

ORIGINAL RESEARCH

A STUDY ON EVALUATION OF SERUM AMYLASE LEVELS IN DUODENAL ULCER PERFORATION AND ITS COMPLICATIONS

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ABSTRACT:

Background: High serum amylase is frequently found in perforated duodenal ulcer (PDU), the rise in serum amylase occurs in cases of perforated peptic ulcer partly as a result of increase leakage of pancreatic enzymes rich fluid from the perforation site with subsequent absorption by peritoneal lymphatics & partly due to damage of pancreases by digestive enzymes that spilled through the perforation. Interestingly, the start of these trends all predated the use of H₂ receptor blockers, or proton pump inhibitors, fibre optic endoscopy, and highly selective vagotomy. However, the incidence of emergency surgery and the death rate associated with peptic ulcers has not decreased nearly so dramatically. **Aims and objectives:** The purpose of this study is to study signs, symptoms, mode of presentation and post operative complications associated with duodenal perforation and importantly to assess the Serum Amylase levels in duodenal perforation and correlate the levels with post operative complications.

Materials and Methods: 60 patients who underwent surgery (Graham's omental patch repair) for perforated duodenal ulcer in Department of General Surgery attached to SVS Medical College were studied from 1-1-2020 to 1-12-2021. The following factors were analysed in terms of morbidity and mortality: age > 18 years; gender; chronic ingestion of NSAIDs; alcohol ingestion and smoking, hemodynamic status on admission; ASA status; site and size of perforation; type of peritoneal collection and Serum Amylase level on the day of admission. Postoperative complications like wound infection, wound dehiscence, postoperative leak, septicaemia, respiratory complications, acute kidney injury and death were assessed and correlated with the Serum Amylase levels.

Results: 60 patients included in this study with proven perforated duodenal ulcer, 54 (90 %) were male and 6 (10 %) were female, male to female ratio was 9 :1. The mean age was 58.4 years, ranging from 31-75 years. The overall mortality was 28%. In 34 patients (57 %), the serum amylase was within normal range, the mortality in this group was NIL. The other 26 patients (43%) had level of 200 or above, the mortality in this group was 48 %. The size of perforation has prognostic significance, for the larger the perforation, the higher the mortality. Patients who were operated after 24 hours of admission and who had shock (systolic BP <90 mm Hg) on admission had significantly elevated Serum amylase levels and mortality in this group was 100%.

Conclusion: Limiting surgical delay in patients with PDU seems to be of paramount importance in reducing the mortality in these patients. In patients with PPD, the high serum amylase the high mortality rate.

Keywords: Peptic ulcer perforation; Morbidity and Mortality; Duration of perforation; Shock on admission; ASA grade; serum amylase.

INTRODUCTION:

Peptic ulcer disease (PUD) represents a worldwide health problem because of its high morbidity, mortality and economic loss.^[1] Globally, the incidence of peptic ulcer disease has fallen in recent years.^[2-4] Despite this and recent advances in both diagnosis and management of peptic ulcer disease, namely the improvement in endoscopic facilities, eradication of *H. pylori* and the introduction of the proton pump inhibitors, complications such as peptic ulcer perforation remain a substantial healthcare problem. This may be due to an increase in the risk factors for peptic ulcer complications. Peptic ulcer disease and its complications remains a frequent clinical problem in our environment predominantly affecting young males not known to suffer from PUD. Simple closure with omental patch followed by *Helicobacter pylori* eradication was effective with excellent results in majority of pts despite patients' late presentation in our country. Peptic ulcer perforation is a serious complication which affects almost 2-10% of peptic ulcer patients on the average.^[5,6] Peptic ulcer perforation presents with an overall mortality of 10% 9 although some authors report ranges between 1.3% and 20%.^[7-9] The most important factor in preventing the post operative morbidity and mortality in patients with PDU is the time factor, so that the shorter the interval between diagnosis and initiation of surgical treatment the less complication rate. A successful outcome could be obtained by prompt recognition of the diagnosis, aggressive resuscitation and early institution of surgical management. The pattern of perforated PUD has been reported to vary from one geographical area to another depending on the prevailing socio-demographic and environmental factors.^[10] In the developing world, the patient population is young with male predominance, patients present late, and there is a strong association with smoking.^[11,12] The diagnosis of perforated DU poses a diagnostic challenge in most of cases. The spillage of duodenal or gastric contents into peritoneal cavity causing abdominal pain, shock, peritonitis, marked tenderness and decreased liver dullness offers little difficulty in diagnosis of perforations.^[13] Since the first description of surgery for acute perforated peptic ulcer disease, many techniques have been recommended. The recent advances in antiulcer therapy have shown that simple closure of perforation with omental patch followed by eradication of *H. Pylori* is a simple and safe option in many centers and have changed the old trend of truncal

vagotomy and drainage procedures.^[14-20] Although surgery is normally the correct treatment for perforated duodenal ulcer, the whole patient and the comorbidity need to be taken into account. Perforations may seal themselves by adherence to liver, gallbladder, or omentum.^[21-25]

Objective:

1. To assess the role of various risk factors like age, sex, use of NSAIDs, smoking and other associated illnesses.
2. To assess importance of time frame to surgery and ASA grading regarding outcome of surgery.
3. To assess postoperative complications in operated cases of peptic ulcer perforation like wound dehiscence and leak etc.
4. To assess Serum amylase levels in perforated peptic ulcer and its association with postoperative complications and mortality.

MATERIALS & METHODS:

This is a prospective study of 60 patients with PDU who attend to the emergency department and treated surgically with explorative laparotomy. The diagnosis of PDU in all patients was based on the presence of history of acute epigastric pain with generalized tenderness and rebound tenderness with board like rigidity. The diagnosis supported by history of chronic dyspeptic symptoms, previous endoscopic finding of DU, with history of long-term ingestion of steroid or NSAID. Blood samples were aspirated from all patients to assess the level of serum amylase in addition to hemoglobin level, blood urea, serum sugar and serum electrolyte (Na⁺, K⁺) and serum Ca²⁺. The normal range of serum amylase in the peripheral circulation is considered to be 80-150 units (somogi). Most of references regard a release of 150, 160, 180 up to 200 somogi unit as upper limit of normal concentration of amylase in serum, in this study, in order to avoid inclusion of technical error, the range of normal was considered to extend to 200 unit. All patients were underwent U/S exam to demonstrate free intraperitoneal fluid. CXR in erect position were done for all patients to detect free gas under diaphragm. All patients underwent an exploratory laparotomy by midline incision under general anesthesia. Data were collected by regarding the demographic information, the radiological, ultrasonography and operative finding, site of perforation, amount of spilled fluid, level of serum amylase by special perform. After preliminary resuscitation with IV fluid in form of crystalloid solution from 0.5 to 2 liters according to the general conditions of the patients and hydration state. Correction of electrolyte disturbance if present. Nasogastric tube inserted to all patients preoperatively. Foleys catheter inserted when indicated. Preoperative antimicrobial therapy given in form of third generation cephalosporin in the form of cefotaxime and metronidazole was used in all cases. Written consents were taken from all patients. All patients underwent explorative laparotomy by midline incision and some of patients (20 patients, 8%) by right paramedian incision. Identification of the site size and nature of the perforation done, closure of the perforation was done with omental patch (Graham's Omentopexy) using 2/0 absorbable suture. Peritoneal lavage done by using 1-3 liters of warmed saline. 2 tube drain were inserted, 1st near the site of repair and second in

the pelvis. The Wound was closed in layers. Patients were followed up during hospitalization and one month after discharging home and complications were recorded.

RESULTS:

The peptic ulcer perforation is one of the most common surgical emergencies. From 12-12-2019 to 11-12-2020 a total of 60 patients with duodenal ulcer perforations were studied. The youngest patient was 31 years old and oldest was 85 years old. Perforation was more common in male compared to female, the ratio being 9:1. Out of 60 cases 54 were male. The mean age of the patients was 58.4 years. The mean ages were, for males 58.7 years and for females 58.2 years. Morbidity was 50% in the age group over 70 years and mortality was 25% in patients with age group 71-80 years and 50% in 81-90 years.

Table 1:Age related morbidity and mortality in patients with PUP

Age group(inyears)	No. ofcases	GoodRecovery	Morbidity	Mortality
31-40	6	4	1	1
41 - 50	11	8	2	1
51-60	11	7	2	2
61-70	82	4	5	5
71-80	8	2	4	2
81-90	2	0	1	1
Total	60	25	15	12

In this study 12 (20%) patients had history of regular ingestion of NSAIDs among which 2(16.7%) of them developed postoperative complications and 3 (5%) patients expired in postoperative period. History of regular smoking was present in 30 (50%) patients, 11 patients developed postoperative complications and 3 patients expired in postoperative period.

History of regular alcohol consumption was present in 35 (58.3%) patients, 11 patients developed postoperative complications and 6 patients expired in postoperative period.

A previous history of dyspepsia or peptic ulcer symptoms was present in 7 out of 50 (14%) patients, 3 of them developed postoperative complications and 2 of them expired during postoperative period. 7 (14%) patients underwent surgery after 24 hours of admission, the rest were operated before 24 hours. All the 7 patients who underwent surgery after 24 hours expired during the postoperative period.

At the time of admission, shock (systolic BP less than 90) was present in 8 (16%) and all of them expired in postoperative period.

Preoperative ASA (American Society of Anaesthesiologists) grade was assessed for all patients with help of anaesthetists, 31 (53%) were grade II, 13 (22%) were grade III, 6 (10%) were grade IV. Morbidity was seen in 7 (12 %) patients with ASA grade II, 8 (53.8%) patients with ASA grade III and 1 (16.6%) patients with grade IV. Mortality was 83.33% in patients with ASA grade IV.

Table 2: Type of peritoneal collection affecting morbidity and mortality in patients with PUP

Parameter		Total	Morbidity	Mortality
Peritoneal Collection	Bilious	33	5	3
	Purulent	17	10	7

On exploration, 33 (56.0%) patients had bilious peritoneal collection and 17 (29%) had purulent collection. All patients were treated surgically by simple omental patch closure of the perforation and good peritoneal wash was given. Patients with purulent peritoneal collection had higher mortality rates than those with bilious collection.

Table 3: Postoperative complications in patients with PUP

Complications	No.
Wound Infection	12
Renal Failure	4
Respiratory failure	3
Septicemia	3
Intra-abdominal abscess	2
Leak	1

15 (26%) patients had postoperative complications. Most common postoperative complication was wound infection followed by acute kidney injury and respiratory failure in 4 and 3 patients respectively which was managed conservatively. 3 patients developed septicemia.

2 patients with respiratory failure required ventilator support in postoperative period.

1 patient had bilious leak through drain in postoperative period. Patients were reexplored and leak was identified from previously closed perforation site. He underwent simple omental patch closure of the perforation.

Two patients had residual intra-abdominal abscess one was managed by ultrasound guided aspiration.

5 patients among the 6 patients of ASA IV expired all of them were male patients. All 5 patients had undergone surgery after 24 hours from onset of symptoms and had shock on presentation.

Table 4: Serum amylase levels in PUP and its complications

No of Cases	Serum amylase levels	Percentage (%)	Morbidity	Death
27	<200	54	8	0
10	200-300	20	6	0
6	300-400	12	1	5
3	400-500	6	0	4
4	>500	8	0	3

There were 2 cases with <24 hours of onset of symptoms and serum amylase was <200 in both of them and mortality among this group was nil. On the other hand remaining 48 cases who presented to emergency after 24 hours of onset of symptoms had elevated serum amylase levels and morbidity as well as mortality was high among these group.

In the analysis of 60 patients, age 50 years and more, ASA grade and purulent peritoneal collection were significant predictors of morbidity. In the analysis of 60 patients, age 50 years and more, duration of perforation of more than 24 hours before surgery, presence of shock on admission, ASA grade, purulent peritoneal collection and Serum amylase levels were significant predictors of mortality.

The factor sex was not dealt with in detail in this analysis and yet has potent influences on the outcome after perforation. The older patients frequently reach aid late. This adds factors of long duration, large fluid spill and often shock. In them the ulcers are often larger and often more numerous. Of further interest with regard to elderly patients are problems of severe associated diseases, reduced healing power and often a reduced diagnostic accuracy. The mortality rate associated with perforation of ulcers is twice as high for women as for men.

DISCUSSION:

Peptic ulcer perforation is one of the commonest surgical emergencies. Although incidence of peptic ulcer diseases has reduced drastically with advent of H2 receptor antagonist and proton pump inhibitors, but complications of PUD such as haemorrhage and perforation has not declined.^[26-29]

PUD is common in third and fourth decade. Mean age of patients with PUP in study by Kocer et al. (2007) was 43 years and that in study by J. C. Dakubo et al. (2009) it was 41 years.^[30-33] However Sharma et al,^[29] (2006) another Indian study showed mean age of 33 years. Study by Irvin (1989) showed older age group patients (mean age 70 years) were commonly affected. Present study matches with studies by Noguiera et al,^[31](2003) and J. C. Testini et al. (2003).

Peptic ulcer perforation was common in the age group of 41-60 years with mean age 58 years in our study. But age is no bar for perforation to occur. It has also been reported in 4 years old child (Bhattacharya, 1969).

Table 5: Sex incidence in patients with PUP in various studies

Study	Male: female ratio
R.B.Satwakaretal.(1978)	9:1
J. Boeyet al.(1982), ^[9]	6.6: 1
Noguieraetal.(2003), ^[31]	2.5:1
Testinietal.(2003), ^[32]	2.9:1
Sharmaetal.(2006), ^[29]	18.2:1
Koceret al.30(2007), ^[30]	8:1
J.C.Dakuboetal.(2009), ^[33]	4.5:1
Presentstudy	7.3:1

In study by Testini et al. (2003),^[32] ratio was 2.9:1 and that in study by Sharma et al. (2006) was 18.2:1. Present study matches with Kocer et al.^[30](2007) with ratio of 8:1 and J. Boey et

al.^[9](1982) with ratio of 6.6:1. In our study 88% were males and 12% were females, and the male- female ratio being 9: 1. In a study by Kocer et al (2007),^[30] 8.9% patients had history of regular ingestion of NSAIDs whereas in study by J. C. Dakubo et al in 2009, it was 36.2%. In our study 24% patients were chronic NSAIDs users. In a study by Kocer et al in 2007,^[30] 73.2% patients had history of regular smoking whereas in study by J. C. Dakubo in 2009, it was 12.6%. In our study 66% patients were chronic smokers. In a study by Kocer et al in 2007,^[30] 12.3% patients had history of regular alcohol consumption whereas in study by J. C. Dakubo in 2009, it was 48.8%. In our study 70% patients were chronic alcoholics. In study by Kocer et al,^[30] in 2007, peptic ulcer perforation was common in younger patients. Smoking among young people was common in Turkey, which explains higher incidence of perforation in young males. In study by J. C. Dakubo et al. in 2009, peptic ulcer perforation was common in younger male patients with low socio- economic status. According to them, males are confronted with stressful life activities and there is an increase in alcohol consumption among the youth. Alcohol intake was statistically significant in predicting postoperative complications and mortality. In our study smoking and alcohol consumption were important risk factors in peptic ulcer perforation but these factors did not affect postoperative morbidity and mortality.

In study by Kocer et al in 2007,^[30] patients older than 50 years had a higher morbidity rate (56.6% vs 16.2%) and mortality rate (37.7% vs 1.4%) when compared to younger patients.

In study by J. C. Dakubo et al. in 2009, patients older than 60 years had a higher mortality rate (26.5% vs 6.8%) when compared to younger patients. Factors like age above 60 years, excessive alcohol intake were statistically significant in predicting postoperative complications and/or mortality in their study.

In our study, patients older than 50 years had a higher morbidity rate (36.4% vs 17.6%) and higher mortality rate (24.2% vs 11.8%) when compared to younger patients. Hence age 50 years and more are statistically significant in predicting postoperative morbidity and mortality in our study. Duration of symptoms before surgery and presence of shock on admission: In a study by Testini et al. in 2003, mortality was 9.8% in case of delayed. In a study by Testini et al. in 2003, mortality was 9.8% in case of delayed surgery, whereas that in study by Kocer et al in 2007,^[30] it was 20% and in study by J. C. Dakubo et al. in 2009, it was 11.8%.

In a study by Testini et al. in 2003, mortality was 55.6% in patients with shock on admission, whereas that in study by Kocer et al in 2007,^[30] it was 68.8% and in study by J.C. Dakubo et al in 2009, it was 20.6%. 12 patients expired in our study. 7 of them had undergone surgery 24 hours after the onset of symptoms and 8 of the 12 expired patients were in shock at the time of admission. In our study, mortality was 100% in patients who underwent surgery 24 hours after the onset of symptoms and in patients with shock on admission. Time of surgery and shock on admission significantly affected postoperative mortality as all the patients who expired had undergone surgery after 24 hours after onset of symptoms and had shock on admission. Delay in surgery caused increased bacterial peritonitis and led to septicemic shock and renal failure in postoperative period.

ASA Grade:**Table 6: ASA Grade affecting Morbidity and Mortality in patients with PUP**

Study	Parameter		ASA grade				
			I	II	III	IV	V
Koceretal (2007), ^[30]	No.ofpatients		14	157	59	32	7
	Morbidity	No.	3	18	18	20	6
		%	21.4	11.5	30.5	62.5	85.7
	Mortality	No.	0	1	4	12	6.0
%		0.0	0.6	6.8	37.5	85.7	
Presentstudy	No.ofpatients		-	31	13	6	-
	Morbidity	No.	-	7	7	1	-
		%	-	22.6	53.8	16.7	-
	Mortality	No.	-	2	3	5	-
%		-	6.5	23.1	83.3	-	

In the study by Kocer et al in 2007,^[30] each increase in ASA score increased morbidity 2 times and mortality 4.5 times in their patients. In our study, each increase in ASA score increased morbidity 2 times. There were 5 deaths among 6 patients of ASA grade IV. Hence ASA grade is also important predictor of postoperative morbidity and mortality. This helps us to explain the amount of risk to the patient.

Table 7: Serum Amylase levels in mortality of patients with PPU

Study	Parameter		Serum amylase				
			<200	200-300	300-400	400-500	>500
Tawfiq J. Al-Marzooq et al. (2015)	No.ofpatients		210	18	12	5	5
	Mortality	No.	21	5	4	2	4
		%	10	27.8	33.3	40.0	80.0
FrankA.Rogerset al.	No.ofpatients		840	72	48	22	18
	Mortality	No.	89	18	11	9	13
		%	10.6	25.0	23.0	41.0	73.0
Presentstudy	No.ofpatients		27	10	6	3	4
	Mortality	No.	0	0	5	4	5
		%	0.0	0.0	60	80	100.0

In a study by Tawfiq J. Al-Marzooq et al. (2015), two hundred fifty patients included in the study with proven PDU, 222 (88.8 %) were male and 28 (11.2 %) were female, male to female ratio is 8:1. The mean age was 38 years, ranging from 22-70 years. The over all mortality was 14.4%. In 210 patients(84%), the Serum amylase was within normal range, the mortality in this group was 10 %. The other 21 patients (16%) had level of 200 or above, the mortality in this group was 37.5 %.

Mortality was 5 % in cases with mild intra peritoneal fluid spillage, 9% in moderate, 25% in large amount & 39 in massive intra peritoneal spillage. The size of perforation has prognostic

significance, for the larger the perforation, the higher the mortality. In a study by Frank A Rogers et al. Serum amylase levels >200 carried 31.9% mortality. In our study among 60 patients, 27 had Serum amylase levels <200 and it was >200 in 23 patients. The mortality rate were very high in patients with elevated Serum amylase.

CONCLUSION:

Perforated duodenal ulcer disease is emerging as a frequent cause of acute abdomen in south India. The perforation is common between age group of 50- 70 years. It is more common in males. The duration of perforation more than 24 hours and presence of shock on admission is associated with increased Serum amylase levels and in turn is associated with significant mortality. Early diagnosis and prompt management of shock and septicemia is important for better prognosis of patients. Patients with purulent peritoneal collection have increased morbidity and mortality. Morbidity rate in our study is 30% and mortality rate is 20%. Age more than 50 years, duration of perforation of more than 24 hours before surgery, presence of shock on admission, ASA grade, purulent peritoneal collection and elevated Serum amylase levels are factors significantly associated with fatal outcomes in patients undergoing emergency surgery for perforated peptic ulcer. Therefore, proper resuscitation from shock, improving ASA grade and decreasing delay in surgery is needed to improve overall results.

ACKNOWLEDGMENT:

The author is thankful to Department of General Surgery for providing all the facilities to carry out this work.

REFERENCES:

1. Thorsen K, Soreide JA, Kvaloy JT, Glomsaker T, Soreide K. "Epidemiology of perforated peptic ulcer; Age-and gender adjusted analysis of incidence and mortality" *W.J.Gastroenterol* 2013; 19(3) : 347- 354.
2. Bin-Taleb AK, Razzaq RA, Al-Kathiri ZO. "Management of perforated peptic ulcer in patients at a teaching hospital" *Saud.Med.J* 2008; 29(2):245-250.
3. Türkdoğan MK, Hekim H, Tuncer İ, Aksoy H " The epidemiological and endoscopic aspects of peptic ulcer disease in Van region". *Eastern Journal of Medicine* 1999; 4(1):6-9.
4. Sung JJY, Kuipers EJ, and El-Serag HB. " Systemic review : the global incidence and prevalence of peptic ulcer disease" *Alimentary pharmacology & Therapeutics* 2009; 24(9) : 938-946.
5. Montalvo-Javé EE, Corres-Sillas O, César A-GC "Factors associated with postoperative complications and mortality in perforated peptic ulcer" *Cir Cir* 2011; 79:128-135.
6. Testini M, Portincasa P, Piccinni G, Lissidini G, Pellegrini F, Greco L "Significant factors associated with fatal outcome in emergency open surgery for perforated peptic ulcer" *World J Gastroenterol* 2003; 9:2338-2340
7. Rajesh V, Sarathchandra S and Smile SR " Risk factors predicting operative mortality in perforated peptic ulcer disease." *Trop Gastroenterol* 2003; 24:148-150.
8. Soll AH: Peptic ulcer and its complications. In *Sleisinger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management*. 6th edition. Edited by

- Feldman M, Scharschmidt BF, Sleisenger MH. Philadelphia, PA: W.B. Saunders; 1998 :620-678.
9. Boey J, Choi KY, Alagaratnam TT and Poon A “ Risk stratification in perforated duodenal ulcers. A prospective validation of predictive factors” *Ann Surg* 1986; 205:22-26.
 10. Hill AG “ The management of perforated peptic ulcer in a resource poor environment” *East Afr Med J* 2001; 78(8):346-348
 11. Rigopoulos A, Ramboiu S and Georgescu I “ A critical evaluation of surgical treatment of perforated ulcer “ *Current Health Science Journal* 2011; 37(2) : 75-78.
 12. Thorsen K, Soreide JM and Soreide K “ What is the best predictor of mortality regression analysis including three critical scoring system “ *J Gastrointest Surg* 2014; 18: 1261-1268.
 13. Di Saverio S, Bassi M, Semerieri N, Masetti M, Ferrara F, Fabbri C, Ansaloni L, Ghersi S, Serenari M, Coccolini F, Naidoo N, Sartelli M, Tugnoli G, Catena F, Cennamo V and Jovine E “ Diagnosis and treatment of Perforated or Bleeding Peptic Ulcer “ *W J Emergency Surgery* 2014; 9 : 45-60.
 14. Moller MH, Adamsen S, Wojdemann M, Moller AM “ Perforated Peptic Ulcer : How to improve outcome “ *Scand. J. Gastroenterol* 2009 ; 44(1): 15-22.
 15. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC “Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality”. *Digestion* 2011;84:102-13.
 16. Lu Y, Loffroy R, Lau JY, Barkun A” Multidisciplinary management strategies for acute non-variceal upper gastrointestinal bleeding”. *Br J Surg* 2014;101:e34-50.
 17. Søreide K, Thorsen K, Søreide JA.” Strategies to improve the outcome of emergency surgery for perforated peptic ulcer”. *Br J Surg* 2014;101:e51-64.
 18. Boey J, Choi SK, Poon A, Alagaratnam TT “Risk stratification in perforated duodenal ulcers. A prospective validation of predictive factors” *Annals of Surgery* 1987;205(1): 22-26.
 19. Egdahl RH. Mechanism of blood enzyme changes following the production of experimental pancreatitis. *Ann Surg.* 1958 Sept; 148:389-399.
 20. Elliott DW, Williams RD, Zollinger RM. The role of trypsin and of bile salts in the pathogenesis of acute pancreatitis. *Surgical Forum.* 1958;9:533-537.
 21. Popper HL. Enzyme studies in edema of the pancreas and acute pancreatitis. *Surgery.* 1940 April;7:566-570.
 22. Popper HL, Nechelis H. Pathways of enzymes into the blood in acute damage of the pancreas. *Proc Soc Exper Biol and Med.* 1940 Jan;43:220-222.
 23. Keith LM Jr, Zollinger RM, McCleery RS. Peritoneal fluid amylase determinations as an aid in the diagnosis of acute pancreatitis. *Arch of Surg.* 1950 Nov; 61:930-936.
 24. Fischer SP, Bader AM, Sweitzer B. Preoperative evaluation. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Young WL. *Miller’s anesthesia.* 7th ed. Philadelphia: Churchill Livingstone Elsevier. 2009:1027.
 25. Lau WY, Leung KL, Zhu XL, Lam YH, Chung SCS, Li AKC. Laparoscopic repair of perforated peptic ulcer. *Br J Surg.* 1995;82(6):814-816.

26. Siu WT, Leong HT, Law BK, Chau CH, Li AC, Fung KH et al. Laparoscopic repair for perforated peptic ulcer: a randomized controlled trial. *Ann Surg.* 2002 Mar;235(3):313-9.
27. Wakayama T, Ishizaki Y, Mitsusada M, Takahashi S, Wada T, Fukushima Y et al. Risk factors influencing the short term results of gastroduodenal perforation. *Surg Today.* 1994;24(8):681-7.
28. Testini M, Portincasa P, Piccinni G, Lissidini G, Pellegrini F, Greco L. Significant factors associated with fatal outcome in emergency open surgery for perforated peptic ulcer. *World J Gastroenterol.* 2003 Oct;9(10):2338-40.
29. Sharma SS, Mamtani MR, Sharma MS, Kulkarni H. A prospective cohort study of postoperative complications in the management of perforated peptic ulcer. *BMC Surg.* 2006 Jun 16;6:8.
30. Kocer B, Surmeli S, Solak C, Unal B, Bozkurt B, Yildirim O et al. Factors affecting mortality and morbidity in patients with peptic ulcer perforation. *J Gastroenterol Hepatol.* 2007 Apr;22(4):565-70.
31. Nogueira C, Silva AS, Santos JN, Silva AG, Ferreira J, Matos E, et al. Perforated peptic ulcer: Main factors of morbidity and mortality. *World J Surg.* 2003 Jul;27(7):782-7.
32. Testini M, Portincasa P, Piccinni G, Lissidini G, Pellegrini F, Greco L. Significant factors associated with fatal outcome in emergency open surgery for perforated peptic ulcer. *World J Gastroenterol.* 2003 Oct;9(10):2338-40.
33. Dakubo JC, Naaeder SB, Clegg-Lampsey JN. Gastro-duodenal peptic ulcer perforation. *East Afr Med J.* 2009 Mar;86(3):100-9.