.56	1.04–2.34	0.03*

AP antipsychotic, *BMI* body mass index, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *DPA* dopamine partial agonist, *MARTA* multi-acting receptor-targeted antipsychotics, *OR* odds ratio, *SDA* serotonin-dopamine antagonist, *VTE* venous thromboembolism

*$p < 0.05$

4 Discussion

We investigated the association of recurrent VTE with AP administration in 8960 patients, and to the best of our knowledge, this is the first study to investigate such an association in the Japanese population using the DPC database. The reported rates of recurrent VTE vary widely, with 0.6–5% at 90 days and 13–25% at 5 years [24–32]. The prevalence of recurrent VTE was 7.7% at 1.5 years in our study.

In this study, the patients in the recurrent group were younger than those in the non-recurrent group. In a meta-analysis by Xuan et al., the incidence of VTE was noted to be threefold higher in young patients taking APs [10]. Our findings are not limited to AP users and do not fully support the result of this meta-analysis. However, our results are meaningful as they highlight the importance of carefully monitoring VTE recurrence not only for the elderly, but also for younger patients with a history of VTE. The OR of VTE recurrence was high for patients with a cumulative AP administration period of exceeding 14 days. In our study population, the proportions of patients with psychiatric disease were approximately 20% in both recurrent group and non-recurrent group, and there was no imbalance in the distribution between the groups. Furthermore, patients with AP prescription exceeding 14 days were significantly higher in the recurrent group. In the recurrent group, there was a possibility that these patients may have been under medication for a longer period because of the severity of VTE in reducing psychiatric symptoms before and after the VTE-related procedure, and may have caused events such as oversedation and immobilization of the patient, which may have been associated with an increased risk of VTE recurrence. [33, 34]. Therefore, patients with a history of VTE should be carefully monitored during long-term use because sedation or immobility due to drug treatment for psychiatric diseases, including APs, has been reported to be related to the onset of VTE. The administration of anticoagulants was significantly higher in the recurrent group and was associated with VTE recurrence. However, more than 90% of patients in the study were treated with administration of anticoagulants. This was considered the appropriate treatment for VTE, and it is possible that mild case without administration of anticoagulant was more likely to be included in the non-recurrent group. Additionally, surgery was significantly higher in the recurrent group and was associated with VTE recurrence. There was a possibility that surgery including VTE-related procedures was more common in the recurrent group during the research period. On the contrary, CCI score (≥ 1) and fracture were significantly lower in the recurrent group and were less associated with VTE

recurrence. These variables were considered comorbidities at admission for initial VTE. These patients may have been carefully monitored after initial VTE, considering comorbidities or medical history, and recurrence of VTE may have been suppressed. The risk of recurrent VTE by AP type was not significantly different in the multivariable logistic regression analyses. Subsequently, we performed univariate logistic regression analyses and multivariable logistic regression analyses in single-type AP users as an exploratory subanalysis. Results of univariate analysis indicated that the risk of recurrent VTE was significantly higher with smoking history and DPA use, while results of the multivariable analysis did not show a significant difference. Because the risk of DPA users was significantly higher in the univariate analysis, multivariable logistic regression analyses were performed for single-type AP users with DPA users as the reference; however, our findings only indicated that the risk of recurrent VTE with phenothiazine was lower than that with DPA. We were interested in the effects on serotonin 5-HT2 receptors other than type-2 dopamine (D2) receptors, which are the mechanism of action of DPA [35]. Consequently, we considered the recurrence of VTE associated with platelet aggregation through the mechanisms of action mediated as coagulation abnormalities by serotonin receptors [36–38]. However, there was no similar tendency between SDA and MARTA, which also have effects on serotonin receptors other than DPA. Therefore, we anticipate their further elucidation from pharmacological mechanisms. Detailed information regarding exploratory subanalysis is provided in the Supplementary information 2.

This study has some limitations. The patients administered APs in this study were part of the entire population (1440/8960, 16.1%). In addition, the information of AP use was used from initial VTE to 1.5 years after the onset of VTE for each patient, as our study was a cross-sectional study. Therefore, AP use before initial VTE was not considered and prevalent user bias of AP use should be recognized. In this study, the use of APs and the presence or absence of psychiatric disease were not found to be imbalanced between the recurrent VTE group and non-recurrent VTE group. However, a cumulative AP administration period (> 14 days) was significantly higher in the recurrent VTE group. There was a possibility that the reasons for prescribing APs may be due to a reason other than the presence or absence of psychiatric illness. Therefore, we should recognize the possibility of confounding by indication. In addition, we have adjusted confounding factors with available information from the MDV database; however, we did not exclude the possibility that there is a residual confounding that cannot be fully adjusted even though we adjusted the possible confounders. Similarly, we recognize the existence of unmeasured confounders, and there was a lack of comprehensive information on transient risk factors, as the administrative database had restrictions on the type of information that was entered into the database. However, we adjusted our analysis for some of the main transient risk factors for VTE onset, such as surgery and fractures. Furthermore, a preliminary analysis of CCI component factors such as advanced cancer, congestive heart failure, and chronic obstructive pulmonary disease, which are considered risk factors for VTE, showed no association with VTE recurrence in our study. The outcome was VTE recurrence, but not primary VTE. The definition of VTE recurrence used in this study was not strict, and the specificity of recurrent VTE diagnosis was not high. As this was a cross-sectional study, the temporal relationship between drug exposure and the onset of the outcome was not clarified. Therefore, we investigate the association between recurrent VTE and each variable, not causality. Patients who developed VTE but were treated in the psychiatric ward along with psychiatric illness care were excluded. Unfortunately, patients not included in the DPC system were not available due to the data characteristics of the MDV database. While VTE is generally considered emergency medicine and treated in a general ward, it is also important to conduct research in the psychiatric ward, and thus, future studies should cover it. To reduce the impact of under-reporting, we excluded patients who did not undergo observation after discharge; however, after the acute phase of VTE treatment, these patients may have been followed up at other medical institutions, such as recovery-phase care hospitals, chronic care hospitals, or family hospitals. Furthermore, patients who take psychiatric drugs, including APs, may be transferred to a psychiatric hospital. While a traceable database is available in Japan, comprehensive and continuous data cannot be collected if patients visit other hospitals, especially in a longitudinal study. These factors may have caused sample size reduction, affected the generalizability of the results, and led to misclassification of the presence or absence of recurrent VTE.

5 Conclusions

In patients with a history of VTE, particular attention should be paid to its recurrence in younger patients. If APs are to be prescribed for > 14 days to patients with a history of VTE, they should be administered cautiously, guided by reported findings on potential risk factors involved. Further evaluations using different databases or populations are required to generalize the findings of this study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-023-00401-2.

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Declarations

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Conflicts of Interest Hiroyuki Hashimoto is an employee of Pfizer R&D Japan and shareholder of Pfizer Inc. The remaining authors report no other conflicts of interest associated with this study.

Availability of Data and material This study was conducted on the basis of a data use agreement with the database vendor. Disclosure to third parties is not permissible.

Ethics Approval The study protocol was approved by the Ethics Review Board of our university (approval number: human medical-2020-013). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki of 1964 and its later amendments or comparable ethical standards.

Consent to Participate The ethics review board of our university waived the need for informed consent because of the study design, which involved a secondary analysis of a claims database and did not directly involve the participants (in designing the research question, selecting the outcome measures, and interpreting and writing the results of this study). The participants were given the opportunity to opt out, which was announced on the study website.

Consent for publication Not applicable.

Code Availability See supplemental information.

Author Contributions Hiroyuki Hashimoto and Ryoka Yamashit were responsible for conceptualization, methodology, data curation, writing: original draft preparation, visualization, and investigation; Shinobu Imai for conceptualization, methodology, software, validation, and writing: reviewing and editing; Anna Kiyomi for conceptualization, methodology, and writing: reviewing and editing; and Munetoshi Sugiura for conceptualization, methodology, writing: reviewing and editing, and supervision. All authors read and approved the final version.

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