

# Stapled side-to-side anastomosis might be benefit in intestinal resection for Crohn's disease

## A systematic review and network meta-analysis

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### Abstract

**Background and aim:** Intestinal anastomosis is an essential step in the intestinal resection in patients with Crohn's disease (CD). Anastomotic configuration such as handsewn end-to-end anastomosis (HEEA), stapled side-to-side anastomosis (SSSA) and so on may be a predictor of prognosis for postoperative CD patients. However, the association between anastomotic types and surgical outcomes are controversial. The aim of this review is to identify the optimal anastomosis for intestinal resection in patients with CD.

**Methods:** Clinical trials comparing anastomosis after intestinal resection in patients with CD were searched in the database of MEDLINE, EMBASE, and the Cochrane Library. Outcomes such as postoperative hospital stay, complications, mortality, recurrence, and reoperation were evaluated. Pairwise treatment effects were estimated through a random-effects network meta-analysis based on the frequency framework by using the STATA software and reported as the estimated summary effect for each comparison between the 2 treatments in the network with a 95% credible interval.

**Results:** A total of 1113 patients in 11 trials were included. In pair-wise comparisons between groups, for overall postoperative complications, SSSA showed a more probability of superiority to HEEA; for complications other than anastomotic leak, anastomotic leak, wound infection, postoperative hospital stay and mortality, there were no significant difference between groups; for clinical recurrence, SSSA showed a more probability of superiority to HEEA; for reoperation, SSSA showed a more probability of superiority to HEEA. The number of eligible randomized controlled trails (RCTs) was small, and more than half of the included trials were retrospective studies; selection bias may lead to a less power in this assessment; follow-up time between different groups was different, which may possibly have affected the interpretation of the analysis of long-term outcome.

**Conclusion:** By comprehensive analyzing all the postoperative outcomes, SSSA appeared to be the optimal anastomotic strategy after intestinal resection for patients with CD.

**Abbreviations:** CD = Crohn's disease, CI = 95% credible interval, GRADE = the grades of recommendations assessment, development and evaluation, HEEA = handsewn end-to-end anastomosis, HESA = handsewn end-to-side anastomosis, HSEA = handsewn side-to-end anastomosis, HSSA = handsewn side-to-side anastomosis, MD = mean differences, NMA = network meta-analysis, NOS = Newcastle–Ottawa scoring system, NPTs = nonrandomized prospective trials, NRTs = nonrandomized retrospective trials, OR = odds ratios, PI = 95% prediction interval, RCTs = randomized controlled trails, SESA = stapled end-to-side anastomosis, SSSA = stapled side-to-side anastomosis, SUCRA = surface under the cumulative ranking curve.

**Keywords:** anastomosis, Crohn's disease, intestinal resection, network meta-analysis

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## 1. Introduction

Crohn's disease (CD) is one kind of inflammatory bowel disease related to an autoimmune disorder. It is characterized by a relapsing transmural bowel inflammation, which can mostly affect the terminal ileum and the proximal colon although any section of the gastrointestinal tract can be involved.<sup>[1]</sup> Although great progress has been made in the medical therapy for CD, surgery remains plays an important role in its management, especially for failure of medication or complications,<sup>[2]</sup> such as stricture, abscess, fistula, haemorrhage, or malignant transformation.<sup>[3]</sup> About 80% CD patients will require surgery during their lifetime, about 15% to 20% will require surgery within the first year after diagnosis.<sup>[1,3,4]</sup>

Surgical techniques such as anastomosis used in the intestinal resection are important strategies for the surgical treatment of CD.<sup>[5]</sup> It is believed that the anastomotic technique affects the surgical outcomes such as postoperative complications, recurrence, reoperation, and so on.<sup>[6]</sup> Growing interest has being raised for the effect of anastomosis on postoperative outcomes recently.

Anastomosis for intestinal resection generally includes proximal-distal bowel side-to-side anastomosis, end-to-end anastomosis, and end-to-side anastomosis. In accordance with the proximal-distal bowel peristalsis direction, side-to-side anastomosis was divided into 2 subtypes, antiperistaltic and isoperistaltic orientation.<sup>[7]</sup> Theoretically, the isoperistaltic oriented side-to-side anastomosis can significantly reduce the postoperative anastomotic recurrence of CD. This may be related to a variety of factors, such as the direction of anastomosis was consistent with the movement of intestine, in which the intestinal contents pass through smoothly and resulting in less intestinal contents accumulated near the anastomotic site. Although side-to-side anastomosis compared to other anastomosis (end-to-end, end-to-side) for the risk of CD relapse were remains controversial, many studies suggested that side-to-side anastomosis can reduce the anastomotic recurrence and the reoperation rate in postoperative patients.<sup>[8]</sup> In addition, the side-to-side anastomosis can significantly reduce the incidence of postoperative complications, hospital stay and medical costs, and the intestinal function recovered faster in patients with side-to-side anastomosis. Before instrumental anastomosis was widely application, those anastomotic configurations mentioned above were mainly performed by hand-fit, handsewn anastomosis.

Since the extensive application of gastrointestinal stapler, CD patients with intestinal anastomosis were more used of stapled side-to-side anastomosis (SSSA) or stapled end-to-side anastomosis (SESA), but traditional handsewn anastomosis is still used in somewhere of the world, such as handsewn end-to-end anastomosis (HEEA). SSSA and HEEA are universally used to restore the continuity of intestinal tract after intestinal resection. With the larger luminal diameter, SSSA was thought theoretically to be more effective than HEEA.

Over the years, many scholars devoted to the relationship between different anastomotic configuration and the outcomes of postoperative. Simillis et al<sup>[9]</sup> have performed a sensitive traditional meta-analysis comparing side-to-side anastomosis with end-to-end anastomosis and shown that side-to-side anastomosis was associated with not only shorter hospital stay, but also fewer anastomotic leaks, fewer postoperative complications. However, the recurrence was identified to be similar with the reoperation rates for recurrence.

However, studies have generated opposite results about the outcomes between SSSA and HEEA. Ikeuchi et al<sup>[10]</sup> have found

that stapled anastomoses for CD might remit reoperation for recurrent patients compared with hand-sewn anastomosis in a prospective randomized trial. In contrary, Mcleod et al<sup>[11]</sup> have conducted a multicenter randomized controlled trial and found that recurrence of CD following ileocolic resection was not influenced by anastomosis. In addition, there are several other anastomoses used for CD surgery, such as handsewn side-to-side anastomosis (HSSA), handsewn side-to-end anastomosis (HSEA), and handsewn end-to-side anastomosis (HESA). The advantage and disadvantage of these anastomoses were rarely commented separately in clinical trials and traditional meta-analysis.

In summary, the relationship between the anastomosis and the surgical outcomes of CD patients, the existing clinical trials have the following defects: the number of participants is not big enough, interventions without multiarms comparison, various control measures without uniform criteria, the evaluation criteria for outcomes are not uniform and so on. This review was designed to identify the optimal anastomosis for different postoperative outcomes in patients underwent intestinal resection because of CD. In order to integrate the conflicting results and the multitreatment from different trials, we performed the network meta-analysis (NMA) comparing effect of multianastomosis on postoperative outcomes for patients with CD.

## 2. Methods

### 2.1. Literature search strategy

Literatures comparing different anastomotic techniques for CD were searched in the database of MEDLINE, EMBASE, and the Cochrane Library. The publication year and language were not restricted. The search strategies were presented in Supplementary Appendix 2, <http://links.lww.com/MD/C189>.

### 2.2. Inclusion and exclusion criteria

The inclusion criteria are listed as follows: compared any kind of anastomosis such as "end-to-end" or "side-to-side" or "end-to-side" or "side-to-end" and so on in CD patients undergoing intestinal resection; trials reported at least one of the postoperative outcomes of interest (complications, mortality, recurrence, and reoperation); when similar studies were reported by the same authors, the one with better quality or published more recently was included.

The exclusion criteria are listed as follows: abstracts, letter to editor, expert opinions, reviews, comments, and case reports; literatures of the full text or data were not available; single arm observations without control.

### 2.3. Data extraction

Data were extracted by 2 authors (JYL and XYC) independently including the following items: first author, year of publication, study and population characteristics, outcome parameters, and so on. For continuous variables, such as postoperative hospital stay, the method documented previously<sup>[12]</sup> was used to estimate the mean and standard deviation. If there were any discrepancies between the 2 observers, consensus was reached by discussing with a third author (JSF).

### 2.4. Quality assessment

Quality assessment was conducted by 2 authors (JYL and JJM). The outcomes of randomized controlled trails (RCTs) were

evaluated by the Grades of recommendations assessment, development, and evaluation (GRADE System). The risk of bias in RCTs was assessed by the Cochrane risk of Bias assessment tool. The qualities of nonrandomized retrospective trials (NRTs) and nonrandomized prospective trials (NPTs) were evaluated by the Newcastle–Ottawa scoring (NOS) system,<sup>[13]</sup> the criteria of which are presented in Supplementary Appendix 1, <http://links.lww.com/MD/C189>. The full score of NOS for evaluating the selection, comparability, outcome in nonrandomized trials was 4, 2, and 3 stars, respectively.

### 2.5. Outcome of interest and definition

Pare-wise comparisons were used to compare different anastomosis in the following postoperative outcomes after intestinal resection for CD: short-term complications included overall postoperative complications, anastomotic leak, wound infection, complications other than anastomotic leak (bowel obstruction/stricture, prolonged ileus, intra-abdominal abscess, wound infection, urogenital infection, pulmonary embolism, and so on); postoperative hospital stay and mortality; long-term complications included clinical recurrence and reoperation for recurrence or complications.

Clinical recurrence was defined as the endoscopic recurrence plus the symptomatic recurrence of CD. Reoperation for recurrence was restricted in perianastomotic recurrence.

### 2.6. Statistical analysis

NMA was performed for each endpoint by using STATA software (version 13.0) based on the frequency framework and the results were reported as the estimated summary effect for each comparison between the 2 treatments in the network, in which the odds ratios (OR) or mean differences (MD) with a 95% credible interval (CI) were calculated. Meanwhile the STATA software (version 13.0) was used to illustrate the related diagrams of this NMA. Network plots presented the relationship of direct and indirect comparisons. Contribution plot shows the weight of each direct and indirect comparison in the entire network. Interval plots present the mean, 95% CI and 95% prediction interval (PI) of the expected value. Surface under the cumulative ranking curve (SUCRA) ranks the probability of all the interventions which is significantly different to the basic treatment. It can be summed up as a simple numerical ranking summary for supplementing the complicated graphic line of each treatment (cumulative rankogram).<sup>[14]</sup> Sensitivity analysis was also conducted by the STATA software (version 13.0) for all the postoperative outcomes.

## 3. Results

### 3.1. Study characteristic

A total of 345 articles were identified with the search strategy, 325 were excluded for duplication and unrelated literatures reviewed by title and abstract. After detailed review, 4 more trials were excluded due to no relevant results. Five studies were excluded as the outcomes were reported inadequately. The remaining 11 trials Appendix 3, <http://links.lww.com/MD/C189> containing 1113 patients were included in this analysis (Fig. 1). Characteristics of included trials were shown in Supplementary Table 1, <http://links.lww.com/MD/C189>. A detailed of assessment of the risk of bias for RCTs are presented in Supplementary Figure 1, <http://links.lww.com/MD/C189>. Details of quality assessment for outcomes of RCTs and non-RCTs were presented

in Supplementary Tables 2 and 3, <http://links.lww.com/MD/C189>, respectively. The contribution of trials to different postoperative outcomes is presented in Supplementary Figure 3, <http://links.lww.com/MD/C189>.

The included trials consisted of 5 prospective studies, included 4 prospective RCTs,<sup>[10,11,15,16]</sup> one nonrandomized prospective trials,<sup>[17]</sup> and 6 nonrandomized retrospective studies.<sup>[18–23]</sup> In the studies of Munoz's<sup>[19]</sup> and Yamamoto's,<sup>[23]</sup> the concept of “wide-lumen stapled anastomosis” and “functional end-to-end anastomosis” were both equal to the concept of SSSA. In quality assessment, we found that, because of the specificity of the intervention, it was impossible for the intervention group to be blind the surgeon. Accounting for the results of GRADE System, all the outcomes of RCTs included were of low quality (Supplementary Table 2, <http://links.lww.com/MD/C189>). Accounting for the results of NOS, all nonrandomized trials included were of high quality (Supplementary Table 3, <http://links.lww.com/MD/C189>).

### 3.2. Short-term complications

Nine trials had reported the short-term complications. In pair-wise comparisons between groups, SSSA showed a more probability of superiority to HEEA for reduction incidence of overall postoperative complications (OR, 0.54; 95%CI, 0.34 to 0.83) (Table 1, Supplementary Figure 4A, <http://links.lww.com/MD/C189>). For complications other than anastomotic leak, anastomotic leak and wound infection, there were no significant difference between groups (Tables 1 and 2, Supplementary Figure 4B–E, <http://links.lww.com/MD/C189>).

Sensitivity analysis of short-term complications is shown in Supplementary Figure 2A–D, <http://links.lww.com/MD/C189>. The effects of treatments were broadly similar for most of trials which interested the outcomes mentioned above.

### 3.3. Postoperative hospital stay

Seven trials had reported the postoperative hospital stay, but there was no significant difference between different anastomotic groups (Table 3, Supplementary Figure 4E, <http://links.lww.com/MD/C189>).

Sensitivity analysis of postoperative hospital stay is shown in Supplementary Figure 2E, <http://links.lww.com/MD/C189>. Results of the treatment effects were broadly similar for most studies in both of these outcomes.

### 3.4. Mortality

Four trials had reported mortality after surgery, there was no significant difference between different anastomotic groups (Table 3, Supplementary Figure 4F, <http://links.lww.com/MD/C189>).

Sensitivity analysis of mortality is shown in Supplementary Figure 2F, <http://links.lww.com/MD/C189>. Results of the treatment effects were broadly similar for most studies. However, 95% CI for the sensitivity analysis was generally wider because they were based on fewer trials.

### 3.5. Clinical recurrence

Seven had reported the clinical recurrence rate. In pair-wise comparisons between groups (Table 4, Supplementary Figure 4G, <http://links.lww.com/MD/C189>), significant superiority was observed when SSSA (OR, 0.32; 95%CI, 0.13 to 0.77)

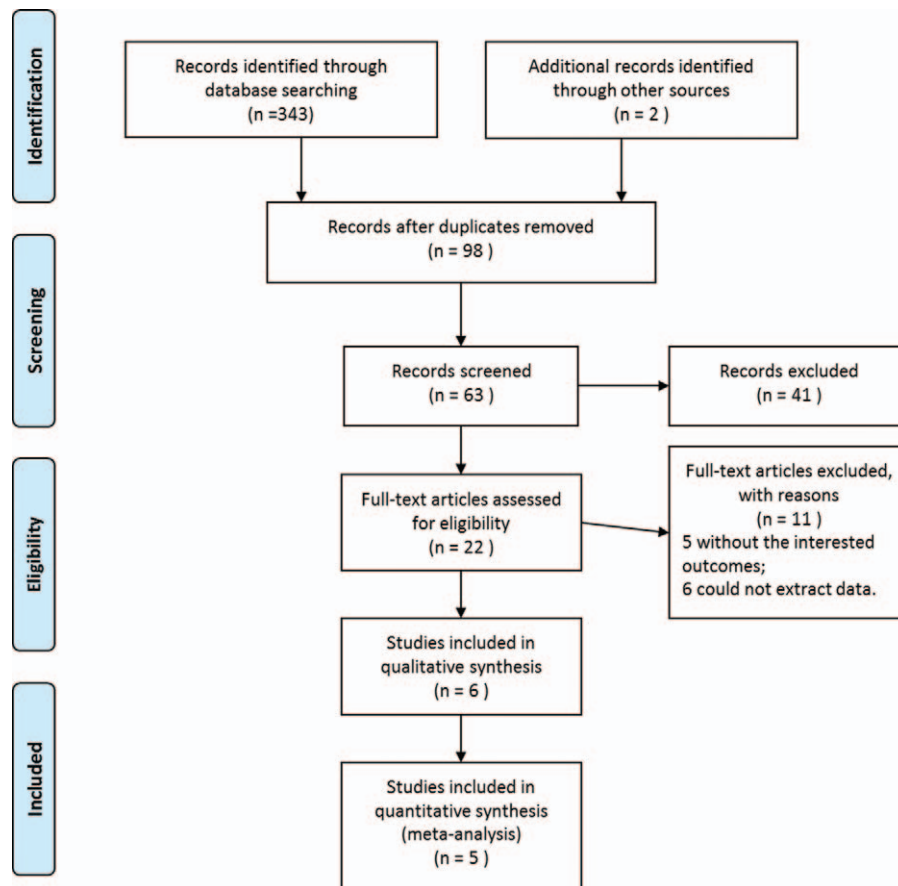


Figure 1. Study flow diagram.

were compared with HEEA for reduction incidence of clinical recurrence.

Sensitivity analysis of clinical recurrence is shown in Supplementary Figure 2G, <http://links.lww.com/MD/C189>. Results of the treatment effects were broadly similar for most studies.

### 3.6. Reoperation

Seven trials had reported the reoperation rate and it was found to be significantly lower in the SSSA group compared with the HEEA group (OR, 0.22; 95%CI, 0.05 to 0.95) (Table 4, Supplementary Figure 4H, <http://links.lww.com/MD/C189>).

Sensitivity analysis of reoperation is shown in Supplementary Figure 2H, <http://links.lww.com/MD/C189>. Results of the treatment effects were different from trials especially in 2 NRTs, Hashemi<sup>[18]</sup> and Muñozjuárez et al,<sup>[19]</sup> which affected the combined effect of other studies if they were excluded respectively. Point estimates of the treatment effects were similar to the results mentioned above.

## 4. Discussion

In addition to removal of the lesion bowel, induced clinical remission, no postoperative complications and other purposes, to delay (or even avoid) anastomotic recurrence is an important symbol of successful CD surgery. In this NMA, we primarily

compare different anastomotic configurations after intestinal resection in patients with CD. The results of this NMA revealed that SSSA with a lower incidence of overall complications, recurrence, and reoperation for recurrence in the SSSA group. However, in terms of anastomotic leak and complications other than anastomotic leak, there was no significant difference between different anastomotic groups, wound infection, postoperative hospital stay and mortality.

In traditional meta-analysis published recently, which cannot identify the details of different anastomotic material such as handsewn or stapled used in the different anastomosis, only compared end-to-end anastomosis to non-end-to-end anastomosis.<sup>[9,24]</sup> In Simillis' study,<sup>[9]</sup> the incidence of anastomotic leak was significant decrease in the side-to-side anastomosis group when only comparing with end-to-end anastomosis group. In Li's study,<sup>[24]</sup> side-to-side anastomosis was compared to non-side-to-side anastomosis. The incidence of overall postoperative complications and recurrence were significant reduced in the side-to-side anastomosis group. Taken together, these results of both the traditional meta-analysis mentioned above demonstrated that side-to-side anastomosis is superior to non-side-to-side anastomosis. The results of our NMA also found that SSSA is superior to any other anastomosis in the interested outcomes.

Postoperative recurrence is common for CD patients. Several potential factors influencing the surgical outcomes have been identified, including familial CD history, gender, age of onset, gestation, smoking, preoperative disease duration, anatomical

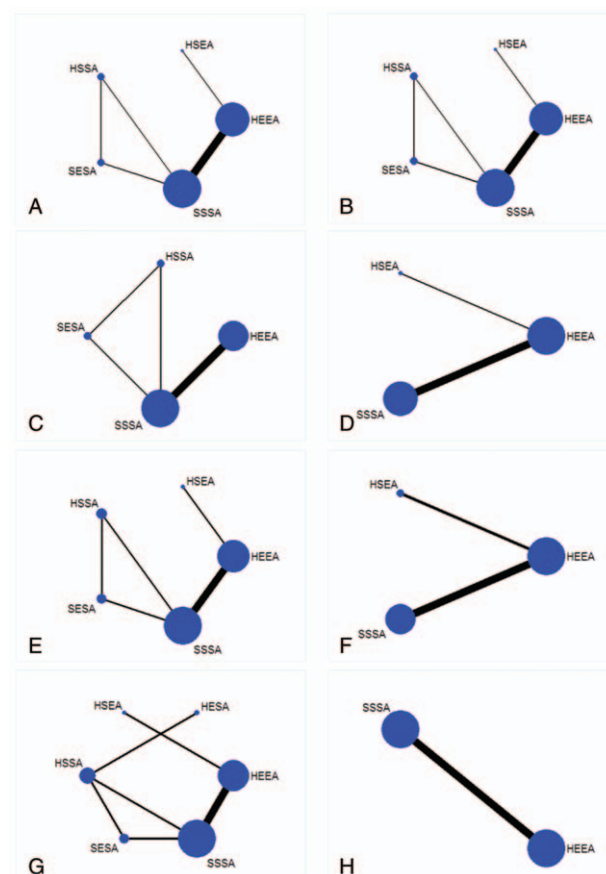
site and extent of involvement, medication, surgical indication, previous resections, length of intestinal resection, anastomosis, residual disease at the resection margins, presence of granulomas in the specimen, perioperative blood transfusions, and postoperative complications.<sup>[6,25]</sup> Among these factors mention above, anastomosis after intestinal resection is considered to be an important factor because patients with permanent end ileostomy seldom suffer from recurrence,<sup>[26]</sup> and nearly 90% of recurrences of disease occur in the preanastomotic segment.<sup>[27]</sup>

Most patients require reoperation for postoperative recurrence.<sup>[28,29]</sup> How to reduce the postoperative recurrence is of great concern. It is believed that, with wide lumen configuration, side-to-side anastomosis may reduce postoperative recurrence by preventing early stenosis, fecal stasis, colonic reflux, and secondary ischemia.<sup>[29,30]</sup> Although women run a higher risk of postoperative recurrence than men,<sup>[31]</sup> symptomatic recurrence particularly beneficial to the subset of patients, such as fewer wound complications, a shorter hospital stay, less tissue trauma and postoperative adhesion, and earlier resumption of oral intake and bowel function.<sup>[2]</sup> A previous observation reported that, in the long-term, HSSA significantly reduced the surgical recurrence rate than SESA,<sup>[21]</sup> which is contradictory to our result of NMA. In this NMA, we found that there was no difference between HSSA and SESA. In addition, we have found that many drug clinical trials with a primary outcome of postoperative endoscopic or clinical recurrence. In our previous analysis, we had found that only biological agents such as adalimumab and infliximab can prevent the endoscopic recurrence,<sup>[32]</sup> but the application of these agents was not used universally, especially in the developing country.

Anastomotic leak from the anastomotic site are life-threatening critical complications, with a reported incidence of approximately 10%.<sup>[33,34]</sup> Base on a series of 122 consecutive CD patients underwent surgery with ileocolonic anastomosis for Crohn's disease, Andrea et al<sup>[20]</sup> have found that SSSA seems to decrease anastomotic leak to a great extent in surgical CD patients, compared with HEEA. In our analysis for anastomotic leak, SSSA has not showed a more probability of superiority to other anastomoses.

For the heterogeneity, the trials in our study differed in several aspects, including the disease severity of the patients, risk of bias, disease severity at the time of randomization, prior exposure to medication, the type of suture used in handsewn anastomosis, anastomotic position, and primary end points. Although heterogeneity between clinical trials merits cautious interpretation, sensitivity analyses only showed marginal differences in the results. We also found consistency between the treatment effects in the NMA and those observed in previous direct (traditional) meta-analysis conducted by others<sup>[33]</sup> and ours (Supplementary Figure 6, <http://links.lww.com/MD/C189>), when direct evidence was available, although there were few closed loops in the evidence network (Fig. 2).

There are several limitations in our NMA. First, the number of eligible RCTs was small. Second, more than half of the included trials were retrospective studies. Selection bias may lead to a less power in this assessment. However, all of these retrospective trials were rated as at least 6 stars in the NOS, indicating a relatively high quality of them. Third, follow-up time between different groups was different, which may possibly have affected the interpretation of the analysis of long-term outcome. Therefore, the reliability of the result, especially about the result of recurrence assessed by the NMA, must be carefully interpreted.



**Figure 2.** Network plots for different outcomes. Nodes represent the competing treatments which are weighted according to the total number of each study; edges represent the available direct comparisons between pairs of treatments which are weighted according to the standard error (SE) of each study. (A) Overall short-term complications; (B) complications other than anastomotic leak; (C) anastomotic leak; (D) wound infection; (E) postoperative hospital stay; (F) mortality; (G) clinical recurrence; (H) reoperation. HEEA=handsewn end-to-end anastomosis, HSEA=handsewn end-to-side anastomosis, HSEA=handsewn side-to-end anastomosis, HSSA=handsewn side-to-side anastomosis, SESA=stapled end-to-side anastomosis, SSSA=stapled side-to-side anastomosis.

Based on our results, SSSA would probably be the optimal anastomosis after intestinal resection for CD. It can significantly reduce incidence of overall postoperative complications, clinical recurrences, and reoperation. In clinical practice, SSSA may be a safer and preferable anastomotic strategy for surgical CD patients. However, owing to the characteristic of the included studies were the retrospective trials and the potential selection bias, more randomized controlled trials should be performed for confirmation.

### Author contributions

**Data curation:** Xiu-yan Chen, Jia-jie Mo.

**Methodology:** Shang-hai Li.

**Software:** Jin-yu Li.

**Supervision:** Jinshan Feng.

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