Persistence of tolvaptan medication for autosomal dominant polycystic kidney disease
A retrospective cohort study using Shizuoka Kokuho Database

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is a rare hereditary disease leading to end-stage renal failure in approximately half of patients by seventy years of age. It is important to continuously take tolvaptan to control disease progression. However, adherence to tolvaptan in a real-world setting, rather than randomized controlled trials (RCTs), has not been sufficiently reported. We aimed to investigate tolvaptan persistence among patients with ADPKD using a large claims database. Using the Shizuoka Kokuho Database, we identified patients diagnosed with ADPKD who were prescribed tolvaptan from March 2014–September 2018 in Japan. The persistence rate of tolvaptan medication was estimated by Kaplan–Meier analysis, and patient background factors associated with treatment discontinuation were exploratively evaluated with log-rank tests. We identified 1714 eligible patients with ADPKD, and among them, 25 patients used tolvaptan medication. We followed up these patients, whose median treatment duration was 21 months. The persistence rates at 12, 24, and 36 months were estimated to be 70.8% (95% confidence interval: 48.2–93.4), 46.5% (23.2–66.9), and 38.7% (16.4–60.8), respectively. In the exploratory analysis, there were no factors that were obviously associated with tolvaptan discontinuation. The persistence rate of tolvaptan in patients with ADPKD in a real-world setting may be lower than that in previous RCTs. Our innovative method, particularly in Japan, to analyze adherence using large claims data should change the way clinical epidemiological research and health policies of rare diseases are designed in the future.

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease, CI = confidence interval, CKD = chronic kidney disease, EHI = employees' health insurance, LEHI = late elders' health insurance, NHI = national health insurance, PMS = postmarketing surveillance, RCTs = randomized controlled trials, SD = standard deviation, SKDB = Shizuoka Kokuho Database.

Keywords: adherence, claims data, rare disease, real-world evidence, tolvaptan

1. Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a rare and inherited kidney disease with a prevalence of approximately 1 in 4000 in Japan.[1] It is characterized by the formation and enlargement of numerous cysts in the kidneys, resulting in systemic damage.[2–4] In 2014, tolvaptan, a vasopressin V2 receptor antagonist, was approved in Japan for the treatment of ADPKD and has benefited many people. Tolvaptan inhibits ADPKD progression, so it is important to take tolvaptan continuously.[5] On

the other hand, tolvaptan sometimes causes adverse events such as strong aquaresis effects and hepatic dysfunction, which interfere with patients' adherence to tolvaptan.[6,7]

Data from randomized controlled trials (RCTs) are useful in obtaining information about medication adherence. In the TEMPO3:4 trial, a pivotal RCT on tolvaptan, the 3-year discontinuation rate for tolvaptan was 23%.[8] In another pivotal RCT, the REPRISE trial, 84.6% of patients completed the study at 1 year after tolvaptan introduction.[9] However, RCTs generally have strict eligibility criteria, and it is not always appropriate to extrapolate their results to a real-world setting with a variety of conditions.[10] For instance, in the TEMPO3:4 trial, the age range for entry was 18 to 50 years, and patients with creatinine clearance below 60 mL/minutes were excluded. Additionally, especially in the field of rare diseases, it is not easy to recruit patients, and RCTs are costly to conduct.[11] Furthermore, postmarketing surveillance (PMS) is often required for all patients who have taken the drug, which requires significant resources.[12,13]

On the other hand, in recent years, real-world data have been increasingly used in clinical epidemiology research.[14–17] Among them, large claims data, which are information on medical practices required for medical institutions to submit insurance claims, are applied to clinical epidemiological research as a secondary use.[18–21] The feature of these data is that they are routinely collected and utilized—under the universal health insurance system in Japan—and can be applied to research at relatively low cost.[14,19,21] Moreover, the process data, such as the procedures performed, are characterized by their relatively high credibility. However, the application of large claims data to the field of rare diseases has not yet been fully developed. If large claims data can be used to analyze adherence to tolvaptan medication in a real-world setting, they may provide useful information for patients with ADPKD and may also change the way clinical epidemiological research in the field of rare diseases is conducted.

In this study, we aimed to investigate adherence to tolvaptan medication in patients with ADPKD in a real-world setting using large claims data. Additionally, an exploratory analysis of factors associated with the discontinuation of tolvaptan treatment was conducted.

2. Materials and Methods

2.1. Data source

We conducted a retrospective cohort study using the Shizuoka Kokuho Database (SKDB), which includes administrative claims data from Shizuoka Prefecture, Japan.[22] There are three main types of public health insurance in Japan, covering almost the entire Japanese population: employees' health insurance (EHI), national health insurance (NHI), and late elders' health insurance (LEHI).[23] To explain it simply, those under 75 who are employed workers (e.g., company employees) and their dependents are enrolled in EHI and are insured by various insurers. Meanwhile, those under 75 who are not employed workers (e.g., self-employed or unemployed) are enrolled in NHI and are

insured by the prefectural and municipal government. Those over 75 are enrolled in LEHI and are insured by the prefecture. The SKDB contains data on NHI and LEHI but not EHI. Shizuoka Prefecture is located at the approximate center of Japan on the Pacific coast and reflects the standard climate, demographics, and economic situation in Japan. As of 2018, it had a population of approximately 3.7 million. The SKDB includes approximately 2.2 million people from the prefecture from April 2012 to September 2018. Insured people account for ~21%, ~73% and ~96% of the prefecture's population of those aged ≤64 years, 65 to 74 years and ≥75 years, respectively.[24] Furthermore, the SKDB contains data on voluntary health checkups, which are performed annually for those aged >40 years, and it includes questionnaire responses and results from laboratory examinations. The proportions of NHI- and LEHI-insured individuals who underwent health checkups in 2018 were 38.7 and 26.6%, respectively.[25,26]

2.2. Study design & patients

The study design is shown in Figure 1. The inclusion criteria were as follows: a new prescription of tolvaptan up to September 2018 (the data collection deadline) and a diagnosis of ADPKD. The International Classification of Diseases 10th revision diagnostic codes and Japanese diagnostic codes were used to identify ADPKD. The exclusion criteria were as follows: those whose look-back period was <6 months from the index month; those with an index month prior to March 2014 when tolvaptan was approved for ADPKD; and those whose dosage of tolvaptan was 15 mg/day or less for the purpose of excluding indications other than ADPKD, namely, heart failure and cirrhosis. Furthermore, we identified patients who had health checkups within 2 years before the index month.

2.3. Outcome

The primary outcome was the persistence of tolvaptan. We estimated the persistence rate at 12, 24, and 36 months after the start of tolvaptan medication. Additionally, we assessed the incidence of dialysis induction and death. In this study, treatment discontinuation of tolvaptan was defined as no tolvaptan prescription for more than 3 months and 84 or fewer prescription days in the last prescription month. Withdrawal from insurance was defined as censoring.

2.4. Definitions of variables

We examined the following patient factors: age, sex, number of medications used, comorbidities (hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, liver cyst, cerebral aneurysm), and chronic kidney disease (CKD) stage. The diagnoses and prescriptions were according to International Classification of Diseases 10th revision diagnostic codes and anatomical therapeutic chemical classification codes[27] (see Table, Supplemental Content, http://links.lww.com/MD/H450). Age was divided into
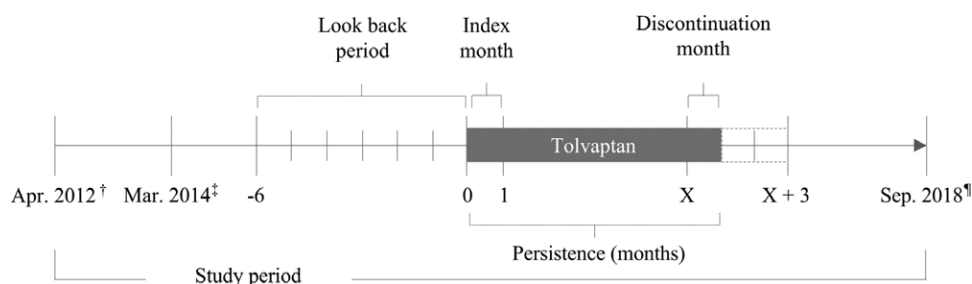

Figure 1. Schematic diagram of the study design. † Beginning of data collection ‡ Tolvaptan was approved for autosomal dominant polycystic kidney disease ¶ Data collection deadline.
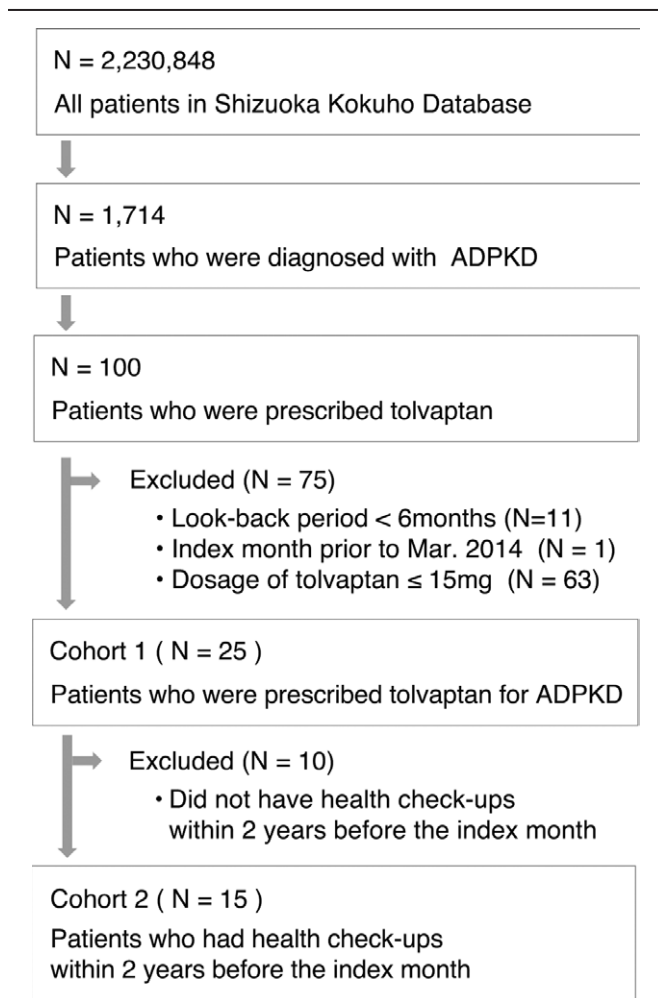
Figure 2. Study cohort selection diagram. ADPKD = autosomal dominant polycystic kidney disease.

Patient characteristics in cohort 1 and cohort 2.

	Cohort 1 (N = 25)		Cohort 2 (N = 15)	
Age, yr				
Median, IQR	66	51–69	67	51–72
Age group, n (%)				
≤64	12	48 (%)	6	40 (%)
≥65	13	52 (%)	8	60 (%)
Sex, n (%)				
Female	13	52 (%)	6	40 (%)
Male	12	48 (%)	8	60 (%)
Number of medications used, n (%)				
1–4	3	12 (%)	2	13 (%)
≥5	22	88 (%)	13	87 (%)
Comorbidity, n (%)				
Hypertension	24	96 (%)	15	100 (%)
Diabetes	0	0 (%)	0	0 (%)
Dyslipidemia	9	36 (%)	5	33 (%)
Hyperuricemia	9	36 (%)	4	27 (%)
Liver cyst	7	28 (%)	5	33 (%)
Cerebral aneurysm	6	24 (%)	4	27 (%)
BMI, kg/m²				
mean (SD)	-	-	22	(1.9)
CKD stage, n (%)				
G1	-	-	0	0 (%)
G2	-	-	2	13 (%)
G3a	-	-	3	20 (%)
G3b	-	-	3	20 (%)
G4	-	-	7	46 (%)
G5	-	-	0	0 (%)
Urine protein, n (%)				
(−)	-	-	10	67 (%)
(±)	-	-	4	27 (%)
(+)	-	-	1	7 (%)

BMI = body mass index, CKD = chronic kidney disease, IQR = interquartile range, SD = standard deviation
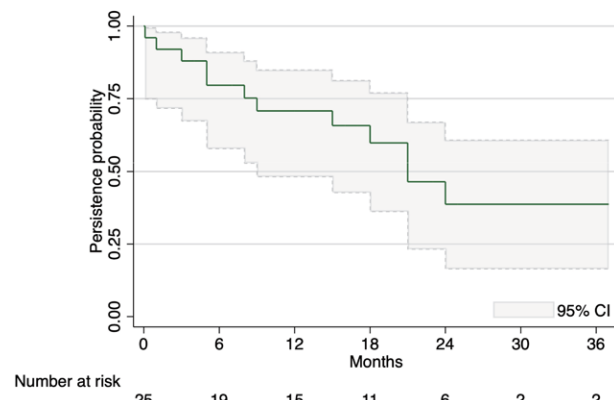
Figure 3. Kaplan–Meier curve and 95% confidence interval in cohort 1.

two categories according to the classification given by the Japan Gerontological Society and the Japan Geriatrics Society.[28] The number of medications used was divided into two categories according to a previous study.[29]

2.5. Statistical analyses

The Kaplan–Meier method was used to estimate the persistence rate of tolvaptan. We exploratively analyzed the association between each patient background factor and treatment discontinuation using the log-rank test. All P values were 2-sided, and $P < .05$ was considered statistically significant. All statistical analyses were conducted using Stata 16.1 (STATA Corp. LP).

2.6. Ethics

The ethics committee of Shizuoka General Hospital approved the study protocol (approval number SGHIRB#2020070). Because of the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the institutional review board of Shizuoka General Hospital.

3. Results

3.1. Study population

The process of subject selection according to the eligibility criteria is shown in Figure 2. There were 1714 patients who were diagnosed with ADPKD. Among them, 25 patients were prescribed

tolvaptan, and we defined them as cohort 1, the study population for the analysis. From cohort 1, 15 patients had undergone medical checkups that contained laboratory data such as kidney function, and we defined them as cohort 2. The patient characteristics of cohort 1 and cohort 2 are shown in Table 1. In cohort 1, the median age was 66 years (interquartile range: 51–69), 13 (52%) patients were female, 22 (88%) patients had five or more medications, 24 (96%) patients had a history of hypertension, and no patient had a history of diabetes mellites. In cohort 2, the mean (standard deviation [SD]) body mass index was 22 (1.9) kg/m², and 10 (67%) patients had a CKD stage worse than G3b.

No patient censoring, including death, was observed during the follow-up period. There were no cases of dialysis induction during the study period, including after discontinuation of tolvaptan medication.
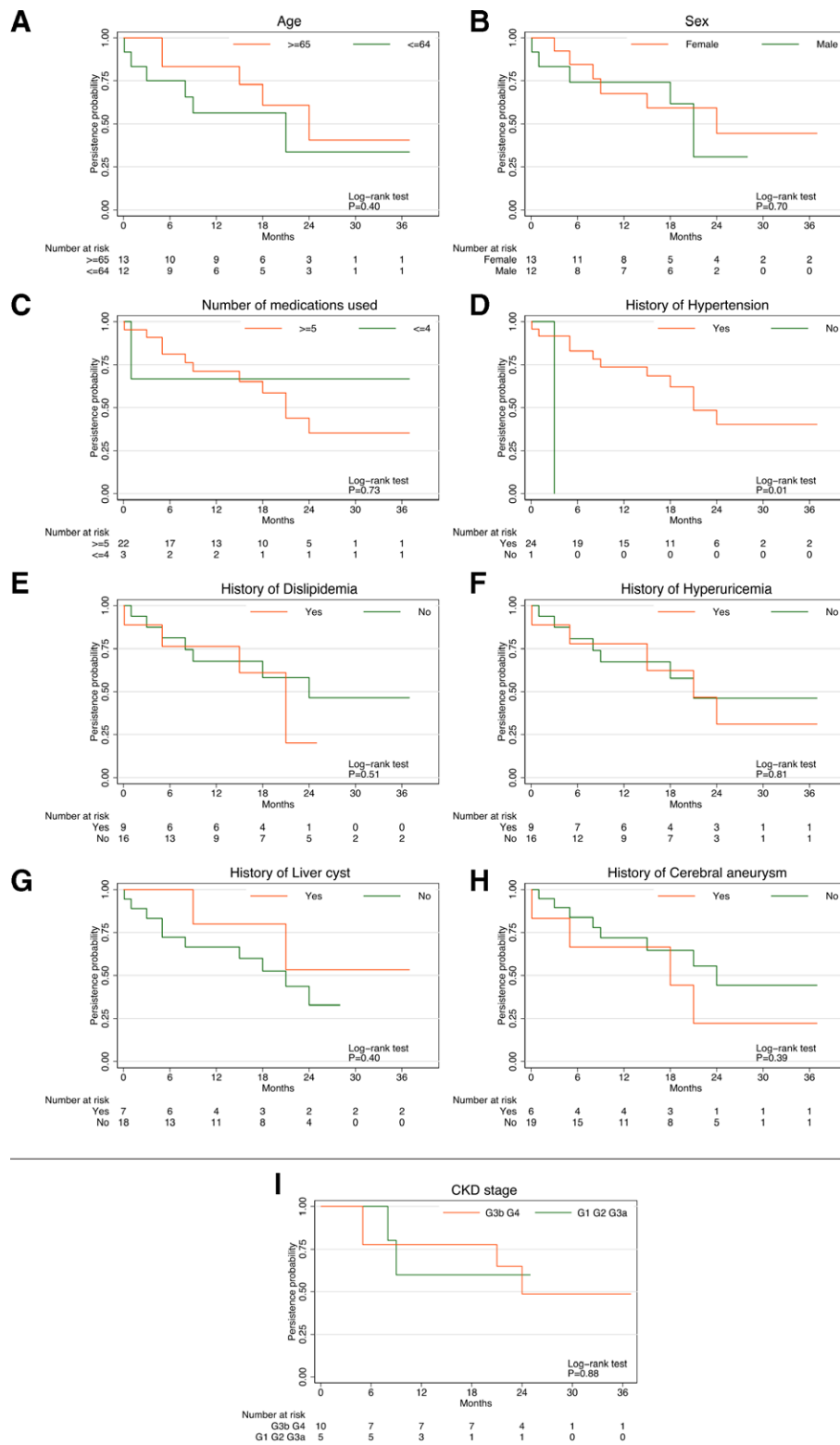
Figure 4. Kaplan–Meier curve stratified by the following patient background factors: (A) age, (B) sex, (C) number of medications used, with or without (D) hypertension, (E) dyslipidemia, (F) hyperuricemia, (G) liver cyst, (H) cerebral aneurysm in cohort 1, and (I) CKD stage in cohort 2. CKD = chronic kidney disease.

3.2. Long-term persistence

The Kaplan–Meier curve and 95% confidence interval (CI) of cohort 1 are shown in Figure 3. The median treatment duration was 21 months. After starting the prescription of tolvaptan, the estimated persistence rates at 12 months, 24 months, and 36 months were 70.8% (95% CI; 48.2–93.4), 46.5% (95% CI; 23.2–66.9), and 38.7% (95% CI: 16.4–60.8), respectively. Treatment discontinuation events were consistently observed throughout the study period in the study cohort.

3.3. Exploratory analysis of factors associated with discontinuation

The Kaplan–Meier curve stratified by patient background factors, such as age, sex, number of medications used, comorbidities and kidney function, is shown in Figure 4(A–I). In this exploratory analysis, we could not find potential factors that were obviously associated with the discontinuation of tolvaptan, except for a history of hypertension. Although patients with a history of hypertension had a significantly higher rate of persistence than those without a history, only one patient did not have hypertension, and the person discontinued tolvaptan during the first three months of medication.

4. Discussion and conclusions

In this study, we investigated adherence to tolvaptan in patients with ADPKD in a real-world setting. The persistence rates were approximately 10% to 40% lower than those in previous RCTs. In the exploratory analysis, we could not find potential factors that were obviously associated with the discontinuation of tolvaptan. To the best of our knowledge, this is the first study worldwide to follow up with each patient over a long period using a large claims dataset.

In the present study, we identified 1714 ADPKD patients from 2.2 million individuals, with a prevalence of approximately 1 in 1300. Our results showed a high prevalence compared with that reported by Higashihara (1998)[1] at approximately 1 in 4000. One reason could be that our database includes information on NHI and LEHI but not EHI, which may have biased the population. Alternatively, the prevalence of ADPKD may have been higher due to changes in diagnostic criteria and advances in diagnostic techniques.[5] Although reported from a single facility, Yoshimoto (2019)[30] reported a prevalence of approximately 1 in 730 to 1471. We also identified 25 patients on tolvaptan medication in cohort 1. Per PMS,[31] the number of cases in Japan as of September 2018 was approximately 4000, and assuming an even distribution, the estimated number of cases in the SKDB was approximately 30, which is a reasonable number compared to the results of this study.

The patient characteristics in this study tended to be different from those previously reported. For example, the median age of cohort 1 was 66 years (interquartile range: 51–69), which was higher than the mean (SD) age of 39 (7) years in the TEMPO3:4 trial, 47.3 (8.2) years in the REPRISE trial, and 49.7 (11.2) years in the PMS interim report SLOW-PKD study.[32] In addition, more than half of the subjects evaluated for renal function in cohort 2 had a CKD stage below G3b. Compared to the TEMPO3:4 trial, in which the mean (SD) eGFR of the subjects was 81.35 (21.02) mL/minutes/1.73 m², there was a trend toward more patients with reduced renal function. In the TEMPO3:4 trial, 23% of patients discontinued treatment at 3 years; in the REPRISE trial, 15.4% discontinued at 1 year after the completion of tolvaptan induction; and in the SLOW-PKD study, 34.7% discontinued at a median treatment duration of 731 days. Given these findings, the persistence rate in our study was approximately 10% to 40% lower. In our exploratory analysis, we were not able to identify factors that were obviously associated with the discontinuation of treatment, suggesting that several factors in a real-world setting may have combined to influence treatment discontinuation.

We analyzed adherence by an innovative method, particularly in Japan, using a large claims dataset, so there is a measure of success in this clinical pharmacoepidemiological research in the field of rare diseases. Collecting clinical data for rare diseases through RCTs is more costly than collecting clinical data for common diseases because of the limited number of patients.[11] In addition, although PMS plays an important role in supplementing the data, it often requires all-case surveillance and intensive human resources at medical facilities and pharmaceutical companies.[12,13] On the other hand, claims data can be routinely collected and utilized and are less costly and easier to analyze than data from RCTs and PMS.[14,18–21] Another strength of this study is its ability to follow up with each patient over a long period. We were able to assess outcomes such as the discontinuation and restarting of tolvaptan medication as well as other outcomes such as the induction of dialysis during the observation period and death, neither of which occurred in our study. These studies allow early detection of signals such as adverse events caused by the drug, which can be used in the decision to conduct a more detailed survey.

Finally, this study has several limitations. First, although we used large-scale data from a prefecture, the sample size was insufficient, and the statistical power may have been limited. In the future, the use of more large-scale data, such as from the National Database of Health Insurance Claims and Specific Health Checkups of Japan,[33] may be needed. Another disadvantage of claims data is the limited availability of patient background and outcome data. Data concerning detailed renal function, renal volume, hematological findings, patient financial status, and lifestyle are also useful in assessing medication adherence, and linkage of claims data with other databases may be required in the future. Such information also predicts disease progression of ADPKD[34] and enhances the assessment of the long-term impact on adherence. Finally, further validation of disease name codes may be necessary.

Using large claims data, we were able to follow up with each patient with ADPKD over a long period and analyze adherence to tolvaptan in a real-world setting. Our results add new knowledge regarding ADPKD medication. This innovative method using routinely collected and utilized data should change pharmacoepidemiological research and health policy for rare diseases in the future.

Author contributions

RS, HY, HK, NI, SN, and HM contributed to the conceptualization and methodology; RS and HY conducted the formal analysis and visualization; RS, HY, and KS contributed to the data curation; HY, KM, YM, and HM managed the project administration; and R.S. and HY drafted the original manuscript. All authors contributed substantially to the interpretation of the results and the writing, review, and editing of the final draft.

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Validation: Ryuta Saito, Hiroyuki Yamamoto.

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