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Are Patients with Perforated Peptic Ulcers Who are Negative for *Helicobacter pylori* at a Greater Risk?

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Abstract

Background: The link between *Helicobacter pylori* infection and peptic ulceration is well established. Recent studies have reported a decrease of *H. pylori*-related peptic ulcer disease; *Helicobacter pylori* eradication is likely the cause of this decrease. We hypothesized that patients with *H. pylori*-positive perforated peptic ulcer disease (PPUD) requiring surgical intervention had worse outcomes than patients with *H. pylori*-negative PPUD.

Patients and Methods: A prospectively collected Acute and Critical Care Surgery registry spanning the years 2008 to 2015 was searched for patients with PPUD and tested for *H. pylori* serum immunoglobulin G (IgG) test. Patients were divided into two cohorts: *H. pylori* positive (HPP) and *H. pylori* negative (HPN). Demographics, laboratory values, medication history, social history, and esophagogastroduodenoscopy were collected. Student t-test was used for continuous variables and χ^2 test was used for categorical variables. Linear regression was applied as appropriate.

Results: We identified 107 patients diagnosed with PPUD, of whom 79 (74%) patients had *H. pylori* serum IgG testing. Forty-two (53.2%) tested positive and 37 (46.8%) tested negative. *Helicobacter pylori*-negative PPUD was more frequent in females (70.27%, $p=0.004$), whites (83.78%, $p=0.001$) and patients with higher body mass index (BMI) 28.81 ± 8.8 ($p=0.033$). The HPN group had a lower serum albumin level (2.97 ± 0.96 vs. 3.86 ± 0.91 $p=0.0001$), higher American Society of Anesthesiologists (ASA; 3.11 ± 0.85 vs. 2.60 ± 0.73 ; $p=0.005$), and Charlson comorbidity index (4.81 ± 2.74 vs. 2.98 ± 2.71 ; $p=0.004$). On unadjusted analysis the HPN cohort had a longer hospital length of stay (LOS; 20.20 ± 13.82 vs. 8.48 ± 7.24 ; $p=0.0001$), intensive care unit (ICU) LOS (10.97 ± 11.60 vs. 1.95 ± 4.59 ; $p=0.0001$), increased ventilator days (4.54 ± 6.74 vs. 0.98 ± 2.85 ; $p=0.004$), and higher rates of 30-day re-admission (11; 29.73% vs. 5; 11.91%; $p=0.049$). Regression models showed that HPN PPUD patients had longer hospital and ICU LOS by 11 days ($p=0.002$) and 8 days ($p=0.002$), respectively, compared with HPP PPUD.

Conclusion: In contrast to our hypothesis, HPN patients had clinically worse outcomes than HPP patients. These findings may represent a difference in the baseline pathophysiology of the peptic ulcer disease process. Further investigation is warranted.

Keywords: *H. pylori*; peptic ulcer; perforation

HELICOBACTER PYLORI INFECTION has been considered the most important cause of peptic ulcer disease since the 1980s [1]. Recent studies have reported a decrease in *H. pylori*-positive (HPP) peptic ulcer disease [2–4]. This reported decreased incidence of *H. pylori* infection is partly the

result of optimizing sanitation, public health education efforts, and a lower childhood acquisition rate [5]. Graham [6] concluded that if the absolute number of *H. pylori*-negative (HPN) idiopathic ulcers remained constant and the incidence of HPP ulcers decreased, a greater proportion of HPN idiopathic

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ulcers would be diagnosed. Contrary to Graham’s hypothesis, Hung et al. [7] reported that from 1997 to 2000 the true incidence of HPN bleeding ulcers had increased four-fold [7].

Recurrent ulcer disease after peptic ulcer perforation occurs mainly in patients with *H. pylori* infection, which suggests that micro-organisms play an important role in complications [8]. We hypothesized that in patients with perforated peptic ulcer disease (PPUD) requiring surgical intervention, positive *H. pylori* serology has worse outcomes than negative serology.

Patients and Methods

A prospectively collected and maintained Acute and Critical Care Surgery (ACCS) registry spanning 2008 to 2015 was searched for patients diagnosed with perforated peptic ulcer (ICD-9 codes 531.1x, 531.2x, 531.5x, 531.6x, 532.1x, 532.2x, 532.5x, 532.6x, and 533.9) requiring emergent operative management. A total of 107 patients were seen in the emergency department who were diagnosed with PPUD and

required surgical intervention. The diagnosis and anatomic location of PPUD was based on the operative findings. Patients were excluded if the etiology of the perforation was caused by ischemia or vascular pathology.

Post-operative serum anti-*H. pylori* immunoglobulin G (IgG) testing was abstracted and patients without serology were excluded from the study. On the basis of the results of the anti-*H. pylori* IgG test, the patients were divided into HPP and HPN cohorts.

Demographics such as age, gender, race, and body mass index (BMI) were abstracted. Laboratory values such as hemoglobin and albumin levels were similarly abstracted. Past medical history including non-steroidal anti-inflammatory drug (NSAID) use, history of gastroesophageal reflux disease (GERD), proton pump inhibitor (PPI) use, dyslipidemia, and peptic ulcer disease history was evaluated and compared. Social history (smoking, drug, and alcohol use) was also collected. We evaluated the outcomes, hospital length of stay (LOS), intensive care unit (ICU) LOS, ventilator days, 30-day re-admission and mortality. Post-operative upper

TABLE 1. DEMOGRAPHICS AND PATIENT CHARACTERISTICS

	Total	HPP	HPN	p
n	79	42 (53.16%)	37 (46.84%)	
Age	56.89 (± 16.51)	50.45 (± 16.06)	64.19 (± 13.92)	0.0001
Gender				0.004
Male	37 (46.84%)	26 (61.90%)	11 (29.73%)	
Female	42 (53.16%)	16 (38.10%)	26 (70.27%)	
Race				0.001
Asian	2 (2.53%)	2 (4.76%)	0 (0%)	
African American	27 (34.19%)	21 (50.00%)	6 (16.22%)	
White	47 (59.49%)	16 (38.10%)	31 (83.78%)	
Other	3 (3.79%)	3 (7.14%)	0 (0%)	
BMI	26.9 (± 7.43)	25.13 (± 5.35)	28.81 (± 8.81)	0.033
Smoking	39 (49.37%)	27 (69.23%)	12 (30.77%)	0.008
Alcohol use	23 (29.11%)	13 (56.52%)	10 (43.48%)	0.940
Drugs	9 (11.39%)	7 (77.78%)	2 (22.22%)	0.277
NSAID use	39 (49.37%)	16 (38.10%)	23 (62.16%)	0.033
GERD	13 (16.50%)	9 (69.23%)	4 (30.77%)	0.204
Location				0.430
Stomach	25 (31.65%)	14 (33.33%)	11 (29.73%)	
Duodenum	40 (50.63%)	19 (45.24%)	21 (56.76%)	
Pyloric channel	11 (13.92%)	8 (19.05%)	3 (8.10%)	
Stomach and duodenum	3 (3.80%)	1 (2.38%)	2 (5.41%)	
Hemoglobin	13.10 (± 2.90)	13.75 (± 2.45)	12.36 (± 3.20)	0.032
Lymphocyte %	8.51 (± 6.43)	9.63 (± 6.74)	7.24 (± 5.90)	0.100
Monocyte %	4.98 (± 3.72)	4.92 (± 4.30)	5.04 (± 3.00)	0.889
Platelets	301.50 (±176.60)	297.52 (±198.14)	305.946 (±151.10)	0.834
Albumin	3.45 (± 1.03)	3.86 (± 0.91)	2.97 (± 0.96)	0.0001
PT	14.54 (± 11.10)	12.98 (± 4.38)	16.14 (± 15.11)	0.219
INR	1.27 (± 0.99)	1.12 (± 0.38)	1.43 (1.34)	0.180
ASA	2.83 (± 0.83)	2.60 (± 0.73)	3.11 (± 0.85)	0.005
Charlson comorbidity index	3.84 (± 2.86)	2.98 (± 2.71)	4.81 (± 2.74)	0.004
Time from perforation to repair	0.27 (± 0.55)	0.29 (± 0.51)	0.24 (± 0.60)	0.733
LOS	13.96 (± 12.25)	8.48 (± 7.24)	20.20 (± 13.82)	<0.0001
ICU LOS	6.18 (± 9.68)	1.95 (± 4.59)	10.97 (± 11.60)	<0.0001
Ventilator days	2.65 (± 5.33)	0.98 (± 2.85)	4.54 (± 6.74)	0.004
UGI barium leak (n=47)	6 (12.77%)	1 (2.13%)	5 (10.64%)	0.029
Mortality	3 (3.80%)	1 (2.40%)	2 (5.41%)	0.483

Statistically significant differences are in bold.

HPN=*Helicobacter pylori*-negative; HPP=*Helicobacter pylori*-positive; BMI=body mass index; NSAID=non-steroidal anti-inflammatory drug; GERD=gastroesophageal reflux disease; PT=prothrombin time; INR=international normalized ratio; ASA=American Society of Anesthesiologists; ICU=intensive care unit; LOS=length of stay; UGI=upper gastrointestinal.

gastrointestinal Gastrografin (Liebel-Flarsheim, North Carolina) study and esophagogastroduodenoscopy (EGD) data were collected if done.

The χ^2 test was used for testing associations between categorical variables and Student t-test was used for continuous variables. Risk factors and outcomes between the two groups (HPP and HPN perforated peptic ulcer), seen on univariable analysis were subjected to multivariable analysis as appropriate. In all analyses, a two-sided p value of <0.05 was regarded as significant. Statistical Package for Social Sciences (SPSS, version 23.0; IBM Corp., Armonk, NY) was used for data analysis.

Results

Of the 107 patients diagnosed with PPUD requiring emergent operative management, 79 (74%) patients had anti-*H. pylori* IgG serology performed. The serology testing was done on average two days (± 2 days).

Of the 79 patients included in the study, 42 (53.16%) were female and 37 (46.84%) were male. The mean age of our patients was 56.89 ± 16.51 years. Perforated peptic ulcer disease was most common in whites (59.49%) followed by African American (34.19%), Asian (2.53%), and others (3.79%; Table 1). The most common site of the perforated peptic ulcer was: duodenum, 40 (50.60%); stomach, 25 (31.70%); pyloric channel, 11 (13.90%); and both stomach and duodenum simultaneously, 3 (3.80%; Table 1).

The result of the serum anti-*H. pylori* IgG test showed that 42 (53.16%) were HPP and 37 (46.84%) were HPN. Patients with HPN PPUD had higher BMI than the HPP group (28.81 ± 8.81 vs. 25.13 ± 5.35 , $p=0.033$). Patients with HPP PPUD were more likely to be smokers than those in the HPN cohort (27, 69.23% vs. 12, 30.77%; $p=0.008$), however, there was no difference found between the cohorts with respect to alcohol or drug history (Table 1). Patients with HPN PPUD were more likely to be on an NSAID pre-operatively (23, 62.16% vs. 16, 38.10%; $p=0.033$), with duodenum (50.60%) being the most common location to be related with the perforated peptic ulcers after the use of NSAID (Table 2). No difference was seen between the cohorts in relation to proton pump inhibitor (PPI) use. Pre-operative laboratory reports showed that the HPN group had lower hemoglobin levels (12.36 ± 3.20 vs. 13.75 ± 2.45 ; $p=0.032$), and serum albumin levels (2.97 ± 0.96 vs. 3.86 ± 0.91 ; $p=0.0001$; Table 1). The ASA and Charlson comorbidity index in the HPN group was 3.11 ± 0.85 and 4.81 ± 2.74 , respectively, which was higher than the HPP group 2.6 ± 0.73 and 2.98 ± 2.71 , respectively ($p=0.005$ and $p=0.004$, respectively; Table 1). The time from

TABLE 2. NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE RELATED TO SITE OF PERFORATION

Location	NSAID use		Total
	No	Yes	
Stomach	13 (32.5%)	12 (30.77%)	25 (31.7%)
Duodenum	17 (42.5%)	23 (58.97%)	40 (50.6%)
Pyloric channel	8 (20.0%)	3 (7.70%)	11 (13.9%)
Stomach and duodenum	2 (5.0%)	1 (2.56%)	3 (3.8%)
Total	40	39	79

NSAID=non-steroidal anti-inflammatory drug.

TABLE 3. LINEAR REGRESSION OF LENGTH OF STAY

Parameters	Coefficient	95% CI	p
HPN	10.87	4.26–17.47	0.002
Age	-0.15	-0.40– 0.11	0.251
BMI	0.39	-0.16– 0.94	0.157
Gender	-1.18	-7.62– 5.25	0.714
Smoking	-0.75	-7.44– 5.93	0.822
NSAID use	-3.99	-11.33– 3.35	0.280
Albumin	-1.46	-5.74– 2.82	0.496
Hemoglobin	0.14	-1.16– 1.44	0.832
ASA	2.82	-1.71– 7.35	0.217
Charlson comorbidity index	1.11	-0.79– 3.02	0.249

Statistically significant differences are in bold.

CI=confidence interval; HPN=*Helicobacter pylori*-negative; BMI=body mass index; NSAID=non-steroidal anti-inflammatory drug; ASA=American Society of Anesthesiologists.

the diagnosis of the perforation to repair was similar in between cohorts (0.29 ± 2.71 vs. 0.24 ± 0.60 , $p=0.733$; Table 1).

In univariable analysis, the patients with HPN had a substantially longer hospital LOS (20.20 ± 13.82 vs. 8.48 ± 7.24 , $p<0.0001$), longer ICU LOS (10.97 ± 11.60 vs. 1.95 ± 4.59 , $p<0.0001$), and more ventilator days (4.54 ± 6.74 vs. 0.98 ± 2.85 , $p=0.004$). They also had a higher re-admission rate of 30 days compared with the HPP group (11, 29.73% vs. 5, 11.91%, $p=0.049$), there was, however, no difference in mortality (Table 1).

Post-operatively, patients underwent upper gastrointestinal Gastrografin (UGI) study to search for a leak. Forty-seven (59.50%) patients had an UGI, of whom 41 (87.23%) did not have a leak. Of the remaining six patients, five (10.64%) from the HPN group and only one (2.13%) patient from the HPP group had a leak ($p=0.029$; Table 1).

Of the patients followed post-operatively for continued symptomatic suspicion for recurrence, patients underwent an EGD on post-operative day 78 (± 45.48). Of the nine patients who underwent an EGD, one (11.1%) patient had a normal EGD and eight (88.9%) patients were found to have a recurrent ulcer. Three (37.5%) of the patients with recurrent ulcers had an associated bleed.

TABLE 4. LINEAR REGRESSION OF INTENSIVE CARE UNIT LENGTH OF STAY

Parameters	Coefficient	95% CI	p
HPN	8.11	3.13–13.10	0.002
Age	-0.09	-0.28– 0.11	0.368
BMI	0.36	-0.06– 0.77	0.088
Gender	0.51	-4.34– 5.36	0.834
Smoking	1.90	-3.14– 6.94	0.453
NSAID use	-2.57	-8.10– 2.07	0.357
Albumin	-0.59	-3.82– 2.64	0.716
Hemoglobin	-0.27	-1.25– 0.71	0.585
ASA	3.33	-0.09– 6.75	0.056
Charlson comorbidity index	0.71	-0.73– 2.15	0.328

Statistically significant differences are in bold.

CI=confidence interval; HPN=*Helicobacter pylori*-negative; BMI=body mass index; NSAID=non-steroidal anti-inflammatory drug; ASA=American Society of Anesthesiologists.

TABLE 5. LINEAR REGRESSION OF VENTILATOR DAYS

Parameters	Coefficient	95% CI	p
HPN	2.30	0.06–4.66	0.056
Age	–0.07	–0.16–0.02	0.119
BMI	0.15	–0.05–0.34	0.142
Gender	–0.02	–2.32–2.28	0.985
Smoking	0.66	–1.72–3.05	0.579
NSAID use	–0.72	–3.35–1.89	0.582
Albumin	–0.49	–2.02–1.04	0.521
Hemoglobin	–0.14	–0.60–0.33	0.552
ASA	1.99	0.38–3.61	0.017
Charlson comorbidity index	0.37	–0.31–1.05	0.278

Statistically significant differences are in bold.

CI=confidence interval; HPN=*Helicobacter pylori*-negative; BMI=body mass index; NSAID=non-steroidal anti-inflammatory drug; ASA=American Society of Anesthesiologists.

We performed multiple linear regression models to adjust for potential outcome confounders. In a linear regression model with LOS as the outcome, HPN PPUD was found to be an independent risk factor for longer LOS (10.87; confidence interval [CI] 4.26–17.47, $p=0.002$; Table 3), similarly with ICU LOS as the outcome, HPN PPUD was again found to be an independent risk factor for longer ICU LOS (8.11; CI 3.13–13.10, $p=0.002$; Table 4). However, with ventilator days as the outcome, *H. pylori* negativity did not have an impact (Table 5).

Discussion

According to previous studies, anti-*H. pylori* serology testing can be used to differentiate the HPP and HPN population. The sensitivity and specificity of all commercially available test kits range from 76%–84% and 79%–90%, respectively [9,10]. The serology test is simple, inexpensive, rapid, accurate, and is useful to assess the global presence of *H. pylori* even when the bacteria are irregularly distributed on the gastric mucosa [11,12]. Studies also show similarities between the various tests for the detection of *H. pylori* [13]. In our study, home medications did not reveal antibiotic use that would eradicate *H. pylori*, causing negative *H. pylori* results. However, the early phase of *H. pylori* infection before IgG seroconversion takes place should be considered in acute PPUD.

In our population the prevalence of *H. pylori* infection in patients with acute PPUD was 53%, which is similar to the study done by Reinbach et al. [14] who found a prevalence of 50%. Only 11.4% of our patients were found to have a previous history of peptic ulcer disease, which is lower than the study by Reinbach et al. [14], however, they reported only perforated duodenal ulcers. As a result of operative evaluation, our patient population had acute PPUD that was not chronic disease.

Helicobacter pylori-negative disease is increasing [15–19]. The role of acid in the pathogenesis of HPN ulcers remains controversial. el-Omar et al. [20] summarized that disturbance in regulation of acid secretion are likely relevant to the mechanism by which *H. pylori* infection predisposes to duodenal ulceration, however, a Japanese study found only one-third of patients with idiopathic ulcers had acid hypersecretion [21]. In our study, only 41% of the patients used PPIs prior to development of the perforation, however, there was no

difference in the use of a PPI and development of HPP or HPN perforated peptic ulcer, which supports the study done by Verdu et al. [22]. Several studies have been conducted to elucidate the role of NSAID use in the development of HPN ulcer disease [4,14,18,23–27]. Fifty percent of our patients had a history of NSAID use. *Helicobacter pylori*-negative perforated ulcers were substantially higher (60%) in the patients with NSAID use, which was consistent with previous studies [14,18,23–25]. Our data suggests that ulcers caused by NSAID use may not be related to the *H. pylori* infection.

Our study shows that the HPN group had lower hemoglobin levels than the HPP group, which is in contrast to previous studies that showed that anemia and HPP ulcers are related [28–30] and that treatment of *H. pylori* infection could be effective in improving anemia [31]. Our patient population is also unique because the HPN group had lower albumin levels suggesting malnutrition and immunosuppression, which contrasts studies in which it was found that the serum albumin levels improved after *H. pylori* eradication [32,33]. The higher rate of re-bleeding or recurrent ulcer formation in the HPN group in our cohort echoed the findings in the previous studies [7,34,35].

This study also shows that the HPN group of patients had almost 10 times longer ICU stay and four times longer ventilator days along with more than twice longer length of stays than the HPP group. The HPN group had higher ASA grade and higher Charlson comorbidity index. The finding of higher ASA grades and Charlson comorbidity indices along with the lower albumin levels in patients with HPN disease suggest that the baseline pathophysiology of HPN PPUD is different than the HPP perforations.

Although our study indicates substantial trends, we were limited by the unavailability of ulcer histology, tissue cultures for *H. pylori*, and other non-invasive testing for *H. pylori* not feasible in an in-patient setting. Furthermore, loss to follow-up may also be a factor. Another notable limitation of the study was the number of patients and the single-center design.

In summary, HPN patients are older and sicker on presentation. *Helicobacter pylori*-negative status is an independent risk factor for increased hospital and ICU LOS, conferring an 11-day and eight-day increase, respectively. Ninety percent of patients with HPN and a clinical suspicion of recurrent disease had a positive EGD for ulcer or ulcer with bleed suggesting awareness for earlier evaluation during follow-up. Lower hemoglobin and albumin levels and LOS along with higher ASA score and Charlson comorbidity index suggest that the HPN perforated peptic ulcers may have a different pathophysiology. Further research is needed to understand etiology of worse outcomes in HPN PPUD patients.

Author Disclosure Statement

No competing financial interests exist.

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