Received: 30 March 2020 | Revised: 3 August 2020 | Accepted: 25 August 2020

DOI: 10.1002/pds.5127

ORIGINAL REPORT

WILEY

# Factors associated with achieving target serum uric acid level and occurrence of gouty arthritis: A retrospective observational study of Japanese health insurance claims data

Ruriko Koto[1] | Akihiro Nakajima[2] | Hideki Horiuchi[1] | Hisashi Yamanaka[3]

[1]Medical Science Department, Teijin Pharma Limited, Tokyo, Japan

[2]Pharmaceutical Development Administration Department, Teijin Pharma Limited, Tokyo, Japan

[3]Institute of Rheumatology Tokyo Women's Medical University, Tokyo, Japan

**Correspondence**
Ruriko Koto, 2-1, Kasumigaseki 3-chome, Chiyoda-ku, Tokyo 100-8585, Japan.
Email: r.koutou@teijin.co.jp

**Present address**
Hisashi Yamanaka, Rheumatology, Sanno Medical Center, Tokyo, Japan

**Funding information**
Teijin Pharma Limited

## Abstract

**Purpose:** This study assessed factors associated with achieving target serum uric acid (sUA) level and occurrence of gouty arthritis in Japanese clinical practice.

**Methods:** Japanese health insurance claims and medical check-up data from October 2015 to March 2017 were analyzed to assess factors associated with target sUA achievement in gout and asymptomatic hyperuricemia and gouty arthritis in gout. Target sUA was further assessed by subgroup analysis of urate-lowering therapy (ULT) prescriptions and outcomes, stratified by renal function.

**Results:** Patients achieving target sUA tended toward older, female, higher ULT dose, higher adherence, more comorbidities, and/or antidiabetic drugs prescribed. Renal dysfunction and/or diuretic prescriptions were associated with reduced achievement of target sUA. Severe renal dysfunction was particularly influential (odds ratio [OR] = 0.22 [95% confidence interval (CI): 0.10-0.48] for <15, 0.15 [0.10-0.23] for ≥15 to <30, compared with eGFR ≥90 mL/min/1.73 $m^2$). Across all renal function categories, mean prescribed ULT dose was low (febuxostat 17.0-21.0 mg/day, allopurinol 123.1-139.6 mg/day), and target sUA achievement was reduced among renal dysfunction patients. Gouty arthritis was more likely in patients with a prior history of such occurrences, and less likely for higher ULT adherence, sUA monitored regularly at medical facilities, and/or more comorbidities.

**Conclusion:** In a real-world setting, severe renal dysfunction is the most important risk factor for failure to achieve the target sUA, suggesting suboptimal disease management in patients with gout or hyperuricemia complicated by this condition. Findings associated with gouty arthritis suggest that these occurrences could be successfully managed by regular monitoring of sUA and closer adherence to ULT.

KEYWORDS

epidemiology, gout, hyperuricemia, pharmacoepidemiology, uric acid

## 1 | INTRODUCTION

Gout is a urate deposition disease caused by persistent hyperuricemia, defined as serum uric acid (sUA) exceeding 7.0 mg/dL.[1] Gouty arthritis occurrences can be reduced by achieving and maintaining sUA at 6.0 mg/dL or below,[2] a level uniformly recommended by international guidelines.[1,3,4] However, although proven and effective urate-lowering therapy (ULT) is available, many gout patients fail to achieve target sUA[5,6]; such patients tend to experience recurring gouty arthritis.[7]

Previous studies in the US, using predictive factors for achieving target sUA, found these targets were more commonly achieved in elderly patients, female patients, and those with lower sUA and BMI at baseline, and that renal dysfunction predicted failure in achieving target sUA.[6,8,9] Recent research has associated greater waist circumference at baseline with failure to achieve target sUA in Japanese patients.[10] Other research has shown that patients with more comorbidities are less prone to occurrences of gouty arthritis, and that patients with higher sUA are at greater risk for first-time onset and for recurrence.[7,11] Inappropriate therapy may also be associated with recurrence.[12]

We investigated real-world treatment of patients with gout or asymptomatic hyperuricemia by referencing data from Japanese health insurance claims, and found that many patients fail to reach their target sUA, suggesting that gout management is suboptimal in Japan.[13] The present study further analyzed those data to determine which background factors are associated with difficulties in reaching target sUA and which are associated with of gouty arthritis occurrences.

**KEY POINTS**

- Achieving target sUA was associated with older age, female sex, higher dose of ULT, higher medication possession ratio, more comorbidities, and/or prescription for antidiabetic drugs.
- Failure to achieve target sUA was associated with decreased renal function and/or prescribed diuretics, and especially with severe renal dysfunction, suggesting that current treatment options may not control sUA in hyperuricemic patients with this condition.
- Regular monitoring of sUA level and greater adherence to ULT were associated with lower likelihood of gouty arthritis; such arthritis may be more successfully managed by regular clinic visits and sustained ULT for sUA may contribute to better management of gouty arthritis.

## 2 | METHODS

### 2.1 | Study design

This study involved a retrospective observational analysis of information from an insurance claims database and data from medical check-ups from October 2015 to March 2017. The study was registered through the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000031503).

We accessed the JMDC Claims Database,[14] which consists of information from multiple organizations that provide health insurance coverage to Japanese employees (the subscribers) and their dependents. The database provided access to anonymized claims data from subscribers, diagnostic codes, and drug prescriptions. Because Japanese health insurance subscribers generally have an employer-sponsored medical check-up every year, the database also provided medical check-up data from each subscriber and from about one-third of the total population in the JMDC database.

Participant data were analyzed for two questions: "What factors were associated with achievement of target sUA?" (Analysis 1) and "What factors were associated with occurrence of gouty arthritis?" (Analysis 2).

### 2.2 | Participants

The study population comprised health insurance subscribers from the JMDC Claims Database (the database population) who satisfied the inclusion criteria and did not have malignant tumors. Inclusion criteria were: (a) Uninterrupted subscription to the insurance program from April 2016 through March 2017, (b) diagnosis of gout or asymptomatic hyperuricemia, (c) age 18 to 65 years.

Analysis 1 participants had met the eligibility criteria, had undergone sUA measurements at medical check-ups, were not on dialysis, had not received ULT or were under treatment with febuxostat monotherapy or allopurinol monotherapy during the 6-month period before the check-up at which sUA was measured, and had data available as explanatory variables for multivariate analysis.

Analysis 2 participants had a diagnosis of gout between April 2016 and March 2017, did not receive ULT or received only febuxostat monotherapy or allopurinol monotherapy between October 2015 and March 2016, and had data available as explanatory variables for multivariate analysis.

The subgroup of analysis by renal function was based on the analysis population but excluded patients who had undergone dialysis between April 2016 and March 2017 and patients for whom eGFR data were not available.

The terms "malignant tumor," "gout," "asymptomatic hyperuricemia" and "gouty arthritis" in this study are defined in Table S1. We applied a modified claims-based algorithm to identify patients with gout.[7,15]

### 2.3 | Study measures

Analysis 1: Factors associated with achieving target sUA (6.0 mg/dL or below) in patients with gout or asymptomatic hyperuricemia.

Subgroup analysis for Analysis 1: To interpret findings for factors associated with achieving target sUA, we conducted further subgroup analysis of factors such as ULT prescription, stratified by renal function. We used the data on estimated glomerular filtration rate (eGFR) calculated from medical check-up data. Patient characteristics (age, number of comorbidities, medication possession ratio [MPR] and mean dose of ULT), ULT prescription, sUA level, and the proportion of patients who achieved target sUA were analyzed by stratifying renal function as represented by eGFR (≥90, ≥60 to <90, ≥30 to <60, ≥15 to <30, and <15 mL/min/1.73 $m^2$).

Analysis 2: Factors associated with occurrence of gouty arthritis in gout patients.

The terms "patient characteristics," "ULT," and "MPR" in this study are defined in Table S1.

### 2.4 | Statistical methods

For Analysis 1, univariate and multivariate logistic regression analyses were performed. The objective variable was whether participants achieved the target sUA level of 6.0 mg/dL or below, generally based on data from annual medical check-ups. If sUA was measured more than once during the year, the most recent value was used. Explanatory variables were patient characteristics and ULT prescription. Values for those explanatory variables were obtained from the database for the 6-month period prior to the month of sUA measurement.

For Analysis 2, univariate and multivariate logistic regression analyses were performed; the objective variable was the occurrence or non-occurrence of gouty arthritis, and explanatory variables were patient characteristics and ULT prescription. Values for those explanatory variables were obtained from the database for the 6-month period between October 2015 and March 2016. Data for the occurrence of gouty arthritis were analyzed between April 2016 and March 2017.

Subgroup analysis was conducted regarding ULT prescription, stratified by renal function, to determine effects on achieving target sUA. The proportion of patients achieving target sUA and the 95% confidence interval (CI) for that proportion were calculated for no ULT and for each dose of febuxostat or allopurinol.

All analyses were performed using SAS version 9.4.

## 3 | RESULTS

### 3.1 | Study population

From among the 67 368 patients in the analysis population, 23 883 patients were selected for Analysis 1. For Analysis 2, the patient population was 17 672 patients (Figure S1).

### 3.2 | Patient characteristics

Both for Analysis 1 and Analysis 2, the target population averaged approximately 50 years of age, was mostly male, and commonly showed complications of hypertension and/or hyperlipidemia. Only a few of those patients met the criteria for renal dysfunction, but among those patients for whom eGFR information from medical check-ups was available in the database, mean eGFR was approximately 70 mL/min/1.73 $m^2$ (Table 1).

### 3.3 | Analysis 1: Factors associated with achieving target sUA (6.0 mg/dL or below) in patients with gout or asymptomatic hyperuricemia

Levels of sUA reached 6 mg/dL or below in 28.1% of all patients (6721/23 883). From the results of multivariate logistic regression analysis, factors that predisposed patients to reach the target sUA were older age, female sex, prescription for higher-dose febuxostat or allopurinol, higher MPR, more comorbidities, and/or prescription for antidiabetic drugs. Patients with lower eGFR and/or a prescription for diuretics were predisposed to fail to achieve the target sUA. The effect of severe renal dysfunction was especially pronounced (odds ratio [OR] = 0.22 [95% CI: 0.10-0.48] for <15 and 0.15 [0.10-0.23] for ≥15 to <30 in comparison to eGFR ≥90 mL/min/1.73 $m^2$) (Figure 1).

### 3.4 | Subgroup analysis: Patient characteristics, ULT prescription, and dose, sUA, and the proportion of patients who achieved the target sUA stratified by renal function

Patients who were prescribed ULT accounted for 66.2% of patients with eGFR ≥90, 73.1% with eGFR ≥60 to <90, 81.3% with eGFR ≥30 to <60, and 94.9% with eGFR <30 mL/min/1.73 $m^2$, suggesting that the percentage of prescriptions for ULT in patients with severe renal dysfunction (eGFR <30 mL/min/1.73 $m^2$) was higher than in patients with normal renal function.

We analyzed patient characteristics by renal function and by ULT (febuxostat or allopurinol). Patients on febuxostat tended to have higher median MPR and more comorbidities, increasing with decreasing renal function (Table 2). This same tendency was seen with allopurinol, except that median MPR did not exceed 45.5 in patients having eGFR<15 mL/min/1.73 $m^2$ (Table 3). The mean prescribed dose was generally low across all categories of renal function for both febuxostat and allopurinol. There was a slight increase in the febuxostat dose in patients with severe renal dysfunction (20.0 mg/day for eGFR ≥15 to <30 and 21.0 mg/day for eGFR <15 in comparison to 17.0 mg/day for eGFR ≥90 mL/min/1.73 $m^2$) and a slight decrease in the allopurinol dose in that same category (133.7 mg/day for eGFR ≥15 to <30 and 123.1 mg/day for eGFR <15 in comparison to 136.0 mg/day for eGFR ≥90 mL/min/1.73 $m^2$) (Tables 2 & 3).

We assessed sUA and the proportion of patients who achieved the target sUA for each prescribed dose of febuxostat, allopurinol, or no treatment, at each level of renal function. Overall, decreased renal

**TABLE 1** Patient characteristics

| | Analysis 1:Factors associated with achievement of sUA target | | | Analysis 2:Factors associated with occurrence of gouty arthritis |
|---|---|---|---|---|
| | Gout N = 6762 | Asymptomatic hyperuricemia N = 17 121 | Total (Gout + asymptomatic hyperuricemia) N = 23 883 | Gout N = 17 672 |
| Age, mean (SD) | 49.6 (8.3) | 50.2 (8.4) | 50.0 (8.4) | 49.2 (9.3) |
| Age, n (%) | | | | |
| 18-19 | 0 | 6 (<0.1) | 6 (<0.1) | 27 (0.2) |
| 20-29 | 102 (1.5) | 301 (1.8) | 403 (1.7) | 582 (3.3) |
| 30-39 | 720 (10.6) | 1590 (9.3) | 2310 (9.7) | 2075 (11.7) |
| 40-49 | 2311 (34.2) | 5455 (31.9) | 7766 (32.5) | 5634 (31.9) |
| 50-59 | 2813 (41.6) | 7484 (43.7) | 10 297 (43.1) | 6948 (39.3) |
| 60-65 | 816 (12.1) | 2285 (13.3) | 3101 (13.0) | 2406 (13.6) |
| Sex, n (%) | | | | |
| Male | 6623 (97.9) | 16 499 (96.4) | 23 122 (96.8) | 17 020 (96.3) |
| Female | 139 (2.1) | 622 (3.6) | 761 (3.2) | 652 (3.7) |
| Comorbidities of interest, n (%) | | | | |
| Hypertension | 2759 (40.8) | 9830 (57.4) | 12 589 (52.7) | 7218 (40.8) |
| Type 2 diabetes | 1487 (22.0) | 5255 (30.7) | 6742 (28.2) | 3858 (21.8) |
| Ischemic heart disease | 407 (6.0) | 1433 (8.4) | 1840 (7.7) | 1099 (6.2) |
| Heart failure | 297 (4.4) | 1239 (7.2) | 1536 (6.4) | 848 (4.8) |
| Cerebrovascular disease | 281 (4.2) | 1138 (6.6) | 1419 (5.9) | 820 (4.6) |
| Hyperlipidemia | 3194 (47.2) | 11 435 (66.8) | 14 629 (61.3) | 8017 (45.4) |
| Renal dysfunction | 365 (5.4) | 1294 (7.6) | 1659 (6.9) | 1009 (5.7) |
| Number of comorbidities | | | | |
| Mean (SD), median | 1.3 (1.3), 1.0 | 1.8 (1.3), 2.0 | 1.7 (1.3), 2.0 | 1.3 (1.3), 1.0 |
| n (%) | | | | |
| 0 | 2265 (33.5) | 2302 (13.4) | 4567 (19.1) | 6154 (34.8) |
| 1 | 1905 (28.2) | 5114 (29.9) | 7019 (29.4) | 4823 (27.3) |
| 2 | 1441 (21.3) | 4967 (29.0) | 6408 (26.8) | 3589 (20.3) |
| 3 | 749 (11.1) | 3084 (18.0) | 3833 (16.0) | 2007 (11.4) |
| 4 | 281 (4.2) | 1081 (6.3) | 1362 (5.7) | 748 (4.2) |
| 5 | 96 (1.4) | 446 (2.6) | 542 (2.3) | 269 (1.5) |
| 6 | 23 (0.3) | 119 (0.7) | 142 (0.6) | 64 (0.4) |
| 7 | 2 (<0.1) | 8 (<0.1) | 10 (<0.1) | 18 (0.1) |
| sUA[a], mg/dL | | | | |
| Patients with data, n | 6762 | 17 121 | 23 883 | 7648 |
| Mean (SD) | 7.00 (1.50) | 6.83 (1.33) | 6.88 (1.38) | 6.98 (1.49) |
| Achieving target sUA[a], n (%) | 1852 (27.4) | 4869 (28.4) | 6721 (28.1) | 2134 (27.9) |
| eGFR[a,b], mL/min/1.73 $m^2$ | | | | |
| Patients with data, n | 6762 | 17 121 | 23 883 | 7366 |
| Mean (SD) | 72.4 (14.7) | 71.3 (15.5) | 71.6 (15.3) | 72.1 (15.1) |
| n (%) | | | | |
| ≥90 | 738 (10.9) | 1761 (10.3) | 2499 (10.5) | 790 (4.5) |
| ≥60, <90 | 4792 (70.9) | 11 791 (68.9) | 16 583 (69.4) | 5211 (29.5) |
| ≥30, <60 | 1200 (17.7) | 3395 (19.8) | 4595 (19.2) | 1310 (7.4) |

**TABLE 1** (Continued)

| | Analysis 1:Factors associated with achievement of sUA target | | | Analysis 2:Factors associated with occurrence of gouty arthritis |
|---|---|---|---|---|
| | Gout N = 6762 | Asymptomatic hyperuricemia N = 17 121 | Total (Gout + asymptomatic hyperuricemia) N = 23 883 | Gout N = 17 672 |
| ≥15, <30 | 27 (0.4) | 143 (0.8) | 170 (0.7) | 29 (0.2) |
| <15 | 5 (<0.1) | 31 (0.2) | 36 (0.2) | 26 (0.1) |
| Not measured | 0 | 0 | 0 | 10 306 (58.3) |
| Concomitant medications, n (%) | | | | |
| Antihyperlipidemic drug | 1961 (29.0) | 7727 (45.1) | 9688 (40.6) | 4991 (28.2) |
| ACE inhibitors | 118 (1.7) | 535 (3.1) | 653 (2.7) | 331 (1.9) |
| ARB | 1673 (24.7) | 6554 (38.3) | 8227 (34.4) | 4390 (24.8) |
| Diuretic drug | 237 (3.5) | 1037 (6.1) | 1274 (5.3) | 704 (4.0) |
| Antidiabetic drug | 525 (7.8) | 2418 (14.1) | 2943 (12.3) | 1411 (8.0) |
| Number of measurements of sUA | | | | |
| Mean (SD) | 2.1 (2.3) | 2.3 (2.5) | 2.2 (2.5) | 2.2 (2.6) |
| n (%) | | | | |
| 0 | 1525 (22.6) | 3713 (21.7) | 5238 (21.9) | 3815 (21.6) |
| 1 | 1969 (29.1) | 4608 (26.9) | 6577 (27.5) | 5123 (29.0) |
| 2 | 1337 (19.8) | 3261 (19.0) | 4598 (19.3) | 3412 (19.3) |
| 3 | 726 (10.7) | 1948 (11.4) | 2674 (11.2) | 1984 (11.2) |
| 4 | 475 (7.0) | 1302 (7.6) | 1777 (7.4) | 1313 (7.4) |
| ≥5 | 730 (10.8) | 2289 (13.4) | 3019 (12.6) | 2025 (11.5) |

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; sUA, serum uric acid.
[a]Data obtained from medical check-ups. For the calculation of percentages, the denominator is "number of patients with data."
[b]eGFR was calculated using the following formula. eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$.

function was associated with higher sUA (Table S2). The proportion of patients who achieved the target sUA tended to decrease as renal function decreased, among both febuxostat and allopurinol patients. In patients with moderate or severe renal dysfunction, the target sUA level was achieved by about 20% of patients who received allopurinol 100 mg and about 50% of patients who received febuxostat 40 mg. Only a few patients with eGFR <30 mL/min/1.73 $m^2$ were treated with allopurinol 200 mg or febuxostat 60 mg (Table S2). In all renal function categories, a higher rate of target sUA achievement was associated with higher dose in both the febuxostat and allopurinol groups (Figure 2).

### 3.5 | Analysis 2: Factors associated with occurrence of gouty arthritis in gout patients

Gouty arthritis occurred in 50.6% of all patients (8939/17 672). From the results of multivariate logistic regression analysis, patients who had a history of gouty arthritis during the previous 6 months were more prone to occurrence of gouty arthritis during the study period. The results also showed that gouty arthritis was less likely to occur in patients with higher MPR, with sUA monitored at medical facilities, and/or with more comorbidities. The effects of age, sex, and concomitant medications were minimal (Figure 3).

## 4 | DISCUSSION

In real-world clinical practice, gout treatment is known to be suboptimal in many countries[16]; we previously reported that this was also the case in Japan.[13] The importance of the treat-to-target approach is recognized for gout, as well as for many other conditions such as diabetes, hypercholesterolemia, and rheumatoid arthritis, and all of these conditions appear to be associated with suboptimal target achievement.[17-19] However, these unsatisfactory outcomes may occur for different reasons in different diseases. We thus consider it of great importance to learn the reasons underlying suboptimal treatment of gout.

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | Proportion | OR (95%CI) | Proportion | OR (95%CI) |
| Age (years) : | 18-29 | 61/409 (14.9%) | 1.00 | 61/409 (14.9%) | 1.00 |
| | 30-39 | 429/2310 (18.6%) | 1.30 (0.97-1.74) | 429/2310 (18.6%) | 1.15 (0.84-1.57) |
| | 40-49 | 1950/7766 (25.1%) | 1.91 (1.45-2.52) | 1950/7766 (25.1%) | 1.53 (1.13-2.06) |
| | 50-59 | 3177/10 297 (30.9%) | 2.55 (1.93-3.35) | 3177/10 297 (30.9%) | 1.96 (1.45-2.66) |
| | 60-65 | 1104/3101 (35.6%) | 3.15 (2.38-4.18) | 1104/3101 (35.6%) | 2.59 (1.90-3.54) |
| Sex : | Male | 6284/23 122 (27.2%) | 1.00 | 6284/23 122 (27.2%) | 1.00 |
| | Female | 437/761 (57.4%) | 3.61 (3.12-4.18) | 437/761 (57.4%) | 6.16 (5.25-7.23) |
| ULT : | No prescription | 2280/13 022 (17.5%) | 1.00 | 2280/13 022 (17.5%) | 1.00 |
| | Febuxostat 10 mg | 821/2083 (39.4%) | 3.07 (2.78-3.38) | 821/2083 (39.4%) | 1.57 (1.38-1.78) |
| | 20 mg | 1333/2608 (51.1%) | 4.93 (4.51-5.38) | 1333/2608 (51.1%) | 2.81 (2.49-3.16) |
| | 40 mg | 275/457 (60.2%) | 7.12 (5.87-8.63) | 275/457 (60.2%) | 4.47 (3.60-5.55) |
| | 60 mg | 14/23 (60.9%) | 7.33 (3.17-16.95) | 14/23 (60.9%) | 4.33 (1.78-10.55) |
| | Allopurinol 50 mg | 33/99 (33.3%) | 2.36 (1.55-3.59) | 33/99 (33.3%) | 0.81 (0.52-1.27) |
| | 100 mg | 1040/3742 (27.8%) | 1.81 (1.67-1.97) | 1040/3742 (27.8%) | 0.76 (0.68-0.86) |
| | 200 mg | 870/1755 (49.6%) | 4.63 (4.17-5.14) | 870/1755 (49.6%) | 2.39 (2.09-2.72) |
| | 300 mg | 55/94 (58.5%) | 6.64 (4.40-10.04) | 55/94 (58.5%) | 4.31 (2.78-6.69) |
| MPR† : | <25% | 1708/10 803 (15.8%) | 1.00 | 1708/10 803 (15.8%) | 1.00 |
| | ≥25%, <50% | 274/1238 (22.1%) | 1.51 (1.31-1.75) | 274/1238 (22.1%) | 1.34 (1.14-1.57) |
| | ≥50%, <75% | 632/2117 (29.9%) | 2.27 (2.04-2.52) | 632/2117 (29.9%) | 1.70 (1.49-1.94) |
| | ≥75% | 4107/9725 (42.2%) | 3.89 (3.65-4.16) | 4107/9725 (42.2%) | 2.77 (2.48-3.10) |
| No. of sUA measurements : | 0 | 2152/9924 (21.7%) | 1.00 | 2152/9924 (21.7%) | 1.00 |
| | 1 | 2245/7603 (29.5%) | 1.51 (1.41-1.62) | 2245/7603 (29.5%) | 1.03 (0.95-1.11) |
| | 2 | 1254/3610 (34.7%) | 1.92 (1.77-2.09) | 1254/3610 (34.7%) | 1.12 (1.02-1.23) |
| | ≥3 | 1070/2746 (39.0%) | 2.31 (2.11-2.52) | 1070/2746 (39.0%) | 1.17 (1.05-1.31) |
| No. of comorbidities‡ : | 0 | 1120/6711 (16.7%) | 1.00 | 1120/6711 (16.7%) | 1.00 |
| | 1 | 1748/6341 (27.6%) | 1.90 (1.75-2.07) | 1748/6341 (27.6%) | 1.32 (1.19-1.46) |
| | 2 | 1928/5830 (33.1%) | 2.47 (2.27-2.68) | 1928/5830 (33.1%) | 1.55 (1.39-1.74) |
| | 3 | 1289/3330 (38.7%) | 3.15 (2.87-3.47) | 1289/3330 (38.7%) | 1.77 (1.54-2.02) |
| | 4 | 444/1137 (39.1%) | 3.20 (2.79-3.66) | 444/1137 (39.1%) | 1.75 (1.46-2.09) |
| | 5 | 150/424 (35.4%) | 2.73 (2.22-3.37) | 150/424 (35.4%) | 1.48 (1.15-1.91) |
| | ≥6 | 42/110 (38.2%) | 3.08 (2.09-4.55) | 42/110 (38.2%) | 1.89 (1.21-2.93) |
| eGFR (mL/min/1.73m$^2$)§ : | ≥90 | 874/2499 (35.0%) | 1.00 | 874/2499 (35.0%) | 1.00 |
| | ≥60, <90 | 4704/16 583 (28.4%) | 0.74 (0.67-0.80) | 4704/16 583 (28.4%) | 0.57 (0.51-0.63) |
| | ≥30, <60 | 1084/4595 (23.6%) | 0.57 (0.52-0.64) | 1084/4595 (23.6%) | 0.30 (0.26-0.34) |
| | ≥15, <30 | 47/170 (27.6%) | 0.71 (0.50-1.00) | 47/170 (27.6%) | 0.15 (0.10-0.23) |
| | <15 | 12/36 (33.3%) | 0.93 (0.46-1.87) | 12/36 (33.3%) | 0.22 (0.10-0.48) |
| Antihyperlipidemic drug : | No | 3589/15 326 (23.6%) | 1.00 | 3589/15 326 (23.4%) | 1.00 |
| | Yes | 3132/8557 (36.6%) | 1.89 (1.78-2.00) | 3132/8557 (36.6%) | 1.19 (1.11-1.28) |
| ACE inhibitors : | No | 6502/23 273 (27.9%) | 1.00 | 6502/23 273 (27.9%) | 1.00 |
| | Yes | 219/610 (35.9%) | 1.44 (1.22-1.71) | 219/610 (35.9%) | 1.04 (0.86-1.26) |
| ARB : | No | 4270/16 328 (26.2%) | 1.00 | 4270/16 328 (26.2%) | 1.00 |
| | Yes | 2451/7555 (32.4%) | 1.36 (1.28-1.44) | 2451/7555 (32.4%) | 0.85 (0.78-0.91) |
| Diuretic drug : | No | 6409/22 789 (28.1%) | 1.00 | 6409/22 789 (28.1%) | 1.00 |
| | Yes | 312/1094 (28.5%) | 1.02 (0.89-1.17) | 312/1094 (28.5%) | 0.60 (0.51-0.70) |
| Antidiabetic drug : | No | 5580/21 232 (26.3%) | 1.00 | 5580/21 232 (26.3%) | 1.00 |
| | Yes | 1141/2651 (43.0%) | 2.12 (1.95-2.30) | 1141/2651 (43.0%) | 1.57 (1.42-1.74) |
| History of gouty arthritis¶: | | | | | |
| | No | 6214/22 141 (28.1%) | 1.00 | 6214/22 141 (28.1%) | 1.00 |
| | Yes | 507/1742 (29.1%) | 1.05 (0.95-1.17) | 507/1742 (29.1%) | 1.12 (0.99-1.26) |

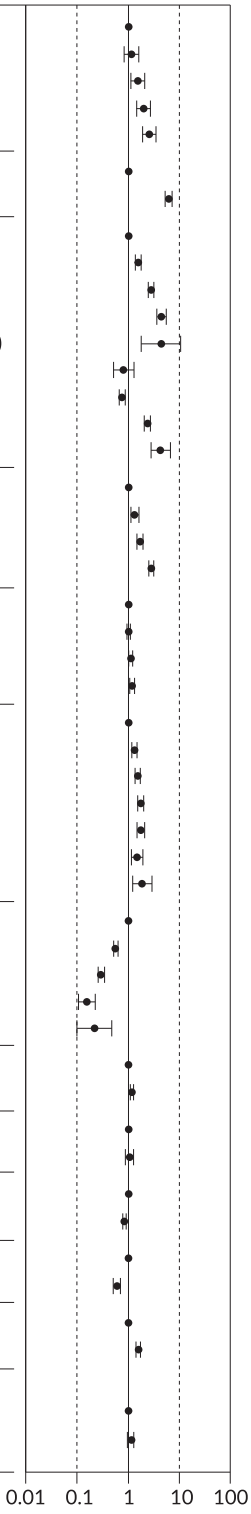


**FIGURE 1** Factors associated with achievement of target sUA (6.0 mg/dL or below): logistic regression analysis. The forest plot shows the point estimate and 95% confidence interval for the odds ratio in multivariate analysis. The objective variable was whether target sUA (6.0 mg/dL or below) had been achieved by the time of medical check-ups, and the explanatory variables were from data on sUA measurements during the 6-month period prior to the medical check-ups. †MPR indicates number of days ULT was prescribed from April 1, 2016 to March 31, 2017/365 days from April 1, 2016 to March 31, 2017. ‡Comorbidities includes hypertension, type 2 diabetes, ischemic heart disease, heart failure, cerebrovascular disease, hyperlipidemia, renal dysfunction. §eGFR was calculated using the following formula. eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$. ¶The most recent 6 months prior to the time of medical check-ups. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MPR, medication possession ratio; OR, odds ratio; sUA, serum uric acid; ULT, urate-lowering therapy

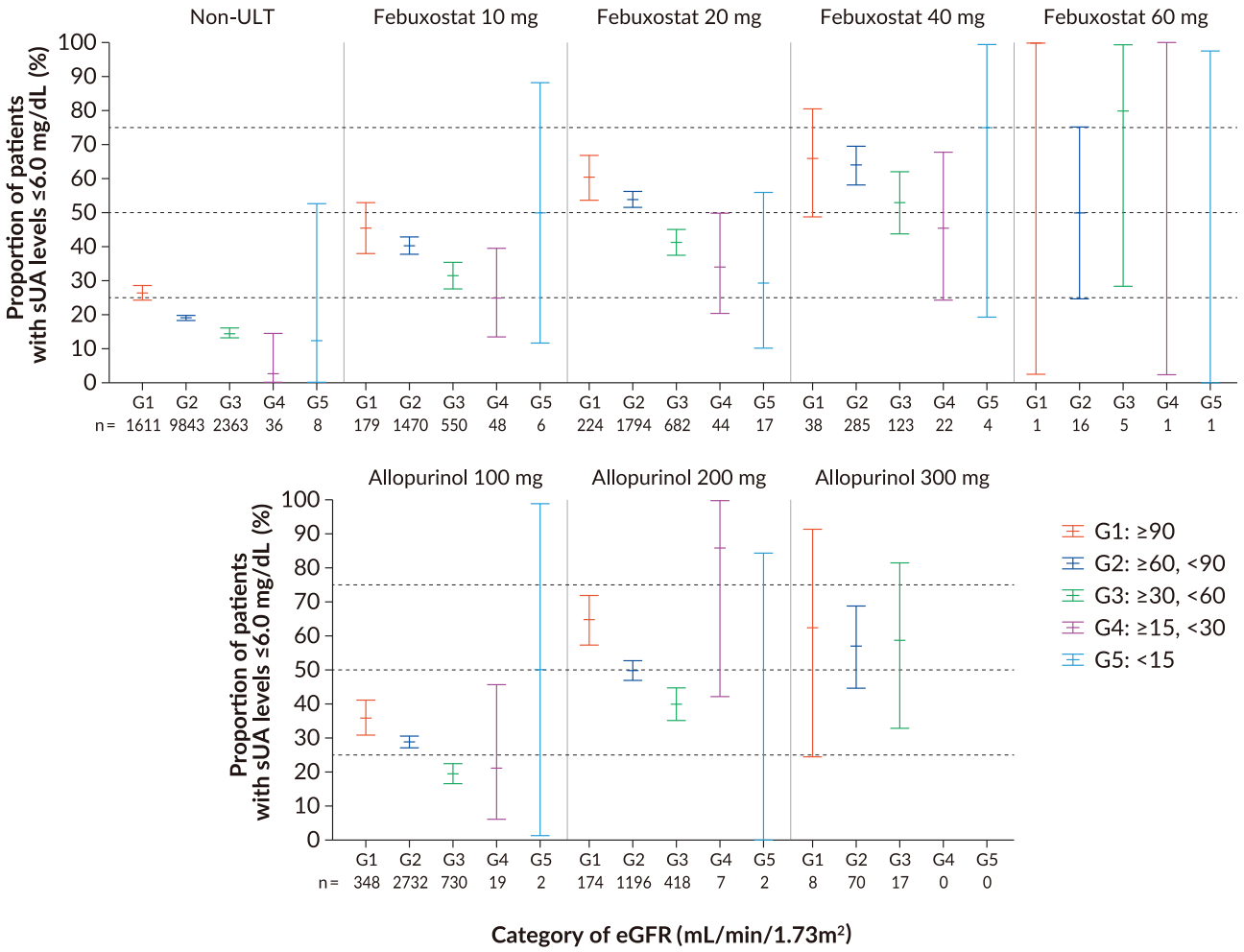


**FIGURE 2** Proportion of patients achieving target sUA, stratified by ULT dose and by renal function. Point estimate and 95% CI were plotted for the proportion of achievement of target sUA. eGFR, estimated glomerular filtration rate; sUA, serum uric acid [Colour figure can be viewed at wileyonlinelibrary.com]

Logistic regression analysis showed that achieving target sUA was more often associated with older age, female sex, higher dose of ULT, higher MPR, more comorbidities, and/or prescription for antidiabetic drugs. Our findings for age and sex supported results from previous studies in the US,[6,8,9] which similarly showed that elderly and female patients were more likely to reach the target sUA. The results for the other related factors also seem reasonable. For example, the higher likelihood of achieving target sUA in patients with more comorbidities could be caused by increased treatment adherence related to those comorbidities, possibly because of more frequent interaction with medical personnel. Such a relationship would be a confounding factor for adherence. The literature indicates that adherence increases proportionally with age[20]; this correlation may be affected by factors that cannot be measured by insurance claims, such as patient awareness of lifestyle and health. Our results also showed that patients with low eGFR and those who were prescribed diuretics tended to fail to achieve their target sUA. The OR for multivariate analysis in comparison to patients with eGFR ≥90 was 0.15 (95% CI: 0.10-0.23) for patients with eGFR ≥15 to <30 and 0.22 (0.10-0.48) for <15 mL/min/1.73 $m^2$, respectively. These results suggest that severe renal dysfunction is the most important predictor for failure to achieve the target sUA within the population that we studied.

In this context, we performed additional analysis of patient characteristics and ULT prescription and outcome, stratified by renal function. Decreased renal function was associated with more comorbidities and higher median MPR, and a higher percentage of those patients had prescriptions for ULT. We found that almost all patients, regardless of the level of renal function, were receiving low-dose ULT. In patients with severe renal dysfunction, the data showed a slight increase in mean febuxostat dose, and a slight decrease in mean allopurinol dose. The observed decrease in the allopurinol dose in our study could be based on treatment guidelines that recommend reducing the allopurinol dose in proportion to the extent of renal dysfunction.[21] This is also in agreement with the finding from a questionnaire survey that many Japanese nephrologists report limiting allopurinol dose to 100 mg/day in patients with CKD stage 4 or 5.[22] Additionally, the overall results for sUA level, and the proportion of target sUA achievement analyzed by renal function and by prescribed ULT dose, trended toward a correlation between higher sUA, lower

**TABLE 2** Patient characteristics stratified by renal function: Febuxostat

| | Total (Gout+asymptomatic hyperuricemia) | | | | | Gout | | | | | Asymptomatic hyperuricemia | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| eGFR[a] | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total |
| N | 868 | 6597 | 2379 | 156 | 36 | 24 211 | 310 | 2346 | 717 | 22 | 6 | 8178 | 558 | 4251 | 1662 | 134 | 30 | 16 033 |
| Age, mean (SD) | 43.9 (9.3) | 48.9 (8.1) | 53.6 (7.0) | 51.4 (8.3) | 49.8 (9.1) | 49.2 (9.4) | 44.0 (8.5) | 48.8 (8.1) | 53.6 (6.5) | 47.5 (8.7) | 51.3 (9.1) | 48.8 (9.3) | 43.8 (9.7) | 49.0 (8.1) | 53.6 (7.2) | 52.0 (8.1) | 49.5 (9.2) | 49.4 (9.4) |
| Number of comorbidities, mean (SD) | 1.4 (1.2) | 1.5 (1.2) | 2.1 (1.4) | 3.6 (1.4) | 3.1 (1.2) | 1.7 (1.4) | 1.1 (1.2) | 1.2 (1.2) | 1.6 (1.3) | 3.4 (1.6) | 3.5 (1.2) | 1.3 (1.3) | 1.6 (1.1) | 1.7 (1.2) | 2.2 (1.4) | 3.6 (1.4) | 3.1 (1.2) | 1.9 (1.4) |
| MPR | | | | | | | | | | | | | | | | | | |
| Mean (SD) | 58.1 (33.2) | 64.5 (32.5) | 71.9 (29.9) | 84.4 (25.6) | 86.1 (22.3) | 65.7 (32.4) | 54.0 (33.5) | 61.2 (33.0) | 66.1 (31.1) | 90.8 (16.5) | 84.7 (22.6) | 61.3 (33.0) | 60.3 (32.8) | 66.4 (32.0) | 74.4 (29.1) | 83.3 (26.7) | 86.4 (22.7) | 67.9 (31.8) |
| Median | 64.4 | 74.3 | 83.0 | 97.3 | 94.7 | 75.9 | 54.0 | 69.3 | 75.1 | 96.7 | 91.4 | 69.0 | 67.5 | 76.2 | 86.3 | 97.5 | 94.8 | 79.5 |
| ≥80%, n (%) | 319/ 868 (36.8) | 2933/ 6597 (44.5) | 1289/ 2379 (54.2) | 116/ 156 (74.4) | 30/ 36 (83.3) | 11 248/ 24 211 (46.5) | 98/ 310 (31.6) | 944/ 2346 (40.2) | 326/ 717 (45.5) | 18/ 22 (81.8) | 5/ 6 (83.3) | 3300/ 8178 (40.4) | 221/ 558 (39.6) | 1989/ 4251 (46.8) | 963/ 1662 (57.9) | 98/ 134 (73.1) | 25/ 30 (83.3) | 7948/ 16 033 (49.6) |
| Mean dose, mean (SD), mg/day | 17.0 (7.9) | 17.1 (8.2) | 17.7 (8.7) | 20.0 (11.1) | 21.0 (11.6) | 17.4 (8.6) | 18.2 (8.3) | 18.5 (9.1) | 19.3 (9.7) | 24.4 (12.6) | 24.6 (17.8) | 19.0 (9.4) | 16.3 (7.6) | 16.3 (7.5) | 17.0 (8.2) | 19.2 (10.7) | 20.3 (10.3) | 16.6 (8.0) |

Abbreviations: eGFR, estimated glomerular filtration rate; MPR, medication possession ratio.

[a]eGFR was calculated using the following formula. eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (Female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$.

achievement of target sUA, and decreased renal function. In patients with renal dysfunction, although sUA increased as renal function decreased, prescriptions for low-dose ULT remained virtually unchanged across all renal function categories. This may explain why patients with renal dysfunction were less likely to achieve their target sUA. Although the proportion of target sUA achievement tended to increase dose-dependently in both the febuxostat and allopurinol groups across all renal function categories, that proportion was generally low in patients with renal dysfunction. These results strongly suggest that management for gout and hyperuricemia in patients with decreased renal function is suboptimal in a real-world clinical setting in Japan.

Treatment options are currently limited for patients who have renal dysfunction and either gout or hyperuricemia. Although recent research outside Japan has shown that allopurinol is effective and safe even when the dose is gradually increased beyond the level considered appropriate for that degree of renal dysfunction,[23,24] the efficacy and safety of high-dose allopurinol have not yet been proven in Japanese patients with reduced renal function. Febuxostat is considered effective and tolerable in patients with mild to moderate renal dysfunction,[25-27] but safety has not been well studied in patients with severe renal dysfunction. Meanwhile, in a randomized clinical trial in the US, in patients with moderate to severe renal dysfunction, 45.2% achievement of target sUA was reported with daily febuxostat 80 mg at 12 months.[28] In our study, target sUA was achieved in only about 50% of patients receiving febuxostat 40 mg, suggesting that the control of sUA in gout and hyperuricemia patients with severe renal dysfunction may be challenging in a real-world setting.

Our results from logistic regression analysis indicated a lower likelihood of gouty arthritis occurrences in gout patients with higher MPR, with sUA monitored at medical facilities, and with more comorbidities. These findings suggest that it may be possible to control gouty arthritis through regular clinic visits and continuing use of ULT. Gouty arthritis is less likely to occur in patients whose sUA levels are appropriately controlled, but in this study annual medical check-up data were used for analysis, so sUA and eGFR were not included in the model because those two parameters were measured infrequently. The results showed that patients with more comorbidities were less likely to experience gouty arthritis, possibly because the presence of comorbidities increases MPR, suggesting confounding by MPR. However, similar results were obtained in a prior study in the US, which showed that a Quan-Charlson comorbidity score above 1 at baseline was associated with lower risk of gouty arthritis during the follow-up period.[7] In this study, the patients with one or more occurrences of gouty arthritis during the previous 6 months were more likely to experience gouty arthritis during the study period. These results appeared consistent with prior research that showed significantly higher risk for gouty arthritis occurrences in patients who had a history of gouty arthritis at baseline.[7]

This study has some limitations. First, insurance claims data are collected for the purpose of payment/reimbursement, not research, which limits the applicability of definitions of terms such as gout,

**TABLE 3** Patient characteristics stratified by renal function: Allopurinol

| | Total (Gout+asymptomatic hyperuricemia) | | | | | | Gout | | | | | | Asymptomatic hyperuricemia | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| eGFR[a] | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total | ≥90 | ≥60 < 90 | ≥30 < 60 | ≥15 < 30 | <15 | Total |
| N | 841 | 6276 | 1821 | 46 | 13 | 20 580 | 267 | 1875 | 523 | 9 | 3 | 6499 | 574 | 4401 | 1298 | 37 | 10 | 14 081 |
| Age, mean (SD) | 47.0 (8.9) | 51.2 (7.6) | 54.8 (6.4) | 52.5 (7.7) | 55.5 (7.3) | 51.3 (8.5) | 47.2 (8.8) | 50.7 (7.7) | 54.3 (6.3) | 50.3 (7.3) | 56.7 (11.0) | 50.8 (8.7) | 46.9 (8.9) | 51.4 (7.5) | 54.9 (6.4) | 53.0 (7.8) | 55.1 (6.6) | 51.5 (8.4) |
| Number of comorbidities, mean (SD) | 1.7 (1.2) | 1.7 (1.2) | 2.0 (1.3) | 3.2 (1.4) | 3.5 (1.3) | 1.8 (1.3) | 1.4 (1.3) | 1.4 (1.2) | 1.7 (1.3) | 3.1 (1.3) | 3.3 (1.2) | 1.5 (1.3) | 1.9 (1.2) | 1.8 (1.2) | 2.2 (1.3) | 3.2 (1.5) | 3.5 (1.4) | 1.9 (1.3) |
| MPR | | | | | | | | | | | | | | | | | | |
| Mean (SD) | 71.4 (31.9) | 73.4 (29.8) | 74.6 (29.4) | 75.3 (33.4) | 55.3 (38.8) | 72.7 (30.4) | 66.1 (33.6) | 67.2 (31.9) | 69.3 (31.6) | 88.4 (12.1) | 55.7 (40.8) | 66.6 (32.5) | 73.9 (30.8) | 76.0 (28.4) | 76.8 (28.2) | 72.2 (36.2) | 55.2 (40.5) | 75.5 (29.0) |
| Median | 85.8 | 86.3 | 86.9 | 94.3 | 45.5 | 85.5 | 78.1 | 78.1 | 81.4 | 94.3 | 40.3 | 78.1 | 88.6 | 88.5 | 89.3 | 94.3 | 49.6 | 88.2 |
| ≥80%, n (%) | 470/ 841 (55.9) | 3614/ 6276 (57.6) | 1087/ 1821 (59.7) | 29/ 46 (63.0) | 5/ 13 (38.5) | 11 677/ 20 580 (56.7) | 131/ 267 (49.1) | 900/ 1875 (48.0) | 269/ 523 (51.4) | 6/ 9 (66.7) | 1/ 3 (33.3) | 3131/ 6499 (48.2) | 339/ 574 (59.1) | 2714/ 4401 (61.7) | 818/ 1298 (63.0) | 23/ 37 (62.2) | 4/ 10 (40.0) | 8546/ 14 081 (60.7) |
| Mean dose, Mean (SD), mg/day | 136.0 (53.5) | 134.7 (53.8) | 139.6 (54.0) | 133.7 (59.7) | 123.1 (43.9) | 136.2 (55.1) | 143.1 (59.8) | 144.4 (58.4) | 146.6 (56.1) | 111.1 (54.7) | 100.0 (0.0) | 145.8 (59.1) | 132.7 (50.0) | 130.5 (51.1) | 136.8 (52.9) | 139.2 (60.3) | 130.0 (48.3) | 131.7 (52.6) |

Abbreviations: eGFR, estimated glomerular filtration rate; MPR = medication possession ratio.

[a]eGFR was calculated using the following formula. eGFR (male) = $194 \times sCr^{-1.094} \times age^{-0.287}$, eGFR (female) = $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$.

gouty arthritis, and comorbidity. Second, results could be confounded by factors that cannot be measured by insurance claims, such as patient awareness of health and lifestyle, socioeconomic factors, and the clinical practice of each physician. Third, the adherence data do not actually prove that patients take their medications. Fourth, because the JMDC database uses information from health insurance societies whose members work primarily for Japanese companies, very little data are available on persons 66 years of age and older, and no data on persons 75 and older. The present study excluded data from persons 66 and older, reducing generalizability from these findings to the general Japanese population. Fifth, because sUA data came from medical check-ups rather than from measurements performed at medical institutions, it was obtained from only a certain portion of patients, individual patients might reduce their use of ULT or other

| | | Univariate | | Multivariate | |
|---|---|---|---|---|---|
| | | Proportion | OR (95%CI) | Proportion | OR (95%CI) |
| Age (years) : | 18-29 | 413/609 (67.8%) | 1.00 | 413/609 (67.8%) | 1.00 |
| | 30-39 | 1320/2075 (63.6%) | 0.83 (0.68-1.01) | 1320/2075 (63.6%) | 1.04 (0.85-1.29) |
| | 40-49 | 3057/5634 (54.3%) | 0.56 (0.47-0.67) | 3057/5634 (54.3%) | 1.00 (0.83-1.22) |
| | 50-59 | 3205/6948 (46.1%) | 0.41 (0.34-0.48) | 3205/6948 (46.1%) | 0.91 (0.75-1.10) |
| | 60-65 | 944/2406 (39.2%) | 0.31 (0.25-0.37) | 944/2406 (39.2%) | 0.79 (0.64-0.98) |
| Sex : | Male | 8566/17 020 (50.3%) | 1.00 | 8566/17 020 (50.3%) | 1.00 |
| | Female | 373/652 (57.2%) | 1.32 (1.13-1.55) | 373/652 (57.2%) | 0.82 (0.68-0.98) |
| ULT (drug, MPR, mean dose): | | | | | |
| | No prescription | 5536/7699 (71.9%) | 1.00 | 5536/7699 (71.9%) | 1.00 |
| | Febuxostat, <75%, ≤20 mg | 767/1565 (49.0%) | 0.38 (0.34-0.42) | 767/1565 (49.0%) | 0.30 (0.27-0.34) |
| | <75%, >20 mg | 153/281 (54.4%) | 0.47 (0.37-0.59) | 153/281 (54.4%) | 0.37 (0.29-0.48) |
| | ≥75%, ≤20 mg | 720/2525 (28.5%) | 0.16 (0.14-0.17) | 720/2525 (28.5%) | 0.18 (0.16-0.20) |
| | ≥75%, >20 mg | 181/554 (32.7%) | 0.19 (0.16-0.23) | 181/554 (32.7%) | 0.19 (0.16-0.23) |
| | Allopurinol, <75%, ≤100 mg | 318/762 (41.7%) | 0.28 (0.24-0.33) | 318/762 (41.7%) | 0.27 (0.23-0.31) |
| | <75%, >100 mg | 387/945 (41.0%) | 0.27 (0.24-0.31) | 387/945 (41.0%) | 0.23 (0.20-0.27) |
| | ≥75%, ≤100 mg | 556/2101 (26.5%) | 0.14 (0.13-0.16) | 556/2101 (26.5%) | 0.17 (0.15-0.19) |
| | ≥75%, >100 mg | 321/1240 (25.9%) | 0.14 (0.12-0.16) | 321/1240 (25.9%) | 0.15 (0.13-0.18) |
| No. of sUA measurements: | 0 | 5664/9288 (61.0%) | 1.00 | 5664/9288 (61.0%) | 1.00 |
| | 1 | 1926/4652 (41.4%) | 0.45 (0.42-0.49) | 1926/4652 (41.4%) | 0.70 (0.64-0.76) |
| | 2 | 736/2115 (34.8%) | 0.34 (0.31-0.38) | 736/2115 (34.8%) | 0.58 (0.52-0.66) |
| | ≥3 | 613/1617 (37.9%) | 0.39 (0.35-0.44) | 613/1617 (37.9%) | 0.70 (0.61-0.80) |
| No. of comorbidities† : | 0 | 5277/8013 (65.9%) | 1.00 | 5277/8013 (65.9%) | 1.00 |
| | 1 | 1744/4172 (41.8%) | 0.37 (0.34-0.40) | 1744/4172 (41.8%) | 0.62 (0.56-0.68) |
| | 2 | 1098/3010 (36.5%) | 0.30 (0.27-0.32) | 1098/3010 (36.5%) | 0.56 (0.49-0.63) |
| | 3 | 554/1645 (33.7%) | 0.26 (0.24-0.29) | 554/1645 (33.7%) | 0.53 (0.45-0.62) |
| | 4 | 192/581 (33.0%) | 0.26 (0.21-0.31) | 192/581 (33.0%) | 0.51 (0.40-0.64) |
| | 5 | 59/197 (29.9%) | 0.22 (0.16-0.30) | 59/197 (29.9%) | 0.47 (0.32-0.68) |
| | ≥6 | 15/54 (27.8%) | 0.20 (0.11-0.36) | 15/54 (27.8%) | 0.36 (0.19-0.71) |
| Antihyperlipidemic drug: | No | 7493/13 450 (55.7%) | 1.00 | 7493/13 450 (55.7%) | 1.00 |
| | Yes | 1446/4222 (34.2%) | 0.41(0.39-0.45) | 1446/4222 (34.2%) | 0.99 (0.90-1.09) |
| ACE inhibitors: | No | 8846/17 373 (50.9%) | 1.00 | 8846/17 373 (50.9%) | 1.00 |
| | Yes | 93/299 (31.1%) | 0.44 (0.34-0.56) | 93/299 (31.1%) | 0.78 (0.59-1.03) |
| ARB: | No | 7541/13 794 (54.7%) | 1.00 | 7541/13 794 (54.7%) | 1.00 |
| | Yes | 1398/3878 (36.0%) | 0.47 (0.43-0.50) | 1398/3878 (36.0%) | 1.00 (0.91-1.11) |
| Diuretic drug: | No | 8740/17 115 (51.1%) | 1.00 | 8740/17 115 (51.1%) | 1.00 |
| | Yes | 199/557 (35.7%) | 0.53 (0.45-0.64) | 199/557 (35.7%) | 1.03 (0.84-1.27) |
| Antidiabetic drug: | No | 8549/16 463 (51.9%) | 1.00 | 8549/16 463 (51.9%) | 1.00 |
| | Yes | 390/1209 (32.3%) | 0.44 (0.39-0.50) | 390/1209 (32.3%) | 0.85 (0.73-0.99) |
| History of gouty arthritis‡: | | | | | |
| | No | 6814/14 466 (47.1%) | 1.00 | 6814/14 466 (47.1%) | 1.00 |
| | Yes | 2125/3206 (66.3%) | 2.21 (2.04-2.39) | 2125/3206 (66.3%) | 4.19 (3.82-4.60) |

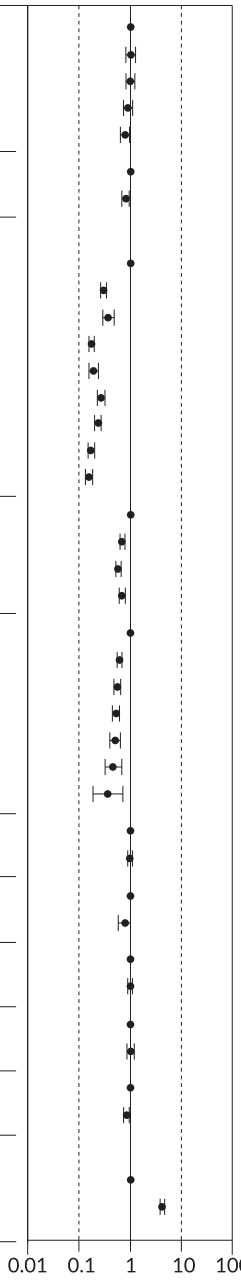


**FIGURE 3** Factors associated with occurrence of gouty arthritis: logistic regression analysis. The forest plot shows the point estimate and 95% CI for the OR in multivariate analysis. The objective variable was whether gouty arthritis occurred between April 2016 and March 2017, and the explanatory variables were from data during the 6-month period between October 2015 and March 2016. † Comorbidities include hypertension, type 2 diabetes, ischemic heart disease, heart failure, cerebrovascular disease, hyperlipidemia, renal dysfunction. ‡ The most recent 6 months prior to the study period. ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; MPR, medication possession ratio; OR, odds ratio; sUA, serum uric acid; ULT, urate-lowering therapy

regular medications on their check-up day, and sUA level was generally measured only once a year. Finally, this was an observational study, making it difficult to show whether achieving the target sUA level caused a reduction in the occurrence of gouty arthritis. Further interventional studies are needed to answer this question.

In conclusion, within the data available in this study, severe renal dysfunction was the most important risk factor for failure to achieve target sUA, indicating that disease management was suboptimal in patients with gout or hyperuricemia complicated by this condition. We also identified the following factors as lowering the likelihood of gouty arthritis: monitoring of sUA level, greater adherence to the use of ULT, and more comorbidities. These findings suggest that occurrence of gouty arthritis could be more successfully managed by regular monitoring of sUA levels and continuing use of ULT.

## ETHICS STATEMENT

This study used anonymized administrative data, so no ethical approval was needed.

## ACKNOWLEDGEMENTS

Support for study planning and information on data handling for the database were provided by JMDC Inc. Review of the statistical analysis plan, clinical study report, and manuscript was provided by Hirotaka Mano, Pharmaceutical Development Administration Department, Teijin Pharma Limited. Medical writing support was provided by EDIT, Inc. (Tokyo, Japan) and was funded by Teijin Pharma Limited.

## CONFLICT OF INTEREST

R. K., A. N., and H. H. are employees of Teijin Pharma Limited. H. Y. reports grants and personal fees from Teijin Pharma Limited.

## PRIOR POSTINGS AND PRESENTATIONS

Portions of these results were presented at the 2019 ACR/ARP Annual Meeting, November 8-13; Atlanta, GA.

## ORCID

*Ruriko Koto* https://orcid.org/0000-0001-9201-1273

## REFERENCES

1. Yamanaka H. Japanese guideline for the management of hyperuricemia and gout: second edition. *Nucleosides Nucleotides Nucleic Acids*. 2011;30:1018-1029.
2. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum*. 2004;51:321-325.
3. 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* 2012;64:1431–1446.
4. Richette P, Doherty M, Pascual E, et al. Updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2016;76:29-42.
5. Pandya BJ, Riedel AA, Swindle JP, et al. Relationship between physician specialty and allopurinol prescribing patterns: a study of patients with gout in managed care settings. *Curr Med Res Opin*. 2011;27:737-744.
6. Hatoum H, Khanna D, Lin SJ, Akhras KS, Shiozawa A, Khanna P. Achieving serum urate goal: a comparative effectiveness study between allopurinol and febuxostat. *Postgrad Med*. 2014;126:65-75.
7. Shiozawa A, Buysman EK, Korrer S. Serum uric acid levels and the risk of flares among gout patients in a US managed care setting. *Curr Med Res Opin*. 2017;33:117-124.
8. Sheer R, Null KD, Szymanski KA, Sudharshan L, Banovic J, Pasquale M. Predictors of reaching a serum uric acid goal in patients with gout and treated with febuxostat. *Clinicoecon Outcomes Res*. 2017;9:629-639.
9. Altan A, Shiozawa A, Bancroft T, Singh JA. A real-world study of switching from allopurinol to febuxostat in a health plan database. *J Clin Rheumatol*. 2015;21:411-418.
10. Katayama A, Yokokawa H, Fukuda H, et al. Achievement of target serum uric acid levels and factors associated with therapeutic failure among Japanese men treated for hyperuricemia/gout. *Intern Med*. 2019;58:1225-1231.
11. Shiozawa A, Szabo SM, Bolzani A, Cheung A, Choi HK. Serum uric acid and the risk of incident and recurrent gout: a systematic review. *J Rheumatol*. 2017;44:388-396.
12. Neogi T, Hunter DJ, Chaisson CE, Allensworth-Davies D, Zhang Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. *J Rheumatol*. 2006;33:104-109.
13. 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*. 2020;1-9. https://doi.org/10.1080/14397595.2020.1784556.
14. 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.
15. Jackson R, Shiozawa A, Buysman E, Altan A, Korrer S, Choi H. Flare frequency, healthcare resource utilisation and costs among patients with gout in a managed care setting: a retrospective medical claims-based analysis. *BMJ Open*. 2015;5:e007214.
16. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis*. 2015;74:661-667.
17. Schmieder RE, Tschöpe D, Koch C, Ouarrak T, Gitt AK. DIALOGUE study group. Individualised treatment targets in patients with type-2 diabetes and hypertension. *Cardiovasc Diabetol*. 2018;17:18.
18. Itoh H, Komuro I, Takeuchi M, et al. Achieving LDL cholesterol target levels <1.81 mmol/L may provide extra cardiovascular protection in patients at high risk: exploratory analysis of the standard versus intensive statin therapy for patients with hypercholesterolaemia and diabetic retinopathy study. *Diabetes Obes Metab*. 2019;21:791-800.
19. Smolen JS. Treat-to-target as an approach in inflammatory arthritis. *Curr Opin Rheumatol*. 2016;28:297-302.
20. Scheepers LEJM, van Onna M, Stehouwer CDA, Singh JA, Arts ICW, Boonen A. Medication adherence among patients with gout: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2018;47:689-702.
21. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. *Am J Med*. 1984;76:47-56.
22. Nakaya I, Namikoshi T, Tsuruta Y, et al. Management of asymptomatic hyperuricaemia in patients with chronic kidney disease by Japanese nephrologists: a questionnaire survey. *Nephrol Ther*. 2011;16:518-521.
23. Stamp LK, Chapman PT, Barclay M, et al. Allopurinol dose escalation to achieve serum urate below 6 mg/dL: an open-label extension study. *Ann Rheum Dis*. 2017;76:2065-2070.

24. Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. *Ann Rheum Dis*. 2017;76:1522-1528.
25. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther*. 2010;12:R63.
26. Hosoya T, Ohno I. A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with impaired renal function in Japan: pharmacokinetic and pharmacodynamic study. *J Clin Rheumatol*. 2011;17(4 Suppl 2):S27-S34.
27. 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.
28. Saag KG, Whelton A, Becker MA, MacDonald P, Hunt B, Gunawardhana L. Impact of febuxostat on renal function in gout patients with moderate-to-severe renal impairment. *Arthritis Rheumatol*. 2016;68:2035-2043.

## SUPPORTING INFORMATION

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

**How to cite this article:** 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. https://doi.org/10.1002/pds.5127