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Research Article

Effect of the Type of Intraoperative Restrictive Fluid Management on the Outcome of Pancreaticoduodenectomy: A Systematic Review and Meta-Analysis

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Background. The perioperative management of pancreaticoduodenectomy is complicated, and the significant morbidity and mortality may be influenced by the method of intraoperative fluid management. Whether intraoperative restrictive fluid therapy can affect the outcomes of pancreaticoduodenectomy or not is controversial. *Methods*. PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov were searched for prospective and retrospective studies comparing restrictive and liberal intraoperative fluids in patients undergoing pancreaticoduodenectomy. Following study identification, a systematic review and meta-analysis were performed. *Results*. Fourteen studies, including six prospective trials and eight retrospective studies, involving 2,596 patients, were included. Intraoperative restrictive fluid regimens had no effect on the mortality compared to liberal fluid regimens in the overall cohort (odds ratio [OR]: 1.39; 95% confidence interval [CI]: 0.82–2.35, $p = 0.773$). Liberal fluid regimens could increase the risk of pulmonary adverse events (OR: 1.66; 95% CI: 1.10–2.50, $p = 0.131$) and prolong the length of hospital stay (SMD -0.10; 95% CI -0.19– -0.01, $p = 0.375$). There were no significant differences in the incidence of pancreatic fistulas. *Conclusions*. Restrictive fluid regimens have a slight effect on the outcomes of pancreaticoduodenectomy. The clinical relevance of this finding needs to be interpreted. The existing evidence may not be adequate; therefore, further studies are warranted.

1. Introduction

Although great efforts had been put into decreasing the morbidity and mortality of pancreaticoduodenectomy (PD), they remain critical concerns to the surgeons and anesthesiologists [1]. The amount of intraoperative fluid might affect the surgical outcome [2]. Theoretically, the intravenous fluid overload may lead to tissue edema, increase the oxygen transfer distance, thus increasing the risk of multiorgan failure and poor surgical-site healing, eventually leading to postoperative complications and a prolonged length of hospital stay (LOS). Conversely, intraoperative hypovolemia could increase the risk of tissue hypoperfusion, leading to organ dysfunction. Thus, little or excess fluid administration is detrimental, and optimal fluid management should aim for a net fluid balance of zero. In the clinical practice, the intraoperative fluid amount is determined by the anesthesiologist's judgment and may considerably change across institutions because of the absence of standard guidelines providing optimal recommendations [3].

Controversial conclusions on this topic existed for a long time, as the most important issue in this field may be the absence of a definition for "restrictive" and for "liberal." In 2002, a small randomized trial reported delayed return of gastrointestinal function and increased LOS in patients with excess water and salt balance [4]. This finding paved the way for a series of trials assessing the impact of restrictive perioperative fluid management in surgical patients [5–7]. While some subsequent trials supported the original findings, demonstrating a reduction in postoperative complications and LOS in patients managed with a restrictive fluid regimen [8], other studies failed to reproduce the benefits

of fluid restriction on postoperative outcomes [9, 10], and some even demonstrated harm [8]. Approximately a decade ago, as a key component of enhanced recovery after surgery (ERAS [11]) theory, perioperative fluid restriction, which may improve the outcomes, had become a perioperative care guideline, with the aim to promote early recovery among patients undergoing major surgery. However, evidences supporting the ERAS theory were derived from colorectal procedures [4], and whether patients undergoing other major abdominal surgeries could benefit from fluid restriction or not was unclear. Although the effect of restrictive fluid regimen on PD was not reported separately, the Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial, which was a high-quality international, randomized, assessor-blinded trial, found that a restrictive fluid regimen was not associated with a higher rate of disability-free survival compared to a liberal fluid regimen for patients undergoing major abdominal surgeries [12].

These publications have generated interest as well as fueled controversy on intraoperative fluid management in patients undergoing PD [13, 14]. Currently, the opinions and practice of intraoperative fluid management in PD varies significantly, as there is no precise definition of a restrictive or liberal fluid regimen. Earlier, meta-analyses had shown lower mortality compared to the liberal intraoperative fluid management strategy [14], but the included studies might not be suitable for this topic.

The aim of the present systematic review and meta-analysis was to critically synthesize past and new evidence comparing restrictive and standard or liberal intraoperative fluid managements in patients undergoing PD to find an association between the restrictive intraoperative fluid management and postoperative outcomes in PD and provide guidance to clinical anesthesiologists.

2. Materials and Methods

This present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guideline.

2.1. Search Strategy and Study Selection. This study could not be registered on a review database because of a competing meta-analysis. PubMed, EMBASE, Cochrane Library, and clinicaltrials.gov were searched from January 1, 1990, to June 31, 2019. Studies were identified through a comprehensive search strategy. The following medical subject headings and keyword terms were used for the search: "Pancreaticoduodenectomy," "Pancreatectomy," "Whipple," and "Fluid." No language limitations were applied. The reference lists of identified studies and meta-analyses on related topics were searched for other eligible studies. Citations were first screened for inclusion based on titles and abstracts. Subsequently, full texts of the remaining citations were screened to generate a list of included studies. Both levels of screening were independently performed by two reviewers (J.W. and X.A.). Disagreements between reviewers were resolved with a discussion or by a senior author (L.P.).

2.2. Eligibility Criteria. The eligibility criteria were prospective and retrospective studies involving patients undergoing PD in which the outcomes had been stratified into restrictive and liberal intraoperative fluid management regimens. The outcomes of eligible studies included postoperative pancreatic fistulas (POPFs), LOS, overall complications, and mortality (in-hospital, 30 or 90 days). Studies that included fluid restriction as a part of clinical management regimens were also included if they met the other inclusion criteria. Studies in which outcomes of interest were not evaluated or not stratified based on the amount of fluid were excluded. Nonhuman studies, case–control studies, case reports, case series, studies of poor quality with a high risk of bias, and other article types (editorials, commentaries, and letters) were also excluded.

2.3. Data Extraction and Bias Assessment. Data were extracted by one reviewer (J.W.) and checked for accuracy by another (X.A.). Discrepancies were resolved through a consensus. The following information was extracted from each included study: date of publication, study design, study objective, dates of included data, patient and surgical details (including age, sex, and type of surgery), 30-day mortality, LOS, overall morbidity, presence of POPFs, delayed gastric emptying, wound infection, and cardiac and pulmonary complications, and the Clavien-Dindo class. Authors were contacted for details of the data when a published manuscript was lacking information or contained unclear information.

The risk of bias and study quality of the included studies was assessed by two reviewers (W.S. and Z.F.). In the event of discrepancies in the classification of study bias, the findings were discussed, and a consensus was reached. The Cochrane Collaboration's tool was used for assessing the risk of bias in randomized controlled trials (RCTs) [15], while the Methodological Index for Non-Randomized Studies (MINORS) was used for observational studies. Studies with a MINORS score of C17 were considered high-quality, as previously published. Retrospective and prospective studies with a high or unclear risk of bias were considered low-quality [16].

2.4. Data Analysis. RCTs and high-quality retrospective observational studies were included for a meta-analysis, which was performed using STATA 14 (StataCorp, USA). Dichotomous variables were analyzed using the Mantel–Haenszel method and expressed as the odds ratio (OR) and 95% confidence interval (CI). Continuous variables were analyzed using the inverse variance method and expressed as the standard mean difference (SMD) and 95% CI. For LOS expressed as the median and range, the mean and standard deviation were estimated using published methods. All analyses were first performed using the fixed-effects model. Study heterogeneity was assessed using the I^2 statistic: <25%, 25%–50%, and >50% were considered low, moderate, and high statistical heterogeneities, respectively. In cases of a high statistical heterogeneity, the random-effects model was used. p values < 0.05 were considered statistically significant in all analyses.

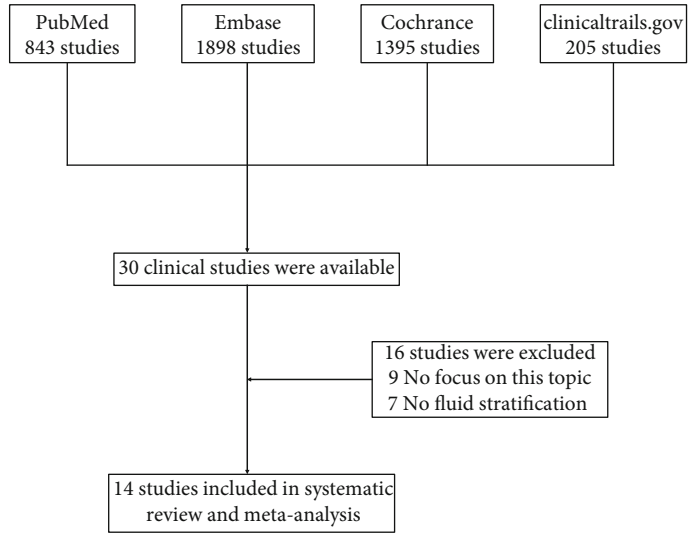

Figure 1: Flow diagram of study selection.

3. Results

3.1. Data Extraction. The literature search on PubMed, Embase, Cochrane Library, and clinicaltrials.gov yielded 843, 1,898, 1,395, and 205 studies, respectively. Subsequently, a review of abstracts led to the retrieval of 30 full-text articles to assess the eligibility (Figure 1). Finally, 16 studies were excluded from the meta-analysis, of which 9 had not focused on the intraoperative fluid restrictive management for PD and 7 had not included stratification based on the intraoperative fluid regimen. This yielded 14 studies (five prospective trials and eight retrospective studies), involving 2,596 patients, including 1,284 patients in the restrictive group and 1,312 patients in the control group. Table 1 summarizes the characteristics of the included studies.

Of the six prospective studies, four reported adequate sequence generation and allocation concealment, one reported adequate blinding of participants and outcome assessors, and one allocated the patients based on the observed fluid balance (Table 2). All eight retrospective studies reported adequate selection and representativeness, outcome assessment, and follow-up (Table 3).

3.2. Main Results. No association between restrictive fluid regimens and reduction in mortality was found in the overall cohort (OR: 1.39; 95% CI: 0.82–2.35, $p = 0.773$; Figure 2). Compared to the liberal fluid regimens, restrictive fluid regimens could reduce the LOS (SMD: 0.10; 95% CI: -0.19–-0.01, $p = 0.375$; Figure 3) after excluding two studies with no LOS data. POPF was analyzed in 11 studies and showed no discrepancies between the two groups (Figure 4). The pulmonary complications were analyzed in eight studies, showing that the liberal fluid regimens could increase the risk of pulmonary adverse events (OR: 1.66; 95% CI: 1.10–2.50, $p = 0.131$; Figure 5).

The heterogeneity was low (<25%) for mortality, LOS, cardiac complications, and POPF and moderate (25–50%) for pulmonary complications. There was no evidence of publication bias on visual inspection of the funnel plot for LOS data or with Egger's test ($p = 0.626$; Figure 6).

4. Discussion

This meta-analysis of restrictive versus liberal fluid therapies revealed that the intraoperative restrictive fluid management regimen in patients undergoing PD might not reduce the mortality or POPF but might reduce LOS and pulmonary complications. The major result of mortality in this study was similar to a recently published RELIEF study [12] but different from a previous meta-analysis [14]. The results of our study suggest that patients undergoing PD may benefit from the restrictive fluid regimen.

The intraoperative fluid management for patients undergoing abdominal surgery had been controversial for decades. Despite Moore and Shires' prescient concept called "moderation," which was proposed more than 50 years ago [27], fluid restriction for surgical patients had not been widely accepted because of the concern regarding underresuscitation, until the ERAS theory became widespread [11]. It had been hypothesized that the intraoperative fluid overload could increase lung tissue edema, which is associated with various postoperative lung complications and may also cause pancreatic anastomosis tissue edema, thus resulting in ischemia and poor healing, and finally, POPF. In contrast, excessive fluid restriction may reduce the intravascular volume and reduce the intraoperative oxygen supply to the tissue, which may impede wound healing, particularly in cases of vasopressor use to maintain tissue perfusion [22]. After the concept of ERAS had been accepted, it seemed that moderation rather than extremes of fluid balance would lead to better patient outcomes. However, excessive resuscitation may be associated with various complications, such as delayed gastric emptying, cardiopulmonary events, and anastomotic complications, as suggested by several clinic trials [8]. Therefore, the best intraoperative fluid management regimen has not been determined.

Table 1: Baseline characteristics of included studies.

Author	Published year	Study type	Age (mean)	ASA ≥ III (%)	Surgical procedure	Restrictive fluid	Liberal fluid	Restrictive group (*n*)	Liberal group (*n*)	Total (*n*)	Mortality
Michal Barak [7]	2006	Prospective study	61	63	PD	Balance 0 to +1000 ml	Balance +1000 to +2000 ml	14	18	32	30-day mortality
Mary Fischer [17]	2010	Prospective study	64.5	28	PD	3900 ml	6250 ml	65	65	130	90-day mortality
Marcovalerio Melis [9]	2011	Retrospective analysis	66.4	49	PD	<6000 ml	>6000 ml	86	102	188	30-day mortality
Oliver S. Eng [18]	2013	Retrospective analysis	64.5	NR	PD	<13.5 ml/kg/hr	>13.5 ml/kg/hr	62	62	124	30-day mortality
Sizhen Wang [19]	2014	Retrospective analysis	53.5	35	PD	<8.2 ml/kg/hr	>8.2 ml/kg/hr	90	57	147	In-hospital
Ganapathy van Samkar [20]	2015	Prospective study	NR	4	P	5 ml/kg/hr	10 ml/kg/hr	34	32	66	In-hospital, 6-year mortality
Florence Grant [10]	2016	Prospective study	65	42	P	6 mL/kg/h	12 mL/kg/h	166	164	330	In-hospital, 60-day mortality
Mark A. Healy [8]	2016	Retrospective analysis	67.1	77	P	<10 ml/kg/h	>15 ml/kg/h	167	152	319	30-day mortality
Birte Kulemann [21]	2017	Retrospective analysis	66	35	PD	<6000 ml	>6000 ml	304	249	553	In-hospital
In Woong Han [22]	2017	Retrospective analysis	62	NR	PD	Actual IOF < planned IOF	Actual IOF ≥ planned IOF	84	98	182	30-day mortality
Laurence Weinberg [23]	2017	Retrospective analysis	66	33	P	4.7 ml/kg/h	7.8 ml/kg/h	47	98	145	30-day mortality
Laurence Weinberg [24]	2017	Prospective study	65	73	PD	2050 ml	4088 ml	26	26	52	NR
Preetjote Gill [25]	2017	Retrospective analysis	64	28	PD	<10 mL/kg/h	>10 mL/kg/h	76	126	202	30-day mortality
Stefano Andrianello [26]	2018	Prospective study	65	30	PD	2500 ml	3700 ml	63	63	126	In-hospital

PD: pancreaticoduodenectomy; P: all pancreatectomy included; NR: not reported; IOF: intraoperative fluid.

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

Author	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall risk of bias
Michal Barak	H	H	H	H	H	H	High
Mary Fischer	L	H	U	L	L	L	Low
Ganapathy van Samkar	L	L	L	L	L	L	Low
Florence Grant	L	H	L	L	L	L	Low
Laurence Weinberg	L	H	L	L	L	L	Low
Stefano Andrianello	U	L	L	L	L	L	Low

H: high risk; L: low risk; U: unclear.

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

Author	Selection	Comparability	Outcome	Overall risk of bias
Marcovalerio Melis	4	1	3	High
Oliver S. Eng	4	2	3	High
Sizhen Wang	4	1	3	High
Mark A. Healy	4	2	2	High
Preetjote Gill	4	2	3	High
Laurence Weinberg	4	1	3	High
In Woong Han	4	1	3	High
Birte Kulemann	4	2	3	High

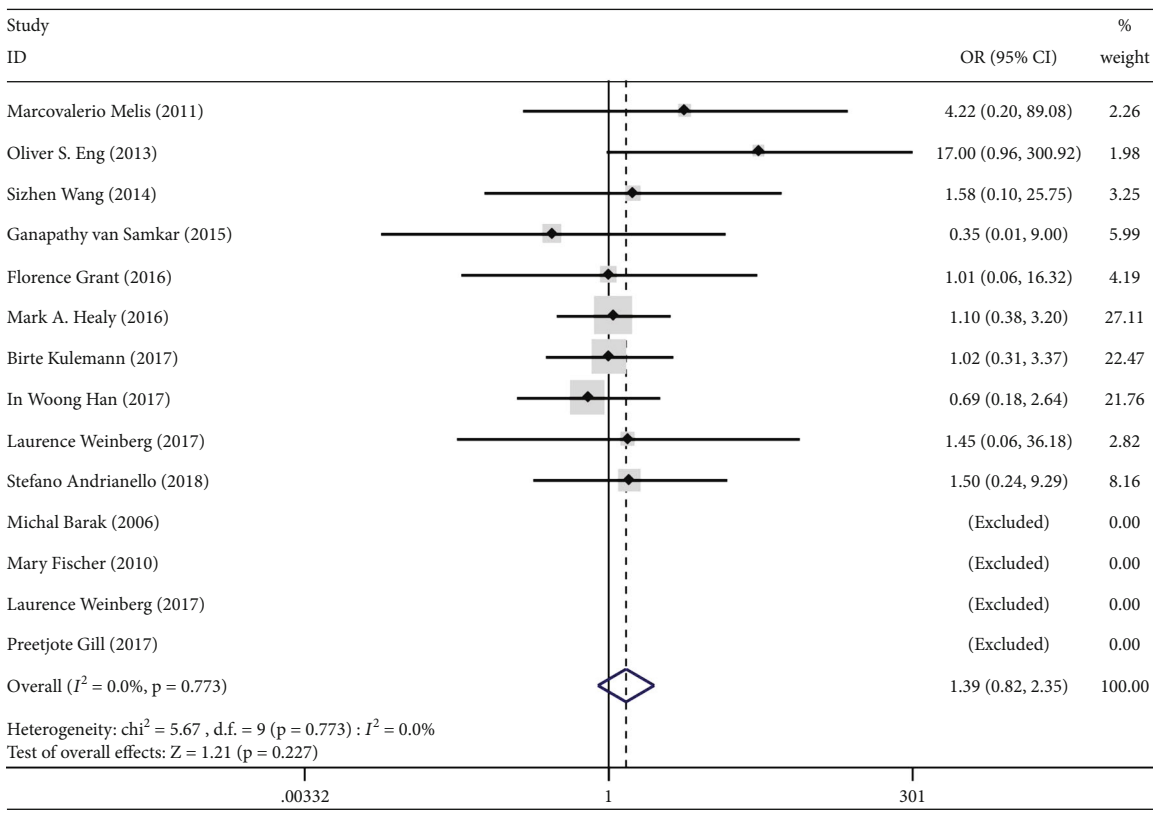

Figure 2: Forest plot for mortality.

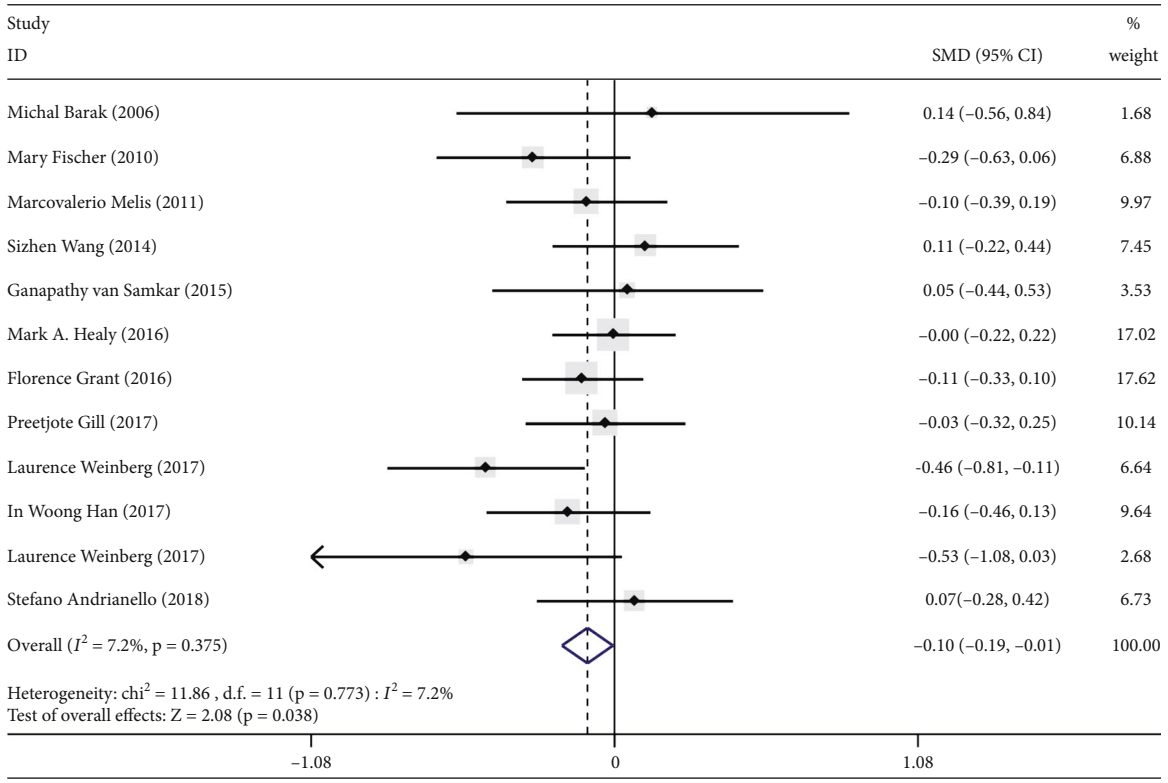

Figure 3: Forest plot for length of stay.

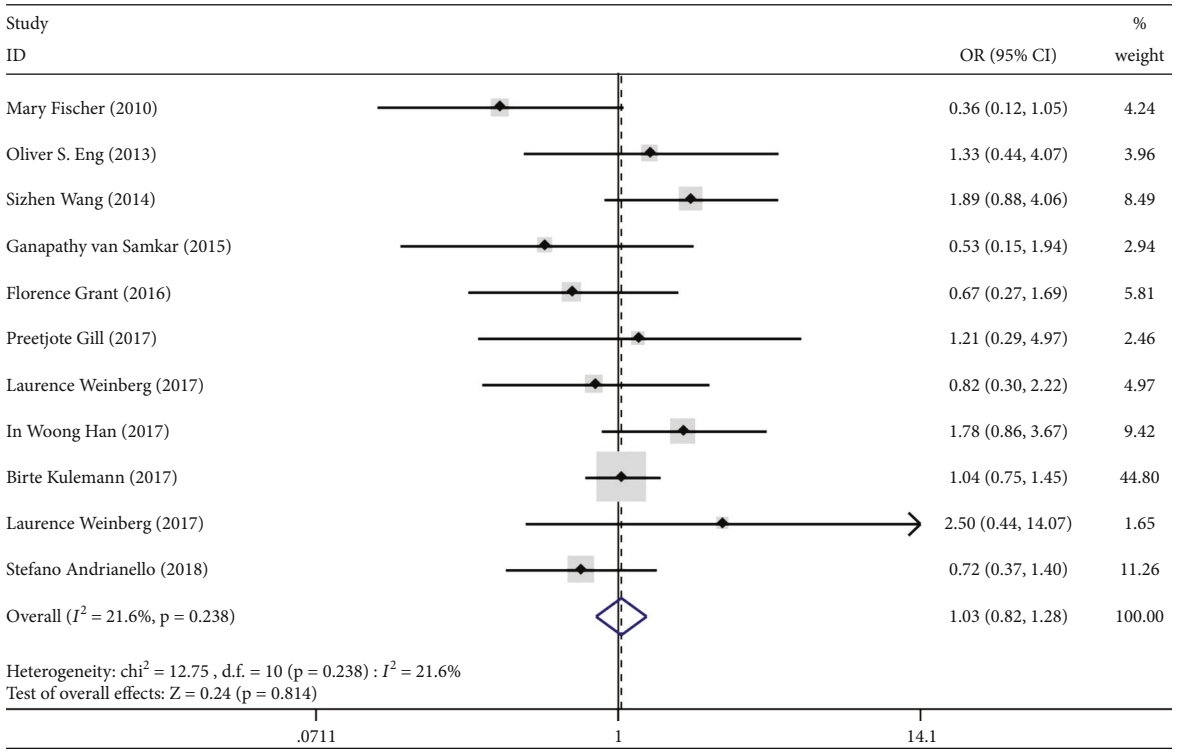

Figure 4: Forest plot for pancreatic fistula.

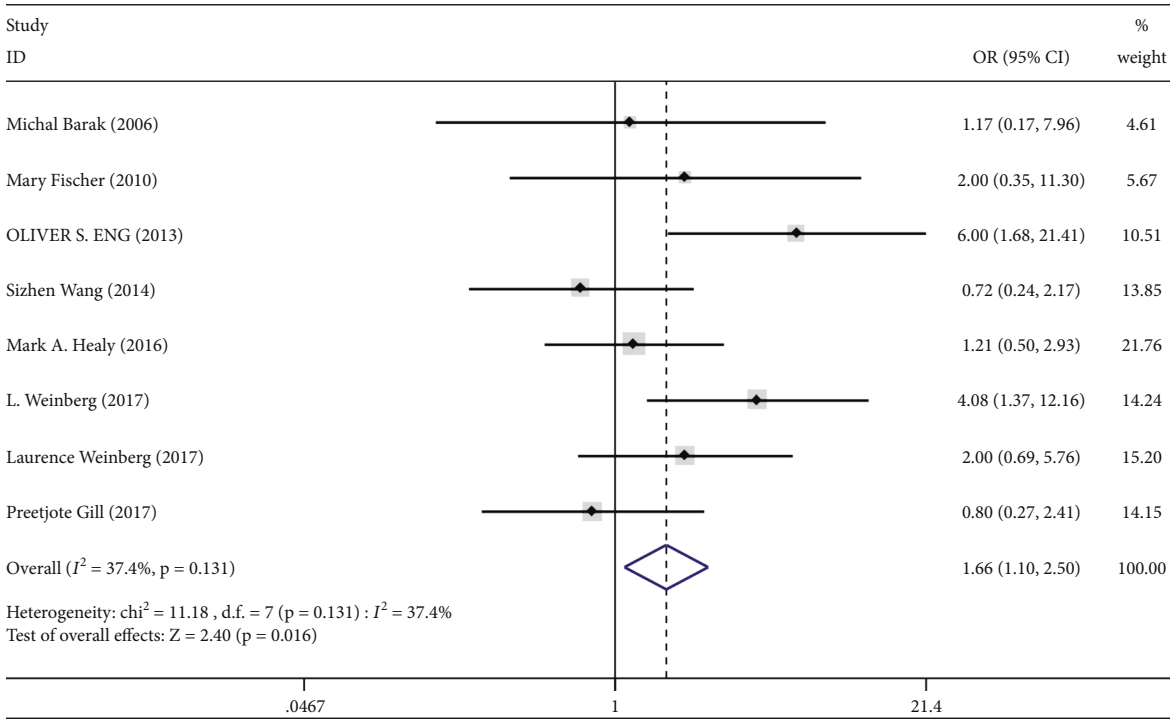

Figure 5: Forest plot for pulmonary complications.

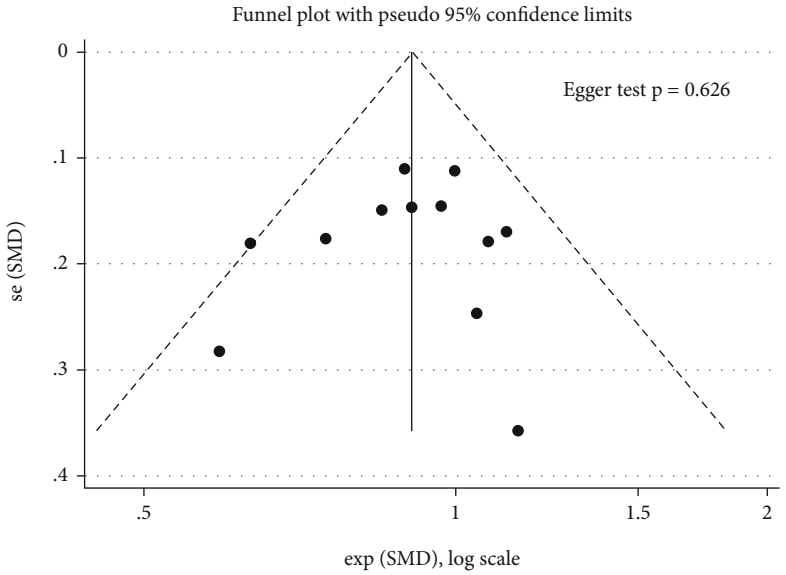

Figure 6: Funnel plot for LOS with nonsignificant Egger's test suggesting no publication bias. Eggers test = 0.32.

Moreover, PD is practically the most complex major abdominal operation, associated with high morbidity rates of 40%–60% [1]. Therefore, the optimal intraoperative fluid management regimen, aimed at reducing the mortality and morbidity of the patient, has been a critical issue to the surgery team comprising of a surgeon and an anesthetist.

Existing evidences on this topic have been inconsistent. For example, the sample size and amount of intraoperative fluid varied widely among the 14 studies included in this meta-analysis across 12 years, leading to diverse conclusions. Eleven studies suggested that the intraoperative fluid management would reduce the postoperative complications [7, 8, 17–19, 21–26], while the other three studies revealed no differences in the overall morbidity between the two groups [9, 10, 20]. Only one study reported associations of the restrictive strategy with decreased mortality and LOS [8], and one study reported an association of the restrictive strategy with grade 1 complications [8].

The diversity in conclusions might be due to the heterogeneity of the study type, study protocol, etc. Moreover, the

lack of a precise definition of restrictive or liberal fluid regimen is an important factor. Therefore, the amounts of intraoperative fluid administration in all individual study may be overlapping. For example, in the study by van Samkar [20], the patients received 5 and 10 mL/kg/h of fluid in the restrictive fluid and liberal fluid groups, respectively, but both groups in the study by Eng were defined as the restrictive fluid group (<13.5 mL/kg/h) [18]. The vague definition of restrictive fluid regimen is a crucial reason behind the debate and controversy.

There was a discrepancy in the results of mortality of each included study, and the pooled analysis suggested no statistically significant difference between the restrictive and liberal fluid therapies. This result was not the same as a previous meta-analysis [14], which may be because of the discrepancy between the included studies. We included all the studies that met our criteria and had available full texts. One study mentioned in the previous meta-analysis was not found in the database that we searched. We excluded one study that evaluated the effect of hypertonic saline within a restrictive fluid regimen after a discussion, as the main objective of that study was focused on hypertonic saline rather than the restrictive fluid regimen [28]. We excluded another study in which the patients and outcomes were stratified based on the fluid balance quartile [29].

The clinical rationale of our results is the following: (1) the procedure of PD is extremely complicated; therefore, mortality and POPF mainly depends on the proficiency of the surgery team. Garland et al. suggested that the volume of facilities might affect the mortality of patients undergoing PD [14], which might be consistent with our viewpoint. (2) The protopathic diseases that lead to PD (such as malignancy) may influence the adverse outcome. In such cases, the fluid regimen as a part of the perioperative management strategies may not play a decisive role in the mortality. (3) With the development of an integrated management strategy, contemporary estimates of the mortality of PD has reduced to approximately 2% [21], which is consistent with our pooled result (2.16% [55/2,544]). This may be the lowest mortality rate in history. We thought that new revolutionary technologies or strategies could lower the current mortality rather than the fluid regimen alone.

In this meta-analysis, two studies that focused on a goal-directed therapy (GDT) [23, 24] were included because the outcomes could be stratified based on restrictive and liberal intraoperative fluid management regimens. Although the GDT regimen has advantages, its practicability in developing countries is doubtful. Furthermore, evaluating the advantages and disadvantages of GDT was beyond the scope of this study.

Consistent with a previous meta-analysis [14], a limitation of our study was the heterogeneity and bias resulting from the inclusion of studies with varying study designs. There was no other choice because of the few studies on this topic. We did not perform subgroup analyses or trial sequential analyses, because the sample size suggested by a previous meta-analysis [14] could not be achieved. Moreover, despite calculating the results of interest, we could not obtain a distinct conclusion on the precise definition of restrictive fluid regimen.

In conclusion, the intraoperative restrictive fluid management regimen in patients undergoing PD might not reduce the mortality or POPF but might reduce the LOS and pulmonary complications.

Data Availability

All data, models, and code generated or used during the study appear in the submitted article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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