



## EPIDEMIOLOGICAL SCIENCE

# 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 transitory 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,<sup>1</sup> 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 al*<sup>2</sup> 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

## Key message

### What is already known about this subject?

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

### What does this study add?

- This study showed that 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.

### How might this impact on clinical practice or future developments?

- These findings warrant further investigation into whether mRNA vaccines have the same effect, which ideally prospectively and with multicentre collaboration.
- This study may inform discussions with patients with gout about the risks of gout flare around the time of COVID-19 vaccination.

no vaccine periods (adjusted OR 1.99; 95% CI 1.01 to 3.89). 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.<sup>3</sup> However, to date, no systemic 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 Biobank Information Management System (BIMS; Haier, China), which took place in the Gout Clinic at the Affiliated Hospital of Qingdao University between February



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2021 and October 2021. All participants had gout according to the 2015 American College of Rheumatology/European League Against Rheumatism gout classification criteria.<sup>4</sup>

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<sup>5</sup> and 40% proportion of gout flare as estimated by the reports.<sup>6</sup>

### 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.<sup>7</sup>

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  $\geq 1$  of the patient's first to second degree relatives affected by gout.<sup>8</sup> 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  $\geq 1$  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.<sup>9</sup> 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 V.26.0 (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  $\chi^2$  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 ( $\text{kg}/\text{m}^2$ ; 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 ( $\text{mg}/\text{dL}$ ; 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 during attack of GIS (57.30 (26.18) vs 63.43 (23.65),  $p=0.04$ ) compared with the non-vaccinated ones. Detailed characteristics are shown in table 1.

### Gout flares following vaccination

For the 462 patients who received COVID-19 vaccine, 203 (43.9%) developed at least one gout flare in the 3 months after any vaccine. Most of these flares were reported within 1 month after the first (99/119 (83.2%)) or second (70/115 (60.9%)) dose of vaccine (table 2). Though the mean (SD) visual analogue score was higher in the second-dose vaccinated patients than the first-dose vaccinated ones (5.65 (2.34) vs 5.02 (2.31),  $p=0.04$ ), the flares were mild or moderate. The main joint sites of gout flare were comparable and most occurred in first metatarsophalangeal, ankle or heel (the first dose: 85.7%; the second dose: 94.8% in total, table 2).

We analysed the odds of a gout flare in the 3 months following COVID-19 flare within the first 3 months after vaccination (model 1: adjusted OR 6.02; 95% CI 3.00 to 12.08) indicating receiving COVID-19 vaccine was associated with sixfold higher odds of gout (table 3). Specifically, patients received Sinovac Life got a significant higher odd of gout flare (model 2: adjusted OR 3.13; 95% CI 1.12 to 8.72, table 3). The OR tended to be higher

**Table 1** Demographic characteristics of the participants

Characteristics	Total (n=549)	No vaccination (n=87)	COVID-19 vaccination (n=462)	P value
<b>Demographics</b>				
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/m <sup>2</sup> ), 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
<b>COVID-19 vaccination</b>				
Vaccination, n (%)	462 (84.2)	–	–	–
Completed	–	–	400 (86.6)	
Not completed	–	–	62 (13.4)	
Vaccination received, n (%)				–
Sinovac Life	250 (54.1)	–	250 (54.1)	
Sinopharm BIBP	174 (37.7)	–	174 (37.7)	
Others	38 (8.2)	–	38 (8.2)	
<b>Gout specific indicators</b>				
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	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
Unmet 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	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.

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

**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)	<b>0.04</b>
Without other specific trigger†, n/N (%)	–	67/119 (56.3)	61/115 (53.0)	0.70
Timing of gout flare (days), n/N (%)	–			<b>&lt;0.001</b>
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 and headache); wheezing or shortness of breath; nausea, vomiting or diarrhoea; flushed and chest tightness.

†Other specific triggers include cold, exercise, alcohol consumption, diuretic use and purine intake.

VAS, visual analogue score; MTP, metatarsophalangeal.

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.

**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 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
<b>Demographics</b>						
Sex (ref: female)	0.82 (0.32 to 2.10)	0.67	4.04 (0.68 to 24.04)	0.13	4.33 (0.73 to 25.82)	0.11
Age (per year)	1.00 (0.99 to 1.02)	0.49	1.01 (0.99 to 1.03)	0.16	1.01 (0.99 to 1.03)	0.18
Body mass index (per kg/m <sup>2</sup> )	1.03 (0.99 to 1.08)	0.16	1.02 (0.97 to 1.08)	0.44	1.02 (0.97 to 1.08)	0.45
Comorbidity† (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)	<b>0.007</b>	0.96 (0.92 to 1.01)	0.09	0.96 (0.92 to 1.01)	0.12
Flare within 3 months prior to first vaccine (ref: no)	0.17 (0.06 to 0.54)	<b>0.003</b>	1.27 (0.21 to 7.68)	0.79	1.27 (0.21 to 7.71)	0.79
Last serum urate done before first vaccine (per mg/dL)	1.22 (1.11 to 1.33)	<b>&lt;0.001</b>	1.14 (1.02 to 1.27)	<b>0.021</b>	1.14 (1.02 to 1.27)	<b>0.025</b>
<b>Vaccination</b>						
COVID-19 vaccination (ref: no)	4.57 (2.66 to 7.84)	<b>&lt;0.001</b>	6.02 (3.00 to 12.08)	<b>&lt;0.001</b>	–	–
Sinovac Life vaccine (ref: no)	2.90 (1.28 to 6.56)	<b>0.011</b>	–	–	3.13 (1.12 to 8.72)	<b>0.029</b>
Sinopharm BIBP vaccine (ref: no)	0.55 (0.28 to 1.10)	0.09	–	–	0.48 (0.2 to 1.14)	0.09
Other vaccines (ref: no)	0.70 (0.34 to 1.41)	0.32	–	–	0.49 (0.20 to 1.19)	0.12
<b>Treatment</b>						
Colchicine prophylaxis (ref: no)	0.38 (0.24 to 0.61)	<b>&lt;0.001</b>	0.53 (0.31 to 0.92)	<b>0.025</b>	0.53 (0.30 to 0.92)	<b>0.024</b>
Febuxostat use at the time of first vaccine (ref: no or missing)	0.89 (0.47 to 1.68)	0.71	–	–	–	–
Benzbromarone 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.

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.<sup>10</sup> The willingness to get vaccinated against COVID-19 in patients with rheumatic diseases is limited by the fear of vaccine side effects.<sup>11</sup> 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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