Systematic Review and/or Meta-analysis

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Efficacy and safety of 13 surgical techniques for the treatment of complex anal fistula, non-Crohn CAF: a systematic review and network meta-analysis

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Background: Considering the difficulty of treating complex anal fistula (CAF), various surgical techniques exist in clinical work. However, none are ideal. Evidence on the efficacy and safety of different surgical treatments is scarce. The authors aimed to compare the outcomes of the 13 surgical techniques and tried to find the best surgical method for treating CAF.

Materials and methods: The authors searched worldwide databases, including Pubmed, Embase, Cochrane Library, Web of Science, CNKI, WanFang, VIP, and SinoMed, from inception to March 2023. All randomized controlled trials comparing the outcomes of 13 surgical techniques were included according to the PICO principles. The indicators of the cure rate, the recurrence rate, the complication rate, the operating time, the postoperative pain on day 1 (VAS), and the postoperative incontinence in month 1 (Wexner) were extracted and analyzed using STATA software 15.1, Review Manager 5.4, and GeMTC14.3.

Results: Twenty-eight randomized controlled trials with a total of 2274 patients were included in the network meta-analysis. There was no statistically significant difference in the comparison among any surgical interventions in terms of the cure rate ($P > 0.05$ Table 2) and recurrence rate ($P > 0.05$ Table 3). However, in terms of complication rate, fistulectomy was lower than FPS (Median: 0.14; 95% CI: 0.02–0.70) or fistulotomy (Median: 0.09; 95% CI: 0.01–0.55), and fistulotomy was lower than EAFR (Median: 0.24; 95% CI: 0.05–0.84), LIFT (Median: 0.17; 95% CI: 0.02–0.66) or LIFT-EAFR (Median: 0.11; 95% CI: 0.01–0.69) ($P > 0.05$ Table 4). The surface estimated the advantages and disadvantages under the cumulative ranking (SUCRA). The ranking results indicated that fistulectomy might have the lowest complication rate (SUCRA = 7.9%). Because the network results of the operating time, the postoperative pain, and the postoperative incontinence contained no closed loops, the results of their probability ranking could only be referenced, demonstrating that fistulectomy might have the shortest operating time (SUCRA = 23.4%), video-assisted modified ligation of the intersphincteric fistula tract (VAMLIFT) might have the lowest postoperative pain on day 1 (VAS) (SUCRA = 0.4%) and LIFT might have the lowest postoperative incontinence in month 1(Wexner) (SUCRA = 16.2%).

Conclusion: Fistulectomy might have the lowest complication rate, which might be the relatively superior surgical technique for treating CAF.

Keywords complex anal fistula, network meta-analysis, surgical techniques

Introduction

A complex anal fistula (CAF) is one common but refractory anorectal disease accounting for 1.7–3.6% of colorectal anal surgeries[1], and its prevalence is 8.6 to 10/per 100 000 of the population every year[2,3]. The symptoms of anal fistulas can include perianal openings with a red, inflamed area, irritation and excruciating pain of the perianal skin, and perianal discharge of pus. Notably, surgery is the primary method of treatment to eliminate the fistulas and preserve the function of the anal sphincter[4]. However, treating CAF is difficult due to the high postoperative recurrence rate and complication rate[5], especially for fecal incontinence. The risk of postoperative incontinence ranges from 6.7 to 52%[6,7], and postoperative recurrence from 10 to 57%[5,8]. Thus, the management of CAF remains challenging[5].

Considering the difficulty of the treatment of CAF, there are various kinds of surgical techniques in the clinical work, such as

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ligation of intersphincteric fistula tract (LIFT)[9], endoanal advancement flap repair (EAFR)[10], video-assisted anal fistule treatment(VAAFT)[11], seton[12], fistulectomy[13], fistulotomy[14], anal fistula plug (AFP)[15], fistulotomy plus seton (FPS) or incision thread drawing[16], LIFT-plug[17], fistulotomy with sphincter reconstruction (FSR)[18], video-assisted modified ligation of the intersphincteric fistula tract (VAMLIFT)[11], tunnel-like fistulectomy plus draining seton combined with incision of the internal opening of anal fistula (TFSIA)[16], and LIFT + EAFR. However, none of these surgical methods are ideal. Although various operative options could treat large numbers of anal fistula, the high rate of postoperative recurrence and fecal incontinence still needs to be addressed.

Given the many surgical options for CAF, the efficacy of each surgical method differs. Thus, it is urgent to increase surgeons' understanding of the CAF and contribute to clinical decision-making during operation. In this study, we obtained 28 RCTs by searching eight authoritative databases and summed up 13 surgical techniques for treating CAF. Until now, scarce research has compared the efficacy and safety of the 13 surgical methods for treating CAF. Therefore, this study was conducted via network meta-analysis to evaluate the differences between various kinds of surgeries, such as the cure rate, the recurrence rate, the complication rate, the operating time, the postoperative pain, and the postoperative incontinence. What we found is significantly meaningful for clinical surgeons' clinical decision-making and is essential to improving patients' suffering.

HIGHLIGHTS

- Fistulectomy might have the lowest complication rate.
- It could be referenced that fistulectomy might have the shortest operating time.
- Video-assisted modified ligation of the intersphincteric fistula tract (VAMLIFT) might have the lowest postoperative pain on day 1.
- LIFT might have the lowest postoperative incontinence in month 1.
- Fistulectomy might be the relatively superior surgical technique for treating the complex anal fistula.

Materials and methods

Search strategy

This network meta-analysis was registered in the Research Registry, an international register website of systematic reviews (www.researchregistry.com). This systematic review and network meta-analysis had been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[19] and AMSTAR 2 (Assessing the methodological quality of systematic reviews) Guidelines[20]. We searched eight worldwide databases, including Pubmed, Embase, Cochrane Library, Web of Science, CNKI, WanFang, VIP, and SinoMed, from inception to March 2023. The articles we selected were published in the language of either English or Chinese. The search items included 'Anal Fistula', 'fistula-in-ano', 'complex anal fistula', 'Ligation of intersphincteric fistula tract', 'Endoanal advancement flap repair', 'Video-assisted anal fistule treatment', 'Seton', 'Fistulectomy', 'Fistulotomy,' 'Anal fistula plug,' 'Fistulotomy Plus Seton or incision thread drawing', 'LIFT-plug', 'Fistulotomy with sphincter reconstruction', and 'Video-assisted modified ligation of the intersphincteric fistula tract', and 'Tunnel-Like Fistulectomy Plus Draining Seton Combined with Incision of Internal Opening of Anal Fistula'. Additionally, the medical subject headings or free-text terms or variants were used in our search strategy. Furthermore, the Boolean Operators 'AND', 'OR', and 'NOT' were applied to connect the search items to constitute the strategy expression. Only RCTs were included in this analysis.

Eligibility and inclusion criteria

Two researchers independently included the articles meeting the criteria according to the PICO principles. Targeted literature for inclusion: P: patients with a definitive diagnosis of CAF[21]: fistula tract crossing more than 30% of the external sphincter, anterior fifistula in a woman, multiple tracts, recurrent fifistula, or preexisting incontinence; patients with other causes of CAF such as inflammatory bowel disease, tuberculosis, trauma, and foreign body infection were excluded; patients with other underlying diseases at the time of treatment, such as severe cardiovascular disease, diabetes mellitus, hematologic disease, and psychiatric disease were also excluded; I: LIFT, EAFR, VAAFT, Seton, Fistulectomy, Fistulotomy, AFP, FPS, LIFT-plug, FSR, VAMLIFT or TFSIA; C: the 13 surgical techniques compared to each other O: complete wound healing was defined as the absence of suppuration of the external orifiifice and full epithelialisation of the wound; recurrence was defined as either non-healing of the wound after 12 weeks or a reappearance of symptoms at the same site; complications refer to the occurrence of another disease or symptom during the treatment, including postoperative urinary retention, infection, anal itching, postoperative bleeding, hematoma, anal wetness, edema at the margins of the wound, wound fissure, or anal incontinence.

In case of disagreement between the two investigators, a consensus result was obtained after consultation, discussion, and consultation with the supervisor. Overall, we obtained 28 RCT studies and their characteristics are clarified below (Table 1).

Data extraction and quality assessment

Two investigators independently extracted the information of the articles, including the publication names, published year, which country the study had been conducted in, research types, kinds of surgical techniques, AF type, age, sample size, sex, follow-up, and outcome indicators (cure rate, recurrence rate, complication rate, duration of operation, VAS score, Wexner incontinence score). Controversial studies were assessed by a third party and unified through discussion.

The quality assessment of the study was done carefully by the two researchers. The quality evaluation and the assessment of the risk of bias of RCTs were assessed using the Cochrane Handbook for Systematic Reviews in the Review Manage software and the CINeMA[42] framework (https://cinema.ispm.unibe.ch).

Statistical analysis

The STATA software version 15.1, Review Manager 5.4, and GeMTC14.3 were used for the network meta-analysis. The cure rate, recurrence rate, complication rate, duration of operation, VAS score, and Wexner incontinence score were compared between each surgical operation. The dichotomous variables were categorized, and their effect sizes were estimated by the relative risk (RR). MD estimated continuous variables. Review Manager 5.4 is a statistical software package for data management and analysis. The STATA

Table 1

Study characteristics.

References	Country	Fistula type(Parks classification)	Anesthesia	Intervention			Control			follow-up (m)	Outcomes
				Treatment	*n*	Years	Treatment	*n*	Years		
Chen *et al.*[22]	China	Transsphincteric fistula	Unknown	LIFT	67	36 ± 9	Fistulotomy	55	40 ± 11	24 (5–59)	①②④
Zhao *et al.*[23]	China	Transsphincteric fistula	Unknown	LIFT	40	46.3 ± 11.6	FPS	40	47.2 ± 10.8	6–12	① ② ③ ④⑤⑥
Guo *et al.*[9]	China	Transsphincteric fistula	Spinal	LIFT + EAFR	20	35.6 ± 11.1	LIFT	20	33.4 ± 10.6	6–12	①②③⑤⑥
Si *et al.*[24]	China	Transsphincteric fistula	Unknown	VAAFT	52	39.27 ± 11.74	FPS	54	36.46 ± 11.47	10 (4–30)	①②⑥
Su *et al.*[25]	China	Transsphincteric fistula	Spinal or sacral canal	LIFT-plug	60	42.9 ± 11.4	FPS	60	43.8 ± 11.1	6	①⑤
Sun *et al.*[17]	China	Transsphincteric anal fistula	Spinal	LIFT	20	33.1 ± 7.3	FPS	21	37.7 ± 7.8	16.6 ± 10.7	① ②③
Ayyar *et al.*[26]	India	Transsphincteric fistula	Spinal	LIFT	30	34.23 ± 9.15	Fistulotomy	30	38.8 ± 11.31	12	①②③④⑤
Buleje *et al.*[27]	Spain	Transsphincteric fistula	Unknown	LIFT	36	47.1	EAFR	36	47.1	12	①②
Han *et al.*[28]	China	Transsphincteric fistula	Lumbar or sacral canal	LIFT-plug	117	35.9 ± 10.1	LIFT	118	36.2 ± 10.8	6	①② ③④
Ho KS *et al.*[29]	Singapore Australia	Transsphincteric fistula	Unknown	EAFR	10	42.5	FPS	10	40.1	15.8	①②
Iqbal *et al.*[30]	Pakistan	Transsphincteric fistula	Unknown	LIFT	25	38.14 ± 10.73	FPS	25	38.14 ± 10.73	6	①②③
Kumar *et al.*[10]	India	Transsphincteric fistula	Local/saddle/spinal	LIFT	42	38.29 ± 11.60	EAFR	42	39.88 ± 10.64	17	①②③④⑤
La Torre *et al.*[31]	Italy	High transsphincteric anal fistula	Unknown	LIFT	26	–	VAAFT	28	–	18	①②③
Madbouly *et al.*[32]	Egypt	High transsphincteric anal fistulas	General or locoregional anesthesia	LIFT	35	45.4 ± 10.6	EAFR	35	40.7 ± 12.3	12	①②③④⑥
Mushaya *et al.*[21]	Australia	Transsphincteric fistula	General anesthesia	LIFT	25	47.5	EAFR	14	48.2	16.4	①②③
Nour *et al.*[33]	Egypt	Transsphincteric anal fistula	Spinal anesthesia	LIFT	39	30.28 ± 7.5	Fistulectomy	39	31.5 ± 8.14	13	①②③④⑤
Perez *et al.*[34]	Spain	Transsphincteric fistula	Unknown	FSR	28	51.4	EAFR	27	47.5	36	①②③
Siddique *et al.*[12]	Pakistan	Transsphincteric fistula	Unknown	VAAFT	40	39.9 ± 12.4	Seton	40	38.3 ± 10.0	36	①②④⑤
Toyonaga *et al.*[35]	Japan	Transsphincteric fistula	Spinal anesthesia	EAFR	35	43.5 (19–70)	Fistulotomy	35	44.2 (25–78)	12	①②③⑥
Wu *et al.*[11]	China	Transsphincteric fistula	Unknown	VAMLIFT	30	–	FPS	30	–	18	①②③④⑤
Yan *et al.*[16]	China	Transsphincteric fistula	Spinal anesthesia	TFSIA	40	41.65 ± 11.07	FPS	40	41.95 ± 13.15	6	①②③④⑤
Zhang *et al.*[36]	China	Parks II anal fistulas	Unknown	VAAFT	37	36.7 ± 9.2	FPS	38	36.8 ± 10.0	6	①②③④⑤⑥
Zheng *et al.*[37]	China	Transsphincteric fistula	Unknown	LIFT-plug	119	–	LIFT	120	–	6	①②③
Bondi *et al.*[38]	Norway; Sweden	Transsphincteric anal fifistula	Unknown	AFP	41	42.2(25.7–65.3)	EAFR	40	53.1 (22.0–69.8)	12 (9–24)	①②③
Ortiz *et al.*[39]	Spain	transsphincteric fistula	general anesthesia	AFP	15	46.5(30~76)	EAFR	16	46.5 (30~76)	12	①②③
Schwandner *et al.*[15]	German	Transsphincteric fistula	Unknown	AFP	43	45.1 ± 13.1	EAFR	39	49.5 ± 13.2	12	①②③④
VanKoperen *et al.*[40]	Netherlands	Transsphincteric perianal fistula	Unknown	AFP	31	45 (24–79)	EAFR	29	42 (24–61)	11 (5–27)	①②③
Ba bai ke re *et al.*[41]	China	Transsphincteric fistula	Spinal or general anesthesia	AFP	45	44.8(18–59)	EAFR	45	45.1 (17–61)	5.7 (5.1–6.4)	①②③

m, month; outcomes: ① cure rate; ② recurrence rate; ③ complication rate; ④ the operating time; ⑤ the postoperative pain on day 1 (VAS); ⑥ the postoperative incontinence in month 1 (Wexner).

15.1 software was used to plot the reticular relationship graphs and calculate closed loops' inconsistency factor (IF) by the 95% CI. It showed that the direct and indirect evidence were consistent if the 95% CI of IF contained 'o'. Otherwise, there was a high possibility of inconsistency. GeMTC14.3 was used for network meta-analysis, applying for the Markov Chain Monte Carlo (MCMC) for Bayesian Inference. While running the WinBUGS procedure, the number of chains was set to 4, the initial values scaling was set to 2.5, the tuning iterations were set to 20 000, the simulation iterations were set to 50 000, and the thinning interval was set to 10. The funnel plot of comparison calibration was used to study whether there was one small sample effect. Finally, the SUCRA score was used to rank the treatment grade of the different surgical techniques.

Results

Search results and study characteristics

Three thousand five hundred seventy literature had been obtained after searching the eight authoritative databases worldwide. There were 2293 articles remaining after duplicating the 1277 overlapped literature finally. Then 2233 records were excluded for unqualified subjects, low simple anal fistula, meta, protocol review, graduation thesis, case report, animal experiment, children, conference summary, tumor or tuberculosis, Crohn's disease, and letter, leaving 60 articles. According to the PICO principles, 28 studies of random controlled clinical trials were included after meeting the inclusion criteria. The detailed flow diagram is shown in Fig. 1. Furthermore, the Cochrane Handbook and CINeMA framework assessed the qualities of the 28 included RCTs for Systematic Reviews. The risk of bias graph and risk of bias summary are shown in Fig. 2. A total of 2274 patients were included in our analysis. The study characteristics are shown in Table 1.

Network meta-analysis of cure rate

Twenty-eight studies reported the cure rate related to 13 surgical methods. The result of the cure rate contained four closed loops, including FPS-LIFT-VAAFT, FPS-LIFT-LIFT-Plug, EAFR-Fistulotomy-LIFT, and EAFR-FPS-LIFT(Fig. 3A). All the IF 95% CIs in the four closed loops contained 'o', demonstrating no significant inconsistency between the direct and indirect evidence (Fig. 4A). Therefore, the consistency model was applied for statistical analysis. According to the network meta-analysis results, there was no statistical significance of the comparison among surgical interventions ($P > 0.05$ Table 2).

Network meta-analysis of recurrence rate

Twenty-seven studies reported the recurrence rate relating to 13 surgical methods. The result of the recurrence rate contained two closed loops, including EAFR-Fistulotomy-LIFT and FPS-LIFT-VAAFT (Fig. 3B). The 95% CI of IF in the 2 closed loops contained 'o', which showed no significant inconsistency between the direct and indirect evidence (Fig. 4B). According to the network meta-analysis results, there was no statistical significance of the comparison among any surgical interventions ($P > 0.05$ Table 3).

Network meta-analysis of complication rate

Twenty-two studies reported the complication rate relating to 12 surgical methods. The result of the complication rate contained two closed loops, including EAFR-Fistulotomy-LIFT and FPS-LIFT-VAAFT (Fig. 3C). The IF 95% CIs in the two closed loops contained 'o', which showed no significant inconsistency between the direct and indirect evidence (Fig. 4C). The treatment of fistulotomy has to be defined as a reference for comparisons.

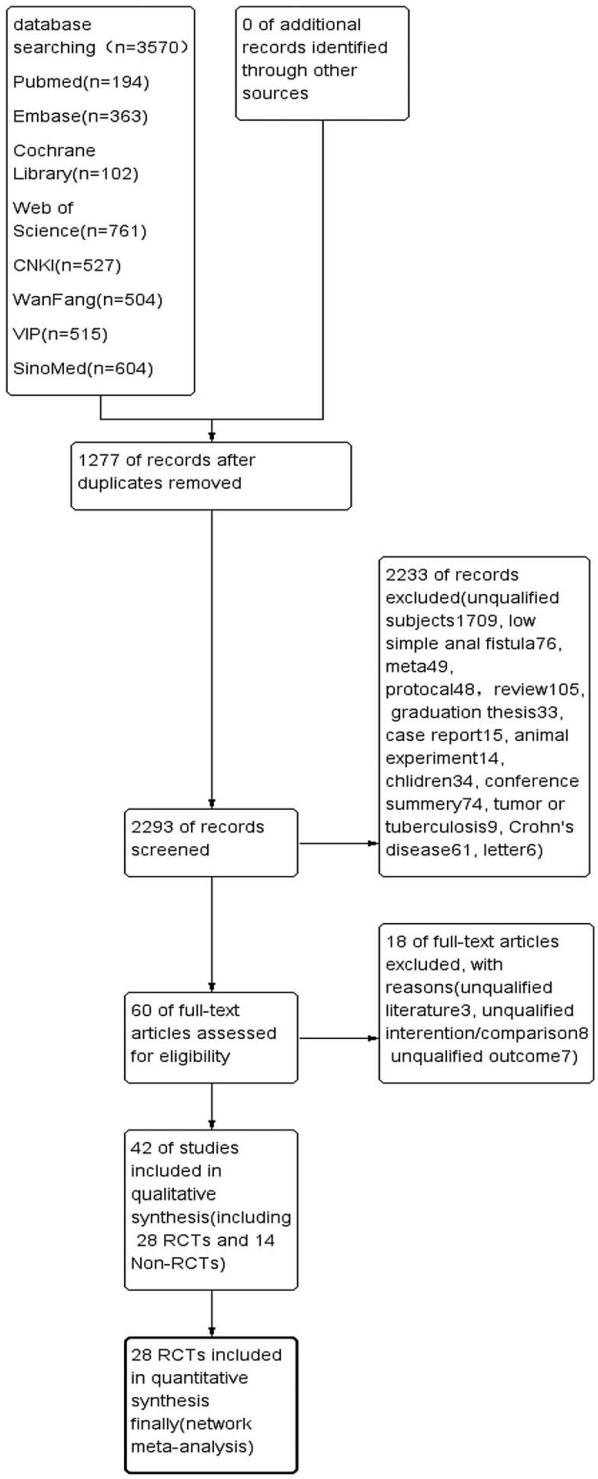

Figure 1. Flowchart of study selection.

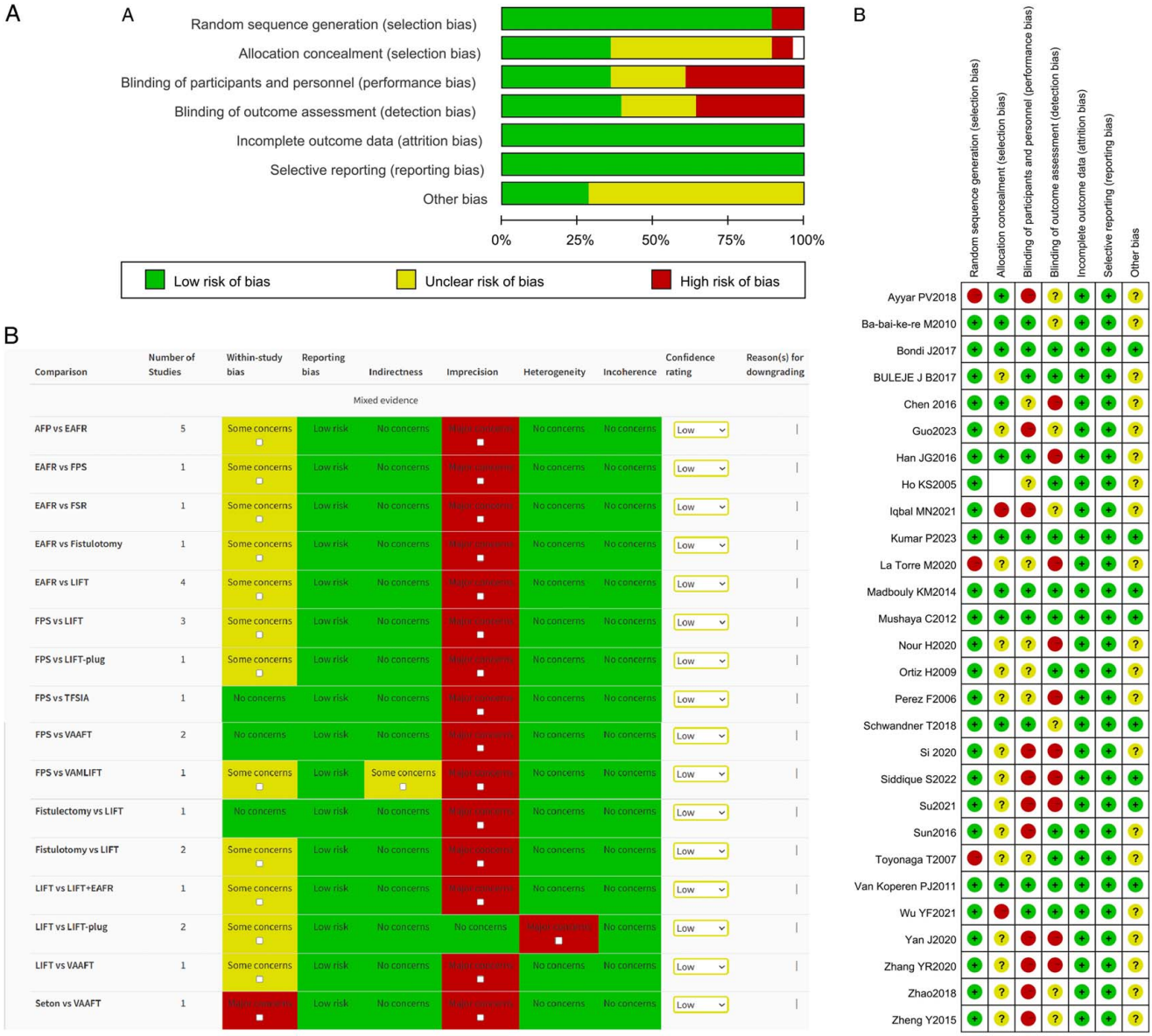

Figure 2. A, Assessment of risk of bias of RCTs by Cochrane (A) risk of bias graph; (B) Risk of bias summary. B, Assessment of risk of bias of RCTs by the CINeMA framework.

Network meta-analysis of operating time

Twelve studies reported the operating time relating to 10 surgical methods. The result of the network meta-analysis contained no closed loops (Fig. 3D). Therefore, the inconsistency between direct and indirect evidence could not be estimated.

Network meta-analysis of the postoperative pain on day 1 (VAS)

Eleven studies reported postoperative pain on day 1 relating to 11 surgical methods. The result of the network meta-analysis contained no closed loops (Fig. 3E). Therefore, the inconsistency between direct and indirect evidence could not be estimated.

Network meta-analysis of postoperative incontinence in month 1 (Wexner)

Six studies reported postoperative incontinence in month 1 relating to six surgical methods. The result of the network meta-analysis contained no closed loops (Fig. 3F). Therefore, the inconsistency between direct and indirect evidence could not be estimated.

Discussion

An AF is a disease secondary to a perianorectal abscess with a chronic abnormal sinus tract[4]. Thus, surgical operation is the optimal method for AF. However, many postoperative problems exist for patients with CAF, including a higher rate of recurrence or complications because of the dysfunction of the anal sphincter,

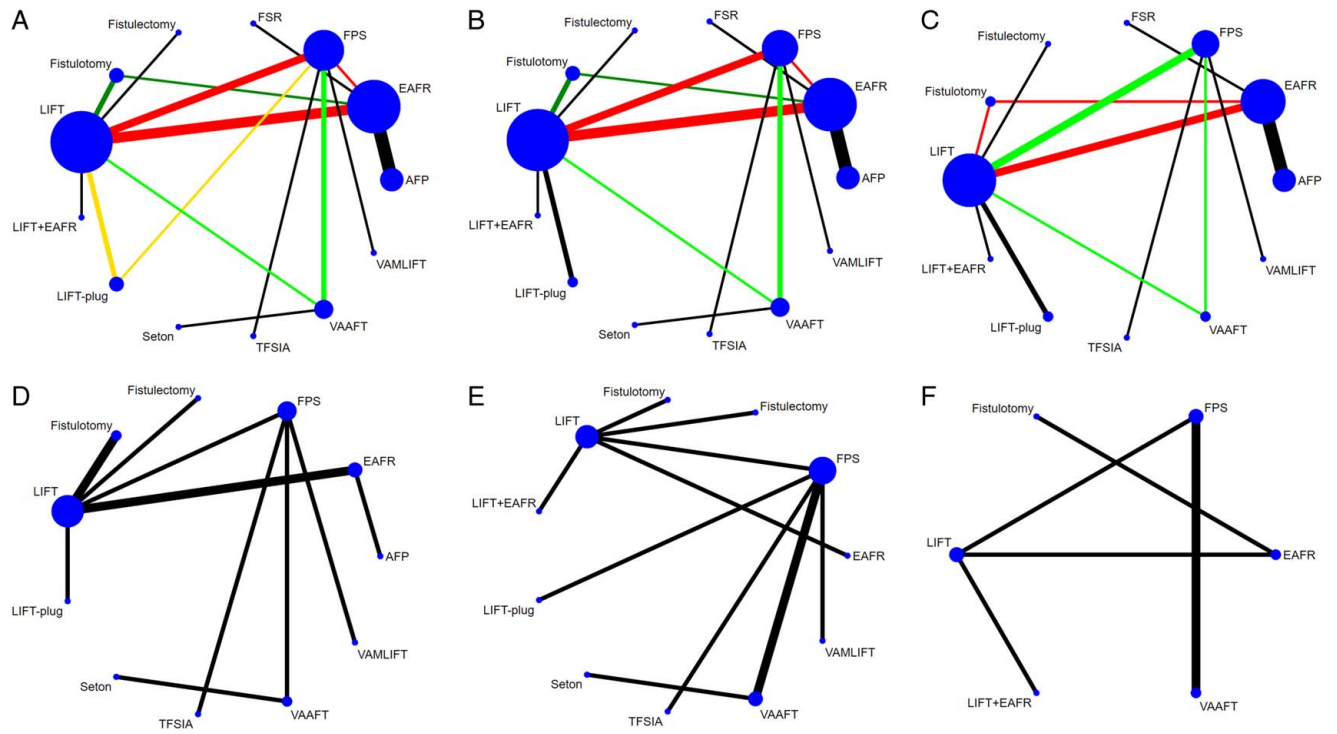

Figure 3. Reticulated evidence diagrams of (A) cure rate, (B) recurrence rate, (C) complication rate, (D) operating time, (E) the postoperative pain on day 1 (VAS), (F) the postoperative incontinence in month 1(Wexner).

especially fecal incontinence. Although numerous surgical techniques have been described, such as LIFT, EAFR, VAAFT, Seton, fistulectomy, fistulotomy, AFP, FPS, LIFT-plug, FSR, VAMLIFT, and TFSIA, none are free of relapse or complications, and most of the time both are involved. Given that the advantages of lesion excision and minimized local destruction seem contradictory, many researchers have been trying to reach a consensus regarding the optimal surgical method for treating intractable CAF via prospective or retrospective studies.

For most surgeons, fistulotomy was believed to be the classic and correct surgical technique with the gold standard in treating the anal fistula[43]. However, the complications of fistulotomy

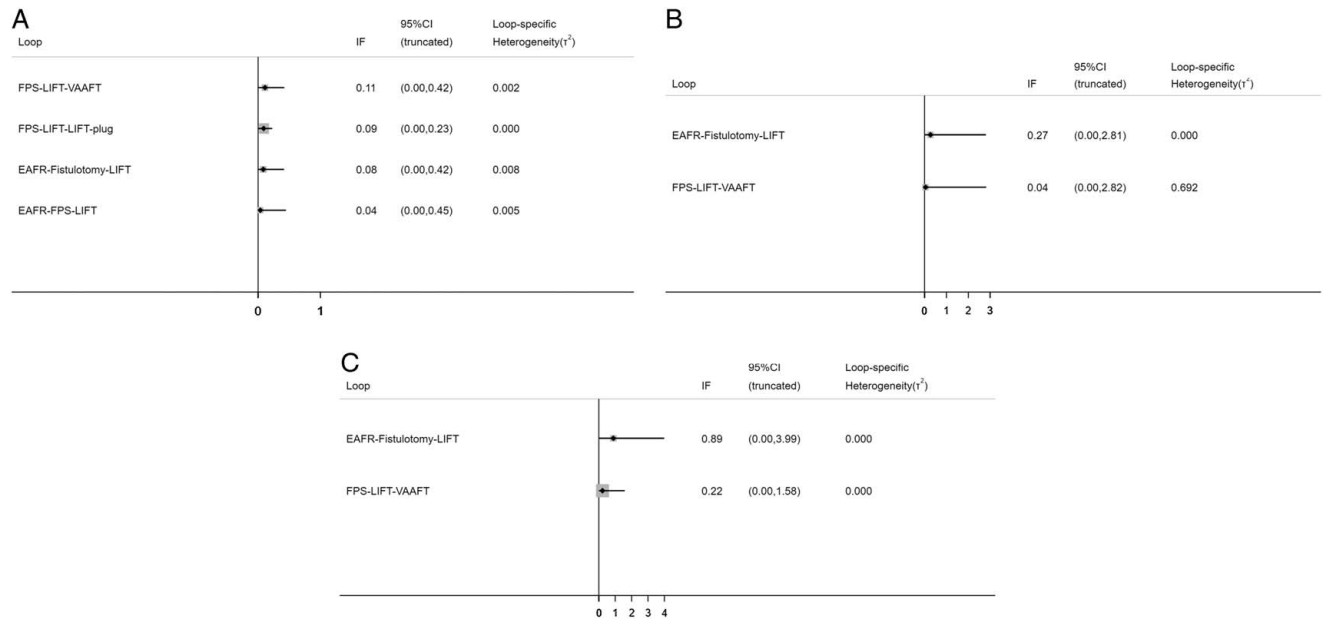

Figure 4. Inconsistency test of (A) cure rate; (B) recurrence rate; (C) complication rate.

Table 2

Network meta-analysis results of cure rate (RR, 95% CI).

AFP	2.27 (0.86–6.41)	1.48 (0.23–10.36)	2.52 (0.10–56.70)	22.29 (0.90–1275.91)	4.43 (0.62–36.49)	2.13 (0.46–10.96)	0.79 (0.04–18.59)	6.70 (0.94–54.65)	4.19 (0.19–97.04)	1.87 (0.10–44.77)	1.65 (0.20–14.97)	3.86 (0.09–303.13)
0.44 (0.16–1.16)	EAFR	0.66 (0.14–3.35)	1.09 (0.05–19.99)	9.63 (0.45–482.02)	1.93 (0.33–12.14)	0.94 (0.27–3.26)	0.35 (0.02–6.85)	2.99 (0.51–18.73)	1.82 (0.09– 37.11)	0.81 (0.05–15.98)	0.72 (0.10–5.18)	1.73 (0.05–106.54)
0.67 (0.10–4.30)	1.51 (0.30, 7.36)	FPS	1.69 (0.05–47.09)	14.52 (0.71–707.51)	2.99 (0.41–19.21)	1.43 (0.43–4.52)	0.54 (0.05–6.26)	4.49 (0.91–21.62)	2.75 (0.20–38.18)	1.25 (0.12–13.20)	1.10 (0.27–4.17)	2.53 (0.10–124.89)
0.40 (0.02–10.08)	0.92 (0.05–19.92)	0.59 (0.02–20.49)	FSR	9.10 (0.13–1363.03)	1.76 (0.06–68.79)	0.85 (0.04–25.07)	0.32 (0.00–23.83)	2.73 (0.09–103.12)	1.61 (0.03–129.86)	0.74 (0.01–51.22)	0.64 (0.02– 25.10)	1.57 (0.01–308.91)
0.04 (0.00–1.11)	0.10 (0.00–2.21)	0.07 (0.00–1.42)	0.11 (0.00–7.57)	Fistulectomy	0.20 (0.00–5.16)	0.10 (0.00–1.55)	0.04 (0.00–1.97)	0.30 (0.01–7.57)	0.19 (0.00–9.42)	0.08 (0.00–4.05)	0.07 (0.00–1.91)	0.17 (0.00–21.57)
0.23 (0.03–1.61)	0.52 (0.08–3.00)	0.33 (0.05–2.45)	0.57 (0.01–17.24)	5.09 (0.19–269.88)	Fistulotomy	0.48 (0.10–2.14)	0.18 (0.01–4.27)	1.53 (0.20–11.85)	0.92 (0.04–21.77)	0.43 (0.02–9.75)	0.37 (0.04–3.32)	0.88 (0.02–57.87)
0.47 (0.09–2.19)	1.06 (0.31–3.69)	0.70 (0.22–2.33)	1.17 (0.04–28.41)	10.35 (0.64–409.08)	2.06 (0.47, 9.78)	LIFT	0.37 (0.03–5.94)	3.17 (0.85–12.41)	1.93 (0.13–29.46)	0.87 (0.07–13.12)	0.77 (0.16–3.63)	1.78 (0.06–93.53)
1.26 (0.05–26.25)	2.84 (0.15–54.88)	1.86 (0.16–21.40)	3.08 (0.04–201.55)	27.93 (0.51–2679.61)	5.58 (0.23–123.13)	2.70 (0.17–37.14)	LIFT-EAFR	8.48 (0.42–147.38)	5.08 (0.13–193.53)	2.31 (0.09–72.47)	2.05 (0.12–33.86)	4.77 (0.08–446.94)
0.15 (0.02–1.06)	0.33 (0.05–1.96)	0.22 (0.05–1.10)	0.37 (0.01–11.63)	3.30 (0.13–182.36)	0.65 (0.08– 4.88)	0.32 (0.08–1.17)	0.12 (0.01–2.38)	LIFT-plug	0.60 (0.03–11.84)	0.28 (0.02–4.56)	0.24 (0.03–1.68)	0.57 (0.01–34.19)
0.24 (0.01–5.35)	0.55 (0.03–11.04)	0.36 (0.03–5.11)	0.62 (0.01–39.28)	5.39 (0.11–566.78)	1.08 (0.05–24.83)	0.52 (0.03–7.98)	0.20 (0.01–7.42)	1.66 (0.08–33.24)	Seton	0.45 (0.01–16.67)	0.40 (0.04–3.67)	0.96 (0.01–100.60)

($P > 0.05$: no statistical significance of the comparison among any surgical interventions).

Table 3

Network meta-analysis results of recurrence rate (RR, 95% CI).

AFP	0.50 (0.13–1.83)	0.46 (0.04–6.84)	0.47 (0.01–18.93)	0.03 (0.00–1.65)	0.17 (0.01–1.97)	0.35 (0.05–2.51)	0.15 (0.00–9.65)	0.36 (0.01–20.81)	0.38 (0.03–6.90)	0.16 (0.00–17.14)
1.99 (0.55–7.70)	EAFR	0.89 (0.10–9.83)	0.93 (0.03–29.37)	0.07 (0.00–2.60)	0.34 (0.04–2.79)	0.70 (0.17–3.11)	0.30 (0.01–16.63)	0.73 (0.02–33.81)	0.75 (0.07–10.39)	0.32 (0.00–30.56)
2.20 (0.15–26.87)	1.12 (0.10–9.67)	FPS	1.03 (0.01–60.11)	0.07 (0.00–3.26)	0.37 (0.02–4.53)	0.79 (0.11–4.26)	0.35 (0.01–10.62)	0.80 (0.04–16.19)	0.83 (0.13–5.32)	0.36 (0.00–17.14)
2.14 (0.05–86.88)	1.08 (0.03–31.85)	0.97 (0.02–66.86)	FSR	0.07 (0.00–11.85)	0.35 (0.01–20.60)	0.75 (0.02–32.14)	0.32 (0.00–56.20)	0.78 (0.00–131.93)	0.81 (0.01–54.75)	0.33 (0.00–87.86)
30.43 (0.60–2758.31)	15.26 (0.38–1127.67)	13.71 (0.31–1241.79)	14.89 (0.08–3180.58)	Fistulectomy	5.12 (0.10–422.60)	10.60 (0.35–685.00)	4.67 (0.04–1051.40)	11.11 (0.09–2225.27)	11.33 (0.23–1081.64)	5.01 (0.01–1618.34)
5.95 (0.51–74.40)	2.97 (0.36–26.26)	2.70 (0.22–41.12)	2.85 (0.05–153.01)	0.20 (0.00–9.74)	Fistulotomy	2.11 (0.33–14.33)	0.90 (0.02–61.54)	2.19 (0.05–120.06)	2.24 (0.15–42.03)	0.96 (0.01–107.42)
2.82 (0.40–20.01)	1.42 (0.32–5.77)	1.26 (0.23–8.72)	1.34 (0.03–56.08)	0.09 (0.00–2.89)	0.47 (0.07–3.07)	LIFT	0.43 (0.01–17.00)	1.02 (0.04–36.10)	1.07 (0.14–9.34)	0.45 (0.00–32.40)
6.68 (0.10–331.42)	3.34 (0.06–136.03)	2.88 (0.09–103.46)	3.16 (0.02–457.57)	0.21 (0.00–27.38)	1.12 (0.02–53.32)	2.35 (0.06–76.08)	Seton	2.40 (0.03–204.20)	2.47 (0.13–44.57)	1.03 (0.00–181.76)
2.76 (0.05–131.03)	1.37 (0.03–50.38)	1.25 (0.06–22.48)	1.29 (0.01–212.71)	0.09 (0.00–11.23)	0.46 (0.01–21.39)	0.98 (0.03–27.70)	0.42 (0.00–38.09)	TFSIA	1.02 (0.03–34.74)	0.44 (0.00–53.83)
2.66 (0.14–39.85)	1.34 (0.10–14.49)	1.20 (0.19–7.85)	1.23 (0.02–82.90)	0.09 (0.00–4.38)	0.45 (0.02–6.72)	0.94 (0.11–6.92)	0.40 (0.02–7.80)	0.98 (0.03–31.03)	VAAFT	0.44 (0.00–31.69)

($P > 0.05$: no statistical significance of the comparison among any surgical interventions).

Table 4

Network meta-analysis results of complication rate (RR, 95% CI).

AFP	0.66 (0.32–1.61)	1.72 (0.37–7.57)	0.86 (0.16–4.68)	0.23 (0.03–1.39)	2.70 (0.68–19.02)	0.46 (0.13–1.58)	0.30 (0.03–2.06)	1.87 (0.22–17.84)	0.54 (0.10–2.83)	1.29 (0.18–10.93)	AFP
1.51 (0.62–3.13)	EAFR	2.55 (0.66–8.05)	1.28 (0.26–5.66)	0.34 (0.06–1.67)	4.13 (1.19–20.33)	0.69 (0.24–1.61)	0.44 (0.05–2.42)	2.75 (0.37–22.02)	0.85 (0.17–3.36)	1.93 (0.28–13.75)	1.51 (0.62–3.13)
0.58 (0.13–2.69)	0.39 (0.12–1.51)	FPS	0.49 (0.07–3.91)	**0.14 (0.02–0.70)**[a]	1.68 (0.32–13.86)	**0.29 (0.12–0.63)**[a]	0.16 (0.02–1.11)	1.12 (0.25–5.86)	0.35 (0.10–1.06)	0.83 (0.19–3.55)	0.58 (0.13–2.69)
1.17 (0.21–6.26)	0.78 (0.18–3.80)	2.03 (0.26–13.59)	**FSR**	0.27 (0.03–2.51)	3.26 (0.47–31.78)	0.58 (0.09–3.15)	0.33 (0.03–3.35)	2.14 (0.18–30.91)	0.67 (0.08–5.05)	1.70 (0.14–20.56)	1.17 (0.21–6.26)
4.32 (0.72–29.07)	2.92 (0.60–17.87)	**7.04 (1.43–40.77)**[a]	3.73 (0.40–37.90)	**Fistulectomy**	**11.67 (1.82–134.58)**[a]	2.05 (0.51–8.41)	1.19 (0.11–11.22)	7.64 (0.94–89.36)	2.45 (0.41–15.75)	5.61 (0.71–61.01)	4.32 (0.72–29.07)
0.37 (0.05–1.46)	**0.24 (0.05–0.84)**[a]	0.60 (0.07–3.14)	0.31 (0.03–2.12)	**0.09 (0.01–0.55)**[a]	**Fistulotomy**	**0.17 (0.02–0.66)**[a]	**0.11 (0.01–0.69)**[a]	0.77 (0.05–6.11)	0.20 (0.02–1.20)	0.51 (0.04–4.06)	0.37 (0.05–1.46)
2.16 (0.63–7.44)	1.46 (0.62–4.16)	**3.45 (1.58–8.61)**[a]	1.72 (0.32–11.00)	0.49 (0.12–1.97)	**5.87 (1.51–42.37)**[a]	**LIFT**	0.59 (0.09–3.25)	4.11 (0.72–27.94)	1.21 (0.39–4.20)	2.86 (0.57–16.87)	2.16 (0.63–7.44)
3.32 (0.49–33.04)	2.27 (0.41–20.12)	6.27 (0.90–52.56)	3.05 (0.30–36.30)	0.84 (0.09–9.16)	**9.23 (1.45–155.16)**[a]	1.71 (0.31–11.67)	**LIFT-EAFR**	6.97 (0.63–100.10)	1.90 (0.28–18.23)	4.90 (0.46–60.60)	3.32 (0.49–33.04)
0.54 (0.06–4.46)	0.36 (0.05–2.73)	0.89 (0.17–4.02)	0.47 (0.03–5.60)	0.13 (0.01–1.07)	1.30 (0.16–19.73)	0.24 (0.04–1.38)	0.14 (0.01–1.59)	**TFSIA**	0.32 (0.04–1.88)	0.75 (0.08–6.25)	0.54 (0.06–4.46)
1.84 (0.35–9.80)	1.18 (0.30–6.02)	2.90 (0.94–10.28)	1.50 (0.20–13.28)	0.41 (0.06–2.43)	4.95 (0.83–50.18)	0.82 (0.24–2.54)	0.53 (0.05–3.63)	3.08 (0.53–27.25)	**VAAFT**	2.22 (0.40–17.21)	1.84 (0.35–9.80)
0.78 (0.09–5.63)	0.52 (0.07–3.52)	1.20 (0.28–5.15)	0.59 (0.05–7.03)	0.18 (0.02–1.41)	1.96 (0.25–24.90)	0.35 (0.06–1.74)	0.20 (0.02–2.20)	1.34 (0.16–12.68)	0.45 (0.06–2.47)	**VAMLIFT**	0.78 (0.09–5.63)

[a](: $P < 0.05$, significant difference; Significant results are in bold.)

vary, including postoperative incontinence, pain, bleeding, or long wound healing time. A study by Alapach *et al.*[44] reported that the incontinence of fistulotomy was 16.2%. Fistulectomy is different from fistulotomy; the latter simply involves opening the fistulous tract to facilitate healing, while the former is one thorough surgical method by excising the fistula tracts entirely and minimizing the risk of secondary tract formation[14]. Therefore, fistulectomy's complication[18] rate, such as incontinence, was significantly reduced with the complete lesion removal, and the recurrence rate of it was reported at 2.56%[5,33]. LIFT is one technique that minimizes sphincter impairment by eliminating the primary sepsis focus of the fistula tract[5]. Though it can preserve the function of the anal sphincter, the other complications mainly consist the postoperative incision dehiscence, relapse, or infection[31]. According to a systematic review and meta-analysis of Stellingwerf *et al.*, the success of LIFT was reported in a range of 59–94%, with an average of 76%[45]. Likewise, EAFR is another surgical method that uses a rectal flap consisting of a mucous layer, submucosa, and some fibers of the internal sphincter to cover the internal opening of CAF[6]. The cure rate of EAFR was reported in a range of 37–80%, with an average of 55%[10]. Notably, EAFR protects the anal anatomy and continence function[10]. However, 9.4–23.5% of patients suffer the incontinence symptom, likely due to intraoperative damage of the internal sphincter[46]. VAAFT is one emerging surgical technique with a range of success from 70.7 to 85.8. Lots of researchers have applied this technique to treat CAF. However, the outcomes varied[11]. Therefore, the outcomes of long-term VAAFT are still expected[31]. Seton is a conventional surgical method in that the silk 1/0 suture was tightened, running through the internal and external openings until the sphincter was slowly cut[12]. Likewise, Andreou *et al.*[47] concords with the study conducted by Siddique *et al.*[12] that there was no incidence of anal incontinence in the Seton method. Wang *et al.*[5] reported that seton was the best surgical method to avoid postoperative anal incontinence. However, the recurrence rate of seton was reported at 12.5% with a follow-up of 3 years[12]. AFP is one kind of suppository consisting of the biological collagen originating from the lyophilized pig's small intestine submucosa[4]. Surgeons pull the tail first from the internal opening to the external opening until it blocks the fistula tract securely[15]. Numerous problems related to the AFP procedure include postoperative infection, incomplete closure of the internal opening, displacement of the plug, or recurrence[48]. The healing rate of AFP was reported at 66.7% in a study conducted by Schwandner *et al.*[15] and the recurrence rate of AFP was 47.7% in the subgroup of RCTs in one meta-analysis performed by Lin *et al.*[49]. FPS is a surgical method that combes the fistulotomy and seton by excising the external opening and inserting the braided thread into the fistula tract tightly[16]. The complication rate of FPS was 32% involving incontinence and recurrence[30]. LIFT-plug is a surgical procedure that combines LIFT and AFP by suturing the opening in the internal sphincter transversely and inserting the plug into the intersphincteric groove blocking the fistula tract and crossing the external sphincter[17]. The cure rate of the LIFT-plug was reported to be 94.0%[28]. In terms of its recurrence rate, three RCTs were found, which Han *et al.*[28] and Zheng *et al.*[37] reported '0', while Su *et al.*'s study missed the data on recurrence[25]. FSR is one surgical method combining fistulotomy and sphincter reconstruction by excising the fistula tract

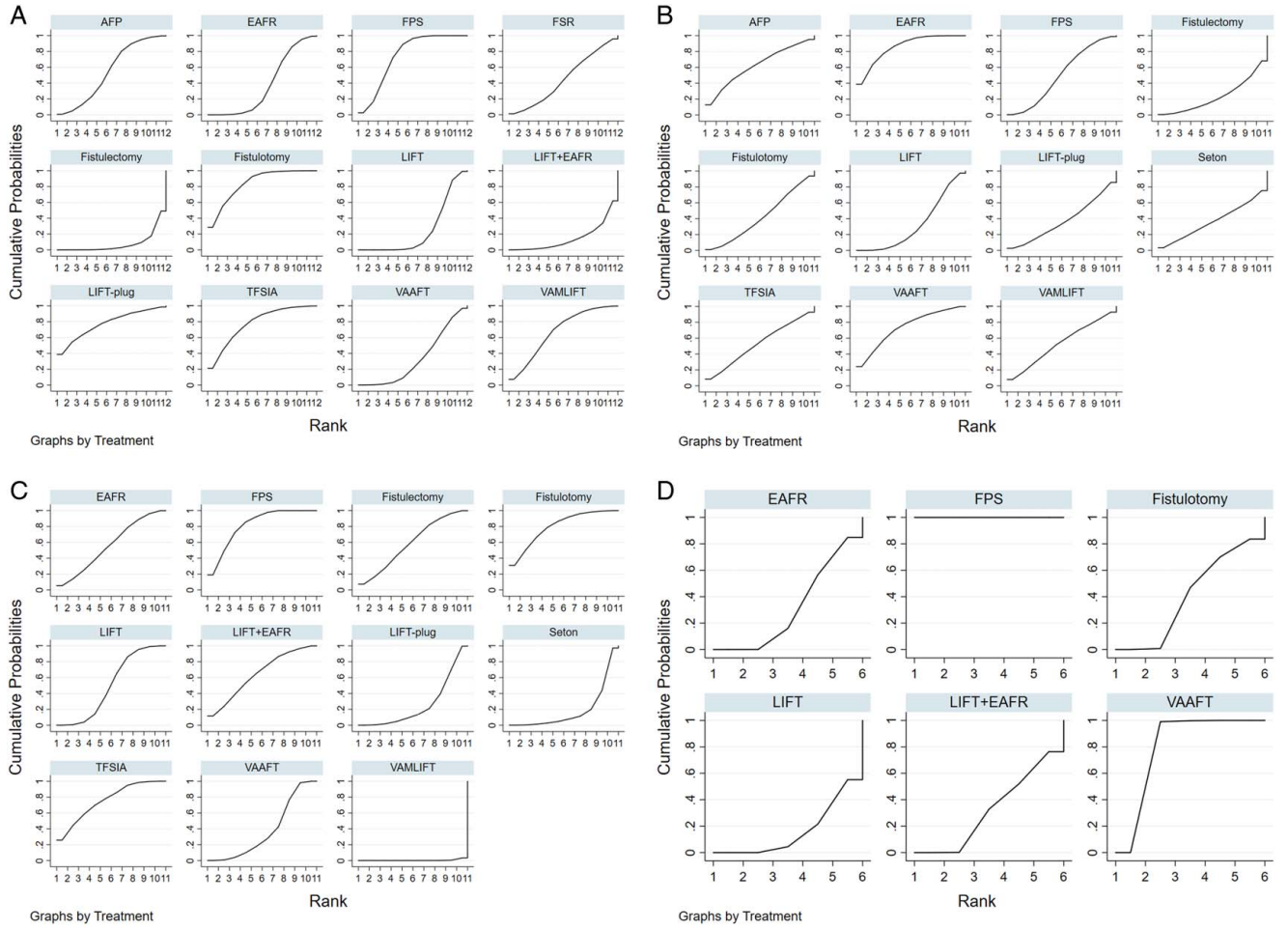

Figure 5. Probability ranking of intervention effects of (A) complication rate; (B) operating time; (C) the postoperative pain on day 1 (VAS); (D) the postoperative contienence in month 1 (Wexner). (Note: Sorted by surface area under the curve, the larger the surface area under the curve, the higher the recommendation rating).

and repairing the internal and external anal sphincter[13]. The recurrence rate and complication rate of FSR were reported at 7.1 and 32.1% in a study conducted by Perez *et al.*[34]. VAMLIFT is one operation of modified LIFT with the assistance of fistulascope debriding the fistula tract[11]. The recurrence rate of VAMLIFT was reported to be 25.0%[12] while the complication rate was 50.0%[31]. Furthermore, TFSIA is similar to TROPIS[16]. The recurrence rate of TFSIA was reported to be 12.5%, with a complication rate of 15.0%[16].

Due to the wide variety of surgical techniques for treating CAF, there were few comparative analyses of the efficacy of different treatments. Only two network meta-analyses were found in the worldwide database, one of which only searched three databases and finally obtained 972 articles. The other one only obtained 880 relevant literature, but 6 included 29 articles that were not RCTs. Those limitations above may affect the conclusion. Therefore, one more established study was expected to estimate the different outcomes of the 13 surgical techniques. In this network meta-analysis, 3570 pieces of literature were identified after searching the eight authoritative databases worldwide. Finally, 28 RCTs with a total of 2274 patients were included in the meta-analysis.

According to the results of the network meta-analysis, there was no statistically significant difference in the comparison among any surgical interventions in terms of the cure rate ($P > 0.05$ Table 2) and recurrence rate ($P > 0.05$ Table 3). However, in terms of complication rate, fistulectomy was lower than FPS (Median: 0.14; 95% CI: 0.02–0.70) and fistulotomy (Median: 0.09; 95% CI: 0.01–0.55). Otherwise, EAFR (Median: 0.24; 95% CI: 0.05–0.84), LIFT (Median: 0.17; 95% CI: 0.02–0.66), and LIFT-EAFR (Median: 0.11; 95% CI: 0.01–0.69) were higher than fistulotomy (Table 4). The results of the probability ranking of complication rate showed: Fistulectomy (7.9%) < LIFT + EAFR (14.9%) < LIFT (25.0%) < VAAFT (33.3%) < EAFR (37.8%) < FSR (45.2%) < AFP (55.0%) < VAMLIFT (67.4%) < FPS (74.5%) < LIFT-plug (77.5%) < TFSIA (77.7%) < fistulotomy (83.9%), suggesting that fistulectomy may be the surgical technique with the lowest complication rate in patients after the operation (Fig. 5A).

Given that the net results of the operating time, the postoperative pain, and the postoperative incontinence contained no closed loops, the inconsistency between direct and indirect evidence could not be estimated. However, the results of the probability ranking of operation time could be referenced: Fistulectomy(23.4%) < LIFT(32.6%) < Seton(36.7%) < LIFT-plug(37.3%) < Fistulotomy(41.9%) < FPS

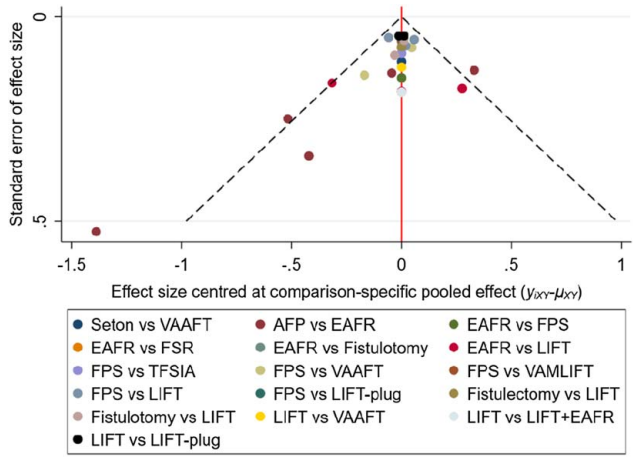

Figure 6. Funnel plot (Note: The points are distributed on both sides of the central axis, and the more the symmetrical distribution, the lower the risk of bias is represented).

(50.5%) < TFSIA (52.5%) < VAMLIFT (53.0%) < AFP(62.4%) < VAAFT(73.6%) < EAFR(85.7%), suggesting that fistulectomy might be the surgical technique with the lowest operating time in patients (Fig. 5B). The results of the probability ranking of the VAS score of the postoperative pain on day 1 could be referenced: VAMLIFT(0.4%) < Seton(19.0%) < LIFT-plug (26.0%) < VAAFT (37.8%) < LIFT(50.2%) < EAFR(56.2%) < Fistulectomy(23.4%) < LIFT + EAFR(64.5%) < TFSIA(75.5%) < Fistulotomy(79.9%) < FPS(81.6%), suggesting that VAMLIFT might be the surgical technique with the lowest postoperative pain on day 1 in patients (Fig. 5C). And the results of the probability ranking of the Wexner score of the postoperative incontinence on month 1 could be referenced: LIFT(16.2%) < EAFR(31.5%) < LIFT + EAFR(32.3%) < Fistulotomy(40.3%) < VAAFT(79.8%) < FPS(100.0%), suggesting that LIFT might be the surgical technique with the lowest Wexner score of postoperative incontinence on month 1 in patients (Fig. 5D).

There were some limitations in this network meta-analysis. First, the number of loops in the network results was too small. Therefore, the results mainly came from the indirect comparison, whose strength of evidence was weaker than the direct comparison. Second, the conclusion is supported by a meager number of cases, and a few trials included more than 100 participants per group in the included list of studies. Thus, these may have been biased due to small study sizes. Third, one limitation should be specified: for recurrence rate, the included studies had different follow-ups (6–36 months), which exposed a risk of underestimation of recurrence rate in shorter follow-up studies and made different RCTs data not correctly comparable for this endpoint. Fourth, though the complications had been defined more precisely in the study, it might also be possible to bias the calculation of complication rates to some extent because the scope of complications is vast, including postoperative urinary retention, infection, anal itching, postoperative bleeding, hematoma, anal wetness, edema at the margins of the wound, wound fissure or anal incontinence. Of all these postoperative complications, anal incontinence is the most serious. Therefore, we studied and discussed anal incontinence as an independent outcome parameter. However, the wide scope of complications was one of the sources of heterogeneity in the article. Fifth, from the specific types of anesthesia in Table 1, we found that the types of anesthesia were unknown in 14 of these 28 articles, likely affecting the incidence of postoperative complications, which might be one of the limitations of our study. Lastly, from the funnel plot of the cure rate, the scatter points of most studies were located symmetrically above the funnel graph, indicating fewer possibilities of publication bias among the included studies. However, some scatter points were located at the bottom of the funnel plot, showing that it might be affected by some small sample effect (Fig. 6).

This network meta-analysis might offer one direction for the subsequent study in the future. The ranking results indicated that fistulectomy might have the lowest complication rate. However, from the assessment of the risk of bias of RCTs by the CINeMA framework (Fig. 2b), the results of the confidence rating were all low. Thus, the article's conclusion needs to be verified in future investigations.

Conclusion

According to the network meta-analysis of the 13 surgical techniques treating CAF, there was no statistical significance of the comparison among any surgical interventions regarding the cure and recurrence rates. However, fistulectomy might have the lowest complication rate, which might be the relatively superior surgical technique for treating CAF.

Ethical approval

This disclosures is not relevant to my manuscript.

Consent

This disclosures is not relevant to my manuscript.

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Author contribution

Y.A.: funding acquisition and writing – original draft; J.G.: funding acquisition and writing – review and editing; J.X.: data curation and software; W.Q.: data curation and formal analysis; L.W.: project administration and supervision; M.T.: conceptualization and methodology.

Conflicts of interest disclosure

We declare that we have no conflicts of interest.

Research registration unique identifying number (UIN)

This network meta-analysis has been registered in Research Registry (Registration UIN: reviewregistry1697), an international register website of systematic reviews http://www.researchregistry.com.

Guarantor

Jihua Gao and Yongkang An.

Data availability statement

We confirm that any datasets generated during and/or analyzed during the current study are publicly available, available upon reasonable request, and data sharing is applicable to this article.

Provenance and peer review

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