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Increased risk of acute coronary syndrome among leptospirosis patients: A nationwide cohort analysis

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ABSTRACT

Background: : Studies on the association between leptospirosis and acute coronary syndrome (ACS) are lacking. Therefore, this study identifies the effects of leptospirosis on the risks of developing ACS with a nationwide retrospective cohort study.
Methods: : We identified adult patients aged ≥20 years who were newly diagnosed with leptospirosis. We also randomly selected a comparison cohort from the general population by using a propensity score matching method. We analyzed the risks of ACS by using Cox proportional hazard regression models.
Results: : Among the 23.74 million people in the cohort, 3690 patients with leptospirosis (68% men, mean age of 52.2 years) and 3690 controls were followed for 13,677 and 15,652 person-years, respectively. The overall incidence of ACS was higher in the leptospirosis cohort than in the nonleptospirosis cohort (4.68 vs 3.71 per 1000 person-years), with a hazard ratio (HR) of 1.69 (95% confidence interval [CI] = 1.12–2.56). Men exhibited a 1.88-fold greater HR of ACS than women did (95% CI = 1.20–2.94). The risk of developing ACS was highest for leptospirosis patients aged ≥65 years (HR = 7, 51% CI = 4.35–12.9) compared with patients aged ≤49 years.
Conclusion: : Leptospirosis is not a previously identified risk factor for ACS. The findings of this nationwide retrospective cohort study indicate that leptospirosis may become an independent risk factor for ACS. Future research to investigate the mechanism is warranted.

1. Introduction

Leptospirosis, an increasingly emerging zoonosis throughout the world, greatly impacts public health in developing countries and tropical regions plagued by frequent flooding [1]. The protean manifestations of leptospirosis range from a mild, flu-like illness to a severe disease typically characterized by jaundice, acute renal and hepatic failure, pulmonary distress, and hemorrhage, which can lead to death [2,3]. However, the frequency and extent of cardiac events after leptospirosis are unclear.

Acute coronary syndrome (ACS) comprises unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). This syndrome is a life-threatening disorder that leads to high morbidity and mortality despite advances in treatment [4,5]. Cerebrovascular diseases (CVAs) and cardiovascular diseases (CADs) share similar traditional risk factors for disorders of the circulatory system [6,7]. Studies have reported that chronic obstructive pulmonary disease (COPD) associated with reduced lung function is a strong risk factor for cardiovascular events, independent of smoking [8,9].

Recent studies on the relationship between infection and atherosclerosis-induced coronary heart disease have reported: an influenza infection can trigger acute myocardial infarction (AMI) [10]; chlamydia pneumonia might be associated with AMI [11]; an HCV infection is an independent predictor of increased coronary atherosclerosis [12]; and human immunodeficiency virus infection increases the risk of AMI [13]. However, the epidemiological relationship between people infected with leptospirosis and subsequent development of ACS remains unclear. Therefore, we conducted a longitudinal nationwide

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retrospective cohort study to determine whether patients with leptospirosis are at an increased risk of subsequently developing ACS.

2. Methods

2.1. Data source

The National Health Insurance Research Database (NHIRD), an electronic claims database of the National Health Insurance (NHI) program, covers more than 99% of the population of Taiwan (23.74 million) and has contracts with 97% of the healthcare institutions in Taiwan [14]. After the Taiwan Ministry of Health and Welfare authorized the National Health Research Institute (NHRI) to manage the claims data, the NHRI cooperated with the Bureau of National Health Insurance to establish the NHIRD for public use.

We used the identification of residents to link 2 data files that included inpatient claims and demographic information. All data were confidential and all people were anonymous. The International Classification of Disease, Ninth Revision of Clinical Modification (ICD-9-CM), is available in the claims data to define disease diagnoses. This study was approved by the Institutional Review Board of China Medical University and Hospital (CMU-REC-101-012).

2.2. Sampled participants

The leptospirosis cohort consisted of adult patients aged ≥20 years selected from inpatient claims who were newly diagnosed with leptospirosis (ICD-9-CM code 100) during 2000–2011. The admission date of initial leptospirosis diagnosis was set as the index date. Patients with a history of ACS (ICD-9-CM codes 410, 411.1, and 411.8) before the index date, or with incomplete age or sex data, were excluded.

Using the same exclusion criteria, we randomly selected the nonleptospirosis patients from the NHIRD by 1:1 matching with the leptospirosis patient on a propensity score. The propensity score was calculated by a logistic regression to estimate the probability of each patient given the baseline variables, including age, sex, hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), CVAs (ICD-9-CM codes 430–438), COPD (ICD-9-CM codes 490–492, 494, 496), and congestive heart failure (CHF; ICD-9-CM code 428).

2.3. Diagnosis of leptospirosis

The clinicians collected urine and blood samples from patients with clinically suspected leptospirosis and confirmed diagnoses by conducting serologic tests (an enzyme-linked immunosorbent assay, a polymerase chain reaction, or a microscopic agglutination test).

2.4. Main outcome

We obtained the main outcome from the hospitalization records of patients with ACS diagnoses during the follow-up. All participants were followed until a diagnosis of ACS was made or until they were censored because of loss to follow-up, death, termination of insurance, or December 31, 2011.

2.5. Statistical analysis

All data processing and statistical analyses were performed using SAS software (version 9.3 for Windows; SAS Institute Inc., Cary, NC). A 2-tailed $P < .05$ was considered statistically significant. A chi-square test examined the differences in the distribution of demographic factors and major CAD risk factors between the cohorts with and without leptospirosis. We calculated the sex-specific and age-specific incidence density rates of ACS with person-years in each cohort. Based on propensity score matching, Cox proportional hazards models stratifying on the matched pairs were also performed to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of developing ACS associated with leptospirosis, compared with nonleptospirosis cohort. The Kaplan–Meier method was used to estimate the cumulative incidence survival curves, the differences between which were compared using a likelihood-ratio test.

3. Results

3.1. Demographic characteristics and major CAD risk factors in the leptospirosis and comparison cohort

Leptospirosis and nonleptospirosis participants were matched on the propensity score effectively (Table 1). Our study included 3690 leptospirosis patients and 3690 participants without leptospirosis, among the sampled participants 68.2% were men. The mean ages for the leptospirosis cohort and nonleptospirosis cohort were 52.2 years (SD = 16.4 years) and 52.8 years (SD = 16.3 years), respectively. Of the 3690 patients in the leptospirosis cohort, some had comorbid medical disorders as hypertension (21.0%), diabetes (14.7%), hyperlipidemia (5.83%), CVA (7.83%), COPD (5.18%) and CHF (4.34%).

3.2. The incidence and hazard ratio of acute coronary syndrome, STEMI, NSTEMI, and unstable angina between 2 cohorts by propensity score matching

During the 12-year follow-up period, the overall incidences for ACS in the leptospirosis cohort, and the propensity score matched nonleptospirosis cohort were 4.68, and 3.71 per 1000 person-years, respectively (Table 2). Leptospirosis patients had a 1.69-fold risk compared with propensity score matched nonleptospirosis patients (95% CI = 1.12–2.56).

Furthermore, we stratified different types of ACS into STEMI, NSTEMI, and unstable angina, and found that the incidence of STEMI and unstable angina subcategories of ACS in the leptospirosis cohort was greater than those of the nonleptospirosis cohort. Leptospirosis patients had a 1.92-fold risk (95% CI = 0.95–3.58) of developing STEMI and 1.80-fold risk (95% CI = 0.96–3.38) of developing unstable angina

Table 1
Distributions of demographic and comorbidity among cohorts with propensity score matching.

Characteristics	Propensity score matched Leptospirosis No (N = 3690) n (%)	 Yes (N = 3690) n (%)	*P*-value
Sex			0.90
Female	1178 (31.9)	1173 (31.8)	
Male	2512 (68.1)	2517 (68.2)	
Age, mean (SD)[a]	52.2 (16.4)	52.2 (16.3)	0.99
Stratify age			0.99
≤34	651 (17.6)	650 (17.6)	
35–49	1039 (28.2)	1044 (28.3)	
50–64	1091 (29.6)	1092 (29.6)	
≥65	909 (24.6)	904 (24.5)	0.52
Major CAD risk factors			
Hypertension	775 (21.0)	773 (21.0)	0.95
Diabetes	548 (14.9)	544 (14.7)	0.90
Hyperlipidemia	210 (5.69)	215 (5.83)	0.80
CVA	296 (8.02)	289 (7.83)	0.76
COPD	196 (5.31)	191 (5.18)	0.79
CHF	165 (4.47)	160 (4.34)	0.78

CVA denotes cerebrovascular accident.
COPD denotes chronic obstructive pulmonary disease.
CHF denotes congestive heart failure.
[a] Chi-square test: two sample T-test.