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Patients With Perforated Peptic Ulcers: Risk Factors for Morbidity and Mortality

Fatih Ciftci[1], Fazilet Erözgen[2]

[1]*Istanbul Gelisim University Vocational School of Health Services, Avcılar, Istanbul, Turkey*

[2]*Istanbul Haseki Education and Research Hospital, Department of General Surgery, Haseki, Istanbul, Turkey*

Perforated peptic ulcers continue to be an important problem in surgical practice. In this study, risk factors for peptic ulcer perforation-associated mortality and morbidity were evaluated. This is a retrospective study of patients surgically treated for perforated peptic ulcer over a decade (March 1999–December 2014). Patient age, sex, complaints at presentation, time lapse between onset of complaints and presentation to the hospital, physical findings, comorbidities, laboratory and imaging findings, length of hospitalization, morbidity, and mortality were recorded. The Mannheim peritonitis index (MPI) and Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated and recorded for each patient on admission to the hospital. Of the 149 patients, mean age was 50.6 ± 19 years (range: 17–86). Of these, 129 (86.5%) were males and 20 (13.4%) females. At least 1 comorbidity was found in 42 (28.1%) of the patients. Complications developed in 36 (24.1%) of the patients during the postoperative period. The most frequent complication was wound site infection. There was mortality in 26 (17.4%) patients and the most frequent cause of mortality was sepsis. Variables that were found to have statistically significant effects on morbidity included age older than 60 years, presence of comorbidities, and MPI ($P = 0.029$, 0.013, and 0.013, respectively). In a multivariate analysis, age older than 60 years, presence of comorbidities, and MPI were independent risk factors that affected morbidity. In the multivariate logistic regression analysis, age older than 60 years [$P = 0.006$, odds ratio (OR) = 5.99, confidence interval (CI) = 0.95] and comorbidities (OR = 2.73, CI = 0.95) were independent risk factors that affected morbidity. MPI and APACHE II scoring were both predictive of mortality. Age older than 60, presentation time, and MPI were independent risk factors for mortality. Undelayed diagnosis and appropriate treatment are of the utmost importance when presenting with a perforated peptic ulcer. We believe close

Corresponding author: Fatih Ciftci, Basaksehir Mah., Erciyes Sok. No:15, Daire 24, Basaksehir, Istanbul, 34306.
Tel.: 90 505 616 4248; Fax: 90 212 462 7056; E-mail: oprdrfatihciftci@gmail.com

observation of high-risk patients during the postoperative period may decrease morbidity and mortality rates.

Key words: Peptic ulcer perforation – Complications – Mortality – High-risk factors – Presentation time – Outcome assessment

Perforation of a peptic ulcer (PPU), gastric or duodenal, is a potentially fatal surgical emergency that remains a formidable health burden worldwide.[1] The need for surgical treatment has decreased substantially, but 10% of patients still require surgery. Treatment of a perforated peptic ulcer remains mainly surgical. Currently, the most preferred approach is simple closure and an omental plug. However, other techniques are also used.[2–4] Factors that affect the prognosis of perforated peptic ulcers include the width of the perforation, age older than 60, the presence of shock, the presence of comorbidities, and the location of the perforation in the stomach.[5,6] Preoperative hemodynamic shock, sepsis, and disseminated peritonitis are major factors affecting morbidity and mortality.[5–9] In this study, we evaluated risk factors for peptic ulcer perforation.

Patients and Methods

We tried to adhere firmly to STROBE recommendations for the duration of our study. In a retrospective analysis of our medical records, data collection was achieved. A total of 149 patients who were operated on and treated with primary closure and omentoplasty between March 1999 and December 2014 at Safa Hospital General Surgery Clinic for a diagnosis of PPU were included. Written consent was obtained from all patients included in the study. Local Ethical Board approval was obtained to the study. The patients treated with other surgical procedures and those who had malignant ulcers were excluded. The variables we recorded for each patient were as: age, sex, complaint at presentation, time lapse between onset of complaint and presentation to the hospital, physical findings, comorbidities, laboratory and imaging findings, hospitalization time, morbidity, and mortality data Additionally, the Mannheim peritonitis index (MPI) and Acute Physiology and Chronic Health Evaluation (APACHE) II score were also calculated and recorded for each patient on presentation to the hospital. APACHE II scoring was based on previous literature of patient's age, chronic health measure, and 12 other physiologic variables measured at the time of presentation to the hospital. Physiologic parameters considered were body temperature, measured rectally; mean arterial blood pressure; heart rate; breathing rate; blood gases; arterial pH; serum sodium; potassium; creatinine; hematocrit; leukocyte count; and Glasgow coma score.[10]

Presentation time was defined as the time lapse between the onset of complaints and presentation to the hospital. Peptic ulcer perforation was diagnosed based on patient history, a physical examination, routine laboratory tests, and radiologic imaging. Comorbidities were recorded. Preoperative shock was defined as systolic blood pressure below 90 mm Hg.

Oral ingestion was stopped and nasogastric and urinary catheters were inserted in all patients presenting with PPU. Patients were taken in for the operation after sufficient fluid resuscitation. Before the operation, ceftriaxone 1 g and ornidazole 500 mg were administered intravenously. Postoperative antibiotic treatment continued for 7 to 10 days. Patients were grouped according to presentation time: <24 versus >24 hours[11,12]; age, <60 versus >60 years; APACHE II score, <11 versus >11[11]; MPI, <26 versus >26[13]; and perforation width, <0.5 versus 0.5 to 1 cm.[14,15] Open surgery was performed on all patients. After the laparotomy, gastrointestinal content that leaked into the abdominal cavity was aspirated and the cavity was irrigated with 1000 mL of warm physiological saline. A Foley drainage catheter was placed in the Morrison pouch in all patients, and another in the pelvis region, as needed. Nasogastric catheters were removed on postoperative day 3 or 4. Patients were allowed to start taking liquid food on postoperative day 4.

Statistical Analyses

We used statistical software (SPSS version 15.0 for Windows; SPSS, Inc, Chicago, Illinois). Quantitative data are expressed as means, ranges, and standard deviations. Student's *t*-test was used to compare parametric data of the groups and the χ^2 test to compare categorical data. Multivariate logistic re-

gression testing was used to analyze risk factors that affected morbidity and mortality. The odds ratio (OR) was calculated for each variable. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

In total, 129 (86.5%) of the patients were males and the mean age was 50.6 ± 19 years (range: 17–86). The mean presentation time was 29.9 ± 29.8 hours (range: 3–237). At the initial presentation to the hospital, 11 (8.05%) of the patients had signs of shock and 42 (28.1%) had at least 1 comorbidity. The most frequent site of perforation was the prepyloric region ($n = 99$ patients, 66.4%). Patients who developed comorbidities had longer hospitalizations ($P < 0.001$). Demographic and clinical characteristics of patients are shown in Table 1. Of the patients, 36 (20.1%) developed comorbidities in the postoperative period. Wound site infection was the most frequent. Death occurred in 26 (17.4%). Causes of postoperative morbidity and mortality are shown in Table 1. Variables found to have statistically significant effects on morbidity included age over 60, presence of comorbidities, perforation width, and MPI ($P = 0.029$, 0.013, and 0.013, respectively; Table 2). In a multivariate logistic regression analysis, age older than 60 [$P = 0.006$, OR = 5.99, confidence interval (CI) = 0.95] and comorbidities (OR = 2.73, CI = 0.95) were found to be independent risk factors that affected morbidity (Table 3). In the univariate analysis, factors found to have effects on mortality were presentation time, shock, comorbidity presence, perforation width, MPI, and APACHE II score ($P < 0.001$, < 0.001, < 0.001, < 0.001, < 0.001, and < 0.001, respectively; Table 4). In the multivariate logistic regression analysis, age older than 60 years ($P = 0.008$, OR = 13.972, CI = 109.069); presentation time ($P = 0.024$, OR = 0.149, CI = 0.781); and MPI ($P = 0.006$, OR = 18.98, CI = 193.87) were found to be independent risk factors (Table 4). Postoperative complications demonstrated after surgery of perforated peptic ulcer according to the Clavien-Dindo grading system (Table 5).

Discussion

Many factors may be associated to the incidence rates of PPU. Epidemiologic studies have revealed that the ones born up to the 1930s were at higher

Table 1 Demographic and clinical characteristics of patients and causes of morbidity and mortality

Sex, n	
Male	129
Female	20
Age, y (range)	50.6 ± 19 (16–89)
Presentation time, h (range)	29.9 ± 29.8 (3–237)
Signs of shock, n (%)	11 (7.3)
Comorbidities, n (%)	
Total	42 (28.1)
Cardiovascular diseases	20 (47.6)
Pulmonary diseases	9 (21.4)
Diabetes mellitus	4 (9.5)
Urinary system disease	2 (4.7)
Malignancy	5 (11.9)
Others	2 (4.7)
Physical examination signs, n (%)	
Tenderness	149 (100)
Defense	129 (86.5)
Rebound	111 (74.4)
Clinical symptoms, n (%)	
Abdominal pain	149 (100)
Nausea/vomiting	51 (34.2)
Unable to discharge stool or gas	71 (47.6)
Perforation width, n (%)	
<0.5 cm	94 (63.0)
0.5–1 cm	48 (32.2)
APACHE II	6.3 ± 6.5 (0–28)
Perforation site, n (%)	
Prepyloric	99 (66.4)
Duodenum	50 (33.5)
WBC, mm^3 (%)	12980 ± 5974 (1100–33,601)
MPI	13.8 ± 6.9 (4–32)
Free or localized fluid in the abdominal cavity on USG, n (%)	89 (59.7)
Free air on direct abdominal X-ray, n (%)	119 (79.8)
Causes of morbidity and mortality, n (%)	
Total morbidity	35 (23.4)
Ileus	1 (2.8)
Delirium	1 (2.8)
Pneumonia	2 (5.6)
Acute kidney failure	1 (2.8)
Urinary system infection	1 (2.8)
Lung edema	1 (2.8)
Fistula	1 (2.8)
Evisceration	1 (2.8)
Pneumonia	2 (5.6)
Wound infection	12 (34.2)
Pleural effusion	9 (25.7)
Atelectasis	3 (8.5)
Mortality, n (%)	26 (17.4)
Sepsis	20 (76.9)
Myocardial infarction	1 (3.8)
Acute kidney failure	1 (3.8)
Fistula	1 (3.8)
Pulmonary causes	3 (3.8)

Table 2 Factors that affect morbidity on univariate analysis

Parameters	Group without comorbidity, *n* (%)	Group with comorbidity, *n* (%)	*P*
Age			
≤60 years	76	10	0.029
>60 years	42	17	
Sex			
Male	103 (88.3)	26 (11.7)	NS
Female	16 (80)	4 (20)	
Presentation time			
≤24 h	81 (80.1)	20 (19.9)	NS
>24 h	41 (85.4)	7 (14.6)	
Comorbidity	29	13	0.029
Shock	9	2	NS
Free air on direct abdominal X-ray	95 (79.8)	24 (20.2)	NS
APACHE II			
≤11	93 (89.4)	21 (10.6)	NS
>11	26 (74.2)	9 (25.8)	
MPI			
≤26	100 (77.5)	29 (22.5)	0.013
>26	20 (100)	0	
Perforation width			
≤0.5 cm	73 (77.6)	21 (22.4)	0.013
0.5–1 cm	39 (81.3)	9 (18.7)	
>1 cm	3 (42.8)	4 (57.2)	
Perforation site			
Prepyloric	80	19	NS
Duodenum	19	11	

risk of PPU than those later born. The speculation of an influence of *Helicobacter pylori* infection on the older population, has been hypothesized as the main cause. On the other hand, *H pylori* infection has been deemed of less importance in perforated peptic ulcer disease (PUD) compared with that of uncomplicated peptic ulcer disease. However, the association between specific birth cohorts and mortality from PUD has been convincing, and a decrease in the incidence of PPU may thus be expected when the cohorts at risk disappear with time.[16–18] Despite this, perforation occurs in ~7% and bleeding in 15% to 20% of PUD patients annually.[19] Peptic ulcer perforation is more prevalent in patients in their 4th and 5th decades and the male-to-female ratio is 2-8:1.[12,20–23] Likewise, in our series, the patients' mean age was 51 years and the male-to-female ratio was 9:1.

It has been reported that free air images are found below the diaphragm in 47.2% to 80% of PPU patients.[20–24] In our study, free air images were found below the diaphragms of 82.4% in our series.

Table 3 Factors affecting morbidity in multivariate logistic regression analysis

Factors	OR	95% CI	*P*
Sex	0.30	0.06–1.09	0.07
Age > 60	5.99	1.59–23.88	0.006
Shock	0.78	0.11–5.58	0.79
Comorbidity	2.79	0.98–7.79	0.045
Presentation time	0.71	0.20–2.61	0.61
MPI	0.84	0.69–0.92	0.02
APACHE II	0.37	0.07–1.86	0.22
Perforation width	1.19	0.59–2.59	0.58
Free air in direct abdominal X-ray	0.99	0.29–2.98	0.88

Postoperative morbidity in PPU varies between 21% and 43%.[12,25,26] Causes of postoperative morbidity are frequently pulmonary and wound site infections. The morbidity rate was 20.3% in our study and the complications were predominantly pulmonary and wound site infections. We found that age older than 60 years, presence of comorbidities, MPI <26, and perforation width were factors that affected the development of comorbidities.

One study highlighted that age older than 60 years and female sex were factors affecting postoperative morbidity.[27] However, in our study, sex had no apparent effect on comorbidity development, even though the patients were predominantly males. In our series, 42.6% of the patients were aged older than 60 years. The effect of age older than 60 years on comorbidity development was found to be statistically significant in univariate and multivariate analyses.

There are reports showing that presentation time longer than 24 hours is unfavorable for the prognosis.[12,21,23] In our study, the mean presentation time was 30.8 to 31.4 hours (range: 2–240). However, we did not find any significant relationship between presentation time and prognosis.

There are reports that the presence of shock at presentation increases the risk of morbidity.[7,8,12,19,23] However, we found no such relationship.

Other studies have reported increased comorbidity rates in PPU patients with comorbidities.[12,27–30] We also found that the comorbidity rate was higher in patients with comorbidities in our series.

Various sites of perforation in PUD have been reported in previous studies.[14,30–32] In our study the site was predominantly prepyloric, in 101 (68.2%) patients. However, the site of perforation had no apparent effect on morbidity rate.

Table 4 Factors affecting mortality in univariate and multivariate logistic regression analysis

Parameters	Group without comorbidity, n (%)	Group with comorbidity, n (%)	*P*
Age			
≤60 y	80 (81.3)	5 (18.7)	<0.001
>60 y	41 (64.0)	23 (36)	
Sex, n (%)			
Male	105 (81.3)	24 (18.6)	NS
Female	16 (80.0)	4 (20.0)	
Shock	4 (36.3)	7 (43.7)	<0.001
Presentation time			
≤24 h	94 (93.0)	7 (7.0)	<0.001
>24 h	27 (56.2)	21 (43.8)	
MPI			
≤26	117 (90.6)	12 (9.4)	<0.001
>26	1 (5.0)	19 (95.0)	
APACHE II			
≤11	109 (92.3)	9 (7.7)	<0.001
>11	9 (29.0)	22 (71.0)	
Free air in direct abdominal X-ray	94 (78.9)	25 (21.1)	NS
Perforation width			
≤0.5 cm	84 (89.3)	10 (10.7)	<0.001
0.5–1 cm	28 (58.3)	20 (41.7)	
>1 cm	6 (66.6)	3 (33.3)	
Perforation site			
Prepyloric	84 (89.3)	15 (10.7)	NS
Duodenum	28 (70.0)	12 (30.0)	
Factors	**OR**	***P* value**	**95% CI**
Sex	0.998	0.897	0.99–9.694
>60 years	13	0.008	1.974–109.069
Shock	972	0.229	0.022–2.386
Comorbidity	1.198	0.639	0.279–5.653
MPI	18.98	18.98	2.18–193.87
APACHE II	0.229	0.229	0.489–4.839
Perforation width	1.495	0.449	0.490–4.838
Free air in direct abdominal X-ray	0.125	0.129	0.008–1.795
Presentation time	0.149	0.024	0.029–0.781

Table 5 Postoperative complications after surgery of perforated peptic ulcer according to the Clavien-Dindo grading system

Grade	Cases, n (%)
1	28 (18.7)
2	6 (4.0%)
3a	Not observed
3b	1 (2.8)
4a	Not observed
4b	20 (13.4)
5	26 (17.6)

A width of perforation greater than 0.5 cm in PPU was reported to significantly increase morbidity.[31,33]

One study reported that MPI was predictive of morbidity.[32,34] In our study, we also found that patients with MPI <26 were at significantly less risk for developing comorbidities.

Postoperative mortality varies between 4% and 30% in PPU patients.[16,23,27,33–35] Causes of mortality are reported to be, predominantly, multiple organ failure and pneumonia. The mortality rate in our study was 18.2%, and the most frequent causes were sepsis and pulmonary. Factors found to affect mortality in our series were age older than 60 years, presentation time longer than 24 hours, presence of shock, MPI >26, APACHE II score >11, and perforation width larger than 0 to 5 cm.

One study reported that mortality rates increased significantly in patients older than 60 years.[23] Another found a mortality rate of 1.4% among patients aged younger than 65 years and 37.7% in those over 65.[12] In our study, we also found that age older than 60 years increased the risk of mortality. However, we found no relationship between sex and mortality.

As in previous reports, we found that presentation time longer than 24 hours significantly increased the risk of mortality.[12,21,23,36] Also, and consistent with other studies, we found that shock at presentation to the hospital significantly increased the mortality risk.[7,8,12,23,35–37] In light of these findings, we consider that fluid-electrolyte resuscitation should be performed in PPU patients who present with shock prior to any operation.

In our series, the presence of comorbidities was found to significantly increase mortality. This result was consistent with other reports.[12,27–29]

Bracho-Riquelme and colleagues[13] reported that MPI scores greater 26 were associated with increased mortality. In our series, we also found significantly increased mortality in association with MPI scores over 26.

Reports on any association of APACHE II scores and mortality remain controversial.[13,32,36–38] In our study, we found higher mortality among patients with APACHE II scores >11.

Postoperative hospitalization of patients with PPU is reported to range between 7 and 12.5 days.[21,22] In our study, the mean hospitalization time was 4.7 ± 3.6 days (range: 0–25). There was significant prolongation of hospitalization in the group of patients who developed morbidity when the patients who died were excluded. Thus, we believe prolonged hospitalization was primarily due to postoperative complications.

Cases of PPU with width >1 cm have been shown to be associated with increased mortality.[37,39] In this study, univariate analysis showed that perforation width was directly associated with increased mortality. Some studies have reported higher mortality rates in association with PPU of gastric origin.[5,6,14] However, we found no significant relationship between mortality and the site of PPU.

Conclusions

Peptic ulcer perforation remains a serious surgical problem despite developments in the treatment of PUD. Patients older than 60 years, who present to the hospital later than 24 hours after onset of symptoms, who have shock findings at presentation, comorbidities, and a perforation width over 0.5 cm have a high risk of developing postoperative morbidity and mortality. MPI is an important scoring system in predicting the development of comorbidities. MPI and APACHE II scoring are both predictive of mortality. We believe close observation of high-risk patients during the postoperative period may decrease morbidity and mortality rates.

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