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ARTICLE

Helicobacter pylori infection and the risk of acute coronary syndrome: a nationwide retrospective cohort study

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Abstract *Helicobacter pylori* infection (HPI) imposes substantial social costs and is of major etiological importance in peptic ulcer disease, gastric cancer, and accelerated cardiovascular diseases. This study determined the risk of acute coronary syndrome (ACS) associated with HPI in a nationwide retrospective cohort study. By using the Taiwan National Health Insurance Research Database (NHIRD), we identified patients diagnosed with HPI from 1998 to 2010. In addition, we randomly selected non-HPI controls frequency-matched by age, sex, and index year from the general population free of HPI. The risk of ACS was analyzed using Cox proportional hazards regression models in which sex, age, and comorbidities were included as variables. We identified 17,075 participants for the HPI group and selected 68,300 participants for the comparison group. The incidence rates were increased in the patients in the HPI group compared with those in the comparison group. Overall, the HPI patients exhibited a 1.93-fold high crude hazard ratio for ACS, and a 1.48-fold adjusted hazard ratio after age, sex, and comorbidities were adjusted. However, the overall adjusted hazard ratio of ACS increased with increasing age with a 3.11 to 8.24 adjusted hazard ratio among the various age groups. Several comorbidities, such as diabetes, hyperlipidemia, and COPD exhibited synergistic effects for ACS risk. We determined a significant association between ACS and comorbidities and provide evidence to encourage clinicians to observe ACS-related comorbidities.

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Introduction

Cardiovascular disease (CVD) is the second leading cause of death in Taiwan [1]. Acute coronary syndrome (ACS) is a critical stage of the clinical manifestation of coronary artery disease (CAD) in CVD [2]. ACS results in substantial morbidity and mortality, accounting for half of all deaths from CVD and contributing to the heavy economic burden of the disease [3].

The effective treatment of ACS is guided by early diagnosis and risk stratification to predict those who are at high risk of short- and long-term adverse outcomes. A family history of premature coronary heart disease (CHD), modifiable risk factors such as hyperlipidemia [4], hypertension, diabetes, and metabolic syndrome [5], and non modifiable risk factors such as sex and age, can be used to predict atherosclerosis development and the risk of presenting with ACS [6].

Atherosclerosis is by far the most frequent cause of CAD. Life-threatening manifestations are typically precipitated by acute thrombosis superimposed on ruptured or eroded

atherosclerotic plaque [7]. Multiple factors contribute to the pathogenesis of atherosclerosis, including endothelial dysfunction, dyslipidemia, inflammatory and immunological factors, plaque rupture, and smoking [8].

The importance of inflammation in the pathogenesis of atherosclerosis derives from the fact that markers of increased or decreased systemic inflammation are associated with the risk of atherosclerosis [9]. Evidence for inflammation in atherosclerotic lesions was obtained from early histological observations, and inflammation is central to understanding the pathogenesis of atherosclerosis [10].

Microbe infection could act according to a number of mechanisms, including direct vascular injury and induction of a systemic inflammatory state, such as that induced by *Helicobacter pylori* (HP) infection (HPI) [11].

HPI is the most common chronic bacterial infection of the human upper gastrointestinal tract [12]. Conservative estimates suggest that half of the world's population is infected with HP [13]. HP is a microaerophilic spiral-shaped Gram-negative bacterium that colonizes the gastric lumen of humans and other primates and is of major etiological importance in peptic ulcer disease and gastric cancer [14]. Increasing evidence from both clinical and experimental observations suggests that inflammation plays a crucial role in CAD Fibre15].

However, subsequent studies have produced conflicting findings. Whether this relationship with inflammation arises from the bacterium itself or its association with other confounding factors related to atherosclerosis, such as a low socioeconomic class, old age, and smoking, primarily modifiable risk factors, such as hyperlipidemia, hypertension, diabetes, and metabolic syndrome, or non-modifiable risk factors, such as sex and age, remains uncertain [17–19]. Confounding by the strong relationship of HPI to other coronary heart disease risk factors, such as age and socioeconomic class may, at least partially, explain the conflicting results that have been obtained [20].

A large population-based study may help clarify the effect of such confounding factors. Therefore, we conducted an investigation by using records from the Taiwan National Health Insurance Research Database (NHIRD) to evaluate whether HPI patients are at risk of developing ACS after accounting for traditional risk factors of ischemic heart disease. The results of this study are provided as a reference to the public and medical professionals.

Materials and methods

Study design and data source

We used the Taiwan NHIRD to conduct a population-based retrospective cohort study. This database was established in 1995 when the Taiwan National Health Insurance (NHI), a comprehensive insurance program, was launched by the Taiwan Department of Health. The NHI covers 99.9 % of the population of Taiwan. The Taiwan National Health Research Institute is responsible for managing various databases, including the registration files of the insured and claims data for reimbursement. Before releasing the electronic files for study, the personal identification numbers were encrypted to protect patient privacy. We used the inpatient claims data as the datasets, and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used to define diseases. The Institutional Review Board of China Medical University (CMU-REC-101-012) approved this study from full ethical review.

Study population

From the inpatient claims data, we selected patients who were newly diagnosed with HPI (ICD-9-CM 041.86) from 1998 to 2010 as the HPI group. For the comparison group, we randomly selected people from the general population who were 4-fold frequency-matched by age, sex, and diagnosis year. We excluded patients with a history of HPI and those with incomplete age or sex information at the baseline. Patients who had a history of comorbidities, such as hypertension (ICD 401–405), diabetes (ICD-9-CM codes 250), hyperlipidemia (ICD-9-CM codes 272), stroke (ICD-9-CM codes 430–438), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–492,494, and 496), and heart failure (ICD-9-CM 428) were included in this study. Both groups were followed up until the observation of an ACS (ICD-9-CM 410, 411.1, and 411.8) event or the end of the study period (December 31, 2010).

Statistical analysis

To compare the distributions of demographic variables and comorbidities between the HPI group and non-HPI group, we analyzed the categorical variables by using a chi-squared test. Two sample *t* tests were used to determine differences in the continuous variables, such as mean age, between the two groups. The sex-, age- and comorbidity-specific incidence densities of ACS per 1,000 person-years of follow-up for each cohort were estimated. The crude hazard ratio (HR) with a 95 % confidence interval (CI) of the HPI group to the comparison group was calculated using univariable Cox proportional hazards regression. Multivariable Cox proportional hazards regression was used to measure the adjusted HR (aHR) of ACS for the HPI group, compared with non-HPI group, after controlling for sex, age, and comorbidities. The interactional effects between the comorbidities and HPI were also assessed using Cox models. All of the statistical analyses in this study were performed using the SAS 9.1 statistical package (SAS Institute Inc., NC, USA). $P<0.05$ in 2-tailed tests was considered significant.

Results

We identified 17 075 patients for the HPI group and selected 68 300 participants for the comparison group (Table 1). After frequency matching, both groups had similar sex and age distributions and more men (62.9 %) and younger participants (34.8 %, ≤49 y). Comorbidities were more prevalent in the HPI group than in the non-HPI group ($P<.0001$).

The incidence of ACS was 1.93-fold higher in the HPI group than in the non-HPI group (6.41 vs 3.33 per 1,000 person-years; aHR=1.48, 95 % CI=1.30–1.69) (Table 2). In both groups, the risks of developing HPI were higher for men than for women. Analysis by sex yielded an aHR of 1.38 (95 % CI=1.09–1.76) for the women and 1.53 (95 % CI= 1.31–1.79) for the men, compared with the non-HPI group.

The risks of developing ACS increased with increasing age in both groups, with a much greater gradient in the HPI group. The participants with comorbidities exhibited higher incidences of ACS in both groups (12.2 vs 9.35 per 1,000 person-years), and the HPI group exhibited a higher aHR of 1.53 (95 % CI=1.29–1.80) compared with the non-HPI group.

Table 3 shows that the HPI group was significantly associated with the development of ACS. The risks of developing ACS increased as age increased. The aHR of ACS was 1.63 times higher among men than among women (95 % CI=1.44–1.85). Compared with the participants without comorbidities, patients with comorbidities such as hypertension (aHR=1.59; 95 % CI=1.37–1.84), diabetes (aHR=2.03; 95 % CI=1.75–2.36), hyperlipidemia (aHR=1.59; 95 % CI=1.28–1.97), COPD (aHR=1.41; 95 % CI=1.16–1.71), heart failure (aHR=1.50; 95 % CI=1.12–2.00), and stroke (aHR=1.14; 95 % CI=0.95–1.36) exhibited a greater risk for developing ACS (all $P<0.05$ except for stroke).

We also estimated risk of ACS in relation to HPI, hypertension, diabetes, hyperlipidemia, COPD, and heart failure, and the interaction among these factors (Table 4). The risk of developing ACS in patients with HPI increased with the existence of any comorbidity. HPI was observed to have an interaction with hyperlipidemia ($P=0.009$) and COPD ($P=0.01$). When HPI and hyperlipidemia were present, the aHR was 4.20 (95 % CI=3.19–5.54), compared with the participants without HPI and hyperlipidemia. The aHR was 2.66-fold higher in the HPI patients with COPD than in the non-HPI/non-COPD participants (95 % CI=2.01–3.52).

Table 1 Demographic characteristics and comorbidity in patients with and without helicobacter pylori infection

Variable	Helicobacter pylori infection		*p*-value
	No *N*=68,300	Yes *N*=17,075	
Sex			0.99
Female	25372 (37.2)	6343 (37.2)	
Male	42928 (62.9)	10732 (62.9)	
Age, years			0.99
≤49	23740 (34.8)	5935 (34.8)	
50–64	19916 (29.2)	4979 (29.2)	
65–74	12432 (18.2)	3108 (18.2)	
75+	12212 (17.9)	3053 (17.9)	
Mean (SD) [a]	57.0 (16.9)	57.4 (16.8)	0.005
Comorbidity			
Hypertension	7007 (10.3)	4590 (26.9)	<0.0001
Diabetes	3930 (5.75)	2966 (17.4)	<0.0001
Hyperlipidemia	1360 (1.99)	1374 (8.05)	<0.0001
Stroke	3223 (4.72)	1662 (9.73)	<0.0001
COPD	1951 (2.86)	1304 (7.64)	<0.0001
Heart failure	670 (0.98)	432 (2.53)	<0.0001

[a] Two sample *T*-test; Chi square test

Discussion

We compared patients with HPI matched by age, sex, and history of comorbidities at the baseline, such as hypertension, hyperlipidemia, stroke, COPD, and heart failure. The risk of developing ACS in patients with HPI increased with the presence of any comorbidity. HPI had a synergistic interaction with hyperlipidemia ($P= 0.009$) and COPD ($P=0.01$). The presence of both HPI and hyperlipidemia yielded an aHR of 4.20 (95 % CI=3.19–5.54) compared with participants without HPI and hyperlipidemia. Patients with COPD yielded an aHR 2.66-fold higher than among non-HPI/non-COPD participants (95 % CI=2.01–3.52). After age and other comorbidities were adjusted for, the results of this study suggested an inverse significant biological gradient for the development of the risk of ACS between the HPI and non-HPI groups.

Previous studies [21] on South Korean adults have shown that HPI is associated with cardiovascular risk factors, particularly levels of triglycerides, HDL-cholesterol, and apolipoproteins, independent of the presence of peptic ulcers. A study from India [22] reported that HPI and diabetes exacerbated glucose tolerance and CHD development. The colonization of CagA-positive HP does not seem to be an independent risk factor for severe CHD [27]. Previous studies provided evidence that HPI stimulates a cascade of inflammation, and subsequent immune responses include cellular and humoral immunity between T and B lymphocytes [24, 25], even bacterial colonization, persistence, virulence, and resulting innate and adaptive immunity play a crucial role in HP-related disease [26, 27]. However, HPI may influence atherogenesis through low-grade, persistent inflammatory stimulation [28] and is significantly associated with risk of short-term adverse outcomes [29]. The reduction in restenosis of coronary vessels after HP eradication could be interpreted as evidence of the

Table 2 Incidence rates stratify by sex, age and comorbidity and Cox model measured hazard ratios of ACS for patients compared between with and without *Helicobacter pylori* infection

Variables	*Helicobacter pylori* infection						Crude HR[b] (95 % CI)	Adjusted HR[c] (95 % CI)
	No			Yes				
	Event	PY	Rate[a]	Event	PY	Rate[a]		
All	818	245918	3.33	361	56414	6.40	1.93 (1.70, 2.18)***	1.48 (1.30, 1.69)***
Sex								
Female	240	88859	2.70	108	20724	5.21	1.94 (1.54, 2.43)***	1.38 (1.09, 1.76)**
Male	578	157059	3.68	253	35690	7.09	1.93 (1.66, 2.24)***	1.53 (1.31, 1.79)***
Age, years								
≤49	61	88946	0.69	39	21272	1.83	2.68 (1.80, 4.01)***	1.67 (1.07, 2.61)*
50–64	180	72783	2.47	100	16678	6.00	2.44 (1.91, 3.11)***	1.57 (1.21, 2.05)***
65–74	231	45706	5.05	98	10075	9.73	1.94 (1.53, 2.45)***	1.39 (1.08, 1.78)*
75+	346	38482	8.99	124	8389	14.8	1.65 (1.34, 2.02)***	1.32 (1.07, 1.63)*
Comorbidity								
No	502	212117	2.37	88	34014	2.59	1.09 (0.87, 1.37)	1.33 (1.06, 1.67)*
Yes	316	33801	9.35	273	22401	12.2	1.30 (1.11, 1.53)**	1.53 (1.29, 1.80)***

[a] Incidence rate per 1,000 person-years[b] Relative hazard ratio

[c] Multivariable analysis including adjustment for age, sex, and comorbidities of hypertension diabetes, hyperlipidemia, stroke, COPD and heart failure

*p<0.05, **p<0.01,***p<0.001

involvement of an HP inflammatory process. Kowalski et al. stated that HP-eradication therapy may prolong the hospitalization-free period for patients with recurrent chest pain [30, 31]. Taiwan and other developing and underdeveloped countries [32, 33] have a high prevalence of HPI; thus, the eradication of HPI may reduce the emerging burden of CVD. Investigating more aggressive HPI and treatment for the disease may be necessary. Randomized controlled trials are required to evaluate the role of HP eradication in these patients. PPIs (proton pump inhibitors) have been shown to decrease the antiplatelet effects of clopidogrel ex vivo [34], raising concerns about the cardiovascular safety of this drug combination. Therefore, more caution when using PPIs for HP eradication is necessary.

Table 3 Cox model with hazard ratios and 95 % confidence intervals of ACS associated with *Helicobacter pylori* infection and covariates

Variable	Crude		Adjusted HR[a]	
	HR (95%CI)		HR (95%CI)	
Age, years				
≤49	1	(Reference)	1	(Reference)
50–64	3.46	(2.75, 4.34)***	3.11	(2.47, 3.92)***
65–74	6.52	(5.21, 8.15)***	5.25	(4.18, 6.60)***
75+	11.2	(9.03, 13.9)***	8.24	(6.58, 10.3)***
Sex (female vs. male)	1.36	(1.20, 1.54)***	1.63	(1.44, 1.85)***
Baseline co-morbidities (yes vs. no)				
HP-I	1.93	(1.70, 2.18)***	1.47	(1.29, 1.68)***
Hypertension	4.14	(3.67, 4.67)***	1.59	(1.37, 1.84)***
Diabetes	4.41	(3.86, 5.04)***	2.03	(1.75, 2.36)***
Hyperlipidemia	3.39	(2.78, 4.15)***	1.59	(1.28, 1.97)***
Stroke	3.56	(3.03, 4.18)***	1.14	(0.95, 1.36)
COPD	3.79	(3.15, 4.56)***	1.41	(1.16, 1.71)***
Heart failure	4.62	(3.50, 6.11)***	1.50	(1.12, 2.00)**

[a] Multivariable analysis including adjustment for age, sex, and comorbidities of hypertension diabetes, hyperlipidemia, stroke, COPD and heart failure

**p<0.01, ***p<0.001

This study used NHIRD claims data and as such has several limitations. The NHI database does not disclose patients' personal histories, socioeconomic status, serum laboratory data, smoking status, or inflammatory markers. And the diagnoses of HPI were involved in several different methods, including blood antibody test, stool antigen test, or carbon urea breath test [35]. However, the most reliable protocol for HPI detection is a biopsy check during endoscopy with a rapid urease test, histological examination, and microbial culture which is only one way for requested insurance benefit in the NHIRD of Taiwan. Therefore the investigation of HPI activity or severity might not be accurately determined in claim data. We could not adjust for environmental factors, such as smoking habits, etc. The evidence suggests that smokers have a risk of ACS, which is compatible with the results of other studies [36]. This may account for much of the risk reduction for smoking-related ACS. However, HPI is not directly related to smoking. Data unadjusted for smoking status may reflect this possible relationship more adequately. In several case–

Table 4 Cox proportional hazards regression analysis for observing whether *Helicobacter pylori* infection interact with comorbidity on the risk of ACS

Variables		*N*	Event, *n*	Adjusted HR[a] (95 % CI)	*P*-value[b]
Helicobacter pylori infection	Hypertension				0.62
No	No	61293	600	1 (Reference)	
No	Yes	7007	218	2.08 (1.77, 2.44)***	
Yes	No	12485	168	1.65 (1.39, 1.95)***	
Yes	Yes	4590	193	3.49 (2.96, 4.11)***	
Helicobacter pylori infection	Diabetes				0.05
No	No	64370	668	1 (Reference)	
No	Yes	3930	150	2.75 (2.30, 3.29)***	
Yes	No	14109	220	1.71 (1.47, 2.00)***	
Yes	Yes	2966	141	4.29 (3.57, 5.15)***	
Helicobacter pylori infection	Hyperlipidemia				0.009**
No	No	66940	767	1 (Reference)	
No	Yes	1360	51	2.80 (2.11, 3.73)***	
Yes	No	15701	307	1.89 (1.66, 2.16)***	
Yes	Yes	1374	54	4.20 (3.19, 5.54)***	
Helicobacter pylori infection	COPD				0.01*
No	No	66349	745	1 (Reference)	
No	Yes	1951	73	1.92 (1.50, 2.45)***	
Yes	No	15771	307	1.99 (1.74, 2.27)***	
Yes	Yes	1304	54	2.66 (2.01, 3.52)***	
Helicobacter pylori infection	Heart failure				0.56
No	No	67630	796	1 (Reference)	
No	Yes	670	22	1.78 (1.17, 2.73)**	
Yes	No	16643	331	1.91 (1.68, 2.17)***	
Yes	Yes	4332	30	4.49 (3.11, 6.48)***	

[a] Adjusted for age and sex

[b] P-value for interaction

*p<0.05, **p<0.01, ***p<0.001

control studies for proved association of HPI and ACS, there were less causal relationship evidence for clarification of HPI and ACS. We used the NHIRD to improve the evidence for clinical significance between HPI and ACS [36]. However, we need further approaches to clarify the relationship between different environmental factors, such as drugs, smoking habits and other individual exposed information, to account for the excessive risk for HPI-related ACS after adjustment for common risk factors for ACS. In the future it would be possible to clarify the detailed exposed information and intervening genetic factors of the host by the National Taiwan Biobank [37].

Conclusion

In this study, we determined a significant association between ACS and comorbidities and provide evidence to encourage clinicians to observe ACS-related comorbidities which might improve preventive ACS complications in the HPI population.

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Conflict of interest The authors declare that they have no conflicts of interest.

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