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Review

Superiority of endoscopic interventions over minimally invasive surgery for infected necrotizing pancreatitis: meta-analysis of randomized trials

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Background and Aim: Infected necrotizing pancreatitis is a highly morbid disease managed by minimally invasive surgical (MIS) or endoscopy-based interventions. This meta-analysis compared the clinical outcomes of patients treated using either approach.

Methods: MEDLINE and EMBASE databases were searched to identify all randomized trials that compared MIS and endoscopy-based interventions for treatment of infected necrotizing pancreatitis. Main outcome measure was to compare rates of complications or death during 6-month follow-up.

Results: Three studies involving 184 patients met inclusion criteria. While there was no significant difference in mortality (14.5% vs. 16.1%, risk ratio [RR] = 1.02, $P = 0.963$), new onset multiple organ failure (5.2% vs. 19.7%, RR = 0.34, $P = 0.045$), enterocutaneous fistula/perforation (3.6% vs. 17.9%, RR = 0.34, $P = 0.034$) and pancreatic fistula (4.2% vs. 38.2%, RR = 0.13, $P < 0.001$) were significantly lower for endoscopic interventions compared to MIS. There was no significant difference in intraabdominal bleeding, endocrine or exocrine pancreatic insufficiency between cohorts. Length of hospital stay was significantly shorter for endoscopy (standardized mean difference, −0.41, $P = 0.010$).

Conclusions: An endoscopy-based treatment approach, as compared to minimally invasive surgery, significantly reduces complications in patients with infected necrotizing pancreatitis.

Key words: complications, endoscopy, necrosectomy, pancreatic necrosis, pancreatitis

INTRODUCTION

ACUTE PANCREATITIS IS the most common gastrointestinal diagnosis that warrants hospitalization with approximately 20% of patients developing pancreatic or peri-pancreatic necrosis.[1,2] While a majority of necrosis remain sterile, 30% of patients develop a superimposed infection that is diagnosed by the presence of gas in the collection, positive culture of the necrotic aspirate, persistent sepsis or ongoing clinical deterioration.[3,4] Given the high morbidity and mortality, infected necrosis, whether pancreatic or peri-pancreatic, requires intervention in most patients.[5] Expert guidelines recommend that the intervention be delayed until the necrosis is well-demarcated.[6,7] Recent evidence suggests that the minimally invasive surgical (MIS) approach that incorporates video-assisted retroperitoneal debridement (VARD) or laparoscopic cystogastrostomy with internal debridement and endoscopic approach that incorporates transluminal drainage via placement of internal endoprosthesis with concomitant percutaneous drainage catheters and/or mechanical debridement using an endoscope are both clinically effective, with treatment outcomes superior to open surgical necrosectomy.[5,8,9] Three randomized trials have compared the endoscopic and MIS options for the treatment of infected necrotizing pancreatitis.[10–12] While the composite of major complications was lower for the endoscopic approach in two randomized trials,[10,11] no significant difference was found in the third.[12]

Given the high disease-related morbidity and major complications attributed to treatment-related interventions, it is important to definitively determine the efficacy and relative advantages of either treatment approach. However, a possible limitation with some of the present studies may be an inadequate sample size, which increases the likelihood of missing a treatment effect, even if it exists. Performing a meta-analysis combines different trials and increases the overall sample size, which in turn increases the statistical power of the analysis as well as the precision of the estimate of the treatment effect.[13] Additionally, a meta-analysis is

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particularly useful when negative results arise from some trials, each of which when taken separately, may be too small to allow a proper conclusion to be drawn regarding the effect of the therapy. Therefore, we conducted a meta-analysis of randomized trials that compared the MIS and endoscopic transluminal interventions in patients with infected necrotizing pancreatitis.

METHODS

Study selection

MEDLINE AND EMBASE databases were searched by two of the authors (JYB, SV) to identify randomized trials comparing the clinical outcomes between endoscopy and minimally invasive surgery for the treatment of necrotizing pancreatitis. The key search terms were "endoscopy", "surgery" and "necrotizing pancreatitis". No restrictions were placed on publication dates or publication language and the last literature search was performed on January 15, 2019. Each study was screened independently by two of the authors (JYB, SV) using the study title and abstract and the full manuscript was reviewed for inclusion in the meta-analysis when necessary. Any discrepancies between the two authors for study inclusion were resolved following consultation with the third author (CMW).

Inclusion and exclusion criteria

All randomized trials published in peer-reviewed journals comparing the clinical outcomes between MIS and endoscopic interventions for infected necrotizing pancreatitis in patients aged 18 years and over were included in this meta-analysis. Studies were included if the rate of adverse events were reported.

Studies other than randomized trials, studies which did not directly compare MIS and endoscopic interventions for necrotizing pancreatitis and studies available only in an abstract format were excluded from the meta-analysis.

Data extraction

The following information was independently extracted from all included studies by two authors (JYB, SV): study design, patient demographics, disease characteristics, details of endoscopic and surgical interventions, details of the main outcome measures that included rates of adverse events, endocrine pancreatic insufficiency, exocrine pancreatic insufficiency and length of hospital stay. Any discrepancies between the two authors on the extracted data were resolved following consultation with the third author (CMW).

Outcome measures

The main outcome measures were comparison of (i) composite endpoint of major complications or death; (ii) individual components of major complications; (iii) endocrine pancreatic insufficiency; (iv) exocrine pancreatic insufficiency; and (v) length of hospital stay between endoscopic and MIS treatment for infected necrotizing pancreatitis.

Assessment of risk of bias

Two authors (JYB, SV) independently assessed the risk of bias for all included studies based on the Cochrane risk of bias tool (Table S1).[14–16] Any discrepancies between the two authors on quality assessment were resolved following consultation with the third author (CMW).

Statistical analysis

Categorical outcome measures were summarized as weighted proportions with 95% confidence intervals for endoscopic and MIS treatment groups. A meta-analysis was conducted using the random effects Mantel-Haenszel method to compare the two treatment arms. *P*-values <0.05 were determined to be statistically significant. The degree of heterogeneity was assessed using the I^2 statistic and funnel plots were constructed to evaluate for publication bias. All statistical analyses were conducted using Stata 14 (Stata Corp., College Station, TX, USA).

RESULTS

Description of included studies

SEARCH OF THE MEDLINE and EMBASE databases revealed 631 and 557 publications, respectively. After screening for eligibility, three randomized trials were retrieved for further review from each database search and after removal of three duplicates, a total of three studies were included in the final meta-analysis (Fig. S1).

Methodological quality of included studies

All three randomized trials fulfilled most of the predetermined list of quality criteria. All three studies had a low risk of bias in all categories except in the risk for performance bias (Table S1).[14,15]

Patient and disease characteristics

A total of 184 patients were included in the meta-analysis (n = 95 in the endoscopy group, n = 89 patients in the

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minimally invasive surgery group). Two of the randomized trials were conducted in the Netherlands and one in the United States. All trials included patients over the age of 18 years with infected (or suspected infected) necrotizing pancreatitis undergoing either endoscopic therapy or MIS therapy. Infected necrotizing pancreatitis was defined in all studies as gas seen on cross-sectional imaging or positive culture of necrotic material. Suspected infected necrosis was defined in all studies as continuing sepsis or clinical deterioration.[10–12] The follow-up period was 6 months after discharge in two studies[10,11] and 6 months after randomization in one study.[12] (Tables 1a–c).

Endoscopic interventions

Percutaneous drains were *in situ* pre-intervention in 0–41% of patients in the endoscopy group, compared to 28–80% in the surgery group. In all studies, endoscopic treatment comprised endoscopic ultrasound (EUS)-guided drainage via cystogastrostomy or cystoenterostomy. Only 7 French (Fr) plastic stents were used in two of the studies,[10,12] while either 7 Fr plastic stents or 15 mm lumen-apposing metal stents (LAMS) were used in one study[11] due to the availability of LAMS from 2015 in the United States. In one study, the multi-gate technique was adopted for collections ≥80 mm, which involved creation of more than one transmural tract.[11] In two of the studies, 6–8.5 Fr nasocystic catheters were also inserted through the cystogastrostomy tract at the time of initial EUS-guided drainage.[10,12]

Following initial EUS-guided drainage, additional interventions varied between the studies. In one study,[11] additional interventions were performed in patients with no clinical improvement (defined as persistent systemic inflammatory response syndrome [SIRS], sepsis or organ failure and <25% decrease in the size of necrotic collection at 72 h) and comprised creation of additional cystogastrostomy tracts in predominantly liquid debris or endoscopic necrosectomy in patients with predominantly solid debris. Plastic stents were inserted through the cystogastrostomy tract and 18–24 Fr catheters were placed following endoscopic necrosectomy. In the other two studies,[10,12] additional endoscopic interventions comprised endoscopic necrosectomy. The indication for endoscopic necrosectomy was defined as the lack of significant clinical improvement in one study (failure of improvement in organ failure or lack of improvement in infection parameters at 72 h)[12]; however, the indication for performing endoscopic necrosectomy was not provided by the authors in the other study.[10] Endoscopic necrosectomy was performed in 32.4–100% of patients across the three studies and open surgical necrosectomy was not performed in any patient in the endoscopy cohorts.

Minimally invasive surgical interventions

The technique of MIS treatment for necrotizing pancreatitis also varied between studies. In the study by Bang *et al*.,[11] MIS treatment comprised laparoscopic cystogastrostomy or VARD depending on the location, extent of necrosis and availability of retroperitoneal access. In the study by Bakker *et al*.,[10] minimally invasive surgery comprised VARD, with reservation of open necrosectomy for patients with no retroperitoneal access in whom VARD could not be performed. In the study by van Brunschot *et al*.,[12] surgical management consisted of the step-up approach in which all patients underwent computed tomography (CT) or ultrasound-guided insertion of percutaneous drains into the necrosis as the initial therapeutic step. VARD was then reserved only for patients who failed to show significant clinical improvement with percutaneous drain placement alone, which constituted 51% of the patients. Also, in this study,[12] laparotomy for necrosectomy was designated as the alternative treatment option for surgical necrosectomy in patients where VARD was not possible. Reintervention in the surgical cohort comprised VARD in all studies.[10–12] Laparotomy for necrosectomy was performed in 0%, 3% and 40% in the surgical cohort.[10–12]

Outcome measures

Composite endpoint of major complications or death

All three randomized trials comprising 184 patients compared the rate of major complications and/or death between endoscopy and minimally invasive surgery. The definition of major complications varied between the studies (Table 3).

The rates of major complications or death were 11.8–43% for endoscopy and 40.6–80% for surgery, with pooled rates of 25.8% (95% confidence interval [CI]: 7.9–49.7%) and 50.8% (95% CI, 33.5–68.0), respectively. There was no significant difference in the rates of major complications or death between endoscopy and surgery with pooled risk ratio (RR) of 0.46 (95% CI, 0.17–1.27; $P = 0.136$; Tables 2 and 3, Fig. 1a). When the rates of major complications or death were compared after the inclusion of pancreatic fistula in all studies, there was still no significant difference between the two treatment modalities, with pooled rates of 26.4% (95% CI, 7.5–51.7%) for endoscopy compared to 57.0% (95% CI, 38.7–74.4%) for surgery and pooled RR of 0.44 (95% CI, 0.19–1.01; $P = 0.053$; Fig. 1b). No significant heterogeneity was observed between the studies ($I^2 = 64.5\%$;

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Table 1 (a) Baseline study and patient characteristics. (b) Baseline characteristics of disease severity. (c) Baseline necrosis characteristics

(a)

Author, year	Study design	No. of patients	Study dates	Follow-up (months)	Age (years)		Male sex: *n* (%)		Duration of symptoms, days: Median (IQR)	
					Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery
Bakker, 2012[10]	Randomized trial	20	8/2008–3/2010	6 months after discharge	62 (58–70)†	64 (46–72)†	6 (60)	8 (80)	48 (36–74)	59 (29–69)
Bang, 2019[11]	Randomized trial	66	5/2014–3/2017	6 months after discharge	59 (46–66)†	57.5 (45–64.5)†	22 (64.7)	21 (65.6)	25 (73.5)§	25 (78.1)§
van Brunschot, 2018[12]	Randomized trial	98	9/2011–1/2015	6 months after randomization	63 (14)‡	60 (11)‡	34 (67)	29 (62)	39 (28–54)	41 (28–52)

(b)

Author, year	ASA class III/IV: *n* (%)		SIRS: *n* (%)		APACHE II score: Median (IQR)		Single organ failure: *n* (%)		Multiple organ failure: *n* (%)		ICU admission: *n* (%)	
	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery
Bakker, 2012[10]	0 (0)	1 (10)	9 (90)	7 (70)	10 (6–14)	11 (7–14)	4 (40)	4 (40)	2 (20)	4 (40)	5 (50)	4 (40)
Bang, 2019[11]	32 (94.1)	31 (96.9)	16 (47.1)	16 (50.0)	30 (26–35)	21 (16–23)	2 (5.9)	3 (9.4)	7 (20.6)	7 (21.9)	24 (70.6)	21 (65.6)
van Brunschot, 2018[12]	5 (10)	2 (4)	33 (65)	38 (81)	9 (5–13)	10 (6–13)	13 (25)	14 (30)	9 (18)	7 (15)	21 (41)	25 (53)

(c)

Author, year	CT Severity Index		Mature necrotic collection: *n* (%)		Size of necrotic collection, cm: Median (IQR)		Extent of necrosis ≥ 30%: *n* (%)		Infected necrosis: *n* (%)		Percutaneous drain *in situ*: *n* (%)	
	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery
Bakker, 2012[10]	8 (4–10)¶	8 (4–10)¶	Not stated	Not stated	Not stated	Not stated	6 (60)	6 (60)	10 (100)	9 (90)	4 (40)	8 (80)
Bang, 2019[11]	33 (97.1)††	29 (90.6)††	21 (61.8)	23 (71.9)	8.7 (6.3–12.8)	9.2 (7.7–12.1)	25 (73.5)	26 (81.3)	31 (91.2)	30 (93.8)	14 (41.2)	9 (28.1)
van Brunschot, 2018[12]	6 (6–8)†	8 (6–10)†	36 (71)	33 (70)	Not stated	Not stated	25 (49.0)	25 (53.2)	46 (90)	46 (98)	0	24 (51)

†Median (IQR).
‡Mean (SD).
§*n* (%) of patients where disease onset ≥ 4 weeks.
¶Median (Range).
††*n* (%) of CTSI ≥ 8.
APACHE II, Acute Physiology And Chronic Health Evaluation II; ASA, American Society of Anesthesiologists; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; SIRS, systemic inflammatory response syndrome.

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Table 2 (a) Summary of major complications or death in individual studies. (b) Summary of secondary outcome measures, including endocrine/exocrine pancreatic insufficiency and length of hospital stay in individual studies

(a)

Author, year	Major complications or death: *n* (%)		Death: *n* (%)		New onset multiple organ failure: *n* (%)		Intraabdominal bleeding: *n* (%)		Enterocutaneous fistula or perforation: *n* (%)		Pancreatic fistula: *n* (%)	
	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery
Bakker, 2012[10]	2 (20)	8 (80)	1 (10)	4 (40)	0	5 (50)	0	0	0	2 (20)	1 (10)	7 (70)
Bang, 2019[11]	4 (11.8)	13 (40.6)	3 (8.8)	2 (6.3)	2 (5.9)	3 (9.4)	0	3 (9.4)	0	5 (15.6)	0	8 (25.0)
van Brunschot, 2018[12]	22 (43)	21 (45)	9 (18)	6 (13)	2 (4)	6 (13)	11 (22)	20 (21)	4 (8)	8 (17)	2 (5)	13 (32)

(b)

Author, year	Incisional hernia: *n* (%)		Surgical site infection: *n* (%)		Pancreatic endocrine insufficiency: *n* (%)		Pancreatic exocrine insufficiency: *n* (%)		No. of necrosectomies: Median (IQR)		Length of hospital stay, days: Median (IQR)	
	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery	Endoscopy	Surgery
Bakker, 2012[10]	N/A	N/A	N/A	N/A	2 (22)	3 (50)	0	3 (50)	3 (2–6)	1 (1–2)	45 (12–69)	36 (17–74)
Bang, 2019[11]	0	2 (6.3)	0	2 (6.3)	6 (27.3)	9 (36.0)	29 (85.3)	28 (87.5)	0 (0–1)	1 (1–1.5)	14 (6–22)	18.5 (11.5–29.5)
van Brunschot, 2018[12]	0	1 (2)	2 (4)	3 (6)	10 (24)	9 (22)	16 (38.1)	13 (31.7)	2 (1–4)	1 (1–1)	35 (19–85)	65 (40–90)

IQR, interquartile range.

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Table 3 Summary of pooled outcome measures and risk ratios

Outcome measure	Number of patients (*n*)		Pooled estimate: mean % (95% CI)		Pooled risk ratio (95% CI)	*P*-value	I^2 statistic (%)
	Endoscopy	Surgery	Endoscopy	Surgery			
Major complications or death[†]	95	89	25.8 (7.9–49.7)	50.8 (33.5–68.0)	0.46 (0.17–1.27)	0.136	74.5
Major complications or death (inc. pancreatic fistula in all studies)	95	89	26.4 (7.5–51.7)	57.0 (38.7–74.4)	0.44 (0.19–1.01)	0.053	64.5
Death	95	89	14.5 (8.3–22.1)	16.1 (5.0–31.8)	1.02 (0.42–2.51)	0.963	17.0
New onset multiple organ failure	95	89	5.2 (1.7–10.4)	19.7 (6.1–38.7)	0.34 (0.12–0.98)	0.045	0
Enterocutaneous fistula/perforation	95	89	3.6 (0.2–11.2)	17.9 (10.8–26.3)	0.34 (0.13–0.92)	0.034	0
Pancreatic fistula	86	83	4.2 (0.4–11.8)	38.2 (19.9–58.5)	0.13 (0.04–0.37)	<0.001	0
Intraabdominal bleeding[‡]	95	89	6.2 (0.2–27.0)	12.3 (3.5–25.4)	0.60 (0.10–3.59)	0.575	45.2
Endocrine pancreatic insufficiency	85	79	22.1 (14.1–31.3)	27.3 (18.0–37.7)	0.78 (0.45–1.36)	0.380	0
Exocrine pancreatic insufficiency	85	79	39.5 (3.7–84.5)	57.8 (17.8–92.5)	0.99 (0.66–1.48)	0.962	34.9
Length of hospital stay (days)	85	79	–	–	SMD −0.41 (−0.71 to −0.095)	0.010	0

[†]In the study by Bang *et al*.,[11] major complications were defined as new onset multiple organ failure/systemic dysfunction, enteral and pancreatic-cutaneous fistula, intraabdominal bleeding and visceral perforation. In the study by Bakker *et al*.,[10] major complications comprised new onset multiple organ failure, intraabdominal bleeding, enterocutaneous fistula, perforation of a visceral organ and pancreatic fistula. In the study by van Brunschot *et al*.,[12] major complications included new onset organ failure, bleeding, perforation of a visceral organ, enterocutaneous fistula and incisional hernia. In this study,[12] although pancreatic fistula was not included in the original definition of major complications, the investigators performed further analyses in which pancreatic fistula was added to the other components of major complications.

[‡]For intraabdominal bleeding, the study by Bakker *et al*. was excluded from meta-analysis for as there were no incidences of bleeding in both cohorts and hence carried zero weight in pooled analysis.

CI, confidence interval; SMD, standardized mean difference.

$P = 0.060$) when pancreatic fistula was included in the analysis in all three studies, but poor symmetry was observed in the funnel plots (Table S2; Fig. S2a,b).

Individual components of composite endpoint of major complications

On comparison of the individual components of major complications, the rates of new onset multiple organ failure were significantly lower in endoscopy (pooled rate 5.2%, 95% CI, 1.7–10.4%) as compared to surgery (pooled rate 19.7%, 95% CI, 6.1–38.7%), with pooled RR of 0.34 (95% CI, 0.12–0.98; $P = 0.045$). In two of the studies,[10,12] the incidence of enterocutaneous fistula and visceral perforation were combined as a composite endpoint. Therefore, in order to minimize heterogeneity, these two components of major complications were also combined from the original database in the third study for the meta-analysis.[11] The rates of enterocutaneous fistula/perforation were significantly lower for endoscopy as compared to surgery, with pooled rates of 3.6% (95% CI, 0.2–11.2%) and 17.9% (95% CI, 10.8–26.3%), respectively, with pooled RR of 0.34 (95% CI, 0.13–0.92; $P = 0.034$). Additionally, the rates of pancreatic fistula were significantly lower for endoscopy as compared to surgery, with pooled rates of 4.2% (95% CI, 0.4–11.8%) and 38.2% (95% CI, 19.9–58.5%) respectively, and pooled RR of 0.13 (95% CI, 0.04–0.37; $P < 0.001$; Tables 2 and 3; Fig. 2a–c). There were, however, no significant differences in the rates of death or intraabdominal bleeding between endoscopy and surgery (Fig. S3a,b).

There was no significant heterogeneity between the studies on comparison of the individual components of major complications; however, poor symmetry was observed in the funnel plots (Figs S4a,b and S5a–c).

Endocrine and exocrine pancreatic insufficiency

The rates of endocrine and exocrine pancreatic insufficiency were compared between endoscopy and surgery in all three studies, comprising 164 patients. The total number of patients in whom these two outcomes were assessed was lower compared to the other outcomes of major complications/death ($n = 184$) as the patients who died were excluded from analysis in two studies.[10,12] In one study,[11] endocrine insufficiency was defined as new onset fasting

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glucose ≥126 mg/dL, 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test or HbA1c ≥6.5%. In the two remaining studies,[10,12] endocrine insufficiency was defined as new requirement for diabetic medication at 6 months following randomization.

The rates of endocrine pancreatic insufficiency were 22–27.3% for endoscopy and 22–50% for surgery, with pooled rates of 22.1% (95% CI, 14.1–31.3%) and 27.3% (95% CI, 18.0–37.7%), respectively. There was no significant difference between endoscopy and surgery with pooled RR 0.78 (95% CI, 0.45–1.36; $P = 0.380$; Tables 2 and 3; Fig. S6a). There was no significant heterogeneity between the studies ($I^2 = 0\%$; $P = 0.483$) but poor symmetry was observed in the funnel plot (Fig. S7a).

All three studies comprising 164 patients compared the rates of exocrine pancreatic insufficiency. In one study,[11] the presence of exocrine pancreatic insufficiency was defined as fecal elastase level <200 μg/g. In the two remaining studies,[10,12] exocrine pancreatic insufficiency was defined as new requirement for pancreatic enzyme supplementation for steatorrhea at 6 months following randomization.

The rates of exocrine pancreatic insufficiency were 0–85.3% for endoscopy and 31.7–87.5% for surgery, with pooled rates of 39.5% (95% CI, 3.7–84.5%) and 57.8% (95% CI, 17.8–92.5%), respectively. There was no significant difference between endoscopy and surgery with pooled RR 0.99 (95% CI, 0.66–1.48; $P = 0.962$; Tables 2 and 3; Fig. S6b). No significant heterogeneity was observed between the studies ($I^2 = 34.2\%$; $P = 0.219$); however, poor symmetry was observed in the funnel plot (Fig. S7b).

Length of hospital stay

All three studies comprising 164 patients compared the length of hospital stay between endoscopy and surgery ($n = 164$ not 184 due to exclusion from analysis of 20 patients who died in two studies[10,12]). The length of hospital stay from index intervention to hospital discharge was calculated in one study.[11] In the other two studies, the length of hospital stay was calculated from the time of randomization.[10,12]

The median length of hospital stay varied from 14 to 45 days in endoscopy compared to 18.5–65 days in surgery. Meta-analysis was performed only with two of the studies[11,12] as the mean length of stay was not provided in the study by Bakker *et al.*[10] When compared, the length of hospital stay was significantly shorter for endoscopy compared to surgery, with standardized mean difference of −0.41 ($P = 0.010$; Tables 2 and 3; Fig. 3). There was no significant heterogeneity between studies ($I^2 = 0\%$; $P = 0.803$) and reasonable symmetry was observed on the funnel plot (Fig. S8).

Two of the studies compared the total costs between endoscopic and surgical treatments.[11,12] In the study by Bang *et al.*,[11] the mean total costs incurred over the 6-month follow-up period were significantly lower for endoscopy compared to surgery at US $75 830 and $117 492, respectively ($P = 0.039$). However, in the study by van Brunschot *et al.*,[12] the mean total costs calculated from the time of randomization to 6-month follow-up were not significantly different between endoscopy and surgery at £60 228 and £73 883, respectively. No cost analysis was performed in the study by Bakker *et al.*[10]

DISCUSSION

OUR META -analysis shows that the endoscopic approach, as compared with minimally invasive surgery, reduces three major complications within the composite endpoint, notably, new onset multiple organ failure, enterocutaneous fistula or perforation and pancreatic fistula. Additionally, patients undergoing endoscopic treatment experience a shorter length of hospital stay as compared to those treated surgically. These findings are important because when considered individually, except for pancreatic fistulae, none of the three randomized trials demonstrated a collective difference in the other two endpoints observed in this meta-analysis. Given that the meta-analysis included only high-quality randomized trials with few methodological limitations (unlike prior publications[17]), we believe that our findings will influence the shift in management strategy for infected necrotizing pancreatitis from minimally invasive surgery towards endoscopic approaches.

It has been reported that the presence of organ failure, irrespective of the presence or absence of infected necrotizing pancreatitis, led to mortality in 30% of patients and that the presence of infected necrotizing pancreatitis, irrespective of the presence or absence of organ failure, led to mortality in 32% of patients.[18] More importantly, the same study observed that mortality was two times higher in patients with both infected necrotizing pancreatitis and organ failure in comparison to patients with only organ failure or only infected necrotizing pancreatitis. While a significant difference in new onset organ failure was observed in only one randomized trial,[10] our meta-analysis suggests that a true difference exists between treatment modalities in favor of the endoscopic approach. This finding is important because organ failure is an important cause of long-term morbidity and death following acute pancreatitis.[19,20]

While the occurrence of pancreatic fistula was found to be significantly higher in the surgical cohort in the three randomized trials and has been subsequently confirmed by this meta-analysis, no significant difference in rates of

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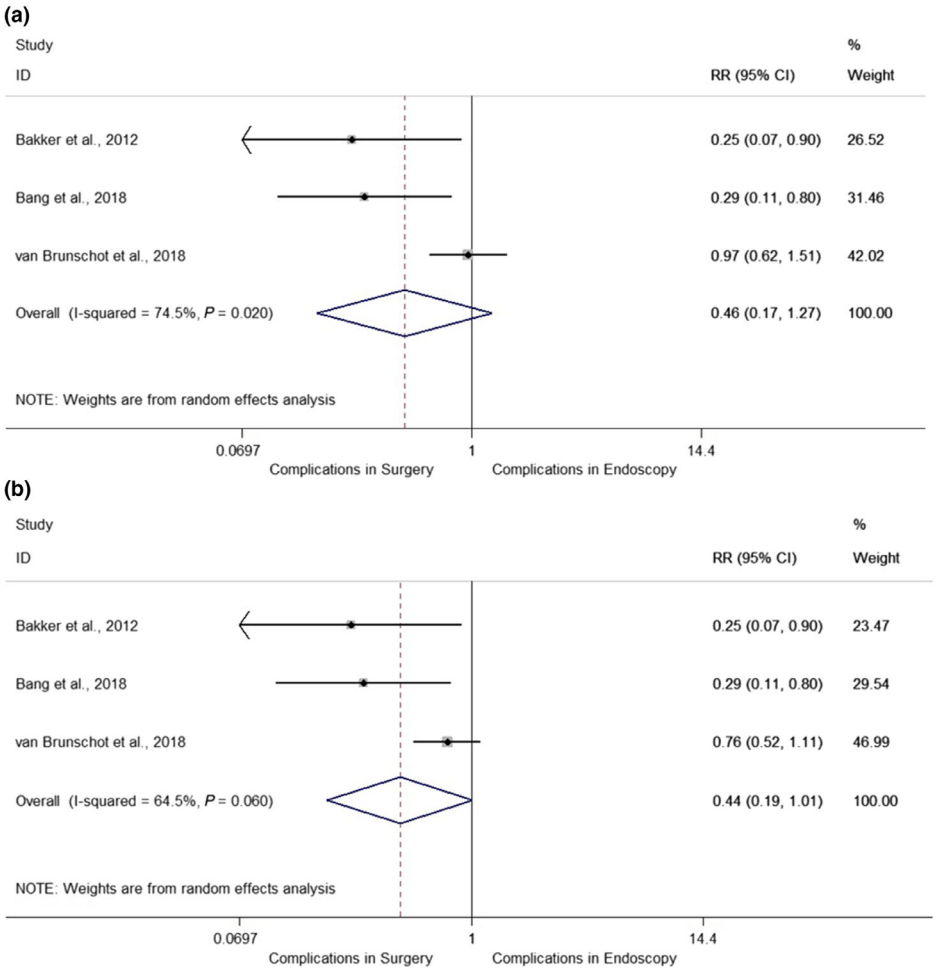

Figure 1 (a) Forest plot comparing the composite of major complications or death between endoscopy and surgery, without inclusion of pancreatic fistula in all studies. (b) Forest plot comparing the composite of major complications or death between endoscopy and surgery, with inclusion of pancreatic fistula in all studies.

enterocutaneous fistula or perforation of a visceral organ requiring an intervention was observed in two of the three studies.[10,12] Remarkably, a significant difference was observed in the meta-analysis for this outcome, favoring the endoscopic approach. While surgical necrosectomy and percutaneous drainage cause external extravasation of inflammatory enzymatic exudates and lead to formation of pancreatic-cutaneous fistulae, the flow of exocrine secretions dissecting through the retroperitoneal tissue planes can cause bowel necrosis due to vascular infarction. This risk can be further compounded by repeated surgical interventions, multiple port placements or pressure necrosis induced by drain placements.[21] While the spontaneous closure of some enterocutaneous fistulae may occur with time, colonic and duodenal fistulae more often require a surgical intervention for control of drainage or repair.[22]

In this meta-analysis, the length of hospital stay was found to be significantly shorter for the endoscopic treatment group as compared to minimally invasive surgery. The reasons for this difference are likely multifactorial: One, the threshold for performing a reintervention after index treatment is likely higher for surgery than endoscopy. Two, complications such as pancreatic or enterocutaneous fistula that are more frequently observed in the surgical group may require additional interventions and/or readmissions. Three, multi-organ failure which is more commonly encountered in the surgical treatment group is associated with long-term morbidity and hence a prolonged hospitalization.

Given the rigorous selection criteria for participation in the three randomized trials, except for procedural methodology, there was no significant heterogeneity for most parameters evaluated in this meta-analysis. The assessment for

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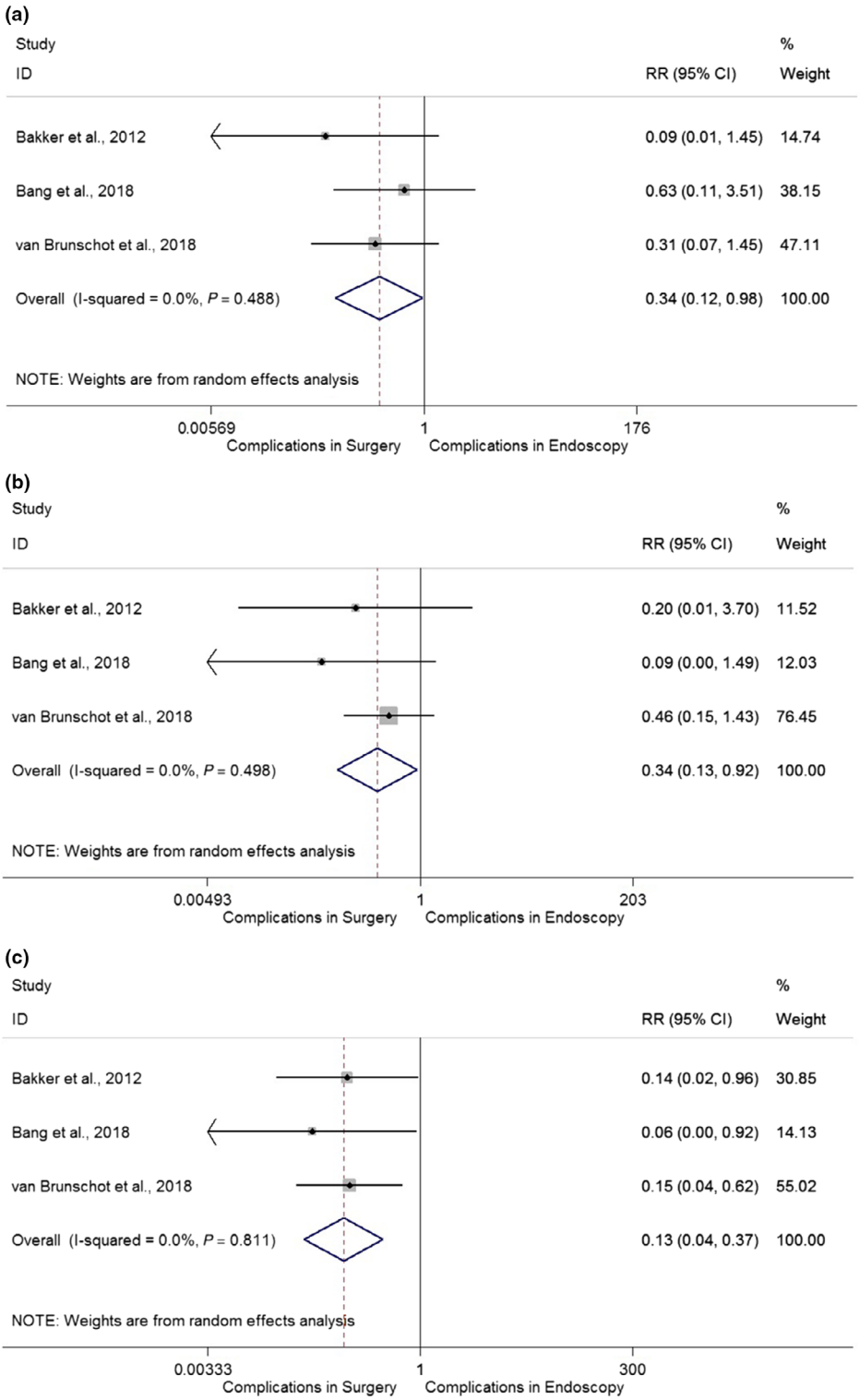

Figure 2 (a) Forest plot comparing new onset multiple organ failure between endoscopy and surgery. (b) Forest plot comparing enterocutaneous fistula or perforation between endoscopy and surgery. (c) Forest plot comparing pancreatic fistula between endoscopy and surgery.

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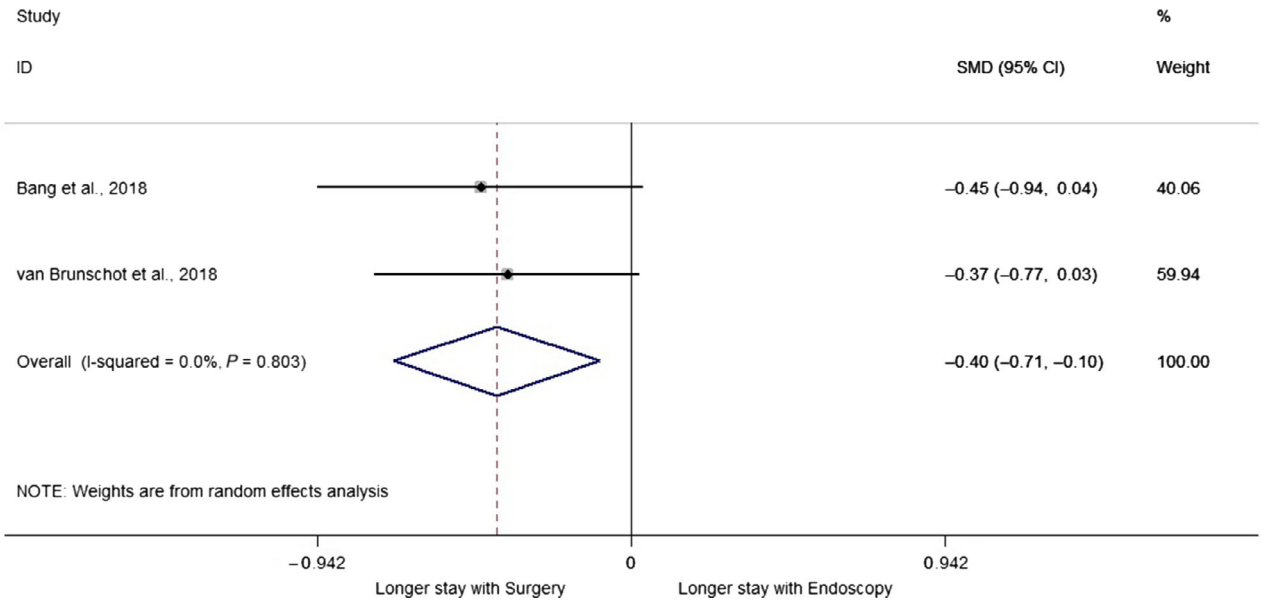

Figure 3 Forest plot comparing length of hospital stay between endoscopy and surgery.

publication bias was more challenging due to the inclusion of only three studies, and hence a difficulty in the assessment of funnel plot symmetry. Although clinical improvement with placement of percutaneous drainage catheters was an exclusion criteria in two studies,[10,11] it was an integral part of the step-up surgical approach in one.[12] Additionally, the creation of multiple transluminal gateways and use of LAMS in the endoscopic cohort may have contributed to fewer number interventions in one study.[11] However, the differences in the types of interventions performed and the threshold for undertaking reinterventions varies between centers as these decisions involve a multidisciplinary team with inherent institutional differences in treatment strategies. Consequently, significant variation between treatment approaches is a limitation that cannot be overcome.

Our meta-analysis shows that the endoscopic treatment approach, as compared to minimally invasive surgery, significantly reduces complications and length of hospital stay in patients with infected necrotizing pancreatitis. Given these promising findings, we believe that when the requisite expertise is available, endoscopic approach should be the first-line treatment strategy. Future investigations must focus on optimizing the procedural techniques, establishing treatment algorithms and developing new devices to further the advancement of endoscopic approaches. Nevertheless, it is important to note that endoscopic approach is conducive only for collections adjacent to the stomach or duodenum and those not amenable to drainage by endoscopy will require drainage by interventional radiology-guided percutaneous drain placement or with VARD.[23] Additionally, patients enrolled in the randomized trials included in this meta-analysis had necrotic collections that were accessible by both treatment approaches. Consequently, the conclusion of this meta-analysis may not be applicable to collections not accessible by either approach. Therefore, a multidisciplinary treatment approach that includes interventional endoscopists, minimally invasive surgeons, interventional radiologists and critical care specialists is pivotal for the provision of optimal care to these challenging patients.

CONFLICT OF INTEREST

JI YOUNG BANG is a Consultant for Boston Scientific Corp. and Olympus America Inc. Shyam Varadarajulu is a Consultant for Boston Scientific Corporation and Olympus America Inc., Covidien, Creo Medical. Juan Pablo Arnoletti and C. Mel Wilcox declare no conflict of interest for this article.

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NONE.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Figure S1 Flow diagram of search history to compare endoscopy and minimally invasive surgery in infected necrotizing pancreatitis.

Figure S2 (a) Funnel plot of the composite of major complications or death without inclusion of pancreatic fistula in all studies. (b) Funnel plot of the composite of major complications or death, with inclusion of pancreatic fistula in all studies.

Figure S3 (a) Forest plot comparing mortality between endoscopy and surgery. (b) Forest plot comparing intraabdominal bleeding between endoscopy and surgery.

Figure S4 (a) Funnel plot of mortality rate. (b) Funnel plot of new onset multiple organ failure.

Figure S5 (a) Funnel plot of enterocutaneous fistula or perforation. (b) Funnel plot of pancreatic fistula. (c) Funnel plot of intraabdominal bleeding.

Figure S6 (a) Forest plot comparing endocrine pancreatic insufficiency between endoscopy and surgery. (b) Forest plot comparing exocrine pancreatic insufficiency between endoscopy and surgery.

Figure S7 (a) Funnel plot of endocrine pancreatic insufficiency. (b) Funnel plot of exocrine pancreatic insufficiency.

Figure S8 Funnel plot of length of hospital stay.

Table S1 Assessment of risk of bias in each study.

Table S2 Summary of I^2 statistics for each outcome measure.

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