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Impact of *Helicobacter pylori* eradication timing on the risk of thromboembolism events in patients with peptic ulcer disease: a population-based cohort study

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ABSTRACT

Objectives To evaluate the impact of *Helicobacter pylori* eradication on venous thromboembolism (VTE) events, and the differences between early and late treatment timing.

Design A population-based cohort study.

Setting Taiwan's National Health Insurance Research Database.

Participants A total of 6736 patients who received *H. pylori* eradication therapy from 2000 to 2010 were identified. We randomly selected 26 944 subjects matching in gender, age and baseline year as comparison cohort.

Primary and secondary outcome measures The incidence rate ratios of VTE in the *H. pylori* eradication cohorts to that of the control cohort were examined. Multivariable Cox proportional hazard regression analysis was used to estimate the relative HRs and 95% CI of VTE development.

Results The total incidence rate of VTE was observed in the late *H. pylori* eradication cohort, the early *H. pylori* eradication cohort and the control cohort (15.2, 3.04 and 2.91 per 1000 person-years, respectively). An age-specific trend was found in the late *H. pylori* eradication cohort, with a greater rate of VTE in the 50–65 years and more than 65 years age groups (adjusted HR 5.44; 95% CI 4.21 to 7.03 and 3.13; 95% CI 2.46 to 3.99). With comorbidities, the late *H. pylori* eradication cohort seemed to have the highest VTE incidence rate and adjusted HR (4.48, 95% CI 3.78 to 5.30).

Conclusions Late *H. pylori* eradication was associated with a significantly increased risk of VTE, and there was a significantly greater risk of VTE in patients with female gender, age more than 50 years and with comorbidities.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study has a large number of subjects selected from national population database to investigate the effect of *Helicobacter pylori* eradication on venous thromboembolism events.
⇒ Multivariate Cox proportional hazard regression was used to control the confounding factors and elucidate the influence of early or late *H. pylori* treatment on venous thromboembolism events.
⇒ The National Health Insurance database lacked some important information of *H. pylori* treatment, such as the compliance and success or failure of *H. pylori* eradication.

INTRODUCTION

Helicobacter pylori infection is one of the most important infections in humans. Chronic *H. pylori* infection causes chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and gastric cancer.[1] Besides gastric diseases, non-gastric events are also associated with *H. pylori* infection, including cardiovascular diseases, lung diseases, haematological diseases, eye and skin diseases, hepatobiliary diseases, diabetes mellitus and neurological disorders.[2 3] *H. pylori* eradication treatment for diagnosed *H. pylori* infection is the standard of care. In recent decades, the clinical guidelines have seen significant scientific advances regarding the management of *H. pylori* infection.[4]

The issue of post-*H. pylori* eradication requires further investigation. *H. pylori* eradication could improve gastric mucosa atrophy and intestinal metaplasia, decrease peptic ulcer and lower gastric cancer risk, but it exacerbates gastro-oesophageal reflux due to acid.[5] The most promising long-term effect of *H. pylori* eradication could decrease the risk of gastric cancer.[6] *H. pylori* could trigger an inflammatory state and induce molecular mechanisms by expressing virulence peptides. Moreover, *H. pylori* infection interferes with the host absorbance of different nutrients, and potentially influences the host's health outside the gastrointestinal tract. Growing evidence has shown that a variety of conditions and disorders are caused by *H. pylori* infection, such as idiopathic

thrombocytopenic purpura, unexplained iron deficiency anaemia and vitamin B_{12} deficiency. However, the associations of *H. pylori* with certain cardiovascular diseases, neurodegenerative diseases and disorders of the digestive system outside the stomach have yet to be fully elucidated.

There are several effects and related issues following *H. pylori* eradication that have yet to be investigated. An early study demonstrated that *H. pylori* eradication could improve symptoms.[7] There were significant long-term improvements in gastric histology following *H. pylori* eradication when compared with patients with persistent infection.[8] It has been clearly established that *H. pylori* eradication can protect against peptic ulcer recurrence and gastric cancer occurrence.[6 9 10] Besides gastric disorders, *H. pylori* eradication could also cause systemic effects, and several clinical events were found to be associated with *H. pylori* eradication, regardless of whether or not the *H. pylori* pathogenic role was defined.[11–16]

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially lethal acute medical event with high morbidity and mortality.[17 18] *H. pylori* infection may be a risk factor for stroke of atherothrombotic origin or cardiovascular diseases in animals and humans.[7 8] A recent large study of *H. pylori* eradication demonstrated that eradication of *H. pylori* could provide metabolic benefits, improving insulin resistance and lipid profile.[19] *H. pylori* eradication provided not only *H. pylori*-associated pathological events, but also systemic effects, such as thromboembolic events. However, there are few studies on the association of *H. pylori* infection or *H. pylori* eradication with VTE. Moreover, the timely eradication of *H. pylori* infection leads to a better overall health status and better clinical outcomes, as well as the prevention of peptic ulcers and gastric cancer.[20–22] Thus, we aimed to investigate *H. pylori* eradication and the timely effect on VTE events due to the systemic effect of treatment using population-based data.

MATERIALS AND METHODS

Data source

The National Health Insurance (NHI) programme was launched on 1 March 1995 and currently covers almost 99% of Taiwan's 23 million residents. Data from the Longitudinal Health Insurance Database 2000 were provided by Taiwan's National Health Research Institutes, and included information on outpatient and ambulatory visits, hospital inpatient care and dental services.[23] The diagnostic codes in the current study were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Sampled participants

Recruited patients were aged 20 years or above with a history of peptic ulcer disease (ICD-9-CM codes 531, 532 and 533), which was subsequently treated with *H. pylori* eradication therapy. According to the insurance payment rules of the NHI system, the diagnosis of most patients who received *H. pylori*-related treatment was confirmed by upper gastrointestinal endoscopy examination. The treatment of *H. pylori* eradication by triple or quadruple therapy was defined as involving multiple medications as follows: a proton pump inhibitor or H2 receptor blocker, clarithromycin or metronidazole, and amoxicillin or tetracycline, with or without bismuth (details of all eligible *H. pylori* eradication regimens were reported previously).[22] These drug combinations were prescribed in the same order, and the duration of therapy was from 7 to 14 days. The early *H. pylori* eradication cohort was defined as patients receiving *H. pylori* eradication therapy within 1 year of diagnosis of peptic ulcer disease, and the late *H. pylori* eradication cohort was defined as patients receiving *H. pylori* eradication therapy more than 1 year after peptic ulcer diseases were diagnosed. The index date for patients was set as the date that they first received *H. pylori* eradication therapy. The exclusion criteria were missing data regarding date of birth, sex or history of VTE (ICD-9-CM 415.1, 453.8 except 415.11) prior to the index date. For comparison, controls were randomly selected from the pool of participants without peptic ulcer disease who did not receive *H. pylori* eradication therapy. According to age (every 5-year span), sex and year of receiving *H. pylori* eradication therapy, controls were 1:4 frequency matched to each *H. pylori* eradication case.

Patient and public involvement

Taiwan NHI programme is a general population healthcare insurance system covering more than 99% population. NHI was initiated on 1 March 1995 in Taiwan, and is still working well now. The de-identified database included medical records of enrollees registered in the National Health Insurance Research Database (NHIRD). A subset of the NHIRD contains data of 1 million randomly selected enrollees from the NHI programme and was used in this study. The claims data were totally encrypted identification information. The disease codes of the database were identified according to the ICD-9-CM. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Variables of interest

The general diagnostic process of the NHI programme was based on physical examination and quantitative ultrasound. All patients were followed up until a diagnosis of VTE was made or they were censored for loss to follow-up, withdrawal from the NHI programme or 31 December 2011, whichever occurred first. Hypertension, diabetes, hyperlipidaemia, coronary artery disease (CAD), heart failure, cancer, stroke, and lower leg fracture or surgery were considered as covariates.

Statistical analysis

The X^2 test and Student's t-test were used to determine differences in categorical and continuous variables between *H. pylori* eradication (including early and late *H.*

Table 1 Comparison of demographics between gastric disease with *Helicobacter pylori* eradication and controls

	Control	Early eradication	Late eradication	Eradication, overall	
	n=26 944 (%)	n=3062 (%)	n=3674 (%)	n=6736 (%)	P value
Age, years					0.99
≤49	11 432 (42.4)	1616 (52.8)	1242 (33.8)	2858 (42.4)	
50–65	9544 (35.4)	986 (32.2)	1400 (38.1)	2386 (35.4)	
≥65	5968 (22.2)	460 (15.0)	1032 (28.1)	1492 (22.2)	
Mean (SD)*	52.6 (14.9)	49.5 (14.1)	56.0 (14.3)	53.0 (14.6)	0.01
Sex					0.99
Female	12 128 (45.0)	1243 (40.6)	1789 (48.7)	3032 (45.0)	
Male	14 816 (55.0)	1819 (59.4)	1885 (51.3)	3704 (55.0)	
Comorbidity					
Hypertension	7890 (29.3)	868 (28.4)	1721 (46.8)	2589 (38.4)	<0.001
Diabetes	2358 (8.75)	298 (9.73)	541 (14.7)	839 (12.5)	<0.001
Hyperlipidaemia	5354 (19.9)	656 (21.4)	1450 (39.5)	2106 (31.3)	<0.001
CAD	3573 (13.3)	434 (14.2)	1224 (33.3)	1658 (24.6)	<0.001
Heart failure	728 (2.70)	56 (1.83)	217 (5.91)	273 (4.05)	<0.001
Cancer	640 (2.38)	71 (2.32)	156 (4.25)	227 (3.37)	<0.001
Stroke	855 (3.17)	77 (2.51)	222 (6.04)	299 (4.44)	<0.001
Low leg fracture or surgery	580 (2.15)	48 (1.57)	126 (3.43)	174 (2.58)	0.03

*Two-sample t-test.
CAD, coronary artery disease.

pylori eradication therapy) and control cohorts. The incidence density rate of VTE was calculated for each instance of early *H. pylori* eradication therapy, late *H. pylori* eradication therapy and for the control cohort. The incidence rate ratios of VTE in the *H. pylori* eradication cohorts to that of the control cohort and the 95% CI were estimated using a Poisson regression model. The relative HRs and 95% CIs of VTE development for the *H. pylori* eradication cohorts were estimated with multivariable Cox proportional hazard regression analysis adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, CAD, heart failure, cancer, stroke, and lower leg fracture or surgery. All data analyses were performed using the SAS statistical package (V.9.4 for Windows; SAS Institute). A two-tailed p<0.05 indicated statistical significance.

RESULTS

Demographic data

From 2000 to 2010, a total of 6736 subjects received *H. pylori* eradication treatment, including 3062 patients who received early *H. pylori* eradication (early eradication cohort), and 3674 patients who received late *H. pylori* eradication (late eradication cohort). There were 26 944 subjects who served as the control cohort for comparison. The demographic data are shown in table 1. There were differences in age among the three cohorts: early eradication, late eradication and control (49.5±14.1, 56.0±14.3, 52.6±14.9; p=0.01). There were no differences in gender ratios among the three cohorts. The late *H. pylori* eradication cohort had more comorbidities compared with the early eradication and control cohorts.

HR and incidence rate of VTE

In table 2, it can be seen that there was no significant difference in risk of VTE between the early *H. pylori* eradication cohort and control cohort. The total incidence rates of VTE were determined for the late *H. pylori* eradication cohort, the early *H. pylori* eradication cohort and the control cohort (15.2, 3.04 and 2.91 per 1000 person-years, respectively). With respect to gender, VTE incidence was higher in the late *H. pylori* eradication cohort in men and women, and female gender in the late *H. pylori* eradication cohort had the highest incidence rate (20.5 per 1000 person-years). The age-specific trend in the late *H. pylori* eradication cohort was found to be greater in the 50–65 years and more than 65 years age groups (adjusted HR 5.44; 95% CI 4.21 to 7.03 and 3.13; 95% CI 2.46 to 3.99). The VTE incidence was lower in the early eradication cohort with more than 65 years old (adjusted HR 0.21; 95% CI 0.08 to 0.56). The early *H. pylori* eradication cohort seemed to have a lower risk of VTE compared with the late *H. pylori* eradication cohort. Regarding comorbidities, the late *H. pylori* eradication cohort seemed to have the highest VTE incidence rate and adjusted HR (4.48, 95% CI 3.78 to 5.30).

HRs of late and early *H. pylori* eradication

Table 3 shows that the risk of VTE was significantly higher in the late *H. pylori* eradication cohort than in the early

Table 2 HRs of venous thromboembolism between control subjects and early or late *Helicobacter pylori* eradication

	Control (N=26 944)		Early eradication (N=3062)			Adjusted HR	Late eradication (N=3674)			Adjusted HR†
	Event	Rate*	Event	Rate*	IRR (95% CI)	(95% CI)	Event	Rate*	IRR (95% CI)	(95% CI)
All	414	2.91	54	3.04	1.04 (0.93 to 1.18)	1.12 (0.84 to 1.49)	272	15.2	5.22 (4.90 to 5.57)‡	3.91 (3.33 to 4.59)‡
Gender										
Female	220	3.46	23	3.14	0.91 (0.75 to 1.10)	0.96 (0.62 to 1.48)	171	20.5	5.92 (5.40 to 6.48)‡	4.39 (3.54 to 5.43)‡
Male	194	2.47	31	2.97	1.20 (1.04 to 1.39)‡	1.29 (0.88 to 1.89)	101	10.6	4.29 (3.91 to 4.71)‡	3.13 (2.43 to 4.03)‡
Age										
≤49	83	1.27	28	2.82	2.23 (1.96 to 2.53)‡	2.07 (1.34 to 3.18)‡	12	1.83	1.45 (1.21 to 1.73)‡	1.29 (0.69 to 2.41)
50–65	138	2.83	22	4.10	1.45 (1.19 to 1.76)‡	1.43 (0.91 to 2.24)	145	22.1	7.78 (7.04 to 8.61)‡	5.44 (4.21 to 7.03)‡
≥65	193	6.92	4	1.62	0.23 (0.14 to 0.40)‡	0.21 (0.08 to 0.56)‡	115	24.2	3.50 (3.09 to 3.96)‡	3.13 (2.46 to 3.99)‡
Comorbidity										
No	133	1.51	26	2.42	1.61 (1.42 to 1.82)‡	1.78 (1.17 to 2.72)§	13	2.01	1.33 (1.12 to 1.58)‡	1.49 (0.84 to 2.64)
Yes	281	5.20	28	3.98	0.77 (0.63 to 0.94)§	0.82 (0.55 to 1.21)	259	22.7	4.36 (4.00 to 4.76)‡	4.48 (3.78 to 5.30)‡

*Incidence rate per 1000 person-years.
†Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
‡P<0.001.
§P<0.01.
IRR, incidence rate ratio.

Table 3 HRs of venous thromboembolism between early and later *Helicobacter pylori* eradication

	Early eradication		Late eradication	
	IRR (95% CI)	Adjusted HR* (95% CI)	IRR (95% CI)	Adjusted HR* (95% CI)
All	1 (reference)	1 (reference)	5.00 (4.25 to 5.90)†	3.56 (2.63 to 4.81)†
Gender				
Female	1 (reference)	1 (reference)	6.52 (4.98 to 8.54)†	4.05 (2.57 to 6.38)†
Male	1 (reference)	1 (reference)	3.57 (2.91 to 4.38)†	2.83 (1.86 to 4.31)†
Age				
≤49	1 (reference)	1 (reference)	0.65 (0.51 to 0.82)†	0.84 (0.43 to 1.67)
50–65	1 (reference)	1 (reference)	5.37 (4.03 to 7.17)†	3.50 (2.18 to 5.60)†
≥65	1 (reference)	1 (reference)	14.9 (7.77 to 28.7)†	16.5 (6.05 to 45.3)†
Comorbidity				
No	1 (reference)	1 (reference)	0.83 (0.66 to 1.05)	0.83 (0.42 to 1.62)
Yes	1 (reference)	1 (reference)	5.70 (4.41 to 7.37)†	5.38 (3.64 to 7.97)†

*Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
†P<0.00.
IRR, incidence rate ratio.

H. pylori eradication cohort (adjusted HR 3.56, 95% CI 2.63 to 4.81). The risk of VTE was significantly greater for both genders, and women had a significantly higher risk compared with men. The age-specific adjusted HR of VTE in the late *H. pylori* eradication cohort compared with the early *H. pylori* eradication cohort was not significant for the younger group (adjusted HR 0.84; 95% CI 0.43 to 1.67). Without comorbidities, the difference of adjusted HR between the late *H. pylori* eradication cohort and the early eradication cohort was not significant (0.83, 95% CI 0.42 to 1.62).

Incidences and adjusted HRs of DVT and PE, according to follow-up period, in the *H. pylori* eradication patients compared with the control patients

Furthermore, we compared incidence densities and HRs of VTE among three cohorts by follow-up duration (table 4). The incidence of VTE was greater in the late *H. pylori* eradication cohort when follow-up duration ≤5 years (25.4 per 1000 person-years). The highest risk occurred during the >5 years of follow-up period (adjusted HR 7.92, 95% CI 4.27 to 14.7) in the late *H. pylori* eradication cohort compared with the early eradication cohort.

DISCUSSION

Our results showed that the timing of *H. pylori* eradication significantly affected risk of VTE. There was a significantly greater risk of late *H. pylori* eradication for VTE for female gender, age over 50 years and with comorbidities.

It is possible that *H. pylori* initiates an inflammatory process in the stomach and may even generate a systemic response throughout the host. *H. pylori* eradication therapy could effectively prevent the progression of the pathological process in the gastric mucosa. The patient may also experience systemic effects, beyond the stomach, from *H. pylori* eradication. The association between *H. pylori* and VTE may not be strong, which would explain why our results showed no significant difference in risk of VTE between the early *H. pylori* eradication and control cohorts. However, late *H. pylori* eradication, particularly with comorbidities, showed a significantly increased risk of VTE compared with early *H. pylori* eradication. The timely eradication of the infection would likely lead to better health status in an *H. pylori*-infected population, not only with respect to prevention of peptic ulcers and gastric cancer, but also in terms of risk of VTE, as shown in the present study.

H. pylori may be an independent risk factor for atherothrombotic events in animals and humans.[24 25] Infection with *H. pylori* did not appear to be associated with DVT in a specific disease.[26] *H. pylori* eradication therapy could cause more extensive beneficial effects, regardless of any relationship with *H. pylori*. Eradicating *H. pylori* infection is currently the standard of care, and could ultimately cause more good than harm. Beyond peptic ulcer recurrence and cancer occurrence, *H. pylori* eradication could cause systemic effects, such as metabolic and inflammatory processes.[14 15] While the association of *H. pylori* and clinical conditions is not directly correlated, *H. pylori* eradication may cause systemic changes within the host that are not immediately apparent. Previous studies were primarily concerned with how *H. pylori* could affect systems within the body, including cardiovascular diseases, neurological disorders, diabetes mellitus, ear and eye diseases, immunological and haematological disorders, liver and bile tract diseases, and gynaecological and respiratory

Table 4 Trends of venous thromboembolism risks by stratified follow-up years

Follow-up time, years	Control (N=26944)		Early eradication (N=3062)		IRR (95% CI)	Adjusted HR† (95% CI)	Late eradication (N=3674)		IRR (95% CI)	Adjusted HR† (95% CI)
	Case	Rate*	Case	Rate*			Case	Rate*		
≤5	216	2.08	42	3.41	1.64 (1.46 to 1.84)‡	1.92 (1.38 to 2.68)‡	165	12.1	5.81 (5.41 to 6.24)‡	4.21 (3.41 to 5.20)‡
>5	198	5.19	12	2.21	0.43 (0.33 to 0.54)‡	0.44 (0.24 to 0.78)‡	107	25.4	4.90 (4.45 to 5.40)‡	3.45 (2.69 to 4.43)‡
≤5					1 (reference)	1 (reference)			3.54 (3.00 to 4.18)‡	2.41 (1.70 to 3.41)‡
>5					1 (reference)	1 (reference)			11.5 (8.43 to 15.8)‡	7.92 (4.27 to 14.7)‡

*Incidence rate per 1000 person-years.
†Multiple analyses including age, sex, and comorbidities of hypertension, diabetes, hyperlipidaemia, coronary artery disease, heart failure, cancer, stroke, and lower leg fracture or surgery.
‡P<0.001.
IRR, incidence rate ratio.

tract diseases.[27 28] Prophylactic eradication therapy is thus considered the standard of care even for extra-gastric diseases. Our results demonstrated that *H. pylori* eradication treatment was associated with VTE, and delayed *H. pylori* eradication was a risk for VTE. *H. pylori* infection may not directly cause VTE events, but late *H. pylori* eradication could be a risk factor for VTE. The processes underlying this phenomenon are unclear, but several possible mechanisms have been suggested. *H. pylori* eradication therapy could have beneficial systemic effects. In addition, a recent study reported that *H. pylori* eradication could lead to changes in the gut microbiome.[29]

In the present study, there was no significant difference in risk of VTE between the early *H. pylori* eradication and control cohort. Early *H. pylori* eradication is associated with decreased risk of VTE especially in the aged patients more than 65 years. After 8 weeks of *H. pylori* eradication, some metabolic benefits on improvement of insulin resistance and lipid profile were reported. Improved metabolic parameter may decrease the risk of VTE. Thus, early eradication of *H. pylori* is recommended.

In the present study, our findings demonstrated differences in VTE risk after early or late *H. pylori* eradication. However, there were limitations in this study. First, the compliance of *H. pylori* eradication for each patient in this study was unknown. We can therefore only assume that patients receiving a prescribed *H. pylori* eradication regimen were fully compliant and completed the course of medications. It is known that the treatment regimen for *H. pylori* eradication may cause mild or severe adverse effects, and therefore, some patients may not have completed the course of treatment. Second, the dataset used in this study did not contain information on the success or failure of *H. pylori* eradication. As such, it was only possible to estimate the general success rate of *H. pylori* eradication. Third, the adherence of post-treatment follow-up and the re-infection rate could not be demonstrated in the database. Finally, the database could not provide the information about usage of other medications, such as hormone therapy or anticoagulant. Those medications might affect the occurrence of VTE.

Besides gastric diseases and cancers, *H. pylori* infection could cause non-gastric systemic effects in humans. *H. pylori* eradication is currently the standard of treatment for preventing recurrence of peptic ulcer diseases and occurrence of cancer. There may be unexpected effects resulting from *H. pylori* eradication. Further study is needed to gain a more comprehensive understanding of the systemic insults and molecular mechanisms involved in *H. pylori* eradication.

CONCLUSIONS

Late *H. pylori* eradication was associated with a significantly increased risk of VTE. The risk of VTE was significantly greater in patients with female gender, age more than 50 years and with comorbidities. Therefore, we recommended administering *H. pylori* eradication therapy early.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of China Medical University and Hospital (CMUH104-REC2-115). The need for informed consent was waived by the IRB of China Medical University.

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