

**A RETROSPECTIVE STUDY ON SURGICAL
APPROACH AND OUTCOME IN GIANT PERFORATED
PEPTIC ULCER DISEASE**

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LIST OF ABBREVIATIONS

PUD- Peptic Ulcer Disease

PPU- Perforated Peptic Ulcer

NSAIDs- Non-Steroidal Anti-Inflammatory Drugs

COX- Cyclooxygenase

TPN- Total Parenteral Nutrition

ICU- Intensive Care Unit

CLO- Campylobacter-like Organism

ASA- American Society of Anesthesiology

ABSTRAK

KAJIAN RETROSPEKTIF MENGENAI PENDEKATAN DAN HASIL PEMBEDAHAN BAGI PENYAKIT KEBOCORAN ULSER PEPTIK BESAR

Pengenalan: Kebocoran ulser peptik berisiko tinggi untuk morbiditi dan mortaliti, rawatan utama ialah pembedahan yang merangkumi pembaikan primer atau reseksi gastrik.

Objektif: Untuk menilai faktor yang mempengaruhi hasil daripada pendekatan pembedahan yang berbeza bagi kebocoran ulser peptic besar.

Kaedah: Semakan retrospektif ke atas semua pesakit kebocoran ulser peptic besar yang menjalani pembedahan dari Januari 2016 hingga Disember 2020 telah dilakukan. Pesakit dengan kebocoran kurang daripada 2 sentimeter telah dikecualikan. Demografi pesakit dan data perioperatif telah direkodkan. Tempoh tinggal, komplikasi selepas pembedahan, keperluan kemasukan ke ICU dan semua punca kematian dilaporkan.

Keputusan: 54 pesakit dengan umur median 60 (dengan julat 15-83) tahun yang mempunyai kebocoran ulser peptic ≥ 2 cm. 18 (33.3%) pesakit yang datang mengalami tanda-tanda dalam masa 24 jam dari permulaan sakit abdomen. Skor median Persatuan Anestesiologi Amerika ialah 3 (dengan julat 1–4). 24 pesakit menjalani pembaikan primer dan 30 pesakit menjalani gastrektomi. Keseluruhan insiden bocor anastomosis, pengumpulan intraabdomen,

pembedahan semula dan kematian 30 hari masing-masing adalah 18.5%, 25.9%, 9.3% dan 27.8%. Tiada perbezaan bagi hasil selepas pembedahan antara kedua-dua kumpulan dikesan: pengumpulan intraabdomen ($p=0.172$), bocor selepas pembedahan ($p=0.754$), pembedahan semula ($p=0.834$) dan kematian semua sebab ($p=0.736$).

Kesimpulan: Kebocoran ulser peptik besar boleh diuruskan sama ada melalui pembaikan primer atau gastrektomi, hasil perioperatif antara dua kumpulan adalah setanding maka pemilihan pendekatan pembedahan yang teliti perlu dibuat dengan mengambil kira faktor perioperatif bagi mengurangkan morbiditi dan mortaliti selepas pembedahan.

Kata kunci: kebocoran ulser peptik, gastrektomi, bocor anastomotik

ABSTRACT

A RETROSPECTIVE STUDY ON SURGICAL APPROACH AND OUTCOME IN GIANT PERFORATED PEPTIC ULCER DISEASE

Introduction: Perforated peptic ulcer (PPU) carries high risk for morbidity and mortality, The mainstay treatment is surgery which includes either primary repair or gastric resection.

Objective: To evaluate the factors affecting outcomes from different surgical approaches in giant PPU.

Methods: A retrospective review of all patients with PPU who underwent surgery from January 2016 to December 2020 was done. Patients with PPU less than 2cm were excluded. Patient demographics and perioperative data were recorded. Length of stay, post-operative complications, need for ICU admission and all-cause mortality are reported.

Results: Fifty-four patients with a median age of 60 (range 15–83) years old had PPU ≥ 2 cm. Eighteen (33.3%) patients presented within 24 hours from the onset of abdominal pain. The median American Society of Anaesthesiology score was 3 (range 1–4). Twenty-four patients had primary repair and 30 patients had gastrectomy. The overall incidence of anastomotic leak, intraabdominal collection, re-operation and 30 days mortality was 18.5%, 25.9%, 9.3% and 27.8%, respectively. No difference in post-operative outcomes between the two groups was detected: intra-abdominal collection ($p=0.172$), post-operative leakage ($p=0.754$), re-operation ($p=0.834$) and all-cause mortality ($p=0.736$).

Conclusions: Giant PPU can be managed by either primary repair or gastrectomy, perioperative outcomes between two groups are comparable hence a careful selection of surgical approach should be made with consideration of perioperative factors to reduce post-operative morbidity and mortality.

Keywords: perforated peptic ulcer, gastrectomy, anastomotic leak

CHAPTER 1

INTRODUCTION

Peptic ulcer disease is a result of dysregulation between the stomach's protective barriers and aggressive luminal factors. It may present with dyspepsia or other gastrointestinal symptoms, or asymptomatic initially and then present with complications such as haemorrhage or perforation. The incidence rates have been steadily falling over the past several decades after the introduction of proton pump inhibitor and eradication therapy for *Helicobacter pylori* infection which remains one of the leading cause of peptic ulcer disease.

Complications of peptic ulcer disease include bleeding, perforation and gastric outlet obstruction. Risk of complication in patients with chronic peptic ulcer disease is 2 to 3% annually. A large systematic review estimated annual incidence rate of hemorrhage in the general population ranged from 19.4 to 57.0 cases per 100,000 individuals, and that annual incidence of ulcer perforation ranges 4 to 14 cases per 100,000 individuals.

The mainstay treatment for perforated peptic ulcer is surgery. The postoperative morbidity ranges from 20 to 50% and the overall mortality ranging from 10 to 40%. The operative treatment includes either simple closures (with or without omental patch) or definitive gastric resection has been debated for decades. One of the considering factor is the size of perforation where the larger size of perforation is associated with higher mortality and post-operative anastomotic leak. Hence careful selection of approach in order to reduce the morbidity and mortality is important.

Our study intended to analyse our experience with perforated peptic ulcer in relation to how surgical approaches and other variable factors affect outcome.

CHAPTER 2

STUDY PROTOCOL

2.1 Documents submitted for ethical approval

RESEARCH PROPOSAL FOR MEDICAL AND HEALTH SCIENCES

Research title:

A retrospective study on surgical approach and outcome in giant perforated peptic ulcer disease

Principal investigator:

Dr. Gan Yiing Yee

Institution: Universiti Sains Malaysia

Co – researcher:

Associate Professor Dr. Ikhwan Sani Bin Mohamad

Institution: Universiti Sains Malaysia

Dr. Hashimah Binti Abdul Rahman

Institution: Hospital Umum Sarawak

Sponsorship: Self – sponsor

Introduction

Peptic ulcer disease is a result of dysregulation between the stomach's protective barriers and aggressive luminal factors. Peptic ulcer disease may present with dyspepsia or other gastrointestinal symptoms, or asymptomatic initially and then present with complications such as haemorrhage or perforation. According to a systematic review [1], the pooled incidence of uncomplicated peptic ulcer disease was approximately one case per 100 person-years in the general population, with the incidence of complications approximately 0.7 cases per 1000 person-years. However, the incidence rates have been steadily falling over the past several decades after the introduction of proton pump inhibitor and eradication therapy for *Helicobacter pylori* infection which remains one of the leading cause of peptic ulcer disease. In a large endoscopy based study of almost 8000 subjects from the University of Malaya Medical Centre [2-3], it showed that *H. pylori* prevalence had declined from 51.7% in 1989/1990 to 30.3% 1999/2000.

Complications of peptic ulcer disease include bleeding, perforation and gastric outlet obstruction. Risk of complication in patients with chronic peptic ulcer disease is 2 to 3% annually. There has been a decrease in the incidence of bleeding and perforation and hospitalization rates due to complications of peptic ulcer disease, presumably reflecting the fall of *H. pylori* prevalence [4]. A large systematic review [5] estimated annual incidence rate of hemorrhage in the general population ranged from 19.4 to 57.0 cases per 100,000 individuals, and that annual incidence of ulcer perforation ranges 4 to 14 cases per 100,000 individuals.

The mainstay treatment for perforated peptic ulcer is surgery. The postoperative morbidity ranges from 20% to 50% and the overall mortality ranging from 10% to 40%.[6-7]. The operative treatment includes either simple closures (with or without omental patch) or definitive gastric resection has been debated for decades. One of the considering factor is the size of perforation where the larger size of perforation is associated with higher mortality and post-operative anastomotic leak [8]. Hence careful selection of approach in order to reduce the morbidity and mortality is important.

The aim of our study is to compare the outcomes of ulcer repair versus gastrectomy in patients with giant perforated peptic ulcer (size of perforation ≥ 20 mm)

1.1 Research Question

Q: What are the operative factors affecting surgical outcomes of giant perforated peptic ulcer

Q: Which approach carries higher mortality and morbidity (primary repair vs gastric resection)

Null hypothesis: There is no difference in terms of mortality and morbidity between patients who underwent gastrectomy and primary ulcer repair.

Alternative hypothesis: There is difference in terms of mortality and morbidity between patients who underwent gastrectomy and primary ulcer repair.

1.2 Objectives and Aims

1.3 Overall Objective

To study factors affecting outcome of giant perforated peptic ulcer post-surgical management

1.4 Specific Aims

1. To determine the incidence of giant PGU
2. To evaluate the comorbidities contributing to PGU
3. To determine the morbidity and mortality associated with PGU
4. To study the association between type of repair and post operative outcome in giant PGU

Literature review

Peptic ulcer disease is associated with two major factors: *Helicobacter pylori* (H. Pylori) infection and the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). H pylori remains one of the commonest infections worldwide representing the key factor in the aetiology of various gastrointestinal diseases ranging from chronic gastritis to peptic ulceration, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma. The mean prevalence of H. pylori infection in patients with perforated peptic ulcer is of only about 65–70% [9-11].

NSAIDs are widely used for its analgesic, anti-inflammatory and anti-pyretic effects. It works by blocking the production of prostaglandins through inhibition of COX to reduce inflammation. Inhibition of COX-1 in the gastrointestinal tract leads to a reduction of prostaglandin secretion and its cytoprotective effects in gastric mucosa. This therefore increases the susceptibility to mucosal injury. About a quarter of chronic NSAID users will develop PUD and 2%-4% will bleed or perforate [13]. Other risk factors include elderly, smoking and alcohol ingestion [7,8,12-14].

Different studies have described risk factors predicting outcomes and morbidity in perforated peptic ulcer disease. Among the most pronounced were increased age, concomitant diseases, presence of shock, size of perforation, ulcer location and recurrence of ulcer [7,8,12-14]. Testini et al [7] also revealed that patients over 65 years have a significantly higher mortality rate after surgery for perforated peptic ulcer than younger patients because of the more frequent presence of comorbid diseases. Boey et al [15] stated that a delay of surgery after onset of symptoms for more than 48 hours, shock upon admission, and a high degree of comorbidity were associated with a 100% mortality when all factors were present.

The postoperative morbidity ranges from 20 to 50% and the overall mortality ranging from 10 to 40% [12-14]. Hence surgery remains the standard approach of management.

Johan Mikulicz-Radecki (1850–1905), often referred to as the first surgeon who closed a perforated peptic ulcer by simple closure, said: ‘Every doctor, faced with a perforated duodenal ulcer of the stomach or intestine, must consider opening the abdomen, sewing up the hole, and averting a possible inflammation by careful cleansing of the abdominal cavity’ [16]. The management of perforated peptic ulcer is still primarily surgical.

In 1992, Feliciano also described 5 points of decision that surgeon needs to take into account. Those decisions include: (1) Is surgery indicated? (2) Is an omental patch sufficient or a definitive ulcer operation indicated? (3) Is the patient stable enough to undergo a definitive ulcer operation? (4) Which definitive ulcer operation should be done? (5) Should the availability of newer medical options influence the choice of operation? With the development of laparoscopic operation in the past few decades, a sixth decision point is proposed; and (6) Should the procedure be performed laparoscopically? [17,18].

According to WSES guideline in 2020 [19], in perforated peptic ulcer and small perforation (<2cm), primary repair is advocated while the adjunct of an omental patch is still debatable. Multiple authors suggest the adjunct of an omental patch in case of large ulcers with friable edges, to reduce the risk of the suture cutting through the edges of the ulcer [20]. While the treatment of a small ulcer is relatively straightforward, the treatment of giant peptic ulcers (diameter > 2 cm) poses different challenges according to the anatomical location.

Giant peptic ulcer is defined as an ulcer greater than 2 cm in diameter[21,22]. It is usually found along the lesser curvature at incisura angularis. It is considered more prone for perforation because of the large size. The larger size of perforation is associated with higher mortality and post-operative anastomotic leak[23]. Furthermore, large gastric ulcers should always raise the suspicion of malignancy. Ergul E, Gozetlik reported that about 10–16% of all gastric perforations are caused by gastric carcinoma[24]. These ulcers were traditionally treated by primary closure after taking a biopsy as it was presumed that patients would not tolerate gastrectomy in an emergency setting as the time taken is longer and prolonged anaesthesia is contraindicated in compromised patients. The controversial point is whether simple closure suffices or a definitive resection. Omental patch repair for large perforated ulcers is reported to have higher morbidity due to an increased risk of suture line leak [23]. Hence, to minimise the risk of leak and to improve clinical outcomes, Gastric resection and reconstruction should be the surgical choice for the treatment of perforated gastric ulcers larger than 2 cm in patient with hemodynamical stability

Turner et al. [25] in 1988 reported a study include one hundred seven patients with perforated gastric ulcers underwent operations from 1955 to 1987. Perforations were treated by simple

closures in 96 patients and by primary gastric resections in 11 patients. Size of perforation only recorded in 86 patients, where ulcer sizes were significantly larger in the 11 patients who underwent primary gastric resections (median, 5.0 cm; 75th percentile, 5.0 cm) than in the 76 patients who underwent simple closures (median, 1.0 cm; 75th percentile, 1.5 cm) ($P = .001$). The overall operative mortality rate was 21%, including 18 deaths (19%) in the patients who had simple closures and five deaths (45%) in the patients who had gastric resections ($P = .056$). Larger gastric perforations are associated with increased postoperative mortality and morbidity.

Kumar P et al [27] conducted a retrospective study analysed 20 cases of perforated giant peptic ulcer (ulcer size more than 2cm) undergoing emergency surgeries in 2014. In the first 4 cases, primary closure was done after taking a biopsy and among these, the 3rd case also underwent partial distal gastrectomy and gastrojejunostomy and the 4th case underwent a radical subtotal gastrectomy with D2 lymphadenectomy and gastrojejunostomy for malignancy. All the remaining 16 cases underwent partial distal gastrectomy and gastrojejunostomy and recovered well. Only one of the patients expired due to multiorgan failure (3rd case). 6 out of 20 cases were histologically proven malignant. They have suggested partial distal gastrectomy and gastrojejunostomy is a better option in giant perforated gastric ulcers.

Chan et al published in European Journal of Trauma and Emergency Surgery in 2019 [28] comparing the outcome of omental patch repair with gastrectomy in 110 patients with perforated peptic ulcer (size more than 2cm), there were 52 patients in the omental patch repair group (Graham patch repair) and 58 patients in the gastrectomy group. They revealed no

statistical difference in perioperative outcomes of omental patch repair versus gastrectomy. A subgroup analysis of patients with giant perforated peptic ulcer (defined as PPU $\geq$ 30 mm) did not show statistically significant differences: intra-abdominal collection (p=0.384), post-operative leakage (p=0.624), re-operation (p=0.793) and all-cause mortality (p=0.254) between the two groups.

A retrospective analysis by Wysocki et al on perforated gastric ulcer in 1999 [26] over the time period of 36 years, included 77 patients with histological proven perforated gastric ulcer. Simple closure was the surgical procedure in 40 patients and *gastric resection* in 34 patients. Mortality rate was markedly higher in simple closure cases (37.5%) as compared to gastric resection group (3%).

Our study intended to analyse our experience with perforated peptic ulcer in relation to how surgical approaches and other variable factors affect outcome.

Overview

Retrospective cohort study

Study Duration

From August 2021 to December 2021

Study Location

Sarawak General Hospital

Study Population

Target population- Patients who diagnosed with perforated peptic ulcer disease in Kuching Sarawak

Source population/Sampling pool- Patients who diagnosed with perforated peptic ulcer disease and underwent surgery in Kuching Sarawak

Sampling frame- Database derived from ward census, operating theatre logs and surgical clinic census in Sarawak General Hospital

Patient Selection

All patients with perforated peptic ulcer disease who underwent surgery with intra-operative finding of perforation equal or more than 2cm between January 2016 to December 2020

Inclusion Criteria

Patients with intra-operative finding of suspected malignant perforation

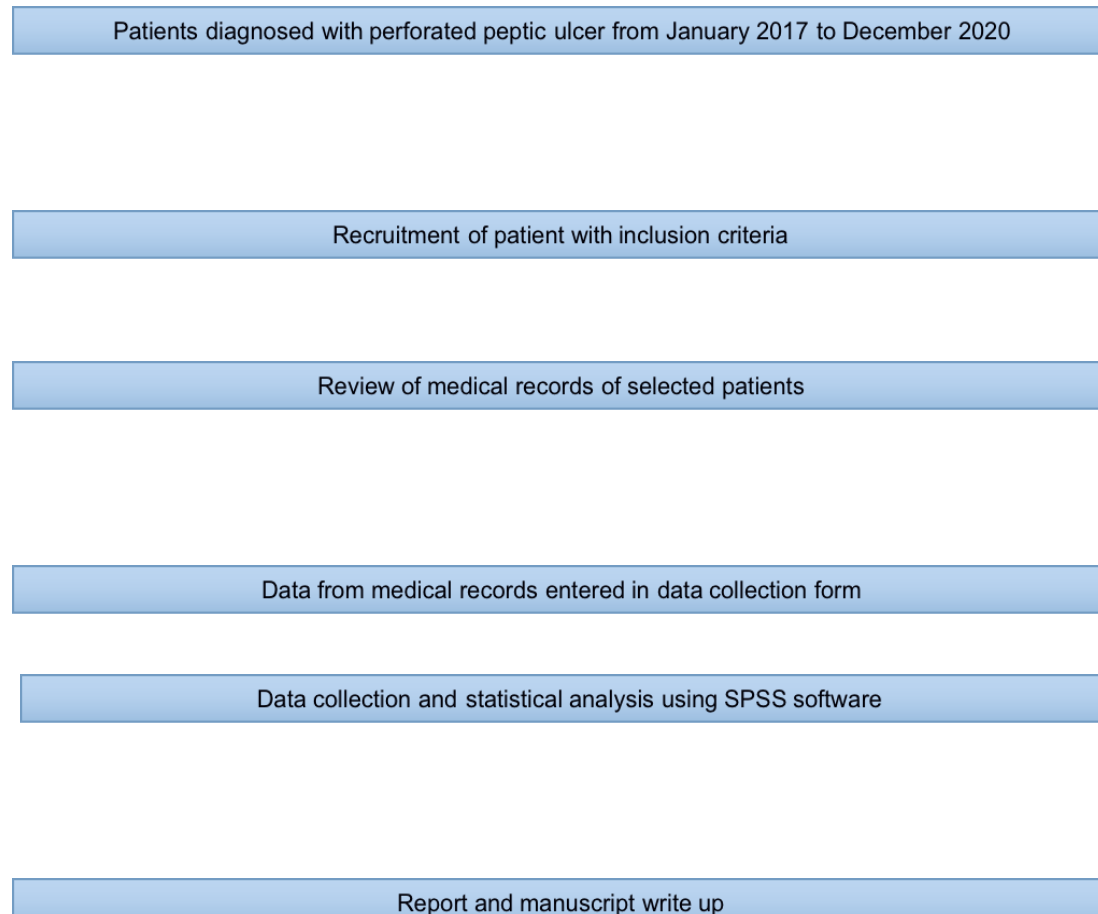
Exclusion Criteria

Patients with perforation site beyond first portion of duodenum

Treatment protocol

Prophylactic antibiotics were administered to all patients undergoing surgery and were continued post-operatively at the discretion of surgeon. Decision of gastrectomy or primary repair were based on operating surgeons depending on patient's general medical condition. All patients who underwent gastrectomy and/or had ulcers of gastric origin were biopsied due to the risk of malignancy. All patients were treated empirically with *Helicobacter pylori* eradication triple therapy and proton pump inhibitor post operatively.

Flow chart



Sample size estimation

Reference from Wysocki et al 2000

Ratio (Unexposed/Exposed): 1.17 (40/34)

	Primary closure (Unexposed) n=40	Gastric resection (Exposed) n=34
Mortality (%)	37.5	3.0

Sample Size: X-Sectional, Cohort, & Randomized Clinical Trials

Two-sided significance level(1-alpha):	90
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1.17
Percent of Unexposed with Outcome:	38
Percent of Exposed with Outcome:	2.9
Odds Ratio:	0.05
Risk/Prevalence Ratio:	0.08
Risk/Prevalence difference:	-34

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	17	15	20
Sample Size-Nonexposed	19	18	23
Total sample size:	36	33	43

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 & 3.19
CC = continuity correction

Sample size required to fulfil objective based on reference paper would be 33-43. Considering dropout rate of 10% (missing or incomplete data), the sample size is estimated to be 40-48.

1.5 Sampling method

Consecutive non randomized,non blinded sampling.

1.6 Collection of Data

Subject cases were selected by reviewing the archives of Sarawak General Hospital(SGH) operation theatre registry for patient who underwent surgery. Data collection were then taken from Surgical Outpatient Department (SOPD), Sarawak General Hospital, Kuching. The demographic, pre-operative presentation, co-morbidities, radiological findings, intra-operative and post-operative data were collected in the data collection form

Study variables and outcome

The study variables were age, gender, time to presentation, predisposing factors of PUD, co-morbidities, risk factors (NSAIDs,and history of peptic ulcer disease),pre-operative laboratory values on day of admission (full blood count and serum urea and creatinine), radiological findings and mortality risk prediction models. The American Society of Anaesthesiologists (ASA) score and Boey's score were calculated from the collected data. Intraoperative factor (perforation site and size) and surgical approach (open vs laparoscopic approach, primary repair vs gastric resection) will be included.Study outcomes that were analysed included total parenteral nutrition (TPN) requirements, length of hospitalisation and intensive care unit (ICU) stay (if required) including mean ICU stay (days) and hemodialysis support, post-operative complications and in-hospital mortality.

1.7 Data Analysis Strategies

Data was collected using Microsoft Excel and was converted to Statistical Package for Social Science (SPSS) software version 23 for analysis. Socio-demographic, intra-operative and post operative parameters were analyzed

Comparison of various preoperative factors, types of approach and outcome of surgery will be analyzed using Chi square to obtain p value

Confidentiality

The information collected from this thesis project was kept with confidentiality. Subject's name was not shown in the data collection. Instead, identification numbers were used in data collection. Only the primary investigator and researchers who collected the data knew the ID numbers and information of each subject. Subjects were not be allowed to view their personal data, as the data were consolidated into database. Publication of the study results will be done without revealing the personal information of the subject.

Declaration of absence of conflict of interest

Principal investigator and supervisor had no conflict of interest during conduct of this study.

Community sensitivities and benefits

Not applicable