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Epidemiology

Correlation between Gout and Coronary Heart Disease in Taiwan: A Nationwide Population-Based Cohort Study

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Background: Gout is the most common inflammatory arthritis in adult males. Patients with gout are at a higher risk of coronary heart disease (CHD). This study aimed to investigate the correlation between gout and CHD.

Methods: This was a retrospective cohort study that used data from the Longitudinal Health Insurance Database of Taiwan. The study subjects were 46,140 patients with new-onset gout during 2003-2010. To avoid selection bias, we used propensity score matching. A Cox proportional hazard model was used to analyze differences in the risk of CHD between patients with and without gout after controlling for related variables.

Results: The patients with gout had a higher risk of CHD than the patients without gout [adjusted hazards ratio (HR) = 1.34, 95% confidence interval (CI): 1.23-1.45]. The risk of CHD increased with older age. Other related factors for CHD included gender (female vs. male, adjusted HR = 0.86, 95% CI: 0.79-0.93), hypertension (adjusted HR = 1.53, 95% CI: 1.42-1.65), hyperlipidemia (adjusted HR = 1.18, 95% CI: 1.07-1.29), and diabetes mellitus (adjusted HR = 1.24, 95% CI: 1.13-1.36).

Conclusions: We found correlations between gout and CHD and other influencing factors including hypertension, hyperlipidemia, and diabetes mellitus. We also found that gender and age were associated with CHD.

Key Words: Coronary heart disease • Gout • Hyperuricemia • Risk factor

INTRODUCTION

Gout is the most common inflammatory arthritis in adult males.[1] It is caused by the crystallization of uric acid within the joints and is often associated with hyperuricemia, with the overall disease burden being substantial and potentially continuing to increase.[2] Substantial evidence suggests that chronic hyperuricemia is an independent risk factor for hypertension (HTN), metabolic syndrome (MS), chronic kidney disease (CKD), and cardiovascular disease (CVD).[3] In addition, the effects of uric acid on the development of CVDs and renal diseases have been demonstrated in animal models.[4]

Studies in selected groups of patients with a high CVD risk [i.e., those with type 2 diabetes mellitus (DM), stroke, congestive heart failure, obstructive sleep apnea, or coronary heart disease (CHD)] have shown an independent association between serum urate and CVD and mortality.[1,3,5] Two large prospective studies reported an independent association between gout and CVD and mortality. The first study showed that gout was associated with a 26% increased risk of acute myocardial infarction [odds ratio (OR) = 1.26; 95% confidence interval (CI): 1.14-1.40].[6] The second study reported links between gout and all-cause mortality (OR = 1.28; 95% CI:

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1.15-1.41), CVD death (OR = 1.38; 95% CI: 1.15-1.66), and fatal CHD (OR = 1.55; 95% CI: 1.24-1.93).[7] Furthermore, a systematic review and meta-analysis study reported that gout increased the risk of mortality from CVD and CHD, but not myocardial infarction.[8]

Using healthcare big data for analysis has become the new trend of cardiology research.[9] Epidemiological data also support the strong association between CVD and gout, and indicate that the prevalence of gout in the general population of Taiwan is 1 in 16 people.[10] In particular, Taiwanese aborigines have a very high prevalence of gout.[11] As patients with gout and hyperuricemia are at a higher risk of CHD, understanding the relationships among these conditions is pertinent for clinicians. Therefore, this study investigated whether gout is associated with CHD by using data from the National Health Insurance Research Database (NHIRD) in Taiwan.

METHODS

This retrospective cohort study investigated the correlation between gout (ICD-9-CM codes 274 and 7906) and CHD (ICD-9-CM codes 410-414) by using data from the Longitudinal Health Insurance Database (LHID), in which 1,000,000 beneficiaries were randomly selected from the NHIRD provided by the National Health Insurance Administration, Ministry of Health and Welfare. The LHID contains all original claims data of outpatient departments (OPDs), emergency departments (EDs) and hospitalizations. In this study, patients with gout were defined as those with at least three diagnoses of gout within one year. Additionally, CHD was defined as at least three diagnoses of CHD within one year. The date of incident CHD was defined as the medical date of the first CHD diagnosis if the patient was found to have CHD.

This study was conducted using 2002-2011 claims data from the LHID. We enrolled patients with and without gout from 2003-2010 as the study subjects, with each patient having at least one year of follow-up. Each patient was followed up until the date of incident CHD, death, or the end of 2011, whichever occurred first. We excluded 3,219 patients with gout who had CHD before a diagnosis of gout. Furthermore, we used propensity score (PS) matching to obtain a 1:5 matched cohort of patients without gout for each patient with gout. PS matching is a statistical matching technique that can reduce potential confounding caused by unbalanced covariates in non-experimental settings. PS is the probability calculated via a logistic regression model. The score is a unit with certain characteristics that was assigned to the gout patients. The scores can be used to reduce or eliminate selection bias in observational studies, and the characteristics we selected for matching were gender, age, monthly insurance salary, and urbanization. After matching, 7,690 patients with gout and 38,450 patients without gout were included in the study. The study subject selection is shown in a flowchart in Figure 1.

The urbanization of study patients was categorized into seven levels on the basis of the urbanization of their residential locations. Level 1 denoted the highest degree of urbanization, and level 7 denoted the lowest degree of urbanization.

We used a Cox proportional hazard model to estimate the hazard ratios (HRs) with 95% CIs for the association between gout and CHD after controlling for related variables. Control variables were gender, age,

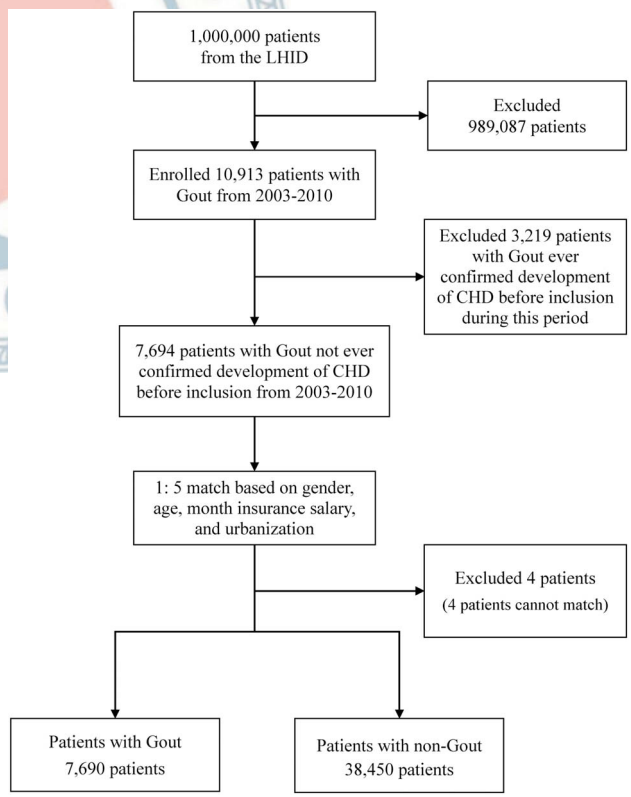

Figure 1. *Flowchart of selection patients for inclusion. CHD, coronary heart disease; LHID, Longitudinal Health Insurance Database.*

monthly insurance salary, urbanization, comorbidities, and the status of major illness. Comorbidities included HTN (ICD-9-CM codes 401-405), hyperlipidemia (HPL) (ICD-9-CM code 272), and DM (ICD-9-CM code 250). In addition, the status of major illness was defined as whether the study subjects had a catastrophic illness and had a certificate during the study period. All statistical analyses in the study were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance in this study was defined as $p < 0.05$.

RESULTS

Table 1 shows the basic characteristics of the patients with and without gout after matching. There were 38,239 (82.88%) males and only 7,901 (17.12%) females. Most of the patients were 45-54 years old (24.93%). The

Table 1. The characteristics of study subjects after propensity score matching

Variables	Non-gout patients		Gout patients		Total	p-value*
	N	%	N	%	N	
Total	38,450	100.00	7,690	100.00	46,140	
Gender#						0.996
Male	31,866	82.88	6,373	82.87	38,239	
Female	6,584	17.12	1,317	17.13	7,901	
Age (years)#	52.27 ± 16.30		53.02 ± 15.40		52.39 ± 16.16	1.000
≤ 34	4,865	12.65	973	12.65	5,838	
35~44	6,551	17.04	1,310	17.04	7,861	
45~54	9,585	24.93	1,917	24.93	11,502	
55~64	7,790	20.26	1,558	20.26	9,348	
65~74	6,150	15.99	1,230	15.99	7,380	
≥ 75	3,509	9.13	702	9.13	4,211	
Month insurance salary (NTD)#						1.000
≤ 17,280	6,465	16.81	1,293	16.81	7,758	
Dependent	7,865	20.46	1,573	20.46	9,438	
17,281~22,800	11,294	29.37	2,258	29.36	13,552	
≥ 22,801	12,826	33.36	2,566	33.37	15,392	
Urbanization#						1.000
Level 1	11,910	30.98	2,382	30.98	14,292	
Level 2	11,310	29.41	2,262	29.41	13,572	
Level 3	5,750	14.95	1,150	14.95	6,900	
Level 4	5,230	13.60	1,046	13.60	6,276	
Level 5	925	2.41	185	2.41	1,110	
Level 6	1,789	4.65	357	4.64	2,146	
Level 7	1,536	3.99	308	4.01	1,844	
HTN						< 0.001
No	32,577	84.73	4,186	54.43	36,763	
Yes	5,873	15.27	3,504	45.57	9,377	
HPL						< 0.001
No	35,339	91.91	4,596	59.77	39,935	
Yes	3,111	8.09	3,094	40.23	6,205	
DM						< 0.001
No	35,317	91.85	6,363	82.74	41,680	
Yes	3,133	8.15	1,327	17.26	4,460	
Major illness						0.001
No	37,396	97.26	7,427	96.58	44,823	
Yes	1,054	2.74	263	3.42	1,317	

* Used Chi-square test to exam the difference of characteristics distribution. # Variables for propensity score matching.
DM, diabetes mellitus; HPT, hyperlipidemia; HTN, hypertension.

average age of the gout patients was 53.02 years [standard deviation (SD) 15.40 years], compared to 52.27 ± 16.30 years in the non-gout patients. Of the gout patients, 3,504 (45.57%) had HTN, 3,094 (40.23%) had HPL, and 1,327 (17.26%) had DM. As expected, the characteristics of the matched variables were similar, including gender, age, monthly insurance salary, and degree of urbanization between the patients with and without gout (p = 1.000), after matching.

The cumulative risk of CHD was significantly higher in the gout patients than in the non-gout patients (Figure 2; log-rank test, p < 0.001). Table 2 shows the HRs for CHD in both groups. The average follow-up time was 4.41 years in the gout patients, and 5.08 years in the non-gout patients. After controlling for other relevant influencing factors, the gout patients had a higher adjusted HR of 1.34 (95% CI: 1.23-1.45) compared to the non-gout patients. Compared to the patients without HTN, the adjusted HR was 1.53 (95% CI: 1.42-1.65) in those with HTN. Compared to the patients without HPL, the adjusted HR was 1.18 (95% CI: 1.07-1.29) in those with HPL. Compared to the patients without DM, the adjusted HR was 1.24 (95% CI: 1.13-1.36) in those with DM. Furthermore, the risk of incident CHD increased with an older age.

DISCUSSION

This retrospective cohort study demonstrated that the patients with gout had a higher risk of CHD than the patients without gout. Moreover, HTN, HPL and DM were influencing factors for CHD. Gender and age were also both related to CHD.

Hyperuricemia is frequently observed in patients with CVDs. The question of whether hyperuricemia is an independent risk factor for CVD was first raised more than five decades ago. Recently, there has been renewed interest in hyperuricemia and its association with HTN and cardiovascular mortality, with studies suggesting that it may have a direct vascular effect.[12] In most patients, hyperuricemia is caused by multiple factors, including genetic and environmental factors, of which many environmental factors are modifiable, potentially correcting the contribution of these factors to hyperuricemia.[13] The relationship between uric acid and CVD has been observed in both patients with frank hyperuricemia and in those with uric acid levels considered to be in the normal to high range.[14] The generally mild serum urate elevation is often documented in patients with uncomplicated obesity, HTN, dyslipidemia, or insulin resistance, which may reflect abnormal renal handling of sodium and uric acid.[15,16] Gout and hyperuricemia have been associated with CHD.

Hyperuricemia is correlated with cardiovascular events in patients with HTN.[17] Uric acid was first found to be associated with primary HTN in 1874. More recent experimental and clinical studies have suggested that uric acid may play a contributory role in the pathogenesis of elevated blood pressure. Uric acid may also be a marker of xanthine oxidase-associated oxidants, and these oxidants may drive the hypertensive response.[18] Moreover, experimental data suggest that uric acid may induce endothelial damage, vascular inflammation, and renin-angiotensin system activation[19] Antihypertensive agents, which are used to treat HTN, may influence serum uric acid (SUA) levels.[20] Our study showed that HTN was associated with CHD in patients with gout and hyperuricemia. These results are similar to those of related studies.

HPL is common in patients with hyperuricemia and gout. A period study indicated that dyslipidemia contributes to coronary artery disease.[21] The most common ab-

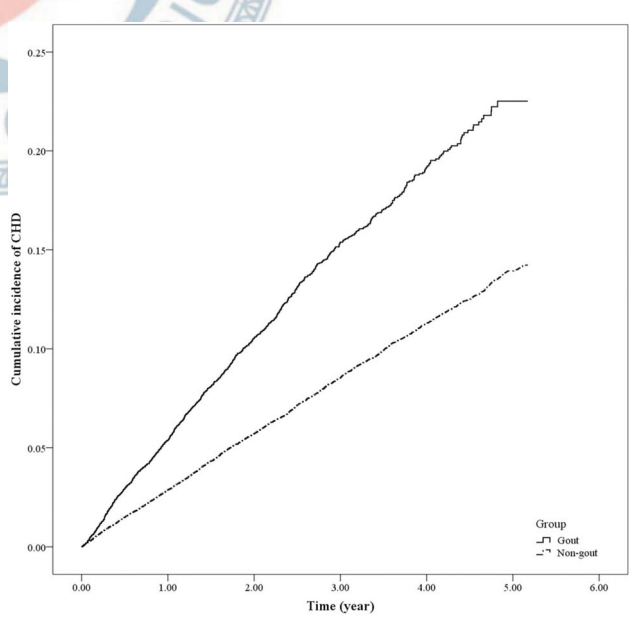

Figure 2. *The cumulative incidence of coronary heart disease between gout patients and non-gout patients (p-value < 0.001, Log-rank test).*

Table 2. Association of CHD in gout patients with multivariable analysis of Cox regression analysis

Variables	Incident CHD (N)	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Total	4,124						
Group							
Non-gout (ref.)	3,155	1			1		
Gout	969	1.75	1.63-1.88	< 0.001	1.34	1.23-1.45	< 0.001
Gender							
Male (ref.)	3,241	1			1		
Female	883	1.36	1.26-1.47	< 0.001	0.86	0.79-0.93	< 0.001
Age (years)							
≤ 34 (ref.)	62	1			1		
35~44	286	3.42	2.60-4.50	< 0.001	3.37	2.55-4.45	< 0.001
45~54	810	6.70	5.18-8.67	< 0.001	6.45	4.96-8.37	< 0.001
55~64	1,049	11.19	8.67-14.46	< 0.001	10.42	8.03-13.52	< 0.001
65~74	1,257	16.56	12.84-21.37	< 0.001	16.44	12.64-21.37	< 0.001
≥ 75	660	17.01	13.11-22.06	< 0.001	14.72	11.25-19.28	< 0.001
Month insurance salary (NTD)							
≤ 17,280 (ref.)	691	1			1		
Dependent	1,130	1.34	1.22-1.47	< 0.001	1.03	0.92-1.14	0.627
17,281~22,800	1,290	1.08	0.98-1.18	0.117	1.02	0.92-1.13	0.724
≥ 22,801	1,013	0.73	0.66-0.80	< 0.001	1.06	0.95-1.19	0.287
Urbanization							
Level 1 (ref.)	1,346	1			1		
Level 2	1,146	0.93	0.86-1.00	0.052	0.90	0.82-0.98	0.011
Level 3	518	0.84	0.76-0.93	0.001	0.81	0.73-0.91	< 0.001
Level 4	582	1.06	0.96-1.17	0.239	0.84	0.76-0.94	0.002
Level 5	118	1.17	0.97-1.42	0.096	0.91	0.74-1.12	0.377
Level 6	229	1.24	1.07-1.42	0.003	0.92	0.79-1.08	0.326
Level 7	185	1.16	0.99-1.35	0.060	0.92	0.77-1.09	0.332
HTN							
No (ref.)	2,566	1			1		
Yes	1,558	2.72	2.55-2.89	< 0.001	1.53	1.42-1.65	< 0.001
HPL							
No (ref.)	3,239	1			1		
Yes	885	2.01	1.87-2.17	< 0.001	1.18	1.07-1.29	< 0.001
DM							
No (ref.)	3,400	1			1		
Yes	724	2.23	2.06-2.41	< 0.001	1.24	1.13-1.36	< 0.001
Major illness							
No (ref.)	3,997	1			1		
Yes	127	1.38	1.16-1.65	< 0.001	0.78	0.65-0.95	0.012

CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HPT, hyperlipidemia; HR, hazards ratio; HTN, hypertension.

normality is hypertriglyceridemia, with a prevalence of 25%-60% in patients with gout,[22] and hyperuricemia has been reported in a considerable number of patients with hypertriglyceridemia.[23] A close correlation has also been reported between the degree of uric acid production and triglyceride metabolism when the influence of alcohol intake is excluded.[24] Our study found that HPL was associated with CHD in the patients with gout and hyperuricemia, which is consistent with previous findings.

Hyperuricemia has been linked to atherosclerosis and diabetes,[12] and several international studies have reported a positive association between SUA levels and DM.[25,26] However, not all studies have found a strong association between the two diseases. In a prospective co-

hort study in Japan, SUA was not associated with an increased risk of DM.[27] Our study showed that DM was associated with CHD in the patients with gout and hyperuricemia.

Men have a higher risk of gout than women due to higher baseline levels of blood uric acid.[1] CHD may affect individuals at any age, but becomes dramatically more common at a progressively older age. The prevalence increases in those aged > 65 years, and is twofold higher in men aged > 75 years. This increased prevalence in older men and women is largely attributed to primary but not secondary gout.[28] Our study indicated that gender and age were both associated with CHD, which is consistent with the findings of previous studies.

Hyperuricemia has long been associated with gout, and more recently, it has been associated with CHD, HTN, stroke, MS, and other disorders. Lowering SUA can improve cardiovascular and renal outcomes, and understanding the therapeutic mechanism of action may provide more clinical benefits to patients.[3]

The strengths of this study are that it was based on a large and representative population cohort, extracted from the NHI system which covers 99% of the population in Taiwan, avoiding bias from selection, non-response, or poor recall. The LHID has been shown to have good levels of accuracy and completeness in recording prescriptions and clinical diagnoses. In addition, we adjusted for many potentially confounding factors and also used PS matching to select non-gout patients as the control group. Therefore, this study showed that the gout patients had a higher risk of CHD with a narrower and statistically significant CI.

There are several limitations to this study. Many factors affecting CHD cannot be obtained from the NHIRD, such as life-related variables including BMI, alcohol consumption and tobacco consumption. Moreover, medications such as hypertensive medications would affect CHD. Medications are a confounding factor for which it is extremely difficult to control, especially in a retrospective cohort study. Each patient in the study period may have received inconsistent prescription patterns during the follow-up period, including drug type, drug dose, and medication duration. Therefore, our study reduced the confounding effect of medications by adjusting for comorbidities. In addition, the severity of gout and disease duration of gout may also affect CHD. This study was a nationwide population-based study. Thus, the study results are accurate and representative, even without the inclusion of medications.

In addition, there are other methods to reduce potential confounding in study subject selection, such as PS weighting, PS stratification, and PS adjustment.[29] This study is an epidemiologic study based on the LHID, and there were nearly 990,000 non-gout patients after enrolling gout patients (Figure 1). Thus, the study used PS matching to select the control group as in previous epidemiologic studies using the LHID.[30-33] Finally, the study may have bias because only ICD codes were used to define disease without any medical procedure codes. This may have led to overdiagnosis, although the study defined incident disease by at least three diagnoses within one year. However, this study is an epidemiologic study that can only provide evidence to show the association between gout and CHD, and cannot show a causal relationship. It is necessary to obtain more information from other databases or questionnaires to conduct a prospective study or randomized controlled trial to investigate such a relationship between gout and CHD in future research.

CONCLUSIONS

We found correlations between gout and CHD and other influencing factors including HTN, HPL, and DM. We also found that gender and age were both associated with CHD.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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