SYSTEMATIC REVIEW

Association between gout and atrial fibrillation: A meta-analysis of observational studies [version 1; referees: awaiting peer review]

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Abstract

Background: Gout is a systemic inflammatory arthritis characterized by the deposition of monosodium urate crystals due to hyperuricemia. Previous studies have explored the link between gout and atrial fibrillation (AF). Given the increasing prevalence and incidence of gout, there is a need to quantify the relationship between gout and the risk of AF. Therefore, we conducted a systematic review and meta-analysis on this topic.
Methods: PubMed and Embase were searched for studies that reported the association between gout and AF using the following search term: ('Gout' and 'Arrhythmia'). The search period was from the start of the database to 3rd August 2018 with no language restrictions.
Results: A total of 75 and 22 articles were retrieved from PubMed and Embase, respectively. Of these, four observational studies (three cohort studies, one case-control study) including 659,094 patients were included. Our meta-analysis demonstrated that gout was significantly associated with increased risk of AF (adjusted hazard ratio: 1.31; 95% confidence interval: 1.00-1.70; P = 0.05; I^2 = 99%) after adjusting for significant comorbidities and confounders.
Conclusions: Our meta-analysis confirms the significant relationship between gout and AF. More data are needed to determine whether this risk can be adequately reduced by urate-lowering therapy.

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Introduction

Gout is a systemic inflammatory arthritis characterized by the deposition of monosodium urate (MSU) crystals due to hyperuricemia. This is defined as serum uric acid levels above 6.8mg/dL and is due to impaired excretion and/or overproduction of uric acid[1]. Atrial fibrillation (AF) is a multifactorial condition whose prevalence increases with age[2–4]. Previous studies have suggested a correlation between pro-inflammatory conditions such as gout and cardiovascular diseases[5–7], and have explored the link between gout and AF[8–13]. Given the increasing prevalence and incidence of gout[14], there is a need to quantify the relationship between gout and the risk of AF.

Methods

The meta-analysis was conducted in accordance with the MOOSE checklist. PubMed and Embase were searched for studies reporting the association between gout and AF using the search terms: ('Gout' and 'Arrhythmia'). The search period was from the start of the database to 3rd August 2018 with no language restrictions. Two researchers (KSKL and MG) independently conducted the search. Any disagreement was resolved by adjudication from a third reviewer (GT). Study selection was carried out by screening titles of full publications to determine compliance with the following inclusion criteria: (1) retrospective or prospective cohort studies in human subjects with gout and non-gout control group; (2) AF occurrence was reported; (3) adjusted hazard ratio (aHR) with 95% confidence intervals (95% CI) was reported or could be calculated. As all of the included studies reported sufficient information, contact with the original study authors was not required.

The quality assessment of these studies included in our meta-analysis was performed using the Newcastle-Ottawa Quality Assessment Scale (NOS). The point score system evaluated the categories of study participant selection, comparability of the results and quality of the outcomes. The following characteristics were assessed: (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study; (5) comparability of cohorts on the basis of the design or analysis; (6) assessment of outcomes; (7) follow-up period sufficiently long for outcomes to occur; and (8) adequacy of follow-up of cohorts.

Data were entered in prespecified spreadsheet in Microsoft Excel. The extracted data elements consisted of (1) surname of first author and publication year; (2) sample size of gout and non-gout cohorts; (3) follow-up duration; (4) population characteristics (age, gender, diabetes mellitus, hypertension, ischemic heart disease or coronary artery disease, chronic heart failure, hyperlipidemia, chronic obstructive pulmonary disease, liver disease).

Statistical analysis was performed using Review Manager (Version 5.3). Heterogeneity was assessed by the I^2 statistic. I^2>50% reflects significant statistical heterogeneity. Therefore, a random-effects model with the inverse variance heterogeneity method was used. Subgroup analyses were not performed due to the fact that not all studies consistently reported the outcomes for the same subgroups.

Results

A total of 97 entries were retrieved from 75 and 22 from PubMed and Embase, respectively. Of these, four observational studies (three cohort studies, one case-control study) including 659,094 patients were included (Figure 1)[4–7]. The main characteristics of the studies are summarised in Table 1. The four different cohorts were recruited from the United Kingdom, United States and Taiwan. All included studies had NOS scores >= 7, indicating that they were of high quality (Table 2 and Table 3). Our meta-analysis demonstrated that gout was significantly associated with increased risk of AF (adjusted HR = 1.31; 95%CI: 1.00- 1.70; P = 0.05; I^2 = 99%) (Figure 2). This was observed after adjusting for comorbidities and confounders of AF.

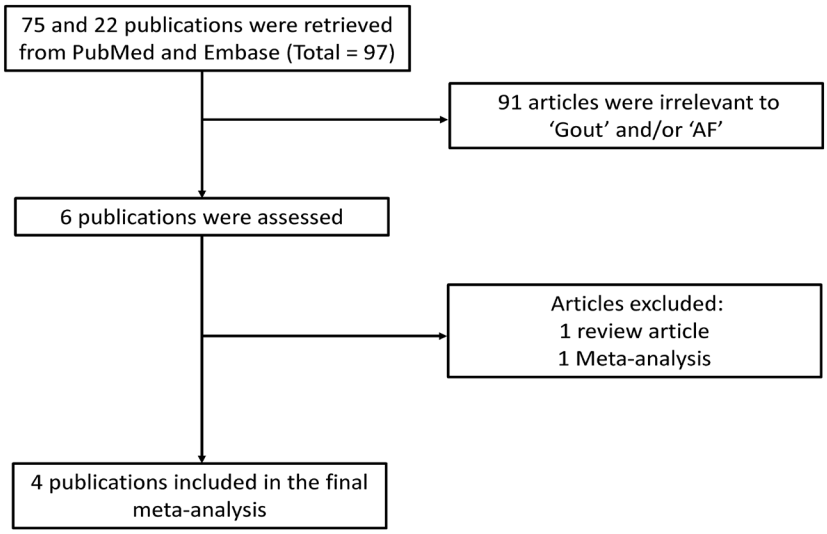

Figure 1. Flow chart for the study screening and selection process.

Table 1. Characteristics for the four studies included in the meta-analysis of gout and atrial fibrillation (AF).

Studies	Subjects	Age (y/o)	Males (n)	Follow-up (years)	DM (%)	HTN (%)	IHD/CAD (%)	CHF (%)	Hyperlipidaemia (%)	COPD (%)	Liver disease (%)
Chang-Fu Kuo 2015	Gout: 45348 Non-Gout: 45348	62.4±15.1 62.39±14.55	33012 33012	9	- (-)	15992 (35.2) 8578 (18.9)	6508 (14.3) 3525 (7.8)	3976 (8.8) 1141 (2.5)	- (-)	- (-)	- (-)
Seoyoung C Kim 2015	Gout: 70015 Osteoarthritis (Non-Gout): 210045	56.8±9.0 56.8±9.0	56992 190976	2	16874 (24.1) 37388 (17.8)	48660 (69.5) 106913 (50.9)	- (-)	- (-)	44740 (63.9) 113844 (54.2)	7422 (10.6) 26466 (12.6)	3011 (4.3) 6721 (3.2)
Singh JA 2018	Gout with incident AF: 10604 Non-Gout with incident AF: 150486	- -	-	-	-	-	-	-	-	-	-
Yu-Jui Kuo 2016	Gout: 63624 Non-Gout: 63624	51.29±16.25 51.29±16.25	47070 47070	6	8933 (14.1) 4867 (7.7)	23412 (37.0) 11153 (17.6)	8868 (14.0) 4779 (7.6)	2783 (4.4) 1265 (2.16)	17119 (27.1) 4719 (7.6)	2199 (3.48) 1583 (2.50)	- (-)

*Data for Singh JA 2018 could not be extracted as data of AF and non-AF group were not separately displayed in the original paper and calculations are not viable.

Table 2. NOS risk of bias scale for included case-control studies.

		Selection					Exposure		
Studies	**Adequate definition of cases**	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability**	**Ascertainment of exposure**	**Same method of ascertainment for subjects**	**Non-response rate**	**Total score (0–9)**
Chang-Fu Kuo 2016	1	1	1	1	1 (age)	1	1	1	8

Table 3. NOS risk of bias scale for included cohort studies.

		Selection					Outcome		
Studies	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest not present at start of study**	**Comparability**	**Assessment of outcome**	**Adequacy of duration of follow-up**	**Adequacy of completeness of follow-up**	**Total score (0–9)**
Chang-Fu Kuo 2016	1	1	1	0	1 (age)	1	1	1	7
Seoyoung C. Kim 2016	1	1	1	1	1 (age)	1	1	1	8
Jasvinder A Singh 2018	1	1	1	0	1 (age)	1	1	1	7

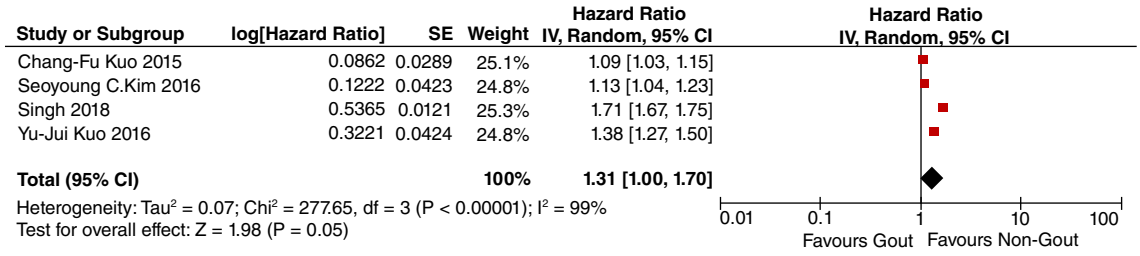

Figure 2. Hazard ratio for the risk of atrial fibrillation in the gout population relative to the non-gout population.

Discussion

Atrial cardiomyopathy, in particularly AF, is a significant clinical problem because it predisposes to stroke, which can be debilitating and increase mortality[15–17]. Numerous predictors of AF have been identified, including co-morbid conditions[18], blood biomarkers[19–26], and electrocardiographic predictors[27–29]. The main finding of this meta-analysis is that gout is associated with a 31% higher risk of AF after adjusting for significant comorbidities and confounders.

Several mechanisms have been proposed to explain this relationship with reactive oxygen species as a critical player in the pro-inflammatory process[13,30]. High serum uric acid levels in gout patients overwhelm the uric acid transporter (URAT1) and their influx causes intracellular accumulation of urate, which in turn stimulates NADPH oxidase and subsequent reactive oxygen species (ROS) production. ROS produced activates the downstream ERK1/2 pathway and upregulates Kv1.5 protein expression, resulting in the attenuation of atrial cellular action potential and electrical remodelling of the left atrium, as illustrated in mice models[31]. Furthermore, the renin-angiotensin-aldosterone system that becomes activated by high urate acid levels in gout patients. Subsequent studies into gout treatment can prevent AF and lower its recurrence rate after pulmonary vein isolation (PVI) ablation[32,33]. In preclinical studies, urate-lowering therapy can reduce oxidative stress and prevent adverse remod-

elling of the cardiac chambers[33,34]. The NLRP3-inflammasome also contributes to the pathogenesis underlying AF in gout and can be activated by MSU crystals in gout[35]. Its activation triggers the maturation and production of the pro-inflammatory cytokine interleukin-1β (IL-1β), which upregulates the expression of TGF-β1, a key mediator for atrial fibrosis[36], which can lead to atrial conduction abnormalities[37,38], promoting AF by re-entry[39,40].

The main strength is that it included the largest cohort of ~660000 patients. However, the following limitations remain. Firstly, as the included studies were retrospective, they are susceptible to bias as in all studies of this study design. Secondly, only four studies were included and future studies are needed to confirm the relationship between gout and AF. Thirdly, definitions of AF also differed between studies. It was based on physician diagnosis or ICD-9 criteria from data obtained using administrative databases. Finally, the type of AF, such as paroxysmal, sustained or permanent, was not reported. These limitations could explain the high heterogeneity observed in this meta-analysis.

In conclusion, our meta-analysis confirms the significant relationship between gout and AF. More data are needed to determine whether this risk can be adequately reduced by urate-lowering therapy.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

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