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Review

Risk Factors for Recurrence after anal fistula surgery: A meta-analysis

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ABSTRACT

Background: Despite a burgeoning literature during the last two decades regarding perioperative risk management of anal fistula, little is known about its risk factors that influence postoperative recurrence. We performed a meta-analysis to summarize and assess the credibility of evidence of potential risk factors for anal fistula recurrence (AFR) after surgery.
Methods: Pubmed and EMBASE without language restriction were searched from inception to April 2018 that reported risk factors which predisposed recurrence after anal fistula surgery. We excluded studies that involved patients with anal fistula associated with Crohn's disease. MOOSE guidelines were followed when this meta-analysis was performed. We used random-effects models to pool relative risks (RRs) with 95% confidence intervals (CIs). Evidence from observational studies was graded into high-quality (Class I), moderate-quality (Class II/III) and low-quality (Class IV) based on Egger's *P* value, total sample size and between-study heterogeneity.
Results: Of 3514 citations screened, 20 unique observational studies comprising 6168 patients were involved in data synthesis. High-quality evidence showed that AFR was associated with high transsphincteric fistula (RR, 4.77; 95% CI, 3.83 to 5.95), internal opening unidentified (RR, 8.54; 95% CI, 5.29 to 13.80), and horseshoe extensions (RR, 1.92; 95% CI, 1.43 to 2.59). Moderate-quality evidence suggested an association with prior anal surgery (RR, 1.52; 95% CI, 1.04 to 2.23), seton placement surgery (RR, 2.97; 95% CI, 1.10 to 8.06), and multiple fistula tract (RR, 4.77; 95% CI, 1.46 to 15.51). High-quality evidence demonstrated no significant association with gender or smoking; moderate-quality evidence also suggested no association with age, tertiary referral, alcohol use, diabetes mellitus, obesity, preoperative seton drainage, high internal opening, postoperative drainage, mucosal advancement flap surgery, supralevator extensions, location or type of anal fistula.
Conclusion: Several patient, surgery and fistula-related factors are significantly associated with postoperative AFR. These findings strengthen clinical awareness of early warning to identify patients with high-risk disease recurrence for AFR.

1. Introduction

Anal fistula is one of the commonest ailments seen by anorectal surgeons. The prevalence of fistula-in-ano is 12.3 cases per 100,000 population in men, and 5.6 cases per 100,000 population in women [1]. Patients with anal fistula usually present with a recurrent abscess or a draining fistula with various severity of symptoms and require surgical interventions. The successful control and eradication of the fistula and preservation of anal continence is the goal of surgical treatment [2,3]. There are two varieties of surgical technique and vary degrees of

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success. Broadly these are partial sphincter-preserving procedures (eg. fistulotomy, fistulectomy and cutting seton) [4–7] and sphincter-conserving procedures (eg. ligation of intersphincteric fistula tract also known as LIFT procedure, drainage seton or mucosal advancement flap) [8–12].

Anal fistula recurrence (AFR) is a common and potentially devastating outcome after anal fistula surgery. It can lead to significant morbidity, multiple operations, increased risk of local fibrosis and scarring and an increased risk continence disturbance [13]. Fistula recurrence can adversely affect the surgeon-patient relationship as well as patients' quality of life [14], particularly as AFR can result in higher health care costs, prolonged wound healing and higher risk of anal stenosis [13]. The reported rate of recurrence after anal fistula surgery is between 3 and 57% [15–18], with varying rates among different procedures.

Multiple factors can affect the development and outcomes of patients with anal fistula, involving patient-related risk factors (eg. patient gender, age, smoking, alcohol, diabetes mellitus or obesity) [13,19–23], surgery-related risk factors (eg. surgical procedure or intraoperative adopted technique) [17,24–26] and fistula-related risk factors (type of fistula, number of fistula tracts and height or location of internal opening) [27,28]. The role of various modifiable risk factors has been described for anal fistula surgery, most notably for postoperative recurrence or surgical failure. To our knowledge, no risk factors for AFR have been systematically summarized to identify the effect on AFR risk. To achieve adequate sample size required for sufficient precision of estimation of associations between these factors and AFR, we conducted a meta-analysis to assess reported risk factors and the risk of AFR.

2. Methods

The protocol for the study was registered in PROSPERO (Registration number: CRD42018102469), an international register website of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/) and was reported according to MOOSE (Meta-Analysis of Observational Studies in Epidemiology) [29], PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines. The MOOSE checklist is reported in eTable 1 in the Supplement.

2.1. Search strategy

We undertook a systematic literature review of articles published from inception through April 2018 in Pubmed and EMBASE that reported risk factors which predisposed recurrence after anal fistula surgery. We used the following search terms: ('anal fistul*' OR 'anus fistul*' OR 'fistula-in-ano' OR 'anorectal fistul*' OR 'perianal fistul*') AND (recur* or relaps* or remission* or 'treatment outcome' or 'treatment failure') (eTable 2 in the Supplement). Fig. 1 presents the literature search and the study selection. No language restrictions were applied. We manually searched reference lists from related reviews for potentially additional eligible studies. In addition, abstracts of scientific meetings or full-texts from major journals on colorectal surgery including the Association of Coloproctology of Great Britain and Ireland (Colorectal Disease), the American Society of Colon and Rectal Surgeons (Diseases of the Colon & Rectum), American and European Surgical Association (Annals of Surgery) and the BJS Society Ltd by John Wiley & Sons Ltd (British Journal of Surgery) were also searched. We did not contact corresponding authors for additional data.

2.2. Study selection

Three authors independently reviewed title and abstract of each identified article, then cross-checked. Studies were included if they satisfied the following PICO(S) (participant, intervention, comparator, outcome (study design)) criteria:

1. Participant: adults aged 18 years and older, undergoing anal fistula surgery.
2. Intervention: assessment of a modifiable patient, fistula and surgery-related risk factors, for example gender, age, smoking, alcohol, obesity and fistula type, surgical procedure, location, height or identification of internal opening, horseshoe or supralevator extensions.
3. Comparator: exposure compared with nonexposure (or lower exposure) to a modifiable risk factor.
4. Outcome: risk of disease recurrence after anal fistula surgery, presented as relative risk (RR) with 95% confidence intervals (CIs), or equivalent.
5. Study design: randomized controlled trials (RCTs), observational studies including cohort, case-control, or cross-sectional studies.

Exclusion criteria were studies that involved patients with anal fistula associated with Crohn's disease, other inflammatory bowel diseases or rectovaginal fistula. We also excluded studies with no outcome data or studies with insufficient data for analysis (eTable 3 in the Supplement).

2.3. Data extraction and quality assessment

Using piloted data extraction forms, two authors independently extracted data on study characteristics, designs and outcomes. Disagreements were resolved by consensus or discussion with a senior author. The extracted data included study source, study years, study type, number of patients, the number of recurrent patients, patient age, surgical procedure, follow-up data, study location, risk factors addressed, significant risk factors and outcomes. A quality score was derived from applying the Cochrane Collaboration's tool and the Newcastle Ottawa Scale for clinical trials [30] and observational studies [31], respectively (meta-analysis checklist was followed and is available in eTable 4 in the Supplement).

2.4. Evaluation of the strength of evidence

The strength of the evidence in the identified associations for observational studies was graded using a set of modified criteria (eTable 5 in the Supplement). We deemed the association as Class I (high-quality) evidence when three conditions of Egger's P value > 0.1, a total population > 1000 and lower between-study heterogeneity $I^2 < 50\%$ were met simultaneously; as Class II (moderate-quality) evidence when two of these three conditions were met. Class III (moderate-quality) evidence association was presented when one of these three conditions was satisfied. That none of these three conditions was met indicated association of Class IV (low-quality) evidence.

2.5. Statistical analysis

The primary outcome was recurrence of anal fistula postoperatively, defined as persistence or recurrence of symptoms or the development of recurrent perianal sepsis or chronic anal fistula within or more than 6 months of surgical intervention. We abstracted adjusted effect estimates preferably. For studies in which adjusted effect estimates were not provided but raw data were reported, we calculated crude RRs and independently cross-verified them by two authors. Original corresponding authors were contacted when the paper suggested that relevant data were available but not reported.

We used Stata Software (version 13.1) for data analyses. For the summation of AFR findings, we calculated rate estimates and 95% CIs using the logit transformation formula. Inverse variance weighting was applied to calculate pooled estimates [32]. Meta-analyses were performed

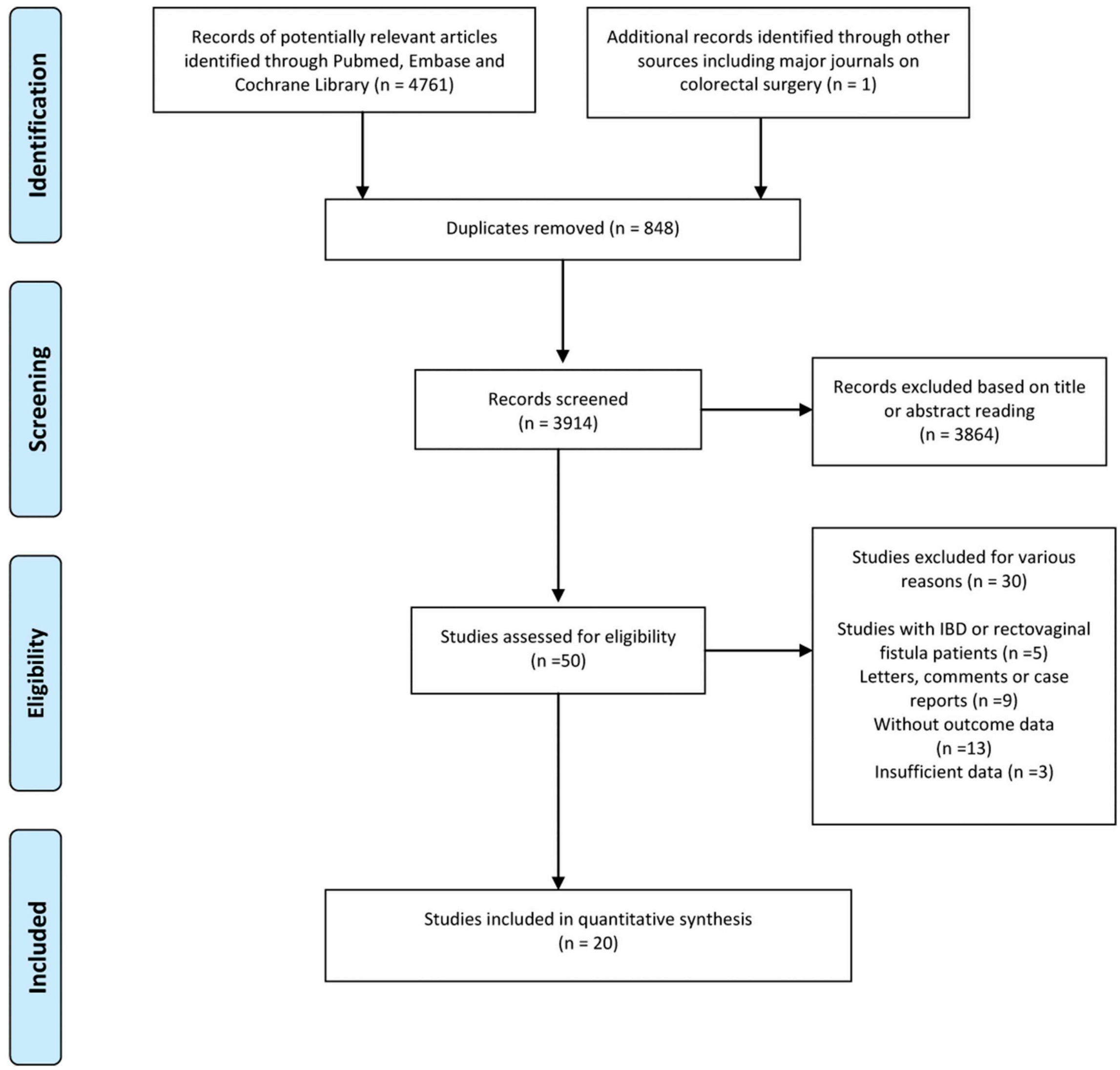

Fig. 1. Flow diagram of the study selection according to the meta-analysis of observational studies in epidemiology.

for recurrence risk of anal fistula and each patient-related factor (including gender, age, smoking, alcohol, obesity, diabetes mellitus, tertiary referral and previous anal surgery), and fistula and surgery-related factor (involving fistula type, surgical procedure, location, height or identification of internal opening, horseshoe or supralevator extensions, number of fistula tracts, seton history and postoperative drainage). For all analyses, we applied random-effects meta-analyses [33] accounting for inherent inter-study heterogeneity in terms of study populations, exposure factors, follow-up length, and other factors. . We used the I^2 statistic to assess between study heterogeneity, with I^2 values of more than 50% indicating significant heterogeneity [34]. We examined publication bias using Egger's test for correlation between the effect estimate and their variances, with a P value < 0.1 indicating significant difference [35]. Sensitivity analyses were also carried out to assess the robustness of the pooled effect estimates by excluding each single study from meta-analyses and by applying Duval's non parametric trim-and-fill method [36]. We undertook a subgroup analysis by surgical procedure to compare different surgical procedure on the pooled effects and heterogeneity. All statistical tests were two-sided with P values of < 0.05 indicating statistical significance.

3. Results

We totally identified 4555 unique records from systematic literature search, of which 50 articles were assessed for eligibility after exclusion of 3464 records when 1041 duplicated records were removed. Finally, data from 6168 individual patients with 723 recurrent cases were included in the meta-analysis of 20 eligible studies [9,15–20,27,28,37–47]. We excluded 5 studies involving patients diagnosed with Crohn's disease and rectovaginal fistula, and patient outcome data were unavailable from 13 additional studies or other reasons (Fig. 1 and eTable 3 in the Supplement). The included studies were conducted in 9 countries across 5 continents: Spain, Egypt, the Netherlands, China, the USA, Japan, Germany, Australia and India. Details of the included studies and quality evaluation are shown in Table 1. The commonest definition of AFR was persistence or recurrence of symptoms or reappearance of the fistulous track with or without associated discharge assessed by endoanal ultrasound from 6-8 weeks to 6 months after surgical intervention (eTable 6 in the Supplement).

Recurrence rates of anal fistula ranged from 2.5% to 57.1% and the pooled recurrence rate was 19% (95% CI, 15%–23%), with significant heterogeneity across studies ($I^2 = 96.8\%$, $P < 0.001$) (eFig. 1 in the Supplement). Additionally, recurrence rates were significantly different when stratified by some baseline study-level factors (almost all $P < 0.001$) such as study region except one according to institution involved (21% in single institutions, and 19% in multiple institutions) ($P = 0.371$) (eTable 7 in the Supplement).

Table 1
Descriptive information of the included studies of risk factors for anal fistula recurrence after surgery.

Source	Study year	Study design	No. of patients	No. of recurrent cases	Age,years	Surgical procedure	Follow-up Data, months	Study region, study set	Risk factors investigated	Significant risk factors	NOS score	Outcomes
Placer Galán et al., 2017	2008–2016	Retrospective cohort study	55	16	Median, 46; range, 34-61	LIFT procedure	Median,32; range, 6-51	Spain, single institution	Type of AF, location of AF, length of AF, technique of LIFT	Type and location of AF	6	Incidence of recurrence and FI
Emile et al., 2017	2009–2016	Retrospective case-control of study	251	26	Mean, 43; range, 17-87	Seton placement	Median,16; range, 6-42	Egypt, single institution	Recurrent AF after previous surgical intervention, location of AF, presence of supralevator extension, and horseshoe fistula, patients' age and gender and the development of infection postoperatively	Recurrent AF after previous surgical intervention, location of AF, presence of supralevator extension, and horseshoe fistula	7	Incidence of recurrence and FI
Boenicke et al., 2017	2012–2015	Prospective cohort study	61	11	Mean,45	Mucosal advancement flap	Mean, 25	Germany, single institution	Age, gender, history of surgical abscess drainage, recurrent fistula, ASA, BMI, smoking, alcohol abuse, diabetes, fistula type, location of fistula, duration seton drainage, abscess formation, horseshoe abscess	Age, history of surgical abscess drainage, BMI, suprasphincteric fistula and horseshoe abscess	8	Incidence of recurrence
Parthasarathi et al., 2016	2013–2014	Prospective cohort study	167	10	Median,44; range,11–85	LIFT procedure	Median,12; range, 4–22	India, single institution	The length of the tract, its course, multiple tracts, secondary abscess formation or extensions of the tract and previous recurrent fistulae	Diabetes mellitus and perianal collections	7	Incidence of recurrence
Visscher et al., 2016	2002–2012	Prospective cohort study	143	40	Mean, 47; range, 22–74	Fistulotomy, 96; fistulectomy, 28; fistulectomy + mucosal advancement flap, 19	Median, 26; range, 2–118	The Netherlands, single institution	Age, gender, previous fistula surgery, type of AF, secondary track formation, surgical treatment	Secondary track formation, surgical treatment	7	Incidence of recurrence
Mijnsbrugge et al., 2016	2013–2015	Prospective cohort study	49	28	Mean, 41; range, 24-67	LIFT procedure	Mean, 10; range, 4-25	The Netherlands, single institution	The location and height of the IFO and EFO	The height of the IFO	6	Incidence of recurrence

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Table 1 (*continued*)

Source	Study year	Study design	No. of patients	No. of recurrent cases	Age,years	Surgical procedure	Follow-up Data, months	Study region, study set	Risk factors investigated	Significant risk factors	NOS score	Outcomes
Li et al., 2016	2013–2015	Retrospective cohort study	1783	45	Mean, 39.1 ± 11.9	Fistulotomy, 396; fistulectomy, 1195; seton placement, 113	NR	China, single institution	Gender, surgical treatment, smoking, diabetes history, previous fistula surgery, complicated with colitis, seton history, location of IPO	High AF, complicated with colitis, seton history, fistula surgery	4	Incidence of recurrence
Ding et al., 2015	2011–2013	Prospective cohort study	196	22	3D-EAUS group: Median,39.73; EUA group:Median,40.25	Fistulectomy, 38; fistulotomy, 79; cutting seton with fistulectomy, 41; advancement flap, 38	1 year after surgery	China, single institution	Three-dimensional endoanal ultrasound	None	7	Incidence of recurrence and FI
Schulze et al., 2015	2008–2013	Prospective cohort study	75	9	Mean, 49.5	LIFT procedure	Mean,14.6	Australia, multiple institutions	NA	The presence of multiple tracts	6	Incidence of recurrence and FI
Zimmerman et al., 2003	1995–2000	Prospective cohort study	105	33	Median,44; range, 19–72	Mucosal advancement flap	Median, 14	The Netherlands, two institutions	Age, sex and BMI, lifestyle factors, such as smoking and drinking habits, previous attempts at repair and the use of a seton for preoperative drainage, bowel preparation, the use of antibiotics, the presence of horseshoe extensions, the location of the internal opening and postoperative drainage of the external wound	Smoking	6	Incidence of recurrence
van Onkelen et al., 2014	2000–2012	Retrospective cohort study	252	103	NR	Mucosal advancement flap	Median, 21; range, 6–136	The Netherlands, single institution	Age, sex, previous attempts at repair, tafR before referral, presence of associated abscesses, preoperative seton drainage, location of the internal opening, horseshoe extension, postoperative drainage, overweight, obesity, smoking, alcohol consumption, diabetes mellitus, and hypertension.	Horseshoe extension	8	Incidence of recurrence

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Table 1 (*continued*)

Source	Study year	Study design	No. of patients	No. of recurrent cases	Age,years	Surgical procedure	Follow-up Data, months	Study region, study set	Risk factors investigated	Significant risk factors	NOS score	Outcomes
Devaraj et al., 2011	2004	Retrospective case-control study	931	80	Mean,59; range,24–93	NA	32.4	USA,single institution	Recent smoking (current/quit smoking)	Recent smoking	6	Development of anal abscess/fistula risk
Abbas et al., 2011	2003–2008	Retrospective cohort study	179	28	Median,45 (22–73)	Fistulotomy, 148; Advancement flap, 19; Anal plug, 12	Median,53 days (6 days–40 months)	USA,single institution	Age, sex, previous operation, fistula type, number of fistula tracts, horseshoe fistula, and intervention type	Horseshoe fistula, and intervention type	6	Rates of operative failure
Schwandner et al., 2011	2007–2009	Prospective cohort study	220	40	BMI < 30: Mean, 39; range, 21-76 BMI ≥ 30: Mean,39; range, 18-64	Mucosal advancement flap	Median, 6; range 3–18	Germany, single institution	Age, tertiary referral, fistula location number of previous attempts to close the fistula, smoking, diabetes, type of surgery	BMI	7	Incidence of recurrence
Yano et al., 2010	2003–2008	Prospective cohort study	205	74	Mean, recurrence group 42.9 ± 12.7; cured group 44.0 ± 13.8	Incision and drainage procedure	NA	Japan, single institution	Gender, sex, BMI, anesthesia method, location of abscess/ fistula, anatomic classification, use of drain, diabetes mellitus, time from onset	Time from onset to surgery	5	Incidence of recurrence
Jordán et al., 2010	1994–1998	Prospective cohort study	279	20	Mean, 46.7	Fistulotomy,132; fistulectomy, 24; seton placement, 30; fistulectomy + sphincter repair, 60; fistulectomy + advancement flap, 26; core-out + IO closure, 7	Mean, 19.2	Spain, two institutions	Type of fistula, type of treatment	Type of fistula, nonidentification of internal opening, recurrent or complex fistulae, and associated chronic abscess.	8	Incidence of recurrence and FI
Hamadani et al., 2009	1995–2007	Retrospective cohort study	148	66	Mean; 43.9 (men) and 42.9 (women)	Incision and drainage	Mean,38; range,1–144	USA, single institution	Age, gender, smoking behavior, perioperative antibiotics use, diabetes, and HIV status.	Age	7	Incidence of recurrence
Poon et al., 2008	2001–2004	Retrospective cohort study	135	18	Mean,44.2	Fistulectomy,15; fistulotomy, 3; combined fistulectomy-fistulotomy, 78; partial fistulectomy-fistulotomy, 7; excision of sinus tract, 22; seton placement ± partial fistulectomy, 9	Mean,40.5	China, single institution	Sex, past history of perianal abscess, previous perianal operations, past history of Crohn's disease, tuberculosis, diabetes mellitus, preoperative MRI mapping and classification of simple or complex fistula, type of fistulas,	Positive history of perianal abscess, previous perianal operation, complex fistula, perianal sinus, lack of identification of internal opening, surgical procedure of sinus tract excision	6	Incidence of recurrence

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Table 1 (*continued*)

Source	Study year	Study design	No. of patients	No. of recurrent cases	Age,years	Surgical procedure	Follow-up Data, months	Study region, study set	Risk factors investigated	Significant risk factors	NOS score	Outcomes
									identification of internal opening, operative procedures and operative findings of abscess formation.			
van Koperen et al., 2008	1995–2003	Prospective cohort study	310	23	Group 1: Median, 39; range, 19–69 Group 2: Median,42; range, 21–67	Fistulotomy, 109; mucosal advancement flap, 70	Median, 76; range 7–134	The Netherlands, single institution	Gender, age, tertiary referral, prior fistula surgery, and smoking, seton drainage and the use of fibrin glue	None	8	Incidence of recurrence
Garcia-Aguilar et al., 1996	1988–1992.	Prospective cohort study	624	31	Mean, 48	Fistulotomy + marsupialization, 299; seton + fistulotomy, 51; cutting seton, 12; Other, 12	Mean, 29; range 2–70	USA, multiple institutions	Type of fistula, the identification and location of the IFO, prior fistula surgery, type of treatment, surgeon	Type of treatment	5	Incidence of recurrence

Abbreviations: AF, anal fistula; BMI, body mass index; EFO, external orifice; FI, fecal incontinence; IFO, internal orifice; LIFT, ligation of intersphincteric fistula tract; NA, not available; NOS, Newcastle Ottawa Scale.

3.1. Quality assessment

After evaluation of methodological safeguards against study quality and the risk of bias, we noticed the reporting was limited among eligible studies, with 50% (10 of 20) not satisfying one or two of the risk of bias items (eTable 4 in the Supplement). Almost all of the studies used hospital-based convenience sample, and no studies used a population-representative sample. Eight studies (40%) either did not provide loss to follow-up information or reported more than 20% loss to follow-up [15,19,27,28,42,43,45,47]. Thirteen studies (65%) reported adequately adjusted multivariate regression models [15,17,20,27,28,37,38,41,43–47]. Seven studies (35%) failed to present results using multivariate regression models for significant and non-significant risk factors in their adjusted analysis [9,16,18,19,39,40,42].

3.2. Patient–related risk factors

Fig. 2 shows the pooled effects of patient–related risk factors including gender, age, tertiary referral, smoking, alcohol use, diabetes mellitus, obesity, prior anal surgery and preoperative seton drainage. We found moderate-quality (Class II) evidence for a significant association between AFR and prior anal surgery (RR, 1.52; 95% CI, 1.04 to 2.23) (Table 2 and eTable 8 in the Supplement). High to moderate-quality (Class I or Class II) evidence showed no significant association between AFR and gender (RR, 1.00; 95% CI, 0.80 to 1.25), age (RR, 1.27; 95% CI, 0.99 to 1.62), tertiary referral (RR, 1.48; 95% CI, 0.78 to 2.83), smoking (RR, 1.20; 95% CI, 0.94 to 1.52), alcohol use (RR, 0.78; 95% CI, 0.59 to 1.01), diabetes mellitus (RR, 1.21; 95% CI, 0.63 to 2.32), obesity (RR, 1.24; 95% CI, 0.95 to 1.63), or preoperative seton drainage (RR, 1.05; 95% CI, 0.51 to 2.16) (Table 3 and eTable 9 in the Supplement).

3.3. Fistula and surgery-related risk factors

We found high-quality (Class I) evidence for a significant association between AFR and high transsphincteric fistula versus low transsphincteric fistula (RR, 4.77; 95% CI, 3.83 to 5.95), internal opening unidentified (RR, 8.54; 95% CI, 5.29 to 13.80), and horseshoe extensions (RR, 1.92; 95% CI, 1.43 to 2.59); and moderate-quality (Class II) evidence for an association with seton placement versus fistulotomy surgery(RR, 2.97; 95% CI, 1.10 to 8.06), and multiple versus single fistula tract (RR, 4.77; 95% CI, 1.46 to 15.51) (Table 2 and eTable 8 in the Supplement).

High-quality (Class I) evidence showed no significant association between AFR and fistulectomy versus fistulotomy surgery (RR, 1.41; 95% CI, 0.73 to 2.73); moderate-quality (Class II) evidence suggested no association between AFR and high versus low internal opening (RR, 2.75; 95% CI, 0.81 to 9.38), lateral versus posterior anal fistula (RR, 0.98; 95% CI, 0.57 to 1.69), anterior versus posterior anal fistula (RR, 0.76; 95% CI, 0.41 to 1.39), postoperative drainage (RR, 1.02; 95% CI, 0.78 to 1.32), low transsphincteric versus suprasphincteric anal fistula (RR, 0.16; 95% CI, 0.04 to 0.67), high transsphincteric versus suprasphincteric anal fistula (RR, 0.45; 95% CI, 0.19 to 1.07); moderate-quality (Class III) evidence also suggested no association between AFR and mucosal advancement flap versus fistulotomy surgery (RR, 1.39; 95% CI, 0.22 to 8.71), supralevator extensions(RR, 1.79; 95% CI, 0.62 to 5.21), and intersphincteric versus suprasphincteric anal fistula (RR, 0.24; 95% CI, 0.02 to 2.40).

3.4. Subgroup analyses and sensitivity analyses

We also conducted subgroup analyses for patients with mucosal advancement flap surgery and found younger age (< 40/45 years) (RR, 1.37; 95% CI, 1.01 to 1.87) and presence of horseshoe extensions (RR, 1.68; 95% CI, 1.21 to 2.34) were identified as the contributing risk factors (eTable 10 in the Supplement).

Sensitivity analysis for outcomes of AFR associated with most of the

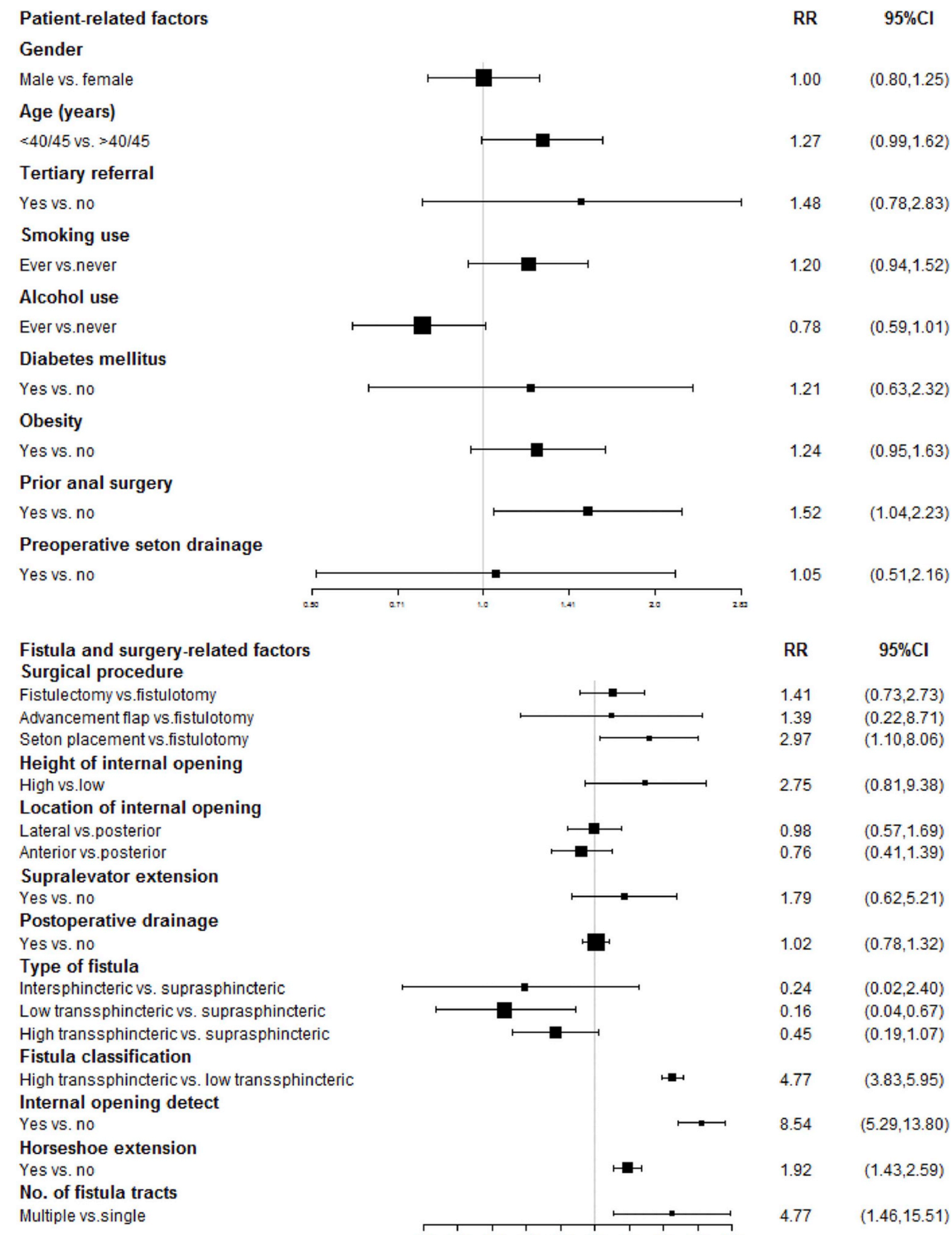

Fig. 2. Meta-analyses of association between anal fistula recurrence and patient-related risk factors, fistula and surgery-related risk factors.

patient-related risk factors, fistula and surgery-related risk factors remained constant, which was further confirmed by trim and filled method (eTable 11 and eTable 12 in the Supplement).

4. Discussion

4.1. Principal findings and clinical interpretation

Understanding risk factors for AFR helps anorectal surgeons and patients coordinate an optimal postoperative management strategy, which is aimed to formulate realistic strategies for complication management mutually agreed on by the surgeon and patient. This meta-analysis aimed to provide the data for evidence regarding predictors for AFR. Overall, 20 studies included in our meta-analysis reported risk factors for AFR with a pooled recurrence rate of almost 20%. Just one patient-related factor of prior anal surgery, followed by five anatomy and surgery-related factors including high *trans*-sphincteric fistula, undetected internal opening, and presence of horseshoe extensions, seton placement surgery and multiple fistula tracts were identified, while for patients with mucosal advancement flap surgery, two factors comprising younger age (< 40/45 years) and presence of horseshoe extensions were identified as the contributing risk factors.

Prior anal surgery is a predictive risk factor of future AFR and this is in agreement with the previous studies by Visscher and Ellis et al. [23,48]. However, patient-related factors in this meta-analysis demonstrated that age (RR, 1.27, 95% CI 0.99 to 1.62), smoking (RR, 1.20, 95%CI 0.94 to 1.52) and obesity (RR, 1.24, 95% CI, 0.95 to 1.63) all had no significant associations with AFR. Despite these findings, we could not exclude these three variables as potential risk factors in that several studies found they were significantly correlated with anal fistula

Table 2
Significant risk factors associated with postoperative anal fistula recurrence.

Significant factors	No. of Studies	No. of Patients	Postoperative Recurrence RR (95% CI)	I^2, %	*P* value	Egger's test *P* value
Prior anal surgery						
No	Ref.		Ref.			
Yes	10	3504	1.52 (1.04–2.23)	53.9	0.017	0.155
Surgical procedure						
Fistulotomy	Ref.		Ref.			
Seton placement	4	2821	2.97 (1.10–8.06)	50.3	0.11	0.635
Fistula classification						
Low transsphincteric	Ref.		Ref.			
High transsphincteric	6	2492	4.77 (3.83–5.95)	0	0.463	0.494
Internal opening detect						
Yes	Ref.		Ref.			
No	3	1038	8.54 (5.29–13.80)	0	0.784	0.69
Horseshoe extension						
No	Ref.		Ref.			
Yes	5	1411	1.92 (1.43–2.59)	3.1	0.389	0.165
No. of fistula tracts						
Single	Ref.		Ref.			
Multiple	3	421	4.77 (1.46–15.51)	42.5	0.176	0.026

Abbreviations: NA, not available; Ref., Reference group; RR, relative risk.

wound healing and post-operative recurrence [19,20,22,23,49]. Thus further clinical research regarding these variables is recommended.

Although beyond the scope of the current meta-analysis, additional research is required concerning the molecular epidemiology of AFR to contributing the interaction between these patient individual factors and potential mechanisms. Despite our findings, obesity has been known as an important risk factor for the advancement of metabolic, endocrine and cardiovascular disorders leading to corresponding systemic diseases [50]. Smoking can produce an environment of tissue hypoxia, leading to delayed or impaired wound healing mediated by vasoconstriction, cellular dysfunction and thrombogenesis [51]. Smoking is often associated with a more sedentary lifestyle, leading to an increased pressure in the anorectal area and reduction in blood flow to the surgical site. It has been shown that blood flow dropped by 15% shortly after smoking a cigarette, as detected by laser Doppler flowmetry in the anorectal mucosa [52]. Being a younger age patient was found to be a risk factor for AFR in patient with mucosal advancement flap, possibly due to the higher sphincter tone found in this age group [53].

Four fistula-related factors were determined to be significantly associated with AFR - high *trans*-sphincteric tract, undetected internal opening, horse-shoe extensions and multiple tracts. These are all associated with operative failure and AFR. Compared with the recurrence rate of 10.7% for low *trans*-sphincteric fistula, the AFR rates were 37.8% for high *trans*-sphincteric tracts and 44.4% for tracts with horseshoe extensions, respectively [27]. Supra-sphincteric tracts have one of the highest rates of AFR [27,54,55] and an undetected internal opening raises the AFR to between 43 and 53% [28,44,56,57].

Our findings suggest that anorectal surgeons should carefully review the preoperative imaging, such as three-dimensional ultrasound, computed tomography scan, and magnetic resonance imaging among patients undergoing anal fistula surgery to obtain the clear anatomy of anal fistula. The first chance for cure is often the best chance. Although the optimal and most cost-effective treatment remains controversial [58], future research must continue to further explore treatments and focus on patient outcomes. Our findings provide additional evidence helpful for shared decision making between anorectal surgeons and patients undergoing anal fistula surgery who are eligible for mucosal advancement flap surgery.

4.2. Strengths

This meta-analysis is strengthened by the implement of its predefined study protocol, comprehensive search strategy, rigorous study inclusion and eligibility criteria, thorough assessment of study quality, and transparent reporting of the findings, which improved objectivity and uniformity.

To our knowledge, this is the first study to comprehensively evaluate a wide range of risk factors for AFR. Moreover, we also assessed the strength of supporting evidence for each investigated risk factor, from Class I to Class IV, based on the combination of inter-study heterogeneity, Egger's *P* value and the number of enrolled patients (Supplementary Table 5) which could potentially help both surgeons and patients interpret the evidence. Furthermore, multiple rigorous methods were applied to examine the robustness of our findings including small study effect analysis, sensitivity analysis, and the trim-and-fill analysis.

4.3. Limitations

Our study should be interpreted with several limitations. Firstly, due to most of the studies we reviewed being retrospective cohorts and the diversity and complexity of related contributing factors for AFR, they were to some extent subject to selection bias. Secondly, few studies involved in the analysis of some of the risk factors, which in this case would be too underpowered to detect significant associations with relatively small effects, re-asserting the need for further high-quality large cohort studies in the future. In addition, we found the effect estimates for some factors were around the boundary with the confidence interval ranging from 0.90 to 1.10 (eg, age, smoking, obesity and prior surgery) (Tables 2–3). To address this issue, we conducted sensitivity analyses for such subsets (eTable 11 and eTable 12 in the Supplement). We consider that as more powered cohort studies were added, more definite and high level evidence would be provided. Moreover, other limitations such as the absence of consistent details in the individual studies made further subgroup analyses impossible. Finally, there have been no gold standard criteria or guidelines to quantitatively assess the strength of evidence for risk factor meta-analysis. We selected three conditions (Egger' *P* value, number of included patients and I^2 statistic) to determine the strength of evidence based on previously published

Table 3
Non-significant risk factors associated with postoperative anal fistula recurrence.

Non-significant patient-related factors	No. of Studies	No. of Patients	Postoperative Recurrence RR (95% CI)	I^2, %	*P* value	Egger's test *P* value
Gender						
Female	Ref.		Ref.			
Male	11	3511	1.00 (0.80–1.25)	0	0.972	0.011
Age (years)						
> 40 or 45	Ref.		Ref.			
≤40 or 45	7	1199	1.27 (0.99–1.62)	53.2	0.046	0.033
Tertiary referral						
No	Ref.		Ref.			
Yes	2	453	1.48 (0.78–2.83)	0	0.676	0.009
Smoking						
Never	Ref.		Ref.			
ever	7	3584	1.20 (0.94–1.52)	8.9	0.361	0.62
Alcohol use						
Never	Ref.		Ref.			
ever	2	357	0.78 (0.59–1.01)	0	0.789	NA
Diabetes mellitus						
No	Ref.		Ref.			
Yes	7	2745	1.21 (0.63–2.32)	55.7	0.035	0.026
Obesity						
No	Ref.					
Yes	4	638	1.24 (0.95–1.63)	49.6	0.114	0.734
Preoperative seton drainage						
No	Ref.		Ref.			
Yes	5	3505	1.05 (0.51–2.16)	71.7	0.007	0.354
Non-significant fistula/surgery-related factors						
Surgical procedure						
Fistulotomy	Ref.		Ref.			
Fistulectomy	4	2340	1.41 (0.73–2.73)	0	0.465	0.934
Advancement flap	3	601	1.39 (0.22–8.71)	80	0.007	0.295
Height of internal opening						
Low	Ref.		Ref.			
High	3	1697	2.75 (0.81–9.38)	84.5	0.002	0.26
Location of internal opening						
Posterior	Ref.		Ref.			
Lateral	6	3023	0.98 (0.57–1.69)	65	0.014	0.884
Anterior	7	3275	0.76 (0.41–1.39)	78.4	< 0.001	0.72
Supralevator extensions						
No	Ref.		Ref.			
Yes	2	356	1.79 (0.62–5.21)	71.2	0.062	NA
Postoperative drainage						
No	Ref.		Ref.			
Yes	2	357	1.02 (0.78–1.32)	0	0.382	NA
Type of fistula						
Suprasphincteric	Ref.		Ref.			
Intersphincteric	2	458	0.24 (0.02–2.40)	60	0.114	NA
Low transsphincteric	3	513	0.16 (0.04–0.67)	46.7	0.153	0.931
High transsphincteric	3	513	0.45 (0.19–1.07)	40.5	0.186	0.526

Abbreviations: NA, not available; Ref., Reference group; RR, relative risk.

criteria [59]. Given the choice of any particular thresholds for each item of the criteria is arbitrary, the evidence classification should serve for illustrative purposes rather than absolute rules.

4.4. Future directions

Multidisciplinary factors to affect postoperative outcomes have been investigated; nevertherless, pragmatic large cohort studies are needed to understand the associations, and maybe the causal factors between specific factors and AFR using objective data synthesis methods. We should not ignore the evidence of patient-related factors for contributing AFR, though only one factor of prior surgery with Class II evidence were identified. These specific variables could be helpful in identifying specific patient groups with an increased risk of recurrence, and individual risk factors should be considered in recommendations on primary prevention of recurrence to make proper strategies to reduce their risks. In the long run, these results may be applied to refine the evolving work on preoperative risk assessment, while providing a renewed call to action for large multicenter cohorts. Not only are unambiguous definitions for each risk factor needed, but also comprehensive, uniform reporting of risk factors and outcomes is necessary to provide optimal care for the increasing number of patients with anal fistula.

5. Conclusions

In conclusion, this meta-analysis has revealed statistically significant increases in risk of AFR with prior anal surgery, high *trans*-sphincteric fistula, undetected internal opening, and presence of horseshoe extensions, seton placement surgery and multiple fistula tracts. For patients with mucosal advancement flap surgery, younger age (< 40/45 years) and presence of horseshoe extensions were identified as the contributing risk factors. Large well-designed studies are still expected to further strengthen the evidence on some risk factors like age, smoking and obesity. Future molecular epidemiology studies are also warranted to establish the underlying mechanisms linking these risk factors with AFR. Our study strengthens clinical awareness of early warning to identify patients with high-risk disease recurrence for AFR.

Provenance and peer review

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Conflicts of interest

The authors declare that they have no conflict of interest.

Role of the funder/sponsor

The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the manuscript. The corresponding author had full access to all the data in the study and has final responsibility for the decision to submit for publication.

Ethical approval

Not applicable.

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Author contribution

Dr. Zubing Mei had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Mei and Wang are co-first authors of this article.

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Acquisition, analysis, or interpretation of data: Zubing Mei, Qingming Wang, Yazhou He, Yi Zhang, Peixin Du, Wei Yang.

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Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Zubing Mei, Yazhou He, Maojun Ge.

Administrative, technical, or material support: All authors.

Study supervision: Zubing Mei.

Research registry number

1. Registry used: PROSPERO (https://www.crd.york.ac.uk/prospero/)
2. Unique Identifying number or registration ID: CRD42018102469
3. Hyperlink to the registration (must be publicly accessible): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=102469

Guarantor

Zubing Mei.

Data statement

This is a summary design study. Data used for meta-analysis was extracted from previously published papers.Acknowledgements

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.08.003.

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