Frequency, Risk, and Cost of Gout-related Episodes Among the Elderly: Does Serum Uric Acid Level Matter?

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ABSTRACT. ***Objective.*** We examined the association between serum uric acid (SUA) level and the frequency, risk, and cost of gout flares among the elderly.

Methods. Data were extracted from the Integrated Healthcare Information Services claims database (1999-2005). Patients were included if they had gout, were aged 65 years and older and had both medical and pharmacy benefits, and electronic laboratory data. Patients with gout and gouty episodes were identified using algorithms based on ICD-9-CM codes and medications. Logistic regression and negative binomial regressions were used to study the relationship between SUA concentration and the annual frequency and one-year risk of gout episodes. Generalized linear models were used to examine the direct healthcare costs associated with gout episodes in the 30 days following each episode.

Results. Elderly patients with gout (n = 2237) with high (6–8.99 mg/dl) and very high (> 9 mg/dl) SUA concentrations were more likely to develop a flare within 12 months compared to patients with normal (< 6 mg/dl) SUA levels (OR 2.1, 95% CI 1.7–2.6; OR 3.4, 95% CI 2.6–4.4, respectively). In multivariate regressions, the average annual number of flares increased by 11.9% ($p < 0.001$) with each unit-increase in SUA level above 6 mg/dl ($p < 0.001$). Among patients with very high SUA levels, average adjusted total healthcare and gout-related costs per episode were $2,555 and $356 higher, respectively, than those of patients with normal SUA levels (both $p < 0.001$).

Conclusion. Higher SUA levels are associated with increased frequency and risk of gout episode, and with higher total and gout-related direct healthcare costs per episode. (J Rheumatol First Release April 15 2009; doi:10.3899/jrheum.080487)

Key Indexing Terms:
GOUT AGING ECONOMICS EPIDEMIOLOGY

Gout currently affects more than 5.1 million people in the US[1], and is the most common cause of inflammatory arthritis in men[2,3]. Further, the prevalence of gout has increased in recent decades, especially among the elderly population[2,4,5]. From 1990 to 1999, the prevalence of gout among individuals aged 65–74 years increased by 30% or more and, over the same period, the prevalence of gout among individuals aged 75 years or older almost doubled[4]. Increases in prevalence of gout extend beyond the US as well, as worldwide increases in incidence have been noted[2,5-10].

The most important risk factor for gout is hyperuricemia, a state of elevated serum uric acid (SUA) concentration[11-15]. Although the physiological pathway between hyperuricemia and gout episodes is well understood, the relationship has not been well studied from an epidemiological perspective. To our knowledge, only 2 studies have directly addressed this relationship[16,17]. While both studies concluded that high SUA is associated with an increased risk of gout episodes, neither study focused on the elderly population, the age group with the highest risk of gout. Moreover, the treatment of gout flares often entails extensive healthcare resources, yet no study to our knowledge has examined the direct healthcare costs of gout flares. Further, relatively few studies have examined the economic effects of lowering SUA in patients with gout, even though a cost-effective approach for management of many diseases is to control the associated risk factors[18,19]. The only study to our knowledge that inves-

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tigated the cost-effectiveness of urate-lowering drugs in patients with nontophaceous recurrent gouty arthritis concluded that the treatment was cost-effective[20]. However, the costs and benefits were estimated based on a hypothetical cohort instead of actual patients' data and the outcome measure was the number of attacks per year, not cost per gout flare.

Our study fills these gaps in the literature by examining the frequency and risk of gout flares among the elderly, and their associated costs. We also assess the association between SUA levels and total and gout-related healthcare costs of gout flares among the elderly population.

MATERIALS AND METHODS

Database. Data for this study were obtained from the Integrated Healthcare Information Services (IHCIS) claims database (1999-2005). IHCIS includes more than 13 million enrollees from 35 health plans that cover all census regions in the US. The IHCIS database contains rich information on health plan eligibility, medical claims, pharmacy claims, and laboratory results, and has been used extensively to study healthcare utilization and healthcare costs[21-24].

Patient selection. This study included all enrollees in the IHCIS database who had gout, who were aged 65 years and older, and who had both medical and pharmacy benefits, as well as electronic laboratory data. An enrollee was defined as having gout if she/he had 2 independent diagnoses of gout [*International Classification of Disease*, 9th Revision, Clinical Modification[25] (ICD-9-CM), 274.xx] or one gout diagnosis and a gout-related prescription claim (i.e., allopurinol, probenecid, colchicines, or sulfinpyrazone) between January 1, 1999, and December 31, 2005. The second criterion was used in order to identify gout patients who may have had insufficient claims data to identify gout based on diagnoses alone. In order to be included in the sample, gout patients also had to have a SUA laboratory test value and a minimum of one year continuous eligibility both before and after the index date, defined as the earliest observed SUA laboratory test since January 1, 2000.

Definition of gout episodes or flares. To our knowledge, a standard epidemiological definition for gout episodes or flares does not exist. Therefore, 2 definitions of gout flares were applied to this study. According to the first definition, a patient was considered to experience a gout flare if she/he had a medical claim for gout (ICD-9-CM, 274.xx) and at least one of the following indicated by pharmacy or medical claims within 7 days following the diagnosis date: any use of nonsteroidal antiinflammatory drugs (NSAID), colchicines, corticosteroids, use of adrenocorticotropic hormone (Healthcare Common Procedure Coding System[26] code J0800), or intraarticular aspiration, or injection (Current Procedure Terminology[27] code 20600, 20605, 20610). According to the second definition, a patient was considered to experience a gout flare if she/he had a medical claim for joint pain (ICD-9-CM, 719.4x) at any time during the study observation period and at least one prescription drug claim for colchicines within 7 days following the diagnosis date. It is important to note that our definition of gout flares is based on claims data only and, to the extent that gout flares were not verified through chart review or direct contact with physicians, the episodes we measure should be considered potential gout flares. Further, to the extent that the outcomes we examined are not associated with gout flares per se, these outcomes should be viewed as those associated with acute gout symptoms. Both these measurement issues are addressed in detail below.

We assessed the frequency of gout flares within 12 months following the index date and the risk of a gout flare within 3, 6, and 12 months following the index date. A gout flare typically lasts 7–10 days but, without treatment, the entire course can last up to a few weeks[28-30]. Therefore, each gout flare was assumed to span the 30-day interval from the first date of a flare. Multiple flares must have occurred beyond this 30-day period to be considered distinct episodes.

Measurement of direct healthcare costs. Direct healthcare costs were estimated based on IHCIS standard cost algorithms. These algorithms are designed by IHCIS to account for differences in pricing across health plans and geographic areas, as well as differences in patient cost-sharing components, such as deductibles and co-payments. The IHCIS cost algorithm adjustments create standard prices for allowed payments and enable valid cost comparisons across patients[31].

Total direct and gout-related direct healthcare costs per flare were calculated based on medical service costs and prescription drug costs during the 30-day period following the onset of a flare. Total direct healthcare costs included inpatient and outpatient services, emergency room visits, and services provided in other locations (e.g., home, ambulatory surgical centers, skilled nursing facilities). Gout-related costs included only costs from medical claims with an ICD-9-CM code of gout and pharmacy claims for gout-related medications (e.g., allopurinol, probenecid). In cases where patients had multiple flares during the one-year period, costs of each flare were accounted for separately. All costs were inflation-adjusted to 2005 US dollars using the medical component of the Consumer Price Index.

SUA level and other patient characteristics. SUA levels were obtained from electronic laboratory data and were classified into 3 groups: normal (< 6 mg/dl), high (6–8.99 mg/dl), and very high (≥ 9 mg/dl). The normal SUA range is consistent with the recommended target levels for individuals with gout[16,32,33]. Research has shown that within this range the majority of gout patients depleted their intraarticular urate crystals[32], and thus had a lower risk of gout flares[16]. This cutoff value was also used in another study examining SUA level and gout flares in a managed-care population[17]. The very high SUA range was chosen because the annual incidence of gouty arthritis was expected to be much higher beyond this level compared with a lower SUA level (4.9% vs 0.1% to 0.5%)[13]. Demographic characteristics (age, sex, geographic region) and comorbidities measured by disease status (e.g., hypertension, diabetes, dyslipidemia) as well as the Deyo-Charlson comorbidity index[34] were also included in the analysis. The Deyo-Charlson index improves upon the Charlson method by relying on sets of ICD-9-CM diagnosis groupings, rather than individual diagnoses.

Statistical analysis. Bivariate association was applied to describe the relationship between the 3 SUA categories and the frequency, risk, and healthcare costs of gout flares. Negative binomial regression, a standard method for modeling count variables, was used to assess the annual frequency of gout flares. Multivariate logistic regression was used to assess the relationship between SUA levels and the risk of gout flares. A restricted cubic spline regression was estimated as well to further examine the nonlinear nature of the relationship between SUA and the risk of gout flares. A generalized linear model with a gamma distribution and log-link function was used to examine the association between SUA levels and healthcare costs. This model specification was used instead of ordinary least-squares regression in order to account for the non-Gaussian distribution of costs. Each of the regression models controlled for age, sex, index year, region, prior comorbidities (hypertension, diabetes, hyperlipidemia, renal impairment, rheumatoid arthritis, lupus), and the Deyo-Charlson comorbidity index. An a priori 2-tailed α level of 0.05 was used for statistical inferences.

RESULTS

Sample characteristics. A total of 2,237 patients with gout met the inclusion criteria of the study (Table 1). We identified 107,558 IHCIS patients who had either (1) 2 diagnoses of gout on different dates or (2) a gout diagnosis and a gout-related pharmacy claim during the date of service period from 1999 to 2005. Of these patients, 52,447 met the 2-year continuous eligibility criteria, and 12,506 patients were also 65 years of age or older. The reduction in sample size from

Table 1. Selection for patients with gout with a least one SUA laboratory test value during the date of service period 1999 to 2005 (n = 2,237).

Category of Patients	No. of Patients
Patients included in IHCIS, selection period 1999–2005	~ 13 million in 2004
Patients with either (1) 2 diagnoses of gout on different dates or (2) gout diagnosis and gout-related pharmacy claim during the date of service period 1999 to 2005	107,558
Patients with minimum of 1 year continuous eligibility both before and after the index date (first date of gout diagnosis)	52,447
Patients age ≥ 65 years at the first date of diagnosis	12,506
Patients with at least one SUA laboratory test value	2,237

IHCIS: Integrated Healthcare Information Services claims database.

12,506 patients to 2,237 patients was due to the requirement that patients needed at least one SUA laboratory test value.

The mean (median) age among patients in the sample was 72.4 (73.0) years (Table 2). The sample was predominantly male (74.4%) and the majority of patients (93.5%) lived in the Atlantic region, a result of the availability of SUA laboratory values. Most patients presented with other prior comorbidities, hypertension being most common (71.3%), followed by hyperlipidemia (38.6%) and diabetes (21.4%). The average Deyo-Charlson comorbidity index was 1.1. Among the gout patients, 633 (28.3%) had a normal SUA value (< 6 mg/dl); 1,173 (52.4%) had a high SUA level (6–8.99 mg/dl); and the remaining 431 (19.3%) patients had a very high SUA level (≥ 9 mg/dl). The prevalence of hypertension and renal impairment increased significantly with SUA level (both $p < 0.001$). The average Deyo-Charlson comorbidity index for the group with very high SUA levels was 1.4, also significantly higher than the other 2 groups, both of which had a mean of 1.0 ($p < 0.001$; Table 2).

Frequency and risk of gout flares. About 40.9% of patients (n = 914) experienced at least one gout flare in the 12-month period following the index date. We found that 92.5% of flares satisfied definition 1 (only), 2.4% of flares satisfied definition 2 (only), and 5.1% of flares satisfied both definitions. Among patients who developed gout flares, 63.3% had one episode within a year, 22.9% had 2, and 13.8% had ≥ 3 episodes (Table 3). The percentage of patients experiencing ≥ 3 flares increased with SUA level (10.6% for SUA < 6 mg/dl, 13.8% for SUA 6–8.99 mg/dl, and 16.2% for SUA ≥ 9 mg/dl). The prevalence of gout flares within 3, 6, and 12 months following the index date was 22.2%, 29.9%, and 40.9%, respectively (Table 3). Again, the results showed a clear positive correlation between the prevalence of flares and SUA levels. The total count of flares within the

Table 2. Characteristics of patients with gout by SUA level.

Characteristics	SUA Level < 6 mg/dl, n = 633	SUA Level 6-8.99 mg/dl, n = 1,173	SUA Level ≥ 9 mg/dl, n = 431	p*	Total, n = 2,237
Demographics					
Age, mean yrs (SD)	72.3 (4.5)	72.4 (4.4)	72.7 (4.2)	0.399	72.4 (4.4)
Male, %	71.4	75.4	75.9	0.126	74.4
Region, %				0.232	
New England	0.2	0.3	0.5		0.3
Atlantic (mid and south)	95.1	93.4	91.2		93.5
Pacific/Mountain	0.2	0.1	0.2		0.1
National	4.6	6.1	7.9		6.0
Other	0.0	0.2	0.2		0.1
Prior comorbidities, %					
Hypertension	66.8	71.2	78.0	0.000	71.3
Diabetes	20.5	21.1	23.4	0.491	21.4
Hyperlipidemia	40.3	38.5	36.4	0.445	38.6
Renal impairment	11.1	12.7	26.0	< 0.001	14.8
Rheumatoid arthritis	3.8	3.0	1.9	0.191	3.0
Lupus	0.0	0.2	0.0	0.436	0.1
Deyo-Charlson comorbidity index, mean (SD)	1.0 (1.5)	1.0 (1.6)	1.4 (1.9)	< 0.001	1.1 (1.6)

* p values for significant differences in percentages across the 3 SUA levels based on chi-square tests; p values for differences by age and comorbidity index across the 3 SUA levels based on ANOVA.

Table 3. Risk and frequency of gout flares by SUA level.

	SUA Level			
	< 6 mg/dl	6-8.99 mg/dl	≥ 9 mg/dl	Total
Total no. gout patients	633	1,173	431	2,237
Frequency of flares within 12 months among gout patients with at least one flare, %				
1 flare	70.0	62.7	60.0	63.3
2 flares	19.4	23.6	23.8	22.9
≥ 3 flares	10.6	13.8	16.2	13.8
Gout patients with at least one flare, %				
Within 3 mo	13.7	23.3	31.8	22.2
Within 6 mo	18.8	31.3	42.5	29.9
Within 12 mo	26.9	43.4	54.5	40.9
No. flares within 12 months among gout patients with at least one flare, mean (SD)	1.5 (0.8)	1.6 (0.9)	1.7 (1.2)	1.6 (1.0)

12-month period amounted to 1,448, with an average of 1.6 (SD 1.0) among patients with at least one gout flare. The average number of gout flares was 1.5 (SD 0.8) for patients with an SUA level < 6 mg/dl, 1.6 (SD 0.9) for those with SUA 6–8.99 mg/dl, and 1.7 (SD 1.2) for those with SUA ≥ 9 mg/dl, indicating a positive association with the SUA value.

Logistic regressions showed that patients with a baseline SUA of 6–8.99 mg/dl were significantly more likely to experience a gout flare within 12 months than those with SUA < 6 mg/dl (OR 2.1, 95% CI 1.7–2.6; Table 4). Patients with SUA ≥ 9 mg/dl were also significantly more likely to have a gout flare compared to those in the lowest SUA category (OR 3.4, 95% CI 2.6–4.4; Table 4). The results for the 3- and 6-month period were consistent with the findings for the 12-month period, albeit with lower odds ratios.

We also examined the total count of gout flares using a multivariate approach. A negative binomial regression model of frequency of gout flares showed that the annual number of gout flares appeared to be unrelated to SUA level when its value was < 6 mg/dl (i.e., that incremental reductions in SUA below 6 mg/dl did not reduce the number of gout flares; Table 5). This result can be seen in both the regression coefficients and in the percentage change in the number of flares. Regarding the coefficients, negative binomial regression models the log of the frequency of gout flares as a function of independent variables, as shown in Table 5. The coefficient can be interpreted as the difference in the number of gout flares (in logs) that is associated with a 1-unit change in the independent variable. The regression coefficients change little with each 1-unit change in SUA when SUA is < 5.99, as does the percentage change in the number of flares. However, when the value exceeded 6

Table 4. Odds ratios (95% confidence intervals) of risk of gout flares by SUA level. Control variables used in the regression are age, sex, index year, region, prior comorbidities (as in Table 2), and Deyo-Charlson comorbidity index. The reference group is a SUA level < 6 mg/dl.

	Time Period from the SUA Date		
SUA Level, mg/dl	Within 3 mo	Within 6 mo	Within 12 mo
< 6	1	1	1
6–8.99	2.0 (1.5–2.5)	2.0 (1.6–2.5)	2.1 (1.7–2.6)
≥ 9	3.1 (2.3–4.3)	3.4 (2.5–4.5)	3.4 (2.6–4.4)

All odds ratios are statistically significant with $p < 0.05$.

Table 5. Multivariate regression coefficients for frequency of gout flare analysis with detailed SUA categories.

Independent Variable	Coefficient	Change in no. of Flares, %	p
Intercept	1.089	197.1	0.058
SUA level, mg/dl			
< 3	–0.862	–57.8	0.006**
3 to 3.99	–1.142	–68.1	< 0.0001**
4 to 4.99	–0.905	–59.5	< 0.0001**
5 to 5.99	–0.897	–59.2	< 0.0001**
6 to 6.99	–0.610	–45.7	< 0.0001**
7 to 7.99	–0.311	–26.8	0.006**
8 to 8.99	–0.241	–21.4	0.041*
9 to 9.99	–0.143	–13.3	0.256
≥ 10	—	—	—
Index year			
2001	–0.301	–26.0	0.011*
2002	–0.214	–19.3	0.051
2003	–0.073	–7.0	0.489
2004	—	—	—
Demographic			
Age at SUA index year	–0.014	–1.4	0.066
Male	0.048	4.9	0.526
Prior comorbidities			
Hypertension	–0.047	–4.6	0.518
Diabetes	–0.292	–25.3	0.001**
Hyperlipidemia	–0.042	–4.1	0.528
Renal impairment	0.181	19.9	0.055
Rheumatoid arthritis	0.716	104.7	< 0.0001**
Lupus	–0.187	–17.0	0.824
Deyo-Charlson comorbidity index	0.004	0.4	0.849
HMO indicator (vs non-HMO)	0.132	14.1	0.111
Dispersion	0.573		

* Significant at 95% level; ** significant at 99% level. HMO: health maintenance organization.

mg/dl, the average number of gout flares increased by 11.9% (95% CI 7.1% to 17.0%) with each unit-increase in SUA (Table 6).

To examine the nonlinear relationship between SUA and gout flares visually, a spline regression with 6 degrees of freedom was estimated, controlling for the same set of covariates as in the previous model. The predicted risk of a gout flare as a function of SUA for a typical patient (i.e., with average covariate values) is shown in Figure 1. Overall, the predicted risks were consistent with the results shown in the descriptive statistics and logistic regression. Moreover, the spline revealed that further reductions in SUA below 5 mg/dl did not lower the risk of a gout flare.

Healthcare costs related to gout flares. Among gout patients who had flares, the average total healthcare cost per flare was $3,096 (SD $9,575). The average gout-related cost per flare was $520 (SD $1,979). Both total healthcare costs and gout-related healthcare costs were positively associated with SUA level (Figure 2). On average, the adjusted total healthcare cost per flare among the group with very high SUA levels was $4,944 (95% CI $4,742–$5,147), $2,555 higher than the group with normal SUA levels ($p < 0.0001$). The mean of the adjusted total healthcare costs among the group with high SUA was $2,523 (95% CI $2,419–$2,626) and this was not significantly different from those with normal SUA levels (mean of $2,389, 95% CI $2,291–$2,487). A similar pattern also existed for the adjusted gout-related costs. Regression adjusted gout-related cost per flare was $620 (95% CI $603–$638) in the highest SUA group, $356 higher than the group with normal SUA levels ($p < 0.0001$). Regression-adjusted gout-related cost per flare was $497 (95% CI $483–$511) in the group with high SUA levels, which was also significantly higher ($233) compared with the group with normal SUA levels ($p < 0.0001$).

DISCUSSION

The existing literature has not examined the relationship between hyperuricemia and gouty episodes, or flares, from an epidemiological perspective, especially among the high-risk elderly, nor have studies investigated the economic burden of gout flares. Our study addressed this void by examining the association between sUA and the frequency, risk, and costs of gout flares among 2,237 elderly patients from a large nationally representative claims database spanning the years 1999 through 2005. The bulk of the reduction in sample size was due to the 2-year continuous eligibility criteria and the age cutoff, 65 years. A sizable reduction was also due to the requirement that patients have at least one SUA laboratory test value. Among the 2,237 patients who met the inclusion criteria, we found that higher SUA levels were associated with increased risk and frequency of gout flares among elderly patients, as well as higher total and gout-related healthcare costs per flare.

More specifically, we found that about 40.9% of patients experienced at least one gouty episode in the 12-month period following the date of the earliest observed SUA laborato-

Table 6. Multivariate regression coefficients for frequency of gout flare analysis focusing on additional increases in SUA above 6 mg/dl.

Independent Variable	Coefficient	Change in no. of Flares, %	p
Intercept	0.150	16.2	0.792
SUA level, mg/dl			
SUA level ≥ 6	–0.285	–24.8	0.163
Each additional unit-increase when SUA ≥ 6	0.113	11.9	< 0.0001**
Index year			
2001	–0.290	–25.2	0.014*
2002	–0.204	–18.5	0.063
2003	–0.064	–6.2	0.540
2004	—	—	—
Demographic			
Age at SUA index year	–0.015	–1.4	0.061
Male	0.053	5.4	0.479
Prior comorbidities			
Hypertension	–0.040	–3.9	0.582
Diabetes	–0.283	–24.6	0.001**
Hyperlipidemia	–0.048	–4.7	0.469
Renal impairment	0.164	17.8	0.084
Rheumatoid arthritis	0.687	98.8	< 0.001**
Lupus	–0.175	–16.1	0.835
Deyo-Charlson comorbidity index	0.002	0.2	0.922
HMO indicator (vs non-HMO)	0.146	15.8	0.077
Dispersion	0.578		

* Significant at 95% level; ** significant at 99% level. HMO: health maintenance organization.

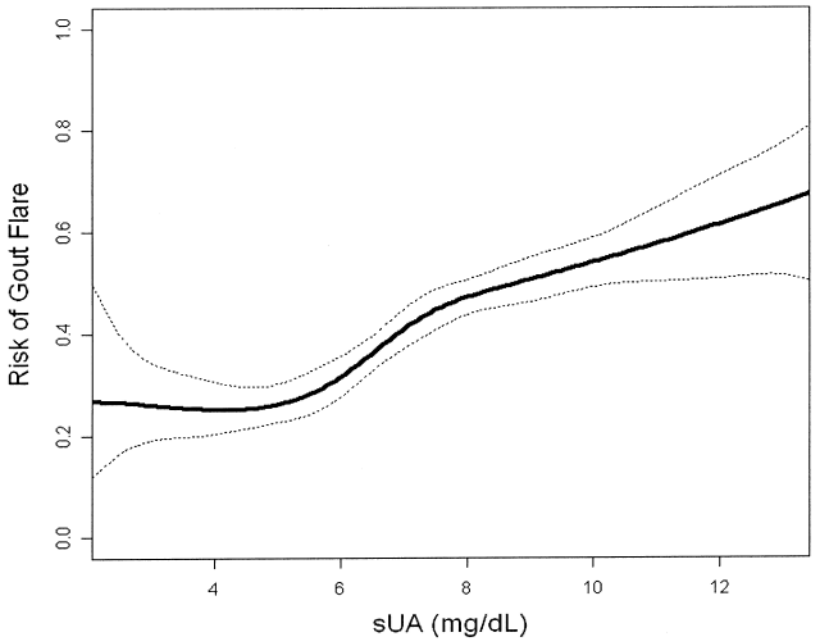

Figure 1. Risk of gout flare as a function of SUA. Based on a spline regression with 6 degrees of freedom, controlling for age, sex, index year, region, prior comorbidities (as in Table 2), and Deyo-Charlson comorbidity index.

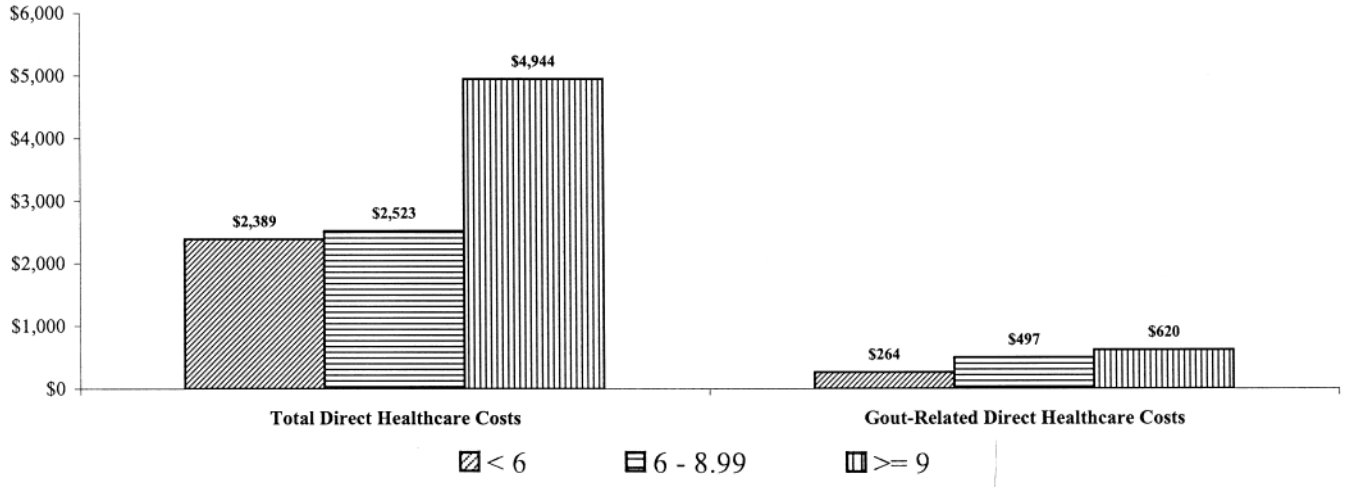

Figure 2. Regression-adjusted 30-day costs per flare by SUA level (2005 US dollars). Costs were estimated after adjustment for age, sex, index year, region, prior comorbidities (as in Table 2), and Deyo-Charlson comorbidity index using generalized linear model.

ry test since January 1, 2000 (the index date). The average number of gout flares was 1.5 (SD 0.8) for patients with an SUA level < 6 mg/dl, 1.6 (SD 0.9) for those with SUA 6–8.99 mg/dl, and 1.7 (SD 1.2) for those with SUA ≥ 9 mg/dl. Using negative binomial regression, we found that among patients with SUA values > 6 mg/dl, the average number of gout flares increased by 11.9% (95% CI 7.1% to 17.0%) with each unit-increase in SUA. The study also addressed the economic implications of having a high SUA level. We found that a high SUA level was associated with increases in both total and gout-related direct healthcare costs. Compared to gout flares among patients with normal SUA levels (< 6 mg/dl), gout flares among patients with very high SUA levels (≥ 9 mg/dl) were associated with approximately $2,500 in additional total healthcare costs during the 30-day period following the index date.

Our findings are consistent with those from Campion, *et al*, whose analysis of 2,046 healthy men from the Normative Aging Study showed that SUA level was a clear predictor of acute gouty arthritis[14]. Our findings are also generally con-

sistent with 2 retrospective studies[16,17]. One, by Shoji and colleagues, was based on an outpatient clinic in Japan[16]. Their analysis found that each unit-reduction in SUA was associated with a reduced risk of recurrent gout flares during a followup period of up to 2 years (OR 0.42, 95% CI 0.31–0.57). The second study, Sarawate, *et al*, investigated the association between SUA and risk and rate of gout flares using managed-care data in the US[17]. Their results demonstrated that patients with SUA levels ≥ 6 mg/dl were more likely to experience a gout flare within one year compared with patients who had SUA levels < 6 mg/dl (OR 1.6, 95% CI 1.2–2.1).

Given the clinical and economic benefits of maintaining an optimal SUA level, appropriate therapies for lowering SUA levels should be considered. Behavioral therapy typically attempts to reduce SUA through changing modifiable risk factors, such as diet, alcohol consumption, and incorrect medications, but these approaches frequently fail due to poor compliance[35]. Pharmacological treatment is then often required as part of the therapy. Researchers have found that in order to prevent recurrent attacks of gout, SUA should be maintained at 4–6 mg/dl[32]. Use of urate-lowering agents can effectively reduce SUA level, and can also reverse the deposition of monosodium urate, which causes the inflammatory response in gout flares[36]. Previous studies demonstrated that urate-lowering drug treatment, usually a lifetime commitment, can be cost-effective or even cost-saving in cases of nontophaceous recurrent gouty arthritis[20]. The development of new pharmacotherapies in treatment of hyperuricemia may present a good opportunity for prevention of gout flares and reduction in healthcare costs related to gout.

Our study has limitations. First, our findings may be specific to elderly patients with gout, as our study population consisted only of individuals aged 65 years and older. Also, it is important to note that the risk of flares is not zero among those patients with SUA levels below the normal range, even though this range is considered to be below the saturation point for monosodium urate. One reason is because SUA is an indirect indication of joint tissue urate levels. SUA levels can vary over time, and normal SUA ranges are influenced by other factors, such as sex and obesity[33].

A second limitation pertains to the definition of gout flares. To our knowledge, no standard epidemiological definition for gout flares exists. Therefore, we used a definition based on ICD-9 codes and medications, and included 2 definitions to address the fact that some information may have been missing in the claims and laboratory data. Neither definition is ideal, however. For example, the first definition could result in false-positives if NSAID are used as prophylaxis, and the second could result in false-negatives because the criteria may be too stringent. Thus, the goal of our study was to assess the risk of gout flares by SUA level. As long as the frequency of any false-positives or false-negatives is consistent across each of the SUA levels, the main findings will remain unbiased. The Outcome Measures in Rheumatology (OMERACT) group, an informal international network studying outcome measurement in rheumatology, is currently working on an appropriate epidemiological definition for gout flare.

Further, gout flares were measured using claims-based diagnoses only, and could not be verified using a second source, such as chart review or direct contact with patients. It is possible, therefore, that some gout patients with flares were not identified in our database because a gout claim did not exist, possibly because the patient did not contact a physician and instead used an over-the-counter NSAID. On the other hand, some patients may have been characterized as having had a gout flare if a physician wrote a prescription for an acute gout medication for the patient to use in case of emergency. This latter issue may be particularly relevant for our study if physicians are more likely to prescribe an acute gout medication when a gout patient has a high SUA level compared to when a patient has low SUA. In such instances, our analysis may expose the effects of gout care, as opposed to gout flares per se. Finally, it is possible that patients were prescribed an NSAID or steroids for the treatment of another condition other than gout, such as low back pain. To the extent that such instances exist among our sample of gout patients, our estimated incremental costs of gout would likely be underestimated due to the presence of patients without a gout flare in the gout cohort.

A recent report evaluated the validity of gout diagnoses based on administrative claims databases by cross-checking administrative claims information with a medical chart review conducted by 2 rheumatologists[37]. Their findings showed that 39% of patients with at least 2 claims-based gout diagnoses over a 5-year period did not have gout or did not have sufficient medical records information to confirm the gout diagnosis (i.e., false-positive). Again, if this was the case in our analyses, then our estimated incremental costs of gout would likely be underestimated due to the presence of gout-free patients in the gout cohort. Separately, use of claims data may also underestimate the true number of gout flares because many flares may be cared for by patients without seeing a physician and without prescription medication (e.g., patients who use over-the-counter medications).

Another potential limitation is that the sample may not be representative of all Medicare patients because Medicare fee-for-service patients, most of whom would not have prescription drug coverage, were not included. Further, most gout patients with a valid SUA value from electronic laboratory data were concentrated in the mid and south Atlantic region, which resulted in a study sample that was not representative of all geographic locations. The sample with an SUA also had fewer comorbidities on average than all gout patients, as indicated by the Deyo-Charlson comorbidity index (1.061 vs 1.146, respectively).

Each of the regression models controlled for age, sex, index year, region, prior comorbidities (hypertension, diabetes, hyperlipidemia, renal impairment, rheumatoid arthritis, lupus), and the Deyo-Charlson comorbidity index. Other confounding factors, such as body mass index, may also influence the relationship between SUA levels and the risk of gout flares, the number of gout flares, or the direct healthcare costs of gout flares. Further, costs were measured as those incurred by patients during the 30-day period following the onset of a flare. These costs could reflect factors beyond gout severity, such as increased healthcare costs due to nonadherence. The relationship between SUA level and cost could also be partly explained by a pattern of behavior in which some physicians requested to see high SUA patients more often than others as a precaution, rather than the decision being a patient-driven one in which healthcare was sought due to illness per se. Regardless of the underlying decision, increased SUA levels were associated with higher costs per flare. Finally, the costs per gout flare reported here could be higher than for a typical flare observed in a "real-world" setting, because mild flares that do not require the attention of a physician may have been excluded. Nonetheless, because the cost of a flare was defined consistently across all SUA levels, our findings in terms of the relationship between SUA and cost per flare remain valid.

Gout is a common disease in the US, and is particularly prevalent among the elderly population. Using claims data for a group of elderly (≥ 65 yrs) patients with gout, we found that patients with very high SUA levels (≥ 9 mg/dl) had more frequent gout flares compared to those with normal SUA levels (< 6 mg/dl) and had a significantly higher risk of experiencing a gout flare. A very high SUA level was also associated with increased direct healthcare costs of gout flares. Reductions in SUA are therefore likely to lower the economic burden of gout through the reduction of both the number of flares and the average cost per flare. Given the substantial effects of higher SUA levels observed in this study, it is desirable from both a clinical and an economic perspective to focus on controlling SUA levels as a method of preventing gout flares.

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