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Endoscopic biliary sphincterotomy: electric current mode

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) associated with biliary sphincterotomy is a procedure performed widely in medical practice. However, this intervention is not an exempt from complications (4–5%) such as acute pancreatitis, bleeding, perforation, cholangitis, or even death (0.02–0.4%)[1-3].

Several studies point to the correlation between the electric current mode (pure cut, blend, pulsed cut, or endocut, and pure cut followed by blend) used in endoscopic sphincterotomy and the incidence of adverse events[4-6]. A better knowledge of the subject based on evidence can assist us in making the best decision in clinical practice.

Our objective is, through a systematic review and meta-analysis, to trace the safety profile of each modality of electric current (pure cut, pulsed cut, blend cut, and pure cut followed by blend) employed in endoscopic biliary sphincterotomy to reduce the incidence of adverse events related to this procedure.

METHODS

A systematic review and meta-analysis of the literature (Medline, Central Cochrane, Embase, LILACS VHL, and grey literature) were carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) recommendations[7]. We used the PICO system (Patient: older than 18 years with the indication of ERCP and biliary sphincterotomy; Intervention and Control: respective modalities of electric current; and Outcome: adverse events such as acute pancreatitis, bleeding, perforation, and cholangitis).

We selected only randomized controlled trials that included patients aged more than 18 years who underwent ERCP with biliary sphincterotomy for various causes (e.g., choledocholithiasis, obstructive neoplasia, benign strictures, and biliary fistulas) randomized to any of the modalities of electric current under evaluation.

The risk of bias in each study was assessed using the Cochrane bias risk tool[8]. The level of evidence for each outcome was evaluated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation)[9].

The data were meta-analyzed using the RevMan 5.3 software, and the results were revealed as forest plots.

RESULTS

After removing duplicates, 12,282 articles were screened, including 10 randomized clinical trials in our study[4,10-18]. Annex Figure 1 summarizes the selection process.

The risk of bias in the included studies is expressed in Annex Table 1.

The characteristics of the studies and results are presented in Chart 1.

Results expressed by comparison:

ENDOCUT VS. *BLEND*

→ Inclusion of two studies with a total of 460 patients[4,12].

Acute pancreatitis

There was no difference between groups for pancreatitis in general (RD 0.01 [-0.03; 0.04], p = 0.62, I^2 = 48%) or in the mild, moderate, and severe subgroups.

Moderate level of certainty.

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Chart 1. Summary of study characteristics and results.

Study	N	Compared groups	ERCP indications	Age (MEAN)	Gender (M/F)	Homogeneous groups	Outcomes
Tanaka[12]	360	Endocut (200)	Choledocolithiasis and CBD stenosis (Benign and malignant)	73 (23-101)	56%/44%	Yes	**Pancreatitis:** 5 mild; 1 moderate; 0 severe **Bleeding:** 14 mild; 0 moderate; 0 severe
		Blend (160)					**Pancreatitis:** 7 mild; 0 moderate; 0 severe **Bleeding:** 18 mild; 0 moderate; 0 severe
Norton[14]	267	Endocut (134)	Choledocolithiasis, stenosis (benign and malignant), SOD, PSC	59 (19-99)	47%/51%	Yes	**Pancreatitis:** 1 mild; 2 moderate; 0 severe **Bleeding:** 4 mild; 4 moderate; 0 severe
		Pure cut (133)					**Pancreatitis:** 1 mild; 0 moderate; 0 severe **Bleeding:** 29 mild; 6 moderate; 0 severe
Macintosh[13]	246	Pure cut (116)	Choledocolithiasis, SOD, pancreatitis, stent insertion	56.4	31%/69%	Yes	**Pancreatitis:** 5 mild; 2 moderate; 2 severe **Bleeding:** 54 mild; 6 moderate; 1 severe
		Blend (130)					**Pancreatitis:** 5 mild; 3 moderate; 0 severe **Bleeding:** 26 mild; 6 moderate; 1 severe
Kida[11]	84	Endocut (41)	Choledocolithiasis, malignant strictures, others	66.2	53%/47%	Yes	**Pancreatitis:** 4 (total) **Bleeding:** 12 mild; 1 moderate; 0 severe
		Pure cut (43)					**Pancreatitis:** 1 (total) **Bleeding:** 22 mild; 6 moderate; 0 severe
Stefanidis[16]	186	Pure cut (62)	Choledocolithiasis	64 (40-86)	56%/44%	Yes	**Pancreatitis:** 2 mild; 0 moderate; 0 severe **Bleeding:** 18 mild; 2 moderate; 1 severe
		Blend (62)					**Pancreatitis:** 8 mild; 0 moderate; 0 severe **Bleeding:** 6 mild; 0 moderate; 1 severe
		Pure cut followed by blend (62)					**Pancreatitis:** 8 mild; 0 moderate; 0 severe **Bleeding:** 9 mild; 0 moderate; 1 severe
Ellahi[18]	86	Endocut (55)	Choledocolithiasis, SOD, Obstructive jaundice and pancreatitis	Unclear	Unclear	Unclear	**Pancreatitis:** 1 mild; 3 moderate; 1 severe **Bleeding:** 1 (total)
		Pure cut (31)					**Pancreatitis:** 0 mild; 0 moderate; 0 severe **Bleeding:** 0 (total)
Gorelick[17]	142	Pure cut (75)	Choledocolithiasis, SOD, biliary stricture, bile leak	Unclear	30%/70%	Yes	**Pancreatitis:** 6 mild; 6 moderate; 2 severe **Bleeding:** 4 mild; 3 moderate; 1 severe
		Pure cut followed by blend (67)					**Pancreatitis:** 5 mild; 5 moderate; 1 severe **Bleeding:** 5 mild; 1 moderate; 0 severe

Continued...

Chart 1. Continuation.

Study	N	Compared groups	ERCP indications	Age (MEAN)	Gender (M/F)	Homogeneous groups	Outcomes
Mahadeva[15]	50	Pure cut (17)	Unclear (but the author states that the indication was homogeneous among groups)	70	Unclear	Yes	**Pancreatitis:** 0 mild; 0 moderate; 0 severe **Bleeding:** 0 moderate; 0 severe
		Blend (15)					**Pancreatitis:** 0 mild; 0 moderate; 0 severe **Bleeding:** 0 moderate; 1 severe
		Pure cut followed by blend (18)					**Pancreatitis:** 0 mild; 0 moderate; 1 severe **Bleeding:** 0 moderate; 0 severe
Kohler[4]	100	Endocut (50)	Choledocolithiasis, chronic pancreatitis, CBD strictures, miscellaneous	Homogeneous	Homogeneous	Yes	**Pancreatitis:** 4 mild; 0 moderate; 0 severe **Bleeding:** 2 mild; 0 moderate; 0 severe
		Blend (50)					**Pancreatitis:** 1 mild; 0 moderate; 0 severe **Bleeding:** 13 mild; 0 moderate; 0 severe
Elta[10]	170	Pure cut (86)	Choledocolithiasis, SOD, stent insertion, miscellaneous	53 (19-96)	35%/65%	Yes	**Pancreatitis:** 3 mild; 0 moderate; 0 severe **Bleeding:** 0 mild; 0 moderate;1 severe
		Blend (85)					**Pancreatitis:** 7 mild; 2 moderate; 1 severe **Bleeding:** 0 mild; 0 moderate; 1 severe
Siegel[10]	100	Bipolar (50)	Unclear	Unclear	Unclear	Unclear	**Pancreatitis:** 0 (total)
		Monopolar (50)					**Pancreatitis:** 6 (total)

n: Number of patients included; compared groups: in parentheses, we have the number of patients randomized to each group; age: mean expressed in years with the range in parentheses when provided in the study; SOD: Sphincter of oddi disfunction; PSC: Primary sclerosing cholangitis; CBD: common bile duct

Bleeding

There was no difference between groups for bleeding in general (RD -0.11 [-0.31; 0.08], p = 0.27, I^2 = 86%) or in the mild, moderate, and severe subgroups.

Very low level of certainty.

Perforation

No difference between groups (absence of cases in both arms).

Moderate level of certainty.

ENDOCUT VS. PURE CUT

→ Inclusion of three studies with a total of 437 patients[11,14,18].

Acute pancreatitis

There was no difference between groups for pancreatitis in general (RD 0.05 [-0.01; 0.11], p = 0.12, I^2 = 57%) or in the mild, moderate, and severe subgroups. In the total of pancreatitis episodes, three studies individually presented more events in the pulsed cut group; however, due to the high heterogeneity, the random effect was used, with no difference between the analyzed arms.

Low level of certainty.

Bleeding

More bleeding in general was observed in the pure cut group (RD -0.19 [-0.25; -0.12], p < 0.00001, I^2 = 96%). This difference

was due to self-limited (mild) bleeding (RD -0.23 [-0.31; -0.15], p < 0.00001, I^2 = 34%), with no difference in the incidence of moderate (RD -0.05 [-0.15; 0.05], p = 0.3, I^2 = 64%) or severe cases (RD 0.00 [-0.02; 0.02], p = 1, I^2 = 0%).

Moderate level of certainty.

Cholangitis

No difference among groups (RD -0.01 [-0.09; 0.06], p = 0.7).

Low level of certainty.

Perforation

Absence of difference between the groups (RD 0.00 [-0.01; 0.02], p = 0.7, I^2 = 0%).

Low level of certainty.

PURE CUT VS. *BLEND*

→ Inclusion of four studies with a total of 572 patients[10,13,15,16].

Acute pancreatitis

Absence of difference for pancreatitis in general (RD -0.03 [-0.07; 0.01], p = 0.17, I^2 = 32%) and in mild (RD -0.03 [-0.07; 0.00], p = 0.08, I^2 = 33%), moderate (RD -0.01 [-0.03; 0.01], p = 0.38, I^2 = 0%), and severe subgroups (RD -0.00 [-0.01; 0.02], p = 0.68, I^2 = 0%).

Low level of certainty.

Bleeding

More bleeding in general was observed in the pure cut group (RD 0.26 [0.61; 0.35], p < 0.00001, I^2 = 0%). This difference was based on self-limited (mild) bleeding (RD 0.24 [0.15; 0.33], p < 0.00001, I^2 = 0%), without difference in moderate (RD 0.01 [-0.02; 0.04], p = 0.51, I^2 = 0%) or severe cases (RD -0.00 [-0.02; 0.02], p = 0.73, I^2 = 0%).

High level of certainty.

Cholangitis

Absence of difference among groups (p = 0.47).

Low level of certainty.

PURE CUT FOLLOWED BY BLEND VS. *BLEND*

→ Inclusion of three studies with a total of 301 patients[15-17].

Acute pancreatitis

Absence of difference for pancreatitis in general (RD 0.06 [-0.02; 0.13], p = 0.12, I^2 = 0%) and in mild (RD 0.04 [-0.02; 0, 10], p = 0.15, I^2 = 23%), moderate (RD 0.00 [-0.04; 0.05], p = 0.91, I^2 = 0%), and severe subgroups (RD 0.01 [-0.02; 0.04], p = 0.45, I^2 = 0%).

Low level of certainty.

Bleeding

Absence of difference for bleeding in general (RD -0.10 [-0.24; 0.04], p = 0.18, I^2 = 61%) and in the mild, moderate, and severe subgroups.

Low level of certainty.

PURE CUT FOLLOWED BY BLEND VS. PURE CUT

→ Inclusion of two studies with a total of 157 patients[15,17].

Acute pancreatitis

Absence of difference for pancreatitis in general (RD -0.01 [-0.11; 0.09], p = 0.82, I^2 = 0%) and in the mild, moderate, and severe subgroups.

Low level of certainty.

Bleeding

Absence of difference in the incidence of mild (RD -0.05 [-0.16; 0.07], p = 0.41, I^2 = 0%), moderate (RD 0.00 [-0.04; 0,04], p = 1.0, I^2 = 0%), or severe bleeding (RD 0.01 [-0.04; 0.06], p = 0.58, I^2 = 0%).

Moderate level of certainty.

DISCUSSION

Mixed current modes (pulsed or endocut and blend) have greater coagulation power when compared to pure cut[4,19]. For this reason, they have been used to prevent bleeding during endoscopic biliary sphincterotomy. However, its greater coagulation power causes deeper dissemination of thermal energy to adjacent tissues and, in the case of biliary sphincterotomy, it is questioned whether this can increase the incidence of acute pancreatitis after ERCP.

While comparing endocut and blend with pure cut, we noted a similar profile, with more cases of pancreatitis in the arms of the mixed mode, but without statistical significance. It is possible that new studies, with an increased sample size, reveal a difference among the methods. It is worth remembering that one of the included studies was interrupted early due to the high incidence of pancreatitis in the arm that used the blend[10].

Regarding bleeding, mixed currents were found to be superior only in cases of self-limited bleeding (considered mild),

with no difference in the incidence of clinically significant bleeding (moderate and severe).

A strategy described to prevent pancreatitis and bleeding is to begin the incision with pure cut (due to its proximity to the pancreatic duct) and to proceed with a mixed current (due to its proximity to thicker vessels). We included three studies that used this strategy, using the blend mode at the end of the incision[15-17]. However, there was no difference in the incidence of acute pancreatitis or bleeding when compared to the pure cut or blend used throughout the incision.

Cholangitis and perforation are uncommon adverse events and have no apparent relation to the electric current modality used in biliary sphincterotomy.

This guideline has some limitations, such as heterogeneity in the bleeding definition, which was circumvented with a new definition applied to each study individually. Another point is the inclusion of articles available only as abstract; however, in these cases, all the outcomes of interest were available. In addition, there is a difference in the inclusion criteria of studies, though the interference of this factor is neutralized by the fact that we included only randomized studies with homogeneous groups. Another limitation is the use of relatively old electrosurgical units in the included studies, which are not used at present in many endoscopic units; however, this is also mitigated by the fact that the principle of each modality of electric current remains in different units, although these strategies are not so modern.

This guideline has a great evidence level since it includes only randomized clinical trials with homogeneous groups in each study. The highly sensitive and systematic literature review followed by the meta-analysis allows us to face the highest level of evidence possible with the current literature.

There is no ideal electric current mode for all situations or sufficient evidence in the literature to recommend one method over others. It is essential to know the effect of each modality to prevent adverse events. We concluded that there is no ideal electric current modality to prevent all adverse events; however, it is essential to understand their respective mechanisms of action and the risk factors of each patient for the endoscopist to make the best decision in clinical practice.

Factors such as the lack of access to information and the limitations of this guideline can hinder the dissemination of the recommendations expressed. Similarly, the wide availability of recommended resources (no impact to obtain resources) and the high level of evidence (systematic review of randomized clinical trials) are facilitators for the dissemination of this guideline.

RECOMMENDATION

For patients undergoing ERCP with endoscopic biliary sphincterotomy, the use of pure cut routinely (or endocut with low effect 1 or 2) is the acceptable strategy. Mixed currents (endocut or blend) are used in cases with increased risk of bleeding or as a rescue strategy for bleeding more than expected during the procedure.

The level of evidence varies from very low to high depending on the outcome analyzed.

AUTHOR'S CONTRIBUTIONS

MPF: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **VMTS:** Conceptualization, Data curation, Formal Analysis. **EGHM:** Conceptualization, Resources, Supervision, Validation, Visualization, Writing – review & editing. **WMB:** Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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ANNEX

Methods

Protocol and Registration

This study was carried out according to PRISMA guidelines and registered in PROSPERO (International Prospective Register of Systematic Reviews) under the record CRD42018109713[7].

Eligibility criteria

Only randomized controlled trials that compared at least two electric current modalities with the necessary data for our analysis were selected. There was no restriction on the language or publication date.

All selected studies included patients older than 18 years who underwent ERCP with biliary sphincterotomy randomized to different modes of electric current.

Studies involving patients with anatomical alterations in the gastrointestinal (GI) tract such as gastrectomy with Billroth II or Roux-en-Y reconstructions or studies involving pancreatic sphincterotomy were excluded.

Search strategy, study selection, and data collection

Initially, two authors performed the search by using title and abstract in the Medline, Embase, Central Cochrane and Lilacs databases, and grey literature. Later, the full text of the studies of interest was assessed. Disagreements were resolved after consensus with a third author. The search strategy was updated till September 2020. All prospective randomized studies that reported the outcomes of interest were included without restriction as to language, modality, or year of publication. The authors used Excel spreadsheets for data collection.

Search strategy

The following search strategy was used on Medline: (((((papillotomy OR Sphincterotomy OR Sphincterotomies OR Sphinc-terotome OR Sphincteroplasty OR Sphincteroplasties) OR ((Retrograde Cholangiopancreatography, Endoscopic OR Cholangiopancreatographies, Endoscopic Retrograde OR Endoscopic Retrograde Cholangiopancreatographies OR Ret-rograde Cholangiopancreatographies, Endoscopic OR Endo-scopic Retrograde Cholangiopancreatography OR ERCP) AND (cut OR electrosurg* OR knife OR blend OR current OR electric* OR Thermocoagulation OR Galvanocautery OR Diathermy OR Fulguration OR vio 200 OR vio 300 OR ERBEOR valley lab OR valleylab OR WEM OR blend OR current OR electrocautery OR cautery OR insulation OR insulated OR coagulation OR endocut OR waves))))))).

In the remaining databases, we used search strategies obtained from the one expressed above.

Data analysis

We used the RevMan 5 software (Review Manager version 5.3.5 – Cochrane Collaboration Copyright© 2014) for the meta-analysis and calculation of the absolute risk difference.

We included only dichotomous variables, employing the risk difference with the Mantel-Haenszel test. Statistically, we considered the 95% confidence interval (CI) and $p < 0.05$. The results were expressed as forest plots.

Heterogeneity was assessed using the Higgins test (I^2), with a fixed effect for low heterogeneity ($I^2 < 50\%$). For $I^2 > 50\%$ (high heterogeneity), we performed a sensitivity analysis using funnel plot to identify outliers. If, after excluding the outlier, $I^2 < 50\%$, the fixed effect was maintained. If, the exclusion of the outlier, $I^2 > 50\%$, the study was maintained (true heterogeneity), and the random effect was applied.

Methodology quality and risk of study bias

The risk of bias in the studies was assessed individually using the Cochrane tool[8].

The quality of the evidence (level of certainty) of each outcome was performed according to the GRADE recommendations, using the GRADEpro software[9].

Heterogeneity in the bleeding definition

Once the definition of bleeding was heterogeneous among the included studies, we made efforts to standardize it. For this, we considered mild bleeding as self-limited (that increased during sphincterotomy, however with no need for any form of intervention); moderate when there was a need for intervention during ERCP and later drop in hematimetric levels or melena; and severe cases involved clinical repercussions with the need for blood transfusion or the need for new therapeutic procedures.

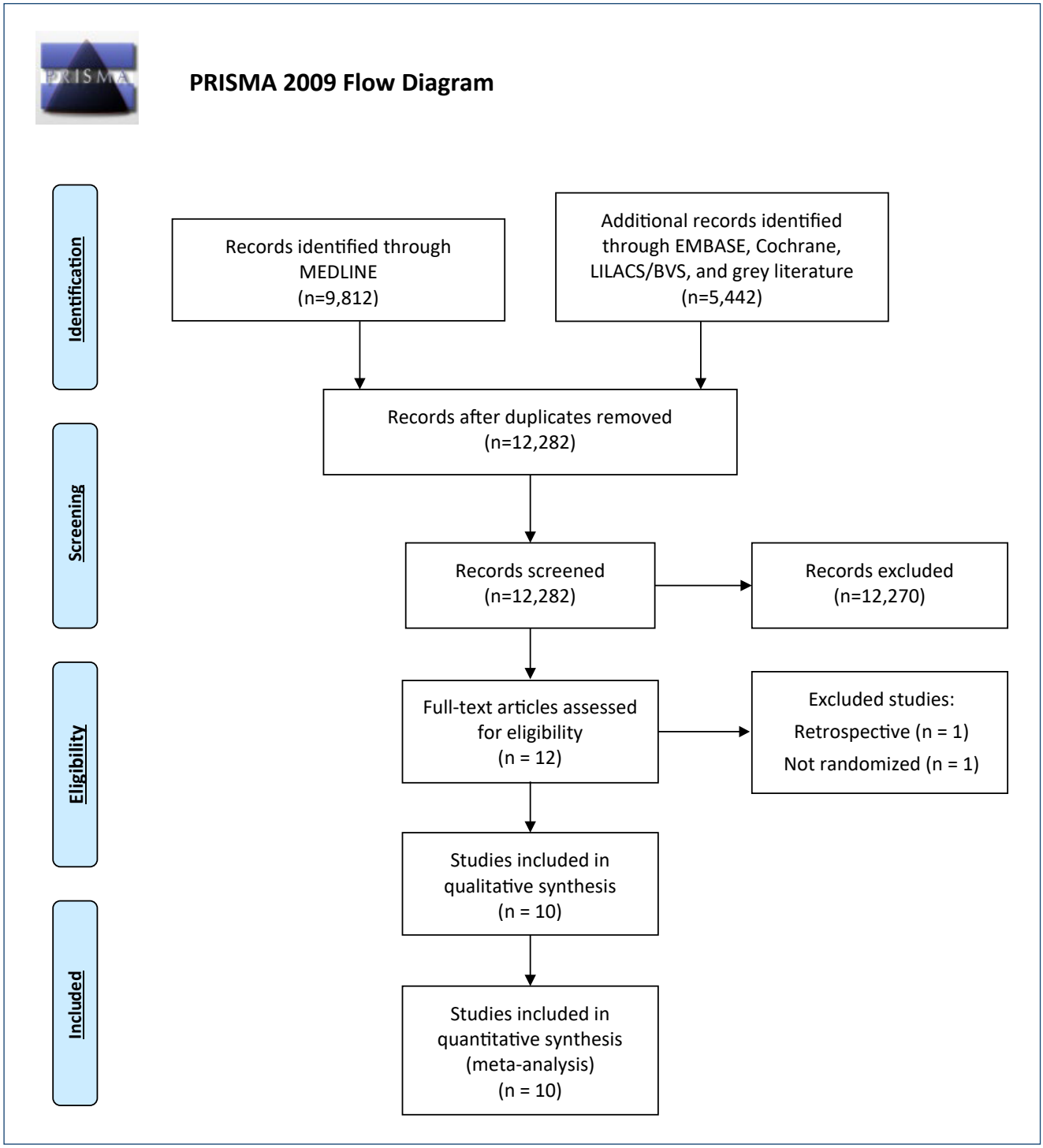

Figure 1. Flowchart of study selection according to PRISMA.

Forest plots

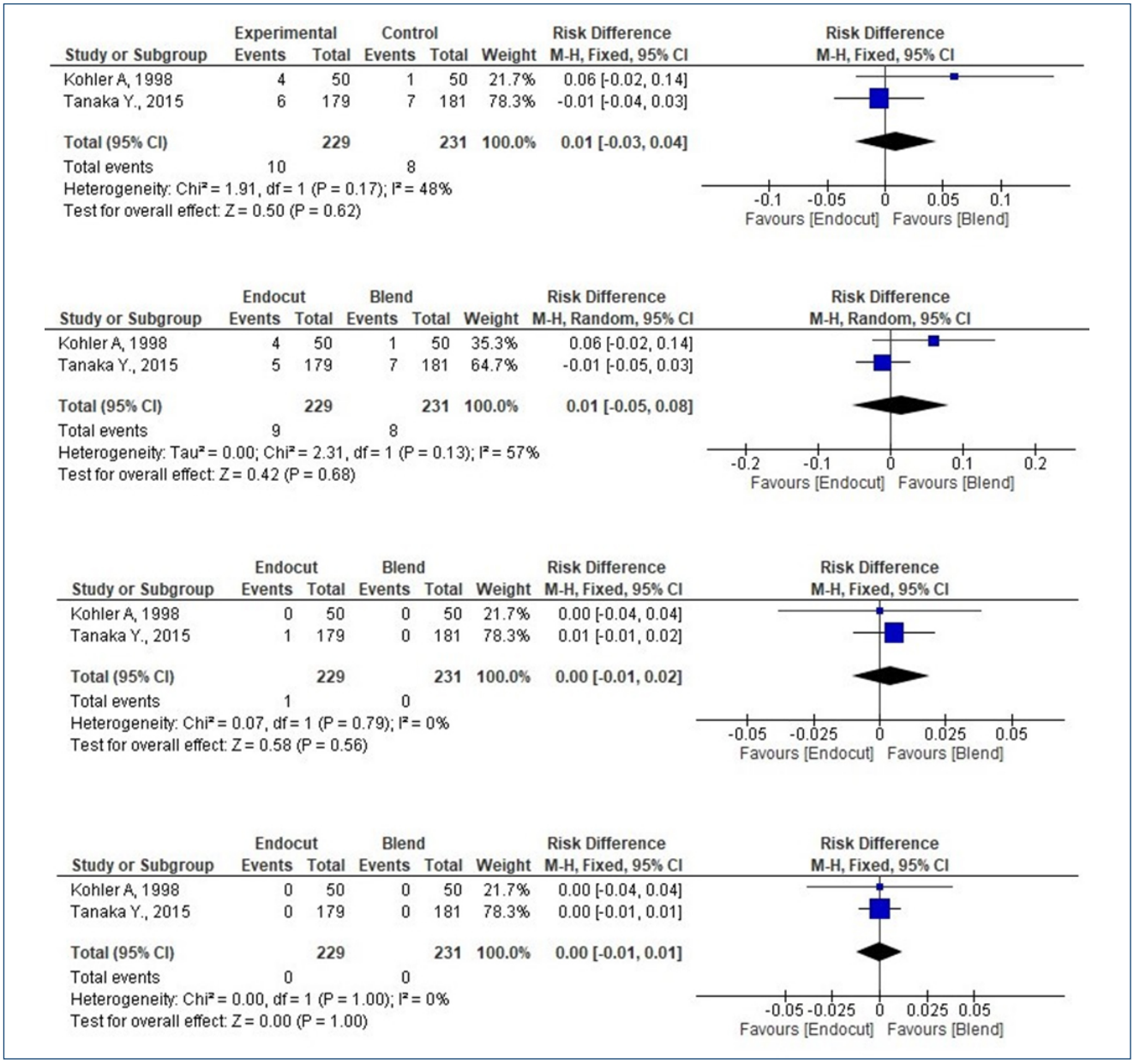

Figure. Pancreatitis in general, mild, moderate, and severe (endocut vs. blend).

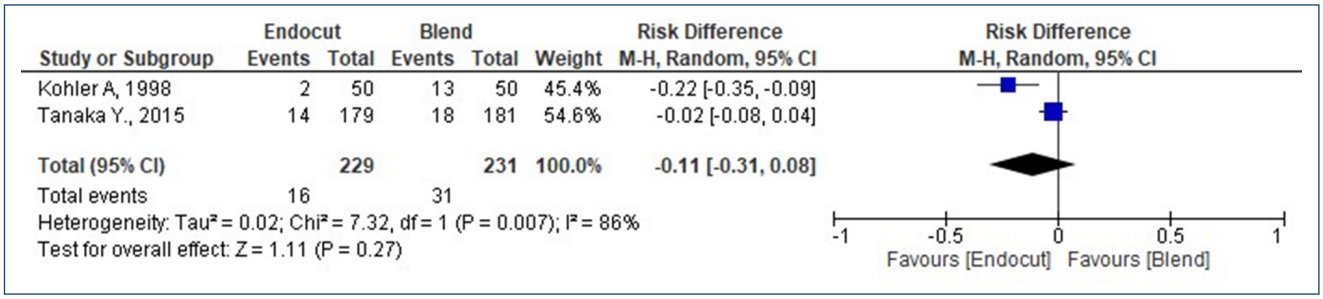

Figure. Bleeding in general (endocut vs. blend).

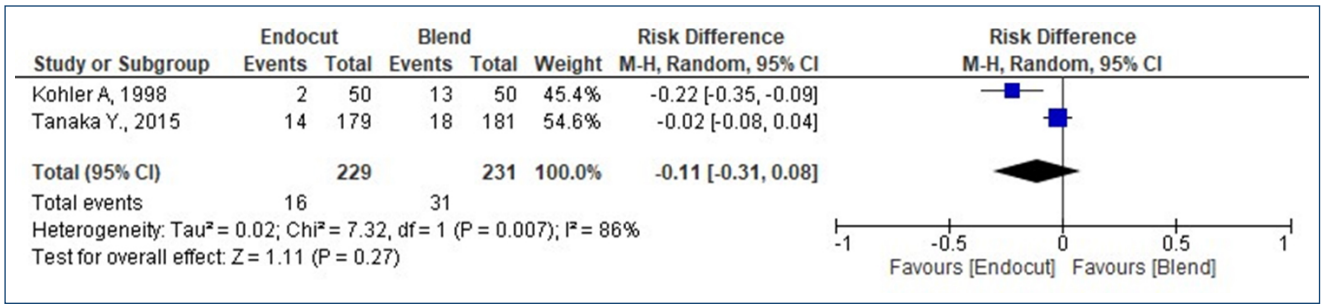

Figure. Mild bleeding (endocut vs. blend).

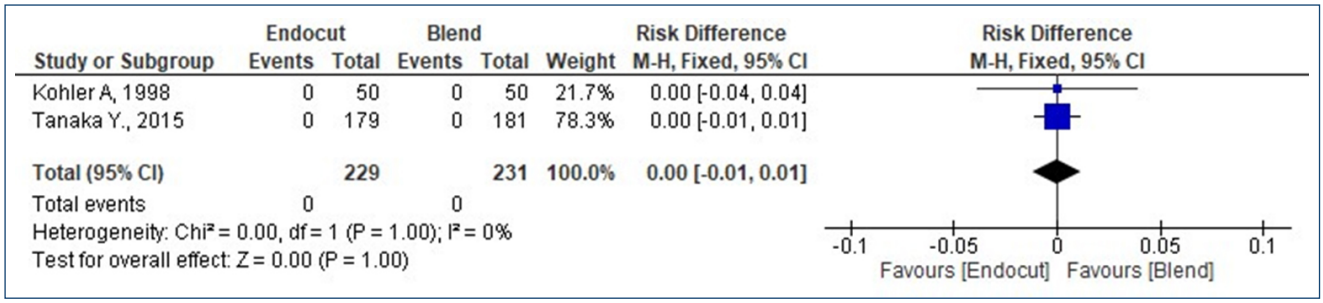

Figure. Moderate bleeding (endocut vs. blend).

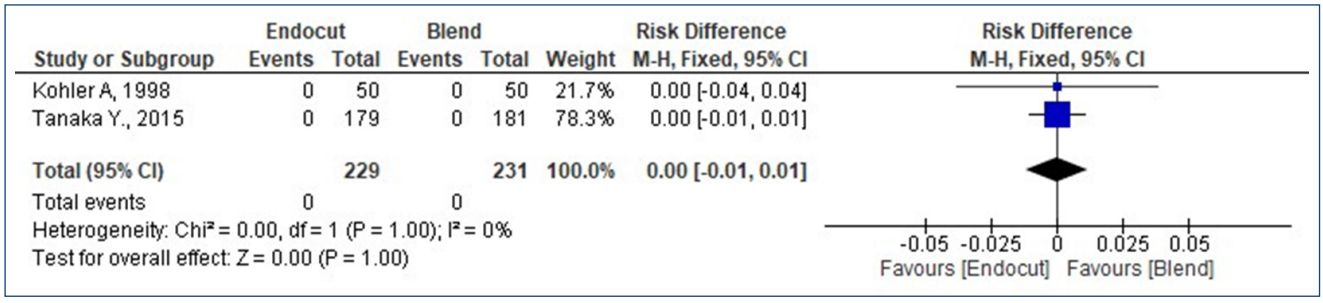

Figure. Severe bleeding (endocut vs. blend).

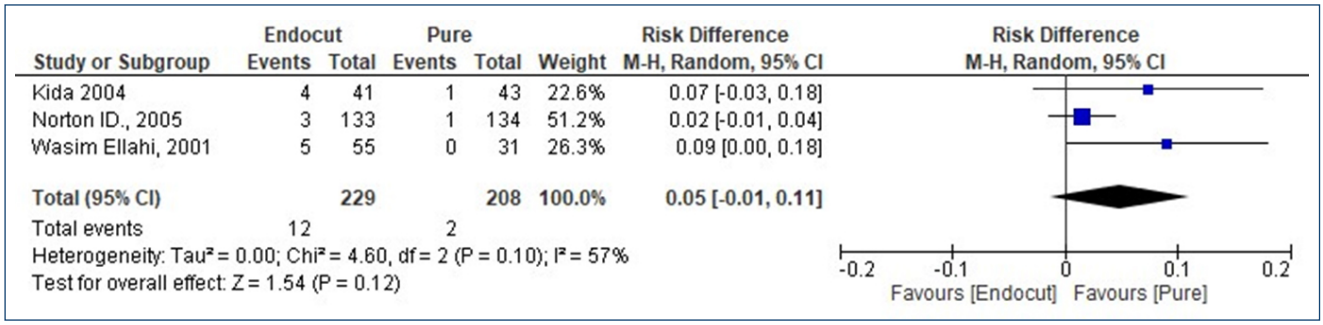

Figure. Pancreatitis in general (endocut vs. pure cut).

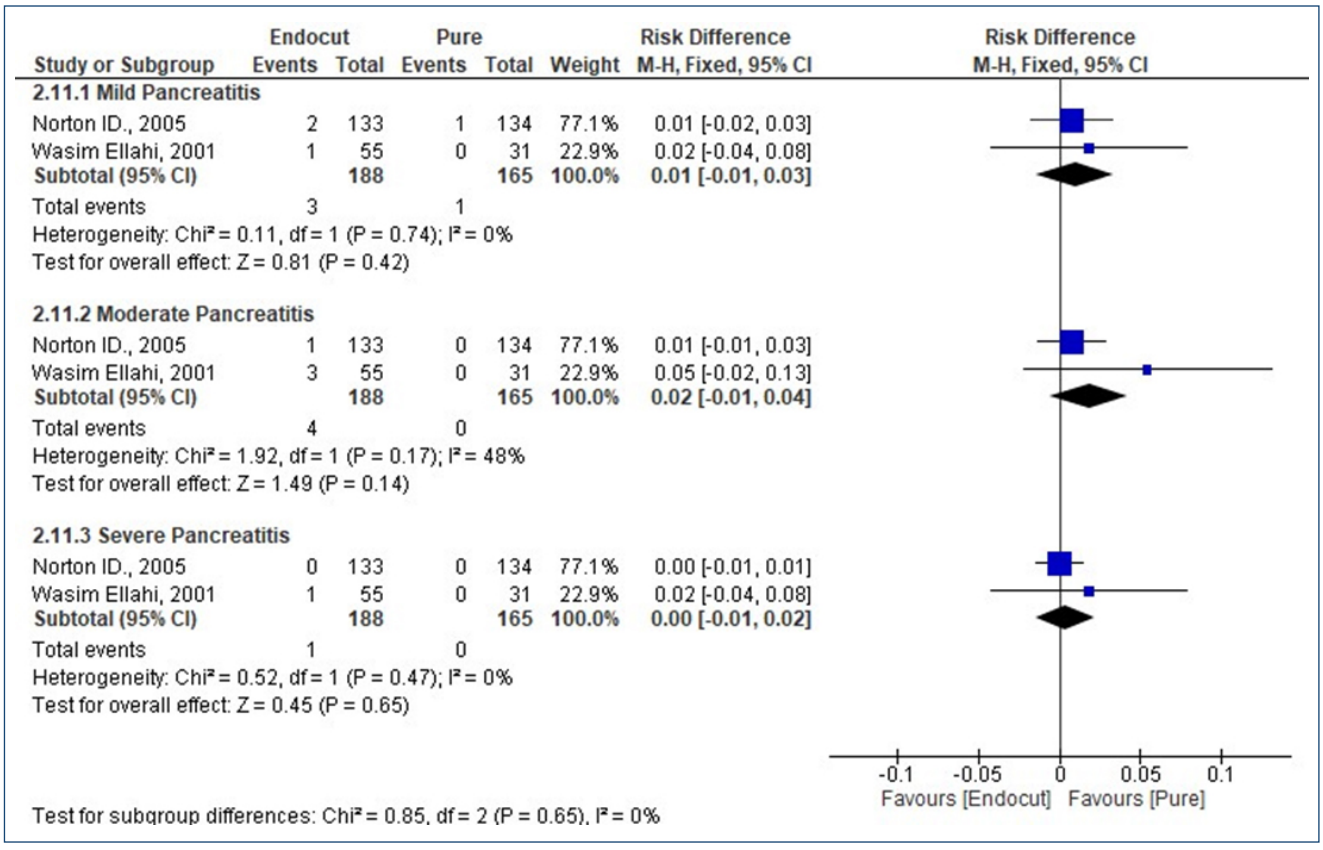

Figure. Mild, moderate, and severe pancreatitis (endocut vs. pure cut).

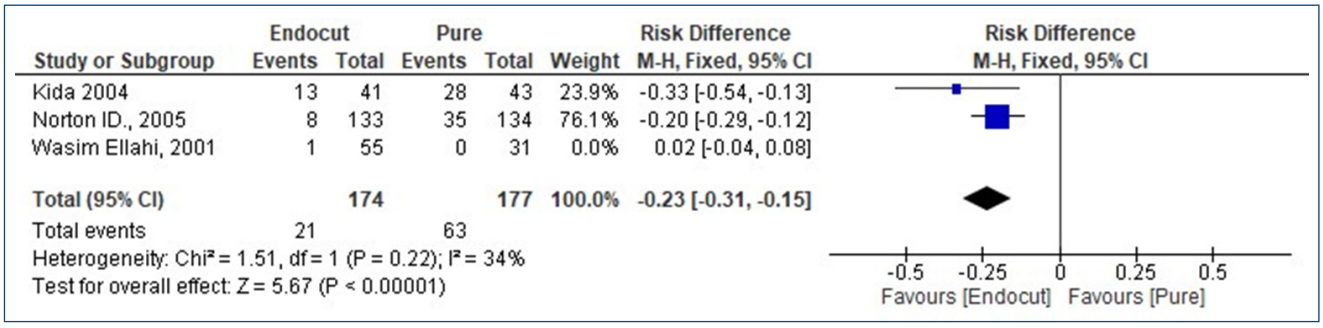

Figure. Bleeding in general (endocut vs. pure cut).

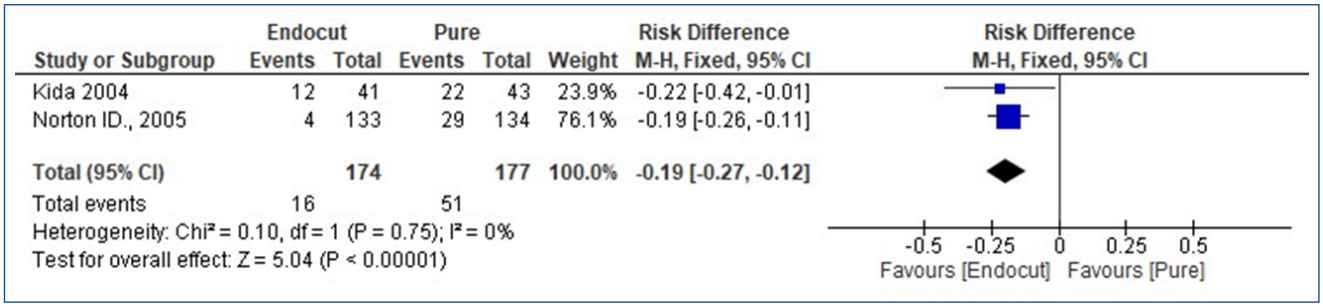

Figure. Mild bleeding (endocut vs. pure cut).

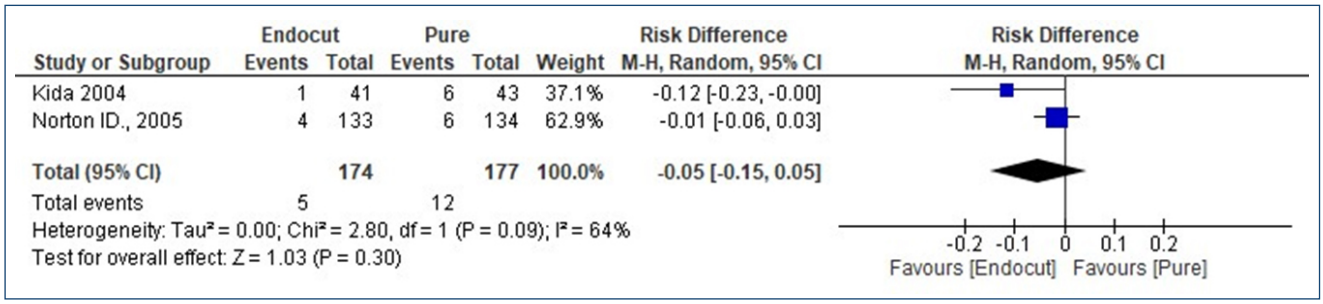

Figure. Moderate bleeding (endocut vs. pure cut).

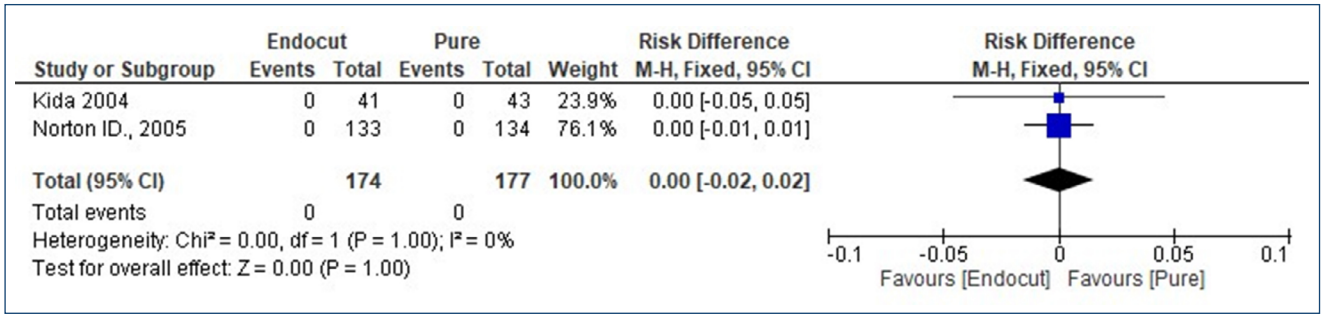

Figure. Severe bleeding (endocut vs. pure cut).

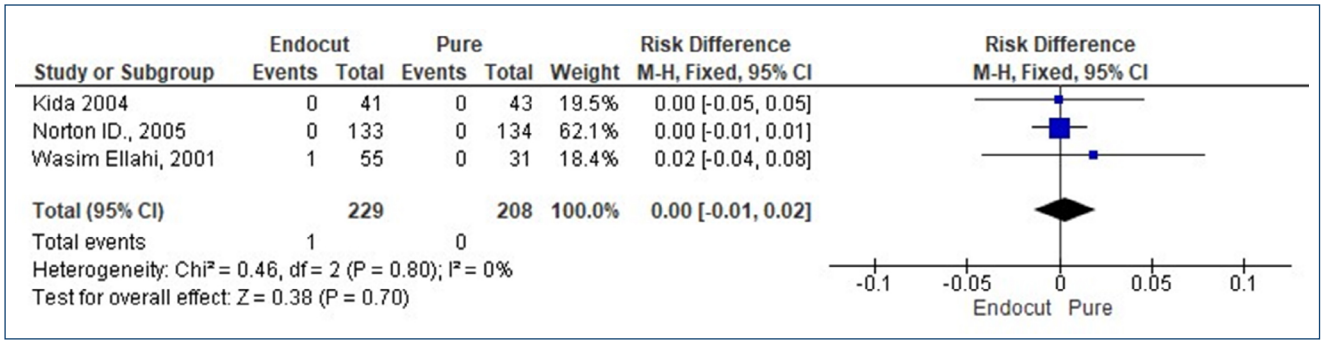

Figure. Perforation (endocut vs. pure cut).

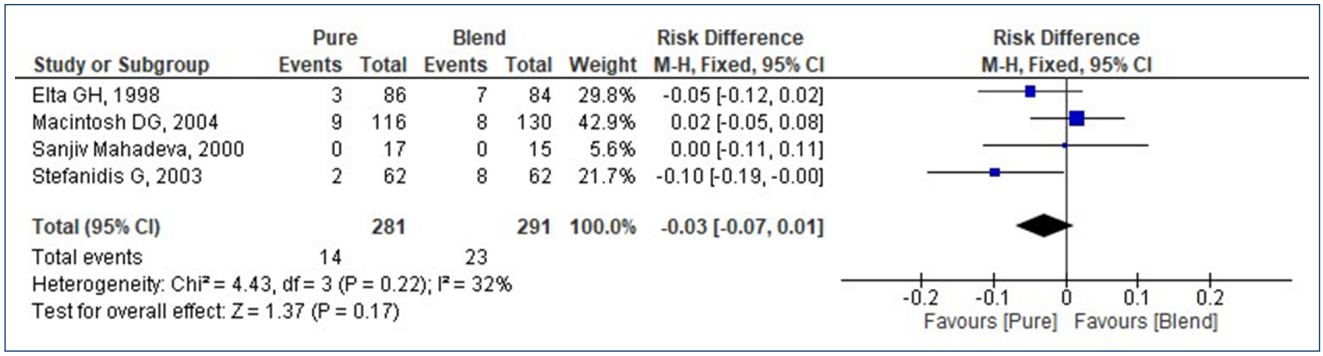

Figure. Pancreatitis in general (pure cut vs. blend).

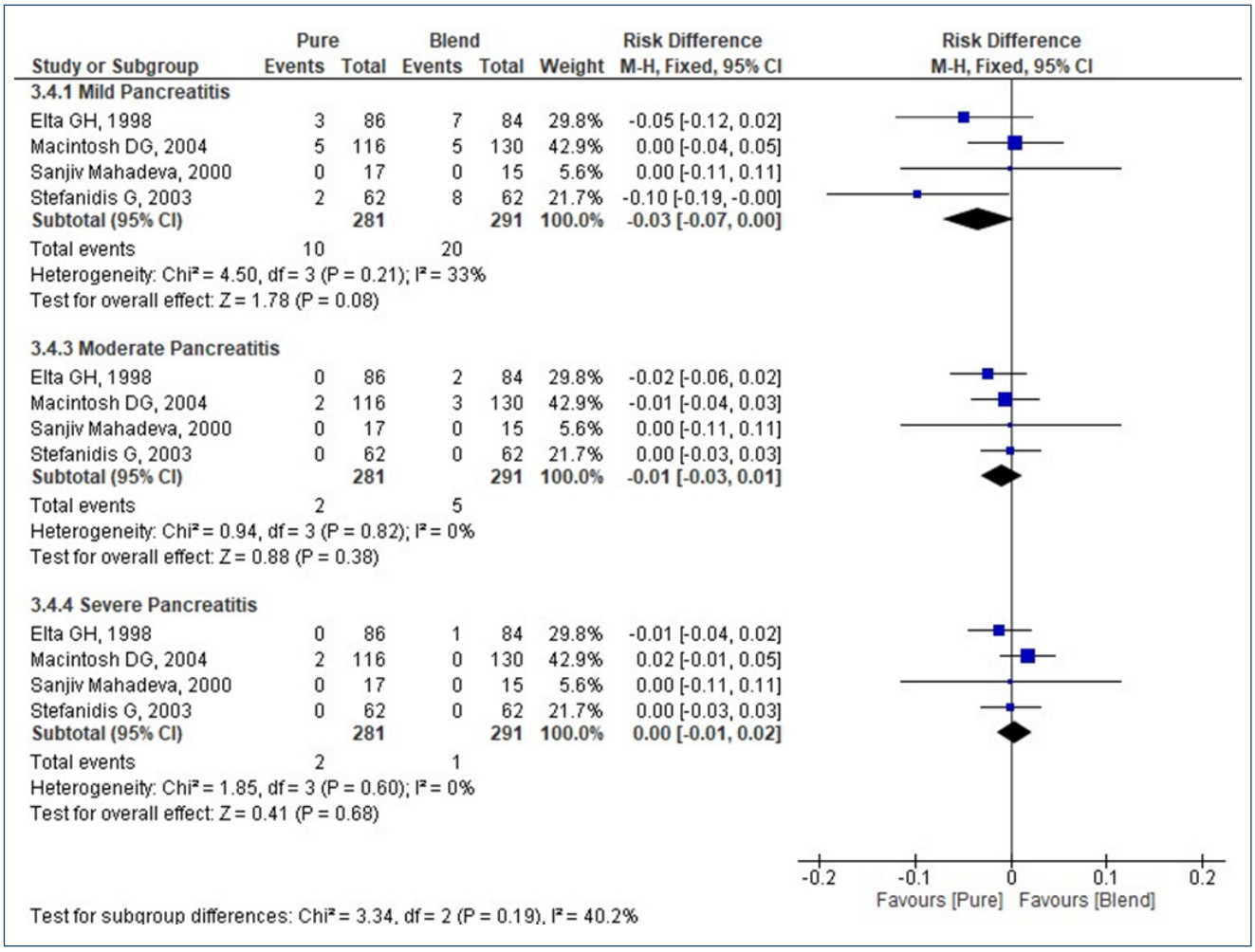

Figure. Mild, moderate, and severe pancreatitis (pure cut vs. blend).

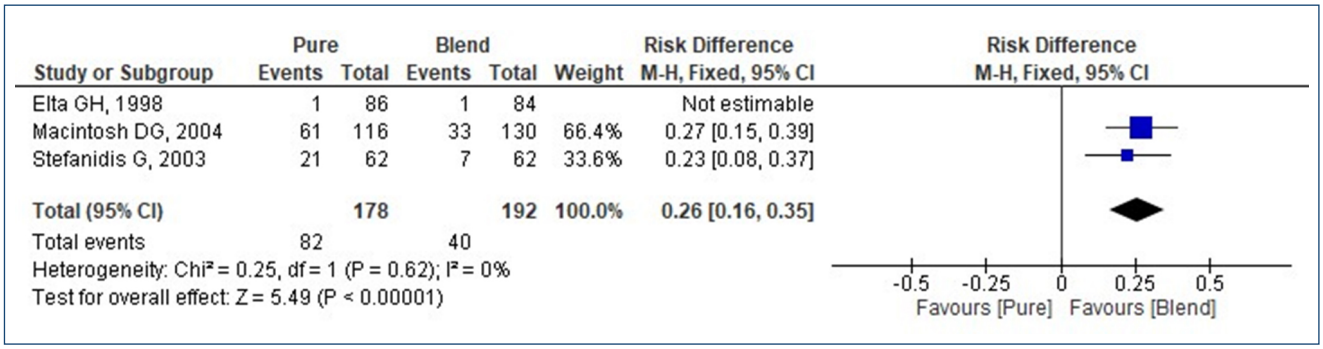

Figure. Bleeding in general (pure cut vs. blend).

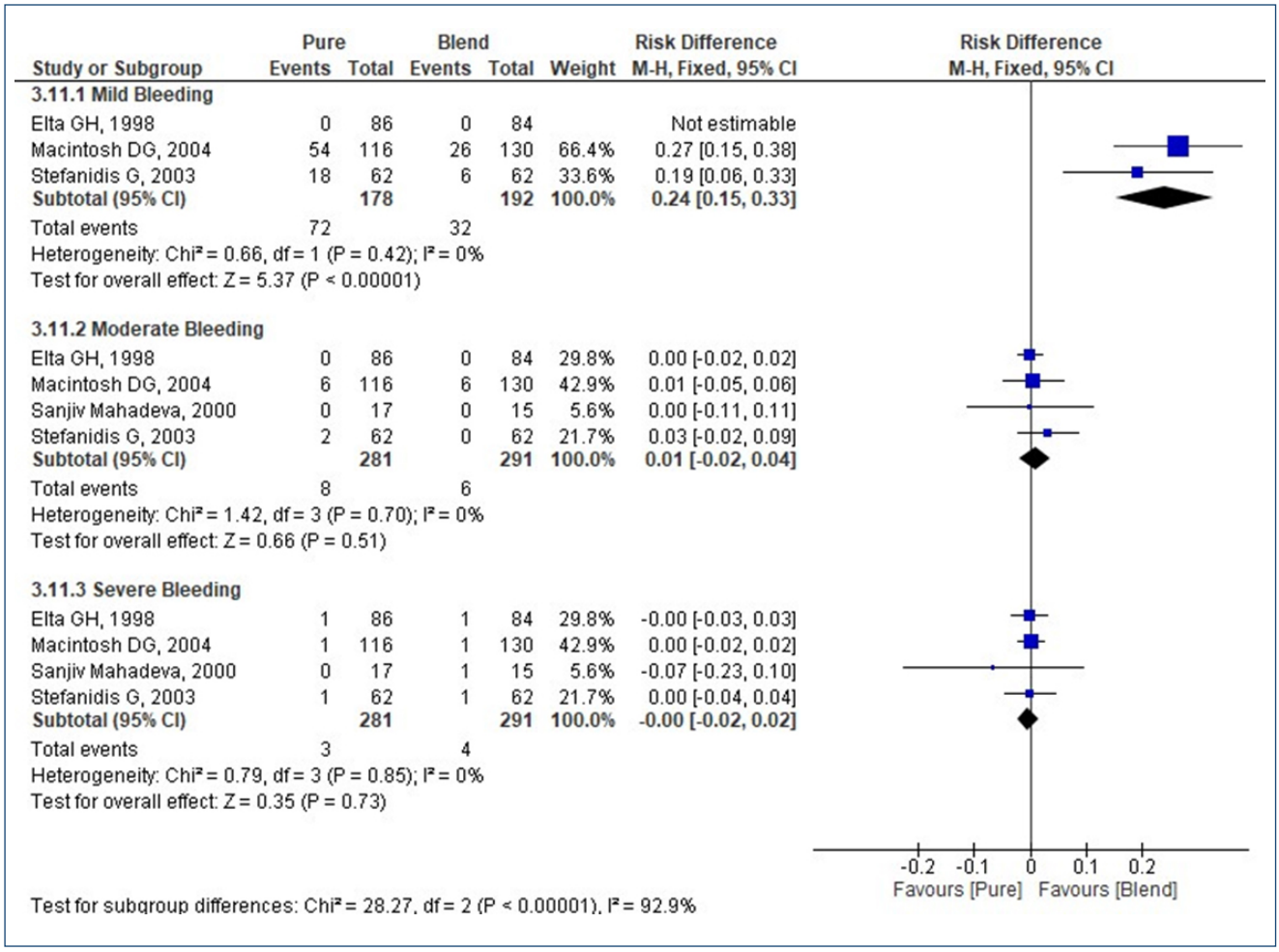

Figure. Mild, moderate, and severe bleeding (pure cut vs. blend).

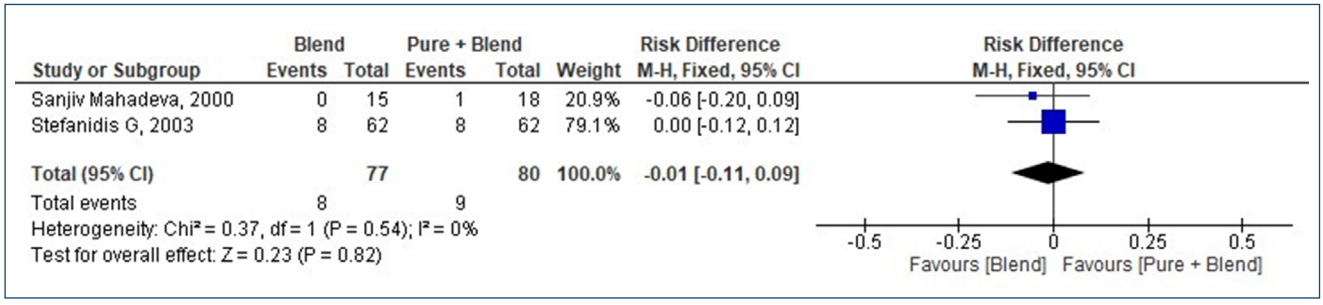

Figure. Pancreatitis in general (pure cut followed by blend vs. blend).

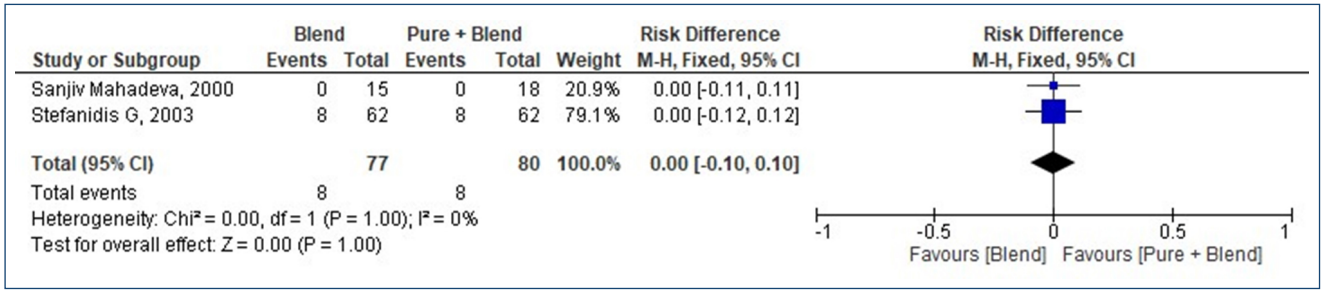

Figure. Mild pancreatitis (pure cut followed by blend vs. blend).

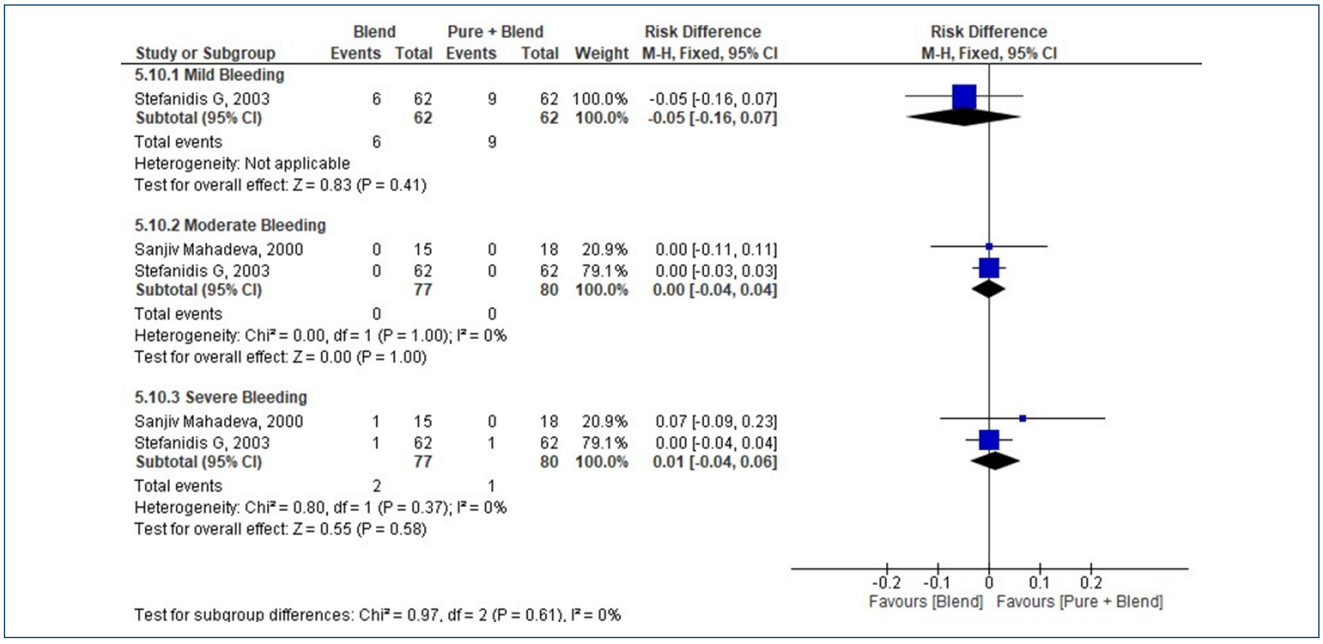

Figure. Mild, moderate, and severe bleeding (pure cut followed by blend vs. blend).

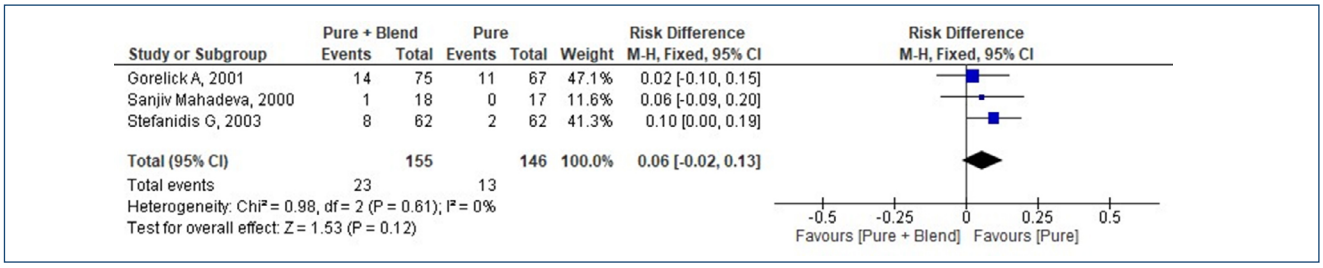

Figure. Pancreatitis in general (pure cut followed by blend vs. pure cut).

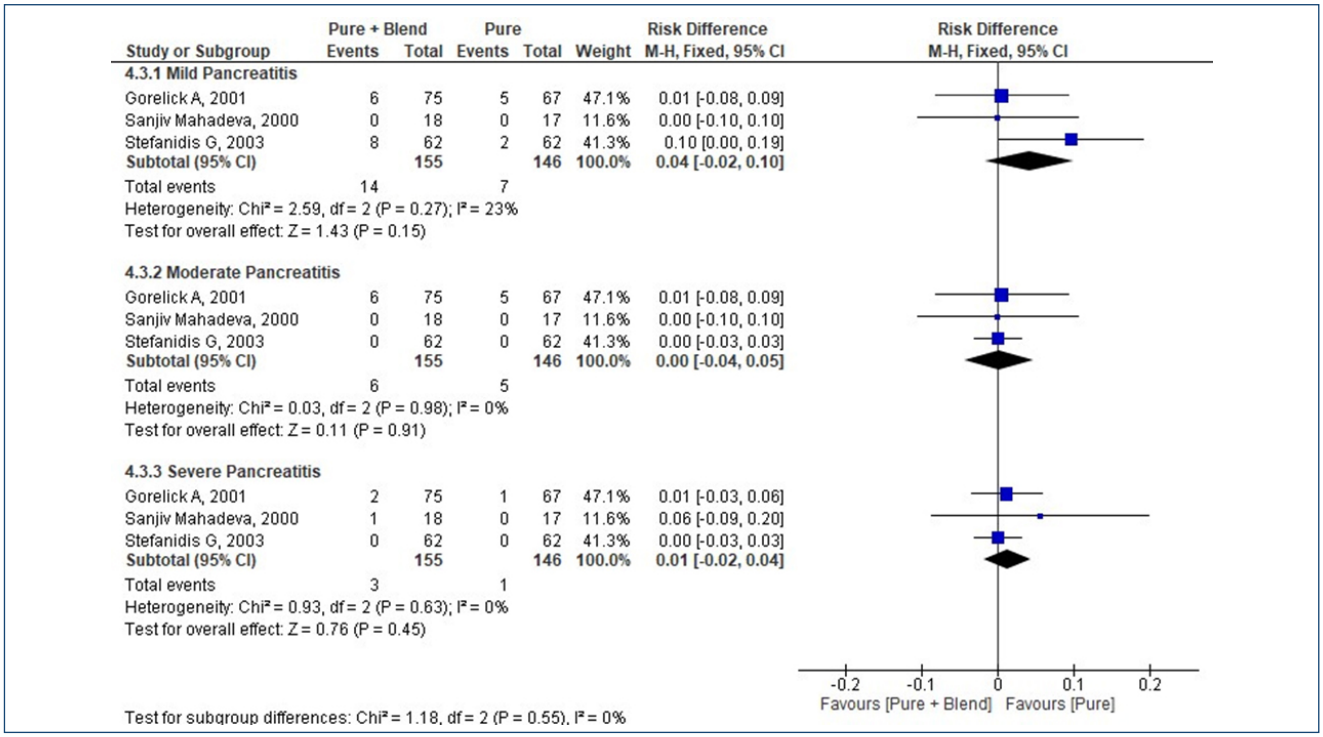

Figure. Mild, moderate, and severe pancreatitis (pure cut followed by blend vs. pure cut).

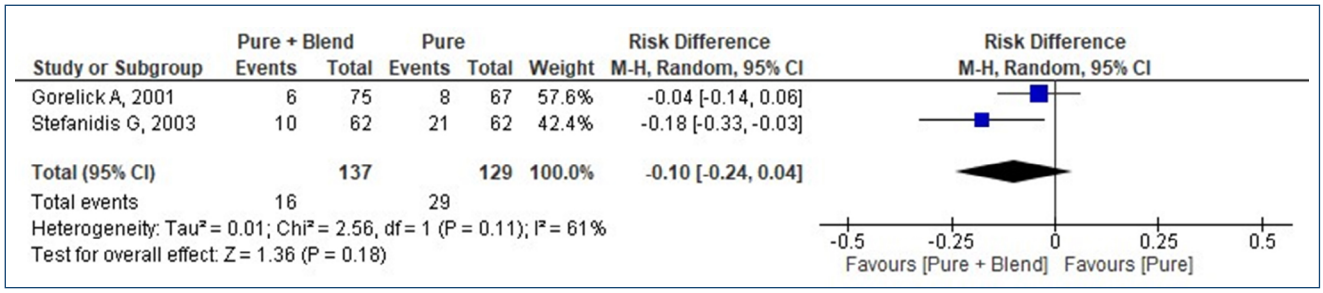

Figure. Bleeding in general (pure cut followed by blend vs. pure cut).

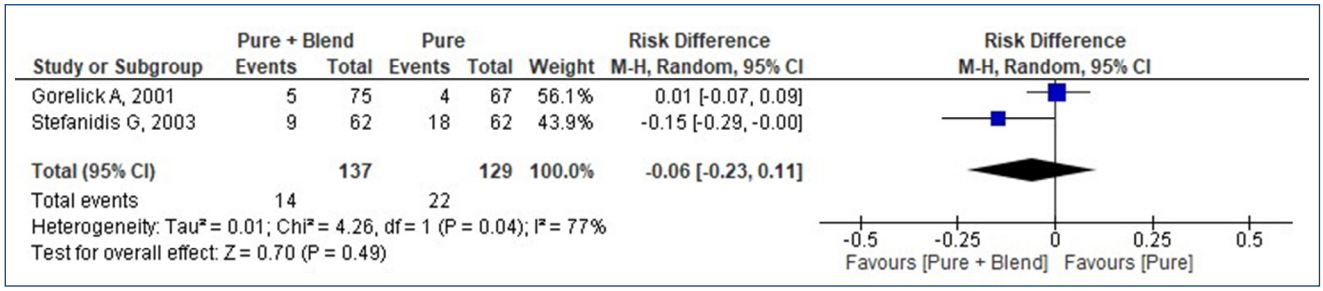

Figure. Mild bleeding (pure cut followed by blend vs. pure cut).

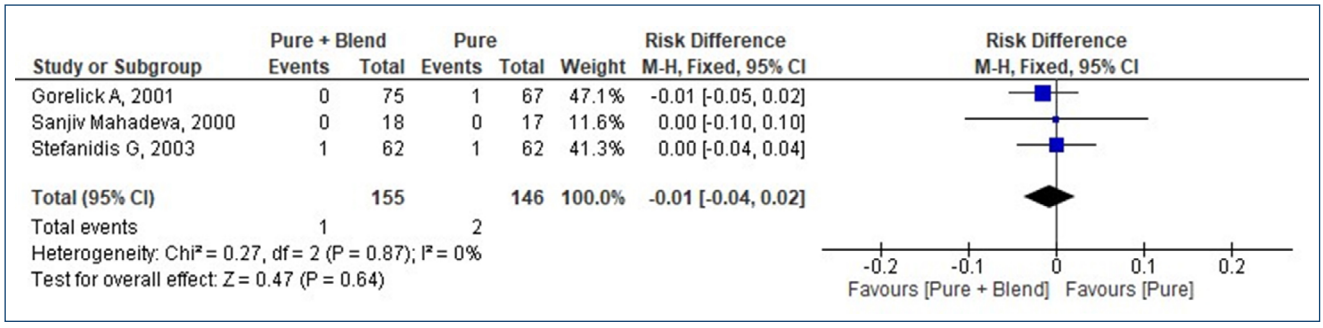

Figure. Severe bleeding (pure cut followed by blend vs. pure cut).

Grade

Evidence quality according to GRADE (endocut vs. blend).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocut	Blend	Relative (95%CI)	Absolute (95%CI)		
Perforation												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Serious[b]	None	0/229 (0.0%)	0/231 (0.0%)	Not estimable	**0 fewer per 1.000** (from 10 fewer to 10 more)	⊕⊕⊕◯ Moderate	
Pancreatitis (total)												
2	Randomized trials	Not serious[a]	Not serious	Not serious	Serious[b]	None	10/229 (4.4%)	8/231 (3.5%)	Not estimable	**10 fewer per 1.000** (from 40 fewer to 30 more)	⊕⊕⊕◯ Moderate	
Bleeding (total)												
2	Randomized trials	Very serious[a]	Very serious[c]	Not serious	Serious[b]	None	16/229 (7.0%)	31/231 (13.4%)	Not estimable	**110 more per 1.000** (from 80 fewer to 310 more)	⊕◯◯◯ Very low	

CI: confidence interval; [a] Kohler with Jadad scale <3 and a few unclear bias evaluation points. None of the studies is a double blind (difficult in endoscopy); [b]. Power < 80%; [c]. I2 > 75%.

Evidence quality according to GRADE (endocut vs. pure cut).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endocut	Pure	Relative (95%CI)	Absolute (95%CI)		
Perforation												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	1/229 (0.4%)	0/208 (0.0%)	Not estimable	**0 fewer per 1.000** (from 20 fewer to 10 more)	⊕⊕◯◯ Low	
Pancreatitis (total)												
3	Randomized trials	Serious[a]	Serious[c]	Not serious	Serious[b]	None	11/229 (4.8%)	2/208 (1.0%)	Not estimable	**50 fewer per 1.000** (from 120 fewer to 30 more)	⊕◯◯◯ Very low	
Bleeding (total)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	21/174 (12.1%)	63/177 (35.6%)	Not estimable	**230 more per 1.000** (from 150 more to 310 more)	⊕⊕⊕◯ Moderate	
Cholangitis												
1	Randomized trials	Serious[d]	Not serious	Not serious	Serious[b]	None	1/55 (1.8%)	1/31 (3.2%)	Not estimable	**10 more per 1.000** (from 60 fewer to 90 more)	⊕⊕◯◯ Low	
Hyperamylasemia												
1	Randomized trials	Serious[d]	Not serious	Not serious	Serious[b]	None	12/41 (29.3%)	5/43 (11.6%)	Not estimable	**180 fewer per 1.000** (from 350 fewer to 10 fewer)	⊕⊕◯◯ Low	

CI: confidence interval; [a] All studies included with Jadad scale < 3. A few unclear bias evaluation points in Kida and Ellahi; [b] Power < 80%; [c] 50–75%; [d] Jadad scale < 3. A few unclear bias evaluation points.

Evidence quality according to GRADE (pure cut vs. blend).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pure	Blend	Relative (95%CI)	Absolute (95%CI)		
Cholangitis												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	0/86 (0.0%)	1/84 (1.2%)	Not estimable	**10 more per 1.000** (from 20 fewer to 40 more)	⊕⊕◯◯ Low	
Pancreatitis (total)												
4	Randomized trials	Serious[c]	Not serious	Not serious	Serious[b]	None	14/281 (5.0%)	23/291 (7.9%)	Not estimable	**30 more per 1.000** (from 10 fewer to 70 more)	⊕⊕◯◯ Low	
Bleeding (total)												
2	Randomized trials	Not serious[d]	Not serious	Not serious	Not serious[b]	None	82/178 (46.1%)	40/192 (20.8%)	Not estimable	**260 fewer per 1.000** (from 350 fewer to 160 fewer)	⊕⊕⊕⊕ High	

CI: confidence interval; [a] Jadad scale < 3. Inappropriate randomization method; [b]Power < 80; [c] Jadad scale < 3 in two studies. Only one (out of four) double blind. A few unclear bias evaluation points in the studies; [d] Stefanidis with Jadad scale < 3 and no sample size. Also not a double blind.

Evidence quality according to GRADE (pure cut followed by blend vs. blend).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pure + Blend	Pure	Relative (95%CI)	Absolute (95%CI)		
Pancreatitis (total)												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	23/155 (14.8%)	13/146 (8.9%)	Not estimable	**60 fewer per 1.000** (from 130 fewer to 20 more)	⊕⊕◯◯ Low	
Bleeding (total)												
2	Randomized trials	Not serious[a]	Serious[c]	Not serious	Serious[b]	None	16/137 (11.7%)	29/129 (22.5%)	Not estimable	**100 more per 1.000** (from 40 fewer to 240 more)	⊕⊕◯◯ Low	

CI: confidence interval; [a] Stefanidis with Jadad scale < 3 and no sample size. A few unclear bias evaluation points in the articles. None of the articles is a double blind (difficult in endoscopy); [b] Power < 80; [c] 50–75%.

Evidence quality according to GRADE (pure cut followed by blend vs. pure cut).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blend	Pure + Blend	Relative (95%CI)	Absolute (95%CI)		
Pancreatitis (total)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	8/77 (10.4%)	9/80 (11.3%)	Not estimable	**10 more per 1.000** (from 90 fewer to 110 more)	⊕⊕◯◯ Low	
Bleeding (total)												
1	Randomized trials	Not serious[c]	Not serious	Not serious	Serious[b]	None	7/62 (11.3%)	10/62 (16.1%)	Not estimable	**50 more per 1.000** (from 50 more to 50 more)	⊕⊕⊕◯ Moderate	

CI: confidence interval; [a] Stefanidis with Jadad scale < 3 and no sample size. A few unclear bias evaluation points in Sanjiv. None of the studies is a double blind; [b] Power < 80; [c] Jadad scale < 3, not a double blind and no sample size.

Table 1. Summary of the risk of bias in the included studies.

Study	Cochrane risk of bias tool								
	Rsg	Acs	Bpp	Boa	Iod	O	Pf	Itt	Ss
Tanaka[12]	+	+	−	+	+	+	+	+	+
Norton[14]	−	?	−	−	+	+	+	+	+
Kida[11]	?	?	?	?	+	+	+	+	?
Macintosh[13]	+	+	+	+	+	+	+	+	+
Stefanidis[16]	+	+	−	+	+	+	+	+	−
Ellahi[18]	?	?	?	?	+	+	?	+	?
Gorelick[17]	+	?	−	+	+	+	+	+	?
Mahadeva[15]	?	?	−	+	+	+	−	−	?
Kohler[4]	?	?	?	?	+	+	+	+	?
Elta[10]	−	?	−	+	+	+	+	+	?

Low risk of bias Unclear risk of bias High risk of bias

Rsg: random sequence generation (selection bias); Acs: allocation concealment (selection bias); Bpp: blinding participants and personnel (performance bias); Boa: blinding of outcome assessment (detection bias); Iod: incomplete outcome data (attrition bias); O: outcome; Pf: prognostic factor; Itt: intention to treat analysis; Ss: sample size