Prevalence of *Helicobacter pylori* Infection in Patients with Perforated Peptic Ulcer in a Tertiary Hospital in Thailand: A Single Tertiary Hospital Study

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**ABSTRACT**

**Objective:** Because of limited resources, the approach in Thailand is to eradicate *Helicobacter pylori* (*H. Pylori*) infection in every patient with peptic ulcer perforation, but without infectious confirmation because of suspected high infection rates. Only one study reported the incidence of infection in perforated disease in Thailand with limited number of patients. Our aims were to study the prevalence of *H. pylori* infection in patients with perforation and to explore associated factors.

**Methods:** In a total 136 patients, infection was confirmed by rapid urease testing during post-operative esophagogastroduodenoscopy. The statistical analysis were Fisher’s exact test and multiple logistic regression analysis.

**Results:** The infection rate was 69.6%. Age ≥ 60 years and male were correlated with infection in multivariable analysis (odds ratio: 3.4 and 4.3, \(p=0.01\) and 0.03, respectively). Only age ≥ 60 years was associated with infection in the univariable analysis (odds ratio: 2.7, \(p=0.02\)) with an infection rate of 81.5%. Three upper gastrointestinal cancers were also seen.

**Conclusion:** The prevalence of *Helicobacter pylori* infection in perforated peptic ulcer patients in our study was high. Male patients ≥ 60 years of age appeared to be more prone to infection. The non-documented infection eradication approach may be more justified in older male patients, especially those with multiple comorbidities.

**Keywords:** *H. pylori* infection; perforated peptic ulcer; prevalence; Thailand (Siriraj Med J 2018;70: 139-144)

**INTRODUCTION**

*Helicobacter pylori* (*H. Pylori*) infection is the established etiology of peptic ulcer disease\(^1\), and perforated peptic ulcer is a significant complication. Most affected patients require surgery, which can increase morbidity and may result in death. Several complicated surgical procedures have been designed to reduce acid secretion to prevent disease recurrence. However, with improved understanding of the pathophysiology and more effective medications, complicated surgery has been replaced with simple closure of the perforation site and/or reinforcing with an omental patch.\(^2,4\)

Studies confirm that *H. pylori* eradication decreases recurrent perforation,\(^5,8\) and the standard recommendation is to confirm and document infection status in all perforated ulcer patients.\(^5,6\) However, in developing countries with limited resources, the recommendation is to eradicate infection in all patients with perforated ulcers regardless of infection documentation, because high infection rates are suspected. This practice has been adopted by most surgeons in Thailand, although there is a lack of supporting documentation and published studies. Surgeons in other countries also take this approach.\(^3\)

The infection rate in Thailand has been reported at approximately 27%-61.4%.\(^9,12\) This wide variation may be a result of regional population differences and/or
sampling differences based on whether patients are seen by gastroenterologists or non-specialists. However, to our knowledge, there was only one study which reported the incidence of infection in perforated disease in Thailand with limited number of patients. The incidence in other countries varies greatly (26%-92%). Our aim in this single-center study was to evaluate the prevalence of H. pylori infection in perforated peptic ulcer patients concurrently with other relevant etiologies and to explore correlated factors that may predict infection.

MATERIALS AND METHODS
Patients
We included all patients with perforated peptic ulcer from January 2014 to December 2016. Following surgery, postoperative rehabilitation, and discharge, patients were subsequently scheduled to return for esophagogastroduodenoscopy (EGD) after obtaining informed consent. EGD was performed in an outpatient setting.

The study was conducted in Sawanpracharak Hospital, a 653-bed public tertiary hospital in Nakhon Sawan province, located in the lower northern part of Thailand. This study was approved by the Sawanpracharak Hospital Medical Ethics Committee (Certification number: 41/2557).

Data collection and diagnostic method to confirm H. pylori infection
The following data was collected: sex, age, ulcer location, type of operation, smoking status (previous, ongoing, or never), recurrent ulcer status, and nonsteroidal anti-inflammatory drug (NSAIDs) use in the two weeks prior to perforation. NSAID and smoking data were obtained from a questionnaire on the endoscopic examination day. The remaining variables were acquired from patients’ medical records. On-going smoking and NSAID use less than two weeks before perforation events, only were included.

H. pylori infection was diagnosed using a rapid urease test (HelicotecUT Plus, Strong Biotech Corp., Taipei, Taiwan). EGD and gastric mucosal sampling are required for this test. Gastric mucosa was collected from both the antrum and body to decrease false negative results from more proximal distribution of the infection in patients who were taking proton-pump inhibitors (prescribed postoperatively in all patients). Interpretation of the test’s color was evaluated approximately 24 hours after the test commenced.

EGD was also used to evaluate whether healed or active ulcers and/or malignancy were present.

Statistical analysis
Variables considered to predict infection (age, sex, ulcer location, smoking, not consuming NSAIDs, and active ulcer) were individually examined for correlation using Fisher’s exact test. Multiple logistic regression analysis was also used and incorporated the same variables. Data were expressed as mean ± standard deviation or percentage with 95% confidence intervals (95% CI). Significance was set at p < 0.05.

RESULTS
We studied a total of 136 patients. Patients’ characteristics and associated variables are summarized in Table 1. Patients’ ages ranged from 16-88 years. The average time between operation and EGD was 30 ± 10.8 days, most patients were male (86.0%), and ulcer locations were: gastric (9.6%), duodenal (47.1%), and pyloric (43.4%). Most surgeries involved simple closure of the perforated ulcer (95.6%).

Including all etiological factors, in a total of 135 patients, H. pylori prevalence was 69.6%. Infection status could not be documented in one patient because of obstructed esophageal cancer. Most patients had a history of smoking (62.5%), and the NSAID consumption rate was 66.9%. Fifteen (11.0%, 95% CI: 6.3-17.5) patients did not have H. pylori infection and had not consumed NSAIDs.

The current episode was recurrent perforation in five (3.7%) patients with four (80%) having infection. Previous infectious eradication information was not available in these patients’ medical records. Ulcers were still active based on EGD in 41 (30.2%) patients with 28 (68.3%, 95% CI: 51.9-81.9) patients infected. Cancer was detected in three (2.2%) patients and confirmed by histology including one gastric cancer (adenocarcinoma) and two upper esophageal cancers (squamous cell carcinoma). All cancer patients were male. In the gastric cancer case, the surgeon was not aware of tumor while performing the ulcer repair operation. Documentation of infection could not be obtained in one esophageal cancer patient, although infection was confirmed in the two other cancer patients.

All relevant factors were examined in both univariable and multivariable analysis, and the results are summarized in Table 2. Age was the only factor that predicted infection in both analyses. However, after adjusting for other factors, male gender also reached statistical significance. Patients ≥ 60 years of age had an 81.5% (95% CI: 68.6-90.7) infection rate compared with 61.7% (95% CI: 50.3-72.3) for those < 60 years of age. Male patients had a 71.8% (95% CI: 62.7-79.7) infection rate compared with 55.6%
**TABLE 1.** Patients’ characteristics, type of operation, and factors associated with the peptic ulcers. Data from 136 patients were analyzed.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Numbers</th>
<th>Percentage</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years) (Mean ± SD)</td>
<td>56.7</td>
<td>(± 13.3)</td>
<td>54.5 – 59.0</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>81</td>
<td>59.6</td>
<td>50.8 – 67.9</td>
</tr>
<tr>
<td>≥ 60</td>
<td>55</td>
<td>40.4</td>
<td>32.1 – 49.2</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>117</td>
<td>86.0</td>
<td>79.0 – 91.4</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>14.0</td>
<td>8.6 – 21.0</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple closure</td>
<td>130</td>
<td>95.6</td>
<td>90.6 – 98.4</td>
</tr>
<tr>
<td>Acid reducing procedure</td>
<td>6</td>
<td>4.4</td>
<td>1.6 – 9.4</td>
</tr>
<tr>
<td>Ulcer type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>13</td>
<td>9.6</td>
<td>5.2 – 15.8</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>64</td>
<td>47.1</td>
<td>38.4 – 55.8</td>
</tr>
<tr>
<td>Pyloric ulcer</td>
<td>59</td>
<td>43.4</td>
<td>34.9 – 52.1</td>
</tr>
<tr>
<td>NSAIDs consumption</td>
<td>91</td>
<td>66.9</td>
<td>58.3 – 74.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>85</td>
<td>62.5</td>
<td>53.8 – 70.4</td>
</tr>
<tr>
<td>H pylori infection*</td>
<td>94</td>
<td>69.6</td>
<td>60.6 – 76.8</td>
</tr>
<tr>
<td>Active ulcer on EGD</td>
<td>41</td>
<td>30.2</td>
<td>22.6 – 38.6</td>
</tr>
<tr>
<td>Recurrence</td>
<td>5</td>
<td>3.7</td>
<td>1.2 – 8.4</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>2.2</td>
<td>0.5 – 6.3</td>
</tr>
</tbody>
</table>

* A total of 135 patients for the H. pylori infection variable.

**Abbreviations:** SD = Standard deviation, NSAIDs = Nonsteroidal anti-inflammatory drugs, H. pylori = Helicobacter pylori, EGD = Esophagogastroduodenoscopy.

**TABLE 2.** Characteristic variables associated with H. pylori infection. Univariable and multivariable analyses in 135 patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
<th>Adjusted odds ratio</th>
<th>95% Confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 yrs</td>
<td>2.7</td>
<td>1.1 – 6.9</td>
<td>0.02</td>
<td>3.4</td>
<td>1.4 – 8.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Male</td>
<td>2.0</td>
<td>0.6 – 6.3</td>
<td>0.18</td>
<td>4.3</td>
<td>1.1 – 16.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.8</td>
<td>0.3 – 1.8</td>
<td>0.70</td>
<td>0.7</td>
<td>0.2 – 1.8</td>
<td>0.44</td>
</tr>
<tr>
<td>No- NSAIDs taking</td>
<td>0.8</td>
<td>0.3 – 1.8</td>
<td>0.55</td>
<td>0.7</td>
<td>0.3 – 1.5</td>
<td>0.33</td>
</tr>
<tr>
<td>Ulcer type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>1.3</td>
<td>0.3 – 8.1</td>
<td>1.00</td>
<td>1.0</td>
<td>0.2 – 4.6</td>
<td>0.99</td>
</tr>
<tr>
<td>Duodenal</td>
<td>0.8</td>
<td>0.4 – 1.8</td>
<td>0.58</td>
<td>0.7</td>
<td>0.3 – 1.7</td>
<td>0.48</td>
</tr>
<tr>
<td>Pyloric</td>
<td>1.1</td>
<td>0.5 – 2.6</td>
<td>0.85</td>
<td>1.0</td>
<td>0.2 – 4.7</td>
<td>0.99</td>
</tr>
<tr>
<td>Active ulcer</td>
<td>0.9</td>
<td>0.4 – 2.2</td>
<td>0.84</td>
<td>0.8</td>
<td>0.4 – 2.1</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Abbreviation:** NSAIDs = Nonsteroidal anti-inflammatory drugs.
(95% CI: 30.8–78.5) for female patients. The infection rate was 88.1% (95% CI: 74.4–96.0) in male patients ≥ 60 years of age.

**DISCUSSION**

*H. pylori* and NSAIDs are two major factors in peptic ulcer pathogenesis. Our study was limited regarding patients’ history of NSAID use. Obtaining NSAID history in Thailand is limited because of patient confusion in terminology between NSAIDs and antibiotics, availability of illegal pain-relief medication containing either NSAIDs or steroid, and lack of education. In the past, simple closure of perforated ulcers was considered inadequate because of high ulcer recurrence. However, with newer more effective acid-reducing medications and a greater understanding of peptic ulcer pathogenesis, simple closer is now more widely used. Considering the high proportion of patients with both main etiological factors in our study (89.0%), simple closure also appeared to be adequate in our center. However, both etiological factors must be controlled postoperatively either by confirming and eradicating the infection or avoiding NSAIDs or using them with acid-reducing medications. Countries with limited resources follow a policy of eradicating the infection in every patient with perforated ulcers regardless of infection documentation, based on a suspected high prevalence of infection. Our results showed an infection prevalence in our hospital of 69.6%. Compared with the prevalence in other countries (26%-92%), our rate is considered high.

Two large nationwide community-based studies of the prevalence of *H. pylori* infection in dyspeptic patients have been performed in Thailand. The prevalence was 48.2% in one study and 45.9% in the other, and both studies reported significant geographic variation. The northern part (our region) was classified as having medium to high prevalence with the highest in the northeast region and the lowest in the southern region. The reported prevalence in Nakhon Sawan province, specifically was 40.3%. Our infection rate was 69.6%. This difference (69.6% vs 40.3%) can be indirectly interpreted that the incidence in perforated disease is higher than in community-based dyspeptic disease. However, compared to previous study in perforated disease, our incidence was lower (69.6% vs 86.3%). This can be explained by differences in geography, timing of examination (after recovery vs intra-operatively) and method of infectious confirmation (rapid ureas test vs rapid urease test and histologic examination).

Age, lower socioeconomic status, lower education level, and some foods are other factors reported to be associated with infection. Differences in socioeconomic status and types of food consumed can explain the geographic variation in infection rates in Thailand. However, in settings like ours (government hospital), most patients have low income and education level, so these factors cannot be used to classify factors associated with infection and may not have practical benefit. Regarding age, our results were similar to certain epidemiological studies, but contrast with large studies in Thailand where the age was either not related or inversely related. Different *H. pylori* genotypes in different pathologies is a possible explanation for this difference, but more evidence is required. Although ulcer location is reportedly related to infection, in our study, perforated ulcer location failed to predict infection. Age was the only variable in our study significantly associated with infection in both uni- and multi-variable analyses. When adjusted for other factors, male gender was also significantly related to infection, and combining these two factors, the infection rate reached as high as 88.1%. This result may be valuable in decision-making, although at a 69.6% infection rate, proceeding with non-documented infection eradication may be a difficult decision. In patients ≥ 60 years of age, the incidence of infection was 81.5%, so the non-documented infection eradication approach appears more reasonable in these patients. Also, in older, frail patients with multiple comorbidities, intensive investigation may be impractical. Some patients may avoid follow-up sessions, which could result in these patients not receiving eradicative treatment.

We also detected a high (2.2% in 3 years) prevalence of upper gastrointestinal cancer in our study, which was much higher than Thailand’s specific cancer incidence for esophageal cancer of 1.6 per 100,000 men and 0.3 per 100,000 women and for gastric cancer of 1.5 per 100,000 men and 1.2 per 100,000 women (approximate rates). Perforated gastric lesions can harbor malignancy, as seen in one of our patients. The upper esophageal squamous cell carcinoma in the other two patients might be pathophysiologically unrelated to the perforated ulcer. The high prevalence of upper gastrointestinal cancer in our study might be explained by smoking as a common risk factor, which was present in 62.5% of our patients. Another relevant explanation might be reflux disease leading to esophageal cancer caused by gastric acid abnormalities, which also occurs in peptic ulcer disease. However, the expected histology of esophageal cancer is distal adenocarcinoma rather than proximal squamous cell cancer. Given the high detection rate of upper gastrointestinal cancer, confirming *H. pylori* infection with EGD is an even more attractive
option. Other noninvasive confirmation methods cannot detect upper gastrointestinal cancer. 28,29 This high cancer detection rate also questions the suitability of the non-documented infection eradication approach because diagnosis of malignancy in some patients (albeit quite a low proportion) could be missed or delayed.

There were certain limitations in our study. First, even within a single country, there are geographic variations of infection prevalence. 9,12 In the southern part of Thailand, the prevalence of infection can be as low as 14.4% (in dyspeptic patients). Second, as a single-hospital study, our results cannot be applied to the national population. Third, the number of subjects in our study was small, and this was reflected in the instability of the odds ratio (wide 95% CI). Fourth, information on certain variables was missing including alcohol consumption, family history, type of foods consumed, socioeconomic variables, preoperative use of acid-regulating medications, and previous H. pylori eradication status in recurrent patients. Fifth, because we relied on the only single test, inaccurate estimation was possible. Lastly, regarding the high incidence of cancer, because of the small sample size, this finding could have occurred by chance because the 95% CI was as low as 0.5%. Further large nationwide studies in specific groups of patients and possibly cost-effective analyses are needed.

CONCLUSION

The rate of H. pylori infection in perforated peptic ulcer patients in our study was high. Age and male gender identified high-risk patients, and older male patients were more likely to be infected. When resources are limited, the non-documented infection eradication approach is useful, especially in male patients ≥ 60 years of age. However, if feasible, documenting infection in every case is highly recommended. EGD with rapid urease testing appears to be the most attractive investigation because of the indirect benefit of malignancy detection. Finally, because of our small sample size, and the single-hospital design, our results should be interpreted with caution. Further larger nationwide studies are needed.

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