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Prevalence, risk factors, and outcomes of gout flare in patients hospitalized for PCR-confirmed COVID-19: A multicenter retrospective cohort study

Short running title: gout flare during COVID-19 hospitalization

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Abstract

Objectives: The study aimed to describe the prevalence and outcomes of gout flare in patients with comorbid gout hospitalized for COVID-19. Factors associated with gout flare, and hospital length of stay were explored.

Methods: This retrospective cohort study included adults with comorbid gout who were hospitalized for PCR-confirmed COVID-19 between March 2020 and December 2021 in three hospitals in Thailand. Prevalence, characteristics, and outcomes of gout flare were described. Factors associated with gout flare were explored using LASSO selection and multivariate logistic regression. Association between gout flare and hospital length of stay was explored using multivariate linear regression.

Results: Among 8697 patients hospitalized for COVID-19, 146 patients with comorbid gout were identified and gout flare occurred in 26 (18%). Compared to those without flare, patients with gout flare had higher baseline serum urate and lower prevalence of use of urate-lowering therapy (ULT) and gout flare prophylaxis medications. One-third of gout flare episodes were treated with two or more anti-inflammatory medications. Logistic regression identified GOUT-36 rule ≥2, a predictive index for inpatient gout flare, as the only factor associated with gout flare (OR 5.46, 95%CI 1.18 to 25.37). Gout flare was found to be independently associated with hospital length of stay and added three days to hospital course.

Conclusion: Gout flare occurred in 18% of patients with comorbid gout hospitalized for COVID-19 and added up to three days to hospital length of stay. Patients with suboptimal ULT appeared to be at high risk for gout flare during COVID-19 hospitalization.

Introduction

Gout is the most common form of inflammatory arthritis in adults.[1] Gout flare is a common complication during hospitalization for medical illness or surgery, with prevalence between 14% and 34%.[2,3] Since inpatient gout flare can add up to six days to hospital length of stay it is important to better understand risk factors for gout flare during a hospital stay.[2] Previously, predictors of gout flare in the inpatient population with comorbid gout have been identified, and these include lack of pre-admission urate-lowering therapy (ULT), lack of pre-admission gout flare prophylaxis, presence of tophus, and pre-admission serum urate above 6 mg/dL.[3] These factors form the components of the GOUT-36 prediction rule, a validated tool that can be completed at admission to help clinicians identify patients at risk of developing inpatient gout flare.[3] Over the last 2 years , coronovirus disease-19 (COVID-19) has been a major reason for hospitalization. Furthermore gout has been associated with increased odds of a COVID-19 diagnosis, as well as COVID-19-related death, most likely due to the high burden of comorbidities in gout population.[4,5] Despite the high prevalance of gout and increased odds of a COVID-19 diagnosis in people with gout, data on gout flare during episodes of COVID-19 has so far been limited to small case series and so the prevalence of gout flare during COVID-19 remains unclear.[6]

During hospitalization for COVID-19, viral and treatment-related factors may influence risk of gout flare. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can activate the inflammasome in infected macrophages generating a highly pro-inflammatory state.[7] This is especially relevant to people hospitalized for COVID-19 because people who develop pneumonia or require invasive ventilation have been found to have higher SARS-CoV-2 viral load compared to asymptomatic people.[8] The priming of macrophages could potentially put

people with COVID-19 at high risk for gout flare, especially when monosodium urate crystals are already present in the joints in people with comorbid gout.[9] Several medications used for COVID-19 treatment may also influence risk of gout flare. Use of colchicine and corticosteroids for COVID-19 may attenuate the risk of gout flare due to their anti-inflammatory effects. In contrast, exposure to favipiravir may initiate a gout flare due to its hyperuricemic effects.[10,11] During hospitalization for COVID-19, invasive ventilation may lead to disruption of established gout therapies and increase the risk of gout flare.[12]

Based on the prevalence of gout flares in hospital and these characteristics of COVID-19 disease or its treatment, we hypothesized that there might be high prevalence of gout flare during COVID-19 hospitalization driven at least partially by COVID-19-specific factors such as favipiravir, COVID-19 pneumonia and ventilator requirement. This primary objective of this study was to describe the prevalence, characteristics, and outcomes of gout flare in people with comorbid gout who were hospitalized for COVID-19. Secondary objectives were to explore factors associated with gout flare during COVID-19 hospitalization, and the association between gout flare and hospital length of stay.

Methods

Study design and population

This retrospective cohort study included adults with comorbid gout who were hospitalized for COVID-19 confirmed on polymerase chain reaction (PCR) between 1 March 2020 and 31 December 2021, in three hospitals in Bangkok metropolitan area; Thammasat University Hospital, Thammasat Field Hospital and Vajira Hospital.

Included study participants met all of the following inclusion criteria; (1) age 18 years or older, (2) hospital admission with COVID-19 (confirmed on PCR on the first day of admission) as the primary admission diagnosis and (3) having gout as comorbid disease at the time of hospital admission. Comorbid gout was defined as having received a gout diagnosis by a doctor before the current admission, according to previous outpatient records, previous hospital discharge notes, or referral letters. Patients were excluded from analysis if they were hospitalized with gout as the primary admission diagnosis or if diagnosed with gout for the first time during the current hospital admission.

Patient identification

Eligible patients were identified from the hospitals' electronic databases in two steps. The first step aimed to identified patients hospitalized for COVID-19. Patients who received International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code for COVID-19 (U071) as primary diagnosis during the study period were extracted from the hospital databases. Electronic records for Thammasat University Hospital and the field hospital were kept in the same database managed by Thammasat University, while electronic records from Vajira Hospital were maintained by Navamindradhiraj University. The second step was to identify patients with comorbid gout among the previously identified COVID-19 cohort. Comorbid gout was identified if the participants received discharge ICD-10 codes for gout (M10) as comorbid diagnosis or if there was mention of any gout key words (gout, tophus, podagra, allopurinol, febuxostat or colchicine) in the participant's electronic discharge letter. The identification of gout key words was done manually by research assistants who had been trained to look for gout key words in hospital discharge letters and had successfully performed similar manual search in another gout study.[3] Manual screening of

discharge letters was necessary because some participants with inactive gout might not have received ICD-10 code for gout at their hospital discharge but gout would still have been mentioned as comorbidity in the letters.

Patient ascertainment

Discharge letters, hospital records and referral letters of all participants identified from initial two-step screening were subsequently reviewed in details by the investigators (KJ and PS) to ensure that the participants met all inclusion criteria and none of the exclusion criteria. During this process, the investigators made sure that the definition of comorbid gout was followed (physician-diagnosed gout). Patients who were initially identified by the key words 'podagra', 'colchicine', 'allopurinol' or 'febuxostat' in the discharge letters would be included in the analysis only if they received explicit gout diagnosis by a doctor in the same discharge letter or in the hospital record or referral letter associated with the same hospital event.

Variables and their definitions

Gout flare is defined as an episode of joint pain and swelling which developed during hospital stay and was judged to be gout by the attending doctor based on hospital notes, or an episode of joint pain that satisfied the Gaffo's definition of gout flare.[13] Duration of gout flare episode was defined as number of days between the onset of acute joint pain and swelling and the resolution of gout flare or date of hospital discharge.

Other variables were divided into five domains: demographics (age, sex), admission data (length of stay, comorbidities), COVID-19 data (pneumonia, oxygen support, invasive ventilation, COVID-19 treatments), gout history (tophus, pre-admission gout medication, in-hospital adjustment of gout medications, serum urate level) and gout flare episodes (joint number

and location, episode duration, treatment). Comorbid diseases included obesity, smoking status and comorbid conditions from the Charlson comorbidity index, which has been associated with poor outcomes in patients hospitalized for COVID-19.[14] **Table 1** lists all variables collected for this study and their descriptions.

Databases and data collection

Electronic and scanned copies of hospital notes were available for review at each participating hospital. Serum urate measurement was performed in-house by the hospital where participants were admitted and the results were available in the same database as the electronic hospital notes. Data were extracted by the investigators (KJ and PS) and recorded in a pre-determined case record form. If a participant had more than one COVID-19 admission during the study period, only the first admission was recorded. If a participant developed gout flare more than once during the same hospital event, only data prior to the first gout flare episode was recorded.

Statistical analysis

Characteristics of the cohort and prevalence of gout flare were described with descriptive statistics. Categorical data were expressed as frequency and percentage and continuous data were expressed as mean (standard deviation, SD) or median (interquartile range, IQR). Comparison between patients who developed gout flare (flare group) and patients who did not had flare (non-flare group) were made using chi-square test for categorical variables and Mann–Whitney U test for continuous variables.

Multivariate logistic regression model

Factors associated with development of inpatient gout flare (dependent variable) were explored using multivariate logistic regression. Fourteen exposure variables were considered for the logistic regression, including traditional predictors of gout flare (GOUT-36 prediction rule, no ULT, no prophylaxis, tophus, serum urate >6 mg/dL, ULT adjustment and prophylaxis stopped/decreased), COVID-19-related variables (COVID-19 pneumonia, invasive ventilation, corticosteroids, favipiravir), demographics (age and sex) and Charlson comorbidity index. These variables were first screened by Least Absolute Shrinkage and Selection Operator (LASSO). LASSO is a type of penalized regression procedure augmented by 10-fold cross validation, which applies penalty factor (λ) to the variables' regression coefficients. Variables that hold little to no discriminatory power would have their regression coefficients shrunk to zero and removed.[15] LASSO was used for variable selection over the traditional univariate logistic regression because LASSO was more robust in handling dataset with small number of outcome events as well as dataset whose variables showed some degree of correlation (multicollinearity).[15,16] Variables selected by LASSO were subsequently fitted into a logistic regression model. Regression coefficients, odds ratios (OR) and their 95% confidence interval (CI) and *P* values were reported.

Two performance indicators were used to assess the logistic regression model; C-statistics and Hosmer-Lemeshow test. C-statistics indicate the ability to distinguish patients with flare from patients without flare (discrimination). The C-statistics range between 0.5 and 1.0, with the latter indicating perfect discrimination. The Hosmer-Lemeshow test indicates how well the predicted event rates match the observed event rates (goodness of fit). A Hosmer-Lemeshow test with non-significant p-value ($\geq$0.05) suggests that there is no evidence of poor model fit in the dataset.

Multivariate linear regression model

We explored the association between gout flare and the length of hospital stay using multivariate linear regression analysis. The primary outcome (dependent variable) was hospital length of stay (days) and exposure variable was inpatient gout flare (yes or no), adjusting for age, sex, Charlson comorbidity index, presence of COVID-19 pneumonia and invasive ventilation. Regression coefficients, their 95%CI and *P* values were presented. We also reported the coefficient of determination (R-squared) of the linear regression model, which indicated the degree of variance in the hospital length of stay that could be explained by the model.

All statistical analyses were performed using IBM SPSS Statistics software (V.25), except the LASSO which was performed in Rstudio (V.2022.02.3+492).

Sample size estimation

Initial database inquiries estimated the number of patients hospitalized for PCR-confirmed COVID-19 at 8000 patients in three participating hospitals. Since the prevalence of gout in the general population ranges between 1% and 4%, we anticipated that at least 80 patients (1%) hospitalized for COVID-19 would have comorbid gout.[1] Assuming that 34% of hospitalized patients with comorbid gout developed gout flare, we anticipated gout flare in 27 patients in our cohort.[3] The event number would be sufficient to support the final logistic regression model that included no more than five exposure variables (five events for each variable).[17]

Ethics approvals

The study protocol was reviewed and approved by the Human Research Ethics Committee of Thammasat University (reference number MTU-EC-IM-1-321/64) and the

Institutional Review Board of the Faculty of Medicine Vajira Hospital (reference number 265/64E) in compliance with the declaration of Helsinki. This was a retrospective, chart review cohort study for which informed consent was not required.

Results

We screened records of 8697 patients hospitalized for PCR-confirmed COVID-19 and identified 146 patients (2%) with comorbid gout (the gout cohort). The mean age of the gout cohort was 64 years and 109 (75%) were male (**Table 2**). Almost all of the cohort (91%) had at least one comorbidity, with diabetes (61/146, 42%), obesity (41/146, 28%) and myocardial infarction (26/146, 18%) as the most common conditions. The majority of the gout cohort (110/146, 75%) had COVID-19 pneumonia, with 14% (21/146) requiring invasive ventilation. The most common medications for COVID-19 were favipiravir (127/146, 87%) and systemic corticosteroids (105/146, 72%).

Gout flare was documented in 26 patients (26/146, 18%) (**Table 2**). All gout flare episodes were explicitly diagnosed by attending physicians according to the hospital notes and 18/26 episodes (69%) also satisfied Gaffo's criteria for gout flare. Participants who developed gout flare had lower prevalence of pre-admission ULT and pre-admission gout flare prophylaxis compared to non-flare group (31% vs. 73% for ULT and 12% vs.41% for gout flare prophylaxis). The mean pre-admission serum urate in the flare participants was significantly higher than that in the non-flare group (8.9 versus 7.2 mg/dL). The majority of patients in the flare group were classified as 'high risk' for inpatient gout flare by the GOUT-36 rule (23/26, 89%), compared to only 40% of the non-flare group. Participants who had gout flare also stayed in hospital longer than participants who did not have a gout flare (13 versus 10 days).

Table 3 describes the characteristics of gout flare episodes. The median number of days between hospital admission and onset of flare was seven days. The majority of flare episodes were monoarticular (79%), with ankle as the most common joint affected (42%), followed by first metatarsophalangeal (32%) and knee joints (26%). Nearly one-third of the flare episodes required two or more medications to treat inflammation.

Fourteen exposure variables were screened in the LASSO model and four were subsequently selected: GOUT-36 ≥2, no pre-admission ULT, no-pre-admission gout flare prophylaxis and invasive ventilation (**Table 4**). From the four selected variables, only GOUT-36 ≥2 was found to be independently associated with gout flare, with OR (95%CI) of 5.46 (1.18 to 25.37). The C-statistic of the regression model was 0.81 (95%CI 0.71 to 0.90, p-value <0.001), indicating good discrimination. Hosmer-Lemeshow chi-square value was 3.768 (p-value 0.708), indicating that there was no evidence of poor model fit.

Association between gout flare and hospital length of stay was explored using linear regression model (**Table 5**). Gout flare was found to be associated with hospital length of stay (OR 5.74, 95%CI 2.49 to 8.98, p-value 0.001), adjusting for demographics, Charlson comorbidity index, COVID-19 pneumonia and invasive ventilation. The coefficient of determination for the model was 0.17, suggesting that the model could explain approximately 17% of the variance of the hospital length of stay.

Discussion

Almost one in five of people (18%) with comorbid gout hospitalized for COVID-19 developed gout flare during their hospital stay, a prevalence similar to those reported in the general inpatient populations.[2,3] Characteristics of gout flare episodes appeared to be similar to

previous reports which were predominantly monoarticular and frequently involving joints of the feet and ankles.[18,19] It may be infered that the inflammatory responses of gout flare episodes in our cohort appeared to be intense as one-third (31%) of the episodes required treatment with two or more anti-inflammatory agents and more than half (58%) of the flare group had also received systemic corticosteroids as part of their COVID-19 treatment. Cases of gout flare occurring during corticosteroid use for COVID-19 treatment have been reported.[6] These break-through flare episodes might be explained by the hyper-inflammatory response in severe COVID-19 which could potentially contribute to a more intense response to MSU crystals in people with comorbid gout.[7,20]

Of the several variables that might be associated with gout flare, including both traditional and COVID-19-related factors, after adjusting for comorbidities and demographics only GOUT-36 rule ≥2 was ultimately found to be independently associated with gout flare. The GOUT-36 rule is a validated composite prediction rule which contained four items; no pre-admission ULT, no pre-admission prophylaxis, tophus and serum urate >6 mg/dL. The rule indicated poor gout control at the time of hospital admission, which greatly increased the risk of gout flare during hospital admission. A recent study of 101 gout patients at the outpatient clinics in Mexico reported higher gout flare frequency and higher serum urate level during COVID-19 pandemic, compared to pre-pandemic period.[21] The observation from the Mexican outpatient study combined with our inpatient cohort suggested that COVID-19 pandemic may have negative impact on gout control overall, which contributed to high risk of flare when gout patients were hospitalized for COVID-19. We did not find an association between the risk of gout flare and COVID-19 specific factors (pneumonia, favipiravir and corticosteroids treatment). Favipiravir has been the standard antiviral therapy in Thailand since the beginning of the

pandemic. Favipiravir was particularly of interest because of its well-established hyperuricemic effects in people who do not have gout and reports of favipiravir-induced gout flare.[10,11] Our cohort however were not suited to fully examine the effects of favipiravir because the majority had serious COVID-19 and were treated with favipiravir.

The gout cohort had a mean age of over 60 years and over 90% of our cohort had at least one comorbidity. Older age and comorbid conditions such cardiovascular disease and diabetes mellitus are known to be associated with mortality in people with COVID-19 as well as people with inflammatory rheumatic diseases (including gout) and COVID-19.[22-24] The high burden of comorbidities likely contributed to the overall high mortality (18%) in our cohort. Of note, all deaths in the gout cohort were found in the non-flare group. Non-flare patients also had higher prevalence of systemic corticosteroids, mechanical ventilation and admission to intensive care unit. The absence of gout flare in patients who died of COVID-19 could have been the result of gout flare under recognition among patients with very severe pneumonia. These patients would likely have been mechanically ventilated and heavily sedated. It would have been difficult for the attending doctors to detect gout flare in this type of situation. In addition, high-dose systemic corticosteroids used in severe COVID-19 pneumonia could have suppressed signs of gout flare if it developed, further increasing the chance that gout flare would be overlooked. Hospital length of stay, another major hospital outcome, was also affected by gout flare, with gout flare group being hospitalized for three days longer than those in the non-flare group. Further analysis with linear regression model, adjusting for demographics, comorbidities, pneumonia and invasive ventilation, confirmed the association between inpatient gout flare and longer hospital length of stay.

One of the strengths of our study was robust patient identification and ascertainment methods. All included patients were admitted primarily for COVID-19 which was confirmed on day of admission by RT-PCR. We included only patients with known physician-diagnosed gout which meant that they would have been evaluated and diagnosed with gout by a doctor before the current admission and therefor minimizing the chance of misdiagnosis. Gout flare was also clearly defined as either physician diagnosis or Gaffo's definition,[13] a short coming of previous gout flare studies. We did not include patients who experienced first gout arthritis episode during admission to prevent erroneous inclusion of COVID-19-related reactive arthritis or septic arthritis.

Our study results however must be interpreted with caution. The cohort included only people with COVID-19 who were hospitalized, indicating that they were severely symptomatic or were considered at high risk of severe COVID-19. It is not known if the same results would be observed in people with COVID-19 managed in the community. Despite our attempt to identify as many patients with comorbid gout as possible from the COVID-19 databases, the prevalence of gout and gout flare were likely underestimated. Gout is a very common comorbid condition, but gout is often overlooked by attending doctors during hospital stay especially where there were minimal symptoms that require additional intervention. We also have not adjudicated the veracity of the prior diagnosis of gout, with a definition based on physican-stated diagnosis, not the more rigorous diagnostic criteria, such as the ACR/EULAR classification criteria.[25] These findings are from three hospitals in one country and in a predominantly Thai population so may not be completely generalizable to other settings.

Conclusion

Gout flare developed in 18% of patients with comorbid gout hospitalized for COVID-19. One-third of gout flare episodes required treatment with two or more anti-inflammatory medications. Inpatient gout flare during COVID-19 admission was associated with GOUT-36 >2 and associated with longer hospital length of stay, with up to three days added to the hospital course. These data suggest people admitted with COVID-19 with a pre-existing diagnosis of gout and who are at high risk for developing gout flare (GOUT-36 rule ≥2) may need closer attention from the attending doctors to ensure that their existing ULT are continued and that gout flare is detected and treated as early as possible.

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Table 1. Extracted variables and their descriptions

Variables	**Descriptions**
Demographics	Age at admission (year), sex (male or female) and ethnicity (Thai or other)
Admission data	
Length of stay	Number of days between date of hospital admission and discharge date
Comorbidities	Conditions from the Charlson comorbidity index, obesity and smoking (ever)
COVID-19 data	
COVID-19 pneumonia	Presence of pulmonary infiltrates on chest radiographs or chest computed tomography judged to be associated with COVID-19 by attending doctor
Oxygen/ventilation support	Oxygen support (nasal cannula, oxygen mask or high-flow nasal cannula), noninvasive positive-pressure ventilation or invasive ventilation
COVID-19 treatment	Systemic corticosteroids (dexamethasone, methylprednisolone, prednisolone), tocilizumab, baricitinib, casirivimab/imdevimab, hydroxychloroquine, azithromycin, ivermectin, antiviral agents (favipiravir, remdesivir, oseltamivir, darunavir, ritonavir, lopinavir) or convalescent plasma
Gout history	
Tophus	Presence of draining or chalk-like subcutaneous nodule under transparent skin at joints, ears, olecranon bursae, finger pads or tendons recorded by a doctor in the admission notes

Pre-admission ULT	Prescription of allopurinol, febuxostat, benzbromarone, probenecid or sulfinpyrazone according to previous outpatient records or previous hospital discharge letters or referral letters
Pre-admission gout flare prophylaxis	Prescription of colchicine, NSAID or prednisolone as continuous therapy according to previous outpatient records or previous hospital discharge letters or referral letters
Adjustment of ULT	Any adjustment of ULT including start, stop, increase or decrease dosage during hospitalization and before onset of gout flare (if any)
Adjustment of flare prophylaxis	Any adjustment of gout flare prophylaxis including stop or decrease dosage during hospitalization and before onset of gout flare (if any)
Pre-admission serum urate	Highest serum urate level tested within one year before admission
Classified as high risk by GOUT-36 prediction rule	Presence of two or more of the following items: no ULT, no prophylaxis, tophus, and serum urate >0.36 mmol/L (6 mg/dL)
Gout flare episode	
Flare onset	Number of days between date of hospital admission and date of flare onset
Duration of flare	Number of days between flare onset and flare resolution or hospital discharge
Number of joints	One (monoarticular), two or three (oligoarticular) and four or more (polyarticular)
Joints involved	e.g., first metatarsophalangeal, ankle, knee
MSU crystal identification	Presence of needle-shaped, strongly birefringent crystals by polarized light microscopy in synovial fluid or tophus aspirates
Medications for gout flare	Colchicine, NSAIDs, systemic corticosteroids or intra-articular corticosteroids

Gaffo's definition of gout flare	Presence of three or more of the following criteria: at least one joint swelling, at least one warm joint, pain score at rest higher than 3 (from a scale of 1 to 10) and patient-defined gout flare
MSU, monosodium urate; NSIAD, non-steroidal anti-inflammatory drugs; ULT, urate-lowering therapy	

Table 2. Cohort characteristics

Characteristics	**Overall cohort (N =146)**	**Non-flare (N =130)**	**Flare (N =26)**	**p-value¥**
Demographics				
Age (years), mean±SD	63.5±15.6	64.2±15.8	60.2±14.7	0.169
Male, n (%)	109 (74.7)	88 (73.3)	21 (80.8)	0.429
Thai ethnicity, n (%)	144 (98.6)	120 (100.0)	24 (92.3)	0.031
Comorbidities				
Charlson comorbidity index, median (IQR)	3.0 (3.0)	3.5 (3.0)	2.5 (3.0)	0.087
Diabetes mellitus, n (%)	61 (41.8)	54 (45.0)	7 (26.9)	0.090
Obesity, n (%)	41 (28.1)	36 (30.0)	5 (19.2)	0.268
Myocardial infarction, n (%)	26 (17.8)	24 (20.0)	2 (7.7)	0.167
Moderate to severe CKD, n (%)	20 (13.7)	15 (12.5)	5 (19.2)	0.356
CVA or TIA, n (%)	13 (8.9)	12 (10.0)	1 (3.8)	0.465
Smoking (ever), n (%)	13 (8.9)	12 (10.0)	1 (3.8)	0.465
Congestive heart failure, n (%)	9 (6.2)	8 (6.7)	1 (3.8)	1.000
Peptic ulcer disease, n (%)	5 (3.4)	4 (3.3)	1 (3.8)	1.000
COPD, n (%)	4 (2.7)	4 (3.3)	0 (0.0)	1.000
Liver disease, n (%)	3 (2.1)	2 (1.7)	1 (3.8)	0.447
Hemiplegia, n (%)	3 (2.1)	3 (2.5)	0 (0.0)	1.000
Solid tumor, n (%)	2 (1.4)	2 (1.7)	0 (0.0)	1.000
AIDS, n (%)	2 (1.4)	2 (1.7)	0 (0.0)	1.000
Connective tissue disease, n (%)	1 (0.7)	0 (0.0)	1 (3.8)	0.178
Dementia, n (%)	1 (0.7)	1 (0.8)	0 (0.0)	1.000

Admission data				
Department, n (%)				
Medical	98 (67.1)	76 (63.4)	22 (84.6)	0.036
Intensive care	20 (13.7)	19 (15.8)	1 (3.8)	0.127
Field hospital	28 (19.2)	25 (20.8)	3 (11.5)	0.411
Length of stay (days), median (IQR)	11.0 (8.0)	10.5 (7.0)	13.0 (16.0)	0.035
Mortality, n (%)	26 (17.8)	26 (21.7)	0 (0.0)	0.005
COVID-19 data				
Pneumonia, n (%)	110 (75.3)	91 (75.8)	19 (73.1)	0.768
Oxygen cannula or mask, n (%)	47 (32.2)	37 (30.8)	10 (38.5)	0.450
High-flow oxygen cannula, n (%)	34 (23.3)	26 (21.7)	8 (30.8)	0.319
NIPPV, n (%)	1 (0.7)	0 (0.0)	1 (3.8)	0.178
Invasive ventilation, n (%)	21 (14.4)	19 (15.8)	2 (7.7)	0.369
COVID-19 treatments				
Favipiravir, n (%)	127 (87.0)	106 (88.3)	21 (80.8)	0.335
Systemic corticosteroids, n (%)*	105 (71.9)	90 (75.0)	15 (57.7)	0.075
Ivermectin, n (%)	25 (17.1)	23 (19.2)	2 (7.7)	0.250
Azithromycin, n (%)	11 (7.5)	8 (6.7)	3 (11.5)	0.414
Remdesivir, n (%)	5 (3.4)	3 (2.5)	2 (7.7)	0.217
Ritonavir, n (%)	4 (2.7)	2 (1.7)	2 (7.7)	0.146
Tocilizumab, n (%)	3 (2.1)	3 (2.5)	0 (0.0)	1.000
Hydroxychloroquine, n (%)	3 (2.1)	0 (0.0)	3 (11.5)	0.005
Baricitinib, n (%)	2 (1.4)	1 (0.8)	1 (3.8)	0.325
Darunavir, n (%)	2 (1.4)	0 (0.0)	2 (7.7)	0.031
Lopinavir, n (%)	2 (1.4)	2 (1.7)	0 (0.0)	1.000

Convalescent plasma, n (%)	2 (1.4)	0 (0.0)	2 (7.7)	0.031
Oseltamivir, n (%)	1 (0.7)	1 (0.8)	0 (0.0)	1.000
Casirivimab/imdevimab, n (%)	1 (0.7)	0 (0.0)	1 (3.8)	0.178
Gout history				
Tophus, n (%)	5 (3.4)	3 (2.5)	2 (7.7)	0.217
Pre-admission ULT	96 (65.7)	88 (73.3)	8 (30.7)	<0.001
Allopurinol, n (%)	78 (53.4)	71 (59.2)	7 (26.9)	0.003
Allopurinol dose (mg/day), median (IQR)	100 (50)	100 (0)	150 (200)	0.069
Febuxostat, n (%)	12 (8.2)	12 (10.0)	0 (0.0)	0.125
Febuxostat dose (mg/day), median (IQR)	60 (40)	60 (40)	NA	NA
Sulfinpyrazone, n (%)	4 (2.7)	3 (2.5)	1 (3.8)	0.548
Sulfinpyrazone dose (mg/day), median (IQR)	150 (250)	100 (0)	200 (0)	0.637
Benzbromarone, n (%)	2 (1.4)	2 (1.7)	0 (0.0)	1.000
Benzbromarone dose (mg/day), median (IQR)	37.5 (0.0)	37.5 (0.0)	NA	NA
Pre-admission colchicine as flare prophylaxis, n (%)	52 (35.6)	49 (40.8)	3 (11.5)	0.005
Colchicine dose (mg/day), median (IQR)	0.6 (0.0)	0.6 (0.0)	0.6 (0.0)	0.375
Adjustment of ULT during hospital stay, n (%)**	36 (24.7)	31 (25.8)	5 (19.2)	0.479
Adjustment of flare prophylaxis during hospital stay, n (%)†	20 (13.7)	17 (14.2)	3 (11.5)	1.000

Highest pre-admission serum urate(mg/dL), mean±SD	7.4±2.4	7.2±2.2	8.9±3.0	0.023
Classified as high risk by GOUT-36 prediction rule‡	70 (47.9)	47 (39.2)	23 (88.5)	<0.001

* Standard dosage of systemic corticosteroids during the study period was dexamethasone 12 mg daily (equivalent to 60 mg of prednisolone).

** Stopping/decreasing in 35 and starting/increasing in 1 patient.

† Stopping/decreasing in 18 and starting/increasing in 2 patients.

‡ Patients were classified as having high risk for inpatient gout flare when they had two or more items from the GOUT-36 prediction rule (no ULT, no prophylaxis, tophus, and serum urate >0.36 mmol/L (6 mg/dL)).

¥ p-value for the comparison between patients with gout flare and patients with no flare.

Table 3. Characteristics of gout flare episodes (N =26)

Characteristics	**Prevalence**
Onset of flare	
Number of days between admission date and flare onset, median (IQR)	7.0 (10.0)
Duration of flare (days), median (IQR)	3.0 (2.0)
Number of joint involved (N =19), n (%)	
1 joint	15 (78.9)
2 or 3 joints	3 (15.8)
4 or more joints	1 (5.3)
Location of flare (N =19), n (%)	
Ankle	8 (42.1)
First metatarsophalangeal joint	6 (31.6)
Knee	5 (26.3)
Wrist	1 (5.3)
Second to fifth metatarsophalangeal joint	1 (5.3)
Gaffo's definition of flare, n (%)	
Presence of 3 or more criteria	18 (69.2)
Pain at rest score >3 (from a scale of 1 to 10)	26 (100.0)
Any swollen joint	19 (73.1)
Any warm joint	18 (69.2)
Patient-defined gout flare*	0 (0.0)
Joint aspiration, n (%)	
Synovial fluid examination performed	4 (15.4)
MSU crystal identified	3 out of 4 (75.0)
Treatment of gout flare, n (%)	

Any medical treatment	23 (88.5)
Colchicine	13 (50.0)
Systemic corticosteroids	10 (38.5)
NSAIDs	9 (34.6)
Combination of two or more medications	8 (30.8)

*Patient-defined gout flare could not be collected from retrospective chart review.

IQR, interquartile range; MSU, monosodium urate; NSAID, non-steroidal anti-inflammatory drug

Table 4. LASSO variable selection and logistic regression exploring factors associated with inpatient gout flare

Variables	**LASSO coefficients***	**Logistic regression**			
		Coefficients	**OR**	**95%CI**	**p-value**
GOUT-36 ≥2 at admission	1.23	1.70	5.46	1.18 to 25.37	0.030
No pre-admission ULT	0.55	0.94	2.56	0.84 to 7.82	0.099
No flare prophylaxis	0.06	0.91	2.49	0.59 to 10.40	0.213
Ventilator support	-0.11	-1.34	0.26	0.05 to 1.31	0.103
Tophus, serum urate >6 mg/dL, ULT adjustment, prophylaxis adjustment, age, male, Charlson comorbidity index, COVID-19 pneumonia, corticosteroids, favipiravir	0 (removed)	-	-	-	-
Intercept	-2.54	-3.66	-	-	-
*Penalty factor (λ) =0.039					

Table 5. Linear regression model exploring association between gout flare and hospital length of stay

Variables	**Regression coefficients**	**95%CI**	**p-values**
Gout flare	5.74	2.49 to 8.98	0.001
Ventilator support	5.68	2.08 to 9.30	0.002
COVID-19 pneumonia	2.46	-0.65 to 5.58	0.120
Charlson comorbidity index	-0.04	-0.78 to 0.69	0.909
Age	-0.28	-0.14 to 0.08	0.620
Male	-1.65	-4.59 to 1.29	0.27
Intercept	11.32	4.34 to 18.29	-