

Clinical characteristics of early- and late-onset gout

A cross-sectional observational study from a Chinese gout clinic

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Abstract

A retrospective cross-sectional study using data from an outpatient clinic in China was conducted to investigate the clinical features of early-onset gout patients.

All patients diagnosed with gout were asked about clinical characteristics of their gout and comorbid diseases. Patients presenting with acute flares were asked about common triggers before the flare. “Early-onset” gout was defined as onset of gout before 40 years and “late-onset” as onset ≥ 40 years. Major joint involvement, flare frequency before presentation, the cumulative number of involved joints, proportions of tophi complications at presentation, flare triggers, as well as any metabolic, cardiovascular, cerebrovascular, and renal comorbidities, were compared between the 2 groups.

A total of 778 gout patients were enrolled in this study, including 449 (57.7%) in the early-onset group and 329 (42.3%) in the late-onset group. Compared with the late-onset gout patients, the early-onset gout patients had a higher proportion of ankle/mid-foot involvement (62.8% vs 48.2%, $P < 0.001$), more frequent flares before presentation (11.2 ± 1.17 vs 6.97 ± 1.03 times per year, $P = 0.01$), higher cumulative number of involved joints (5.2 ± 0.26 vs 3.8 ± 0.26 , $P < 0.001$), and more likely to have alcohol consumption as a flare trigger (65.2% vs 53.9%, $P = 0.03$); whereas early-onset gout patients had fewer metabolic, cardiovascular, cerebrovascular, or renal complications.

Early- and late-onset gout patients had different clinical features. Early-onset seems to be influenced more by lifestyle, while late-onset patients have more complications because of comorbidities.

Abbreviations: ABCG2 = ATP-binding cassette family, G-subfamily, No. 2, BMI = body mass index, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, IRB = Institutional Review Board, MTP1 = first metatarsophalangeal, PUMCH = Peking Union Medical College Hospital, RR = relative risk, SNP = single nucleotide polymorphism, SUA = serum uric acid, TG = total triglyceride.

Keywords: clinical features, comorbidity, early onset, gout, lifestyle

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1. Introduction

Gout is a common form of chronic arthritis with distinct clinical features. In addition to resulting in erosive arthritis, gout is also a risk factor for renal, cardiovascular, and cerebrovascular diseases, causing a decreased quality of life and increased social and medical burdens.^[1] Gout has been commonly believed to be a disease of elderly men, with an average onset age of 60 years or more.^[2] In contrast, in recent years, Chen et al^[3] and Yu^[4] found a trend of earlier gout onset in Taiwan, and Kuo et al^[5] reported a second peak of incidence at 30 to 39 years of age and a trend of younger disease onset. Studies on early-onset gout, however, are lacking. Chen and Shen^[6] published a cohort study on juvenile gout, finding that a significant percentage of these patients were overweight and had a family history. Yamanaka^[7] reviewed the causes of gout and hyperuricemia in the young, emphasizing secondary and genetic diseases. Finally, Matsuo et al^[8] found that an ATP-binding cassette family, G-subfamily, No. 2 (ABCG2) gene polymorphism was associated with early-onset gout. All other literature on this topic consists of case reports. However, the clinical features of early-onset gout are still poorly characterized.

We observed a large number of young gout patients at the GOUT clinic of Peking Union Medical College Hospital

(PUMCH) from 2008 to 2014. We retrospectively reviewed data from the GOUT clinic with the aim of studying the clinical and genetic characteristics of gout patients with an early disease onset.

2. Methods

2.1. Subjects

A retrospective observational study was conducted in patients presenting to the GOUT clinic of PUMCH from June 2008 to July 2014. Patients with microscopically identified monosodium urate crystals, or with at least 6 of the 12 classification criteria of the 1977 American College of Rheumatology criteria for gout, were consecutively enrolled. Patients with prior tumors, secondary gout, or missing information regarding the age of onset were excluded. This study was approved by the Institutional Review Board (IRB) at PUMCH, and each subject signed the informed consent.

Patients with a disease onset at less than 40 years of age were defined as the “early-onset” group, and those with an onset at 40 years or older were defined as the “late-onset” group.^[4]

2.2. Parameters

All patients enrolled were asked about demographic and geographic (local or nonlocal based on residential address) information, clinical characteristics of their gout, and comorbid diseases. Demographic information included sex, birth, and race. Clinical features included the age of gout onset, disease duration (years), self-reported gout flare frequency during the year following the first gout flare (first year flare frequency, times per year) and self-reported gout flare frequency during the year before presentation (recent flare frequency, times per year), the cumulative number of joints involved (joint number), the pattern of joint involvement, the presence of tophi (yes or no), and the peak serum uric acid (SUA) level. Comorbid diseases included previously physician-diagnosed hypertension, type 2 diabetes, cardiovascular diseases, cerebrovascular diseases, and chronic renal diseases caused by hyperuricemia or gout.

In addition, patients presenting with acute gouty flares, characterized by acute pain, redness, and swelling of 1 joint as assessed by an experienced physician, were asked whether they had encountered the following triggers 48 hours before the flare: alcohol intake, high-purine food ingestion, diuretics or aspirin intake, sports, or trauma.

The estimated glomerular filtration rate (eGFR) was calculated using the CGC1 (Cockcroft-Gault) equation: $eGFR (mL/min/1.73 m^2) = (140 - \text{age}) \times \text{weight (kg)} \times \text{constant/serum creatinine } (\mu\text{mol/L})$ (the constant is 1.23 in men and 1.04 in women), and renal damage was defined as an $eGFR < 60 mL/min/1.73 m^2$. According to the 2011 Chinese Expert Consensus on Obesity, obesity was defined as a body mass index (BMI) $\geq 28 kg/m^2$. Dyslipidemia was defined as having one of the following 4 items: total triglyceride (TG) $\geq 1.7 mmol/L$, total cholesterol $\geq 5.17 mmol/L$, low-density lipoprotein cholesterol $\geq 3.36 mmol/L$, or high-density lipoprotein cholesterol (HDL-C) $< 0.9 mmol/L$ in men or $< 1.0 mmol/L$ in women. Metabolic syndrome was defined as having 3 or more of the 4 items: BMI $\geq 25.0 kg/m^2$, fasting blood glucose $\geq 6.1 mmol/L$ and/or a history of diabetes, systolic blood pressure/diastolic blood pressure $\geq 140/90 mm Hg$ and/or a history of hypertension, and TG $\geq 1.7 mmol/L$ and/or HDL-C $< 0.9 mmol/L$ in men or $< 1.0 mmol/L$ in women.

2.3. Genetic study

The genetic study started in January 2013, after which patients enrolled in this study were asked to sign an additional informed consent to participate in the genetic study if they agreed to do so. This genetic study was also approved by the IRB at PUMCH. The ABCG2 gene abnormality, assessed by 2 single nucleotide polymorphisms (SNPs) rs2231142 and rs72552713, has been reported to be associated with early-onset gout.^[8] Thus, we sequenced the 2 SNPs using a direct sequencing method (Roche Diagnosis 454 GS FLX+ platform, Majorbio Bio-pharm Tech[®], Shanghai, China). ABCG2 protein functions were estimated according to the model proposed by Matsuo et al^[8]: normal function (genotypes CC and CC, respectively), 3/4 function (CA and CC, respectively), 1/2 function (AA and CC, respectively, or CC and CT, respectively), and 1/4 or less function (CA and CT, respectively, or AA and CT, respectively).

2.4. Statistical analysis

Continuous variables between early- and late-onset groups were compared with the *t* test, and categorical variables were compared with the χ^2 test or Fisher exact test. Linear regression analysis was used to analyze the association between gout severity (recent flare frequency and cumulative number of involved joints) and disease parameters (gout age of onset, disease duration, and SUA). Sex, BMI, metabolic syndrome, and eGFR were then adjusted for analyzing the association between gout severity and the 3 disease parameters. Missing data were omitted. A value of $P < 0.05$ was defined as significant. Stata 10.0 (StataCorp, College Station, TX) was used for the statistical analysis.

3. Results

A total of 778 gout patients were enrolled in this study, including 449 (57.7%) in the early-onset group (onset age < 40 years) and 329 (42.3%) in the late-onset group (onset age ≥ 40 years). All patients were ethnic Chinese Han. Women constituted 2.1% of the whole cohort. Nonlocal residents constituted the majority of the patients, especially in the early-onset group (Table 1).

3.1. Early- and late-onset gout patients had distinct clinical features of gout

The average age of gout onset in the whole cohort was 38.3 ± 0.45 years, 29.5 ± 0.29 in the early-onset group and 50.4 ± 0.48 in the late-onset group. The average disease duration was 6.7 ± 0.23 years, which was significantly increased in the early-onset group (7.8 ± 0.32 years) compared with the late-onset group (5.4 ± 0.30 years, $P < 0.001$). The average SUA was $571.4 \pm 5.39 \mu\text{mol/L}$, which was significantly higher in the early-onset group ($595.8 \pm 7.09 \mu\text{mol/L}$) compared with the late-onset group ($536.8 \pm 7.77 \mu\text{mol/L}$, $P < 0.001$) (Table 1).

First metatarsophalangeal (MTP1) involvement is characteristic of gouty arthritis. Ankle and mid-foot involvement are also among the most commonly involved joints in patients with gout. Thus, we analyzed the involvement pattern of these joints. Nearly 3/4 of the gout patients had MTP1 involvement at some point, but the incidence was slightly but significantly lower in the early-onset gout patients (72.4%) than in the late-onset patients (82.2%, $P = 0.002$). More than half of the patients had ankle or mid-foot involvement, with a higher incidence in the early-onset gout patients (62.8%) than in the late-onset patients (48.2%, $P = 0.001$).

Table 1**Clinical and genetic features of the early- and late-onset gout groups.**

| | Total | Early onset (<40y) | Late onset (≥40y) | P |
|--|-------------|--------------------|-------------------|--------|
| Geographic features | (n=778) | (n=449) | (n=329) | |
| Female, % | 2.1 | 1.3 | 3.0 | 0.098 |
| Nonlocal, % | 62.7 | 68.0 | 55.4 | <0.001 |
| Clinical features of gout | (n=778) | (n=449) | (n=329) | |
| Age of onset, y; mean±SE | 38.3±0.45 | 29.5±0.29 | 50.4±0.48 | <0.001 |
| Disease duration, y; mean±SE | 6.7±0.23 | 7.8±0.32 | 5.4±0.30 | <0.001 |
| SUA, μmol/L; mean±SE | 571.4±5.39 | 595.8±7.09 | 536.8±7.77 | <0.001 |
| MTP1 involvement, % | 76.6 | 72.4 | 82.2 | 0.002 |
| Ankle or mid-foot involvement, % | 56.6 | 62.8 | 48.2 | 0.001 |
| First year flare frequency [*] , mean±SE | 2.34±0.10 | 2.41±0.13 | 2.25±0.17 | 0.452 |
| Recent flare frequency [†] , mean±SE | 9.43±0.81 | 11.21±1.17 | 6.97±1.03 | 0.010 |
| No. of involved joints, mean±SE | 4.57±0.19 | 5.2±0.26 | 3.8±0.26 | <0.001 |
| Tophi [‡] , % | 23.5 | 24.5 | 22.2 | 0.453 |
| Flare triggers | (n=358) | (n=204) | (n=154) | |
| Alcohol, n (%) | 60.30 | 65.2 | 53.9 | 0.030 |
| Beer, n (%) | 32.40 | 37.3 | 26.0 | 0.024 |
| Spirits, n (%) | 31.80 | 35.3 | 27.3 | 0.107 |
| Wine, n (%) | 2.50 | 3.4 | 1.3 | 0.202 |
| High-purine food, n (%) | 69.60 | 72.5 | 64.9 | 0.156 |
| Red meat, n (%) | 40.30 | 41.2 | 39.2 | 0.709 |
| Seafood, n (%) | 27.90 | 30.4 | 24.7 | 0.233 |
| Animal organs, n (%) | 14.20 | 15.7 | 12.3 | 0.369 |
| Medication, n (%) | 5.00 | 3.9 | 6.5 | 0.270 |
| Sports and trauma, n (%) | 37.90 | 44.1 | 29.9 | 0.005 |
| Others, n (%) | 5.80 | 6.9 | 4.6 | 0.365 |
| Metabolic diseases | (n=741) | (n=416) | (n=281) | |
| Obesity [§] , % | 35.30 | 37.90 | 31.60 | 0.082 |
| BMI, kg/m ² ; mean±SE | 26.89±0.13 | 27.12±0.186 | 26.58±0.183 | 0.047 |
| Dyslipidemia [¶] , % | 66.50 | 64.80 | 68.80 | 0.271 |
| Triglycerides, mmol/L; mean±SE | 2.78±0.133 | 3.03±0.215 | 2.45±0.113 | 0.016 |
| HDL-C, mmol/L; mean±SE | 1.04±0.015 | 1.02±0.018 | 1.06±0.0252 | 0.259 |
| Hypertension, % | 65.5 | 59.9 | 73.1 | <0.001 |
| Diabetes mellitus, % | 11.0 | 6.7 | 16.9 | <0.001 |
| Metabolic syndrome [#] , % | 38.2 | 31.7 | 47.1 | <0.001 |
| Cardiovascular events | (n=778) | (n=461) | (n=317) | |
| Coronary artery disease, % | 3.2 | 1.3 | 5.8 | <0.001 |
| Cerebrovascular disease, % | 3.3 | 1.1 | 6.4 | <0.001 |
| Renal complication | (n=439) | (n=155) | (n=284) | |
| Renal damage ^{**} , % | 16.4 | 4.5 | 22.9 | <0.001 |
| eGFR, mL/min/1.73 m ² ^{††} ; mean±SE | 84.84±1.360 | 101.63±2.429 | 75.68±1.350 | <0.001 |
| ABCG2 protein function | (n=142) | (n=83) | (n=59) | |
| Normal, % | 17.6 | 20.5 | 13.6 | 0.373 |
| Abnormal function, % | 82.4 | 79.5 | 86.4 | |

BMI = body mass index, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, MTP1 = first metatarsophalangeal, SE = standard error, SUA = serum uric acid.

* First year flare frequency (times per year): self-reported flare frequency during the year after the first gout flare.

† Recent flare frequency (times per year): self-reported flare frequency during the year before presentation.

‡ Tophi: the proportion of patients complicated with tophi at presentation.

§ Obesity is defined as BMI ≥ 28 kg/m² by the 2011 Chinese Expert Consensus on Obesity.

|| BMI is calculated by the equation BMI = weight (kg)/height (m) × height (m).

¶ Dyslipidemia is defined as total triglyceride ≥ 1.7 mmol/L, total cholesterol ≥ 5.17 mmol/L, low-density lipoprotein cholesterol ≥ 3.36 mmol/L, high-density lipoprotein cholesterol < 0.9 mmol/L in men or < 1.0 mmol/L in women by the 2011 Chinese Expert Consensus on Obesity.

Metabolic syndrome is defined as 3 or more of the 4 items: BMI ≥ 25.0 kg/m², fasting blood glucose ≥ 6.1 mmol/L and/or history of diabetes; systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg and/or a history of hypertension; triglycerides ≥ 1.7 mmol/L and/or HDL-C < 0.9 mmol/L in men or < 1.0 mmol/L in women.

** Renal damage is defined as eGFR < 60 mL/min/1.73 m².

†† eGFR is calculated by the CGC1 equation: eGFR (mL/min/1.73 m²) = (140 - age) × weight (kg) × constant/serum creatinine (μmol/L) (constant is 1.23 in men and 1.04 in women).

The flare frequency increased as the disease course progressed. Although the flare frequency during the first year was similar in the 2 groups, the self-reported recent gout flare frequencies were higher in the early-onset group, 11.21 ± 1.17 times per year, as compared with 6.97 ± 1.03 times per year in the late-onset group, $P=0.010$. The cumulative number of joints involved at presentation was also higher in the early-onset group (5.2 ± 0.26) compared with the late-onset group (3.8 ± 0.26, $P < 0.001$).

Both groups had nearly 1/4 of patients complicated with tophi at presentation (Table 1).

In linear regression analysis, age of disease onset ($\beta = -0.114$, $P=0.003$), disease duration ($\beta = 0.300$, $P < 0.001$), and SUA ($\beta = 0.244$, $P < 0.001$) were all significantly associated with recent flare frequency. Similarly, age of disease onset ($\beta = -0.155$, $P < 0.001$), disease duration ($\beta = 0.461$, $P < 0.001$), and SUA ($\beta = 0.190$, $P < 0.001$) were also significantly associated

Table 2**Crude and adjusted linear regression analysis for recent flare frequency and cumulative number of involved joints.**

| | Crude | | | | Adjusted (model 1) | | | | Adjusted (model 2) | | | |
|---|--------|-------|---------|----------|--------------------|-------|---------|----------|--------------------|-------|---------|----------|
| | Coef | SE | β | <i>P</i> | Coef | SE | β | <i>P</i> | Coef | SE | β | <i>P</i> |
| Recent flare frequency | | | | | | | | | | | | |
| Onset age* | -0.047 | 0.016 | -0.114 | 0.003 | -0.007 | 0.019 | -0.015 | 0.735 | -0.047 | 0.027 | -0.109 | 0.085 |
| Duration† | 0.284 | 0.035 | 0.300 | <0.001 | 0.276 | 0.043 | 0.283 | <0.001 | 0.354 | 0.048 | 0.375 | <0.001 |
| SUA‡ | 0.011 | 0.002 | 0.244 | <0.001 | 0.009 | 0.002 | 0.214 | <0.001 | 0.006 | 0.002 | 0.128 | 0.011 |
| Cumulative number of involved joints | | | | | | | | | | | | |
| | Coef | SE | β | <i>P</i> | Coef | SE | β | <i>P</i> | Coef | SE | β | <i>P</i> |
| Onset age* | -0.063 | 0.015 | -0.155 | <0.001 | -0.009 | 0.016 | -0.023 | 0.574 | -0.022 | 0.031 | -0.053 | 0.473 |
| Duration† | 0.407 | 0.029 | 0.461 | <0.001 | 0.302 | 0.030 | 0.399 | <0.001 | 0.263 | 0.055 | 0.272 | <0.001 |
| SUA‡ | 0.008 | 0.002 | 0.190 | <0.001 | 0.006 | 0.001 | 0.155 | <0.001 | 0.009 | 0.002 | 0.201 | <0.001 |

Adjusted model 2 = further adjusted for sex; Adjusted model 1 = adjusted for disease onset age, disease duration, and serum uric acid level; BMI = metabolic syndrome and eGFR.

* Onset age: disease onset age.

† Duration: disease duration.

‡ Coef = coefficient, SE = standard error, SUA = serum uric acid level.

with the cumulative number of joints involved (Supplementary figure, <http://links.lww.com/MD/B411>). After adjustment for disease onset age, disease duration, SUA level, sex, BMI, metabolic syndrome, and eGFR, the associations by age of disease onset were attenuated for both recent flare frequency ($P=0.085$) and the cumulative number of joints involved ($P=0.473$); while disease duration and SUA remained significantly associated with recent flare frequency and the cumulative number of joints involved ($P=0.011$ to $\sim<0.001$) (Table 2). In subgroup analysis, disease duration was consistently associated with both disease severity parameters in both early- and late-onset groups; however, SUA was significantly associated with recent flare frequency and was marginally significantly associated with cumulative number of involved joints only among early-onset group (Supplementary table, <http://links.lww.com/MD/B411>).

3.2. A higher proportion of early-onset gout patients had alcohol consumption before gout flares

A total of 358 patients presented with acute flares, confirmed by an experienced physician. Among these patients, 60.3% reported alcohol intake and 69.6% reported high-purine food intake before their gout flare. Compared with the late-onset group, a higher proportion of patients in the early-onset group had consumed alcohol (65.2% vs 53.9%, $P=0.030$), especially beer, before the gout flare (37.3% vs 26.0%, $P=0.024$). The proportions of patients reporting high-purine food intake before gout flare were similar in the 2 groups. More patients in the late-onset group reported diuretics and/or aspirin intake before their gout flare (6.5% vs 3.9%, $P=0.27$), while more patients in the early-onset group reported sports or trauma before their gout flare (44.1% vs 29.9%, $P=0.005$) (Table 1).

3.3. Cardiovascular, cerebrovascular, and renal comorbidities were more prevalent in late-onset gout patients

The proportions of obesity and dyslipidemia were similar between the 2 groups, whereas BMI and serum triglyceride levels were slightly higher in the early-onset group (Table 1). In contrast, the proportions of hypertension, diabetes mellitus, and metabolic syndrome at presentation were significantly lower in

the early-onset group (59.9%, 6.7%, and 31.7%, respectively) compared with the late-onset group (73.1%, 16.9%, and 47.1%, respectively). The proportions of coronary artery disease and cerebrovascular disease were also significantly lower in the early-onset group (1.3% and 1.1%, respectively) than in the late-onset group (5.8% and 6.4%, respectively) (Table 1).

Compared with the late-onset group, patients in the early-onset group had relatively preserved renal function, with higher eGFR levels (101.63 ± 2.429 vs 75.68 ± 1.350 mL/min/1.73 m², $P < 0.001$) and fewer patients with renal damage (eGFR < 60 mL/min/1.73 m²) (Table 1).

3.4. Genetic study revealed a high prevalence of ABCG2 protein dysfunction but no difference between the 2 groups

A total of 142 patients consented to the genetic study. An ABCG2 protein function abnormality was detected in 82.4% of the patients, 79.5% in the early-onset group and 86.4% in the late-onset group (Table 1). The average ages of disease onset in the full protein function group, 3/4 function group, 1/2 function group, and 1/4 function group were 37.1 ± 1.96 , 36.7 ± 1.29 , 38.0 ± 2.29 , and 30.4 ± 5.45 years, respectively; no significant differences were observed.

4. Discussion

Within this Chinese cohort of gout patients, we described a group of 449 patients with an age of disease onset of less than 40 years (early-onset group) and 329 patients with an age of disease onset age of 40 years or more (late-onset group). Compared with patients with a late disease onset, patients with an early disease onset had more frequent flares and more joints involved after a long disease duration but a lower proportion of cardiovascular, cerebrovascular, and renal comorbidities at presentation.

MTP1 was the most commonly involved joint in both groups. However, a large proportion of patients with early-onset gout had ankle/mid-foot involvement, which might be explained by the higher proportions of engagement in sports and trauma observed in these patients. Engagement in sports and trauma may specifically provide templates and collagen fibers for crystal nucleation, thus precipitating monosodium urate formation and

precipitate gout flares.^[9] Previously, De Leonardis et al^[10] reported that in elderly gout patients (onset age of ≥ 65 years), gout often involves the hand joints, with unusual localization of tophi on osteoarthritic nodes. Thus, the joint involvement pattern of early- and late-onset gout patients differs.

In previous studies, tophus formation was used as a marker for gout severity.^[4] In the present study, because the proportion of patients presenting with tophi were similar between the early- and late-onset patients, we chose recent flare frequency (self-reported gout flare frequency during the year before presentation) and the joint numbers (cumulative number of involved joints) as markers of gout severity. Patients in the early-onset group had more severe gout. Adjusted linear regression analysis revealed that the association between gout severity and age of gout onset were attenuated when disease duration and SUA were included in the model. Thus, the greater severity of gout in patients in the early-onset group might have been due to the longer disease duration and higher SUA level.

Although we lack data on general lifestyle, data about flare triggers might provide a clue to the patients' habitual lifestyle to some extent. In the present study, alcohol and high-purine food consumption were significant triggers in both groups, and compared with the late-onset patients, early-onset patients had a slightly but significantly higher proportion of having alcohol consumption, especially beer, as a gout trigger. Alcohol consumption, particularly beer, is known to be a significant risk factor for gout. In 1 longitudinal study, alcohol consumption showed a dose-dependent increased risk of gout, with a multivariate relative risk (RR) per 10g increase in daily alcohol intake of 1.17 (95% confidence interval [CI] 1.11–1.22) and a multivariate RR per 12oz beer per day of 1.49 (95% CI 1.32–1.70).^[11] In addition, the early-onset gout patients had significantly higher levels of serum TGs, which was associated with Western dietary patterns.^[12,13] Moreover, early-onset gout patients also had a slight but significantly higher BMI, which is in accordance with the findings of Chen and Shen.^[6] Thus, early-onset gout patients might be more influenced by lifestyle factors.

Higher proportions of aspirin and diuretics usage as gout triggers were seen in late-onset gout patients. Although high doses of aspirin (>3 g/d) inhibit urate reabsorption, low doses (1–2g/d) trans-stimulate urate reabsorption and therefore increases SUA levels.^[14] Low-dosage aspirin, commonly used for cerebrovascular and cardiovascular preventive therapy, was associated with a 1.8-fold increased risk of recurrent gout.^[15] Commonly used diuretics, including loop, thiazide, and thiazide-like diuretics, are known to enhance urate absorption in the renal tubules^[16] and to increase gout risk by 1.7- to 2.64-fold.^[17] Moreover, the proportions of hypertension, diabetes, and metabolic syndrome as well as coronary artery and cerebrovascular diseases were all significantly lower in the early-onset group than in the late-onset group, while renal function was relatively preserved in the early-onset gout patients compared with the late-onset patients. These results suggest less influence of baseline cardiovascular and renal comorbidities in early-onset gout patients. However, in a meta-analysis, Liu et al^[18] found a gradual increase in myocardial infarction risk in patients with early-onset gout (gout onset age 20–44, 45–69, ≥ 70 years; RR 2.82, 95% CI 1.38–5.79; RR 1.85, 95% CI 1.22–2.82; and RR 1.52, 95% CI 1.22–1.88; respectively). In addition, in the present study, the proportions of hypertension, diabetes, and metabolic syndrome in patients younger than 40 years at presentation were 59.9%, 6.7%, and 31.7%, respectively, higher than the prevalence in the general Chinese population within the same

age ranges (20%,^[19] 3.2%,^[20] and 6.1%,^[21] respectively). Therefore, although patients with early-onset gout had fewer cardiovascular comorbidities compared with late-onset gout patients, these patients possessed higher risks for further cardiovascular events compared with the general population, and therefore, careful evaluation and more intensive health management should probably be initiated early.

Previous reports suggested that positive family history was common in early-onset gout patients, while familial juvenile hyperuricemic nephropathy may only constitute 15% of juvenile gout patients,^[4,6] suggesting other genetic factors in these patients. In recent years, genome-wide association studies have identified multiple risk loci associated with gout.^[22] *ABCG2*, encoding a unidirectional transporter *ABCG2* involved in urate secretion in both the kidney and the intestine, is one of the most consistent and strong loci associated with gout.^[23] SNP rs2231142 results in an abnormal protein structure and decreased protein expression, reducing the protein's function by 54%,^[24] and rs72552713 reduces the protein's function by nearly 100%.^[25] Matsuo et al^[8] reported that patients with both SNPs and therefore severe *ABCG2* abnormality (1/4 function or less) have very early disease onset and that patients with very early disease onset have more severe *ABCG2* abnormality. Although our results did not reach significance, likely due to the small sample size, we did find a trend of earlier gout onset in patients with more severe *ABCG2* abnormality. In addition, the findings that SUA was associated with recent flare frequency and cumulative number of involved joints among early-onset group suggested the importance of *ABCG2* gene in early-onset patients and that it might be a reliable biomarker in earlier gout onset.

This study had several limitations. First, this is a retrospective study and depends on patient-reported responses and therefore there may be misclassification bias, since patients with a longer disease duration tend to not recollect clearly the exact date of onset and frequency of flare in the first year, which might result in bias in our final results. Second, PUMCH is a general medical center, and patients presenting to our clinic usually had a more severe disease, which might have caused patient bias. Third, this is a cross-sectional study of an outpatient clinic, the sample size was small, and the rate of successful follow-up was relatively low. A well designed prospective study, such as one using national electrical medical records that could follow the entire disease course, would be helpful for further studies of the clinical and genetic characteristics of early- and late-onset gout patients.

Nevertheless, this study described a group of early-onset gout patients with distinct clinical features, which suggests a higher influence of lifestyle and physical characteristics and less association with cardiovascular and renal diseases. However, patients with early-onset gout might suffer from more severe gout as disease progresses and be at a higher risk for future cardiovascular events. Further study of early-onset gout patients might be of importance for controlling the rising prevalence of gout and hyperuricemia in the younger population.

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