Joint Bone Spine 86 (2019) 389–391

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Letter to the Editor

Association between gout and cardiovascular disease risk: A nation-wide case-control study

ARTICLE INFO

Keywords:
Gout
Cardiovascular disease
Heart disease
Arthritis

Gout is a progressive, painful and common form of inflammatory arthritis in adult males [1]. The prevalence of gout has been increasing worldwide, affecting 1.4% of the population in the UK and Germany and 4% in the USA [2,3]. Previous literature have been shown that gout is associated with several conditions such as insulin resistance syndrome, obesity, hypertension that could reduce survival [4]. Recently, concern has been raised due to the association between gout and cardiovascular disease (CVD). Gout lead CVD due to both hyperuricemia and crystal-induced inflammation. We, therefore, investigate the magnitude of the association between gout and risk of CVD.

A population-based case-control study was conducted using National Health Insurance Database (NHID) which cover 99% of the 23 million inhabitants of Taiwan. This database contains overall information on patient's demographics (encrypted patient's identification numbers, birthdate, sex), in-patients, and out-patients claim data, length of hospital stay, number of hospitalization, diagnostic test, date of visits, laboratory, and pharmacy data. All the patients who were aged ≥ 20 year, had gout before the index date included in this study. Gout patients were identified by International Classification of Disease, Clinical Modification, Ninth Revision codes [ICD-9-274.xx and patients who received first-line treatment with a xanthine oxidase inhibitor (i.e., allopurinol or febuxostat) at least 30 days. The cases were defined as the patients who had a primary diagnosed cardiovascular disease in between 1st January 2009 and 31st December 2011. Patients with CVD was defined as an ICD-9-CM diagnosis (410.xx-438.xx) [Appendix A, Table S1; See the supplementary material associated with this article online], at of coronary artery disease (CAD)/coronary heart disease, and cerebrovascular disease. Coronary artery disease specific major CVD events require evidence of myocardial infraction (MI) or coronary revascularization [5]. However, MI patients were identified by discharge diagnosis ICD-9 code of 410.xo or 410.x1, and revascularization was defined as coronary artery bypass graft and/or percutaneous revascularization procedure. Cerebrovascular disease related CVD included ischemic or hemorrhagic stroke, transient ischemic attack (TIA), and other cerebrovascular disease revascularization. Patients were classified as having an ischemic or hemorrhagic stroke, TIA, other cerebrovascular disease if they had ≥ 1 inpatient claims with a discharge ICD-9-CM diagnosis code (primary or secondary) of 433.x1, 434.xx-436.xx (ischemic), or 430.xx-431.xx (hemorrhagic) or 435.xx (TIA) or 437.xx-438.xx (other cerebrovascular disease). The controls were defined as the patients without cardiovascular disease between 2009 and 2011. Several covariates that were established risk factors, were used to adjust multivariate analysis. A conditional logistic regression model was used to estimate the adjusted odd ratio (AORs) and 95% confidence intervals (CI) for quantify the effect of gout and cardiac disease risk. Data were analyzed with the R (V.3.5) statistical packages. All statistical tests were two-sided and $P \leq 0.05$ was considered statistically significant.

A total of 99,220 patients with CVD were identified between 2009 and 2011. Among those, 73,694 patients had heart disease and 40,896 had cerebrovascular disease. The relationship between gout and cardiovascular risk is shown in Table 1. The adjusted odd

Table 1
Association between gout and cardiovascular disease risk.

Disease	Non-gout		Gout		Adjusted odds ratio (95% CI)	*P*-value
	No	Yes	No	Yes		
CVD	155,359 (63.1%)	90,733 (36.9%)	8409 (53.5%)	7295 (46.5%)	1.49 (1.44–1.53)	<0.0001
Heart	179,094 (72.8%)	66,998 (27.2%)	9882 (62.9%)	5822 (37.1%)	1.57 (1.52–1.63)	<0.0001
Cerebrovascular	208,539 (84.7%)	37,553 (15.3%)	12,688 (80.8%)	3016 (19.2%)	1.32 (1.27–1.38)	<0.0001
Diabetes	203,302 (82.6%)	42,790 (17.4%)	12,224 (77.8%)	3480 (22.2%)	1.35 (1.30–1.41)	<0.0001
Chronic liver disease	238,697 (97%)	7395 (3%)	14,787 (94.2%)	917 (5.8%)	2.0 (1.87–2.15)	<0.0001
Hypertension	124,836 (50.7%)	121,256 (49.3%)	3048 (19.4%)	12,656 (80.6%)	4.27 (4.11–4.45)	<0.0001
Renal failure	238,612 (97%)	7480 (3%)	14,234 (90.6%)	1470 (9.4%)	3.29 (3.11–3.49)	<0.0001

Cerebrovascular disease: ICD-9 code 430–438 were used to identify patients.
Heart disease (ischemic heart disease, heart failure, ill-defined descriptions and complications of heart disease): ICD-9 code 410–414, 428,429 were used to identify heart patient.

https://doi.org/10.1016/j.jbspin.2018.06.011

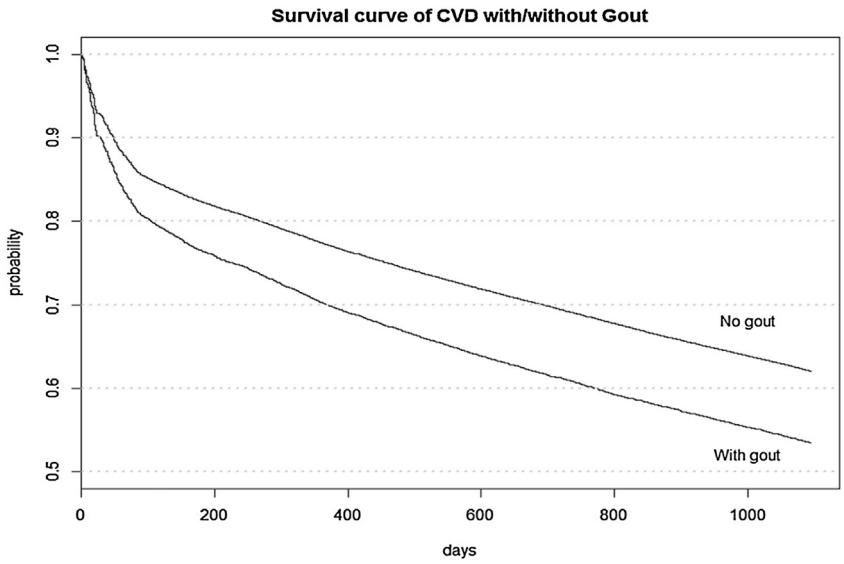

Fig. 1. Survival of CVD patients with gout and without gout.

ratio for gout and overall cardiovascular risk was 1.49 (95% CI: 1.44–1.53). In addition, an increased risk was observed in heart disease (OR: 1.57; 95% CI: 1.52–1.63) and cerebrum disease (OR: 1.32; 95% CI: 1.27–1.38) in-patients with gout. When we stratified CVD risk patients with gender, female patients showed higher risk (OR: 2.06; 95% CI: 1.94–2.20) than male patients (OR: 1.26; 95% CI: 1.21–1.31). The probability of surviving CVD patients with or without gout is shown in Fig. 1.

This is the first comprehensive study compared the risk of CVD patients with gout and without gout. In this large population-based case-control study showed that gout was significantly associated with increased the risk of CVD. However, female patients with gout showed higher risk than male patients. Several studies mentioned that the exact role of gout and CVD risk is still unclear because gout and CVD share some common risk factors (hypertension, obesity, etc.) which might be confounding factors of this study. Contrary, biological studies mentioned that systemic inflammation reads to atherogenesis via endothelial dysfunction. This process drives to decrease an arterial compliance as well as impaired blood flow [6]. Additionally, Clarson et al. [7] reported their meta-analysis that gout increased the risk of mortality from CVD and CHD. However, our results could be interpreted with caution and physicians should be monitor gout patients on timely basis to reduce unintended adverse outcome. There are several limitations of our study that need to address. First, duration of gout disease and cardiovascular risk was not evaluated. Second, some potential confounding factors such as lifestyle, body mass index, alcohol consumption, smoking data were not considered for risk stratification. Third, we did not consider impact of individual gout therapy (Febuxostat, Allopurinol, Probenecid) and major cardiovascular events. Although, White et al. [8] reported that gout patient's treatment with febuxostat had major adverse cardiovascular events similar to those associated with allopurinol. Therefore, more epidemiological studies with large follow-up, randomized control, and biological studies are warranted to find an exact role of gout for increasing the risk of CVD.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgement

This work was financially supported by the "TMU Research Center of Cancer Translational Medicine" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jbspin.2018.06.011.

References

[1] Yang H-C, Nguyen PAA, Islam M, et al. Gout drugs use and risk of cancer: a case-control study. Joint Bone Spine 2018, http://dx.doi.org/10.1016/j.jbspin.2018.01.008.
[2] Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis 2008;67:960–6.
[3] Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheumatol 2011;63:3136–41.
[4] Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093–103.
[5] Fooody J, Turpin RS, Tidwell B, et al. Major cardiovascular events in patients with gout and associated cardiovascular disease or heart failure and chronic kidney disease initiating a xanthine oxidase inhibitor. Am Health Drug Benefits 2017;10:393–401.
[6] Brook RD, Yalavarthi S, Myles JD, et al. Determinants of vascular function in patients with chronic gout. J Clin Hypertens 2011;13:178–88.
[7] Clarson L, Chandratre P, Hider S, et al. Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis. Eur J Prev Cardiol 2015;22:335–43.
[8] White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018;378:1200–10.

Chia-Wei Liang[a,b,1]
Md. Mohaimenul Islam[a,b,1]
Tahmina Nasrin Poly[a,b]
Hsuan-Chia Yang[b]
Yu-Chuan Jack Li[a,b,c,d,*]
[a] *Graduate Institute of Biomedical Informatics, College of Medicine Science and Technology, Taipei Medical University, 110 Taipei, Taiwan*

[b] *International Center for Health Information Technology, Taipei Medical University, 110 Taipei, Taiwan*
[c] *Department of Dermatology, Taipei Medical University, Wan Fang Hospital, 110 Taipei, Taiwan*
[d] *TMU Research Center of Cancer Translational Medicine, Taipei, Taiwan*

[*] Corresponding author at: Graduate Institute of Biomedical Informatics, Taipei Medical University, 250 Wu-Hsing Street, 110 Taipei, Taiwan.
E-mail addresses: jack@tmu.edu.tw, jaak88@gmail.com (Y.-C. Jack Li)

[1] Equal contribution.

Available online 17 July 2018