

# Colchicine is associated with a decreased Risk for myocardial infarction in patients with Gout: A systematic review and meta-analysis

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## Research article

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# Abstract

**Objective:** This meta-analysis aimed to identify the effects of Colchicine on myocardial infarction (MI) in patients with Gout.

**Methods:** In July 2018, a systematic computer-based search was conducted in PubMed, EMBASE, and Cochrane Database of Systematic Reviews. Data on patients with Gout that compared Colchicine versus others (non-used Colchicine) were retrieved. The endpoints were the incidence rate for MI. After testing for heterogeneity between studies, data were aggregated for random-effects models when necessary.

**Results:** Three clinical studies with 114371 patients (Colchicine group=1063, control group=113308) were finally included in the meta-analysis. Colchicine was associated with a decreased Risk for myocardial infarction (95% CI, 0.25, 0.33, P=.000).

**Conclusions:** Colchicine was efficacious in the reduction of the incidence rate for MI in patients with Gout.

## Background

Myocardial infarction (MI) is the main cause of death in some chronic diseases, especially in patients with inflammatory diseases[1]. Gout, the common types of inflammatory arthritis caused by deposits of monosodium urate (MSU) crystals, is associated with the increasing of cardiovascular disease (especially MI) morbidity and mortality[2]. Gout causes cardiovascular diseases (CVD) mainly due to hyperuricemia and serum uric acid induced inflammatory response[3]. Therefore, the main treatment of this disease is anti-inflammatory and uric acid lowering[4]. Recently, several studies and a meta-analysis have illustrated a protective effect of urate-lowering therapies (febuxostat and allopurinol) against MI [5–7]. However, early use of anti-inflammatory drugs (such as: colchicine) therapy for gout patients weather can also reduce cardiovascular events[8].

Colchicine is derived from the bulb-like corms of the *Colchicum autumnale* plant, also known as autumn crocus, and is widely used for treatment of acute gout flares, prophylaxis against gout flare [9, 10]. Several retrospective observed studies have assessed the efficacy of Colchicine in the reduction of the incidence rate for MI in patients with Gout [11–13]. Other trials contained non-controlled observational studies and demonstrated inconsistent results [8, 14]. Additionally, large sample clinical studies are emerging, and it is necessary to reevaluate the efficacy of Colchicine for reducing the incidence rate for MI in patients with Gout. The aim of this meta-analysis was to assess whether Colchicine can decrease the incidence rate for MI in patients with Gout.

## Methods

This systematic review and meta-analysis was reported according to the previous reporting items as follow PRISMA guidelines[15].

## Literature search and study selection

The following databases were searched in August 2018 without limitations on location, language or publication types: Web of science (1950–2018), EMBASE (1974–2018), the Cochrane Library (August 2018). The Mesh terms and their combinations used in the search were as follows: “myocardial infarction” OR “MI” OR “Cardiovascular disease” OR “CVD” AND “colchicine” AND “gout” [Mesh terms]. All related reviews, case series, case reports, original articles were searched for any correlated studies, including RCTs and ROS regarding gout patients. Those studies were selected on the basis of their titles and abstracts and then on their full text and duplicates were removed.

Studies were deemed eligible if they fulfilled the inclusion criteria: (a) diagnosis criteria fulfilled the American Rheumatology Association diagnostic for gout[16]; (b) studies that used colchicine to treat gout; (c) studies that assessed the relationship between colchicine using and MI; (d) studies that provided enough data for per patient with gout or other statistics to calculate RR; (e) studies that included 20 or more patients;(f) articles that were reported without language restrictions.

The following studies were excluded: (a) reviews, (b) case report, (c) no reports associated with gout and MI, (d) data cannot be extracted.

## Data extraction and quality assessment

Two searchers (ZX and LY), collected data on the study design, sample size, treatments, research group and control group according to the previous formulation. (age, sex, disease duration et al.), definition of the outcome measures: In the gout patients who used colchicine in total, the number of MI cases occurred. Differences were settled by consensus. The quality evaluation of the eventually included studies that meet the criteria was carried out.

The quality evaluation of all included trials suitable for meta-analysis was independently evaluated by 2 reviewers according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (<http://handbook.cochrane.org/>)[17]. Quality evaluation was carried out as followed 7 aspects: random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias, general characteristic balance, and intent to treat. Each domain was evaluated as follow: low bias, unclear bias, or high bias under the guidance of Cochrane Handbook for Systematic Reviews of Interventions[17].

## Statistical analysis

Bicategorized variables (In the gout patients who used colchicine in total, the number of MI cases occurred) were represented by a risk ratio (RR) with 95% confidence intervals (95% CI).  $p < 0.05$  was considered to have statistical significance. Variables of meta-analysis were calculated by RevMan V.5.3 (Cochrane Collaboration, London, UK). The  $\chi^2$  Cochran’s Q test, at  $p < 0.05$  and the  $I^2$  statistic were used to evaluate the statistical heterogeneity of the study. High values indicated that the study had high heterogeneity. Significant heterogeneity of meta-analyses used a random-effects model. Statistical

analysis was performed by RevMan V.5.3.  $p < 0.01$  was as statistically significant. Publication bias was performed by funnel plots and Egger's test.

## Results

### Eligible studies

In the preliminary search, finally, 64 studies were searched from the electronic databases (EMBASE = 4, Web of Science = 55, Cochrane Library = 5). In order to delete duplicate papers, all papers were imported into Endnote X9 (Thomson Reuters Corp., USA) software. A total of 63 papers were reviewed and 61 papers were removed according to the inclusion criteria at abstract and title levels. Finally, 3 papers (including an additional records identified through other sources) with 114371 patients (Colchicine group = 1063, control group = 113308) were included in the meta-analysis [11–13].

### Study characteristics

The flow diagram for the included studies can be seen in Fig 1. The general characteristics of the included studies can be seen in Table 1. Quality assessment was performed according to QUADAS–2. The results were conducted by RevMan5.3 as depicted in Fig 2.

### Outcomes of the meta-analysis

We included three studies comparing MI incidence between colchicine ever users and never users (see Table 1) [11–13]. In a nested case-control research, presented as an abstract from the 2014 ACR annual meeting, incidence of MI was not decreased among patients with RA with colchicine use (RR 0.28 (95% CI 0.24 to 0.32))[11]. In a retrospective, cross-sectional study, MI risk was reduced with colchicine treatment (RR 0.46 (95%CI 0.19 to 1.06))[12]. In a retrospective research of an incident Gout cohort, colchicine use relative to the decreased incidence of MI (RR 0.40 (95% CI 0.23 to 0.68))[13]. MI incidence was lower for colchicine ever users than never users (pooled RR 0.29 (95% CI 0.25 to 0.33,  $p = 0.00001$ )) (Fig 3).

## Discussion

By searching literature, this is the first systematic review with meta-analysis of the correlation between Colchicine using and a decreased incidence of MI in patients with Gout. According to our results, Colchicine has a positive impact on reducing incidence of MI in patients with Gout.

Our meta-analysis showed lower incidence of MI in patients with Gout for Colchicine users than Colchicine non-users. Our literature search highlighted two other studies consistent with this findings but data could not be extracted for meta-analysis[18]. This finding was confirmed in several publications [12, 13, 18], reporting reduced MI/CVE incidence with Colchicine use among patients with Gout. However, Dubreuil, M.[11]also reported that colchicine use was not associated with a reduced risk of MI among persons with gout, which could be related to not rule out some potential confounding factors.

So, according to our results, early using Colchicine could have significant benefit for reducing the MI incidence in patients with Gout. Yet, RCT studies are lacking, and Future studies should identify a larger sample of continuous colchicine users to clarify its potential cardio-protective role in Gout.

## Conclusion

In conclusion, gout patients who took colchicine may reduce incidence of MI versus those who did not take colchicine.

### Limitations

Several limitations as follow up: First, no specialized RCTs about this topic to date, Only part data from observational studies was extracted, which certainly was bound to produce some unavoidable bias, comprising: namely design bias, selection bias, treatment bias and publication bias. Moreover, patients with history of CVD were from these observational studies. Finally, By summarizing some published studies, we can find out the incidence of cardiac infarction in each study take the place of individual patient-level data, so producing confounding and selection bias could not be avoided in these studies.

## Abbreviations

MI = myocardial infarction, CVD = Cardiovascular disease, CVE = Cardiovascular events, CI = confidence interval, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, ROS = retrospective observed trials, RR = risk ratio.

## Declarations

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### Availability of data and materials

All data and materials are presented in this published article.

### Authors' contributions

ZX undertook the literature search, screening of titles and abstracts. LY performed the statistics. ZX and XD wrote the paper. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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## Tables

Table 1 Description of the studies included in the meta-analysis

First author, year	Study design	Underlying disease	Age(years) Mean±SD/Period	Female gender (%)	EVENT of MI/Total	follow- up
Crittenden, D. B. et al.,  2012	retrospective, cross- sectional study	GOUT	Group1: 71.3 ± 11.8  Group2: 71.3± 11.9	Group1: 0.4  Group2: 0.8	Group1: 7/576  Group2: 19/712	-
Dubreuil, M. et al.,  2014	nested case-control study	GOUT	18-89	-	Group1: 211/55509  Group2: 763/55509	-
Solomon, D. H. et al.,  2016	retrospective cohort study	GOUT	Group1: 72.2±10.6  Group2: 73.0±12.3	Group1: 36.3  Group2: 36.3	Group1: 18/501  Group2: 45/501	16.5 months

Group 1: Colchicine group, Group2: Control group, MI: myocardial infarction

## Figures

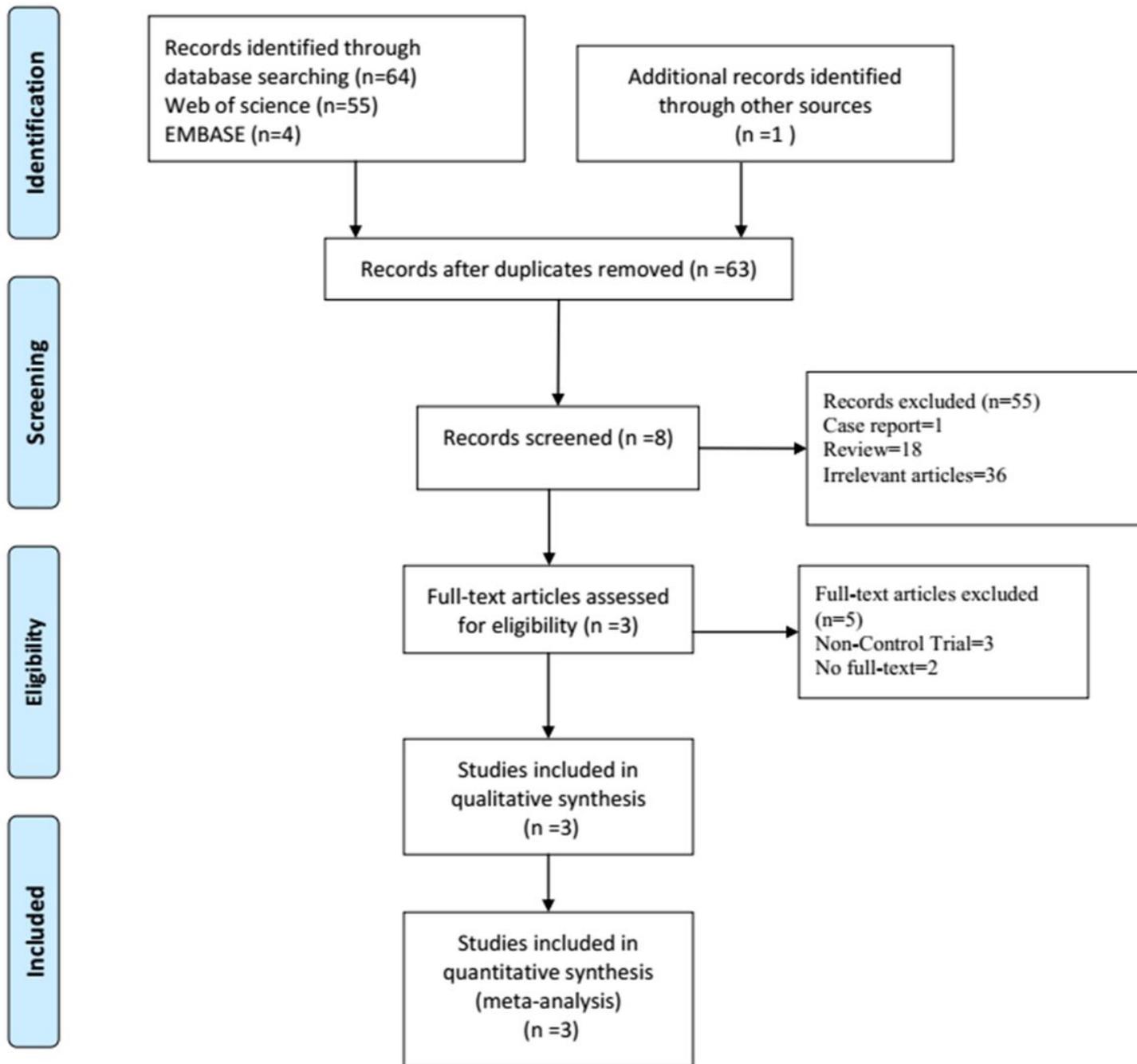


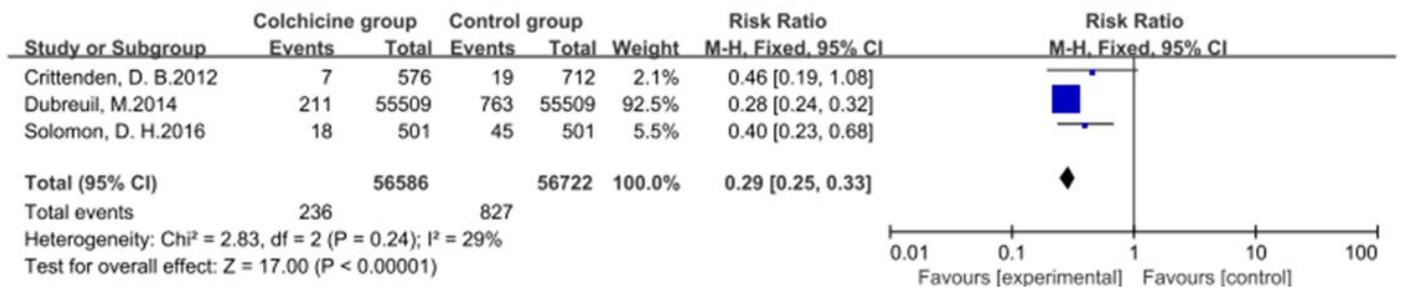
Figure 1

Elaborated searching strategies of the systematic literature review with meta-analysis.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Crittenden, D. B.2012	⊖	⊖	⊕	⊕	⊕	⊕	⊕
Dubreuil, M.2014	⊖	⊖	⊕	⊕	⊕	⊕	⊕
Solomon, D. H.2016	⊖	⊖	⊕	⊕	⊕	⊕	⊕

Figure 2

Risk of bias of all included trials.



**Figure 3**

Forest plots of RR for MI incidence among Colchicine ever users and never users.