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Helicobacter pylori infection and gastroduodenal diseases in Vietnam: a cross-sectional, hospital-based study

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Abstract

Background: The rate of *H. pylori* infection in Vietnam is reportedly high, but the spectrum of *H. pylori*-associated gastroduodenal diseases has not been systematically investigated. Moreover, despite the similarities of ethnicity and diet, the age-standardized incidence rate of gastric cancer in the northern city of Hanoi is higher than that in the southern city of Ho Chi Minh, but the reason for this phenomenon is unknown. The virulence of Vietnamese *H. pylori* has also not been investigated in detail.

Methods: Individuals undergoing esophagogastroduodenoscopy were randomly recruited. *H. pylori* infection status was determined based on the combined results of culture, histology, immunohistochemistry, rapid urine test and serum ELISA. Peptic ulcer (PU) and gastroesophageal reflux disease was diagnosed by endoscopy, and chronic gastritis was determined histologically. *H. pylori* virulence factors were investigated by PCR and sequencing.

Results: Among the examined patients, 65.6% were infected with *H. pylori*. The prevalence of infection was significantly higher in those over 40 years of age than in those aged ≤ 40 . Chronic gastritis was present in all *H. pylori*-infected individuals, 83.1% of whom had active gastritis, and 85.3% and 14.7% had atrophy and intestinal metaplasia, respectively. PU was present in 21% of infected patients, whereas its incidence was very low in non-infected individuals. The prevalence of PU was significantly higher in Hanoi than in Ho Chi Minh. The prevalence of *vacA m1*, which has been identified as an independent risk factor for PU in Vietnam, was significantly higher among *H. pylori* isolates from Hanoi than among those from Ho Chi Minh.

Conclusions: *H. pylori* infection is common in Vietnam and is strongly associated with PU, active gastritis, atrophy and intestinal metaplasia. *vacA m1* is associated with an increased risk for PU and might contribute to the difference in the prevalence of PU and gastric cancer between Hanoi and Ho Chi Minh.

Background

Helicobacter pylori (*H. pylori*) is a spiral, Gram-negative bacterium that chronically infects more than half of the world's population, and is currently recognized to play a causative role in the pathogenesis of gastritis, gastroduodenal ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [1,2]. Infection with *H. pylori* almost always results in chronic

gastritis, but more severe diseases such as peptic ulcer and gastric cancer develop in only a small proportion of infected patients, suggesting that the clinical outcomes are probably determined by the interaction of bacterial virulence, host genetic susceptibility and environmental factors [2,3]. To date, several *H. pylori* virulence factors associated with severe clinical outcomes have been reported, including *cagA*, *cagE*, *vacA*, *babA*, *oipA*, *iceA* and *homb* [4-11].

In Vietnam, the rate of *H. pylori* infection is reportedly high [12], but the spectrum of *H. pylori*-associated gastroduodenal diseases has not been investigated

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systematically. Moreover, despite the similarities of ethnicity and diet, the age-standardized incidence rate (ASR) of gastric cancer in the northern city of Hanoi is about 1.5 times higher than that in the southern city of Ho Chi Minh (27.0 vs. 18.7 cases per 100,000 males and 13.2 vs. 8.1 cases per 100,000 females, respectively) [13], but the reason for this intriguing phenomenon is unknown. Additionally, the ASR of gastric cancer in Vietnam is approximately 3 times lower than that in Japan and Korea [13], despite the fact that the prevalence of *H. pylori* infection in Vietnam is reportedly higher [12]. This phenomenon, regarded as an “Asian enigma”, is thought to be partly attributable to geographic variations in bacterial virulence [14,15]. Nevertheless, the virulence of Vietnamese *H. pylori* strains has not been extensively investigated. Therefore, we carried out the present cross-sectional study to clarify these unresolved issues.

Methods

Patients

Individuals undergoing esophagogastroduodenoscopy at the endoscopy centers of two major hospitals in Hanoi and Ho Chi Minh were randomly selected. Local ethics approval and written informed consent from all participants were obtained before the study. Exclusion criteria included a history of partial gastric resection, *H. pylori* eradication therapy and treatment with antibiotics, bismuth-containing compounds, H₂-receptor blockers or proton pump inhibitors within 1 month before the study. Overall, the study subjects comprised 270 participants (153 females and 117 males) aged 14 to 86 years (mean age, 42.5 years), including 134 from Hanoi and 136 from Ho Chi Minh (Table 1).

Before endoscopy, participants were interviewed by trained medical staff to ascertain their medical history and lifestyle factors. During endoscopy, 5 biopsy specimens (two from the antrum, two from the corpus and one from the upper part of the lesser curvature) were taken and subsequently used for *H. pylori* culture and histopathologic examination. Peptic ulcer disease (PU) including gastric ulcer (GU), duodenal ulcer (DU) and gastroduodenal ulcer (GDU), and gastroesophageal reflux disease (GERD) were diagnosed by endoscopic observation, while chronic gastritis was determined histologically. After endoscopy, urine and blood samples from all participants were collected on the same day and tested using the rapid urine test and a serum ELISA kit, respectively.

Determination of *H. pylori* infection status

To maximize the diagnostic accuracy, 5 different methods were combined for the diagnosis of *H. pylori* infection, including culture, histology, immunohistochemistry, rapid urine test and serum ELISA.

Table 1 Characteristics of the study population

	<i>H. pylori</i> -positive	<i>H. pylori</i> -negative	Total
No. of participants (%)	177 (65.6%)	93 (34.4%)	270
Number (%) in region			
Hanoi	89 (66.4%)	45 (33.6%)	134
Ho Chi Minh	88 (64.7%)	48 (35.3%)	136
Sex, no. (%)			
Female	101 (66%)	52 (34%)	153
Male	76 (65%)	41 (35%)	117
Age group, no. (%)			
≤40	67 (57.8%)	49 (42.2%)	116
≤20	6 (66.7%)	3 (33.3%)	9
21-30	24 (53.3%)	21 (46.7%)	45
31-40	37 (59.7%)	25 (40.3%)	62
> 40	110 (71.4%)	44 (28.6%)	154
41-50	62 (71.3%)	25 (28.7%)	87
51-60	30 (69.8%)	13 (30.2%)	43
>60	18 (75.0%)	6 (25.0%)	24
Mean age (range)	43.7 (14-83)	40.2 (18-86)	42.5 (14-86)
Disease			
Peptic ulcer	37	1	38
Gastric cancer	0	0	0
MALT lymphoma	0	0	0
Chronic gastritis	177	68	145
Active	147	11	158
Non-active	30	57	87
Atrophy	151	53	204
Intestinal metaplasia	26	5	31
GERD	4	5	9
Normal	0	25	25

For *H. pylori* culture, two biopsy specimens from the antrum and body were homogenized in saline and inoculated onto Mueller Hinton II Agar medium (Becton Dickinson, NJ, USA) supplemented with 7% horse blood without antibiotics. The plates were incubated for up to 10 days at 37°C under microaerophilic conditions (10% O₂, 5% CO₂ and 85% N₂). *H. pylori* was identified on the basis of colony morphology, gram staining and positive reactions for oxidase, catalase, and urease. Isolated strains were stored at -80°C in Brucella Broth (Difco, NJ, USA) containing 10% dimethylsulfoxide and 10% horse serum.

HE and Giemsa staining, and immunohistochemistry with anti-*H. pylori* polyclonal antibody (Dako, Denmark) were performed using serial sections of three specimens from the antrum, corpus and upper part of the lesser curvature, as described previously [16]. Results were judged by an experienced pathologist (T.U.) who was unaware of other information about the subjects.

Urine and blood samples were collected and tested using the urine RAPIRUN test (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and E Plate kit (Eiken Chemical Co., Ltd., Tokyo, Japan), respectively, in accordance with the manufacturers' instructions.

H. pylori-positive status was determined by positive culture or, in the case of negative culture, by at least two positive results among the following tests: histology, immunohistochemistry, rapid urine test and serum ELISA. Patients were diagnosed as *H. pylori*-negative when all five tests gave negative results. If only one test other than culture was positive, patients were considered to have undetermined *H. pylori* infection status and were excluded from further analysis.

Diagnosis and scoring of chronic gastritis

Biopsy specimens were stained with HE and examined by an experienced pathologist (T.U.). For each biopsy specimen, the grades of neutrophil infiltration, mononuclear cell infiltration, atrophy and intestinal metaplasia were scored on the basis of the updated Sydney System (0, none; 1, mild; 2, moderate; and 3, severe).

Active gastritis was classified into four groups as described previously: (i) non-active gastritis, (ii) antrum-predominant gastritis (AP), (iii) corpus-predominant gastritis (CP) and (iv) pangastritis (PAN) [17,18].

Investigation of *H. pylori* virulence factors

H. pylori was subcultured from the stock. Multiple colonies on agar plates were harvested, and genomic DNA was extracted using the standard phenol-chloroform method.

The virulence factors of *H. pylori*, including *cagA*, *cagE*, *vacA s/m/i*, *iceA*, *babA* and *homB*, were examined using PCR as described previously elsewhere [5,7,8,19-22]. The status of *oipA*, "on" or "off", was determined by examining its signal sequence, as described previously [10]. Sequencing was performed with a Big Dye Terminator v3.1 Cycle Sequencing Kit on a ABI Prism 310 Genetic Analyzer (Applied Biosystems, CA, USA) in accordance with the manufacturer's instructions. All the primers used in this study were purchased from Sigma-Aldrich Japan.

Statistical analysis

Chi-squared test, Fisher's exact test, one-way ANOVA test, and multivariate analysis were used. Differences at $p < 0.05$ were regarded as statistically significant. Data analysis was performed using SPSS statistical software v.16.0 (SPSS Inc., Chicago, USA).

Results

Prevalence of *H. pylori* infection

Among the 270 participants, 100, 131, 133, 143 and 141 gave positive results by culture, histology, immunohistochemistry,

rapid urine test and serum ELISA, respectively. Based on the combined results of these tests, 177 patients (65.6%) were judged to be infected with *H. pylori*, 93 (34.4%) were *H. pylori*-negative, and none was considered to have undetermined *H. pylori* infection status (Table 1). There was no significant difference in the prevalence of infection between females and males (66.0% vs. 65.0%), or between Hanoi and Ho Chi Minh (66.4% vs. 64.7%) (Table 1). The prevalence of infection did not differ significantly among the 10-year age groups, but was significantly higher in persons over 40 years of age than in those aged ≤ 40 years (71.4% vs. 57.8%, $p = 0.021$) (Table 1).

H. pylori infection and gastroduodenal diseases

Among the 270 participants, 38 (14.1%) were endoscopically diagnosed as having PU, including 21 DUs, 6 GUs and 11 GDUs (DU/GU ratio, 3.5); gastric cancer and MALT lymphoma were not detected (Table 1). The prevalence of PUD was 37/177 (20.9%) in the *H. pylori*-infected group but only 1/93 (1.1%) in the non-infected group (Table 1). Multivariate analysis showed that the presence of PU was strongly associated with *H. pylori* infection (adjusted OR, 27.8; 95% CI, 3.6 - 200; $p = 0.001$), but not with other factors such as sex, age group, alcohol and coffee consumption, and smoking.

The prevalence of PU was 20.1% (27/134) in Hanoi but much lower in Ho Chi Minh, 8.1% (11/136). For *H. pylori*-infected subjects, the prevalence was 30.3% (27/89) and 11.4% (10/88) in Hanoi and Ho Chi Minh, respectively. Multivariate analysis showed that subjects in Hanoi had a higher risk for PU than those in Ho Chi Minh, with an adjusted OR of 2.6 (95% CI, 1.2 - 5.9; $p = 0.02$) for the overall population and 3.0 (95% CI, 1.3 - 7.0; $p = 0.01$) for *H. pylori*-infected subjects. Among *H. pylori*-related PU, the proportion of GDU was significantly higher in Hochiminh than in Hanoi. In contrast, the proportion of GU in Hanoi appeared to be higher than that in Hochiminh but this difference did not reach the statistical significance (Table 2).

GERD was diagnosed endoscopically in 9 cases (3.3%) and was not inversely associated with *H. pylori* infection status ($p = 0.282$).

H. pylori infection and chronic gastritis

Chronic gastritis was present in all *H. pylori*-infected persons, the majority of whom (147/177, 83.1%) had active gastritis, including AP (57.1%), CP (3.4%) and PAN (22.6%). Atrophic gastritis had developed in the majority of them (151/177, 85.3%), even in younger individuals, and its prevalence appeared to increase with age (Figure 1). About 14.7% (26/177) of infected persons had intestinal metaplasia, which was always accompanied by atrophy (Table 1 and Figure 1). The prevalence

Table 2 Clinical outcomes among *H. pylori*-infected patients in Hanoi and Hochiminh

Disease	Hanoi (n = 89)	Hochiminh (n = 88)	p
Peptic ulcer	27 (30.3%)	10 (11.4%)	< 0.05
Duodenal ulcer	19	2	N.S
Gastric ulcer	6	0	N.S
Gastroduodenal ulcer	2	8	< 0.05
Chronic gastritis	89 (100%)	88 (100%)	N.S
Active gastritis	70 (78.7%)	77 (87.5%)	N.S
Antrum-predominant gastritis	42	59	< 0.05
Corpus-predominant gastritis	3	3	N.S
Pangastritis	25	15	< 0.05
Atrophy	76 (85.4%)	75 (85.2%)	N.S
Intestinal metaplasia	15 (16.9%)	11 (12.5%)	N.S

N.S, not significant

of antrum-predominant gastritis among *H. pylori*-infected patients was significantly lower in Hanoi than in Hochiminh, whereas the prevalence of pangastritis in Hanoi was significantly higher than that in Hochiminh. However, there was no significant difference in the prevalences of atrophy and intestinal metaplasia between the two cities (Table 2).

Multivariate analysis showed that *H. pylori* positivity was strongly associated with active inflammation (adjusted OR, 41.7; 95% CI, 18.9 - 90.9; $p < 0.001$), chronic inflammation (adjusted OR, 19.2; 95% CI, 5.5 - 66.7; $p < 0.001$), atrophy (adjusted OR, 4.2; 95% CI, 2.3 - 7.7; $p < 0.001$) and intestinal metaplasia (adjusted OR, 3.2; 95% CI, 1.1 - 9.8; $p = 0.036$) in the

gastric mucosa. An age of >40 years conferred an increased risk for atrophy (adjusted OR, 3.0; 95% CI, 1.6 - 5.5; $p < 0.001$) and intestinal metaplasia (adjusted 3.1; 95% CI, 1.2 - 7.9; $p = 0.02$).

***H. pylori* virulence factors and peptic ulcer**

An important focus of our interest was why the prevalence of PU was significantly higher in Hanoi than in Ho Chi Minh. It is currently accepted that the clinical outcomes of *H. pylori* infection are determined by the interaction of bacterial virulence, and host and environmental factors. Because the ethnicity, environmental factors and prevalence of *H. pylori* infection in the two regions are similar, we focused on bacterial virulence. We investigated genetic factors of *H. pylori* that are reportedly associated with gastroduodenal diseases, including *cagA*, *cagE*, *vacA* (*s/m/i*), *babA*, *oipA*, *iceA*, and *hombB*, in 100 clinical strains (53 from Hanoi and 47 from Ho Chi Minh), of which 24 and 76 strains were isolated from patients with PU and chronic gastritis, respectively. Details of the results are presented in Table 3. Multivariate analysis showed that only *vacA m1* was an independent risk factor for PU (adjusted OR, 3.0; 95% CI, 1.1 - 8.4; $p = 0.034$). Moreover, infection with *H. pylori* that simultaneously possessed *vacA m1* together with *cagA*, *cagE* and *babA* (quadruple positivity) conferred an increased risk for PU (OR, 4.2; 95% CI, 1.5 - 11.3, $p = 0.005$). Interestingly, the prevalences of *vacA m1* and quadruple positivity were significantly higher among *H. pylori* isolates from Hanoi than among those from Ho Chi Minh (58.5% vs. 36.2%, $p = 0.029$ and 54.7% vs. 34.0%, $p = 0.046$, respectively) (Table 4). In addition, comparison of virulence factors of

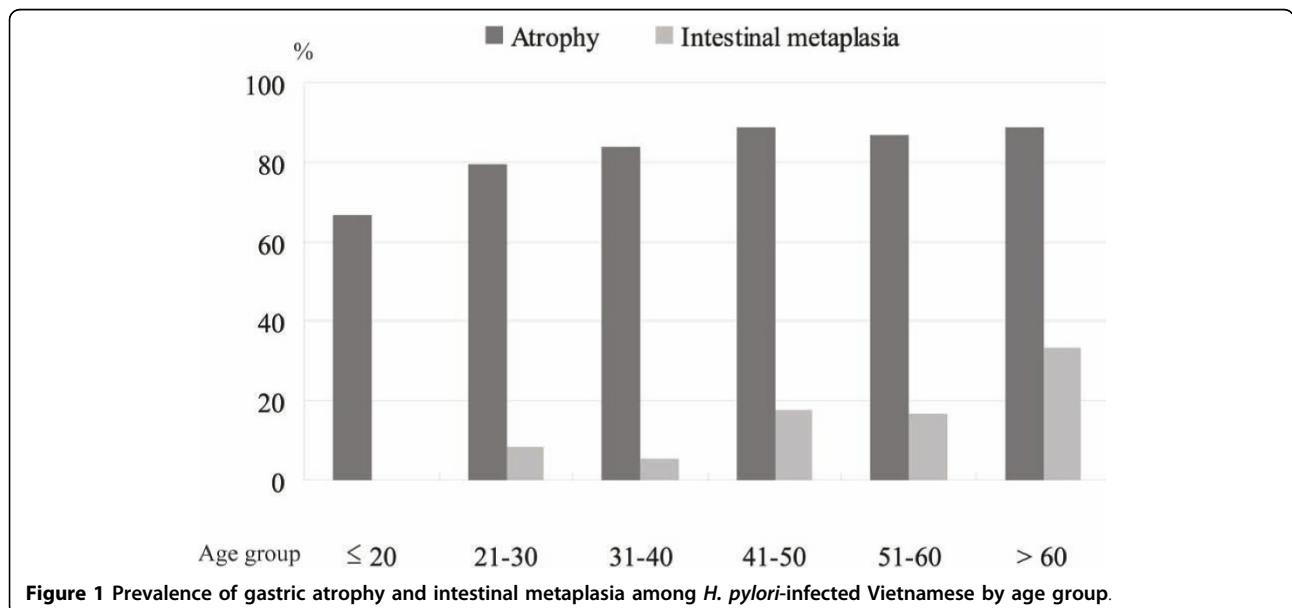


Figure 1 Prevalence of gastric atrophy and intestinal metaplasia among *H. pylori*-infected Vietnamese by age group.

Table 3 Virulence factors of *H. pylori* from Vietnam

	Total (n = 100)	Peptic ulcer (n = 24)	Chronic gastritis (n = 76)	p
<i>cagA</i>				> 0.05
Positive	95 (95%)	24 (100%)	71 (93.4%)	
Negative	5 (5%)	0 (0%)	5 (6.6%)	
<i>cagE</i>				> 0.05
Positive	88 (88%)	24 (100%)	64 (84.2%)	
Negative	12 (12%)	0 (0%)	12 (15.8%)	
<i>vacA m</i> †				< 0.05
<i>m1</i>	48 (48%)	17 (70.8%)	31 (40.8%)	
<i>m2</i>	52 (52%)	7 (29.2%)	45 (59.2%)	
<i>vacA s</i>				> 0.05
<i>s1</i>	100 (100%)	24 (100%)	76 (100%)	
<i>s2</i>	0 (0%)	0 (0%)	0 (0%)	
<i>vacA i</i>				> 0.05
<i>i1</i>	94 (94%)	24 (100%)	70 (92.1%)	
<i>i2</i>	6 (6%)	0 (0%)	6 (7.9%)	
<i>babA</i>				> 0.05
Positive	92 (92%)	24 (100%)	68 (89.5%)	
Negative	8 (8%)	0 (0%)	8 (10.5%)	
<i>oipA status</i>				> 0.05
On	100 (100%)	24 (100%)	76 (100%)	
Off	0 (0%)	0 (0%)	0 (0%)	
<i>iceA</i>				> 0.05
<i>iceA1</i>	50 (50%)	13 (54.2%)	37 (48.7%)	
<i>iceA2</i>	44 (44%)	11 (45.8%)	33 (43.5%)	
Both <i>iceA1/2</i>	3 (3%)	0 (0%)	3 (3.9%)	
None	3 (3%)	0 (0%)	3 (3.9%)	
<i>homb</i>				> 0.05
Positive	39 (39%)	7 (29.2%)	32 (42.1%)	
Negative	61 (61%)	17 (70.8%)	44 (57.9%)	
Quadruple positivity †				< 0.05
Yes	45 (45%)	17 (70.8%)	28 (36.8%)	
No	55 (55%)	7 (29.2%)	48 (63.2%)	

† Prevalence was significantly different between peptic ulcer and chronic gastritis

H. pylori infecting DU and GU patients revealed no significant difference (data not shown).

Discussion

We found that the prevalence of *H. pylori* infection in Vietnam was about 66%, being somewhat similar to that in several other Asian countries [12]. In this study, *H. pylori* infection was proved to be strongly associated with active gastritis, atrophy, intestinal metaplasia, and especially PU (adjusted OR, 27.8; p = 0.001). We did not detect any case of gastric cancer or MALToma, possibly due to their low prevalence and the small sample size. *H. pylori* is probably a very important cause of PU in Vietnam, as PU

Table 4 Prevalence of *H. pylori* virulence factors in Hanoi and Ho Chi Minh

	Hanoi (n = 53)	Ho Chi Minh (n = 47)	p (Hanoi vs. Ho Chi Minh)
<i>cagA</i>			N.S
Positive	51 (96.2%)	44 (93.6%)	
Negative	2 (3.8%)	3 (6.4%)	
<i>cagE</i>			N.S
Positive	49 (92.5%)	39 (83.0%)	
Negative	4 (7.5%)	3 (6.4%)	
<i>vacA m</i>			0.034
<i>m1</i>	31 (58%)	17 (36.2%)	
<i>m2</i>	22 (41.5%)	30 (63.8%)	
<i>vacA s</i>			N.S
<i>s1</i>	53 (100%)	48 (100%)	
<i>s2</i>	0 (0%)	0 (0%)	
<i>vacA i</i>			N.S
<i>i1</i>	50 (94.3%)	44 (93.6%)	
<i>i2</i>	3 (5.7%)	3 (6.4%)	
<i>babA</i>			N.S
Positive	50 (94.3%)	42 (89.4%)	
Negative	3 (5.7%)	5 (10.6%)	
<i>oipA status</i>			N.S
On	53 (100%)	48 (100%)	
Off	0 (0%)	0 (0%)	
<i>iceA</i>			N.S
<i>iceA1</i>	26 (49.1%)	24 (51.1%)	
<i>iceA2</i>	23 (43.4%)	21 (44.7%)	
Both <i>iceA1/2</i>	2 (3.8%)	1 (2.1%)	
None	2 (3.8%)	1 (2.1%)	
<i>homb</i>			N.S
Positive	19 (35.8%)	20 (42.6%)	
Negative	34 (64.2%)	27 (57.4%)	
Quadruple positivity			0.046
Yes	29 (54.7%)	16 (34.0%)	
No	24 (45.3%)	31 (66.0%)	

N.S, not significant.

was observed in approximately 21% of infected patients, while it was virtually absent in non-infected subjects.

We discovered that the majority of *H. pylori* isolates from Vietnam possessed *cagA*, *cagE*, *babA*, *oipA* "on", *vacA s1* and *vacA i1*, while other genes such as *vacA m1*, *homb* and *iceA1* were less frequent. Among these virulence factors, only *vacA m1* was identified as an independent risk factor for PU (adjusted OR, 3.0). Moreover, the co-existence of *vacA m1* with *cagA*, *cagE* and *babA* conferred an increased risk for PU, perhaps due to a synergic effect among them. Current evidence indicates that the ASR of gastric cancer in Hanoi is about 1.5 times higher than that in Ho Chi Minh [13], and this appeared to accord with the differences

between the two cities in the prevalences of antrum-predominant gastritis and pangastritis. Moreover, in the present study the prevalence of PU in Hanoi was also proved to be significantly higher. Our results suggest that the higher prevalence of PU in Hanoi might be attributable to the higher prevalence of *H. pylori* strains carrying *vacAm1* and quadruple positivity in Hanoi, in comparison with Ho Chi Minh. Because *H. pylori* virulence was associated with both PU and gastric cancer, our data, although not direct, are the first to indicate a reason for the difference in the ASR of gastric cancer between these two regions of Vietnam.

Compared with Japan, the ASR of gastric cancer in Vietnam is much lower [13], and this seems to be reflected by the DU/GU ratio as well as the pattern of chronic gastritis observed in Vietnamese patients. The DU/GU ratio has been regarded as a good marker for evaluating the risk of gastric cancer in certain populations because DU patients have low risk of developing gastric cancer whereas the opposite is true for GU patients [18,23]. The DU/GU ratio in Vietnam is about four times higher than that in Japan, but still much lower than that in India, where the ASR of gastric cancer is very low [13,23]. Corresponding well to the high DU/GU ratio, the majority of infected Vietnamese have antrum-predominant gastritis (57%) whereas the rate of corpus-predominant gastritis is low (3.4%) in comparison with Japan (14~17%) [17,18].

Because *H. pylori* virulence is thought to contribute partly to the geographic variation in the ASR of gastric cancer [14,15], we compared various virulence factors of Vietnamese strains with those of Japanese ones. From the literature, it is evident that nearly all Japanese *H. pylori* strains simultaneously carry *cagA*, *cagE*, *vacAm1/s1/i1*, *babA* and *oipA* "on" [6,10,11,22,24], while among Vietnamese strains, this figure is around 45%. Furthermore, the prevalence of *homB*-positive strains is also higher in Japan than in Vietnam (over 90% vs. 39%) [8,25]. From these data, it is tempting to speculate that the difference in ASR of gastric cancer is attributable partly to the difference in bacterial virulence between the two countries.

Conclusions

Our study indicates that *H. pylori* infection is common in Vietnam and is strongly associated with the development of PU, active gastritis, atrophy and intestinal metaplasia. Moreover, *H. pylori vacA m1* is associated with an increased risk for PU and might contribute to the difference in the prevalence of PU and gastric cancer between Hanoi and Ho Chi Minh.

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Authors' contributions

TLN and TU carried out the experiments, data analysis and drafting of the manuscript. YT, DTT, LT, BHM, SHL, KDT, DDH, HHH, TM, and TO participated in the collection of patients and contributed to the manuscript. MK, KM, TF, YY and MM participated in the design, coordination and analysis of the study. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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