



Review Paper

# Risk factors for postoperative intra-abdominal septic complications after surgery in Crohn's disease: A meta-analysis of observational studies

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## Abstract

**Background and Aims:** Postoperative intra-abdominal septic complications [IASCs] are the most feared risks of surgery for Crohn's disease[CD]. The risk factors for IASCs still remain controversial. The aim of this study was to assess the risk factors for IASCs in CD patients undergoing abdominal surgery.

**Methods:** MEDLINE, Cochrane Library, and EMBASE were searched to identify observational studies reporting the risk factors for IASCs in CD patients. A meta-analysis was conducted to investigate the impact of various risk factors on IASCs in CD. The GRADE [Grading of Recommendations Assessment, Development and Evaluation] approach was used for quality assessment of evidence on outcome levels.

**Results:** This review included 15 studies evaluating 3807 patients undergoing 4189 operations. The meta-analyses found that low albumin levels (odds ratio [OR]: 1.93; 95% confidence interval [CI]: 1.362.75), preoperative steroids use [OR: 1.99; 95% CI: 1.54–2.57], a preoperative abscess [OR: 1.94; 95% CI: 1.263.0], previous surgery history [OR: 1.50; 95% CI: 1.151.97] may be risk factors for IASCs. There were no associations between anastomosis methods [OR: 0.94; 95% CI: 0.58–1.53], biologics therapy [OR: 1.29; 95% CI: 0.792.11], and immunomodulator use [OR: 1.07; 95% CI: 0.661.73] with the risk of IASCs. Due to observational design, the quality of evidence was regarded low or moderate for these risk factors by the GRADE approach.

**Conclusions:** This meta-analysis provides some evidence that steroids use, previous surgical history, a preoperative abscess, and low albumin levels may be associated with higher rates of IASCs in CD. Knowledge about those risk factors may influence treatment and procedure-related decisions, and possibly reduce the ss rate.

**Keywords:** Crohn's disease; risk factors; postoperative intra-abdominal septic complications

## 1. Introduction

Nearly 70–90% of Crohn's disease [CD] patients will undergo at least one operation during the course of CD.<sup>1,2</sup> The term 'anastomosis-related postoperative intra-abdominal septic complications'

[IASCs] involves an anastomotic leakage, intra-abdominal abscess, or enterocutaneous fistula. These are the most severe complications and are often the underlying causes of death following surgery.<sup>3</sup> IASCs are associated with increased mortality and morbidity,

longer hospital stays, higher treatment costs, and greater individual suffering.<sup>4</sup> Moreover, the recurrence rates in patients with IASCs were significantly higher than in those without IASCs.<sup>5</sup> Therefore, IASCs should be evaluated separately from other complications. The frequency of reported IASCs has ranged between 2.7% and 16%, according to several publications.<sup>5,6,7</sup> However, the risk factors for IASCs still remain controversial. Some risk factors related to higher rates of IASCs include the following: preoperative steroids use,<sup>8,9</sup> a preoperative abscess,<sup>8,9</sup> poor nutritional status,<sup>5,9</sup> low albumin levels,<sup>10</sup> advanced age,<sup>11,12</sup> immune-modulating medications,<sup>7</sup> the method of anastomosis,<sup>6</sup> operating time,<sup>6,13</sup> duration of symptoms leading to surgery,<sup>5,14</sup> and a colo-colonic anastomosis.<sup>7,13</sup> However, other studies have found that some of these factors were not associated with IASCs.<sup>3,4,5,15</sup> Therefore, it is important to uncover the risk factors for IASCs to determine appropriate therapeutic strategies. Knowledge about these risk factors may help individualize treatment for each patient; for instance, may improve selection of patients not suited for primary anastomosis.

## 2. Methods

### 2.1. Search strategy

The Cochrane Library and the MEDLINE and EMBASE databases were searched [from inception to August 31, 2014]. Two reviewers [WPH and YFS] working independently and in duplicate conducted a systematic literature search. For Medline, the term Crohn's disease and exploded terms such as inflammatory bowel disease, regional enteritis were used to identify papers on CD. The terms intra-abdominal septic complications, anastomotic leakage, intra-abdominal abscess, enterocutaneous fistula, and exploded terms were used to identify papers related to IASCs. The four sets of terms were combined using the set operator OR. Search was limited to titles or abstracts, to narrow the search results. The two sets of terms CD and IASCs were then combined using the set operator AND. Individually fitted search strategies with similar search terms were also performed in the EMBASE database. Only published journal studies were included; unpublished data were not sought. No language restrictions were applied. The 'related articles' function from PubMed was used to broaden the search, and reference lists of included studies were searched for additional relevant studies. All abstracts, studies, and citations scanned were reviewed. For studies deemed eligible for inclusion, available full papers were obtained and evaluated in detail. For the study selection process, see [Figure 1](#).

### 2.2. Study selection

Inclusion criteria for the selected studies included the following.

1. Studies had to report risk factors for IASCs in CD patients who underwent intestinal resection with primary anastomosis and/or stricturoplasty [diverting a stoma without anastomosis was excluded].
2. IASCs must have met one of the three criteria: anastomotic leakage, intra-abdominal abscess, or enterocutaneous fistula.
3. Risk factors must have been analysed with multivariate regression analyses to reduce the risk of confounding in the observational studies.

When two studies were reported by the same institution and/or authors on the same patient cohorts, the larger, higher-quality study was included in the analysis.

Exclusion criteria for this study included the following.

1. Studies observing IASCs occurrence more than 1 month after surgery were excluded, because late IASCs are mainly caused by recurrent diseases which are not surgical complications.
2. Studies only involving pediatric patients and studies which incorporated both CD and ulcerative colitis patients without clear distinction were excluded.
3. Studies where it was impossible to extrapolate or calculate the necessary data [eg IASCs were included in the total postoperative complications without separate analysis].

When there was disagreement over the eligibility of a study, an additional reviewer [YBT] assessed the article until a consensus was reached.

### 2.3. Quality assessment

The Newcastle-Ottawa Scale<sup>16</sup> was adopted to assess the quality of the included studies. Studies achieving seven or more stars were considered to be of a higher quality.

The GRADE [Grading of Recommendations Assessment, Development and Evaluation] Approach<sup>17</sup> was adopted to assess the quality of evidence on outcome level for the analyses. The quality may be rated as high, moderate, low, or very low. GRADE scoring was performed using the software GRADEpro, version 3.6.1 for Windows.

Newcastle-Ottawa Scale [NOS] and GRADE scoring were performed individually by YFS and WPH. Discrepancies were settled by discussion.

### 2.4. Data extraction

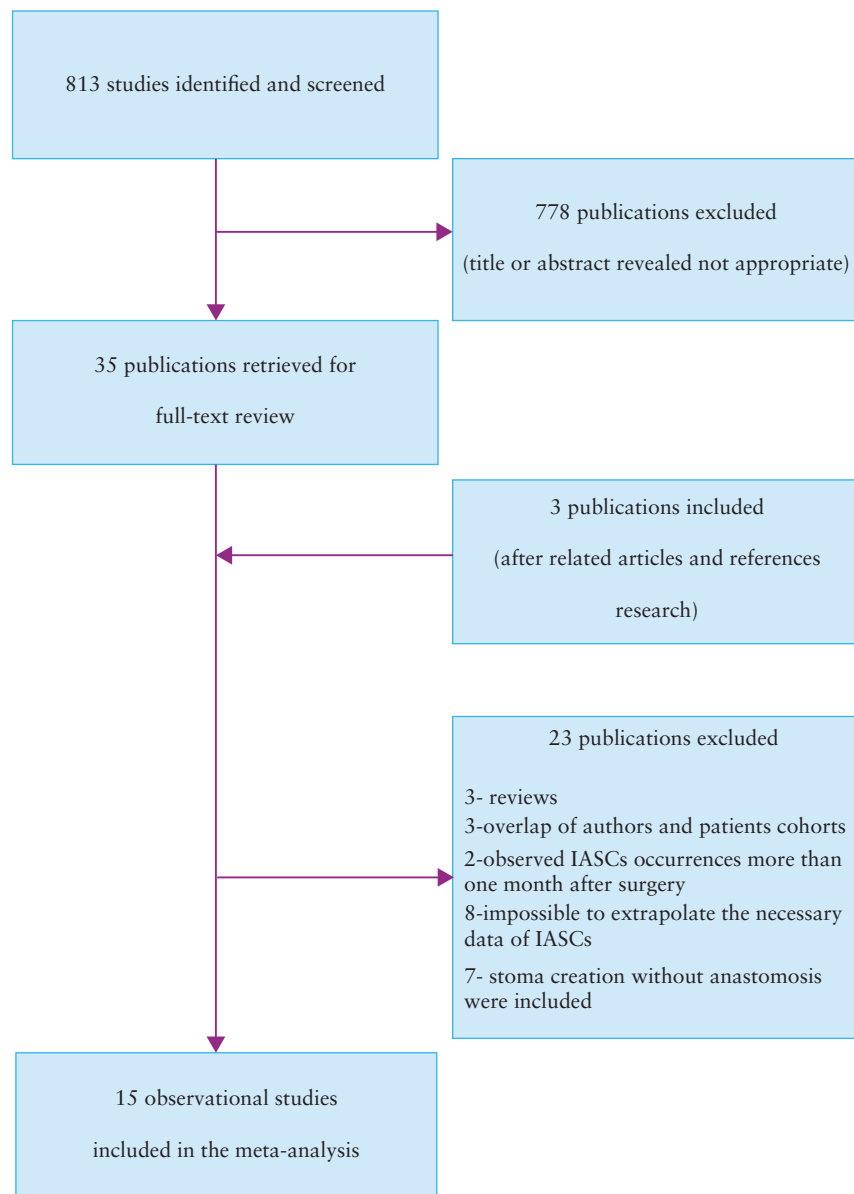
Two reviewers [WPH and YFS] independently extracted the following data from all eligible studies: first author, year of publication, country of origin, study design, number of subjects, and risk factors involving IASCs. For the risk factors involving IASCs, we mainly focused on factors that had previously been identified as independent factors including: low albumin levels, preoperative abscess, method of anastomosis, previous surgery history, preoperative steroids, biologics, and immunomodulation therapy.

### 2.5. Statistical analysis

A meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement.<sup>18</sup> An odds ratio [OR] was used as the statistical measure for dichotomous outcomes. ORs were calculated from the original data and reported with 95% confidence intervals [CIs]. Pooled odds ratios were calculated for the effect of each variable on the incidence of IASCs. Pooled outcome measures were determined using random effects models as described by Der Simonian and Laird.<sup>19</sup>

Heterogeneity was quantified using  $I^2$ . Low heterogeneity might account for less than 30% of the variability in point estimates, and notable heterogeneity for substantially more than 50%.<sup>20</sup> The pooled estimates are presented with forest plots. Several measures were taken to quantitatively assess heterogeneity: [1] reanalysis of the data using a fixed effects model instead of a random effects model; [2] funnel plots with an Egger test were used to evaluate publication bias; and [3] sensitivity analyses were performed by excluding each study, one at a time, and estimating the overall OR with the remaining studies.

Statistical analyses were performed using the software STATA, version 12.0 [Stata Corporation, College Station, TX, USA].



**Figure 1.** The study selection process.

### 3. Results

#### 3.1. Search results

Our predefined search strategy identified a total of 813 studies; 778 of these studies did not meet the inclusion criteria and were excluded from further analysis. The remaining 35 studies were retrieved for full text articles<sup>3,4,5,6,7,8,9,12,13,14,15,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44</sup>; a related articles search and an examination of the bibliography of these references identified three studies of possible interest.<sup>10,45,46</sup> In total, 38 studies were acquired for further analysis. Three reviews<sup>26,34,46</sup> were excluded. Three studies<sup>10,39,40</sup> were excluded because of an overlap of authors and possibly of patient cohorts. Therefore, the higher quality studies<sup>3,28,41</sup> were included. Two studies<sup>30,41</sup> that observed IASC occurrences more than 1 month after surgery were excluded. Studies<sup>25,29,35,37,42,43,44,45</sup> were excluded because IASCs were included in the total postoperative complications and it was impossible to extrapolate the necessary data from the studies. Studies<sup>5,15,32,22,27,31,36</sup> were excluded

because stoma creation without anastomosis was included in the total operative procedures, so it was impossible to extrapolate the data for bowel resection with primary anastomosis. Therefore, 15 studies<sup>3,4,6,7,8,9,12,13,14,21,23,24,28,33,38</sup> that met the inclusion criteria were included in the final meta-analysis. The included studies had a total population of 3807 patients who underwent 4189 operations. The overall IASCs rate for the entire study cohort was 9.2%.

#### 3.2. Quality assessment

The included studies were assessed for risk of bias using the Newcastle-Ottawa Scale. The median score was 7.7 [range: 7–8] for all studies. Most of the studies had a low risk of bias and had good quality in the assessment of outcome [Table 1].

The GRADE approach was adopted to assess the quality of evidence on outcome level for the analyses. The quality of evidence was regarded moderate or low for these risk factors [Table 2].

**Table 1.** Characteristics of the 15 studies included in the meta-analyses to assess the risk of postoperative intra-abdominal septic complications in CD patients.

Source	Study design	No. of patients [no. of operations]	Surgical procedure	Newcastle- Ottawa scale
Yamamoto <i>et al.</i> 2000 UK	Case-control	343[566]	BR+SP	8
Tay <i>et al.</i> 2003 USA	Cohort	100[100]	BR+SP	7
Alves <i>et al.</i> 2007 France	Case-control	161[161]	IR	8
Myrelid <i>et al.</i> 2009 Sweden	Case-control	306[343]	BR+SP	8
Tzivanakis <i>et al.</i> 2012 UK	Case-control	173[173]	IR	8
Kanazawa <i>et al.</i> 2012 Japan	Case-control	550[633]	BR	8
EL-hussuna <i>et al.</i> 2012 Denmark	Cohort	417[417]	BR+SP	7
Shental <i>et al.</i> 2012 Israel	Case-control	166[166]	IR	8
Serradori <i>et al.</i> 2013 France	Case-control	217[217]	IR	7
Huang <i>et al.</i> 2013 China	Case-control	91[120]	BR	7
Wang <i>et al.</i> 2013 China	Case-control	114[114]	BR	8
Myrelid <i>et al.</i> 2014 Sweden	Cohort	298[298]	BR	8
Nasir <i>et al.</i> 2010 USA	Cohort	370[370]	BR+SP	8
Appau <i>et al.</i> 2008 USA	Cohort	389[389]	IR	8
Resegotti <i>et al.</i> 2005 Italy	Cohort	112[112]	IR	8

BR, bowel resection; SP, stricturoplasty; IR, ileocecal [or ileocolic] resection.

**Table 2.** Summary finding of risk factors eligible for meta-analysis.

Risk factor	Number of patients/studies	Regarded a risk factor	Pooled odds ratio	Quality of evidence [GRADE]
Low albumin levels	2127/8	Yes	1.93 [95% CI: 1.36-2.75]	⊕⊕○○ Low
A preoperative abscess	3132/12	Yes	1.94 [95% CI: 1.263-0]	⊕⊕○○ Low
Preoperative steroid use	3502/13	Yes	1.99 [95% CI: 1.54-2.57]	⊕⊕⊕○ Moderate
Previous surgery history	2737/9	Yes	1.50 [95% CI: 1.151-97]	⊕⊕⊕○ Moderate
Biologics use	1833/6	No	1.29 [95% CI: 0.792-1.11]	⊕⊕○○ Low
Immunomodulation use	2146/6	No	1.07 [95% CI: 0.661-73]	⊕⊕○○ Low
Anastomosis methods	2532/8	No	0.94 [95% CI: 0.58-1.53]	⊕⊕○○ Low

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

### 3.3. Risk factors for IASCs

#### 3.3.1. Serum albumin levels

A total of eight studies<sup>3,4,6,7,14,21,24,33</sup> [ $n = 2127$ ] evaluated serum albumin as a risk factor. A meta-analysis on these studies found a pooled OR of 1.93 [95% CI: 1.36-2.75] in the random effects model, suggesting that low serum albumin was associated with a high risk of IASCs [Figure 2a]. There was no heterogeneity [ $p = 0.88$ ;  $I^2 = 0\%$ ] among the studies and no evidence of a significant publication bias was found using funnel plots [not shown] and an Egger test [ $p = 0.86$ ]. The quality of the evidence was regarded as low based on the GRADE approach.

#### 3.3.2. Preoperative abscess

Twelve studies<sup>3,4,6,7,8,9,13,14,21,23,24,33</sup> [ $n = 3132$ ] evaluated a preoperative abscess as a risk factor. A meta-analysis on these studies found a pooled OR of 1.94 [95% CI: 1.2-63.0] in the random effects model, suggesting that a preoperative abscess was associated with a high risk of IASCs [Figure 2b]. There was mild heterogeneity [ $p = 0.03$ ;  $I^2 = 49.1\%$ ] among the studies. There was no evidence of a

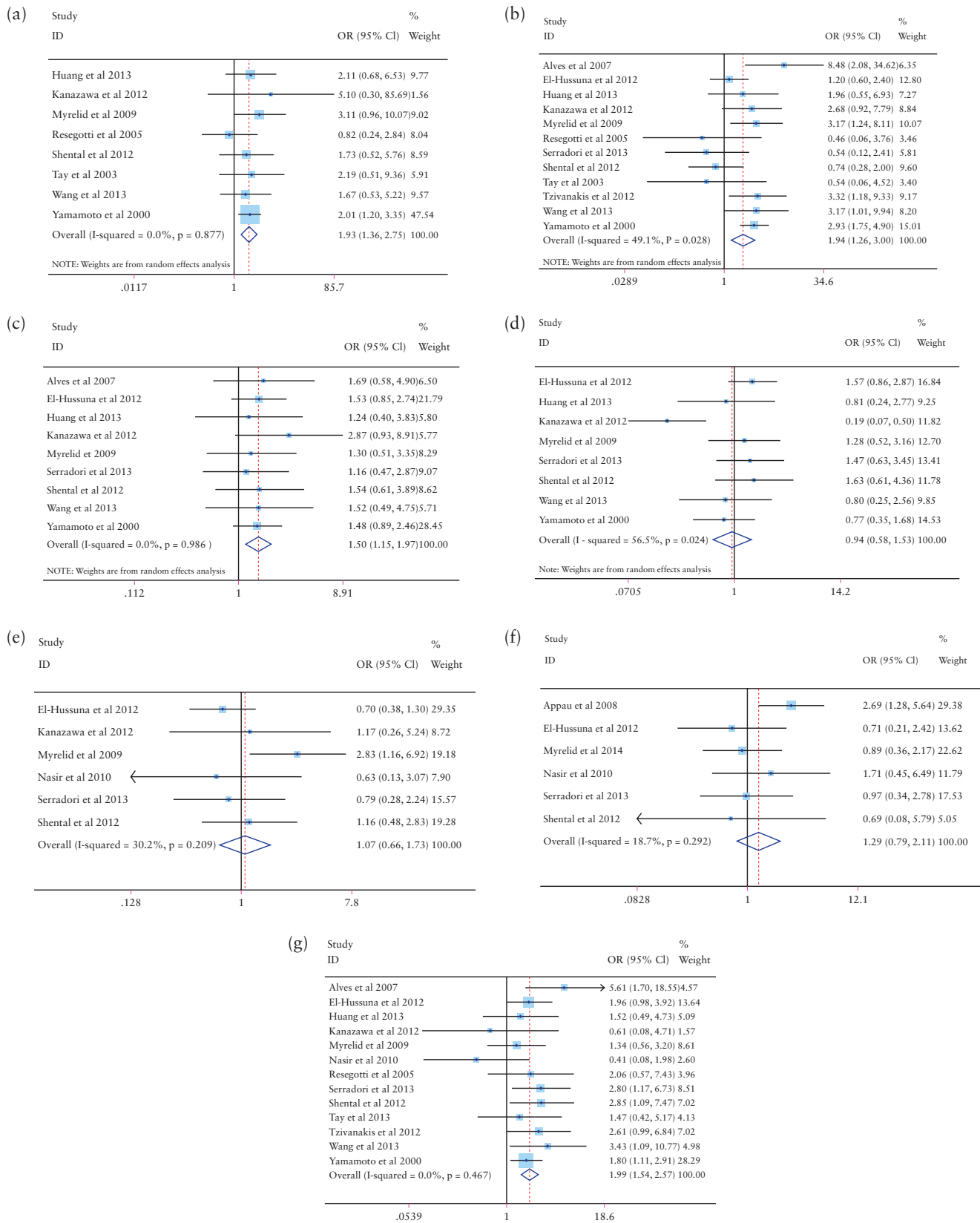
significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.33$ ]. The quality of the evidence was regarded as low based on the GRADE approach.

#### 3.3.3. Previous surgery history

Nine studies<sup>3,6,7,9,13,14,21,23,33</sup> [ $n = 2737$ ] evaluated previous surgery history as a risk factor. A meta-analysis on these studies found a pooled OR of 1.50 [95% CI: 1.15-1.97] in the random effects model, suggesting that a previous surgical history was associated with a high risk of IASCs [Figure 2c]. There was no heterogeneity [ $p = 0.99$ ;  $I^2 = 0\%$ ] among the studies and no evidence of a significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.67$ ]. The quality of the evidence was regarded as moderate based on the GRADE approach.

#### 3.3.4. Method of anastomosis

Eight studies<sup>3,6,7,13,14,21,23,33</sup> [ $n = 2532$ ] evaluated the method of anastomosis as a risk factor. A meta-analysis on these studies found a



**Figure 2.** Forest plots for risk factor eligible for meta-analysis. (a) Serum albumin levels as a risk factor. (b) Preoperative abscess as a risk factor. (c) Previous surgery history as a risk factor. (d) Method of anastomosis as a risk factor. (e) Immunomodulation as a risk factor. (f) Biologics as a risk factor. (g) Steroids as a risk factor.

pooled OR of 0.94 [95% CI: 0.58–1.53] in the random effects model, suggesting that the method of anastomosis was not a risk factor for IASCs [Figure 2d]. There was significant heterogeneity [ $p = 0.024$ ;  $I^2 = 56.5\%$ ] among the studies. A sensitivity analysis performed by excluding the Kanazawa study changed the heterogeneity from 57 to 0, but did not alter the statistical significance of the estimate. There was no evidence of a significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.31$ ]. The quality of the evidence was regarded as low based on the GRADE approach.

### 3.3.5. Immunomodulation

Six studies<sup>6,7,12,13,14,23</sup> [ $n = 2146$ ] evaluated immunomodulation as a risk factor. A meta-analysis on these studies found a pooled OR of 1.07 [95% CI: 0.66–1.73] in the random effects model, suggesting that immunomodulation was not a risk factor for IASCs [Figure 2e]. There was mild heterogeneity [ $p = 0.21$ ;  $I^2 = 30.2\%$ ] among the studies and no evidence of a significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.80$ ]. The quality of the evidence was regarded as low based on the GRADE approach.

### 3.3.6. Biologics

Six studies<sup>12,13,14,23,28,38</sup> [ $n = 1833$ ] evaluated biologics as a risk factor. A meta-analysis on these studies found a pooled OR of 1.29 [95% CI: 0.79–2.11] in the random effects model, suggesting that biologics were not a risk factor for IASCs [Figure 2f]. There was low heterogeneity [ $p = 0.29$ ;  $I^2 = 18.7\%$ ] among the studies and no evidence of a significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.25$ ]. The quality of the evidence was regarded as low based on the GRADE approach.

### 3.3.7. Steroids

A total of 13 studies<sup>3,4,6,7,8,9,12,13,14,21,23,24,33</sup> [ $n = 3502$ ] evaluated steroids use as a risk factor. A meta-analysis on these studies found a pooled OR of 1.99 [95% CI: 1.54–2.57] in the random effects model, suggesting that steroids use was associated with a high risk of IASCs [Figure 2g]. There was no heterogeneity [ $p = 0.47$ ;  $I^2 = 0\%$ ] among the studies. There was no evidence of a significant publication bias found using funnel plots [not shown] and an Egger test [ $p = 0.65$ ]. The quality of the evidence was regarded as moderate based on the GRADE approach.

Comparing these results with a fixed effect model, as well as leaving out any one of the included studies, would not change the statistical significance for any of the outcomes.

## 4. Discussion

This is the first meta-analysis of observational studies designed to assess risk factors for IASCs in patients with CD. Our findings demonstrate that low albumin levels, preoperative steroids use, a preoperative abscess, and previous surgical history are risk factors for IASCs. There were no associations between method of anastomosis, biologics therapy, and immunomodulator use with the risk of IASCs. On the basis of the GRADE approach on outcome of meta-analyses, the quality of evidence was regarded low or moderate. The studies included in the meta-analysis had good quality in assessment of outcome according to NOS evaluation. So, the low quality of the outcomes was not a result of biases across studies, but mostly was a result of the observational nature of the studies which at the starting point are considered as low quality in GRADE.

Serum albumin is an important material for wound healing and collagen synthesis at the anastomosis site. Hypoproteinemia can result in tissue oedema and collagen synthesis disorders, which

may contribute to an anastomotic leakage.<sup>47</sup> Moreover, hypoproteinaemia has an adverse effect on the immune system. Thus, infections were commonly found in patients with low albumin levels.<sup>48</sup> Albumin levels have a major impact on surgical outcomes and postoperative complications. Low albumin levels are also associated with an increased risk of postoperative morbidity and mortality. Furthermore, according to some studies, serum albumin has been used as a predictor of surgical outcomes.<sup>49,50</sup> Hypoproteinemia justifies the use of a protective diverting colostomy/ileostomy in patients with low albumin levels.<sup>51</sup> This is consistent with our finding that albumin levels play an important role in the development of IASCs in CD patients undergoing surgery. The correction of severe hypoalbuminaemia is necessary during preoperative management.

A preoperative abscess is a common complication of CD, with the incidence ranging between 10% and 30%.<sup>3,9,25,52</sup> This might reflect an advanced disease activity and is regarded as an independent significant risk factor for IASCs,<sup>3,8,9</sup> which was confirmed by our study. The conclusion was consistent with the current opinion that an abdominal abscess should be treated with conservative strategies [eg use percutaneous drainage and antibiotics to avoid surgery in an acute setting].<sup>53</sup> Some studies have demonstrated the efficacy of percutaneous abscess drainage to reduce the incidence of IASCs.<sup>52,54</sup> Currently, it is accepted that percutaneous drainage prior to surgery is the best option, allowing a one-step procedure without a stoma to be performed later, or even avoidance of surgery.

To our knowledge, no studies have identified previous surgical history as a risk factor for IASCs. However, the meta-analysis showed that previous abdominal surgery was associated with an increased IASCs rate. Previous surgery would result in a greater amount of adhesions, which make surgery more difficult to perform. Combined with the nature of CD such as fistulas, abscesses, intestinal inflammation, and tissue fibrosis, patients who have had abdominal surgery may be more prone to developing IASCs. Although the results cannot modify the preoperative strategy, the knowledge of a previous surgical history can be used for the evaluation of the risk for IASCs, especially for patients presenting with other risk factors.

Stapled anastomoses are now widely accepted in gastrointestinal surgery, but there is no clear evidence indicating that stapled anastomoses are superior to handsewn anastomoses in patients with CD. Some studies reported that stapled anastomoses were associated with less anastomotic leakage.<sup>24,55</sup> Other studies showed no difference in anastomotic leakage between handsewn anastomoses and stapled anastomoses.<sup>52,56</sup> The advantage of stapled anastomoses may be in lowering intraoperative septic contamination and reducing tissue inflammation. However, the intestinal wall is often thick and oedematous in CD patients and may not staple well, which contributes to an increased risk of anastomotic leak. This meta-analysis demonstrates that employing either a handsewn or stapled anastomosis does not appear to affect the incidence of IASCs. A heterogeneity between the studies was caused by the work of Kanazawa *et al.*,<sup>6</sup> which indicated that the anastomotic leakage rate in the handsewn group was much higher than that in the stapled group. In that study, the number of patients in the handsewn group [ $n = 88$ ] was far less than those in the stapled group [ $n = 528$ ], leading to a somewhat reduced statistical reliability. Sensitivity analysis performed by leaving out the Kanazawa *et al.* study did not change the statistical significance of the outcome, which confirmed the stability of the result.

Almost all CD patients are taking immunomodulator therapy at the time of surgery; many of them are receiving combinations of multiple agents such as steroids, thiopurines, and infliximab. The use of these agents has proven to be effective in induction and maintenance of remission in CD patients. However, the impact of

immunosuppressive agents on surgical outcome is debatable. Some studies show that these agents may be independently associated with postoperative complications<sup>38,46</sup>; other studies do not show any association between adverse complications after surgery and the use of immunosuppressive agents.<sup>37,44</sup> One study<sup>4</sup> has reported improved perioperative outcomes for patients receiving immunomodulating agents. So, this meta-analysis provides a comprehensive evaluation of the impact of immunomodulating agents [steroids, immunosuppressive medication, and biologic agents] on IASCs in CD patients. There are two important limitations involved in this risk factor, which lead to statistical heterogeneity for the outcome measures: [1] concomitant use of immunomodulators; and [2] the cut-off time of immunomodulator therapy before surgery varied considerably [a cut-off time of 2 or 3 months was used among the included studies and some studies included patients who received immunomodulators after surgery]. So it is difficult to approach with accuracy the net effect of different immunomodulators on IASCs as an independent risk factor.

It is unclear from the literature what influence steroids use has on IASCs. Steroids use was associated with a high risk of IASCs in some studies,<sup>3,8,9,13</sup> but not in others.<sup>4,5,6</sup> Steroids have been shown to reduce anastomotic healing and increase the risks of complications following surgery.<sup>57</sup> Prolonged use of steroids can lead to worsening of the general condition of patients. Tzivanakis<sup>8</sup> preferred a temporary stoma to a primary anastomosis when two risk factors [steroids usage and preoperative abscess] were present. Our results also suggest that preoperative steroids use is a risk factor for IASCs.

The influence of immunosuppressive therapy on surgical outcome in CD patients is controversial. According to clinical and laboratory data, immunosuppressive medication has a negative impact on postoperative outcome; for instance, it may impair wound and anastomotic healing and increase the rates of infectious complications. However in CD, immunomodulator drugs may be effective in the treatment and prophylaxis for the exacerbation of inflammation after surgery, which would improve perioperative outcomes. Some studies show that immunosuppressive medication does not influence the postoperative complications,<sup>31,32</sup> and other studies report either positive or negative effects on early postoperative outcome.<sup>4,7</sup> A meta-analysis<sup>58</sup> showed there was no association between the use of immunomodulator drugs and postoperative complications. This is in line with our study: preoperative immunosuppressive agents are not associated with increased rates of IASCs after bowel resection.

Biologic agents have been postulated to be associated with adverse effects on account of potent immunosuppressive action: the attenuated immune response may increase risk of anastomotic leak and septic complications. However, the influence of biologic agents on surgical outcome in CD patients is debatable. Some studies found anti-TNF [tumor necrosis factor] treatment is associated with an increased risk of postoperative complications,<sup>22,38</sup> and other studies showed there was no association between the use of anti-TNF and postoperative complications.<sup>12,31</sup> The outcomes of meta-analyses on the effect of anti-TNF treatment on the anastomotic complications are controversial as well. El-Hussuna *et al.*<sup>34</sup> found anti-TNF treatment increased the risk of anastomotic complications, whereas Papaconstantinou *et al.*<sup>26</sup> suggested there was no significant association between anti-TNF treatment and anastomosis-related complications. Both of the meta-analyses included studies involving various surgical procedures, which led to statistical heterogeneity for the outcome measures. The present meta-analysis only included studies involving intestinal resection with primary anastomosis and/or strictureplasty, which provides a more homogeneous group. Our results

suggest that anti-TNF treatment is not associated with increased rates of IASCs after bowel resection in CD patients.

There are some limitations to the present review. The risk factor for IASCs can only be investigated in observational studies, which entails a risk of bias that cannot be eliminated through adjusted analyses. Randomized controlled trials were regarded as high quality, whereas observational studies were considered low quality. Therefore, our reported conclusions are based on lesser-quality studies. The included studies varied in terms of risk factors for IASCs, severity, location, and duration of the disease, surgical indications, and the type of surgical procedure. This resulted in a certain degree of statistical heterogeneity for a few of our outcomes. Therefore, we applied random effects models in the meta-analyses, which yielded a more conservative conclusion in case of heterogeneity. We only included studies involving intestinal resection with primary anastomosis and/or strictureplasty in CD patients, which provides a more homogeneous group. We tried to reduce the risk of confounding in the observational studies by selecting studies using multivariate regression. However, without the inclusion of all known and unknown confounders, this risk cannot be entirely eliminated.

In summary, preoperative steroids use, low albumin levels, previous surgical history, and a preoperative abscess were shown to be associated with higher rates of IASCs in CD patients undergoing abdominal surgery. This may help surgeons to better decide the appropriate therapeutic strategies for individual patients. For example, surgeons may decide to postpone surgery or to use a protecting stoma instead of a primary anastomosis when several risk factors are present simultaneously in very high-risk patients. These decisions possibly indirectly reduce the IASCs rate in CD patients.

## Conflict of Interest

No conflicts of interest exist in this manuscript for any author.

There was no funding support for this project.

## Acknowledgments

WH and YS were responsible for study design, data acquisition, and analysis, interpretation of the data, and preparation of the draft of the manuscript. LN was responsible for statistical analysis. YT was responsible for study concept and design, interpretation of the data, study supervision, and revision of the manuscript.

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