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Global 30-day morbidity and mortality of surgery for perforated peptic ulcer: GRACE study

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Abstract

Background There is little international data on morbidity and mortality of surgery for perforated peptic ulcer (PPU). This study aimed to understand the global 30-day morbidity and mortality of patients undergoing surgery for PPU and to identify variables associated with these.

Method We performed an international study of adults (≥ 18 years) who underwent surgery for PPU from 1st January 2022 to 30th June 2022. Patients who were treated conservatively or had an underlying gastric cancer were excluded. Patients were divided into subgroups according to age (≤ 50 and > 50 years) and time from onset of symptoms to hospital presentation (≤ 24 and > 24 h). Univariate and Multivariate analyses were carried out to identify factors associated with higher 30-day morbidity and mortality.

Results 1874 patients from 159 centres across 52 countries were included. 78.3% ($n = 1467$) of the patients were males and the median (IQR) age was 49 years (25). Thirty-day morbidity and mortality were 48.5% ($n = 910$) and 9.3% ($n = 174$) respectively. Median (IQR) hospital stay was 7 (5) days. Open surgery was performed in 80% ($n = 1505$) of the cohort. Age > 50 years [(OR = 1.7, 95% CI 1.4–2), (OR = 4.7, 95% CI 3.1–7.6)], female gender [(OR = 1.8, 95% CI 1.4–2.3), (OR = 1.9, 95% CI 1.3–2.9)], shock on admission [(OR = 2.1, 95% CI 1.7–2.7), (OR = 4.8, 95% CI 3.2–7.1)], and acute

Rishi Singhal and Kamal Mahawar have contributed equally to this study.

The collaborators of GRACE Study Collaborative Group are listed in Acknowledgements section.

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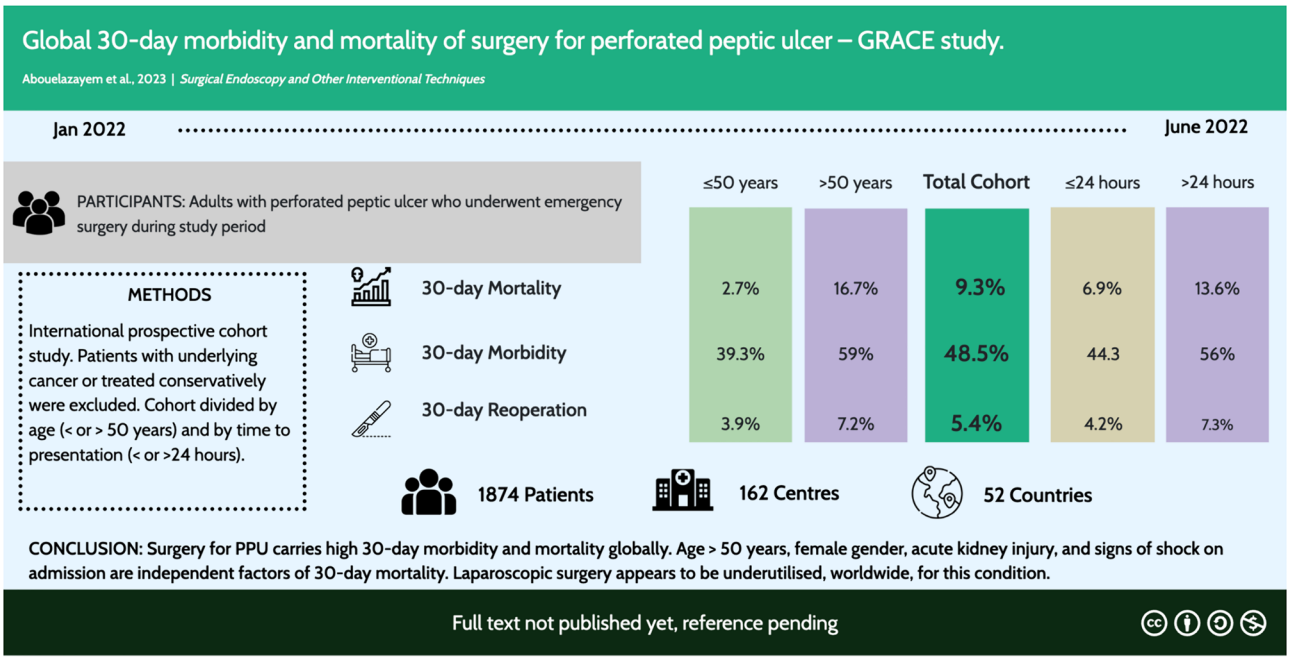
kidney injury [(OR = 2.5, 95% CI 1.9–3.2), (OR = 3.9), 95% CI 2.7–5.6)] were associated with both 30-day morbidity and mortality. Delayed presentation was associated with 30-day morbidity [OR = 1.3, 95% CI 1.1–1.6], but not mortality.

Conclusions This study showed that surgery for PPU was associated with high 30-day morbidity and mortality rate. Age, female gender, and signs of shock at presentation were associated with both 30-day morbidity and mortality.

Graphical abstract



Keywords Global surgery · Perforated peptic ulcer · Gastrointestinal

Peptic ulcer disease (PUD) is a common condition, with a lifetime prevalence of 5–10% and an annual incidence of 0.1–0.3% [1]. The management of PUD has evolved over the last two decades due to the advancement in anti-ulcer medications, resulting in a significant reduction in the requirement for elective surgery [2, 3]. Despite these advances, some ulcers do perforate, and perforated peptic ulcer (PPU) remains a surgical emergency affecting 2–10% of PUD patients, with a reported mortality rate of 16–30% and a morbidity rate of 20–50% [2–5].

Surgery is the mainstay treatment for PPU, with most patients undergoing primary closure of the perforation. Gastric resection with reconstruction is usually reserved for large perforations [6]. Traditionally, the surgery is performed using open technique through a laparotomy, but more recently, laparoscopic approach is being used and may be associated with reduced mortality, less post-operative pain, and shorter hospital stay [7, 8].

Non-operative management of PPU with nasogastric decompression, antibiotics, and radiological drainage of abscesses or collections is usually reserved for those presenting late or unfit for surgical repair [9–11]. It is also an option for some, carefully selected surgically fit patients with mild symptoms or localised peritonitis where the perforation is deemed to have sealed spontaneously [12, 13].

Published studies reporting on the early morbidity and mortality of surgery for PPU are mostly either single-centre or national [6, 14–16]. The inferences from such studies are difficult to generalise due to their small sample size and restricted population [4, 5, 15–20]. Though there are some larger studies, they are also limited to one particular country [21–23]. To the best of our knowledge, there is no global data on this topic. This study aimed to assess the global 30-day morbidity and mortality of surgery for PPU and the factors influencing it.

Methodology

Study design

We conducted a prospective, global, multicentre, observational cohort study of adult (≥ 18 years) patients who underwent emergency surgery for PPU between 01/01/2022 and 30/06/2022.

Patients with a PPU in a bypassed stomach after previous bariatric surgery such as Roux-en-Y Gastric Bypass, One Anastomosis Gastric Bypass, or Sleeve Gastrectomy were included but those with underlying gastric cancer, those who had other surgery along with surgery for PPU, and those treated non-operatively were excluded.

The study was registered as a multinational audit (Number 4935) at the Shrewsbury and Telford Hospital NHS (National Health Service) Foundation Trust, UK, and was disseminated globally to the members of The Upper Gastrointestinal Surgery Society (TUGSS) and more widely to the surgical community through social media channels (Twitter, LinkedIn, and Facebook). Each country's National coordinator was assigned to disseminate the study further and assist the participating centres in obtaining local approvals.

Collaborators were responsible for obtaining local approvals and patient consent and documenting it in the patient record.

Data collection

We collected data on patient demographics, pre-operative data (shock on admission, alcohol consumption, non-steroidal anti-inflammatory drugs (NSAID) use, smoking, history of bariatric surgery, time from onset of symptoms to presentation to hospital, comorbidities, laboratory results, and American Society of Anaesthesiologists (ASA) score), details of surgery (Laparoscopic or open, location of the ulcer, type of repair, omentopexy, size of perforation, and vagotomy), and 30-day morbidity and mortality. The definition of some variables like shock and acute kidney injury was left to the clinical teams.

We used the Clavien–Dindo (CD) system [24] to record morbidity. This study focused on the number of patients who developed complications rather than the number of complications. We used the highest CD score if a given patient experienced more than one complication.

Collaborators collected anonymised patient data using a Microsoft Excel sheet. This was submitted as a password-protected file to an NHS email address and the password was shared separately. After submission, we examined the data for incomplete or missing information, and collaborators were contacted for clarification if needed. A study flowchart is presented in Fig. 1.

Amendments to protocol

The study was conducted as per the study protocol. We used standard descriptive statistics for primary outcomes. One amendment was to further analyse the effect of clinically relevant variables on the study outcomes, and this was agreed by consensus among the study core team.

Fig. 1 Study flowchart showing different stages of the study

Statistical analysis

Univariate and bivariate analyses were performed using standard classical descriptions, *t* test for numerical variables, and χ^2 test for categorical variables. Multivariate analysis was performed in R software for statistical programming using generalized linear models with the logit function. Variables in the multivariate model were not selected a priori. After data analysis, clinically relevant variables were selected and agreed upon by consensus among the study core group. Variance Inflation Factor (VIF) for the multivariate model was close to one, showing that collinearity did not affect the analysis.

Odds Ratio, confidence interval, and other metrics were extracted from the generated models to compare the influence of the different variables. Shapiro–Wilk test was used to assess normality of the variables. Missing data were low in numbers overall. In Univariate analysis, we did not

exclude patients with few missing data. In multivariate analysis, patients with missing data were excluded.

Patients were divided into subgroups to study the influence of some variables. These were age (≤ 50 and > 50 years) and time from onset of symptoms to hospital presentation (≤ 24 and > 24 h).

Results

Patients' demographics

The study included 1874 patients, with a median age of 49 years (IQR 25). Males comprised most of the cohort, representing 78.3% ($n = 1467$) of the participants, with a male-to-female ratio of 3.6:1. Asian ethnicity accounted for 41.9% ($n = 786$), followed by Caucasians (31.5%, $n = 590$), and other ethnicities (15.4%, $n = 289$).

Almost half of the cohort (47%, $n = 881$) were older than 50 years. We found a notable difference in age distribution across regions. The median age among patients from Europe and the United States of America (USA) was 56 (IQR 28), while in Africa and Asia, it was nearly a decade younger at 45 (IQR 22) and 46 (IQR 24) years, respectively (Fig. 2). A total of 45 patients (2.4%) had a history of bariatric surgery, 21 had sleeve gastrectomy, 18 had Roux-en-Y Gastric bypass and 6 had One Anastomosis Gastric Bypass. In this group of patients, we expected the pathology of PPU in the bypassed stomach or after sleeve gastrectomy not to be different from normal population.

Most patients (65%, $n = 1209$) presented to the hospital within 24 h of symptom onset. The most common comorbidities were hypertension (26.4%), diabetes (17.6%), and ischemic heart disease (10.1%). Most patients (62.8%, $n = 1165$) were current or ex-smokers, and 41.5% ($n = 778$) had a history of NSAID use. Table 1 provides a detailed breakdown of patient demographics.

Presentation and laboratory results

Approximately 23.5% ($n = 441$) of the patients had features of shock at presentation to the hospital. Patients > 50 years old (32.3% vs. 15.7%) and those who presented > 24 h after the onset of symptoms (33.5% vs. 18%) were more likely to present with features of shock. Most patients had an ASA score of I (39.5%, $n = 732$) or II (31.9%, $n = 591$).

The median haemoglobin (Hb) concentration was 130 g/L (IQR 38.9), and the white cell count (WCC) was 14×10^9/L (IQR 7.2). The median C-reactive protein (CRP) level was 25 mg/L (IQR 98), and the creatinine level was 95.5 µmol/L (IQR 59.5). There were no significant differences in Hb and WCC across the different groups. However, the levels of CRP and creatinine were higher in those > 50 years compared to the ≤ 50 years group (CRP 80.2 vs. 60, Creatinine 138 vs. 109) and in those who presented after > 24 h compared to the ≤ 24 h group (CRP 79.4 vs. 64.5, Creatinine 143 vs. 111).

Surgical details

Most of the patients underwent open surgery (80%, $n = 1505$), 16.4% ($n = 307$) had laparoscopic surgery, and 3.1% ($n = 59$) had laparoscopic converted to open surgery. Laparoscopic surgery accounted for 16.5% of the patients in the ≤ 50 years group and 16.2% in the > 50 group. When analysed by presentation, 21.1% of those who presented in ≤ 24 h underwent laparoscopic surgery compared to 7.6% of those presenting > 24 h after the onset of symptoms.

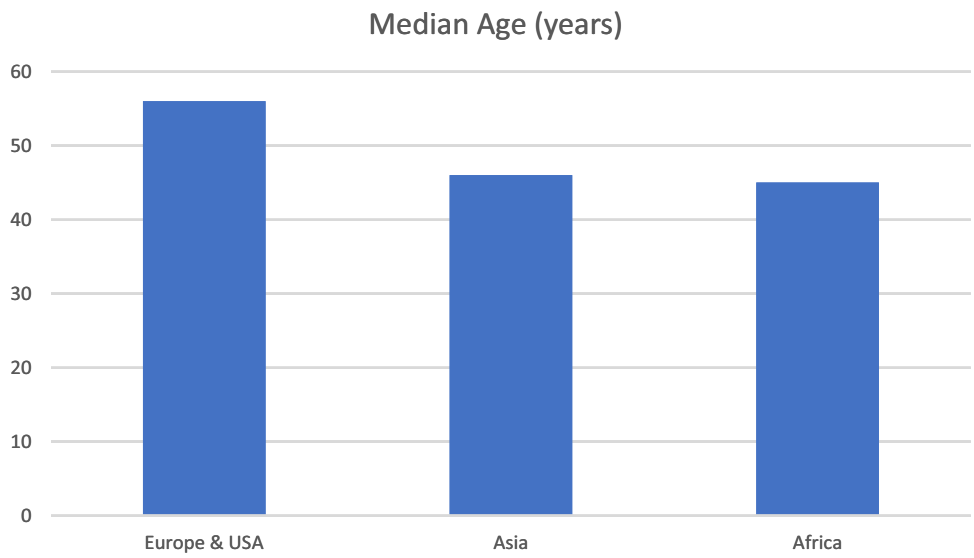


Fig. 2 Differences in median age of patients from different continents

Table 1 Demographics

	Total cohort *n* (%)	≤ 50 years *n* (%)	> 50 years *n* (%)	Presentation to hospital ≤ 24 h *n* (%)	Presentation to hospital > 24 h *n* (%)
Total number	1874	993 (53)	881 (47)	1209 (64.9)	654 (35.1)
Age (median (IQR))	49 (25)	38 (15)	63 (14.5)	48 (25)	51 (24)
Gender					
Males	1467 (78.3)	816 (82.2)	651 (73.9)	928 (76.8)	529 (80.9)
Females	405 (21.6)	175 (17.6)	230 (26.1)	279 (23.1)	125 (19.1)
Others	2 (0.1)	2 (0.2)		2 (0.2)	
Ethnicity					
Afro-Caribbean	155 (8.3)	113 (11.4)	42 (4.8)	113 (9.3)	41 (6.3)
Asian	786 (41.9)	439 (44.2)	347 (39.4)	414 (34.2)	372 (56.9)
Caucasian	590 (31.5)	242 (24.4)	348 (39.5)	447 (37.0)	136 (20.8)
Hispanic	54 (2.9)	24 (2.4)	30 (3.4)	42 (3.5)	12 (1.8)
Others	289 (15.4)	175 (17.6)	114 (12.9)	193 (16.0)	93 (14.2)
History of bariatric surgery					
Gastric bypass					
RYGB	18 (1)	6 (0.6)	12 (1.4)	16 (1.3)	2 (0.3)
OAGB	6 (0.3)	1 (0.1)	5 (0.6)	6 (0.5)	
Sleeve gastrectomy	21 (1.1)	9 (0.9)	14 (1.6)	21 (1.7)	2 (0.3)
Comorbidities					
Diabetes	329 (17.6)	101 (10.2)	228 (25.9)	197 (16.3)	128 (19.6)
IHD	190 (10.1)	50 (5)	140 (15.9)	120 (9.9)	68 (10.4)
HTN	494 (26.4)	110 (11.1)	384 (43.6)	309 (25.6)	180 (27.5)
CKD	87 (4.6)	20 (2)	67 (7.6)	43 (3.6)	42 (6.4)
COPD	144 (7.7)	27 (2.7)	117 (13.3)	81 (6.7)	63 (9.6)
Others	329 (17.6)	104 (10.5)	225 (25.5)	200 (16.6)	124 (19)
History of smoking					
Never	692 (37.3)	350 (35.7)	342 (39)	434 (36.3)	253 (38.9)
Ex-smoker	974 (52.5)	66(6.7)	125 (14.3)	113 (9.4)	77 (11.8)
Current smoker	191 (10.3)	564 (57.6)	410 (46.8)	650 (54.3)	321 (49.3)
Missing	17				
History of alcohol consumption					
Yes	546 (29.1)	278 (28)	268 (30.4)	350 (29)	194 (29.7)
No	1319 (70.4)	708 (71.3)	611 (69.4)	852 (70.5)	458 (70)
Missing	9				
Shock on admission					
Yes	441 (23.5)	156 (15.7)	285 (32.3)	218 (18)	219 (33.5)
No	1432(76.4)	837 (84.3)	595 (67.5)	990 (81.9)	435 (66.5)
Missing	1				
History of NSAIDs	778 (41.5)	366 (36.9)	412 (46.8)	484 (40.0)	292 (44.6)

SD standard deviation, *OAGB* one anastomosis gastric bypass, *RYGB* Roux-en-Y gastric bypass, *IHD* ischemic heart disease, *HTN* hypertension, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *NSAIDs* non-steroidal anti-inflammatory drugs

The median size of the perforation was 1 cm (IQR 0.6). Most of the patients (82.5%, $n = 1546$) had a primary repair of the perforation with omentopexy. Approximately 10.8% ($n = 202$) had a primary repair without omentopexy, and 4.1% ($n = 77$) required a gastric resection (Table 2).

Post-operative outcomes

The median hospital stay was 7 days (IQR 5) for the whole cohort. Overall, the 30-day morbidity rate was 48.5% ($n = 910$). Approximately 34% ($n = 637$) of the

Table 2 Surgical details

	Total cohort *n* (%)	≤ 50 years *n* (%)	> 50 years *n* (%)	Presentation to hospital ≤ 24 h *n* (%)	Presentation to hospital > 24 h *n* (%)
Surgical technique					
Missing	3 (0.2)	2 (0.2)	1 (0.1)	3	
Laparoscopic	307 (16.4)	164 (16.5)	143 (16.2)	255 (21.1)	50 (7.6)
Open	1505 (80.3)	802 (80.8)	703 (79.8)	913 (75.5)	583 (89.1)
Lap converted to open	59 (3.1)	25 (2.5)	34 (3.9)	38 (3.1)	21 (3.2)
Site of perforation					
Duodenum	961 (51.3)	–	–	–	–
Antrum	743 (39.6)	–	–	–	–
Other	170 (9.1)	–	–	–	–
Diameter of perforation (cm)					
Missing	24	12	12	16	5
Median (IQR)	1 (0.6)	1 (0.5)	1 (0.8)	1 (0.5)	1 (1)
Repair technique					
Suture repair without omentopexy	202 (10.8)	93 (9.4)	109 (12.4)	153 (12.7)	49 (7.5)
Suture repair with omentopexy	1546 (82.5)	841 (84.7)	705 (80)	992 (82.1)	546 (83.5)
Others	126 (6.7)	59 (5.9)	67 (7.6)	64 (5.3)	59 (9)
Simultaneous gastric resection	77 (4.1)	29 (2.9)	48 (5.4)	49 (4.1)	26 (4)
Vagotomy					
No vagotomy	1542 (97.8)	816 (98)	726 (97.6)	974 (96.7)	561 (99.6)
Truncal vagotomy	20 (1.3)	7 (0.8)	13 (1.7)	18 (1.8)	2 (0.4)
Selective or highly selective vagotomy	15 (1.0)	10 (1.2)	5 (0.7)	15 (1.5)	
Operating time (min)					
Missing	11	2	9	3	4
Median (IQR)	90 (60)	85 (52)	90 (55)	83 (60)	90 (50)

cohort had a CD grade of ≤ 3a morbidity, and 14.5% ($n = 273$) had a CD grade ≥ 3b morbidity/mortality. The 30-day reoperation rate was 5.4% ($n = 102$), and the most common morbidity was wound infection (17.4%, $n = 327$). The 30-day mortality rate was 9.3% ($n = 174$) (Table 3). Median age was higher and features of shock on admission was more likely in those who developed a morbidity. (Table 4).

Outcomes by age groups

In the > 50 years group, the median hospital stay (8 vs. 6 days), rate of complications (59% vs. 39.3%), and 30-day reoperation rate (7.2% vs. 3.9%) were higher compared to the younger cohort. Wound infection was the most common complication in both groups (17% vs. 17.9%). Chest infection (14.9% vs. 4.7%) and gastrointestinal (GI) leakage (7.4% vs. 2.9%) were also more likely in the older group. The 30-day mortality rate was higher in this group (16.7% vs. 2.7%) compared to the ≤ 50 years group.

Outcomes by time to presentation to hospital

Participants who presented to the hospital > 24 h from the onset of symptoms had a higher overall rate of complications (56% vs. 44.3%), wound infection (22.8% vs. 14.6%), chest infection (14.5% vs. 6.9%) and GI leak (7% vs. 3.7%). In this group, 30-day reoperation rate (7.3% vs. 4.2%) and mortality rates were also higher (13.6% vs. 6.9%).

Univariate analysis for 30-day morbidity and mortality

On univariate analysis, age > 50 years [($p < 0.001$), (OR = 2.2), (95% CI 1.8–2.7)], presentation to hospital after 24 h of symptom onset [($p < 0.001$), (OR = 1.6), (95% CI 1.3–1.9)], female gender [($p < 0.001$), (OR = 2), (95% CI 1.6–2.5)], shock on admission [($p < 0.001$), (OR = 3.4), (95% CI 2.7–4.3)], acute kidney injury [($p < 0.001$), (OR = 3.7), (95% CI 2.9–4.7)], NSAID use [($p = 0.001$), (OR = 1.3), (95% CI 1.1–1.6)], and comorbidities such as diabetes [($p < 0.001$), (OR = 2), (95% CI 1.6–2.6)], ischemic heart disease [($p < 0.001$), (OR = 2), (95% CI 1.5–2.7)], hypertension [($p < 0.001$), (OR = 2.5), (95% CI 2–3.1], chronic

Table 3 Post operative outcomes

	Total cohort *n* (%)	≤ 50 years *n* (%)	> 50 years *n* (%)	Presentation to hospital ≤ 24 h *n* (%)	Presentation to hospital > 24 h *n* (%)
Total	1874	993	881	1209	654
Hospital stay (days)					
Missing	5	5	0	3	2
Median (IQR)	7 (5)	6 (4)	8 (7)	6 (5)	7 (6)
Complications after surgery	910 (48.5)	390 (39.3)	520 (59)	536 (44.3)	366 (56)
Wound	327 (17.4)	169 (17)	158 (17.9)	177 (14.6)	149 (22.8)
Chest	178 (9.5)	47 (4.7)	131 (14.9)	83 (6.9)	95 (14.5)
GI leak	94 (5)	29 (2.9)	65 (7.4)	45 (3.7)	46 (7)
Bleeding	37 (2)	10 (1.0)	27 (3.1)	26 (2.2)	11 (1.7)
MI	34 (1.8)	4 (0.4)	30 (3.4)	17 (1.4)	16 (2.4)
Stroke	13 (0.7)	2 (0.2)	11 (1.2)	6 (0.5)	7 (1.1)
Others	227 (12.1)	129 (13)	98 (11.1)	182 (15.1)	42 (6.4)
30 day re-operation	102 (5.4)	39 (3.9)	63 (7.2)	51 (4.2)	48 (7.3)
COVID 19 post operatively	84 (4.5)	35 (3.5)	49 (5.6)	55 (4.6)	29 (4.4)
Clavien-Dindo grade					
0	964 (51.4)	603 (60.7)	361 (41)	673 (55.7)	288 (44)
1	389 (20.8)	233 (23.5)	156 (17.7)	267 (22.1)	119 (18.2)
2	204 (10.9)	77 (7.8)	127 (14.4)	115 (9.5)	89 (13.6)
3a	44 (2.3)	16 (1.6)	28 (3.2)	22 (1.8)	22 (3.4)
3b	57 (3)	25 (2.5)	32 (3.6)	31 (2.6)	24 (3.7)
4a	29 (1.5)	8 (0.8)	21 (2.4)	13 (1.1)	13 (2)
4b	13 (0.7)	4 (0.4)	9 (1)	5 (0.4)	10 (1.5)
5	174 (9.3)	27 (2.7)	147 (16.7)	83 (6.9)	89 (13.6)

SD standard deviation

kidney disease [($p < 0.001$), (OR = 3.3), (95% CI 2–5.5)], and chronic obstructive pulmonary disease [($p < 0.001$), (OR = 2.3), (95% CI 1.6–3.4)], were significantly associated with 30-day morbidity. Previous bariatric surgery and alcohol consumption were not associated with 30-day morbidity (Table 5). Age > 50 years [($p < 0.001$), (OR = 7.1), (95% CI 4.7–11)], presentation to hospital after 24 h of symptom onset [($p < 0.001$), (OR = 2.1), (95% CI 1.6–2.9)], female gender [($p < 0.001$), (OR = 2.4), (95% CI 1.7–3.3)], shock on admission [($p < 0.001$), (OR = 8.9), (95% CI 6.4–12.7)], and acute kidney injury [($p < 0.001$), (OR = 7.9), (95% CI 5.7–11.1)] were also significantly associated with 30-day mortality.

Multivariate analysis for 30-day morbidity and mortality

On multivariate analysis, 30-day morbidity was significantly associated with age > 50 years [(OR = 1.7), (95% CI 1.4–2)], presentation to hospital after 24 h of symptom onset [(OR = 1.3), (95% CI 1.1–1.6)], female gender [(OR = 1.8), (95% CI 1.4–2.3)], shock on admission [(OR = 2.1), (95% CI 1.7–2.7)], and acute kidney injury [(OR = 2.5), (95% CI 1.9–3.2)]. 30-day mortality was significantly associated with age > 50 years [(OR = 4.7), (95% CI 3.1–7.6)], female gender [(OR = 1.9), (95% CI 1.3–2.9)], acute kidney injury [(OR = 3.9), (95% CI 2.7–5.6)], and shock on admission [(OR = 4.8), (95% CI 3.2–7.1)]. Presentation to the hospital after 24 h of symptom onset and alcohol consumption were not associated with 30-day mortality on multivariate analysis. Details of the analysis are presented in Table 5.

Discussion

This study involving 1874 patients from 159 medical centres across 52 countries is the first global study examining 30-day morbidity and mortality of adult patients undergoing surgery for PPU. We found that the 30-day morbidity of surgery for PPU was 48.5%, and the 30-day mortality was 9.3%. Age over 50 years, female gender, shock on admission, and acute kidney injury were independent factors associated with 30-day morbidity and mortality. Delayed presentation to the hospital after 24 h of symptom onset was only associated with 30-day morbidity.

There are wide variations in the reported morbidity and mortality rates for PPU in the scientific literature with

Table 4 Complications vs no complications

	No complications *n* (%)	Complications *n* (%)	*P* value
Total number	964	910	
Age (Median (IQR))	45 (21)	55 (26)	< 0.001
Gender			< 0.001
Males	809 (83.9)	658 (72.3)	
Females	153 (15.9)	252 (27.7)	
Others	2 (0.2)		
History of bariatric surgery			0.748
RYGB	9 (0.9)	9 (1.0)	
OAGB	4 (0.4)	2 (0.2)	
Sleeve gastrectomy	11 (1.1)	12 (1.3)	
Comorbidities			
Diabetes	122 (12.7)	207 (22.7)	< 0.001
IHD	69 (7.2)	121 (13.3)	< 0.001
HTN	172 (17.8)	322 (35.4)	< 0.001
CKD	22 (2.3)	65 (7.2)	< 0.001
COPD	47 (4.9)	97 (10.7)	< 0.001
History of NSAIDs	365 (37.9)	413 (45.4)	< 0.001
Time between onset of symptoms and presentation to hospital (h) (mean ± SD)	15 (24)	24 (40)	< 0.001
Shock on admission	129 (13.4)	312 (34.3)	< 0.001
Laboratory results (median (IQR))			
Hemoglobin (g/L)	135 (31)	125 (40)	0.149
WCC ($n \times 10^9$/L)	14 (6.5)	13.5 (8.4)	0.39
CRP (mg/L)	17 (70.9)	42 (137)	< 0.001
Creatinine (µmol/L)	87 (40.4)	106 (79)	0.007

Table 5 Univariate and multivariate analysis of risk factors for 30-day morbidity and mortality

Variables	Univariate analysis				Multivariate analysis			
	Morbidity		Mortality		Morbidity		Mortality	
	P value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age > 50	< 0.001	2.21 (1.84–2.67)	< 0.001	7.08 (4.72–11.01)	< 0.001	1.68 (1.37–2.04)	< 0.001	4.74 (3.07–7.55)
Delayed presentation > 24 h	< 0.001	1.59 (1.31–1.93)	< 0.001	2.13 (1.56–2.93)	0.016	1.29 (1.05–1.59)	0.104	1.36 (0.94–1.96)
Female gender	< 0.001	2.03 (1.62–2.54)	< 0.001	2.38 (1.71–3.3)	< 0.001	1.83 (1.44–2.34)	0.001	1.93 (1.29–2.88)
Shock on admission	< 0.001	3.37 (2.68–4.25)	< 0.001	8.97 (6.41–12.68)	< 0.001	2.12 (1.65–2.74)	< 0.001	4.8 (3.28–7.08)
Alcohol consumption	0.383	1.09 (0.9–1.33)	0.27	1.2 (0.86–1.67)	0.27	1.13 (0.91–1.41)	0.574	1.12 (0.75–1.68)
NSAID use	0.001	1.36 (1.13–1.63)	0.71	0.94 (0.68–1.29)	0.155	1.16 (0.95–1.41)	0.011	0.62 (0.42–0.89)
Acute kidney injury	< 0.001	3.72 (2.92–4.75)	< 0.001	7.94 (5.72–11.11)	< 0.001	2.48 (1.91–3.23)	< 0.001	3.9 (2.69–5.67)

OR odds ratio, *CI* confidence interval

morbidity rates ranging from 15.4 to 62% [16–21] and mortality rates ranging from 7.8% up to 30.4% [4, 5, 15, 18, 19, 22, 23]. This variation probably stems from the population differences, as most of these studies are either from a single-centre [4, 5, 15–20] or a single country [18, 21, 22].

Age is known to be an important determinant of morbidity and mortality after surgery for PPU. A recent meta-analysis reported a mortality rate as low as 1.11% in some African countries (with younger populations) [25], while some European studies, where the population is typically older, have reported a mortality rate of 25.5% [26]. Over half of the patients (53%) in this study were ≤ 50 years old, and the median age was 49 years (IQR 25). This aligns closely with findings from Tas et al. [27] and Lohsiriwat et al. [20],

who reported mean ages of 51.7 and 52 years, respectively. Recent studies from the USA have reported mean ages of 56 and 61 [6, 17], while Yalcin et al. [28] reported a mean age of 41 in Turkey, and Bupicha et al. [16] noted a much younger mean age of 32 years in a study from Ethiopia. These findings reflect an ageing population in the western world. Our study also confirmed this with differences in the median age in patients from different continents.

Several studies have established a clear link between age and 30-day morbidity and mortality in patients undergoing PPU surgery [16, 18, 29, 30]. Byrne et al. reported a 5% increase in mortality risk for each year of age [22]. Consistent with these findings, our study demonstrated that patients over 50 years old had a significantly higher risk of 30-day morbidity (59% vs. 39%, OR = 2.2, 95% CI 1.8–2.6) and mortality (16.7% vs. 2.7%, OR = 3.9, 95% CI 1.9–8.5).

Our study confirmed that most patients undergoing surgery for PPU are males (78.3%, $n = 1467$). This is consistent with findings from previous studies [23, 28, 31]. Consistent with some published studies [5, 32, 33], we also found that female gender to be associated with 30-day morbidity on both univariate and multivariate analyses. However, other authors have not observed this association [18, 19]. We further found a significant association between female gender and 30-day mortality. This is in contrast to studies by Byrne et al. [22] and Thorsen et al. [4]. In our cohort, the median age in females was 54 (IQR 29.5) years compared to 47 (IQR 25) in males. This might partly account for the higher 30-day morbidity and mortality observed in this group.

Overall, 25% of our cohort had features of shock on admission. Older age group (> 50 years) and those with delayed presentation to hospital (> 24 h after symptom onset) were twice more likely to present with shock. Pre-operative shock has been identified as an independent risk factor for mortality in previous studies [18, 34, 35]. Our study confirms that finding. We also found it to be an independent risk factor for 30-day morbidity.

Several studies have investigated the impact of delay in presentation and surgery on morbidity and mortality. Meraj et al. and Kim et al. found no significant association between a delay of > 24 h of presentation and morbidity or mortality on multivariate analysis. However, Bupicha et al. and Noguiera et al. showed that delay was significantly associated with higher morbidity and mortality [16, 18, 19, 32]. In addition, Buck et al. reported that for each hour of delay to surgery during the first day of admission, there was a 2.4% decrease in survival [36]. In contrast, Byrne et al. found no association between time from admission to surgery and mortality [22]. Various factors can contribute to delays from admission to surgery, such as pre-operative optimization or trial of conservative management. We used time to presentation to the hospital to better understand the effects of delays on outcomes. Our findings showed that a delay of > 24 h (from onset of symptoms) to presentation was significantly associated with higher morbidity and mortality on univariate analysis. However, on multivariate analysis, it was only associated with morbidity, not mortality.

Our study found that only 16.4% ($n = 307$) of the cohort underwent laparoscopic surgery for PPU, indicating perhaps that laparoscopy is underutilised in emergency surgery worldwide. Previous studies have compared laparoscopy to open surgery in treating PPU and reported some benefits of laparoscopy over open surgery [6, 37]. Further research and training are warranted to increase global adoption of minimally invasive techniques for these patients.

Strengths and weaknesses

The global nature of the study, high data completion rate, and large sample size are some of the obvious strengths of this study. At the same time, some limitations should be considered while interpreting this data. Important ones are self-reported complication rates by collaborators, posteriori selection of variables in multivariate analysis, and lack of information on Helicobacter Pylori infection status. Other limitations of this study are lack of information on the use of drains, antibiotics, proton pump inhibitors, and oral intake. Non-inclusion of patients who underwent conservative management is another limitation, as we focused on those undergoing surgery in this study.

Conclusion

Surgery for PPU was found to be associated with a 30-day morbidity and mortality of 48.5% and 9.3% respectively in this large, global study. Age > 50 years old, female gender, acute kidney injury, and signs of shock upon admission were associated with 30-day mortality. Laparoscopic surgery appears to be underutilised for this condition.

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