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Original article

Elevated risk of mortality among gout patients: A comparison with the National Population in Taiwan

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ABSTRACT

Objectives: Accumulating evidence suggests that gout is associated with increased overall and cardiovascular mortality. Using data from a large consecutive cohort of gout sufferers who were followed for 8 years, we investigated mortality among gout sufferers and compared the results with data from the general population of Taiwan.
Methods: The study comprised 6631 people who had gout diagnosis at outpatient department of the Chang Gung Memorial Hospital in 2000. Survival status and cause of death were ascertained by examining the National Death Registry of Taiwan through 2008.
Results: During 53,048 person-years of follow-up in 6631 gout patients, 1273 (male, 941; female, 332) deaths were identified, corresponding to the crude mortality rate was 21.3 (male, 20.0; female, 26.1) per 1000 patient-years, which was significantly higher than that of the national population. As compared with the national population of Taiwan in 2000, the all-cause standardized mortality ratio (95% confidence interval) was 1.29 (1.21–1.37) for men and 1.70 (1.53–1.89) for women. Both men and women in this cohort had higher standardized mortality ratios for death due to kidney diseases (men, 3.10; women, 3.54), endocrine and metabolic diseases (men, 2.24; women, 2.71), and cardiovascular diseases (men, 1.58; women, 1.81). Multivariate Cox regression showed no difference in mortality between genders.
Discussion/Conclusions: Individuals with gout have increased mortality risk in both sexes; however, the extent of risk increment is higher in women. Kidney diseases, endocrine and metabolic diseases, and cardiovascular diseases are primary causes of death.

1. Introduction

Gout is a disease of purine metabolism and is characterized by hyperuricemia, recurrent attacks of acute arthritis, intercritical gout and chronic tophaceous gout. The burden of gout is enormous, as gout often coexists with other medical conditions, including metabolic syndrome [1], diabetes mellitus [2], hypertension [3] and chronic kidney disease [4]; all of which are related to reduced long-term survival.

Gout is particularly a major health issue in Taiwan. In a national survey during 1993 to 1996, 23% of adult male had hyperuricemia [5]. Gout prevalence is higher in Taiwan and seems to be increasing. An earlier study conducted in 1994 reported that the prevalence of gout in suburban and urban areas was 0.67%. A community-based study, conducted in 2000, reported that gout prevalence in men aged more than 30 years was 1.3% [6]. Our recent study, with an older age distribution, found that 3.6% of subjects undergone a health screening program had gout [7]. Therefore, it is important to understand the health impact of gout in Taiwan.

Few studies have investigated the survival impact of gout [8–10]. Evidence for mortality risk in women with gout was particularly scarce. Earlier studies observed no increase in cardiovascular mortality in individuals with gout [11,12] but two recent epidemiologic studies demonstrated that individuals with gout had higher risks of all-cause and cardiovascular mortality [9,10]. These two studies all focused on men. In a previous study, we investigated a cohort of gout sufferers who had undergone health screenings, and observed a hazard ratio of 1.97 (95% confidence interval [CI], 1.08–3.59) for cardiovascular death [13]. Although

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our prior study included both men and women, we did not analyze women separately.

Herein, to further examine the survival impact of gout for both genders, we describe a large consecutive gout cohort with a follow-up period of 8 years and compare with data from the general population of Taiwan. This updated report extends and consolidates our earlier study of the association between gout and increased mortality by comparing mortality with the national population and examining this relationship in both genders separately.

2. Methods

The study has been approved by Institutional Review Board of the Chang Gung Memorial Hospital (CGMH), Taiwan. The present study was conducted with full compliance with local, national, ethical, and regulatory principles. We identified patients with gouty arthritis from the records of the outpatient department in CGMH, which is the largest medical center in Taiwan.

2.1. Study cohort

A computerized search of the entire outpatient database was performed to identify patients with gout. The case definition of gout in the present study was an outpatient diagnosis of gout on at least two occasions (International Classification of Diseases, Ninth Revision [ICD-9] codes: 274) and at least once hyperuricemia. As the prevalence of hyperuricemia was high in Taiwan [5,6] and mean serum uric acid (SUA) levels was higher in Taiwan [6] than the Western country [14], the cutoff of hyperuricemia in the present study (an SUA level higher than 7.7 mg/dL in men or higher than 6.6 mg/dL in women) was based on a recent national survey [5]. In this study, we enrolled patients aged older than 20 years who fulfilled gout case definition and had outpatient visits during year 2000.

2.2. Baseline characteristics and comorbidities

We also obtain sex, age at time of gout diagnosis, medication uses at every outpatient visit, and diagnoses of chronic illnesses, including diabetes mellitus (DM; ICD-9 codes: 250), hypertension (ICD-9 codes: 401-405), coronary heart disease (CHD; ICD-9 codes: 410–414), stroke (ICD-9 codes: 430–438) and chronic kidney disease (CKD, ICD-9 codes: 585).

2.3. Mortality and causes of death

Survival status and cause of death from 2000 through 2008 were ascertained by using the National Death Registry in Taiwan, which records the deaths of all citizens; causes of death are coded from death certificates. The accuracy of the coding has been validated by previous studies [9,10]. We linked our cohort with the death registry by the national identification number, which is unique for each citizen in Taiwan. Died gout patients were identified by matched national identification number.

Causes of death were death from any cause and specific causes including infectious diseases (ICD-9 codes: 001–139), neoplasms (ICD-9 codes: 140–239), endocrine and metabolic diseases (ICD-9 codes: 240–279), cardiovascular diseases (ICD-9 codes: 390–459), respiratory diseases (ICD-9 codes: 460–519), gastro-intestinal diseases (ICD-9 codes: 520–579) and kidney diseases (ICD-9 codes: 580–599). National demographic data was obtained from the Office of Statistics, Directorate-General of Budget, Accounting and Statistics, Taiwan. National death registry was obtained from the Bureau of Health Promotion, Department of Health, Taiwan.

Table 1
Baseline characteristics of subjects.

	Male (n = 5219)	Female (n = 1412)	P
Age (years old)	53.2 ± 14.3	60.2 ± 12.2	<0.001
HTN (n, %)	2107, 40.4%	778, 55.1%	<0.001
DM (n, %)	846, 16.2%	426, 30.2%	<0.001
CAD (n, %)	528, 10.1%	123, 8.7%	<0.001
Stroke (n, %)	473, 9.1%	129, 9.1%	0.917
CKD (n, %)	903, 17.3%	268, 19.0%	0.146
With DM	176 (19.5%)	96 (35.8%)	<0.001
With HTN	532 (58.9%)	163 (60.8%)	<0.001
With both	134 (14.8%)	66 (24.6%)	<0.001
Use of aspirin (n, %)	640, 12.3%	186, 13.2%	0.358

DM: diabetes mellitus; CKD: chronic kidney disease; CAD: coronary heart disease; eGFR: estimated glomerular filtration rate; HTN: hypertension.

2.4. Statistical analysis

Summary statistics were expressed as a percentage for categorical data and mean ± SD for approximately normally distributed continuous variables. Mortality was compared by using standardized mortality ratios (SMRs: the ratio of observed to expected deaths), with the national population in 2000 as reference. We calculated the expected number of deaths by multiplying the number of patients in each sex and 5-year age group by the corresponding national mortality rates. The SMRs for both all-cause mortality and selected causes of death were calculated. Calculation of confidence intervals for SMRs was based on the assumption that the observed number of deaths is the mean of a Poisson distribution [15].

All-cause mortality between genders was compared by using the log-rank test. Cox proportional hazards models were used to explore gender difference in all-cause mortality, controlling for age, DM, hypertension, CHD, stroke, CKD and use of aspirin. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. A 2-sided P-value less than 0.05 was considered statistically significant. All analyses were performed using PASW Statistics, version 18 and PASW Modeler, version 13 (SPSS Inc. Chicago, Illinois).

3. Results

3.1. Baseline characteristics and mortality rates

A total of 6631 (5219 men, 1412 women) subjects were enrolled in the study during an 8-year follow-up period. Table 1 showed the baseline characteristics of the cohort. The mean age was 56.6 ± 14.3 years and women were significantly older. The prevalences of DM and hypertension were 19.2 and 43.5%; both were more common in women than in men (P < 0.001). Men had higher prevalence of CHD, but not stroke and CKD. As both DM and hypertension were more often found in women, DM and hypertension related CKD was also more prevalent. The prevalences of DM, hypertension, CHD, stroke and CKD are shown in Table 1. There were 3264 patients (49.2%) of subjects in this cohort were free of DM or hypertension (2774 men; 490 women).

3.2. All-cause and cause-specific standardized mortality ratios

During study period, 1273 (941 men, 332 women) deaths were identified. The 1-, 2- and 5-year survival rates were 96.9, 94.0 and 85.9%. In comparison, the 1-, 2- and 5-year mortality rates of the national population in 2000 were 99.4, 98.8 and 96.9%, respectively. The crude mortality rate was 21.3 (male, 20.0; female, 26.1) per 1000 patient-years, which was significantly higher than that of the national population (total, 8.5; male, 10.3; female, 6.6 per 1000 patient-years). Cardiovascular diseases (n = 337, 26.5%), neoplasms (n = 276, 21.7%), endocrine and metabolic diseases (n = 177,