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Outcomes of Endoscopic Drainage in Children with Pancreatic Fluid Collections: A Systematic Review and Meta-Analysis

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Purpose: Endoscopic drainage is an established treatment modality for adult patients with pancreatic fluid collections (PFCs). Available data regarding the efficacy and safety of endoscopic drainage in pediatric patients are limited. In this systematic review and meta-analysis, we aimed to analyze the outcomes of endoscopic drainage in children with PFCs.
Methods: A literature search was performed in Embase, PubMed, and Google Scholar for studies on the outcomes of endoscopic drainage with or without endoscopic ultrasonography (EUS) guidance in pediatric patients with PFCs from inception to May 2021. The study's primary objective was clinical success, defined as resolution of PFCs. The secondary outcomes included technical success, adverse events, and recurrence rates.
Results: Fourteen studies (187 children, 70.3% male) were included in this review. The subtypes of fluid collection included pseudocysts (60.3%) and walled-off necrosis (39.7%). The pooled technical success rates in studies where drainage of PFCs were performed with and without EUS guidance were 95.3% (95% confidence interval [CI], 89.6–98%; I^2=0) and 93.9% (95% CI, 82.6–98%; I^2=0), respectively. The pooled clinical success after one and two endoscopic interventions were 88.7% (95% CI, 82.7–92.9%; I^2=0) and 92.3% (95% CI, 87.4–95.4%; I^2=0), respectively. The pooled rate of major adverse events was 6.3% (95% CI, 3.3–11.4%; I^2=0). The pooled rate of recurrent PFCs after endoscopic drainage was 10.4% (95% CI, 6.1–17.1%; I^2=0).
Conclusion: Endoscopic drainage is safe and effective in children with PFCs. However, future studies are required to compare endoscopic and EUS-guided drainage of PFCs in children.

Keywords: Pancreatic pseudocyst; Endoscopy; Endosonography; Drainage

INTRODUCTION

The incidence of acute pancreatitis in children has increased over the past two decades [1]. Acute peripancreatic fluid collections are common during the course of acute pancreatitis. Although acute fluid collections resolve in most cases, pseudocysts may form in a proportion (8–41%) of these cases [2]. Conservative management is usually sufficient for cases of asymptomatic pancreatic fluid collections (PFCs). However, symptomatic PFCs require some form of drainage via percutaneous, surgical, or endoscopic approaches. There is

ample evidence regarding the utility of endoscopic drainage of PFCs in adult patients [3-6]. Emerging data also suggests that endoscopic drainage may be a safe and effective treatment in children and adolescents [7]. Unlike adults, pediatric studies on the role of endoscopic drainage are limited by the study design and small sample size, which precludes drawing firm conclusions.

In this systematic review and meta-analysis, we aimed to analyze the clinical success of endoscopic drainage in children with PFCs.

MATERIALS AND METHODS

The present systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [8]. A literature search was performed in PubMed, Embase, and Google Scholar databases. The search was limited to studies in English language and the following key terms were used in different combinations: 'pancreatic fluid collection' OR 'pseudocyst' OR 'walled off necrosis' AND 'endoscopy' OR endoscopic ultrasound OR 'EUS' (**Supplementary Fig. 1**). Two independent investigators (ZN and RT) performed the search and data extraction, and assessed the quality of the studies. Any conflict between the two researchers were resolved by consensus discussion and the opinion of a third investigator (SL).

Criteria for study inclusion and exclusion

The eligibility of the studies for inclusion in the review was judged individually by two different investigators (ZN and RT). The following types of studies published as full-texts or abstracts were included in this meta-analysis: randomized controlled trials, prospective cohorts, or retrospective studies. The inclusion criteria were age ≤18 years, sample size ≥5 cases, and clinical success. The following types of studies were excluded: studies with fewer than five cases, animal model, studies published in languages other than English, editorials, and reviews. In cases of overlapping study cohorts by the same authors, the most recent study was considered eligible for inclusion in the review.

Data abstraction and quality assessment

The following parameters were recorded from the selected studies: study characteristics (design, year of publication, and sample size), endoscopic drainage procedure-related parameters (with or without endoscopic ultrasonography [EUS] guidance, adverse events), demographic characteristics of the study population (mean/median age in years, sex, size of collection), mean or median follow-up duration in months, clinical success as defined by resolution of PFCs, recurrence, and re-intervention rates. The data obtained from the included studies were systematically recorded in a database (Microsoft Excel® 2021, Version 16.48; Microsoft, Redmond, WA, USA).

Outcomes assessed

The primary objective of the study was clinical success, as defined by the resolution of PFCs after endoscopic drainage of PFC. Secondary objectives included technical success, adverse events related to endoscopic drainage, recurrence rates, and rates of re-interventions. Any difference in opinion between the two investigators was resolved by consensus and judgement of a third researcher (SL).

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Assessment of quality of studies

The quality of the studies was evaluated using the methodological index for nonrandomized studies (MINORS). The tool comprises eight questions that assess various domains related to the quality of the study [9]. The answer to each question was rated from 0 to 2 (0=not reported; 1=reported but inadequate; and 2=reported, adequate). The best possible score for the study was 16. The final ratings of the included studies were given as 'good', 'fair', or 'poor' by two independent researchers (ZA/RT), and any discrepancy in the rating was resolved by a third reviewer (SL).

Statistical analysis

The outcomes of interest are presented as pooled data with a 95% confidence interval (CI). Numerical data, available as a range or interquartile interval, were transformed to standard deviation before analysis using the method described by Hozo et al. [10] and Wan et al. [11]. Heterogeneity among the studies was identified by examination of forest plots and I^2 statistics and graded as low (I^2 0–30%), moderate (31–60%), substantial (61–75%), and considerable (76–100%). A random-effects model (Der Simonian and Laird) was used for the analysis [12]. Forest plots were constructed for the primary and secondary outcomes. All analyses were performed using Comprehensive Meta-Analysis software (version 3.0; Biostat, Englewood, NJ, USA).

Publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's test of the intercept [13]. Egger's test utilizes a linear regression of the intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate.

Duval and Tweedie's trim and fill method was used to address publication bias and to determine the imputed point estimate in case a significant publication bias was suspected on visual inspection of the funnel plot [14].

RESULTS

Baseline characteristics of the studies

A preliminary literature search revealed 5,136 records (**Supplementary Fig. 1**). After screening for eligibility, a total of 14 studies were included in this review. The included studies were published as full-text (10) or abstracts (4) between 2008 and 2021 [15-28]. All the included studies were retrospective in nature. The details of the selection process according to the PRISMA guidelines and the summary of the included studies are presented in **Fig. 1** and **Table 1**, respectively.

Patients' characteristics

Overall, the studies involved a total of 187 children with a pooled mean age of 11.7 years (95% CI, 10.2–13.2 years). The aetiology of pancreatitis was described in nine studies (137 children), and were idiopathic in 76 (55.5%), trauma in 32 (23.3%), biliary in 13 (9.5%), chronic pancreatitis in 5 (3.6%), pancreas divisum in 3 (2.2%), genetics in 3 (2.2%), and others in 5 (3.6%) children [15-17,20-24,27]. The characteristics of fluid collection in 13 studies were pseudocysts in 108 (60.3%) and walled-off necrosis (WON) in 71 (39.7%). In one study, the proportions of pseudocysts and WON were not clearly defined [25]. The pooled mean PFC size was 11.5 cm (95% CI, 9.9–13.1 cm; I^2=84.7%) (**Table 1**).

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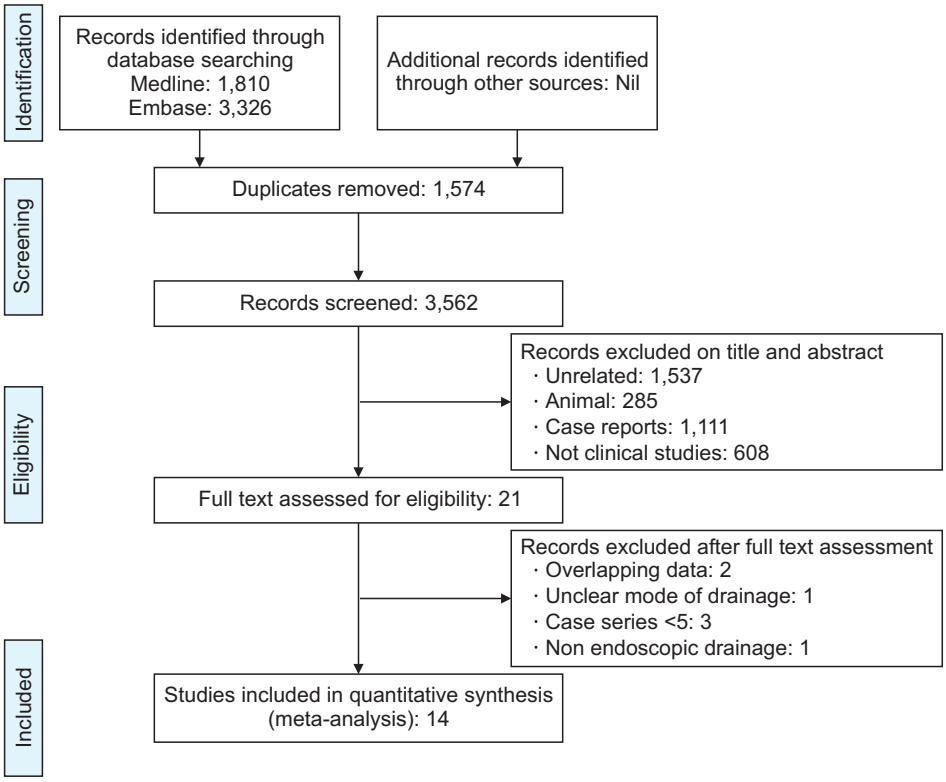

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis) flow diagram demonstrating study selection process.

Technique of endoscopic drainage

Endoscopic drainage procedures were performed under general anesthesia in four studies [16,17,20,21]. Moderate sedation (ketamine, midazolam, or diazepam with or without propofol) was used in five studies [15,18,22,23,27] (**Supplementary Table 1**).

Endoscopic drainage of PFCs was performed under EUS guidance in 10 studies [18-26,28] and without EUS guidance in three studies [15,17,27]. In one study, drainage procedures were performed using both techniques [16]. The most common route for drainage was transgastric (n=139), followed by transesophageal (n=4) and transduodenal (n=2). The drainage route was not reported in three studies [18,21,28] (**Table 2**).

The type of stent used for endoscopic transmural drainage was reported in 10 studies including one or more plastic stents in six studies [15-17,20,22,27], either plastic or metal stents in three studies [21,24,25], and exclusively metal stents in one study [23].

Other details, including the type of scope and the technique of drainage utilized in each study, are outlined in **Table 2**.

Technical outcomes

The pooled technical success rate of endoscopic drainage was 94.9% (95% CI, 90.5–97.3%; I^2=0) (**Fig. 2A**). The pooled technical success rates in studies where drainage of PFCs were performed with and without EUS guidance were 95.3% (95% CI, 89.6–98%; I^2=0) and 93.9% (95% CI, 82.6–98%; I^2=0). There was no heterogeneity among the included studies regarding technical success.

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Table 1. Demographic characteristics of children in different studies

Study	Country/Study design	Study period	N	Age in years (mean±SD)	Sex (M/F)	Size of PFC (cm)†	Nature of PFC (PC or WON)	Aetiology of pancreatitis	Duration of collection
Sharma and Maharshi, 2008 [15]	India/R	1994–2004	9	9.6±4.42	6/3	12.4±3.9	All PC	Trauma 8, idiopathic chronic pancreatitis 1	3–30 mo
Jazrawi et al., 2011 [16]	USA/R	Jan 2004–Oct 2009	10	11.8±4.9	4/6	7.2±3.2	All PC	Biliary 4, trauma 2, divisum 1, familial 1, idiopathic 2	NR
Makin et al., 2012 [17]	UK/R	Jan 2001–Dec 2010	7	12.2±3.1	5/2	14.1±4.3	All PC	Trauma 2, divisum 1, idiopathic 1, drug 1, genetic 1, biliary 1	6 mo (1–9)
Ramesh et al., 2013 [20]	USA/R	Oct 2007–Jan 2012	7	8.4±2.1	4/3	12.3±2.6	PC 6, WON 1	Trauma 5, hereditary 1, idiopathic 1	4 wk (IQR 2–6)
Agarwal et al., 2013 [18]*	India/R	Jan 2009–Dec 2012	20	NR	NR	NR	All PC	NR	NR
Bai, 2013 [19]*	China/R	Jan 2006–Oct 2012	5	10–14	NR	NR	All PC	NR	NR
Bang and Varadarajulu, 2016 [21]	USA/R	April 2009–May 2015	6	13.5±3.1	1/5	13.3±6.3	WON	Idiopathic 3, biliary 2, drug 1	5.3±1.5 mo
Nabi et al., 2017 [22]	India/R	Jan 2013–June 2016	30	13±3.4	22/8	9.5 (6.1–17.5)	PC 13, WON 17	Trauma 6, biliary 1, idiopathic 23	63 d (28–1,126)
Nabi et al., 2019 [23]	India/R	NR	32	15 (9–18)	28/4	NR	All WON	Idiopathic 26, biliary 2, alcohol 2, divisum 1, eosinophilic 1	NR
Farr et al., 2020 [24]	USA/R	2008–2019	5	NR	NR	10.6±3.4	All PC	Trauma 5	5.8±0.8 wk
Lal et al., 2020 [25]	India/R	Jan 2015–July 2019	6	10 (IQR 10–11)	5/1	9.9 (7.6–14.7)	PC and WON	NR	NR
Poddar et al., 2021[27]	India/R	June 2013–Dec 2017	31	14 (3–17)	22/9	13.6 (8.5–21)	WON 12, PC 17	Idiopathic 19, chronic pancreatitis 5, trauma 4, biliary 3	2 mo (1–10)
Seol et al., 2021 [28]*	South Korea/R	Sept 2002–April 2020	14	NR	NR	NR	PC 11, WON 3	NR	NR
Ghoneem et al., 2021 [26]*	Egypt/R	May 2017–June 2020	5	NR	NR	NR	All PC	NR	NR

PFC: pancreatic fluid collection, PC: pseudocyst, WON: walled-off necrosis, R: retrospective, NR: not reported, SD: standard deviation, IQR: interquartile range.
*Abstracts. †Max reported dimension.

Table 2. Technical and clinical outcomes of endoscopic drainage of pancreatic fluid collections

Study	EUS or endoscopic	Route (CG or CD)	Tech success (%)	Stent (plastic/metal)	Adverse events	Clinical success (%)	Recurrence	Re-intervention	Follow-up
Sharma and Maharshi, 2008 [15]	Endoscopic	CG 8, CD 1	9 (100)	Plastic	0	All	0	0	5.7 y (2–10)
Jazrawi et al., 2011 [16]	Endoscopic 5 *EUS 5	CG	10 (100)	Plastic	0	All	0	0	6 mo
Makin et al., 2012 [17]	Endoscopic	CG	7 (100)	Plastic	0	5 (71.4)	1	2	18 mo (5–108)
Ramesh et al., 2013 [20]	EUS	CG	7 (100)	Plastic	0	5 (71.4) 7 (100)	0	2	34 mo (IQR 193–1,167 d)
Agarwal et al., 2013 [18]	EUS	NR	20 (100)	NR	2	20 (100)	NR	NR	NR
Bai, 2013 [19]	EUS	CG	5 (100)	NR	0	5 (100)	0	0	21 mo (10–32)
Bang and Varadarajulu, 2016 [21]	EUS	NR	6 (100)	Plastic 5, Metal 1	0	4 (66.7) 6 (100)	0	2	29.2±26.1 mo
Nabi et al., 2017 [22]	EUS	CG 26, TE 4	29 (96.7)	Plastic	10 (2 major-bleeding, perforation)	28 (93.3)	2	3	829 d (150–1,230)
Nabi et al., 2019 [23]	EUS	CG	32 (100)	Metal	NR	29 (90.6)	5	3	15.2±15.9 mo
Farr et al., 2020 [24]	EUS	CG	5 (100)	Plastic 3, Metal 2	NR	5 (100)	NR	NR	23±28.6 mo
Lal et al., 2020 [25]	EUS	CG	6 (100)	Plastic 1, Metal 5	0	6 (100)	NR	NR	NR
Poddar et al., 2021 [27]	Endoscopic	CG 28, CD 1	29 (93.5)	Plastic	11 (major: bleeding 1, pneumoperitoneum 1)	28 (90.3)	3	0	26 mo (5–48)
Seol et al., 2021 [28]	EUS	NR	14 (100)	NR	1 (peritonitis)	14 (100)	NR	NR	NR
Ghoneem et al., 2021 [26]	EUS	CG	5 (100)	NR	1 (fever+vomiting)	5 (100)	NR	NR	NR

EUS: endoscopic ultrasonography, CG: cystogastric, CD: cysto-duodenal, TE: trans-esophageal, NR: not reported, IQR: interquartile range.
*EUS used to identify the puncture site and deploy a plastic stent.

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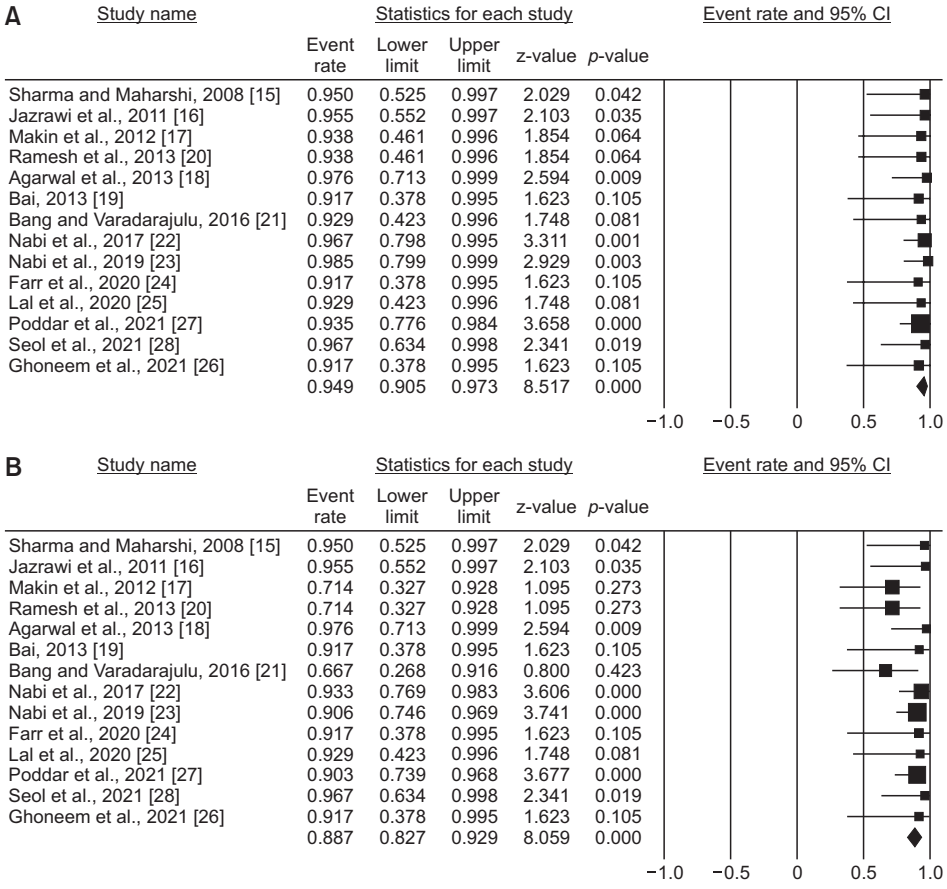

Fig. 2. (A) Forest plot demonstrating pooled technical success of endoscopic drainage. (B) Forest plot demonstrating pooled clinical success of endoscopic drainage.
CI: confidence interval.

Clinical outcome

The pooled clinical success rate after a single endoscopic intervention was 88.7% (95% CI, 82.7–92.9%; I^2=0) (**Fig. 2B**). The overall pooled clinical success rate after the second endoscopic intervention was 92.3% (95% CI, 87.4–95.4%; I^2=0) (**Supplementary Fig. 2**).

Recurrence and re-intervention

The pooled mean follow-up duration after endoscopic drainage reported in 10 studies was 26.6 months (95% CI, 20.9–32.3 months; I^2=78%) [15-17,19-24,27]. Significant heterogeneity in the follow-up period was due to the shorter follow-up in the study by Nabi et al. [23] and relatively longer follow-up in the study by Sharma and Maharshi [15]. The pooled rate of recurrent PFCs after endoscopic drainage was 10.4% (95% CI, 6.1–17.1%; I^2=0) (**Supplementary Fig. 3**). The pooled rate of re-intervention after the index drainage procedure was 13.2% (95% CI, 7.5–22.3%; I^2=11.6%) (**Fig. 3A**). In most cases (11 out of 12, 91.7%), endoscopic re-interventions were performed (**Supplementary Table 2**).

Adverse events

The pooled rates of overall and major adverse events reported in 12 studies were 16.8% (95% CI, 9.8–27.2%; I^2=28.6%) and 6.3% (95% CI, 3.3-11.4%; I^2=0), respectively (**Fig. 3B**) [15-22,25-28]. The pooled rates of adverse events in the studies where endoscopic drainage procedures

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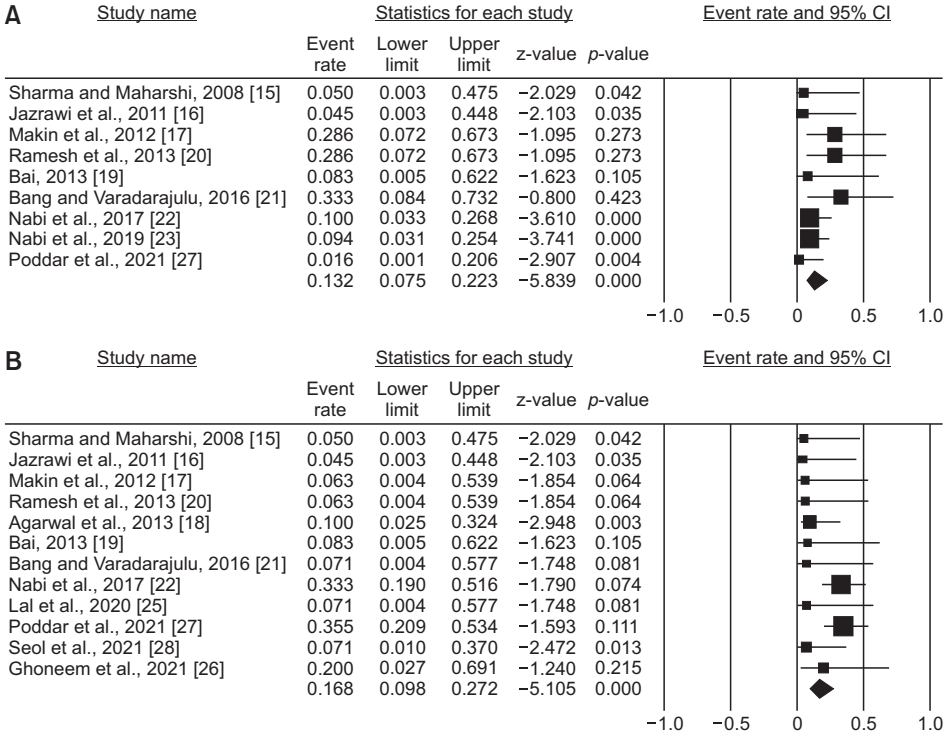

Fig. 3. (A) Forest plot demonstrating pooled rates of re-intervention after endoscopic drainage. (B) Forest plot demonstrating pooled rates of adverse events associated with endoscopic drainage.
CI: confidence interval.

were performed with and without EUS guidance were 15.8% (95% CI, 8.3–27.9%; I^2=18.5%) and 16.7% (95% CI, 3.5–52.6%; I^2=51.8%), respectively.

Publication bias

Visual inspection of the funnel plot suggested no publication bias with respect to the technical success, recurrence, and re-intervention rates. With regard to clinical success and adverse events, publication bias was suspected upon visual inspection of the funnel plot. Egger's test revealed an intercept (B0) of 0.85 (95% CI, −0.61 to 2.29; p=0.114) for clinical success and −1.95141 (95% CI, −2.50401, −1.39881; p=0.00001) for adverse events. Using Trim and Fill, the imputed clinical success rate was 87.3% (95% CI, 80.9–91.7%). The imputed values were unchanged for adverse events (**Fig. 4**).

Quality of studies

The overall quality of the studies was rated as fair, with a median MINORS score of 8 (range 6–10). All the included studies performed well with respect to 'clearly stated aim' and 'endpoints appropriate to the aim of the study'. Most studies performed well with respect to 'appropriate follow-up period' (n=13 ≥1-year mean follow-up) and 'loss to follow-up <5%' (n=11). However, most of the studies did not include or report whether consecutive children were included, raising the possibility of selection bias. None of the included studies performed a prospective calculation of the study size or an unbiased or blinded assessment of the study endpoints. The details of individual assessment of the studies on the MINORS scale are outlined in **Supplementary Table 3**.

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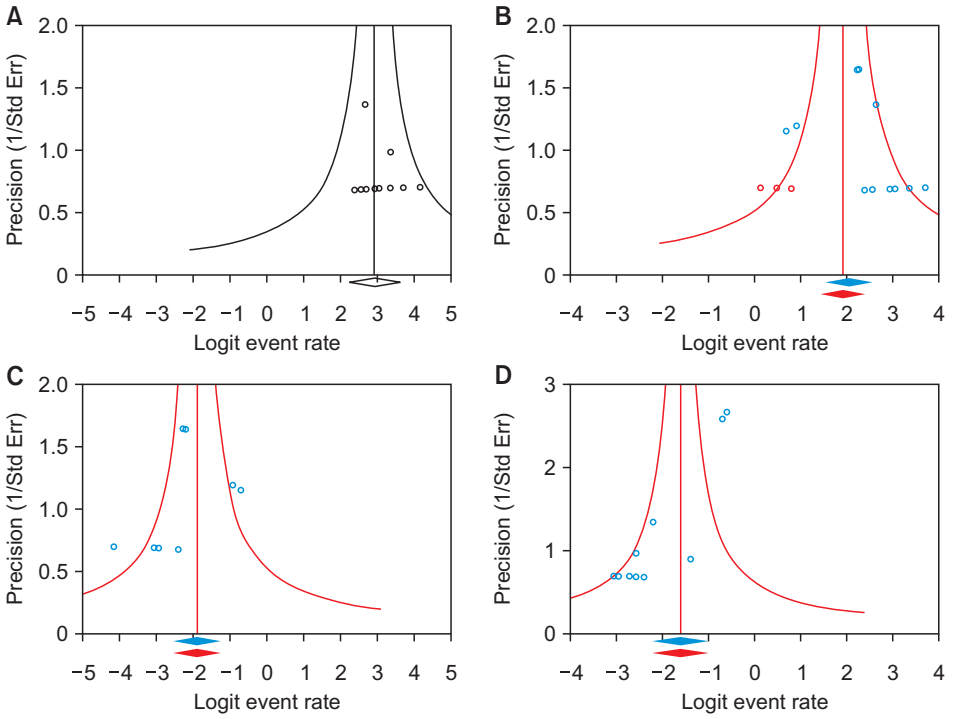

Fig. 4. (A) Funnel plot related to technical success of endoscopic drainage. (B) Funnel plot related to clinical success of endoscopic drainage (imputed clinical success depicted in red). (C) Funnel plot pertaining to rates of re-intervention after endoscopic drainage. (D) Funnel plot related to adverse events after endoscopic drainage. Std Err: standard error.

DISCUSSION

Endoscopic drainage has emerged as the treatment of choice in adults with PFCs [6,29-32]. In contrast, data regarding the safety and efficacy of endoscopic drainage in pediatric patients are limited. The predominant reasons are technical issues related to the size of therapeutic EUS scopes, lack of expertise, and requirement for general anesthesia. In this systematic review and meta-analysis, we analyzed the outcomes of endoscopic drainage in children and adolescents with PFCs including pseudocysts and WON. We found that endoscopic drainage with or without EUS assistance was a safe and effective treatment modality for pediatric patients with PFCs.

Endoscopic drainage procedures were successfully performed in most cases, and technical failure was rare. While general anesthesia is preferred for therapeutic EUS procedures, drainage procedures could be successfully performed under moderate sedation (midazolam, ketamine, and propofol) in five studies included in this review. Interestingly, all five studies in which moderate sedation was used were performed in India. While the choice of sedation may differ among centers, it may not be reasonable to presume that general anesthesia is not mandatory for the endoscopic drainage of PFCs.

The drainage procedures were performed under EUS guidance in most studies. Importantly, the pooled rates for technical success were similar in studies that performed drainage procedures with or without EUS guidance (EUS 95.3% vs. non-EUS 93.9%). In contrast, few randomized trials in adult patients have concluded the superiority of EUS-guided drainage

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over endoscopic drainage, especially in non-bulging collections [33,34]. One possible reason for this discrepancy in the present review may be the selective inclusion of cases with luminal bulge in which both drainage techniques (endoscopic versus EUS) may have comparable success rates [34]. On the same note, EUS-guided drainage may not be technically feasible in smaller children (<15 kg) owing to the large tip diameter of therapeutic echoendoscopes [35]. Therefore, caution is advised when considering the high technical success rate of EUS-guided drainage in pediatric patients.

The overall clinical success after one and two endoscopic interventions were 89% and 92%, respectively. This finding suggests that endoscopic drainage is an effective modality for drainage in pediatric patients with PFCs. This finding is substantiated by the low rate of re-interventions (13%) over a mean follow-up of about 2 years. These results are comparable to those reported in adult studies, where the overall success rate of endoscopic drainage has been reported in 63–100% cases [5].

The pooled rate of adverse events associated with endoscopic drainage was 17%, with no significant difference between the EUS-and non-EUS-guided approaches (16% vs. 17%). Notably, most studies did not use a standardized definition to report adverse events. As a result, some of the inconsequential events, such as minor bleeding episodes, were reported as adverse events in some studies that possibly inflated the overall rate of adverse events [22,27]. Furthermore, major adverse events were uncommon (6%), including perforation or peritonitis (n=3), and major bleeding episodes (n=2).

The present systematic review and meta-analysis has several strengths. To the best of our knowledge, this is the first systematic review to analyze the outcomes of endoscopic drainage of pediatric PFCs. Overlapping study cohorts were avoided by rigorous screening. However, we acknowledge certain drawbacks, which include the retrospective design of the studies included in this review, small sample size, and inclusion of four studies available in the abstract form. The limited number of pediatric studies pertaining to endoscopic drainage in children justifies the inclusion of abstracts for this systematic review and meta-analysis.

Moreover, data regarding the primary objective of this review (i.e., clinical success) were available in all the included studies. Since endoscopic drainage was performed in carefully selected cases (rather than consecutive cases), caution is advised when concluding the high technical success in this review. The results of endoscopic drainage of PFCs were not stratified according to the age or etiology of pancreatitis because of the limited information available from the studies. Other important caveats in existing literature include a lack of standardized reporting of adverse events and the absence of categorization of fluid collections (WON or pseudocyst). Moreover, the role of endoscopic necrosectomy and the impact of the disconnected duct on recurrence in pediatric patients with WON need to be evaluated in future studies [36].

In conclusion, endoscopic drainage with or without EUS guidance is a safe and effective treatment modality for pediatric patients with PFCs. Prospective comparative trials are required to compare endoscopic and EUS-guided drainage in the pediatric population.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Type of scope, sedation, and technical details of endoscopic drainage

Click here to view

Supplementary Table 2

Recurrence and re-intervention rates after endoscopic drainage of pancreatic fluid collection

Click here to view

Supplementary Table 3

Assessment of study quality using MINORS tool

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Supplementary Fig. 1

Preliminary search results from Embase and Medline.

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Supplementary Fig. 2

Forest plot revealing clinical success after second endoscopic intervention.

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Supplementary Fig. 3

Forest and funnel plots related to recurrence of fluid collection after endoscopic drainage.

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