Colchicine prophylaxis is associated with fewer gout flares after COVID-19 vaccination

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ABSTRACT

Objectives COVID-19 vaccination often triggers a constellation of transient inflammatory symptoms. Gout is associated with several comorbidities linked to poor outcomes in COVID-19, and gout flares can be triggered by some vaccinations. We analysed the risk of gout flares in the first 3 months after COVID-19 vaccination with inactivated virus, and whether colchicine can prevent gout flares following post-COVID-19 vaccination.

Methods A clinical delivery population-based cross-sectional study was conducted in the Gout Clinic at the Affiliated Hospital of Qingdao University between February and October 2021. Study participants were selected using a systematic random sampling technique among follow-up patients with gout. We collected data, including vaccinations and potential risk factors, using a combination of interviews, health QR codes and medical records. Logistic regression was used to adjust for covariates.

Results We enrolled 549 gout participants (median age 39 years, 84.2% vaccinated). For the 462 patients who received COVID-19 vaccine, 203 (43.9%) developed at least one gout flare in the 3 months after vaccination. Most of these flares were experienced within 1 month after the first (99/119 (83.2%)) or second (70/115 (60.9%)) dose of vaccine. Compared with unvaccinated participants, COVID-19 vaccination was associated with higher odds of gout flare within 3 months (adjusted OR 6.02; 95% CI 3.00 to 12.08). Colchicine use was associated with 47% less likelihood of postvaccine gout flare.

Conclusion COVID-19 vaccination was associated with increased odds of gout flare, which developed mainly in month 1 after each vaccine dose, and was negatively associated with colchicine prophylaxis.

INTRODUCTION

Vaccines against SARS-CoV-2 represent a pivotal and effective countermeasure to contain the COVID-19 pandemic. Given gout is associated with many risk factors (eg, age and comorbidities) for poor COVID-19 outcomes,1 vaccination of patients with gout is of high priority.

Risk factors for gout flare include dietary factors, medications and comorbidities. Recently, a case-crossover study conducted by Yokose et al5 revealed that recombinant herpes zoster vaccine (RZV) in the prior 2 days was associated with a twofold increased odds of gout flare when compared with no vaccine periods (adjusted OR 1.99; 95% CI 1.01 to 3.95). A study conducted by the European Alliance of Associations for Rheumatology Coronavirus Vaccine physician-reported Registry reported 4.4% of flare following mRNA vaccination in inflammatory/autoimmune rheumatic and musculoskeletal disease cases from 30 countries.3 However, to date, no systematic analysis, even real-world data, investigated the association between COVID-19 vaccine and gout flare.

We analysed the risk of gout flares in the first 3 months after COVID-19 vaccination with inactivated virus, and whether colchicine associates with reduced gout flares following post-COVID-19 vaccination.

METHODS

Study design and participants

We performed a clinical delivery population-based observational and cross-sectional study, based on face-to-face electronic questionnaires and individual medical records from the Biomedical Information Management System (BIMS; Haier, China), which took place in the Gout Clinic at the Affiliated Hospital of Qingdao University between February
2021 and October 2021. All participants had gout according to the 2015 American College of Rheumatology/European League Against Rheumatism gout classification criteria. A sample size of 544 was calculated by using a formula for calculating sample size for cross-sectional study, assumed a 90% CI, 5% non-response rate, 70% COVID-19 vaccination rate in Shandong Province and 40% proportion of gout flare as estimated by the reports.

Assessments and procedures
After written informed consent was obtained, all eligible participants completed a structured interview questionnaire, with the help of trained research staff. The questionnaire includes a Gout Assessment Questionnaire (GAQ 2.0), data of gout flare and the type and date of each vaccine. Gout-specific health-related quality of life (HRQoL) was assessed by the Gout Impact Scale (GIS) of the GAQ 2.0 (Chinese version), a 24-item instrument with five scales: gout concern overall, gout concern during gout flare, medication side effects, unmet gout treatment need and well-being during flare, each with a 0–100 score (higher score indicating more concern/need).

Patients were asked to recall the data of gout flare regarding times of onset, clinical signs and symptoms within 3 months before the first dose vaccine and after any of the vaccines. These data were double-checked in each patient’s standardised medical record to ensure the reliability and accuracy.

The type and date of each vaccine were collected by uploading their personal health QR code, a vaccination certificate, which was launched by Chinese government.

Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. A positive family history of gout was defined as ≥1 of the patient’s first to second degree relatives affected by gout. Comorbidities were defined as present if formally recorded in the past history of the medical record, or if the patient was currently receiving comorbidity specific drug treatment, and included hypertension, renal disease, hyperlipidaemia, tumour, fracture, cardiovascular, digestive, respiratory or mental diseases. Last serum urate (SU) done before the first vaccine and the urate-lowering treatment at the time of the first vaccine were traced by the BIMS. Prophylactic colchicine usage was defined as taking 0.5 g colchicine once or twice daily ≥1 month at any time during the vaccination period (online supplemental figure 1).

In total, we enrolled 2983 patients with 2036 follow-up patients as estimated by the last year’s numbers of patients who visited our clinical centre. New patients, who were the first time to visit our clinic, were excluded. Eligible patients were invited to participate using a systematic random sampling technique. The sampling fraction was determined by dividing the total 8-month follow-up numbers by the sample size. The first participant was selected as his or her first visiting sequence on our research initiating date and every second interval was included using systematic random sampling. Six hundred and seventy-eight were selected for questionnaire interview. Completed questionnaires were returned by 646 out of 678 respondents, with a response rate of 95.3%. There were 96 patients excluded because of insufficient medical record data. Finally, 549 were enrolled for the analysis (online supplemental figure 1).

This study was initiated at the very beginning of COVID-19 vaccination in China. The vaccination programme was started from December 2020 and greatly expanded in April, May and June 2021. We matched the data of gout flare by the first vaccination date of vaccinated patients in the non-vaccination participants. Most patients in non-vaccination group were vaccinated subsequently as government advocacy and sufficient vaccine supply developed. All clinical data were corrected and confirmed by personal medical records.

Statistical analysis
All analyses were performed using SPSS V26.0 (IBM). Continuous variables were expressed as mean (SD) or median (IQR) and were compared by independent sample t-test or Wilcoxon sign-rank test. Categorical variables were expressed as number (percentage) and were compared by χ² test. Logistic regression analyses were used to assess the association of variables with gout flare. P value <0.05 was considered statistically significant.

RESULTS
Study participants
The study included 549 participants (531 (96.7%) men), with a median (IQR) age of 39 years (32–49) (table 1). Four hundred and sixty-two (84.2%) received COVID-19 vaccine, in which 400 (86.6%) had received two doses. Most patients (250 (54.1%)) received the Sinovac Life vaccine, 174 (37.7%) had the Sinopharm BIBP and 38 (8.2%) the others (recombinant COVID-19 vaccine (CHO cell) or recombinant COVID-19 Vaccine (adenovirus type 5 vector)). Both Sinovac Life and Sinopharm BIBP vaccines contain aluminium hydroxide adjuvant. Mean (SD) time between the first and second dose of the vaccine (if applicable) was 36 (13) days. The non-vaccination and vaccination participants displayed comparable means (SD) of BMI (kg/m²): 26.95 (3.59) vs 27.67 (4.15), p=0.15), duration of gout (year; 7.74 (6.33) vs 6.40 (5.34), p=0.11), gout flare per person within last 3 months before the first vaccine (0.56 vs 0.56), last SU done before the first vaccine (mg/dL; 7.63 (2.22) vs 7.45 (1.97), p=0.55) and proportions of comorbidities (46.0% vs 50.7%, p=0.48), prophylactic colchicine usage (32.2% vs 24.7%, p=0.14), achieving the treatment urate target in recent year (29.9% vs 24.9%, p=0.35) and urate-lowering drugs use at the time of the first vaccine (p=0.44). However, the vaccinated patients had a higher proportion of patients with gout flares within last 3 months after vaccination (43.9% vs 32.2%, p=0.04) and a lower mean (SD) score of well-being (70% COVID-19 flare (model 1: adjusted OR 6.02; 95% CI, 5% non-
among participants with high last serum urate levels before the first-dose vaccine (adjusted OR 1.14; 95% CI 1.02 to 1.27). On the contrary, colchicine prophylaxis was associated with 47% less likelihood of having an increase in gout flare burden after vaccination (model 1: adjusted OR 0.53; 95% CI 0.31 to 0.92, model 2: adjusted OR 0.53; 95% CI 0.30 to 0.92, table 3).

**DISCUSSION**

The findings of this clinical delivery population-based cross-sectional study provide important implications for COVID-19 vaccine administration in people with gout. Our data indicate a higher odds of gout flare within 3 months after COVID-19 vaccine and that colchicine prophylaxis is associated with markedly reduced odds of postvaccine gout flare. The percentage of medically confirmed flares reported within 3 months after COVID-19 vaccination was 203/462 (43.94%). Most patients developed a flare within 1 month after the first (99/119 (83.19%)) or second (70/115 (60.87%)) vaccine. Notably, Sinovac Life vaccine received as well as higher SU levels before the first vaccine are all associated with increased risk of the postvaccine gout flare.

The main limitation of this study is its observational and cross-sectional nature, with retrospective collection of gout flare data that may be subject to recall bias. Substantially, personal medical records were checked to verify the gout flare data, thereby minimising the bias. Also, we could not fully account for confounding factors. The percentage of patients developing at least one gout flare within 3 months after vaccination was 244/462 (52.80%). The percentage of patients developing at least one gout flare within 3 months after vaccination was 244/462 (52.80%). The percentage of patients developing at least one gout flare within 3 months after vaccination was 244/462 (52.80%).

### Table 1 Demographic characteristics of the participants

| Characteristics | Total (n=549) | No vaccination (n=87) | COVID-19 vaccination (n=462) | P value |
|-----------------|--------------|---------------------|-----------------------------|---------|
| Demographics    |              |                     |                             |         |
| Age (years), mean (SD)/median (IQR) | 41.01 (12.65)/39 (32–49) | 40.75 (14.50)/37 (28–52.5) | 41.05 (12.36)/39.5 (32–48) | 0.86    |
| Male sex, n (%) | 531 (96.7) | 82 (94.3) | 449 (97.2) | 0.18    |
| Body mass index (kg/m²), mean (SD) | 27.55 (4.06) | 26.95 (3.59) | 27.67 (4.15) | 0.15    |
| Completed college (n, %) | 358 (65.2) | 50 (57.5) | 308 (66.7) | 0.81    |
| Smoking, n (%) |              |                     |                             | 0.08    |
| Never | 286 (52.1) | 44 (50.6) | 242 (52.4) |         |
| Sometimes | 74 (13.5) | 10 (11.5) | 64 (13.9) |           |
| Regular | 114 (20.8) | 26 (29.9) | 88 (19.1) |           |
| Quit | 75 (13.7) | 7 (8.5) | 68 (14.7) |           |
| Alcohol drinking, n (%) |              |                     |                             | 0.37    |
| Never | 130 (23.7) | 19 (21.8) | 111 (24.0) |         |
| Sometimes | 259 (47.2) | 42 (48.3) | 217 (47.0) |           |
| Regular | 80 (14.6) | 17 (19.5) | 63 (13.6) |           |
| Quit | 80 (14.6) | 9 (10.3) | 71 (15.4) |           |
| Comorbidities*, n (%) | 274 (49.9) | 40 (46.0) | 234 (50.7) | 0.48    |
| COVID-19 vaccination |              |                     |                             |         |
| Vaccination, n (%) | 462 (84.2) | – | – | – |
| Completed | – | – | 400 (86.6) |           |
| Not completed | – | – | 62 (13.4) |           |
| Vaccination received, n (%) |              |                     |                             | –       |
| Sinovac Life | 250 (45.1) | – | 250 (54.1) |         |
| Sinopharm BIBP | 174 (31.7) | – | 174 (37.7) |           |
| Others | 38 (8.2) | – | 38 (8.2) |           |
| Gout specific indicators |              |                     |                             |         |
| Age at onset (years), mean (SD) | 35.90 (11.1) | 35.57 (13.7) | 35.97 (10.5) | 0.81    |
| Duration of gout (years), mean (SD) | 6.64 (5.5) | 7.74 (6.3) | 6.40 (5.3) | 0.11    |
| Positive family history, n (%) | 101 (18.4) | 14 (16.1) | 87 (18.8) | 0.55    |
| Palpable tophus, n (%) | 66 (12.0) | 8 (9.2) | 58 (12.6) | 0.38    |
| Gout impact scale scores†, mean (SD) |              |                     |                             |         |
| Gout concern overall | 82.62 (22.36) | 82.54 (20.60) | 82.63 (22.7) | 0.97    |
| Gout concern during attack gout | 71.65 (20.55) | 73.61 (19.96) | 71.29 (20.66) | 0.33    |
| Medications side effects | 71.47 (19.9) | 72.72 (19.22) | 71.23 (20.03) | 0.52    |
| Ummot gout treatment need | 60.93 (15.82) | 62.45 (16.76) | 60.64 (15.63) | 0.33    |
| Well-being during attack | 58.27 (25.88) | 63.43 (23.65) | 57.30 (26.18) | 0.04    |
| Colchicine prophylaxis, n (%) | 142 (25.9) | 28 (32.2) | 114 (24.7) | 0.14    |
| Achieving the treatment urate target in recent year, n (%)‡ | 141 (25.7) | 26 (29.9) | 115 (24.9) | 0.35    |
| Last serum urate done before first vaccine (mg/dL), mean (SD) | 7.51 (2.01) | 7.63 (2.22) | 7.45 (1.97) | 0.55    |
| Gout flares per person within last 3 months before first vaccine, mean | 0.56 | 0.56 | – | – |
| Gout flares within last 3 months after any vaccine, n (%) | 231 (41.1) | 28 (32.2) | 203 (43.9) | 0.04    |
| Urate-lowering drugs use at the time of the first vaccine, n (%) |              |                     |                             | 0.44    |
| Febuxostat | 304 (55.4) | 53 (60.9) | 251 (54.3) |         |
| Benzbromarone | 48 (8.6) | 8 (9.2) | 40 (8.7) |           |
| No or missing | 197 (35.9) | 26 (29.9) | 171 (37.0) |           |

*Comorbidities include diabetes, hypertension, renal disease, hyperlipidemia, tumour, fracture, cardiovascular, digestive, respiratory or mental diseases.
†Gout impact scale scores: 0~100 where 100 indicates worse condition.
‡Achieving the treatment urate target in recent year indicates serum urate < 6 mg/dL.
Table 2  Characteristics of patients after the first and second dose COVID-19 vaccines

| Characteristics                          | Total (n=462) | First dose | Second dose | P value |
|------------------------------------------|---------------|------------|-------------|---------|
| Vaccination completed, n (%)            | 400 (86.6)    | –          | –           | –       |
| Vaccination received, n (%)             | –             | –          | –           | –       |
| Sinovac Life                             | 251 (54.3)    | –          | –           | –       |
| Sinopharm BIBP                           | 173 (37.5)    | –          | –           | –       |
| Others                                   | 38 (8.2)      | –          | –           | –       |
| Side effects after any vaccination*, n (%)| 141 (30.5)    | –          | –           | –       |
| Gout flare after any vaccination*, n (%) | 203 (43.9)    | –          | –           | –       |

Flare ratio, n/N (%) – 119/203 (58.6) 115/203 (56.7) 0.65
VAS, mean (SD) – 5.02 (2.3) 5.65 (2.3) 0.04
Without other specific trigger†, n/N (%) – 67/119 (56.3) 61/115 (53.0) 0.70
Timing of gout flare (days), n/N (%) – <0.001
Within 1 week – 36/119 (30.3) 22/115 (19.1)
1 week ~1 month – 63/119 (52.9) 48/115 (41.7)
1~3 months – 20/119 (16.8) 45/115 (39.1)
Main joint site of gout flare, n/N (%) – 0.07
First MTP – 49/119 (41.2) 58/115 (50.4)
Ankle and heel – 53/119 (44.5) 51/115 (44.4)
Knee – 15/119 (12.6) 4/115 (3.5)
Wrist – 2/119 (1.7) 2/115 (1.7)

*Side effects after vaccination includes cold symptoms (fatigue, cough, fever, muscle pain nd headache); wheezing or shortness of breath; nausea, vomiting or diarrhoea; flustered and chest tightness.
†Other specific triggers include cold, exercise, alcohol consumption, diuretic use and purine intake.
VAS, visual analogue score; MTP, metatarsophalangeal.

Table 3  Variables associated with a gout flare in the 3-month period*

| Variables for gout flare                        | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
|                                                 | OR (95% CI)         | P value               |
|                                                 | Model 1             | Model 2               |
| Demographics                                    | OR (95% CI)         | P value               |
| Sex (ref: female)                               | 0.82 (0.32 to 2.10) | 0.67                  |
| Age (per year)                                  | 1.00 (0.99 to 1.02) | 0.49                  |
| Body mass index (per kg/m²)                     | 1.03 (0.99 to 1.08) | 0.16                  |
| Comorbidities† (ref: no)                        | 0.92 (0.67 to 1.29) | 0.64                  |
| Tophi (ref: no)                                 | 1.01 (0.59 to 1.70) | 0.98                  |
| Disease duration (per year)                     | 0.96 (0.92 to 0.99) | 0.007                 |
| Flare within 3 months prior to first vaccine (ref: no) | 0.17 (0.06 to 0.54) | 0.003                 |
| Last serum urate done before first vaccine (per mg/dL) | 1.22 (1.11 to 1.33) | <0.001                 |
| Vaccination                                    | 4.57 (2.66 to 7.84) | <0.001                 |
| Sinovac Life vaccine (ref: no)                  | 2.90 (1.28 to 6.56) | 0.011                 |
| Sinopharm BIBP vaccine (ref: no)                | 0.55 (0.28 to 1.10) | 0.09                  |
| Other vaccines (ref: no)                        | 0.70 (0.34 to 1.41) | 0.32                  |
| Treatment                                       | 0.38 (0.24 to 0.61) | <0.001                 |
| Colchicine prophylaxis (ref: no)                | 0.89 (0.47 to 1.68) | 0.71                  |
| Benzbranorine use at the time of first vaccine (ref: no or missing) | 0.66 (0.36 to 1.21) | 0.18                  |

Model 1: fully adjusted by COVID-19 vaccination, sex, age, body mass index, disease duration, flare within 3 months prior to the first dose vaccine, last serum urate done before the first dose vaccine, colchicine prophylaxis and urate-lowering drugs use at the time of the first dose vaccine.
Model 2: fully adjusted by vaccine types (Sinovac Life, Sinopharm BIBP and others including recombinant COVID-19 vaccine (CHO cell) or recombinant COVID-19 Vaccine (adenovirus type 5 vector)), sex, age, body mass index, disease duration, flare within 3 months prior to the first dose vaccine, last serum urate done before the first dose vaccine, colchicine prophylaxis and urate-lowering drugs use at the time of the first dose vaccine.
Bold values indicate P<0.05.
*Gout flare within 3 months after any vaccine in COVID-19 vaccination participants or the matched time period in the non-vaccination participants.
†Comorbidities include hypertension, renal disease, hyperlipidaemia, tumour, fracture, cardiovascular, digestive, respiratory or mental diseases.
factors affecting the relevant outcomes. Importantly, we only investigated the effects of inactivated virus COVID-19 vaccines on gout flare, the only approved vaccines currently in China. Other vaccine types (eg, mRNA, viral vector or protein subunit type) need to be studied for validation, ideally prospectively and with multicentre collaboration.

In conclusion, this study suggests that COVID-19 vaccination is associated with a higher odds of postvaccine gout flares. Colchicine prophylaxis was associated with marked reduction of gout flares after COVID-19 vaccine. Surprisingly, mention of gout, a disease so frequently linked with obesity, type 2 diabetes, hypertension and advanced age, has been omitted from recent rheumatology society recommendations for COVID-19 vaccination in patients with rheumatic disease. The willingness to get vaccinated against COVID-19 in patients with rheumatic diseases is limited by the fear of vaccine side effects. This study may inform discussions with patients with gout about the risks of gout flare around the time of COVID-19 vaccination.

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Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY. 25th May 2023.

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Supplementary Figure 1. Study profile.

2,983 patients with gout who visited our Gout Clinic between February and October, 2021

New visitors → 947 excluded

Follow-up patients

2,036 were numbered by their visiting sequence

Systematic random sampling

678 patients face-to-face visit

33 without response excluded

Vaccinated patients
Non-vaccinated patients

Clinical data were matched by the first vaccination date of vaccinated ones based on personal medical records

Data analysis

First dose

Second dose

Flares up to 3 months

Colchicine prophylaxis

ULDs use

Last SU done

All clinical data were checked by personal medical records

96 with insufficient medical records excluded
Flare likely after vaccination, but can be prevented with colchicine

COVID-19 vaccination associated with increased likelihood of gout flare

INTRODUCTION
Gout is a very common condition, affecting up to 2–4% of adults in developed countries. The symptoms tend to flare every so often, developing over a few hours and causing severe pain in the joints. It is caused by deposits of crystals of a substance called uric acid (urate) in the joints, which leads to inflammation.

COVID-19 is the disease caused by a new type of coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It was declared a pandemic by the World Health Organization on 11 March 2020. COVID-19 has forced people to change their behaviours to try to limit the spread of infection.

Gout is associated with several other diseases (comorbidities) that are linked to poor outcomes in COVID-19, and gout flares can be triggered by some vaccinations.

WHAT DID THE AUTHORS HOPE TO FIND?
The authors hoped to learn whether COVID-19 vaccination affects the risk of gout flares. They also wanted to see whether a medicine called colchicine could reduce the risk of gout flares after COVID-19 vaccination.

WHO WAS STUDIED?
The study looked at 549 people with gout. Of these, 462 had received a COVID-19 vaccine based on an inactivated virus – the only one currently available in China.

HOW WAS THE STUDY CONDUCTED?
This was a non-interventional observational study of people seen at one clinic in China. The authors used medical records and face-to-face interviews to collect data about vaccinations and people’s potential risk factors that might make them more likely to have a gout flare.

The interviews were based on a questionnaire about gout disease activity, flares, and the type and date of each vaccine. Everyone was asked to recall the date of any gout flares, and any clinical signs and symptoms within 3 months before and after receiving the COVID-19 vaccine. This information was cross-checked in each person’s medical record.

The information collected was used to analyse the risk of gout flares in the first 3 months after COVID-19 vaccination with inactivated virus. They also investigated whether taking colchicine was associated with reduced gout flares after COVID-19 vaccination.

WHAT WERE THE MAIN FINDINGS OF THE STUDY?
The main finding was that gout flares were more common after COVID-19 vaccination, particularly in the month after vaccination. Compared with unvaccinated people, those who had received a COVID-19 vaccine were 6-times more likely to have a gout flare in the following 3 months. However, people using colchicine were 47% less likely to have a flare after their vaccination.

ARE THESE FINDINGS NEW?
Yes, this is the first study to report whether gout flares occur more often after COVID-19 vaccination.

WHAT ARE THE LIMITATIONS OF THE STUDY?
The main limitation of this study is its observational design, and collecting data in interviews might be subject to recall bias. Also, the results may not apply to other COVID vaccine types such as those based on mRNA, viral vector, or protein subunits. More studies are needed to examine the rate of gout flares after other kinds of COVID-19 vaccination.
WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?
The authors are doing a prospective study to confirm their conclusions.

WHAT DOES THIS MEAN FOR ME?
If you have gout, you may experience flares around the time of your COVID-19 vaccination. Knowing this means you can plan ways to prevent the flares through medicine and diet, and treat them quickly if they do occur.

If you have any concerns about your disease or its treatment, you should speak to your doctor.

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