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ORIGINAL SCIENTIFIC REPORT

Long-Term Mortality in Patients Operated for Perforated Peptic Ulcer: Factors Limiting Longevity are Dominated by Older Age, Comorbidity Burden and Severe Postoperative Complications

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Abstract

Background Perforated peptic ulcer (PPU) is a surgical emergency associated with high short-term mortality. However, studies on long-term outcomes are scarce. Our aim was to investigate long-term survival after surgery for PPU.

Materials and Methods A population-based, consecutive cohort of patients who underwent surgery for PPU between 2001 and 2014 was reviewed, and the long-term mortality was assessed. Survival was investigated by univariate analysis (log-rank test) and displayed using Kaplan–Meier survival curves. Multivariable analysis of risk factors for long-term mortality was assessed by Cox proportional hazards regression and reported as hazard ratio (HR) with 95 % confidence intervals (CI).

Results A total of 234 patients were available for the calculation of ninety-day, one-year and two-year mortality, and the results showed rates of 19.2 % (45/234), 22.6 % (53/234) and 24.8 % (58/234), respectively. At the end of follow-up, a total of 109 of the 234 patients (46.6 %) had died. Excluding 37 (15.2 %) patients who died within 30 days of surgery, 197 patients had long-term follow-up (median 57 months, range 1–168) of which 36 % (71/197) died during the follow-up period. In multivariable analyses, age >60 years (HR 3.95, 95 % CI 1.81–8.65), active cancer (HR 3.49, 95 % CI 1.73–7.04), hypoalbuminemia (HR 1.65, 95 % CI 0.99–2.73), pulmonary disease (HR 2.06, 95 % CI 1.14–3.71), cardiovascular disease (HR 1.67, 95 % CI 1.01–2.79) and severe postoperative complications (HR 1.76, 95 % CI 1.07–2.89) during the initial stay for PPU were all independently associated with an increased risk of long-term mortality. Cause of long-term mortality was most frequently (18 of 71; 25 %) attributed to new onset sepsis and/or multiorgan failure.

Conclusion The long-term mortality after surgery for PPU is high. One in every three patients died during follow-up. Older age, comorbidity and severe postoperative complications were risk factors for long-term mortality.

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Introduction

Perforated peptic ulcer (PPU) is the most serious complication related to peptic ulcer disease (PUD) and annually accounts for 70 % of deaths caused by PUD globally [1]. Demographic differences in the incidence and presentation of PUD have developed over time and exist between regions. In the Western world, patients who suffer a PPU are typically older and present with significant additional comorbidity [2]. In contrast, patients with PPU in developing countries are often younger and predominantly male and have little or no additional comorbidity [3]. Consequently, both short-term mortality and long-term outcomes may be affected by age and the existence of comorbidity on presentation, which may add to the risk for these patients in the long term.

Recent population-based studies [4, 5] have reported a 30-day mortality rate between 16 and 27 % for patients surgically treated for PPU. In contrast to short-term mortality, only a few studies, some of which are clearly dated, have reported the long-term mortality for this particular group of patients [6–8].

As data on the long-term outcomes of patients with PPU remain scarce [2], we aimed to investigate the long-term mortality in a well-described, population-based cohort.

Materials and methods

Study ethics

The study was approved as a quality control assurance project according to the Regional Ethics Committee (REK Vest # 2011/713).

Study population

Stavanger University Hospital (SUH) is the only hospital in the greater Stavanger area and has an urban–rural catchment area of approximately 350,000 inhabitants. Because SUH is the only hospital in this region in the southwestern part of Norway, referral bias is minimal. A detailed description of the catchment area and the management of patients with PPU have been previously reported [9, 10].

All consecutive patients who underwent surgery for a perforated gastric (GU) or duodenal ulcer (DU) admitted between January 2001 and December 2014 were identified from the hospital administrative electronic database using ICD-10 diagnostic codes (K25 and K26) and codes for surgical procedures (i.e., JDA 60 gastrorrhaphy, JDA 61 Laparoscopic gastrorrhaphy, JDH 70 duodenorrhaphy, JDH 71 Laparoscopic duodenorrhaphy).

Patients with a malignant ulcer, patients treated conservatively (i.e., non-operatively) and patients identified at autopsy were excluded. We also excluded patients who were foreign residents and thus not available for follow-up. Patients who were admitted more than once for PPU during the study period were only registered for their index admission for long-term follow-up analyses.

Long-term follow-up

Long-term mortality was the main outcome measured in this study. To assess long-term mortality after surgery, only patients alive at 30 days after surgery were included in the Kaplan–Meier plots. The patients were followed until April 30, 2015. Updated survival information was obtained from the National Population Registry, which is linked to the hospital's electronic journal system. Any death was coded as an event, and patients alive were censored on the last date of follow-up.

Definitions

Active cancer included all patients with cancer and/or metastatic cancer who were currently being treated with chemotherapy or radiation. This definition did not include previously treated cancers currently regarded without evidence of relapse.

Death from multiorgan failure (MOF) was defined as failure of more than one organ system (heart, lung, kidney or liver) leading to fatality. Sepsis-related causes of death included pyelonephritis, pneumonia and peritonitis. Because of the large number of causes of death and occasionally multiple causes listed for a single patient, wide categories were employed to describe trends.

Cardiovascular events included myocardial infarction, heart failure, pulmonary embolism and stroke. Pulmonary disease included chronic obstructive pulmonary disease, asthma and pulmonary fibrosis. Severe complications were defined as Clavien–Dindo classification grade 3 and 4 [11]. Hypoalbuminemia was defined as an albumin level of <37 g/L, and hyperbilirubinemia was defined as a bilirubin level >19 µmol/L, based upon optimal cutoff points found in a previous receiver operating characteristics curve (ROC) analysis [10].

Scoring systems

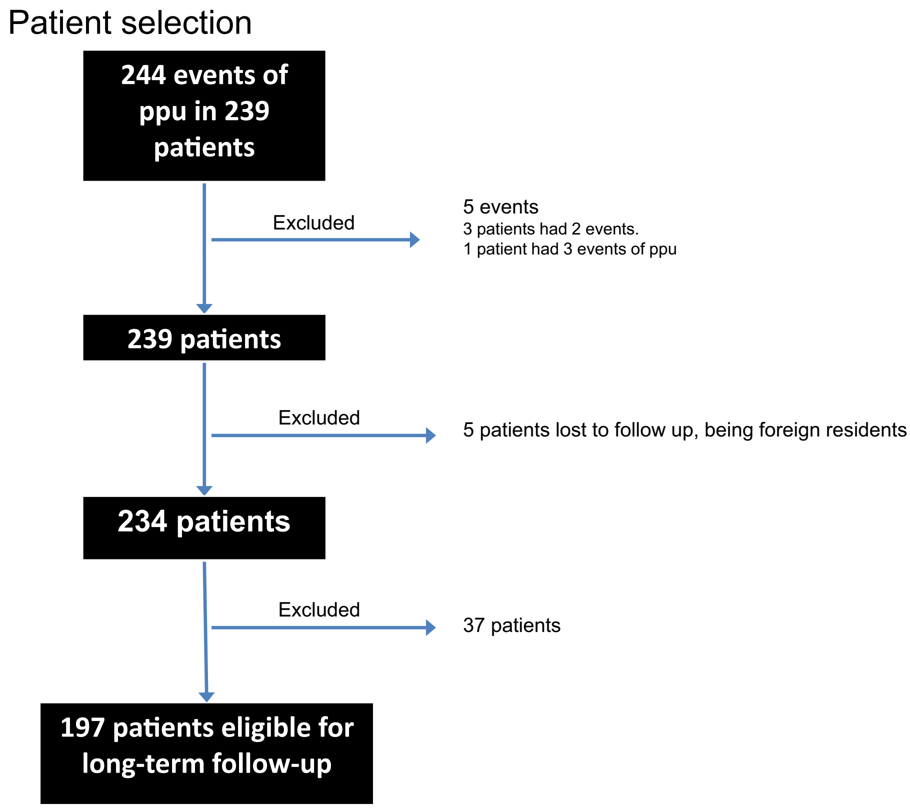
The Charlson comorbidity index (CCI) score [12] takes into account several diseases ranked from 1–6 points; for example, hypertension yields 1 point, complicated diabetes mellitus 2 points and metastatic cancer 6 points. Angina pectoris does not yield any points. Age >40 years yields 1 point for each decade of increasing age.

ROC analysis [13] of the CCI score was conducted to assess the best cutoff with regard to one-year mortality. A CCI score ≥ 6 was classified as high risk and applied for long-term survival analysis.

Statistical analysis

Statistical analyses were performed using SPSS for Mac, version 22.0. Descriptive analysis was conducted for

Fig. 1 Flowchart of patient selection



simple frequency analysis, and a Chi-square analysis or the Fisher's exact test was used to compare categorical data, where appropriate. Survivals were displayed by calculation of Kaplan–Meier curves, and comparisons of survivals between subgroups were calculated by the log-rank test. Cox proportional hazard regression was used for multivariable analysis for associations between independent variables and long-term mortality, and results are presented as the hazard ratio (HR) with 95 % confidence interval (95 % CI). Factors with a p value of <0.10 in univariate analyses were included in the multivariable analyses, which was additionally adjusted for age, sex and operation method (laparoscopy versus laparotomy). All tests were two-sided, and p values <0.050 were regarded as statistically significant.

Results

Over 14 years, 244 events of PPU were surgically treated at SUH. Five patients were excluded due to multiple events (3 patients had 2 events of PPU and 1 patient had 3 PPU events). Hence, patients were only included once for long-term follow-up analyses. Additionally, 5 patients with a foreign address were lost to follow-up. One patient was admitted 3 times for PPU during the study period but died within 30 days after the third admission. Thus, 234 patients were included for the estimation of 90-day, 1-year and 2-year mortality, while 37 patients who died within 30 days postoperatively (30-day postoperative mortality 15.2 % (37/244)) were excluded from the long-term survival analysis (Fig. 1). Hence, 197 patients surviving beyond 30-days were included in the long-term survival analysis (Fig. 1). Differences in clinical characteristics of the patients who died after surviving 30 days compared to those who were alive at follow-up were analyzed and are presented in Table 1.

Long-term follow-up and outcomes

The 90-day mortality was 19.2 % (45/234). Seven patients died between postoperative day 30 and 90 from various causes including lung cancer, peritonitis due to intestinal ischemia with multiple intestinal perforations, heart attack, metastatic cancer, pulmonary embolus, respiration failure, acute respiratory distress syndrome (ARDS) and one of the 'unknown' causes. The 1- and 2-year mortality rates were 22.6 % (53/234) and 24.8 % (58/234), respectively. At last follow-up, 46.6 % (109/234) of the patients were deceased. With a median follow-up time of 57 months, Kaplan–Meier analysis showed a 10-year median survival estimate of 119 months (range 0–168).

Table 1 Characteristics of patients available for long-term analysis (*n*=197)

Factors	Died during follow-up *N*=71 (36 %)	Long-term survivors *N*=126 (64 %)	*p* value*
Sex			
Male	32 (45%)	65 (51.6%)	0.380
Female	39 (55%)	61 (48.4%)	
Age (years)			
<60	8 (11.4%)	64 (51.1%)	<0.001
≥60	63 (88.6%)	62 (48.9%)	
ASA risk score			
ASA 1–2	3 (7%)	28 (22.2%)	0.001**
ASA ≥3	68 (93%)	98 (77.8%)	
Comorbidity			
Low (CCI) <6	36 (50.1%)	108 (84.4%)	<0.001
High (CCI) ≥6	35 (49.9%)	18 (15.6%)	
Ulcer location			
Gastric	51 (71.8%)	83 (65.9%)	0.389
Duodenal	20 (28.2%)	43 (44.1%)	
Severe compl.			
No	44 (62%)	97 (77%)	0.025
Yes	27 (38%)	29 (23%)	
Preoperative shock			
No	55 (77.5%)	109 (86.5%)	0.103
Yes	16 (22.5%)	17 (13.5%)	
*Preoperative sepsis**			
No	38 (53.5%)	68 (54%)	0.988
Yes	32 (45.0%)	57 (45.2%)	
Laboratory tests			
CRP <21	29 (40.1%)	76 (60.3%)	0.009
CRP ≥21	42 (59.9%)	50 (39.7%)	
Creatinine <118	51 (71.8%)	108 (85.7%)	0.022
Creatinine ≥118	19 (26.8%)	17 (13.5%)	
Bilirubin <19	62 (87.3%)	109 (86.5%)	0.780
Bilirubin ≥19	8 (11.3%)	16 (12.7%)	
Surgical repair			
Laparoscopy	19 (26.8%)	65 (51.6%)	0.001
Laparotomy	52 (73.2%)	61 (48.4%)	

Severe compl. = severe complications (Clavien–Dindo 3 and 4)

CRP measured in mg/L; creatinine and bilirubin measured in µmol/L

Two patients missing data for sepsis

Two patients missing data for creatinine

Two patients missing data for bilirubin

* *Chi-square test*

** Fisher's exact test

In further long-term analyses, 197 patients who survived >30 days were included (Fig. 1); of these patients, 36 % (71/197) died during the follow-up period. Postoperative complications (Clavien–Dindo 1–4) were seen in 42.6 % (84/197) of the patients, while severe postoperative complications (Clavien–Dindo 3 and 4) were encountered in 24.4 % (56/197). Women constituted 51 % of the long-term survivors (100/197). The median age was 61 and 72 years for men and women, respectively ($p < 0.001$).

Associations with mortality

Univariate long-term survival analysis by log-rank test revealed significantly worse survival in patients aged >60 years compared to the younger patients (Fig. 2a) and with an active cancer present at time of diagnosis (Fig. 2b), in patients with hypoalbuminemia (Fig. 3a), pulmonary disease (Fig. 3b) and cardiovascular disease (Fig. 4a) as well as those who had severe postoperative complications (Fig. 4b).

By means of log-rank testing, a significant difference in long-term survival was found for CCI score with 75 % (108/144) of patients alive at follow-up in the CCI score <6 group compared to 34 % (18/53) in the CCI score ≥6 group ($p < 0.001$). The ROC analysis for the cutoff points for the CCI score are shown in the Appendix. Further, in the American Society of Anesthesiologists (ASA) score <3 group, 90 % (28/31) of patients were alive at follow-up compared to 59 % (98/166) in the ASA ≥3 group ($p < 0.001$). Preoperative shock was seen in 33/197 (16.8 %) patients with 66.5 % (109/164) of patients alive at follow-up for those without preoperative shock compared to 51.5 % (17/33) for those with preoperative shock ($p < 0.012$). For patients with creatinine <118 µmol/L, 67.5 % (108/160) of patients were alive at follow-up compared to 47 % (17/36) ($p < 0.007$) for those with creatinine ≥118 µmol/L. For patients with a preoperative CRP <21 mg/L, 72 % (76/105) of patients were alive at follow-up compared to 54 % (50/92) for patients with a preoperative CRP ≥21 mg/L (p=0.002). Active smoking status, sex, surgical access (i.e., laparoscopy compared to laparotomy), PPU location, preoperative sepsis nor hyperbilirubinemia were significantly associated with long-term mortality by univariate log-rank calculations.

The cause of long-term mortality was most frequently attributed to sepsis and/or MOF, accounting for 25 % (18/71) of the late deaths. A high proportion of the late deaths occurred outside of the hospital. Accordingly, detailed information on causes of death was generally unreachable. The obtained information on causes of death is presented in Table 2.

In the multivariable Cox proportional hazard analysis, age ≥60 years, active cancer, hypoalbuminemia, pulmonary disease, cardiovascular disease and severe postoperative complications remain included in the multivariable model for association with long-term mortality, after adjusting for preoperative shock, elevated creatinine >118 µmol/L, preoperative CRP >21 mg/L, sex and laparoscopy compared to laparotomy (Table 3).

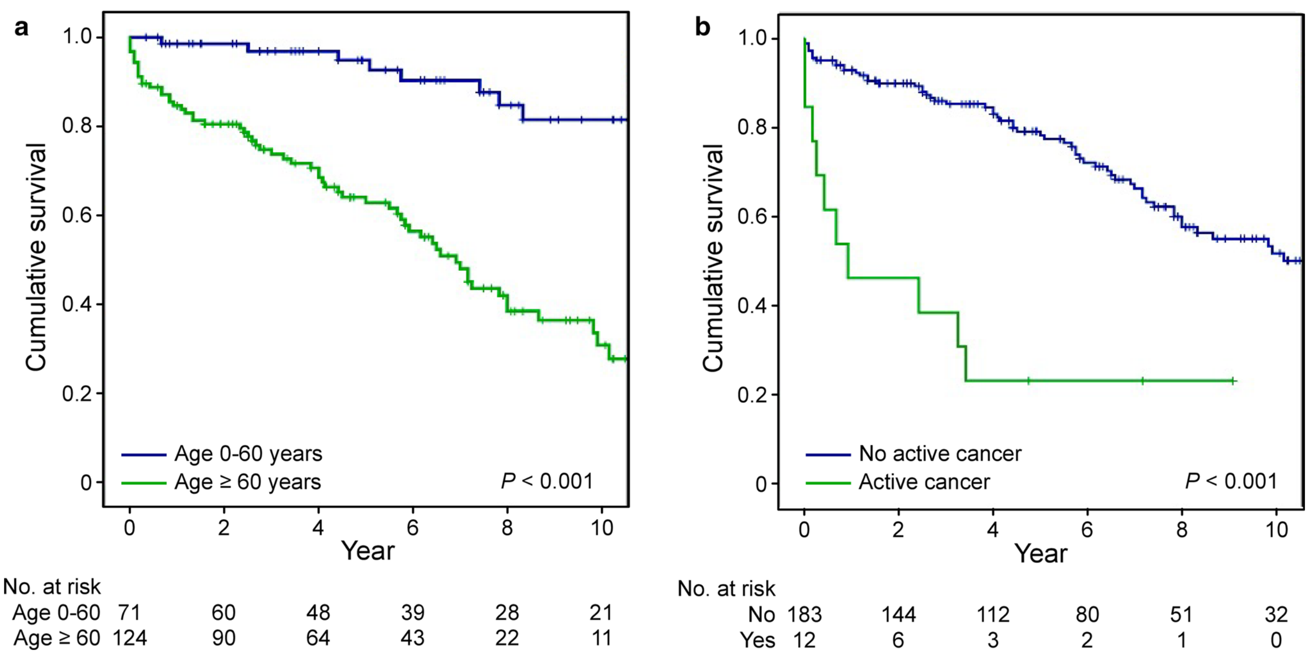


Fig. 2 **a**, **b** Long-term outcome according to age and presence of cancer

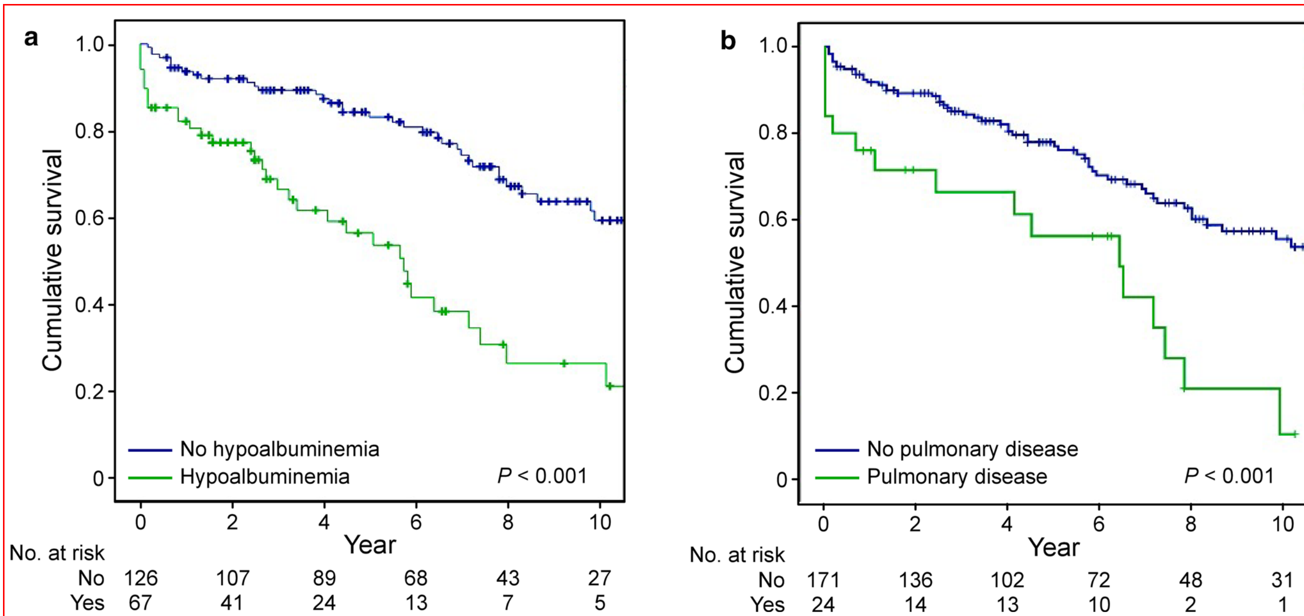


Fig. 3 **a**, **b** Long-term outcome according to hypoalbuminemia and pulmonary disease

Discussion

This long-term follow-up study after surgery for perforated peptic ulcer demonstrates that almost half of all patients were deceased at the end of follow-up. Excluding the early postoperative deaths within 30 days, about one-third of the patients eligible for follow-up died within the ensuing follow-up period. In the adjusted analysis, older age, active cancer, hypoalbuminemia, pulmonary disease, cardiovascular disease and severe postoperative complications were significant risk factors associated with an increased long-term mortality.

Patients with active cancer, age >60 years and hypoalbuminemia have previously been found to predict 30-day

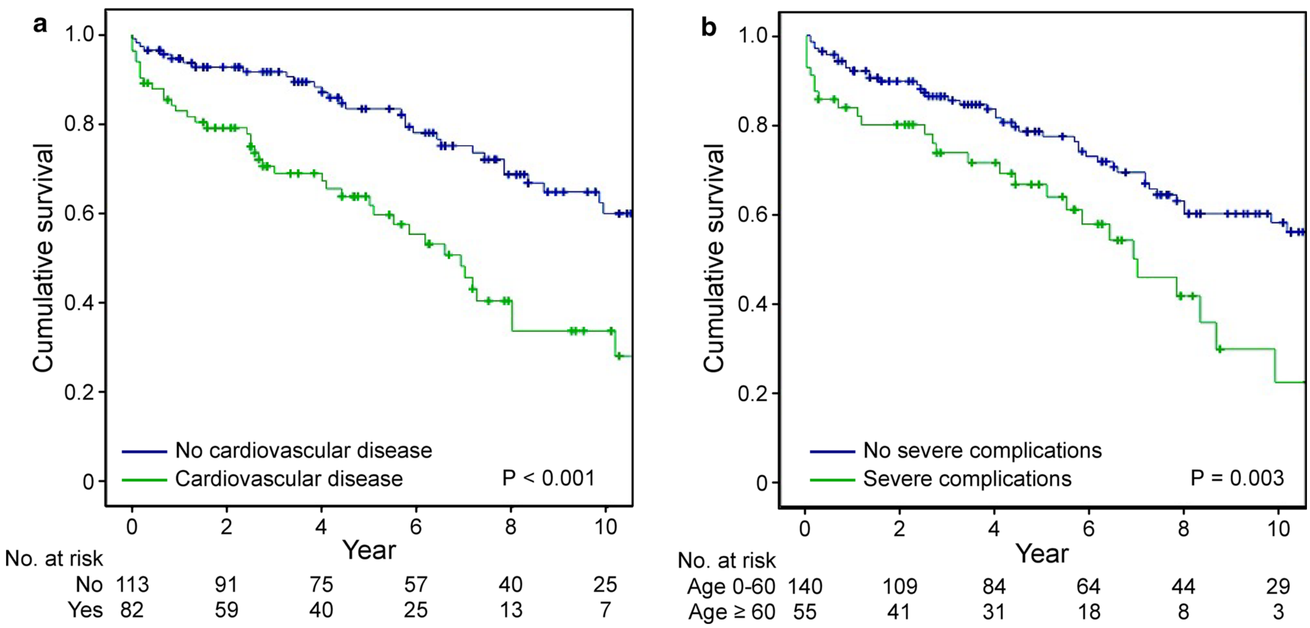


Fig. 4 **a**, **b** Long-term outcome according to cardiovascular disease and postoperative complications

Table 2 Causes of late deaths according to age groups

Causes of death	Age <60 years	Age ≥60 years	Total
Cardiovascular	1	8	9
MOF	0	6	6
Sepsis related	2	10	12
Cancer	1	8	9
Other	1	0	1
Unknown	3	31	34
Total	8	63	71

MOF multiorgan failure

Table 3 Factors remaining in the Cox multivariable regression analysis after adjusting for cofactors

Factor	Hazard ratio (HR)	95 % CI	*p* value
Pulmonary disease	2.06	1.14–3.71	0.017
Cardiovascular disease	1.67	1.01–2.79	0.048
Active cancer	3.49	1.73–7.04	0.001
Severe complications	1.76	1.07–2.89	0.027
Albumin <37 g/L	1.65	0.99–2.73	0.051
Age ≥60	3.95	1.81–8.65	0.001

Adjusted for sex, laparoscopy versus laparotomy, preoperative shock, crp >21 and elevated creatinine

mortality in the same cohort [10, 14], which now emphasizes their detrimental effects also for long-term mortality. The fact that also pulmonary and cardiovascular disease was highly associated with long-term outcome is not surprising, due to the unfavorable implications of these disorders. However, the association between severe complications after surgery for PPU and long-term outcome has been described only once in the past [8], although postoperative complications have been associated with unfavorable outcomes in other fields of gastrointestinal surgery and was also found in a study from the National Surgical Quality Improvement Program (NSQIP) of patients undergoing 8 types of major surgery [15, 16]. These associations emphasize an associated risk of death with higher age and increased comorbidity. Notably, we do not have data to support the possibility of long-term organ failure or reduced organ function as a consequence of severe complications, but this may partly explain why severe complications were associated with decreased long-term survival.

Increased long-term mortality in the elderly with higher comorbidity also points to the concept of frailty, which can be easily understood but difficult to evaluate, especially in the emergency setting [17]. Frailty implies a lack of resilience toward stressors as the human physiology is challenged with age [18]. Thus, elderly people who experience an insult, including a PPU, may have difficulty in recovering properly. Thus, subsequent new events, such as a pulmonary infection or a cardiac event, may further challenge a limited physiologic capacity and eventually hasten death.

Age is one of the most prominent general risk factors for short-term mortality. As shown in this study, age as an unmodifiable factor is also associated with long-term survival. Along with higher age, the comorbidity increases [18], and thus the risk of death, which in this study is reflected by a high fatality rate for cardiovascular events and infection-related fatal outcomes (sepsis, MOF) in patients >60 years of age [19].

The presence of active cancer has been associated with both short- and long-term mortality in patients with PPU. Indeed, the comprehensive study by Svanes et al. [6] demonstrated that most causes of death in the long term were related to smoking-associated diseases, including a high rate of cancer-related deaths. In a more recent German study [8], age and the presence of comorbidities were also found to be risk factors for long-term mortality. A Danish study is the only cohort with follow-up data on long-term outcomes for patients with PPU who underwent surgery after the 2000s, with 2-year mortality as the final endpoint of follow-up [7]. Consistent with our findings, both age and a high degree of comorbidity were associated with increased long-term mortality [7, 8].

Smoking was found to be strongly associated with long-term mortality, mainly due to smoking-related illnesses measured by the excessive standard mortality ratio in a previous study [6]. In the present study, smoking was not found to be significantly associated with long-term mortality in the univariate analysis. This may partly be explained by the fact that patients with PPU in Scandinavia to a considerable extent are smokers with a high level of comorbidity, which is also reflected by the factors associated with long-term mortality in this study. In addition, as shown in a previous study [9], non-smokers were significantly younger than smokers. Hence, the patients who died from PPU despite being non-smokers already had comorbidities of clinical importance, in addition to a higher age, which put them at risk.

Preoperative hypoalbuminemia has been previously linked to 30-day mortality in both patients with PPU and in patients with other conditions [10]. Hypoalbuminemia may be an indicator of preoperative poor nutritional status, presence of chronic disease or cancer, or presence of sepsis/severe infection on admission. The presence of this condition has been linked to excessive 1-year mortality in patients >70 years of age undergoing emergency abdominal surgery [20]. The finding that hypoalbuminemia is also associated with long-term outcome may represent an indicator of the underlying frailty in these patients, the presence of an underlying chronic disease or an age-related decline in appetite and a reduced adequate intake of nutrients. These factors may all increase a person's susceptibility to the new onset of disease, including acute or chronic organ failure, and may diminish reserves to withstand further ailments in the long term [21].

The CCI and ASA scores were both highly associated with long-term mortality in the univariate analysis. However, due to interaction of these factors with comorbidity, we chose to keep the scoring systems out of the multivariable model. In the past, the CCI score has been found to be associated with short-term mortality in patients with PPU [22]. To date, CCI score has not been demonstrated to be associated with long-term mortality in patients with PPU. However, a CCI score >4 has also been linked to excessive 1-year mortality for patients >70 years of age undergoing emergency abdominal surgery [20]. The CCI score has also been shown to predict 1-year mortality in patients admitted to the intensive care unit (ICU) [23]. One advantage of the CCI score is that it is a quantifiable scoring system that can be easily calculated. While many factors and scoring systems are associated with short-term mortality in patients with PPU [12, 24], few studies on long-term mortality have been conducted.

The ASA score, as a more general score, is based on vague and user-dependent definitions, although this score has predicted short-term mortality in several studies of PPU and other conditions [12]. The ASA score has also been applied to predict long-term mortality after emergency abdominal surgery [20] and other illnesses, although not for PPU.

In this study, we found a significant lower mortality at the time of follow-up in the group treated laparoscopically compared to laparotomy by means of Chi-square testing. However, the log-rank test did not show any differences between the groups and the Chi-square testing does not consider the time element. Laparoscopy versus laparotomy was also adjusted for in the multivariable Cox regression analyses. A selection bias in favor of less comorbidity in the laparoscopy group as compared to the laparotomy group may also have taken place. In addition, laparotomy was more frequently employed in the early period of this study, while laparoscopy became the method of choice when possible during the most recent period. Hence, patients with a laparotomy generally have a longer observation period in this study. Consequently, we believe no causality can be drawn between long-term mortality and choice of surgical repair.

Finally, the question arises whether patients with PPU should receive closer follow-up after surgical treatment. Currently, only a 6-week follow-up period with upper endoscopy is recommended after surgical treatment of gastric ulcers (if not biopsied at surgery), but the evidence for this practice and for how clinical follow-up of patients with PPU should be conducted is poor [2]. Patients with PPU are clearly at risk of future adverse events and have a high mortality rate several years after the event. We assume that the increased mortality reflects the older age and associated disease burden with added comorbidity in this group of elderly, sick patients. Whether further investigations into secondary intervention, surveillance and preventive measures are warranted remains unclear. Nevertheless, the factors contributing to a long-term detrimental prognosis may be valuable information that both the surgeon and the general practitioner can use to counsel patients. Simple means of counseling and prevention such as smoking cessation, focus on nutritional support and cardiopulmonary protective measures should be strongly considered.

Conclusion

Our findings revealed that one in three patients who underwent surgery for PPU died during a median follow-up time of 57 months. Older age, the presence of hypoalbuminemia and comorbidities such as pulmonary disease, cardiovascular disease and active cancer were identified as independent risk factors for this fatal long-term outcome. Notably, severe postoperative complications were associated with an increased risk of long-term mortality, which underlines that patients with PPU may be a frail group with an increased risk of death also in a long-term perspective.

Appendix: ROC analysis of Charlson score for cutoff points

See Table 4.

Table 4 Coordinates of the curve: test result variable(s): Charlson score

Positive if greater than or equal to[a]	Sensitivity	1—specificity
−1.00	1.000	1.000
0.50	0.981	0.909
1.50	0.981	0.800
2.50	0.962	0.720
3.50	0.962	0.566
4.50	0.849	0.383
5.50	0.660	0.246
6.50	0.453	0.109
7.50	0.340	0.029
8.50	0.283	0.023
9.50	0.189	0.023
10.50	0.113	0.000
11.50	0.057	0.000
13.00	0.000	0.000

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