

A Clinicopathological Study of Patients Presenting with Peptic Perforation to Hamidia Hospital Bhopal

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Abstract

Introduction: Although the incidence of peptic ulcer disease has reduced, the peptic ulcer perforation rates remain constant. The incidence of perforated peptic ulcer is approximately 7 to 10 cases per 100000 population per year; with short term morbidity and mortality upto 30% and 50% respectively [1]. Worldwide variation in demography, socioeconomic status, *Helicobacter pylori* prevalence and prescription drugs make investigation into risk factors for PPU difficult. Appropriate risk-assessment and selection of therapeutic alternatives becomes important to address the risk for morbidity and mortality.

Material and Methods: The study was carried out in Gandhi Medical College and Associated Hamidia Hospital, Bhopal with sample size of 124 between January 2016 and May 2017 Focus of the study was to elicit etiological factors, gender and age distribution, clinical presentation, laboratory and radiological investigations, type of perforation, size and site of perforation, post-operative recovery and complications, peritoneal fluid culture, biopsy from margin and *H. pylori* positivity. All the observations are recorded in a tabular form. Finally a statistical analysis has been done to highlight the factors contributing to morbidity and mortality and various scores predicting post-operative outcome.

Results and Observations: Overall incidence of gastric perforation was more than duodenal perforation with prepyloric region being the most common site. Male: female ratio was 4.85:1. Incidence of duodenal perforation was more in younger age group as compared to gastric perforation which is common in the elderly population. Alcohol intake, smoking, tobacco chewing and NSAIDs were important risk factors for development of perforated peptic ulcer. The signs of symptoms were consistent with those of peritonitis in all patients. Deranged pre-operative renal function tests and arterial blood gas analysis, and presence of pre-operative co-morbidities was consistent with poorer post-operative outcomes. None of the patients underwent any definite ulcer surgery during operative management showing an increasing trend towards use of post-operative proton pump inhibitors. *E. coli* was the most common organism isolated from the peritoneal fluid (24.4%) followed by *Klebsiella*. A total of 77 patients out of 124 patients reported complications, of which, lung complications (37 patients) and wound complications (43 patients) were the most common. Mortality was seen in 26 patients (20.96%) and it was higher in older patients. Histopathology was positive for malignancy in only one patient showing that malignancy is a rare cause of perforated peptic ulcer in the Indian Sub-continent. *H. pylori* positivity was found in 54.54% of the study. Prognostic scores- Boey Score and MPI Score was used to predict outcome. Boey Score of 3 was associated with higher mortality and Mannheim Peritonitis Index Score >26 was associated with increased morbidity and mortality.

Conclusion: In patients of gastroduodenal perforation risk of complications increases with age and other co-morbidities, thus special consideration and efforts should be made to treat the elderly patient to prevent morbidity and mortality. Boey Score can be used as good predictor in terms of post-operative mortality and Mannheim Peritonitis Index can predict the outcome in terms of post-operative morbidity.

Keywords: Peptic Ulcer Perforation; Gastroduodenal Perforation; MPI; Boey Score; *H. pylori*

Abbreviations

PUD: Peptic Ulcer Disease; PPU: Perforated Peptic Ulcer; *H. pylori*: *Helicobacter pylori*; MPI: Mannheim Peritonitis Index; ROC: Receiver Operator Characteristics; AUC: Area Under Curve

Introduction

Perforated gastric and duodenal ulcer is a common surgical emergency worldwide which is associated with high morbidity and mortality. Each year peptic ulcer disease (PUD) affects 4 million people around the world [1]. Complications are encountered in 10%-20% of these patients and 2% - 14% of the ulcers will perforate [2]. Perforated peptic ulcer (PPU) is a life threatening disease and the mortality varies from 10% - 40%

Globally the incidence of peptic ulcer disease is said to have fallen in recent years. Also recent advances have taken place in both diagnosis and management of peptic ulcer disease, namely improvements in endoscopic diagnostic and therapeutic facilities, the increased use of proton pump inhibitors and *Helicobacter pylori* eradication therapies. In spite of all these, peptic ulcer perforation rates have remained unchanged [3] and therefore remain a major health challenge. The pattern of perforated PUD is said to vary from one geographical area to another, depending on some socio-demographic and perhaps environmental factors [4]. In a developing country such as ours, the patients presenting with perforated PUD are comparatively young with a dominant male preponderance [5,6]. This is in contrast to the developed countries where the patient population with perforated PUD are mainly the elderly with less pronounced incidence differences between sexes. It is probable that the very strong association with smoking and alcohol among the young male population may account for the high incidence in developing countries. Certainly in the West the high incidence is due to ulcerogenic drug ingestion amongst the elderly population [7]. At least half of the world's population are infected by *H. pylori* making it one of the most wide spread infections in the world. Actual infection rate vary from nation to nation; developing countries have a much higher infection rate as compared to the developed countries where rates are estimated to be around 25%. Despite high rates of infection in certain areas of the world, the overall frequency of *H. pylori* infection is declining.

PPU presents as an acute abdominal condition, with localized or generalized peritonitis and a high risk for developing sepsis and death. Clinical prediction rules are used, but accuracy varies with study population. Early surgery, either by laparoscopic or open repair, and proper sepsis management are essential for good outcome. Appropriate risk-assessment and selection of therapeutic alternatives becomes important to address the risk for morbidity and mortality. The paucity in clinical progress and basic understanding of perforated peptic ulcers begs for increased attention in order to reduce morbidity and mortality.

Materials and Methods

The present study was carried out in Gandhi Medical College and Associated Hamidia Hospital, Bhopal with sample size of 124 between January 2016 and May 2017

Objectives

1. To evaluate the etiological factors of peptic perforation commonly presenting in Hamidia Hospital, Bhopal.
2. To evaluate the accuracy of history, clinical parameters, Laboratory and Radiological investigations in the diagnosis.
3. To compare and evaluate post-operative recovery and complications till time of discharge.
4. Accuracy of outcome predictions of different scoring systems-Boey Score and Mannheim Peritonitis Index (MPI).

Inclusion Criteria

1. Patients above 14 years of age.
2. Both male and female patients.

Exclusion Criteria

1. Patients presenting with features of gastric perforation who were managed conservatively.
2. Patients with associated solid organ injury and other hollow viscus injury (excluding stomach and first part of duodenum).

Following Plan of work

Preoperative work-up: Preoperative work-up included general information of the patient, symptoms and signs at the time of presentation, co-morbidities, general physical and per abdomen examination, routine blood investigations including renal function, arterial blood gas analysis and radiological investigations. All patients underwent pre-operative resuscitation, nasogastric tube insertion and catheterization.

All of the patients were operated under general anesthesia and preferable incision was midline. During operation following points were recorded: Amount of bilio-pyoperitoneum, site of perforation, size of perforation, surrounding wall and margin of perforation, lymph node status and any additional findings on exploration. One perioperative marginal biopsy was taken. The peritoneal soiling was cleared by peritoneal lavage and lavage fluid was suctioned out, the definitive procedure then performed. The choice of definitive procedure was dependent upon the condition of patient and the competency of the surgeon.

Post-operative work up: Post-operative work up included vital monitoring, routine blood investigations, culture sensitivity of lavage fluid, serology for H. pylori, and removal of drains, ryle’s tube and catheter. Post-operative complications and mortality was noted.

Prognostic Scoring: Two scores were used namely Boey Score and Mannheim Peritonitis Index.

Boey Score

Boey’s score, which is a score based on scoring factors as shock on admission, confounding medical illness, and prolonged perforation, has been found to be a useful tool in predicting outcome.

Risk factors included:

1. No of hours since perforation
 - Less than 24 hours score 0
 - More than 24 hours score 1
2. Concomitant severe medical illness
 - Absent score 0
 - Present score 1
3. Preoperative shock (Shock was defined as persistent hypotension with 1.Systolic BP less than 90 mm of Hg 2. Mean arterial pressure less than 60 3. Reduction in Systolic BP more than 40 mm of Hg from baseline.)
 - Absent score 0
 - Present score 1

Mannheim Peritonitis Index

Risk Factor	Weightage, if any
Age > 50 years	5
Female Gender	5
Organ Failure*	7
Malignancy	4
Preoperative duration of peritonitis > 24 hours	4
Origin of sepsis not colonic	4
Diffuse generalised peritonitis	6
Type of Exudate	
Clear	0
Cloudy, Purulent	6
Faecal	12

**Definitions of organ failure: Kidney: creatinine > 177 µmol/L, urea > 167 µmol/L, oliguria < 20 ml/h; Lung: pO₂ < 50 mmHg, pCO₂ > 50 mmHg; Shock: hypodynamic or hyperdynamic; Intestinal obstruction (only if profound): Paralysis > 24h or complete mechanical ileus.*

Statistical Analysis: Multivariate Regression Analysis was performed using SPSS Statistics 19, and Receiver Operating Characteristic (ROC) and Area Under Curve were calculated.

Observations and Results

Table 1 shows incidence of the sub-type of perforation and their relation to sex. Out of the total 124 patients, 102 patients (82.25%) show gastric perforation and 22 patients (17.75%) show duodenal perforations. Females show a slightly higher incidence of gastric perforation as compared to their male counterparts and vice versa for duodenal perforation.

S. No.		Total Cases N = 124		Incidence in Male N = 103		Incidence in Female N = 21	
1.	Gastric Perforation	102	82.25%	84	81.55%	18	85.71%
2.	Duodenal perforation (first part of duodenum)	22	17.75%	19	18.45%	3	14.29%

Table 1: Incidence of sub-types of perforation and their relation to sex.

Table 2 shows age-wise distribution of gastro-duodenal perforation. The youngest patient in the series was a 22 year old male and the oldest patient in the series was an 86 year-old female. The maximum number of patients belonged to age group between 40 - 70 years. Incidence of duodenal perforation was more in age group 40 - 60 years as compared to gastric perforation which showed higher incidence in age group > 60 years.

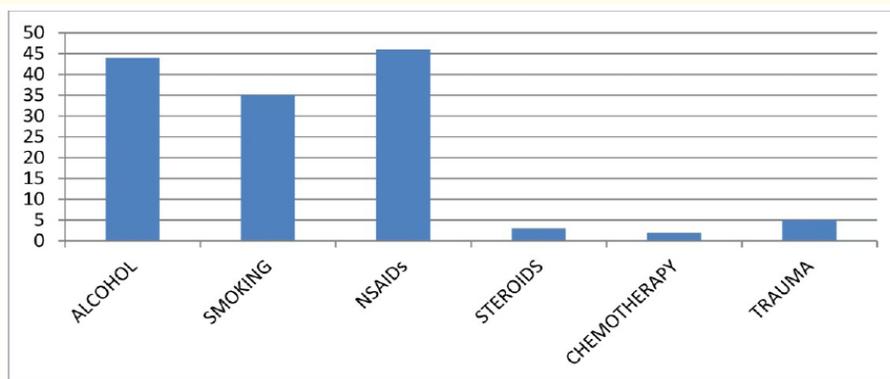
Age (years)	Gastric perforation (102)	Duodenal perforation (22)	Total (124)	Percentage
20 - 30	3	0	3	2.41
31 - 40	11	2	13	10.48
41 - 50	15	8	23	18.54
51 - 60	21	6	27	21.77
61 - 70	28	2	30	24.19
71 - 80	21	3	24	19.35
> 80	3	1	4	3.26

Table 2: Age-wise distribution.

Risk factor	Number	Percentage
Alcohol Intake	44	35.48%
Smoking and Tobacco	35	28.22%
NSAIDs	46	37.09%
Steroids	3	2.41%
Chemotherapy	2	1.61%
Trauma	5	4.03%

Table 3: Risk factors.

Out of the total 102 patients with gastric perforation, 32 (38.23%) gave history of regular NSAIDs use; as compared with duodenal perforation where 31.81% (7 patients) out of the total 22 patients gave similar history, signifying that NSAIDs is an important etiological factor for both gastric and duodenal ulcer perforation.



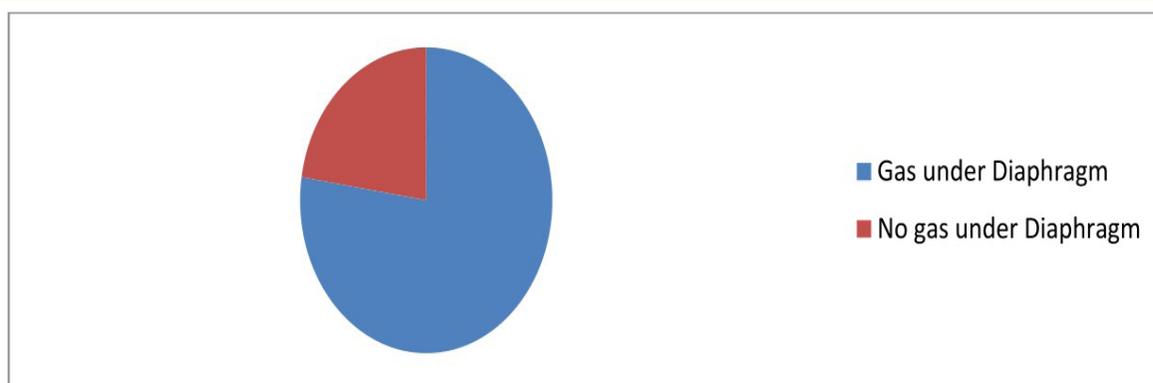
Graph 1: Risk factors for gastroduodenal perforation.

Presenting complaint	Number	Percentage
Presentation within 24 hours	21	16.93%
Pain	124	100%
Distension	124	100%
Vomiting	93	75%
Not passing flatus and motion (> 24 Hours)	117	94.35%
Fever	49	39.51%
Altered sensorium	31	25%
Decreased urine output	36	29.03%
Previous history of Dyspeptic symptoms	39	31.46%
Abdominal Tenderness	124	100%
Abdominal Guarding	118	95.16%
Abdominal Rigidity	113	91.12%
Absent bowel sounds	96	77.41%
Tachycardia (Pulse > 90/min)	116	93.54%
Hypotension (SBP < 90 mm Hg)	57	45.96%
Tachypnoea (respiratory rate > 26/min)	41	33.06%
Oliguria	42	33.87%
Shock (pulse and blood pressure not palpable)	18	14.51%

Table 4: Patient presentation.

Co-morbid conditions	Number	Percentage
Diabetes Mellitus	6	4.86%
Hypertension/CAD	14	11.29%
COPD/Asthma/past history of Tuberculosis	21	16.93%
Malignancy	2	1.61%
Absent	81	65.32%

Table 5: Presence of co-morbid conditions.



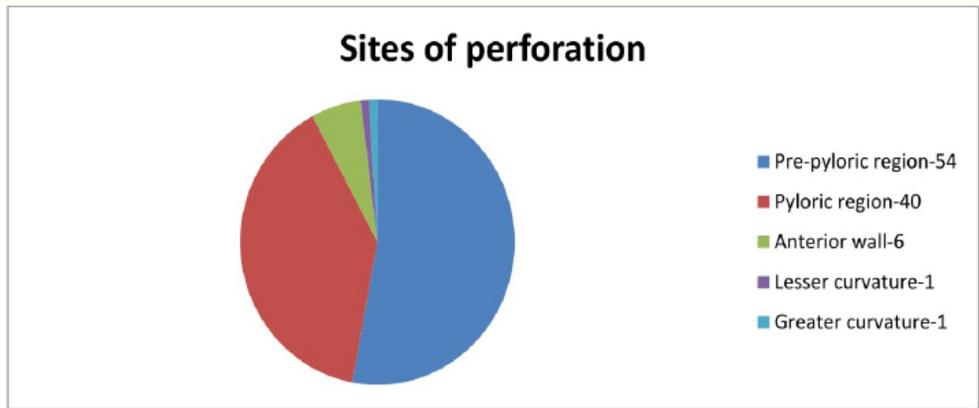
Graph 2: Radiological investigations.

All the patients underwent plain erect radiograph of chest and abdomen out of which 96 (77.4%) patients had gas under diaphragm. Out of the remaining 28 patients, 23 patients underwent ultrasound of abdomen which revealed septate ascites with internal air echoes.

Investigations	Finding	Number	Percentage
Haemoglobin	Less Than 9 Gm%	31	25%
Total Leucocyte count	More than 11,000 cells/cumm or less than 4500 cells/cumm	67	54.03%
Blood Urea	> 45 mg/dl	48	38.70%
Serum Creatinine	> 1.5 mg/dl	45	36.29%
Serum Sodium	> 145 mEq/L or < 130 mEq/l	53	42.74%
Serum Potassium	> 5.5 mEq/L or < 3.5 mEq/L	27	21.77%

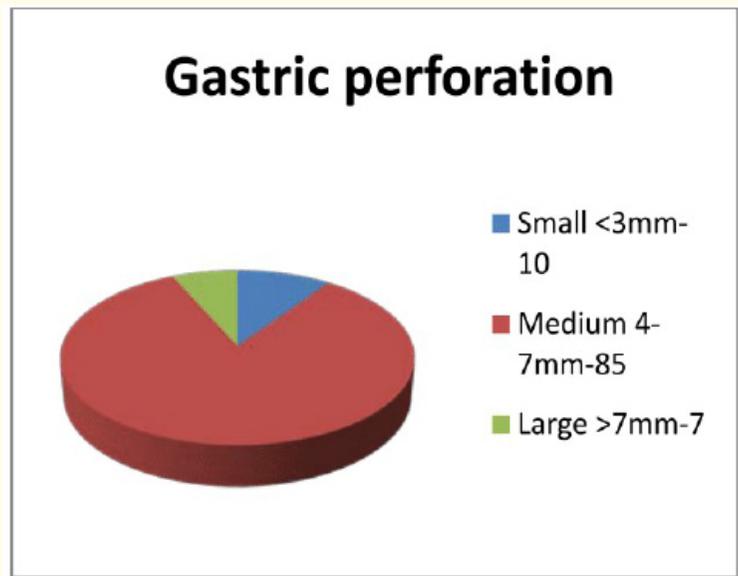
Table 6: Routine blood investigations.

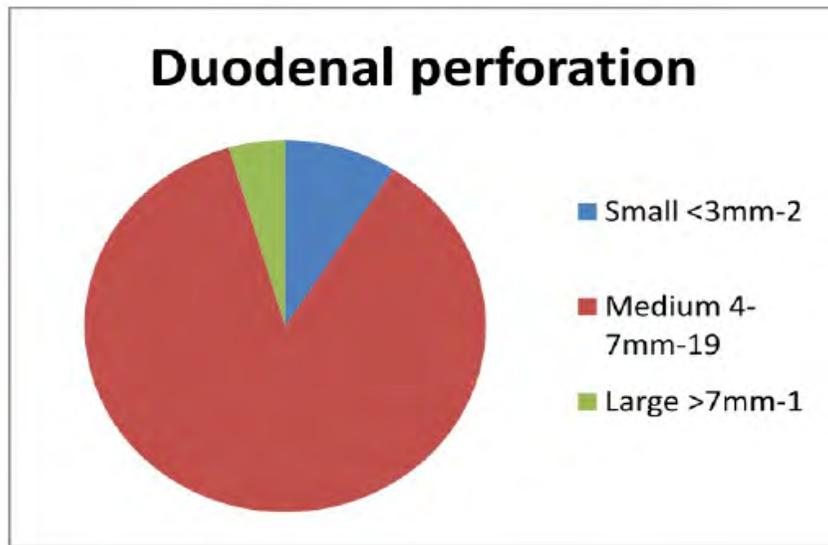
Poorer outcomes were associated with the following derangements in the routine blood investigations-haemoglobin less than 9 gm%, total leucocyte count more than 11,000 cells per cu mm or less than 4500 cells per cu mm, deranged renal function tests and deranged serum electrolytes.



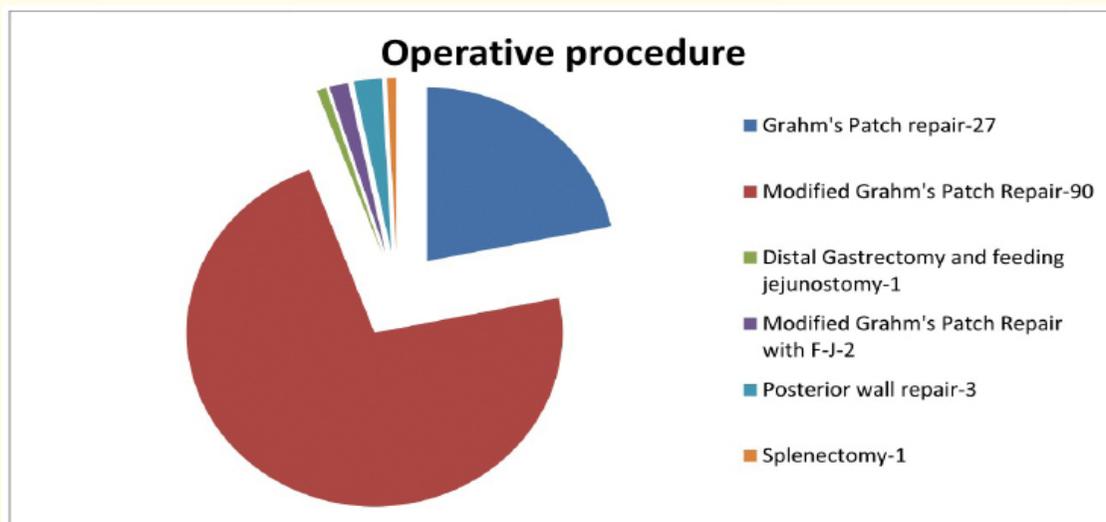
Graph 3: Sites of perforation.

Out of the total 102 patients with gastric perforation, maximum patients showed perforation in the pre-pyloric region of stomach (52.92%), followed by the pyloric region (39.21%), anterior wall (5.88%) and equal incidence in the lesser and the greater curvature (0.80%). Out of the patients with anterior gastric wall perforation, 5 patients had history of trauma. Out of these 5 trauma patients, 3 patients had a concomitant perforation in the posterior wall of stomach. For the purpose of this study, perforation in only the first part of duodenum is considered.





Graph 4: Size of perforation.



Graph 5: Operative procedures.

Peritoneal Cultures: The peritoneal fluid was obtained for culture and sensitivity in the 119 patients who presented with bilio-pyoperitoneum. *E. coli* was the most commonly isolated organism (24.40%) followed by *Klebsiella* (19.01%). *Bacteroides* sp. (anaerobic bacilli) and *Candida* sp. were isolated in almost 19% patients. Sterile cultures were found in 16.93% patients. Incidence of sterile culture was more in gastric perforation as compared with duodenal perforation however due to small number of cases of duodenal perforation as compared to gastric perforation, findings may be insignificant.

Complications	Number	Percentage (N = 124)	Remarks
Pneumonia and other lung complications	37	29.83%	Lung complications also include atelectasis, pleural effusion
Wound infection/Wound dehiscence	43	34.67%	Wound infections more common in patients with lung complications
Urinary tract infection (documented)	22	17.74%	Associated with prolonged catheterisation > 7 days
Suture leak	17	13.70%	Seen more in patients with older age, poor nutrition
Prolonged post-operative Ileus	12	9.67%	For the purpose of study defined as delay in GI motility beyond 5 days
Fistula	4	3.22%	All patients had concomitant wound infection or dehiscence
Sepsis	35	28.22%	More common in older patients, deranged renal function, poor nutrition
Mortality	26	20.96%	Older age patients were found to be at higher risk

Table 7: Post-operative complications.

Out of the total 124 patients, 77 patients reported complications

Out of the total 77 patients with complications, complications were seen more in older age group patients. Highest incidence was seen in patients of more than 80 years of age.

Biopsy: Out of the total 124 patients, biopsy from perforation margin was taken in 119 patients. The biopsy predominantly showed chronic inflammatory changes in 62.9% patients as compared to acute inflammation in only 15.32% patients. Malignancy was discovered only in 1 patient out of the total 119 biopsies.

H. pylori positivity: Out of the total 124 patients, 119 patients underwent *H. pylori* testing. 64.74% patients (66) with gastric perforation and 54.54% patients (12) with duodenal perforation showed increased titres of *H. pylori* antibodies in their serum.

Boey Score	Number	Morbidity	Percentage Morbidity	p-Value (Chi Square)
0	14	0	0	X ² = 23.24 df = 3 p < 0.001
1	46	15	32.60%	
2	45	30	66.6%	
3	19	19	100%	
Boey Score	Number	Mortality	Percentage Mortality	p-Value (Chi Square)
0	14	0	0	X ² = 78.54 df = 3 p < 0.001
1	46	0	0	
2	45	8	17.7%	
3	19	18	94.7%	

Table 8: Prognostic score predicting mortality-boey's score.

Regression Analysis was performed using SPSS Statistics 19. Receiver–operating characteristic (ROC) curve analysis demonstrated high predictive value of Boey score in predicting postoperative mortality (Figure 1.1) and morbidity (Figure 1.2) in our study. The area under the curve (AUC) in ROC curve analysis was 0.935 and 0.774 for mortality and morbidity, respectively. So although the Boey score was a good predictor of mortality and morbidity, its predictive ability was higher for post-operative mortality.

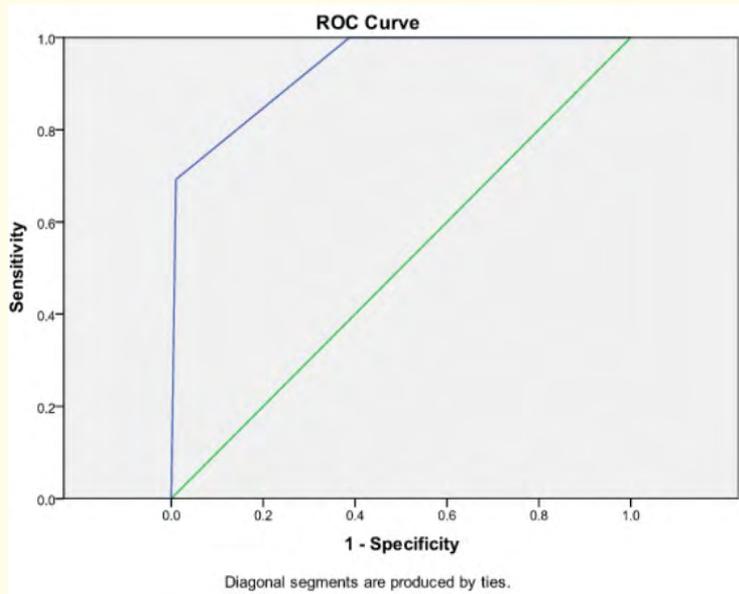


Figure 1.1: Mortality.

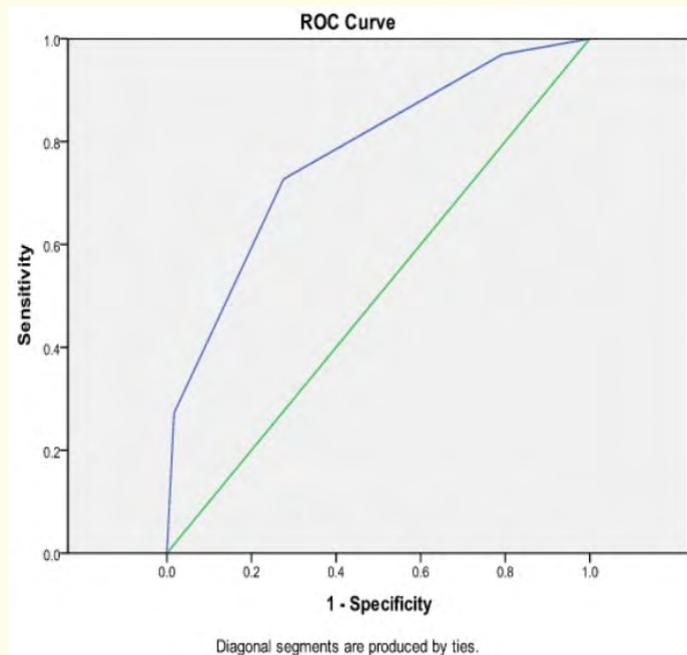


Figure 1.2: Morbidity.

Regression Analysis was performed using SPSS Statistics 19. Receiver–operating characteristic (ROC) curve analysis demonstrated high predictive value of MPI score in predicting postoperative mortality (Figure 2.1) and morbidity (Figure 2.2) in our study. The area under the curve (AUC) in ROC curve analysis was 0.892 and 0.920 for mortality and morbidity, respectively. So although the MPI score was a good predictor of mortality and morbidity, its predictive ability was higher for post-operative morbidity.

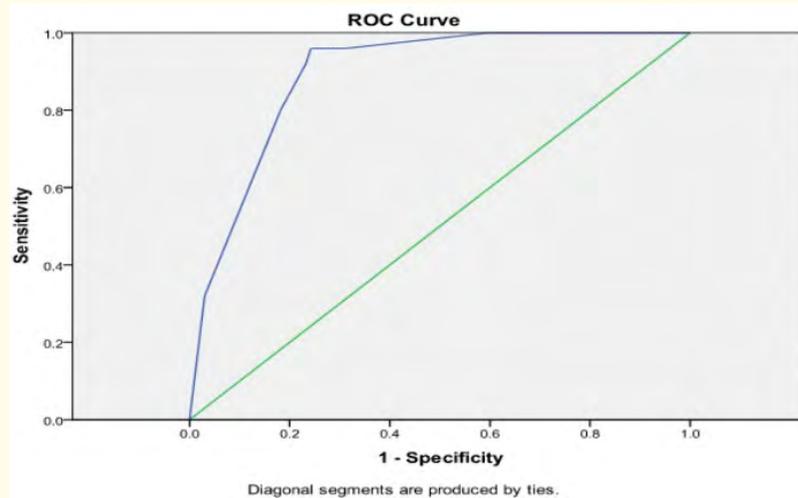


Figure 2.1: Mortality.

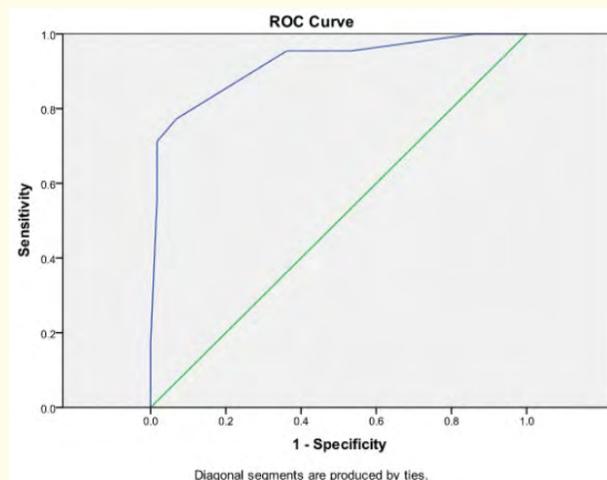


Figure 2.2: Morbidity.

Discussion

In developing countries, gastroduodenal perforation is predominantly seen in middle aged males. This is in contrast to developed countries where perforation is mainly seen in the elderly population with less pronounced differences in sex [5,6]. The male: female ratio in our study was 4.85:1. African cohorts from Nigeria, Kenya, Ethiopia, Tanzania and Ghana report of male rates from 6 to 13 times that of females. Similar patterns are reported from the middle East and Arab countries and parts of southern Asia [8-10]. Incidence of duodenal perforation was more in age group 40 - 60 years as compared to gastric perforation which showed higher incidence in age group > 60 years. In developing countries, the median age at diagnosis has increased by over 2 decades (from mid 30 - 40s to the 60s and above) [11-14].

As far as risk factors are concerned, alcohol intake, smoking, tobacco abuse and NSAIDs use emerged as important risk factors. Anderson, et al. in 107 patients of perforated peptic ulcer and 214 patients with bleeding ulcer showed that alcohol intake was more associated with bleeding ulcer rather than perforated ulcer [15]. A retrospective study by DS Collier, et al. on 269 patients showed elderly especially women were unduly susceptible to NSAID associated peptic ulcer perforation [16]. Another study by FH Smedley, et al. in 272 patients of gastroduodenal perforation confirmed the association of NSAID and complicated peptic ulcer in patients of over 65 years and highlighted the particular susceptibility of the gastric mucosa to their injurious effect [17].

Only 21 patients out of the total 124 patients presented to the emergency department within 24 hours. Average time lapse between onset of symptoms and presentation to tertiary centre was 2.5 days. Common symptoms at time of presentation were pain and abdominal distension. Only 39 patients had previous history of dyspeptic symptoms. Presence of co-morbidities was associated with poorer prognosis. Poorer outcomes were associated with the following derangements in the routine blood investigations-haemoglobin less than 9 gm%, total leucocyte count more than 11,000 cells per cu mm or less than 4500 cells per cu mm, deranged renal function tests and deranged serum electrolytes. Out of these parameters renal function was a major determinant in the outcome of the patients, which is also evident in the studies conducted by Testini M., et al. [18], Makela JT, et al. [3], Sillakivi T, et al [19].

Most common site of perforation was the pre-pyloric region followed by pyloric region. However, distinction between duodenal and gastric location can be difficult in the juxtapyloric region and in very inflamed and contaminated settings. Most patients underwent Modified Graham's Patch repair. None of the patients underwent any definitive surgery for peptic ulcer signifying a declining trend towards definitive procedure and an increasing trend towards use of proton pump inhibitors and *H. pylori* therapy.

Amongst the total 124 patients, 77 patients reported complications. Pneumonia and other lung complications were seen in 37 patients (29.83%). Wound infection and/or dehiscence was seen in 43 patients (34.67%) most of which overlapped with lung complications. Complications were higher in older patients. out of the total 77 patients, maximum complications was seen in the age group 60 - 80 years (36 patients), followed by 40-60 years (30 patients), 20 - 40 years (8 patients) and > 80 (3 patients). However, considering total number of individuals in the particular age group, maximum complications were seen in patients above 80 years of age (75%) followed by 60 - 80 years (66.66%).

Malignancy was discovered only in 1 patients out of the total 119 biopsies. Gastric malignancy is rare in the Indian Sub-continent and only 5 - 10% of all gastric perforations are caused by gastric carcinoma [20,21].

64.74% patients with gastric perforation and 54.54% patients with duodenal perforation showed increased titres of *H. pylori* antibodies in their serum. All the patients were given *H. pylori* kit containing proton pump inhibitor and two antibiotics. Dogra B., et al. in a study on 50 patients with peptic perforation found prevalence of *H. pylori* infection to be 92%, whereas, Aman., et al. in their study, found the prevalence of 85.1% [22,23]. Metzger J., et al. studied 45 patients with acute perforation of a gastric or duodenal ulcer, and found the prevalence of *H. pylori* was 73.3%. In contrast with the literature, they found roughly the same incidence of *H. pylori* infection for both gastric and duodenal ulcers [24]. Another study by Mahim Koshariya., et al. on 70 patients with gastro-duodenal perforation showed that perforated gastroduodenal ulcer was associated with *H. pylori* infection as a strong etiological factor and *H. pylori* infection status should be assessed at the initial endoscopy or operation, regardless of concomitant NSAID intake. If *H. pylori* infection is found, an appropriate eradication therapy should be initiated as soon as possible, as not only it is beneficial for eradication of *H. pylori* but it is also valuable in prevention of ulcer [25].

Receiver-operating characteristic (ROC) curve analysis demonstrated high predictive value of Boey score and MPI in predicting post-operative mortality and morbidity. Although both Boey score and MPI index were good predictors of morbidity and mortality, Boey score was a better predictor for mortality and MPI score > 26 was a better predictor of morbidity. In another study by Gulzar JS., et al. on 50 patients, logistic regression coefficient of Boey's score revealed that the risk increases with Boey's score. The accuracy of Boey's score in predicting morbidity and mortality was shown in terms of AUC (95% CI) which was 0.887 (0.790 - 0.985) for morbidity and 0.849 (0.730- 0.968) for mortality [26]. Kusumoto yoshiko., et al. evaluated the reliability of the MPI in predicting the outcome of patients with peritonitis in 108 patients. A comparison of MPI and mortality showed patients with a MPI score of 26 or less to have mortality of 3.8%, whereas those with a score exceeding 26 had mortality of 41.0% [27].

Conclusion

Although the incidence of peptic ulcer disease had reduced significantly over the past decade, the incidence of perforated peptic ulcer remains fairly constant and carries a high mortality. The classic triad of sudden onset of pain, tachycardia and abdominal rigidity is hallmark of perforated ulcer. Erect chest radiograph may not establish a diagnosis and a high index of suspicion is essential. Early diagnosis, prompt resuscitation, timely referral and an urgent surgical intervention are essential to improve outcomes. The risk of complications increases with age and other co-morbidities, thus special consideration and efforts should be made to treat the elderly patient to prevent morbidity and mortality. Although various scoring systems are used to prognosticate the outcome in peptic ulcer perforation patients, Boey Score can be used as good predictor in terms of post-operative mortality and Mannheim Peritonitis Index can predict the outcome in terms of post-operative morbidity.

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