Systematic Review and Meta-Analysis

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An updated systematic review and meta-analysis of the use of octreotide for the prevention of postoperative complications after pancreatic resection

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Abstract

Background: The use of octreotide prophylaxis following pancreatic surgery is controversial. We aimed to evaluate the effectiveness of octreotide for the prevention of postoperative complications after pancreatic surgery through this systematic review and meta-analysis.

Methods: Literature databases (including the MEDLINE, EMBASE, and Cochrane databases) were searched systematically for relevant articles. Only randomized controlled trials (RCTs) were eligible for inclusion in our research. We extracted the basic information regarding the patients, intervention procedures, and all complications after pancreatic surgery and then performed the meta-analysis.

Results: Thirteen RCTs involving 2006 patients were identified. There were no differences between the octreotide group and the placebo group with regard to pancreatic fistulas (PFs) (relative risk [RR] = 0.79, 95% confidence interval [CI] = 0.62–0.99, $P = .05$), clinically significant PFs (RR = 1.01, 95% CI = 0.68–1.50, $P = .95$), mortality (RR = 1.21, 95% CI = 0.78–1.88, $P = .40$), biliary leakage (RR 0.84, 95% CI = 0.39–1.82, $P = .66$), delayed gastric emptying (RR = 0.83, 95% CI = 0.54–1.27, $P = .39$), abdominal infection (RR = 1.00, 95% CI = 0.66–1.52, $P = 1.00$), bleeding (RR = 1.16, 95% CI = 0.78–1.72, $P = .46$), pulmonary complications (RR = 0.73, 95% CI = 0.45–1.18, $P = .20$), overall complications (RR = 0.80, 95% CI = 0.64–1.01, $P = .06$), and reoperation rates (RR = 1.18, 95% CI = 0.77–1.81, $P = .45$). In the high-risk group, octreotide was no more effective at reducing PF formation than placebo (RR = 0.81, 95% CI = 0.67–1.00, $P = .05$). In addition, octreotide had no influence on the incidence of PF (RR = 0.38, 95% CI = 0.14–1.05, $P = .06$) after distal pancreatic resection and local pancreatic resection.

Conclusion: The present best evidence suggests that prophylactic use of octreotide has no effect on reducing complications after pancreatic resection.

Abbreviations: CI = confidence interval, DP = distal pancreatectomy, ISGPF = International Study Group for Pancreatic Surgery, MD = mean difference, PD = pancreaticoduodenectomy, PFs = pancreatic fistulas, POPF = postoperative pancreatic fistula, PPPD = pylorus-preserving pancreaticoduodenectomy, RCTs = randomized controlled trials, RR = relative risk, RRs = risk ratios, SMD = standardized mean difference.

Keywords: meta-analysis, octreotide, pancreatic fistula, pancreatic resection

1. Introduction

Surgery involving the pancreas is performed to treat pancreatic, bile duct, and periampullary malignant diseases, chronic pancreatitis, trauma, and so on. The incidence of complications after pancreatic surgery remains as high as 28% to 58%[1–3] despite constant exploration and striving to improve surgical techniques and intensive care. Pancreatic fistula (PF) and other complications caused by postoperative PF (POPF) are the most important complications after pancreatic surgery and may even lead to death. Various methods have been tried to reduce the incidence of POPF; however, the incidence of PF is not significantly lower than previously.[4–6] Surgeons are constantly exploring different surgical procedures and using different anastomosis instruments and different medicines to prevent complications. One of the most common methods used is prophylactic somatostatin or synthetic somatostatin analogues to decrease the incidence of PF by inhibiting the exocrine secretions of the pancreas.[7–9]

Octreotide is a synthetic octapeptide analogue of endogenous somatostatin with more specific, more potent,

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HZ and JQ have contributed equally to this work as co-first authors.

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and longer-acting inhibitory effects.[10–12] Although many clinical trials have evaluated the function of octreotide to decrease complications after pancreatic surgery, the results of the research are still controversial.[13–15] Despite the disputes regarding octreotide, it is very common to use octreotide to prevent complications in many clinical centers. Therefore, we conducted an updated meta-analysis of randomized controlled trials (RCTs) to further evaluate the effectiveness of prophylactic use of octreotide to prevent complications after pancreatic surgery. We hope to provide the present best evidence regarding if prophylactic octreotide is necessary after pancreatic resection.

2. Methods

Ethical approval or patient consent was not required since the present study was a review of previous published literature.

2.1. Search strategy and selection criteria

We identified relevant studies by searching databases including MEDLINE, EMBASE, and the Cochrane Controlled Trial Register on the Cochrane Library from inception to July 2018. The references of the identified studies were also searched to identify further relevant studies. The research was not restricted by language. We used the following terms and keywords: "pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy or PD or PPPD or pancreatic resection or pancreatectomy or distal pancreatectomy or DP" and "octreotide or octreotide acetate or somatostatin analogue," and "randomized controlled trial or RCT or controlled clinical trial or randomized or clinical trials as topic or placebo or randomly or trial." The inclusion criteria were as follows: the study included all published RCTs that included adults (aged older than 18 years) who underwent surgery involving partial pancreatectomy (surgery for pancreatic cancer, pancreatic-related benign tumors,

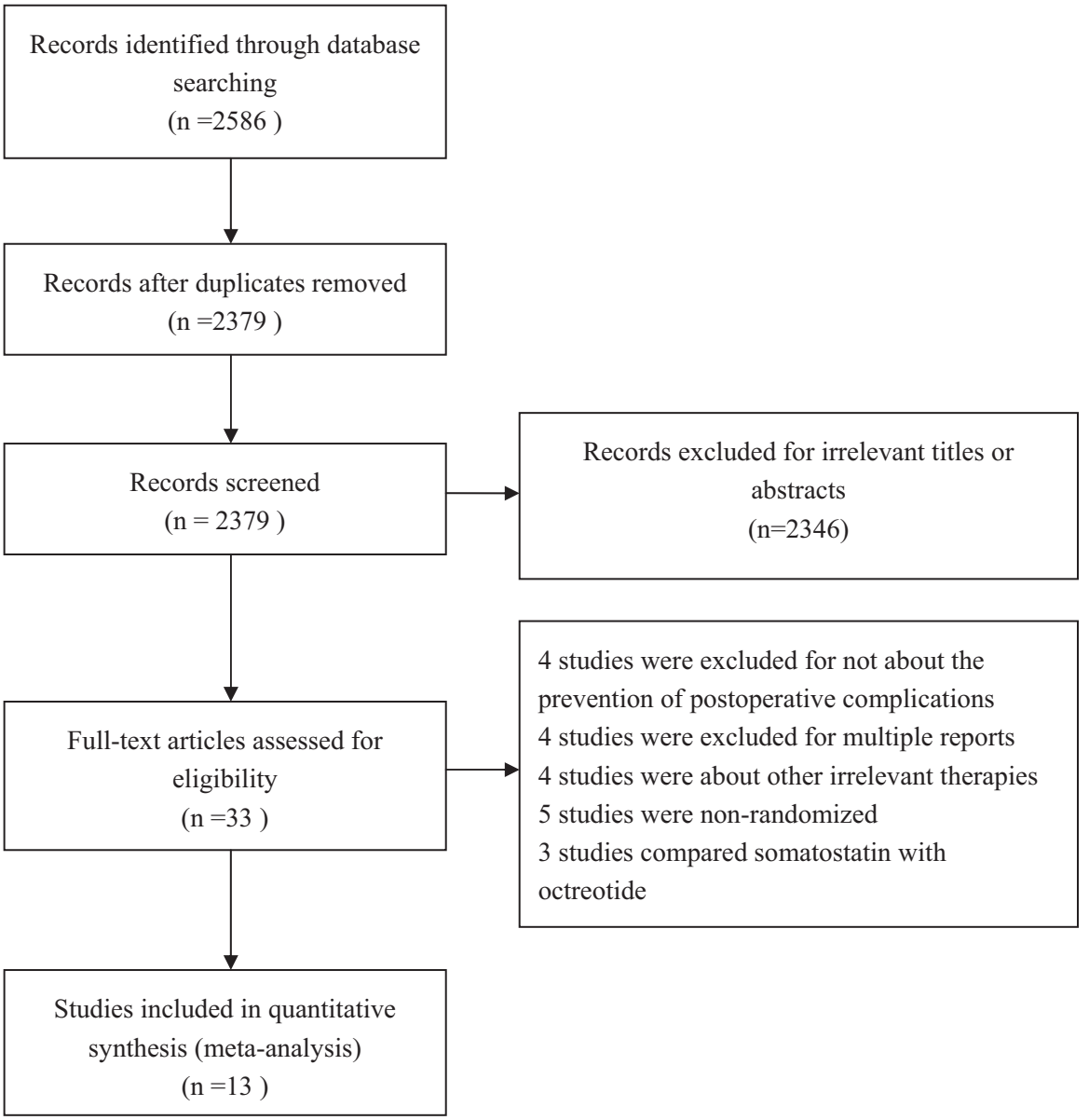

Figure 1. Flow diagram of studies screening according to PRISMA guidelines. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1

Characteristics of included studies.

Author, year	Multi or single center	Patients per group	Mean age	Administration methods	Surgical approach	Pathology	Pancreatic fistula definition	Pancreatic fistula
El Nakeeb et al, 2018[19]	Single center	Octreotide 52	54.4	100 μg per 8 h until fluids intake	PD	Malignancy;	According to the ISGPF	10
		Control 52	55.5			Chronic pancreatitis; Other tumor		11
Kurumboor et al, 2015[20]	Single center	Octreotide 55	58 ± 9.2	100 μg per 8 h for 5 days	PD	Periampullary	According to the ISGPF	33
		Control 54	56 ± 11.6			Or pancreatic tumor		34
Fernandez et al, 2013[21]	Single center	Octreotide 32	69	100 μg per 8 h for 10 days	PPPD	Malignancy;	According to the ISGPF	2
		Control 30	69			Other tumor		3
Kurumboor et al, 2012[22]	Single center	Octreotide 24	NS	100 μg per 8 h for 5 days	PD	NS	NS	18
		Control 21						16
Kollmar et al, 2008[23]	Single center	Octreotide 35	59.9 ± 2.0	100 μg per 8 h for 7 days	PD	Malignancy;	Any volume after day 3 with amylase contents >3 times normal serum amylase	9
		Control 32	64.8 ± 2.0		PPPD	Chronic pancreatitis; Other tumor		6
Hesse et al, 2005[24]	Single center	Octreotide 55	59.93 ± 12.5	100 μg per 8 h for 7 days	PD	Cancer;	>100 mL/d of amylase-rich fluid >5 times the NSA after day 3 and persisting beyond POD7 with rising temperature and proseptic conditions	6
		Control 50	58.98 ± 13.7		PPPD	Benign tumor; Chronic pancreatitis		6
Suc et al, 2004[25]	Multicenter	Octreotide 122	56 ± 14	100 μg per 8 h for 10 days	PD	Malignancy;	>4 times normal serum values of amylase for 3 days or clinical/radiologically as anastomotic leak	21
		Control 108	57 ± 12		PPPD DP	Benign; Chronic pancreatitis; Other tumor		20
Yeo et al, 2000[26]	Multicenter	Octreotide 104	63.9 ± 1.3	250 μg per 8 h for 7 days	PD	Malignancy;	>50 mL/d amylase-rich fluid and >3 times normal serum values on or after day 10 or radiological pancreatic anastomosis disruption	11
		Control 107	65.5 ± 1.1		PPPD	Chronic pancreatitis; Other tumor		10
Lowy et al, 1997[27]	Single center	Octreotide 57	63	150 μg per 8 h for 5 days	PD	Malignancy	Amylase-rich fluid >2.5 times NSA with fever, leucocytosis, or sepsis or need for percutaneous drainage	16
		Control 53	65					11
Friess et al, 1995[28]	Multicenter	Octreotide 122	48	100 μg per 8 h for 8 days	PD PPPD	Chronic pancreatitis	Amylase and lipase >3 times serum concentration, >3 days postoperative, >10 mL/h	12
		Control 125	47		DPPHR Left resection Pancreatico-Jejunostomy			28
Montorsi et al, 1995[29]	Multicenter	Octreotide 111	59.4 ± 10.8	100 μg per 8 h for 7days	PD Whipple	Pancreatic and periampullary cancer;	>10 mL/d amylase-rich fluid >3 times normal serum amylase since the POD 3	10
		Control 107	56.9 ± 12.5		LR SP Enucleationother	Chronic pancreatitis; Other tumor		21
Pederzoli et al, 1994[30]	Multicenter	Octreotide 122	52.6 ± 1.1	100 μg per 8 h for 7 days	Whipple	Pancreatic and periampullary cancer;	Amylase >3 times the maximum normal and >10 mL per 24 h for at least 4 days from POD 4	11
		Control 130	53.6 ± 1.2		PPPD LP other	Chronic pancreatitis; others		24
Buchler et al, 1992[31]	Multicenter	Octreotide 125	51	100 μg per 8 h for 7 days	PD	Pancreatic and periampullary cancer;	Amylase and lipase >3 times serum concentration and >10 mL/d, >3 days postoperatively	22
		Control 121	52		PPPD LR other	Chronic pancreatitis; others		46

DP = distal pancreatectomy, LR = left resection (left pancreatectomy), NSA = normal serum amylase, PD = pancreaticoduodenectomy, POD = postoperative day, PPPD = pylorus-preserving pancreaticoduodenectomy, SP = subtotal pancreatectomy.

common bile duct cancer, periampullary cancer, chronic pancreatitis, and trauma). Octreotide was administered prophylactically in the intervention group, and placebo or no intervention was used in the control group. The aim of using octreotide prophylaxis was to prevent complications after pancreatic resection. The primary outcome was the incidence of PF after pancreatic surgery. The secondary endpoints included mortality and other postoperative complications.

The exclusion criteria were as follows: patient information that was unclear and studies that compared octreotide with other prophylactic interventions.

2.2. Data extraction

Two reviewers independently identified the trials according to the predesigned protocol. The basic details were extracted including the name of first author, publication year, country, study design, number of patients, mean age, surgical procedure, administration methods of octreotide, definition of PF, complications in each group, primary endpoints including the incidences of PF and clinically significant PF, and secondary endpoints including the incidences of mortality, overall complications, abdominal infection, bleeding, pulmonary complications, reoperation, biliary leakage, and delayed gastric emptying.

2.3. Assessment of quality

Two reviewers independently screened, extracted, and evaluated the relevant information from the articles. Risk of bias in the included studies was assessed by the Cochrane Collaboration tool.[16] The quality of the included studies was evaluated by 7 parameters: random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The items were estimated as "low risk," "unclear risk," or "high risk." Any disagreement was resolved by a discussion until a consensus was reached.

2.4. Statistical methods

Meta-analysis was conducted using Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark). The pooled risk ratios (RRs) and 95% confidence interval (CIs) were calculated for dichotomous outcomes. The pooled mean difference (MD) or standardized mean difference (SMD) with the 95% CI was estimated for continuous outcomes. Heterogeneity among the studies was investigated with the Q test and I^2 test with Revman software. If $P < 0.05$ and $I^2 > 50\%$, there was significant heterogeneity; if $P \geq .05$ and $I^2 \leq 50\%$, there was no significant heterogeneity. If there was significant heterogeneity, we analyzed data using a random effects model. If there was not significant heterogeneity, we used a fixed effects model.[17,18] A funnel plot was used to explore publication bias. We performed a subgroup analysis based on the level of risk (low-risk stratum vs high-risk stratum) and the surgical procedures (PD vs DP and local pancreatic resection). Pancreas with soft texture and non-dilated pancreatic ducts were considered to belong to the high-risk stratum. A P value $<.05$ was considered statistically significant.

3. Results

3.1. Description of studies

A total of 2586 records were identified by the search strategy. A total of 207 duplicates and 2346 clearly irrelevant references identified by reading the titles and abstracts were excluded. Thirty-three references were retrieved for further assessment. Of the 33 references, 4 studies were not about the prevention of postoperative complications, 4 studies were multiple reports, 4 studies were about other irrelevant therapies, 5 studies were non-randomized, and 3 studies compared somatostatin with octreotide (Fig. 1). Finally, 13 RCTs were included in the meta-analysis (Table 1).

All of the studies were in English. The meta-analysis involved a total of 2006 patients: 1016 were randomized to the octreotide group, and 990 were randomized to the control group. Seven trials had single-center designs, and 6 trials had multicenter designs. The characteristics of the 13 studies including the different definitions of PF are presented in Table 1.

3.2. Risk of bias within studies

The risk of bias of the included studies is presented in Figs. 2 and 3. Overall, the included studies were sufficiently evaluated as

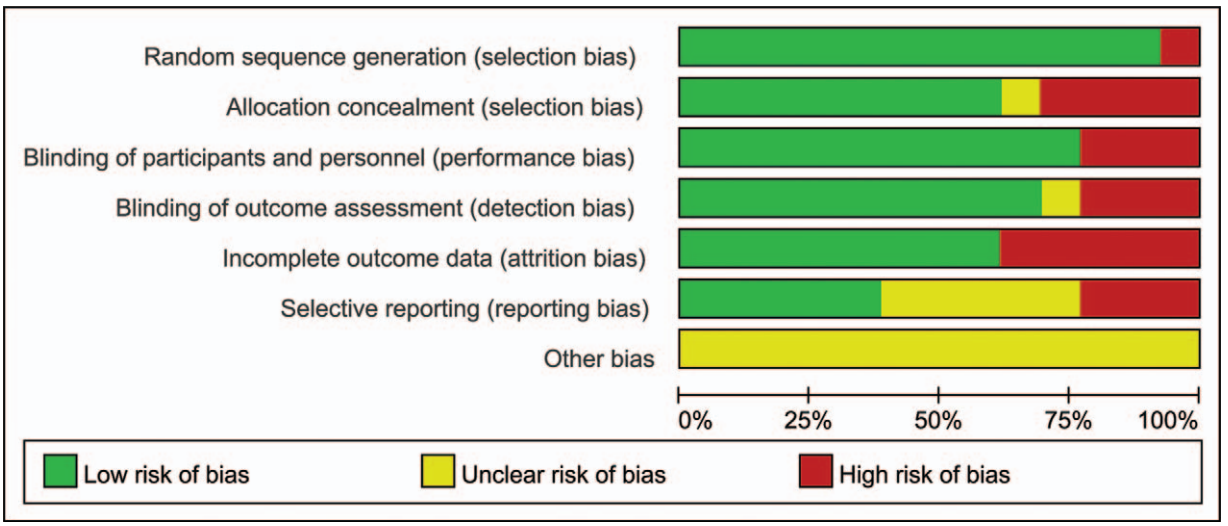

Figure 2. Risk of bias of the included studies using the Cochrane Risk of Bias tool. The items were judged as "low risk" (green), "unclear risk" (yellow), or "high risk" (red).

having a low risk or moderate risk of bias across the domains. Of the 13 studies, 12 studies provided the details of the generation of the randomization sequence,[19–26,28–31] and only 1 study used an improper randomization method.[27] Eight studies used a double-blind method,[19,22,23,26,28–31] 4 studies adopted a single-blind or open-label method[21,24,25,27] and 1 study did not mention the blinding method.[20] There was a low risk of attrition bias due to the low rate of loss of follow-up, making it unlikely to cause significant bias. The "other risk of bias" was reported as unclear in all the studies.

3.3. Results of the meta-analyses

3.3.1. Primary outcomes: PF and clinically significant PF.

There were no differences between the 2 groups in the incidences of PF and clinically significant PF. After pooling all the trials, 414 PFs occurred (414/2006, 20.6%), including 180 in the octreotide group (180/1016, 17.7%) and 234 in the control group (234/990, 23.6%). The pooled RR was 0.79 (95% CI 0.62–0.99, $P=.05$) (Fig. 4). Eighty-eight clinically significant PFs occurred (88/832, 10.6%), including 46 in the octreotide group (46/432, 10.6%) and 42 in the control group (42/400, 10.5%). The pooled RR was 1.01 (95% CI 0.68–1.50, $P=.95$) (Fig. 5).

3.3.2. Secondary outcome: postoperative complications.

There were no significant differences between the 2 groups in the incidences of mortality (RR = 1.21, 95% CI = 0.78–1.88, $P=.40$) (Fig. 6), biliary leakage (RR 0.84, 95% CI = 0.39–1.82, $P=.66$) (Fig. 7), delayed gastric emptying (RR = 0.83, 95% CI = 0.54–1.27, $P=.39$) (Fig. 8), abdominal infection (RR = 1.00, 95% CI = 0.66–1.52, $P=1.00$) (Fig. 9), bleeding (RR = 1.16, 95% CI = 0.78–1.72, $P=.46$) (Fig. 10), pulmonary complications (RR = 0.73, 95% CI = 0.45–1.18, $P=.20$) (Fig. 11), overall complications (RR = 0.80, 95% CI = 0.64–1.01, $P=.06$) (Fig. 12), and reoperation rates (RR = 1.18, 95% CI = 0.77–1.81, $P=.45$) (Fig. 13).

3.4. Subgroup analyses

In subgroup analyses, the included studies stratified patients into 2 groups: high-risk and low-risk groups. The pooled analysis showed that there was no significant difference in the incidence of PF in the high-risk group (RR = 0.81, 95% CI = 0.67–1.00, $P=.05$) and the low-risk group (RR = 0.58, 95% CI = 0.14–2.35, $P=.45$) (Fig. 14). Additionally, there was no significant difference between the PD group (RR = 1.01, 95% CI = 0.83–1.22, $P=.96$) and the DP and local pancreatic resection group (RR = 0.38, 95% CI = 0.14–1.05, $P=.06$) (Fig. 15).

3.5. Publication bias

We assessed the publication bias based on the results of PF and clinically significant PF. No evidence of publication bias existed in the studies included in the meta-analysis (Figs. 16 and 17).

4. Discussion

POPF is the most frequent major complication after pancreatic resection and may lead to secondary intra-abdominal abscess formation and septic and hemorrhagic complications and even death.[32,33] Pancreatic exocrine secretions are considered a major contributor to the development of POPF after pancreatic resection. Thus, inhibition of these secretions may reduce the incidence of POPF after pancreatic resection. Octreotide is known to inhibit exocrine secretions from the pancreas and may reduce the incidence of PF after pancreatic surgery.[34,10] Since 1979, several clinical trials have evaluated the effect of octreotide and attempted to determine whether octreotide can prevent complications after pancreatic resection. However, until now, the results were still quite conflicting.

The purpose of our meta-analysis was to evaluate the efficacy of prophylactic octreotide for the prevention of complications after pancreatic resection. The present evidence suggests that prophylactic octreotide had no effective role in reducing the incidence of complications after pancreatic surgery, including the

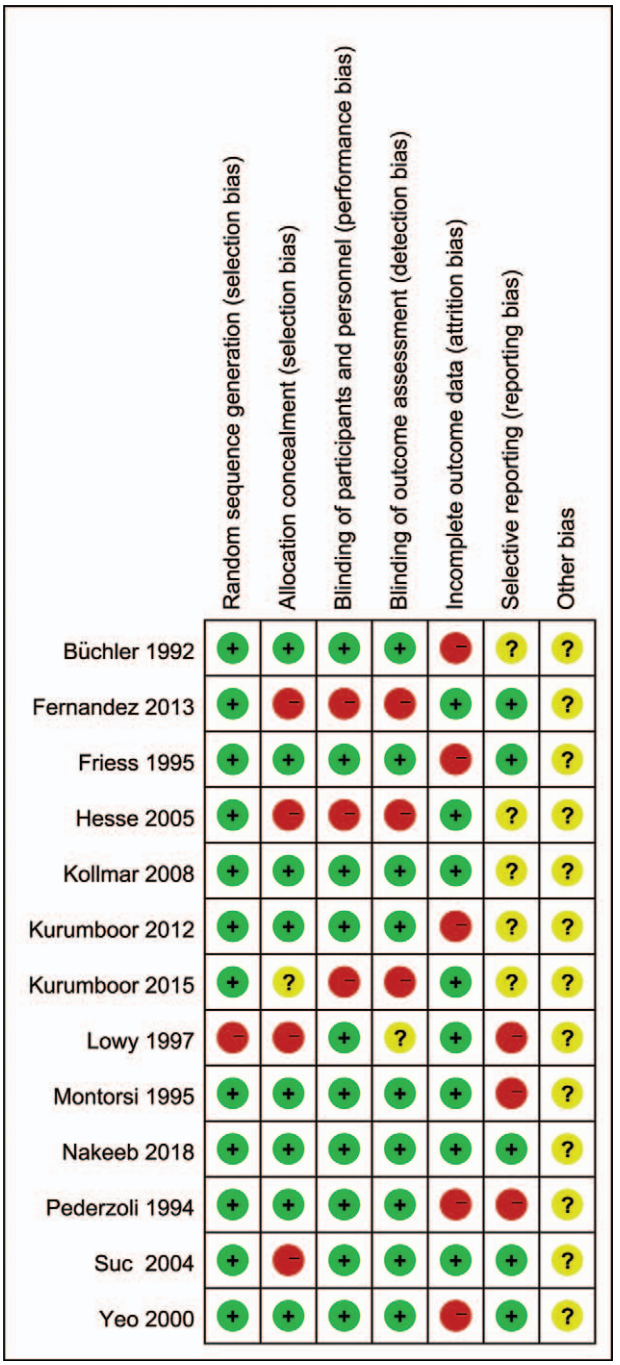

Figure 3. Risk of bias summary: review author's judgement about each risk of bias item for each included study, presented as percentages.

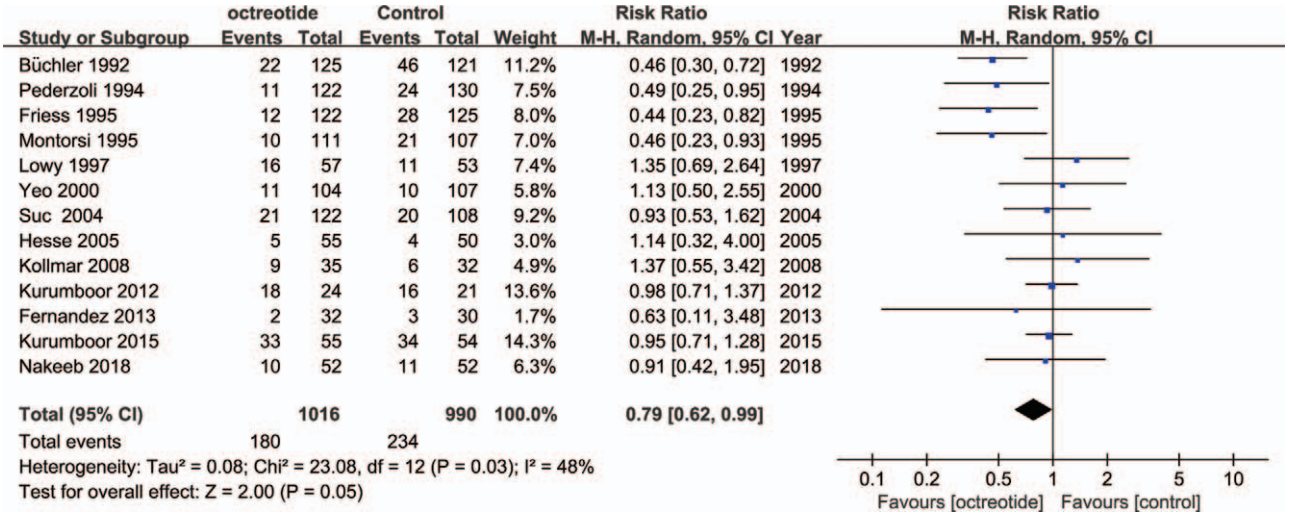

Figure 4. Forest plot of meta-analysis comparing octreotide with control group in pancreatic fistula.

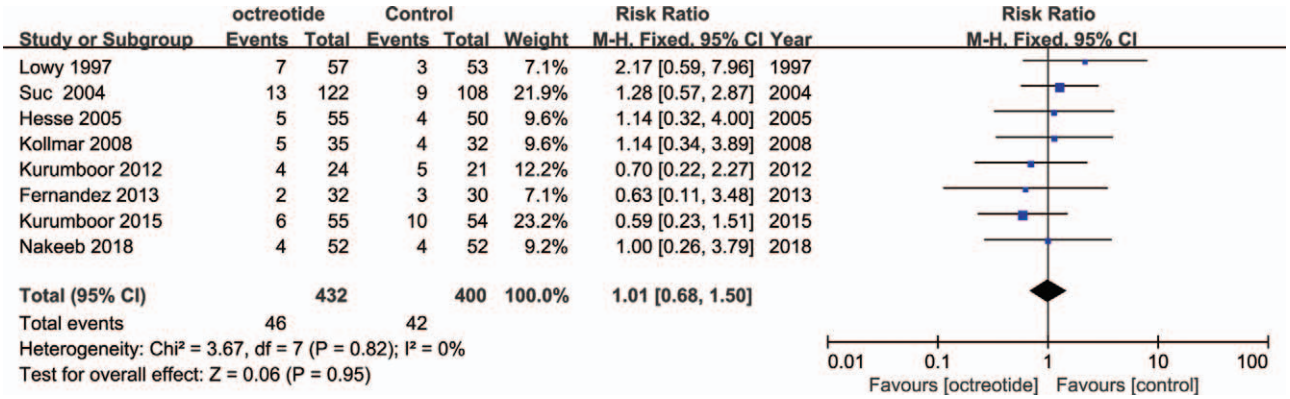

Figure 5. Forest plot of meta-analysis comparing octreotide with control group in clinically significant pancreatic fistula.

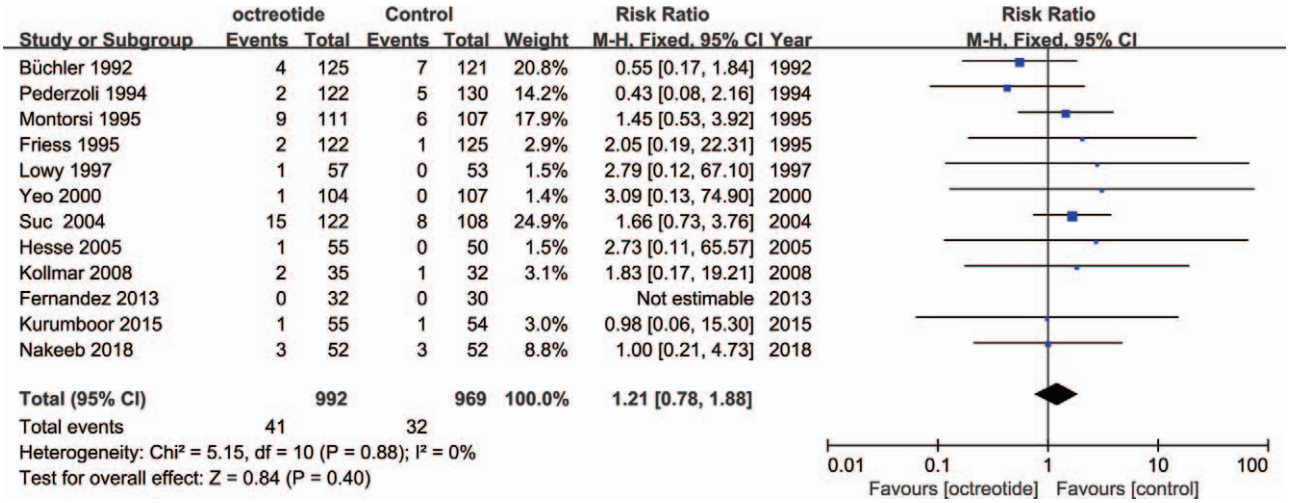

Figure 6. Forest plot of meta-analysis comparing octreotide with control group in mortality.

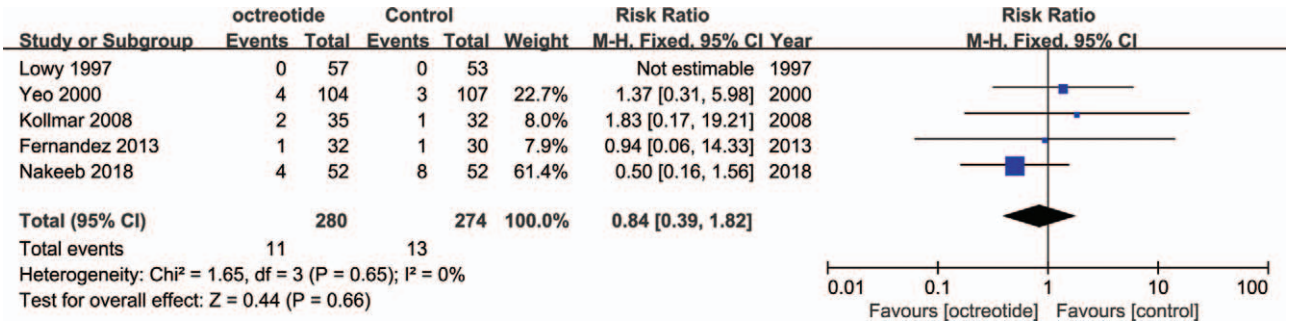

Figure 7. Forest plot of meta-analysis comparing octreotide with control group in biliary leakage.

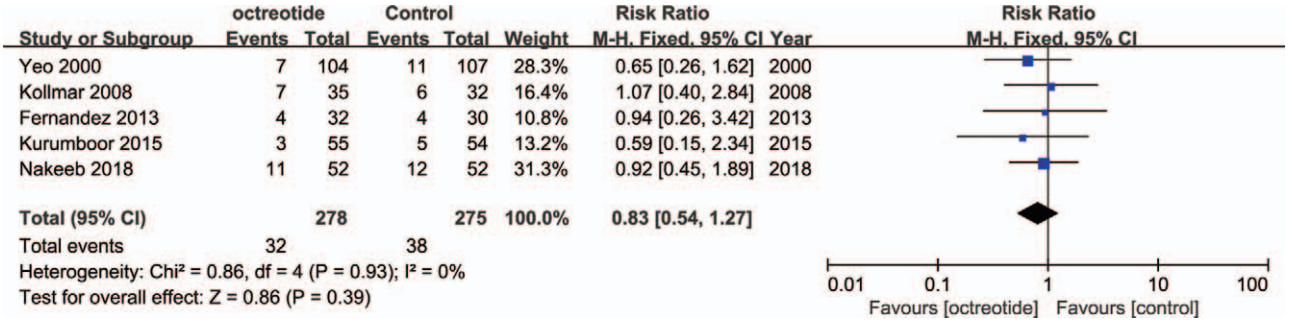

Figure 8. Forest plot of meta-analysis comparing octreotide with control group in delayed gastric emptying.

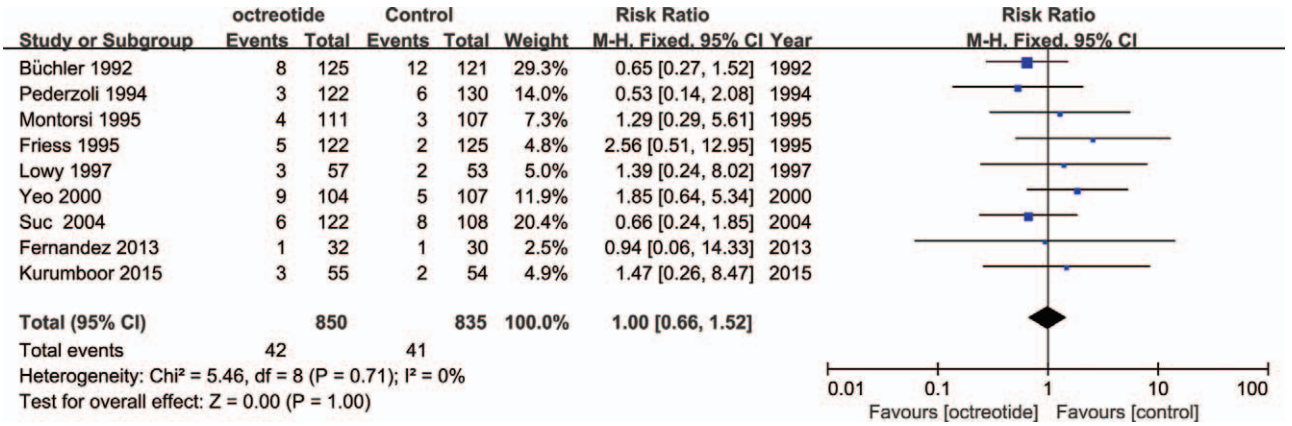

Figure 9. Forest plot of meta-analysis comparing octreotide with control group in abdominal infection.

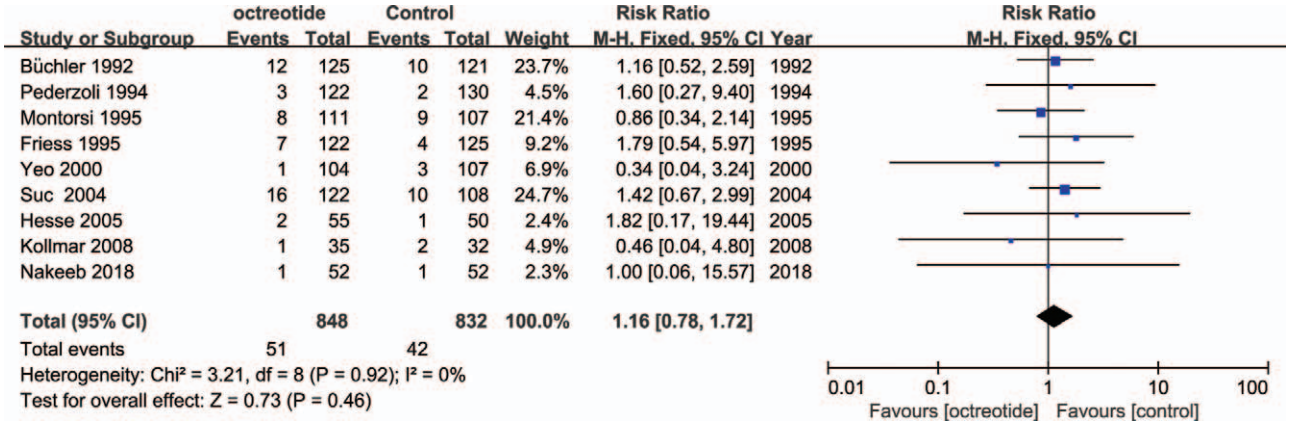

Figure 10. Forest plot of meta-analysis comparing octreotide with control group in bleeding.

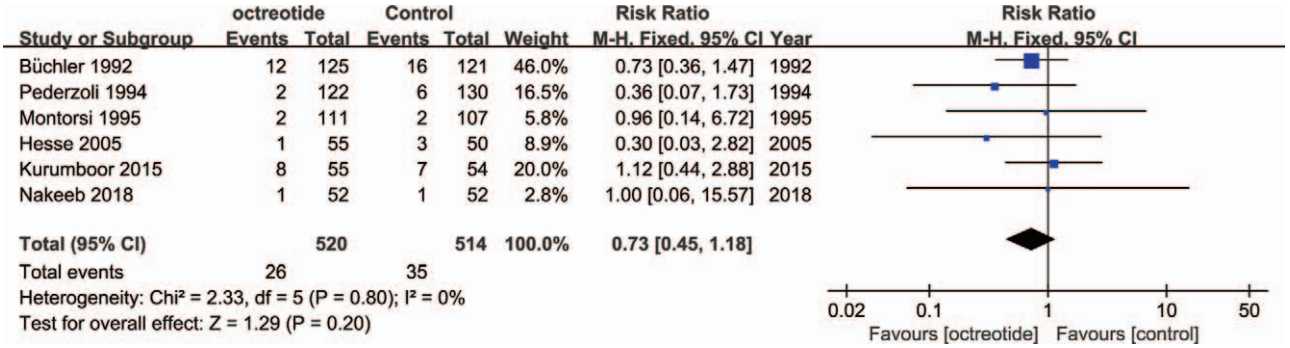

Figure 11. Forest plot of meta-analysis comparing octreotide with control group in pulmonary complications.

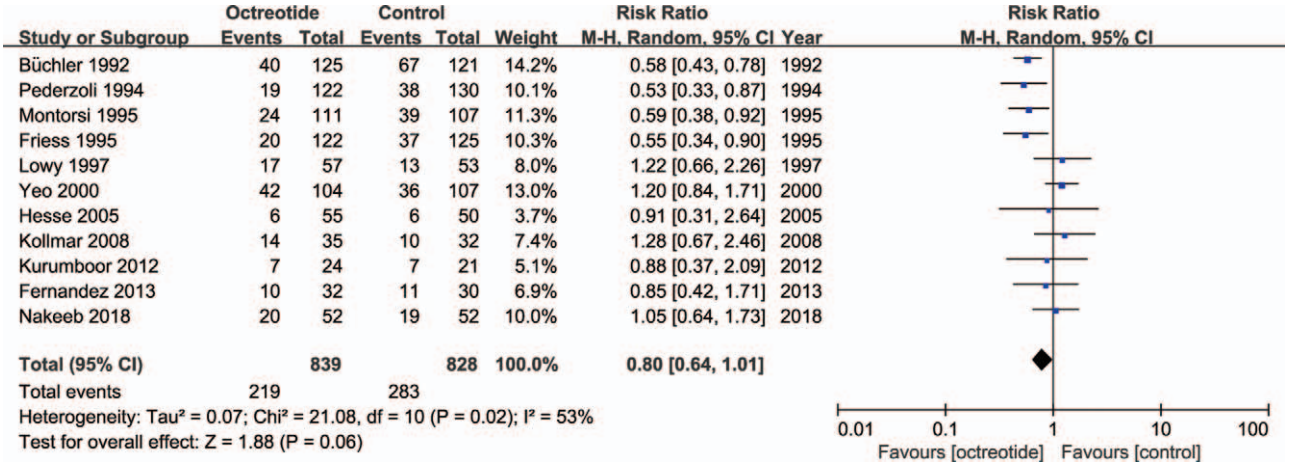

Figure 12. Forest plot of meta-analysis comparing octreotide with control group in overall complications.

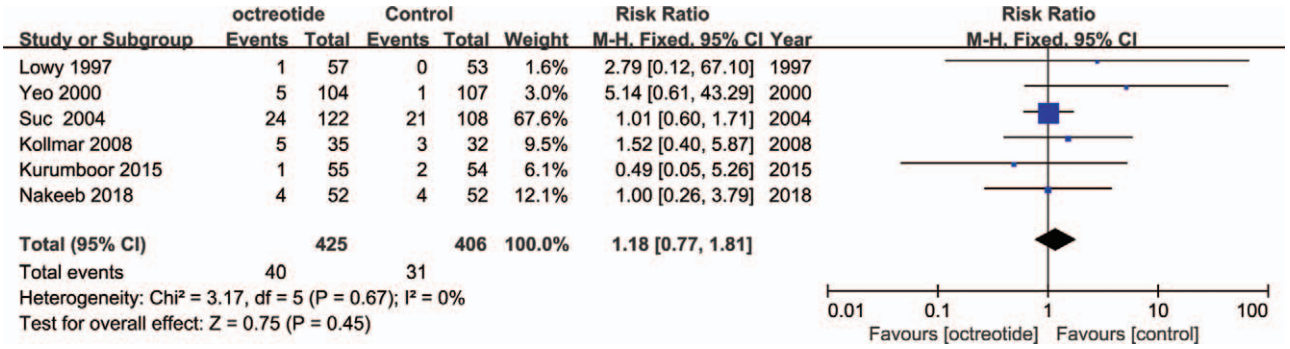

Figure 13. Forest plot of meta-analysis comparing octreotide with control group in reoperation rates.

incidence of PF. The results were different from those of previous meta-analyses[35–37] that showed that the prophylactic use of octreotide could significantly reduce the incidence of some complications, especially PF. Some previous studies recommended the prophylactic use of octreotide.

Because of these different results, there are many things that need to be further discussed. First, the studies included in our meta-analysis did not use the same standard definitions of PF. In 2005, the definition of PF achieved uniformity, and POPF was graded as A, B, and C. Grade A fistulas are transient and have no clinical importance. Grade B and C fistulas have significant clinical impact, require changes in treatment and may cause an increase in morbidity and mortality.[38] In 2016, the International Study Group for Pancreatic Surgery (ISGPS) redefined Grade A PF to no longer be a true PF.[39] In our study, only 3 trials used the International Study Group for Pancreatic Fistula (ISGPF) definition,[19–21] and other trials used their own definitions of PF. Therefore, potential clinical heterogeneity could not be absolutely excluded. Furthermore, lack of high-quality RCTs, different surgery procedure and experience, different preopera-

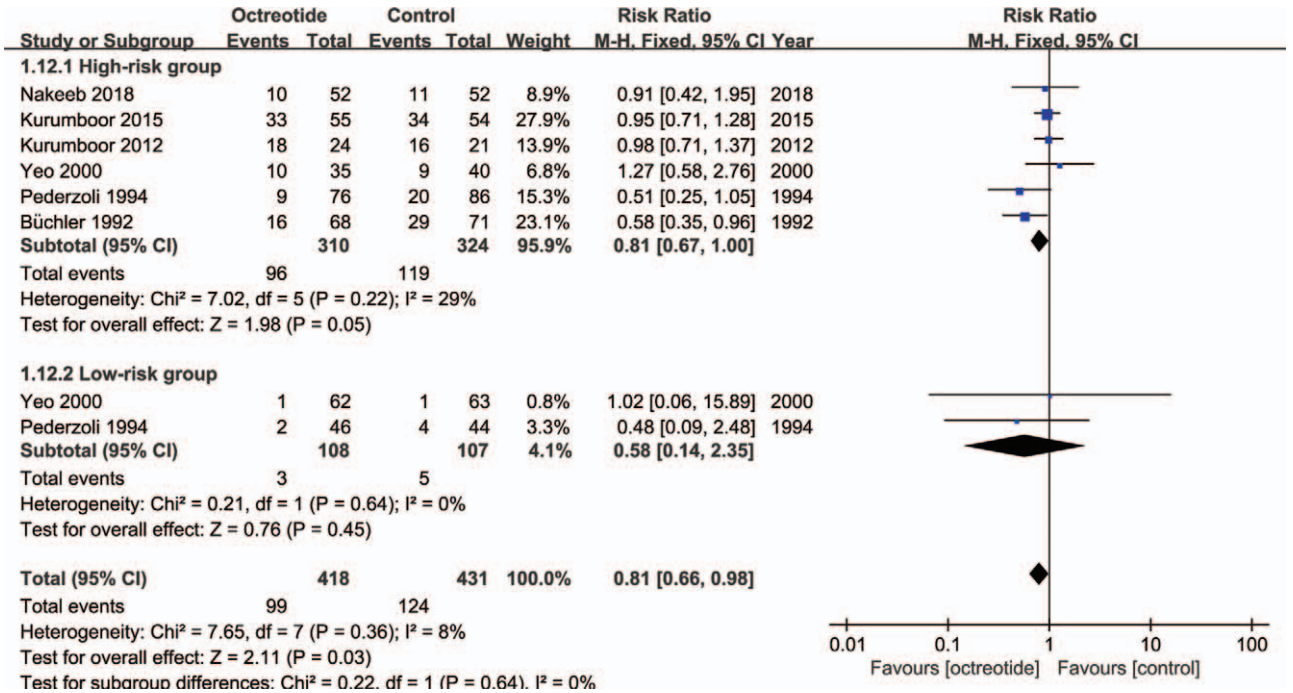

Figure 14. Forest plot of meta-analysis comparing octreotide with control group with the risk factor with pancreatic fistula.

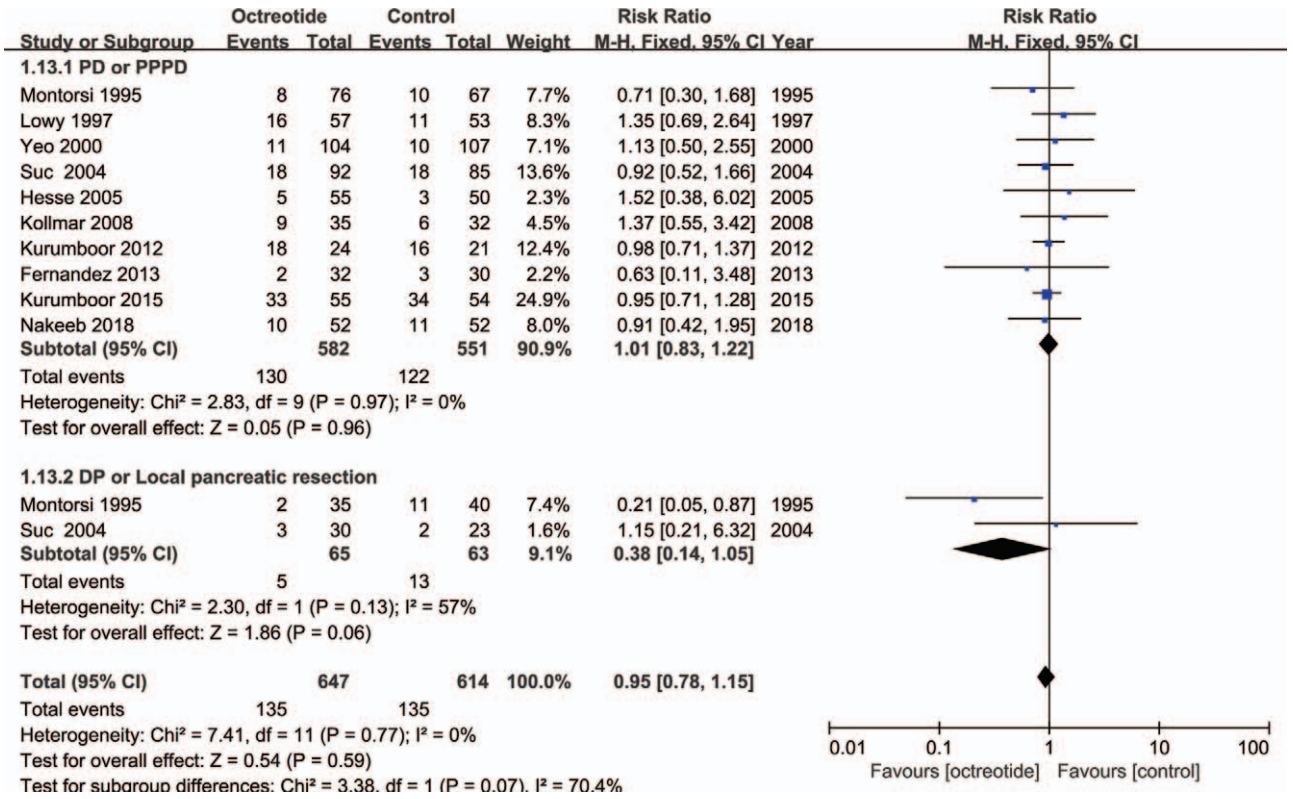

Figure 15. Forest plot of meta-analysis comparing octreotide with control group with the surgical procedures with pancreatic fistula following pancreatic resection.

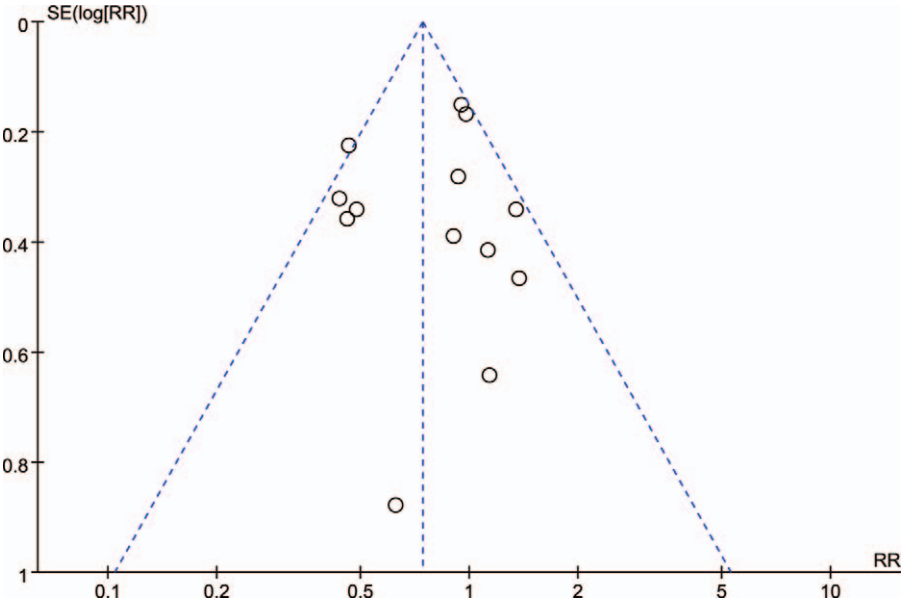

Figure 16. Funnel plot illustrating meta-analysis of the incidence of pancreatic fistula.

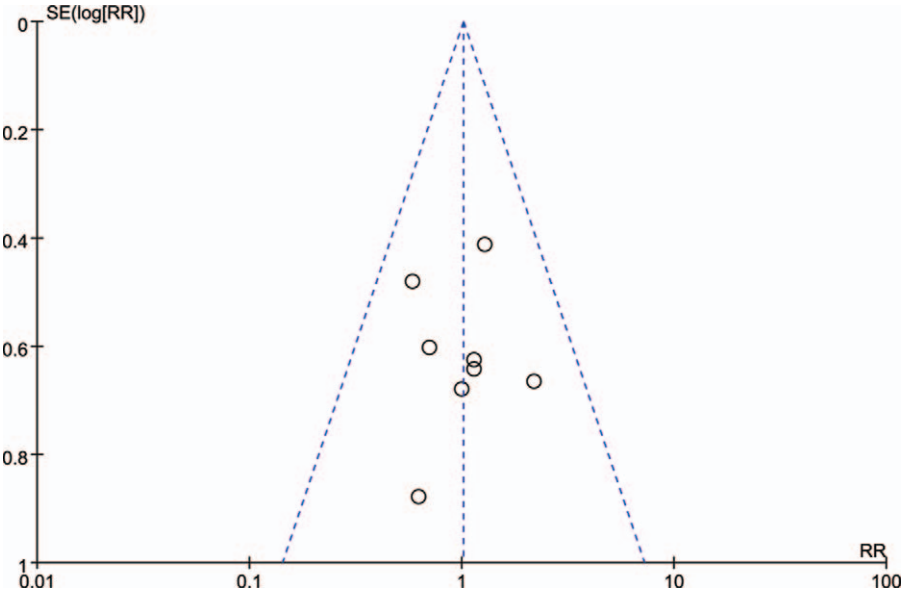

Figure 17. Funnel plot illustrating meta-analysis of the incidence of clinically significant pancreatic fistula.

tive nutritional status, and other reasons may also cause potential clinical heterogeneity. Second, soft texture and a non-dilated pancreatic duct are independent risk factors for POPF.[40] The study by Callery et al[41] reported that patients with ampullary, duodenal, cystic, or islet cell pathology are more likely to develop POPF than patients with pancreatic cancer or chronic pancreatitis. An explanation may be the soft pancreatic texture and non-dilated pancreatic duct in pancreases with ampullary, duodenal, cystic, or islet cell pathology. Some studies have classified postoperative patients into high-risk and low-risk groups based on the pathology of the disease, texture of the pancreas, and diameter of the pancreatic duct. These studies have shown that the prophylactic use of octreotide might decrease the incidence of PF in high-risk patients.[28,31] However, in our study, the meta-analysis of the subgroup high-risk patients showed that octreotide could not decrease the incidence of PF in these high-risk patients. Therefore, we believe that the prophylactic use of octreotide for high-risk patients should not be recommended. Third, the clinical trials included many types of pancreatic resections. There is a significantly different incidence of POPF between different types of pancreatic surgery procedures (such as PD and DP).[42] The study by Montorsi et al[29] reported that the prophylactic use of octreotide could reduce the occurrence of PF in patients who underwent DP but not in patients who underwent

PD. However, the study by Suc et al[25] reported the different results, which revealed that octreotide could be useful in patients who underwent PD by pancreatojejunostomy and had a high risk of PF (a main pancreatic duct measuring <3 mm) but not in those who underwent DP. In our study, the meta-analysis of subgroups of different surgery methods showed that octreotide could not reduce the rate of PF after DP and local pancreatic resection. Therefore, additional high-quality RCTs to evaluate the efficacy of octreotide to prevent postoperative complications after DP and local pancreatic resection are needed. Fourth, different methods of anastomosis (such as pancreatojejunostomy and pancreatogastrostomy) may cause different rates of PF. Because pancreatic enzymes cannot activate in gastric tissue, the use of octreotide may be useless after pancreatogastrostomy. If octreotide can reduce the rate of PF after surgery, the reason for this effect may not be that octreotide reduces pancreatic enzyme secretion. A study by Suc et al[25] reported that the prophylactic use of octreotide can reduce the incidence of intra-abdominal complications after pancreatojejunostomy but cannot reduce the incidence of intra-abdominal complications after pancreatogastrostomy. However, this article did not further analyze the reason why octreotide reduces the incidence of complications between these 2 methods of anastomosis. Therefore, more RCTs with a greater number of patients and using the ISGPS standard PF definition and standard surgical procedures are needed to evaluate the efficacy of octreotide in different methods of anastomosis. Last but not least, the adverse effects of octreotide are worth consideration. The prophylactic use of octreotide may result in prolonged recovery time of the intestine and increase delayed gastric emptying due to decreased secretion of digestive enzymes.[43,44] Some studies have also revealed that octreotide can inhibit the anabolism of the body and suppress the secretion of tropic hormones, which may delay the healing of each anastomosis.[45,46] A study by Jenkins et al[47] showed that octreotide can decrease the volume of pancreatic juice. However, a low volume of pancreatic juice may cause a high concentration of enzymes, which may delay the healing of anastomosis sites. However, in our meta-analysis, prophylactic octreotide did not significantly prolong gastric emptying after pancreatic resection and cause other serious adverse effects. The adverse effects of octreotide were mainly minor and well tolerated. The reason for the results of this meta-analysis may be that although octreotide can reduce pancreatic exocrine secretions, octreotide can also shrink the visceral vessels and decrease gastrointestinal blood flow, which reduces the blood supply to the pancreaticointestinal anastomosis and can also reduce the secretion of growth hormone (GH).[13] These factors are not helpful for the healing of the anastomosis site and may cause other complications.

5. Conclusion

The best available evidence showed that octreotide had no influence on the incidence of PF and other complications after pancreatic resection. The prophylactic use of octreotide is not recommended. However, further high-quality RCTs to assess which subgroup of patients may benefit from prophylactic octreotide administration are urgently needed.

Author contributions

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