

Intraoperative biopsy in peptic ulcer perforation: Is it necessary? A comprehensive analysis of prognostic factors for mortality and ICU admission

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ABSTRACT

Introduction: The necessity of routine intraoperative biopsy during emergency surgery for peptic ulcer perforation (PUP) remains controversial when malignancy is not suspected. This study evaluated the diagnostic yield of intraoperative biopsy and identified prognostic factors for mortality and intensive care unit (ICU) admission.

Materials and Methods: This retrospective single-center cohort included 77 adults undergoing emergency laparotomy for PUP, excluding tumor perforations and cases with radiological suspicion of malignancy. Clinical, laboratory, and perioperative variables, including Boey and PULP scores, were analyzed. Outcomes were compared between patients with and without intraoperative biopsy, and according to mortality and ICU admission. Postoperative endoscopy at one month was used for secondary malignancy screening.

Results: Intraoperative biopsy was performed in 58.4% of patients, detecting malignancy in only one case (1.3%). No malignancy was found on postoperative endoscopy in patients without intraoperative suspicion. Overall mortality was 11.7% and was significantly associated with advanced age, delayed presentation, larger perforation size, comorbidity, higher Boey and PULP scores, elevated creatinine, and hypoalbuminemia. ICU admission (84.4%) showed similar associations. Intraoperative biopsy had no significant impact on mortality or ICU requirement.

Conclusions: Routine intraoperative biopsy provides minimal diagnostic benefit in the absence of macroscopic suspicion of malignancy. A selective approach, guided by intraoperative findings and supported by early postoperative endoscopy, appears safe and sufficient. Prognosis is mainly determined by patient-related and physiological factors, perforation severity, and established risk scores.

Keywords: Biopsy, emergency surgery, gastric malignancy, intraoperative peptic ulcer perforation



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Introduction

Despite advances in proton pump inhibitor therapy and widespread implementation of *Helicobacter pylori* eradication protocols, peptic ulcer disease remains clinically significant, particularly among elderly patients and those with substantial comorbidities.^[1,2] Among its complications, peptic ulcer perforation represents a life-threatening condition characterized by sudden-onset severe abdominal pain, diffuse peritonitis, and rapid physiological deterioration, necessitating urgent surgical intervention. Mortality rates in perforated ulcer cases increase markedly with advanced age, delayed presentation, septic physiology, and diminished physiological reserve, often reaching double-digit values in high-risk subgroups. Consequently, rapid, evidence-based diagnostic and therapeutic decision-making is essential for optimizing outcomes in this patient population.

Surgical management of peptic ulcer perforation typically consists of primary closure or omental patch repair (Graham patch), although resection may be required in selected cases.^[3] However, the potential for an underlying malignancy—particularly in gastric ulcer perforations—has long been a concern for surgeons.^[4] The perforation site is often inflamed, edematous, and partially necrotic, factors that impair macroscopic assessment and raise doubts regarding the diagnostic sensitivity of limited intraoperative biopsies.^[5] This has fueled ongoing debate regarding whether routine biopsy of the perforation margin is justified or whether biopsy should be reserved for cases with suspicious intraoperative findings.

Existing literature suggests that the prevalence of malignancy detected during surgery for peptic ulcer perforation is low, with most perforations arising from benign ulcer disease.^[6] Nevertheless, in many centers, intraoperative biopsy continues to be performed routinely in all patients with gastric perforation—often driven by habit or defensive surgical practice—despite limited evidence supporting its clinical value or cost-effectiveness.^[5] This practice also raises questions regarding operative time, bleeding risk, technical difficulty, pathology workload, and the true contribution of biopsy results to postoperative management.^[7] Furthermore, the contemporary availability of routine early postoperative upper gastrointestinal endoscopy—a highly effective diagnostic tool for identifying underlying malignancy—further challenges the necessity of intraoperative biopsy in all cases.^[8]

Multiple risk stratification systems, including the Boey score and the Peptic Ulcer Perforation (PULP) score, have been developed to assess prognosis in perforated ulcer disease.^[9,10] These models incorporate variables such as age, significant comorbidities, presence of shock, time from perforation to surgery, and laboratory parameters to estimate mortality and morbidity risk.^[9,10] However, the number of studies evaluating the real-world performance of these scores—particularly their relationship with intensive care unit (ICU) requirements, postoperative mortality, and surgical outcomes within the same patient cohort—remains limited. Additionally, there is a lack of comprehensive analyses examining how perforation size, anatomical location (gastric, duodenal, or anastomotic), renal function indicators (creatinine), nutritional markers (albumin), and systemic inflammatory parameters (WBC, CRP) collectively influence both mortality and ICU admission rates.^[11]

The potential drawbacks of intraoperative biopsy must also be considered, particularly in this high-risk population. Obtaining a biopsy may prolong operative time, increase bleeding or technical difficulty, add pathology-related costs, and potentially delay incorporation of results into clinical decision-making.^[6] In elderly, comorbid, or hemodynamically unstable patients for whom minimizing operative duration is essential, the true clinical value of routine or broad-indication biopsy warrants scrutiny. The exceptionally low malignancy detection rate reported in surgical series of peptic ulcer perforation supports a more selective, rather than routine, approach.^[12] Nonetheless, this assumption has largely been based on small case series and heterogeneous cohorts, and no clear consensus exists.^[13]

Accordingly, evaluating the clinical utility of intraoperative biopsy—both in terms of its ability to detect underlying malignancy and its implications for postoperative course and resource utilization—remains an important question in the management of peptic ulcer perforation. Assessing its relationship with clinically relevant outcomes, such as mortality and ICU admission, within the same well-defined cohort may help refine surgical decision algorithms and inform future guideline recommendations.

In this study, we aimed primarily to determine whether intraoperative biopsy is necessary in adult patients undergoing emergency surgery for peptic ulcer perforation after excluding tumor perforations and cases in which overt malignancy was identified macroscopically intraop-

eratively. We compared clinical, laboratory, and perioperative characteristics between patients who did and did not undergo intraoperative biopsy to evaluate its diagnostic contribution. As a secondary objective, we examined prognostic factors associated with postoperative mortality and ICU requirement—including age, time to hospital presentation, perforation size and location, comorbidity status, preoperative shock, ASA class, Boey and PULP scores, creatinine, albumin, WBC, and CRP. Through this approach, we sought to provide a comprehensive assessment that both questions the rationale for routine intraoperative biopsy and delineates the risk profile associated with adverse clinical outcomes in patients with perforated peptic ulcer disease.

Materials and Methods

This study was designed as a single-center retrospective cohort analysis aimed at evaluating clinical outcomes in adult patients undergoing emergency surgery for peptic ulcer perforation. The investigation was conducted in the Department of General Surgery at Erciyes University Faculty of Medicine, following approval from the institutional Clinical Research Ethics Committee (No: 2025/440, Date: 10/09/2025). All components of the study were performed in accordance with the principles of the Declaration of Helsinki. Data were collected retrospectively from patient medical records, operative notes, anesthesia charts, ICU databases, pathology reports, and endoscopy findings. Statistical analyses were carried out using SPSS software, version 22.0.

All adult patients (≥ 18 years) who underwent emergency laparotomy with a preoperative diagnosis of peptic ulcer perforation were eligible for inclusion. Patients with a known malignant tumor prior to surgery, or those in whom preoperative endoscopy or contrast-enhanced computed tomography demonstrated a mass at the perforation site suggestive of malignancy, were excluded. Accordingly, the study population consisted solely of patients without preoperatively recognized malignancy who required emergency surgery for perforation. Importantly, patients in whom the surgeon identified suspicious features at the ulcer base intraoperatively and therefore performed biopsy or resection were not excluded; these cases were included, and their histopathological results were incorporated into the analyses. Based on these criteria, a total of 77 patients were included in the final cohort.

For each patient, demographic characteristics, comorbidities, time to hospital presentation, hemodynamic status,

ASA physical status classification, presence of preoperative shock, laboratory parameters (creatinine, WBC count, CRP level, albumin), perforation site, perforation size, surgical technique (Graham patch versus resection), intraoperative biopsy status, postoperative intubation requirement, ICU admission, and in-hospital mortality were systematically recorded. The Boey and PULP scores were calculated for all patients to allow objective assessment of preoperative risk. In the postoperative period, patients who were clinically stable underwent routine upper gastrointestinal endoscopy at approximately one month, and additional biopsies were obtained when indicated.

All surgical procedures were performed via a standard midline laparotomy. Following inspection of the abdominal cavity, primary closure reinforced with an omental patch (Graham patch) was performed whenever appropriate. In cases where the perforation site exhibited irregular margins, induration, large defect size, or was located in the stomach—features raising suspicion for an underlying lesion—the decision to obtain an intraoperative biopsy or to perform resection was left to the surgeon's clinical judgment. To evaluate the potential influence of intraoperative pathology on operative decision-making in this preoperatively non-malignant cohort, biopsy results were recorded in detail. All biopsy and resection specimens were examined in the institutional pathology laboratory using routine hematoxylin–eosin staining and assessed for benign ulcer features, inflammation, dysplasia, or malignancy.

Normality of continuous variables was tested using the Shapiro–Wilk test, and none met criteria for normal distribution. Therefore, these variables were summarized using medians, interquartile ranges, and minimum–maximum values; mean \pm standard deviation was additionally reported for descriptive purposes. Comparisons of continuous variables between groups were made using the Mann–Whitney U test, while categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when expected cell counts were insufficient. Clinical variables were compared between patients who did and did not undergo intraoperative biopsy, between survivors and non-survivors, and between patients requiring ICU admission and those managed without ICU care. A *p*-value of < 0.05 was considered statistically significant. Because of the limited sample size—particularly within the mortality subgroup—analyses were restricted to univariate comparisons, and multivariable regression modeling was not performed.

Results

A total of 77 patients who underwent surgery for peptic ulcer perforation and had no evidence of tumor-related perforation were included in the study. Baseline clinical and laboratory characteristics are presented in Table 1. The median age of the cohort was 58 years (IQR: 38.5–69.5; range: 19–92), with a mean age of 54.95 ± 20.11 years. The median time to hospital presentation was 1 day (IQR: 1–2). The median perforation location score was 1 (IQR: 1–2), corresponding predominantly to duodenal perforations, followed by gastric and anastomotic/perianastomotic sites. Median serum creatinine, WBC count, CRP level, and albumin level were 0.98 mg/dL (0.82–1.67), $11.75 \times 10^3/\mu\text{L}$ (8.22–15.51), 11.75 mg/L (8.22–15.51), and 3.67 g/dL (3.19–4.37), respectively. The median Boey and PULP scores were 1 (0–1) and 1 (0–3), respectively (Table 1).

Demographic, clinical, and perioperative characteristics are summarized in Table 2. Of the cohort, 67.5% were male and 32.5% were female. ICU admission rates were high, with 84.4% of patients requiring postoperative intensive care. Postoperative intubation was necessary in 50.6% of cases. Duodenal perforations constituted the majority (71.4%), followed by gastric (20.8%) and anastomotic/perianastomotic perforations (7.8%). Comorbidities were present in 58.4% of patients, and most patients were classified as ASA II (66.2%). Preoperative shock was identified in 18.2% of the cohort. Graham patch repair was performed

in 92.2% of cases, whereas resection was required in 7.8%. Intraoperative biopsy was taken in 45 patients (58.4%), yielding benign results in 44 (57.1%) and malignancy in 1 (1.3%). At one-month postoperative endoscopic follow-up, malignancy was identified in only one patient (1.3%). The overall in-hospital mortality rate was 11.7% (Table 2).

A comparison of patients with and without intraoperative biopsy is provided in Table 3. No significant differences were observed between groups regarding age, time to hospital presentation, WBC count, CRP level, albumin level, Boey score, or PULP score (all $p > 0.05$). However, perforation size was significantly larger in patients who underwent biopsy (mean rank 44.24 vs. 31.63; $p = 0.005$). Serum creatinine levels exhibited a trend toward higher values in the biopsy group, although this did not reach statistical significance ($p = 0.059$).

Continuous variables associated with postoperative mortality are summarized in Table 4. Patients who died postoperatively had significantly higher mean rank values for age (56.67 vs. 36.66; $p = 0.012$), longer time to hospital presentation ($p = 0.021$), larger perforation size ($p = 0.025$), and higher Boey and PULP scores (both $p < 0.001$). Serum creatinine levels were also significantly higher in the mortality group ($p = 0.002$). Conversely, albumin levels were significantly lower among non-survivors ($p = 0.001$). Significant differences were observed in CRP levels but not WBC between survivors and non-survivors ($p = 0.002$).

Table 1. Baseline clinical and laboratory characteristics of patients undergoing surgery for peptic ulcer perforation

Variable	Median (IQR)	Min–Max	Mean \pm SD
Age (years)	58 (38.5–69.5)	19–92	54.95 \pm 20.11
Time to hospital admission (days)	1 (1–2)	1–2	1.32 \pm 0.47
Perforation location ¹	1 (1–2)	1–3	1.36 \pm 0.63
Serum creatinine (mg/dL)	0.98 (0.82–1.67)	0.00–7.80	1.57 \pm 1.47
WBC ($\times 10^3/\mu\text{L}$)	11.75 (8.22–15.51)	1.44–42.30	12.56 \pm 6.79
CRP (mg/L) ²	42.3 (4.4–218.1)	0–492	108.02
Albumin (g/dL)	3.67 (3.19–4.37)	1.65–5.06	3.65 \pm 0.83
Boey score	1 (0–1)	0–3	0.96 \pm 0.98
PULP score	1 (0–3)	0–7	1.64 \pm 1.72

WBC: White blood cells; PULP: Peptic Ulcer Perforation; CRP: C-reactif protein. Continuous variables demonstrated non-normal distribution based on the Shapiro–Wilk test ($p < 0.05$) and are reported as median (interquartile range) and minimum–maximum values. Mean \pm standard deviation is additionally provided for descriptive purposes. Perforation location¹ refers to gastric (1), duodenal (2), and other sites (3). CRP² values were reported together with WBC, as both represent inflammatory markers in this cohort.

Table 2. Distribution of demographic, clinical, and perioperative characteristics in patients undergoing surgery for peptic ulcer perforation

Variable	n	%
Female	25	32.5
Male	52	67.5
ICU admission		
No	12	15.6
Yes	65	84.4
Postoperative intubation		
No	38	49.4
Yes	39	50.6
Perforation location		
Duodenum (1 st part)	55	71.4
Stomach	16	20.8
Anastomotic/perianastomotic perforation	6	7.8
Comorbidity		
Present	45	58.4
Absent	32	41.6
ASA score		
I	11	14.3
II	51	66.2
III	15	19.5
Preoperative shock		
Yes	14	18.2
No	63	81.8
Surgical procedure		
Graham patch	71	92.2
Resection	6	7.8
Intraoperative biopsy		
Performed	45	58.4
Not performed	32	41.6
Intraoperative biopsy pathology		
Benign	44	57.1
Malignant	1	1.3
No biopsy taken	32	41.6
In-hospital mortality		
Yes	9	11.7
No	68	88.3
Peroperative biopsy result		
Benign	76	98.7
Malignant	1	1.3

Table 2 (Cont). Distribution of demographic, clinical, and perioperative characteristics in patients undergoing surgery for peptic ulcer perforation

Variable	n	%
1-month postoperative endoscopic pathology		
Benign	76	98.7
Malignant	1	1.3

Values are presented as numbers and percentages. Perforation location categories: duodenal (first part), gastric, and anastomotic/perianastomotic sites. Graham patch includes omental patch repair. Intraoperative biopsy pathology reflects histology from selectively obtained specimens. Perioperative biopsy result refers to surgical specimen evaluation in resection cases. Postoperative endoscopic pathology represents routine 1-month follow-up endoscopy findings.

Categorical variables associated with mortality are shown in Table 5. Although mortality was more frequent among women, the difference was not statistically significant ($p=0.414$). All mortality cases required ICU care, although this did not reach statistical significance ($p=0.340$). Postoperative intubation was more common among non-survivors but approached rather than reached statistical significance ($p=0.083$). Gastric perforations were significantly more frequent among patients who died (66.7% vs. 14.7%; $p=0.004$). Comorbidities were also significantly more common in the mortality group ($p=0.049$). Preoperative shock demonstrated a strong association with mortality, occurring in 88.9% of patients who died ($p<0.001$). Surgical technique (Graham patch vs. resection) and intraoperative biopsy status were not associated with mortality ($p=0.538$ and $p=0.594$, respectively).

Continuous variables associated with ICU admission are detailed in Table 6. Patients requiring intensive care were significantly older ($p<0.001$) and had higher ASA, PULP, and Boey scores (all $p\leq 0.003$). Larger perforation size, elevated serum creatinine, higher WBC and CRP levels, and lower albumin levels were also significantly associated with ICU admission (all $p<0.05$). Time to hospital presentation did not differ significantly between patients with and without ICU admission ($p=0.550$).

Categorical variables related to ICU admission are presented in Table 7. Female sex was significantly associated with ICU requirement ($p=0.015$). Comorbidity presence significantly increased the likelihood of ICU admission ($p=0.002$).

Table 3. Comparison of clinical and laboratory variables between patients with and without intraoperative biopsy during surgery for peptic ulcer perforation

Variable	Biopsy Performed (n=45) Mean Rank	Biopsy Not Performed (n=32) Mean Rank	Mann–Whitney U	Z	p
Age (years)	42.39	34.23	567.5	−1.577	0.115
Time to hospital admission (days)	39.33	38.53	705.0	−0.191	0.848
Perforation size (cm)	44.24	31.63	484.0	−2.798	0.005
Serum creatinine (mg/dL)	43.06	33.30	537.5	−1.887	0.059
WBC ($\times 10^3/\mu\text{L}$)	35.84	43.44	578.0	−1.468	0.142
CRP (mg/L)	40.94	36.27	632.5	−0.904	0.366
Albumin (g/dL)	36.43	42.61	604.5	−1.194	0.233
Boey score	41.28	35.80	617.5	−1.130	0.258
PULP score	42.82	33.63	548.0	−1.831	0.067

WBC: White blood cells; PULP: Peptic Ulcer Perforation; CRP: C-reaktif protein. All comparisons were performed using the Mann–Whitney U test due to non-normal data distribution. Data are reported as mean rank values. Statistically significant p-values ($p < 0.05$) are presented in bold. Perforation size reflects the intraoperatively measured maximal diameter of the perforation site.

Table 4. Comparison of continuous clinical and laboratory variables between survivors and non-survivors after surgery for peptic ulcer perforation

Variable	Survivors (n=68) Mean Rank	Non-Survivors (n=9) Mean Rank	Mann–Whitney U	Z	p
Age (years)	36.66	56.67	147.0	−2.522	0.012
Time to hospital admission (days)	37.26	52.17	187.5	−2.316	0.021
Perforation size (cm)	37.18	52.72	182.5	−2.246	0.025
Boey score	35.45	65.83	64.5	−4.085	<0.001
PULP score	35.40	66.17	61.5	−3.993	<0.001
Serum creatinine (mg/dL)	36.15	60.56	112.0	−3.076	0.002
Albumin (g/dL)	42.04	16.00	99.0	−3.282	0.001
WBC ($\times 10^3/\mu\text{L}$)	38.93	39.56	301.0	−0.079	0.937
CRP (mg/L)	36.09	61.00	108.0	−3.139	0.002

WBC: White blood cells; PULP: Peptic Ulcer Perforation; CRP: C-reaktif protein. All analyses were conducted using the Mann–Whitney U test due to non-normal distribution of continuous variables. Data are presented as mean rank values. Statistically significant p-values ($p < 0.05$) are shown in bold. Mortality reflects in-hospital postoperative death.

Although preoperative shock was more frequent in patients who required ICU care, this did not reach statistical significance ($p = 0.109$). Perforation location, surgical technique, and intraoperative biopsy status were not significantly associated with ICU admission (all $p > 0.05$).

Discussion

In this study, we examined the role of intraoperative biopsy in adult patients undergoing emergency surgery for peptic ulcer perforation in whom malignancy was not known preoperatively, and we evaluated these findings alongside

Table 5. Association between postoperative mortality and clinical categorical variables in patients undergoing surgery for peptic ulcer perforation

Variable	Survivors (n=68)	Non-survivors (n=9)	Test	p
Gender				
Female	21 (30.9%)	4 (44.4%)	$\chi^2=0.667$	0.414 ¹
Male	47 (69.1%)	5 (55.6%)		
ICU admission				
No	12 (17.6%)	0 (0.0%)	Fisher's	0.340 ¹
Yes	56 (82.4%)	9 (100%)		
Postoperative intubation				
No	36 (52.9%)	2 (22.2%)	$\chi^2=3.00$	0.083 ²
Yes	32 (47.1%)	7 (77.8%)		
Perforation localization				
Duodenum	52 (76.5%)	3 (33.3%)	Fisher's	0.004 ³
Gastric	10 (14.7%)	6 (66.7%)		
Anastomotic	6 (8.8%)	0 (0.0%)		
Comorbidity				
Present	37 (54.4%)	8 (88.9%)	$\chi^2=3.89$	0.049 ⁴
Absent	31 (45.6%)	1 (11.1%)		
Preoperative shock				
Present	6 (8.8%)	8 (88.9%)	$\chi^2=34.25$	<0.001 ⁵
Absent	62 (91.2%)	1 (11.1%)		
Surgical technique				
Graham patch	63 (92.6%)	8 (88.9%)	Fisher's	0.538 ⁶
Resection	5 (7.4%)	1 (11.1%)		
Intraoperative biopsy				
Performed	39 (57.4%)	6 (66.7%)	$\chi^2=0.284$	0.594 ⁷
Not performed	29 (42.6%)	3 (33.3%)		

Categorical variables were compared using Pearson's chi-square or Fisher's exact test, depending on expected cell counts. Exact tests were adopted when assumptions for chi-square were not met. Statistically significant p-values ($p < 0.05$) are shown in bold. Mortality reflects in-hospital postoperative death. Perforation localization categories include duodenal, gastric, and anastomotic sites.

prognostic factors associated with mortality and ICU admission. Two central observations emerged from our analysis: With respect to detecting underlying malignancy, the surgeon's intraoperative macroscopic impression appeared to be the key determinant, and routine biopsy of the perforation margin provided no additional diagnostic value when the operative field did not raise suspicion for cancer; and overall prognosis was shaped predominantly by age, comorbidity burden, hemodynamic instability, perforation size, and established clinical risk scores such as Boey and PULP.^[14,15] Taken together, these findings support a selective—not routine—approach to intraoperative biopsy, guided primarily by the surgeon's intraoperative judgment.

In our cohort, intraoperative biopsy was performed in 45 patients, with malignancy detected in only one case. Importantly, none of the patients in whom the surgeon did not suspect malignancy—and therefore did not obtain a biopsy—were found to have cancer during the planned postoperative endoscopic evaluation at one month. This pattern suggests that the surgeon's macroscopic assessment of the perforation and ulcer bed may possess a high negative predictive value in excluding underlying malignancy.^[16] In practical terms, the absence of macroscopic features such as induration, irregular or elevated ulcer margins, mass-like thickening, or overtly atypical appearance corresponded to an exceedingly low probability of detecting malignancy on

Table 6. Comparison of continuous clinical and laboratory variables according to intensive care unit admission status after surgery for peptic ulcer perforation

Variable	ICU No Mean Rank	ICU Yes Mean Rank	U	Z	p
Age (years)	15.33	43.37	106.0	-3.990	<0.001
ASA score	24.08	41.75	211.0	-3.006	0.003
PULP score	18.13	42.85	139.5	-3.623	<0.001
BOEY score	22.50	42.05	192.0	-2.966	0.003
Perforation size (mm)	25.54	41.48	228.5	-2.602	0.009
Serum creatinine (mg/dL)	20.75	42.37	171.0	-3.076	0.002
WBC ($\times 10^3/\mu\text{L}$)	53.00	36.42	222.0	-2.359	0.018
CRP (mg/L)	24.79	41.62	219.5	-2.395	0.017
Albumin (g/dL)	57.63	35.56	166.5	-3.139	0.002
Time to hospital admission (hours)	36.13	39.53	355.5	-0.597	0.550

All analyses were performed using the Mann-Whitney U test due to non-normal distribution of continuous variables. Data are presented as mean rank values. Statistically significant p-values ($p < 0.05$) are shown in bold. ICU = intensive care unit.

Table 7. Association between intensive care unit admission and categorical clinical variables in patients undergoing surgery for peptic ulcer perforation

Variable	ICU No n (%)	ICU Yes n (%)	Test	p
Gender				
Female	0 (0.0)	25 (38.5)	Pearson $\chi^2=6.834$; Fisher	0.015
Male	12 (100)	40 (61.5)		
Comorbidity				
Present	2 (16.7)	43 (66.2)	Pearson $\chi^2=10.214$; Fisher	0.002
Absent	10 (83.3)	22 (33.8)		
Preoperative shock				
Present	0 (0.0)	14 (21.5)	Pearson $\chi^2=3.159$; Fisher	0.109
Absent	12 (100)	51 (78.5)		
Perforation localization				
Duodenum (1 st part)	11 (91.7)	44 (67.7)	Pearson $\chi^2=2.983$; Fisher	0.315
Stomach	1 (8.3)	15 (23.1)		
Anastomotic leak	0 (0.0)	6 (9.2)		
Surgical procedure				
Graham patch	11 (91.7)	60 (92.3)	Pearson $\chi^2=0.006$; Fisher	1.000
Resection	1 (8.3)	5 (7.7)		
Intraoperative biopsy				
Performed	6 (50.0)	39 (60.0)	Pearson $\chi^2=0.417$; Fisher	0.540
Not performed	6 (50.0)	26 (40.0)		

Categorical variables were compared using Pearson's chi-square or Fisher's exact test, depending on expected cell counts. Exact tests were preferred when chi-square assumptions were not met. Statistically significant p-values ($p < 0.05$) are shown in bold. ICU = intensive care unit.

histology.^[17] Conversely, cases with prominent, irregular, or particularly large gastric perforations—particularly those raising intraoperative concern—were more likely to yield diagnostic benefit from biopsy or resection, reinforcing the rationale for a selective strategy.

These findings call into question the longstanding practice—still widely adhered to in many centers—of obtaining a biopsy from all gastric perforations as a matter of routine.^[5,7] The fact that no malignancy was detected in any patient for whom the surgeon had no intraoperative suspicion and thus did not sample the perforation suggests that the diagnostic yield of routine biopsy in this setting is extremely low. Moreover, planned postoperative upper endoscopy provides a reliable second-stage evaluation of the perforation site and allows targeted biopsy when needed, thereby substantially mitigating the risk of missing an occult malignancy.^[18] Thus, a two-step diagnostic strategy—macroscopic intraoperative assessment as the primary filter, combined with systematic early postoperative endoscopy as a confirmatory measure—appears to offer a more rational and resource-conscious approach than routine biopsy.^[19]

The potential impact of intraoperative biopsy on operative time, technical complexity, and pathology workload must also be considered. Inflammatory changes, edema, and friable tissue at the perforation site can render tissue sampling technically challenging and may increase the risk of bleeding or further tissue injury. In elderly, comorbid, or hemodynamically unstable patients, avoiding unnecessary extension of the operative duration is an important priority. In our study, intraoperative biopsy was not associated with increased mortality or ICU admission, suggesting that it does not directly worsen short-term outcomes. However, given its limited benefit in detecting malignancy, the routine use of biopsy in all perforation cases seems clinically unjustified. Selective biopsy guided by intraoperative suspicion provides a more balanced strategy, maintaining patient safety while avoiding unnecessary procedures.

The second major component of our study involved identifying prognostic factors associated with postoperative mortality and ICU requirement. Our findings align closely with previously reported risk determinants in the literature. Advanced age, delayed presentation, larger perforation size, and significantly elevated Boey and PULP scores were all strongly associated with mortality.^[20] In addition, higher creatinine levels and markedly reduced albumin concentrations among non-survivors indicate that impaired organ reserve and systemic physiological deterioration contrib-

ute substantially to poor outcomes.^[21] The predominance of gastric perforations among mortality cases may reflect both a more severe septic burden and the potential underlying malignant biology inherent to this anatomical location.^[22] In contrast, single-point inflammatory markers such as WBC count did not discriminate between survivors and non-survivors, whereas CRP levels were significantly higher among non-survivors.^[23] These findings reinforce the importance of multiparametric scoring systems, such as Boey and PULP, when used alongside clinical judgment.

The patterns observed in patients requiring ICU admission similarly reflect the overall severity of illness. Those admitted to the ICU were older, had higher ASA, Boey, and PULP scores, larger perforation sizes, elevated creatinine and inflammatory markers, and significantly lower albumin levels—characteristics consistent with a physiologically vulnerable population requiring heightened postoperative support.^[23] The association of female sex and comorbidity with ICU admission suggests that frailty-related factors may also influence postoperative care needs.^[24] Notably, perforation location, surgical technique, and intraoperative biopsy status were not associated with ICU requirement, emphasizing that systemic physiological status, rather than anatomical features, primarily dictates the need for intensive care.

Taken together, these findings underscore two major strategic principles for the surgical management of peptic ulcer perforation. First, high-risk patients should be identified early using a combination of age, comorbidities, hemodynamic instability, perforation characteristics, laboratory parameters such as creatinine and albumin, and validated scoring systems including Boey and PULP.^[25] Early resuscitation, preoperative optimization, proactive ICU planning, and vigilant postoperative monitoring are particularly critical for these patients.^[26] Second, malignancy assessment should follow a rational, stepwise approach: A selective intraoperative biopsy performed only when macroscopic findings raise concern, followed by a structured early postoperative endoscopic evaluation for all patients.^[26] The complete absence of malignancy among patients with no intraoperative suspicion and no biopsy in our cohort provides strong observational support for the safety and feasibility of this two-tiered approach.

This study possesses several strengths. By excluding patients with known preoperative malignancy, we specifically targeted a cohort representing true “malignancy-unknown perforations.” Consistent surgical practices within

a single center reduced procedural heterogeneity, and we incorporated both classical risk scores and laboratory parameters in our assessment of mortality and ICU outcomes. The systematic integration of postoperative endoscopy also strengthened our ability to detect malignancies potentially missed intraoperatively.

However, certain limitations must be acknowledged. The retrospective design and single-center setting raise the possibility of selection and information biases, and they may restrict generalizability to other populations. The decision to perform biopsy was at the discretion of the operating surgeon, introducing inherent selection bias between biopsy and non-biopsy groups. The limited sample size—particularly within the mortality subgroup—precluded multivariable modeling, preventing a more nuanced analysis of interacting risk factors. Furthermore, despite planned routine postoperative endoscopy, incomplete adherence cannot be fully excluded, and the possibility of extremely late-presenting malignancies, although improbable, cannot be entirely dismissed.^[4]

Conclusion

This study demonstrates that the diagnostic value of routine intraoperative biopsy in patients undergoing surgery for peptic ulcer perforation without preoperative suspicion of malignancy is extremely limited.^[4,7,27] Our findings indicate that the surgeon's macroscopic intraoperative assessment should be the principal determinant in deciding whether a biopsy is warranted and in effectively excluding the risk of underlying malignancy. In cases where no intraoperative features raise concern for cancer, routine biopsy of the perforation margin appears unnecessary, and early postoperative endoscopic evaluation provides a safe and adequate means of secondary assessment.^[28] Conversely, parameters such as advanced age, comorbidities, hemodynamic instability, perforation size, and elevated Boey and PULP scores emerged as the major determinants of mortality and ICU admission.^[9,10,28] These observations support shifting from a routine to a selective biopsy approach guided by the surgeon's clinical judgment, while reinforcing the importance of systematic use of validated risk scoring systems in prognostic evaluation. Future multicenter, prospective studies incorporating comprehensive multivariable analyses are needed to confirm these findings and to refine evidence-based recommendations for the surgical management of peptic ulcer perforation at the guideline level.

Disclosures

Ethics Committee Approval: The study was approved by the Board of Ethical Committee Members of Universiti Kebangsaan Malaysia (PPI/111/8/JEP-2022-100) and the Malaysia Ministry of Health Medical Research and Ethics Committee (MREC) (NMRR ID-22-00168-TWV) (Date is not provided).

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