Research Article

Risk factors in perforated peptic ulcer disease: Incidence and relation to morbidity and mortality

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Abstract

Background: Today, the hospital admission and surgical management for peptic ulcer disease is largely restricted to the treatment of its complications.

Aims: To study the risk factors of perforated peptic ulcer.

Patients and Methods: A prospective study of 118 patients presented with perforated peptic ulcers between January 2009 and December 2011 at Al- Yarmouk Teaching Hospital. A detailed history was documented including the proposed risk factors of age, gender, occupation, social habits and associated medical illnesses.

Results: The total number of patients was 118 patients. Out of these, 101 were males (86%) and 17 were females (14%); with the male: female ratio being 6:1. Patients in the fourth decade constituted the highest proportion of cases (38%); 78% non-professional employers; 43.2% used ulcerogenic drugs; 72.9% were smokers and 14.4% consumed alcohol. Negative history of peptic ulcer diseases were documented in 64.4%; 19.5% had associated medical; 44% had blood group O and *H. pylori* infection was positive in 75% of cases. Regarding the risk factors, *H. pylori* and smoking were more related.

Conclusions: Nonprofessional employer males in the fourth decade of life were the commonest in this collection. Combined risk factors of *H. pylori* and the use of NSAID formed the highest risk. Negative past history, those with group O and smoking were important risk factors in this study. Regarding the relation of risk factors to morbidity and mortality, medical co-morbidities & smoking had significant relation.

Keywords: Peptic ulcer, Perforation, Risk factors

INTRODUCTION

Peptic Ulcer Disease (PUD) remains a major public health problem worldwide, and it is one of the most common and costly GI diseases (including lost work time and productivity, are estimated to be above 8 billion (USD) per year in the US).[1] Globally the life time prevalence of PUD is 10% of the population.[2]

Duodenal ulcers are twice as common as gastric ulcers and males out number females by a factor of 4.[3] The population with gastric ulcers tends to be older,(so higher mortality than duodenal ulcer), this is due to the increasingly common use of NSAIDs including aspirin in this elderly cohort, many of whom also have *H. pylori* infection.[4] PUD is more prevalent in low socioeconomic

groups and considerably more common in the developing world than in the west.[1, 4]

Risk factors:

Helicobacter pylori (H.pylori): It is now widely accepted that infection with *H. pylori* is the most important factor in the development of peptic ulceration.[1, 3] Sometimes it can disrupt the mucous layer and inflame the lining of the stomach or duodenum, producing an ulcer.[2]

NSAIDs: (non-steroidal anti-inflammatory drugs): After *H. pylori* infection, ingestion of NSAIDs is a common predisposing factor of PUD.[3] The prevalence of peptic ulcer in chronic NSAID users is about 25% (15% gastric and 10% duodenal). Complications of PUD (specifically hemorrhage and perforation) are much more common in patients taking NSAIDs.[1, 3]

Smoking: Smoking increases gastric acid secretion and duodenogastric reflux. Smoking decreases both gastroduodenal prostaglandin production and pancreaticoduodenal bicarbonate production, which can increase a person's chance of getting an ulcer, also slows the healing of existing ulcers and contributes to ulcer recurrence.[1, 5]

Caffeine: Beverages and foods that contain caffeine can stimulate acid secretion in the stomach. This can aggravate an existing ulcer, but the stimulation of stomach acid can't be attributed solely to caffeine.[6]

Alcohol: Alcohol is commonly mentioned as a risk factor for PUD,[7] but confirmatory data are lacking.[1] PUD often linked to heavy alcohol consumption.[6]

Stress: Emotional stress is no longer thought to be a cause of ulcers, but people who are experiencing emotional stress often report increased pain of existing ulcers.[1]

*Blood Group:*Recently, Borén and coworkers[8] have shown that persons with blood group O have more *H. pylori* receptors.

PATIENTS AND METHODS

This is a prospective case series study of 118 patients who presented with perforated peptic ulcers (PPU) at the surgical department of Al-Yarmouk Teaching Hospital in Baghdad between Jan. 2009 and Jan. 2012.

A detailed history was documented with the risk factors that are related to the condition including age, gender, occupation, family, social and drug history with medical associated illnesses. The numbers of PPU cases are recorded in different seasons of the year to study its variation.

All patients in this study were resuscitated on admission in the casualty department. Examination and investigations were done and a decision for surgical intervention was taken. All patients included in the study have a proven diagnosis of perforated peptic ulcer (PPU) intra-operatively.

H. pylori infection was assessed by serology, Immunoglobulin G (IgG) antibody against *H. pylori* by using the ELISA method (Enzyme-linked immunosorbent assay), and blood samples for this test were obtained preoperatively or 1st day postoperative. Morbidity and mortality were recorded.

On discharge, positive serology patients for *H.pylori* were put on triple regime to eradicate *H. Pylori*, and were followed in the out-patient department for up to 2 months after surgery.

All data were analyzed using statistical package for social sciences (SPSS) computer software version 19 using Chi square (chi^2) and multivariate analysis with a probability value of <0.05 as a statistically significant value.

RESULTS

Regarding the gender of patients, 101 were males (85.6%) and 17 were females (14.4%); with the male: female ratio being 6:1. (Fig.1)

The mean age (±SD) was 38.8±14years (range: 18-82 years), the median age was 35 years. The mean age of female patients (44.7±12 years) was higher than males (37.7±14 years).

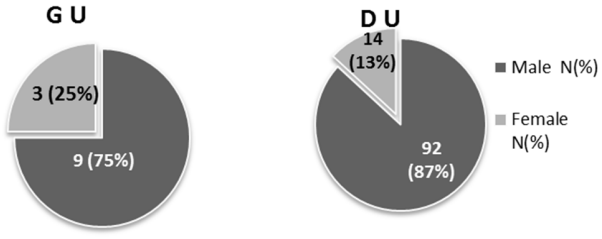

Figure 1. Sex distribution for perforated gastric and duodenal ulcer.

The incidence of PPU was highest among patients whether male or female in the 4th decade of life (45 patients; 38.1%). (Tab. 1)

Table 1. Distribution of Different Age Groups

Age (years)		11-20	21-30	31-40	41-50	51-60	>60	Total
D U	Male	2	27	38	7	10	8	92
	Female	0	1	6	3	2	2	14
	No. (%)	2 (1.9	28 (26.4)	44 (41.5)	10 (9.4)	12 (11.4)	10 (9.4)	106 (100)
G U	Male	0	0	1	3	4	1	9
	Female	0	0	0	1	2	0	3
	No. (%)	0	0	1 (8.3)	4 (33.4)	6 (50)	1 (8.3)	12 (100)
Total (%)		2 (1.7)	28 (23.7)	45 (38.1)	14 (11.9)	18 (15.3)	11 (9.3)	118 (100%)

The occupations were classified to three main groups (categories):

A) Non-Employed (dependent on others for living).

B) Nonprofessional employee (non-educated)

C) Professional (educated)

The highest percentage (78%) of PPU was recorded in the nonprofessional group and the lowest (6%) was recorded in professional group (6%). (Table2)

Table 2. Occupation Distribution

	D U	%	G U	%	Total (%)
A (Dependent)	14	13.2	5	41.7	19 (16)
B (Employers)	86	81.1	6	50	92 (78)
C (Professional)	6	5.7	1	8.3	7 (6)
Total	106	89.8	12	10.2	118 (100)

According to the NOAA (National Oceanic and Atmospheric Administration); national Climatic Data Center in USA:

http://www.ncdc.noaa.gov/oa/climate/afghan/iraq-narrative.html.

The seasonal weather for Iraq is classified as shown below:

Spring (April &May), Summer (June-September), Autumn (October & November) and Winter (December-March).

Table 3. Month and season distribution of patients

Season	Month	No of patients /Month	Patients/total patients % per season
Spring	April	8	17/118 = **14.5%**
	May	9	
Summer	June	10	39/118 = **33%**
	July	11	
	August	8	
	September	10	
Autumn	October	4	13/118 = **11%**
	November	9	
Winter	December	13	49/118 = **41.5%**
	January	12	
	February	13	
	March	11	
TOTAL		**118**	**100%**

The commonest presentation was in the winter {49(4105%)} patients followed by summer season {39(33&)}. The highest presentation was in February and December (13 patients in each) as shown in Tab. 3.

Fifty one patients (43.2%) were current ulcerogenic drugs users; out of them, 48 (40.7%) patients were using NSAIDs and only 3 patients were steroid users (2.5%). The type of NSAIDs was mainly acetylsalicylate (either Aspirin or Aspegic) in 58.8% of them (30/51). (Fig.3). A higher percentage of NSAIDs ingestion was found in perforated gastric ulcer (9/12; 75%) than perforated duodenal ulcer (42/106; 39.6%).

Table 4. Risk factors

	No.	%(per total)	Combined Risk Factors	No.	%(per total)
NSAID	51	43.2	NSAID + Smoking	11	9.3
Active Smokers	86	72.9	Smoking + Alcohol	10	8.5
Alcoholic	17	14.4	NSAID + Alcohol	7	6
(HP) Infection	89	75.4	*H. pylori* + NSAID	27	22.8
			Total	**55**	**46.6**

Social history of smoking habit was recorded in 86 patients (72.9%); most of them were regular active smokers for more than 5 years and smoke more than one pack per day (20 cigarettes/day); out of those 86 patients 5 were females (5.8%) and 81 were males (94.2%). Drinking alcohol was reported in 14.4% (17/118), all of them were males. (Tab.3)

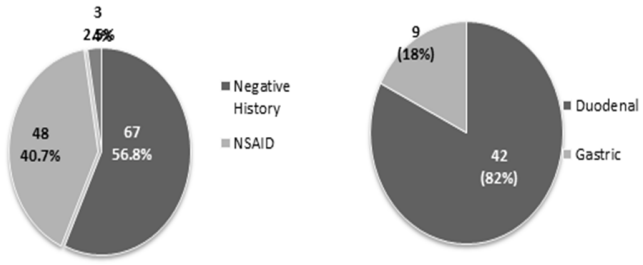

Figure 2. Drug history.

Out of 118 cases, 42 (35.6%) were previously diagnosed as having peptic ulcer prior to perforation and the remaining 76 (64. 4%) had no past history. Out of 42 patients, 2 patients were currently under anti-ulcer treatment at the time of perforation and the remaining had taken medical treatment at one time. (Fig.3)

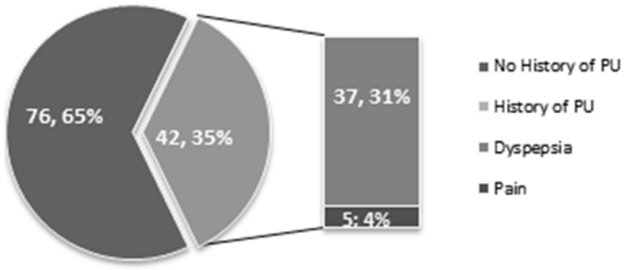

Figure 3. History of peptic ulcer.

Twenty three patients (19.5%) had associated comorbid diseases. Cardiovascular (IHD and Hypertension), and diabetes mellitus were the most frequently associated conditions. (Fig.4)

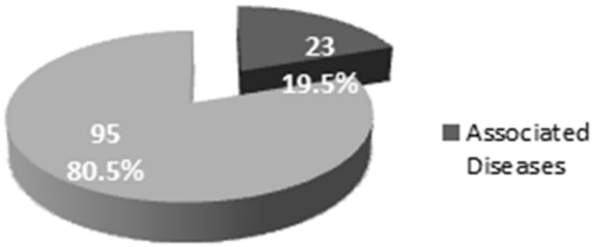

Figure 4. History of medical illness.

In our study, we found that the highest number of patients have blood group O [52 patients (44%)] and the lowest found in group AB [10 patients (8%)]. Most of blood groups were rhesus positive (Rh^+) (95%). (Tab.5)

The Helicobacter pylori infection was positive in 75.4% (89/118) divided into 8 patients of PGU (6.8%), and 81 patients of PDU (68.6%). (Fig.6) *H. pylori* eradication with a 2-weeks triple-drug regimen was given to every patient who was serology positive for *H. pylori*. Only 36 patients (30.5%) were attended for subsequent follow up and accepted to have endoscopy, 31 patients were serology positive for *H. pylori. H. pylori* eradication was achieved in 23 patients of them (74.1%). (Tab.14)Endoscopic healing was achieved in 91.6% of them (33/36).

Tab.5 Distribution of Patients between Different Blood Groups

Blood Groups		A	B	AB	O	Total
DU	Male	14	29	7	42	92
	Female	3	4	2	5	14
	No. (%)	17 (16)	33 (31.1)	9 (8.5)	47 (44.4)	106 (100)
GU	Male	2	3	1	3	9
	Female	1			2	3
	No. (%)	3 (25)	3 (25)	1(8.3)	5 (41.7)	12 (100)
Total patients(%)		20 (17)	36 (30.5)	10 (8.5)	52 (44)	118 (100)

Regarding the relation of risk factors to morbidity and mortality, co-morbidities & smoking had significant relation as shown in table.6

In this series, 26(22%) patients had 45 complications. The commonest were chest infection and wound infection. Overall 30-day mortality was 7 patients (5.9%). The relation of risk factors to morbidity and mortality shows higher morbidities in patients having medical co-morbidities. A strong relation was found between associated medical diseases and smoking with smoking.

Table 6. relation of risk factors to morbidity and mortality on chi square analysis

Variables		n	%	Morbid n	%	P value	Died n	%	P value
Gender	Male	101	85.6	22	18.6	0.072	5	4.2	0.046*
	Female	17	14.4	4	3.4		2	1.7	
Age (years)	< 50	89	75.4	17	14.4	0.061	4	3.4	0.042*
	> 50	29	24.6	9	7.6		3	2.5	
Type of ulcer	DU	106	89.8	23	19.5	0.071	6	5.1	0.056
	GU	12	10.2	3	2.5		1	0.8	
NSAIDs	yes	51	43.2	12	10.1	0.072	3	2.5	0.074
	no	67	56.8	14	11.9		4	3.4	
Tobacco	yes	86	72.9	19	16.1	0.075	3	2.5	0.042*
	no	32	27.1	7	5.9		4	3.4	
Alcoholism	yes	17	14.4	5	4.2	0.065	1	0.8	0.075
	no	101	85.6	21	17.8		6	5.1	
Co-morbidities	yes	23	19.5	12	10.1	0.031*	5	4.2	0.002*
	no	95	80.5	14	11.9		2	1.7	
History of PUD	yes	42	35.6	9	14.4	0.074	2	1.7	0.067
	no	76	64.4	17	7.6		5	4.2	
Blood type	O	52	44	12	10.1	0.070	4	3.4	0.067
	B	36	30.5	7	5.9		2	1.7	
	A	20	17	5	4.2		1	0.8	
	AB	10	8.5	2	1.8		0		
	definitive	3	2.5	2	1.7		1	0.8	
* *P*< 0.05 statically significant									

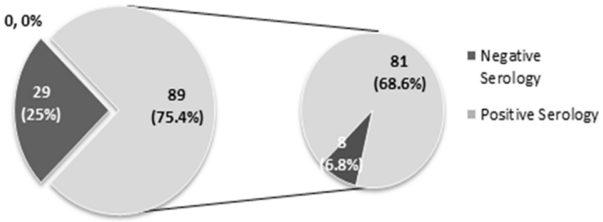

Figure 5. H. pylori infection in PDU and PGU.

DISCUSSION

Though the number of hospital admissions for uncomplicated peptic ulcer (PU) has decreased dramatically with advances in medical therapy for PUD, there is an increasing trend toward hospitalization for its complications such as hemorrhage and perforation.[9]

In our study, PPU was more common in males than females with a male:female ratio of 6:1. This was close to a study from Turkey[10] and a study from Europe[11] in each, the male:female ratio was 7:1. The mean age for men was younger (37.7 y) than that of women (44.7 years). These findings have also been observed by other studies,[12, 13] A possible explanation for these findings may be that some behaviors, such as smoking and drinking alcohol, are more frequent among men, thus increasing the risk of PUD and perforation, especially in young adults.

The present study showed highest incidence in the 3rd and 4th decade of life. Some studies reported most of the patients with PPU in the 3rddecade of life[14] while other was close to our study.[11] There is shift of age towards elderly in other parts of the world. It may be due to difference in lifestyle, psychological stress, and increasing use of aspirin and NSAIDs in that population.

The perforation rate was very high (78%) in non-professional people and low socioeconomic class and this is mostly due to poor compliance with medical treatment of known cases of peptic ulcer and high rate of infection with *H. pylori*, and stress in various forms. These results were very similar to the literature done in both developing and developed countries.[3, 15]

The relation of PPU and season was discussed in many studies, but frank association was not found.[16] In our study, the highest rate of perforation was noted during the months of winter (January, February and December). Sankar from India found the same trend.[17] There is no obvious explanation for this trend, but might be due to higher rates of NSAIDs ingestion in these months (i.e. winter) for joint pain and common cold.

More than one study reported that the incidence of ulcer perforations is influenced by the use of NSAIDs, which increase the risk of perforation, 3-5 times[18] and even to 8 times in some series. In several different populations it has been estimated that 15-35% of all peptic ulcer complications are due to NSAIDs.[19]

In this study, there were 51cases (43.2%) giving definitive history of recent ingestion of ulcerogenic drugs. Higher figures (56%) were reported in a study from Spain[20] and less (15%) in another one from Portugal.[21]

Higher percentage of NSAIDs related perforated gastric ulcer (PGU) 75% (9/12) compared with NSAIDs related perforated duodenal ulcer (PDU) 37% (39/106). This may be explained by the observation that most of PGU cases were chronic users for NSAIDs either as a part of their medical treatment (joint and back pains) or as a prophylactic antiplatelet therapy. This observation goes with the literature[3] and with a study from Pakistan.[22]

In the present series, (72.9%) were smokers and (14.4%) were alcoholics. In fact the evidence that tobacco or alcohol uses are risk factors for peptic ulcers is not conclusive.[23] A previous study reported that smoking is harmful to the gastroduodenal mucosa, and *H. pylori* infiltration is denser in the gastric antrum of smokers.[24] A prospective study of more than 47,000 men with duodenal ulcer did not find an association between alcohol intake and duodenal ulcer.[6] Another study found that the local irritative effects of ethanol and acute exposure to high concentrations are followed by severe gastric epithelial damage.[25]

In our study, alcoholic cases (14%) are markedly less than other series that estimated alcohol consumer in PPU were 25-50%.[17, 26]

We found a combination of social risk factors in our patients (like smoking with NSAIDs, or *H. pylori* with NSAID) in 55 patients (46.6%). These combinations were mentioned to increase the risk of PPU.[25] Although the idea was initially controversial, most evidence now supports the assertion that *H pylori* and NSAIDs are synergistic with respect to the development of PUD.[27] The steroid intake is associated with an increased risk of peptic ulcer only for patients concurrently taking NSAIDs, and for patients with a prior history of ulcer.[28]

In agreement with other studies[29] more than 60% of patients had no past history suggestive of PUD before the onset of perforation, and those with a known history of PUD were not on regular treatment. This is in sharp contrast to Nuhu[30] in Nigeria and Khan[31] in Pakistan who reported that about 60% of cases had previous history of peptic ulcer disease. It has been reported that in many developing countries, the diagnosis of PUD is first made in many instances after perforation.[15] The present study confirms this observation because more than 60% of the patients with perforation were not diagnosed previously as cases of PUD and were not on treatment. Patients with no previous diagnosis of PUD have a higher risk of PPU than patients with a known history of ulcer disease. This may be explained by the assumption that preventative measures are more likely to have been taken in patients with a known history of ulcer. Furthermore, these patients are perhaps more likely to seek treatment earlier.

Associated premorbid illness was documented in 23 patients (19.5%). Associated premorbid illnesses have been reported to influence the outcome of patients with PPUs.[32] One or more associated diseases are one of the significant factors associated with increased morbidity and mortality in patients undergoing surgery,[33] as reported in our study ($p< 0.05$).

In this study Group O was the most prevalent blood group (44%) followed by B (30%). Sharma *et al.*[34] from India found that PPU with blood group O (55%) was most common followed by B (22%), and Eduardo *et al.* from Mexico noted that the predominant blood group type in PPU was O (70%) then B (17%).[29]

Helicobacter pylori infection was most common in the lowest socio-economic class (85%). Developing countries have a higher rate of *H. pylori* infection.[3] Although the relationship between *H. pylori* infection and peptic ulcer has been well defined, the relationship with perforated ulcer is more controversial.[35] A report from Hong Kong found a high prevalence of *H. pylori* infection of up to 80% in patients with PPU.[36] Several studies found that the mean prevalence of *H. pylori* infection in PPU is only 68%, being similar to that reported in other peptic ulcer complications, such as gastric outlet obstruction.[37]

In our study the prevalence of *H. pylori* infection was (75%), out of them 31 patients were available for subsequent follow up. *H. pylori* eradication was achieved in 23patients (74.1%).

The prevalence of *H. pylori* infection in PPU varies markedly among studies [Tab. 7]. These controversial results may be due, at least partly, to several factors, as differences in frequency of NSAID use, the sensibility and specificity of diagnostic methods of *H. pylori*, or the possibility that the infection could have been eradicated by procedures aimed to treat the ulcer.[38]

Endoscopic healing was achieved in 91.6% (33/36) patients, and this coincides with results from other studies.[33, 39, 40] A lower percentage noticed in a study from India.[36]

Conclusion: Nonprofessional employer males in the fourth decade of life were the commonest in this collection. Combined risk factors of H. pylori and the use of NSAID formed the highest risk. Negative past history, those with group O and smoking were important risk factors in this study. Regarding the relation of risk factors to morbidity and mortality, medical co-morbidities & smoking had significant relation.

Table 7. H. pylori infection frequency and eradication in perforated ulcers in other studies

Author [reference]	Site of PPU	No. of patients	Diagnosis of *H. pylori*	*H. pylori* Prevalence (%)	*H. pylori* Eradication (%)
Rodríguez et al., University Hospital Marque´s de Valdecilla, Santander, Spain, 2005 [35]	DU, GU	92	S, Cu, RUT, UBT	68/92 (74%)	46/68 (67%)
Bose et al., Department of Surgery, Pondicherry, India, 2007 [36]	DU	93	RUT, H	60/93 (64%)	43/53 [b](81%)
Tran et al., faculty of medicine, Ho Chi Minh, Vietnam.2002[40]	GU, DU	111	RUT, H, S	107/111 (96%)	102/107 (95%)
Kumar et al. Safdarjang Hospital, New Delhi, India 2002 [41]	DU	30	RUT, H	17/30 (57%)	4/17 [a](23%)
Our study, Al-Yarmouk Teaching Hospital, Baghdad, Iraq. 2012	DU, GU	118	S, H	89/118 (75%)	23/31 [c](74%)

PPU: perforated peptic ulcer, DU: duodenal ulcer, GU: gastric ulcer, RUT: rapid urease test, H: histology, S: serology, UBT: urea breath test, Cu: culture.
a **Eradication therapy involved only ranitidine in this study.**
b **7 patients were not available for subsequent follow up.**
c **66 patients with *H. pylori* serology positive did not attend for follow up.**

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