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An Independent Risk of Gout on the Development of Deep Vein Thrombosis and Pulmonary Embolism

A Nationwide, Population-Based Cohort Study

Chien-Chung Huang, MD, Po-Hao Huang, MD, Jiunn-Horng Chen, MD, PhD,
Joung-Liang Lan, MD, Gregory J. Tsay, MD, PhD, Hsiao-Yi Lin, MD, Chun-Hung Tseng, MD,
Cheng-Li Lin, MSc, and Chung-Yi Hsu, MD, PhD

Abstract: Previous studies indicated that gout is a risk factor of cardiovascular diseases. This study aimed to determine if patients with gout have an increased risk of deep vein thrombosis (DVT) or pulmonary embolism (PE).

We used the Longitudinal Health Insurance Database, a subset of the national insurance claim dataset, which enrolled 1 million Taiwanese to identify 57,981 patients with gout and 115,961 reference subjects matched by sex, age, and entry date of diagnosis. The risk of DVT and PE was analyzed using the Cox proportional hazards model.

In this Taiwanese dataset observed from 2000 to 2010, we found the incidence of DVT was 5.26 per 10^4 person-years in the gout cohort, which was twofold higher than the incidence of 2.63 per 10^4 person-years in the reference cohort. After adjusting for age, sex, and 9 comorbidities, the hazard ratio (HR) of developing DVT was 1.66 (95% confidence interval [CI] = 1.37–2.01). Among patients with gout, the youngest age group had the highest increase in the risk of developing DVT (HR [95% CI] = 2.04 [1.24–3.37] for ages 20 to 49 years, 1.80 [1.28–2.51] for ages 50 to 64 years, and 1.45 [1.11–1.91] for ages ≥65 years). The incidence of PE was about one-fifth that of DVT in gout patients, but the effect of gout on the risk was similar (HR [95% CI] = 1.53 [1.01–2.29]).

Our analysis confirmed that gout increased the risk of DVT and PE. Further exploration is needed in the future.

(*Medicine* 94(51):e2140)

Abbreviations: CI = confidence interval, CVD = cardiovascular disease, DAMPs = damage-associated molecular patterns, DVT = deep vein thrombosis, HR = hazard ratio, ICD-9-CM = International Classification of Diseases 9th Revision Clinical Modification, IRR = incidence rate ratio, LHID2000 = Longitudinal Health Insurance Database 2000, MSU = monosodium urate, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PE = pulmonary embolism, ROS = reactive oxygen species, VTE = venous thromboembolism.

INTRODUCTION

Gout is the most common form of inflammatory arthritis and presents with intermittent acute arthritis and chronic deformed joints with tophus formation. The prevalence of gout in the adult population was estimated at 3.23% (5.17% in men and 1.34% in women) in the United Kingdom,[1] 3.9% in the United States,[2] and 3.8% in Taiwan.[3] The incidence and prevalence of gout has been increasing since the 1980s,[4,5] and this may be related to the growing prevalence of obesity[6,7] and metabolic syndrome,[8] both of which are risk factors for venous thromboembolism (VTE).[9,10]

VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE), both of which are common acute diseases that are potentially lethal.[11] PE is 1 of the most common causes of cardiovascular disease (CVD) mortality after myocardial infarction and cerebral stroke.[11,12] The world reported incidence of VTE was 1.43 per 10^3 person-years in Norway[13] and 1.22 per 10^3 person-years in Quebec, Canada.[12] A slightly higher incidence has been reported for men than for women. In addition to obesity and metabolic syndrome, as noted above, cigarette smoking, hypertension, and diabetes are other known risk factors for VTE.[11] On the other hand, although the reported incidence of VTE in Taiwan was much smaller, the annual incidence has increased gradually from 0.12 per 10^3 persons in 1998 to 0.23 per 10^3 persons in 2008.[14]

Recent studies have reported a significant risk association between gout and CVD.[3,15,16] Both the Framingham study and the National Health Professional Follow-up Study reported a greater risk of coronary heart disease in men with gout than in

men without gout (hazard ratio [HR] 1.60 and 1.55, respectively).[17,18] The Multiple Risk Factor Intervention Trial[19] and a recent report in Taiwan reported similar results.[20] However, whether gout is an independent risk factor for VTE is still unconfirmed.

DVT and PE have a common pathophysiology, namely inflammation, hyper-coagulation, endothelial injury, and hemostasis with thromboembolism,[21] with other forms of CVD.[22] We hypothesized that the modest but persistent inflammation in gout may promote atherosclerosis and thrombogenesis and thus the development of CVD[23] and VTE.[24] This study aimed to examine the risk of VTE, including both DVT and PE, in patients with gout.

METHODS

Data Source

The National Health Insurance Research Database (NHIRD) was used for this population-based cohort study. Studies using this dataset have been published elsewhere.[25,26] The accuracy and validity of diagnoses in the NHIRD have been reported.[27,28] The subjects of interest were extracted from 1 million participants from all insured beneficiaries by a systemic sampling of the patient dataset (the Longitudinal Health Insurance Database 2000; LHID2000) in the NHIRD for the period of January 1, 1996 to December 31, 2000 in Taiwan and were followed up until the year 2010. This study was approved by the ethical review board of the China Medical University in Taiwan (DMR96-IRB-241, DMR99-IRB-074, and CMUH103-REC1-020).

Criteria for Selecting Study Subjects

The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code was used for coding

the diseases of interest in the present study.[29,30] To prevent medical fraud with overbilling for healthcare or inappropriate charges based on unconfirmed diagnoses, NHI sets strict rules on disease coding and regularly monitors coding and claims submitted for reimbursement by all participants of NHI beneficiaries. NHIRD provides reliable information for the proposed studies to explore the risk of VTE development in patients with gout.

In the LHID2000, there were 58,614 enrollers with the new diagnosis of gout (ICD-9-CM 274) identified during the study period (1998–2008), excluding the possible prevalent gout during 1996 to 1998. The date of gout diagnosis for each patient was defined as the entry date. Patients were excluded from the study if they were diagnosed with VTE before they were diagnosed with gout (n = 633). The remaining 57,981 patients with incident gout were identified as the gout cohort. The reference subjects were selected from people without gout and without VTE history in the LHID2000. The entry date of reference subjects was randomly assigned to match the entry date of a gout patient. For each identified gout patient, there were 2 reference subjects matched for age (within a 5-year age span), gender, and year of entry date (n = 115,961, only 1 reference subject was not satisfied for the matching criteria).

Outcome and Relevant Variables

The primary end point was the occurrence of VTE during the study period (1998–2010) including occurrence of DVT (ICD-9-CM 453.8) or PE (ICD-9-CM 415.1) after excluding iatrogenic PE (ICD-9-CM 415.11). All subjects were followed from the entry date until the date of VTE diagnosis, withdrawal from the NHI program or the end of 2010. The variables of relevance were age, gender, and the following comorbidities: hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250), atrial fibrillation (ICD-9-CM

TABLE 1. Demographic Characteristics and Comorbidities in Patients With Gout and in Reference Subjects Without Gout

Variable	Gout		P Value
	Yes, N = 57,981	No, N = 115,961	
Sex			0.99
Female, n (%)	15,163 (26.2)	30,326 (26.2)	
Male, n (%)	42,818 (73.9)	85,635 (73.9)	
Age, mean (SD)	52.5 (16.0)	51.9 (16.2)	
Stratified age groups			0.99
20–34 y, n (%)	9126 (15.7)	18,252 (15.7)	
35–49 y, n (%)	17,530 (30.2)	35,060 (30.2)	
50–64 y, n (%)	16,569 (28.6)	33,138 (28.6)	
≥65 y, n (%)	14,756 (25.5)	29,511 (25.5)	
Comorbidity			
Atrial fibrillation, n (%)	523 (0.90)	621 (0.54)	<0.001
Diabetes, n (%)	10,567 (18.2)	11,104 (9.58)	<0.001
Hyperlipidemia, n (%)	20,188 (34.8)	11,624 (10.0)	<0.001
Hypertension, n (%)	26,417 (45.6)	26,697 (23.0)	<0.001
Stroke, n (%)	6689 (11.5)	9062 (7.81)	<0.001
Heart failure, n (%)	1923 (3.32)	1745 (1.50)	<0.001
Lower leg fracture or surgery, n (%)	743 (1.28)	1245 (1.07)	<0.001
Cancer, n (%)	2162 (3.73)	4135 (3.57)	0.09
Pregnancy, n (%)	551 (0.95)	1307 (1.13)	<0.001

Data are n (%) unless otherwise stated. *P* values are from chi-squared tests for all variables except for age (2-sample *t* test).
SD = standard deviation.

427.31), stroke (ICD-9-CM 430–438), heart failure (ICD-9-CM 428), fracture of lower limbs with/without operation (ICD-9-CM 820, 821, 823, 81.51, 81.52, 81.53, and 81.54), all cancer (ICD-9-CM 140–208), and pregnancy (ICD-9-CM procedure 72–74 or ICD-9-CM 640.x1–676.x1, 640.x2–676.x2, and 650–659). All comorbidities were defined before the entry date.

Statistical Analysis

The demographic factors and comorbidities were compared between the gout cohort and the reference cohort using a chi-squared test for categorical variables and a Student *t* test for continuous variables. Person-years were calculated from the entry date to the date censored. A Kaplan–Meier survival curve was used to compare the incidence of DVT or PE between cohorts and was tested using a log-rank test. The gender-, age-, and comorbidity-specific incidence rates (per 10^4 person-years) of VTE were compared between the case and reference cohorts. We used a Poisson regression model to estimate the incidence rate ratio (IRR) and corresponding 95% confidence interval (CI) of DVT and PE in gout patients relative to the reference subjects. The multivariate-adjusted HR and the corresponding 95% CI of DVT and PE in gout patients relative to the reference subjects were derived by the Cox proportional hazard regression model with adjustment for age, gender, and comorbidities of atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, fracture of lower limbs with/without operation, cancer, and pregnancy. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. Results showed that there was no significant relation between Schoenfeld residuals for gout and follow-up time in either the model evaluating DVT risk ($P = 0.97$) or the model evaluating PE risk ($P = 0.53$). We further compared the risk of VTE development in patients with gout after stratification with respect to gender, age, and comorbidity. The age subgroups were 20 to 49, 50 to 64, and ≥ 65 years. Medication to treat gout, especially urate lowering agents, was considered to modify the risk of CVD in gout patients.[31] The risk of VTE in gout patients who did not use urate lowering agents was compared with the 1-to-2 matched reference subjects of nonusers (no gout, no urate lowering agent use). A 2-tailed *P* value of <0.05 was considered significant. SAS version 9.1 (SAS Institute Inc., Carey, NC) was used for all analyses.

RESULTS

In the LHID2000, we identified 57,981 gout patients as the gout cohort and 115,961 matched subjects without gout as the reference cohort (ratio of 1:2), for a total of 1,358,378 person-years of follow-up. The mean age of the gout cohort was 52.5 ± 16.0 years. Among the 173,942 investigated subjects, the proportion of men was 2.8 times higher than that of women (73.9% vs 26.2%). The age of gout patients was split into subgroups: 15.7% of patients were ages 20 to 34 years, 30.2% were ages 35 to 49 years, 28.6% were ages 50 to 64 years, and 25.5% were ages ≥ 65 years. The prevalence of co-morbidities including hypertension, diabetes, hyperlipidemia, atrial fibrillation, stroke, heart failure, and fracture of lower limbs with/ without operation was significantly higher in the gout cohort than in the reference cohort (Table 1).

Although the reported incidence of VTE in Taiwan was small,[14] we used the LHID2000 to estimate the standardized prevalence and incidence of VTE with respect to the Taiwanese population in 2010 as 6.39 (4.79 for DVT and 1.87 for PE) per 10^4 person-years and 1.69 (1.41 for DVT and 0.32 for PE) per
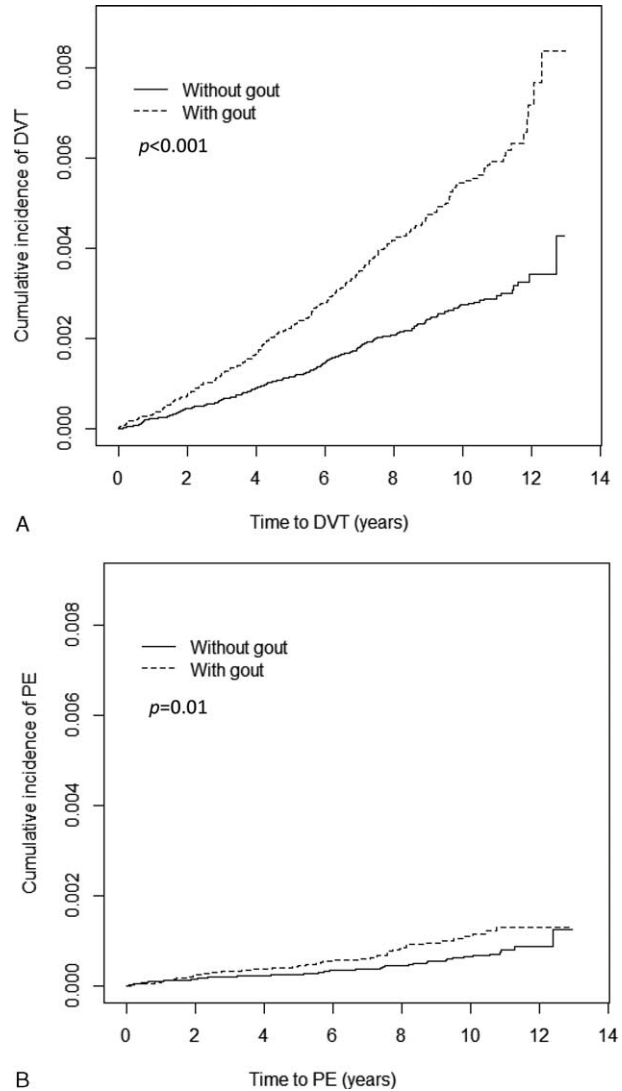
FIGURE 1. Cumulative incidence of DVT (A) and PE (B) in patients with gout and reference subjects without gout. Data were analyzed with the log-rank test. DVT = deep vein thrombosis, PE = pulmonary embolism.

10^4 person-years, respectively. Figure 1 shows the cumulative incidences of the gout and reference cohorts for DVT and PE during 11 years of follow-up (all $P \leq 0.01$, log-rank test). During the study period, 243 patients with gout (5.26 per 10^4 person-years) and 236 reference subjects (2.63 per 10^4 person-years) developed DVT, with a significant IRR of 2.00 (95% CI = 1.93–2.07) and an adjusted HR of 1.66 (95% CI = 1.37–2.01; Table 2). The effect of gout on the risk of DVT was similar for men and women. It is noteworthy that the greatest effect of gout on the risk of DVT was in the youngest subgroup and the risk steadily declined with increasing age (Table 2). We further investigated if gout patients had a higher risk of PE. During the study period, 49 patients with gout (1.06 per 10^4 person-years) and 59 reference subjects (0.66 per 10^4 person-years) developed PE (adjusted HR = 1.53; 95% CI = 1.01–2.29; Table 2). However, the event number was too small to have a reliable estimate.

TABLE 2. IRR and HR of DVT and PE Stratified by Sex and Age

| | Gout | | | | | | Compared to Reference Group | |
| | Yes | | | No | | | | |
Variable	Event	PY	Rate[†]	Event	PY	Rate[†]	IRR (95% CI)	Adjusted HR (95% CI)
DVT								
All[‡]	243	461,760	5.26	236	896,618	2.63	2.00 (1.93–2.07)[***]	1.66 (1.37–2.01)[***]
Sex[§]								
Female	95	117,509	8.08	90	231,379	3.89	2.08 (1.95–2.22)[***]	1.68 (1.23–2.30)[***]
Male	148	344,251	4.30	146	665,239	2.19	1.96 (1.88–2.04)[***]	1.66 (1.30–2.13)[***]
Stratified age[‖]								
20–49 y	45	221,775	2.03	32	432,416	0.74	2.74 (2.60–2.90)[***]	2.04 (1.24–3.37)[**]
50–64 y	86	133,976	6.42	79	265,034	2.98	2.15 (2.02–2.29)[***]	1.80 (1.28–2.51)[***]
≥65 y	112	106,008	10.6	125	199,167	6.28	1.68 (1.58–1.79)[***]	1.45 (1.11–1.91)[**]
Comorbidity[¶,#]								
No	41	174,836	2.35	84	622,932	1.35	1.74 (1.65–1.83)[***]	2.27 (1.56–3.31)[***]
Yes	202	286,924	7.04	152	273,686	5.55	1.27 (1.21–1.33)[***]	1.45 (1.17–1.79)[***]
PE								
All[‡]	49	462,465	1.06	59	897,236	0.66	1.61 (1.55–1.67)[***]	1.53 (1.01–2.29)[*]
Sex[§]								
Female	20	117,791	1.70	26	231,658	1.12	1.51 (1.41–1.63)[***]	1.29 (0.69–2.42)
Male	29	344,675	0.84	33	665,578	0.50	1.70 (1.62–1.78)[***]	1.71 (1.00–2.91)[*]
Stratified age[‖]								
20–49 y	11	221,923	0.50	7	432,495	0.16	3.06 (2.88–3.26)[***]	2.84 (1.03–7.82)[*]
50–64 y	16	134,223	1.19	20	265,273	0.75	1.58 (1.47–1.70)[***]	1.56 (0.76–3.21)
≥65 y	22	106,319	2.07	32	199,467	1.60	1.29 (1.20–1.39)[***]	1.22 (0.68–2.18)
Comorbidity[¶,#]								
No	7	174,984	0.40	29	623,138	0.47	0.86 (0.80–0.92)[***]	1.02 (0.44–2.34)
Yes	42	287,480	1.46	30	274,098	1.09	1.33 (1.26–1.41)[***]	1.58 (0.99–2.54)

CI = confidence interval, DVT = deep vein thrombosis, HR = hazard ratio, IRR = incidence rate ratio, PE = pulmonary embolism, PY = person-years.

[†] Incidence rate per 10^4 person-years.

[‡] Adjusted HR was calculated with the Cox proportional hazard regression and adjusted for age, sex, and the following comorbidities: atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy.

[§] Adjusted HR was calculated with the Cox proportional hazard regression and adjusted for age and the following comorbidities: atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy.

[‖] Adjusted HR was calculated with the Cox proportional hazard regression and adjusted for sex and the following comorbidities: atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy.

[¶] Adjusted HR was calculated with the Cox proportional hazard regression and adjusted for age and sex.

[#] The comorbidity group was comprised of patients with any 1 of the following comorbidities: atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy.

[*] $P < 0.05$.

[**] $P < 0.01$.

[***] $P < 0.001$.

TABLE 3. Cox Proportional Hazards Regression Analysis for the Combined Effect of Gout and Comorbidity on the Risk of DVT and PE

Group	Gout	Comorbidity[†]	N	Number of Events	Adjusted HR[‡] (95% CI)
DVT	No	No	76,992	84	1 (Reference)
	No	Yes	21,377	41	2.11 (1.45–3.07)[***]
	Yes	No	38,969	152	1.92 (1.34–2.77)[***]
	Yes	Yes	36,604	202	2.83 (1.95–4.12)[***]
PE	No	No	76,992	29	1 (Reference)
	No	Yes	21,377	7	1.06 (0.46–2.42)
	Yes	No	38,969	30	1.33 (0.63–2.83)
	Yes	Yes	36,604	42	2.27 (1.04–4.91)[*]

CI = confidence interval, DVT = deep vein thrombosis, HR = hazard ratio, PE = pulmonary embolism.

[†] The comorbidity group was comprised of patients with any 1 of the following comorbidities: atrial fibrillation, diabetes, hyperlipidemia, hypertension, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy.

[‡] Adjusted HR was calculated with the Cox proportional hazard regression and adjusted for age and sex.

[*] $P < 0.05$.

[***] $P < 0.001$.

The impact of comorbidities on outcomes was examined by stratifying the gout and reference cohorts with respect to the status of comorbidities. The risk of DVT was significantly increased in gout patients with comorbidity (HR = 1.45, 95% CI = 1.17–1.79) and in gout patients without comorbidity (HR = 2.27, 95% CI = 1.56–3.31) relative to their respective reference subjects (Table 2). However, the event number of PE was also too small to make significant estimates after stratification.

To explore the joined effect of gout and comorbidity on DVT or PE (as both individual *P* values for interaction were >0.05), we stratified the gout patients and reference subjects using a 2 × 2 stratification with respect to the status of comorbidity (Table 3). Relative to the reference subjects without comorbidity, gout patients with and without comorbidity had significantly higher risk of DVT, and gout patients with comorbidity had a significantly higher risk of PE (Table 3). Figure 2 demonstrates the joined effect of gout and each comorbidity on DVT (Figure 2A) and PE (Figure 2B). Relative to the reference subjects without comorbidity, the gout patients without comorbidity had a significantly higher risk of DVT, with HRs ranging from 1.87 to 2.32 across comorbidities (Figure 2A, red lines). The HR of gout for DVT was significant for each comorbidity and was higher than the HR of the reference subjects with comorbidities for each comorbidity except cancer, because cancer is a major risk factor for DVT.[26] Relative to the reference subjects without comorbidity, the gout patients with comorbidity had a significantly higher risk of DVT, with HRs ranging from 2.21 to 3.33. Figure 2B shows the joined effects of gout and each comorbidity on PE. Relative to the reference subjects without comorbidity, the gout patients without comorbidity had a significantly higher risk of PE, with HRs ranging from 1.58 to 1.75 across comorbidities except hypertension[11] (Figure 2B, red lines).

Figure 3 demonstrates the risk of DVT and PE in the gout patients and reference subjects with respect to the number of comorbidities. The effect of gout on the risk of DVT and PE was comparable to that of any single comorbidity. However, the effect of gout combined with any other comorbidity on the risk of DVT and PE was higher than the effect of any 2 comorbidities combined.

During the follow-up, there were 35,795 gout patients prescribed with urate lowering agents. These constituted 61.7% of total gout patients and can possibly modify the risk estimates of VTE in gout patients. We compared the risk of VTE between those 22,186 gout patients who did not use urate lowering agents and the matched reference subjects. The risks were markedly enhanced in the untreated gout patients with HRs of 2.16 (95% CI = 1.59–2.92) for DVT and 2.28 (95% CI = 1.17–4.46) for PE relative to the matched reference subjects.

DISCUSSION

The present study of a large Taiwanese database confirmed that gout increased the risk of VTE by 50% to 60% after adjusting for age, sex, and comorbidities (metabolic syndrome of diabetes, hyperlipidemia, hypertension, and atrial fibrillation, stroke, heart failure, lower leg fracture with/without operation, cancer, and pregnancy). These estimates are comparable to those of the effect of gout on CVD,[17–19] which emphasizes the importance of gout as a risk factor for DVT and PE. Besides, the risk of DVT was higher in gout patients without comorbidity than in gout patients with comorbidity, and the risk of VTE in gout patients with any single comorbidity was markedly higher than that in reference subjects without gout but with any combination of 2 comorbidities. These findings support for an independent effect of gout on VTE.

Urate lowering therapy in the United Kingdom was only received in 37.63% of gout patients and 39.66% of whom were adherent to treatment.[1] Obviously, the current management of gout is suboptimal,[32] even though the risk factors and treatment of gout are best understood. In this study, more than 2 times increased risk of VTE in gout patients who did not receive urate lowering agents relative to the reference subjects were demonstrated. This finding can imply that under-treatment of gout may have serious negative consequences for VTE.

Although prolonged immobilization or elevated body mass index is associated with the risk of VTE,[21] the relationship between gout and VTE is less well evidenced. However, several lines of evidence can provide a possible biological explanation to support the increased VTE risk in gout patients. The monosodium urate (MSU) crystals that form during gout[33] represent 1 of the damage-associated molecular patterns (DAMPs) that trigger toll-like receptors, and contribute to the cyclic activation and resolution of chronic gouty inflammation.[34] The persistent deposition of MSU crystals with tophi formation in the intercritical phase of gout may sequentially induce inflammatory mediators.[33] Low-grade inflammation around asymptomatic tophus can be demonstrated by imaging studies including Doppler ultrasonography,[35] and the immune-histological method can also reveal proinflammatory cytokines around coronal zone of tophus.[36] Oxidative stress induced by intracellular uric acid activates nicotinamide adenine dinucleotide phosphate oxidase.[37] Nitric oxide production is thus reduced while reactive oxygen species is increased in blood vessels. Both aggravate vascular inflammation inhibit endothelial-cell growth and result in proliferation of vascular smooth muscle cells.[38] Uric acid in the kidney damage can be similarly through activation of renin-angiotensin system, decreased nitric oxide production with microvascular rarefaction, afferent arteriolopathy, interstitial inflammation, and tubulointerstitial fibrosis.[15,39] Multiple organs and systems may thus be systemically involved.[40] Taken together, these results indicate that the inflammation in gout may have potentiated arthrosclerosis and thrombogenesis to increase the likelihood of endothelial dysfunction and VTE development.[41]

Several limitations were noted in this study. First, gout patients may have been misclassified in the population of LHID2000, because patients in the case cohort with a clinical diagnosis of gout defined by the physicians did not necessarily meet the classification criteria of American College of Rheumatology.[42,43] However, the utility and validity of using claims dataset of LHID2000 to identify gout has been assessed.[3] In agreement with published reports,[1,2] the gout patients in the present study were predominately male and were most often in the middle-age subgroups (age 35–64 years). These characteristics support the validity of the current approach of identifying gout patients from the LHID2000.[3] Second, the LHID2000 does not include variables such as body mass index; inflammatory index; uric acid level; and synovial fluid analysis; the results of imaging studies and personal habits such as diet, cigarette smoking, and alcohol drinking; therefore, we were unable to include these variables as covariates in the current analysis. Although smoking and metabolic syndrome are reported as risk factors of VTE,[44–46] we were unable to assess the impact of smoking on the risk of VTE in gout patients, and we can only assess the effect of respective component of metabolic
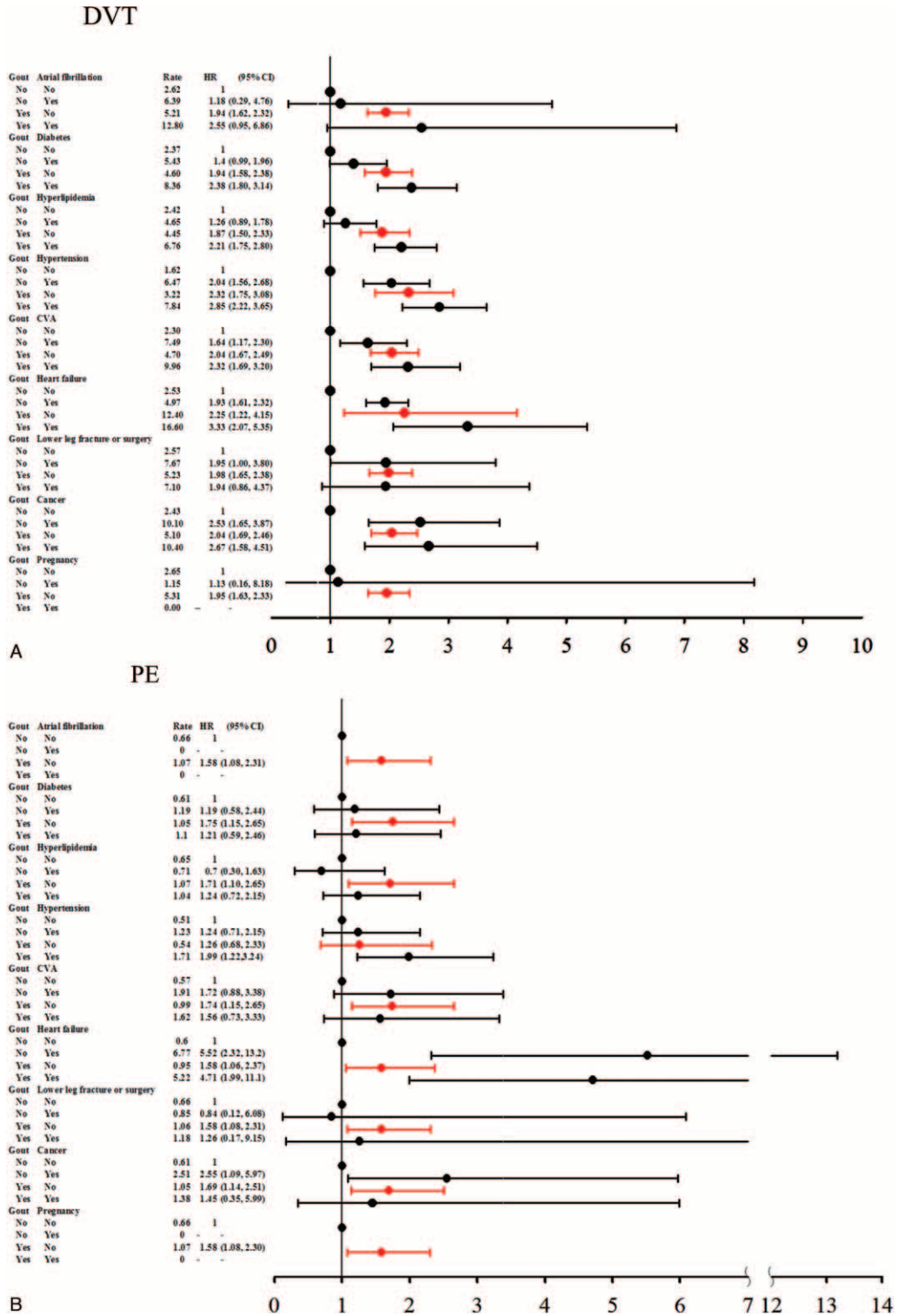
FIGURE 2. The combined effect of gout and each comorbidity (atrial fibrillation, hypertension, diabetes mellitus, stroke, heart failure, fracture of lower limbs with/without operation, all cancer, and pregnancy) on the occurrence of DVT (A) and PE (B). The hazard ratio of VTE in gout patients without comorbidity relative to the reference subjects without comorbidity is marked in red. DVT = deep vein thrombosis, CVA = cerebral stroke, PE = pulmonary embolism, VTE = venous thromboembolism.
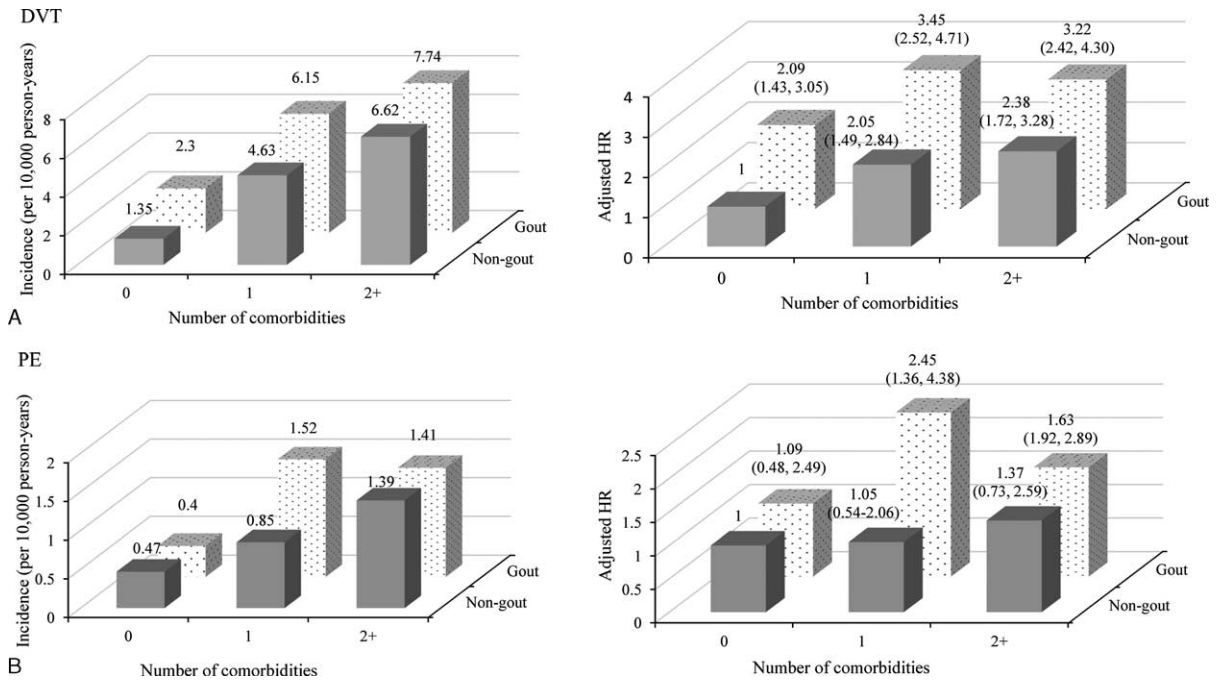
FIGURE 3. The relation between the number of comorbidities in patients with gout and reference subjects without gout and the risk of DVT (A) and PE (B) expressed as the incidence rate (per 10^4 person-years) (left) and adjusted HR (95% CI) (right). CI = confidence interval, DVT = deep vein thrombosis, HR = hazard ratio, PE = pulmonary embolism.

syndrome except obesity on VTE. However, patients with gout had a significantly higher prevalence of comorbidities than the reference cohort, and may have impacted the VTE risk. Nevertheless, the independent risk of gout for VTE was confirmed by adjusting for comorbidities and by sequential stratifications by comorbidity in both patients and reference subjects. The VTE risk persisted in gout patients without comorbidities and was higher in younger patients, which strengthens our conclusion that gout is an independent risk factor for VTE. Third, due to a difficulty in resolving the potential bias from indication of urate lowering agents, whether intervention in gout patients can reduce risk for DVT and/or PE[31] were not demonstrated. However, a marked enhanced risk of VTE in the untreated gout patients was shown relative to the matched reference subjects. Fourth, people can still argue that other residual confounding factors can exist; however, with the huge national insurance data and large sample size, these confounders may become nondifferential bias and all these evidences may strengthen the contention that gout can be an independent risk factor for VTE.

This population-based cohort study has several strengths. First, the NHIRD encompasses >22 million individuals in Taiwan who are enrolled in a national insurance program and therefore includes >98% of the population. The Bureau of NHI monitors and audits the insurance claims for reimbursement rigorously to prevent healthcare fraud, and thus the reliability of the diagnosis recorded for insurance claims is strengthened by this stringent NHI surveillance program. Second, the statistical power gained from the large sample size made subgroup analyses possible and allowed us to ascertain the impact of gout on VTE risk. Although the increased risk of DVT in gout patients was significant across all age subgroups, the risk of VTE in gout patients was highest in the youngest subgroup and declined with increasing age. The findings of increased risk in young people who often have a low prevalence of traditional

risk factors and comorbidities[23] support an independent risk of gout on VTE. Third, the long observation period further increased the accuracy with which we could assess the effect of gout on future VTE development.

In conclusion, the present study extends research on the risk of gout for CVD development to confirm an independent effect of gout on VTE. This message can further raise attention to the systemic effect of gout in addition to the intermittent arthritis attack and joint deformity, and also add to our current understanding of the association between gout and CVDs.

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