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REVIEW

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Alternative treatments to treat perforated peptic ulcer: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Introduction Perforated peptic ulcers (PPU) represent a critical surgical emergency. Despite the historical predominance of open surgical repair, laparoscopic and endoscopic approaches have shown promise in reducing morbidity and hospital stay. This study aimed to conduct a network meta-analysis comparing open, laparoscopic, and endoscopic interventions for PPU repair.

Methods A systematic search of Medline (PubMed), Embase, Cochrane Library, Google Scholar, and the National Institute for Health and Clinical Excellence (NICE) databases identified randomized controlled trials (RCTs) comparing these approaches. The primary outcomes were 30-day mortality and morbidity.

Results Eight RCTs including 657 patients were analyzed. Endoscopic interventions were associated with fewer respiratory complications and shorter hospital stays, while the laparoscopic approach demonstrated fewer surgical site infections and less postoperative pain compared to open repair. Other outcomes demonstrated non-significant differences across interventions.

Conclusions Prompt resuscitation and surgical repair, either laparoscopic or open, remains the gold standard for PPU. Endoscopic techniques are viable alternatives for small perforations and in selected cases where general anesthesia is contraindicated.

Keywords Peptic ulcer, Perforated peptic ulcer, Peptic ulcer disease, Laparoscopy, Open surgery, Endoscopy

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Introduction

Peptic ulcer disease (PUD) is a prevalent condition with a reported incidence of 1.5–3%, affecting approximately 4 million individuals annually [1, 2]. While complications arise in 10–20% of PUD cases, perforation occurs in approximately 5%, with reported mortality rates ranging from 5 to 10% [1–4]. The mortality increases to 50% when patients present for treatment more than 24 h post-perforation [5–7]. Clinical presentation includes sudden epigastric pain, tachycardia, and abdominal rigidity, with diagnosis confirmed through imaging such as erect chest radiography or CT scans [6, 8, 9].

Historically, 80% of PPU cases have been managed with open surgical interventions [1, 6, 10–12]. However, laparoscopy has demonstrated superior outcomes in reduced pain, lower infection rates, and shorter hospital stays [1, 6, 10–12]. Recent advances in endoscopic methods further expand treatment options, particularly for small perforations and patients unsuitable for general anesthesia [1, 6, 10–12].

This network meta-analysis of randomized controlled trials (RCTs) evaluates the comparative effectiveness of these treatment modalities, addressing gaps in the existing literature and providing evidence for clinical decision-making.

Materials and methods

Study design and inclusion criteria

The study protocol was registered in the PROSPERO database (provisional registration number: 656470) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements checklist and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines [13, 14]. The literature search strategy and study selection criteria were outlined according to the PICOS framework. RCTs comparing open, laparoscopic, and endoscopic treatments for PPU in adult patients were included. Retrospective and observational studies, case reports, narrative and systematic reviews, and non-English articles were excluded. The primary study outcomes were the 30-day mortality and morbidity rates.

Literature search strategy

A systematic search was conducted from January 2004 to December 2023 in Medline (PubMed), Embase, Cochrane Library, Google Scholar, and NICE databases using MeSH terms and free-text keywords related to PPU and its treatment approaches, as follows: "*peptic ulcer disease*", "*perforated peptic ulcer*", "*duodenal ulcer*", "*omental patch*", and "*laparoscopic repair*".

Study selection, data extraction, and risk of bias assessment

Two independent researchers (PG and SDS) performed the literature search. The relevance of the records was assessed based on their titles and abstracts. Only those excluded by both reviewers were removed. The two reviewers then independently conducted a full-text analysis of the pre-selected articles. Any disagreements regarding study inclusion or exclusion were resolved through discussion. Both reviewers also independently evaluated the risk of bias using appropriate tools based on the study design. Lastly, the two independent researchers (PG and SDS) extracted data on study design, patient demographics, intervention details, and outcomes.

Statistical analysis

Pairwise meta-analysis assessed direct comparisons, while network meta-analysis evaluated relative effectiveness. The analyses were performed in R using the gemtc package [15, 16]. In the pairwise meta-analysis, a random-effects model (DerSimonian and Laird method) was applied to pool odds ratios (OR) for dichotomous outcomes and mean differences (MD) for continuous outcomes. When minimal heterogeneity was identified, a fixed-effect model was also considered to confirm consistency with the random-effects approach. In the network meta-analysis, a Bayesian hierarchical framework was employed in gemtc, assuming consistency and transitivity across the network. Markov chain Monte Carlo (MCMC) simulations were run using multiple chains to ensure convergence, which was monitored via the Gelman-Rubin statistic. The relative effectiveness of each treatment compared with every other treatment was then estimated, providing both point estimates and 95% credible intervals. A point estimate of $p < 0.05$ was considered statistically significant in all pairwise analyses. Following the standard meta-analytical approach, continuous outcomes were evaluated using MD, while dichotomous outcomes were assessed using OR. The I^2 test was used to evaluate heterogeneity, and cut-off values of 25%, 50%, and 75% were considered low, moderate, and high, respectively [17–19].

Results

Search results

The systematic search identified 1,545 records, of which eight RCTs comprising 657 patients met inclusion criteria and were considered for the updated pairwise and network meta-analysis [20–27] (Fig. 1). Thirty-two retrospective and six prospective studies were excluded (Supplementary Table 1). Of 657 included patients, 322 (49%) underwent laparoscopic repair, 272 (41.4%) underwent

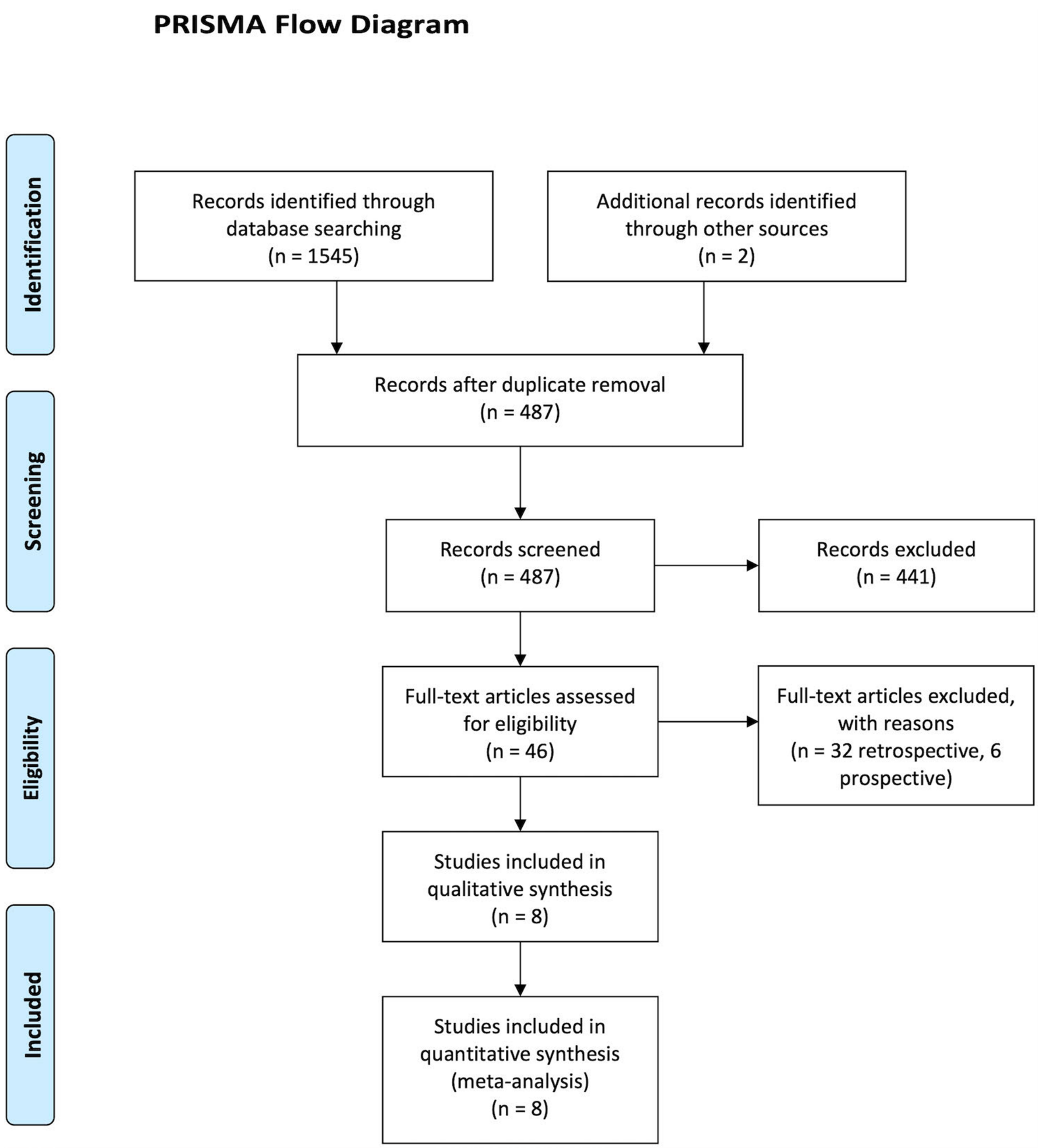

Fig. 1 Flow diagram of search strategy

open surgery, and 63 (9.6%) underwent endoscopic interventions (Table 1). The mean age ranged from 46 to 80 years old, with older patients predominantly in the endoscopic group. Male patients constituted 75.5% of the overall study population. The studies were conducted across Asia, Europe, and Africa.

Risk of bias assessment

Blinding of participants and outcome assessment were identified as limitations in all studies. However, allocation concealment and sequence generation were adequately described.

Statistically significant differences

There is evidence that significantly older patients were included in the endoscopic cohort but not in the laparoscopic or open cohorts. The network meta-analysis revealed that endoscopic interventions significantly reduced respiratory complications compared to laparoscopic and open approaches. Similarly, the mean length

Table 1 Characteristics of the included studies

Author (year)	Period	Country	Groups	N° patients	Gender (M/F)	Age	Site of perforation
Lau et al. [20]	1992–1994	China	Laparoscopy vs. Open	24–21[1]	20/4–17/4[1]	52.3 ± 13.8–51.1 ± 19.7[1]	Duodenum: 20–16[1] Juxtapyloric: 3–2[1] Gastric: 1—3 [1]
				24–24[2]	22/2–20/4 [2]	47.8 ± 17.5–44.9 ± 18.8[2]	Duodenum: 19–21 [2] Juxtapyloric: 4–2 [2] Gastric: 1—1 [2]
Siu et al. [21]	1994–1997	China	Laparoscopy vs. Open	63–58	53/10–45/13	53.8 ± 18.4–56.1 ± 19.0	Duodenum: 45–48 Pylorus: 2—4 Prepyloric: 15–6 Stomach: 1–0
Bertleff et al. [22]	1999–2005	Netherlands	Laparoscopy vs. Open	52–49	29/23–32/17	66 ± 25.8–59 ± 29.5	Pyloric: 8–12 Postpyloric: 20–14 Prepyloric: 19–22
Shah et al. [23]	2009–2011	India	Laparoscopy vs. Open	25–25	20/5–21/4	50.4 ± 18.6–51.2 ± 18.2	Duodenum: 16–13 Pylorus: 3–2 Prepyloric: 6–10
Zedan et al. [24]	2012–2014	Egypt	Laparoscopy vs. Open	21–24	14/7–18/6	40 ± 9.4–42 ± 13.4	Duodenum: 21—24
Ge et al. [25]	2010–2014	China	Laparoscopy vs. Open	58–61	49/9–54/7	46.4 ± 20.4–46.5 ± 18	Duodenal: 39–31 Gastric: 19–30
Arroyo Vázquez et al. [26]	2014–2018	Sweden	Endoscopy vs. Laparoscopy	13–15	6/7–7/8	80 ± 48–75 ± 68	Duodenum: 13–15
Negm et al. [27]	2019–2021	Egypt	Endoscopy vs. Surgery (40 laparoscopic and 10 open)	50–50	33/17–36/14	47 ± 9–36 ± 27	Duodenum: 29–35 Gastric: 21–15
Total	1992–2021			657 patients Laparoscopy: 322 (49%) Open: 272 (41.4%) Endoscopic: 63 (9.6%)	496 males (75.5%), 161 females (24.5%)	46–80	Duodenum: 439 (66.8%)

[1] Laparoscopic/open suture

[2] Laparoscopic/open sutureless (with gelatin sponge and fibrin glue)

of hospital stay was markedly shorter in the endoscopic cohort (Table 2).

Laparoscopic repair demonstrated superior outcomes in terms of surgical site infections, which occurred in only 2% of cases compared to the 8.5% observed in the open surgery group. Additionally, postoperative pain was significantly reduced in laparoscopic patients, with a mean pain score improvement of −1.21 (95% CI − 2.09 to − 0.33) compared to open surgery (Table 3).

Non-significant differences

There was evidence of non-significant differences in postoperative complications, operative time, abdominal abscesses, and repair-site leakage between the laparoscopic, open, and endoscopic procedures (Table 2). Furthermore, the pairwise meta-analysis demonstrated non-significant differences in mortality, reoperation rates, and time to oral diet between the laparoscopic and open approaches (Table 3).

Discussion

To the best of our knowledge, this study represents the first network meta-analysis of RCTs comparing laparoscopic, open, and endoscopic procedures for PPU treatment. The results reinforce the growing role of minimally invasive techniques in managing PPU. These findings align with recent trends favoring less invasive surgical approaches, reflecting the need to minimize postoperative morbidity and enhance patient recovery.

While open surgery has been the most widely used approach due to its historical precedence and reliability, minimally invasive techniques are increasingly favored for their potentially superior outcomes. A previous pairwise meta-analysis, including retrospective, prospective cohort studies and RCTs, compared laparoscopic and open approaches and reported shorter hospital stay, lower risks of mortality, wound infections, septic shock, and renal failure, as well as a higher risk of suture leakage and longer operative time for laparoscopy [28]. Risk

Table 2 Outcomes of interest: network meta-analysis of laparoscopic vs open vs endoscopic

Age		
Laparoscopic	−0.246 (−4.704, 3.842)	**10.500 (0.017, 20.941)**
	Open	**10.783 (1.138, 20.414)**
		Endoscopic
Operative Time		
Laparoscopic	−18.866 (−44.670, 4.699)	−49.299 (−103.015, 2.835)
	Open	−30.367 (−76.158, 16.643)
		Endoscopic
Postoperative Complications		
Laparoscopic	1.484 (0.488, 4.063)	0.713 (0.111, 4.765)
	Open	0.474 (0.114, 2.384)
		Endoscopic
Repair-site Leakage		
Laparoscopic	0.214 (0.019, 1.558)	0.046 (0.001, 1.162)
	Open	0.222 (0.010, 2.980)
		Endoscopic
Pneumonia		
Laparoscopic	2.004 (0.232, 14.455)	**0.000 (0.000, 0.064)**
	Open	**0.000 (0.000, 0.032)**
		Endoscopic
Abdominal Abscess		
Laparoscopic	0.746 (0.072, 6.251)	0.267 (0.005, 9.996)
	Open	0.374 (0.013, 7.139)
		Endoscopic
Length of Hospital Stay		
Laparoscopic	0.755 (−1.217, 2.746)	**−5.246 (−9.523, −1.164)**
	Open	**−6.003 (−9.807, −2.392)**
		Endoscopic

Comparison of the included interventions: mean difference or odds ratio (95% CrI). Each cell gives the effect of the column-defining intervention relative to the row-defining intervention. Statistically significant results are highlighted in bold

Table 3 Outcomes of interest: pairwise meta-analysis of laparoscopic vs open

Outcomes of interest	**Number of studies and patients (%; events/total)**	**Statistical method, estimated effect, 95% CI**	***p*-value**	**I^2 (%)**
Return to diet	5, 378	MD = −0.50 (−1.35,0.35) (RE)	0.25	66
Postoperative pain	6, 479	MD = −1.21 (−2.09,—0.33) (RE)	**0.007**	94
Reoperations	4, 333 (4; 7/169 vs. 2; 3/164)	OR = 1.93 (0.57, 6.50) (FE)	0.08	43
Surgical Site Infections	6, 479 (2; 5/242 vs. 8.5; 20/237)	OR = 0.28 (0.11, 0.74) (FE)	**0.01**	0
Mortality	5, 434 (3; 6/221 vs. 4; 9/213)	OR = 0.60 (0.20, 1.78) (RE)	0.08	28

MD mean difference; *OR* Odds ratio; *FE* fixed-effects model; *RE* random-effects; *p*-values highlighted in bold favor laparoscopy

factors significantly influencing PPU prognosis encompass patient-related factors (e.g., age, gender, comorbidities, steroid/NSAID use, delayed presentation), disease-related factors (e.g., perforation size, shock at presentation, elevated urea/creatinine, gastric vs. duodenal location, underlying malignancy, anemia/hypoalbuminemia), and treatment-related factors (e.g., blood transfusion, gastric resection, complications, parenteral nutrition, intensive care unit admission) (Table 4) [6].

PPU management typically involves three primary approaches: laparoscopic or open surgery, endoscopic

Table 4 Risk factors determinants of the prognosis of the perforated peptic ulcer

Risk factors Determinants the Prognosis of patients with PPU		
Patient factors	Disease factors	Treatment factors
Age	Size of perforation	Blood transfusion
Gender	Shock at presentation	Complications
Comorbidities	Elevated urea and creatinine	Need for gastric resection
Use of steroids and/or NSAIDs	Gastric vs duodenal location	Parenteral nutrition
Delay in presentation	Underlying malignancy	Intensive care unit
	Anaemia	
	Hypoalbuminemia	

Duodenal Perforation		
Contained Perforation	**Non-Contained Perforation**	
Stable patient Gastroduodenogram to prove self-sealing	Minor Perforation <2cm	Major perforation >2cm
Conservative treatment	Surgical treatment	Surgical treatment
NG tube IV Fluids IV Antibiotics NPO High Dependency Unit Monitoring H Pylori eradication treatment	1. Primary closure by interrupted sutures 2. Primary closure by interrupted sutures covered with pedicled omentoplasty 3. Cellan-Jones repair: plugging the perforation with pedicled omentoplasty 4. Graham patch: plugging the perforation with free omental patch	Pyloric exclusion and formation of a gastrojejunostomy Duodeno-duodenostomy Roux-en -Y duodenojejunostomy Antrectomy and gastrojejunostomy Pancreatoduodenectomy Tube duodenostomy
NG: nasogastric tube NPO: nothing per os	Endoscopic options	Endoscopic option
	Perforation size<1cm TTSC Perforation size 1-3cm OTSC endoloop with clips or SEMS	SEMS
		SEMS: self-expandable metal clips TTSC: through-the scope clips OTSC: over-the scope clips

Scheme 1 Algorithm of treatment management of perforated peptic ulcer

intervention, and conservative management (Scheme 1). Conservative management, predicated on gastroduodenogram confirmation of self-sealing perforation, has been reported to be effective in 50–70% of cases [29]. Endoscopic procedures are generally recommended for patients presenting early, typically within 24 h of perforation, when inflammatory changes are less pronounced [30]. Non-contained PPU necessitates surgical intervention (laparoscopic or open) or endoscopic treatment based on factors such as perforation location, size, surrounding tissue quality, and underlying etiology (Scheme 1) [31]. Factors such as age > 60 years, delayed intervention (> 24 h), hemodynamic instability (systolic blood pressure < 100 mmHg), and significant comorbidities are established predictors of increased morbidity and mortality, potentially doubling the mortality rate [32, 33]. Based on these known risk factors, Boey's score has emerged as a valuable prognostic tool, aiding in risk stratification and clinical decision-making [5, 34]. The morbidity and mortality rates escalated sharply with higher Boey's scores. For instance, patients with a Boey 0 score experienced a morbidity rate of 17.4% and mortality of 1.5%, while those with a Boey 3 score faced a 100% mortality rate (Table 5). This underscores the value of Boey's score in guiding treatment decisions and predicting outcomes.

This meta-analysis underscores the shifting paradigm in PPU management with most patients treated by laparoscopy. Our analysis included only RCTs with a final cohort of 657 patients, of which 75.5% were male (Table 1). No significant age difference was observed between the laparoscopic and open groups. However, the NMA demonstrated a significant age difference, with older patients predominantly included in the endoscopic cohort compared to both laparoscopic and open cohorts (Table 2). This finding suggests potential selection bias, as elderly patients with comorbidities and contraindications to general anesthesia may have been preferentially selected for less invasive endoscopic procedures. This potential bias may also explain the significantly lower incidence of pneumonia observed in the endoscopic group compared to laparoscopic and open groups. Further investigation of how patient age and comorbidity profiles influence intervention choice could help refine selection criteria and improve outcomes in this demographic. In addition, most studies included patients with a Boey score of 0–2, indicating varying levels of risk but generally excluding those in critical condition.

Table 5 Boey's Score related to morbidity and mortality

Boey score	Morbidity rate	Mortality rate
Boey 0	17.4%	1.5%
Boey1	30.1%	14.4%
Boey 2	42.1%	32.1%
Boey 3		100%

Endoscopic interventions, although less commonly employed, showed unique advantages for selected patient populations. Patients in the endoscopic group, who were predominantly older and had more comorbidities, experienced fewer respiratory complications and significantly shorter hospital stays. These results suggest that endoscopic approaches may be particularly beneficial for high-risk patients who are contraindicated for general anesthesia. However, the limited availability of skilled endoscopists and the requirement for advanced equipment may restrict its wider adoption. The reduction in surgical site infections and postoperative pain observed with laparoscopic repair aligns with findings from prior studies, which have also demonstrated the feasibility and safety of laparoscopic techniques for PPU repair. Interestingly, mortality rates, postoperative complications, repair site leakage, abdominal abscesses, and reoperation rates were not significantly different across the treatment modalities, underscoring the importance of individualized patient management. Factors such as the surgeon's expertise, the size and location of the perforation, and the patient's overall health status are critical in determining the most appropriate intervention. Additional work clarifying how these factors interact may further optimize surgical decision-making and standardize the care provided to PPU patients.

However, several limitations warrant a cautious interpretation of our findings. These include relatively small sample size, lack of blinding for both participants and outcome assessors, the inherent urgency of surgical interventions, and the potential influence of younger surgeon experience and learning curves on outcomes. Furthermore, the limited sample size of the endoscopic cohort introduces some uncertainty in these findings. Significant heterogeneity was observed in postoperative complications, pain, operative time, and length of hospital stay. In addition, no study reported data on retroperitoneal perforations, which were inconsistently excluded in the reviewed studies. The studies exhibited heterogeneity in the inclusion criteria, particularly concerning the size and location of the perforation. Finally, the lack of long-term outcome data represents a significant limitation of this study. None of the included studies systematically reported long-term outcomes, such as recurrence rates or patient-reported quality of life, which limits the generalizability of findings. Variability in surgical expertise and institutional practices likely contributed to the differences in outcomes. Lastly, sensitivity analysis based on different PPU locations, sizes, and symptoms onset was not possible because data were not separately available in the majority of the included RCTs. Addressing these limitations in future research will be essential for establishing a more robust evidence base, ultimately guiding more nuanced clinical decisions for PPU patients in diverse contexts.

Implications for research

Given the global prevalence of PUD and the increasing elderly population in both developed and developing nations, optimizing emergency care is crucial for mitigating the burden of PPU. This necessitates international collaboration to conduct robust trials investigating various aspects of the disease [35].

Firstly, further research is needed to define precise selection criteria for conservative management, differentiating between healthy and frail patient cohorts. Moreover, establishing standardized criteria for disease severity will facilitate the development of tailored management strategies and improve treatment outcomes.

Future RCTs should rigorously compare laparoscopic and open approaches, utilizing robust endpoints such as morbidity and mortality. Furthermore, future studies should focus on identifying risk factors for less common but potentially serious complications, such as reoperation and intra-abdominal abscesses.

Concerning operative variables, further investigation is warranted to determine the optimal use of omental patches and to establish evidence-based guidelines for antibiotic and antifungal prophylaxis.

Lastly, studies reporting long-term outcomes, particularly in younger populations, are urgently required to better analyze recurrence rates and patient-reported quality-of-life measures [35].

Conclusions

Minimally invasive techniques, including laparoscopic and endoscopic interventions, represent viable alternatives to open surgery for PPU. While laparoscopic repair offers distinct advantages in reducing surgical site infections and postoperative pain, endoscopic approaches may be particularly beneficial for high-risk patients. Individualized treatment plans considering patient characteristics and perforation features are crucial to optimizing outcomes and reducing the burden of PPU. Randomized trials with larger sample sizes and multicenter collaborations are essential to validate the findings of this analysis and provide further robust evidence for clinical guidelines.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13017-025-00599-2.

Supplementary file 1

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None to declare.

Author contributions
All authors made substantial contributions to the conception of the work, the acquisition, analysis, and interpretation of data, drafted the work and revised it critically for important intellectual content, approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability
Datasets analyzed during the current study are available upon reasonable request to the authors.

Declarations

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Informed consent
Not applicable.

Competing interests
The authors declare no competing interests.

Institutional review board approval
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