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Original Article

Long-term risk of acute coronary syndrome in patients with cholangitis: A 13-year nationwide cohort study☆

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ABSTRACT

Background & aims: Patients with cholangitis may exhibit repeated and chronic inflammation of the biliary tract despite successful medical or surgical treatments. This nationwide cohort study examined the association between cholangitis and the subsequent development of acute coronary syndrome (ACS).
Methods: We identified a cohort of 37 676 patients who were diagnosed with cholangitis between January 1998 and December 2010, and a comparison cohort of 150 704 subjects frequency matched by age, sex, and index year after excluding comorbidities for ACS. Both cohorts were followed until the end of 2010 to measure the incidence of ACS. Both incidence rate ratios and hazard ratios of ACS were estimated by age and sex.
Results: Sex-specific analysis showed that males were at a higher incidence of ACS than females in both groups with (16.2 vs 11.5 per 10 000 person-years) and without (18.7 vs 12.5 per 10 000 person-years) cholangitis. The incidence of ACS also increased with age no matter having or not having cholangitis. The age stratified analysis revealed that the risk of ACS was significantly higher in patients with cholangitis younger than 65 years old. The multivariable Cox proportional hazard model demonstrated that cholangitis was significantly associated with ACS (adjusted hazard ratio [HR] = 1.18; 95% confidence interval [CI], 1.03–1.35) after adjusting age and sex in the model.
Conclusions: This study suggests that patients with cholangitis are at an elevated risk of ACS. Awareness of the potential ACS risk for patients with cholangitis is important for patients and clinicians.

1. Introduction

Cholangitis is the inflammation or infection of any segment of the biliary tract. The underlying pathophysiology of cholangitis typically includes: first, the obstruction or reflux of bile flow within the biliary system; second, increased bacterial growth in the bile duct; and third, elevated intraductal pressure in the bile duct, which allows the translocation of bacteria or endotoxins into the vascular and lymphatic system (cholangiovenous or lymphatic reflux) [1]. The primary etiology of cholangitis is cholelithiasis. Other significant etiologies include the stenosis of the biliary tract, which can result from congenital anomalies, benign or malignant tumors, medical complications, autoimmune diseases, or external compression.

A significant proportion of cholangitis patients have latent or recurring cholangitis even after a successful initial treatment. The long-term recurrence rate of common bile stones after an endoscopic removal ranged from 11.0% to 17.4% [2,3]. Cholangitis occurred in approximately 10% of patients who underwent biliary reconstructions [4,5]. These studies have suggested that patients experiencing cholangitis may exhibit chronic biliary inflammation, which theoretically results in adverse long-term effects on the cardiovascular system [6].

To our knowledge, no previous studies have examined the risks of cardiovascular events in cholangitis patients. In the present study, we investigate whether cholangitis is associated with an increased risk of acute coronary syndrome (ACS) based on a cohort study and data from the Taiwan National Health Insurance Research Database.

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2. Methods

2.1. Data sources

The Taiwan National Health Insurance Program was established in March 1995 by the Bureau of National Health Insurance, Department of Health, and covered over 99% of the Taiwanese population (23.74 million insurants) in 2009 [7,8]. The identification numbers linked to patient files with personal information were scrambled to ensure patient confidentiality. We used 2 data files including the registries of beneficiaries and inpatient claims. The accuracy and high validity of the diagnoses in the National Health Insurance Research Database (NHIRD) have been previously demonstrated [9,10]. The International Classification of Diseases, ninth edition clinical modification (ICD-9-CM) was used to identify the diagnoses. In addition, Taiwan launched a national health insurance (NHI) in 1995, operated by a single-buyer, the government. All insurance claims should be scrutinized by medical reimbursement specialists and peer review. Therefore the diagnosed codes in NHIRD should be accurate and reliable. With the NHI's and China Medical University's approval, this study was approved by the Institutional Review Board of China Medical University in central Taiwan (CMU-REC-101-012).

2.2. Study patients

We conducted a retrospective cohort study of patients who were first hospitalized for cholangitis (ICD-9 code 576.1) in 1998–2010, and the index date was the date of the diagnosis. The diagnoses of acute coronary syndrome (ACS) (ICD-9 code 410–411.1) were based on the ICD-9 code determined by clinical physicians according to the clinical symptoms and signs, the electrocardiogram (EKG), imaging and blood tests.

Patients younger than 20 years of age and those with previous incidence of acute coronary syndrome (ACS) (ICD-9 code 410–411.1), hypertension (ICD-9 code 401–405), diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272), chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490–496), chronic kidney disease (CKD) (ICD-9 code 585), and heart failure (ICD-9 code 428) were excluded. A comparison cohort was randomly selected among patients that were not diagnosed with cholangitis during 1998–2010 and frequency matched on age (every 5 years), sex, and index year at a 1:4 ratio. The same exclusion criteria were also applied to the non-cholangitis cohort.

2.3. Outcome definition

All patient data were examined for incidence of ACS until the date of death, date of loss (withdrawal from insurance), or December 31, 2010.

2.4. Statistical analysis

The differences in demographic characteristics between the cholangitis cohort and non-cholangitis cohort were tested using a chi-square test for categorical variables and a *t*-test for continuous variables. We calculated the incidence density rate of ACS developed in both cholangitis and non-cholangitis cohorts. In order to estimate the sex-, and age-specific risk of ACS between the two study cohorts, we used the univariable and multivariable Cox proportional hazard model to estimate strata-specific adjusted hazard ratio (HR) and 95% confidence interval (CI) of developing ACS in patients with cholangitis compared with the non-cholangitis cohort. The multivariable model was used for controlling age and sex. We estimated the cohort-specific cumulative incidences by 1 − (Kaplan–Meier survival) for unadjusted curves and 1 − (direct adjusted survival function) for considering age and sex in the Cox model under the assumption of no other competing risks; while the difference in cumulative incidence curves between the two cohorts was tested by log-rank test and likelihood-ratio test, respectively. The analyses were performed using the SAS statistical package (version 9.3; SAS Institute Inc., Cary, NC, USA). The statistical significance was accepted at a two-tailed *P* value lower than .05.

3. Results

The eligible patients comprised 37 676 persons in the cholangitis cohort and 150 704 persons in the non-cholangitis cohort (Table 1). The distributions of age and gender were similar in both cohorts by the design of frequency matching. In the present study, 53.4% were males and 46.5% were over 65 years.

Table 2 lists the overall sex- and age-specific incidence density rate of ACS in both cohorts. The sex-specific analysis showed that male patients had a higher risk of ACS in both the cholangitis cohort (18.7 vs. 12.5 per 10 000 person-years) and the non-cholangitis cohort (16.2 vs. 11.5 per 10 000 person-years). However, the ACS risk associated with cholangitis was similar in both males (HR = 1.19, 95% CI = 1.00–1.42) and females (HR = 1.16, 95% CI = 0.94–1.44).

As expected, the age-specific incidence ACS increased with age in both cohorts, especially that the highest incidence of ACS was found in the cholangitis patients over 75 years of age (27.2 per 10 000 person-years). Nevertheless, patients suffering from cholangitis were at the highest risk for ACS in those ≤49 years of age (crude HR = 2.02, 95% CI = 1.14–3.57) with an adjusted HR of 2.11 (95% CI = 1.20–3.74). The corresponding adjusted HRs for those 50–64 years of age were also significant but smaller (adjusted HR = 1.54, 95% CI = 1.18–2.01). Our findings suggested that cholangitis was associated with an excessive risk of ACS in younger patients who usually exhibited a lower ACS risk. Table 3 summarizes the mutually adjusted main effects of age, sex, and cholangitis on ACS by Cox proportional hazard models. Male gender was at a higher risk for ACS (adjusted HR = 1.40, 95% CI = 1.26–1.56). The risk of ACS increased with age (adjusted HR = 4.44 for aged 50–64 years (95% CI = 3.34–5.91), adjusted HR = 10.7 for those aged 65–74 years (95% CI = 8.12–14.1), adjusted HR = 12.3 (95% CI = 9.29–16.2) for the oldest patients compared with the youngest patients). After adjusted for gender and age, individuals with cholangitis had a 1.18-fold higher risk for ACS (95% CI = 1.03–1.35).

Fig. 1 presents the 13-year cumulative incidence curves of ACS by cholangitis status without any adjustment (A) and adjusted for age and sex (B). The difference in the cumulative incidence curves of ACS between the patients with cholangitis and those without cholangitis during the 13 years of follow-up was more pronounced in the adjusted curves ($P = 0.04$) than the unadjusted curves ($P = 0.07$).

4. Discussion

The present study is the first to address the long-term risk of ACS in patients with cholangitis. This population-based cohort study demonstrates that the long-term risk of ACS is significantly increased in patients with cholangitis, with an adjusted HR of 1.18 (95% CI: 1.03, 1.35) for ACS within 13 years, after adjusting for confounding factors.

Table 1
Demographic characteristics in patient with and without cholangitis.

Variable	Cholangitis	
	No	Yes
	N = 150704	N = 37676
Gender	n (%)	n (%)
Female	70 228 (46.6)	17 557 (46.6)
Male	80 476 (53.4)	20 119 (53.4)
Age, mean(SD)	61.2 (16.0)	61.9 (15.9)
≤49	35 752 (23.7)	8983 (23.7)
50–64	44 980 (29.9)	11 245 (29.9)
65–74	35 052 (23.3)	8763 (23.3)
75+	34 920 (23.2)	8730 (23.2)

SD: standard deviation.