CLINICAL AND ENDOSCOPIC CHARACTERISTICS OF NON-HELICOBACTER PYLORI, NON-NSAID PEPTIC ULCER DISEASE AT THE UNIVERSITY OF SANTO TOMAS HOSPITAL: A PROSPECTIVE STUDY

KC de Lunas MD, GT Ang MD, JD Sollano MD.
Section of Gastroenterology, University of Santo Tomas, Manila, Philippines

Background/Aims
As the prevalence of Hp-associated ulcers is decreasing, non-Hp, non-NSAID ulcers are increasingly recognized. These ulcers are associated with more complications, recurrent bleeding and resistance to treatment; hence recognition is important. This study aims to determine the clinical and endoscopic characteristics of non-Hp, non-NSAID PUD at the UST Hospital from July to December 2015.

Method
Patients who underwent EGD from July to December 2015 in UST Hospital were included. Age, gender, smoking/alcohol intake, comorbidities, and medications were recorded. Patients with antiplatelet, anticoagulant, and NSAID intake were identified. Biopsies were taken for RUT/histology. Ulcer size, location, number, and Forrest classification were noted. T-test and Chi square were used to compare characteristics between idiopathic versus Hp/NSAID ulcers.

Results
Of 837 EGDs, 102 patients had PUD wherein 64% were NSAID and/or Hp positive while 36% were neither NSAID nor Hp-related. Mean age was 62±15 and was similar between the groups. Fifty-two percent were males and 48% were females. There were more females in the non-Hp, non-NSAID group (p 0.04). No difference was seen in smoking/alcohol intake (p 0.8). Hp/NSAID ulcers are more commonly associated with comorbidities (p 0.03). Cirrhosis was more frequently seen in idiopathic ulcers. Most common presentations were bleeding (38%) and abdominal pain (37%). No difference in location, Forrest classification, size, and number between the 2 groups was seen.

Conclusion
Non-Hp, non-NSAID ulcers were seen in 36% of PUD patients. Idiopathic ulcers were female-predominant and comorbidities were not contributory in these ulcers. Endoscopic findings did not differ between non-Hp, non-NSAID and Hp, NSAID-related ulcers.

TABLE OF CONTENTS

INTRODUCTION

Peptic ulcer disease (PUD) remains to be an important cause of morbidity and mortality among patients. Helicobacter pylori (Hp) infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are two of the most important etiologies for the development of PUD. The prevalence of Hp in a series done from 2009 to 2011 ranged between 7 to 87% (1). However, generally, the prevalence is declining mostly attributed to improved sanitation and hygiene and to better detection and emergence of effective treatment of this infection. This has translated to a decreasing proportion of Hp-negative ulcers. Meanwhile, the use of ASA with or without clopidogrel as prevention or treatment of cardiovascular diseases as well as intake of NSAIDs has been on the rise. This led to increasing proportions of patients with ulcers attributed to such medications. (2)

On the other hand, both relative proportion and actual numbers of patients with non-NSAID and non-Hp ulcers have increased. This type of ulcers are said to be more common among the elderly, patients with advance comorbidities, smokers among others (3). More importantly, its relation to complications, recurrent ulcer bleeding and complex treatment makes it a challenging disease entity that deserves attention in the field of PUD.

OBJECTIVES

General Objective

- to determine the clinical and endoscopic characteristics of non-*Helicobacter pylori*, non-NSAID peptic ulcer disease at the University of Santo Tomas Hospital from July 1, to December 31, 2015

Specific Objectives

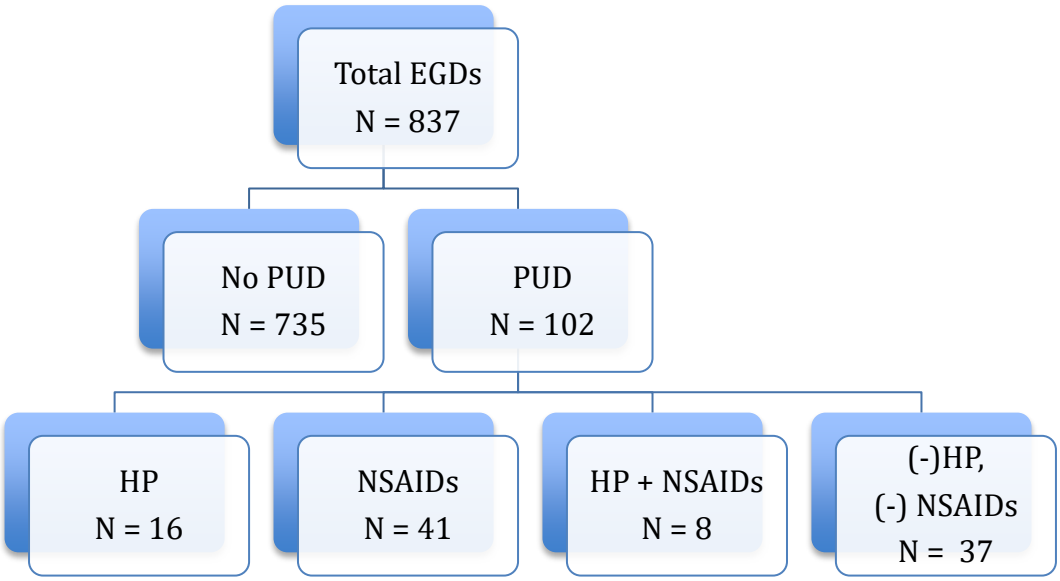
- to determine proportion of patients with peptic ulcers who have no *H pylori* infection and have not taken 1) ASA 2) NSAIDs 3) antiplatelet agents and 4) anticoagulant agents at the University of Santo Tomas Hospital (USTH) from July 1 to December 31, 2015
- to evaluate other variables (smoking, alcohol intake, comorbid illnesses) which may contribute to the development of non-Hp, non-NSAID, non-anticoagulant, non-antiplatelet peptic ulcers
- to investigate the clinical presentation of non-*Helicobacter pylori*, non-NSAID peptic ulcer disease patients
- to identify the endoscopic characteristics of non-*Helicobacter pylori*, non-NSAID peptic ulcer disease patients

METHODOLOGY

Patients who underwent upper GI endoscopy from July 1, 2015 to December 31, 2015 at the University of Santo Tomas Hospital were included in this study. Age, gender, alcohol and smoking history, comorbid illnesses, and medications were recorded. The severity of co-morbid illness was graded according to the American Society of Anesthesiology (ASA) classification: grade 1 = normal healthy patient, grade 2 = mild systemic illness, grade 3 = severe but incapacitating systemic illness, grade 4 = life-threatening systemic illness, and grade 5 = morbid illness. A list of locally available Aspirin, anticoagulants, antiplatelets, NSAIDs, including their generic and brand names, was presented to the subject to facilitate recollection of recent intake. Aspirin, anticoagulants, antiplatelets, NSAIDs use is defined as intake of at least 1 dose within 4 weeks prior endoscopy. An ulcer is defined as a mucosal break with an apparent depth and a diameter measuring at least 5 mm. Biopsy specimens were taken from the antrum and body of the stomach. Hp infection was assessed using rapid urease test (RUT) (CLO test) and histology (hematoxylin and eosin stain and Giemsa stain). A positive Hp is demonstrated as change of color from yellow to pink using the CLO test kit or presence of Hp in histologic specimens. True non-Hp, non-NSAID ulcers are defined as the absence of HP infection and exposure to Aspirin, anticoagulants, antiplatelets, NSAIDs within 4 weeks prior endoscopy. Ulcer size, location, and number were also recorded.

Nominal data were expressed as percentage, whereas mean ± standard deviation for parametric data. T-test was used for continuous variables, while the Chi square test was used for categorical variables. p value < 0.05 was considered significant.

CONCEPTUAL FRAMEWORK



RESULTS

Among 837 patients who underwent upper GI endoscopy between July 1, 2015 and December 31, 2015, 102 (12.2%) were diagnosed with peptic ulcers. Mean age was 62±15 years. There were 53 (52%) male subjects while 49 (48%) were females. There were significantly more female patients in the non-NSAID, non-Hp group than in the NSAID/Hp group (p = 0.04). No significant difference was seen in smoking and alcohol intake between the two. However, patients with NSAID/Hp intake and Hp infection presented with more comorbid illnesses than patients in the non-NSAID, non-Hp group (p = 0.03).

Table 1. Patient demographics

	Non-NSAID, Non-Hp	**NSAID, Hp**	***p* value**
Age	62±15	62±15	0.2
Gender			
Male	5 (29.4)	48 (56.5)	0.04
Female	12 (70.6)	37 (43.5)	
Smoking	3 (17.6)	18 (21.2)	0.7
Alcohol	3 (17.6)	17 (20)	0.8
Comorbid illneses	17 (16.7)	85 (83.3)	0.03
ASA 1	11 (64.7)	30 (35.3)	
ASA 2	3 17.6)	44 (51.8)	
ASA 3	3 (17.6)	11 (12.9)	
ASA 4	0	0	
ASA 5	0	0	

Regardless of etiology, majority of the patients were in the elderly age group at 50 years or more, particularly between the 60-69 age range. Median age was 67 years. There was no significant difference between the means of the non-Hp, non-NSAID group (62±15) versus the Hp/NSAID group (62±15).

Table 2. Frequency of ulcers according to age group

Age Group	Non-Hp, non-NSAID	Hp	NSAID	Hp + NSAID
20-29	2 (5.4)	1 (6.3)	1 (2.4)	0
30-39	3 (8.1)	1 (6.3)	2 (4.9)	0
40-49	3 (8.1)	1 (6.3)	2 (4.9)	1 (12.5)
50-59	4 (10.8)	2 (12.5)	5 (12.2)	5 (62.5)
60-69	15 (40.5)	3 (18.8)	16 (38)	1 (12.5)
70-79	6 (16.2)	8 (50)	12 (29.3)	1 (12.5)
80-89	4 (10.8)	0	3 (7.3)	0
≥90	0	0	1 (2.4)	0

Across all ASA classes, there were significantly more comorbidities in the NSAID/Hp group than in the non-Hp, non-NSAID group. Most of the patients had hypertension (35%), followed by diabetes (10.8%) and coronary artery disease (CAD) (10.8%), and liver cirrhosis (6.9%). In the non-Hp, non-NSAID group, majority did not have any comorbid illness (20.6%). In this group, most commonly seen was hypertension in 7.8% followed by cirrhosis in 4.9%.

Table 3. Comorbid illnesses

Comorbid illness	Non-Hp, non-NSAID	Hp	NSAID	Hp + NSAID
Hypertension	8 (7.8)	6 (5.8)	18 (17.6)	4 (3.9)
Diabetes	1 (0.9)	2 (1.9)	6 (5.8)	2 (1.9)
CAD	0	1 (0.9)	7 (6.8)	3 (2.9)
Cirrhosis	5 (4.9)	1 (0.9)	1 (0.9)	0
Arthritis	0	0	5 (4.9)	1 (0.9)
Dyslipidemia	1 (0.9)	0	0	0
Bronchial asthma	0	7	0	0
COPD	1 (0.9)	0	0	0
Cholelithiasis	1 (0.9)	0	0	0
Dermatomyositis	1 (0.9)	0	1 (0.9)	0
Polycythemia	1 (0.9)	0	1 (0.9)	0
Stroke	1 (0.9)	1 (0.9)	0	0
Goiter	1 (0.9)	0	0	0
None	21 (20.6)	6 (5.8)	13 (12.7)	1 (0.9)

The most common initial presentations were upper GI bleeding in 40% and abdominal pain in 36%. Other symptoms included symptomatic anemia, reflux and bloatedness.

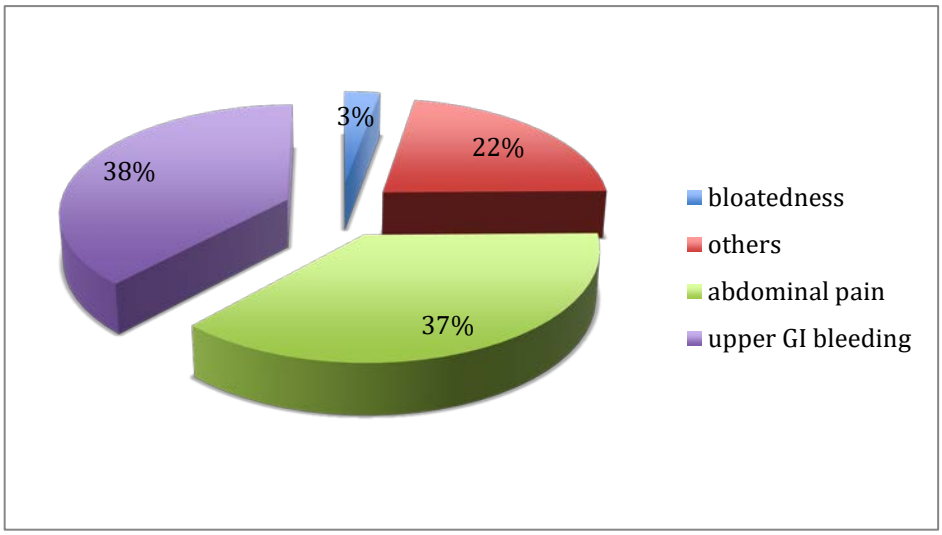


Figure 1. Indications for esophagogastroduodenoscopy in patients found to have peptic ulcer disease

Of the 102 ulcers, 16 (15%) of these patients had documented Hp infections, 41 (40.2%) had history of Aspirin, anticoagulant, antiplatelet, NSAID intake, and 8 (8%) were positive for both. There were 37 (36%) patients who had negative Hp and NSAID/ASA intake.

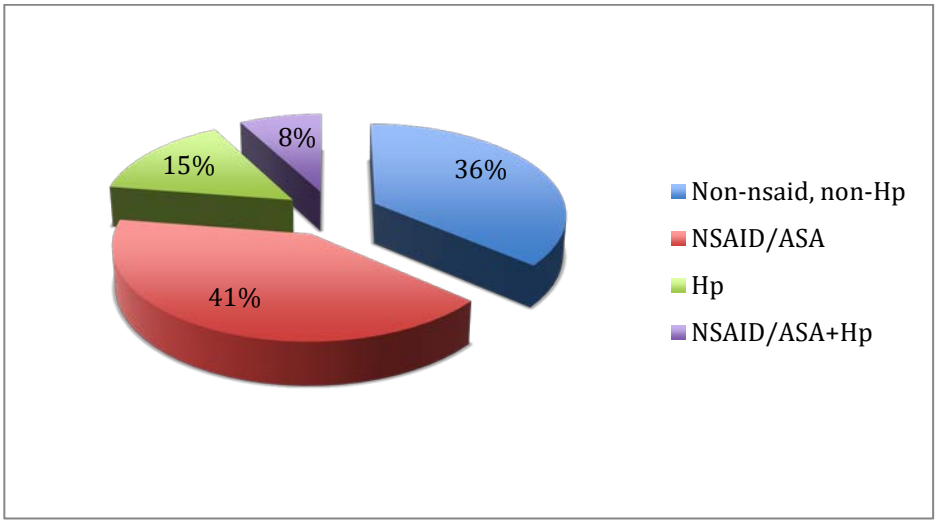


Figure 2. Distribution of ulcers according to etiology

Seventy-four (73%) were located in the stomach, 16 (16%) were in the duodenum, while 12 (11%) involved both the stomach and duodenum. Most of the ulcers were clean-based (77%), while 23% had stigmata of recent hemorrhage. Seventy nine (77%) measured 0.5 to 1 cm, only a minority were large ulcers measuring >2 cm (2.9%). There were no significant differences in terms of location, Forrest classification, size, and number of the ulcers between the 2 groups.

Table 4. Endoscopic characteristics

	Non-NSAID, Non-Hp	NSAID, Hp	*p* value
Location			0.6
Gastric	14 (82.4)	60 (70.6)	
Duodenum	2 (11.8)	14 (16.5)	
Gastric + duodenum	1 (8.3)	11 (12.9)	
Forrest			
Clean-based	15 (88.2)	64 (75.3)	0.6
With stigmata of recent hemorrhage	2 (11.8)	21 (24.7)	
Size			
0.5-1 cm	14 (82.4)	74 (87.1)	0.7
1-2 cm	2 (11.8)	9 (10.6)	
>2 cm	1 (5.9)	2 (2.4)	
Number			
Single	10 (58.8)	61 (59.8)	0.9
Multiple	7 (41.2)	41 (40.2)	

DISCUSSION

In this study, most of the ulcers were attributed to intake of NSAIDs, ASA, anticoagulants, antiplatelets at 40.2% while Hp-related ulcers were seen in 15%. Combined NSAID and Hp ulcers were noted in 8%. On the other hand, 36% were non-Hp, non-NSAID ulcers. These observations are similar to those of Chow and Sung wherein NSAID-related ulcers and ulcers not related to NSAID intake and Hp infection are increasing in contrast to Hp-related ulcers whose proportion is decreasing. This is related to the impact of eradication of Hp across the globe (2, 4). Locally, this was demonstrated by Wong, et al wherein the prevalence of Hp infection decreased significantly from 1996 to 2002 for both GU and DU (68.13 *vs* 33.48%, $P < 0.0001$; and 76.67 *vs* 36.50%, $P < 0.0001$, respectively), which corresponded to a decreased in the prevalence of PUD (5). In another study by de Lunas, et al, a declining incidence of Hp from 32% to 9% was recorded between 2004 and 2013 (6). Meanwhile, several studies have already proved an increasing prevalence of non-NSAID, non-Hp ulcers. Based on 6 reports published in 1999 to 2003, proportions of non-NSAID, non-Hp ulcers ranged from 1.3 to 4.1% versus reports in 2005 to 2006 wherein 10 to 30% were recorded (7).

Several risk factors predispose patients to develop idiopathic ulcers. Among them are age, comorbid illnesses, and smoking which were included in the analysis of this study. A number of studies have shown that idiopathic ulcer patients are significantly older than those with Hp and/or NSAID ulcers (7). Older age is associated with lower levels of prostaglandins, which are known to protect the gastric mucosa from damage making it vulnerable to ulcerogenic factors. In this study, although most of the patients belonged to the elderly age group, age did not significantly differ between the idiopathic and NSAID/Hp

groups.

According to Ijima et al, serious systemic complications are risk factors for idiopathic ulcers. This is based on data collected among patients in the intensive care units whose ulcers are unrelated to Hp infection (7). In a 7-year prospective cohort study in Prince of Wales Hospital, 50% of idiopathic ulcers were associated with ASA ≥3. This group of patients also had higher recurrent bleeding and mortality (8). In contrast to these prevailing reports, this study showed that non-Hp, non-NSAID ulcer patients had less comorbid illnesses than those of the NSAID group. This can be attribute to the association of hypertensive and CAD patients with the antiplatelet and anticoagulant use. However, in the review of the frequency of comorbid illnesses, cirrhosis ranked second to hypertension among idiopathic ulcer patients. Cirrhotic patients may be more susceptible to PUD because of impaired mucosal defense due to decreased prostaglandin synthesis (8). Portal hypertension also plays a role owing to visceral congestion disturbing the normal blood flow thereby inhibiting mucosal repair (7).

Smoking is also a risk factor for PUD primarily by impairing mucosal healing as well increase in xanthine oxidase activity, production of leukotrienes and nitric oxide, and neutrophil infiltration into the gastric mucosa (4). However, in this study, smoking did not significantly differ between the 2 groups.

Although the results of this study differ from other published studies, it was shown that non-NSAID, non-Hp ulcers are increasingly seen and are becoming significant causes of PUD. It will be interesting to investigate on other etiologies, long-term management, response to treatments, and outcomes of these patients to broaden our understanding of this disease.

CONCLUSION

Out of 837 EGDs, 102 (12%) patients had peptic ulcer. Non-Hp, non-NSAID ulcers were seen in 36% of these patients. Mean age was 62±15 and was similar between the 2 groups. Fifty-three (52%) were males and 49 (48%) were females. There were more females in the non-Hp, non-NSAID group than males (*p* 0.04). No significant difference was seen in smoking and alcoholic intake between the two groups (*p* 0.8). In this study, comorbid illnesses were not contributory in this type of ulcers (*p* 0.03). Patients with ulcers associated with Hp and NSAIDs are more commonly associated with comorbidities owing to their frequent use of Aspirin, antiplatelets, and anticoagulants. Cirrhosis was more frequently seen among patients with idiopathic ulcers because of impaired mucosal defense due to decreased prostaglandin synthesis as well as to disturbed mucosal blood flow because of portal hypertension. Most commonly, patiens presents with upper GI bleeding (38%) and abdominal pain (37%). Ulcer location, Forrest classification, size, and number did not differ between the non-HP, non-NSAID and the HP, NSAID groups.

REFERENCES

(1) Feldman, M., Friedman, L., and Brandt, L. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 10th edition. Saunders. 2016. pp 884-885.

(2) Chow, D. and Sung, J. *Best Practice & Research Clinical Gastroe*nterology 2009. 23: 3–9.

(3) Iijima, K., et al. Helicobacter pylori -negative, non-steroidal anti-inflammatory drug: Negative idiopathic ulcers in Asia. *World Journal of Gastroe*nterology 2014 January 21; 20(3): 706-713.

(4) Chung, C., Chiang, T., and Lee, Y. A systematic approach for the diagnosis and treatment of idiopathic peptic ulcers. *Korean Journal of Internal Medicine* 2015; 30:559-570.

(5) Wong, S., et al. Changing trends in peptic ulcer prevalence in a tertiary care setting in the Philippines: A seven-year study. *Journal of Gastroenterology and Hepatology* April 2015; 20: 4, 628-632.

(6) de Lunas, K., Romano, R., and Sollano, J. (2015). Decreasing Trend of Gastric Cancer and *Helicobacter pylori* Infection in the Philippines: A 10-year Observational Study. Unpublished manuscript.

(7) Iijima, K., et al. Helicobacter pylori -negative, non-steroidal anti-inflammatory drug: Negative idiopathic ulcers in Asia. *World Journal of Gastroe*nterology 2014 January 21; 20(3): 706-713.

(8) Wong, G., et al. High Incidence of Mortality and Recurrent Bleeding in Patients With Helicobacter pylori–Negative Idiopathic Bleeding Ulcers. *Gastroenterology* 2009; 137:525–531.

(9) Rajabalinia, H., et al. Non-Helicobacter pylori, non-NSAIDs peptic ulcers: a descriptive study on patients referred to Taleghani hospital with upper gastrointestinal bleeding. *Gastroenterology and Hepatology From Bed to Bench* 2012; 5(4):190-196.

(10) Chan, H., et al. Is non-Helicobacter pylori, non-NSAID peptic ulcer a common cause of upper GI bleeding? A prospective study of 977 patients. *Gastrointestinal Endoscopy* 2001. 53: 4, 2001.