THERAPEUTIC ADVANCES in
*Musculoskeletal Disease*

*Original Research*

# Gout increases length of stay in patients hospitalized for heart failure exacerbation

*Ther Adv Musculoskelet Dis*

2022, Vol. 14: 1–7

DOI: 10.1177/1759720X221102853



**Daniel DeMizio, Guojing Wu, Ying Wei, Joan Bathon and Runsheng Wang**

***Abstract***

**Background:** It is unclear whether patients with a history of gout have longer hospitalizations in general, or only when suffering a flare. This study examines the effect of gout diagnosis and gout flare on the length of stay (LoS) in patients admitted for heart failure (HF) exacerbation.

**Methods:** We conducted a matched retrospective cohort study and searched electronic medical records for patients admitted for HF with a prior diagnosis of gout from 1 July 2012 to 30 June 2017 and matched them to patients admitted for HF without gout. Cases who had a gout flare during the admission were identified. The log of the length of stay (log LoS) was utilized for normalization of the data. We used a linear mixed-effect model to compare the adjusted LoS of gout patient with flare, gout patient without flare, and controls.

**Results:** A total of 978 admissions for HF exacerbation in 738 patients, including 246 individual with gout and 492 matched controls, were identified and included in the analysis. The log LoS was significantly longer in cases ($1.86 \pm 0.95$) compared with controls ($1.72 \pm 0.94$; $p = 0.0278$). The log LoS was significantly longer in those with gout who flared ($2.41 \pm 0.96$) compared to those without gout ($1.72 \pm 0.94$, $p < 0.0001$). After adjusting for potential confounders, the log LoS of patients who flared ($p < 0.0001$) remained significantly longer than controls, as well as those who did not flare ($p = 0.042$), but to a lesser extent.

**Conclusion:** HF patients with gout had significantly longer hospitalizations than those without gout, a finding driven primarily by gout flare during hospitalization.

***Keywords:*** gout, heart failure, healthcare

Received: 11 November 2021; revised manuscript accepted: 27 April 2022.

Correspondence to:
**Daniel DeMizio**
Division of Rheumatology, Columbia University Irving Medical Center, 630 West 168th Street, Suite 3-450, New York, NY 10032, USA.
**dd2936@cumc.columbia.edu**

**Runsheng Wang**
Division of Rheumatology, Columbia University Irving Medical Center, 630 West 168th Street, Suite 3-450, New York, NY 10032, USA.
**rw2646@cumc.columbia.edu**

**Guojing Wu**
**Ying Wei**
Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, USA

**Joan Bathon**
Division of Rheumatology, Columbia University Irving Medical Center, New York, NY, USA

## Significance and innovations

Heart failure (HF) patients with a concomitant diagnosis of gout have significantly longer hospitalizations compared to matched controls with a diagnosis of HF alone.

This effect is driven primarily by the occurrence of gout flares during hospitalization, with a median length of stay of 4 days longer than those without a diagnosis of gout and those gout patients who did not flare.

Interventions that aim to improve gout outcomes and diminish the preponderance of flares in this high-risk population are warranted.

## Introduction

Gout is the most common inflammatory arthritis in the United States. There is growing evidence that both the prevalence of gout and its burden on healthcare costs has increased over recent decades.[1,2] This trend starkly contrasts with the declining hospitalization rates for other inflammatory arthritides, such as rheumatoid arthritis.[2] The basis for these trends is, in part, driven by suboptimal gout care. A recent analysis of data from the National Health and Nutrition Examination Survey (NHANES) by Chen *et al.*[3] revealed that only approximately one-third of patients with an indication for urate-lowering therapy successfully reach a target serum urate level of <6 mg/dL.

Trends studied from 1993 to 2011 using the Nationwide Inpatient Database suggest that the annual hospitalization rate for gout had increased from 4.4 to 8.8 per 100,000 US adults.[2] While

such increases have undoubtedly contributed to the rising burden of gout on healthcare costs, flares in hospitalized patients after admission contribute as well. Population-based studies, such as those by Zleik *et al.*,[4] have suggested that rates of incident gout flares were significantly increased during hospitalization compared to that in an outpatient setting over a similar time frame. In their study, cardiovascular disease was the most common reason for initial admission, accounting for approximately 25% of the inpatient admission diagnoses associated with incident gout flares. Given that heart failure (HF) in particular is likely a high-risk admission diagnosis for risk of gout flares due to associated diuresis and volume contraction, our study serves to explore gout-related inpatient utilization trends within our own hospital system.

We aimed to compare the length of stay for patients with both gout and HF who were admitted for a primary diagnosis of HF exacerbation to those with HF without a gout diagnosis. We hypothesized that patients admitted to the hospital for HF exacerbation with a prior diagnosis of gout would have lengthier hospitalizations than those without a prior diagnosis of gout. Similarly, we hypothesized that patients admitted to the hospital for a primary HF exacerbation who then suffer a concomitant gout flare would likely have longer hospitalizations than those who do not experience concomitant gout flares.

## Materials and methods

### *Study sample and case ascertainment*

We conducted a matched retrospective cohort study using electronic medical record data from Columbia University Irving Medical Center. We included all patients >18 years of age with an inpatient hospitalization occurring at any point from 1 July 2012 to 30 June 2017 for a primary discharge diagnosis of HF exacerbation using identified International Classification of Disease: 9th Revision (ICD-9) and 10th Revision (ICD-10) codes (ICD-9: 428.x, ICD-10: I50.x).[5] A cohort of exposed 'cases' with gout was defined as those with two or more gout diagnoses (ICD-9: 274.0–274.9; ICD-10: M10.0 to M10.9) prior to their HF admission. A manual review of 50 random cases was performed (DJD) and showed a positive predictive value of the ICD diagnosis of 92%, against clinical documentation of gout. A comparison cohort of unexposed 'controls' admitted for HF exacerbation without prior history of gout from the same study population was matched 2:1, on the basis of age at the first admission for HF, sex, and total number of HF admissions during the study period.

Gout flare was defined as any clinician documentation of a flare during an inpatient hospitalization and was ascertained by manual chart review performed by one rheumatologist (DJD). The definition for gout flare included any patients with a prior history of gout developing acute swelling of one or more joints, rheumatology consult for gout flare, arthrocentesis with crystal analysis revealing intracellular monosodium urate crystals, intra-articular corticosteroid injection, or the use of prednisone, methylprednisolone, colchicine, or anakinra for an indication of gout during the hospitalization.

### *Study outcomes and variables*

We queried the electronic medical record and manually curated the following variables: age, sex, race, admission, and discharge time and dates, body mass index (BMI), and baseline laboratory data on admission, including serum urate, presence or absence of elevated troponin, brain natriuretic peptide, and sodium, creatinine. Baseline laboratory data were defined as the first value obtained on the day of admission. If a laboratory value was not available during the admission to discharge window, we used the laboratory values closest to admission and within 10 days prior to the admission. Ejection fraction, as determined by echocardiogram occurring during the admission or within 1 year prior to hospitalization, was also collected. As a correlate for socioeconomic status, primary insurance and zip code were obtained. Zip codes were used to estimate annual gross income according to 2013 Internal Revenue Service Tax Statistic.[6]

### *Statistical analysis*

Descriptive statistics were used to summarize the data for both exposed gout cases and unexposed controls. Primary outcome was length of stay (LoS), defined as the difference between discharge and admission date. The log of the length of stay (log LoS) was utilized for normalization of the data.[7] We dichotomized troponin, as 'elevated' or 'not elevated' and considered any missing

troponin values as 'not elevated', assuming that if a clinician did not order this test, the clinical picture likely did not fit a situation where that provider would expect an elevated value.

We used two-sample *t*-test to compare the log LoS between cases and controls. We used linear mixed effect model with random intercept to adjust for potential confounders and compared the adjusted LoS of gout patients with flare, gout patients without flare, and controls. Statistical analyses were performed using Stata version 16 (StataCorp LLC) and R version 3.6.1 (R Foundation for Statistical Computing). The reporting of this study conforms to the STROBE statement.[8]

This study was approved by the Institutional Review Board of Columbia University Irving Medical Center (Protocol: AAAS3014). Informed consent was waived for this study due to its minimal risk. All patient details have been de-identified such that the identity of the patients may not be ascertained in any way.

## Results

### *Patient characteristics*

We identified 545 admissions for HF exacerbation in 293 patients with a history of gout and 5461 admissions for HF exacerbation in 3798 patients without a history of gout during the study period. After matching, a total of 246 cases and 492 matched controls were included in our analysis. This reduction in cases was due to no match present in the initial cohort on the basis of age, sex, and the number of HF admissions. The average number of admissions per patient in each group was 1.325 ($\pm$0.61), for a total of 978 admissions (652 control admissions and 326 case admissions). Individual baseline data for cases and controls are summarized in Table 1. Both cases and controls tended to be overweight (BMI of 29.04 in cases *vs* 28.28 in controls) with a degree of baseline chronic kidney disease that was more pronounced in cases compared to controls (mean baseline creatinine 2.22 mEq/L *vs* 1.76 mEq/L). Measures of severity of HF were similar in the two groups, as indicated by ejection fraction (38.96% *vs* 36.97%) and brain natriuretic peptide level (5145.41 mEq/L *vs* 5539.3 mEq/L) in cases and controls, respectively. Controls tended to have a higher frequency of elevated troponin compared to cases (22.6% *vs* 15.9% respectively).

### *Gout flares and length of stay*

The median LoS for patients with gout was 6 days (interquartile range (IQR) = 9), and median LoS for controls was 6 days as well, but with a much shorter IQR (IQR = 7). The log LoS was significantly longer in patients with gout ($1.86 \pm 0.95$) compared with patients without gout ($1.72 \pm 0.94$; $p = 0.0278$).

Out of 326 case admissions, a gout flare was confirmed to have occurred in 42 (13%) admissions. The median LoS for those gout patients who flared was 10 days (IQR = 10), compared to 6 days in those without flare (IQR = 8), and 6 days in patients without a history of gout (IQR = 7). The log LoS was significantly longer in those with gout who flared ($2.41 \pm 0.96$) compared to those without gout ($1.72 \pm 0.94$, $p < 0.0001$). The log LoS in those with gout who did not flare was not different from controls ($1.82 \pm 0.83$; $p = 0.2465$).

After adjusting for age, baseline electrolytes, kidney function, BMI, cardiac function, and socioeconomic status, having a gout flare remained significantly associated with a longer log LoS (coefficient = 0.629, $p < 0.0001$; Table 2); and to a lesser extent, a history of gout but no flare (coefficient = 0.145, $p = 0.04$) was associated with longer hospital stay as well. Predicted median LoS for those without gout was 5.68 days, compared to 6.0 and 10.96 days for those with gout who did not flare and those with gout who flared, respectively. Elevated troponin (coefficient = 0.36, $p < 0.0001$) and adjusted gross income (coefficient = 0.001, $p = 0.011$) had a significantly positive association with log LoS in this model. Age (coefficient = $-0.009$, $p = 0.0008$), BMI (coefficient = $-0.016$, $p = 0.0004$), and baseline sodium (coefficient = $-0.026$, $p = 0.0002$) had significantly negative association with log LoS in this model.

## Discussion

Our study shows that HF patients with a diagnosis of gout have significantly longer hospitalizations than those without gout. Those gout patients who flare during hospitalization primarily drive this effect, with a median length of stay of 4 days longer than those without a diagnosis of gout and those gout patients who did not flare.

**Table 1.** Baseline characteristics of patients with prior gout diagnosis (Gout) and patients without prior gout diagnosis (non-gout).

| | Non-gout (*n* = 492) | Gout (*n* = 246) |
|---|---|---|
| Age, years | 71.67 (±13.95) | 71.67 (±13.95) |
| Sex, no. (%) | | |
| Male | 304(61.7%) | 152(61.7%) |
| Female | 188 (38.2%) | 94(38.2%) |
| BMI | 28.28 (±11.55) | 29.04(±8.00) |
| Ejection fraction, % | 36.97 (±18.97) | 38.96 (±18.55) |
| Baseline Na, mEq/L | 137.78 (±4.78) | 138.51 (±4.43) |
| Baseline Cr, mEq/L | 1.76 (±1.48) | 2.22 (±1.60) |
| Baseline BNP, mEq/L | 5539.3 (±11,574.2) | 5145.41 (±8596.18) |
| Elevated troponin, no.(%) | 111 (22.6%) | 39 (15.9%) |
| Insurance, no.(%) | | |
| Commercial | 243 (49.4%) | 111 (45.1%) |
| Medicare | 217 (44.1%) | 126 (51.2%) |
| Self-Pay | 7 (1.4%) | 2 (0.8%) |
| Medicaid | 25 (5.1%) | 7 (2.9%) |
| Adjusted gross income, US dollars | 59,125 (±55,682) | 53,602 (±48,183) |
| Length of stay (days) | | |
| Mean | 9.17 (+ 13.55) | 11.46 (+23.44) |
| Median (IQR) | 6 (7) | 6 (9) |
| Log (length of stay) | 1.721 ± 0.94 (1.64–1.79) | 1.86 ± 0.95 (1.75–1.96) |

Except where indicated otherwise, values are mean ± SD. BMI, body mass index; BNP, brain natriuretic peptide; Cr, creatinine; Na, sodium; SD, standard deviation.

Previous data indicate that the burden of gout on healthcare systems is increasing, leading to increasing hospital costs.[2] A multicenter retrospective study employed by Singh and Yu[9] using US National Emergency Department Sample (NEDS), revealed that of 205,1252 emergency department visits from 2009 to 2012 for a primary diagnosis of gout, 7.7% resulted in hospitalizations lasting an average of 4 days in duration. Their multivariate model suggested that factors such as older age, renal failure, and HF were associated with longer hospital stays in patients admitted for a primary diagnosis of gout. Given the frequent comorbid presence of gout in patients with HF, and their propensity to flare, we chose to specifically focus on a subset of patients with a diagnosis of HF with admission for an HF exacerbation.

Compared to the findings of Singh and Yu,[9] the patients in our cohort tended to have longer hospital stays, approximately 11 days for cases and 9 days for controls. Our cohort was generally ill, comprised primarily of elderly patients with severe HF and frequent readmissions, likely explaining this discordance. Similarly, a 5-year population-based single-center cohort study by Zleik *et al.*[4] including 429 patients with incident

**Table 2.** Multivariable linear mixed-effect analysis of gout and length of stay.

| Parameters | Coefficient | SE | *P* value |
|---|---|---|---|
| Gout (flare) | 0.6293 | 0.1605 | 0.00009 |
| Gout (no flare) | 0.1452 | 0.0713 | 0.0423 |
| Elevated troponin | 0.3637 | 0.0784 | 0.000004 |
| Insurance | | | |
| Insurance: commercial | –0.1823 | 0.1258 | 0.1477 |
| Insurance: Medicaid | –0.1594 | 0.1298 | 0.2201 |
| Insurance: Medicare | –0.1473 | 0.1905 | 0.4396 |
| Insurance: self-pay | –0.1112 | 0.2749 | 0.6857 |
| Creatinine | –0.0373 | 0.0213 | 0.0813 |
| Sodium | –0.0261 | 0.0070 | 0.0002 |
| BMI | –0.0160 | 0.0045 | 0.0004 |
| Age | –0.0093 | 0.0027 | 0.0008 |
| Ejection fraction | 0.0018 | 0.0018 | 0.081 |
| Adjusted gross income | 0.0015 | 0.0006 | 0.0111 |
| Brain natiuretic peptide | –0.0006 | 0.00003 | 0.0502 |

BMI: body mass index.

gout showed that the risk of gout flare during hospitalization was 10-fold higher compared to those in the outpatient setting. In their study, flares significantly increased the average hospital stay by 1.8 days compared to hospitalized patients without gout flare. In their study, reason for initial admission was widely variable; however, cardiovascular disease accounted for the most frequent reason for initial admission at approximately 25%. Factors that have been implicated in increasing the risk for gout flares during hospitalization include preadmission serum urate, tophi, initiation or increase of gout prophylaxis, diuretic use, volume depletion, and kidney injury.[10,11]

These risk factors are frequently found in patients admitted for HF exacerbation and likely contribute to their propensity for flare. Risk stratification tools such as the GOUT-36 model established by Jatuworapruk *et al.*[12] have incorporated such risk factors and may be utilized to stratify patients at highest risk for inpatient gout flare.

In our study, focused specifically on this high-risk subpopulation of patients with gout and HF, the median length of stay for cases that flared was 4 days longer than both controls and cases that did not flare. It may be argued that gout flares are biased to occur in the sickest and most aggressively treated patients who are more likely to have longer hospitals stays. While additional confounders may exist, after adjusting for age, baseline electrolytes, kidney function, BMI, cardiac function, and socioeconomic status, this significant increase in hospital duration persisted and suggests that the gout flare is contributing to longer LoS. This is a finding which supports our initial hypothesis and is a logical conclusion that is well expected, as the occurrence of a gout flare during the hospitalization and the need for additional diagnostic studies, inpatient consultations, and therapies could certainly contribute to longer hospitalizations on average.

The main methodological limitations of our study include our single center study design thereby potentially limiting the generalizability of our findings compared to that gained by a more population-based approach. Similarly, our study cohort came from a tertiary referral center, and as

a result, outpatient records may be incomplete if patients with prior history of gout never had an outpatient encounter in our center. This could lead to misclassification of gout patients into the control group. Such misclassification could make it harder to observe a difference in the LoS between cases and controls, but does not appear to have ultimately affected our conclusion. Additional methodological weaknesses are those inherent to retrospective design, particularly in regards to the validity of our ascertainment of gout diagnosis by the presence of two ICD codes. Several studies have examined the validity of this approach with variable success, with PPV (Positive Predictive Value) ranging from approximately 60% to 85%.[10,13–16] While manual review of a small portion of the cases in our center yielded a PPV of 92%, there is a high likelihood that inappropriate classification of a gout diagnosis occurred. Similarly, the validity of retrospective ascertainment of the occurrence of gout flares has not been extensively studied. Our flare rate of 13% was in close concordance with that seen in previous similar studies.[4] Finally, due to technical limitations of our electronic medical record, medication reconciliation (i.e. potentially contributory medications at varying dosages), serum urate levels, and comorbidities were not included in our analyses. Failure to assess these factors could theoretically affect risk of gout flare and/or length of stay.

Future considerations include evaluating additional factors that might predispose this subset of patients for risk of flare, such as whether failure to continue urate-lowering therapy during admission is significantly associated with inpatient flares. Various patient, provider, and healthcare system factors serve as potential barriers to effective gout management. Our findings suggest that addressing these barriers and promoting better control of gout, both in the outpatient and inpatient setting, may potentially diminish the preponderance of inpatient gout flares and lead to shorter lengths of stay. Risk stratification tools to identify patients at highest risk for inpatient gout flares may help target these interventions to appropriate patients. Research evaluating the effectiveness of interventions that promote improved gout control is warranted.

## Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Columbia University Irving Medical Center (Protocol: AAAS3014). Informed consent was waived for this study due to its minimal risk. All patient details have been de-identified such that the identity of the patients may not be ascertained in any way.

## Consent for publication

All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

## Author contribution(s)

**Daniel DeMizio:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Writing – original draft.

**Guojing Wu:** Data curation; Methodology.

**Ying Wei:** Methodology.

**Joan Bathon:** Writing – review & editing.

**Runsheng Wang:** Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – review & editing

## ORCID iD

Daniel DeMizio https://orcid.org/0000-0001-6868-4806

## Acknowledgements

None

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

## Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article. Additional raw data may be available from the corresponding author (DD, RW) upon reasonable request.

## References

1. Kuo C-F, Grainge MJ, Zhang W, *et al*. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol* 2015; 11: 649–662.

2. Lim SY, Lu N, Oza A, *et al*. Trends in gout and rheumatoid arthritis hospitalizations in the

United States 1993–2011. *JAMA* 2016; 315: 2345–2347.

3. Chen-Xu M, Yokose C, Rai SK, *et al.* Contemporary prevalence of gout and hyperuricemia in the United States and decadal trends: the national health and nutrition examination survey, 2007–2016. *Arthritis Rheumatol* 2019; 71: 991–999.
4. Zleik N, Elfishawi MM, Kvrgic Z, *et al.* Hospitalization increases the risk of acute arthritic flares in gout: a population-based study over 2 decades. *J Rheumatol* 2018; 45: 1188–1191.
5. World Health Organization. International classification of diseases [Internet], 2020, http://www.who.int/classifications/icd/en/index.html
6. Internal Revenue Services. SOI tax stats: county data – 2013 [Internet], 2020, https://www.irs.gov/statistics/soi-tax-stats-county-data-2013
7. Chazard E, Ficheur G, Beuscart JB, *et al.* How to compare the length of stay of two samples of inpatients? A simulation study to compare type I and type II errors of 12 statistical tests. *Value Health* 2017; 20: 992–998.
8. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
9. Singh JA and Yu S. Gout-related inpatient utilization: a study of predictors of outcomes and time trends. *Arthritis Res Ther* 2016; 18: 57.
10. Choi HK, Mount DB and Reginato AM. Pathogenesis of gout. *Ann Intern Med* 2005; 143: 499.
11. Jatuworapruk K, Grainger R, Dalbeth N, *et al.* Development of a prediction model for inpatient gout flares in people with comorbid gout. *Ann Rheum Dis* 2020; 79: 418–423.
12. Jatuworapruk K, Grainger R, Dalbeth N, *et al.* The GOUT-36 prediction rule for inpatient gout flare in people with comorbid gout: derivation and external validation. *Rheumatology* 2021; 61: 1658–1662.
13. Harrold LR, Saag KG, Yood RA, *et al.* Validity of gout diagnoses in administrative data. *Arthritis Rheum* 2007; 57: 103–108.
14. Dehlin M, Stasinopoulou K and Jacobsson L. Validity of gout diagnosis in Swedish primary and secondary care: a validation study. *BMC Musculoskelet Disord* 2015; 16: 149.
15. Malik A, Schumacher HR, Dinnella JE, *et al.* Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. *J Clin Rheumatol* 2009; 15: 22–24.
16. Singh JA. Veterans Affairs databases are accurate for gout-related health care utilization: a validation study. *Arthritis Res Ther* 2013; 15: R224.