Association of onset-to-surgery time with morbidity and mortality among patients with perforated peptic ulcer: an observational cohort study

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Research Article

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Abstract

Background

Rapid surgery is recommended to improve outcomes after peptic ulcer perforation (PPU), but understanding of the optimal onset-to-surgery time for PPU is limited. The purpose of this study was to assess the optimal time of onset to surgery for PPU that improved patient outcomes.

Methods

Data of eligible patients with PPU at three hospitals from 2019 to 2021 were retrospectively reviewed. Patients were categorized as a onset-to-surgery time of ≤ 12 h (early surgery [ES]) or > 12 h (late surgery [LS]). The primary outcome was 30-day sepsis morbidity. Secondary outcomes included 30-day postoperative morbidity and 30-day mortality. Patients' characteristics and surgical outcomes were also compared. A *P* value of < 0.05 is considered as statistically significant.

Results

Of 245 patients, 231 (94.3%; mean [SD] age, 62.6 [18.2] years; 153 [70.5%] male)were included in the final analysis. Among the remaining cases, 50.7% underwent ES and 49.3% underwent LS. LS was associated with increased sepsis morbidity within 30 days (OR_{adj} 5.71, 95% CI 2.02–16.10, *P* = 0.001). In secondary analyses, LS was associated with an increased risk of postoperative morbidity (OR_{adj} 1.93, 95% CI 1.06–3.53, *P* = 0.032). The 30-day mortality was 0.9% in the ES group and 4.7% in the LS group (OR_{adj} 3.93, 95% CI 0.43–36.05, *P* = 0.227). In addition, the estimated blood loss during ES was significantly less than that during LS (*P* = 0.004). The operative time and hospital stay were shorter in the ES group (both *P* < 0.005). Moreover, patients in the LS group were more likely to need for ICU admission (39.3% vs 22.7%, *P* = 0.008).

Conclusions

This cohort study found evidence that more favorable outcomes were achieved when surgery was performed within 12 hours after the onset of severe abdominal pain among patients with PPU. These findings provide more clarity around the optimal time of onset to surgery for patients with PPU. However, more well powered researches are needed to confirm the findings.

Introduction

Globally, perforated peptic ulcer (PPU) is a life-threatening surgical emergency with high mortality rate that approaches 30% [1]. Most of this mortality is due to sepsis, defined as organ dysfunction caused by a dysregulated host response to infection [2, 3]. Sepsis is a major contributor to healthcare problems and economic burden in China and worldwide [4–6].Abdominal sepsis remains the second most common source of sepsis. Abdominal sepsis is only possible by prompt reducing, and even eliminating infections [7].

Early surgery and aggressive treatment of sepsis in patients with PPU are the mainstays of therapy [3].Delayed treatment after PPU increased the risk morbidity and mortality [8]. A nationwide cohort study has found that delay in source control in PPU leads to 6% increased risk of death per hour [9]. Additionally, surgical treatment for PPU within 24 hours of onset has been associated with improved mortality and morbidity [10]. Surgery interval more than 36 hours after perforation was found to be significantly associated with an increase in postoperative mortality and morbidity [11].

However, robust evidence on the optimal timing of onset-to-surgery is still lacking. Important adverse effects of delayed surgery have not been sufficiently studied previously. A better understanding of the optimal onset-to-surgery time in patients with PPU will facilitate improved outcomes. Thus, this study was to compare outcomes of early versus late surgery for PPU using a multicenter database, and to assesses the optimal time of onset-to-surgery to achieve the better outcomes.

Methods

Patients

All consecutive eligible patients with PPU were confirmed from three hospital branches of Guangdong Provincial Hospital of Chinese Medicine located in different districts of Guangzhou city between January 2019 and December 2021. These three hospitals were one of the main referral centres for Yuexiu, Liwan, and Panyu district. Demographic, clinical, pathological, and imaging features together with the management and outcomes were carefully reviewed. Written informed consent was acquired from patients preceding the surgical procedures. This study was approved by the ethical committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2022-034).

The inclusion criteria: patients surgically treated for benign peptic ulcer perforation. The exclusion criteria: (i) age < 18 years; (ii) pregnant and breastfeeding women; (iii) malignant ulcer perforation; (iv) transfer from other hospital; or (v) diagnostic laparoscopy/laparotomy with no further surgical procedures performed.

Data collection

Patients were classified into two groups, based on the onset of severe abdominal pain to surgery time, which was either ≤ 12 h (early surgery [ES]) or > 12 h (late surgery [LS]). The surgical approach was decided by the individual gastrointestinal surgeon based on a combined assessment of clinical status, intraoperative findings, and imaging features. Data were collected in a prospectively maintained database from clinical report forms.

The demographic and clinical data included age, gender, body mass index (BMI), preoperative white blood cell (WBC), preoperative hemoglobin (Hb), perforation location, American Society of Anesthesiologists (ASA), operative time, estimated blood loss, surgical procedure, hospital stay, and hospital branch. Preoperative WBC or Hb was defined as WBC or Hb measured closest to the operation time before operation. Perforation location was divided into the following two sections: stomach, and duodenum. Surgical procedures consisted of two categories: simple closure and subtotal gastrectomy. Hospital branches included Dadelu General Hospital, Daxuecheng Hospital, and Fangcun Hospital.

Outcome measurements

The primary outcome measure was 30-day sepsis morbidity. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to intra-abdominal infection from perforated peptic ulcer. Organ dysfunction was represented by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more. Secondary outcomes were 30-day postoperative morbidity and 30-day mortality. Postoperative morbidity included renal complications, cardiac complications, pulmonary embolism, deep vein thrombosis, surgical site infection, pneumonia, bleeding, reoperation, and transfusion. The length of hospital stay, need for ICU (intensive care unit) admission, estimated blood loss, and operative time were also analyzed.

Statistical analysis

Data are presented as mean (standard deviation, SD) for quantitative variables and numbers with percentages for categorical variables. Quantitative variables were compared using the Student's t-test. Categorical variables were analysed using the Chi-square test or Fisher's exact test. Cox proportional hazards models were performed to calculate odds ratio and 95% confidence interval for associations of onset-to-surgery time with morbidity and mortality. A two-sided *P* value of less than 0.05 was considered to be statistically significant. Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Study population

Between January 1, 2019, and December 31, 2021, 245 patients with PPU were collected from three hospital branches of Guangdong Provincial Hospital of Chinese Medicine. Of these, 28 cases were excluded. Among the remaining 217 cases, 50.7% (110/217) underwent early surgery and 49.3% (107/217) underwent late surgery. (Figure. 1).

Baseline clinical characteristics of the total cohort and subgroup are outlined in Table 1. All variables in both groups were well balanced, including age, gender, BMI, preoperative WBC count, preoperative hemoglobin level, ASA classification, perforation location, surgical approach, surgical procedure, and hospital branch.

Primary outcome

30-day sepsis morbidity

In total, 28 (12.9%) patients suffered sepsis within 30 days after hospitalization, 5 (4.7%) in the early surgery group and 23 (21.5%) in the late surgery group. Late surgery was associated with increased sepsis morbidity within 30 days (OR_{adj} 5.71, 95% CI 2.02–16.10, $P = 0.001$; Table 2).

Secondary outcomes

30-day postoperative morbidity and 30-day mortality

In total, 71 (32.7%) patients had postoperative complications within 30 days after surgery, 28 (25.5%) after ES and 43 (40.2%) after LS. In multivariable adjusted analyses, we found a significant association between late surgery and postoperative morbidity (OR_{adj} 1.93, 95% CI 1.06–3.53, $P = 0.032$; Table 2). The 30-day mortality occurred in 1 (0.9%) of ES group (due to pulmonary dysfunction) and 5 (4.7%) of LS group (OR_{adj} 3.93, 95% CI 0.43–36.05, $P = 0.227$; Table 2). The causes of death were sepsis (50.0%), pulmonary dysfunction (16.7%), heart failure (16.7%), and upper gastrointestinal bleeding (16.6%).

Table 1
Comparison of characteristics of patients between the two groups (early surgery versus late surgery)

Variables	All patients (n = 217)	ES group (n = 110)	LS group (n = 107)	*P* value
Age (years), mean (SD)	62.6 (18.2)	60.6 (19.4)	64.7 (16.7)	0.101
Age ≥ 65 years				0.199
Yes	106 (48.8)	49 (44.5)	57 (53.3)	
No	111 (51.2)	61 (55.5)	50 (46.7)	
Gender				0.055
Male	153 (70.5)	84 (76.4)	69 (64.5)	
Female	64 (29.5)	26 (23.6)	38 (35.5)	
BMI (kg/m2), mean (SD)	21.5 (3.5)	21.3 (2.9)	21.7 (4.1)	0.492
WBC Count, mean (SD)	12.9 (7.6)	13.2 (8.8)	12.5 (6.2)	0.544
WBC > 12,000/μL				0.635
Yes	108 (49.8)	53 (48.2)	55 (51.4)	
No	109 (50.2)	57 (51.8)	52 (48.6)	
Hb, mean (SD)	131.3 (28.7)	135.0 (25.1)	127.6 (31.6)	0.058
ASA classification				0.704
I /II	90 (41.5)	47 (42.7)	43 (40.2)	
III / IV	127 (58.5)	63 (57.3)	64 (59.8)	
Perforation location				0.465
Stomach	119 (54.8)	63 (57.3)	56 (52.3)	
Duodenum	98 (45.2)	47 (42.7)	51 (47.7)	
Surgical approach				0.067
Laparoscopic surgery	205 (94.5)	107 (97.3)	98 (91.6)	
Open surgery	12 (5.5)	3 (2.7)	9 (8.4)	
Surgical procedure				0.098
Simple closure	208 (95.9)	108 (98.2)	100 (93.5)	

Data are expressed in n (%) unless otherwise indicated. ES: early surgery; LS: late surgery; SD, standard deviation; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; ASA, American Society of Anesthesiology.

Variables	All patients (n = 217)	ES group (n = 110)	LS group (n = 107)	*P* value
Subtotal gastrectomy	9 (4.1)	2 (1.8)	7 (6.5)	
Hospital branches				0.413
Dadelu General Hospital	119 (54.8)	56 (50.9)	63 (58.9)	
Daxuecheng Hospital	39 (18.0)	20 (18.2)	19 (17.7)	
Fangcun Hospital	59 (27.2)	34 (30.9)	25 (23.4)	

Data are expressed in n (%) unless otherwise indicated. ES: early surgery; LS: late surgery; SD, standard deviation; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; ASA, American Society of Anesthesiology.

Table 2
Results of morbidity and mortality associated with late surgery

Variables	ES (n = 110)	LS (n = 107)	Unadjusted analysis		Adjusted analysis*	
			OR (95% CI)	*P* value	OR_{adj} (95% CI)	*P* value
30-day sepsis morbidity	5 (4.5)	23 (21.5)	5.75 (2.10-15.77)	0.001	5.71 (2.02–16.10)	0.001
30-day postoperative morbidity	28 (25.5)	43 (40.2)	1.97 (1.11–3.51)	0.022	1.93 (1.06–3.53)	0.032
renal complications	7 (6.4)	19 (17.8)	3.18 (1.28–7.91)	0.013	3.31 (1.30–8.44)	0.012
cardiac complications	6 (5.5)	18 (16.8)	3.51 (1.33–9.21)	0.011	3.56 (1.34–9.45)	0.011
pulmonary embolism	0	0	NA	NA	NA	NA
deep vein thrombosis	0	3 (2.8)	NA	NA	NA	NA
surgical site infection	1 (0.9)	8 (7.5)	8.90 (1.09–72.42)	0.041	7.46 (0.89–62.57)	0.064
pneumonia	13 (11.8)	25 (23.4)	2.28 (1.09–4.73)	0.028	2.49 (1.12–5.38)	0.020
bleeding	1 (0.9)	4 (3.8)	4.28 (0.47–38.88)	0.197	4.12 (0.44–39.34)	0.214
reoperation	0	5 (4.7)	NA	NA	NA	NA
transfusion	10 (9.1)	19 (17.8)	2.16 (0.95–4.89)	0.065	2.06 (0.89–4.75)	0.090
30-day mortality	1 (0.9)	5 (4.7)	5.34 (0.61–46.51)	0.129	3.93 (0.43–36.05)	0.227

Data are expressed in n (%) unless otherwise indicated. ES: early surgery; LS: late surgery; OR, odds ratio; OR_{adj}, adjusted odds ratio; NA, not applicable.

*Adjustments included hospital branch, surgical approach, and surgical procedure.

Surgical outcomes

The surgical results in both groups are presented in Table 3. The estimated blood loss during ES was significantly less than that during LS ($P = 0.005$). In the ES group, the operative time and hospital stay were shorter than those in the LS group (both $P < 0.005$). Patients in the LS group were more likely to need for ICU admission (39.3% vs 22.7%, $P = 0.008$).

Table 3
Comparison of surgical outcomes of patients between the two groups

Variables	ES (n = 110)	LS (n = 107)	*P* value
Operative time (min), mean (SD)	82.2 (38.9)	103.6 (66.2)	0.004
Estimated blood loss (ml), mean (SD)	15.2 (16.2)	25.9 (35.0)	0.005
Hospital stay (days), mean (SD)	7.2 (3.2)	9.6 (7.2)	0.002
need for ICU admission	25 (22.7)	42 (39.3)	0.008
Data are expressed in n (%) unless otherwise indicated. ES: early surgery; LS: late surgery; SD, standard deviation; ICU, intensive care unit.			

Discussion

This cohort study distinctly characterizes the association between onset-to-surgery time for PPU against 30-day sepsis morbidity, postoperative morbidity and mortality. Surgery within 12 hours after onset significantly reduced the morbidity of sepsis and postoperative complications. Patients in the ES group have better surgical outcomes. And there was a significantly reduced the need for ICU admission in the ES group. On the basis of this analysis and previous work, the optimal time of onset to surgery for PPU is within 12 hours.

For the past decades, there has been a significant trend towards early surgery if the indications for surgical treatment are clear, especially in patients with delayed presentation [12]. Early in the year 1994, a study from Norway has found that delayed treatment exceeded 12 hours after PPU reduced survival, increased complications, and prolonged hospital stay [13]. In 2013, a cohort study from Denmark showed that every hour of delay in the first 24 hours from admission to surgery was associated with an adjusted 2.4% decreased of survival compared with the previous hour [14]. Recently, a nationwide cohort study from United Kingdom demonstrated that hourly delay to surgery in patients with PPU leads to 6% increased risk of 90-day mortality [9]. In our study, the higher 30-day mortality was observed among patients undergoing surgery exceeded 12 hours. And only 50.7% of the patients with PPU received surgery within 12 hours, highlighting the potential need to improve timely access to diagnosis and treatment for patients presenting to the hospital with severe abdominal pain.

Surgery is the most effective means to control the source of infection in patients with PPU [16]. However, the long-term mortality after surgery for PPU is high, mainly attributing to new onset sepsis and/or multi-organ failure [17]. Sepsis is a major healthcare problem, affecting millions of people worldwide each year and imposing a growing economic burden [5, 18]. Sepsis is a time critical medical emergency that occurs when an infection exceeds local tissue containment. Early prevention and blocking, especially adequate source control, can reduce the occurrence of sepsis [19]. Currently, whether early surgery for PPU can decrease sepsis morbidity is rarely reported. A study published in 1982 has found that late surgery (after 48 hours) significantly increased the risk of severe peritoneal contamination, positive cultures, and septic complications [20]. Another study published in 2016 from Switzerland showed that the duration of symptoms more than 24 hours increased septic complications [21]. In our study, 12.9% of patients with PPU suffered sepsis within 30 days after hospitalization, and sepsis accounted for 50% of fatalities. Compared with patients who underwent surgery exceeded 12 hours, we found that the 30-day sepsis morbidity was significantly decreased in patients who received surgery within 12 hours, which indicates that early surgery for PPU can reduce the incidence of sepsis. Therefore, raising awareness and leading to early presentation to hospital can reduce the sepsis morbidity through timely and appropriate medical care.

Risk factors affecting postoperative complications in patients with PPU has been widely reported. A systematic review performed in 2010 provided strong evidence that shock upon admission, preoperative metabolic acidosis, tachycardia, acute renal failure, low serum albumin level, high ASA score, and delayed surgery (> 24 h) were significant factors for increased risk of postoperative morbidity [22]. A cohort study among Black Africans with PPU in Côte d'Ivoire indicated that the risk factors of postoperative complications or mortality were comorbidities, tachycardia, purulent intra-abdominal fluid collection, hyponatremia, delayed hospital admission (> 72 h), and delayed surgery (between 24 and 48 h). Another recent study from India showed that the overall postoperative morbidity was 62.5% and found that advanced age, preoperative shock, delayed presentation (> 24 h) and raised serum creatinine were significantly associated with the postoperative morbidity [23]. Consistently with previous studies, delayed surgery was associated with an increased risk of postoperative complications in our study. 40.2% of patients had 30-day postoperative complications after late surgery (onset-to-surgery time > 12 h), while only 25.5% in the ES group. Thus, we can consider that the earlier the surgery, the less postoperative complications.

Delayed surgery affects not only the morbidity and mortality but surgical outcomes such as operative time, estimated blood loss and hospital stay. Our data showed longer operation time, more estimated blood loss, longer length of hospital stay, and more need for ICU admission in the LS group. With regard to hospital stay, some studies have found that surgical delay (> 12 h) was one of major factors associated with longer length of hospital stay [13, 24].

Our study has several limitations. First, a selection bias existed due to its retrospective design. To reduce this, we used rigorous data collection procedures. As a result, this factor was not significant source of bias. Second, the statistical power is insufficient because the number of patients enrolled may not be sufficient, especially in the mortality analysis. Third, patients transferred from other hospitals were not collected, which might be different between both groups and thus have influenced outcomes. Fourth, the clinical pathway varied among surgeons, which might lead to a potential bias. Finally, only three centres participated in our research, which may not represent the current situation in China.

Looking forward, there is obviously a drive to reduce morbidity and mortality and lead to a better outcome by raising awareness and implementing change. The SMASH trial from Sweden is ongoing, seeks to determine whether a new standardised perioperative protocols consisting of rapid start of operation in emergency abdominal surgical procedures leads to a better outcome compared with the present standard in Swedish routine health-care [25]. In China, the Abdominal Pain Center model has been in place for several years and has demonstrated a better management and in-hospital clinical outcomes of patients with abdomen. To minimize delays to diagnosis and treatment in PPU, we recommend that time points should be audited include: from arrival to CT/X-ray scan, from arrival to diagnosis, and from decision to surgery. Moreover, the time from onset of severe abdominal pain to arrival is a factor which needs to minimize delays by better education.

Conclusions

This cohort study suggests that surgery for PPU should ideally be provided within 12 hours after the onset of severe abdominal pain. Surgery exceeded 12 hours after onset significantly increased the morbidity of sepsis and postoperative complications, decreased the surgical outcomes. Interventions to reduce time from symptom onset to surgery may be warranted if these findings are independently confirmed by other cohorts.

Abbreviations

PPU, peptic ulcer perforation; ES, early surgery; LS, late surgery; h, hour or hours; BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; ASA, American Society of Anesthesiologists; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; OR, odds ratio; OR_{adj}, adjusted odds ratio; CI, confidence interval; SD, standard deviation; CT, computed tomography.

Declarations

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Authors’ contributions

K.L.T., Z.J.T., H.L.L., J.J.G., and Y.C.X. collected and analyzed the data. K.L.T., and R.S.X. performed statistical analysis. K.L.T. and Z.J.T. drafted the manuscript. Z.Q.C., and B.Q.C. performed the procedure, conceived of and designed the study. Z.Q.C. critically revised all the intellectual content of the manuscript. All authors read and approved the final manuscript.

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Ethics approval

This study was approved by the ethical committee of Guangdong Provincial Hospital of Chinese Medicine (No. ZE2022-034).

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to patient privacy restrictions, but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Conflicts of interests

The authors declare that there is no conflict of interests in this study.

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Figures

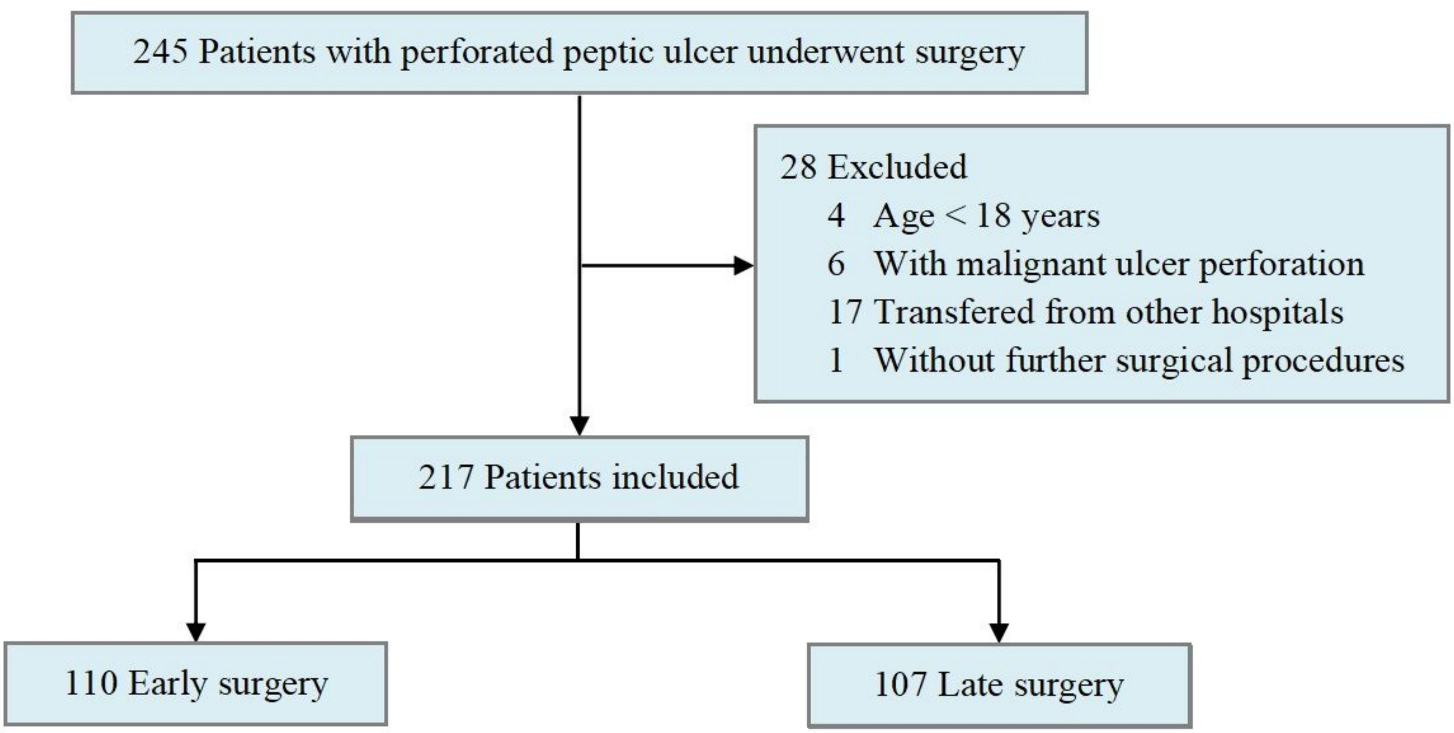

Figure 1

Flow-diagram of patient inclusion