Journal of Epidemiology xxx (2017) 1–4

Contents lists available at ScienceDirect

Journal of Epidemiology

journal homepage: http://www.journals.elsevier.com/journal-of-epidemiology/

Original Article

Hemorrhoid is associated with increased risk of peripheral artery occlusive disease: A nationwide cohort study

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ARTICLE INFO

Article history:
Received 14 July 2016
Accepted 12 December 2016
Available online xxx

Keywords:
Cohort study
Comorbidity
Hemorrhoid
Peripheral artery occlusive disease

ABSTRACT

Background: This study was conducted to evaluate the association between hemorrhoid and risk of incident peripheral artery occlusive disease (PAOD).
Methods: Using the Taiwanese Longitudinal Health Insurance Database 2000, we compared the incident PAOD risk between the hemorrhoid and the non-hemorrhoid cohorts. Both of these cohorts were followed up from the index date until the date of PAOD diagnosis, withdrawal from the National Health Insurance program, or the end of 2011.
Results: The mean follow-up period was 6.82 (standard deviation [SD], 3.22) and 6.70 (SD, 3.23) years in the hemorrhoid and non-hemorrhoid cohorts, respectively. The plot of the Kaplan–Meier analysis showed that, by the end of the 12-year follow-up period, the cumulative incidence of PAOD was significantly higher for the hemorrhoid cohort than for the non-hemorrhoid cohort (log-rank test: $p < 0.001$).
Conclusions: A significantly increased PAOD risk in patients with hemorrhoids was found in this nationwide cohort study.

Introduction

Hemorrhoid, which varies clinically from asymptomatic to manifestations of bleeding, prolapse, and thrombosis, is becoming a huge medical burden worldwide.[1–4] Several theories have been proposed for the development of the hemorrhoid; among them, inflammation is one of the pathogenic processes that has gained attention recently.[1–6]

Peripheral artery occlusive disease (PAOD) is one of the leading causes of mortality worldwide.[7–10] Patients with PAOD are usually asymptomatic and are easily overlooked.[7–12] The risk factors of developing PAOD have been well established in previous investigations.[13–15]

Matrix metalloproteinases (MMPs), key players in the pathogenesis of PAOD, have recently been reported to be associated with hemorrhoid development.[5,16–18] However, no study has addressed the relationship between hemorrhoid and the risk of incident PAOD. Therefore, this study was designed to evaluate the association between hemorrhoid and the subsequent PAOD risk using a nationwide population-based database.

Methods

Data source

A nationwide population-based retrospective cohort study was performed using the Taiwanese Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000 comprises one million randomly sampled beneficiaries enrolled in the National Health Insurance (NHI) program, which collected all records on these individuals from 1996 to 2011. The NHI program includes the complete medical information of more than 23.74 million Taiwanese residents, with a coverage rate of over than 99%.[19] The NHI program and LHID2000 have been described in detail previously.[20,21] The identification numbers of patients have been scrambled to protect the privacy of insured residents before releasing the LHID2000.

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Peer review under responsibility of the Japan Epidemiological Association.

http://dx.doi.org/10.1016/j.je.2016.12.015

Diseases diagnoses were identified and coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The Ethics Review Board of China Medical University and Hospital in Taiwan approved this study (CMUH-104-REC2-115).

Sampled participants

Subjects with hemorrhoids (ICD-9-CM code 455) newly diagnosed from January 2000 through December 2010 were included in the hemorrhoid cohort. The first date of hemorrhoid diagnosed was defined as the entry date. We excluded patients with a history of PAOD (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9) before the entry date or those aged <20 years. The non-hemorrhoid cohort was identified from the LHID2000 during the same period of 2000–2010, with exclusion criteria similar to the hemorrhoid cohort. Patients in the hemorrhoid and non-hemorrhoid cohorts were selected by 1:1 frequency matching by sex, age (every 5-year span), index year, and comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, and 496), heart failure (ICD-9-CM code 428), coronary artery disease (CAD) (ICD-9-CM codes 410–414), stroke (ICD-9-CM codes 430–438), and asthma (ICD-9-CM code 493). The comorbidities diagnosed before the end of the study were included for adjustment. Both these cohorts were followed up from the index date until the date of PAOD diagnosis, withdrawal from the NHI program, or the database ended (December 31, 2011), whichever came first.

Statistical analysis

Distributions of demographic variables, including sex, age, and comorbidities were compared between the hemorrhoid and the non-hemorrhoid cohorts. The categorical variables were analyzed using the chi-square test, and the continuous variables of the baseline characteristics of these cohorts were analyzed using the Student *t*-test. To assess the difference of the cumulative incidence of PAOD between the hemorrhoid and non-hemorrhoid cohorts, we applied the Kaplan–Meier analysis and the log-rank test. We computed the incidence density rate (per 1000 person-years) of PAOD for each cohort. Cox proportional hazard model was used to assess the risk of PAOD between the hemorrhoid and the non-hemorrhoid cohorts. Sex, age, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, and asthma were included in the multivariable model for adjustment. We estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) using the Cox model. We performed all statistical analyses using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), with $p < 0.05$ in two-tailed tests considered significant.

Results

Eligible study patients included 37,992 patients with hemorrhoids and 37,992 patients without hemorrhoids (Table 1). No significant differences regarding the distributions of sex, age, and comorbidities between the hemorrhoid and non-hemorrhoid cohorts were found. Males represented the majority of the study cohorts (54.3% vs. 54.2%); most people were less than 50-years-old (60.5% vs. 60.5%). The mean age of the patients in the hemorrhoid and the non-hemorrhoid cohorts was 47.2 (standard deviation [SD], 15.8) and 47.0 (SD, 16.2) years, respectively.

The mean follow-up period was 6.82 (SD, 3.22) and 6.70 (SD, 3.23) years in the hemorrhoid and non-hemorrhoid cohorts, respectively. The plot of the Kaplan–Meier analysis showed that, by the end of the 12-year follow-up period, the cumulative incidence of PAOD was significantly higher for the hemorrhoid cohort than for the non-hemorrhoid cohort (log-rank test: $p < 0.001$) (Fig. 1).

Table 1
Demographic characteristics and comorbidities in patients with and without hemorrhoids.

Variable	Hemorrhoid		*p*-value
	No	Yes	
	$n = 37{,}992$	$n = 37{,}992$	
Sex			0.93
Female	17,387 (45.8)	17,375 (45.7)	
Male	20,605 (54.2)	20,617 (54.3)	
Age, years, mean (SD)	47.0 (16.2)	47.2 (15.8)	0.05
Age groups, years			0.89
≤49	22,966 (60.5)	22,983 (60.5)	
50–64	8855 (23.3)	8865 (23.3)	
≥65	6161 (16.2)	6144 (16.2)	
Comorbidity			
Diabetes	4125 (10.9)	4157 (10.9)	0.71
Hypertension	13,400 (35.2)	13,405 (35.3)	0.97
Hyperlipidemia	10,920 (28.7)	10,968 (28.8)	0.70
COPD	3924 (10.3)	3957 (10.4)	0.69
Heart failure	1523 (4.01)	1558 (4.10)	0.52
CAD	7419 (19.5)	7454 (19.6)	0.75
Stroke	7841 (20.6)	7869 (20.7)	0.80
Asthma	2391 (6.29)	2415 (6.36)	0.72

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation. Values are reported as *n* (%), unless otherwise noted.

The overall, sex-, age-, and comorbidity-specific incidence density rates and HR of these two cohorts are shown in Table 2. The overall incidence rate of PAOD was significantly higher in the hemorrhoid cohort than in the non-hemorrhoid cohort (3.61 vs. 2.88 per 1000 person-years) with an adjusted hazard ratio (aHR) of 1.25 (95% CI, 1.14–1.38). The risk of PAOD for the hemorrhoid relative to the non-hemorrhoid cohort was significantly higher in both women (aHR 1.27; 95% CI, 1.10–1.47) and men (aHR 1.24; 95% CI, 1.08–1.41). The incidence of PAOD increased with age in both cohorts, and the age-specific aHR of PAOD for the hemorrhoid relative to the non-hemorrhoid cohort was significantly higher for

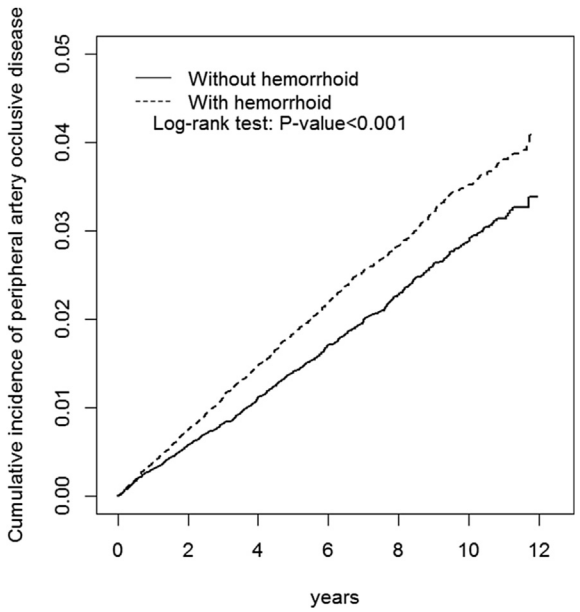

Fig. 1. Cumulative incidence curves of peripheral artery occlusive disease (PAOD) for patients with and without hemorrhoid.

Please cite this article in press as: Hu W-S, Lin C-L, Hemorrhoid is associated with increased risk of peripheral artery occlusive disease: A nationwide cohort study, Journal of Epidemiology (2017), http://dx.doi.org/10.1016/j.je.2016.12.015