



Restrictive Versus Liberal Fluid Regimens in Patients Undergoing Pancreaticoduodenectomy: a Systematic Review and Meta-Analysis

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Abstract

Background Pancreaticoduodenectomy is associated with significant morbidity and mortality which may be influenced by perioperative fluid management. It remains unclear whether liberal and restrictive fluid regimens impact mortality and morbidity in patients undergoing pancreaticoduodenectomy.

Methods Medline, EMBASE, Cochrane Library and clinicaltrials.gov were searched for studies comparing restrictive and liberal perioperative fluids in patients undergoing pancreaticoduodenectomy. Both prospective and retrospective studies in those undergoing pancreaticoduodenectomy were eligible for inclusion where the patient outcomes were stratified to restrictive and liberal perioperative fluid management regimens, with mortality as the primary outcome. Following study identification, a systematic review and meta-analysis with trial sequential analysis was completed.

Results Thirteen studies including five prospective trials and eight retrospective analyses totalling 3062 patients were included. Restrictive fluid regimens were associated with a significant reduction in mortality compared to liberal fluid regimens for the overall cohort (odds ratio 0.54; 95% CI 0.31–0.94, $p = 0.03$). There were no significant differences in complication profile. Subgroup analysis revealed this result was contributed to significantly by retrospective studies. The results of the trial sequential analysis suggest this mortality benefit may be due to a type I statistical error and that further patient numbers are required for definitive conclusions.

Conclusions Restrictive fluid regimens are associated with a reduction in mortality following pancreaticoduodenectomy. The clinical relevance of this finding needs to be interpreted pragmatically given the lack of association with significant causes of morbidity and in considering the results of the recently published RELIEF study.

Keywords Fluid therapy · Pancreaticoduodenectomy · Mortality

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Introduction

Pancreaticoduodenectomy (PD), predominantly performed for carcinoma of the pancreas or biliary tree, is associated with an extended anaesthetic and surgical time followed by a prolonged postoperative recovery period. Despite continual improvement in perioperative care, complications such as pancreatic fistula, sepsis and cardiopulmonary events are frequent, with up to 62% of patients in some series experiencing serious morbidity.^{1–3} To further improve outcomes in patients undergoing PD, the contribution of perioperative fluid therapy to adverse outcomes needs to be scrutinised to determine if an optimal strategy exists which could be implemented through standardisation of care.^{4–6}

Surgical patients have historically received large amounts of fluid perioperatively in an attempt to compensate for the

extravasation of fluid (“third spacing”) from the intravascular to the interstitial compartment.^{7,8} More recently, there has been a move to fluid restrict patients to avoid the complications associated with fluid overload.^{8–11} Both strategies have inherent advantages; however, it is unclear at what fluid balance an individual patient undergoing pancreatic surgery will obtain an optimum outcome, especially in the absence of well-validated goal-directed monitoring.¹²

The Enhanced Recovery After Surgery (ERAS) Society recommends near zero fluid balance with the avoidance of salt and water overload during the perioperative and immediate postoperative period for patients undergoing PD. This recommendation is derived from data from patients undergoing colorectal surgery.¹³ In contrast to these recommendations, the recently published RELIEF trial demonstrated an increase in renal and wound complications in a heterogenous cohort of patients undergoing abdominal surgery who were exposed to a restrictive fluid regimen, while earlier meta-analyses have shown no difference in morbidity and mortality when compared with a liberal perioperative fluid management strategy.^{12,14–17}

This is a systematic review and meta-analysis of perioperative fluid regimens in patients undergoing PD and its effect on mortality and complication rates, with the aim of clarifying the optimal fluid management in these patients.

Materials and Methods

Search Strategy and Eligibility Criteria

The study protocol complied with PRISMA guidelines.¹⁸ This study was unable to be registered on a review database due to a competing meta-analysis. Medline (Ovid), EMBASE, Cochrane Library and clinicaltrials.gov were searched from 1 January 1969 to 4 December 2017. The following MeSH and keyword terms were used for Medline: “Pancreaticoduodenectomy/OR Pancreatectomy/OR Whipple*.mp. OR Pancreaticoduodenectomy.mp. OR Pancreatectomy.mp. AND Fluid*.mp. Language limits were not applied. The reference lists of identified studies and previous meta-analyses on related topics were searched for other eligible studies.

Eligibility criteria included both prospective and retrospective studies in patients undergoing pancreaticoduodenectomy where the outcomes were stratified to restrictive and liberal perioperative fluid management regimens, with mortality as the primary outcome. The perioperative period for the purpose of this meta-analysis was defined as from the start of the operative procedure to 24 h postoperatively. Using previous consensus definitions, a restrictive fluid administration strategy was defined as either less than

the median for the cohort or less than 10 ml/kg/h intraoperatively.¹⁶

Data Extraction and Bias Assessment

Data was extracted independently and in duplicate by two reviewers (MLG and NJL). Studies identified with the search strategy were combined with a dataset published in the proceedings of a meeting (Lightfoot, 2015).¹⁹ Authors were contacted for additional data if published manuscripts were lacking information or were unclear. Extracted data included baseline characteristics of age, gender, preoperative ASA classification, weight, height and BMI. Patient outcomes collected included 30-day mortality, pancreatic fistulae, hospital length of stay, delayed gastric emptying, wound infection, overall morbidity, cardiac or pulmonary complications and Clavien-Dindo classification.

Bias was assessed independently by two reviewers (MLG and NJL) using the Ottawa-Newcastle Scale and the Cochrane Assessment of Bias Tool for retrospective and prospective studies, respectively.^{20,21} In the event of discrepancies of study bias classification, the findings were discussed and consensus reached. Retrospective studies and prospective studies with high or unclear risk of bias were classified as low quality.

Outcomes

The primary outcome was perioperative mortality defined as in-hospital death or death within 30 days postoperatively.

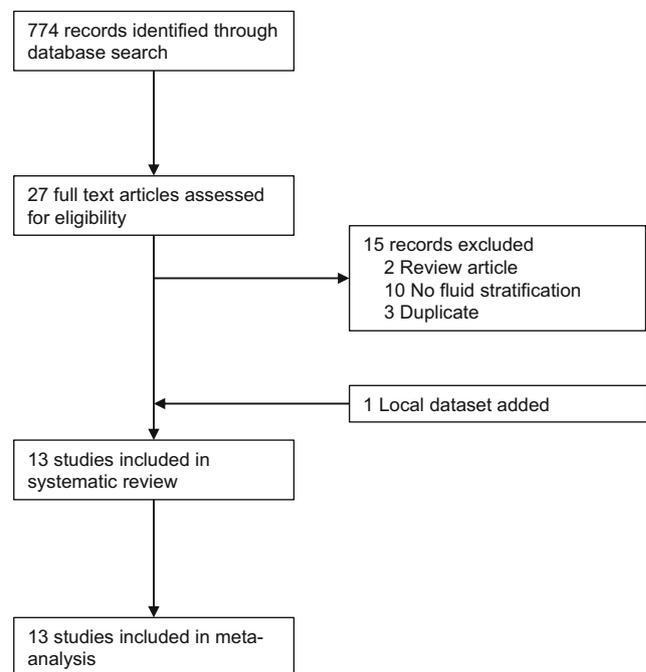


Fig. 1 Flow diagram of selection of studies

Table 1 Baseline characteristics of included studies

	Study type	Age ^a	ASA % I–II/III– IV	Surgical procedure	Restrictive fluid	Liberal fluid	Restrictive group (n)	Liberal group (n)	Total (n)	Mortality
Barak et al. ³⁰	Prospective RCT	61.4 (14.4)	37/63	PD	Balance 0 to + 1000 ml	Balance + 1000 to + 2000 ml	14	18	32	30-day mortality
Behman et al. ³¹	Retrospective cohort	65.7 (12.9)	10/90	PD	Fluid balance quartiles	Fluid balance quartiles	126	125	251	90-day mortality
Eng et al. ³²	Retrospective cohort	64.5 (13.3)	NR	PD	< 13.95 ml/kg/h	> 13.95 ml/kg/h	62	62	124	30-day mortality
Fischer et al. ³³	Prospective RCT	64.5 (11.1)	72/28	PD	3900 ml	6250 ml	65	65	130	In-hospital or 90-day
Grant et al. ³⁴	Prospective RCT	65.0 (9.85)	58/42	P	< 6 ml/kg/h	> 12 ml/kg/h	111	107	218	In-hospital or 60-day
Healy et al. ³⁵	Retrospective cohort	67.1 (13.2)	23/77	P	< 10 ml/kg/h	> 15 ml/kg/h	167	152	319	30-day mortality
Kulemann et al. ³⁶	Retrospective cohort	60.0 (20.2)	65/35	PD	< 6000 ml	> 6000 ml	304	249	552	30-day mortality
Lavu et al. ³⁷	Prospective RCT	67.5 (11.0)	25/65	PD	10 ml/kg/h	15 ml/kg/h	132	132	264	30-day mortality
Lightfoot et al. ¹⁹	Retrospective cohort	62.5 (12.0)	26/74	PD	< 6000 ml	> 6000 ml	313	314	627	30-day mortality
Melis et al. ³⁸	Retrospective cohort	66.4 (11.5)	51/49	PD	< 6000 ml	> 6000 ml	86	102	188	In-hospital or 30-day
Van Samkar et al. ³⁹	Prospective RCT	62.3 (9.50)	96/4	PD	5 ml/kg/h	10 ml/kg/h	24	16	40	30-day mortality
Wang et al. ⁴⁰	Retrospective cohort	53.5 (10.7)	65/35	PD	< 8.2 ml/kg/h	> 8.2 ml/kg/h	90	57	147	30-day mortality
Wright et al. ⁶	Retrospective cohort	65.2 (12.0)	42/58	PD	Balance < + 4325 ml	Balance > + 4326 ml	85	84	169	90-day mortality

^a Values are mean (standard deviation)

PD pancreaticoduodenectomy, P all pancreaticectomy included, NR not reported, n number of patients

Table 2 Quality assessment of prospective studies using the Cochrane Assessment of Bias Tool

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall risk of bias
Barak et al. ³⁰	H	H	H	H	H	H	High
Fischer et al. ³³	L	H	I	L	L	L	Low
Grant et al. ³⁴	L	H	L	L	L	L	Low
Lavu et al. ³⁷	L	I	H	L	L	L	Low
Van Samkar et al. ³⁹	L	L	L	L	L	L	Low

H high risk, L low risk, I indeterminate

Secondary outcomes included pancreatic fistulae, hospital length of stay, delayed gastric emptying, wound infection, overall morbidity, cardiac or pulmonary complications and Clavien-Dindo classification (serious morbidity was classified as Clavien-Dindo classification III–V). Overall morbidity was defined as the percentage of participants with any complication, not the sum of the total number of complications per patient.

Statistical Analysis

Analyses were completed using RevMan 5.3 software and heterogeneity assessed with the I^2 statistic.²² Heterogeneity was regarded as low when I^2 was less than 25% and high when I^2 was greater than 50%.²³ The results were calculated as odds ratios (OR) and 95% confidence intervals (CI) using the Mantel-Haenszel method for discrete and continuous data through a random effects model. Publication bias was assessed graphically using a funnel plot and asymmetry assessed through Egger’s test with Meta-Essentials Software.²⁴

Subgroup analysis was completed for seven relevant subgroups. Prospective trials were compared with retrospective trials. Medical risk was defined as low if greater than 50% of study participants were ASA I-II and high if greater than 50% of study participants were ASA III–IV. Other analyses included elderly patients (mean age \geq 65 years) compared with younger patients, surgical

procedure (pancreaticoduodenectomy versus distal or total pancreatectomy) and presence or absence of a thoracic epidural. The effect of the dataset published in meeting proceedings was also assessed. Finally, early studies (2006–2013) were compared with later studies (2014–2017). Where there were statistically significant differences between subgroups, the test of interaction was applied. The analysis is used to compare a treatment effect for different subgroups, for example two different age groups and mortality or two different studies and mortality.²⁵ A test of interaction is deemed significant (there is a significant difference in treatment effect between two subgroups) if $p < 0.05$.

Trial Sequential Analysis

Trial sequential analysis (TSA) is used to reduce the risk of random error in meta-analyses. Type I error is common in meta-analyses due to repeated significance testing as more trials are published and due to the accumulation of multiple small studies with high risk of bias.^{26–28} TSA calculates monitoring boundaries that adjust the p value to maintain an overall risk of type I error at 5%.

This method also calculates the required information size for the meta-analysis to detect a treatment effect with a 20% risk of type II error and power of 80%. The required information size was calculated based on an assumption of plausible reductions in odds ratio of 33% for mortality and

Table 3 Quality assessment of retrospective studies using the Newcastle-Ottawa Scale

	Selection	Comparability	Outcome	Overall risk of bias
Behman et al. ³¹	4/4	2/2	3/3	High
Eng et al. ³²	4/4	2/2	3/3	High
Healy et al. ³⁵	4/4	2/2	2/3	High
Kulemann et al. ³⁶	4/4	2/2	3/3	High
Lightfoot et al. ¹⁹	4/4	2/2	3/3	High
Melis et al. ³⁸	4/4	1/2	3/3	High
Wang et al. ⁴⁰	4/4	2/2	3/3	High
Wright et al. ⁶	4/4	1/2	3/3	High

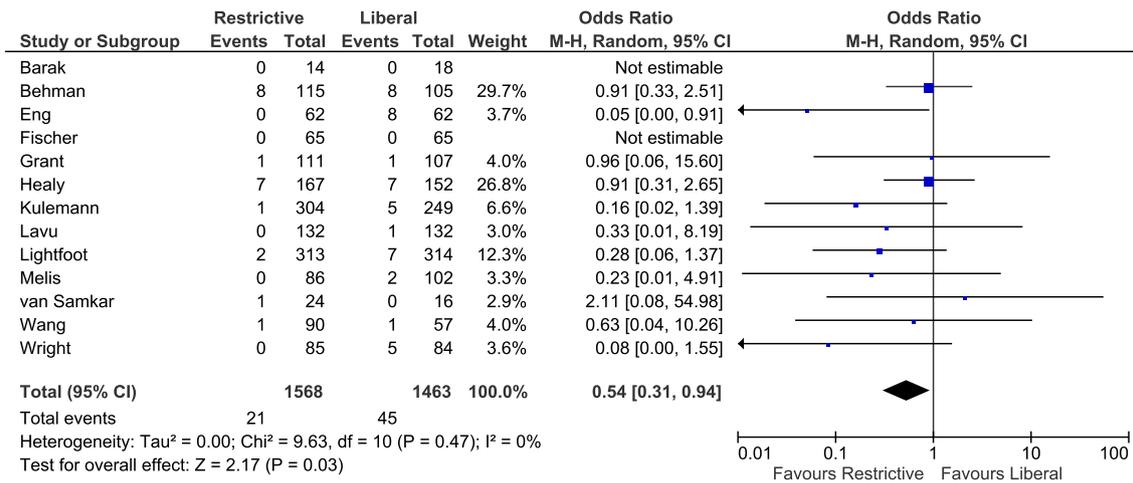


Fig. 2 Forest plot for mortality

morbidity based on rates found in this meta-analysis. Exclusion of zero-event trials may inflate pooled treatment effect estimates; thus, to account for this, an empirical continuity correction of 0.01 was used so that these trials were not excluded.²⁹

Results

Data Extraction

The literature search identified 774 studies, which following review of abstracts leads to 27 full text articles being retrieved for assessment of eligibility (Fig. 1). As a result, 15 studies were excluded for meta-analysis. Two were review articles, ten did not stratify by perioperative fluid regimen, and three were duplicates of previously published works. This left 12 studies (five prospective trials and seven retrospective studies) totalling 2420 patients. The

earliest study was published in 2006. This was combined with further data from a quaternary pancreatic surgical centre of 627 patients, previously published as a poster and in meeting proceedings, giving a total of 3062 patients. There were 1579 (52%) patients in the restrictive group and 1483 (48%) patients in the control group.

The baseline characteristics and bias assessments of each study are presented in Tables 1, 2, and 3. The definitions used for restrictive and liberal fluid regimens were heterogeneous (Table 1). Six studies used rate of fluid administration in millilitres per kilogramme per hour, using thresholds of 5, 6, 8.2, 10, 10 and 13.95 ml/kg/h, three studies divided groups by overall fluid balance, a further three divided groups by median fluid amount (6000 mL) and one used the avoidance of normovolaemic haemodilution.

Of the five prospective studies, four reported adequate sequence generation and allocation concealment and one reported adequate blinding of participants and outcome assessors (Table 2). Of the eight retrospective studies, all reported

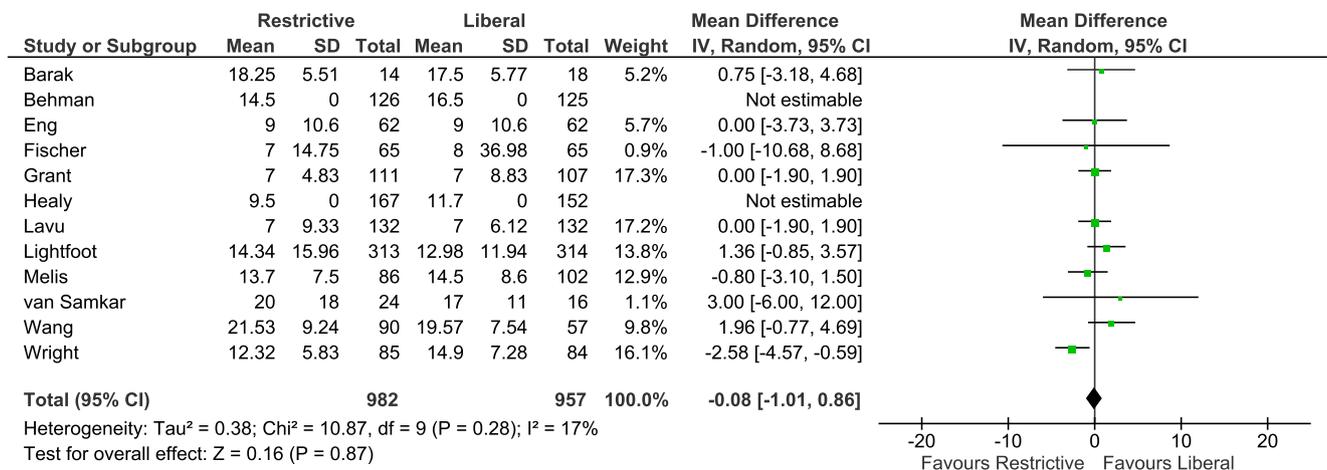


Fig. 3 Forest plot for length of stay

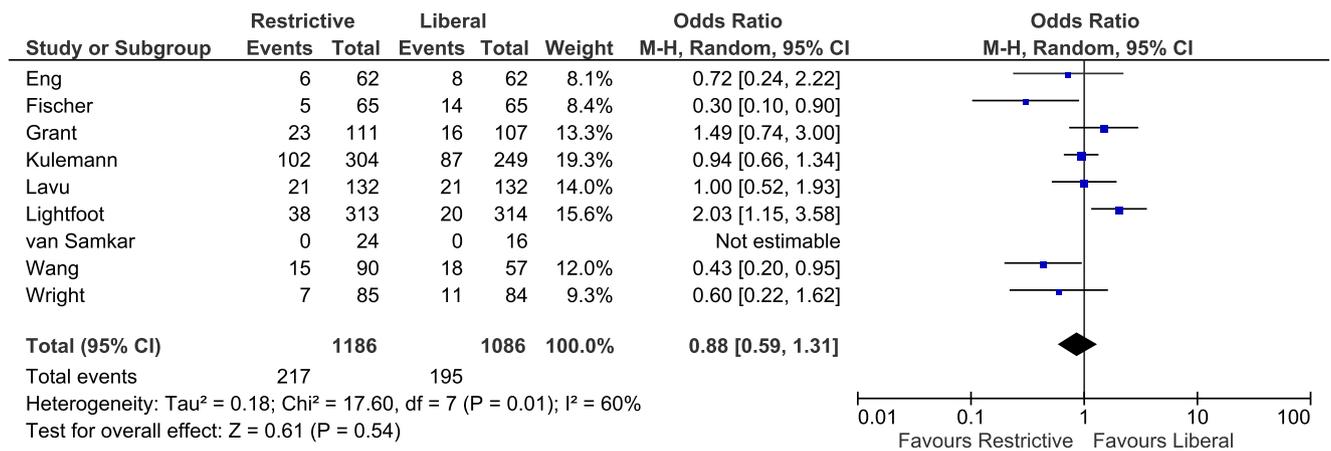


Fig. 4 Forest plot for pancreatic fistula

adequate selection and representativeness, outcome assessment and follow-up (Table 3). On the basis of the quality assessment, four studies were deemed as low risk of bias,^{33,34,37,39} while the remainder were deemed at high risk of bias.

Main Results

Restrictive fluid regimens were associated with a significant reduction in mortality compared to liberal fluid regimens for the overall cohort (odds ratio 0.54; 95% CI 0.31–0.94, *p* = 0.03; Fig. 2). There were no significant differences for length of hospital stay; nor incidences of pancreatic fistula, delayed gastric emptying or wound infection; overall morbidity; cardiac or pulmonary complications; and Clavien-Dindo classification (Figs. 3, 4, 5, 6, 7, 8, 9, and 10).

Heterogeneity was low (< 25%) for mortality, length of stay and cardiac and pulmonary complications, moderate (25–50%) for pancreatic fistula, delayed gastric emptying, wound infection and Clavien-Dindo classification and high (> 50%) for overall morbidity. There was no

evidence of publication bias on visual inspection of the funnel plot for mortality data, nor with Egger’s test (*p* = 0.32; Fig. 11).

Subgroup analysis demonstrated that the beneficial effect of fluid restriction on mortality was driven by the disproportionate contribution of patients from retrospective studies (77% retrospective, 23% prospective) (Table 4). Analysis of the prospective studies revealed no difference in mortality between the two groups. However, the analysis was underpowered to detect this outcome as there were only four deaths in the five prospective trials. The test for interaction showed that the difference in findings between retrospective and prospective studies was not significant. There were no significant differences in retrospective and prospective studies for pancreatic fistula, length of hospital stay, wound infection or overall morbidity.

Of the 13 studies included, five (38%) had a patient population with a mean age greater than 65 years. Further subgroup analysis revealed no evidence of a differential treatment effect between younger and older patients across the reported outcomes (Table 4). Of the 12 studies with ASA data, six (50%)

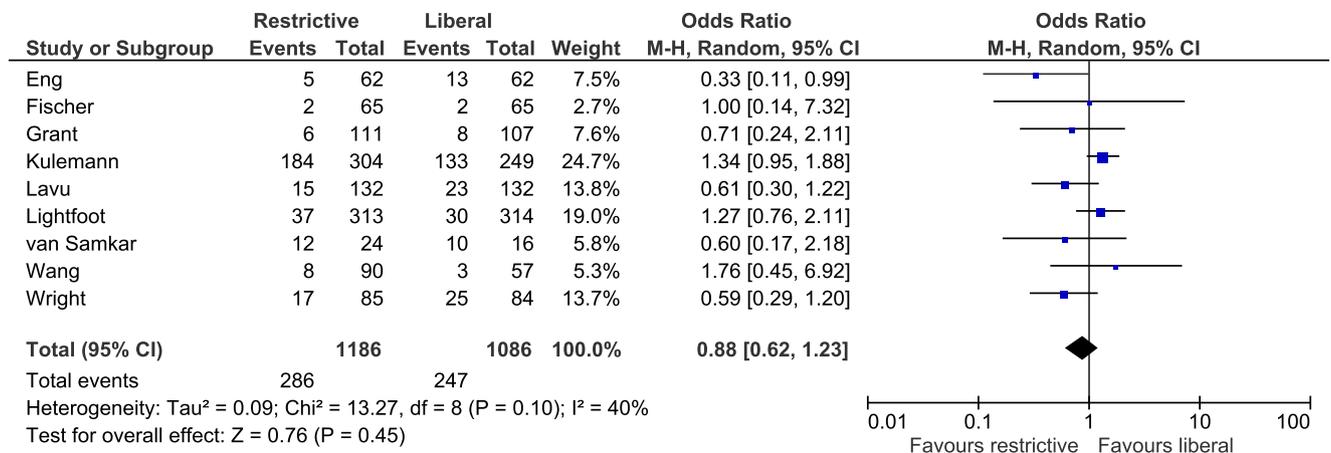


Fig. 5 Forest plot for delayed gastric emptying

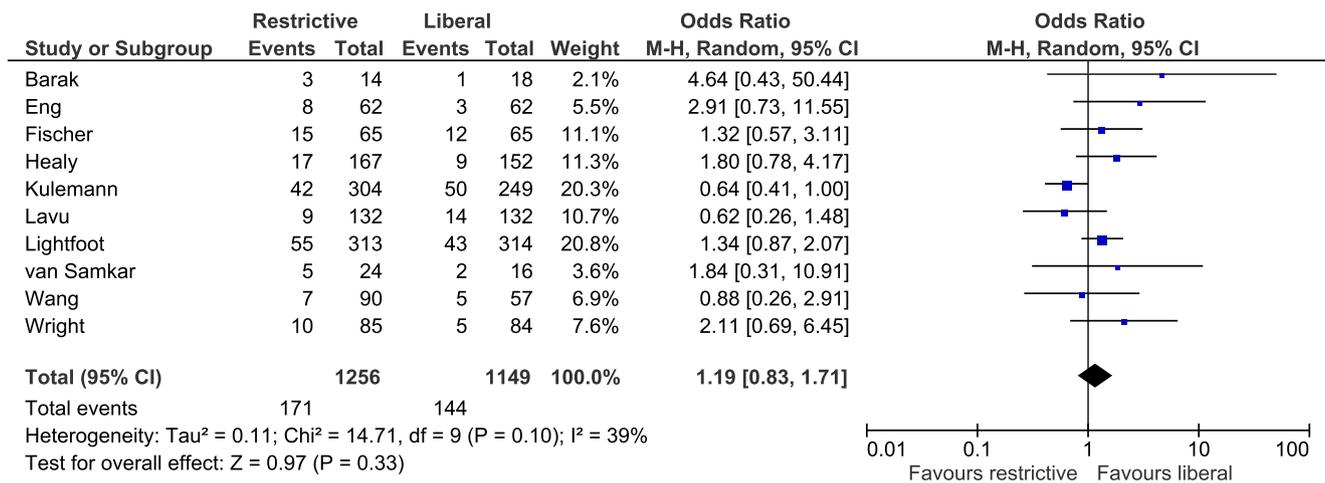


Fig. 6 Forest plot for wound infection

studies enrolled more than 50% high-risk (ASA III–IV) patients and there was no difference in mortality data across these subgroups.

Three studies utilised epidural analgesia as a part of a standardised care package, whereas two studies reported the avoidance of epidural use. There were three studies with selective epidural use and five with no data on epidural use. There was no evidence to suggest an interaction between epidural use and the reported outcomes. There was no change in the reported outcomes when the unpublished retrospective data set was removed from the analysis of the primary outcome. Likewise, analysis of studies by date of publication revealed no difference in recorded outcomes.

A trial sequential-monitoring boundary was created for an intervention effect on mortality suggested by mortality rates in this meta-analysis (Fig. 12). The required sample size to detect mortality differences was 7653 participants. This was calculated using the mortality estimate provided by all the trials due to the small number of events in the prospective studies deemed at low risk of bias. As this boundary was not crossed by the cumulative Z curve, the presence of a significant result ($p = 0.03$) may be due to random error. The required information size calculated

for morbidity and wound infection was 8030 and 9122 participants, respectively (Figs. 13 and 14). Neither the trial sequential-monitoring boundaries nor the traditional boundaries were crossed for morbidity or wound infection.

Discussion

This meta-analysis of restrictive versus liberal fluid therapies has found that a restrictive fluid management regimen in PD reduces mortality, without a change in the frequency of recorded complications between the two strategies. This result was driven predominantly by retrospective studies; the TSA boundary was not crossed, suggesting the body of evidence contains insufficient numbers of patients to reach this conclusion. Blood loss was identified as a significant confounder in the retrospective studies. It may be inferred that patients self-select for the liberal group in the presence of bleeding which is known to alter a patient's morbidity and mortality.

The debate surrounding fluid management for patients undergoing abdominal surgery is longstanding. Current trends suggest that moderation rather than extremes of fluid balance will lead to optimal patient outcomes.^{9–11} It

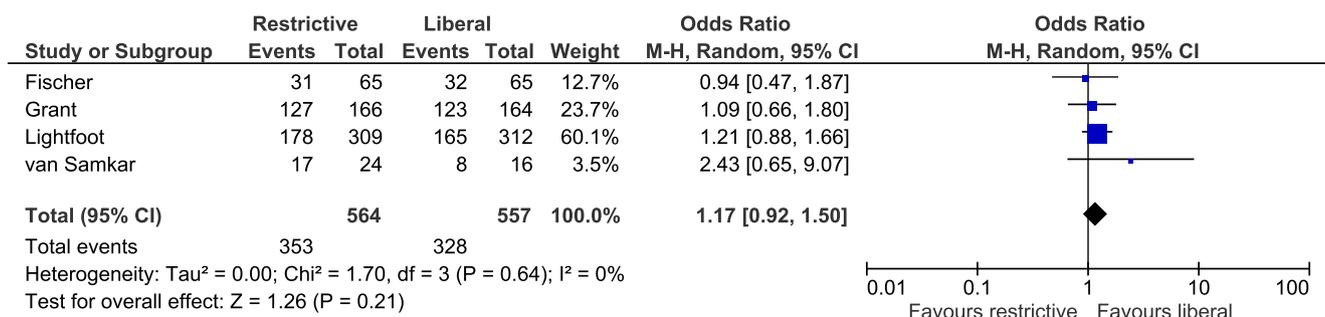


Fig. 7 Forest plot for morbidity

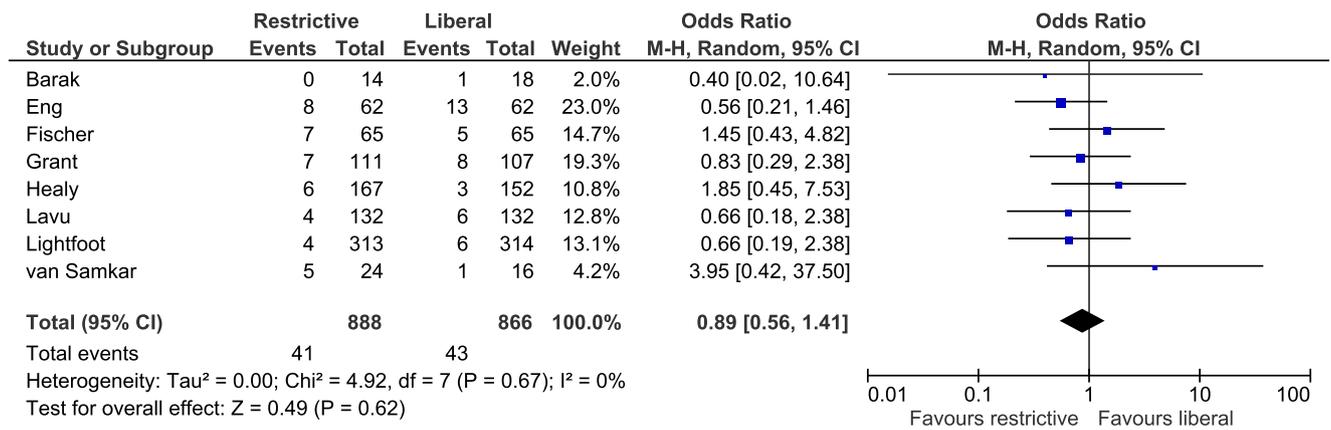


Fig. 8 Forest plot for cardiac complications

is hypothesised that fluid overload can precipitate cardiac failure and pneumonia in susceptible patients.⁴¹ It may also increase gut oedema, leading to postoperative ileus, bowel anastomotic dehiscence and delayed wound healing.⁴² Fluid restriction may impede wound healing, with the depletion of intravascular volume leading to reduced tissue oxygen tension, particularly in the context of the increased vasopressor requirement to defend mean arterial pressure. In tenuous circulations such as wounds and anastomoses, this may manifest as increased rates of wound infection.⁴³ This dichotomy is further complicated by the contribution of goal-directed therapy. There is currently no validated strategy nor monitor of tissue perfusion that has been proven to consistently alter outcomes in pancreatic surgery.⁴⁴

The individual results of the prospective studies included in this meta-analysis by and large suggest that a restrictive fluid strategy was not associated with any change in mortality. The subgroup analysis looking at the prospective data supports this conclusion with no reduction in mortality seen between groups of patients randomised to either a liberal or restrictive fluid strategy. This analysis was

limited by the small number of deaths observed in both groups. Many of the prospective studies originated from high-volume pancreatic surgical centres which have a low incidence of post-surgical complications.^{45–47} As such, strong conclusions are unable to be reached. The difference in mortality is largely driven by the retrospective cohorts where the differences in the definition of a restrictive strategy were especially apparent. The trial sequential analysis suggests that the number of patients enrolled in this meta-analysis was drastically less than the calculated sample size (3062 versus 7653) meaning that this result may be explained through a type II error.

The current literature surrounding fluid management in abdominal surgery is conflicted due to the utility of fluid restriction being superimposed on the effects of goal-directed therapy. Wang et al. recently published a meta-analysis on this in *Zhonghua wai ke za zhi* [*Chinese Journal of Surgery*] which included only four prospective trials.^{33,34,37,39,48} They found no significant differences in complication profile or mortality between the two groups.⁴⁸ Corcoran et al. found that a group exposed to goal-directed therapy when compared to a liberal fluid

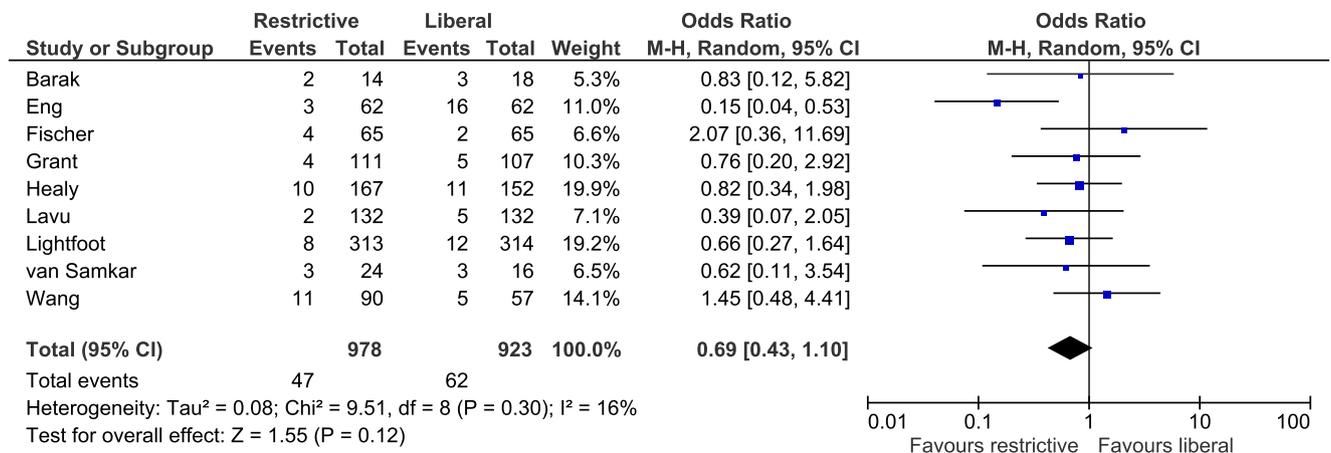


Fig. 9 Forest plot for pulmonary complications

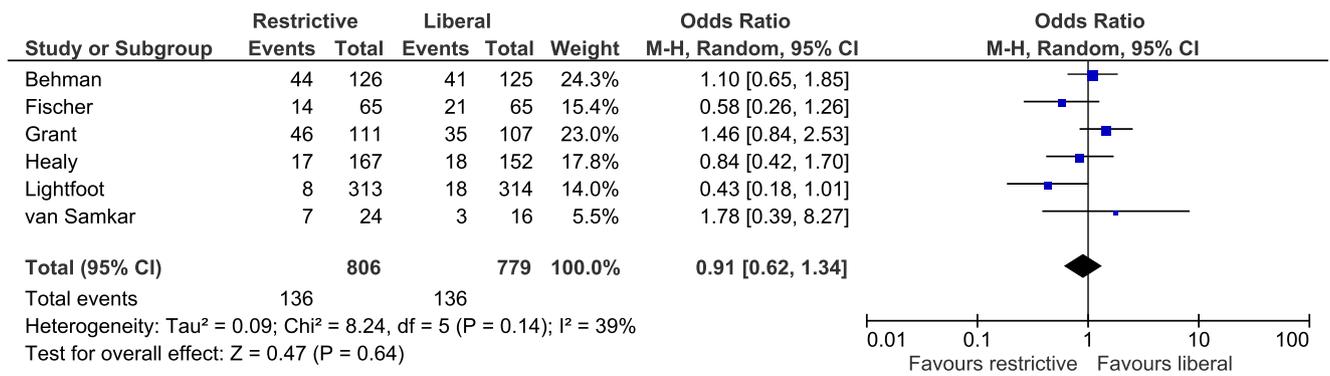


Fig. 10 Forest plot for Clavien-Dindo III–V complications

regimen received almost the same amount of fluid. Liberal regimens were associated with increased rates of pulmonary complications and longer hospital stays.¹² This is in contrast to Boland et al. who found no differences in morbidity, mortality and length of stay in patients undergoing abdominal surgery.¹⁴ More recently, Jia et al. found restrictive fluid regimens were associated with shorter hospital stay and shorter time to first flatus, with no difference in cardiopulmonary complications or mortality.¹⁵ These trials have been completed in parallel with the widespread introduction of Enhanced Recovery After Surgery or fast-track protocols making it difficult to tease out the effect of fluid therapy on any improvements in a patient’s perioperative journey.⁴⁹

In PD, prospective studies have reached disparate conclusions with regard to the effect of fluid management on the complication profile. In 2006, Barak et al. prospectively randomised a small group of 32 patients undergoing pancreaticoduodenectomy to postoperative positive fluid balance of between 0 and 1000 mL and 1000–2000 mL.

They reported no in-hospital mortality and a similar complication profile between the two groups.³⁰ Fischer et al. prospectively randomised 130 patients undergoing pancreaticoduodenectomy to acute normovolaemic haemodilution (ANH) and standard management. The 65 patients in the ANH group received over 2 L more fluid intraoperatively than the control group. The ANH group had significantly more pancreatic anastomatic complications than the standard (restrictive) group. However, there were no differences in overall morbidity between the two groups and no reported deaths across the study.³³

The HYSLAR trial by Lavu et al. randomised 264 pancreaticoduodenectomy patients to restrictive perioperative fluid (9 ml/kg/h Lactated Ringer’s with 1 ml/kg/h 3% hypertonic saline) and liberal perioperative fluid (15 ml/kg/h lactated Ringer’s). At 30 days postoperatively, there was only one death across the two groups. They found the restrictive group experienced less complications overall but similar rates of reoperations, length of hospital stay, and readmission.³⁷

Fig. 11 Funnel plot for mortality with non-significant Egger’s test suggesting no publication bias. Eggers test = 0.32

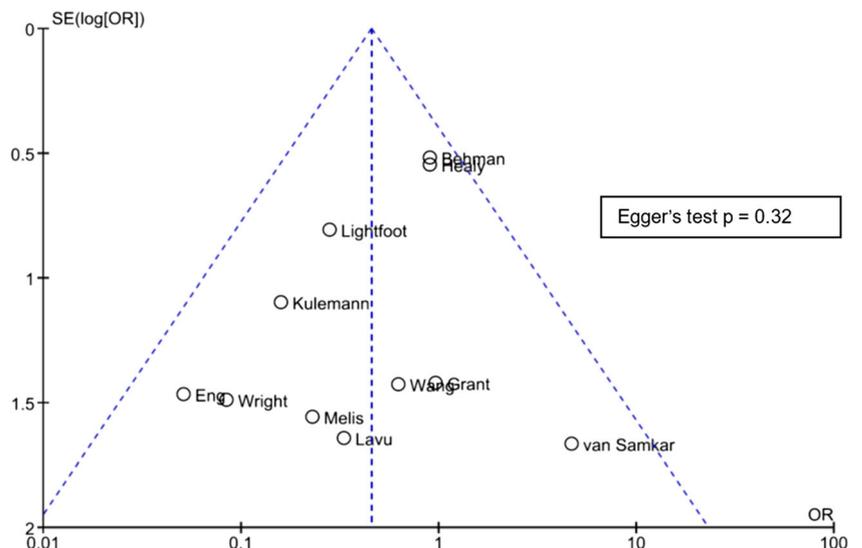


Table 4 Subgroup analyses

	Mortality		Length of stay	
	<i>n/N</i>	OR (95% CI)	<i>n/N</i>	MD (95% CI)
Type of study				
Prospective	R 2/338; L 2/346	0.88 [0.15, 5.13]	R 338; L 346	0.12 [−1.13, 1.37]
Retrospective	R 19/1222; L 43/1125	0.44 [0.22, 0.90]	R 867; L 834	−0.11 [−2.21, 1.98]
Interaction <i>p</i> value		0.475		
Medical risk categories				
High	R 17/837; L 28/825	0.65 [0.33, 1.28]	R 544; L 548	−0.27 [−2.13, 1.59]
Low	R 4/672; L 9/604	0.45 [0.13, 1.51]	R 368; L 355	0.22 [−1.05, 1.49]
Interaction <i>p</i> value				
Age				
Elderly (> 65 years)	R 9/529; L 17/530	0.63 [0.27, 1.46]	R 414; L 425	−0.82 [−2.04, 0.40]
Young (< 65 years)	R 12/1031; L 28/941	0.43 [0.18, 1.06]	R 560; L 540	1.24 [−0.18, 2.65]
Interaction <i>p</i> value				
Surgical procedure				
PD	R 13/1282; L 37/1212	0.43 [0.22, 0.84]	R 863; L 858	−0.06 [−1.18, 1.07]
Pancreatectomy	R 8/278; L 8/259	0.91 [0.34, 2.48]	R 111; L 107	0.00 [−1.90, 1.90]
Interaction <i>p</i> value				
Epidural				
Yes	R 1/115; L 5/126	0.39 [0.02, 9.39]	R 115; L 126	−0.98 [−3.89, 1.92]
No	R 1/243; L 2/239	0.61 [0.07, 4.99]	R 243; L 239	0.00 [−1.34, 1.34]
Interaction <i>p</i> value				
Effect of unpublished data set				
With	R 21/1568; L 45/1463	0.54 [0.31, 0.94]	R 982; L 957	−0.08 [−1.01, 0.86]
Without	R 19/1255; L 38/1149	0.59 [0.33, 1.07]	R 669; L 643	−0.33 [−1.28, 0.62]
Interaction <i>p</i> value	0.831			
Timing of studies				
2006–2013	R 0/227; L 10/247	0.10 [0.01, 0.85]	R 227; L 247	−0.34 [−2.06, 1.39]
2014–2018	R 21/1341; L 35/1216	0.61 [0.35, 1.09]	R 755; L 710	−0.09 [−1.33, 1.51]
Interaction <i>p</i> value	0.062			
	Wound infection	Any fistula		
	<i>n/N</i>	OR (95% CI)	<i>n/N</i>	OR (95% CI)
Type of study				
Prospective	R 32/227; L 29/239	1.11 [0.58, 2.12]	R 54/325; L 54/328	0.94 [0.52, 1.69]
Retrospective	R 139/1021; L 115/918	1.25 [0.78, 2.00]	R 75/550; L 67/517	0.83 [0.42, 1.63]
Interaction <i>p</i> value				
Medical risk categories				
High	R 94/711; L 72/700	1.35 [0.88, 2.08]	R 69/530; L 57/530	1.13 [0.63, 2.01]
Low	R 69/475; L 69/395	0.81 [0.54, 1.21]	R 51/282; L 52/253	0.74 [0.35, 1.56]
Interaction <i>p</i> value				
Age				
Elderly (> 65 years)	R 19/217; L 19/216	1.08 [0.33, 3.59]	R 52/328; L 50/323	1.03 [0.67, 1.58]
Young (< 65 years)	R 152/1031; L 125/941	1.24 [0.83, 1.84]	R 77/546; L 71/522	0.81 [0.39, 1.66]
Interaction <i>p</i> value				
Surgical procedure				
PD	R 154/1081; L 135/1005	1.13 [0.77, 1.67]	R 105/763; L 103/738	0.82 [0.50, 1.32]
Pancreatectomy	R 17/167; L 9/152	1.80 [0.78, 4.17]	R 24/111; L 18/107	1.36 [0.69, 2.69]
Interaction <i>p</i> value				
Epidural				
Yes	R 18/115; L 8/126	2.27 [0.94, 5.47]	R 9/101; L 11/108	0.80 [0.21, 3.03]

Table 4 (continued)

	Mortality		Length of stay	
No	R 9/132; L14/132	0.62 [0.26, 1.48]	R 45/243; L 39/239	1.16 [0.72, 1.87]
Interaction <i>p</i> value				
Effect of unpublished data set				
With	R 171/1256; L 144/1149	1.19 [0.83, 1.71]	R 129/882; L 121/837	0.89 [0.59, 1.35]
Without	R 116/943; L 101/835	1.19 [0.77, 1.84]	R 88/569; L 96/523	0.77 [0.53, 1.12]
Interaction <i>p</i> value				
Timing of studies				
2006–2013	R 26/141; L 16/145	1.80 [0.90, 3.60]	R 16/127; L 27/127	0.54 [0.27, 1.06]
2014–2018	R 145/115; L 128/1004	1.07 [0.72, 1.60]	R 113/755; L 94/710	1.03 [0.66, 1.62]
Interaction <i>p</i> value				
	Morbidity	CD III–V		
	n/N	OR (95% CI)	n/N	OR (95% CI)
Type of study				
Prospective	R 255/322; L 278/322	0.85 [0.32, 2.28]	R 67/192; L 59/196	1.07 [0.53, 2.15]
Retrospective	R 671/1167; L 632/1081	0.95 [0.64, 1.39]	R 83/671; L 98/656	0.76 [0.50, 1.14]
Interaction <i>p</i> value				
Medical risk categories				
High	R 508/833; L 508/823	0.97 [0.47, 1.97]	R 69/606; L 77/591	0.80 [0.48, 1.33]
Low	R 418/656; L 402/580	0.74 [0.58, 0.96]	R 67/192; L 59/196	1.07 [0.53, 2.15]
Interaction <i>p</i> value		0.485		
Age				
Elderly (> 65 years)	R 380/540; L 422/550	0.72 [0.31, 1.66]	R 90/237; L 76/232	1.26 [0.86, 1.84]
Young (< 65 years)	R 546/949; L 488/853	1.05 [0.74, 1.49]	R 46/561; L 60/555	0.67 [0.43, 1.05]
Interaction <i>p</i> value				
Surgical procedure				
PD	R 747/1211; L 756/1144	0.83 [0.54, 1.28]	R 73/520; L 83/528	0.77 [0.45, 1.33]
Pancreatectomy	R 179/278; L 154/259	1.36 [0.91, 2.02]	R 63/278; L 53/259	1.16 [0.68, 1.96]
Interaction <i>p</i> value				
Epidural				
Yes	R 35/99; L 49/102	0.99 [0.31, 3.22]	R 7/16; L 3/24	1.78 [0.39, 8.27]
No	R 193/243; L 219/239	0.42 [0.07, 2.43]	R 46/111; 35/107	1.46 [0.84, 2.53]
Interaction <i>p</i> value				
Effect of unpublished data set				
With	R 375/564; L 328/557	1.73 [0.96, 3.12]	R 136/806; L 136/779	0.91 [0.62, 1.34]
Without	R 197/255; L 163/245	2.19 [0.79, 6.07]	R 128/493; L 118/465	1.05 [0.76, 1.45]
Interaction <i>p</i> value				
Timing of studies				
2006–2013	R 53/65; L 32/65	4.55 [2.06, 10.07]	R 14/65; L 21/65	0.58 [0.26–1.26]
2014–2018	R 322/499; L 296/492	1.21 [0.93, 1.57]	R 122/741; L 115/714	0.99 [0.66, 1.50]
Interaction <i>p</i> value	0.999			

Interaction *p* value supplied where subgroup analyses appear statistically significant. Significant interaction *p* value is < 0.05

R restrictive group, *L* liberal group, *OR* odds ratio, *MD* mean difference, *CI* confidence interval, *PD* pancreaticoduodenectomy

Van Samkar et al. randomised 66 patients to standard (10 ml/kg/h) and restricted (5 ml/kg/h) perioperative fluid regimens; 32 patients underwent pancreaticoduodenectomy with the remainder receiving palliative bypass procedures. There were no reported differences in in-hospital mortality nor 6-

year survival between the groups. There was one death within 30 days across this study population. The authors reported an overrepresentation of pancreaticoduodenectomy in the restrictive group (*n* = 23) versus the standard group (*n* = 13) which could have biased outcomes.³⁹

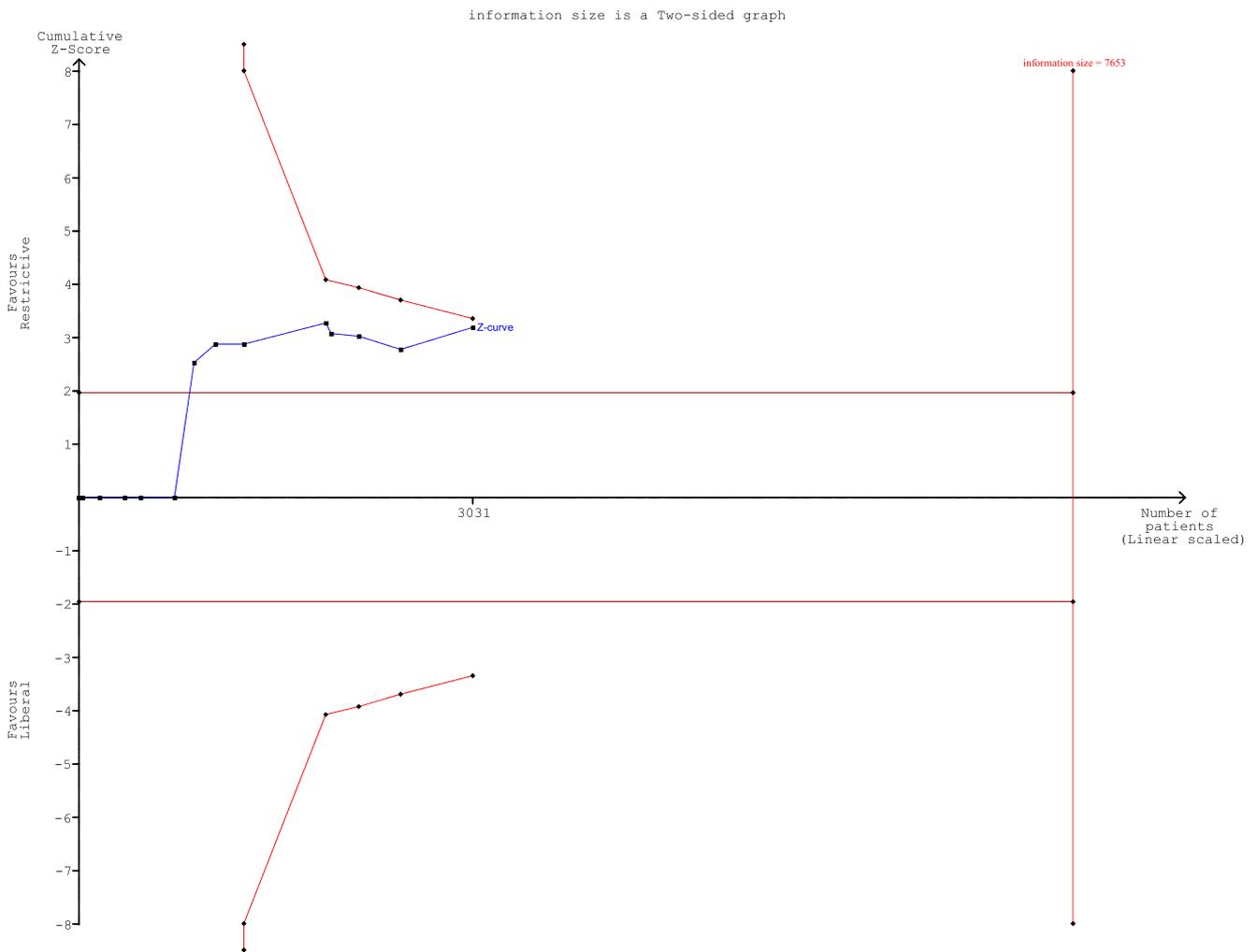


Fig. 12 Trial sequential analysis for mortality. The required sample size to detect significant mortality difference was calculated as 7653 participants. The cumulative Z curve was not crossed with 3031 participants suggesting random error

In the most recent prospective trial, Grant et al. randomised 330 pancreatic surgical patients to restrictive (6 ml/kg/h crystalloid) and liberal (12 ml/kg/h crystalloid) fluid regimens and found no difference in mortality, complication rate or length of stay. Once again, this population had a low mortality rate, with two deaths at 60 days. The overall fluid regimens differed approximately 1.6-fold between the two groups and the authors postulated this was not enough to affect mortality in a large volume institution.³⁴

In the RELIEF study by Myles et al., patients were randomised to receive either a restrictive or liberal fluid regimen for the first 24 h after the induction of anaesthesia.¹⁷ Two hundred and seventy-two patients, accounting for 9.1% of the total study population, underwent hepatopancreaticobiliary surgery. The median fluid exposure was approximately 5 ml/kg/h in the restrictive group after a 5-ml/kg bolus and 8 ml/kg/h after a 10-ml/kg bolus in the liberal group. No differences were seen in mortality and disability-free survival at 12 months post-procedure.

Those exposed to a restrictive fluid regimen had a significantly greater chance of developing both renal failure and surgical wound infections.¹⁷

Two explanations are offered for the results produced by this meta-analysis. There is significant variation in mortality based on case volume for many surgical procedures. This is especially true for pancreatic surgery where the mortality rate may range from close to zero for large high-volume centres to up to 14% for medium and small volume facilities.^{45–47} When looking at the prospective studies alone, the pooled mortality rate was 0.6% (4/648) suggesting patient enrolment comes from large, high-volume facilities where the individual impact of an intervention such as a change in fluid management may be masked by inherent advantages of increased case volume. When the retrospective cohorts were included, the mortality rate increased to 2.2% (66/3031) which is in line with contemporary estimates of approximately 2%.^{36,37,50} This highlights the importance of including retrospective analyses to guide

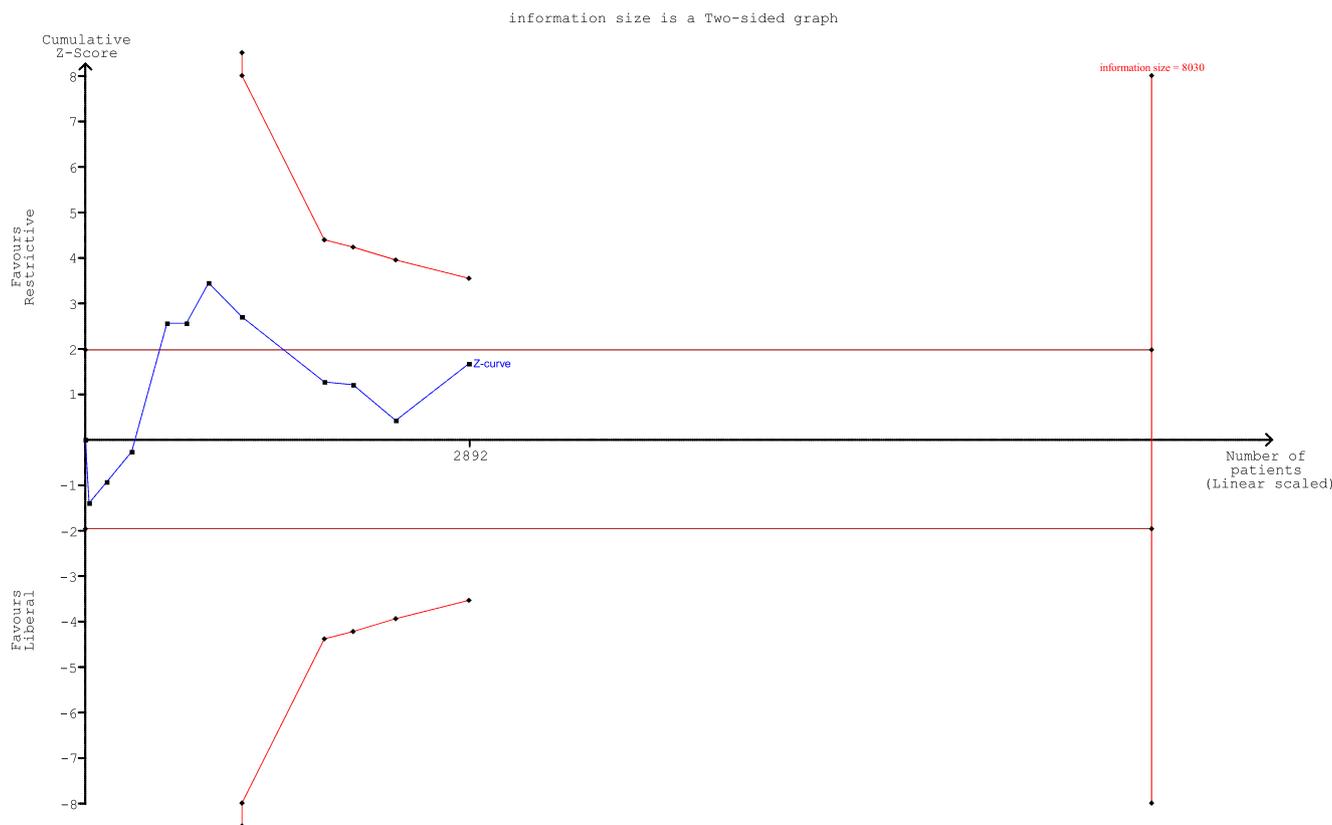


Fig. 13 Trial sequential analysis for morbidity. The required sample size to detect significant morbidity differences was calculated as 8030 participants. The cumulative Z curve was not crossed with 2892 participants

practice given the significant cost associated with large multi-centre prospective trials.

Secondly, blood loss may act as a confounding factor. Overall, no difference in estimated intraoperative blood loss was seen between the two groups. On review of the retrospective cohorts, the restrictive group experienced a significant reduction in the estimated blood loss while no difference was seen in the prospective studies. This may suggest that increases in blood loss may drive the increased fluid administration and could push a patient from the restrictive to the liberal group. The data was inadequate to conduct a subgroup analysis on transfusion rates. It is postulated that liberal patients with greater blood loss received more transfusions, which may explain the mortality difference between groups.⁵¹

No standard definition of what constitutes a restrictive or liberal fluid regimen currently exists. Previous studies have based definitions of “standard” fluid administration on textbook or expert opinion. This considers the fluid deficit from fasting, maintenance, third spacing and blood loss.^{16,52,53} More recently, Shin et al. retrospectively divided a cohort of 92,094 surgical cases to quintiles and found that a moderately restrictive fluid management strategy, with a mean rate of administration of 7.6 ml/kg/h, was associated with minimisation of both morbidity and

mortality.⁵² This group constituted the second quintile meaning that both further reductions and increases in fluid administration lead to an increase in morbidity and mortality. This rate is 40% lower than the current “textbook” recommendation for fluid administration.⁵³ These differences and the heterogeneity presented in the meta-analysis highlight the lack of clear guidance which exists with regard to perioperative fluid therapy. The discussion is further complicated by the composition of fluids used to provide both resuscitation and maintenance.

An important limitation of this meta-analysis is the heterogeneity and introduction of bias afforded by the inclusion of a wide variety of study designs. This was necessary given the small number of studies on fluid management and PD. This significant limitation was somewhat mitigated by subgroup analyses and trial sequential analysis. Importantly, the overall findings of the meta-analyses reflected the results of the prospective studies included; there is limited consensus on the optimal management of perioperative fluids in PD.

In conclusion, the question surrounding liberal and restriction fluid regimens in pancreaticoduodenectomy is yet to be answered. Although this meta-analysis has revealed a lower mortality in patients exposed to restrictive fluid management strategies, there is no clear reason as to why this is the case.

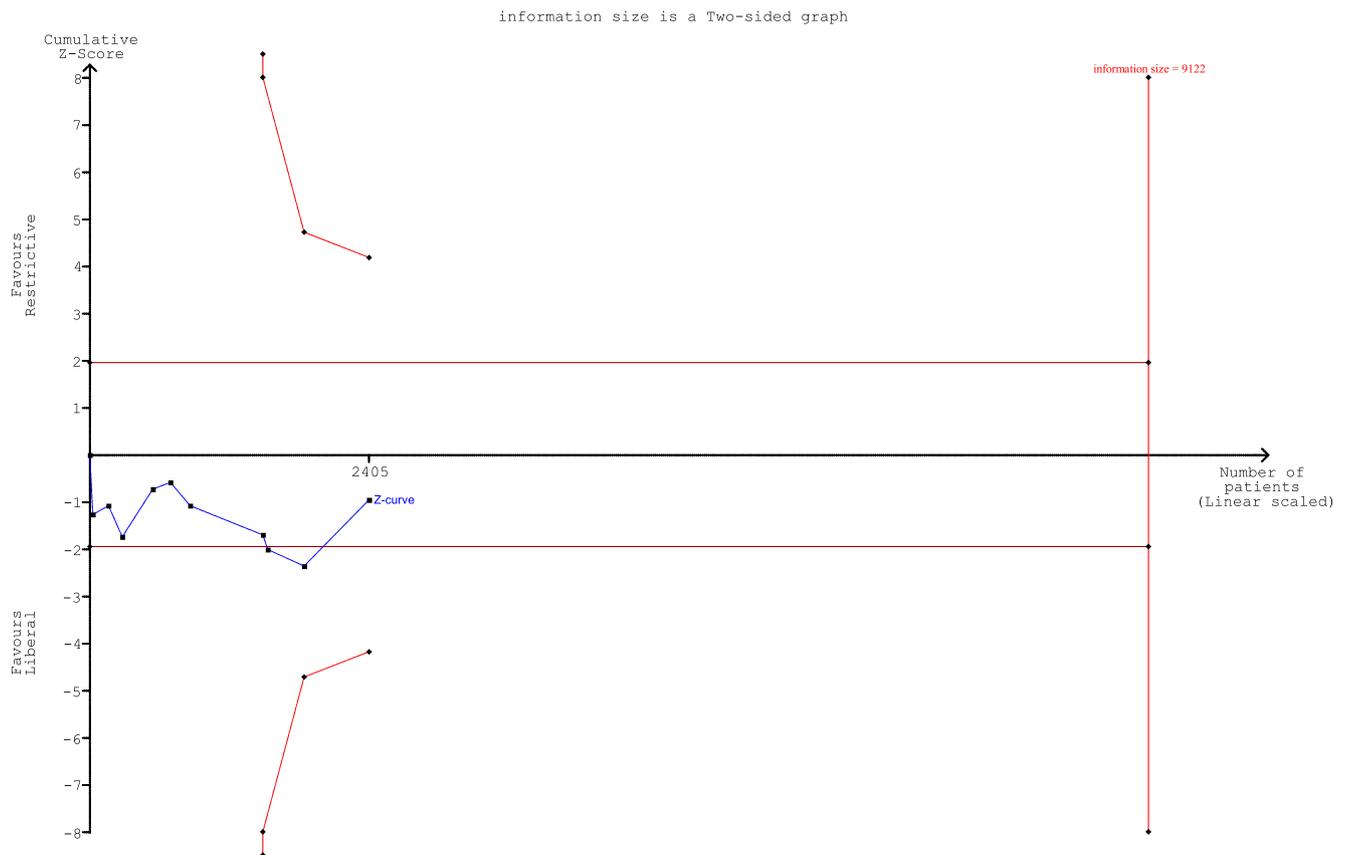


Fig. 14 Trial sequential analysis for wound infection. The required sample size to detect significant wound infection differences was calculated as 9122 participants. The cumulative Z curve was not crossed with 2405 participants

One strategy to answer this question would be the conduct of a large scale randomised controlled trial. This is likely to be impractical due to difficulties in recruitment, changes in surgical practice towards minimally invasive or robotic techniques and differences in resection strategies between centres. The establishment of a pancreatic surgical registry or the modification of pre-existing registries akin to the legion of Orthopaedic Arthroplasty data repositories to collect data on fluid management may be an achievable option. Although this is clearly retrospective cohort data, it becomes a powerful tool in collating and analysing predictors of complications with a low background incidence. This is clearly not just the domain of the anaesthesiologists who administer the fluid in the operating room; rather, it could be seen as an area where collaboration occurs between the surgeons who manage the patients and their complications, anaesthesiologists and critical care physicians who can alter a patient's fluid balance in the hours and days after surgery.

Goal-directed fluid management strategies as they currently stand lack easily measurable and minimally invasive targets against which to direct therapy. Further developments in applied physiology including the use of patient specific rather than population metrics may positively contribute to the management of surgical patients. Until these advances have been

made, individualisation of fluid therapy rather than adherence to dogma should be strongly considered.

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HSM participated in study conception and design, analysis, drafting of the article, and critical revision of the manuscript.

ADM participated in study conception and design and critical revision of the manuscript.

SAM participated in study conception and design, acquisition of data, and critical revision of the manuscript.

NJL participated in study conception and design, acquisition of data, analysis, interpretation of data, drafting of the article, and critical revision of the manuscript.

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