AGA Clinical Practice Guideline on *Management of Local Complications of Acute Pancreatitis*

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ABSTRACT

Background & Aims

Local complications of acute pancreatitis represent a heterogeneous group of problems that develop from the tissue necrosis and marked inflammation of the pancreas and surrounding structures. They lead to a range of peri-pancreatic and systemic manifestations. The American Gastroenterological Association developed this Guideline to provide evidence-based recommendations for the management of select local complications.

Methods

The American Gastroenterological Association (AGA) convened a multidisciplinary panel to develop clinical practice recommendations for adults with local complications of acute pancreatitis. Systematic reviews were performed for seven prioritized clinical questions. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to prioritize clinical outcomes and assess evidence, and GRADE's Evidence-to-Decision Framework was used to develop recommendations.

Results

The Panel reviewed the evidence and agreed on 7 recommendations. Conditional recommendations were issued for delayed over immediate drainage, minimally invasive surgical step-up over open surgical techniques, and endoscopic transluminal over minimally invasive surgical step-up approaches for patients with suspected infection of pancreatic and/or peripancreatic collections. A conditional recommendation was made for the use of either double pigtail plastic or lumen-apposing metal stents for endoscopic drainage. The panel made a conditional recommendation for the use of either an upfront or on-demand endoscopic necrosectomy. In patients with disconnected pancreatic duct who require drainage, the AGA suggested placing transluminal double-pigtail stents over no stents after the initial stent has been removed. A conditional recommendation was made to anticoagulate splanchnic vein

thrombosis following acute pancreatitis based on very low certainty data. An expert implementation remark noted that isolated splenic vein thrombosis are not routinely anticoagulated.

Conclusions

This document provides recommendations for commonly seen local complications in acute pancreatitis. Providers should engage in multi-disciplinary shared decision making based on patient preferences. Limitations and gaps in the evidence are highlighted to guide future research opportunities.

Key Words: Pancreatitis; Drainage; Pancreatic Pseudocyst; Walled off necrosis; Thrombosis; Anticoagulation; Necrosectomy; Debridement.

EXECUTIVE SUMMARY

Description of the Health Problem

Acute pancreatitis is an inflammatory condition defined by the combination of acute abdominal pain, significantly elevated amylase or lipase, and/or supportive imaging findings. Local complications result from tissue injury secondary to unregulated spillage of pancreatic enzymes and other mechanism(s). The ensuing inflammatory reaction involves the pancreatic parenchyma, surrounding fat, and vascular structures as well as provoking a systemic inflammatory response.[1] Local complications, including infected or suspected infected pancreatic and peri-pancreatic fluid or necrotic collections, may result in symptoms of abdominal pain, vomiting, fever, failure to thrive, and ultimately clinical deterioration. Untreated patients may develop sepsis and have a morbid course with substantial health care costs and compromised quality of life. A significant proportion of patients develop local complications; while many resolve with conservative management, some symptomatic necrotic collections require interventions. In the past 25 years, there has been a paradigm shift from open surgical approaches to endoscopic, percutaneous, and minimally invasive operative techniques. Furthermore, the decision to treat splanchnic vein thrombosis continues to challenge clinicians.[2]

Aims and Objectives of the Guideline

The purpose of these guidelines is to provide evidence-based recommendations for the management of local complications of acute pancreatitis based on a comprehensive assessment of the literature and a thorough and robust analysis of available data.

The primary objectives are to identify management strategies which reduce mortality, new onset organ failure, intra-abdominal bleeding and fistula (pancreatic or entero-cutaneous), and the need for repeat interventions. Secondary objectives are to define optimal approaches that minimize length of stay and mitigate delayed sequelae including exocrine pancreatic insufficiency, diabetes mellitus, and incisional hernias.

Target Audience

While the Guideline Panel is aware that this guideline will be read by a wide audience, including policymakers and industry, that is not the guideline's intended primary audience. This guideline, like all AGA guidelines, is primarily targeted towards healthcare professionals in the fields of gastroenterology and primary care who depend on our expert, evidence-based recommendations to inform their clinical practice and shared decision-making with patients. Rather than represent a specific standard to adhere to, we intend these recommendations to be used by clinicians to guide their patient management decisions and to inform considerations of benefits and harms of treatments in each individual case. If used in this way, this guideline's recommendations will contribute to improved, personalized health care for all gastroenterology patients.

Recommendations

The summary of Guideline recommendations is provided in Table 1. This guideline should be read in conjunction with the Supplementary Materials, which contains additional tables, figures, and supporting text. Clinicians may find the Clinical Decision Support Tool (CDST), Figure 1 and the Guideline Spotlight helpful instruments to inform patient management.

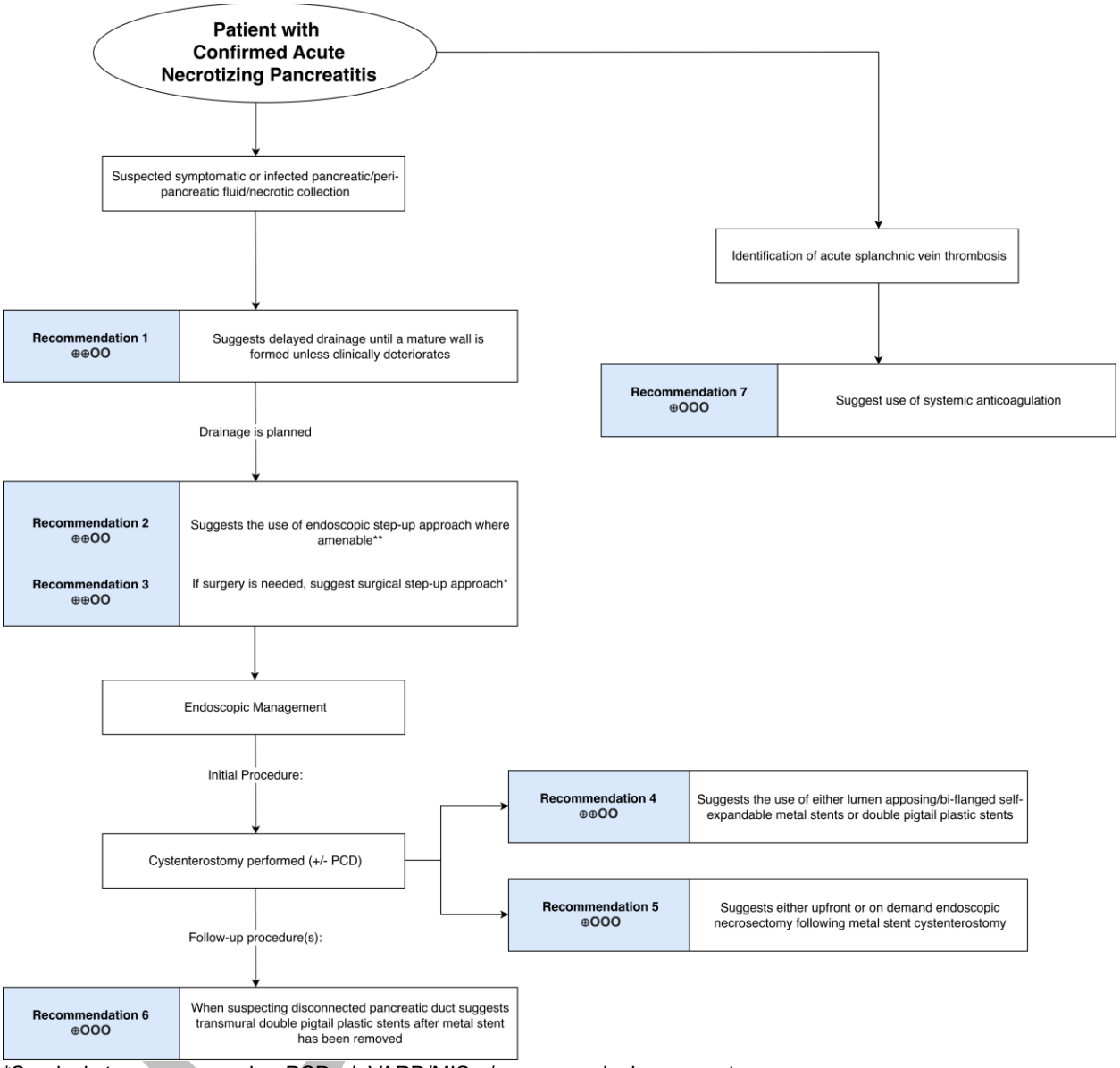
123 **Table 1: Guideline Recommendations and Implementation Considerations**

	RECOMMENDATION	STRENGTH	COE
1	**In individuals with suspected infection of pancreatic and/or peripancreatic collections in the early phase of acute pancreatitis, the AGA suggests delayed drainage over immediate drainage.** *Implementation Considerations:* • *Delayed drainage allows time to assess efficacy of antibiotics, nutrition, and other best-practice conservative measures, may obviate the need for drainage, and also allows time for encapsulation of the collection.* • *Drainage may be performed through an endoscopic and/or percutaneous approach.* • *Local expertise, location of collections, clinical condition of the patient, and degree of encapsulation of the collection should guide the approach.*	Conditional	Low
2	**In individuals with suspected infection of pancreatic and/or peripancreatic collections, the AGA suggests minimally invasive step-up approach over open surgical necrosectomy for management.** *Implementation Considerations:* • *Minimally invasive step-up approach involves initial drainage by endoscopic and/or percutaneous route followed by repeated drainage procedure and necrosectomy if there is no improvement.* • *If minimally invasive step-up approach is unsuccessful or not feasible, open surgical necrosectomy may be implemented*	Conditional	Low
3	**In individuals with suspected infected or symptomatic pancreatic and/or peripancreatic collections, amenable to endoscopic drainage who require intervention, the AGA suggests the use of endoscopic transluminal approach over minimally invasive surgical step-up approach as the initial interventional strategy.**	Conditional	Low

	RECOMMENDATION	STRENGTH	COE
	Implementation Considerations: • *If the collection is not adjacent to the stomach and duodenum and is located in the deep retroperitoneum or pelvis, a minimally invasive surgical step-up approach may be required instead of/or combined with endoscopic transluminal approach.*		
4	**In individuals with suspected infected or symptomatic pancreatic and/or peripancreatic collections who are undergoing endoscopic transluminal drainage, the AGA suggests the use of either lumen-apposing metal stents or double pigtail plastic stents.** *Implementation Considerations:* • *When a lumen-apposed metal stent is used, expert panel practice includes removal within 4 weeks from placement (but after a stable tract has been formed), when feasible, to reduce risk of stent-related complications particularly bleeding.*	Conditional	Low
5	**In individuals undergoing endoscopic transluminal drainage for suspected infected or symptomatic pancreatic and/or peripancreatic collections, the AGA suggests either upfront or on-demand endoscopic necrosectomy.** *Implementation Considerations:* • *Safe upfront necrosectomy generally requires a lumen-apposing or bi-flanged self-expandable metal stent to maintain the tract and reduce the risk of separation of the gastrointestinal lumen from the collection* • *Upfront necrosectomy requires a stable patient who can tolerate a longer procedure.* • *May favor upfront necrosectomy if the lumen apposing metal stent has concern for immediate occlusion from necrosis or very large collections with solid necrotic burden.*	Conditional	Very Low

	RECOMMENDATION	STRENGTH	COE
6	**In individuals who underwent endoscopic transluminal drainage of walled off necrosis/pancreatic fluid collection with suspected disconnected pancreatic duct, the AGA suggests placing transluminal double pigtail plastic stents over no stent after the initial metal stent has been removed.** *Implementation Considerations:* • *There may be instances when the cavity completely collapses and the replacement of plastic stents is not anatomically feasible.*	Conditional	Very Low
7	**In individuals with acute splanchnic vein thrombosis following acute pancreatitis, the AGA suggests anticoagulation over no anticoagulation.** *Implementation Considerations:* • *Patients and providers may choose against anti-coagulation if bleeding risk is high or if bleeding risk is prioritized over potential benefit* • *Expert panel practice is to generally anticoagulate for superior mesenteric vein and portal vein thrombosis and not routinely for isolated splenic vein thrombosis*	Conditional	Very Low

Figure 1: Clinical Decision Support Tool



*Surgical step-up approach = PCD +/- VARD/MIS +/- open surgical necrosectomy

**Endoscopic step-up approach = endoscopic cystenterostomy (+/- PCD) +/- DEN

Certainty of Evidence Legend:

High (⊕⊕⊕⊕): Very confident that the true effect lies close to the estimate of the effect.

Moderate (⊕⊕⊕O): Moderately confident; the true effect is likely close to the estimate but may be substantially different.

Low (⊕⊕OO): Limited confidence; the true effect may be substantially different from the estimate.

Very Low (⊕OOO): Very little confidence; the true effect is likely to be substantially different from the estimate.

Abbreviations: DEN, direct endoscopic necrosectomy; MIS, minimally invasive surgery; PCD, percutaneous catheter drainage; VARD, video-assisted retroperitoneal debridement.

1. GUIDELINE DEVELOPMENT PROCEDURES

1.1 Overview

This document represents the official recommendations of the AGA. It was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. and adheres to best practices in guideline development as outlined by the National Academy of Medicine (formerly Institute of Medicine), using a process outlined previously.[3]

1.2 Organization and Panel Composition

The Guideline Panel was comprised of eight members (Supplemental Table 1); all selected based on their specific expertise. There were six clinical content experts with clinical and/or research expertise in the clinical topic, and two methodologists with specialized GRADE guideline development skills. A librarian assisted the Panel members with designing and executing the required literature searches. All Panel members participated in evidence review and the Senior Methodologist oversaw data synthesis and analysis. All members of the Guideline Panel then reviewed the results of the analysis, contributed to consensus development, and constructed the final recommendations.

1.3 Conflict of Interest

Each nominee to this Guideline Panel underwent a vetting process that required them to report all commercially funded and other relevant activities within the previous 24 months. All reported financial or intellectual conflicts were reviewed by the Chair of the AGA Institute Clinical Guidelines Committee (CGC) and adjudicated against rules and criteria in the CGC COI Policy. Only nominees whose COI status complied with this policy were appointed as Guideline Panel members. (Supplemental Table 2.)

1.4 Guideline Funding

AGA provided all financial support for the development of this guideline. No funding from industry was offered or accepted to support the writing effort.

1.5 Document Review

(To be added prior to publication)

1.6 Guideline Updates

Guidelines should be "living" products. To remain useful, they need to be updated as new information accumulates. This document will be updated when major new research is published. The need for an update will be determined by the Guideline Panel members and the CGC.

2. METHODS

2.1 Scope

Acute pancreatitis results in >300,000 hospitalizations and >5,000 deaths in the United States alone, with a cost exceeding $5 billion annually.[4-6] Most morbidity is attributable to local complications, which include fluid collections with variable levels of necrosis, disconnected pancreatic duct, and vascular complications. Clinical manifestations include abdominal pain, symptoms of gastric or biliary obstruction, and sepsis. Furthermore, the long-term sequelae of acute pancreatitis, including development of endocrine and exocrine pancreatic insufficiency, and progression to chronic pancreatitis, are strongly correlated with local complications, especially necrosis.[7-9] Drainage with or without necrosectomy is the primary management of symptomatic infected or suspected infected fluid collections that do not respond to medical therapy. Adverse events following interventions such as fistulae, bleeding, and hernias are additional sources of morbidity. Treatment modalities including endoscopic, percutaneous, and minimally invasive surgical approaches have been developed to manage local complications and reduce treatment-related adverse events. Additionally, splanchnic vein thrombosis is a relatively common complication and the decision to anticoagulate is a frequent conundrum among clinicians. In the context of the compelling societal burden and dynamic treatment landscape, the Guidelines Panel focused its systematic review and research questions on the evidence-based management of local complications of acute pancreatitis.

2.2 Formulation of Clinical Questions

The clinical research questions which underpin this guideline were developed by the Guideline Panel, with methodologists and clinical content experts working together to develop specific questions which address current knowledge gaps in this area. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome(s) for each clinical question. (Supplemental Table 3)

The panel selected desirable and undesirable patient-important outcomes (benefits and harms). A patient representative provided feedback on selected outcomes, priorities, balance between desirable and undesirable outcomes and, where applicable, how patients' values and

preferences may affect the strength of recommendations. Critical and important outcomes for decision-making for all the interventions included in this review are summarized in the evidence profiles (see section 2.5).

Several additional clinical complications were considered for PICO questions, such as pancreatico-colonic fistula formation and hemorrhage, but given their comparatively low incidence, were not prioritized by the panel for inclusion in the Guideline and a systematic review was not performed. In the context of pancreatic fluid collections, the Guideline development panel gave priority to comparison of traditional versus minimally invasive step-up approaches and timing of intervention. Given increased recognition of disconnected pancreatic duct syndrome as a frequent cause for recurrent pancreatic fluid collection, its management was also addressed by the Guideline. While indirectly related to fluid collections, the complication of acute splanchnic vein thrombosis was selected as an important topic due to wide variation in clinical practice regarding the therapeutic role of anticoagulation. While comparisons of peroral endoscopic transluminal versus minimally invasive surgical as well as metal versus plastic stents were performed, comparison of different types of stents and other devices was out of the scope of this review. Additionally, the question of up-front necrosectomy during index procedure versus sequential treatment was systematically evaluated, but specific technical approaches for necrosectomy could not be evaluated. Lastly, supportive care is recognized as fundamental management of acute pancreatitis; this Guideline does not directly address fluid resuscitation, antibiotic or nutritional support strategies, which have been comprehensively addressed in [10]

2.3 Search Strategy

The systematic review process was guided by a search protocol developed *a priori* by the Guideline Panel members in collaboration with a medical librarian. The librarian conducted a comprehensive search of the following databases: Embase (via Elsevier), Medline (via Ovid), Cochrane CENTRAL (via Wiley), and Web of Science (SCI-Expanded, SSCI, AHCI, CPCI-Science, BCI-Science, ESCI, CCR, and IC from inception to March 2026 using a combination of controlled vocabulary terms supplemented with keywords. The search was limited to English language and human adults. The final strategy is available in Supplemental Table 4. The bibliography and included references of prior guidelines on this topic were searched to identify

relevant studies that may have been missed. Additionally, content experts helped identify any ongoing studies with results expected soon.

2.4 Study Selection, Data Collection, and Analysis

The inclusion and exclusion criteria were based on the clinical research questions developed by the Guideline Panel. Searches from all databases were combined in Rayyan bibliographic software. The Guideline Panel sought to identify randomized controlled trials; however, when these were not available or were sparse, observational studies were also considered, giving preference to observational studies with control arms over single arm studies. A consensus was reached on study inclusion (Supplemental Figure 1, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram). Any disagreements were resolved with adjudication by the Guideline Panel Chair and Senior Methodologist. Data were extracted from each study, including study characteristics such as year of publication, study site, study population, intervention, comparison group, outcomes, and methods for risk-of bias assessment.

Meta-analyses were conducted when more than one study contributed data for the same intervention and outcome. Dichotomous outcomes were combined to obtain a relative risk (RR) and 95% CI. For the meta-analyses, the generic inverse-variance method of weighting was used and the random-effects model applied. However, if three or fewer studies were available, a fixed-effects model was used due to the instability of between-study variance. The Guideline Panel assessed the statistical heterogeneity using the I^2 index. The Panel used meta-analysis software for the comparative studies: https://oaltayar.shinyapps.io/ma_meta_app/. We used the Cochrane Risk-of-Bias tool to assess the risk of bias in the included studies incorporated in RevMan. This tool assesses the risk of bias in the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Robvis tool was used to create plots.[11] (Supplemental Figures 6 to 44)

2.5 Certainty of the Evidence

The Guideline Panel used the GRADE approach to assess the certainty of evidence for the effect of the intervention on each outcome using the GradePro Guideline Development Tool software (https://gradepro.org). The GRADE approach considers factors such as study design, population studied, risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias to rate the certainty of evidence as high, moderate, low, or very low (Table 2 - Interpretation of the Certainty of Effects Using the GRADE Framework). The results of certainty assessment are reported in evidence profiles available in **Supplemental Tables 8, 12, 16, 20, 24, 28, and 32** for all the interventions included in this review.

Table 2: Interpretation of the Certainty of Effects Using the GRADE Framework

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

2.6 Development of Recommendations

The process of translation of evidence into guideline recommendations followed the GRADE Evidence to Decision framework and was achieved by means of discussion during virtual meetings of the Guideline Panel. The Evidence to Decision framework considers the certainty of evidence, balance of benefits and harms, patient values and preferences, feasibility, acceptability, equity, and resource use. Evidence to Decision tables are presented in Supplemental Tables 9, 13, 17, 21, 25, 29, and 33. Group consensus was reached for all the recommendations.

The interpretation of strength of recommendations is summarized in Table 3. The certainty of evidence and the strength of recommendation are provided for each clinical question. As per GRADE methodology, recommendations are labeled as “strong” or “conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. In situations when the recommendation is only supported with very low certainty for the benefits and very low certainty for the harm outcomes, the guideline panel placed a higher value on risk avoidance. Additionally, a search for studies on health equity and disparities was performed and if any identified references were found, they were reviewed and utilized in the evidence to decision framework process. For this guideline, no direct comparative data pertinent to the specific PICOs was found.

Table 3: **Interpretation of strong and conditional recommendations using the GRADE framework**

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with his or her values and preferences. Use shared-decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

3. RECOMMENDATIONS

3.1 Should delayed versus immediate drainage management strategy be used for suspected infection of pancreatic/peri-pancreatic collections in the early phase of acute pancreatitis?

Recommendation 1. In individuals with suspected infection of pancreatic and/or peripancreatic collections in the early phase of acute pancreatitis, the AGA suggests delayed drainage over immediate drainage. *(conditional recommendation, low certainty of evidence)*

Implementation Considerations:

- Delayed drainage allows time to assess efficacy of antibiotics, nutrition, and other best-practice conservative measures, may obviate the need for drainage, and also allows time for encapsulation of the collection.
- Drainage may be performed through an endoscopic and/or percutaneous approach.
- Local expertise, location of collections, clinical condition of the patient, and degree of encapsulation of the collection should guide the approach.

3.1.1 Summary of the Evidence

Evidence informing the recommendation for the timing of drainage for suspected infected pancreatic or peri-pancreatic necrotic/fluid collections was derived from one RCT.[12] Boxhoorn et al randomized a total of 104 participants to immediate versus postponed intervention with outcomes determined through 6 months of follow-up.[12] The study defined infected necrosis as air within the necrosis on imaging or positive Gram stain or culture from FNA within the first 14 days after onset of acute pancreatitis. After the first 14 days, persistent organ failure or fever (>38.5 degrees Celsius) and elevated CRP/leukocyte counts for 3 consecutive days was used to diagnose infection. Most participants were diagnosed based on gas findings on imaging or clinical suspicion of infected necrosis. Antibiotics were given to patients in both groups. Immediate drainage was defined as within 24 hours from randomization and postponed intervention was defined as waiting for necrotic collections to be largely/fully encapsulated or if

already encapsulated, draining it following clinical deterioration or lack of improvement. The median time to drainage after onset of symptoms in the immediate and postponed drainage groups was 24 days (interquartile range, 20 to 30) and 29 days (interquartile range, 24 to 40), respectively. (Supplementary Table 6).

3.1.2 Benefits and Harms

The critical outcomes for this question were mortality and new-onset organ failure. Both mortality and new onset organ failure favored delayed drainage (12.7% vs 10.2%, RR 1.25, 95% CI 0.42-3.68; 25.5% vs 22.4%, RR 1.13, 95% CI 0.57-2.26, respectively) in this trial. Other secondary outcomes assessed were perforation or enterocutaneous fistula, bleeding, and need for at least one procedure. Delayed drainage was associated with less perforation (or enterocutaneous fistula) (9.1 vs 8.2%, RR 1.11, 95% CI 0.32 – 3.91), but with more bleeding that required an intervention (14.5% vs 20.4%, RR 0.71, 95% CI 0.71-1.66).

Thus, an immediate drainage strategy may lead to 380 more per 1000 patients receiving a drainage procedure compared to delayed drainage (Supplementary Table 8).

3.1.3 Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was low (Supplemental Tables 8 and 9). Results were very uncertain for mortality due to extremely serious imprecision. Thus, the other critical outcome, new onset organ failure, along with important benefits and harms, guided decision making. For these outcomes, we also downgraded for very serious imprecision related to the low event rate, crossing the *priori* minimal important difference (MID) threshold of 5%, wide confidence intervals and concern for optimal information size. No serious risk of bias was found.

3.1.4 Discussion

Results from a single RCT suggest it may be preferable to delay drainage of a suspected infected pancreatic fluid collection based on the balance of potential benefits and harms.[12] Perhaps the largest benefit is the potential avoidance of a drainage procedure. However, the clinical decision making at an individual patient level is complex and requires careful consideration.

The question of early versus delayed drainage assumes significance in patients who are not improving or worsening with medical treatment in the first weeks of illness. Invasive intervention is generally not technically feasible (or indicated) in the first two weeks of acute pancreatitis because of largely solid and heterogeneous (peri) pancreatic necrosis and ill-defined collections. However, as the disease progresses into the third and fourth weeks of illness, the collections start maturing. It is during this period that the issue of drainage might arise if there is persistent fever and rising leukocyte count, which suggests that even though the initial sterile inflammation is perhaps resolving, the secondary infection of the fluid collections is evolving, necessitating escalation of therapy. In patients not responding to nutritional support and broad-spectrum antibiotics, drainage of the collection(s) may be required. The choice and efficacy of any drainage procedure is determined by three important variables: 1. degree of encapsulation, 2. timing and 3. location of the collection (i.e. proximity to the gastroduodenal wall). The timing and encapsulation are related, but there is heterogeneity in the time course between patients. A recent observational study showed the degree of encapsulation is more important than the time elapsed after the onset of AP in terms of successful drainage, complications, and mortality.[13] The limitation with early drainage in patients who lack an even partially encapsulated necrotic collection is that the drainage is often ineffective.

For patients who do not respond to maximal supportive therapy, nutritional supplementation, and combination antibiotics, the decision to drain early or later should be individualized depending on the clinical course and the factors mentioned above. If pursued, early drainage should only be performed in tertiary care centers with adequate expertise and back-up. Collections located adjacent to the gastroduodenal wall are amenable to endoscopic

transluminal drainage while those difficult to reach from the gastrointestinal lumen are best treated with percutaneous drainage. The relative solid content within the collection might also determine the approach of initial drainage and subsequent stepping-up of therapy to necrosectomy, if required.

The panel excluded two studies by Ke et al published in 2021 and 2025, because they did not meet PICO inclusion criteria.[14, 15] Specifically, the trials included participants with acute pancreatitis and organ failure. While related, the panel did not consider organ failure and necrosis to be synonymous. In the more recent trial, 120 participants with acute necrotizing pancreatitis and early persistent or worsening organ failure were randomized to receive either early percutaneous catheter drainage or standard care. The primary composite outcome of major complications or death during the index admission did not differ between the groups (33.3% in the early intervention group and 36.8% in the standard care group (risk difference [RD], − 3.5%; 95% CI, − 20.6% to 13.6%; P = 0.69).[15] Observational data from a meta-analysis including 855 patients (320 early drainage and 535 delayed drainage) also supported delayed drainage; the complication rates (rate ratio 1.06, 95% CI 0.79-1.42; P=0.69) and need for necrosectomy (OR 2.15, 95% CI 0.86-5.35; P=0.09;) were similar in both groups. Mortality was slightly higher in the early drainage group (OR 1.94, 95%CI 1.05-3.59; P=0.03). [16]

Moreover, a major benefit of delayed drainage is the potential avoidance of a drainage procedure (and, therefore, any intervention-related complications). In the Boxhoorn et al trial, 39% in the delayed drainage group were treated medically with antibiotics and did not require drainage. Longer-term follow-up from this trial (median 51 months) demonstrated similar rates of mortality and major complications but with significantly fewer number of interventions in the delayed drainage group (median 4 vs. 1 intervention, P = 0.001).[17]

3.1.5 Evidence Gaps and Future Research

The certainty of evidence is low indicating the need for additional controlled trials to assess the optimal timing of intervention for suspected infected fluid collections. Clinical trial registries show there are at least two ongoing RCTs to address this question and these results are awaited.

While delayed drainage may be preferable, diagnostic biomarker(s) such as CRP and procalcitonin to differentiate between a patient with systemic inflammation in the setting of a sterile collection versus infected pancreatic necrosis may be informative to guide decision-making regarding when escalation to intervention may be beneficial. Further advances in the medical management of necrotizing pancreatitis (e.g., fluid management, optimal antibiotic regimens, etc.) may further reduce the need for procedural interventions.

3.2 Should minimally invasive surgical step-up approach versus open surgical necrosectomy be used for an initial interventional strategy in patients with suspected infection of pancreatic/peri-pancreatic collections?

Recommendation 2. In individuals with suspected infection of pancreatic and/or peripancreatic collections, the AGA suggests a minimally invasive step-up approach over open surgical necrosectomy for management. *(conditional recommendation, low certainty of evidence)*

Implementation Considerations:

- Minimally invasive step-up approach involves initial drainage by endoscopic and/or percutaneous route followed by repeated drainage procedure and necrosectomy if there is no improvement.
- If minimally invasive step-up approach is unsuccessful or not feasible, open surgical necrosectomy may be implemented

3.2.1 Summary of the Evidence

Evidence informing the recommendation for minimally invasive surgical step-up approach over open surgical necrosectomy is derived from one RCT and supplemented by a large, pooled analysis of primarily observational data. The trial by vanSantvoort et al included 88 participants with a mean age of 57 years and 6-month follow-up.[18] Open surgical necrosectomy consisted of laparotomy through bilateral subcostal incision, blunt removal of necrotic tissue, then placement

of two large bore drains for postoperative lavage. Minimally invasive step-up approach consisted of percutaneous retroperitoneal (or endoscopic transgastric) drainage with escalation to an additional drain after 72 hours if there was no clinical improvement. If no further drain could be placed or no improvement after 72 hours of an additional drain, video-assisted retroperitoneal debridement (VARD) was pursued. Given the extremely serious imprecision for the outcome of mortality, a 2018 pooled analysis of individual data of 1980 participants was included to represent observational data.[19] The overall certainty was very low.

3.2.2 Benefits and Harms

The critical outcomes for this PICO were mortality, new onset organ failure, intraabdominal bleeding requiring intervention, and pancreatic fistula. Important outcomes included exocrine pancreatic insufficiency, new onset diabetes, incisional hernia, need for necrosectomy, and length of stay. In the RCT, mortality was found to be 18.6% in the minimally invasive group and 15.6% in the open surgical group (RR 1.20, 95% CI 0.48, 3.01). In the pooled data analysis, mortality was categorized by endoscopic drainage versus open surgical (10.8% vs 30.4%; RR 0.35 95% CI 0.21, 0.59) and percutaneous drainage versus open surgical (18.6% vs 23.1%; RR 0.8, 95% CI 0.61, 1.06), both of which favored the minimally invasive approaches. Mortality data were deemed to be very uncertain, so the other critical outcomes influenced decision making. In the RCT, the rate of new onset multiple organ failure (or systemic complication) was lower in the minimally invasive group (11.6% vs 42.2%; RR 0.28; 95% CI 0.11, 0.67). Similarly, intraabdominal bleeding (16.3% vs 22.2%; RR 0.73, 95% CI 0.31, 1.75) and pancreatic fistula rates (27.9% vs 37.8%; RR 0.74, 95% CI 0.40, 1.36) were also lower in the minimally invasive arm compared to open surgical necrosectomy. Amongst the important outcomes, the need for necrosectomy via laparotomy or VARD was lower in the minimally invasive approach (60.5% vs 100%, RR 0.61, 95% CI 0.48, 0.77). Data regarding the other important outcomes and overall judgements can be found in Supplemental Tables 12 and 13.

3.2.3 Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was low. Results were very uncertain for mortality, which was primarily due to imprecision and thus the other critical outcomes drove decision making. However, results for new onset organ failure or systemic complications were also found to have serious imprecision. The rest of the outcomes were found to have serious to very serious imprecision. Imprecision concern was mainly due to low event rate and sample size and crossing the *a priori* minimally important difference thresholds. No serious risk of bias was found.

3.2.4 Discussion

Considering the large effect size of harm reductions, the panel concluded minimally invasive (percutaneous or endoscopic) approaches should likely be the first approach to treat infected pancreatic necrosis compared to open surgical necrosectomy. This recommendation is conditional based on a paucity of high quality RCTs. Nevertheless, the collectively pooled data suggest that minimally invasive approaches were associated with less frequent and less significant complications including organ failure, bleeding, need for open surgical necrosectomy, and endocrine and exocrine insufficiency. Long-term follow-up from the van Santvoort trial analyzed costs and found no significant difference between minimally invasive and open surgical groups. [17]

There are some important clinical considerations for implementation. First, the results of the single RCT may not be generalizable to all patients with necrotizing pancreatitis illustrated by the enrollment of only 88 patients amongst 378 who were screened.[18] Secondly, there may be limited instances where an operative approach may be a stronger consideration. For example, in the scenario of a patient with gallstone etiology, a single stage approach (i.e., necrosectomy in conjunction with cholecystectomy) may be considered at an institution with appropriate surgical expertise. Individual institutional expertise in advanced endoscopy and interventional radiology should also be considered when selecting a minimally invasive approach and

treatment decisions made after multidisciplinary discussions among pancreatic surgeons, advanced endoscopists, and interventional radiologists.

3.2.5 Evidence Gaps and Future Research

Techniques for managing necrotizing pancreatitis have evolved over the last two decades, including the use of minimally invasive techniques. At this time, it is seems unnecessary to continue studying and attempting to refine open techniques. Rather, further standardization and studying newer approaches are highly needed. However, novel trial designs will likely be needed to address these problems due to disease heterogeneity and variable institutional expertise.

3.3 Should per-oral endoscopic transluminal approach compared to minimally invasive surgical step-up approach be used for initial management strategy for suspected infected or symptomatic pancreatic and/or peri-pancreatic collections that require invasive treatment?

Recommendation 3. In individuals with suspected infected or symptomatic pancreatic and/or peripancreatic collections, amenable to endoscopic drainage who require intervention, the AGA suggests the use of endoscopic transluminal approach over minimally invasive surgical step-up approach as the initial interventional strategy. *(conditional recommendation, low certainty of evidence)*

Implementation Considerations:

- If the collection is not adjacent to the stomach and duodenum and is located in the deep
- retroperitoneum or pelvis, a minimally invasive surgical step-up approach may be required instead of/or combined with endoscopic transluminal approach.

3.3.1 Summary of the Evidence

Evidence comparing the per-oral endoscopic transluminal approach versus minimally invasive surgical step-up approach was informed by a systematic review (SR) and meta-analysis (MA) of RCT's. A shared search for PICOs 1-5 identified 1016 studies. A unique search for this PICO identified an additional 2979 studies (Supplementary Table 5). Artificial intelligence (AI) assisted screening tool was used for initial screening.[20] AI excluded 2956 studies. Two reviewers independently assessed the eligibility of the articles and included five RCTs in the final MA.[21-25] Studies were from Western countries (3 studies)[22, 23, 25] and India (two studies)[21, 24]. All studies were fully published articles. Participants assigned to the per-oral endoscopic transluminal approach underwent endoscopic ultrasound (EUS) guided drainage using plastic stents in 3 studies [22, 24, 25] and either plastic stents or lumen apposing metal stents (LAMS) in two studies. [21, 23] Participants assigned to the minimally invasive surgical step-up approach underwent laparoscopic transperitoneal cystogastrostomy (2 studies) [21, 24], VARD (2 studies) [22, 25] or either approach (1 study).[23] Participants in surgical step-up approach using VARD underwent percutaneous catheter drainage first, followed by minimally invasive surgical necrosectomy. Participants with percutaneous catheter drainage prior to intended treatment were excluded from three studies [21, 24, 25] and permitted in two studies. [22, 23]

3.3.2 Benefits and Harms

The critical outcomes that informed the benefits for this PICO question were new onset organ failure, development of fistula (pancreatic or enterocutaneous), bleeding, and perforation. Meta-analysis of five RCTs (including 140 participants in per-oral endoscopic transluminal group and 144 minimally invasive surgical step-up) demonstrated less new onset single or multi-organ failure compared to minimally invasive surgical step-up (4% vs 12.1%; RR: 0.41 (95% CI: 0.15 – 1.10). Per-oral endoscopic approach had lower risk for fistula formation (2.1% vs 21.5%; RR: 0.14 (95% CI: 0.05-0.39). There was less bleeding (8.6% vs 9.7%; RR 0.95, 95% CI 0.47, 1.92) and perforation (3.6% vs 7.4%; RR 0.55, 95% CI 0.21, 1.43) associated with the endoscopic approach. Mortality data was noted to be of very low certainty and thus the other critical

outcomes drove decision making. Important outcomes and details of the evidence can be found in Supplemental Table 16.

3.3.3 Certainty in Evidence of Effects

The overall certainty in the evidence was low (Supplemental **Table 16).** For the critical outcomes of new onset organ failure (any), respiratory failure, and bleeding, the certainty of evidence was low. Although no risk of bias or inconsistency was identified, the imprecision of the effect estimates was rated as very serious due to the low number of events and the wide confidence intervals, which crossed the minimally important difference threshold. For the critical outcome of fistula formation, the certainty of evidence was rated as moderate, primarily due to imprecision in the effect estimate resulting from the low event rate.

3.3.4 Discussion

Due to several advantages associated with the endoscopic approach, the guideline panel suggests endoscopic approach over surgery for initial treatment of suspected infected or symptomatic pancreatic and/or peri-pancreatic collections. The meta-analysis showed that an endoscopic approach compared to minimally invasive surgery for the treatment of infected necrotizing pancreatitis was associated with lower rates of new onset organ failure, fistulae (pancreatic and enterocutaneous), bleeding, perforation and length of stay. Conversely, there may be a trivial increase in the number of procedures with this approach.

Available data also suggests moderate cost saving with per-oral endoscopic approach. In the study by Bang et al.[3] from the US, the total cost of the per-oral endoscopic approach was $75,830, compared with $117,492 for the minimally invasive surgical approach (P=0.039). The number of quality-adjusted life years (QALYs) gained was 0.452 (benefit cost analysis [BCa] 95% CI, 0.434–0.472) in the endoscopy group and 0.450 (BCa 95% CI, 0.427–0.468) in the surgery group with a mean difference of 0.002 (95% CI, –0.025 to 0.029). Similar findings were observed in Europe by Van Brunschot et al.[5]

Minimally invasive surgical procedures are typically longer compared to the endoscopic approach. Prolonged general anesthesia, which can sustain systemic inflammation in critically ill patients, the invasive nature of surgery, and longer recovery period likely contribute to the higher incidence of new onset organ failure observed with surgery versus endoscopy.[26] The presence of organ failure is an important predictor of mortality, associated with 30% mortality in acute pancreatitis. [27]

Endoscopy has another apparent advantage over surgery, with lower incidence of pancreatic and enterocutaneous fistulae. Fistula formation is due to extravasation of pancreatic juice, inflammatory exudate and bowel necrosis from passage of inflammatory exudate into the retroperitoneal tissue. This occurs more readily during percutaneous drain placement and surgical necrosectomy).[28] Pancreatic and enterocutaneous fistulae are associated with significant morbidity, prolonged hospitalization and often require surgical intervention[29] supporting our recommendation of endoscopy over surgery for treatment of necrotizing pancreatitis. Nevertheless, disease heterogeneity and variable local expertise in advanced endoscopy, surgery, and interventional radiology will impact the approach for individual cases.

3.3.5 Evidence Gaps and Future Research

Further research is needed to refine the endoscopic approach, including development of standardized terminology for describing collections and development and testing of standardized algorithms for management. There are situations where pancreatic fluid collections may not be accessible from the gastric or small bowel lumen. Thus, additional work is needed to consider how to categorize and systematically study alternative interventional approaches (e.g., percutaneous drainage, surgical drainage and/or necrosectomy) for these situations.

3.4 Should metal versus plastic stents be used for initial per-oral endoscopic transluminal drainage in patients with suspected infected or symptomatic pancreatic/peri-pancreatic collections?

Recommendation 4. In individuals with suspected infected or symptomatic pancreatic and/or peripancreatic collections who are undergoing endoscopic transluminal drainage, the AGA suggests the use of either lumen-apposing metal stents or double pigtail plastic stents. *(conditional recommendation, low certainty of evidence)*

Implementation Considerations:

- When a lumen-apposed metal stent is used, expert panel practice includes removal within 4 weeks from placement (but after a stable tract has been formed), when feasible, to reduce risk of stent-related complications particularly bleeding

3.4.1 Summary of the Evidence

Evidence comparing plastic versus metal stents for per-oral endoscopic transluminal drainage was informed by six RCTs (176 participants with metal stents, 175 with double pigtail plastic stents).[30-35]. (Supplemental Table 18). Studies were from Western countries (3 studies)[30, 31, 33], India (2 studies)[32, 34] and East Asia (1 study).[35] All studies were fully published articles. Included participants had complete encapsulation in 4 studies [30, 31, 34, 35] and status of encapsulation was not reported in the remaining two studies. The proportion of participants with confirmed infected necrosis ranged from 13% to 100% across studies. Individuals were randomized to either EUS-guided drainage with metal stents or double-pigtail plastic stents. Endoscopic drainage with metal stent was performed using electrocautery-enhanced lumen-apposing metal stents (LAMS) (4 studies) [30, 31, 33, 35], bi-flanged self-expandable metal stents (1 study) [34] and either electrocautery-enhanced LAMS or bi-flanged self-expandable metal stents (1 study).[32] The metal stents were removed within 6 weeks (4 studies) [32-35] or at median of 6 weeks (1 study).[31] One study [30] removed the metal stent at 3 weeks post-intervention if the WON had resolved. Endoscopic drainage with plastic stents was performed using one or two 7 Fr or 10 Fr double pigtail plastic stents.

3.4.2 Benefits and Harms

Adverse events (AEs) were considered critical outcomes for this PICO. The meta-analysis demonstrated no significant difference between metal and plastic stents for endoscopic transluminal drainage with regard to adverse events. The risk of bleeding was not significantly increased with metal stents (RR 1.37, 95% CI 0.56–3.37), corresponding to an absolute risk increase of 17 per 1,000 patients (from 20 fewer to 108 more). The risk of perforation was similarly not significantly different (RR 0.76, 95% CI 0.07–8.81) with an absolute risk reduction of 3 per 1,000 (95% CI: 11 fewer to 89 more). Stent -related AEs did not differ between the two groups (RR 1.06, 95% CI 0.37–3.05) with an absolute risk increase of 12 per 1,000 (95% CI: 128 fewer to 415 more) with metal stents.

The need for surgical necrosectomy was also not significantly different (RR 2.15, 95% CI 0.60–7.72; 13 more per 1000 with metal stent; 95% CI 5 fewer to 77 more). Finally, the number of procedures required to achieve clinical success was comparable, with a mean difference of 0.54 additional procedures with metal stents (95% CI: 1.25 fewer to 2.35 more).

The important outcomes that informed benefits for this PICO question were length of procedure and length of hospital stay. The length of procedure was 9.9 minutes shorter with metal stents (from 16.8 shorter to 3.1 minutes shorter). Additionally, the length of hospital stay was about 1.5 days shorter with metal stents (from 6.0 shorter to 3.0 days longer).

3.4.3 Certainty in Evidence of Effects

The overall certainty in the evidence was low (Supplemental **Table 20**). For the critical outcomes of AEs (bleeding, perforation, stent related adverse event), the certainty of evidence was low to very low. This was mainly due to the imprecision of the effect estimates as the wide confidence intervals crossed the minimally important difference threshold of 5%.

3.4.4 Discussion

The Guideline panel suggested the use of either metal or plastic stents for drainage of pancreatic fluid collections. There were no major differences in multiple outcomes assessed, so this suggestion is largely influenced by similar risk of harms. Overall, there was no substantial difference in length of stay, requirement for surgical necrosectomy, or number of procedures required to achieve clinical success. Based on Poiseuilles's law, (i.e., flow is directly related to radius and inversely related to length (Flow=πp(radius)^4/(8υ length)) it has been hypothesized that lumen apposing stents with a shorter length and greater diameter than plastic stents should provide superior drainage. Supporting the hypothesis, there were more favorable rates of re-intervention free survival in the metal stent arms of the trials by Koduri et al.[34] and Bang et al.[30] Nevertheless, collectively, there were no clinically significant differences in success across multiple outcome measures (including need for surgical necrosectomy) in the meta-analysis of six available RCTs.

Technical expertise commentary from the panel is that existing "all-in-one" metal stent deployment system in which the EUS guided access needle, cautery ring, and metal stent are part of a single device simplifies placement, providing a practical advantage relative to plastic stent deployment (which requires multiple device exchanges over a wire using a Seldinger type process). This improved efficiency for metal stent placement likely explains a shorter procedure time demonstrated in our meta-analysis.

There was no major difference in overall adverse events for metal versus plastic stents. However, in the trial by Bang et al, the duration of LAMS indwelling correlated with bleeding.[30] There were 3 delayed bleeds at >4 weeks, which were hypothesized to be related to in-growth and pseudoaneurysm around the distal flange of the lumen apposing stents. This prompted a protocol revision which required removal at 3 weeks. This observation was congruent with a cohort study showing removal >4 weeks after placement was associated with delayed bleeding and supports the current practice of removing LAMS within a 4-week timeframe (but after a stable tract has formed), when feasible. The panel acknowledges that LAMS may be required

past the 4-week mark in select cases for further necrosectomy but encourages removal as soon as possible in these scenarios.

The guideline panel did not identify a significant difference in cost between metal and plastic stents for endoscopic drainage in the US and Europe. Bang et al.[30] reported that although the initial cost for LAMS was higher than double pigtail plastic stent ($12,155 vs. $6,609, respectively, P <0.001), the overall total cost per patient was similar between the two groups (LAMS: $53,117 vs. PS: $50,132; P= 0.775). Similarly, Gornals et al.[31] found minimal difference in total cost per patient in a European study comparing metal and plastic stents (LAMS: $41,565 vs. PS: $41,971, difference of $406 per patient).

3.4.5 Evidence Gaps and Future Research

Larger trials stratified by degree of necrosis, status of infection and fluid collection size are needed to inform this clinical question. To date, there has only been one multicenter trial, which was stopped prematurely during the COVID-19 pandemic.[31] Importantly, existing trials were also performed at tertiary centers.. Future research should expand outcomes to include rates of re-intervention and formal cost analyses.

3.5 Should upfront transluminal endoscopic necrosectomy versus endoscopic drainage (i.e., drainage followed by subsequent on-demand necrosectomy) be used for patients with suspected infected or symptomatic walled off necrotic collections?

Recommendation 5. In individuals undergoing endoscopic transluminal drainage for suspected infected or symptomatic pancreatic and/or peripancreatic collections, the AGA suggests either upfront or on-demand endoscopic necrosectomy. *(conditional recommendation, very low certainty of evidence)*

Implementation Considerations:

- Safe upfront necrosectomy generally requires a lumen-apposing or bi-flanged self-expandable metal stent to maintain the tract and reduce the risk of separation of the gastrointestinal lumen from the collection
- Upfront necrosectomy requires a stable patient who can tolerate a longer procedure.
- May favor upfront necrosectomy if the lumen apposing metal stent has concern for immediate occlusion from necrosis or very large collections with solid necrotic burden.

3.5.1 Summary of the Evidence

Evidence comparing upfront versus on-demand endoscopic necrosectomy in patients who underwent per-oral endoscopic transluminal drainage was informed by five RCTs (134 patients upfront necrosectomy, 135 patients on-demand necrosectomy). Studies were conducted in the US (1 study), Europe (1 study), Middle east (1 study) and Asia (2 studies). All studies were fully published articles. Two studies included exclusively patients with fully encapsulated collections, and the remaining studies enrolled predominantly such patients or did not delineate details. Of studies that reported the timing of endoscopic drainage, it was comparable between the two groups and was generally performed at 4–6 weeks following acute pancreatitis. Initial endoscopic drainage was performed using LAMS in 4 studies and predominantly LAMS in one study (Saito et al.), except for two participants (DPPS). The median size of WON was comparable between the upfront and on-demand necrosectomy groups within each study; however, the study by Olsen et al included larger collections (median 21.7–23 cm) compared with the other studies, in which median WON size was approximately 10-15 cm.

3.5.2 Benefits and Harms

The critical outcomes that informed the benefits for this PICO question were procedure related AEs, bleeding, perforation, need for surgical necrosectomy (escalation of care to surgery), and new onset organ failure. Meta-analysis of 5 RCTs (134 upfront, 135 on-demand) demonstrated slightly fewer procedure related AEs with upfront compared to on-demand necrosectomy RR: 0.89 (95% CI: 0.51 -1.53). Specifically, upfront necrosectomy may be associated with slightly

higher bleeding (12.7% vs 10.4%; RR 1.31, 95% CI 0.64-2.66), but slightly lower perforation risk (2.2% vs 3.7%; 95% CI 0.21-2.63). Upfront necrosectomy was associated with less need for surgical necrosectomy RR: 0.40 (95% CI: 0.10-1.55) with an absolute risk reduction of 36 fewer cases per 1000 patients (from 53 fewer to 33 more). There was no significant difference in new onset organ failure RR: 1.00 (95% CI: 00.46-2.18). Other important outcomes including LOS, 6-month readmission, and total number of interventions are presented in the supplement. Sub-group analysis for length of stay was performed with exclusion of the Olsen trial, which was stopped early. Length of stay of the sub-group analysis showed that upfront necrosectomy may be associated with lower length of stay (MD: 3.95 days shorter; 95% CI 11.43 lower to 3.53 higher).

3.5.3 Certainty in Evidence of Effects

The overall certainty in the evidence was very low (Supplemental **Table 24).** For the critical outcomes, this was driven by the imprecision of the effect estimates due to the low number of events (n <300) and the wide confidence interval, which crossed the minimally important difference (MID) of 5%. No serious risk of bias or inconsistency was identified in the critical outcomes.

3.5.4 Discussion

As the use of endoscopic strategies to manage symptomatic necrotic collections has propagated, competing approaches of up-front versus on-demand necrosectomy following drainage have emerged. The up-front approach usually involves necrosectomy during the same session as initial endoscopic drainage, while in the on-demand pathway it is performed only if the patient fails to improve. The Guideline panel suggested the use of either up-front or on-demand endoscopic necrosectomy for symptomatic pancreatic collections given similar rates of clinically meaningful procedure-related adverse events. Additionally, the meta-analysis failed to show a marked benefit in the need for surgical necrosectomy or development of new onset organ failure. Additionally, the upfront strategy was associated with decreased length of stay, however the certainty of evidence was very low.

The DESTIN and WONDER-01 multicenter trials indicate that up-front necrosectomy accelerated the resolution of systemic inflammatory response syndrome and organ failure, time to improvement in inflammatory markers, reduction in collection size, shortened hospitalization relative to the on-demand strategy.[36, 37]. The ACCELERATE trial preferentially enrolled patients with larger WON resulting in a somewhat distinctive study population (median was >21 cm).[38] The trial was halted early, after 25 participants were enrolled, given that more participants in the on-demand arm developed the composite endpoint of organ failure, fistula, bleeding, death, or prolonged hospitalization, compared to the up-front arm.

In contrast, in the recent RCT by Mohamadnejad et al, clinical success was not better for up-front necrosectomy and resulted in more necrosectomy sessions and adverse events. Additionally, 44% in the on-demand group improved without necrosectomy.[39] Additionally, in the WONDER-01 trial, the step-up approach required fewer median necrosectomy procedures and shorter total median procedure time than the up-front approach. Importantly, there were 4 deaths with up-front versus 2 with the step-up approach.[37]

Data regarding cost effectiveness are heterogeneous. Up-front necrosectomy theoretically results in less procedures, while the on–demand approach achieves shorter index procedure and entirely obviates necrosectomy in a sizable proportion of patients who improve with drainage alone. The DESTIN trial showed lower mean per patient cost for up-front rather than on-demand necrosectomy, though it did not reach statistical significance.[36] WONDER -1 revealed a higher cost for the index hospitalization, for up-front necrosectomy but no difference in cost of all treatment related hospitalization.[37] In ACCELERATE, the cost was higher for the step-up approach, but it did not reach statistical significance.[38]

Thus, the best evidence suggests that both the up-front and on-demand necrosectomy approaches are reasonable management approaches for suspected and symptomatic necrotic pancreatic fluid collections. The choice is likely influenced by patient specific characteristics. For the upfront strategy, necrotic collection must be fully mature and walled-off, and necrosectomy may be pursued only if the patient is stable and can tolerate a prolonged procedure. Immediate necrosectomy is not appropriate after placement of plastic stents, because removing these

stents or advancing a gastroscope through an immature cystgastrostomy tract carries a concerning risk for perforation. The ACCELERATE trial suggests that up-front necrosectomy may be favored for very large collections[38] and multivariate analysis in the recent trial by Mohamadnejad et al suggests it may be most advantageous in those with a higher percentage of solid necrosis.[39] However, in patients with coagulopathy or who will not tolerate longer procedures, an on-demand approach is likely favored. Additionally, there are important technical considerations. If the consistency of the necrosis is such that it may immediately occlude the drainage tract, then at least some necrosectomy may be needed to maintain drainage.

3.5.5 Evidence Gaps and Future Research

Same as 3.1.5, above.

There are many opportunities to improve endoscopic techniques, including the development of dedicated accessories for endoscopic necrosectomy, in a manner that improves patient safety, optimizes the efficiency of drainage and debridement, and reduces procedural time. The guidance techniques used in neurosurgery to target dissection and avoid vessels may be integrated to enhance safety[40, 41] Additionally, these delicate procedures may likely be enhanced by new dedicated accessories designed to clear necrotic tissue and introduction of robotics to enhance endoscopic procedures requiring complex spatial assessment.[42-44] Thus, both further high-quality trials and introduction of rapidly evolving technology may influence recommendations for future iterations of this Guideline.

3.6 Should transluminal plastic stents versus no stents be used following endoscopic drainage of walled-off necrosis/pancreatic fluid collections for individuals with suspected disconnected pancreatic duct after initial metal stent has been removed?

Recommendation 6. In individuals who underwent endoscopic transluminal drainage of walled off necrosis/pancreatic fluid collection with suspected disconnected pancreatic duct, the AGA

suggests placing transluminal double pigtail plastic stents over no stent after the initial metal stent has been removed. (condition recommendation, very low certainty of evidence)

Implementation Considerations:

- There may be instances when the cavity completely collapses and the replacement of plastic stents is not anatomically feasible.

3.6.1 Summary of the Evidence

Evidence comparing placement of transluminal plastic stents versus no stents in patients with suspected disconnected pancreatic duct syndrome (DPDS) after the initial stent has been removed was informed by our systematic review and meta-analysis. Two reviewers independently assessed the eligibility of the articles and included a total of 4 studies in the meta-analysis (1 RCT[45] and 3 observational cohort studies [46-48] (Supplemental Table 26). These studies encompassed 172 and 106 participants treated with and without transmural plastic stents, respectively. Studies were from the US (n=2) and India (n=2). All studies were fully published articles. Two studies included both pseudocysts and WON ([46, 48]) while the others included WON only ([45, 47]). Initial drainage of the pancreatic fluid collection was performed using LAMS in all studies. In these studies, DPDS was defined as complete disruption of the main pancreatic duct, resulting in a portion of the upstream viable pancreas parenchyma becoming isolated from the main pancreatic duct downstream. This was determined based on magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Participants who underwent transmural plastic stent placement had one or two 7 Fr or 10 Fr double pigtail stents placed. The median (or mean) follow-up ranged between 18 and 20 months.

3.6.2 Benefits and Harms

The critical outcome that informed the benefits for this PICO question was the need for repeat drainage. Recurrent fluid collection was defined by re-accumulation of PFC in the same location

on follow-up imaging. Our meta-analysis of the 4 studies demonstrated lower need for repeat drainage with transluminal PS (RR 0.25 (95% CI: 0.08-0.79) corresponding with an absolute risk reduction of 113 fewer cases per 1000 (from 139 fewer to 32 fewer)). When considering the RCT only, the RR was 0.73 (0.17-3.07) which corresponded with 26 fewer cases per 1000 (from 79 fewer to 197 more). AEs were also considered critical outcomes. There were no bleeding or perforations reported in either group in the included studies. The need for escalation to surgery was not significantly different between the two groups (RR: 1.41 (95% CI: 0.20-9.73).

3.6.3 Certainty in Evidence of Effects

The overall certainty in the evidence was very low (**Supplemental Table 28**). This was primarily due to imprecision, as the confidence intervals were wide and crossed the minimally important difference threshold. Additional concerns included risk of bias, since 3 of the 4 included studies were observational introducing risk for selection bias and unmeasured confounders. Furthermore, there was variability in follow-up duration between groups in the studies, which may have contributed to differences. Another important limitation was that the comparator group in the observational studies was largely composed of participants in whom plastic stent placement had failed after removal of the metal stent, rather than patients who had not received a stent. As such, the control group may not have represented a true comparator.

3.6.4 Discussion

Acute necrotizing pancreatitis may result in either partial disruption or complete disconnection of the pancreatic duct, referred to as disconnected pancreatic duct (DPD).[49] DPD may occur in approximately one-quarter of patients with necrotizing pancreatitis, especially in those with necrosis involving the neck or body.[50] Continuous secretion of enzyme-rich pancreatic juice from the disconnected viable upstream pancreatic parenchyma results in recurrent pancreatic fluid collection (PFC), external pancreatic fistulae, and pancreatitis of the upstream pancreatic remnant, collectively referred to as disconnected pancreatic duct syndrome (DPDS).[49] Thus, patients undergoing endoscopic transluminal drainage for necrotic collections with suspected DPD, may develop recurrent PFC after removal of transluminal stents. Maintaining the patency

of the cystenterostomy tract, after resolution of necrotic collection by leaving double pigtailed plastic stents in place, is considered to prevent recurrent PFC. While LAMS are often used as the initial cystenterostomy stent for WON, they ideally should not be left in situ for more than 4 weeks given risk of delayed bleed (see PICO 4).[30] Therefore, current practice involves exchanging the LAMS to plastic stents (PS). Double pigtail stents are used rather than straight plastic stents in this scenario as the proximal and distal ends coil in the gastrointestinal lumen and necrotic cavity, respectively.

The panel made a conditional recommendation favoring placement of a transmural double pigtailed plastic stents after the initial endoscopic drainage with LAMS to provide unimpeded drainage of the disconnected upstream pancreatic gland. The panel acknowledges the limitations of primarily basing their conclusions on observational studies with a lack of an optimal comparator.

The panel noted that it may be technically challenging and risky to exchange LAMS to double pigtail stents when the necrotic cavity completely collapses. For example, one study noted that plastic stent exchange may not be feasible in up to 25% of patients.[48] It is therefore important to consider proactively changing from LAMS to plastic when near-complete resolution of PFC is achieved.

The panel also noted that some studies showed similar recurrence rates in PFCs with and without plastic stents. The single randomized trial did not show a difference in recurrent pancreatic fluid collections but was limited by small sample size, high dropout rate and short-term follow-up.[45] It is important to consider that some recurrences are clinically inconsequential including those that regress spontaneously without need for reintervention.[45, 51] These discordant results may be explained by heterogeneity with regards to the site of disconnection and volume and health of the disconnected pancreatic parenchyma. Proximal duct disruption, absence of atrophy of the disconnected segment of pancreas, or clinical symptoms of exocrine and endocrine insufficiency are associated with recurrent PFC.[52] This indicates potential need to prioritize changing LAMS to double pigtail stents for patients at high risk of recurrent PFC with proximal disconnection (e.g., at the neck) and preservation of the disconnected (distal) gland.

3.6.5 Evidence Gaps and Future Research

Given the heterogeneity in clinical outcomes following DPD, it is imperative to conduct prospective studies to refine the prediction of clinically relevant recurrent PFCs. These include approaches to better identify pancreatic duct disruption including the selective use of MRCP. These data can support individualized management strategies by helping us distinguish which patients may benefit from stent exchange from those who do not need stenting. Future studies are needed to address the optimal size, number and length of the double pigtailed plastic stents which need to remain in situ to prevent RFC. The length of time the double pigtail stents should remain is a controversial topic with a need for better data regarding clinical and financial consequences.

3.7 Should anticoagulation versus no anticoagulation be used for acute splanchnic vein thrombosis in acute pancreatitis

Recommendation 7. In individuals with acute splanchnic vein thrombosis following acute pancreatitis, the AGA suggests anticoagulation over no anticoagulation. (conditional recommendation, very low certainty of evidence)

Implementation Considerations:

- Patients and providers may choose against anti-coagulation if bleeding risk is high or if bleeding risk is prioritized over potential benefit
- Expert panel practice is to generally anticoagulate for superior mesenteric vein and portal vein thrombosis and not routinely for isolated splenic vein thrombosis

3.7.1 Summary of the Evidence

Evidence informing the recommendation for anticoagulation over no anticoagulation for acute splanchnic vein thrombosis in acute pancreatitis is derived from our systematic review and meta-analysis of 17 comparative observational studies, four of which were published in abstract form.[53-56] No RCTs were identified to address this PICO. The *a priori* definition of acute

thrombosis was the occurrence of consistent imaging within 6 months of the acute pancreatitis episode. Sources of heterogeneity in the disease included vessels affected (splenic vein, portal vein, superior mesenteric vein, or a combination) and degree of vessel patency (complete vs. partial), with variability in treatments including anticoagulant type and duration. Moreover, there was inconsistent reporting of each of these data elements as well as the definitions used for bleeding and recanalization. Study details can be found in Supplemental Table 30.

3.7.2 Benefits and Harms

The critical outcomes for this PICO were mortality, bleeding, gut/hepatic ischemia, and recanalization. An important outcome was the development of esophageal and gastric varices. The data were deemed to be very uncertain overall. The expert panel did not feel there was enough data to decide based on mortality, and gut/hepatic ischemia, so the critical outcomes of recanalization and bleeding risk primarily influenced decision making even though it was noted that certainty of evidence was very low. Pooled analysis of fifteen studies showed higher rates of bleeding with anticoagulation compared to no anticoagulation (13.5% versus 10.2%; RR 1.34, 95% CI 1.06, 1.70). For absolute risks, this translated to 35 more bleeds per 1000 people (6 to 74 more). Pooled analysis of 11 observational studies showed 48.9% recanalization rate in those treated with anticoagulation versus 19.8% rate in those who were not (RR 1.51, 95 CI 1.04, 2.19). This translated to 101 more recanalization with anticoagulation per 1000 people (95% CI: 8 more to 235 more). The other important outcomes and overall judgements can be found in Supplemental Tables 32 and 33.

3.7.3 Certainty in Evidence of Effects

The overall certainty in the evidence across the critical outcomes and considering both benefits and harms was very low. Results were very uncertain for all outcomes driven by very serious risk of bias and serious to extremely serious imprecision for most outcomes. For risk of bias, there was concern for selection bias, residual confounders, and lack of data for outcomes stratified by patterns of vascular involvement. Multiple studies did not report duration of treatment or follow-up. Also, the indication for starting anticoagulation was not consistently

reported, which introduces risk for bias towards inclusion of patients with more severe disease into anticoagulation groups. Imprecision concerns were mainly due to low event rate and crossing *a priori* minimally important difference (MID) thresholds. Lastly, for the outcome of recanalization, there was serious inconsistency given moderately high I^2 and indirectness as recanalization was selected as a surrogate for clinical outcomes.

3.7.4 Discussion

The panel provided a conditional recommendation to suggest anticoagulation over no anticoagulation due to moderate benefit of recanalization with the trivial to small risk of bleeding. The ultimate clinical goal of using anticoagulation is to prevent the development of portal hypertension and its sequelae. However, since most studies only provided short term follow-up and/or did not systematically report all endpoints, the panel accepted, albeit imperfect, vascular recanalization as a surrogate outcome for clinical benefit.

There was substantial deliberation from the panel regarding whether the vessel(s) involved should be considered in the recommendation for anticoagulation. Based on the nature of data reporting and lack of direct or indirect comparative data, the panel was unable to assess outcomes based on vessel involvement and therefore we have provided an overarching recommendation related to any splanchnic vessel. However, in general, the experts do not routinely anticoagulate isolated acute splenic vein thrombosis in patients with acute pancreatitis due to the small clinical consequences of withholding treatment.[57] Isolated splenic vein thrombosis accounted for at least one-third of cases in the observational series where details of vascular involvement were provided (Supplemental Table 30).

In the pooled data, there was small risk for anticoagulation-related bleeding, which should be considered when making personalized decisions. While splanchnic thromboses can develop in patients with AP of mild clinical severity, it is much more likely to occur in the setting of severe AP with necrosis. [58] Thus, there may be scenarios where this risk may be further increased (e.g., need for serial interventions) or the benefits may be lower (e.g., isolated splenic vein involvement). When anticoagulation is utilized for this complication, the experts typically treat for

a duration of 3-6 months. Treatment may be stopped earlier if there is a shift in the benefits/harms profile, including development of bleeding complications or vascular collaterals.

3.7.5 Evidence Gaps and Future Research

There is an immediate need for a randomized controlled trial to address the clinical decisions related to anticoagulation for acute splanchnic thrombosis in the setting of acute pancreatitis. Considering the differing consequences based on vascular territory, randomization should likely be stratified based on the vessel(s) involved. Other important considerations for study design and analysis include assessing patient or disease-related characteristics that may contribute to thrombosis (e.g., cigarette smoking, systemic inflammation, extent of necrosis (if present), etc.) or treatment response (e.g., degree of vascular obstruction). Additionally, clinically important outcomes with clear downstream consequences should be used instead of re-canalization, which is a surrogate, in future studies. Finally, the ideal duration to continue anticoagulation should be addressed.

Evidence Gaps for Local Complications of Pancreatitis

Substantial gaps exist in current published data, largely related to both disease and therapeutic heterogeneity. One important question is how disease manifestations (i.e., morphology) should influence therapeutic approaches. Location of necrosis (e.g., retrogastric, multi-field) as well as parenchymal involvement are important but understudied factors. The treatment for ill-localized and extensive collections is often not standardized and needs further study. Another major gap lies in the fact that few cost effectiveness data are available. Consistent definitions of disease endpoints such as necrosis clearance and return to function remain undefined. Similarly, classifications systems for disconnected pancreatic duct syndrome and splanchnic venous thrombosis are needed. There have been advances in randomized trials over the last two decades, but additional, larger studies are needed, especially related to DPD and anticoagulation for thrombosis. We anticipate this evidence based clinical Guideline will be refined as these data become available.

Conclusion

This AGA Guideline critically assessed the available literature for managing local complications of acute pancreatitis. For patients with infected (or suspected infected) pancreatic/peripancreatic collection(s) a minimally invasive approach rather than open surgical necrosectomy may be used for management and when feasible this intervention should be delayed to allow the wall around the collection to mature and necrotic debris to liquify. If collection(s) are equally accessible, the per-oral endoscopic transluminal route may be used over invasive surgical step-up approach with placement of either metal or plastic stents. Among patients with disconnected pancreatic duct, who are initially drained with a metal stent, plastic stents may be used upon its removal to prevent fluid collection recurrence. Among those with acute pancreatitis complicated by splanchnic vein thrombosis, therapeutic anticoagulation is suggested.

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AGA Clinical Practice Guideline on Acute Pancreatitis: Supplemental Material

COMPILED DRAFT — August 13, 2026

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SUPPLEMENTAL TABLES

Supplemental Table 1. Guideline Panel Members

Name	Role	Institution
Raj Shah, MD	Methodology and Clinical Chair	Ohio State University
James Buxbaum, MD	Clinical Lead	University of Southern California
Tarek Sawas, MD	Junior Methodologist	University of Texas Southwestern
Ji Young Bang, MD	Content Expert	Orlando Health
Philip Hart, MD	Content Expert	Ohio State University
Pramod Garg, MD	Content Expert	AIIMS, New Delhi, India
Guru Trikudanathan, MD	Content Expert	University of Minnesota
Nicholas Zyromski, MD	Content Expert	Indiana University

Supplemental Table 2. Conflict of Interest Disclosures

PANEL MEMBER	PANEL POSITION	INSTITUTION	GRANTS/ RESEARCH	MEDICOLEGAL CONSULTING	OTHER CONSULTING	DSMB OR SIMILAR STUDY COMMITTEE	TEACHING/ SPEAKING ACTIVITIES	STOCK, OPTIONS, OR OTHER OWNERSHIP	GI SOCIETIES	INCIDENTALS (FOOD, BEVERAGE, TRAVEL)
Raj Shah, MD	Methodology and Clinical Chair	Ohio State University	N/A	N/A	N/A	N/A	N/A	N/A	ASGE Bariatric Committee.	N/A
James Buxbaum, MD	Clinical Lead	University of Southern California	N/A	N/A	Boston Scientific; Nov 2023, ongoing; Arrivo; Nov 2023, ongoing; Interpace; Olympus.	N/A	Medscape; completed May 2023.	N/A	N/A	N/A
Tarek Sawas, MD	Junior Methodologist	University of Texas Southwestern	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ji Young Bang, MD	Content Expert	Orlando Health	Boston Scientific; Olympus America In.	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Philip Hart, MD	Content Expert	Ohio State University	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pramod Garg, MD	Content Expert	AIIMS, New Delhi, India	N/A	N/A	N/A	N/A	N/A	N/A	International Association of Pancreatology; Indian Pancreas Club.	N/A
Guru Trikudanathan, MD	Content Expert	University of Minnesota	N/A	N/A	N/A	N/A	Boston Scientific (speaker honorarium, hands-on course, and travel reimbursement, ASGE Annual Advanced Endoscopy fellows course, 2023).	N/A	N/A	N/A
Nicholas Zyromski, MD	Content Expert	Indiana University	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Osama Altayar, MD, MS	Co-author	Washington University School of Medicine	Site PI for clinical trials on celiac disease: Takeda (4/2022–2/2025); Pfizer (5/2023–8/2025); Sanofi (2/2024–present).	N/A	N/A	N/A	N/A	N/A	SSCD; ACG; Syrian American Medical Society.	N/A

Supplemental Table 3. PICO Questions

PICO	Focused Question	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)
1	In patients with suspected infected pancreatic and/or peripancreatic collections in the early phase of acute pancreatitis, should delayed drainage or immediate drainage be used?	Patients with suspected infected pancreatic and/or peripancreatic collections in the early phase of acute pancreatitis	Delayed drainage	Immediate drainage	Mortality; new-onset organ failure
2	In patients with suspected infected pancreatic and/or peripancreatic collections, should a minimally invasive step-up approach or open surgical necrosectomy be used?	Patients with suspected infected pancreatic and/or peripancreatic collections	Minimally invasive step-up approach	Open surgical necrosectomy	Mortality; new-onset organ failure; intra-abdominal bleeding requiring intervention; pancreatic fistula
3	In patients with suspected infected or symptomatic pancreatic and/or peripancreatic collections amenable to endoscopic drainage who require intervention, should an endoscopic transluminal approach or a minimally invasive surgical step-up approach be used as the initial interventional strategy?	Patients with suspected infected or symptomatic pancreatic and/or peripancreatic collections amenable to endoscopic drainage who require intervention	Endoscopic transluminal approach	Minimally invasive surgical step-up approach	New-onset organ failure; development of fistula (pancreatic or enterocutaneous); bleeding; perforation
4	In patients with suspected infected or symptomatic pancreatic and/or peripancreatic collections undergoing endoscopic transluminal drainage, should lumen-apposing metal stents or double pigtail plastic stents be used?	Patients with suspected infected or symptomatic pancreatic and/or peripancreatic collections undergoing endoscopic transluminal drainage	Lumen-apposing metal stents	Double pigtail plastic stents	Adverse events (e.g., bleeding, perforation, stent-related)
5	In patients undergoing endoscopic transluminal drainage for suspected infected or symptomatic pancreatic and/or peripancreatic collections, should upfront or on-demand endoscopic necrosectomy be used?	Patients undergoing endoscopic transluminal drainage for suspected infected or symptomatic pancreatic and/or peripancreatic collections	Upfront endoscopic necrosectomy	On-demand endoscopic necrosectomy	Procedure-related adverse events; bleeding; perforation; need for surgical necrosectomy (escalation of care to surgery); new-onset organ failure
6	In patients who underwent endoscopic transluminal drainage of walled-off necrosis/pancreatic fluid collection with suspected disconnected pancreatic duct, should transluminal double pigtail plastic stents or no stent be placed after the initial metal stent has been removed?	Patients who underwent endoscopic transluminal drainage of walled-off necrosis/pancreatic fluid collection with suspected disconnected pancreatic duct	Transluminal double pigtail plastic stents (after metal stent removal)	No stent	Need for repeat drainage (recurrent fluid collection)
7	In patients with acute splanchnic vein thrombosis following acute pancreatitis, should anticoagulation or no anticoagulation be used?	Patients with acute splanchnic vein thrombosis following acute pancreatitis	Anticoagulation	No anticoagulation	Mortality; bleeding; gut/hepatic ischemia; recanalization

Supplemental Table 4. Search Strategy

Databases: Ovid MEDLINE. No Embase or Cochrane CENTRAL strategy was supplied. Presented as one strategy per PICO.

Pancreatitis Searches (in Ovid Medline format)

PICO 1. In patients with a suspected infection of pancreatic and/or peri-pancreatic collections in the early phase of acute pancreatitis, should immediate vs delayed drainage in those who require intervention drainage be used for as a management strategy?

1. exp Pancreatitis/ or exp Pancreatitis, Acute Necrotizing/ or exp Pancreatic Pseudocyst/
2. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
3. ((necrotizing or necrotising OR hemorrhag*) adj2 pancrea*).tw,kw
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Drainage/
8. (drain OR draining OR drainage or necrosectom* OR intervention?).tw,kw
9. 7 OR 8
10. 6 and 9
11. exp Treatment Delay/
12. exp Time-to-Treatment/
13. exp Time Factors/
14. exp Early Medical Intervention/
15. ((time adj2 (treatment or factor*)) or "treatment delay" or "door to treatment time" or "onset to treatment time" or "time to therapy").tw,kw.
16. ((delay* or earlier or early or late or later or postpone* or immediate*) adj5 (drain* or treat* or therapy or intervention*)).tw,kw.
17. OR/11-16
18. 10 AND 17
19. exp randomized controlled trial/
20. Controlled clinical trial.pt
21. (randomised OR randomized).tw,kw
22. Drug therapy.fs
23. Randomly.ab
24. Trial.ab
25. Groups.ab
26. OR/19-25
27. exp animals/ not humans.sh
28. 26 not 27
29. 18 and 28
30. 29 not (“case reports” OR editorial or “systematic review” or “meta-analysis” or review).pt

31. ..dedup 30

PICO 2: In patients with a suspected infection of pancreatic and/or peri-pancreatic collections should minimally invasive surgical step-up approach versus open surgical necrosectomy be used as an initial interventional management strategy?

1. exp Pancreatitis/ or exp Pancreatitis, Acute Necrotizing/ or exp Pancreatic Pseudocyst/
2. ((necrotizing or necrotising or hemorrhag*) adj2 pancrea*).tw,kw.
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Drainage/
8. (drain or draining or drainage or (minimal* adj5 (intervention or internations)) or ((minimal* or endoscopic or laparoscopic or retroperitoneal) adj5 necrosectom*)).tw,kw.
9. exp Minimally Invasive Surgical Procedures/ or exp Debridement/
10. ((minimal* adj5 surg*) or "mini-invasive" or miniinvasive).tw,kw.
11. (("step-up" or stepup) adj3 (protocol* or approach*)).tw,kw.
12. or/7-11
13. ((open adj3 approach*) or laparotomy or (open adj5 surg*) or ((open or surgical or laparotomy) adj5 necrosectom*)).tw,kw.
14. 6 and 12 and 13
15. exp randomized controlled trial/
16. controlled clinical trial.pt.
17. (Randomized or randomised).tw,kw.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. or/15-21
23. exp animals/ not humans.sh.
24. 22 not 23
25. 14 and 24
26. remove duplicates from 25
27. 26 not ("case reports" or editorial or "systematic review" or "meta-analysis" or review).pt.

PICO 3: In patients with suspected infected or symptomatic pancreatic and/or peri-pancreatic collections who require invasive treatment, should a per-oral endoscopic transluminal approach versus minimally invasive surgical step-up approach be used as an initial interventional management strategy?

1. exp Pancreatitis/ or exp Pancreatitis, Acute Necrotizing/ or exp Pancreatic Pseudocyst/
2. ((necrotizing or necrotising or hemorrhag*) adj2 pancrea*).tw,kw
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Drainage/
8. (drain or draining or drainage or (minimal* adj5 (intervention or internations)) or ((minimal* or endoscopic or laparoscopic or retroperitoneal) adj5 necrosectom*)).tw,kw.
9. exp Minimally Invasive Surgical Procedures/ OR exp Debridement/
10. ((minimal* adj5 surg*) or "mini-invasive" or miniinvasive).tw,kw.
11. (("step-up" or stepup) adj3 (protocol* or approach*)).tw,kw.
12. OR/7-11
13. 6 AND 12
14. exp Endoscopy/
15. exp Laparoscopy/
16. (endoscop* or laparoscop* or peritoneoscop* or transluminal or eus).tw,kw.
17. OR/14-16
18. 13 AND 17
19. exp randomized controlled trial/
20. Controlled clinical trial.pt
21. (randomised OR randomized).tw,kw
22. Drug therapy.fs
23. Randomly.ab
24. Trial.ab
25. Groups.ab
26. OR/19-25
27. exp animals/ not humans.sh
28. 26 not 27
29. 18 and 28
30. 29 NOT (“case reports” OR editorial or “systematic review” or “meta-analysis” or review).pt
31. ..dedup 30

PICO 4: In patients with suspected infected or symptomatic pancreatic and/or peri-pancreatic collections who are undergoing initial per-oral endoscopic transluminal drainage, should plastic versus metal stents be used?

1. exp Pancreatitis/ or exp Pancreatitis, Acute Necrotizing/ or exp Pancreatic Pseudocyst/
2. ((necrotizing or necrotising or hemorrhag*) adj2 pancrea*).tw,kw
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatides or pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Stents/ or stent*.tw,kw
8. exp Plastics/ or plastic*.tw,kw
9. 7 and 8
10. exp Metals/ or metal*.tw,kw
11. 7 and 10
12. 6 and 9 and 11
13. exp randomized controlled trial/
14. Controlled clinical trial.pt
15. (randomised OR randomized).tw,kw
16. Drug therapy.fs
17. Randomly.ab
18. Trial.ab
19. Groups.ab
20. OR/13-19
21. exp animals/ not humans.sh
22. 20 not 21
23. 12 and 22
24. 23 not (“case reports” OR editorial or “systematic review” or “meta-analysis” or review).pt
25. ..dedup 24

PICO 5:In patients with suspected infected or symptomatic walled off necrotic collections (WON), should upfront transluminal endoscopic necrosectomy versus endoscopic drainage (i.e drainage followed by subsequent on demand necrosectomy) be used as a management strategy?

1. exp Pancreatitis/ or exp Pancreatitis, Acute Necrotizing/ or exp Pancreatic Pseudocyst/
2. ((necrotizing or necrotising or hemorrhag*) adj2 pancrea*).tw,kw.
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.

5. (pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Treatment Delay/ OR exp Time-to-Treatment/ OR exp Time Factors/ OR exp Early Medical Intervention/ OR ((time adj2 (treatment or factor*)) or "treatment delay" or "door to treatment time" or "onset to treatment time" or "time to therapy").tw,kw. OR ((delay* or earlier or early or late or later or postpone* or immediate*) adj5 (drain* or treat* or therapy or intervention*)).tw,kw.
8. exp endoscopy/ or endoscop*.tw,kw
9. 7 and 8
10. ((upfront OR direct OR immediate) adj5 endoscop*).tw,kw
11. 9 or 10
12. exp Drainage/ OR (drain OR draining OR drainage).tw,kw
13. 6 AND 11 AND 12
14. exp randomized controlled trial/
15. Controlled clinical trial.pt
16. (randomised OR randomized).tw,kw
17. Drug therapy.fs
18. Randomly.ab
19. Trial.ab
20. Groups.ab
21. OR/14-20
22. exp animals/ not humans.sh
23. 21 not 22
24. 13 and 23
25. 24 not (“case reports” OR editorial or “systematic review” or “meta-analysis” or review).pt
26. ..dedup 25

PICO 6: In patients who underwent endoscopic drainage of walled off necrosis for suspected disconnected pancreatic duct, should transluminal plastic stents be placed or no stent placed after the initial metal stent(s) has been removed?

1. exp Pancreatitis/
2. exp Pancreatic Pseudocyst/
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.
4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatides or pancreatitis or pseudocyst or won or wopn).tw,kw.
6. or/1-5
7. exp Pancreatic Ducts/
8. (duct OR ducts OR wirsung* OR santorini OR papilla).tw,kw
9. 7 or 8

10. exp Stents/ or stent*.tw,kw
11. exp Plastics/ or plastic*.tw,kw
12. 10 and 11
13. exp Metals/ or metal*.tw,kw
14. 10 and 13
15. 6 and 9 and 12 and 14
16. exp randomized controlled trial/
17. Controlled clinical trial.pt
18. (randomised OR randomized).tw,kw
19. Drug therapy.fs
20. Randomly.ab
21. Trial.ab
22. Groups.ab
23. or/16-22
24. exp animals/ not humans.sh
25. 23 not 24
26. 15 and 25
27. exp cohort studies/
28. cohort*.tw
29. controlled clinical trial.pt OR observational study.pt
30. epidemiologic methods/
31. limit 30 to yr=1966-1989
32. exp case-control studies/
33. (case* and control*).tw
34. (case* and series).tw
35. or/27-29,31-34
36. exp animals/ not humans.sh
37. 35 not 36
38. 15 and 37
39. 26 or 38
40. 39 not (“case reports” OR editorials or “systematic review” or “meta-analysis” or review).pt
41. ..dedup 40

PICO 7: In patients with acute pancreatitis complicated by acute splanchnic vein thrombosis should therapeutic anticoagulation versus no anticoagulation be used for treatment?

1. exp Pancreatitis/
2. exp Pancreatic Pseudocyst/
3. ((peripancreatic or 'peri-pancreatic' or pancreatic) adj2 (necrosis or necroses or necrotizing or necrotising or 'fluid collection')).tw,kw.

4. ('pancreas pseudocyst' or 'walled off necrosis' or 'walled off pancreatic necrosis' or 'walled off pancreas necrosis' or 'acute necrotic collection' or 'peripancreatic fluid collection' or 'peripancreatic necrosis' or 'pancreas necrosis' or 'pancreatic fluid collection').tw,kw.
5. (pancreatides or pancreatitis or pseudocyst or won or wopn).tw,kw.
6. exp Thrombosis/ and (exp Splenic Vein/ or Portal Vein/)
7. ((portal or splenic or mesenteric) adj3 (thrombosis or thromboses)).tw,kw.
8. ("porto thromboses" or pylethrombosis or svt or smv or mvt or pvt).tw,kw.
9. or/1-8
10. exp Anticoagulants/
11. (anticoagulation or anticoagulant*).tw,kw.
12. exp Warfarin/
13. (warfarin or adolsine or aldocumar or athrombinek or befarin or circuvit or coumadin* or coumafene or coumaphene or dagonal or farin or jantoven or kumatox or marevan or martefarin or orafin or panwarfarin or panwarfin or prothromadin or sofarin or tedicumar or tintorane or uniwarfin or waran or warfant or warfar or warfarine or warfilone or warnerine).tw,kw.
14. exp Heparin/
15. (heparin or beparine or clarin or contusol or disebrin or eleparon or elheparin or elheparon or hepaflex or heparine or heparinic or hepcon or liquaemin or liquemin or liquemine or menaven or monoparin or nevparin or noparin or uniparin or vetren or vister or vr496 or 'vr 496' or lmwh).tw,kw.
16. (apixaban or eliquis or aboxoma or apixaben or eliques or lunast or bms562247 or 'bms 562247' or 'bms 562247 01').tw,kw.
17. exp Rivaroxaban/
18. (rivaroxaban or assubex or kriva or naxat or rivaro or rivaolto or rivxa or throsaben or xanirva or xerdoxo or xindus or xarelto or 'bay 59-7939' or 'bay 597939' or 'bay 59 7939').tw,kw.
19. exp Dabigatran/
20. (pradaxa or pradax or pradaxar or rendix or telexer or trangian or wasedoc or abagat or abidoax or dabicat or dabikaste or dabiperel or dabitex or daxirem or dabigatran or 'bibr 1048').tw,kw.
21. or/10-20
22. 9 and 21
23. exp randomized controlled trial/
24. Controlled clinical trial.pt.
25. (randomised or randomized).tw,kw.
26. Drug therapy.fs.
27. Randomly.ab.
28. Trial.ab.
29. Groups.ab.
30. or/23-29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 22 and 32
34. exp cohort studies/
35. cohort*.tw.
36. (controlled clinical trial or observational study).pt.

37. epidemiologic methods/
38. limit 37 to yr=1966-1989
39. exp case-control studies/
40. (case* and control*).tw.
41. (case* and series).tw.
42. or/34-36,38-41
43. exp animals/ not humans.sh.
44. 42 not 43
45. 22 and 44
46. 33 or 45
47. 46 not ("case reports" or editorials or "systematic review" or "meta-analysis" or review).pt.
48. remove duplicates from 47

Supplemental Table 5. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Phase	Shared search	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5	PICO 6	PICO 7
Initial literature search								
Records screened	1016	919	166	2979	99	74	692	1605
Records excluded	938	909	164	2956	96	73	680	1564
Reports assessed for eligibility	78	10	2	23	3	1	12	41
Studies included in SR/MA	—	1	1	5	6	5	4	17
Updated search, March 2026								
Records screened	—	372	124	683	87	113	124	341
Records excluded	—	366	120	679	85	108	121	333
Reports assessed for eligibility	—	6	4	4	2	5	3	8
Additional studies included in SR/MA	—	0	0	0	0	4	0	3

Records identified from the initial literature search: n = 7550. Records identified from the updated literature search, March 2026: n = 1844. Of the records excluded in the initial search, PICO 3 (n = 2956) were excluded using an AI-assisted screening tool. Counts transcribed directly from the PRISMA flow diagram in the source file; screened minus excluded equals assessed for every column, and the per-column screened totals sum to the stated identified totals for both waves.

Source: Page MJ, et al. BMJ 2021;372:n71.

Supplemental Table 6. PICO 1 Baseline Characteristics — Immediate versus delayed drainage

PICO 1 Table 1: Baseline characteristics of studies comparing immediate vs delayed drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections																				
1st Author last name	**Year**	**Country**	**Abstract or Full article**	**Study design**	**Total number of patients, n (%)**	**Definition of infected necrosis**	**Definition of Immediate vs delayed drainage**	**Number of patients with immediate drainage, n (%)**	**Number of patients with delayed drainage, n (%)**	**Age, mean or median years, (SD or IQR)**	**Men, n (%)**	**Cause of pancreatitis, Gallstone, alcohol, TG, other, n (%)**	**Number of patients with severe pancreatitis, (breakdown of severe and moderate), n (%)**	**Degree of encapsulation, n (%)**	**Number of patients with necrosis,<30% 30-50%, >50%, n (%)**	**Number of patients with infected necrosis, n (%)**	**Number of patients required necrosectomy, n (%)**	**Number of patients with endoscopic/catheter drainage, n (%)**	**Time to drainage, mean/median days, mean/median (SD, IQR)**	**Follow up time, days**
Boxhoorn	2021	Netherlands	Full	RCT	104	Gas in necrosis on imaging, positive culture or clinical evidence of infection	Immediate drainage: within 24 h of randomization; Delayed drainage: postponing drainage until when necrotic collections were largely or fully encapsulated	55 (52.9)	49 (47.1)	I: 60 (SD 14), D 59 (SD 11)	I: 32 (58), D: 32 (65)	I: gallstone 36 (65), alcohol 8 (15); D: gallstone 29 (59), alcohol 7 (14)	I: 7 (2), D: 6 (2)	None 1: 6 (11), D: 8 (16) Medium: 16 (29) 19 (39) Large 19 (35), 11 (22) Fully: 14 (25), 11(22)	I: <30%: 35 (64), 30-50%: 8 (15), >50%: 12 (22), D: <30%: 33 (67), 30-50%: 7 (14), >50%: 9 (18)	I: 55 (52.9), D: 49 (47.1)	I: 28 (51), D: 11 (22)	I: 55 (100), D: 30 (61)	I: 24 d (IQR: 20 - 30), D: median 29 d (IQR: 24-40)	I: 180, D: 180

D: delayed drainage, I: Immediate drainage, NA: not applicable, NR: not reported, RCT: randomized control trial, TG: triglyceride

Supplemental Table 7. PICO 1 Outcomes — Immediate versus delayed drainage

PICO 1 Table 2. Outcomes of studies comparing immediate vs delayed drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections														
1st Author last name	**Mortality, n (%)**	**AE Composite, n (%)**	**AE Perforation or enterocutaneous fistula, n (%)**	**AE bleeding, n (%)**	**New onset organ failure, n (%)**	**Respiratory failure (intubation), n (%)**	**AKI (new onset), n (%)**	**Cardiovascular failure (new onset), n (%)**	**Renal replacement therapy (new onset), n (%)**	**Multi-organ failure (new onset), n (%)**	**Need for rescue surgical necrosectomy, n (%)**	**30-day re-admission, n (%)**	**LOS, days**	**Number of interventions required (immediate)**
Boxhoorn	I: 7 (13), D: 5 (10)	NR	I: 5 (9), D 4 (8)	I: 8 (15), D: 10 (20)	I: 14 (25), D: 11 (22)	I: 5 (9), D: 8 (16)	I: 3 (5), D: 4 (8)	I: 11 (20), D: 9 (18)	NR	I: 4 (7), D: 4 (8)	NR	NR	I: 59 (50 to 70), D: 51 (40 to 65)	I: 4.4, D: 2.6

AE: Adverse events, AKI: Acute kidney injury, I: immediate drainage, D: delayed drainage, LOS: length of hospital stay, NR: not reported

Supplemental Table 8. PICO 1 Evidence Profile — Immediate versus delayed drainage

Question: Immediate compared to delayed drainage in patients with a suspected infection of pancreatic and/or peri-pancreatic collections in the early phase of acute pancreatitis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	immediate	delayed drainage	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious[a]	not serious	not serious	extremely serious[b]	none	7/55 (12.7%)	5/49 (10.2%)	**RR 1.25** (0.42 to 3.68)	**26 more per 1,000** (from 59 fewer to 273 more)	⨁◯◯◯ Very low[a,b]	CRITICAL
New Onset Organ Failure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	14/55 (25.5%)	11/49 (22.4%)	**RR 1.13** (0.57 to 2.26)	**29 more per 1,000** (from 97 fewer to 283 more)	⨁⨁◯◯ Low[a,c]	CRITICAL
Perforation or enterocutaneous fistula												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	5/55 (9.1%)	4/49 (8.2%)	**RR 1.11** (0.32 to 3.91)	**9 more per 1,000** (from 56 fewer to 238 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Bleeding												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	8/55 (14.5%)	10/49 (20.4%)	**RR 0.71** (0.31 to 1.66)	**59 fewer per 1,000** (from 141 fewer to 135 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Respiratory Failure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	5/55 (9.1%)	8/49 (16.3%)	**RR 0.56** (0.20 to 1.59)	**72 fewer per 1,000** (from 131 fewer to 96 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Renal Failure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	3/55 (5.5%)	4/49 (8.2%)	**RR 0.67** (0.16 to 2.84)	**27 fewer per 1,000** (from 69 fewer to 150 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Cardiovascular Failure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	11/55 (20.0%)	9/49 (18.4%)	**RR 1.09** (0.49 to 2.40)	**17 more per 1,000** (from 94 fewer to 257 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Avoidance of procedure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	0/55 (0.0%)	19/49 (38.8%)	**RR 0.02** (0.00 to 0.37)	**380 fewer per 1,000** (from 244 fewer to --)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Need for at least one procedure												
1	randomised trials	not serious[a]	not serious	not serious	very serious[d]	none	55/55 (100.0%)	30/49 (61.2%)	**RR 1.62** (1.30 to 2.02)	**380 more per 1,000** (from 184 more to 624 more)	⨁⨁◯◯ Low[a,d]	IMPORTANT
Number of interventions required												
1	randomised trials	not serious[a]	not serious	not serious	very serious[c]	none	55	49	-	MD **1.8 interventions more** (0.6 more to 3 more)	⨁⨁◯◯ Low[a,c]	IMPORTANT
Length of hospital stay												
1	randomised trials	not serious[a]	not serious	not serious	very serious[e]	none	55	49	-	MD **8 days more** (9 fewer to 23 more)	⨁⨁◯◯ Low[a,e]	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Four participants in immediate were delayed for mean of 4 days versus 1 in the delayed group. Small number of participants impacted and mean of 4 days and thus less likely to impact outcomes such as number of procedures (already less in delayed group) or complications.
b. Crosses MID 1.4% multiple times and low event rate (less than 300)
c. Ratio of lower to upper CI meets at least ~3 for RR. Additionally, event rate is less than 300. Thus, downgraded twice.
d. Low event rate (less than 300)
e. Confidence interval shows both appreciable benefit and less desirable outcome. Additionally much smaller than OIS.

Supplemental Table 9. PICO 1 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	**Moderate**	High			No included studies
Cost effectiveness	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Supplemental Table 10. PICO 2 Baseline Characteristics — Minimally invasive surgical step-up approach versus open surgical necrosectomy

PICO2 Table 1: Baseline characteristics of studies comparing minimally invasive surgical step-up approach to open surgical necrosectomy as an initial management strategy In patients with a suspected infection of pancreatic and/or peri-pancreatic collections

1st Author last name	Year	Country	Abstract or full article	Study design	Total number of patients, N (%)	Definition of infected necrosis	Number of patients with open surgical necrosectomy, N (%)	Number of patients with surgical step-up approach, N (%)	Age, mean or median years, (SD or IQR)	Men, No (%)	Cause of pancreatitis, N (%) gallstone, alcohol, Tg, other	Number of patients with severe pancreatitis, N (%)	Degree of encapsulation	Number of patients with necrosis,<30 % 30-50%, >50%, N (%)	Number of patients with infected necrosis, N (%)	Number of patients required necrosectomy, N (%)	Number of patients with endoscopic/catheter drainage, N (%)	Time to drainage, mean/median days, mean/median (SD, IQR)	Follow up time, days
Van Santvoort (PANTER)	2010	Netherlands	full	RCT	88 (100)	pos culture, pos gas, or clinical suspicion; "confirmed infection" rates - o-42(93; s-39(91)	45	43	O: 57.4+/-2.0; S: 57.6+/-2.1	O: 33(73); S: 31(72)	O: gallstone: 29(64), alcohol 5(11), TG: nr, other: 11 (24); S: gallstone 26(60), alcohol: 3(7), TG: nr, other: 14(33)	nr	nr	O: 19(42), 10(22), 16(36); S: 17(40), 14(33), 12(28)	O: 45 (100); S: 43 (100)	O: 45 (100); S: 26 (60.5) (via VARD+laparotomy)	O: 0 (0); S: 43 (100)	O: 29 (12-25), S 30 (11-71) *	nr

IQR: interquartile range, NR: not reported, O: open surgical necroscetomy, S: surgical step-up approach, SD: standard deviation, TG: Triglyceride, VARD: video assisted retroperitoneal debridement.
*Time since the onset of symptoms

Supplemental Table 11. PICO 2 Outcomes — Minimally invasive surgical step-up approach versus open surgical necrosectomy

PICO2 Table 2: Outcome of studies comparing minimally invasive surgical step-up approach to open surgical necrosectomy as an initial management strategy In patients with a suspected infection of pancreatic and/or peri-pancreatic collections																	
1st Author last name	**Mortality**	**Intubation, n (%)**	**AKI, n (%)**	**Cardiovascular failure, n (%)**	**hypotension /pressers, n (%)**	**New onset multi-organ failure or systemic complication, n (%)**	**Procedural AE composite, n (%)**	**Bleeding, n (%)**	**Fistula, n(%)**	**Incisional hernia, n (%)**	**long term AE, n (%)**	**EPI, n (%)**	**DM, n (%)**	**Need for cross over to other therapy, n (%)**	**Number of interventions required, n (%)**	**30-day readmission, n (%)**	**LOS, median days (range or IQR)**	**Need for necrosectomy, n(%)**
Van Santvoort (PANTER)	O: 8 (19), S: 7 (16)	nr	nr	nr	nr	O: 19 (42), S: 5 (12)	nr	O: 10 (22), S: 7(16)	O: 17(38), S: 12(28)	O: 11(24), S: 3(7)	nr	O: 15 (33), S: 3 (7) - defined by use of PERT	O: 17 (38), S: 7 (16)	O: 0 (0), S: 30 (65)	nr	nr	O: 60 (range 1-247), S: 50 (1-287)	O: 45 (100), S: 26 (60)

AKI: acute kidney injury, AE: adverse events, EPI: exocrine pancreatic insufficiency, DM: diabetes mellitus. IQR: interquartile range, NR: not reported, O: open surgical necrosectomy, S: step-up approach surgical approach

Supplemental Table 12. PICO 2 Evidence Profile — Minimally invasive surgical step-up approach versus open surgical necrosectomy

Question: Minimally invasive surgical step-up approach compared to open surgical necrosectomy for an initial interventional management strategy in patients with suspected infected pancreatic and/or peri-pancreatic collections

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	minimally invasive surgical step-up approach	open surgical necrosectomy	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	not serious	not serious	not serious	extremely serious[a]	none	8/43 (18.6%)	7/45 (15.6%)	**RR 1.20** (0.48 to 3.01)	**31 more per 1,000** (from 81 fewer to 313 more)	⊕◯◯◯ Very low[a]	CRITICAL
Mortality (observational) (minimally invasive step up/catheter)												
15	non-randomised studies	not serious[b]	not serious[c]	not serious	very serious[d]	none	70/376 (18.6%)	87/376 (23.1%)	**RR 0.80** (0.61 to 1.06)	**46 fewer per 1,000** (from 90 fewer to 14 more)	⊕◯◯◯ Very low[b,c,d]	CRITICAL
Mortality (observational) (endoscopic)												
15	non-randomised studies	not serious[b]	not serious	not serious	serious[e,f]	none	17/158 (10.8%)	48/158 (30.4%)	**RR 0.35** (0.21 to 0.59)	**197 fewer per 1,000** (from 240 fewer to 125 fewer)	⊕◯◯◯ Very low[b,e,f]	CRITICAL
New onset multiple-organ failure or systemic complication (follow-up: 6 months)												
1	randomised trials	not serious	not serious	not serious	serious[e,g]	none	5/43 (11.6%)	19/45 (42.2%)	**RR 0.28** (0.11 to 0.67)	**304 fewer per 1,000** (from 376 fewer to 139 fewer)	⊕⊕⊕◯ Moderate[e,g]	CRITICAL
Intraabdominal bleeding requiring intervention												
1	randomised trials	not serious	not serious	not serious	very serious[e,h]	none	7/43 (16.3%)	10/45 (22.2%)	**RR 0.73** (0.31 to 1.75)	**60 fewer per 1,000** (from 153 fewer to 167 more)	⊕⊕◯◯ Low[e,h]	CRITICAL
Pancreatic fistula												
1	randomised trials	not serious	not serious	not serious	very serious[h]	none	12/43 (27.9%)	17/45 (37.8%)	**RR 0.74** (0.40 to 1.36)	**98 fewer per 1,000** (from 227 fewer to 136 more)	⊕⊕◯◯ Low[h]	CRITICAL
Exocrine pancreatic insufficency (assessed with: Use of pancreatic enzymes)												
1	randomised trials	not serious	not serious	serious[i]	serious[e]	none	3/43 (7.0%)	15/45 (33.3%)	**RR 0.21** (0.07 to 0.67)	**263 fewer per 1,000** (from 310 fewer to 110 fewer)	⊕⊕◯◯ Low[e,i]	IMPORTANT
New onset diabetes												
1	randomised trials	not serious	not serious	serious[j]	serious[k]	none	7/43 (16.3%)	17/45 (37.8%)	**RR 0.43** (0.20 to 0.94)	**215 fewer per 1,000** (from 302 fewer to 23 fewer)	⊕⊕◯◯ Low[j,k]	IMPORTANT
Incisional hernia												
1	randomised trials	not serious	not serious	not serious	very serious[f,k]	none	3/43 (7.0%)	11/45 (24.4%)	**RR 0.29** (0.09 to 0.95)	**174 fewer per 1,000** (from 222 fewer to 12 fewer)	⊕⊕◯◯ Low[f,k]	IMPORTANT
Need for necrosectomy (laparotomy or VARD)												
1	randomised trials	not serious	not serious	not serious	serious[f]	none	26/43 (60.5%)	45/45 (100.0%)	**RR 0.61** (0.48 to 0.77)	**390 fewer per 1,000** (from 520 fewer to 230 fewer)	⊕⊕⊕◯ Moderate[f]	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	minimally invasive surgical step-up approach	open surgical necrosectomy	Relative (95% CI)	Absolute (95% CI)		
Length of stay												
1	randomised trials	not serious	not serious	not serious	very serious[l]	none	Step up: median 50 days (range 1-287) Open: median 60 days (range 1-247) p value: 0.53				⨁⨁◯◯ Low[l]	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Crossed minimally important difference threshold of 1.4% multiple times. Low event rate. Additionally, upper to lower boundary of CI is more than 3 for risk ratio. Confidence interval includes both appreciable harm and benefit.
b. Confounding and publication of unpublished studies included, however started at low
c. Utilized patient level data and thus did not assume inconsistency with adjustment calculations
d. Crossed MID of 1.4%, low event rate, confidence interval includes both appreciable harm and benefit
e. low sample size (less than 400) in the setting of large effect side (.25 or above/below)
f. Low event rate (less than 300)
g. Using a threshold of 5%, the clinically meaningful difference is not crossed
h. Crosses minimally important threshold of 5% for both benefit and clear harm
i. use of pancreatic enzymes is surrogate marker for exocrine pancreatic insufficiency
j. new use of oral anti-diabetic medication or insulin is surrogate
k. Crosses minimally important threshold of 5%
l. Overall low sample size and insignificant p value in setting of no confidence interval and only median ranges

Supplemental Table 13. PICO 2 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	**Large**		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Supplemental Table 14. PICO 3 Baseline Characteristics — Endoscopic transluminal approach versus minimally invasive surgical step-up approach

PICO3 Table 1: Baseline characteristics of studies comparing per-oral endoscopic transluminal approach to minimally invasive surgical step-up approach as the initial management strategy in patients with a suspected infection of pancreatic and/or peri-pancreatic collections																				
1st Author last name	Year	Country	Abstract or Full article	Study design	Total number of patients, N (%)	Definition of infected necrosis / notes on eligibility	Number of patients with initial per-oral endoscopic transluminal approach, N (%)	Number of patients with surgical step-up , N (%)	Method of surgical drainage	Method of endoscopic drainage	Age, mean or median years, (SD or IQR)	Men, No (%)	Cause of pancreatitis, N (%) Gallstone, alcohol, Tg, other	Number of patients with severe pancreatitis, N (%) (breakdown of severe and moderate)	Degree of encapsulation	Number of patients with necrosis, <30% 30-50%, >50%, N (%)	Number of patients with infected necrosis, N (%)	Number of patients required necrosectomy, N (%)	Number of patients with endoscopic/catheter drainage, N (%)	Time to drainage, mean/median days, mean/median (SD, IQR)	Follow up time, days
Angadi	2021	India	full article	RCT	40	Inclusion: WON >4wks and >6 cm plus 'symptom'; infection was clinical suspicion or pain or obstruction (GOO or biliary)	20	20	Laparoscopic transperitomial cystogastrostomy	Different stenting (PS vs LAMS) depending on the degree of necrosis	Endo: 36 (21-51); surg: 32 (16-60)	Endo: 17 (85); Surg: 18(90),	Endo: 3 (15), 5(25), nr, 12 (60);surg :2(10), 8(40), nr, 10(50)	endo - mod 16 (80), sever 4 (20); surg: mod 16 (80) sever 4 (20)	100% had mature wall	Endo: 15 (60) <1/3; surg: 15(75) <1/3	endo 1(5); surg 2(10)	nr	Endo: 20 (100); surg: 3(15)	nr	nr
Bakker (PENGUIN)	2012	Netherlands	full article	RCT	20 (2 were excluded from surg necrosectomy arm)	FNA, gas, or suspicion	10	10	CARDs and If not feasible then open necrosectomy Through laparotomy using a bilateral subcostal incision (40%)	nr	endo: 62 (IQR: 58-70); surg: 64(IQR: 46-72)	endo 6(60); surg-8(80)	Endo: 6(60), 2(20), nr, (2(20); surg:7(70), 2(20), nr, 1(10)	nr	nr	Endo: 3(30), 2(20), 4(40); surg: 3(30), 2(20), 4(40);	endo 10(100); surg 9(90)	Endo; surg 10 (100)	endo 4(40); surg 8(80)	endo 48(IQR: 36-74); surg: 59 (IQR: 29-69)	nr
Bang	2019	US	full article	RCT	66	FNA, gas, or suspicion	34	32	Laparoscopic transperitomial cystogastrostomy or VARDS	nr	endo 59(IQR: 46-66); surg 57.5 (IQR45-64.5)	endo 22 (65); surg 21(66)	Endo: 14(41), 6(18), nr, 14(41); surg:8(25), 11(34), 1(3), 13(41)	nr	endo 21(62) were WON; surg 23(72) were WON;	nr	endo 31(91;)surg 30(94);	Endo; surg 32(100);	PCD prior to intervention endo 14(41); surg 9 (28)	reported as categorical	nr, 6 month follow-up
Garg	2019	India	full article	RCT	60	Pseudocysts or WON<30%; infection defined by fever	29	30	Laparoscopic cystogastrostomy	nr	endo 37.6(12.9); surg 34.1(12.7)	endo 22(73); surg (22(73)	endo 14 (47), 8(27), nr, 8(27); surg 13 (43), 9(30), nr, 8(27);	nr	100% for both groups	none with >30%	endo 2(7); surg 4(13)	nr	nr	endo 28.2(24.7); surg 20.1 (16.4),	all for at least 6 months; total median was 22 months (3-38) months
van Brunschot	2018	Netherlands	full article	RCT	98	FNA used for confirmed infected necrosis; surg group got catheter first	51	47	VARDS	nr	endo 63(14); surg 60(11)	endo 34 (67); surg 29(62)	endo 26 (51), 7(14), nr, 18(35); surg 30(64), 7 (15), nr, 10(21)	nr	endo 36(71) complete ; surg 33(70) were complete ,	Endo: 26(51), 15(29), 10(20); surg - 22(47), 10(21), 15(32)	endo 46(90); surg 46(98)	nr	nr	endo 39(28-54); surg 41(28-52)	

FNA: fine needle aspiration: IQR: interquartile range; nr: not reported RCT: randomized control trial; SD: standard deviation; VARDs: video-assisted retroperitoneal debridement; WON: walled-off necrosis

Supplemental Table 15. PICO 3 Outcomes — Endoscopic transluminal approach versus minimally invasive surgical step-up approach

PICO3 Table 2: Outcome of studies comparing per-oral endoscopic transluminal approach to minimally invasive surgical step-up approach as an initial management strategy In patients with a suspected infection of pancreatic and/or peri-pancreatic collections																		
First author	**Mortality**, n (%)	**Composite** AEs, N (%)	**Perforation**, N (%)	**Bleeding**, n (%)	**cutaneous fistula**, n (%)	**DM**, n (%)	**EPI**, n (%)	**New onset organ failure**, n (%)	**resp failure intubation**, n (%)	**AKI**, n (%)	**Dialysis**, n (%)	**cardiovascular (hypotension/pressor)**, n (%)	**New onset Multi-organ failure**, n (%)	**Need for salvage differed method for necrosectomy or second surgery (**escalation**)**, n (%)	**# of interventions required (count the original intervention as 1)**, mean/median (SD or IQR-range)	**LOS**, mean/median (SD or IQR-range)	**30-day readmission**, n (%)	**comments**
Angadi	endo 1(5); surg 0 (0)	-	endo 0 (0); surg 1(5)	endo 1(5); surg 1(5)	EC: endo 0 (0); surg 0 (0)	nr	nr	nr	nr	nr	nr	nr	nr	nr	nr	endo 4(IQR: 4-8); surg 6(IQR: 5-9);	nr	primary outcome was resolution of WON at 4 weeks - not recorded in table
Bakker (PENGUIN)	endo 1 (10), surg 4 (40)	-	endo 0 (0); surg 2 (20)	Endo 0 (0); surg: 0 (0)	endo 1 (10); surg 8 (80)	endo 2(22); surg 3 (50)	endo 0 (0); surg 3 (50)	nr	nr	nr	nr	nr	endo 0 (0); surg 5 (50)	endo 2 (20); surg 0 (0)	endo 3 (2-6); surg 1(1-2)	endo 45 (12-69); surg 36(17-74)	nr	primary outcome was serum IL6; in contrast to Angadi and Bang they did NOT exclude previous PCD
Bang (MISER)	endo 3(9); surg 2(6)	endo 4(11); surg 13(41)	Endo 0 (0); surg: 0 (0)	endo 0 (0); surg 3(9)	endo 0 (0); surg 9(28)	endo 6(27); surg 9(36)	endo 29(85); surg 28(88)	nr	nr	nr	nr	Endo 1 (2.9), surg 2 (5.7)	endo 2(6); surg 3(9)	endo 11 (32); surg 31(97)	Endo: 1(IQR: 1-2); surg: 1(IQR: 1-2)	endo 14 (IQR: 6-22); surg 19(IQR: 12-30)	nr	many had perc drains after randomization, but prior to intervention
Garg	Endo 0 (0); surg: 0 (0)	nr	endo 1(3); surg 0 (0)	endo 3 (10.3); surg 8(27)	EC: endo 0 (0); surg 1(3)	nr	nr	nr	Endo: 1 (3.4); surg 1(3)	nr	nr	Endo 0 (0), surg 1 (3.3)	Endo 1 (3.4), surg 1 (3.3)	endo 2 (6.8); surg 30 (100)	nr	endo 8 (range: 3-69); surg 7(range: 4-52)	nr	
van Brunschot	endo 9(18); surg 6(13)	endo 22(43); surg 21(45)	endo 4(8); surg 8(17)	endo 11(22); surg 10(21)	Endo: 2 (4.1), surg 13 (27.7)	endo 10 (23.8); surg 9 (22)	endo 22 (52.4); surg 19 (46.3)	nr	endo 4(8); surg 7(15)	endo 2(4); surg 6(13),	nr	endo 3(6); surg 9(19)	endo 2(4); surg 6(13)	endo 2(4); surg 0 (0)	endo 3(2-6); surg 4(2-6)	nr	nr	

AEs: adverse events; AKI: acute kidney injury; DM: diabetes mellitus; EC: enterocutaneous fistula; Endo: endoscopic transluminal drainage; EPI: exocrine pancreatic insufficiency; IQR: interquartile range; LOS: length of stay; nr: not reported; SD: standard deviation; surg: surgical step-up drainage

Supplemental Table 16. PICO 3 Evidence Profile — Endoscopic transluminal approach versus minimally invasive surgical step-up approach

Question: Per-oral endoscopic transluminal approach compared to minimally invasive surgical step-up approach for as initial interventional management strategy for suspected infected or symptomatic pancreatic and/or peri-pancreatic collections who require invasive treatment,

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	per-oral endoscopic transluminal approach	minimally invasive surgical step-up approach	Relative (95% CI)	Absolute (95% CI)		
Mortality												
5	randomised trials	not serious[a]	not serious	not serious	extremely serious[b,c,d]	none	14/140 (10.0%)	12/144 (8.3%)	**RR 1.23** (0.58 to 2.60)	**19 more per 1,000** (from 35 fewer to 133 more)	⊕◯◯◯ Very low[a,b,c,d]	CRITICAL
New onset single or multi-organ failure (assessed with: When MOF reported - was used.)												
4	randomised trials	not serious	not serious	not serious	very serious[c,e]	none	5/125 (4.0%)	15/124 (12.1%)	**RR 0.41** (0.15 to 1.10)	**71 fewer per 1,000** (from 103 fewer to 12 more)	⊕⊕◯◯ Low[c,e]	CRITICAL
Fistula formation (pancreatic or enterocutaneous, pancreatic used when EC combined with perforation)												
5	randomised trials	not serious[a]	not serious	not serious	serious[c]	none	3/140 (2.1%)	31/144 (21.5%)	**RR 0.14** (0.05 to 0.39)	**185 fewer per 1,000** (from 205 fewer to 131 fewer)	⊕⊕⊕◯ Moderate[a,c]	CRITICAL
Bleeding												
5	randomised trials	not serious[a,f]	not serious	not serious	very serious[c,d,e]	none	12/140 (8.6%)	14/144 (9.7%)	**RR 0.95** (0.47 to 1.92)	**5 fewer per 1,000** (from 52 fewer to 89 more)	⊕⊕◯◯ Low[a,c,d,e,f]	CRITICAL
Perforation												
5	randomised trials	not serious[a]	not serious	serious[g]	serious[c,e]	none	5/140 (3.6%)	11/148 (7.4%)	**RR 0.55** (0.21 to 1.43)	**33 fewer per 1,000** (from 59 fewer to 32 more)	⊕⊕◯◯ Low[a,c,e,g]	CRITICAL
Respiratory failure												
2	randomised trials	not serious	not serious	not serious	very serious[c,e,h]	none	4/80 (5.0%)	8/77 (10.4%)	**RR 0.50** (0.17 to 1.49)	**52 fewer per 1,000** (from 86 fewer to 51 more)	⊕⊕◯◯ Low[c,e,h]	IMPORTANT
Renal failure												
1	randomised trials	not serious	not serious	not serious	extremely serious[c,d,e]	none	2/51 (3.9%)	6/47 (12.8%)	**RR 0.31** (0.07 to 1.45)	**88 fewer per 1,000** (from 119 fewer to 57 more)	⊕◯◯◯ Very low[c,d,e]	IMPORTANT
Cardiovascular failure												
3	randomised trials	not serious[i]	not serious	not serious	very serious[c,e]	none	4/113 (3.5%)	12/112 (10.7%)	**RR 0.35** (0.12 to 0.99)	**70 fewer per 1,000** (from 94 fewer to 1 fewer)	⊕⊕◯◯ Low[c,e,i]	IMPORTANT
Diabetes												
3	randomised trials	not serious[j,k]	not serious	not serious	extremely serious[c,d,e]	none	18/87 (20.7%)	21/88 (23.9%)	**RR 0.87** (0.50 to 1.51)	**31 fewer per 1,000** (from 119 fewer to 122 more)	⊕◯◯◯ Very low[c,d,e,j,k]	IMPORTANT
EPI												
3	randomised trials	not serious[j]	not serious	serious[l]	extremely serious[c,d,e]	none	51/87 (58.6%)	50/88 (56.8%)	**RR 1.92** (0.81 to 1.28)	**523 more per 1,000** (from 108 fewer to 159 more)	⊕◯◯◯ Very low[c,d,e,j,l]	IMPORTANT
Need for escalation to more invasive intervention or repeat surgery at time of original intervention or future intervention for adverse event or pancreatic disease (6 month data used when able)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	per-oral endoscopic transluminal approach	minimally invasive surgical step-up approach	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	not serious[m]	not serious	not serious	very serious[c,e]	none	9/144 (6.3%)	14/144 (9.7%)	**RR 0.68** (0.31 to 1.52)	**31 fewer per 1,000** (from 67 fewer to 51 more)	⨁⨁◯◯ Low[c,e,m]	IMPORTANT
Number of intervention												
3	randomised trials	not serious	not serious[n]	not serious	very serious[d,o]	none	95	91	-	MD **0.22 procedure higher** (0.21 lower to 0.64 higher)	⨁⨁◯◯ Low[d,n,o]	IMPORTANT
LOS												
5	randomised trials	not serious	not serious[p]	not serious	very serious[h,o]	none	145	141	-	MD **3.61 days lower** (8.58 lower to 1.36 higher)	⨁⨁◯◯ Low[h,o,p]	IMPORTANT
Enterocutaneous fistula												
4	randomised trials	not serious	not serious	serious[g]	serious[e]	none	4/105 (3.8%)	10/113 (8.8%)	**RR 0.48** (0.18 to 1.33)	**46 fewer per 1,000** (from 73 fewer to 29 more)	⨁⨁◯◯ Low[e,g]	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Angadi2021: per protocol denominator of 17 was used instead of 20 to be conservative as 3 never got allocated endoscopic treatment.
b. Crosses MID of 1.4% at multiple thresholds
c. Low event rate (less than 300)
d. Crosses both meaningful benefit and harm
e. Crosses MID of 5%
f. Garg2019: bleeding from puncture sites (2) was not counted as bleeding as controlled bleeding during surgery or endoscopy was deemed part of the procedure as it did not involve "escalation of care."
g. A study reported EC fistula and perforation together
h. CI includes both meaningful benefit and no effect
i. Garg2019: septic shock was counted for CV failure to capture it, but not in overall new organ failure outcome
j. Per protocol data was used for certain study as was presented in this manner. Given conservative nature of using per protocol for harms and did not assume that majority in ITT would have gotten disease, did not assume risk of bias
k. vanbrunschot2018- used endocrine insufficiency
l. Definition of EPI is heterogenous and unreliable. When pancreatic elastase proportions were available, this was used.
m. Unclear escalation in Brunschot2018 in surgery arm for adverse event etc, however overall did not downgrade for risk of bias
n. Bakker 2012: surgery # of necrosectomy, endoscopy # of procedure. Bang 2019: # of endoscopic and surgery procedures only, Brunchot 2018: # of drainage procedures including percutaneous
o. Low sample size (less than 400)
p. LOS may be from time of intervention or randomization

Supplemental Table 17. PICO 3 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Supplemental Table 18. PICO 4 Baseline Characteristics — Metal stents versus plastic stents

PICO 4 Table 1: Baseline characteristics of studies comparing the use of plastic versus metal stents for initial per-oral endoscopic transluminal drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections

1st Author last name	Year	Country	Abstract or Full article	Study design	Total number of patients, n (%)	Definition of infected necrosis	Number of patients with endoscopic drainage with plastic stents, n (%)	Number of patients with endoscopic drainage with metal stent, n (%)	Age, mean or median years, (SD or IQR)	Men, No (%)	Cause of pancreatitis, N (%) Gallstone, alcohol, Tg, other	Number of patients with severe pancreatitis, N (%) (breakdown of severe and moderate)	Degree of encapsulation	Number of patients with necrosis,< 30% 30-50%, >50%, n (%)	Number of patients with infected necrosis, n (%)	Number of patients required necrosectomy, n (%)	Number of patients with endoscopic/catheter drainage, n (%)	Time to drainage, mean/median days, mean/median (SD, IQR)	Follow up time, days
Bang	2019	US	Full	RCT	60	inclusion - suspected infected or symptomatic WON	**29**	**31**	MS: 55.8(15.6), PS: 60.3(13.0)	MS: 20(65), PS: 16(55)	MS: 6(19), 9(29), 0, 16(51); PS: 10(35), 5(17), 0, 14(48)	nr	100% encapsulated	nr	MS: 27(87), PS: 26(90)	MS: 4 (12.9), PS: 6 (20.7)	MS: 2 (6.5), PS: 5 (17.2)	nr	6 months for MS and PS
Gornals (PROMETHEUS)	2024	Spain	Full	RCT	64	inclusion are unclear; gas, FNA, suspicion	33	31	MS: 60(13.5), PS: 62(15)	MS: 25(76), PS: 20(64)	MS: 19(59), 9(28), nr, 4(13); PS: 18(58), 8(25), nr, 5(16)	nr	100% WON	<50% - M 22(66), P 11(36); >50% M 11(33), P 19(63)	MS: 13 (40), PS: 13(42)	MS: 1 (3.2), PS: 0 (0)	nr	nr	nr
Kakadiya	2023	India	Full	RCT	48	inclusion symptomatic WON	24	24	MS: 35.4(11.8), PS: 38.2 (12.7)	MS: 18(75), PS: 20(83)	MS: 10(42), 9(38), nr, 5(21); PS: 10(42), 10(42), nr, 4(17)	nr	nr	nr	MS: 9(38), PS 3(13)	nr	nr	MS: 8(17.5), PS: 12(10) weeks	nr
Karstensen	2023	Denmark	Full	RCT	42	inclusion symptomatic WON, including infxn	22	20	MS: 59.4 (13), PS 61.1 (14.3)	MS 15(75); PS 17 (77)	MS 14(70), 5(25), nr, 1(5); PS: 10(46), 5 (23), nr, 7(33)	nr	nr	nr	MS 20(100), PS 20(91)	MS 8(42), PS 11(50)	MS 3(15), PS 1(5)	MS: 28 (21-41), PS: 25 (22-41)	nr
Koduri	2024	India	Full	RCT	92	inclusion - symptomatic WON	46	46	MS: 34.9(12.4); PS: 36.8(11.1)	MS: 38(83), PS: 38(83)	MS: 16(35), 14(30), nr, 16(35); PS: 7(15), 21(46), nr, 18(39)	nr	100% mature en-capsulted	nr	MS 31(67), PS 33(72)	nr	PTC MS 2(4), PS 7(15)	nr	nr
Moon	2024	South Korea	Full	RCT	46	FNA, gas, suspicion	23	23	MS: 38.5 (38.5-60), PS: 49(41.5-62)	MS: 16(70), PS: 11(48)	MS: 0, 8(35), 1(4), 15 (65); PS: 1(4), 9(39), 1(4), 11(48)	nr	100% well defined capsule	nr	nr	nr	PTC 2(9) MS 8(35)	nr	nr

IQR: interquartile range; FNA: fine needle aspiration; MS: metal stent; nr: not reported; P: plastic stent; RCT: randomized control trial; SD: standard deviation; Won: walled-off necrosis

Supplemental Table 19. PICO 4 Outcomes — Metal stents versus plastic stents

PICO 4 Table 2. Outcomes of studies comparing the use of plastic versus metal stents for initial per-oral endoscopic transluminal drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections											
1st Author last name	**Composite AEs, n (%)**	**perforation, n (%)**	**bleeding, n (%)**	**stent dysfunction (migrated, occluded, etc) , n (%)**	**Need for surgical necrosectomy (escalation), n (%)**	**# of endoscopic sessions required,** mean/median (SD, IQR)	**LOS hospital, mean/**median (SD, IQR)	**30-day re-admission, n (%)**	**duration of procedure (minutes), mean/**median (SD, IQR)	**amount of time before exchanging initial stent and characterize when bleeding occurred**	**comments**
Bang	nr	MS: 0 (0), PS: 0 (0)	MS: 7 (22.6), PS: 1 (3.4)	MS: 10(32), PS: 2(7)	MS: 1 (3.2), PS: 0 (0)	MS: 8 (1.2), PS: 2 (1.5)	MS: 6.2(9), PS: 12.2 (21.1)	readmissions during 6 months - M-10 (33), P 11 (39)	MS: 18(15.5), PS: 41.6 (25.7)	prior to protocol>3wks: M8(26), P0; after protocol change M 2(7), P 2 (6.9)	
Gornals (PROMETHEUS)	nr	MS: 1 (3), PS: 0 (0)	MS: 5 (15), PS: 3 (10)	MS: 12 (36.4), PS: 14 (45.2)	MS: 1(3), PS: 0 (0)	MS: 3(2-3), PS: 3(2-4)	MS: 5(3-16), PS: 15(5-24)	nr	MS 35(24-50), PS 45(38-63)	nr	
Kakadiya	nr	MS: 0 (0), PS: 0 (0)	MS: 1(4), PS: 1(4)	MS: 0 (0), PS: 3(13)	MS: 1 (4), PS: 0 (0)	MS: 2.8(1), PS: 2.2(1)	MS: 8.5 (11), PS: 5 (5)	nr	MS 13(5.3), PS: 25 (7)	Metal stent replaced with plastic in 15 pts	
Karstensen	MS: 1(5) PS: 3 (14)	MS: 0 (0), PS: 2 (9)	MS: 0 (0), PS: 1 (5)	nr	MS: 3 (16), PS: 1 (5) (VARD or surgical nec)	MS: 5(3-10), PS: 7 (5-11)	M 58(40-86), P 43 (40-67)	nr	MS: 30(28-54), PS: 59(36-67)	nr	1 death in each group
Koduri	nr	MS: 0 (0), PS: 0 (0)	MS: 0 (0), PS: 1 (2)	MS: 3 (7), PS: 0 (0)	MS: 0 (0), PS: 0 (0)	MS: 5, PS: 9	MS 7(3.4), PS 21 (9)	nr	MS 19.6 (7.5), PS: 21.4 (9)	nr	
Moon	nr	MS: 0 (0), PS: 0 (0)	MS: 0 (0), PS: 1 (4)	MS: 6 (26), PS: 12 (52)	MS: 0 (0), PS: 1 (4)	MS: 9(8-9), PS 4(2.5-5)	nr	nr	MS: 6.8(4.4-10.7), PS: 8.5(7.8-9.9)	nr	**note that this study includes a minority of CP and postop patients (35%); Also reported death in 0 in metal group and 2(9) in plastic group

AEs: adverse events; IQR: interquartile range; LOS: length of stay; MS: metal stent; nr: not reported; P: plastic stent; SD: standard deviation; VARD: video assisted retroperitoneal debridement; Won: walled-off necrosis

Supplemental Table 20. PICO 4 Evidence Profile — Metal stents versus plastic stents

Question: Metal stents compared to plastic stents for initial per-oral endoscopic transluminal drainage In patients with suspected infected or symptomatic pancreatic and/or peri-pancreatic collections

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	metal stents	plastic stents	Relative (95% CI)	Absolute (95% CI)		
Bleeding												
6	randomised trials	not serious	not serious	not serious	extremely serious[a,b]	none	13/176 (7.4%)	8/175 (4.6%)	**RR 1.37** (0.56 to 3.37)	**17 more per 1,000** (from 20 fewer to 108 more)	⊕◯◯◯ Very low[a,b]	CRITICAL
Perforation (symptomatic or required treatment)												
6	randomised trials	not serious	not serious	not serious	very serious[a,b,c]	none	1/176 (0.6%)	2/175 (1.1%)	**RR 0.76** (0.07 to 8.81)	**3 fewer per 1,000** (from 11 fewer to 89 more)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
Stent-related adverse event (defined by study)												
5	randomised trials	not serious[d]	not serious	not serious[e]	extremely serious[a,b,c]	none	31/157 (19.7%)	31/153 (20.3%)	**RR 1.06** (0.37 to 3.05)	**12 more per 1,000** (from 128 fewer to 415 more)	⊕◯◯◯ Very low[a,b,c,d,e]	CRITICAL
Need for surgical necrosectomy (inclusive of VARD)												
6	randomised trials	not serious	not serious	not serious	very serious[a,b,c]	none	6/176 (3.4%)	2/175 (1.1%)	**RR 2.15** (0.60 to 7.72)	**13 more per 1,000** (from 5 fewer to 77 more)	⊕⊕◯◯ Low[a,b,c]	CRITICAL
Number of procedures to achieve clinical success (endoscopic priority, perc drain if combined)												
6	randomised trials	not serious[f,g]	serious[h]	not serious	very serious[i,j]	none	176	175	-	MD **0.54 procedure higher** (1.28 lower to 2.35 higher)	⊕◯◯◯ Very low[f,g,h,i,j]	IMPORTANT
Length of procedure												
6	randomised trials	not serious	not serious	not serious	serious[j]	none	176	175	-	MD **9.93 minutes lower** (16.75 lower to 3.11 lower)	⊕⊕⊕◯ Moderate[j]	IMPORTANT
Length of of hospital stay												
5	randomised trials	not serious	not serious	not serious	very serious[j,k]	none	153	152	-	MD **1.47 days lower** (5.98 lower to 3.04 higher)	⊕⊕◯◯ Low[j,k]	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Crosses minimally important threshold of 5%
b. Low event rate
c. Wide confidence interval
d. Bang et al made a protocol amendment for 6 week CT to 3 weeks
e. High inconsistency index, however suspect this is due to varying definition of stent related adverse events
f. One study dilated the plastic stent group to maintain patency, which is not the typical treatment algorithm and this does increase the number of procedures in the plastic stent group.
g. Unclear risk of bias given no blinding and thus difficult to assess for performance bias during necrosectomy and varying tools used. Additionally, a minority of studies also did not have defined objective definitions for when to escalate for necrosectomy
h. Endoscopic procedures were given priority when presented, however some studies reported composite data inclusive of percutaneous which was usually more in pigtail arm. One study was a clear outlier (Moon 2024), which could not be accounted for and thus in conjunction for ROB downgrading was only done once.
i. CI includes both less and more procedures.
j. Low sample size (less than 400)
k. CI includes both less and more days

Supplemental Table 21. PICO 4 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	**Low**	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Supplemental Table 22. PICO 5 Baseline Characteristics — Upfront versus on-demand endoscopic necrosectomy

PICO 5 Table 1: Baseline characteristics of studies comparing upfront transluminal endoscopic necrosectomy versus on demand subsequent necrosectomy after initial endoscopic drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections subsequent																			
1st Author last name	Year	Country	Abstract or Full article	Study design	Total number of patients, N (%)	Definition of infected necrosis	Number of patients with upfront transluminal endoscopic necrosectomy , N (%)	Number of patients with endoscopic on demand necrosectomy , N (%)	Age, mean or median years, (SD or IQR)	Men, N (%)	Cause of pancreatitis, N (%) Gallstone, alcohol, Tg, other	Number of patients with severe pancreatitis , N (%) (breakdown of severe and moderate)	Degree of encapsulation	Number of patients with necrosis,<30% 30-50%, >50%, N (%)	Number of patients with infected necrosis, N (%)	Number of patients required necrosectomy, N (%)	Number of patients with endoscopic/ catheter drainage, N (%)	Time to drainage, mean/median days, mean/median (SD, IQR)	Follow up time, days
Bang	2024	USA	Full	RCT	70	Gas in the necrotic collection on CT, positive culture of necrotic tissue, decompensation or sepsis	37 (53)	33 (47)	U: 45.7 (14.4), S: 53.2 (14.9)	U 26 (70), S 20 (61)	U- Gallstone 10 (27), alcohol 12 (32), idiopathic 6(16), other 9 (24%), S - Gall stone 4(12), alcohol 6(18), idiopathic 17(52), other 6 (18)	nr	U: 35(95%), S: 29(88%) WON	<30 0 both groups	U 37 (100), S 33 (100)	U 37 (100), s 26(79)	U 4 (11), S 9 (27)	nr	nr
Olsen	2026	Denmark	Full	RCT	25	Culture-verified infection.	12	13	U: 56.5 (34.5–70.0), S: 53.0 (48.0–74.0)	U: 7 (58), 8 (62)	U: Gallstone: 9 (75), alcohol: 2 (17), idiopathic: 1 (8), S: Gallstone: 9 (69), alcohol: 1 (8), drug: 1 (8), PEP: 1 (8), idiopathic: 1 (8)	nr	nr but appears 100%	U: 55%, S: 45%	U: 12 (100), S: 12 (92)	U: 4.0 (3.0–5.3), S: 4.5 (1.8–6.3)	U: 3 (25), S: 6 (50), VARD: U: 0 (0), S: 3 (25)	U: 28.0 (22.8–45.8), S: 26.0 (23.0–31.0)	nr
Mohamad nejad	2026	Iran	Full	RCT	50	positive WON's Gram stain or culture obtained during the index procedure, presence of gas in necrosis on CT, presence of two inflammatory markers (T >38.5°C, elevated CRP) or leukocyte count) in the absence of another focus of infection, presence of persistent organ failure	25 (50)	25 (50)	U: 53.2 (15.2), S: 50.9 (16.4)	U: 19 (76), S: 14 (56)	U: Gallstone 16 (64), alcohol 3 (12), PEP 0 (0), hypertriglyceridemia 2 (8), post-surgical 2 (8), Idiopathic 2 (8), S: Gallstone 18 (72), alcohol 1 (4), PEP 2 (8), hypertriglyceridemia 1 (4), post-surgical 2 (8l, Idiopathic 1 (4)	nr	U 25 full encapsulation, S: 25 full encapsulations	U: 20 to 32%: 10 (40), 33 to 49%: 11 (44), >50% 4 (16), S: 20 to 32%: 8 (32), 33 to 49%: 7 (28), >50% : 10 (40)	U: 25 (100), S: 25 (100)	U: 25 (100), S 14 (56)	U: 1 (4), S: 1 (4)	U: 4 to 6 weeks: 21 (84), > 6 weeks: 4 (16), S: 4 to 6 weeks: 18 (72), > 6 weeks 7 (28)	nr

PICO 5 Table 1: Baseline characteristics of studies comparing upfront transluminal endoscopic necrosectomy versus on demand subsequent necrosectomy after initial endoscopic drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections subsequent																		
Saito	2026	Japan	Full	RCT	70	nr	33 (47)	37 (53)	U: 59 (15.5), S: 59.8 (17.8)	U 22 (67), S: 28 (76)	U: Gallstone: 8 (24), alcohol, 12 (36), other: 8 (24), idiopathic: 5 (15), S: Gallstone: 14 (38), alcohol: 9 (24), other: 7 (19), idiopathic: 7 (19)	nr	U: Complete: 28 (85), partial 5 (15), S: complete: 29 (78), 8 (22)	U: < 30%: 2 (6.1), 30–59%: 27 (82), ≥ 60%: 4 (12), S: 30%:5 (14), 30–59%: 31 (84), ≥ 60%: 1 (2.7)	U: 25 (76), S: 25 (68)	U: 33 (100), 17 (46)	U: 3 (9.1), S: 4 (11)	U: 30 (26-44), S: 41 (30-68)	nr
Ancil	2016	India	Full	RCT	54	either a positive culture of the necrotic tissue obtained before the procedure or at the index intervention, or the presence of gas foci within the WON on computed tomography, Clinically suspected infected WON was defined as persistent (>72 hours), worsening, or new-onset systemic inflammatory response syndrome (SIRS) and/or organ failure occurring after 2weeks from disease onset	27 (50)	27 (50)	U: 39.3 (13.2) S: 38.2 (12.2)	U: 22 (81.5), S: 18 (66.7)	U: Alcohol: 8 (29.6), Gall stone 13 (48.1), Idiopathic 6 (22.2) S: Alcohol 11 (40.7), gallstone 13 (48.1), Idiopathic 2 (7.4)	nr	nr	U: < 30%:0 (0), 30-50%: 21 (77.8), >50%: 6 (22.2) S: <30%: 0 (0), 30-5-%: 19 (70.4), >50%: 8 (29.6)	U: 27 (100), S: 27 (100)	U: 27 (100), S 15 (55.6	nr	nr	Nr

CRP: C-reactive protein; IQR: interquartile range; nr: not reported; PEP: post ERCP pancreatitis; PTC: percutaneous transhepatic cholangiography; RCT: randomized control trial; S: subsequent necrosectomy; SD: standard deviation; U: upfront necrosectomy; WON: walled-off necrosis

Supplemental Table 23. PICO 5 Outcomes — Upfront versus on-demand endoscopic necrosectomy

PICO 5 Table 2. Outcomes of studies comparing upfront transluminal endoscopic necrosectomy versus on demand subsequent necrosectomy after initial endoscopic drainage In patients with a suspected infection of pancreatic and/or peri-pancreatic collections subsequent										
1st Author last name	AEs, n (%)	Perforation, n (%)	bleeding, n (%)	stent dysfunction (migrated, occluded, etc), n (%)	need for surgical necrosectomy, escalation of care to surgery, n (%)	new onset organ failure, n (%)	# of endoscopic sessions required, mean/median (SD, IQR)	LOS for hospital stay, mean/median (SD, IQR)	30-day readmission, n (%)	Mortality , n (%)
Bang	U: 4(11), S-8 (24)	nr	U: 4 (11), S: 3 (12)	U: 0 (0), S-1 (3)	U: 0 (0), S: 0 (0)	-	U 1(0-1), S 2 (1-4)	Hospital stay from index intervention to discharge, days U- 9 (7 to 20) S-19 (9 to 33), Hospital stay from admission to discharge, U-21 (10 to 31), S-24 (12 to 43)	U-18 (49), S-19 (58)	U 0 (0), 2 (6)
Olsen	**Major AE:** U: 0 (0), S: 6 (46) **Procedure related AE:** U: 2 (17), S: 5 (39)	U: 0 (0), S: 2 (15.4) *	Intraprocedural bleeding: U: 1 (8.3), S: 2 (15.4) Major bleeding: U: 0 (0), S: 3 (23.1) **	nr	U: 0 (0), S: 3 (25) (3 VARDs) [a 4th one required diverting ileostomy for fistula closure)	U: 0 (0), S: 3 (25)	U: 4 (3-5.3), S: 4.5 (1.8-6.3) (number of endoscopic necrosectomy)	U: 32.5 (17.5-38.2), S: 68.5 (35.5-97.8)	U 5 (42), S: 6 (50) (6 months readmission not 30-day)	U: 0 (0), S: 1 (8)
Mohamadnejad	**Procedure related AE: U**: 10 (40), S: 6 (24)	nr	Major bleeding U: 2 (8), S: 0 (0) Any bleeding: U: 4 (16), S 1 (4)	U: 1 (4), S: 1 (4)	U: 1 (4), S: 0 (0)	U 2 (8), S: 2 (8)	U: 2 (1-3), S: 1 (0-2)	U: 14 (5-22), S: 8 (5-26)	nr	U: 2 (8), S: 3 (12)
Saito	**Both disease and procedure AE:** U: 14 (42), S: 14 (38) **Procedure related AE:** U: 8 (24), S: 8 (22) **Disease-related AEs:** U: 10 (30), S: 8 (22)	U: 2 (6.1), S: 2 (5.4)	U: 7 (21), S: 4 (11)	U: 2 (6), S: 5 (14)	U: 1 (3), S: 3 (8.1)	U: 8 (24.1), S: 4 (11)	U: 5 (2–9), S: 0 (0–4)	U: 34 (19–58), S: 36 (19–55)	nr	U: 4 (12), S: 2 (5.4)
Ancil	U: 3 (11.1), S: 4 (14.8)	U: 0 (0), S:1 (3.7)	U: 2 (7.4), S 2 (7.4)	U: 1 (3.7), S: 1 (3.7)	U: 0 (0), S: 2 (7.4)	U: 3 (11.1), S: 4 (14.8)	U: 1(1.5), S: 2 (1.5)	U: 4 (6.7). S: 12 (12.6)	U: 5 (18.5), S: 12 (44.4)	U: 3 (11.1), S: 5 (18.5)

AEs: adverse events, IQR: interquartile range, LOS: length of hospital stay, S: step-up approach, SD: standard deviation, U: upfront necrosectomy, VARDs: video-assisted retroperitoneal debridement,
* perforation or enterocutaneous fistula
** Requiring intervention or blood transfusion

Supplemental Table 24. PICO 5 Evidence Profile — Upfront versus on-demand endoscopic necrosectomy

Question: Upfront transluminal endoscopic necrosectomy compared to endoscopic drainage (i.e drainage followed by subsequent on demand necrosectomy) for patients with suspected infected or symptomatic walled off necrotic collections (updated)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	upfront transluminal endoscopic necrosectomy	endoscopic drainage (i.e drainage followed by subsequent on demand necrosectomy)	Relative (95% CI)	Absolute (95% CI)		
Procedure related adverse events (perforation, bleeding, stent dysfunction, defined by study etc)												
5	randomised trials	not serious	not serious	not serious	extremely serious[a,b]	none	27/134 (20.1%)	31/135 (23.0%)	**RR 0.89** (0.51 to 1.53)	**25 fewer per 1,000** (from 113 fewer to 122 more)	⊕◯◯◯ Very low[a,b]	CRITICAL
Perforation												
5	randomised trials	not serious	not serious	not serious	extremely serious[a,c]	none	3/134 (2.2%)	5/134 (3.7%)	**RR 0.74** (0.21 to 2.63)	**10 fewer per 1,000** (from 29 fewer to 61 more)	⊕◯◯◯ Very low[a,c]	CRITICAL
Bleeding												
5	randomised trials	not serious	not serious	not serious	very serious[a,b]	none	17/134 (12.7%)	14/135 (10.4%)	**RR 1.31** (0.64 to 2.66)	**32 more per 1,000** (from 37 fewer to 172 more)	⊕⊕◯◯ Low[a,b]	CRITICAL
Need for surgical necrosectomy (escalation of care to surgery)												
5	randomised trials	not serious[d]	not serious	not serious	extremely serious[a,e]	none	2/134 (1.5%)	8/135 (5.9%)	**RR 0.40** (0.10 to 1.55)	**36 fewer per 1,000** (from 53 fewer to 33 more)	⊕◯◯◯ Very low[a,d,e]	CRITICAL
New onset organ failure												
4	randomised trials	not serious[f]	not serious	not serious	extremely serious[a,c]	none	11/97 (11.3%)	13/102 (12.7%)	**RR 1.00** (0.46 to 2.18)	**0 fewer per 1,000** (from 69 fewer to 150 more)	⊕◯◯◯ Very low[a,c,f]	CRITICAL
LOS without Olsen												
3	randomised trials	serious[g]	not serious	not serious	extremely serious[h]	none	122	122	-	MD **3.95 days lower** (11.43 lower to 3.53 higher)	⊕◯◯◯ Very low[g,h]	IMPORTANT
Length of Hospital Stay												
4	randomised trials	serious[g]	serious[i]	not serious	serious[h]	none	134	135	-	MD **6.36 days lower** (15.13 lower to 2.42 higher)	⊕◯◯◯ Very low[g,h,i]	IMPORTANT
6 month readmission (30 day not reported)												
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	28/76 (36.8%)	37/73 (50.7%)	**RR 0.72** (0.50 to 1.04)	**142 fewer per 1,000** (from 253 fewer to 20 more)	⊕⊕◯◯ Low[a]	IMPORTANT
Total number of interventions (3-6 months; majority of trials assessed for clinical success)												
4	randomised trials	not serious	not serious[j]	not serious[j]	extremely serious[k]	none	107	107	-	MD **0.41 SD lower** (1.36 lower to 0.54 higher)	⊕◯◯◯ Very low[j,k]	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Low event rate and wide confidence interval
b. Crosses MID for appreciable harm/benefit multiple times
c. Possible appreciable harm and possible benefit
d. Unblinded and decision to undergo surgery based on criteria, but variable interventions could be done potentially instead of surgery
e. Possible appreciable benefit and possible harm
f. Definition for Wonder01 trial for persistent organ failure, unclear if truly new onset
g. Unblinded and thus possible for ROB for decision making of discharge date
h. Does not meet optimal information size with wide confidence interval and appreciable benefit and harm
i. Olsen drives difference, sub group performed and thus difference is not clinically significant
j. Mix of re-intervention and total number of procedures
k. does not meet optimal information size

Supplemental Table 25. PICO 5 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	**Trivial* for critical outcomes**	**Small* for important outcomes**	Moderate	Large		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	**Very low**	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Supplemental Table 26. PICO 6 Baseline Characteristics — Transluminal plastic stents versus no stent

PICO 6 Table 1: Baseline characteristics of studies comparing placement vs no placement of transluminal plastic stents after the initial metal stent(s) removal in patients with walled off necrosis and suspected disconnected pancreatic duct

1st Author last name	Year	Country	Abstract or Full article	Study design	Total number of patients, N	Initial size of the pancreatic collection, mean/median (SD, IQR)	Number of patients with suspected DPD, N	Definition of DPD (MRCP, EUS, ERCP), n (%)	Site of DPD, head, body, tail, n (%)	location of the initial drainage (trans-gastric or trans-duodenal), n (%)	ERCP with trans-papillary stent, n (%)	Manifestation of DPD, (Pseudocyst, pancreatitis upstream, ascites, fistula), n (%)	Age, mean or median years, (SD or IQR)	Men, No (%)	Cause of pancreatitis, N (%) Gallstone, alcohol, Tg, other	Number of patients with severe pancreatitis, N (%) (breakdown of severe and moderate)	Number of patients with transluminal plastic stent after resolution , N (%)	Number of patients without transluminal plastic stent after resolution , N (%)	Number of DPSs used, 1: N (%), 2N (%), >2 : N (%)	Follow up time, months mean/median (SD, IQR)
Chavan	2022	India	full	RCT	236	DPS - median 12.4 cm (IQR 10.72-14.65); no DPS median 11.4 cm (IQR 6.1-19)	104	104 (100) had both MRP and ERCP "nonprojected segment of pd with isolated portions of upstream duct on MRCP", on ERP, compete cut-off of main pd with no contrast opacification of upstreatm pd"	stent h:5(9.6)/neck&body 16 (82)tail 4(7.7) no stent head 2(3.8) neck&body 17 (82) tail 3(5.8)	stent TG100% no-stent TG 100%,TD1 (2%)	0	nr	34 (IQR: 26-44.7)	94(90)	gallstone 19(18); etOH 34(33)	nr	**52**	**52**	7Fr 104 (100)	DPS 19(14.75-23.25) no-DPS: 18 (14.5-20.5)
Pawa	2022	USA	full	Retrospective	48	mean 13.5 (10.52)	48	MRCP 33(69), ERP15(31) complete disruption of main pd with presence of viable pancreatic tissue beyond main pd cut off on MRCP resulting in secretion of pancreatic juices by the disconnected functional pancreatic gland causing ascites, persistent PFC, or pancreatico-cutaneous fistula	nr	TG43(90)TD4(8)T.eso(1(2)	0	nr	53.1(14.5)	29(60)	Gallstone 16(33)etOH 17(35)TG3(6) other 9(19)	nr	21(44)	27 (56)	nr	median 20.1
Rana	2023	India	Full	Retrospective	53	Stent 9.5cm(1.3), no stent 9.2 (1.5)	53	MRCP and ERCP	100% head/neck	nr	nr	nr	S 35.7, NS 33.4	S 34(87), NS 11(78.5)	nr	nr	**39 (74)**	**14 (26)**	7Fr 35 (90), 10FR 4 (10)	nr
Bang	2021	USA	Full	Prospective	94			ERCP 75 (80), MRCP 19 (20)				Fluid collection along PD, upstream variable parenchyma		nr	nr	nr	70(75)	24(26)	NA	NA

IQR: interquartile range; FNA: fine needle aspiration; MS: metal stent; nr: not reported; P: plastic stent; RCT: randomized control trial; SD: standard deviation; Won: walled-off necrosis

Supplemental Table 27. PICO 6 Outcomes — Transluminal plastic stents versus no stent

PICO 6, Table 2. Outcomes of studies comparing placement vs no placement of transluminal plastic stents after the initial metal stent(s) removal in patients with walled off necrosis and suspected disconnected pancreatic duct								
1st Author last name	**Recurrent collection**, n (%	**Need for repeat drainage intervention**	AEs	**Perforation**	**Bleeding**	**Need for surgical resection (escalation of care to surgery)**	**Development of diabetes**	**Development of EPI**
Chavan	DPS: 3 (5.8), no-DBS: 3 (5.8) (at 3 months) DPS: 7 (13.5), no-DBS: 13 (25) at 1 year	DPS: 3 (5.8) (EUS-guided drainage in 1, surgical cystogastrostomy in 1, distal pancreatosplenectomy in 1); No-DPS: 4 (7.7) (EUS-guided drainage in all 4)	2 (3.8) complication associate with plastic stent deployment in stent group	DPS: 0 (0), no-DPS: 0 (0)	DPS: 0 (0), no-DPS: 0 (0)	DPS: 2 (3.8), no-DPS: 0 (0)	nr	nr
Pawa	DPS: 1 (4.8), no-DPS: 10 (37)	DPS: 1 (4.8) (surgical management), no-DPS: 4 (14.8) (2 with endoscopic and 2 surgical treatment	nr (reported for LAMS but not after removal)	DPS: 0 (0), no-DPS: 0 (0)	DPS: 0 (0), no-DPS: 0 (0)	DPS: 1 (4.8), no-DPS 2 (7.4)	nr	nr
Rana	DPS 2 (5), no-DBS: NS 6 (43)	DPS 1 (3) no-DBS 5 (36)	DBS: 1 (2.5), no-DBS 0	DBS: 1 (2.5), no-DBS 0	nr	DPS: 0 (0), no-DPS: 0 (0)	nr	nr
Bang	DPS: 1 (1.4), no-DBS: 6 (25)	nr	DPS: 0 (0), no-DPS: 0 (0)	DPS: 0 (0), no-DPS: 0 (0)	DPS: 0 (0), no-DPS: 0 (0)	DPS: 0 (0), no-DPS: 0 (0)	nr	nr

AEs, adverse events; DPS: double pigtail stent; EPI: exocrine pancreatic insufficiency; nr: not reported.

Supplemental Table 28. PICO 6 Evidence Profile — Transluminal plastic stents versus no stent

Question: Transluminal plastic stents compared to no stent for patients who underwent endoscopic drainage of walled of necrosis/pancreatic fluid collection for suspected disconnected pancreatic duct after initial metal stent has been removed

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	transluminal plastic stents	no stent	Relative (95% CI)	Absolute (95% CI)		
Need for repeat drainage procedure												
4	non-randomised studies	very serious[a,b,c,d,e]	not serious	serious[f,g,h]	not serious[i]	none	6/172 (3.5%)	16/106 (15.1%)	**RR 0.25** (0.08 to 0.79)	**113 fewer per 1,000** (from 139 fewer to 32 fewer)	⨁◯◯◯ Very low[a,b,c,d,e,f,g,h,i]	CRITICAL
Need for repeat drainage procedure (RCT)												
1	randomised trials	not serious[d]	not serious	not serious	extremely serious[i,j]	none	3/42 (7.1%)	4/41 (9.8%)	**RR 0.73** (0.17 to 3.07)	**26 fewer per 1,000** (from 81 fewer to 202 more)	⨁◯◯◯ Very low[d,i,j]	CRITICAL
Need for escalation to surgery												
4	non-randomised studies	very serious[a]	not serious	not serious	extremely serious[i]	none	3/172 (1.7%)	2/106 (1.9%)	**RR 1.41** (0.20 to 9.73)	**8 more per 1,000** (from 15 fewer to 165 more)	⨁◯◯◯ Very low[a,i]	CRITICAL
Perforation after metal stent removal												
3	non-randomised studies	very serious[a,k]	not serious	not serious	very serious[l]	none	0/143 (0.0%)	0/103 (0.0%)	not estimable		⨁◯◯◯ Very low[a,k,l]	CRITICAL
Bleeding after metal stent removal												
3	non-randomised studies	very serious[a,k]	not serious	not serious	very serious[l]	none	0/143 (0.0%)	0/103 (0.0%)	not estimable		⨁◯◯◯ Very low[a,k,l]	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational studies in which it was unclear risk of bias as there is a possibility for selection bias
b. One observational study did not clarify breakdown by intervention for recurrence. To be conservative, 1 was assumed in DPS group and 3 in the no DPS rather than all 4 in the no DPS group.
c. Observational studies not blinded and some studies may not define recurrence clearly which could create variability in decision making for outcome assessors.
d. Per-protocol used for RCT data to ensure that the 6 patients that failed were not contributing to the recurrent intervention predominately, however assumption of 2 patients of the ITT did not have recurrence. Small number, but low event rate.
e. Median follow up for Pawa 2022 differed between two groups favoring the no DPS to capture more events.
f. A minority of patients had chronic pancreatitis in one study, but it was unclear which cohort they were in. An unclear indirectness versus risk of bias, but we did not downgrade for this specific reason
g. Observational studies mainly assessed the comparator as those who had unsuccessful plastic stent placement rather than an equal comparison of those who did not get one. Unclear if this would be a different population. Indirectness for this and the chronic pancreatitis reason, we downgraded once
h. Recurrence collections were only counted if needed repeat drainage
i. Crosses the MID of 5%
j. Low event rate
k. Unclear risk of bias, however the comparison of harms did include the plastic stent replacement attempt by design of the observational studies as the comparator was those who had an unsuccessful
l. Low event rate and sample size

Supplemental Table 29. PICO 6 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of required resources	**Very low**	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Supplemental Table 30. PICO 7 Baseline Characteristics — Anticoagulation versus no anticoagulation

PICO 7 table 1. Baseline characteristics of studies comparing anticoagulation vs no-anticoagulation with patients with acute pancreatitis and acute splanchnic vein thrombosis																	
1st Author last name	Year	Country	Abstract or Full article	Total number of patients, N	Total with acute SVT, N	Total with acute SVT with data on AC, N	SV only	PV only	SMV only	SV+PV	SV+ SMV	PV+SMV	SV+PV+SMV	Number treated with anticoagulation , N, (%)	Number not treated with anticoagulation, N (%)	Anticoagulation type , (DOAC, heparin LMWH, Warfarin..) N (%)	Duration of AC, mean/median months (SD, IQR)
Bjornsson	2020		abstract	1102	20	20	4	2	0	4	0	5	5	12	8	nr	nr
Brotherton	2022	US	abstract	nr	121	121	-	-	-	-	-	-	-	68	53	nr	nr
Dalal	2022	US	abstract	104390	1500	1500	-	-	-	-	-	-	-	550	950	mix of Warfarin, Rivaroxaban, Apixaban	nr
Easler	2014	US	full	162	22	22	13	1	1	2	0	1	4	6	16	nr	nr
Gonzelez	2011	UK	full	127	20	20	8	5	1	4	1	0	1	4	16	LMWH, then Warfarin for all	nr
Guo	2024	China	full	3048	808	808	-	-	-	-	-	-	-	38	770	LMWH or coumadin	med 13 d (IQR 18d)
Harris	2013	US	full	2454	45	45	17	7	4	4	4	4	5	17	28	LMWH or UFH, then Warfarin	range 3-12 months
Maire	2025	France	Full	711	88	88	29	24	14	-	-	-	-	69	19	tinzaparin N=36, enoxaparin N=20, VitK n=5, unfractionated n=4, apixaban N=1	5 months and 11 days (2-8 months)
Junare	2020	India	full	105	24	24	11	0	0	4	0	0	9	12	12	nr	nr
McGurk	2023	UK	abstract	172	10	10	3	2	3	2	0	0	0	7	3	LMWH, then DOAC x3 months	3 months
Oyon	2023	Spain	full	1655	60	46	23	9	4	1	4	2	3	33	13	LMWH, then Warfarin for 3-6 months	3-6 months
Pagliari	2020	Italy	full	221	27	27	9	1	0	2	10	1	4	16	11	LMWH, then fondaparinux (n=5)or Warfarin (n=7)or apixaban (n=4)	range 1.5-9 months
Sissingh	2024	Netherlands	full	432	97	88	32	20	15	11	5	7	7	17	71	LMWH (n=12), Warfarin (n=4), UFH (n=1)	nr
Thejasvin	2022	UK	full	401	109	109	46	0	0	0	0	36	27	74	35	LMWH, then apixaban	med 3 m (range 0-6 m)
Chowdhury	2024		Abstract	814	92	70	47	-	-	-	-	-	-	14	56	nr	
Jajoo	2025	USA	Full	897	29	29	-	-	-	-	-	-	-	18	11	DOAC: (70%), Warfarin: (10%)	
Maire	2025	France	Full	711	121	88	21	24	14	-	-	-	-	69	19	LMWH (n=56), Warfarin (n=5), unfractionated heparin (n = 4), apixaban (n = 1)	
Eltweri	2024	UK and Australia	Full	98	98	98	98	0	0	0	0	0	0	39	59	heparin, LMWH, warfarin or DOAC	

AC: anticoagulation, DOAC: Direct oral anticoagulation, IQR: interquartile range, LMWH: low molecular weight heparin, nr: not reported, PV: Portal vein, SVT: Splanchnic vein thrombosis, SMV: Superior mesenteric vein, SV: Splenic vein, UFH: unfractionated heparin

Supplemental Table 31. PICO 7 Outcomes — Anticoagulation versus no anticoagulation

PICO 7 Table 2. Outcomes of studies comparing anticoagulation vs no-anticoagulation with patients with acute pancreatitis and acute splanchnic vein thrombosis												
Study	Number of patients on AC, n	Number of patients not on AC, n	Mortality AC, n	Mortality no AC, n	Bleeding AC, n	Bleeding no AC, n	Ischemia AC, n	Ischemia no AC, n	Recanalization AC, n	Recanalization no AC, n	Varices AC, n	Varices no AC, n
Gonzelez 2011	4	16	-	-	0	0	-	-	2	4	-	-
Harris 2013	17	28	2	1	2	5	-	-	2	3	-	-
Easler 2014	6	16			1	0	-	-	-	-	-	-
Junare 2020	12	12	1	2	1	0	4	0	6	5	3	4
Bjornsson 2020	12	8	0	0	0	0	-	-	5	6	-	-
Pagliari 2020	16	11	0	0	0	0	-	-	11	3	-	-
Brotherton 2022	68	53	7	2	24	14	-	-	-	-	-	-
Thejasvin 2022	74	35	13	6	5	0	-	-	44	11	-	-
McGurk 2023	7	3	0	0	0	0	-	-	-	-	-	-
Oyon 2023	33	13	1	0	1	0	-	-	18	4	-	-
Guo 2024	38	770	-	-	4	91	-	-	14	97		-
Sissingh 2024	17	71	-	-	2	8	0	4	6	40	-	-
Maire 2025	69	19	-	-	10	2	-	-	28	9	26	13
Chowdhury 2024	14	56	-	-	-	-	-	-	9	31	-	-
Jajoo 2025	18	11	1	4	9	0	0	1	-	-	8	2
Dalal 2022	550	950	-	-	70	90	4**0**	60	-	-	30	70
Eltweri 2024	39	59	1	1	-	-	-	-	18	9	2	5

AC: anticoagulation

Supplemental Table 32. PICO 7 Evidence Profile — Anticoagulation versus no anticoagulation

Question: Therapeutic anticoagulation compared to no anticoagulation for acute splanchnic vein thrombosis

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	therapeutic anticoagulation	no anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	non-randomised studies	very serious[a,b]	not serious	not serious	extremely serious[c]	none	25/284 (8.8%)	16/225 (7.1%)	**RR 1.07** (0.57 to 2.00)	**5 more per 1,000** (from 31 fewer to 71 more)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Bleeding												
15	non-randomised studies	very serious[a]	not serious	not serious[d]	serious[e]	none	131/968 (13.5%)	211/2067 (10.2%)	**RR 1.34** (1.06 to 1.70)	**35 more per 1,000** (from 6 more to 71 more)	⨁◯◯◯ Very low[a,d,e]	CRITICAL
Gut or hepatic Ischemia (gut/bowel reported as priority)												
4	non-randomised studies	very serious[a,b,f]	not serious	serious[g]	not serious	none	44/597 (7.4%)	65/1044 (6.2%)	**RR 1.15** (0.79 to 1.69)	**9 more per 1,000** (from 13 fewer to 43 more)	⨁◯◯◯ Very low[a,b,f,g]	CRITICAL
Development of gastric or esophageal varices												
5	non-randomised studies	very serious[a,b,f]	not serious	serious[h]	serious[e]	none	69/688 (10.0%)	94/1051 (8.9%)	**RR 0.68** (0.52 to 0.91)	**29 fewer per 1,000** (from 43 fewer to 8 fewer)	⨁◯◯◯ Very low[a,b,e,f,h]	IMPORTANT
Re-canalization												
11	non-randomised studies	very serious[a]	serious[i]	serious[j]	very serious[e]	none	135/276 (48.9%)	213/1078 (19.8%)	**RR 1.51** (1.04 to 2.19)	**101 more per 1,000** (from 8 more to 235 more)	⨁◯◯◯ Very low[a,e,i,j]	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study with possible selection bias, residual confounders. Some studies have unclear follow up time and decision to start anticoagulation could be based on clinical worsening as opposed to equal cohorts of comparison.
b. Outcomes categorized by vessel affected were limited
c. Confidence interval crosses minimally important difference of 1-1.4%
d. 1 study used transfusions instead of bleeding. No downgrading was done for this
e. CI contain the value of minimal clinical significant threshold of 5%
f. One study was database study that used ICD codes and numbers were rounded
g. Definition was variable and unclear downstream consequences
h. Unclear downstream consequences
i. Moderately high I^2 Inconsistency index
j. Surrogate for downstream effects of thrombus

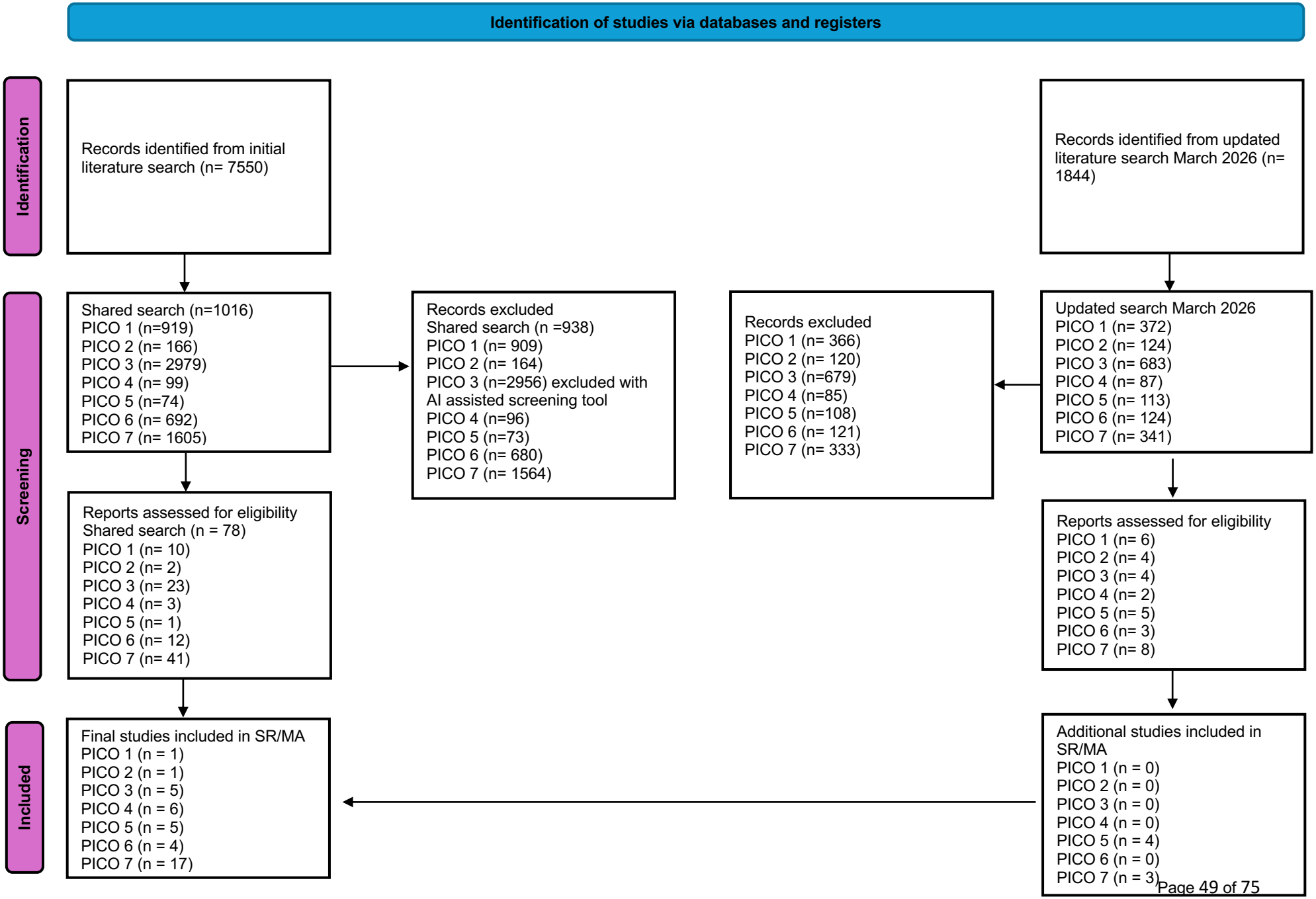
Supplemental Table 33. PICO 7 Evidence to Decision Framework

Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
Resources required	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	**Very low**	Low	Moderate	High			No included studies
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
Equity	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

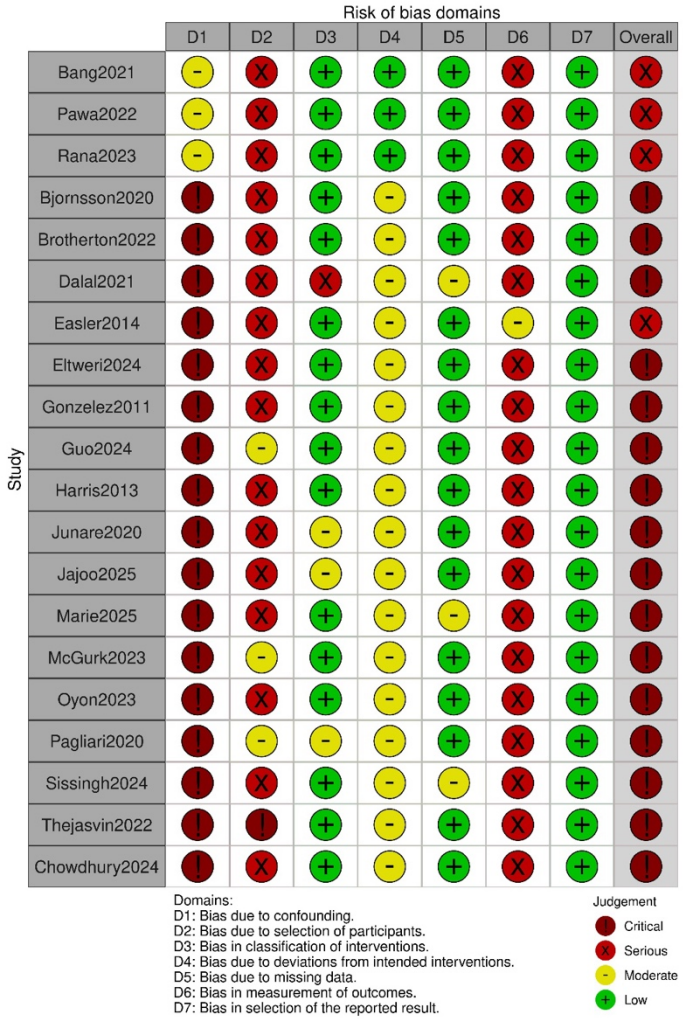
SUPPLEMENTAL FIGURES

Supplemental Figure 1. PRISMA Flow Diagram

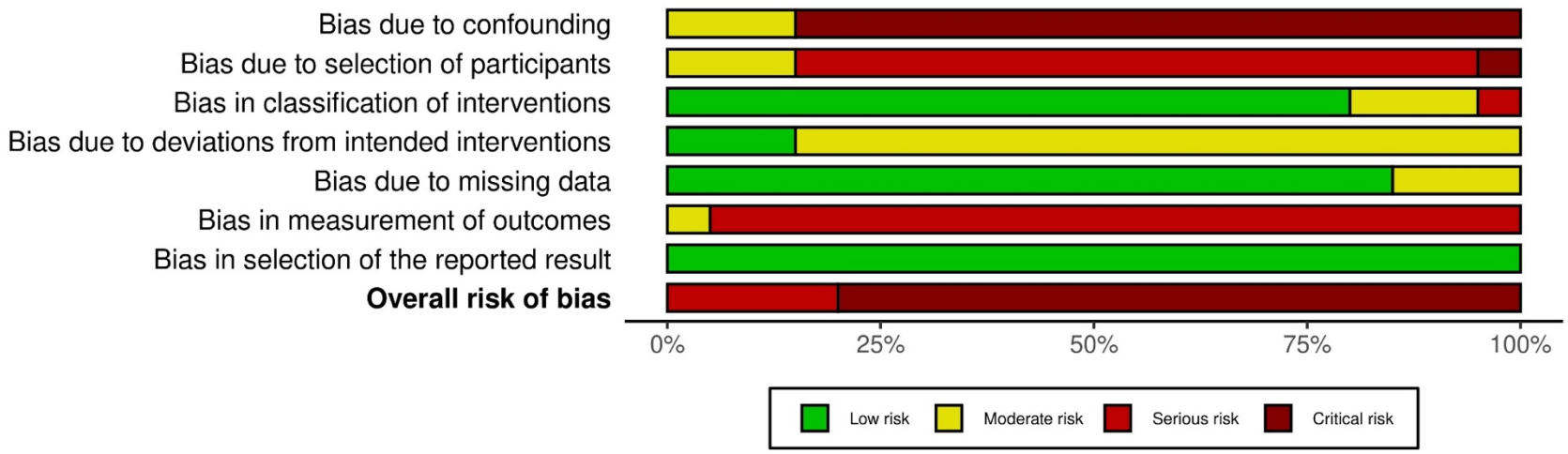


Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

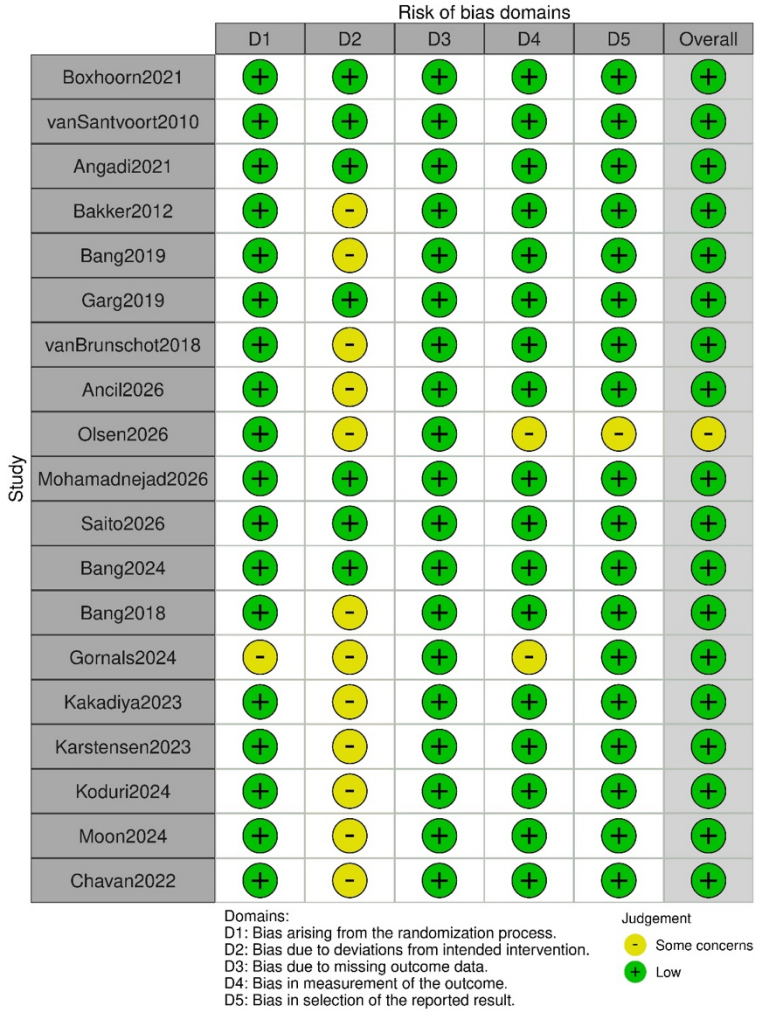
Supplemental Figure 2. Risk of Bias Assessment — Traffic-light plot (7 bias domains)



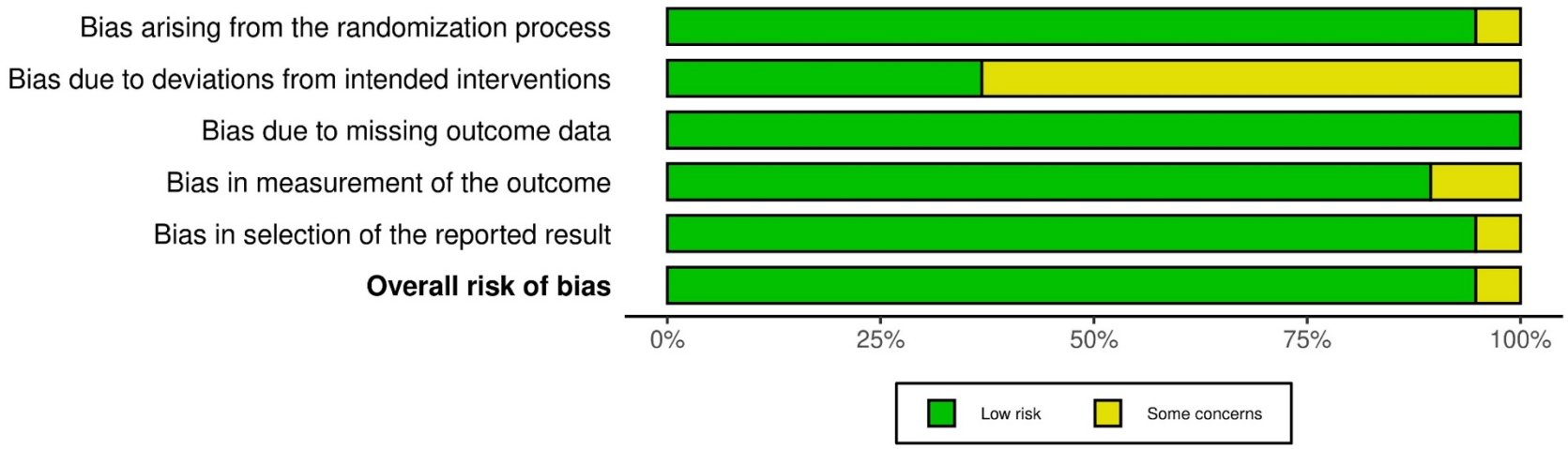
Supplemental Figure 3. Risk of Bias Assessment — Summary bar chart (7 bias domains)



Supplemental Figure 4. Risk of Bias Assessment — Traffic-light plot (5 bias domains)



Supplemental Figure 5. Risk of Bias Assessment — Summary bar chart (5 bias domains)

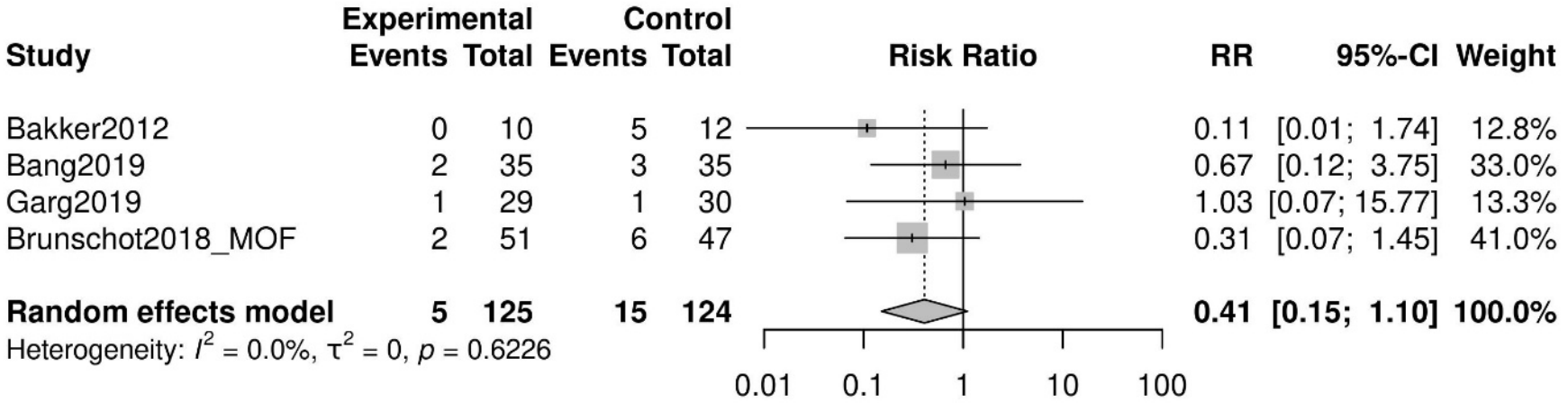


LABEL NOTE: the four risk of bias figures carry no captions in the source file. The domain counts above were read off the plots; which set is randomized and which is non-randomized still needs confirming.

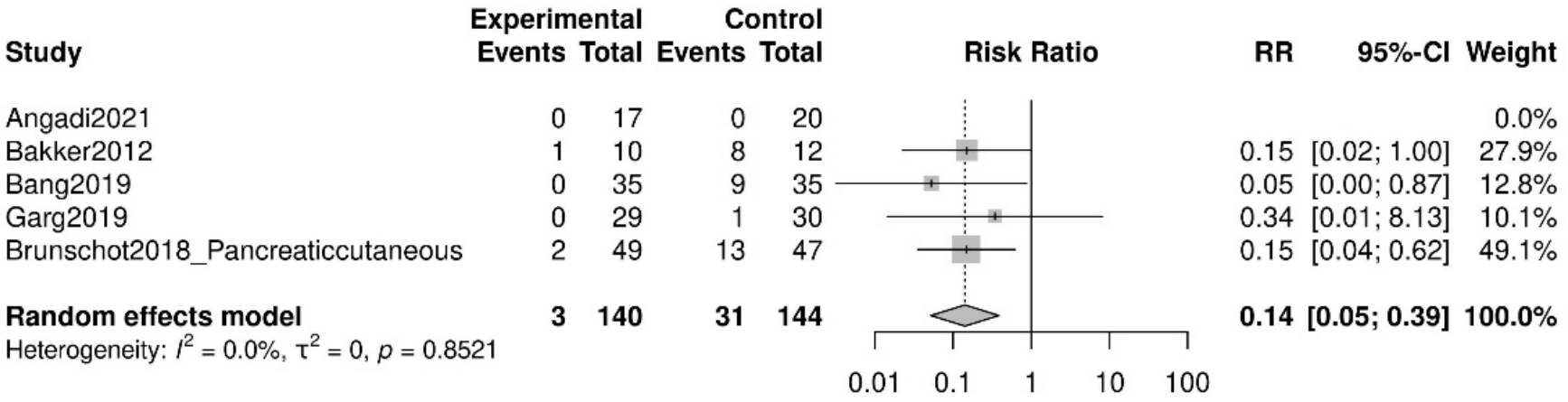
PICO 1. Immediate versus delayed drainage- No forest plots

PICO 2. Minimally invasive surgical step-up approach versus open surgical necrosectomy- No forest plots

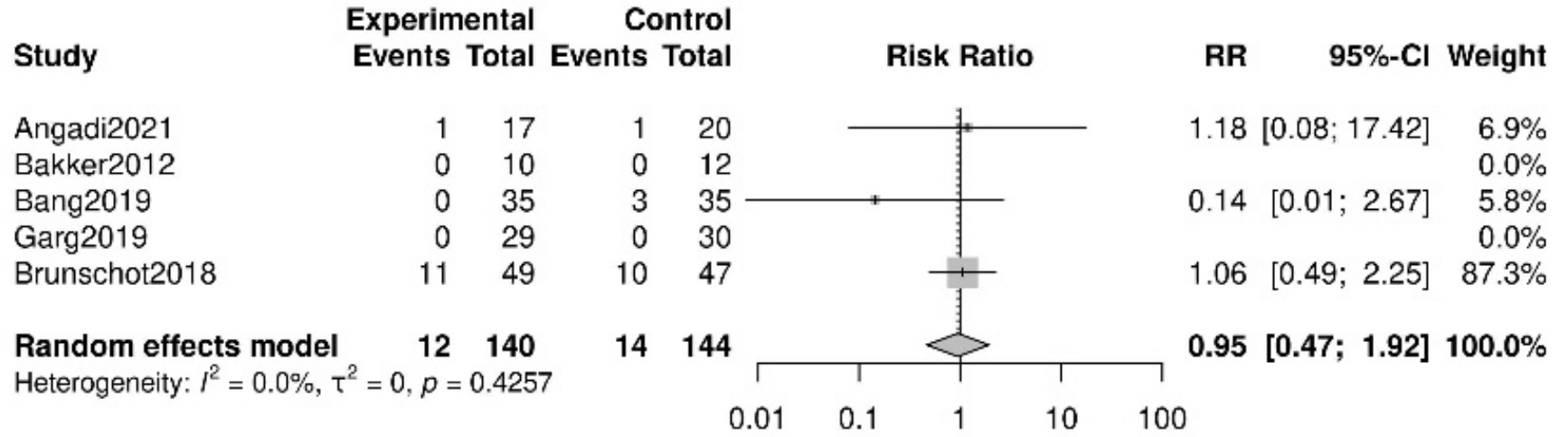
Supplemental Figure 6. Forest Plot — New onset organ failure (PICO 3)



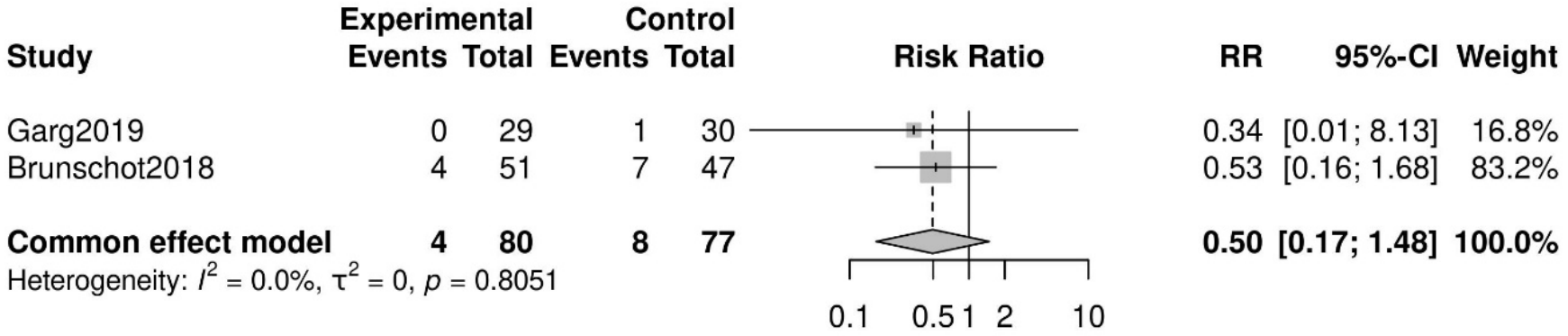
Supplemental Figure 7. Forest Plot — Fistula (PICO 3)



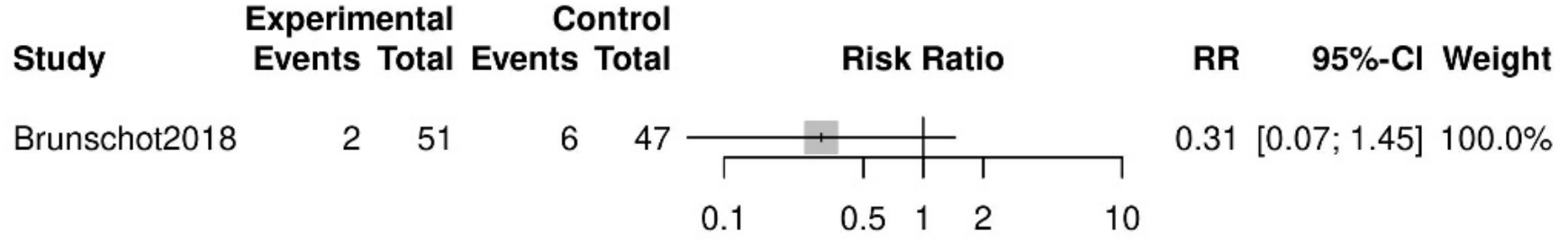
Supplemental Figure 8. Forest Plot — Bleeding (PICO 3)



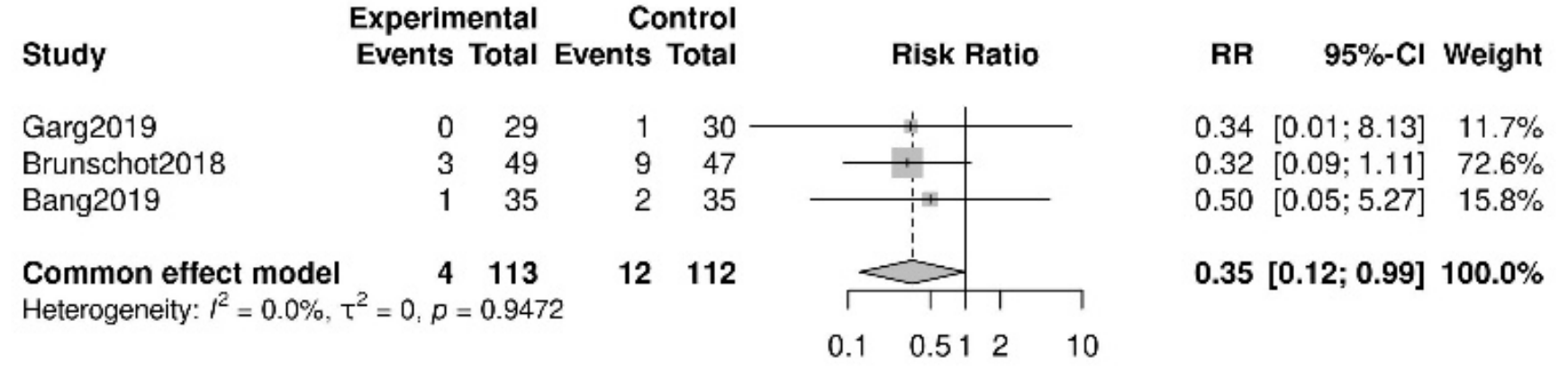
Supplemental Figure 9. Forest Plot — Respiratory failure (PICO 3)



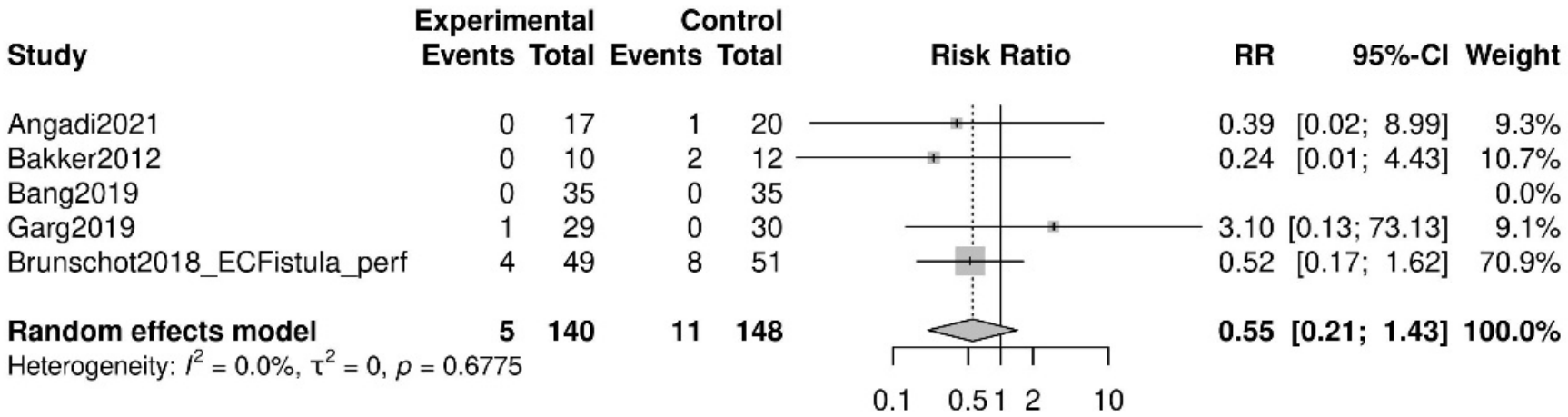
Supplemental Figure 10. Forest Plot — Renal Failure (PICO 3)



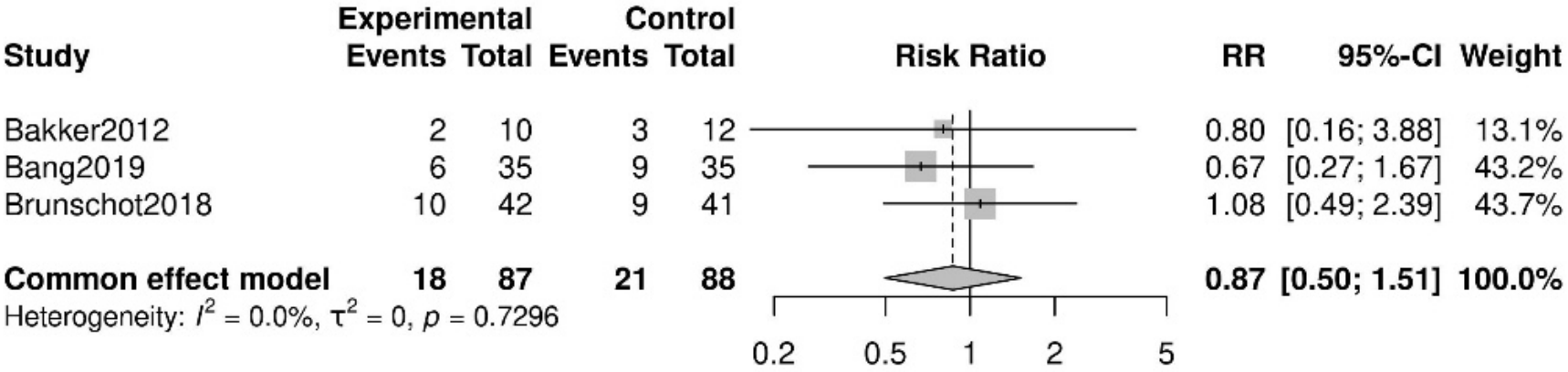
Supplemental Figure 11. Forest Plot — Cardiovascular failure (PICO 3)



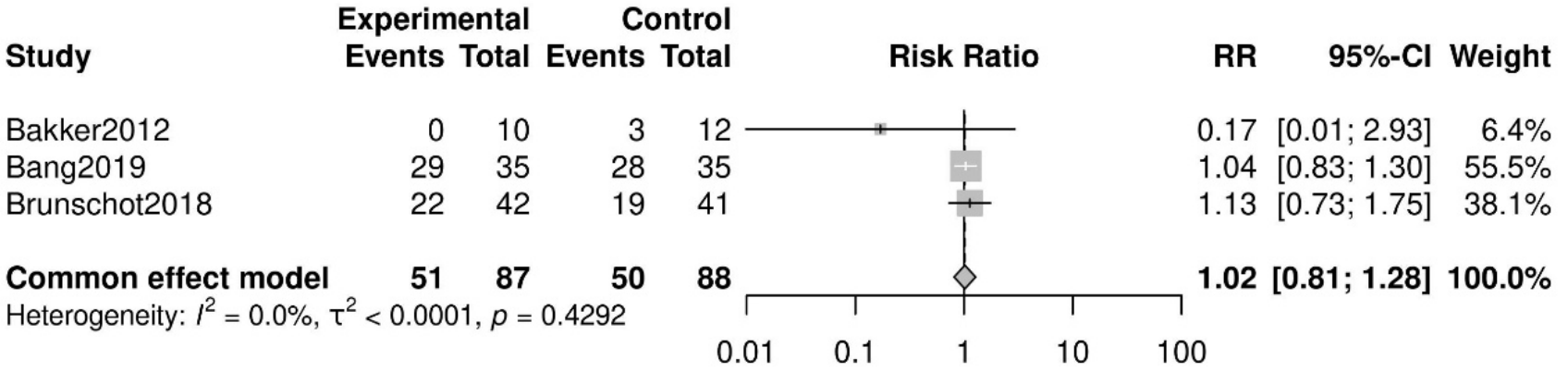
Supplemental Figure 12. Forest Plot — Perforation (PICO 3)



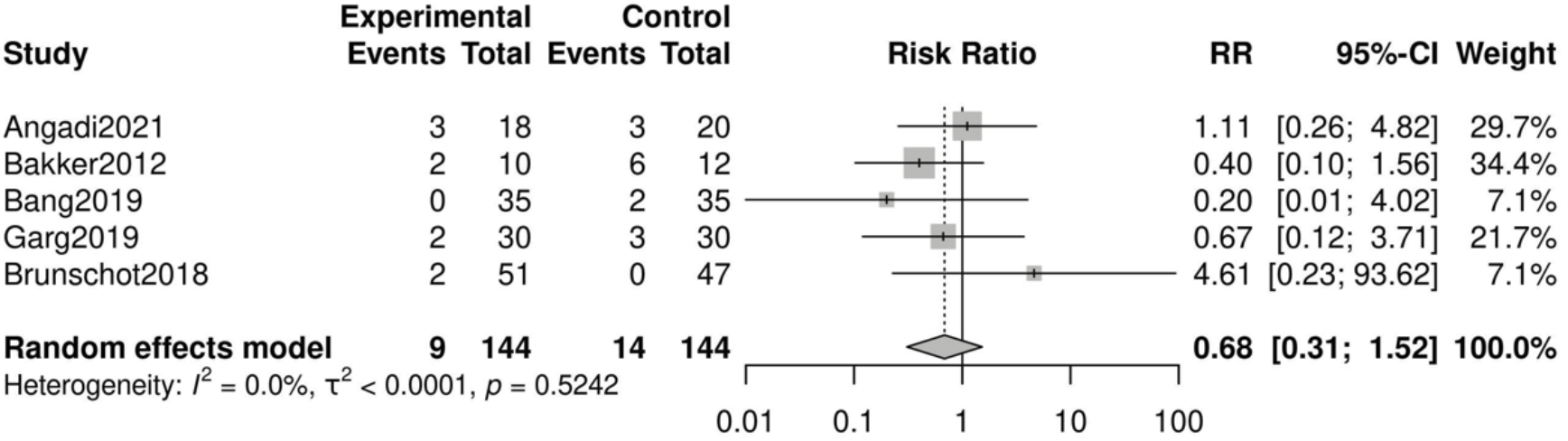
Supplemental Figure 13. Forest Plot — Diabetes (PICO 3)



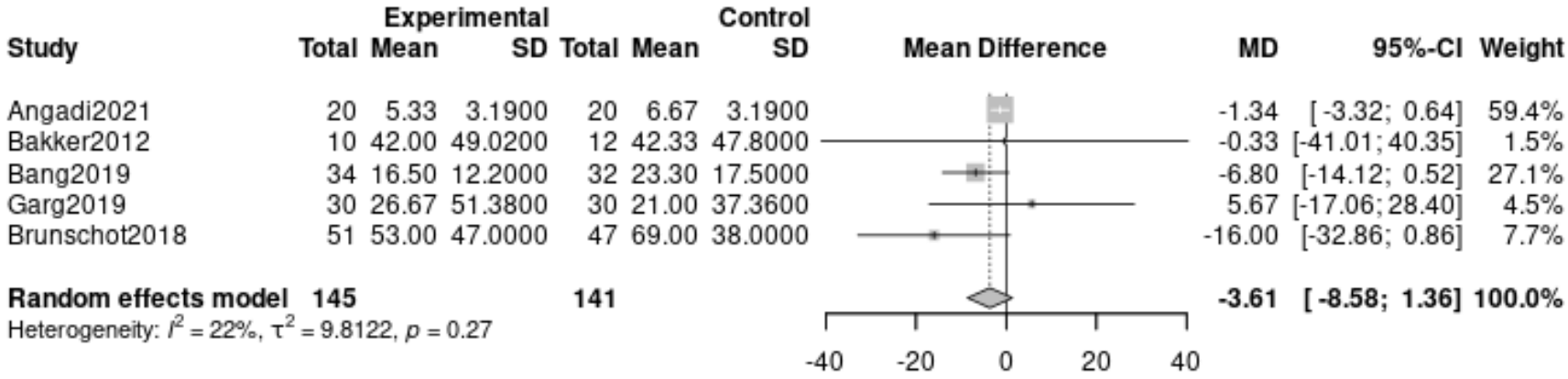
Supplemental Figure 14. Forest Plot — Exocrine Pancreatic Insufficiency (PICO 3)



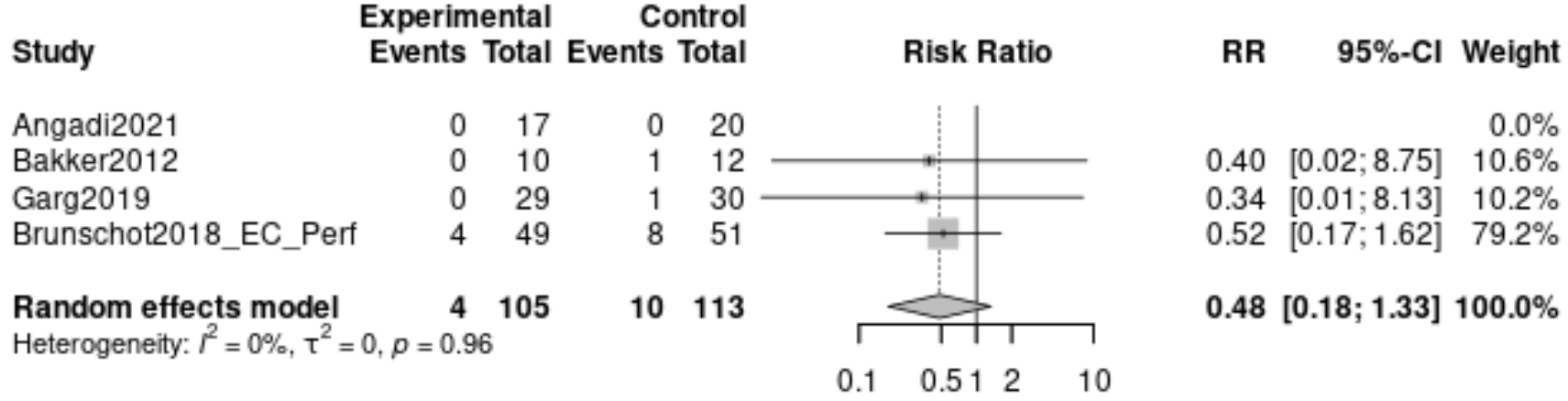
Supplemental Figure 15. Forest Plot — Need for escalation (PICO 3)



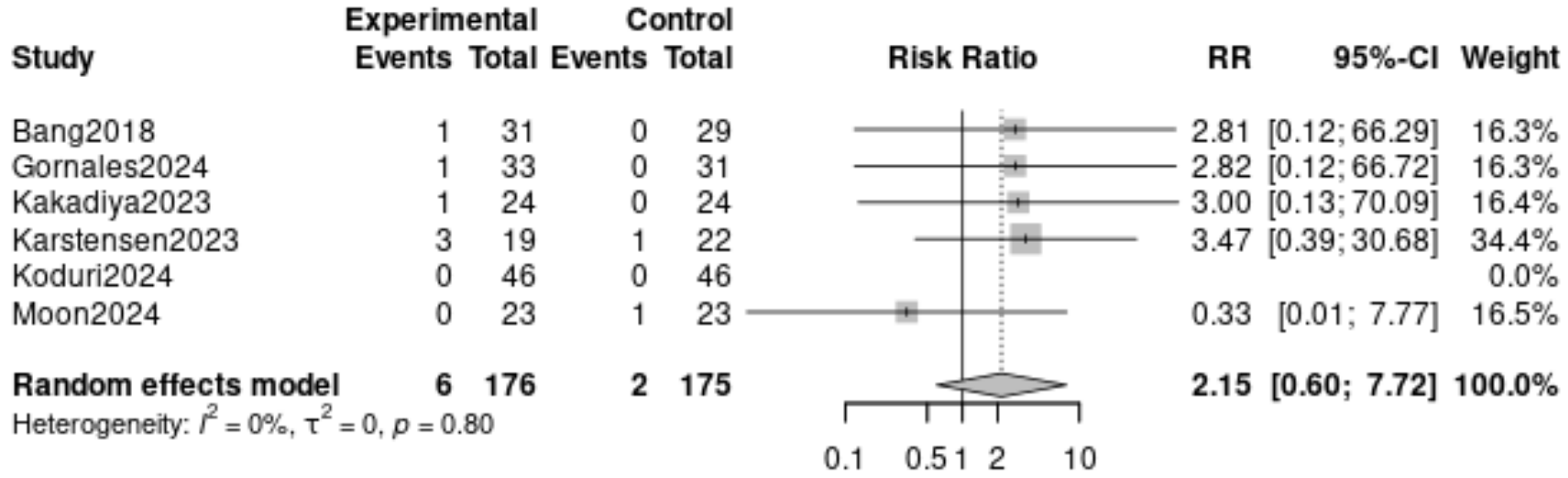
Supplemental Figure 16. Forest Plot — Length of stay (PICO 3)



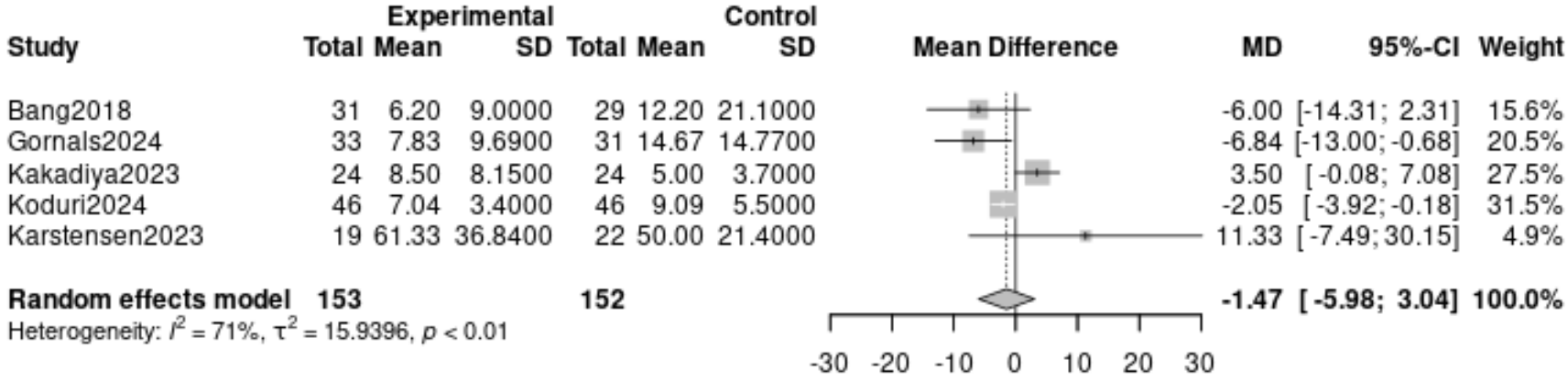
Supplemental Figure 17. Forest Plot — Enterocutaneous fistula only (PICO 3)



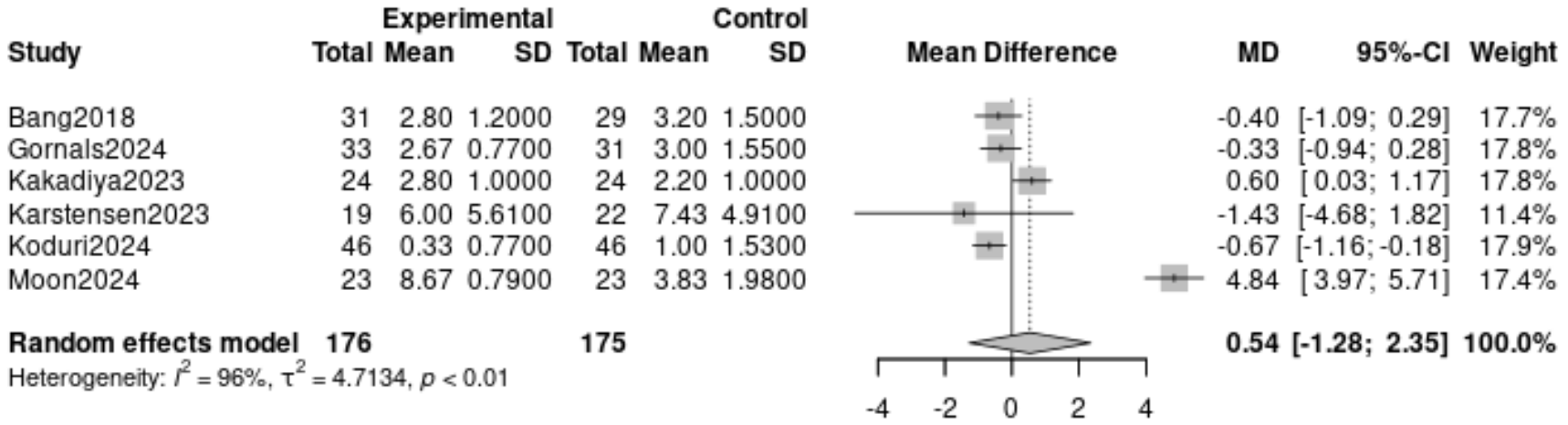
Supplemental Figure 18. Forest Plot — Need for surgical necrosectomy (PICO 4)



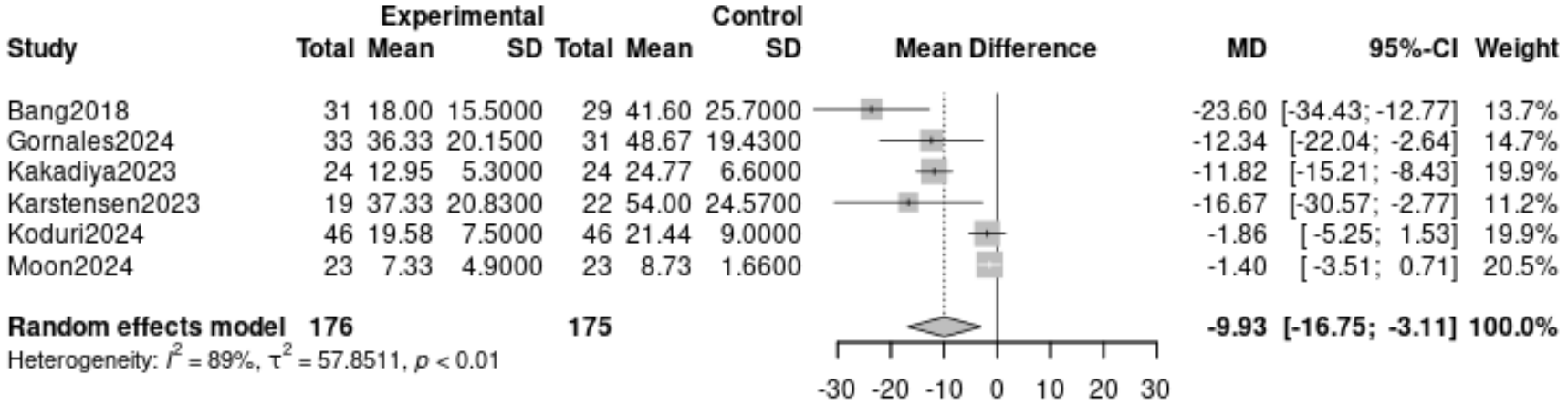
Supplemental Figure 19. Forest Plot — LOS (PICO 4)



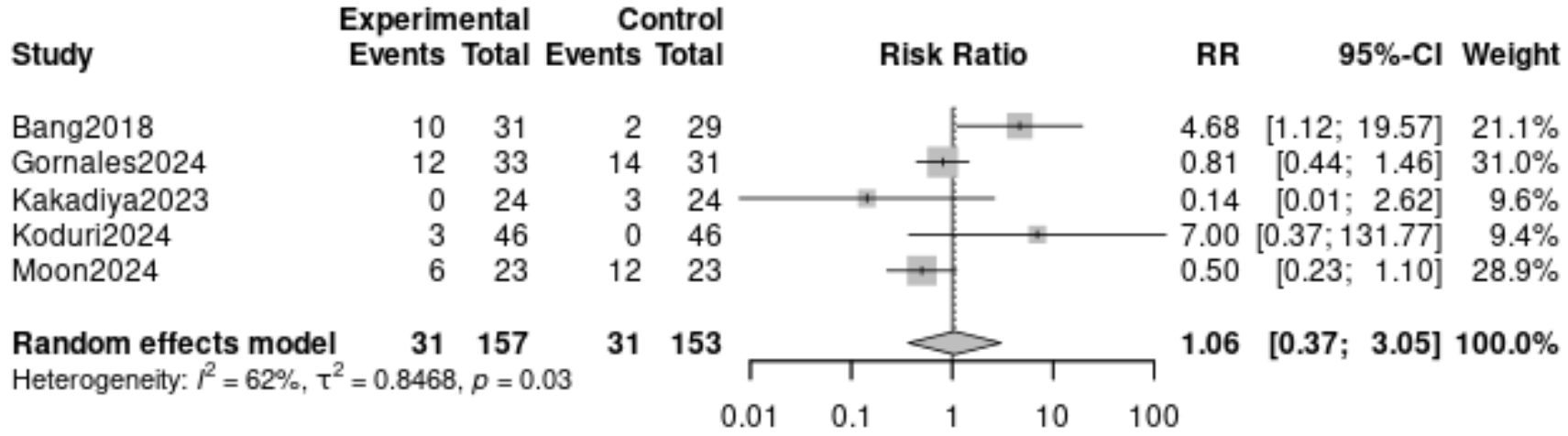
Supplemental Figure 20. Forest Plot — # of procedures (PICO 4)



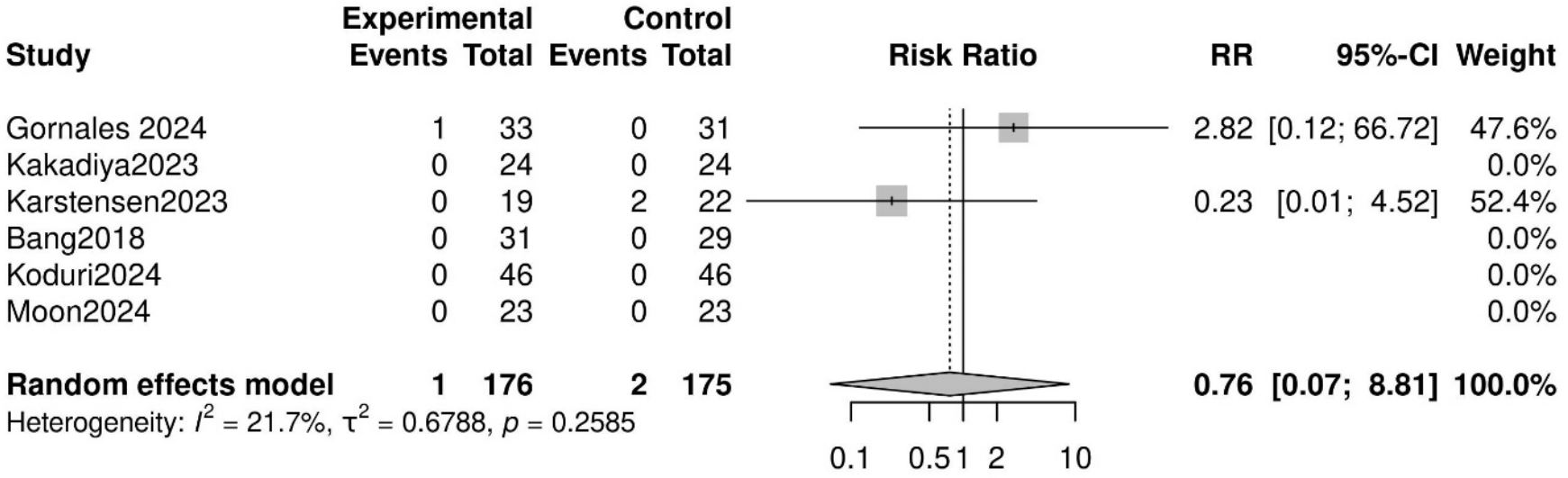
Supplemental Figure 21. Forest Plot — Procedure duration (PICO 4)



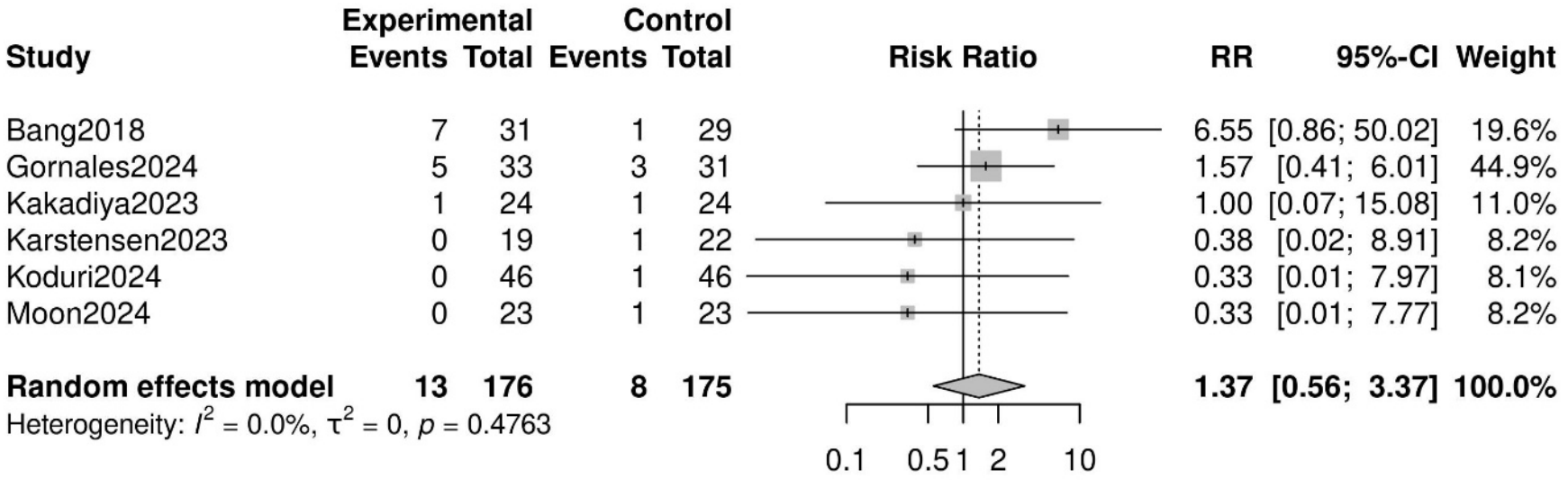
Supplemental Figure 22. Forest Plot — Stent dysfunction (PICO 4)



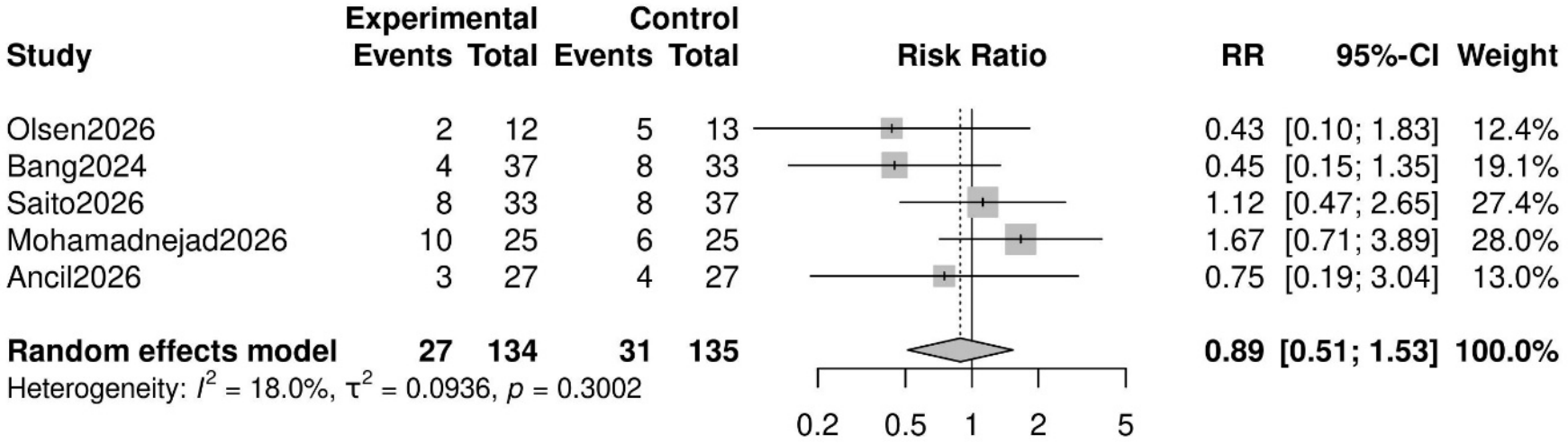
Supplemental Figure 23. Forest Plot — Perforation (PICO 4)



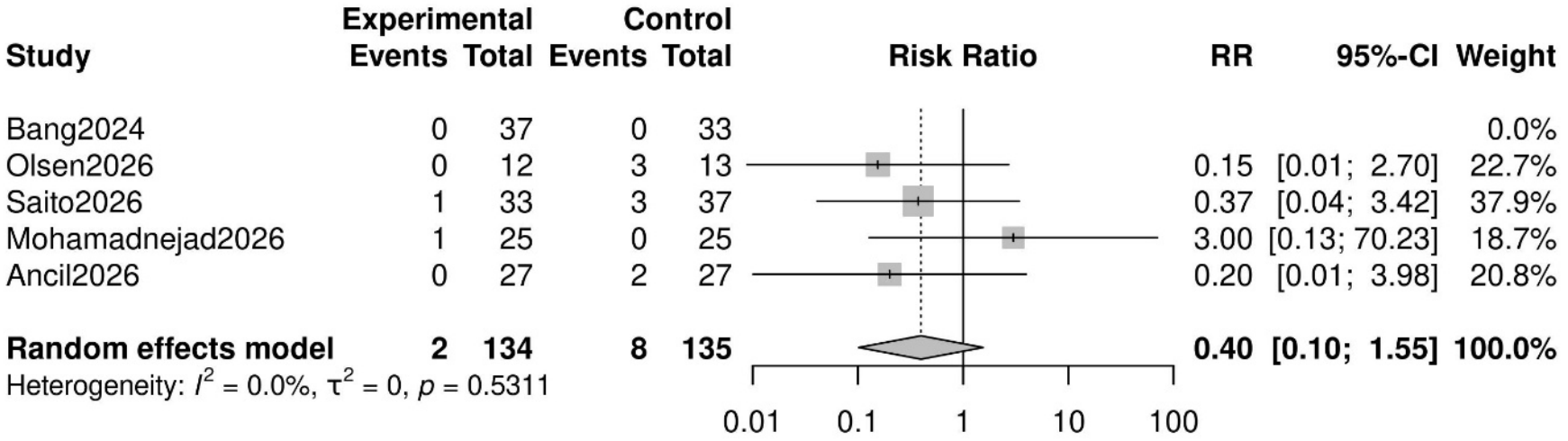
Supplemental Figure 24. Forest Plot — Bleeding (PICO 4)



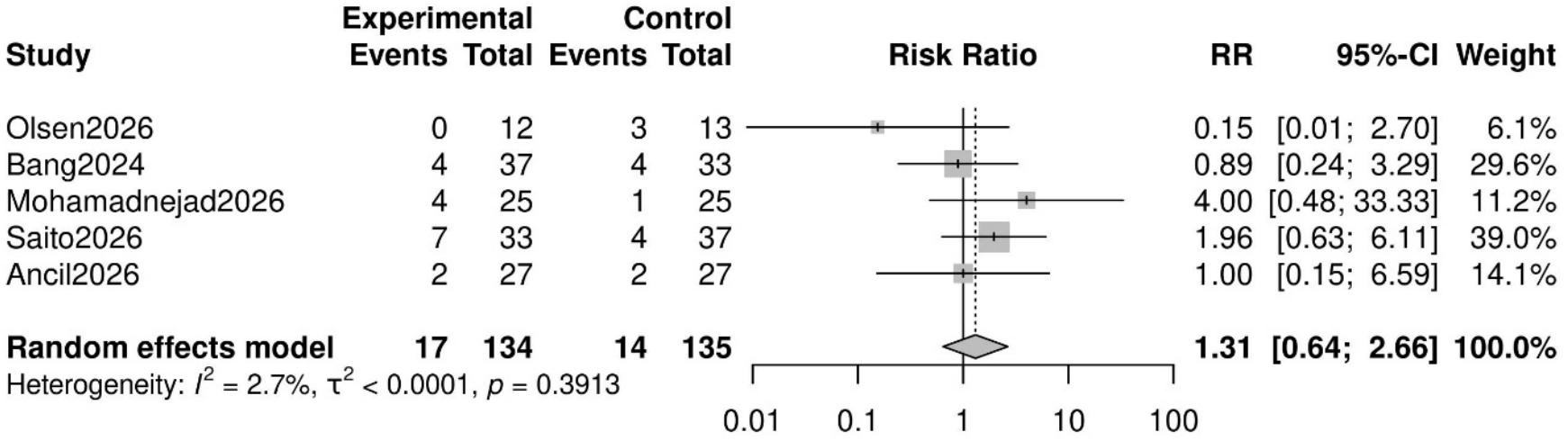
Supplemental Figure 25. Forest Plot — Procedure related adverse events (PICO 5)



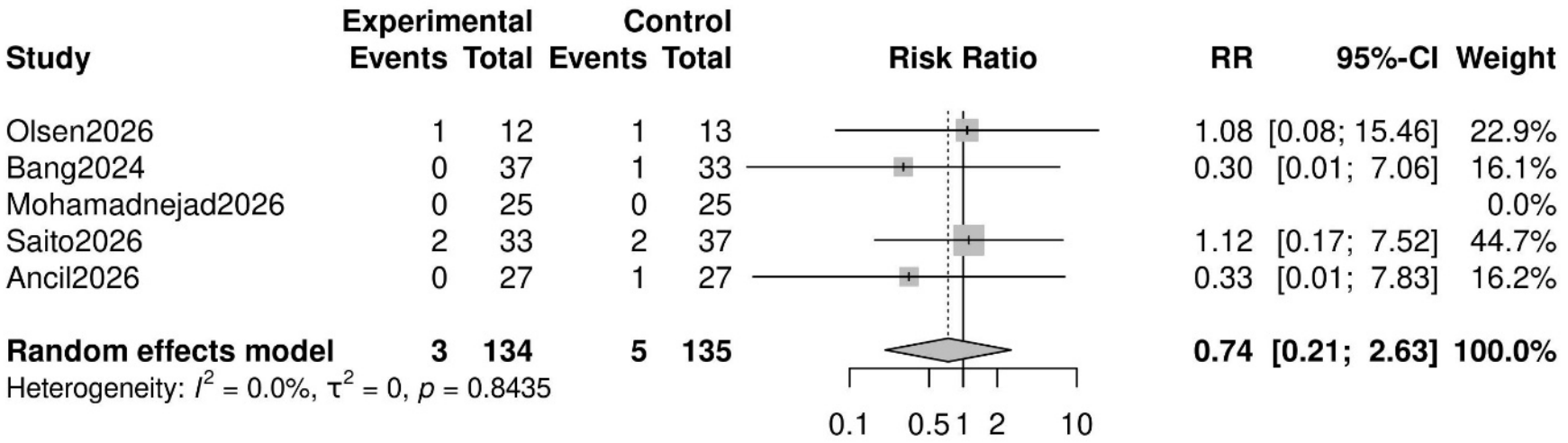
Supplemental Figure 26. Forest Plot — Need for surgical necrosectomy (PICO 5)



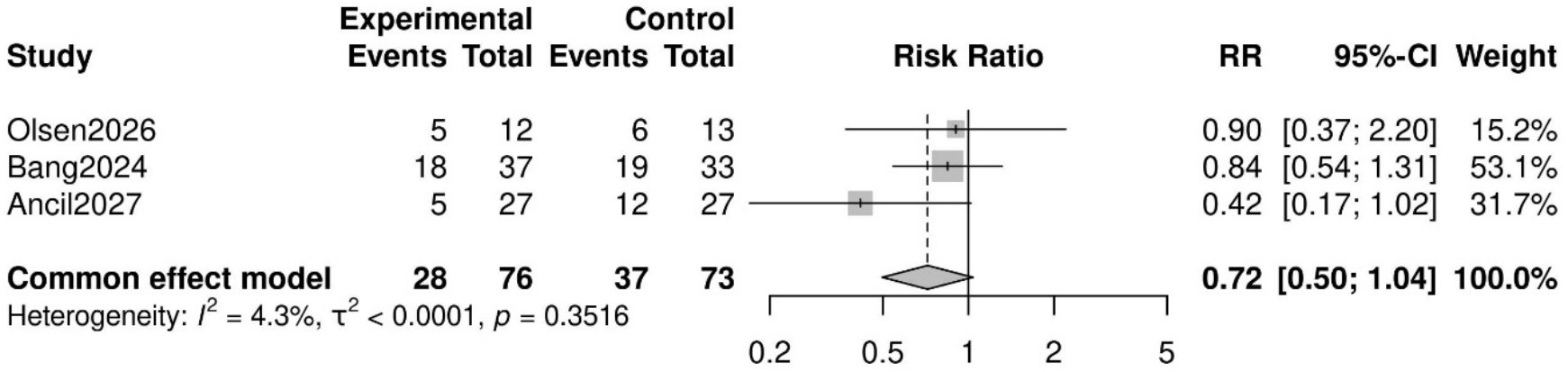
Supplemental Figure 27. Forest Plot — Bleeding (PICO 5)



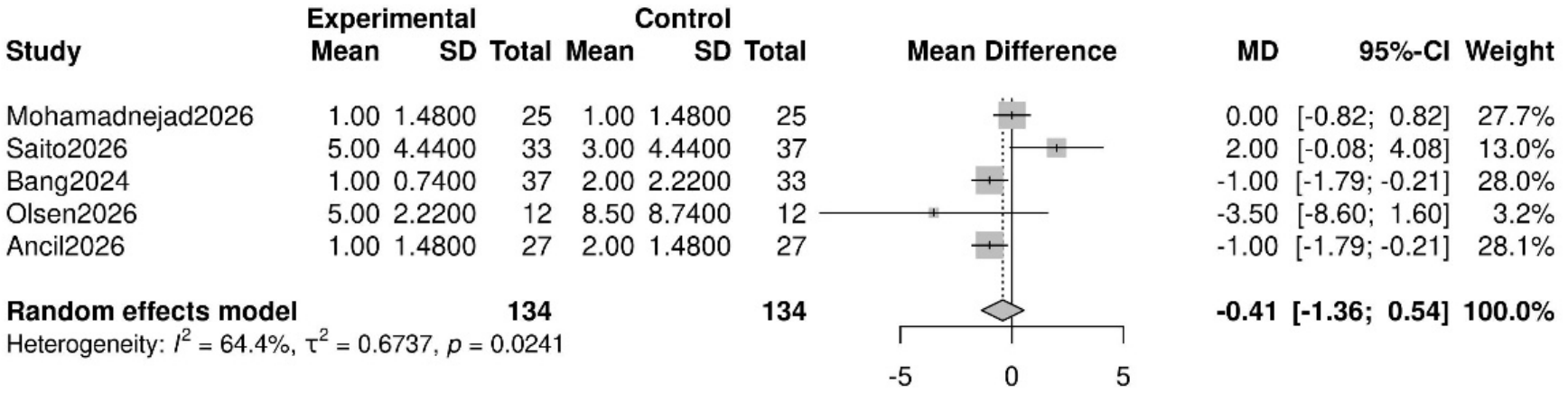
Supplemental Figure 28. Forest Plot — Perforation (PICO 5)



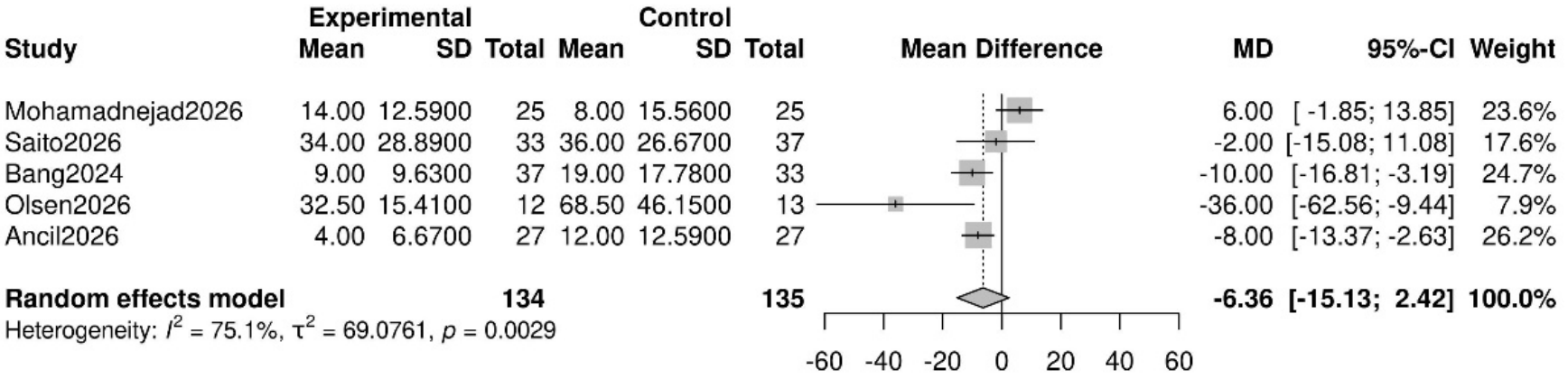
Supplemental Figure 29. Forest Plot — 6 month readmission (PICO 5)



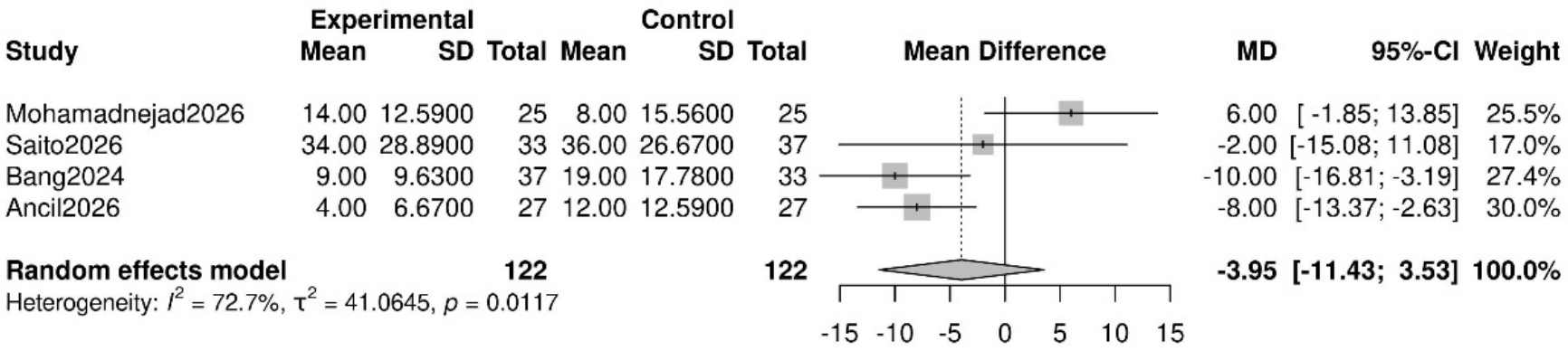
Supplemental Figure 30. Forest Plot — Number of interventions (PICO 5)



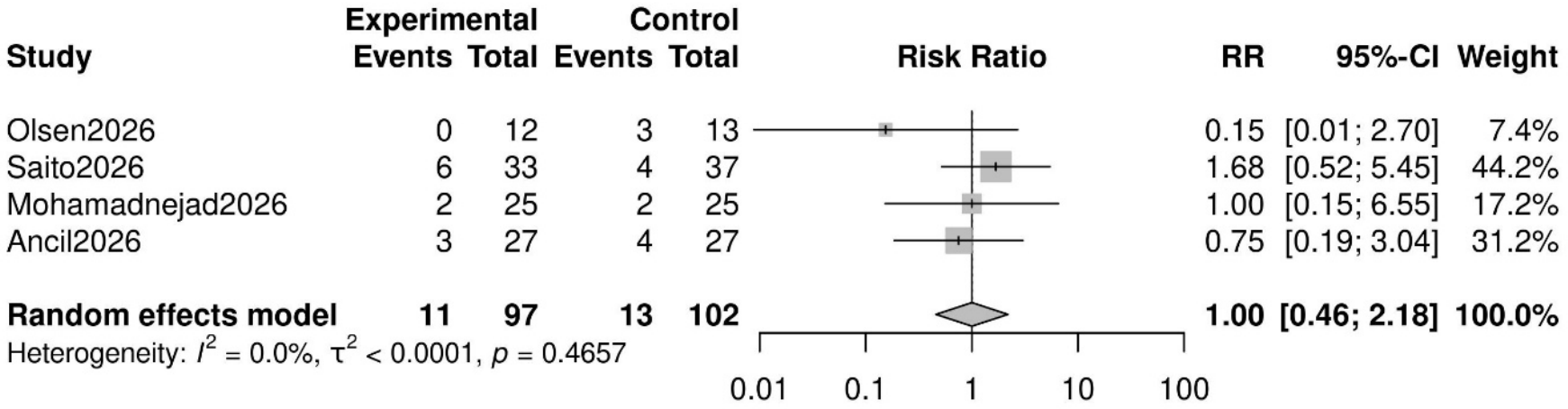
Supplemental Figure 31. Forest Plot — LOS (PICO 5)



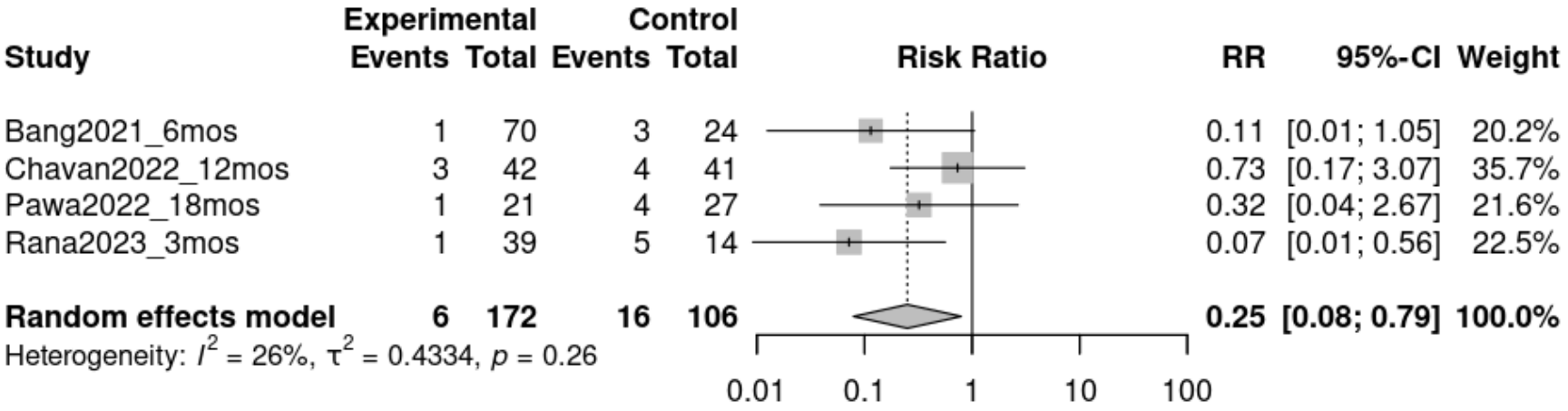
Supplemental Figure 32. Forest Plot — LOS without Olsen (PICO 5)



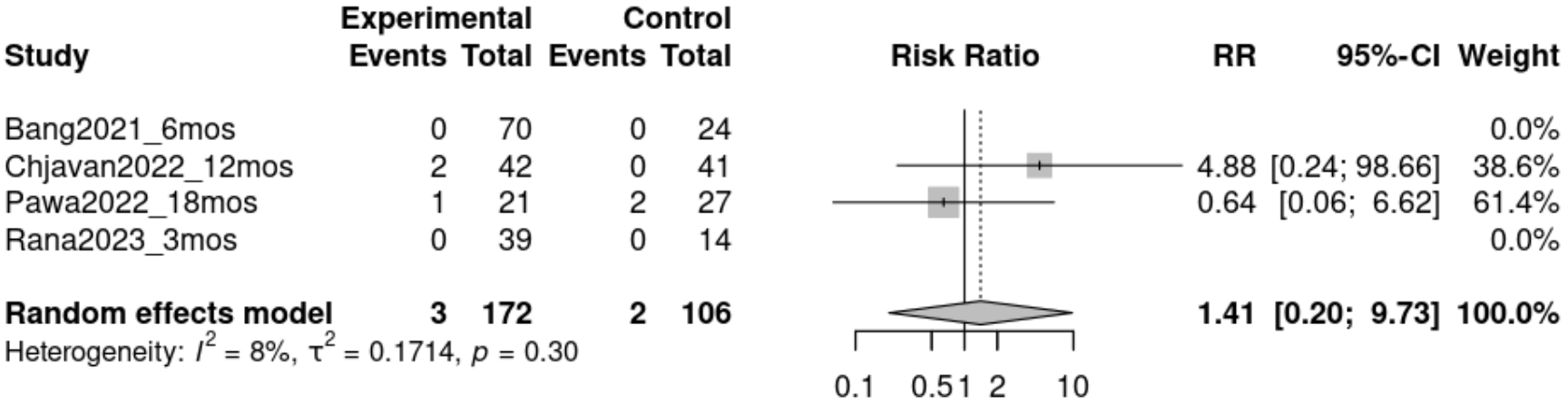
Supplemental Figure 33. Forest Plot — New onset organ failure (PICO 5)



Supplemental Figure 34. Forest Plot — Recurrence – need for repeat procedure (PICO 6)



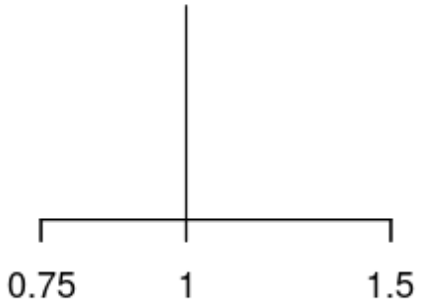
Supplemental Figure 35. Forest Plot — Escalation of surgery (PICO 6)



Supplemental Figure 36. Forest Plot — Perforation (PICO 6)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio	RR 95%-CI	Weight
Bang2021	0	70	0	24			0.0%
Chavan2022	0	52	0	52			0.0%
Pawa2022	0	21	0	27			0.0%
Random effects model	**0**	**143**	**0**	**103**			**100.0%**

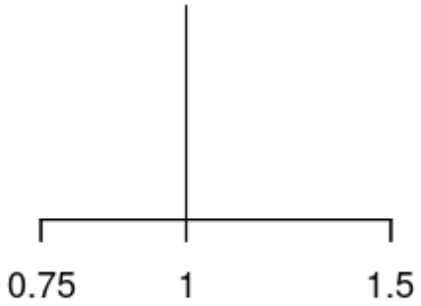
Heterogeneity: I^2 = NA%, τ^2 = NA, p = NA



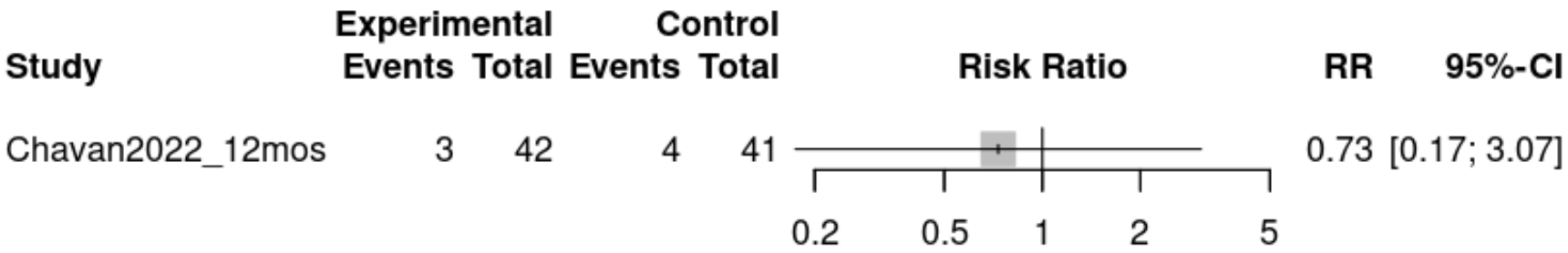
Supplemental Figure 37. Forest Plot — Bleeding (PICO 6)

Study	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio	RR 95%-CI	Weight
Bang2021	0	70	0	24			0.0%
Chavan2022	0	52	0	52			0.0%
Pawa2022	0	21	0	27			0.0%
Random effects model	**0**	**143**	**0**	**103**			**100.0%**

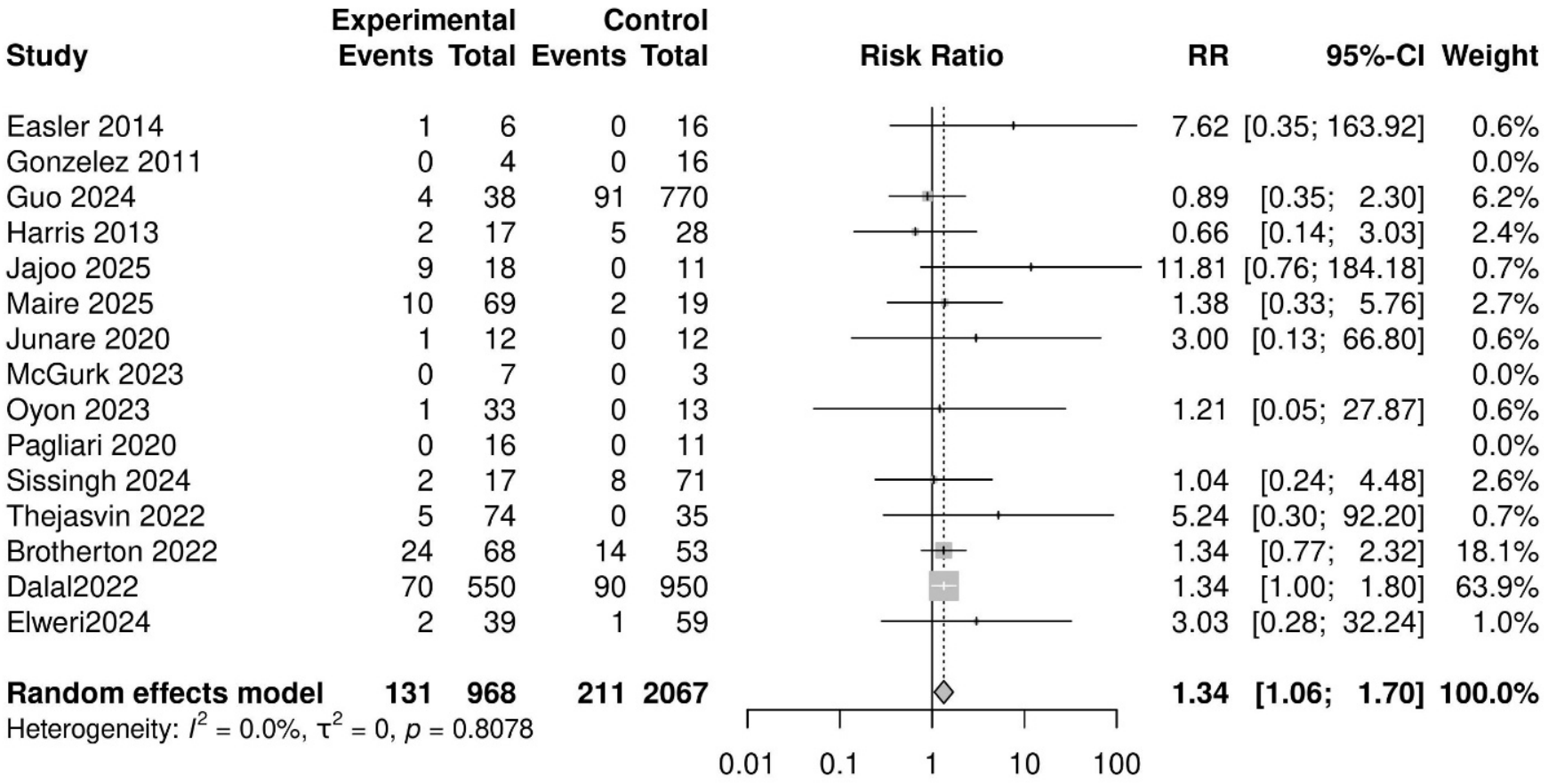
Heterogeneity: I^2 = NA%, τ^2 = NA, p = NA



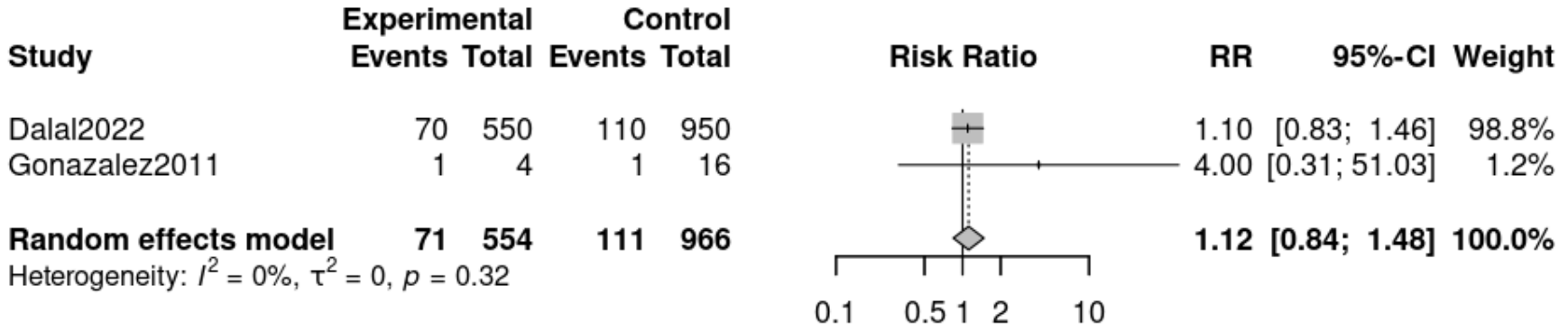
Supplemental Figure 38. Forest Plot — Recurrence need for procedure RCT only (PICO 6)



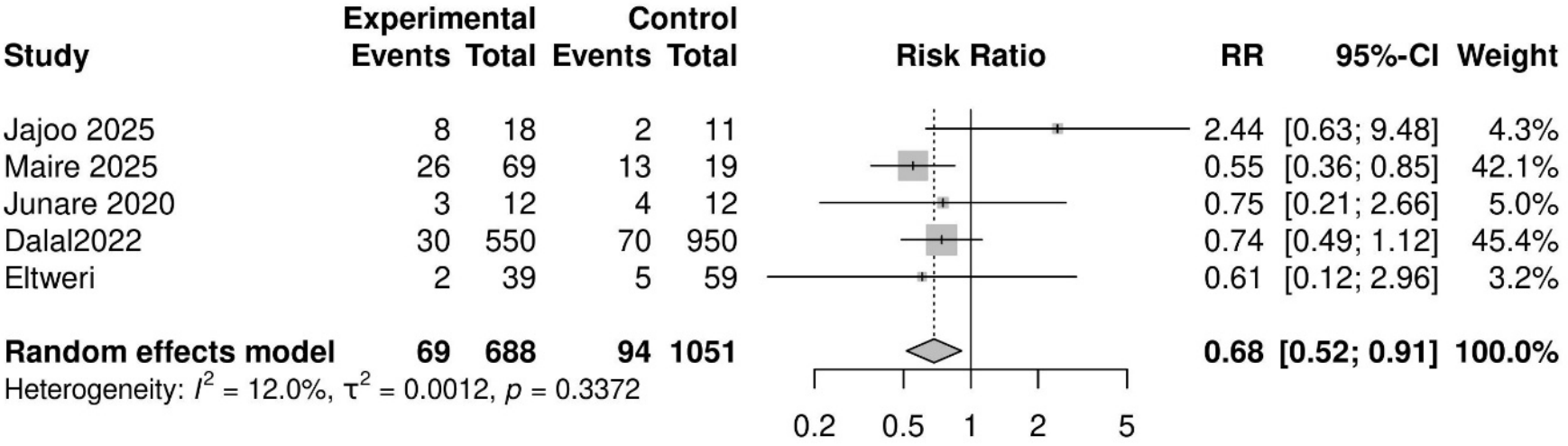
Supplemental Figure 39. Forest Plot — Bleeding (PICO 7)



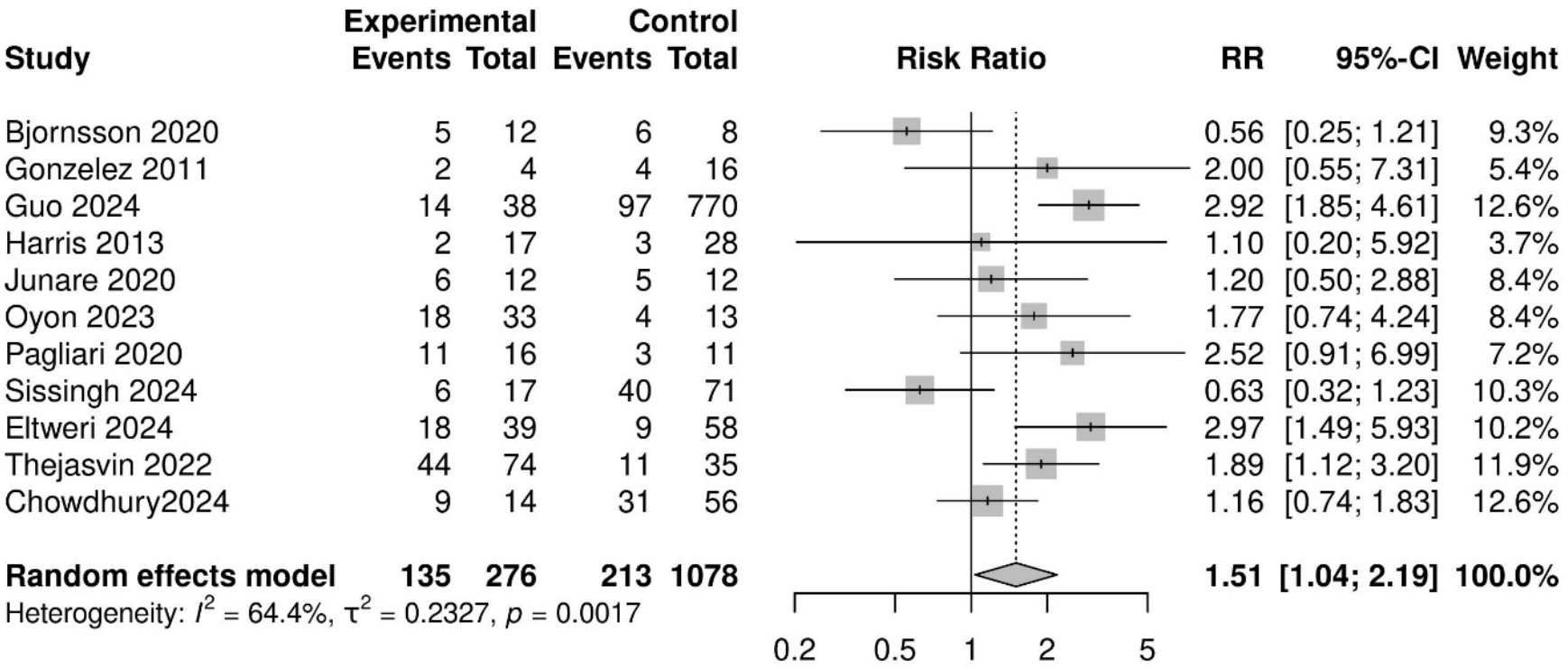
Supplemental Figure 40. Forest Plot — Ascites (PICO 7)



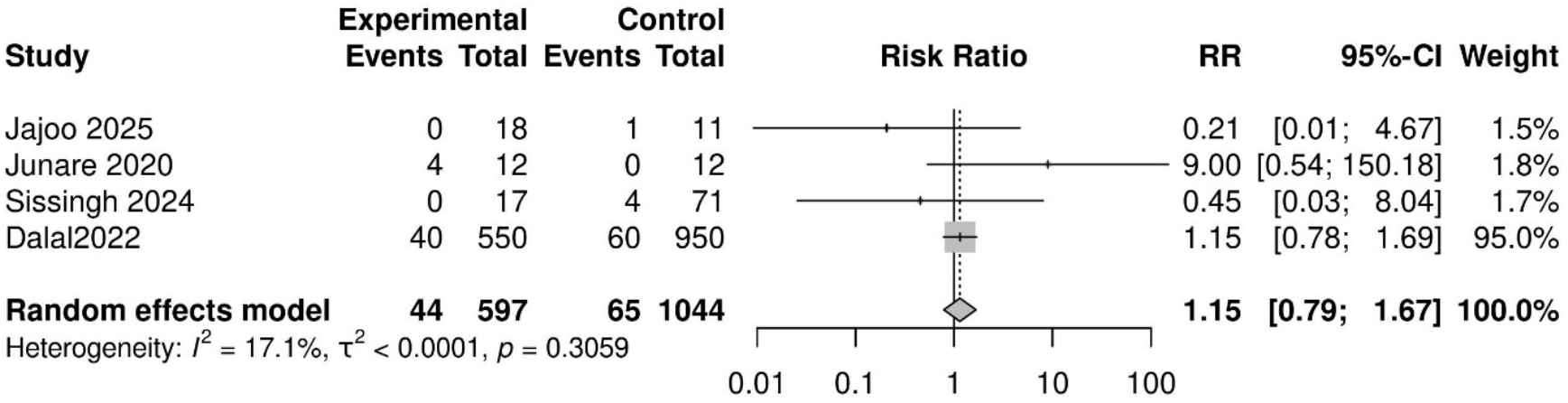
Supplemental Figure 41. Forest Plot — Varices (PICO 7)



Supplemental Figure 42. Forest Plot — Recanalization (PICO 7)



Supplemental Figure 43. Forest Plot — Ischemia (PICO 7)



Supplemental Figure 44. Forest Plot — Mortality (PICO 7)