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Risk factors influencing morbidity and mortality in perforated peptic ulcer disease

İlhan Taş[1], Burak Veli Ülger[2], Akın Önder[2], Murat Kapan[2], Zübeyir Bozdağ[2]

ABSTRACT

Objective: Peptic ulcer perforation continues to be a major surgical problem. In this study, risk factors that influence morbidity and mortality in perforated peptic ulcer disease were examined.

Material and Methods: Files of 148 patients who were included in the study due to peptic ulcer perforation between January 2006 and December 2010 were retrospectively analyzed. Data regarding age, gender, complaints, time elapsed between onset of symptoms and hospital admission, physical examination findings, co-morbid diseases, laboratory and imaging findings, length of hospital stay, morbidity and mortality were recorded.

Results: The study group included 129 (87.2%) male and 19 (12.8%) female patients. The mean age was 51.7±20 (15-88) years. Forty five patients (30.4%) had at least one co-morbid disease. In the postoperative period, 30 patients (20.3%) had complications. The most common complication was wound infection. Mortality was observed in 27 patients (18.2%). The most common cause of mortality was sepsis. Multivariate analysis revealed age over 60 years, presence of co-morbidities and Mannheim peritonitis index as independent risk factors for morbidity. Age over 60 years, time to admission and Mannheim peritonitis index were detected as independent risk factors for mortality.

Conclusion: Early diagnosis and proper treatment are important in patients presenting with peptic ulcer perforation.

Key Words: Peptic ulcer perforation, morbidity, mortality, risk factors, time to admission

INTRODUCTION

Peptic ulcer disease (PUD) is a disease that results from an imbalance between aggressive factors such as stomach acid and pepsin and mucosa defense barriers (1). Although the need for elective surgery has decreased as a result of advances in medical treatment, 10% of the patients require surgery. The choice of treatment for peptic ulcer perforation (PUP) remains to be surgery. Currently, the most preferred surgical method is simple closure and omental plug. Different techniques are also applied (2-4). Factors that influence the prognosis of PUP are listed as follows: time to hospital presentation, large perforation diameter, age over 60 years, presence of shock, presence of concomitant diseases and localization of the perforation in the stomach (5, 6). Preoperative hemodynamic shock, sepsis and generalized peritonitis are important factors influencing morbidity and mortality (5-8). In this study, we examined the risk factors affecting morbidity and mortality in PUD.

[1]Clinic of General Surgery, Ministry of Health Cizre State Hospital, Şırnak, Turkey

[2]Department of General Surgery, Dicle University Faculty of Medicine, Diyarbakır, Turkey

Address for Correspondence
Burak Veli Ülger
Department of General Surgery, Dicle University Faculty of Medicine, Diyarbakır, Turkey
Phone: +90 505 434 19 23
e-mail: bvulger@gmail.com

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MATERIAL AND METHODS

The files of 148 patients, who were operated on at Dicle University, School of Medicine, General Surgery Clinic as diagnosed with PUD and received primary closure + omentoplasty were retrospectively examined after the obtainment of approval from Dicle University, School of Medicine, Ethics Committee with the date and number 18.07.2012/663. Written consents indicating that they allowed their data to be used in medical research were obtained from all our patients. The patients who underwent different surgical procedures or had malignant ulcer perforations were excluded from the study. The age, sex, symptoms at presentation, time between onset of symptoms and presentation to the hospital, physical examination findings, concomitant diseases, laboratory and imaging findings, hospital stay duration, morbidity and mortality information of these patients were recorded.

The time to presentation was considered to be the time elapsing between the onset of symptoms and presentation to the hospital. Peptic ulcer perforation diagnosis was made on the basis of history, physical examination, routine laboratory studies and radiologic imaging. Patients with concomitant diseases were recorded. Preoperative shock was defined as a systolic blood pressure below 90 mm-Hg (9).

The Mannheim Peritonitis Index (MPI) (Table 1) (10) and APACHE II scores of all patients were calculated. The APACHE II scoring system included patient's age, chronic health measurement and 12 physiological variables measured at presentation. The physiological parameters that were taken into consideration were rectal fever, mean arterial pressure, pulse rate, respiratory rate, arterial blood gas, arterial pH, serum Na, K, creatinine, hematocrit, leukocyte count and Glasgow coma score (11).

Table 1. Mannheim peritonitis index

Factors	Score
Age>50	5
Female gender	5
Organ failure*	7
Malignancy	4
Preoperative peritonitis duration>24 hours	4
Non-colonic sepsis source	4
Diffuse generalized peritonitis	6
Intra-abdominal fluid (exudate)	
Clean	0
Contaminated, purulant	6
Fecaloid	12

*Renal failure: creatinin level>177 µmol/L or urea level>67 mmol/L or oliguria<20 mL/hour. Pulmonary failure: PO_2<50 mm-Hg or PCO_2>50 mm-Hg. Intestinal obstruction: paralysis >24 hours or complete mechanical obstruction. Shock: hypodynamic or hyperdynamic

The oral intake of patients who were diagnosed with PUP was discontinued, and urinary catheters and nasogastric tubes were placed. Following adequate fluid resuscitation, the patients were taken to surgery. Ceftriaxone 1 g and ornidazole 500 mg were administered before the operation. Post-operative antibiotic treatment was maintained for 7-10 days.

Open surgery was performed in all the patients. After aspiration of the free gastrointestinal content in the abdomen, irrigation was performed using at least 1000 cc physiological serum. A Foley drain was placed to Morrison pouch in all the patients and in the pelvic site if necessary. Their nasogastric tubes were withdrawn on post-operative days 3-4. On post-operative day 4, the patients were started on liquid diet.

The patients were grouped as ≤24 hours and >24 hours (12) according to their presentation, ≤60 years and >60 years as per their age, ≤11 and >11 (11) according to the APACHE 2 score, ≤26 and >26 (13) as per MPI, ≤0.5 cm, 0.5-1 cm and ≥1 cm (14) according to the perforation diameter (15).

Statistical Analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows 13.0 software was used for statistical analysis. The quantitative data were expressed as mean ± standard deviation. Student t-test was used for analysis of parameters and chi-square test for the assessment of different categorical data. To evaluate the risk factors influencing morbidity and mortality, multivariate logistic regression test was used. Odds ratio (OR) was calculated for every variable. A value of $p<0.05$ for all variables was considered significant.

RESULTS

129 (87.2%) of the patients were male and the mean age was 51.7±20 (15-88) years. The mean time for presentation to the hospital was 30.8±31.4 (2-240) hours. While 12 (8.1%) of the patients had shock at presentation, 45 of them (30.4%) were identified to have at least one concomitant disease. It was identified that perforation was most frequent in the pre-pyloric region (101 patients, 68.2%). The length of hospital stay was longer in patients that developed morbidity ($p<0.001$). The demographic and characteristic clinical findings of the patients are indicated in Table 2.

In the post-operative period, 30 patients (20.3%) developed morbidity. The most frequent morbidity was wound infection. 28 (18.2%) patients died. The most frequent reason for mortality was sepsis. The reasons for morbidity and mortality in the post-operative period are shown in Table 3.

Age above 60, presence of a concomitant disease, perforation diameter and MPI were found statistically significant factors influencing morbidity, on univariate analysis (p=0.031, p=0.030, p=0.014 and p=0.014, respectively) (Table 4). In the multivariate logistic regression analysis, age above 60 (p=0.007, OR=6.28, CI=24), presence of a concomitant disease (p=0.046, OR=2.83, CI=7.88) and MPI (p=0.01, OR=0.83, CI=0.95) were found to be independent risk factors influencing morbidity (Table 5).

Age above 60, time to presentation at the hospital, shock, presence of a concomitant disease, perforation diameter, MPI and APACHE II score were identified as statistically significant factors influencing mortality, on univariate analysis ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.00$ and $p<0.001$, respectively) (Table 6). In the multivariate logistic regression analysis, age above 60 (p=0.009, OR=14.781, CI=110.073), time to presentation (p=0.025, OR=0.157, CI=0.793) and MPI (p=0.007, OR=19.72, CI=196.96) were found to be independent risk factors influencing mortality (Table 7).

DISCUSSION

Although the incidence and prevalence of peptic ulcer disease varies, its frequency is estimated to be 1500-3000 per 100.000 people (16). The lifetime possibility for a person to develop PUD is approximately 5% (17). Peptic ulcer disease is a disease with multi-factorial etiology and mostly the use of non-steroid anti-inflammatory drugs and Helicobacter pylori have been kept responsible. The widespread use of H_2 receptor blockers and proton pump inhibitors in recent years for the treatment of PUD has resulted in a decrease in elective ulcer surgery (18). In spite of these developments, PUD patients experience perforation at a rate of 7%, and bleeding at a rate of 15-20% per year (19). Peptic ulcer perforation is frequently seen in the 4th and 5th decades and its male/female ratio is in the range of 2-8/1 (12, 20-23). While the mean age of our patients was 51 in a way similar to the literature, the male/female ratio was 9/1.

It was reported that free sub-diaphragmatic air was identified in the direct X-ray images of 47.2-80% of patients with PUP (12, 20, 24). Parallel with these data, 82.44% of the patients in our study were identified to have free air in their X-ray images.

The post-operative morbidity rate in peptic ulcer perforation ranges between 21-42% (9, 12, 25, 26). Pulmonary and wound site infections are often considered among post-operative morbidity reasons. In our study, the morbidity rate was 20.3%. Parallel with the literature, our patients were identified to have wound site infections and pulmonary complications. We found in our study that age above 60, presence of a concomi-

Table 2. Patients' demographic and characteristic clinical signs

Age (year)	51.7±20 (15-88)	
Gender, n (%)		
	Male	129 (87.2)
	Female	19 (12.8)
Admission time (hours)		30.8±31.4 (2-240)
Shock signs, n (%)		12 (8.1)
Comorbidities, n (%)	Total	45 (30.4)
	Cardiovascular disease	23 (51.1)
	Pulmonary disease	11 (24.4)
	Diabetes mellitus	6 (13.3)
	Urinary system disease	4 (8.9)
	Malignancy	7 (15.5)
	Other	5 (11.1)
Clinical signs, n (%)		
	Abdominal pain	148 (100)
	Nausea-vomiting	48 (32.4)
	Failure to defecate	67 (45)
Physical examination findings, n (%)		
	Tenderness	148 (100)
	Guarding	131 (88.5)
	Rebound tenderness	109 (73.6)
WBC (/mm^3)		13129±6684 (1200-34900)
Free air on AXR, n (%)		122 (82.4)
Free intraabdominal fluid and/or fluid collection, n (%)		91 (82.7)
MPI		14.9±7.8 (5-33)
APACHE II		6.7±6.9 (0-28)
Perforation site, n (%)		
	Pre-pyloric	101 (68.2)
	Duodenum	47 (31.8)
Perforation diameter, n (%)	<0.5 cm	93 (62.8)
	0.5-1 cm	47 (31.8)
	>1 cm	8 (5.4)
Morbidity, n (%)		30 (20.3)
Mortality, n (%)		27 (18.2)
Length of hospital stay (days)		8.7±4.6 (0-44)

AXR: upright abdominal X-ray; US: ultrasonography; WBC: white blood cell count; MPI: Mannheim peritonitis index; APACHE II: acute physiology and chronic health evaluation

Table 3. Morbidity and mortality causes

Morbidity, n (%)	Total	30 (20.3)
	Wound infection	13 (43.3)
	Pleural effusion	10 (33.3)
	Atelectasis	4 (13.3)
	Pneumonia	3 (10)
	Acute renal failure	3 (10)
	Delirium	2 (6.7)
	Intestinal obstruction	1 (3.3)
	Evisceration	1 (3.3)
	Intraabdominal abscess	1 (3.3)
	Fistula	1 (3.3)
	Pulmonary edema	1 (3.3)
	Urinary tract infection	1 (3.3)
Mortality, n (%)	Total	27 (18.2)
	Sepsis	20 (74)
	Pulmonary etiology	4 (14.8)
	Myocardial infarction	1 (3.7)
	Acute renal failure	1 (3.7)
	Fistula	1 (3.7)

tant disease, MPI ≤26 and perforation diameter were factors that influenced morbidity.

Kim et al. (27) stated that age above 60 and female sex constituted the risk factors that influenced post-operative morbidity. In our study, PUP was often seen among men whereas sex was not a significantly influencing factor for morbidity. In our study, 42% of our patients were above the age of 60. In the univariate and multivariate analysis, age above 60 was identified to have a significant influence on morbidity.

There are studies in the literature indicating that the time to presentation at the hospital being over 24 hours had a negative effect on the progress of the disease (12, 21, 23). In our study, the average time to presentation was calculated to be 30.8±31.4 (2-240) hours. However, we did not identify any correlations between the time to presentation and development of morbidity.

It has been stated that the presence of shock on presentation increases mortality (7, 8, 12, 19, 23). On the other hand, we did not identify any association between presence of shock and morbidity.

There are studies indicating that morbidity rates increase depending on the presence of concomitant diseases in patients with peptic ulcer perforation (12, 27-29). Similarly, we identified that our patients who had concomitant diseases had higher morbidity rates.

Different results were reported in terms of perforation site in PUD (14, 30). In our study, 101 (68.2%) patients were identified to have a pre-pyloric perforation; however, the influence of the perforation site on morbidity was not significant.

It was demonstrated that morbidity was significantly increased if perforation diameter was wider than 0.5 cm in PUP (31). In our study, perforation diameter had an influence on morbidity according to univariate analysis.

Billing et al. (32) specified that MPI was effective in the prediction of morbidity. Similarly, in our study, we determined that patients with an MPI ≤26 had a significantly lower morbidity rate.

The post-operative mortality rate in peptic ulcer perforation ranges between 4-30% (12, 16, 23, 27, 33, 34). Mortality has

Table 4. Factors influencing morbidity on univariate analysis

Parameters	Group without morbidity n (%)	Group with morbidity n (%)	p
Gender			
Male	104 (80.6)	25 (19.4)	NS
Female	14 (73.7)	5 (26.3)	
Age			
<60 years	74 (85.9)	12 (14.1)	0,031
>60 years	44 (71.4)	18 (28.6)	
Admission period			
<24 hours	79 (78.2)	22 (21.8)	NS
>24 hours	39 (83)	8 (17)	
Shock	10 (83.3)	2 (16.7)	NS
Co-morbidities	31 (68.9)	14 (31.1)	0.030
Free air on AXR	97 (79.5)	25 (20.5)	NS
MPI			
<26	99 (76.7)	30 (23.3)	0.014
>26	19 (100)	0 (0)	
APACHE II			
<11	95 (80.5)	23 (19.5)	NS
>11	23 (76.7)	7 (23.3)	
Perforation site			
Prepyloric	81 (80.2)	20 (19.8)	NS
Duodenum	37 (78.7)	10 (21.3)	
Perforation diameter			
<0.5 cm	74 (79.6)	19 (20.4)	0.014
0.5-1 cm	41 (87.2)	6 (12.8)	
>1 cm	3 (37.5)	5 (62.5)	

AXR: upright abdominal X-ray; MPI: Mannheim peritonitis index; APACHE II: acute physiology and chronic health evaluation; NS: not significant

been reported to be due to multiple organ failure and pneumonia. In our study, our mortality rate was 18.2%. The most frequent reasons for mortality in our patients were sepsis and pulmonary problems.

The factors influencing mortality in our patients were as follows: age above 60, time to presentation longer than 24 hours, shock at the time of presentation, APACHE II score above 11 and perforation diameter wider than 0.5 cm.

Arıcı et al. (23) reported that mortality significantly increased in PUP patients above the age of 60. Koçer et al. (12) stated that mortality was 1.4% below the age of 65, while it was 37.3% above 65 years of age. In our study, being above the age of 60 was found to have a significant influence on mortality. However, we determined that sex did not have an influence on mortality.

Table 5. Factors influencing morbidity on multivariate logistic regression analysis

Factors	p	Odds ratio	CI 95%
>60 years	0.007	6.28	1.64-24.00
Gender	0.08	0.29	0.07-1.17
Admission period (>24 hours)	0.58	0.69	0.19-2.52
Shock	0.85	0.83	0.12-5.60
Co-morbidities	0.046	2.83	1.01-7.88
Free intraabdominal air on AXR	0.96	1.02	0.33-3.18
Perforation diameter	0.60	1.22	0.56-2.64
APACHE II	0.24	0.39	0.08-1.88
MPI	0.01	0.83	0.72-0.95

AXR: upright abdominal X-ray; MPI: Mannheim peritonitis index; APACHE II: acute physiology and chronic health evaluation

Table 6. Factors influencing mortality on univariate analysis

Parameters	Group without morbidity n (%)	Group with morbidity n (%)	p
Gender			
Male	107 (82.9)	22 (17.1)	NS
Female	14 (73.7)	5 (26.3)	
Age			
<60 years	82 (96.5)	3 (3.5)	<0.001
>60 years	39 (61.9)	24 (38.1)	
Admission period			
<24 hours	93 (92.1)	8 (7.9)	<0.001
>24 hours	28 (59.6)	19 (40.4)	
Shock	3 (25)	9 (75)	<0.001
Co-morbidities	28 (62.2)	17 (37.8)	<0.001
Free air on AXR	98 (80.3)	24 (19.7)	NS
MPI			
<26	119 (92.2)	10 (7.8)	<0.001
>26	2 (10.5)	17 (89.5)	
APACHE II			
<11	111 (94)	7 (6)	<0.001
>11	10 (33.3)	20 (66.7)	
Perforation site			
Prepyloric	85 (84.2)	16 (15.8)	NS
Duodenum	36 (76.6)	11 (23.4)	
Perforation diameter			
<0.5 cm	85 (91.4)	8 (8.6)	<0.001
0.5-1 cm	29 (61.7)	18 (38.3)	
>1 cm	7 (87.5)	1 (12.5)	

AXR: upright abdominal X-ray; MPI: Mannheim peritonitis index; APACHE II: acute physiology and chronic health evaluation; NS: not significant

Table 7. Factors effecting mortality on multivariate logistic regression analysis

Factors	p	Odds ratio	CI %95
>60 years	0.009	14.781	1.985-110.073
Gender	0.986	1.020	0.107-9.729
Admission period (>24 hours)	0.025	0.157	0.031-0.793
Shock	0.233	0.241	0.023-2.497
Comorbidities	0.747	1.277	0.288-5.663
Free air on AXR	0.132	0.126	0.009-1.865
Perforation diameter	0.456	1.545	0.492-4.846
APACHE II	0.056	0.232	0.052-1.041
MPI	0.007	19.72	2.29-196.96

AXR: upright abdominal X-ray; MPI: Mannheim peritonitis index; APACHE II: acute physiologic and chronic health evaluation

Parallel with studies indicating that time to presentation longer than 24 hours influenced the development of mortality, we identified that mortality was significantly increased in patients whose time to presentation was longer than 24 hours (12, 21, 23).

In accordance with publications reporting that the presence of shock at the time of presentation increased mortality, we determined that our patients who had shock on presentation had a significantly increased mortality (7, 8, 12, 23, 35). Therefore, we think that patients presenting with PUP, especially with the presence of a shock, need to be taken into the operating room immediately after the correction of fluid-electrolyte imbalance.

According to literature, the presence of concomitant diseases in PUP patients influenced mortality rates (12, 27-29). We also found that the presence of a concomitant disease had a significant influence on mortality.

Bracho-Riquelme et al. (13) have reported that an MPI score above 26 increased mortality at a rate of 40/3. We also determined that MPI above 26 significantly increased mortality in our patients.

There are various studies in the literature regarding mortality prediction by the APACHE II score (13, 32, 36). In our study, we identified that patients who had an APACHE II score above 11 had a significantly higher mortality.

There are studies stating that mortality rate was higher in perforations larger than 1 cm (37). Similarly, in our study, it was identified in the univariate analyses that the perforation diameter influenced mortality. Although there are publications in the literature reporting a higher mortality rate with peptic ulcer perforations of stomach origin, we determined that perforation site did not have an influence on mortality in our patients (5, 6, 14).

The hospital stay duration following surgery in patients with PUP ranges between 7-12.5 days (21, 22). In our study, the mean length of hospital stay was 8.7±4.6 (0-44) days. After exclusion of patients who developed mortality from the assessment, length of hospital stay was found to be significantly higher in the group that developed morbidity. We think that this period was longer as a result of the complications that developed in the post-operative period.

CONCLUSION

In spite of the developments in peptic ulcer disease treatment, peptic ulcer perforation remains a serious surgical problem. Patients above the age of 60, with a time to presentation longer than 24 hours, presence of shock at the time of presentation and concomitant diseases, and a perforation diameter wider than 0.5 cm are patients at high risk for post-operative morbidity and mortality. MPI scoring system is reliable in predicting morbidity, and MPI and APACHE II in predicting mortality. We believe that close post-operative follow-up of patients under risk can help in reducing morbidity and mortality rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dicle University Faculty of Medicine (18.07.2012/663).

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