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Review

Internal pancreatic duct stent does not decrease pancreatic fistula rate after pancreatic resection: a meta-analysis

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Pancreatic anastomosis;
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Meta-analysis

Abstract

BACKGROUND: The use of an internal pancreatic duct stent to improve postoperative outcomes of pancreatic anastomosis remains a matter of debate.

METHODS: A meta-analysis including comparative studies providing data on patients with and without internal stenting during pancreaticojejunostomy anastomosis was performed.

RESULTS: Seven articles including 724 patients were identified for inclusion: 1 randomized controlled trial, 1 quasi–randomized controlled trial, and 5 observational clinical studies. The meta-analysis revealed that there were no significant differences between groups regarding operative outcomes. The use of an internal pancreatic duct stent was not associated with a statistically significant reduction in pancreatic fistula ($P = .31$), hospital mortality ($P = .64$), or delayed gastric emptying ($P = .17$), but it was associated with a higher risk of pancreatic fistulas in soft pancreases ($P = .05$) and overall morbidity ($P = .04$).

CONCLUSIONS: The current literature suggests that the use of an internal pancreatic duct stent does not help to reduce the leakage rate of pancreatic anastomosis after pancreatic resection, and it may increase the risk of pancreatic fistulas in soft pancreases.

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Pancreaticoduodenectomy is the primary means of treating various benign and malignant diseases of the pancreatic head and periampullary region. Associated mortality rates have dropped dramatically in the past decade, but morbidity rates remain high.[1,2] Despite a significant amount of research, postoperative leakage of pancreatic anastomoses, possibly leading to postoperative pancreatic fistulas, continues to be the most frequent and potentially the most life-threatening complication.[3] In addition, pancreatic fistula can be associated with additional complications such as intra-abdominal hemorrhage and abscess, which lead to a prolonged hospital stay. A pancreatic fistula rate of 10% to 20% after pancreaticoduodenectomy has been reported even in high-volume centers, and it has not declined significantly in the last 30 years.[4–6]

Surgeons have attempted to reduce the incidence of pancreatic fistulas by numerous surgical modalities, such as the use of the duct-to-mucosa technique, stapling off the transected end

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of the pancreas, omental wrapping of the anastomosis, early removal of the drain, and other various techniques.[7–11] Another technical modification in pancreatic anastomosis is the use of a transanastomotic stent for the internal drainage of pancreatic secretion. Theoretically, a stent may help divert away the pancreatic secretion from the anastomosis, and it allows more precise placement of sutures, thus protecting the pancreatic duct from suture injury and reducing the risk of iatrogenic pancreatic duct occlusion, but studies on the outcome of patients who underwent internal stenting for pancreaticoduodenectomy are scarce and their results are inconsistent.[12–18] In such circumstances, a meta-analysis providing a critical appraisal of the available evidence might be helpful to obtain more precise estimates of treatment efficacy and safety. Therefore, we conducted a meta-analysis of current studies to evaluate the perioperative outcome and survival of patients who underwent internal stenting during pancreaticoduodenectomy.

Methods

Literature search

To identify relevant studies, we searched the medical literature for articles published up to January 31, 2012, using MEDLINE (from 1966), EMBASE (from 1980), and the Cochrane Database of Systematic Reviews. The search terms included "stent," "stents," "stenting," "pancreaticoduodenectomy," "pancreaticojejunostomy," "Whipple," and "pancreatic resection." In addition, the reference lists of relevant articles were manually searched to find other potentially eligible studies. No language restriction was imposed.

Study selection

The titles and abstracts of the search findings were screened for potentially eligible studies. We included all cohort studies (prospective or retrospective) and all case-control studies that evaluated internal stenting for pancreaticoduodenectomy. We excluded reviews, comments, letters, case reports, and articles with less than 10 patients who underwent internal stenting for pancreaticoduodenectomy. To be included in the meta-analysis, studies had to cite the odds ratio (OR) or relative risk of postoperative outcomes by internal stenting or provide sufficient data to allow us to calculate it.

Data abstraction and quality assessment

Two reviewers (Z.Y. and Q.B.Z.) independently extracted the following data from each study: first author, year of publication, study period, study design, sample size, baseline characteristics of the study cohort, number of subjects operated on with each procedure, definition of pancreatic fistula, number of pancreatic leaks, number of delayed gastric emptying, wound events, bile leak, intra-abdominal abscess, intra-abdominal collection, hemorrhage, morbidity, hospital mortality rate, and length of hospital stay.

The randomized controlled trials (RCTs) were scored using the Jadad composite scale,[19] which evaluates studies based on appropriate randomization, proper blinding, and an adequate description of withdrawals and dropouts. The nonrandomized studies were scored on the following basis: prospective versus retrospective data collection, assignment to stenting or nonstenting by means other than surgeon preference, and an explicit definition of pancreatic fistula (studies were given a score of 1 for each of these areas, score 1–4).[20]

Data analysis

Meta-analyses were performed for studies that provided comparative data on the outcomes of patients who underwent pancreaticoduodenectomy with or without internal stents. Subgroup analyses were conducted if necessary. The OR was chosen as an effect measure for dichotomous outcomes and a weighted mean difference (WMD) for continuous variables, which were reported along with the corresponding 95% confidence intervals (CIs). All results were investigated for clinical and statistical heterogeneity. Clinical heterogeneity was defined as the existence of an inhomogeneous study population, the variability of interventions, and the insufficient definition of outcome parameters or major variability in perioperative management. Clinical heterogeneity was explained when appropriate and possible. Statistical heterogeneity was explored by inspection of the forest plot and I^2 statistic; an I^2 value of more than 50% was considered to indicate high statistical heterogeneity.[21] According to whether the studies had given a clear definition of the outcome parameter, data were calculated by using the random effects model or the fixed effects model (Review Manager, Version 5.1 for Windows; The Cochrane Collaboration).

Results

The literature search yielded a total of 523 studies. After detailed assessment, 7 studies were detected that matched the eligibility criteria for inclusion in this meta-analysis (Table 1). There were 5 observational clinical studies, 1 RCT, and 1 quasi-RCT. In total, these studies included 724 patients: 379 in the internal stenting group and 345 in the nonstenting group. Two identified studies were conducted in the United States, 2 in Japan, 1 in Greece, 1 in Hong Kong, and 1 in Taiwan. The 2 Japanese studies were from the same institution, but only 1 reported the pancreatic fistula rate.

The definition for pancreatic fistulas proposed by the International Study Group on Pancreatic Fistula[2] (ie, the presence of amylase-rich fluid >3 times the upper limit of normal in the serum of any measurable volume on or after postoperative day 3) was used in 5 of the 7 studies.[12–16]

Table 1 Baseline characteristics of studies included in the meta-analysis

Reference	Country	Year	Inclusion period	Study type	Sample size	Group	Patients	M/F	Age
Lai et al[12]	HongKong	2011	1999–2008	Prospective	24/49	Stenting	24	11/13	63.7 ± 12.4
						Nonstenting	25	13/12	60.0 ± 12.7
Suzuki et al[13]	Japan	2011	1990–2006	Retrospective	24/45	Stenting	24	14/10	61.2 ± 2.7
						Nonstenting	21	11/10	62.3 ± 3.4
Smyrniotis et al[14]	Greece	2010	2000–2008	Quasi-RCT	41/82	Stenting	41	26/15	60 ± 10
						Nonstenting	41	24/17	59 ± 11
Suzuki et al[15]	Japan	2009	1990–2006	Retrospective	49/72	Stenting	49	31/18	63.7 ± 1.8
						Nonstenting	72	44/29	66.4 ± 1.5
Winter et al[16]	United States	2006	2004–2005	RCT	115/234	Stenting	115	67/48	63 (27–89)
						Nonstenting	119	65/54	67 (33–88)
Moket al[17]	TaiWan	1999	1991–1998	Retrospective	57/128	Stenting	71	NR	NR
						Nonstenting	57	NR	NR
Grace et al[18]	United States	1986	1975–1984	Retrospective	55/65	Stenting	55	NR	NR
						Nonstenting	10	NR	NR

F = female; M = male; NR = not reported.

The decision on whether to perform the anastomosis with or without a stenting tube was based on the judgments of the surgeons in 5 of the 7 identified studies[12,13,15,17,18] and using an alternating technique or a random number pattern in the other 2 studies.[14,16] Four studies restricted the anastomosis to the end-to-side, duct-to-mucosa method.[12–15] Two studies reported the pancreatic fistula rate in soft pancreases.[15,16] The patient characteristics and perioperative outcomes of patients who underwent pancreaticojejunostomy with and without internal stent are summarized in Tables 1 and 2.

Meta-analysis of operative outcomes

As Table 2 shows, no study showed significant differences in operative time, blood loss, or transfusion requirement. The study by winter et al [16] reported results of operative time and blood loss as median values because the data were not normally distributed; therefore, this study was excluded from the meta-analysis. Another study was excluded because of the different anastomosis method used in each group. Only 2 of the 7 studies were included in the meta-analysis; a meta-analysis of these studies revealed no difference regarding the operative time (WMD = 5.33; 95% CI, −8.56 to 19.23) and blood loss (WMD = −14.02; 95% CI, −173.77 to 145.72). The transfusion requirement was not analyzed because of insufficient data.

Meta-analysis of pancreatic fistula

Data on pancreatic fistulas were available in 6 of the studies. Five of them reported a higher percentage of pancreatic fistulas in the group with internal stents, and only 1 study reported a lower percentage of pancreatic fistulas in the group without internal stents. Overall, pancreatic fistulas were described in 13.8% of patients in the stenting group and 11.1% in the nonstenting group, with no significant difference in favor of stenting or nonstenting in the meta-analysis (reported by 6 trials, OR = 1.28; 95% CI, .39–.81; P = .31). A subgroup analysis of studies involving stenting performed by surgeon preference showed the rate of pancreatic fistulas was 8.0% in the stenting group and 5.5% in the nonstenting group, with no significant difference in the meta-analysis (reported by 4 trials, OR 1.13; 95% CI, .47–2.7; P = .78). A subgroup analysis of studies in which whether to stent a tube or not was not based on the judgements of surgeons showed that the rate of pancreatic fistulas was 8.0% in the stenting group and 5.5% in the nonstenting group, with no significant difference in the meta-analysis (reported by 2 trials, OR = 1.36; 95% CI, 0.76–2.42; P = .3). Another subgroup analysis of studies that standardized the anastomosis method with an end-to-side, duct-to-mucosa method revealed no significant difference (reported by 3 trials, OR = 1.79; 95% CI, .60–5.29; P = .29; Figs. 1 and 2). Soft pancreatic texture was found to be a risk factor for pancreatic fistulas in some studies.[22] A subgroup analysis showed an increased pancreatic fistula rate in patients with soft pancreases among stented patients (reported by 2 trials, OR = 2.03; 95% CI, .99–4.16; P = .05; Fig. 3).

Meta-analysis of the other postoperative outcomes

Overall, hospital mortality was described in 1.8% of patients in the stenting group and 2.3% in the nonstenting group, with no significant difference in the meta-analysis (reported by 4 trials, OR = .74; 95% CI, .21–2.64; P = .64). Morbidity was described in 33.3% of patients in the stenting group and 22.0% in the nonstenting group, with a significant difference in favor of nonstenting in the meta-analysis (reported by 4 trials, OR = 1.74; 95% CI, 1.03–2.94; P = .04).

Table 2 Outcomes of included studies

Reference	Group	Patients	Operation time	Blood loss	Transfusion requirement	PF (%)	PF of soft pancreas (%)	DGE (%)	WI (%)	BL (%)	IAC (%)	IAA (%)	IAH (%)	ReO (%)	Overall morbidity (%)
Lai et al[12]	IS+	24	270.5 ± 56.5	772.9 ± 732.6	NR	16.7	NR	16.7	NR	4.2	16.7	NR	4.0	4.2	45.8
	IS−	25	263.6 ± 61.8	665.3 ± 410.4	NR	16.0	NR	8.0	NR	4.0	4.0	NR	4.0	8.0	40.0
Suzuki et al[13]	IS+	24	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29.1
	IS−	21	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	14.3
Smyrniotis et al[14]	IS+	41	210 ± 30	400 ± 350	14	4.9	NR	4.9	4.9	NR	2.4	NR	2.4	4.9	29.3
	IS−	41	205 ± 40	450 ± 480	19	2.4	NR	7.3	4.9	NR	2.4	NR	2.4	4.9	26.8
Suzuki et al[15]	IS+	49	NR	NR	NR	6.1	12.5	14.3	NR	NR	NR	2.0	2.0	NR	32.7
	IS−	72	NR	NR	NR	1.4	3.3	2.8	NR	NR	NR	5.6	0	NR	15.3
Winter et al[16]	IS+	115	345 (230–680)*	750 (100–3,700)*	0(0–6)*†	27.0	47.4	13.9	13.0	3.5	NR	7.0	NR	4.4	NR
	IS−	119	350(234–600)*	675 (150–2400)*	0(0–5)*†	21.9	33.9	12.6	18.5	2.5	NR	5.1	NR	8.4	NR
Moket al[17]	IS+	71	351±15	NR	NR	4.2	NR	NR	NR	NR	NR	NR	NR	NR	NR
	IS−	57	362±19	NR	NR	1.8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Grace et al[18]	IS+	55	NR	NR	NR	10.9	NR	NR	NR	NR	NR	NR	NR	NR	NR
	IS−	10	NR	NR	NR	30.0	NR	NR	NR	NR	NR	NR	NR	NR	NR

BL = bile leak; DEG = delayed gastric emptying; IAA = intra-abdominal abscess; IAC = intra-abdominal collection; IAH = intra-abdominal hemorrhage; IS+ = internal stenting; IS− = nonstenting; NR = not reported; PF = pancreatic fistula; ReO = reoperation; WI = wound infection.

*Medians with ranges in parentheses.

†Units of transfused red blood cells.

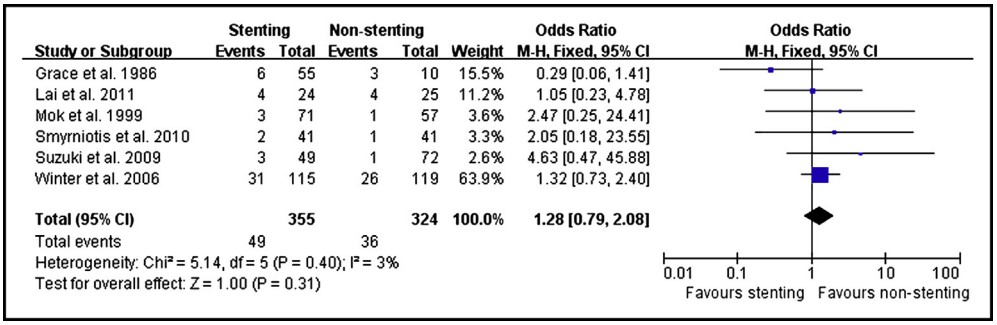


Figure 1 A forest plot depicting the results of the meta-analysis on pancreatic fistulas of 6 studies.

Concerning other complications, there was no significant difference in delayed gastric emptying in the 2 groups (reported by 4 trials, stenting = 12.7%, nonstenting = 8.5%, $P = .17$), wound events (stenting = 10.9%, nonstenting = 15%, $P = .28$), bile leak (stenting = 3.6%, nonstenting = 2.8%, $P = .69$), intra-abdominal abscess (stenting = 5.5%, nonstenting = 5.2%, $P = .96$), intra-abdominal collection (stenting = 7.7%, nonstenting = 3.0%, $P = .24$), and hemorrhage (stenting = 2.6%, nonstenting = 1.4%, $P = .56$). Four studies reported on the length of hospital stay; 2 studies were excluded because the data concerning the hospital stay showed abnormal distribution.[15,16] A meta-analysis of the remaining 2 studies showed that there was no significant difference between the stenting and nonstenting groups in hospital stay ($P = .76$).

Studies standardized pancreaticojejunostomy with a duct-to-mucosa anastomosis

An analysis of 4 studies revealed that internal stent use was not associated with any statistically significant difference in pancreatic fistulas (OR = 1.79; 95% CI, .6–5.29; $P = .29$) or hospital mortality (OR = 1.24; 95% CI, .17–9.08; $P = .83$). Overall morbidity in the stenting group was higher than in the nonstenting group (OR = 1.74; 95% CI, 1.03–2.94, $P = .038$). Delayed gastric emptying was found to be lower in the nonstenting group compared with the stenting group although the difference was not significant (OR = 2.33; 95% CI, .91–5.98; Fig. 4; Table 3).

Publication bias

A funnel plot of studies included in our primary outcome of the pancreatic fistula rate was created to explore publication bias (not shown). This is a scatterplot of the treatment effects estimated from individual studies plotted on the horizontal axis (OR) against the standard error of the estimate shown on the vertical axis standard error estimate (SE). The effect estimate and CIs were shown on the funnel plot and showed a symmetric distribution around the effect estimate, indicating there may be minimal publication bias in the studies.

Comments

This meta-analysis found that there was no benefit with the placement of an internal stent in pancreatic anastomosis for improving postoperative outcomes. In contrast, a trend

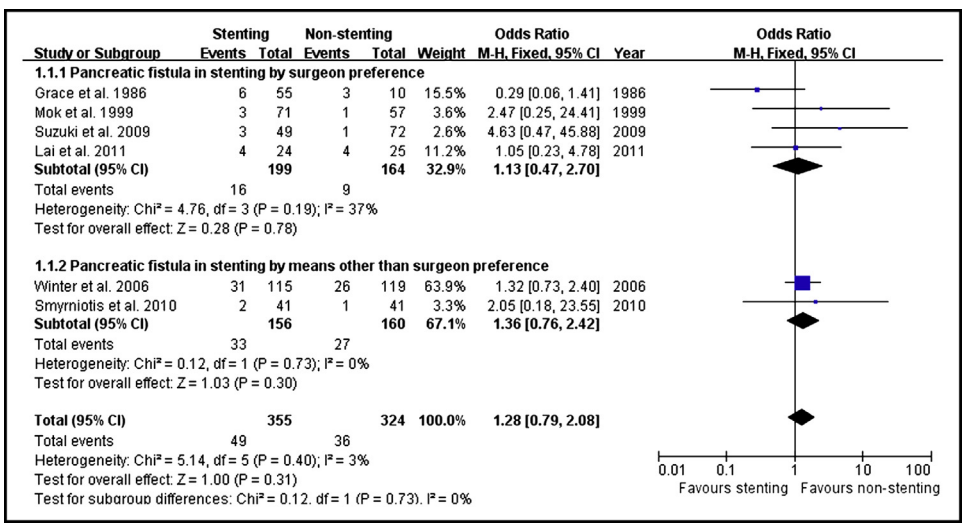


Figure 2 A forest plot depicting the results of subgroup analysis for pancreatic fistulas.

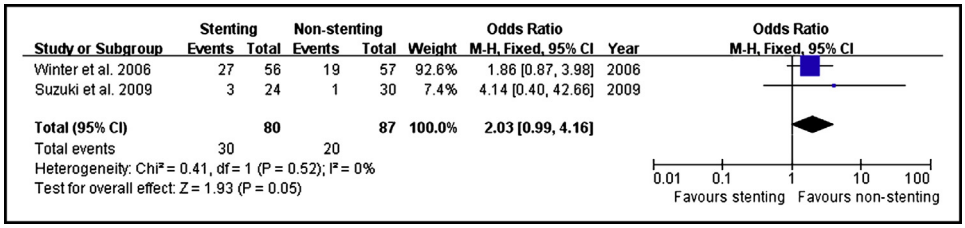


Figure 3 A forest plot depicting the results of the meta-analysis on pancreatic fistulas in soft pancreases.

was observed toward increased pancreatic fistulas in patients with soft pancreatic remnants and stents. Although a number of recent reports have shown that pancreaticoduodenectomy can be performed safely and the mortality rate has been reported to be less than 5%,[23] postoperative complications are still high. The safe anastomosis of the pancreas and gastrointestinal tract after pancreaticoduodenectomy is still a challenge. One of the modifications in pancreaticojejunostomy is the use of internal or external pancreatic duct stents. An internal stent may divert away the pancreatic secretion from the anastomosis, facilitate the placement of sutures during anastomosis, and protect the duct from suture injury.

A controlled study in a canine model showed that the use of an internal stent could prevent anastomotic leakage and occlusion in pancreaticojejunostomy anastomosis.[24] Internal stenting of the anastomosis has been reported to reduce pancreatic fistulas after pancreaticoduodenectomy in some studies.[25,26] Dai et al[27] reported a 0% pancreatic leak rate with the use of an internal pancreatic duct stent in 256 patients; however, these studies did not include a comparative group. In a randomized comparative study by Winter et al,[16] no benefit was observed for pancreatic duct stenting, and the trial was stopped early because of the real possibility that pancreatic stents were causing harm. Other prospective studies with the same anastomosis methods in both the stenting and nonstentings group revealed a higher rate of pancreatic fistula in the stenting group although there were no significant differences between groups in the 2 studies.[12,14] In our experience, migration of the stent is a potential shortcoming, and inserting the stent might harm the pancreatic duct. On the other hand, whether the foreign body effect can stimulate exocrine function is also worth considering.

The recent studies of the effectiveness of nonstent pancreaticojejunostomy and pancreaticogastrostomy showed that duct-to-mucosa anastomosis can decrease pancreatic fistulas regardless of the internal stenting tube.[28,29] In the present study, the meta-analysis of studies using standardized pancreaticojejunostomy with a duct-to-mucosa anastomosis showed that it was useless to stent an internal tube during performing the anastomosis, and the rate of pancreatic fistulas without stenting could be as low as 16% even in the group with an 84% percentage of soft pancreases. Meanwhile, in this analysis, the delayed gastric emptying rate in the stenting group was higher than that in the nonstenting group. Although the exact pathogenesis of delayed gastric emptying remains unproven, some authors found that a clinically relevant pancreatic fistula is one of the independent factors for delayed gastric emptying.[30,31] The results indicate that placing an internal stent is unnecessary during end-to-side, duct-to-mucosa pancreaticojejunostomy.

The accumulated experience concerning the factors involved in fistula formation has shown that a normal soft pancreas is an obvious risk factor[32] because it is very hard to anastomose a narrow pancreatic duct and a fragile parenchyma to the jejunum or stomach and the exocrine function

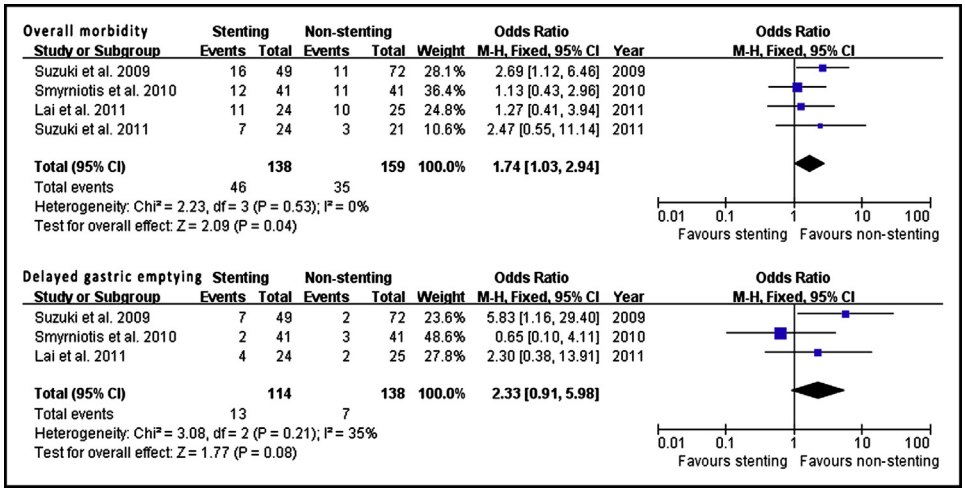


Figure 4 A forest plot depicting the results of the meta-analysis on studies standardizing pancreaticojejunostomy with a duct-to-mucosa anastomosis.

Table 3 Analysis of studies standardizing pancreaticojejunostomy with a duct-to-mucosa anastomosis

Outcomes	Number of studies	Number of patients		OR	95% CI	*P* value	I^2, %
		Stenting	Nonstenting				
Pancreatic fistula	3[12,14,15]	114	138	1.79	.60–5.29	.29	0
Delayed gastric emptying	3[12,14,15]	114	138	2.33	.91–5.98	.08	35
Overall morbidity	4[12–15]	138	159	1.74	1.03–2.94	.04	0
Hospital mortality	3[12,14,15]	114	138	1.24	.17–9.08	.83	0

I^2 = heterogeneity.

of a normal soft pancreas is much stronger than a firm one. Once pancreatic fistula occurs, the healing takes many days because of vigorous pancreatic secretions.[33] Therefore, surgeons may prefer to perform pancreatic anastomosis with stenting in order to prevent a pancreatic fistula. Dramatically, our meta-analysis of the fistula rate in soft pancreases showed an increased rate in patients with soft pancreases among stented patients. In our opinion, it is insufficient for such an internal stent to drain the pancreatic fluid away because the stent is short and does not have active aspiration function itself. Instead, the placement of a stent may stimulate a normal soft pancreas with good endocrine and exocrine function, so that it may cause excess production of pancreatic juice.

One previous meta-analysis by Zhou et al[34] evaluated the effect of external pancreatic duct stents, and it showed that the use of external pancreatic duct stents could reduce the leakage rate of pancreatic anastomosis after pancreatic resection. It should be noted that their pooled study examined the effect of external stents, whereas the present study examined the effect of internal stents. The different results suggest that external stents might be more useful than internal stents in decreasing the pancreatic fistula rate. There some reasons supporting the usefulness of an external pancreatic stent to reduce pancreatic fistulas are the following: (1) stenting a tube in the pancreatic duct allows more precise placement of sutures during pancreatic anastomosis; (2) compared with a short internal stent, an external pancreatic duct could drain pancreatic juice from the anastomosis more completely and prevent activation of pancreatic enzymes by enterokinase in small bowel mucosa soon after surgery; (3) the possibility of radiologic imaging of the anastomotic site in order to visualize a potential fistula[34]; (4) external drainage allows quantitative collection of the pancreatic juice in patients with pancreatic fistulas; and (5) internal stents fall off spontaneously into the bowel lumen at variable postoperative delays, but external stents could decrease the chance of stent migration compared with the use of a short internal stent.[35]

This study has some limitations. It incorporated low-quality studies; most of the data come from nonrandomized studies. Another limitation is that potential publication bias might be present. Authors might be more likely to report positive findings in an international English-language journal and negative findings in a local journal, and studies with significant results are more likely to get published than those with nonsignificant results. In addition, certain studies have attempted to show a benefit of stenting when possibly the improved outcomes could be attributed to their shift toward the performance of the duct-to-mucosa anastomosis rather than the use of transanastomotic pancreatic ductal stents.

In conclusion, the present study showed that the use of an internal pancreatic duct stent cannot reduce the leakage rate of pancreatic anastomosis after pancreatic resection, and it may increase the risk of a pancreatic fistula in a soft pancreas. More evidence from randomized studies is needed, and the impact of stenting on pancreatic fistulas should be discussed in soft and firm pancreases separately.

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