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Original research

Preoperative infliximab use and postoperative complications in Crohn's disease: A systematic review and meta-analysis

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ABSTRACT

Background: Infliximab revolutionized the treatment paradigm of Crohn's disease (CD), but did not reduce the need for surgery. The impact of biologic agents on surgical complication rates remains debated. The aim of this study was to determine the effect of preoperative infliximab use on early postoperative complications in patients with CD undergoing abdominal surgery.

Method: PubMed and Embase databases were searched to identify comparative studies that investigated postsurgical morbidity in CD patients receiving infliximab preoperatively with those not on infliximab. We used meta-analysis with random-effects model to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs) for total complication rate as well as major, minor, infectious, and non-infectious complications.

Results: A total of 18 studies involving 5769 patients included in this systematic review. There was significant association between infliximab therapy prior to surgery and total (OR = 1.45, 95% CI 1.04–2.02; 13 studies, 2538 patients), infectious (OR = 1.47, 95% CI 1.08–1.99; 10 studies, 2116 patients) and non-infectious (OR = 2.29, 95% CI 1.14–4.61; 3 studies, 729 patients) postoperative complications respectively. There was no significant disparity in the major (OR = 1.39, 95% CI 0.85–2.27; 9 studies, 3696 patients) and minor (OR = 1.39, 95% CI 0.57–3.40; 5 studies, 753 patients) complication rates between infliximab and control groups. No publication bias was detected.

Conclusion: Preoperative infliximab use modestly increases the risk of total early postoperative complications, and particularly infectious complications in CD patients.

1. Introduction

Infliximab, a chimeric anti-tumor necrosis factor alpha (anti-TNF-α) antibody, revolutionized the therapeutic regime of Crohn's disease (CD).[1] However, evidences from population-based survey showed that the introduction of infliximab since 1998 did not alter the natural history of the disease, and neither reduced the need for surgery.[2] At least 50% of patients will require surgical treatment in the first ten years of disease and approximately 70–80% will require surgery during their lifetime.[1,2]

The immunosuppressive effects of infliximab may induce patients at an increased risk of infection.[3] Moreover, surgery itself causes a complex stress on the human body that leads to some reduction of cell mediated immunity.[4] Therefore, the impact of biologic agents on surgical complication rates becomes a major concern in clinical practice. Previous observational studies evaluating the association between preoperative therapy of infliximab and postoperative complications resulted in inconsistent outcomes. Even two previous meta-analyses in an attempt to answer this question produced contrary conclusions.[5,6] Kopylov et al. found that preoperative infliximab treatment is associated with an increased risk of postoperative infectious complications, and with a trend toward an increased risk of non-infectious and total complications.[5] Whereas the pooled results by Rosenfeld et al. demonstrated no significant disparity in the major complication, minor complication, reoperation, and 30-day mortality rates between infliximab and control groups. So they considered that infliximab may be safe to continue in the preoperative period without increasing the risk of postoperative complications for CD patients.[6]

The purpose of our study was to perform a comprehensive systematic review of the existing literature to evaluate the effect of preoperative infliximab use on early postoperative complications in patients with CD undergoing abdominal surgery. We would determine the nature of these complications if infliximab treatment in the preoperative period increased the overall complication rate.

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2. Material and methods

2.1. Search strategy

Potentially relevant studies were identified by searching the electronic databases including PubMed and Embase. Reference lists from all available review articles and primary studies were hand-searched to identify additional relevant publications. The search terms contained '(infliximab or tumor necrosis factor or TNF) and (postoperative or post-operative or surgical complications) and (inflammatory bowel disease or Crohn's disease)'. We performed the final search on 17 May, 2013.

2.2. Study selection

Two reviewers (Z.Y. and L.H.) independently evaluated all of the retrieved studies according to pre-specified selection criteria. Discrepancies were resolved by consensus or with the consultation of a third reviewer (D.F.). There was no language restriction. The following eligibility criteria was applied: (1) population: patients with CD undergoing abdominal surgery; (2) intervention: infliximab treatment prior to surgery; (3) comparator: controls not receiving infliximab preoperatively; (4) outcomes: short-term complications either reported as total, major, minor, infectious or non-infectious, or listed individually to allow classification by the reviewers. We summarized a list of the definition of major, minor, infectious and non-infectious complications in each study in Supplemental Table 1.

Studies were excluded if they did any of the following: (1) reported duplicate results that were published in other articles; only the most recent and complete data were included in the systematic review. (2) studies that included CD and ulcerative colitis (UC) patients as one group; we tried to contact the corresponding authors to obtain the data in their CD patients separately.

2.3. Data extraction and quality assessment

Two reviewers (Z.Y. and Q.W.) independently extracted the data using a pre-defined form (Supplemental Table 2) and then cross checked the extracted data. We collected information on the following items: first author and year of publication, country of origin, study period, type of publication, duration of infliximab exposure, duration of complications after surgery, number of patients, demographic characteristics (sex, age at surgery, body mass index, smoking status), disease characteristics (duration, severity, concomitant medications) and surgical characteristics (indication, proportion of previous surgery and emergency, type and approach of operation). The quality of the study reports was evaluated using the Newcastle-Ottawa scale (NOS), a method for assessing the quality of nonrandomised studies in meta-analysis.[7] The scales allocate stars, maximum of nine, for quality of selection, comparability, exposure and outcome of study participants. We considered studies with a score of 7 or above as high quality.

2.4. Statistical analysis

Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were generated using a random-effects model that considered both within and between-study variations. The χ^2-based Q-test and the I^2 statistic were used to evaluate statistical heterogeneity. Specifically, a Q statistic of $P < 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity among studies. To detect and evaluate clinical heterogeneity, we performed sensitivity analysis without the less-qualified studies or the study, which has shown the most significant difference accordingly. We plotted Begg's funnel plot to test for publication bias. We also used Egger's weighted regression method to calculate the P value for bias. All analyses listed above were conducted using the software Stata (Version 12.0; Stata Corporation, College Station, TX, USA).

3. Results

3.1. Search results

The initial search identified 2332 potentially relevant citations, of which 2289 were discarded after title and abstract screening. A total of 43 citations were retrieved for detailed evaluation. Eight meeting abstracts duplicated with the corresponding full-text articles published subsequently. Thirteen studies were excluded for

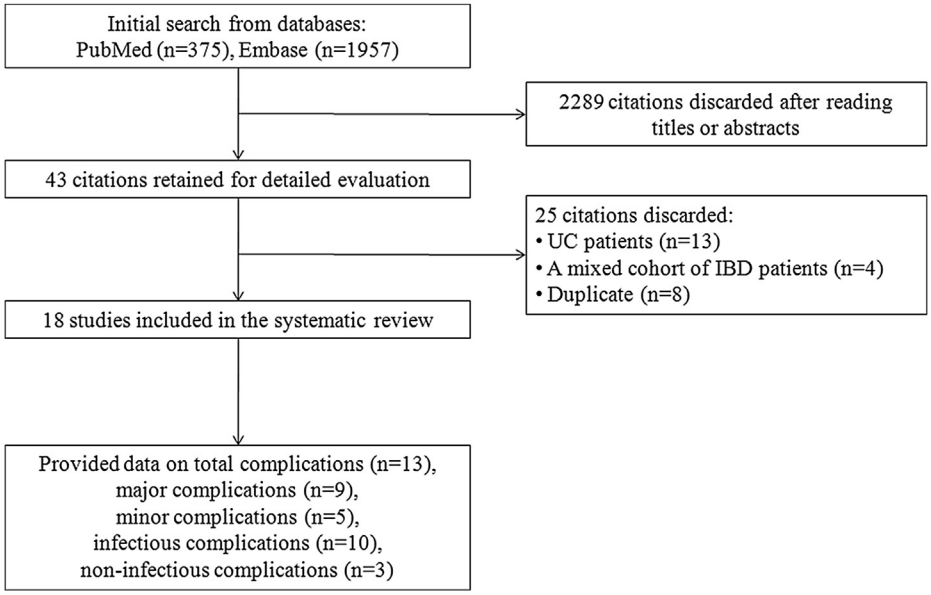

Fig. 1. Study flow diagram.

addressing data on UC population alone. Additional four studies did not distinguish CD patients from a mixed cohort of inflammatory bowel disease (IBD) patients,[8–11] although we contacted these corresponding authors. Finally, 18 observational studies with 5769 patients (median: 210.5; range: 76–2293) published from 2002 to 2013 were included in this systematic review (Fig. 1).[12–29] Total complication rates could be assessed in 13 of these studies.[14–23,25,27,29] Major, minor, infectious and non-infectious complications were assessed in nine,[12–14,16,20,22,23,26,28] five,[12,14,16,22,23] ten,[13–16,18,20,22,27–29] and three studies respectively.[16,22,27]

3.2. Study and patient characteristics

The characteristics of studies and patients are shown in Supplemental Table 2. Eleven studies were performed in the United States, five in Europe, one in Japan, and one in Brazil. Fourteen studies published as full-text articles, while the other four as abstracts. In all, 1116 out of 5769 (19.3%) patients included in our systematic review received infliximab and 4653 (80.7%) did not. Five studies included a minority of patients treated with adalimumab and certolizumab pegol (196/1116, 17.6%).[19,21,24,26,28] Infliximab was given within 12 weeks prior to surgery in eight studies,[16,20,22–27] 8 weeks in three studies,[13,17,28] 8 weeks before surgery or 4 weeks after it in three studies,[12,15,19] and 4 weeks in one study.[21] The duration of follow-up was reported at 30 days in 13 studies,[13,15–17,19–21,23–28] and at 10 days in one study,[14] and without available information in four studies.[12,18,22,29] Only 4 out of 18 studies were considered as high-quality ones based on the NOS.[14,22,24,28]

There were 2156 (42.8%) males from the available data about the sex in 14 studies.[13–17,19–26,28] Data on the proportion of emergent

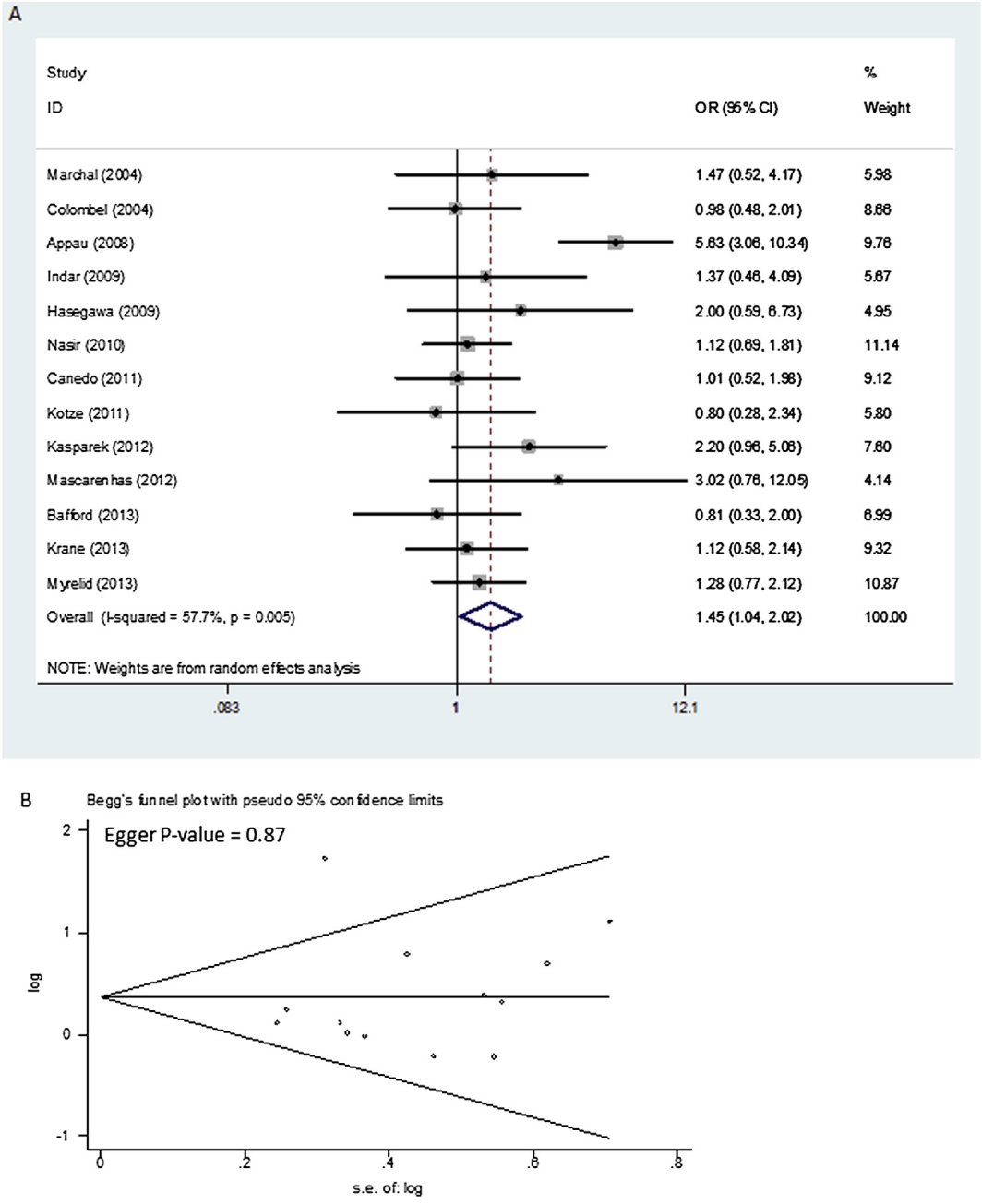

Fig. 2. Pooled outcome for development of total complications in patients exposed to IFX preoperatively vs. controls: A. Forest plots; B. Funnel plots.

surgery were available in eight studies including 2015 patients,[13,15,17,19,20,24,25,28] of whom 289 (14.3%) underwent urgent operation. The type of surgery among the studies was quite different. Some studies included patients undergoing only one specific type of surgery, whereas some others included patients undergoing any intestinal surgery. Data on the surgical approach were available in 11 studies including 2417 patients,[13,15–20,22,25,27,28] of whom 953 (39.4%) underwent laparoscopic operation. We could not conduct subgroup analyses for specific operative interventions due to the variability of surgical parameters included in the studies.

Data on concomitant medications, stratified by infliximab treatment, were available in 10 studies.[13,14,16,17,19,22–24,26,28] Corticosteroids were equi-frequently used between infliximab and non-infliximab groups (OR = 1.10, 95% CI 0.92-1.31, 10 studies, 4274 patients). Patients in the infliximab group had a more frequent use of immunomodulators (azathioprine and methotrexate) (OR = 1.70, 95% CI 1.34–2.16, 5 studies, 1613 patients).

3.3. Total complications

There were a total of 2538 patients (663 in the infliximab group and 1875 in the control group) in 13 studies reporting total complications after operation in CD patients receiving infliximab preoperatively. The summary OR was 1.45 (95% CI 1.04–2.02; $P_{heterogeneity} = 0.01$, $I^2 = 57.7\%$), indicating a significantly increased risk, but with significant heterogeneity among studies (Fig. 2A). When we excluded the studies published as abstracts or the studies with some patients treated with other anti-TNF-α agents, the increase in total complications remained statistically significant. When we limited to the studies with infliximab use in 12 weeks prior to surgery or the studies with reporting complications for 30 postoperative days, a trend towards increased risk was observed but without statistical significance (Table 1). No publication bias was detected according to the symmetry of the funnel plot and the Egger's *P*-value (Fig. 2B).

3.4. Major and minor complications

When the complications were divided into major and minor ones, nine studies that reported major complications included 653 patients who received infliximab preoperatively and 3043 controls, and five studies that reported minor complications included 202 patients who received infliximab preoperatively and 551 controls. The summary OR for major complications was 1.39 (95% CI 0.85–2.27; $P_{heterogeneity} < 0.01$, $I^2 = 71.5\%$), suggesting that there was no association between preoperative infliximab use and major complications, but a significant heterogeneity among studies (Fig. 3A). The summary OR for minor complications was 1.39 (95% CI 0.57–3.40; $P_{heterogeneity} = 0.07$, $I^2 = 53.5\%$), also indicating no association but a significant heterogeneity among studies (Fig. 3C). Similar results were obtained in the sensitivity analyses (Table 1). Only when we limited to the studies with full-text or the studies with infliximab use in 12 weeks prior to surgery, a significant increase in minor complications was observed. No publication bias was detected on the basis of the symmetry of the funnel plot and the Egger's *P*-value (Fig. 3B and D).

3.5. Infectious and non-infectious complications

When the complications were grouped into infectious and non-infectious ones, ten studies that reported infectious complications included 626 patients who received infliximab preoperatively and 1490 controls, and three studies that reported non-infectious complications included 171 patients who received

Table 1
Results of sensitivity analysis.

	Total complications						Major complications						Minor complications					
	No. of studies	No. of patients	OR (95%CI)	P_h	I^2, %	*P*	No. of studies	No. of patients	OR (95%CI)	P_h	I^2, %	*P*	No. of studies	No. of patients	OR (95%CI)	P_h	I^2, %	*P*
All available studies	13	2538	1.45 (1.04–2.02)	0.01	57.7	0.03	9	3696	1.39 (0.85–2.27)	<0.01	71.5	0.20	5	753	1.39 (0.57–3.40)	0.07	53.5	0.47
Studies with full-text	10	2074	1.51 (0.99–2.30)	<0.01	66.2	0.05	8	3600	1.50 (0.88–2.56)	<0.01	73.6	0.13	4	657	2.11 (1.07–4.15)	0.71	0	0.03
Duration of IFX exposure ≤12 weeks preoperatively	8	1431	1.58 (0.91–2.77)	<0.01	71.4	0.11	7	3521	1.49 (0.84–2.63)	<0.01	77.3	0.17	3	578	2.62 (1.18–5.85)	0.85	0	0.02
30-day postoperative complications	9	1975	1.38 (0.86–2.20)	<0.01	70.2	0.18	6	3425	1.57 (0.82–3.03)	<0.01	80.9	0.18	2	482	3.45 (0.73–16.25)	0.69	0	0.12
Only IFX use (no other anti-TNF-α agents)	11	2092	1.57 (1.06–2.31)	<0.01	61.1	0.02	7	1078	1.59 (0.80–3.16)	<0.01	70.2	0.19	5	753	1.39 (0.57–3.40)	0.07	53.5	0.47

Infectious complications						Non-infectious complications					
No. of studies	No. of patients	OR (95%CI)	P_h	I^2, %	*P*	No. of studies	No. of patients	OR (95%CI)	P_h	I^2, %	*P*
10	2116	1.47 (1.08–1.99)	0.14	33.9	0.01	3	729	2.29 (1.14–4.61)	0.12	52.5	0.02
8	1728	1.48 (1.04–2.10)	0.14	35.8	0.03	3	729	2.29 (1.14–4.61)	0.12	52.5	0.02
6	1379	1.56 (1.10–2.20)	0.23	27.6	0.01	3	729	2.29 (1.14–4.61)	0.12	52.5	0.02
6	1553	1.50 (1.03–2.18)	0.15	38.1	0.04	2	633	1.98 (0.69–5.70)	0.05	74.2	0.21
9	1791	1.43 (0.99–2.07)	0.10	39.7	0.06	3	729	2.29 (1.14–4.61)	0.12	52.5	0.02

OR, odds ratio; CI, confidence interval; P_h, *P* value of *Q*-test for heterogeneity test; IFX, infliximab; TNF, tumor necrosis factor.

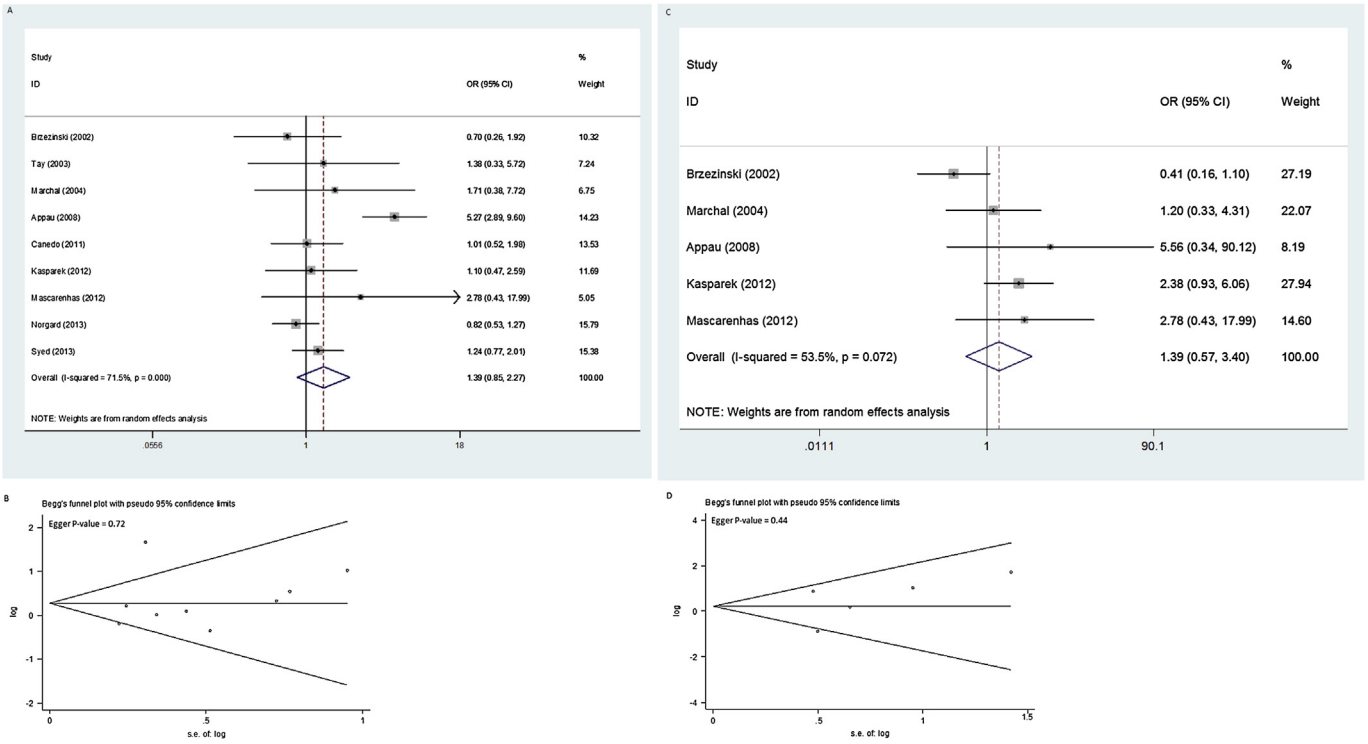

Fig. 3. Pooled outcome for development of major and minor complications in patients exposed to IFX preoperatively vs. controls: A. Forest plots for major complications; B. Funnel plots for major complications; C. Forest plots for minor complications; D. Funnel plots for minor complications.

infliximab preoperatively and 558 controls. The summary OR for infectious complications was 1.47 (95% CI 1.08-1.99; $P_{\text{heterogeneity}} = 0.14$, $I^2 = 33.9\%$), indicating a significantly increased risk (Fig. 4A). The summary OR for non-infectious complications was 2.29 (95% CI 1.14–4.61; $P_{\text{heterogeneity}} = 0.12$, $I^2 = 52.5\%$), suggesting a significantly increased risk, but with a little heterogeneity among studies (Fig. 4C). Similar results were obtained in the sensitivity analyses (Table 1). Only when we limited to the studies

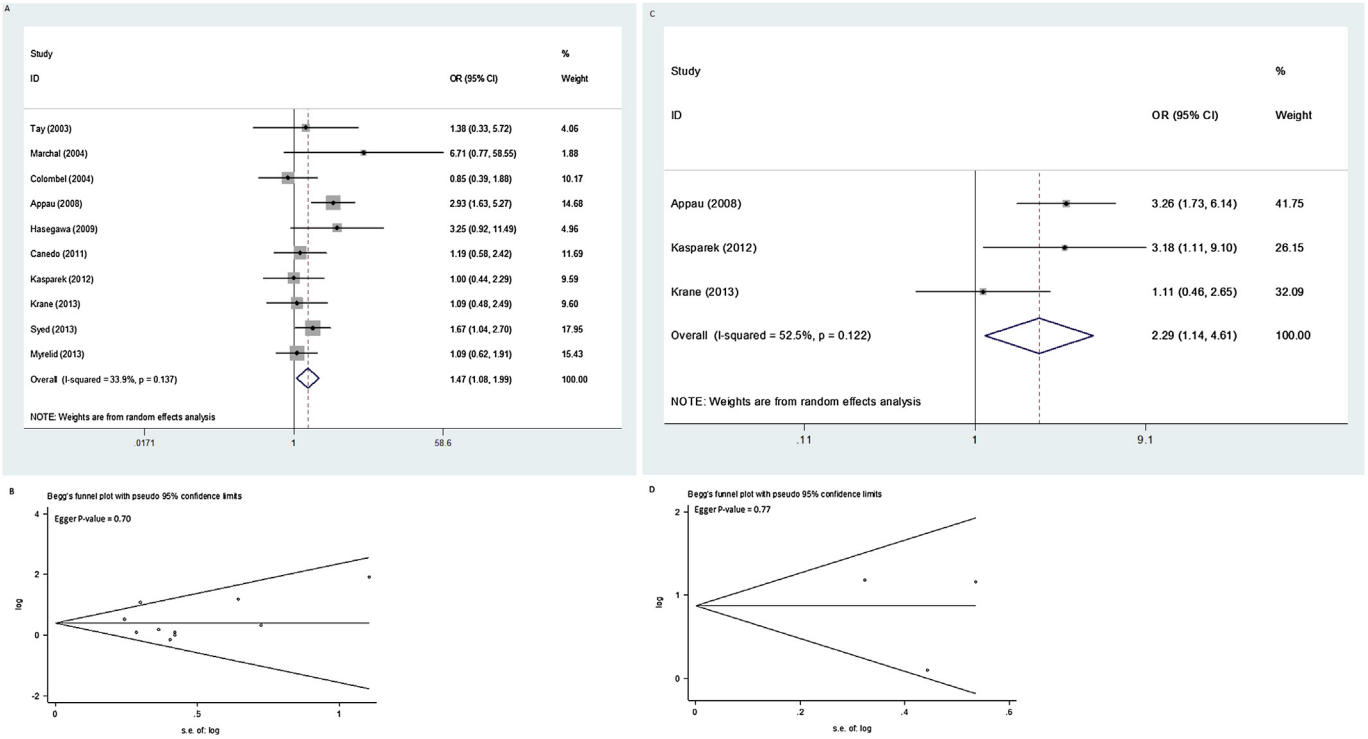

Fig. 4. Pooled outcome for development of infectious and non-infectious complications in patients exposed to IFX preoperatively vs. controls: A. Forest plots for infectious complications; B. Funnel plots for infectious complications; C. Forest plots for non-infectious complications; D. Funnel plots for non-infectious complications.

with reporting complications for 30 postoperative days, there was no association between preoperative infliximab use and non-infectious complications, with a significant heterogeneity among studies. No publication bias was detected on the basis of the symmetry of the funnel plot and the Egger's *P*-value (Fig. 4B and D).

4. Discussion

This systematic review displayed that preoperative treatment of infliximab was associated with a small but statistically significant increase in total complication rate following abdominal surgery for CD patients. The major source of these complications was the postoperative infection, although the non-infectious complications were also increased in the pooled result of the three included studies.

Our systematic review differed from the previous evaluations in several respects.[5,6] The first difference was the inclusion of recently published articles. We conducted an exhaustive literature search and included several additional recent studies with large numbers of target patients (>100) who received infliximab preoperatively. Second, although we found an increased risk of total postoperative complications, there was high degree of statistical heterogeneity between studies. We did sensitivity analyses limited to several specific subgroups to examine the robustness of our results with respect to the choice of study method and other confounding factors. Third, we used two classifications to determine the nature of the complications. There was no association between preoperative infliximab use and postoperative outcomes in either major or minor complications, and with high heterogeneity among studies. However, the pooled outcome on increased risk of infectious postoperative complications was substantial in statistics. Thus it will be more appropriate to sort the complications as infectious and non-infectious in future studies.

Our previous meta-analysis focusing on the similar topic in UC patients summarized the postsurgical outcomes affected by preoperative therapy of infliximab from 13 observational studies.[30] In contrast to the results of this systematic review, infliximab use in the preoperative period was not associated with an increase in total, infectious, and non-infectious complications in patients with UC undergoing abdominal surgery. It illustrated to some extent that CD and UC are quite different in terms of medical and surgical management.[1] Surgery does not cure CD, and up to 40% of patients will eventually need secondary operation.[2] The postsurgical morbidities for CD patients may be different from UC due to the larger number of surgeries and more aggressive medications in order to minimize the impact of disease. Therefore, the two recent meta-analyses combining CD and UC as a whole to deal with this issue might be inappropriate and unpractical, although they performed subgroup analyses for CD and UC patients separately.[31,32]

Similar to other meta-analyses in this field, the current systematic review has several limitations. First, given the nature of all included studies were retrospective, the major limitation of these studies was the incomparability between infliximab and control groups. The primary objective in a few studies was not limited to infliximab-treated versus untreated patients. Only four studies received high points on the NOS score. Secondly, there was high degree of heterogeneity among the included studies in the syntheses, which might stem from the various inclusion criteria and nonuniform definitions of the complications (Supplemental Table 1). In addition, although we conducted sensitivity analyses to discern the influence of the timing of the last preoperative infliximab on the rate of complications and the timing of the assessment of complications, it was impossible to stratify the meta-analysis results for some other important confounders with respect to disease-related and surgery-related parameters as a result of insufficient data and nonuniform presentations (Supplemental Table 2). Thirdly, patients treated with infliximab were more likely to be treated with immunomodulators (OR = 1.70, 95% CI 1.34–2.16), indicating that they suffered from more aggressive disease condition than patients who did not receive preoperative anti-TNF-α therapy. These patients usually had additional risk factors for adverse surgical outcomes such as malnutrition, anemia, fistulae, past surgeries, and urgent indications for operation.

In conclusion, preoperative infliximab use slightly increases the incidence of total early postoperative complications, and particularly infectious complications in CD patients. The surgical intervention for CD patients should be considered according to the immunosuppressive therapy prior to surgery. However, these results need to be interpreted with caution due to the study limitations. Future prospective studies controlling potential confounding variables and using homogenous classification of postoperative complications are urgently seeking to confirm our findings.

Ethical approval

This article is a systematic review. There is no need for ethical approval.

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Author contribution

Conception and design: Z.-P. Yang, K.-C. Wu and D.-M. Fan.

Collection and assembly of data: Z.-P. Yang, L. Hong and Q. Wu.

Data analysis and interpretation: Z.-P. Yang, L. Hong, Q. Wu, K.-C. Wu and D.-M. Fan.

Manuscript writing: Z.-P. Yang, L. Hong, Q. Wu and D.-M. Fan.

Final approval of manuscript: Z.-P. Yang, L. Hong, Q. Wu, K.-C. Wu and D.-M. Fan.

Conflict of interest

No potential conflict of interest existed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijsu.2013.12.015.

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