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Does *Helicobacter pylori* Eradication Reduce the Risk of Open Angle Glaucoma in Patients With Peptic Ulcer Disease?

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Abstract: To investigate whether *Helicobacter pylori* (*H pylori*) eradication would influence the risk of primary open angle glaucoma (POAG) in patients with peptic ulcer disease.

From the Longitudinal Health Insurance Database 2000, 6061 patients with peptic ulcer and receiving *H pylori* eradication therapy were recruited. The study cohort was subdivided into early (within 1 year) and late (after 1 year) eradication cohorts. The 24,244 control cohort subjects were those who without peptic ulcer and without receiving *H pylori* eradication therapy and were frequency-matched with the *H pylori* eradication cohort by age, sex, and the year of receiving *H pylori* eradication therapy.

The higher incidence of POAG was observed in late *H pylori* eradication cohort and in early *H pylori* eradication cohort than in control cohort (1.57, 1.32, and 0.95, per 1000 person-year, respectively). However, overall risk of glaucoma was not significantly higher in the late eradication than in the early eradication (adjusted hazard ratio = 0.85, 95% confidence interval = 0.48–1.53). The POAG incidence was greater in the late *H pylori* eradication cohort when follow-up duration ≤5 years (1.59, per 1000 person-years). However, when follow-up duration >5 years, the incidence of POAG was greater in the early *H pylori* eradication cohort (1.68, per 1000 person-years). These relationships were not associated with a significantly increased or decreased risk of POAG in multivariable analyses.

Either early or late *H pylori* eradication does not significantly reduce the risk of glaucoma in patients with peptic ulcer disease compared with normal control.

(*Medicine* 94(39):e1578)

Abbreviations: aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, *H pylori* = *Helicobacter pylori*, HR = hazard ratio, IRB = Institutional Review Board, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = Taiwan National Health Insurance, NHIRD = National Health Insurance Research Database, POAG = primary open angle glaucoma.

INTRODUCTION

Glaucoma is the leading cause of blindness, but many pathogenesis remain to be clarified.[1] *Helicobacter pylori* infection has been noted to play some role in pathogenesis of glaucoma.[1,2] Some molecular mechanisms were proposed to explain the relationship between glaucoma and *H pylori* infection,[3] including proinflammatory and vasoactive materials release, platelet and platelet-leukocyte aggregation promotion, and apoptotic cascades influence.[4–7]

Previous studies provide important evidence for the potential roles of *H pylori* infection in glaucoma pathogenesis; however, there is still no clear answer as to whether *H pylori* eradication therapy prevents future glaucoma development.[4,8] Based on the hypothesis that *H pylori* eradication may be a feasible method for glaucoma prevention, we conducted a population-based retrospective cohort study of patients with peptic ulcer disease who received *H pylori* eradication therapy over a 10-year period. The primary outcome of interest was whether early *H pylori* eradication is associated with decreased risk of primary open angle glaucoma (POAG) in patients with peptic ulcer disease.

METHODS

Data Source

This retrospective cohort study was retrieved from the Longitudinal Health Insurance Database (LHID2000), derived

TABLE 1. Comparison of Demographics and Comorbidity Between Gastric Disease With *H pylori* Eradication and Controls

	Control (N = 24,244)		Early HP Eradication (N = 2876)		Late HP Eradication (N = 3185)		Total (N = 6061)		P Value
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Age, yr									0.99
≤49	10,696	(44.1)	1522	(52.9)	1152	(36.2)	2674	(44.1)	
50–65	8344	(34.4)	919	(32.0)	1167	(36.6)	2086	(34.4)	
≥65	5204	(21.5)	435	(15.1)	866	(27.2)	1301	(21.5)	
Mean (SD)*	52.0	(14.9)	49.4	(14.1)	55.3	(14.4)	52.5	(14.6)	0.02
Sex									0.99
Female	10,624	(43.8)	1159	(40.3)	1497	(47.0)	2656	(43.8)	
Male	13,620	(56.2)	1717	(59.7)	1688	(53.0)	3405	(56.2)	
Comorbidity									
Hypertension	6558	(27.1)	756	(26.3)	1332	(41.8)	2088	(34.5)	<0.001
Diabetes	1989	(8.20)	267	(9.28)	432	(13.6)	699	(11.5)	<0.001
Hyperlipidemia	3966	(16.4)	549	(19.1)	1076	(33.8)	1625	(26.8)	<0.001
CAD	2641	(10.9)	350	(12.2)	866	(27.2)	1216	(20.1)	<0.001

Chi-squared test and Fisher's exact test compared to total gastric Disease.
CAD = coronary artery disease; HP = *Helicobacter pylori*; SD = standard deviation.
* Two sample *t* test.

from the Taiwan National Health Insurance (NHI) program. The NHI program, launched in 1995, covers more than 99% of the population, which is currently 23 million (http://www.nhi.gov.tw/english/index.aspx). This mandatory universal program offers comprehensive medical coverage, including outpatient, inpatient, emergency, dental, and traditional Chinese medicine services and prescription drugs, to all Taiwanese residents. The LHID2000 contained 1 million insurant randomly selected from the year 2000 Registry for Beneficiaries under the NHI program. This secondary dataset was encrypted prior to its release for research purposes to protect privacy. The study was approved from full review by the Institutional Research Ethic Committee (CMU-REC-101–012). Diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Sampled Participants

From the LHID 2000, patients who were diagnosed of peptic ulcer (ICD-9-CM codes: 531, 532, and 533) and received *H pylori* eradication therapy at the same time were recruited. *Helicobacter pylori* eradication with triple or quadruple therapy was defined as proton pump inhibitor or H2 receptor blocker, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without Bismuth (details for all eligible *H pylori* eradication regimens are reported previously).[9] These drug combinations were prescribed within the same prescription order, and the duration of therapy was between 7 and 14 days. One year was chosen as the cutoff value based on the distribution of *H pylori* eradication date after diagnosed of peptic ulcer. Patients who received *H pylori* eradication therapy within the first year after the diagnosis of peptic ulcer were included in the "early eradication cohort." Patients included in the "late eradication cohort" were given *H pylori* eradication therapy 1 year or more after diagnosed of peptic ulcer. The date of the first received *H pylori* eradication therapy was used as the index date. We excluded patients diagnosed with POAG (ICD-9-CM 365.1) at the baseline and <20 years old and those without information on age and sex. Fourfold of control patients were

randomly selected from LHID 2000 beneficiaries without peptic ulcer and without receiving *H pylori* eradication therapy and applied the same exclusion criteria used in selecting *H pylori* eradication cohort. The control cohort patients were frequency-matched with the *H pylori* eradication cohort by age (every 5-year span), sex, and the year of receiving *H pylori* eradication therapy.

Outcome and Comorbidities

All patients were followed up until a diagnosis of POAG, loss to follow-up, death, the date of withdrawing from the insurance, and the end of 2011, whichever date came first. We considered several well-known risk factors of POAG including hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD) (ICD-9-CM codes 410–414), to be the comorbidities.

Statistical Analysis

The differences between the covariates of the *H pylori* eradication and control cohorts were analyzed using the Chi-squared test for categorical variables or *t* test for continuous variables. The incidence of POAG was calculated for each *H pylori* eradication subgroup (early and late) and for the control cohort. Poisson regression model was used to assess glaucoma incidence rate ratios (IRRs) for *H pylori* eradication cohort when compared to control cohort. Multivariable Cox proportional hazard regression analysis was performed to estimate the relative hazard ratios (HRs) of POAG development for *H pylori* eradication cohort with adjustment of age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, and CAD when compared with the control cohort. The risk changed over time was further evaluated by stratifying the follow-up duration into 2 periods (≤5 and >5 years), with both IRR and HR measured for *H pylori* eradication cohort when compared with control cohort. All models were also used to estimate the risk of POAG for late *H pylori* eradication cohort when compared with the early

H pylori eradication cohort. All analyses were performed using the SAS statistical package (version 9.2 for Windows; SAS Institute, Inc., Cary, NC). A 2-tailed *P* value of <0.05 indicated the statistical significance level.

RESULTS

In total, we included 6061 subjects receiving *H pylori* eradication therapy, among whom 2876 were early *H pylori* eradication cohort, and 3185 were late *H pylori* eradication cohort. The control cohort consisted of 24,244 subjects. The baseline characteristics of the patients in the 3 cohorts are presented in Table 1. Among the 3 cohorts, the majority of patients were <49 years (52.9% in early *H pylori* eradication, 36.2% in late *H pylori* eradication, and 44.1% in control cohort, respectively) and were male (59.7% in early *H pylori* eradication, 53.0% in late *H pylori* eradication, and 56.2% in control cohort, respectively). The mean age was 52.5 ± 14.6 years in the *H pylori* eradication cohort and 52.0 ± 14.9 years in the control cohort. Compared with the control cohort, the *H pylori* eradication cohort was more likely to have all of the listed comorbidities in Table 1. Compared with the patients in early *H pylori* eradication, those in late *H pylori* eradication were more likely to have comorbidities. The mean duration of follow-up for control cohort was 6.71 years, approximately 0.5 year longer than that for early *H pylori* eradication (6.08 years), and late *H pylori* eradication (6.26 years) (data not shown).

The higher incidence of POAG was observed in the late *H pylori* eradication cohort and in the early *H pylori* eradication cohort than in the control cohort (1.57, 1.32, and 0.95, per 1000 person-year, respectively; Table 2). The POAG incidence was greater in women in the late *H pylori* eradication cohort (2.10, per 1000 person-year). The glaucoma incidence increased with age in all 3 cohorts. The age-specific early *H pylori* eradication to control relative risk was greater for the ages 50 to 65 years (adjusted HR = 1.94; 95% confidence interval [CI] = 1.05–3.60). The glaucoma incidence increased with comorbidity in all 3 cohorts. We further analyzed the association between late *H pylori* eradication and the risk of POAG stratified by comorbidity and the result shows that 2.93-fold of POAG risk was significantly observed in patients without comorbidity (95% CI = 1.52–5.64).

Table 3 shows that the overall risk of glaucoma was not significantly higher in late *H pylori* eradication cohort than in early *H pylori* eradication cohort (adjusted HR = 0.85, 95% CI = 0.48–1.53). The age-specific adjusted HR of glaucoma in the late *H pylori* eradication cohort to early *H pylori* eradication cohort was not significant for the younger group (adjusted HR = 3.68; 95% CI = 0.95–14.3). Furthermore, we compared incidence densities and HRs of POAG among 3 cohorts by follow-up duration (Table 4). The incidence of glaucoma was greater in the late *H pylori* eradication cohort when follow-up duration ≤5 years (1.59, per 1000 person-years). On the contrary, when follow-up duration >5 years, the incidence of POAG was greater in the early *H pylori* eradication cohort (1.68, per 1000 person-years). However, these relationships were not associated with a significantly increased or decreased risk of POAG in multivariable analyses.

DISCUSSION

The risk of glaucoma among patients with *H pylori* infection has been widely studied. Higher prevalence of *H pylori* infection was found in the sera of patients with POAG and PXFG patients compared with control group.[5] A possible

association between *H pylori* infection and glaucoma was supported again that glaucoma-related parameters were improved in the subgroup of patients in whom *H pylori* eradication was successful.[8] There are additional published data further reinforcing the association glaucoma and *H pylori* infection in other ethnicities, including Greece, Turkey, Iran, Korea, India, and China, by using serology, aqueous humor and anti-*H pylori* IgG antibodies and/or histology.[10–12] In Zavos's study,[12] *H pylori* bacteria have been detected histologically in eye biopsies of POAG patients. On the contrary, in a Canadian study, the authors suggest *H pylori* infection is not associated with POAG based on serum test.[13] And in a Israel study,[14] no association between *H pylori* infection or CagA-bearing strains and glaucoma was noted. Because of different study designs and methods, it is not suitable to directly compare the outcomes among all these studies. Here, in our study, we aim to clarify the role of *H pylori* infection in glaucoma; therefore, the study cohort was subdivided into 2: early eradication cohort (2876 subjects) and late eradication cohort (3185 subjects). Logically, early eradication cohort should have shorter period of *H pylori* exposure time than late eradication cohort. Slightly higher incidence of POAG was observed in the late *H pylori* eradication cohort and in the early *H pylori* eradication cohort than in the control cohort (1.57, 1.32, and 0.95, per 1000 person-year, respectively). This finding first confirms our hypothesis that longer period of *H pylori* exposure would have slightly higher POAG risk compared to shorter period exposure of *H pylori*. The glaucoma incidence increased with age and with comorbidity in all 3 cohorts. The age-specific early *H pylori* eradication to control relative risk was greater for the ages 50 to 65 years (adjusted HR = 1.94; 95% CI = 1.05–3.60). We further analyzed the association between late *H pylori* eradication and the risk of POAG stratified by comorbidity, and the result shows that 2.93-fold of POAG risk was significantly observed in patients without comorbidity (95% CI = 1.52–5.64). This result again supports our presumed thought that longer exposure of *H pylori* would increase POAG risk even without the effect of comorbidity.

Interesting finding was noted that the overall risk of glaucoma was not significantly higher in late *H pylori* eradication cohort than in early *H pylori* eradication cohort (adjusted HR = 0.85, 95% CI = 0.48–1.53); and the age-specific adjusted HR of glaucoma in the late *H pylori* eradication cohort was not significant higher for the younger group (adjusted HR = 3.68; 95% CI = 0.95–14.3) when compared to early *H pylori* eradication cohort. All these results suggest that glaucoma risk was not significantly different between early eradication cohort and late eradication cohort.

To understand whether different follow-up duration would influence glaucoma risk, further analysis was performed. Logically, follow-up duration means the *H pylori* exposure duration. Although incidence of POAG was greater in the late *H pylori* eradication cohort when follow-up duration ≤5 years (1.59, per 1000 person-years) and was greater in the early *H pylori* eradication cohort (1.68, per 1000 person-years) when follow-up duration >5 years. However, all these results were not associated with a significantly increased or decreased risk of POAG in multivariable analyses. Again, POAG risk was not significantly different related to the follow-up duration (*H pylori* exposure duration).

To solve the hypothesis if *H pylori* eradication plays some role in glaucoma treatment, the optimal timing for eradication is an important issue. Although our result infers the slightly higher risk of POAG in *H pylori* eradication cohort but not achieve

TABLE 2. Hazard Ratios of Glaucoma Between Gastric Disease With Late HP Eradication and Control Subjects as Well as Gastric Disease With Early HP Eradication and Control Subjects Stratified by Demographics and Comorbidity

	Control (N=24,244)		Early HP Eradication (N=2876)				Late HP Eradication (N=3185)			
	Case	Rate†	Case	Rate†	IRR (95% CI)	Adjusted HR‡ (95% CI)	Case	Rate†	IRR (95% CI)	Adjusted HR‡ (95% CI)
All	127	0.95	23	1.32	1.40 (1.24, 1.57)***	1.45 (0.92, 2.26)	26	1.57	1.66 (1.49, 1.86)***	1.22 (0.80, 1.88)
Gender										
Female	53	0.90	8	1.12	1.24 (1.02, 1.51)*	1.23 (0.59, 2.60)	16	2.10	2.33 (2.01, 2.70)***	1.72 (0.97, 3.05)
Male	74	0.98	15	1.46	1.49 (1.29, 1.73)***	1.60 (0.92, 2.80)	10	1.12	1.14 (0.96, 1.36)	0.84 (0.43, 1.65)
Age										
≤49	27	0.42	3	0.31	0.73 (0.58, 0.92)*	0.72 (0.22, 2.36)	7	1.09	2.59 (2.20, 3.03)***	2.31 (0.99, 5.37)
50–65	50	1.12	13	2.47	2.20 (1.86, 2.60)***	1.94 (1.05, 3.60)*	8	1.36	1.21 (0.98, 1.48)	0.97 (0.45, 2.07)
≥65	50	1.92	7	2.95	1.53 (1.17, 2.01)**	1.37 (0.62, 3.04)	11	2.59	1.35 (1.08, 1.69)**	1.11 (0.57, 2.16)
Comorbidity										
No	47	0.52	10	0.89	1.70 (1.47, 1.97)***	1.88 (0.95, 3.74)	11	1.50	2.88 (2.51, 3.31)***	2.93 (1.52, 5.64)**
Yes	80	1.81	13	2.12	1.17 (0.97, 1.42)	1.28 (0.71, 2.31)	15	1.63	0.90 (0.75, 1.08)	0.89 (0.51, 1.55)

CI = confidence interval; HP = *Helicobacter pylori*; HR = hazard ratio; IRR = incidence rate ratio.
†Rate, incidence rate, per 1000 person-years.
‡Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, and coronary artery disease.
*P < 0.05, **P < 0.01, ***P < 0.001.

TABLE 3. Hazard Ratios of Glaucoma Between All Gastric Disease Patients With Early HP Eradication and With Late HP Eradication Stratified by Demographic Characteristics and Comorbidity

	Early HP Eradication		Late HP Eradication	
	IRR (95% CI)	Adjusted HR[†] (95% CI)	IRR (95% CI)	Adjusted HR[†] (95% CI)
All	1 (Reference)	1 (Reference)	1.19 (1.00, 1.41)[*]	0.85 (0.48, 1.53)
Gender				
Female	1 (Reference)	1 (Reference)	1.87 (1.43, 2.46)[***]	1.48 (0.62, 3.53)
Male	1 (Reference)	1 (Reference)	0.77 (0.61, 0.97)[*]	0.52 (0.22, 1.18)
Age				
≤49	1 (Reference)	1 (Reference)	3.55 (2.66, 4.76)[***]	3.68 (0.95, 14.3)
50–65	1 (Reference)	1 (Reference)	0.55 (0.41, 0.73)[***]	0.52 (0.21, 1.29)
≥65	1 (Reference)	1 (Reference)	0.88 (0.61, 1.27)	0.77 (0.29, 2.00)
Comorbidity				
No	1 (Reference)	1 (Reference)	1.69 (1.33, 2.14)[***]	1.48 (0.62, 3.51)
Yes	1 (Reference)	1 (Reference)	0.77 (0.60, 0.98)[*]	0.62 (0.29, 1.32)

CI = confidence interval; HP = *Helicobacter pylori*; HR = hazard ratio; IRR = incidence rate ratio.
[†]Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, and coronary artery disease
[*]$P < 0.05$, [***]$P < 0.001$.

statistically meaningful result compared to normal controls, glaucoma risk is not significantly different among 3 cohorts. This finding has important value because it is the few one which addressed the risk of POAG and *H pylori* eradication in patients with peptic ulcer disease based on a large nationalized health insurance database in a Chinese population. Based on some limitations of present study design and method, it is a pity that we could not achieve definite conclusion regarding the role of *H pylori* eradication in glaucoma treatment.

There are several limitations to our study. First, our observations were a retrospective cohort study based on claimed database from Taiwan NHIRD. Certain selection biases may exist, and caution must be taken in extrapolating our results to other ethnic populations. Second, the definitions of early and late eradication cohorts (1 year) was referred from another published work also from Taiwan NHIRD.[9] Different definition

for early or late should have different outcome. Third, we did not analyze the relative risk of glaucoma in patients with peptic ulcer diseases without *H pylori* eradication therapy. According to our observations about general clinical practice pattern in Taiwan, patients with *H pylori* infection almost receive eradication therapy; therefore, the *H pylori* infection case without eradication therapy is quite few. Fourth, we were unable to get data to verify whether *H pylori* eradication was effective based on this database. Therefore, we can only calculate and compare the IRRs and HRs in early and late eradication cohorts, not among those in whom *H pylori* was eradicated and not eradicated.[9] As we know so well that eradication therapy with proton pump inhibitor, clarithromycin and amoxicillin has been extensively used for years, although it fails in a considerable percentage of patients.[15] Also in a community-based study from Taiwan, the eradication rate was around 86.9%.[16] Although we

TABLE 4. Trends of Glaucoma Risks by Stratified Follow-Up Years

Follow-Up Time, yr	Control (N = 24,244)		Early HP Eradication (N = 2876)				Late HP Eradication (N = 3185)			
	Case	Rate[†]	Case	Rate[†]	IRR (95% CI)	Adjusted HR[‡] (95% CI)	Case	Rate[†]	IRR (95% CI)	Adjusted HR[‡] (95% CI)
≤5	93	0.95	14	1.16	1.22 (1.07, 1.39)[**]	1.27 (0.72, 2.23)	20	1.59	1.68 (1.50, 1.87)[***]	1.21 (0.74, 1.99)
>5	34	0.94	9	1.68	1.80 (1.55, 2.10)[***]	1.84 (0.88, 3.86)	6	1.51	1.62 (1.35, 1.94)[***]	1.24 (0.51, 3.02)
≤5					1 (Reference)	1 (Reference)			1.37 (1.14, 1.64)[***]	0.79 (0.45, 1.38)
>5					1 (Reference)	1 (Reference)			0.90 (0.69, 1.18)	0.54 (0.26, 1.14)

CI = confidence interval; HP = *Helicobacter pylori*; HR = hazard ratio; IRR = incidence rate ratio.
[†]Rate, incidence rate, per 1000 person-years.
[‡]Adjusted HR: multiple analysis including age, sex, and co-morbidities of hypertension, diabetes, hyperlipidemia, and coronary artery disease.
[**]$P < 0.01$, [***]$P < 0.001$.

suppose the failure rates of early and late eradication cohorts should be similar, the influence of the uncalculated failure rates may still bias the statistics. However, this is an inevitable study limitation in this kind of claims database study. Fifth, the glaucoma definition was completely relied on ICD coding (365.1) based on NHIRD; and it is potentially not completely accurate. Miscoding problem might exist in this study.

In conclusion, in this nationwide, long-term cohort study, glaucoma risk is not significant different among normal population, early eradication cohort and late eradication cohort. The role of *H pylori* eradication in glaucoma treatment is not yet clear based on the current result, further large-scale prospective study should be carried on to further elucidate this important issue.

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