

Original Article

Assessment of Prognostic Factors in Perforated Peptic Ulcers Patients

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Abstract - Perforated peptic ulcer is a life-threatening condition requiring emergency intervention due to high morbidity and mortality. Aim: The aim of this study is to evaluate the prognostic factors associated with outcomes of perforated ulcers. Materials and Methods: An observational prospective analytic study was conducted in adult patients diagnosed with perforated peptic ulcers who underwent modified Graham patch repair. They were selected from the General Surgery department at Tishreen University Hospital. Sociodemographic variables, with morbidity and mortality and their associated factors, were analyzed. Results: A total of 40 patients, 31 males (77.5%) and 9 females (22.5%), were included in the study. They had a mean age of 51.67 ± 13.8 years, 20% had the concomitant disease, and 57.5% of the patients presented within 6-24 hours. Complications occurred in 15 patients (37.5%), and mortality in 6 cases (15%). Pre-operative duration (OR 3.4), age older than 65 years (OR 3.2), comorbidities (OR 3.4), size of perforation (OR 2.9), and use of NSAIDs (OR 3.1) were independent factors that were associated with the risk of progression of complications. Pre-operative duration (OR 2.9), age older than 65 years (OR 3.6), comorbidities (OR 3.02), and size of perforation (OR 3.2) were factors that were associated independently with the risk of mortality. Conclusion: Early detection of perforation and urgent intervention are considered crucial, and the presence of older patients, delayed surgical intervention, comorbidities, and large perforations are all warning flags that may predispose to poor prognosis.

Keywords - Morbidity, Mortality, Peptic ulcer, Perforated, Risk factors.

1. Introduction

Peptic ulcers represent defects in the gastrointestinal mucosa that extend into muscularis mucosa and submucosa or deeper [1]. It results from an imbalance between naturally protective factors, including mucus and prostaglandins and damaging factors of acid and pepsin in the lumen [2]. Epigastric pain represents the main clinical manifestation of ulcers that result from surrounding nerve irritation, with associated symptoms that include nausea, bloating, and early satiety [3,4]. Complications such as bleeding, perforation, obstruction and ulcers might have only been brought to medical attention due to complications [5,6].

Perforated peptic ulcer represents the second in frequency after bleeding. It is an ulcer that goes through all wall layers and forms a hole in which acid, bile or food material spills into the peritoneal cavity [7]. Despite the decreasing number of peptic ulcers, the prevalence of perforations appears to be unchanged, which might be explained by increases in many risk factors, such as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), especially in the elderly with the presence of comorbidities and smoking [8,9]. Patients might present with severe sudden abdominal pain, tachycardia and cold extremities during the first two hours [10]. Within 2 to 12 hours of onset, chemical peritonitis develops as a result of releasing gastrointestinal contents into the peritoneal cavity, and patients become unstable hemodynamically after 12 hours [11,12].

Perforated ulcers are considered an important problem in emergency and general surgery. Early diagnosis and rapid intervention are crucial to improve outcomes, especially in the case of septic shock, to avoid multiple organ failure (MOF) [13,14]. Various risk factors are known for poor prognosis, which includes: metabolic acidosis, presence of shock on admission, acute kidney injury, and delayed surgical intervention [15,16]. It is essential to identify risk factors for complications in perforated peptic ulcers and develop effective prevention strategies [17]. Therefore, this study aimed to investigate the risk factors for mortality and complications in patients with perforated ulcers.

2. Patients and Methods

After approval by the local research ethics committee, an observational prospective analytic study was conducted on adult patients attending the Department of General Surgery at Tishreen University Hospital over the period of one year, 2021-2022.

• Inclusion Criteria were as Follows

Patients with perforated peptic ulcers (gastric, duodenal) who underwent urgent surgical intervention.

• Exclusion Criteria

Patients who underwent conservative treatment, presence of tumor perforation, or perforations due to non-peptic ulcer etiologies.



A rapid ABC (airway, breathing, and circulation) evaluation was done in the emergency department. A detailed history was taken, which included characteristics of pain (onset, location, intensity, radiation, and response to analgesics), fever, nausea, emesis, patient's medical history, past surgical history and habits. Physical examination was performed, which included monitoring of vital signs, abdominal examination (tenderness, rebound tenderness, guarding) and detection of shock (hypotension, tachycardia, tachypnea, decreased urine output, and altered mental state). Routine laboratory studies including white blood cell count WBC, C-reactive protein CRP, urea, creatinine, amylase, glucose, prothrombin time PT, partial thromboplastin time PTT, serum sodium Na, serum potassium K, and arterial blood gas were performed.

Chest and abdominal X-rays were performed as the initial routine diagnostic assessment. Abdominal ultrasound was performed to detect the presence of intra-abdominal free fluid. In contrast, the computed tomography CT scan was performed when the x-ray was negative with the presence of perforation signs. Characteristics of perforation regarding size and location were detected, and all patients underwent modified Graham patch repair. Patients were regularly followed up for complications or death (2 weeks, 1 month after surgery).

2.1. Ethical Consideration

All patients were provided with complete and clear informed consent after the discussion about the study.

2.2. Statistical Analysis

Statistical analysis was performed by using the IBM SPSS version20. Basic Descriptive statistics included means, standard deviations(SD), median, frequency and percentages. The chi-square test examined the relationships and comparisons between the two groups. Multivariate logistic regression analysis was performed to estimate independent risk factors. This model included risk factors first identified through univariate analysis. All the tests were considered significant at a 5% type I error rate($p < 0.05$), β :20%, and power of the study:80%.

Table 1. Distribution of the study population according to demographic characteristics

Variable	Result
Age(years)	51.67±13.8(18-87)
Age groups	
≤65	36(90%)
>65	4(10%)
Gender	
Male	31(77.5%)

Female	9(22.5%)
Habits	
Smoking	34(85%)
Alcohol consumption	4(10%)
Comorbidities	
Hypertension	3(7.5%)
Peptic ulcer	3(7.5%)
Diabetes mellitus	1(2.5%)
Lung cancer	1(2.5%)
Drugs history	
Steroids	3(7.5%)
Nonsteroidal anti-inflammatory drugs(NSAIDs)	21(52.5%)

Table 2. Distribution of the study population according to the clinical and laboratory characteristics

Variable	Result
Clinical manifestations	
Acute abdominal pain	40(100%)
Muscular guarding	40(100%)
Tachycardia	27(67.5%)
Fever	21(52.5%)
Emesis	14(35%)
Shock	7(17.5%)
Pre-operative duration (hours)	
<6	8(20%)
6-24	23(57.5%)
>6	9(22.5%)
Laboratory findings	
Elevated WBC*	35(87.5%)
Elevated NEU**	28(70%)
Elevated CRP***	32(80%)
Metabolic acidosis	18(45%)
Elevated amylase	14(35%)
Elevated creatinine	12(30%)

*WBC, White blood cells count- **Neu, Neutrophil- ***Crp, C-Reactive protein.

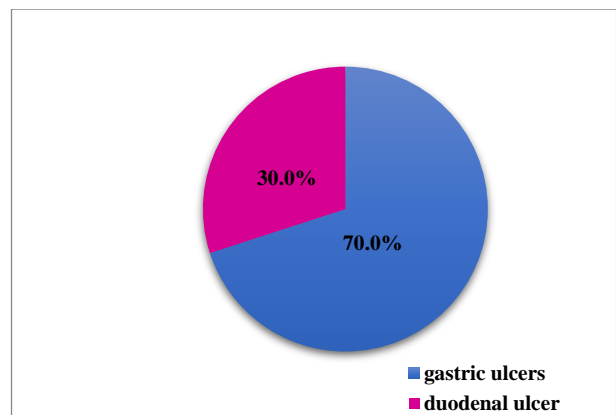


Fig. 1 Distribution of ulcers according to location

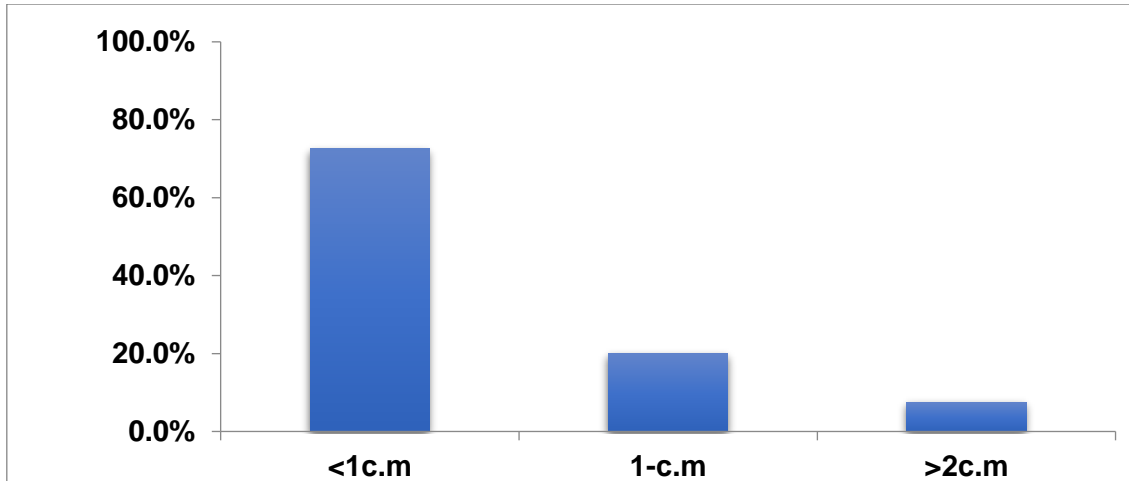


Fig. 2 Distribution of ulcers according to perforated ulcer size

Table 3. Distribution of the study population according to the complications

Variable	Result
Complications	
Acute kidney injury	6(15%)
Surgical site infection	5(12.5%)
Pleural effusion	3(7.5%)
Myocardial infarction	1(2.5%)
Wound dehiscence	1(2.5%)
Pulmonary embolism	1(2.5%)
Death	6(15%)

Table 4. Distribution of the complications according to the demographic characteristics

Variable	Complication		P value*
	Present	Absent	
Gender			
Male	12(38.7%)	19(61.3%)	0.7
Female	3(33.3%)	6(66.7%)	
Age older than 65 years	3(75%)	1(25%)	0.02
Habits			
Smoking	12(35.3%)	22(64.7%)	0.4
Alcohol consumption	2(50%)	2(50%)	0.5
Drugs history			
Steroids	2(66.7%)	1(33.3%)	0.06
Nonsteroidal anti-inflammatory drugs (NSAIDs)	13(61.9%)	8(38.1%)	0.04
Comorbidities	6(75%)	2(25%)	0.003

*P-value is significant at the 0.05 level.

Table 5. Distribution of the complications according to the characteristics of ulcers

Variable	Complication		P value
	Present	Absent	
Location of perforation			
Gastric ulcers	12(42.9%)	16(57.1%)	0.2
Duodenal ulcers	3(25%)	9(75%)	
Size of perforation(cm)			
<1	8(27.6%)	21(72.4%)	0.03
1-2	4(50%)	4(50%)	
>2	3(100%)	0(0%)	
Pre-operative duration(hours)			0.02

<6	2(25%)	6(75%)	
6-24	7(30.4%)	16(69.6%)	
>24	6(66.7%)	3(33.3%)	
Metabolic acidosis	10(55.5%)	8(44.5%)	0.2
Presence of intra-abdominal free fluid	12(44.4%)	15(55.6%)	0.5

Table 6. Risk factors for complications of the study population

Variable	OR [CI 95%]	P value
Pre-operative duration	3.4[1.6-7.7]	0.002
Age older than 65 years	3.2[2.2-8.1]	0.01
Comorbidities	3.4[1.2-7.3]	0.001
Size of perforation	2.9[1.7-6.9]	0.01
Use of NSAIDs	3.1[1.1-6.7]	0.02

Table 7. Distribution of death according to the demographic characteristics

Variable	Deaths		P value
	Present	Absent	
Gender			
Male	3(9.7%)	28(90.3%)	0.08
Female	3(33.3%)	6(66.7%)	
Age older than 65 years	4(100%)	0(0%)	0.0001
Habits			
Smoking	4(11.8%)	30(88.2%)	0.1
Alcohol consumption	0(0%)	4(100%)	0.3
Drugs history			
Steroids	0(0%)	3(100%)	0.06
Nonsteroidal anti-inflammatory drugs(NSAIDs)	2(9.5%)	19(90.5%)	0.09
Comorbidities	5(62.5%)	3(37.5%)	0.003

Table 8. Distribution of death according to the characteristics of ulcers

Variable	Death		P value
	Present	Absent	
Location of perforation			
Gastric ulcers	5(17.9%)	23(82.1%)	0.4
Duodenal ulcers	1(8.3%)	11(91.7%)	
Size of perforation(cm)			
<1	3(10.3%)	26(89.7%)	0.01
1-2	2(25%)	6(75%)	
>2	1(33.3%)	2(66.7%)	
Pre-operative duration(hours)			
<6	0(0%)	8(100%)	0.002
6-24	3(13%)	20(87%)	
>24	3(33.3%)	6(66.7%)	
Metabolic acidosis	4(22.2%)	14(77.8%)	0.04
Presence of intra-abdominal free fluid	4(14.8%)	23(85.2%)	0.01
Complications			
Pleural effusion	2(66.7%)	1(33.3%)	0.02
Acute kidney injury	3(50%)	3(50%)	1
Myocardial infarction	0(0%)	1(100%)	0.2
Surgical site infection	0(0%)	5(100%)	0.08
Wound dehiscence	0(0%)	1(100%)	0.5
Pulmonary embolism	1(100%)	0(0%)	0.6
Shock	4(57.1%)	3(42.9%)	0.04

Table 9. Risk factors for death of the study population

Variable	OR [CI 95%]	P value
Pre-operative duration	2.9[0.8-7.5]	0.001
Age older than 65 years	3.6[1.4-8.9]	0.005
Comorbidities	3.02[1.1-6.9]	0.001
Size of perforation	3.2[1.2-9.8]	0.02

3. Results

A total of 40 cases of perforated peptic ulcers in adults were studied during the study period. Ages range from 18 years to 87 years (mean 51.67 ± 13.8 years), and 90% of the patients were younger than 65 years. Ages range from 40 years to 87 years in gastric ulcers (mean 56.28 ± 11.2 years), whereas in duodenal ulcers range from 18 to 73 years (mean 40.91 ± 13.5 years). The maximum number of cases in the study were males constituting 31 (77.5%), and females, 9 (22.5%) with male to female ratio was 3.4:1. 34 cases (85%) of the patients reported smoking, and 4 cases (10%) consumed alcohol. There was recurrent vague epigastric pain in 27 cases (67.5%), and perforation represented the first clinical manifestation in 10 cases (25%). Comorbidities of significance were hypertension (7.5%), peptic ulcer (7.5%), diabetes mellitus (2.5%), and Lung cancer (2.5%). 52.5% of the patients received NSAIDs, and 7.5% received steroids, table (1). The most common presenting symptoms were acute abdominal pain (100%) and muscular guarding (100%), followed by tachycardia (67.5%), fever (52.5%), emesis (35%), and shock (17.5%). The number of patients in each pre-operative symptom duration was as follows: < 6 hours- 8 patients, 6-24 hours- 23 patients, and >24 hours-9 patients. The percentage of patients who showed elevated levels of WBC, NEU, CRP, amylase, and creatinine was as follows; 87.5%, 70%, 80%, 35% and 30%, respectively. Metabolic acidosis was detected in 18 cases (45%). Erect chest/abdominal x-ray was performed in 40 cases. It was positive (presence of air under diaphragm "pneumoperitoneum") in 29 cases (72.5%), whereas abdominal ultrasound was performed in 40 cases and was positive (intra-abdominal free fluid) in 27 cases (67.5%). CT-scan was performed in 11 cases and was positive (presence of air under diaphragm) in 10 cases (90.9%), table (2). 28 cases (70%) were gastric ulcers, and 12 cases (30%) were duodenal ulcers, Figure (1). Perforated peptic ulcers were classified according to their perforation size into three groups; <1 cm (29 cases:72.5%), 1-2 cm (8 cases:20%), and > 2 cm (3 cases:7.5%), figure (2). Acute kidney injury represented the most frequent complication, which was observed in 6 cases (15%), followed by surgical site infection (12.5%), pleural effusion (7.5%), myocardial infarction (2.5%), wound dehiscence (2.5%) and pulmonary embolism (2.5%). The death occurred in 6 cases (15%), without any case of cutaneous intestinal fistula, abdominal abscesses, or repair site leak, table (3). The overall complications rate was 37.5 %, with no significant difference in relation to sex (p:0.7), smoking (p:0.4), consumption of alcohol(p:0.5), and use of Steroids(p:0.06). Complicated patients were significantly older than 65 years (75% versus 25%, p:0.02), had more comorbidities (75% versus 25%, p:0.003), with the widespread use of NSAIDs (61.9% versus 38.1,p:0.04), table(4). There were no significant differences in relation to the location of perforation(p:0.2), presence of metabolic acidosis(p:0.2), and presence of intra-abdominal free fluid(p:0.5). Complications were increased significantly with increasing size of perforation (27.6% in size < 1 cm versus 100% in size >2 cm, p:0.03) and duration pre-operative (25% in duration <6 hours versus 66.7% in duration longer than 24

hours, p:0.02). In addition, complications occurred in all patients who presented with shock (7 cases:100%), table(5). In the multivariate logistic regression analysis, pre-operative duration (OR 3.4,95% CI 1.6-7.7, p=0.002), age older than 65 years (OR 3.2,95% CI 2.2-8.1, p=0.01), comorbidities (OR 3.4,95% CI 1.2-7.3, p=0.001), size of perforation (OR 2.9,95% CI 1.7-6.9, p=0.01), and use of NSAIDs (OR 3.1,95% CI 1.1-6.7, p=0.02) were factors that associated with the risk of progression complications, Table (6). The overall mortality rate was 15%, with no significant difference in relation to sex(p:0.08), smoking(p:0.1), consumption of alcohol(p:0.3), use of steroids(p:0.06) and NSAIDs(p:0.09). Patients who died were significantly older than 65 years (100% versus 0%, p:0.0001) with the presence of comorbidities (62.5% versus 37.5%, p:0.003), table(7). There were no significant differences in relation to the location of perforation(p:0.4) and the presence of complications except for pleural effusion(p:0.02) and shock(p:0.04). The rate of mortality was increased significantly with increasing size of perforation (10.3% in size < 1 cm versus 33.3% in size >2 cm, p:0.01) and pre-operative duration (0% in duration <6 hours versus 33.3% in duration longer than 24 hours, p:0.002). Metabolic acidosis was present in 22.2% of complicated patients, with the presence of intra-abdominal free fluid in 14.8% of complicated patients, table(8). In the multivariate logistic regression analysis, pre-operative duration (OR 2.9,95% CI 0.8-7.5, p=0.001), age older than 65 years (OR 3.6,95% CI 1.4-8.9, p=0.005), comorbidities (OR 3.02,95% CI 1.1-6.9, p=0.001), and size of perforation (OR 3.2,95% CI 1.2-9.8, p=0.02) were factors that associated with the risk of death, Table (9).

4. Discussion

In this observational prospective analytic study, we report the risk factors associated with outcomes among individuals who experienced perforated peptic ulcers. There were no local studies about the prevalence and risk factors of morbidity and mortality in perforated peptic ulcer patients.

The current study of 40 patients with perforated peptic ulcers shows that the majority of patients were males, which might be explained by a high frequency of smoking [18] and consumption of alcohol [19]. Perforated gastric ulcers were observed more frequently than duodenal ones due to the high prevalence of gastric ulcers in non- developed countries [20], frequent use of NSAIDs in our study and NSAIDs-related ulcers are observed more frequently in the stomach [26], and the majority of patients in the current study were elderly where gastric ulcers are common [22]. Pre-operative duration ranged from 6 to 24 hours in approximately two-thirds of patients. Acute kidney injury (AKI), surgical site infection and pleural effusion represented the most observed complications, and the occurrence of septic shock might explain AKI in 17.5% and fluid disorders. Compared with the uncomplicated group, pre-operative duration, older age, comorbidities, size of perforation, and use of NSAIDs were factors that were associated significantly with a risk ratio of complications.

Pre-operative duration, age older than 65 years, comorbidities, and perforation size represented factors associated with mortality. The results of the current study are consistent with the previous studies.

Chalya et al. (2011) showed in a study conducted on 84 patients with perforated peptic ulcers that the male-to-female ratio was 1.3:1 with a median age of 28 years. Use of NSAIDs, alcohol and smoking was detected in 10.7, 85.7%, and 64.3%, respectively, and the majority of perforations were located in the duodenum. The rate of complications was 29.8%, and mortality was 10.7%. Risk factors associated with complications were: delay of treatment and concomitant diseases, whereas mortality was more frequent in older age, delayed presentation (longer than 24 hours), presence of shock on admission, concomitant diseases, and gastric ulcers [23]. The difference with the current study is that patients were younger; the majority of ulcers were duodenal, with low use of NSAIDs, high consumption of alcohol, and some factors associated with mortality (shock and location of ulcer).

Unver et al. (2015) demonstrated in a study conducted on 239 patients diagnosed with perforated peptic ulcers that the male-to-female ratio was 2.7:1 without any effect of sex on the occurrence of complications that developed in 43.9%. Respiratory infections, surgical site infections, and cardiac complications represented the most frequent complications. Risk factors associated with mortality were advanced age and concomitant diseases [24]. The difference with the current study was that the rate of complications was lower in our study, and AKI represented the most frequent complication, without any effect of pre-operative duration and size of perforation on the mortality rate in the Unver study.

Teshome et al. (2020) demonstrated in a study conducted on 136 patients during a period of 4 years that ulcers were observed more frequently in males than females, with a mean age of 36.5 ± 16.56 years. 52.2% of the patients presented after 24 hours due to patients being from rural regions, and the majority of ulcers were located in the

duodenum. The rate of complications was 22.8%, in which surgical site infection and wound dehiscence were the most frequent complications, with a rate of mortality of 6.6%. Older age, females, presence of comorbidities, delayed presentation and shock were associated significantly with morbidity and mortality [25]. Differences with the current study were that patients in our study were older, presented frequently during 6 to 24 hours, perforations were located frequently in the stomach, and acute kidney injury represented the most frequent complication without any effect of gender on outcomes.

In summary, early diagnosis and management of perforated ulcers are essential to improve outcomes. In addition, it is necessary to reduce the consumption of NSAIDs and perform a study to compare the outcome of traditional surgery and laparoscopic in managing perforated ulcers.

5. Conclusion

Early detection of perforation and urgent intervention are considered crucial. The presence of older patients, delayed surgical intervention, comorbidities, and large perforations are all warning flags that may predispose to poor prognosis.

Availability of data and materials

Most of the data were in the article, and other data can be asked from the corresponding author.

Author contributions

All authors performed the measurements and wrote the article. The literature review was done by Dr. Habib Wakkaf, and all authors performed analytic calculations and performed numerical simulations.

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References

- [1] Angel Lanas, and Francis K L Chan, "Peptic Ulcer Disease", *Lancet*, vol.390, no.10094, pp.613-24, 2017. *Crossref*, [https://doi.org/10.1016/S0140-6736\(16\)32404-7](https://doi.org/10.1016/S0140-6736(16)32404-7)
- [2] Alan Barkun, and Grigorios Leontiadis, "Systematic Review of the Symptom Burden, Quality of Life Impairment and Costs Associated with Peptic Ulcer Disease," *The American Journal of Medicine*, vol. 123, no. 4, pp.358-366, 2010. *Crossref*, <https://doi.org/10.1016/j.amjmed.2009.09.031>
- [3] Montri Gururatsakul et al., "Association between Clinical Manifestations of Complicated and Uncomplicated Peptic Ulcer and Visceral Sensory Dysfunction," *Journal of Gastroenterology and Hepatology*, vol.25, no.6, pp.1162-9, 2010. *Crossref*, <https://doi.org/10.1111/j.1440-1746.2010.06269.x>
- [4] Sang Pyo Lee et al., "Risk Factors for the Presence of Symptoms in Peptic Ulcer Disease," *Clinical Endoscopy*, vol. 50, no.6, pp.578-584, 2017. *Crossref*, <https://doi.org/10.5946/ce.2016.129>
- [5] J. Y. Lau et al., "Systematic Review of The Epidemiology of Complicated Peptic Ulcer Disease: Incidence, Recurrence, Risk Factors and Mortality," *Digestion*, vol.84, no. 2, pp.102-13, 2011. *Crossref*, <https://doi.org/10.1159/000323958>
- [6] J .Sadik et al., "Bleeding Peptic Ulcer-Time Trends in Incidence, Treatment and Mortality in Sweden," *Alimentary Pharmacology & Therapeutics*, vol.30, no. 4, pp. 392-398, 2009. *Crossref*, <https://doi.org/10.1111/j.1365-2036.2009.04058.x>

- [7] Kin Tong Chung, and Vishalkumar G Shelat, "Perforated Peptic Ulcer - An Update," *World Journal of Gastrointestinal Surgery*, vol. 9, no. 1, pp.1-12, 2017. *Crossref*, <https://doi.org/10.4240/wjgs.v9.i1.1>
- [8] Antonio Tarasconi et al., "Perforated and Bleeding Peptic Ulcer: WSES Guidelines," *World Journal of Emergency Surgery*, vol. 15, no. 3, pp. 1-24, 2020. *Crossref*, <https://doi.org/10.1186/s13017-019-0283-978>
- [9] Kenneth Thorsen et al., "Epidemiology of Perforated Peptic Ulcer: Age and Gender Adjusted Analysis of Incidence and Mortality," *World Journal of Gastroenterology*, vol. 19, no. 3, pp. 347-54, 2013. *Crossref*, <https://doi.org/10.3748/wjg.v19.i3.347>
- [10] Kenneth Thorsen et al., "Perforated Peptic Ulcer," *Lancet*, vol. 386, no. 10000, pp.1288-1298, 2015. *Crossref*, [https://doi.org/10.1016/S0140-6736\(15\)00276-7](https://doi.org/10.1016/S0140-6736(15)00276-7)
- [11] Charles HN. Johnson et al., "An Evaluation of the Epidemiology, Management and Outcomes for Perforated Peptic Ulcers Across the North of England Over 15 Years: A Retrospective Cohort Study," *International Journal of Surgery*, vol. 64, no. 1, pp. 24-32, 2019. *Crossref*, <https://doi.org/10.1016/j.ijssu.2019.03.005>
- [12] Mariëtta J O E Bertleff, and Johan F Lange, "Perforated Peptic Ulcer Disease: A Review of History and Treatment," *Digestive Surgery*, vol. 27, no. 3, pp.161-169, 2010. *Crossref*, <https://doi.org/10.1159/000264653>
- [13] M. H Moller et al., "Trial of a Perioperative Protocol to Reduce Mortality in Patients with Peptic Ulcer Perforation," *British Journal of Surgery*, vol. 98, no. 6, pp. 802-10, 2011. *Crossref*, <https://doi.org/10.1002/bjs.7429>
- [14] Sushama Surapaneni, Rajkumar S, and A Vijaya Bhaskar Reddy, "The Perforation-Operation Time Interval; An Important Mortality Indicator in Peptic Ulcer Perforation," *Journal of Clinical and Diagnostic Research for doctors*, vol. 7, no. 5, pp. 880-2, 2013. *Crossref*, <https://doi.org/10.7860/JCDR/2013/4925.2965>
- [15] G.Bas et al., "Risk Factors of Morbidity and Mortality in Patients with Perforated Peptic Ulcer," *Acta Chirurgica Belgica*, vol. 108, no. 4, pp.424-27, 2008. *Crossref*, <https://doi.org/10.1080/00015458.2008.11680254>
- [16] Belma Kocer et al., "Factors Affecting Mortality and Morbidity in Patients with Peptic Ulcer Perforation," *Journal of Gastroenterology and Hepatology*, vol. 22, no. 4, pp. 565-570, 2007. *Crossref*, <https://doi.org/10.1111/j.1440-1746.2006.04500.x>
- [17] K.Soreide, K.Thorsen, J.Soreide, "Strategies to Improve The Outcome of Emergency Surgery for Perforated Peptic Ulcer," *British Journal of Surgery*, vol. 101, no. 1, pp. 51-64, 2014. *Crossref*, <https://doi.org/10.1002/bjs.9368>
- [18] Janet M. Torpy, "Peptic Ulcer Disease," *JAMA*, vol. 307, no. 12, pp.1329, 2012. *Crossref*, <https://doi.org/10.1001/jama.2012.184>
- [19] Donald Garrow, and Mark H Delegege, "Risk Factors for Gastrointestinal Ulcer Disease in the Us Population," *Digestive Diseases and Sciences*, vol. 55, no. 1, pp.66-72, 2010. *Crossref*, <https://doi.org/10.1007/s10620-008-0708-x>
- [20] J. J. Y. Sung, E. J. Kuipers, H. B. EL-Serag, "Systematic Review: The Global Incidence and Prevalence of Peptic Ulcer Disease," *Alimentary Pharmacology & Therapeutic*, vol. 29, no. 9, pp. 938-946, 2019. *Crossref*, <https://doi.org/10.1111/j.1365-2036.2009.03960.x>
- [21] R.Sathiya, R.Kalaimagal, "A Review on Computational Approaches for Disease Diagnosis in Wireless Capsule Endoscopy Images" *International Journal of Engineering Trends and Technology*, vol. 67, no. 8, 29-48, 2019. *Crossref*, <https://doi.org/10.14445/22315381/IJETT-V67I8P206>
- [22] Emma Sverden et al., "Peptic ulcer disease," *BMJ*, vol. 367, no. 1, pp.15495, 2019. *Crossref*, <https://doi.org/10.1136/bmj.15495>
- [23] Phillipo L Chalya et al., "Clinical Profile and Outcome of Surgical Treatment of Perforated Peptic Ulcers in Northwestern Tanzania: A Tertiary Hospital Experience," *World Journal of Emergency Surgery*, vol. 6, no.31, pp.1-10, 2011. *Crossref*, <https://doi.org/10.1186/1749-7922-6-31>
- [24] Mutlu Unver et al., "Prognostic Factors in Peptic Ulcer Perforations: A Retrospective 14-Year Study," *International Surgery*, vol.100, no. 3, pp. 942–948, 2015. *Crossref*, <https://doi.org/10.9738/INTSURG-D-14-00187.1>
- [25] Henok Teshome, Mekbib Birega, and Mekdim Taddese, "Perforated Peptic Ulcer Disease in a Tertiary Hospital, Addis Ababa, Ethiopia: Five Year Retrospective Study," *Ethiopian Journal of Health Sciences*, vol. 30, no. 3, pp. 363-370, 2020. *Crossref*, <https://doi.org/10.4314/ejhs.v30i3.7>
- [26] Jordi Castellsague et al., "Individual NSAIDs and Upper Gastrointestinal Complications," *Drug Safety*, vol. 35, no. 12, pp. 1127-1146, 2012. *Crossref*, <https://doi.org/10.2165/11633470-000000000-00000>