

Comparative Outcomes of EUS-Guided Lumen-Apposing Metal Stents Drainage for Pancreatic Pseudocysts and Walled-off Necrosis: Case Series and Meta-Analysis

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Research

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Abstract

Background and Aims: Endoscopic ultrasound-guided transmural drainage for pancreatic fluid collections (PFCs) has become the first-line treatment with quicker recovery and less injury compared with surgery and percutaneous drainage. The efficacy of stents implantation and drainage for different types of PFCs remains controversial, especially lumen-apposing metal stents (LAMS). This study aims to compare efficacy and safety of LAMS drainage for pancreatic pseudocysts (PPC) and walled-off necrosis (WON).

Methods: A meta-analysis was performed for LAMS drainage for WON and PPC by systematically searching PubMed, Cochrane, and Embase databases from January 2010 to January 2020. From 2017 to 2019, 12 patients who were treated with LAMS drainage for PFCs in our medical center were also reviewed and included in this study.

Results: Combining 11 searched literatures with the data from our medical center, a total of 585 patients with PFCs were enrolled in this meta-analysis, including 343 patients with WON and 242 with PPC. The technical success rate in WON is not significantly different from that of PPC ($P = 0.08 > 0.05$). The clinical success of LAMS placement was achieved in 99% versus 89% in PPC and WON, respectively (RR = 0.92, 95% CI: 0.86–0.98, $P = 0.01 < 0.05$). Further intervention of direct endoscopic necrosectomy was required in 60% of patients in WON group. There was no significant difference in the incidence of adverse events after LAMS placement between WON and PPC, including infection, bleeding, stent migration and stent occlusion.

Conclusions: Endoscopic ultrasound-guided LAMS for PFCs is feasible, effective with preferable technical and clinical success rates. The clinical effect of LAMS on PPC is better than that of WON, but its adverse reactions still need to be verified in a large-sample prospective study.

Background

Approximately 20–40% of patients with severe acute pancreatitis will develop pancreatic and peripancreatic infection¹. Pancreatic fluid collections (PFCs) with amylase-rich collections usually occur after acute or chronic pancreatitis and pancreatic injury. According to the revised 2012 Atlanta Classification, PFCs were classified as peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst and walled-off necrosis (sterile or infected)². It is reported that the majority of PFCs can resolve spontaneously, but the collections with the diameter of more than 5 cm may accompany with higher risk of complications, particularly in absence of decreasing collection size over 6 weeks³. Delaying intervention at least for 4 weeks after onset of acute pancreatitis is currently regarded as a favorable approach to drainage for PFCs^{3–5}.

By establishing a channel between the digestive tract and the cyst to achieve the internal drainage of the cyst, endoscopic ultrasound-guided stents placement for the drainage of PFCs has recently become the preferred therapeutic approach. Compared with surgery, it has considerable curative effect, less trauma, faster recovery and less cost⁶. A novel lumen-apposing metal stent (LAMS) emerging after plastic stents and self-expanding metal stents, shaped like saddle on both ends and covered with silicone, has been broadly used in recent years. These stents have a certain anchoring effect and can adapt to the situations between the wall of the gastrointestinal tract and the cyst. Baron et al.⁷ firstly reported the treatment of walled-off necrosis (WON) with endoscopic debridement in 1996, laying the foundation for the application of direct endoscopic necrosectomy (DEN). The larger luminal diameter of LAMS provides a convenient passage for a gastroscope into the cyst to visualize the necrotic material and perform DEN when needed. Even if there is a large diameter drainage channel, if DEN is not performed, solid necrotic tissue in WON cannot be completely drained out spontaneously with undesirable clinical effect⁸.

Research shows that the outcome of endoscopic drainage is closely related with the types of PFCs, the clinical success rate of organized necrosis was significantly lower than other collections^{9,10}. Hasan et al.⁴ proposed that it is crucial to distinguish pancreatic pseudocyst (PPC) from WON due to the more additional interventions and lower success rate of definitive resolution in patients with WON than PPC. However, a meta-analysis from Hammad et al published in 2018, aiming to compare the efficacy of LAMS drainage for PFCs with plastic stents, reported endoscopic LAMS drainage for WON has no difference with that of PPC¹¹, meanwhile another meta-analysis from Renelus et al.¹² included metal and plastic stents published in 2019 also supported this finding. With regard to the controversial results of stents in the management of PFCs, we have carried out a comparative study centering on the efficacy of LAMS for PPC and WON through a meta-analysis combined with a series of medical records from our medical center to evaluate the outcomes of different types of PFCs.

Material And Methods

Present Series

Consecutive patients who were treated in Beijing Friendship Hospital, Capital Medical University and underwent EUS-guided LAMS placement for PPC or WON from January 2017 to December 2019 were retrospectively recruited in this present series. Written informed consent was obtained from each included patient before procedure. This case-series study was approved by Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University.

Inclusion criteria for the case series included^{13,14}: (i) patients with PPC or WON aged 18–75 years; (ii) the collection occurs over 6 weeks after onset of acute pancreatitis and the diameter of cyst is larger than 6 cm, or in the presence of persistent pain and complications, such as infection and mass effect. Patients with regional varices, suspected cystic neoplasms, coagulopathy (INR > 1.5), thrombocytopenia (platelets < 50,000/mm³) were excluded from the study.

According to 2012 revision of the Atlanta classification and definitions of acute pancreatitis, WON was identified as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis, and PPC were encapsulated collections of fluid within a well-defined inflammatory wall usually surround the pancreas with minimal or no solid necrotic tissue.

Treatment and Follow-up

All procedures were performed under general anesthesia or conscious sedation depending on the patient's condition, and all patients underwent procedures by endoscopists with more than 5 years of endosonographic experience. Intravenous antibiotics were administered systematically before and after the procedure. CT or magnetic resonance imaging was performed to define quantification of solid debris in PFCs before procedure, and the amount of solid debris was graded as minimal (< 10%), moderate (10–50%) and profound (> 50%)¹⁵.

Firstly, the location and size of the collection was identified by endoscopic ultrasound, then a 19-gauge needle was selected to puncture the cyst through the gastric and duodenal wall provided that interposed vessels were excluded at the puncture site. In five patients, a 0.035-inch guidewire was passed through the needle and was coiled in the PFCs in necessity, then AXIOS stents (Boston Scientific, United States) were released over guidewire under fluoroscopic and EUS guidance. In the remaining 7 patients, the puncture site was further dilated by balloon and cystotome, and followed by deployment of double mushroom head stents (DMHS, Micro-Tech Co., Nanjing, Jiangsu Province, China) over guidewire. Additional endoscopic interventions, such as direct endoscopic necrosectomy, saline irrigation or placement of a nasocystic tube were adopted at the discretion of endoscopists according to the clinical course of the patients. Follow-up imaging with computed tomography was performed at 1 month after the initial LAMS placement to evaluate treatment outcome. Patients with slow resolution on imaging were further followed based on medical judgement. The follow-up period of adverse events was 3 months after deployment.

Outcomes

Clinical success was defined as at least a 60% decrease or resolution of the PFCs to < 2 cm in the PFC size based on cross-sectional imaging at one month along with symptoms relief. Technical success was defined as successful insertion of the LAMS during the PFC drainage. Safety was evaluated according to the number of adverse events mainly consisted of postoperative infection, postoperative bleeding, stent occlusion and stent migration. Postoperative infection was defined as a new septic event that occurred after the procedure, associated with fever accompanied by the increased leukocyte count or positive blood culture. Postoperative bleeding was noted as gastrointestinal hemorrhage presenting as hematemesis, melena, hematochezia, or decrease of hemoglobin necessitating blood transfusion, with endoscopic or radiologic demonstration of oozing blood from the fistula, it included immediate bleeding (< 7 days) and delayed bleeding (> 7 days). Stent occlusion was defined as a stent with a lumen obstructed by necrosis or refluxed food under the endoscopic view. Stent migration was defined as the need to retrieve the stent either from cyst or the enteral lumen.

Systematic Review and Meta-analysis

Search Strategy

Relevant published studies were systematically searched and identified from 3 English databases including PubMed, Cochrane Library and Embase database and 3 Chinese databases, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (CQVIP) and Wanfang Database. The search terms were as follows: ("pancreatic pseudocysts" OR "pancreatic fluid collections" OR "peripancreatic fluid collection") AND ("walled-off necrosis" OR "pancreatic abscess") AND ("lumen-apposing metal stents" OR "self-expandable metallic stents" OR "biflanged metal stents" OR "metal stents"). References of the searched studies and the bibliographies of recently published review articles were also screened. The details of the search strategy were showed in **Supplementary Table 1**.

Inclusion and Exclusion Criteria

The inclusion criteria of the studies were as follows: (i) the PPC and WON patients were simultaneously included and all of these patients received endoscopic ultrasound-guided LAMS drainage; (ii) the clinical success rates were reported or could be calculated; (iii) the publication language should be in either English or Chinese. The exclusion criteria were as follows: (i) reviews, letters and case reports; (ii) other types of stents; (iii) lack of sufficient data.

Data Extraction

Data were retrieved by two investigators independently for articles screening and data extraction. Discrepancies in articles screen and data collection were referred to a senior methodologist for resolution. The following variables were extracted with the agreement of the two investigators: the basic information including research design, first author, publication year, sample size, and related data information including the cyst type, stent type, technical success rate, clinical success rate, and incidences of adverse events: postoperative infection and bleeding, stent migration and stent occlusion.

Quality Assessment

The Newcastle-Ottawa Scale (NOS; Ottawa Hospital, Ottawa, ON) was used to assess the quality of the included studies by two investigators. Discrepancies in quality assessment were also referred to a senior methodologist for resolution. The scale evaluates the studies from three domains: selection, comparability, and exposure/outcome, with a total score of 9 points. Studies with scores of 7 or higher were evaluated as high quality, and studies scored 5 or 6 were assessed as moderate quality¹⁶.

Statistical Analysis

The primary outcome was the clinical success rates. The technical success rates and the adverse events rates constituted the secondary outcome. The absolute number of observed events were collected and the proportions were calculated. The dichotomous outcomes of clinical success rates, technical success rates and adverse events rates were expressed and calculated as percentage. The relative risk (RR) with 95% confidence intervals (CI) were calculated and summary statistics were estimated using meta-analysis models¹⁷. The proportions and RR with 95% CI values from individual studies were presented in forest plots. The I^2 statistics and P values were used to examine whether variations were caused by heterogeneity. Fixed effect model was applied when the result of heterogeneity showed of $P > 0.05$ or $I^2 < 50\%$. Random-effects model was applied when the result of the heterogeneity proved to be significant ($P < 0.05$ or $I^2 > 50\%$). Freeman-Tukey double arcsine transformation method was implemented to calculate an overall proportion. The number of 0.5 was added to

each cell frequency for studies with a zero cell count. Publication bias was assessed by visual examination of the funnel plots and Egger's test of weighted linear regression. Statistical analysis was conducted with R software (version 3.5.1) with the "meta" package. *P* value below 0.05 was considered statistically significant.

Results

Present Series

A total of 12 patients with PFCs were included in this series as they met selection criteria, including 2 patients with PPC and 10 with WON. The mean age of the 12 present case series was 47.2 ± 11.9 years old with age ranged from 28 to 62 years old, including 8 males and 4 females. Regarding the etiology of acute pancreatitis, 5 cases were alcohol or hypertriglyceridemia, 6 cases were gallstone, and 1 case was idiopathic. For the location of PFCs, 2 cases were in the pancreatic head, 2 cases in the head and body, and 8 cases in the body and tail. The average maximal diameter of PFCs was 12.5 ± 4.0 cm. The symptoms of patients with PFCs were mainly abdominal pain, fever, or abdominal distention, in which 8 cases were mainly manifested by abdominal pain and fever, 2 cases were mainly manifested by abdominal distention and diarrhea, and 2 cases were found by cross-sectional image without obvious discomfort. Minimal solid debris was noted in 4 cases (33.3%), moderate solid debris in 7 cases (58.3%) and profound solid debris in 1 case (8.3%). The details of the demographic characteristics of these 12 patients are showed in Table 1.

Table 1
Characteristics of 12 patients with pancreatic fluid collections.

Characteristics	PFCs (n = 12)
Age, year (mean \pm SD)	47.2 ± 11.9
Male/female	8/4
Etiology of pancreatitis, n (%)	
Alcohol or hypertriglyceridemia	5(41.7%)
Gallstone	6(50.0%)
Idiopathic	1(8.3%)
Complaints, n (%)	
Abdominal pain and fever	8(66.7%)
Bloating and diarrhea	2(16.7%)
No symptoms	2(16.7%)
Location of fluid collection, n (%)	
Head	2(16.7%)
Head and body	2(16.7%)
Body and tail	8(66.7%)
Triglycerides, mmol/L (mean \pm SD)	1.8 ± 0.9
Maximal diameter of PFCs, cm (mean \pm SD)	12.5 ± 4.0
<i>Abbreviations: PFCs, pancreatic fluid collections; SD, standard error.</i>	

Endoscopic debridement through LAMS was performed in 3 patients with WON, and 1 patient with WON was treated with saline cystic irrigation through LAMS. In terms of efficacy of LAMS, stents placement was technically successful in 12 patients with the technical success rate of 100%. Endoscopic therapy using the LAMS was successful in 8 of 10 patients with WON compared with 2 of 2 patients with PPC, and the clinical success rate in patients with WON and PPC was 83.3% and 100%, respectively. Treatment failure occurred in two patients, in which one patient with moderate solid debris required surgical intervention due to pseudoaneurysm and another with profound solid debris had poor drainage with cyst infection, followed by nasal cyst drainage as complementary endoscopic interventions, and the collection resolved partially across cross-sectional imaging at one month after LAMS placement.

Stent removal was performed after a median of 29.6 days (range 18–45). In terms of procedure-related adverse events, infection occurred in 1 patient with PPC and 6 patients with WON, and 1 patient with WON had a stent migration and stent blockage concurrently. Immediate bleeding or delayed bleeding was not observed in any patients. Procedural characteristics and clinical outcomes of PFCs are showed in Table 2.

Table 2
Procedural characteristics and clinical outcomes of present series

	PFCs (n = 12)	PPC (n = 2)	WON (n = 10)
Type of LAMS, n (%)			
DMHS	7(58.3%)	1(50.0%)	6(60.0%)
AXIOS	5(41.7%)	1(50.0%)	4(40.0%)
Total no. of endoscopic reinterventions			
0	9	3	6
1	1	0	1
> 1	2	0	2
Cyst irrigation, n (%)	1(8.3%)	0	1(8.3%)
Technical success, n (%)			
YES	12(100%)	2(100%)	10(100%)
Clinical success, n (%)			
YES	10(83.3%)	2(100%)	8(80.0%)
NO	2(16.7%)	0	2(20.0%)
Adverse events, n (%)			
Infection	6(50%)	1(50%)	5(50%)
Bleeding	0	0	0
Stent migration	1(8.3%)	0	1(10.0%)
Stent occlusion	1(8.3%)	0	1(10.0%)
Duration of procedure, min (mean ± SD)	65.6 ± 24.3	51.5 ± 23.3	68.4 ± 24.7
Hospital stay, days (mean ± SD)	17.1 ± 8.6	16.5 ± 3.5	17.2 ± 9.4
Days to stent removal, days [range]	29.6[18–45]	27.5[27–28]	30.1[18–45]
<i>Abbreviations: LAMS, lumen-apposing metal stents; PFCs, pancreatic fluid collections; PPC, pancreatic pseudocysts; WON, walled-off necrosis; SD, standard error</i>			

Literature Search

The flowchart of the literature search process is illustrated in Fig. 1. The retrieval time was from January 2010 to January 2020. According to the search strategy, a total of 271 articles were enrolled during database searching, including 225 English articles and 46 Chinese articles. Among these articles, 39 articles were excluded due to duplicates, 203 articles were excluded after the review of title and abstract, 20 articles were excluded after full-text review for the following reason: 13 articles had no sufficient data and 7 articles targeted on other types of stents or mixed. We included 2 articles from the reference of the screened articles and a record from our center in addition. Finally, 585 patients from 12 studies were included in the meta-analysis.

Study and Population Characteristics

The studies and population characteristics in the meta-analysis are shown in Table 3. Data from our series was added to the meta-analysis as well. Among the 12 retrospective or prospective studies, the cases data came from 4 in Asia, 3 in Europe, 1 in Oceania and 4 in North America. All these treatments were implemented between the years of 2011 to 2019. Most of the used LAMS subtypes were AXIOS stents or Nagi stents (Taewoong Medical, South Korea), the rest were DMHS and HANARO stents (MI-Tech, South Korea). The definitions of clinical success used in the included individual studies are shown in **Supplementary Table 2**.

A total of 585 patients with PFCs were included in the meta-analysis, in which 343 patients with WON and 242 with PPC. The age of these patients were around 50 years old except for the study from Sundeeep et al. The clinical success rates varied from 50–100%. Postoperative infection, bleeding, stent migration and stent occlusion were the most common complications after LAMS placement. Due to missing data in some studies, 11 patients were finally excluded for calculating clinical success, adverse events (574/585), in which four patients were lost to follow-up in Dennis et al. (1 and 3 in PPC and WON, respectively), and two patients with PPC were lost to follow-up and one patient with WON is being followed up in Rajat et al. Besides, in Daisy et al., data on four patients were limited to technical procedure and excluded from the further analysis (1 and 3 in PPC and WON, respectively).

Table 3
The characteristics of the included studies and population.

No	First author	Publication year	Country	Research period	No. of study institutes	Study design	Sample size	Study arm		LAMS subtype	Mean age	Gender, Female/Male	N
								WON	PPC				
1	Natsuyo et al ¹⁸	2013	Japan	2011–2012	2	Retrospective	9	4	5	Nagi	49	3/6	7
2	Daisy et al ¹⁹	2015	European countries	2011–2012	15	Prospective	61	46	15	AXIOS	55	23/38	7
3	Sujievvan et al ²⁰	2015	Australia	2013	13	Retrospective	47	9	38	Nagi	51 [#]	16/32 ^Δ	8
4	Ali A et al ²¹	2016	US	2012–2014	4	Retrospective	82	68	14	AXIOS	51	33/48 ^Δ	8
5	Josep et al ²²	2017	US	NA	2	Retrospective	25	22	3	AXIOS	50	11/14	9
6	Shuntaro et al ²³	2017	Japan	2015–2016	1	Prospective	12	8	4	HANARO	66	2/10	7
7	Suresh et al ²⁴	2017	UK and Ireland	2015–2016	11	Prospective	116	70	46	AXIOS	53	38/78	8
8	Dennis et al ²⁵	2018	US	2010–2016	Multi-center	Retrospective	122	64	58	AXIOS	60	43/79	7
9	Sundeep et al ²⁶	2018	Korea	NA	NA	Prospective	5	4	1	Nagi	29	0/5	6
10	Maria et al ²⁷	2018	Italy	2013–2016	7	Retrospective	67	23	44	Nagi	59	21/46	8
11	Rajat et al ²⁸	2019	US	2014–2017	1	Retrospective	27	15	12	AXIOS	54	15/12	7
12	This center	NA	China	2016–2019	1	Retrospective	12	10	2	AXIOS and DMHS	47	4/8	N

Notes: # The age derived from Sujievvan et al was median age, and ages derived from other studies were mean ages. Δ The gender distribution was derived directly from the articles or calculated from gender ratio provided from the studies, which might bring the inconsistent with the total sample size.

Quality assessment

The included studies showed moderate to high quality. The specific scoring rules of the included trials according to NOS are showed in **Supplementary Table 3**. The NOS scale showed of one study with the score of 6 (moderate quality) and 10 studies were scored higher than or equal to 7 (high quality). The quality assessment showed of an acceptable quality of the included studies.

Risk ratio of technical success between WON and PPC

A total of 10 studies provided the data on the technical success rates of WON and PPC after LAMS placement. The overall risk ratio using fixed effect model ($I^2 = 0\%$, $P = 0.84$) was 1.04 (95%CI: 1.00–1.08) (Fig. 2). It showed no significance in technical success between WON and PPC ($Z = 1.78$, $P = 0.08$).

Clinical success rates of WON and PPC

Firstly, we summarized the overall clinical success rates of LAMS for patients with WON and PPC. As showed in Fig. 3a, the clinical success rates of LAMS for WON ranged from 50–100%, with the overall clinical success rate of 89% (95%CI: 85%–93%) in fixed effect model ($I^2 = 26\%$, $P = 0.19$). The clinical success rates of LAMS for PPC ranged from 83–100%, with the overall clinical success rate of 99% (95%CI: 95%–100%) in fixed effect model ($I^2 = 0\%$, $P = 0.80$), showed in Fig. 3b.

In order to clarify if the difference existed in the clinical success rates between LAMS in WON and PPC, the risk ratios of WON compared with PPC were calculated and showed in Fig. 4. The overall RR of WON compared with PPC was 0.92 (95%CI: 0.86–0.98) in the fixed effect model ($I^2 = 0\%$, $P = 0.48$). The combined Z-test value was -2.73 ($P = 0.01$). The clinical effectiveness of LAMS in patients with WON was 0.92 times compared with LAMS in patients with PPC. LAMS drainage showed better clinical efficacy in PPC than that of WON.

The cumulative meta-analysis was also used on the clinical success rate (comparison of the efficacy of LAMS between PPC and WON) in the order of publication year and sample size, reflecting the dynamic trend in the included studies. In the cumulative meta-analysis of publication year, the risk ratio in the efficacy of LAMS between WON and PPC tended to be stable after the year of 2017 (**Supplementary Fig. 1a**). In the cumulative meta-analysis of sample size, the risk ratio between WON and PPC tended to be stable with sample size larger than 30 patients (**Supplementary Fig. 1b**).

The studies were divided into three subgroups: Nagi group, AXIOS group, and other group (including HANARO stents, AXIOS stents and DMHS mixed). Subgroup analysis of clinical success in different subtypes of LAMS showed the significant risk ratio in AXIOS group (RR = 0.92, 95%CI: 0.86–0.99). In Nagi and other groups, the RR showed no significance success rates in different subtypes of LAMS. The clinical efficacy of AXIOS stents in PPC were better than WON (Fig. 5).

Safety evaluation on postoperative complications

In this review, the most common adverse events included postoperative infection, bleeding, stents migration and stent occlusion. There were at least five articles provided the data on each of these four complications. The summarized proportions of adverse events were showed in **Supplementary Fig. 2** and **Supplementary Fig. 3**. All the four complications showed no significance on the complication rates between patients with WON and PPC in fixed effect model (all the $I^2 < 50\%$ and $P > 0.05$) (Fig. 6). As showed in **Fig. 6a**, the summary of RR on the postoperative infection was 1.57 (95% CI: 0.73–3.39) in fixed effect model, and no significance was found in the RR of WON cases compared with PPC cases ($Z = 1.15$, $P = 0.25$) on postoperative infection. The summary of RR on postoperative bleeding was 0.84 (95% CI: 0.34–2.09) (Fig. 6b). We also found no significance in the RR of WON cases compared with PPC cases ($Z = -0.37$, $P = 0.71$) on postoperative bleeding. The summary of RR on the complication of migration was 1.04 (95% CI: 0.51–2.12) in the fixed effect model (Fig. 6c). There was once again no significance in the RR of WON cases compared with PPC cases ($Z = 0.11$, $P = 0.91$) on stent migration. Figure 6d showed that the summary of RR on the complication of stents occlusion was 1.66 (95% CI: 0.92–2.98) in the fixed effect model. No significance was also found in the RR of WON cases compared with PPC cases ($Z = 1.70$, $P = 0.09$) on stent occlusion.

The proportion of patients undergoing DEN in WON cases

A total of 10 studies provided the information of DEN among WON cases. The summary proportion of patients undergoing DEN was 60% (95% CI: 34%–84%) in the random effect model ($I^2 = 94\% > 50\%$, $P < 0.01$). The results showed of 100% DEN proportion in the studies of Ali A et al. and Sujievvan et al (Fig. 7). Other studies with relative larger weight showed of low proportion of patients undergoing DEN in patients with WON ranged from 30–53%.

Publication bias

Finally, the publication bias was evaluated on the main outcome of RR in clinical success rates. The results of funnel plot showed that the studies distributed roughly symmetrical (Fig. 8). Statistical analysis using Egger's test confirmed that there was no evidence of publication bias in the clinical success risk ratio between WON and PPC ($P = 0.07$).

Discussion

Although the majority of the individual studies have shown that endoscopic transmural LAMS in PPC have a higher clinical success rate than WON, many of which did not demonstrate statistical significance^{20,29}. Since the treatment success of LAMS drainage for PFCs is more than 80% in general, it is difficult for studies with a relatively small sample to prove the superiority on PPC. As for efficacy of LAMS in different types of PFCs, we found there was no significant difference in the technical success rate between PPC and WON, it can be comprehended that the existence of necrosis or the proportion of solid debris in the cyst would not affect the ease of stents placement.

Given most patients with PPC in our center are prone to choose plastic stent for drainage with less cost and good efficacy, there is a small sample of patients with PPC undergoing LAMS drainage ($n = 2$) in our series. We found that the clinical success rate of LAMS drainage in WON and PPC was 83.3% and 100%, respectively. Further, our meta-analysis showed that the endoscopic transmural LAMS drainage in PPC showed higher clinical success rate than in WON (99% vs. 89%), which was inconsistent with the two meta-analysis as previous mentioned. The main reason may lie in selection bias and inclusion criteria with different study aims. Studies of patients with either WON or PPC in absence of comparative analysis were enrolled in the meta-analysis of Hammad et al¹¹, designated to evaluate the cumulative efficacy and safety of LAMS in the management of PFCs. While for our meta-analysis with a directly comparative aims, only studies included WON and PPC simultaneously were enrolled with the study aim of comparing efficacy and safety of LAMS drainage for PPC and WON. On the other hand, the different techniques of LAMS deployment, treatment protocols and endoscopists with varying level of experiences might also be the reasons for the inconsistency with consideration of the heterogeneity of the previous studies. Another previously published meta-analysis conducted by Renelus et al¹² included not merely metal stents, but also plastic stents, which has a confounding impact on the outcome of PFCs. The study from Varadarajulu et al.³⁰ in favor of our findings also showed clinical success was significantly higher for PPC and pancreatic abscess compared to WON. This may be explained by the fact that WON containing varying amounts of necrotic fluid and solid debris, comparing to PPC with minimal or no necrosis, has lower response rate to EUS-guided drainage and higher risk of complications, such as stent occlusion and stent migration^{11,27}.

For the efficacy of different types of stent drainage of PFCs, there are no related reports about the comparative effects of different subtypes of LAMS on different types of PFCs. Our study mainly included AXIOS stents and Nagi stents, which were made from different manufacturers with various specifications for clinical choosing. Subgroup analysis of LAMS showed that the clinical efficacy of AXIOS stents in PPC were better than in WON (RR = 0.92, 95%CI: 0.86–

0.99). The similar trends of clinical success rates ratios between WON and PPC were also showed in the subgroups of Nagi (RR = 0.92, 95%CI: 0.79–1.07) and other stents (RR = 0.85, 95%CI: 0.58–1.25), in spite of no statistical significance. A large sample size of AXIOS stents (74.3%) might play the major role in the summarized results. As we cannot obtain available data about the size of LAMS from the literature for analysis, the efficacy of different diameter and length of LAMS on PFCs may be more invaluable to clinical application.

A multivariate analysis of 304 patients about pooled adverse reactions of LAMS, published in 2020, showed that the risk of adverse events in patients with WON was 2.18 times higher than in patients with PPC, in which the classification of adverse events was not further discussed³¹. However, our subgroup analysis showed no significant difference in the incidence of the main adverse reactions between WON and PPC, including infection, bleeding, stent migration and stent occlusion. The results might owe to multitude of reasons. Postoperative bleeding was not observed in our case series, meanwhile the rate of overall bleeding in PPC and WON from our meta-analysis was both 1%, which was in accordance with previously reported data. Because of the insufficient data about the occurrence time of bleeding provided by literature, the immediately bleeding and delayed bleeding cannot be further assessed discretely. On the other hand, a cumulative risk analysis from Garcia-Alonso et al.³² revealed that the incidences of bleeding after 1 week, 3 and 6 months were 3.4%, 4.4% and 5.4%, respectively, which reflected a low risk of delayed bleeding following LAMS placement. A newly published protocol also revealed half of LAMS related bleeding occurs within the first week and procedural factors rather than stent dwell time impact risk of bleeding³³. In addition, the overall stent migration rates with the exclusion of asymptomatic displacement in PPC and WON were noted as 1% and 2%, respectively. Some research reported a higher rate of stent migration ranging from 19%–48.9%^{32,34}. The differences may lie in different definitions either asymptomatic migration or endoscopic interventions were required in case of clinically serious issue. Hence adverse events may be stratified for further analysis according to the severity grading system of the ASGE lexicon³⁵.

Regrading to postoperative infection, 5/10 patients with WON had infection in the case series from our center, of which 4 patients with postprocedural infection had moderate to profound solid debris evaluated by CT. Most of them were discharged after anti-infective therapy in combination with endoscopic reinterventions (i.e. DEN or saline lavage). Compared with previously published studies, our case series showed a higher rate of postoperative infection (50%) after LAMS placement. We speculated this was related to the higher mean proportion of solid debris roughly calculated by CT in infection group (32%) than non-infection group (15%). Watanabe et al. also proposed that patients with WON with a high proportion of necrotic tissue had lower treatment success rate³⁶. Although we found no statistical difference in postoperative infection between WON and PPC, the summary of RR on the postoperative infection may indicate that the potential risk in WON (9%) was 1.57 times (95%CI: 0.73–3.39) higher than PPC (2%). Yang et al.²⁵ proposed that the assessment of the proportion of necrotic tissue in WON cases can accurately predict the clinical outcome of LAMS drainage and provide a reference for selecting the best clinical protocol, such as LAMS with DEN, LAMS with double plastic stents, and only LAMS.

It has been reported that patients with PPC have stent blockage with food²⁴, and patients with WON containing large pieces of necrotic debris in cyst are more likely to stent occlusion resulting in secondary infection in the same way¹⁹. In our series, one stent occlusion episode was present in a patient with WON containing 45% solid necrosis. Our meta-analysis showed no significance in the RR of patients with WON compared with patients with PPC on stent occlusion, but the results may potentially reflect a tendency of 1.66 times (95% CI: 0.92–2.98) higher risk of stent occlusion in WON (9%) than PPC (2%). Recently, a novel LAMS with an anti-reflux valve has been developed to prevent food refluxing into the cyst cavity and causing secondary infection³⁷. Above all, more studies on larger sample size may be needed to draw reliable conclusions about adverse events between WON and PPC.

Taking into account the existence of necrotic tissue in WON, more endoscopic procedures are needed. Our meta-analysis including a total of 8 studies showed that approximately 60% of patients with WON underwent DEN. Due to paucity of data about the use of DEN in both arms provided, a good comparison for the use of DEN was not performed. The included literature also reported LAMS placement combining with other reasonable endoscopic treatments based on the available clinical expertise, such as the double pigtail plastic stent placed coaxially in LAMS²⁵, the double pigtail plastic stent replaced after the removal of LAMS²⁸, nasal cyst drainage tube placement, endoscopic retrograde pancreatic drainage²¹ and percutaneous catheter drainage^{24,26}, which may have a contribution in the outcome of PFCs. Even with an inevitable effect of the above combination therapies, the clinical success rate of WON is still lower than that of PPC.

Although the clinical outcomes of WON have been improved by the development of DEN, several adverse events may be unavoidable during the endoscopic treatment course, such as ruptured pseudoaneurysm with bleeding²³. It has been in discussion whether DEN is burdened by an increased risk of adverse events. Fugazza et al.³¹ thought endoscopic necrosectomy usually performed haven't increased such risk. But two systematic review showed that the average sessions of DEN under endoscopy were 4–5, the clinical success rates were 81–88% and the incidences of complications were as high as 28–36%^{38,39}, among which the risks of stent displacement and bleeding after DEN were higher³⁹, and further endoscopic intervention is required to reset the stents to ensure effective drainage. It had been reported that the stent was retrieved and redeployed under direct visualization after the stent migration⁴⁰. Considering the risks of the DEN itself, intervention in a sterile WON may carry with secondary iatrogenic infection. Not all patients with WON need endoscopic mechanical debridement, the research by Joan et al.⁴¹ showed that saline lavage combined with LAMS drainage for WON can simplify the procedure of DEN with good efficacy. Siddiqui et al.⁴² also reported that necrotic tissue was irrigated with hydrogen peroxide solution under endoscope, where hydrogen peroxide decomposes and releases oxygen to loosen the necrotic tissue through its foaming effect.

Therefore, the patients with PFCs should be carefully selected for DEN combined with endoscopic LAMS implantation. It's more appropriate that such complex procedures should be performed by skilled endoscopists, as well as the creation of multiple transluminal gateway in necessity⁴³. At the same time, a multidisciplinary approach involving specialized radiologists and surgeons can be carried out if necessary, such as angioembolization under interventional radiologic guidance, endoscopic and percutaneous drainage or surgery. An open necrosectomy served as a maximally invasive salvage therapy offers the possibility to control critical complications such as bleeding and perform a further necrosectomy when other treatments have failed⁴⁴. On the other hand,

although DEN has certain procedure related adverse events, it is still a good choice compared to conventional surgery and can also be used as a bridge for successful surgery to stabilize the state of critical patients and optimize their clinical status before surgery ²⁰.

A large update of the literature published in the recent five years from various regions were embraced in our study, along with our own case series from China. Most of the studies comparing WON and PPC were multi-center studies. The complications were stratified and the effect of subtypes of LAMS on the drainage of PFCs were further analyzed. Meanwhile we calculated the proportion of DEN in patients with WON to consider its possible impact on outcomes of LAMS. The main limitation of this meta-analysis was related to the study design of included studies. All these studies were retrospective or prospective longitudinal cohort studies. The lack of randomization in the treatment and varied duration of the follow-up time might cause the limitation of the evidence. Several variations in the technology of releasing LAMS and subsequent interventions without standardized treatment decision-making process, as well as inconformity of clinical success and adverse events in some studies may result in overestimation or underestimation. A longer period of follow-up for LAMS drainage may increase number of adverse events reported. However, the high homogeneity of this study in the statistics showed acceptable results and supports our views. Another limitation existed in the relative smaller sample size in PPC cases than WON cases, which might reduce the statistical power. At last, the language bias may exist since only English and Chinese articles were retrieved and studies published in other languages might be omitted in this meta-analysis.

Conclusion

The placement of the LAMS drainage through intestinal wall has promising clinical efficacy and safety for PFCs. The clinical outcomes of LAMS drainage for pancreatic pseudocysts is better than walled-off necrosis, but larger sample size and high-quality follow-up studies are required to determine its adverse reactions. Meanwhile more randomized controlled trials are needed to evaluate the role of DEN in walled-off necrosis.

Abbreviations

PFCs: pancreatic fluid collections

LAMS: lumen-apposing metal stents

PPC: pancreatic pseudocysts

WON: walled-off necrosis

DEN: direct endoscopic necrosectomy

DMHS: double mushroom head stents

CNKI: China National Knowledge Infrastructure

NOS: The Newcastle-Ottawa Scale

RR: relative risk

CI: confidence intervals

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Beijing Friendship hospital, Capital Medical University. Written informed consent was obtained from individual or guardian participants.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interest

The authors declared no conflicts of interest.

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Author contributions

SZ and PL designed the research study. JL, AZ, WW, CL, XL and GZ collected the data. JL, QZ, XS, YW, MJ and YW analyzed and interpreted the data. JL, QZ and PL drafted the manuscript. AZ, WW, CL, XL, GZ, XS, YW, MJ, YW and SZ critically revised the manuscript for intellectual content. All the authors have approved of the final version of the manuscript.

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Figures

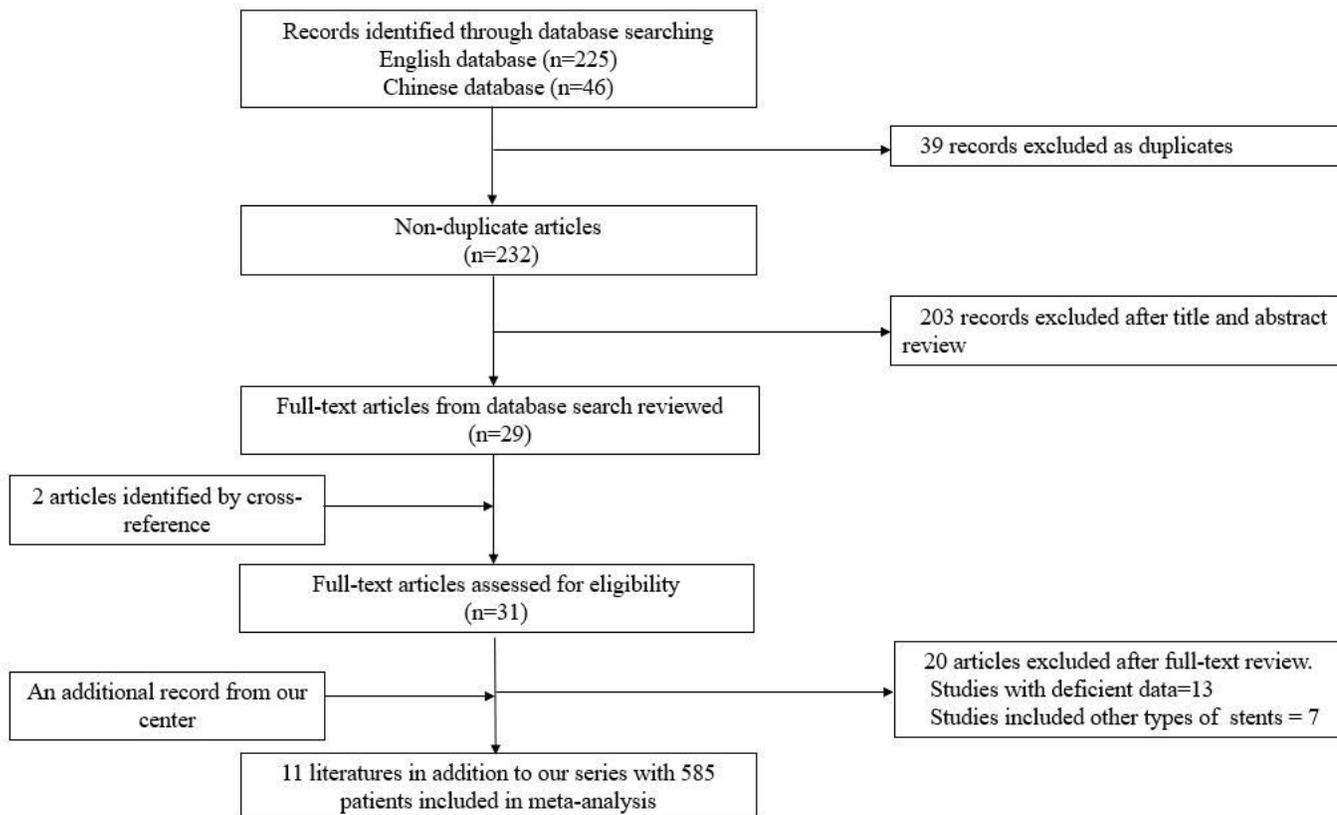


Figure 1

PRISMA flowchart of studies included in the meta-analysis.

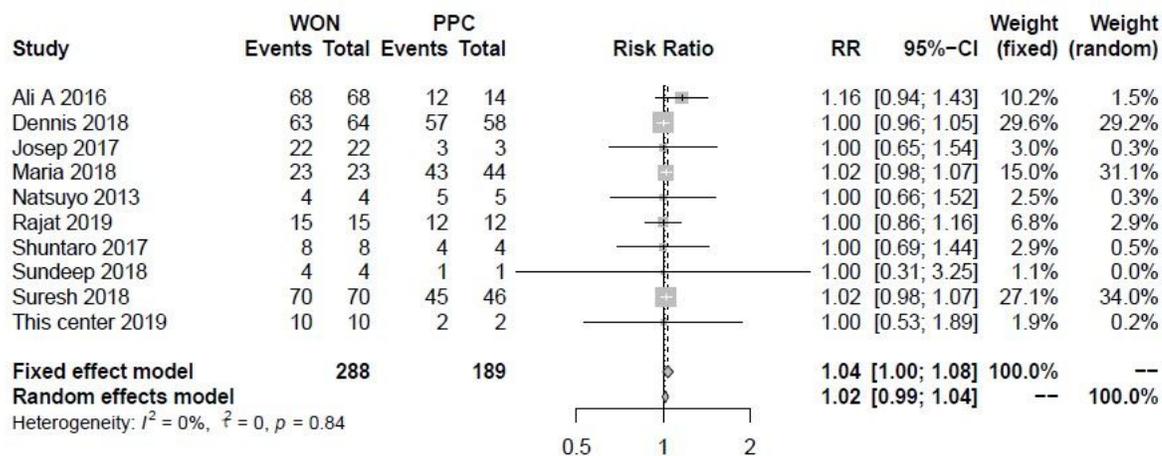


Figure 2

The forest plot of meta-analysis on risk ratio of technical success rates of LAMS between WON and PPC.

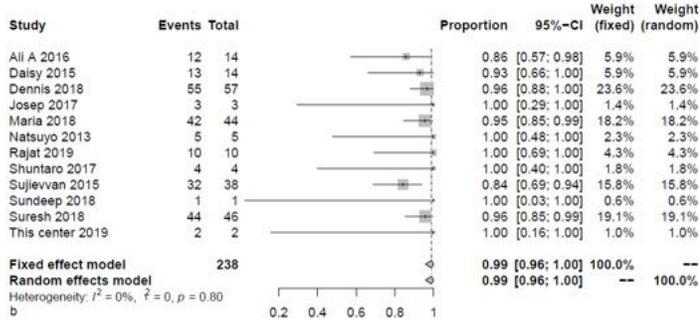
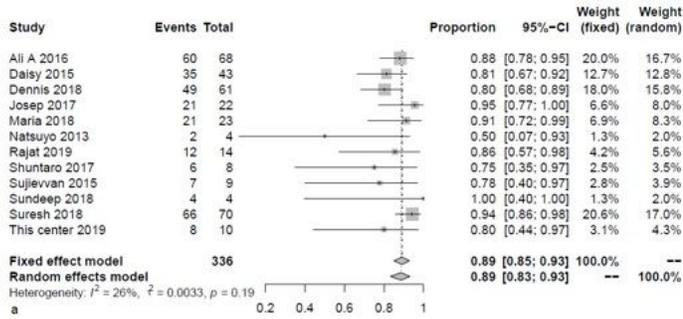


Figure 3

The clinical success rates of LAMS drainage for WON (a) and PPC (b).

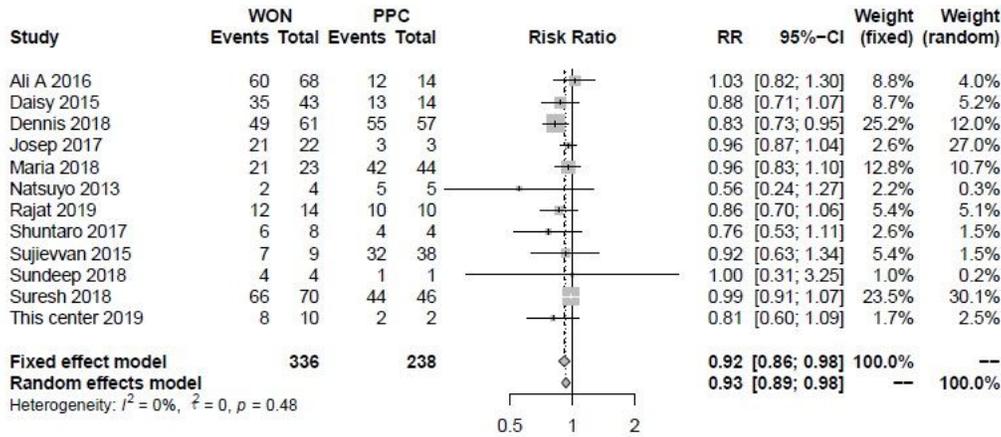


Figure 4

The forest plot in risk ratio of clinical success rates of LAMS between WON and PPC.

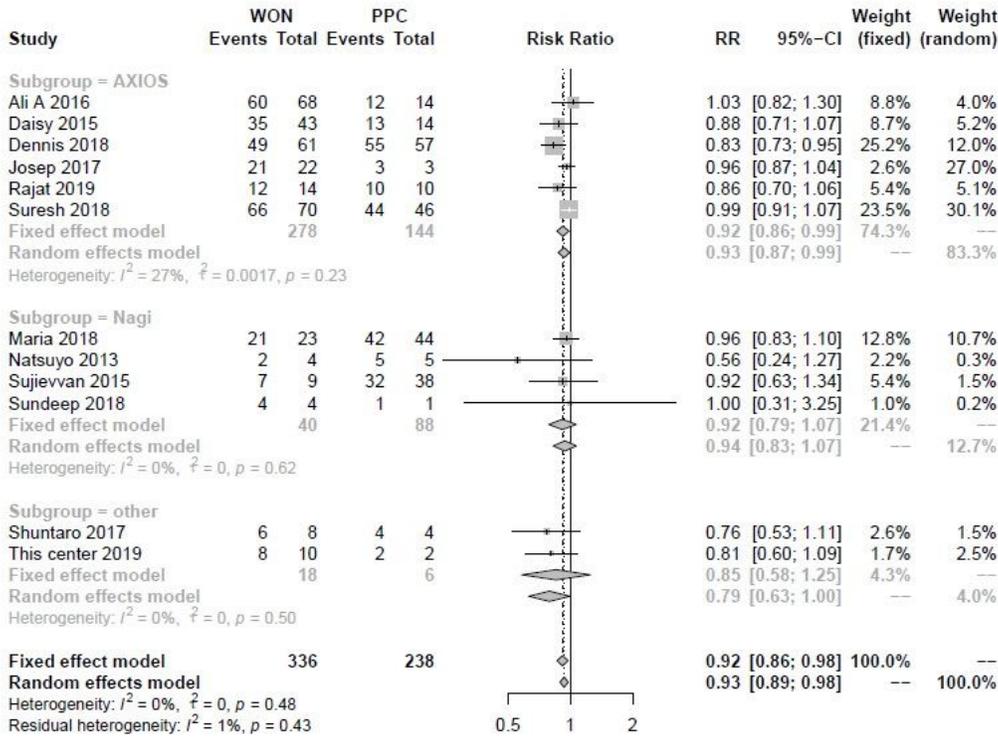


Figure 5

The forest plot of subgroup meta-analysis on risk ratio of clinical success rates between WON and PPC.

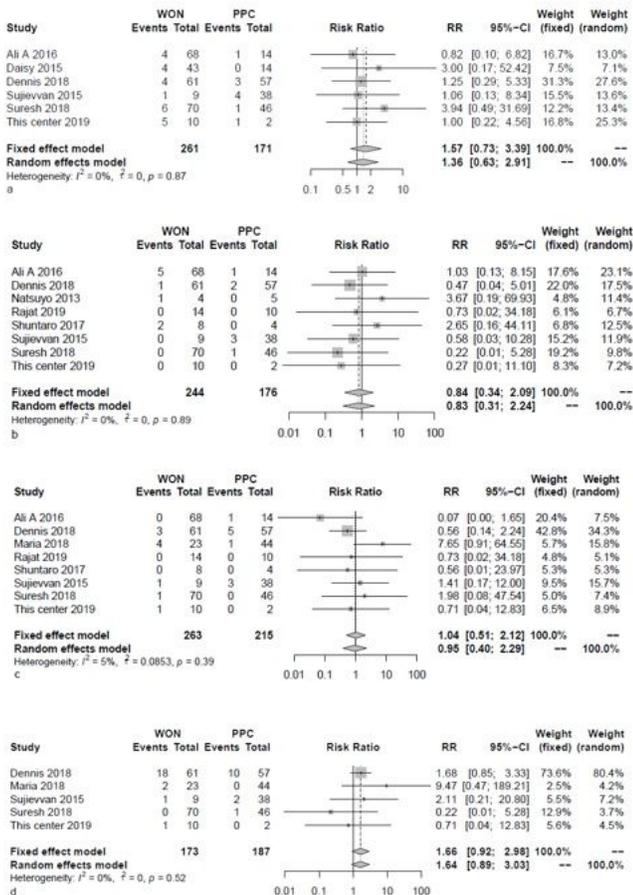


Figure 6

The forest plot of meta-analysis on risk ratio of adverse events rates between WON and PPC. (a, postoperative infection; b, postoperative bleeding; c, stents migration; d, stents occlusion).

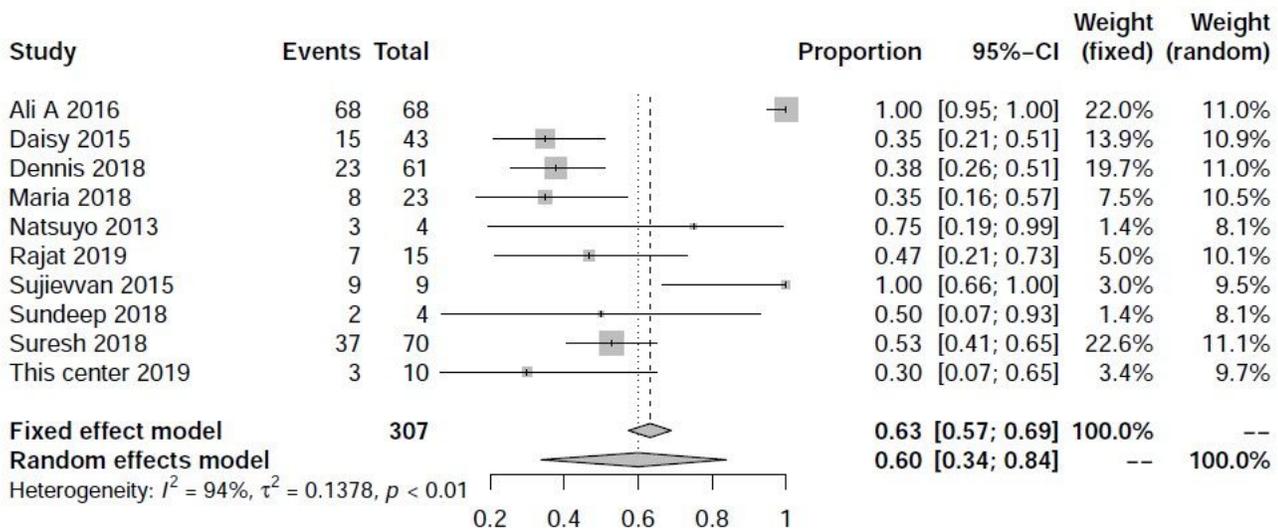


Figure 7

The forest plot of meta-analysis on the proportion of patients undergoing DEN in patients with WON.

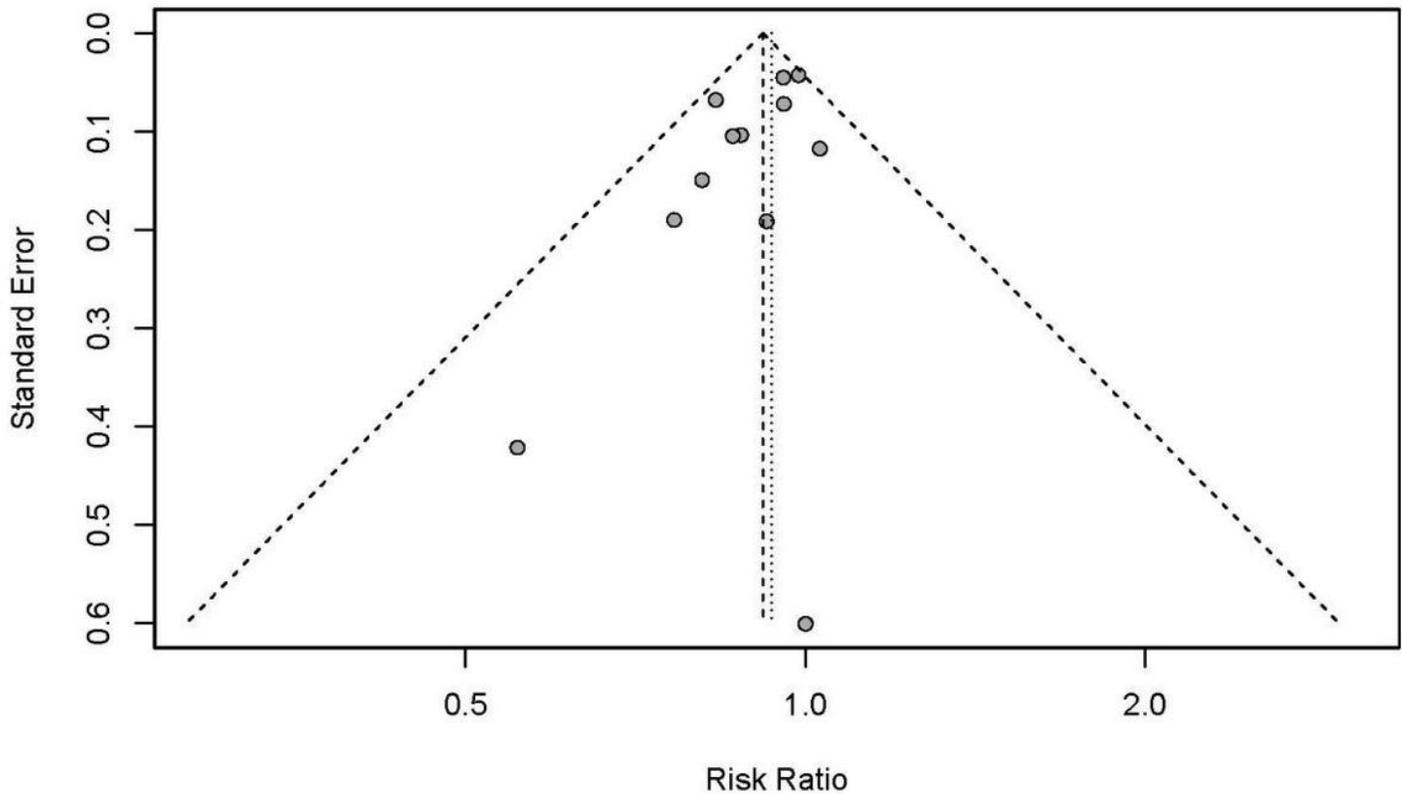


Figure 8

The funnel plot of publication bias.

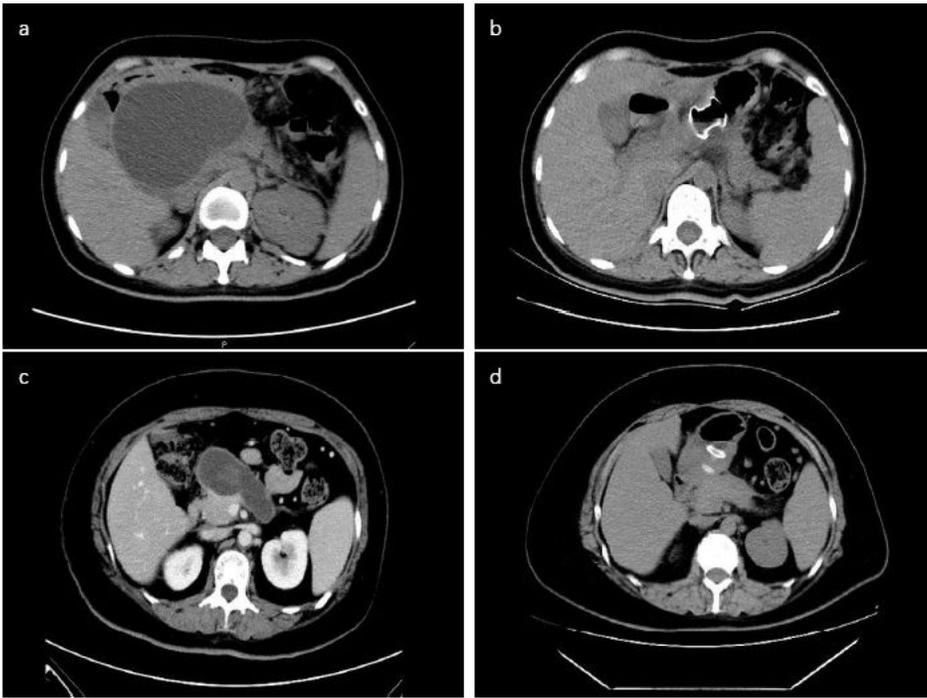


Figure 9

a. The computed tomography scan shows the widespread fluid collection without solid necrotic tissue around pancreas before LAMS placement. b. The computed tomography scan shows resolution of the cyst after LAMS deployment. c. The computed tomography scan shows the walled off necrosis with non-liquid components in the head of pancreas before LAMS placement. d. The computed tomography scan shows significantly shrinking of the cyst after LAMS deployment.

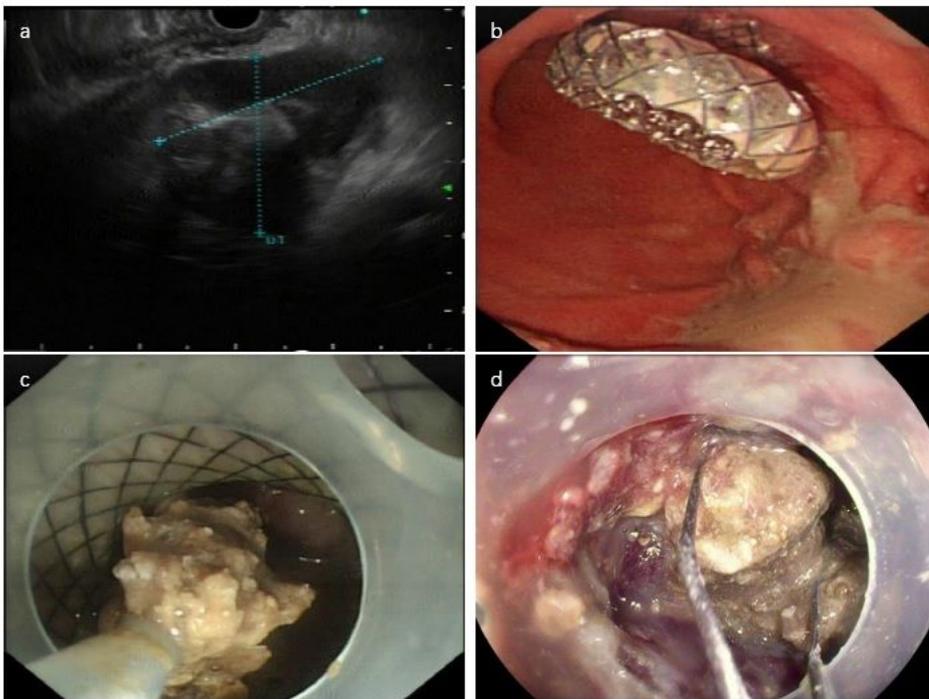


Figure 10

a. Endosonographic view of the walled-off necrosis cavity (8.0*5.0cm). b. An endoscopic view of the fully deployed LAMS across the cystogastrostomy tract, and a large amount of pus was discharge. c and d. Endoscopic view from inside the WON when performing direct endoscopic necrosectomy through the stent: retrieval of a fragment of necrosis with forceps or a snare.

Supplementary Files

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