Received: 31 March 2022 | Revised: 27 May 2022 | Accepted: 1 June 2022

DOI: 10.1111/jch.14539

ORIGINAL ARTICLE

WILEY

The reality of treatment for hyperuricemia and gout in Japan: A historical cohort study using health insurance claims data

Seigo Akari MS[1] | Takashi Nakamura PhD[1] | Kenichi Furusawa PhD[1] | Yuichi Miyazaki MS[1] | Kazuomi Kario MDPhD[2]

[1]Medical Affairs Department, Sanwa Kagaku Kenkyusho Co., Ltd., Aichi, Japan

[2]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

Correspondence
Seigo Akari MS, Medical Affairs Department, Sanwa Kagaku Kenkyusho Co., Ltd., 35 Higashisotobori-cho, Higashi-ku, Nagoya Aichi 461–8631, Japan.
Email: s_akari@skk-net.com

Abstract

Hyperuricemia causes gout and has also been associated with metabolic syndrome and cardiovascular disease. Uric acid-lowering drugs (ULDs) are used to reduce uric acid levels for the treatment of hyperuricemia and gout. However, there is a lack of robust and real-world data on the history and treatment of patients with newly diagnosed hyperuricemia or gout in Japan. This retrospective, longitudinal, historical cohort study determined the characteristics of patients with hyperuricemia and/or gout, and prescription of, and adherence to, ULDs using data from the JMDC Claims Database. The primary evaluation population included 64 677 patients with newly diagnosed hyperuricemia and/or gout. Of these, only 26 501 (41.0%) had a prescription for ULDs at diagnosis. Even when ULDs were prescribed, the persistence rate of prescriptions declined over time, with a 54.4% persistence rate for ULDs at 12 months after the index diagnosis. In subgroups of patients with or without hypertension and diabetes, the rate of ULD prescription continuation was significantly higher in those with comorbidities than in those without (76.8% vs. 42.6% in those with vs. without hypertension, and 78.7% vs. 52.2% in those with vs. without diabetes). These finding suggest that therapeutic interventions to lower serum uric acid levels are under-utilized for patients with newly diagnosed hyperuricemia and/or gout in Japan.

KEYWORDS
database, gout, historical cohort, hyperuricemia, uric acid

1 | INTRODUCTION

The number of patients with gout and hyperuricemia is increasing worldwide[1,2] and in Japan.[3] Hyperuricemia has been reported to be associated not only with gout[4,5] but also with metabolic syndrome and cardiovascular diseases, including hypertension, dyslipidemia, diabetes, obesity, and chronic kidney disease (CKD).[6–13]

Uric acid-lowering drugs (ULDs) are used to treat hyperuricemia and gout, and consist of two main types of medication: uric acid production inhibitors and uricosuric agents. Several recently published database studies conducted in Japan have reported on the reality of medical treatment for hyperuricemia and gout.[14–16] Koto and coworkers reported that severe renal dysfunction was the most important risk factor for failure to achieve target serum uric acid levels, that gout and asymptomatic hyperuricemia are often treated with low-dose ULDs, and that gout management in Japan may be suboptimal because many patients fail to achieve the target serum uric acid level.[15,16]

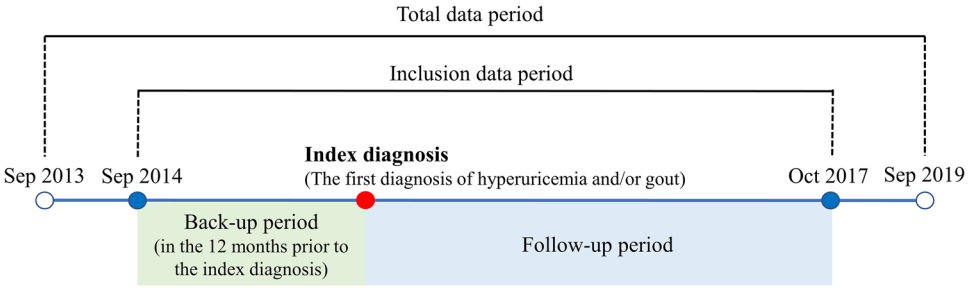


FIGURE 1 Overview of study design

Higa and coworkers reported that the accurate prevalence of hyperuricemia in the Japanese population was 26.8% in male patients and 0.9% in female patients, arguing that it is also important to increase awareness of hyperuricemia in society and reduce the burden of hyperuricemia-related diseases.[14] However, because these studies were cross-sectional, the actual history and treatment of patients with newly diagnosed hyperuricemia or gout remain unclear. Therefore, this study was designed to examine specific characteristics and the reality of treatment in individuals with a first diagnosis of hyperuricemia or gout using the JMDC Claims Database,[17] a Japanese health insurance claims database.

2 | METHODS

2.1 | Study design

This retrospective, longitudinal, historical cohort study (UMIN000045426) was based on the JMDC Claims Database. An overview of study design is provided in Figure 1. All data were anonymized, de-identified, and compliant with the International Conference on Harmonization guidelines regarding the protection of human patients in observational studies.[18] The study received ethical approval from the Ethics Committee of Research Institute of Healthcare Data Science: approval No. RI2020007.

2.2 | Data source and patient selection

The JMDC Claims Database uses standardized disease classifications and anonymous record linkage.[17] It provides information on the beneficiaries (including encrypted personal identifiers, age, sex, International Classification of Diseases 10th revision [ICD-10] diagnostic and procedural codes), and the name, dose, and the number of days supplied for prescribed and/or dispensed drugs. The database also includes clinical and laboratory data from annual health check-ups.

The database for this study ("total data period") was constructed based on monthly claims from medical institutions and pharmacies submitted from September 2013 to September 2019, which included approximately 6.67 million insured persons (aged 0–75 years), and consisted mainly of company employees and their family members. The inclusion period ("inclusion data period") was set from September 2014 to October 2017. The final study population included health insurance subscribers who were in the JMDC Claims Database over that period and met the following inclusion criteria:

1. Database registrations within the total data period.
2. Subscribers of the health insurance association registered in the database at the end of the total data period.
3. The first (oldest) diagnosis of hyperuricemia or gout ("index diagnosis") was within the inclusion data period.
4. Twelve months of observations were available retrospectively from the time of the index diagnosis.
5. No record of ULD prescription prior to the index diagnosis.
6. Age ≥20 years at the index diagnosis.

2.3 | Definitions

An index diagnosis of hyperuricemia was identified using the ICD-10 code E790, and an index diagnosis of gout was identified using the ICD-10 code M10 (see Table S2 for ICD-10 code definitions). ATC code definitions for ULDs are shown in Table S1. Comorbidities were defined as the presence diagnoses at the time of the index diagnosis (see Table S2 for ICD-10 code definitions). Hypertension, dyslipidemia, and diabetes mellitus were defined as diagnoses accompanied by a prescription for the respective treatment in an outpatient setting at the time of the index diagnosis (ATC codes used to define prescription history are shown in Table S3), as defined previously.[14,19] This avoids issues with ICD-10 codes in the claim databased not accurately reflecting clinical manifestations.

2.4 | Endpoints

This study was analyzed data to determine the following parameters for newly diagnosed patients with hyperuricemia or gout: baseline characteristics; actual treatment received; rate of continuation with ULD treatment.

Laboratory data were collected from the latest annual medical check-up performed prior to the index diagnosis. The expected duration of ULD treatment continuation was defined as the period from the

date of ULD prescription to the date of prescription plus the number of days of prescription minus one day. The actual duration of treatment continuation was defined as a condition in which the next prescription of a ULD was received no later than 90 days after the end of the expected duration of medication because prescriptions for chronic conditions in Japan are often issued to provide drug supply for 60–90 days of treatment. Lack of treatment continuation was defined as the period of treatment that continued until the last scheduled date of medication during the continuation of treatment. The same definitions were also applied to other treatments.

2.5 | Statistical analyses

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean ± standard deviation. The rate of treatment continuation was estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). In all analyses, a two-sided p-value of < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Study participants

The JMDC Claims Database population included 6 671 294 individuals enrolled between September 2013 and September 2019. Of these, 152 974 patients had a first diagnosis of hyperuricemia or gout within the inclusion data period (September 2014 to October 2017), and 67 104 patients were retrospectively observed for 12 months from this first diagnosis. There were 65 830 patients who had no previous prescription record for ULDs prior to the index diagnosis, of whom 1153 were aged < 20 years and were therefore excluded (Figure 2). Therefore, the primary evaluation population included 64 677 patients with an index diagnosis of hyperuricemia alone ($n = 46\,280$), gout only ($n = 14\,519$), or hyperuricemia and gout ($n = 3878$) (Figure 2).

Most of the patients were male (89%) and aged between 40 and 64 years (70%) (Table 1). Liver disease, hypertension and dyslipidemia were common comorbidities (Table 1). More than half of all patients (59%) had no prescription for ULDs at the index diagnosis or in following month, while the remaining patients (41%) were prescribed ULDs over this period (Table 1). The prescription rate of ULDs was 38% in patients with hyperuricemia only, 42% in those with gout only, and 70% in patients with both hyperuricemia and gout (Table 1). Uric acid production inhibitors (xanthine oxidereductase [XOR] inhibitors) accounted for the majority of ULD prescriptions (39%), and febuxostat was the most commonly used XOR inhibitor (Table 1). With respect to the prescription rate of concomitant medications, 23.9% of patients were using antihypertensives, 17.4% were taking lipid-lowering drugs, and 5.9% were using antidiabetic agents (Table 1).

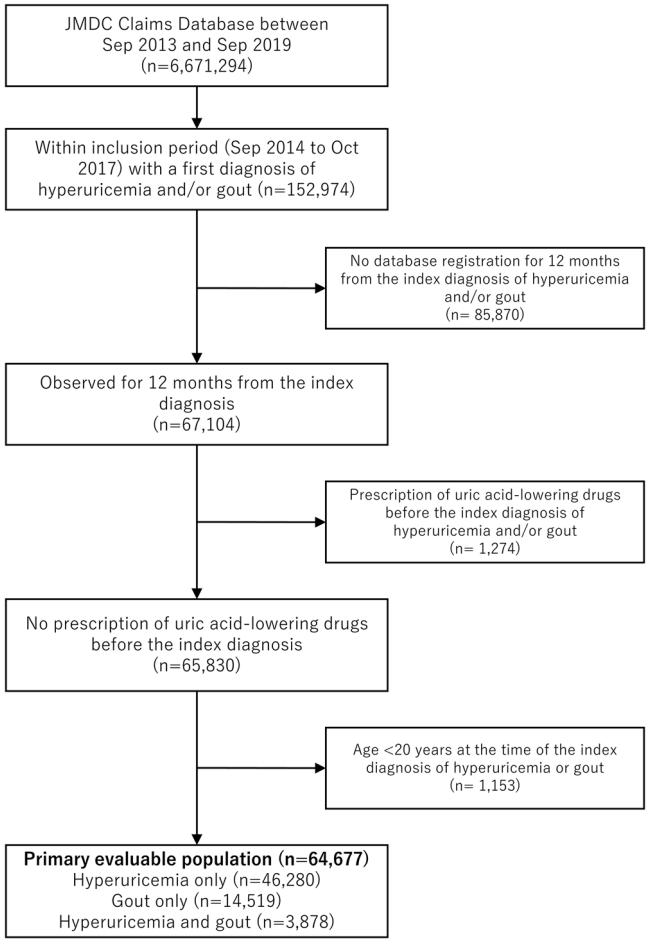


FIGURE 2 Flow chart of patient selection

Based medical check-up data from the 20 892 patients for whom serum uric acid could be measured, the mean serum uric acid level was 7.69±1.39 mg/dl, and 77% of patients had a serum uric acid level of ≥7.0 mg/dl. For the 46 482 patients with available body mass index (BMI) data, mean BMI was 25.2 kg/m^2, with 52% of patients having a BMI ≥25 kg/m^2.

3.2 | Treatment continuation duration

Use of ULDs declined over time from the index diagnosis (Figure 3). The treatment continuation rate for ULDs in patients with newly diagnosed hyperuricemia and/or gout was 54.4% at 12 months after the index diagnosis (Figure 3A). This rate was significantly lower than the continuation rate for antihypertensive drugs in patients with hypertension (66.7%) or antidiabetic agents in those with diabetes (74.9%) (Figure S1). The ULD continuation rate was significantly higher in patients with hyperuricemia only compared with gout only or hyperuricemia + gout (Figure 3B). In addition, the ULD continuation rate was significantly higher in patients with versus without hypertension (76.8% vs. 42.6%; Figure 3C) or diabetes (78.7% vs. 52.2%; Figure 3D). Females versus males, older versus younger individuals, those with a

TABLE 1 Clinical and demographic characteristics of the study population at baseline, overall and in patient subgroups based on diagnosis

Parameter	Overall ($n = 64\,677$)	Hyperuricemia ($n = 46\,280$)	Gout ($n = 14\,519$)	Hyperuricemia and gout ($n = 3878$)
Age, years	47.1±11.3	47.0±11.4	47.5±11.0	47.4±10.3
Age group, *n* (%)				
20–39 years	16 170 (25.0)	11 894 (25.7)	3436 (23.7)	840 (21.7)
40–64 years	45 081 (69.7)	31 900 (68.9)	10 305 (71.0)	2876 (74.2)
≥65 years	3426 (5.3)	2486 (5.4)	778 (5.4)	162 (4.2)
Sex, *n* (%)				
Male	57 758 (89.3)	40 875 (88.3)	13 148 (90.6)	3735 (96.3)
Female	6919 (10.7)	5405 (11.7)	1371 (9.4)	143 (3.7)
Follow-up duration, months	36.5±13.8	36.5±13.9	36.6±13.6	36.8±13.3
Comorbidities, *n* (%)				
Hypertension[a]	16 643 (25.7)	13 378 (28.9)	2636 (18.2)	629 (16.2)
Dyslipidemia[b]	12 525 (19.4)	10 331 (22.3)	1755 (12.1)	439 (11.3)
Diabetes mellitus[c]	4051 (6.3)	3373 (7.3)	589 (4.1)	89 (2.3)
Angina	2905 (4.5)	2340 (5.1)	466 (3.2)	99 (2.6)
Acute myocardial infarction	419 (0.6)	346 (0.7)	62 (0.4)	11 (0.3)
Intracerebral hemorrhage	174 (0.3)	144 (0.3)	22 (0.2)	8 (0.2)
Cerebral infarction	1061 (1.6)	839 (1.8)	168 (1.2)	54 (1.4)
Heart failure	3395 (5.2)	2792 (6.0)	506 (3.5)	97 (2.5)
Atrial fibrillation and flutter	1196 (1.8)	953 (2.1)	199 (1.4)	44 (1.1)
Malignant tumor	2266 (3.5)	1819 (3.9)	369 (2.5)	78 (2.0)
Renal disease	6377 (9.9)	5425 (11.7)	760 (5.2)	192 (5.0)
Liver disease	17 388 (26.9)	14 517 (31.4)	2252 (15.5)	619 (16.0)
Uric acid-lowering medications, *n* (%)				
None	38 176 (59.0)	28 554 (61.7)	8443 (58.2)	1179 (30.4)
Uric acid production inhibitors				
XOR inhibitors	24 908 (38.5)	16 904 (36.5)	5485 (37.8)	2519 (65.0)
Allopurinol	6776 (10.5)	4484 (9.7)	1548 (10.7)	744 (19.2)
Febuxostat	16 585 (25.6)	11 337 (24.5)	3656 (25.2)	1592 (41.1)
Topiroxostat	1788 (2.8)	1202 (2.6)	356 (2.5)	230 (5.9)
Uricosuric drugs	1852 (2.9)	919 (2.0)	696 (4.8)	237 (6.1)
Benzbromarone	1693 (2.6)	873 (1.9)	614 (4.2)	206 (5.3)
Probenecid	113 (0.2)	25 (0.1)	66 (0.5)	22 (0.6)
Bucolome	48 (0.1)	21 (0.0)	18 (0.1)	9 (0.2)
Concomitant medications, *n* (%)				
Antihypertensive drugs	15 455 (23.9)	12 812 (27.7)	2122 (14.6)	521 (13.4)
ACE inhibitors	822 (1.3)	689 (1.5)	109 (0.8)	24 (0.6)
ARBs	10 233 (15.8)	8547 (18.5)	1347 (9.3)	339 (8.7)
Calcium channel blockers	10 084 (15.6)	8272 (17.9)	1457 (10.0)	355 (9.2)
Diuretic drugs	3044 (4.7)	2633 (5.7)	335 (2.3)	76 (2.0)
Antihyperlipidemic drugs	11 247 (17.4)	9473 (20.5)	1409 (9.7)	365 (9.4)
Statins	8448 (13.1)	7106 (15.4)	1082 (7.5)	260 (6.7)

(Continues)

TABLE 1 (Continued)

Parameter	Overall ($n = 64\,677$)	Hyperuricemia ($n = 46\,280$)	Gout ($n = 14\,519$)	Hyperuricemia and gout ($n = 3878$)
Fibrates	1969 (3.0)	1667 (3.6)	234 (1.6)	68 (1.8)
Antidiabetic drugs	3784 (5.9)	3212 (6.9)	496 (3.4)	76 (2.0)

Values are mean ± standard deviation or number of patients (%).
Abbreviations: ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; XOR, xanthine oxidereductase.
[a]Hypertension was defined as diagnoses accompanied by prescription containing angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, β-blockers, or other antihypertensive drugs (see Table S3 for details) for treatment in an outpatient setting at the time of the index diagnosis.
[b]Dyslipidemia was defined as diagnoses accompanied by prescription containing statins, fibrates or other cholesterol- and triglyceride- regulating drugs (see Table S3 for details) for treatment in an outpatient setting at the time of the index diagnosis.
[c]Diabetes mellitus was defined as diagnoses accompanied by prescription containing antidiabetic drugs (see Table S3 for details) in an outpatient setting at the time of the index diagnosis.

BMI ≥25 versus < 25 kg/m^2, or patients with versus without renal disease had significantly higher rates of ULD continuation (Figure S2).

4 | DISCUSSION

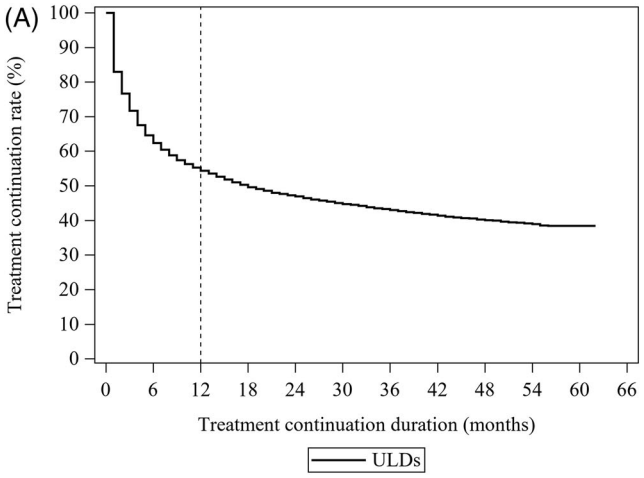
There were two new findings in this study. Firstly, nearly half of patients with newly diagnosed hyperuricemia and/or gout did not receive a specific treatment to lower serum uric acid levels. Secondly, persistence with ULD therapy in these patients was worse than that for antihypertensive drugs in hypertension or antidiabetic drugs in diabetes mellitus, and the presence of both these comorbidities was associated with better persistence with ULD treatment.

The population of this study represented approximately 1% of the entire JMDC Claims Database, and the most common diagnosis was hyperuricemia. This result may that there are more patients with asymptomatic hyperuricemia than with gout in Japan. The Japanese guidelines do recommend pharmacological treatment for asymptomatic hyperuricemia in patients with serum uric acid levels of ≥8.0 mg/dl and complications such as kidney disease, urolithiasis, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome, etc., or serum uric acid levels of ≥9.0 mg/dl.[20] However, it remains to be determined whether ULD therapy can reduce event rates in patients with hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome etc.[20] In contrast, the situation is different in the US[21] and European Union.[22] Based on the available data, the mean serum uric acid level in our study population was 7.69 mg/dl, reflecting the serum uric acid level at the time of the index diagnosis without therapeutic intervention. More than half of all patients (51.9%) with available data had a BMI of 25 kg/m^2 or higher, suggesting that hyperuricemia or gout may be closely related to obesity. This is consistent with the findings of previous epidemiological reports[8,14] showing that the incidence of hyperuricemia increases with the presence of obesity and with increasing BMI.

Our study population had a lower rate of comorbidities, including hypertension, dyslipidemia and diabetes mellitus, compared with previous studies.[15] This may be due to the differences of the definition in preexisting disease and the fact that patients in the current study had a new diagnosis of hyperuricemia and/or gout.

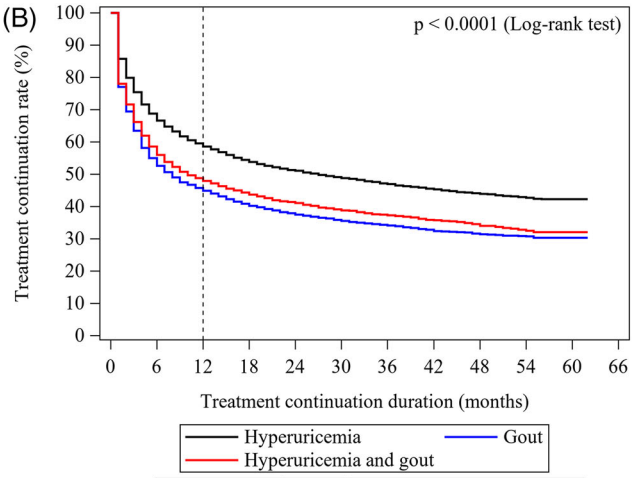
In patients with newly diagnosed hyperuricemia or gout, prescription of ULDs at the time of index diagnosis was relatively low, at 41%. In many cases, follow-up with lifestyle guidance was performed, and the rate of therapeutic intervention was limited. Poor adherence to ULDs has been reported previously,[23,24] which is consistent with the results of this study. It has also been reported that, in United States, approximately 70% of prescription interruptions occur in patients newly started on ULDs.[25] This may be due to insufficient understanding of the necessity to continue taking ULDs even in the absence of gouty arthritis, and lack of awareness of the need to prevent gouty arthritis.[26] Thus, it may be that disease risk is widely recognized in hypertension and diabetes but not sufficiently recognized in hyperuricemia. In Japan, another study using the JMDC database has shown that controlling serum uric acid levels below 6.0 mg/dl, which is the target level for managing both hyperuricemia and gout, can suppress the occurrence of gout.[27] Epidemiological data showed that the risk of death in patients with hyperuricemia and gout was significantly reduced after more than 2 years of treatment with ULDs compared with an untreated group.[28] However, it is still controversial as to whether ULDs should be used to treat asymptomatic patients with high serum uric acid levels.[29–31]

Our finding that the presence of hypertension or diabetes markedly increased the rate of persistence with ULD treatment is consistent with previous data showing that adherence to treatment in patients with gout increases in proportion to the number of complications experienced.[24] Epidemiologically, levels of uric acid and XOR have been reported to be independent risks factor for hypertension.[6,32-36] The presence of elevated serum uric acid levels has also been reported to be associated with the risk of cardiovascular events in patients with hypertension, even when blood pressure is well controlled.[37] In addition, treatment with the XOR inhibitor topiroxostat in hypertensive patients with hyperuricemia has been shown to improve the urine albumin-to-creatinine ratio (UACR) and blood pressure.[38] Furthermore, several meta-analyses have demonstrated that administration of allopurinol reduces blood pressure.[39,40] Moreover, in



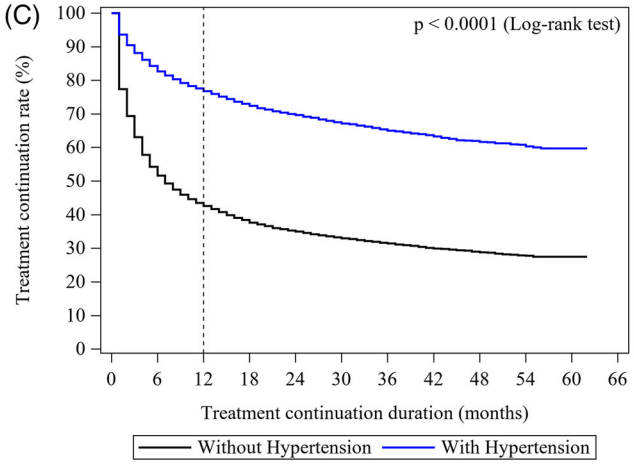
n	Estimates		
	Median	95%CI Lower	95%CI Upper
26,501	18.0	17.0	19.0

At 12-month			
at risk	Treatment continuation rate (%)		
	rate	95%CI Lower	95%CI Upper
13,555	54.4	53.8	55.0



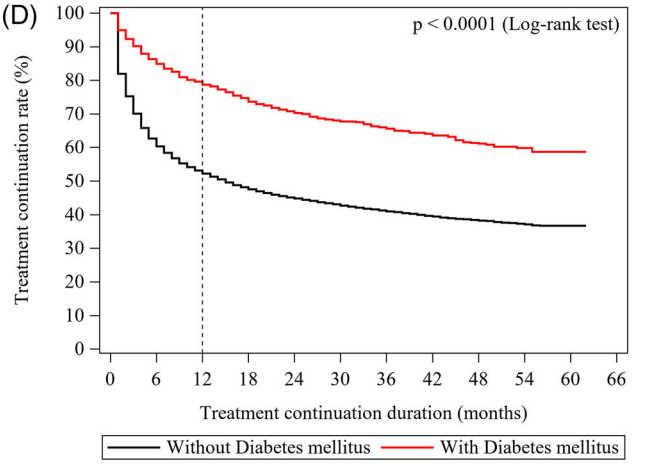
Index diagnosis	n	Estimates		
		Median	95%CI Lower	95%CI Upper
Hyperuricemia	17,726	27.0	25.0	29.0
Gout	6,076	8.0	7.0	9.0
Hyperuricemia and gout	2,699	10.0	9.0	12.0

Index diagnosis	At 12-month			
	at risk	Treatment continuation rate (%)		
		rate	95%CI Lower	95%CI Upper
Hyperuricemia	9,729	58.6	57.9	59.3
Gout	2,583	44.9	43.6	46.2
Hyperuricemia and gout	1,243	48	46	49.9



	n	Estimates		
		Median	95%CI Lower	95%CI Upper
Without Hypertension	17,327	7.0	7.0	8.0
With Hypertension	9,174	-	-	-

	At 12-month			
	at risk	Treatment continuation rate (%)		
		rate	95%CI Lower	95%CI Upper
Without Hypertension	7,039	42.6	41.8	43.3
With Hypertension	6,516	76.8	75.9	77.7



	n	Estimates		
		Median	95%CI Lower	95%CI Upper
Without Diabetes mellitus	24,329	15.0	14.0	16.0
With Diabetes mellitus	2,172	-	-	-

	At 12-month			
	at risk	Treatment continuation rate (%)		
		rate	95%CI Lower	95%CI Upper
Without Diabetes mellitus	12,013	52.2	51.6	52.9
With Diabetes mellitus	1,542	78.7	76.9	80.4

FIGURE 3 Continuation of treatment with uric acid-lowering drugs (ULDs) for the overall study population (**A**), by treatment indication (**B**), and in patients with versus without hypertension (**C**) or diabetes mellitus (**D**). CI, confidence interval

the Framingham Heart Study, individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes, independent of other known risk factors.[41] Urinary uric acid clearance also appears to decrease in proportion to increases in insulin resistance in normal volunteers, leading to an increase in serum uric acid concentration.[42] Thus, it appears that modulation of serum uric acid concentration by insulin resistance is exerted at the level of the kidney.[42,43] A Japanese study in patients with hyperuricemia and diabetic nephropathy reported significant reductions in serum uric acid level and glycosylated hemoglobin in those treated with high-dose topiroxostat.[44] Therefore, it may be beneficial to consider concomitant use of ULDs and antihypertensives or antidiabetics to improve therapeutic effects and adherence to uric acid-lowering therapy in patients with hyperuricemia and hypertension or diabetes.

This study has several limitations. First, the JMDC Claims Database only includes individuals insured by health insurance associations,

meaning that the population may not reflect a broad range of socioeconomic backgrounds. However, from a clinical point of view, this database includes all claims for members of all the health insurance societies for which the JMDC collects data, and enables patient-based tracking of visits and treatment flows even if the patient was transferred to another hospital during treatment or was completely cured, unlike databases sourced from medical institutions.[45] Nevertheless, it does only cover a small subset of the Japanese population. In addition, the results of this study may not be generalizable to some sectors of the population, including the elderly aged ≥ 65 years, because the surveyed population does not include many patients in this age group, and information on those aged ≥ 75 years is completely lacking. Second, prescription history does not provide any information about whether a patient prescribed the medication actually took it. Third, we do not have any information on laboratory test results other than the annual check-up, and serum uric acid levels were determined based on information from one of these annual medical check-ups. Therefore, we were not able to follow the effects of treatment, including changes in serum uric acid levels, after the prescription of ULDs. However, this does not necessarily mean that clinicians who prescribed ULDs were not subsequently monitoring changes in serum uric acid during therapy. In addition, there is a possibility of bias because data on test results from specific medical check-ups can only be obtained from people who have undergone these tests. Finally, due to the lack of data, we were unable to assess the reasons for treatment discontinuation, which need to be clarified in future studies. This information could be useful in developing strategies to improve patient adherence to ULD treatment.

5 | CONCLUSIONS

Therapeutic interventions to reduce serum uric acid levels in patients with newly diagnosed hyperuricemia or gout are underutilized, and the rate of continuation with ULD treatment was lower than that for antihypertensive drugs in patients with hypertension or antidiabetic drugs in those with diabetes.

ACKNOWLEDGMENTS

The authors would like to thank JMDC Inc. independent data analysis. English language editing assistance was provided by Nicola Ryan, independent medical writer, funded by Sanwa Kagaku Kenkyusho, Co., Ltd.

DISCLOSURES

Seigo Akari, Takashi Nakamura, Kenichi Furusawa and Yuichi Miyazaki are full-time employees of Sanwa Kagaku Kenkyusho Co., Ltd. Kazuomi Kario has received research grants from Astellas Pharma Inc., Eisai Co., Otsuka Pharmaceutical Co., Sanwa Kagaku Kenkyusho Co., Daiichi Sankyo Co., Taisho Pharmaceutical Co., Sumitomo Dainippon Pharma Co., Takeda Pharmaceutical Co., Mitsubishi Tanabe Pharma Co., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb K.K. and Mochida Pharmaceutical Co., and honoraria from Novartis, Daiichi Sankyo Co. and Takeda Pharmaceutical Co., Bristol-Myers K.K., Mylan EPD and participation on an Advisory Board of Novartis.

AUTHOR CONTRIBUTIONS

Study conception and design: Seigo Akari, Takashi Nakamura and Kazuomi Kario. Data preparation: Seigo Akari. Data analysis and interpretation: Seigo Akari, Takashi Nakamura and Kazuomi Kario. Drafting and revising of the manuscript: all authors. Final approval of the submitted manuscript: all authors.

ORCID

Seigo Akari MS https://orcid.org/0000-0001-6641-1062
Takashi Nakamura PhD https://orcid.org/0000-0003-2324-3569
Kazuomi Kario MDPhD https://orcid.org/0000-0002-8251-4480

REFERENCES

1. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol*. 2015; 11: 649-662.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum*. 2011; 63: 3136-3141.
3. Hakoda M, Kasagi F. Increasing trend of asymptomatic hyperuricemia under treatment with urate-lowering drugs in Japan. *Mod Rheumatol*. 2019; 29: 880-884.
4. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med*. 1987; 82: 421-426.
5. Dalbeth N, Phipps-Green A, Frampton C, et al. Relationship between serum urate concentration and clinically evident incident gout: an individual participant data analysis. *Ann Rheum Dis*. 2018; 77: 1048-1052.
6. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2011; 63: 102-110.
7. Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. *Arterioscler Thromb Vasc Biol*. 2005; 25: 1038-1044.
8. Kuwabara M, Niwa K, Hisatome I, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year Japanese cohort study. *Hypertension*. 2017; 69: 1036-1044.
9. Lv Q, Meng XF, He FF, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. *PLoS One*. 2013; 8: e56864.
10. Mori K, Furuhashi M, Tanaka M, et al. U-shaped relationship between serum uric acid level and decline in renal function during a 10-year period in female subjects: BOREAS-CKD2. *Hypertens Res*. 2021; 44: 107-116.
11. Verdecchia P, Schillaci G, Reboldi G, et al. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. *Hypertension*. 2000; 36: 1072-1078.
12. Yuan H, Yu C, Li X, et al. Serum uric acid levels and risk of metabolic syndrome: a dose-response meta-analysis of prospective studies. *J Clin Endocrinol Metab*. 2015; 100: 4198-4207.
13. Zhu P, Liu Y, Han L, Xu G, Ran JM. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies. *PLoS One*. 2014; 9: e100801.
14. Higa S, Yoshida M, Shima D, et al. A retrospective, cross-sectional study on the prevalence of hyperuricemia using a Japanese healthcare database. *Arch Rheumatol*. 2020; 35: 41-51.

15. Koto R, Nakajima A, Horiuchi H, Yamanaka H. Real-world treatment of gout and asymptomatic hyperuricemia: a cross-sectional study of Japanese health insurance claims data. *Mod Rheumatol*. 2021; 31: 261-269.
16. Koto R, Nakajima A, Horiuchi H, Yamanaka H. Factors associated with achieving target serum uric acid level and occurrence of gouty arthritis: a retrospective observational study of Japanese health insurance claims data. *Pharmacoepidemiol Drug Saf*. 2021; 30: 157-168.
17. Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. *J Epidemiol*. 2010; 20: 413-419.
18. Dixon JR Jr. The International Conference on harmonization good clinical practice guideline. *Qual Assur*. 1998; 6: 65-74.
19. Hara K, Tomio J, Svensson T, et al. Association measures of claims-based algorithms for common chronic conditions were assessed using regularly collected data in Japan. *J Clin Epidemiol*. 2018; 99: 84-95.
20. Hisatome I, Ichida K, Mineo I, et al. Japanese society of gout and uric & nucleic acids 2019 guidelines for management of hyperuricemia and gout 3rd edition. *Gout and Uric & Nucleic Acids*. 2020; 44 (Supplement): 1-40.
21. Khanna D, Fitzgerald JD, Khanna PP, et al. American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012; 64: 1431-1446.
22. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017; 76: 29-42.
23. Roddy E, Zhang W, Doherty M. Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann Rheum Dis*. 2007; 66: 1311-1315.
24. Scheepers L, van Onna M, Stehouwer CDA, et al. Medication adherence among patients with gout: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018; 47: 689-702.
25. Harrold LR, Andrade SE, Briesacher B, et al. The dynamics of chronic gout treatment: medication gaps and return to therapy. *Am J Med*. 2010; 123: 54-59.
26. Chaichian Y, Chohan S, Becker MA. Long-term management of gout: nonpharmacologic and pharmacologic therapies. *Rheum Dis Clin North Am*. 2014; 40: 357-374.
27. Koto R, Nakajima A, Horiuchi H, Yamanaka H. Serum uric acid control for prevention of gout flare in patients with asymptomatic hyperuricaemia: a retrospective cohort study of health insurance claims and medical check-up data in Japan. *Ann Rheum Dis*. 2021; 80: 1483-1490.
28. Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. *J Rheumatol*. 2015; 42: 1694-1701.
29. Zhang L, An K, Mou X, et al. Effect of urate-lowering therapy on the progression of kidney function in patients with asymptomatic hyperuricemia: a systematic review and meta-analysis. *Front Pharmacol*. 2021; 12: 795082.
30. Chen Q, Wang Z, Zhou J, et al. Effect of urate-lowering therapy on cardiovascular and kidney outcomes: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2020; 15: 1576-1586.
31. Kimura K, Hosoya T, Uchida S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis*. 2018; 72: 798-810.
32. Lanaspa MA, Andres-Hernando A, Kuwabara M. Uric acid and hypertension. *Hypertens Res*. 2020; 43: 832-834.
33. Lee SW, Kim HC, Nam C, et al. Age-differential association between serum uric acid and incident hypertension. *Hypertens Res*. 2019; 42: 428-437.
34. Tatsumi Y, Asayama K, Morimoto A, et al. Hyperuricemia predicts the risk for developing hypertension independent of alcohol drinking status in men and women: the Saku study. *Hypertens Res*. 2020; 43: 442-449.
35. Qin T, Zhou X, Wang J, et al. Hyperuricemia and the prognosis of hypertensive patients: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*. 2016; 18: 1268-1278.
36. Kario K, Nishizawa M, Kiuchi M, et al. Comparative effects of topiroxostat and febuxostat on arterial properties in hypertensive patients with hyperuricemia. *J Clin Hypertens (Greenwich)*. 2021; 23: 334-344.
37. Furuhashi M, Higashiura Y, Koyama M, et al. Independent association of plasma xanthine oxidoreductase activity with hypertension in nondiabetic subjects not using medication. *Hypertens Res*. 2021; 44: 1213-1220.
38. Yoshida S, Kurajoh M, Fukumoto S, et al. Association of plasma xanthine oxidoreductase activity with blood pressure affected by oxidative stress level: MedCity21 health examination registry. *Scientific Reports*. 2020; 10: 4437.
39. Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. *J Clin Hypertens (Greenwich)*. 2013; 15: 435-442.
40. Qu LH, Jiang H, Chen JH. Effect of uric acid-lowering therapy on blood pressure: systematic review and meta-analysis. *Ann Med*. 2017; 49: 142-156.
41. Bhole V, Choi JW, Kim SW, de Vera M, Choi H. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med*. 2010; 123: 957-961.
42. Vuorinen-Markkola H, Yki-Järvinen H. Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab*. 1994; 78: 25-29.
43. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA*. 1991; 266: 3008-3011.
44. Mizukoshi T, Kato S, Ando M, et al. Renoprotective effects of topiroxostat for hyperuricaemic patients with overt diabetic nephropathy study (ETUDE study): a prospective, randomized, multicentre clinical trial. *Nephrology (Carlton)*. 2018; 23: 1023-1030.
45. Nagai K, Tanaka T, Kodaira N, et al. Data resource profile: JMDC claims databases sourced from Medical Institutions. *J Gen Fam Med*. 2020; 21: 211-218.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Akari S, Nakamura T, Furusawa K, Miyazaki Y, Kario K. The reality of treatment for hyperuricemia and gout in Japan: A historical cohort study using health insurance claims data. *J Clin Hypertens*. 2022;24:1068–1075. https://doi.org/10.1111/jch.14539