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Meta-Analysis: The Influence of Preoperative Infliximab Use on Postoperative Complications of Crohn's Disease

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Background: Infliximab (IFX) is a breakthrough treatment for refractory Crohn's disease (CD) whose effect on postoperative complications of CD remains controversial. The purpose of this study was to conduct a meta-analysis examining the effect of IFX on postoperative complications of CD.

Methods: We searched "PubMed," "EMBASE," and "Cochrane Library" databases from inception of each database until March 2018. All eligible articles were screened according to the inclusion criteria. The cumulative overall, major, minor, infectious, noninfectious, surgical, and medical complications, as well as reoperation, readmission, and mortality of CD patients who received IFX and underwent ileocolonic resection were extracted and analyzed using Review Manager 5.3. The random effects model was used to calculate the odds ratio (OR) and 95% confidence interval (CI).

Results: A total of 18 nonrandomized controlled trial studies, with 1407 patients who received IFX and 4589 patients who did not were identified. The incidence of complications was 9.38%–60.56% in the IFX group and 12.73%–53.85% in the control group. Overall, major, minor, infectious, noninfectious, surgical, and medical complications could be assessed in 16, 12, 11, 14, 12, 12, and 11 studies, respectively. There were no statistically significant differences between the 2 groups for any complication ($P > 0.05$, all comparisons). Reoperation ($P = 0.70$), readmission ($P = 0.22$) and mortality ($P = 0.86$) showed no significant difference between the 2 groups. Subgroup analysis showed that complications were not significantly different among the countries represented in the studies.

Conclusions: Based on this analysis, there does not appear to be an association between preoperative IFX treatment and postoperative complications of CD; IFX appears relatively safe for preoperative use in the treatment of CD.

Key Words: infliximab, Crohn's disease, postoperative complications, biologics, preoperative

INTRODUCTION

One-third of Crohn's disease (CD) patients require surgical treatment when the duration of disease is more than 5 years[1]; 70% of CD patients are inevitably operated on during their lifetime.[2] The emergence of infliximab (IFX) has increased the clinical response and remission rates of active CD, especially for refractory disease, which is not responsive to other therapies.[3,4] Patients treated with IFX have even achieved mucosal healing. However, evidence reported by de Buck et al[5] showed that treatment with IFX did not alter the natural history of CD or reduce the need for surgery. Accordingly, it was concluded that the inhibitory effect of IFX on the immune response potentially increased the risk of postoperative complications. However, this view has not been uniformly accepted and research in the field remains controversial.

A study by Appau et al[6] showed that preoperative use of IFX for 3 months before surgery increased postoperative abscess and sepsis in CD patients. Kotze et al[7] reports the opposite, suggesting that tumor necrosis factor alpha (TNF-α) inhibitors did not influence postoperative morbidity after elective surgical resection in CD. Even more surprising is that the results of 2 meta-analysis studies by Kopylov et al[8] and Rosenfeld et al[9] conducted using the same research yielded inconsistent results. The purpose of this study was to conduct a meta-analysis of research in this area and fully elucidate the effect of IFX in preoperative CD clinical applications.

METHODS

Search Strategy and Study Selection

We used the MeSH terms "Crohn Disease," "Postoperative Complications," "Infliximab," and their entry terms (Crohn Disease: Crohn's Enteritis; Regional Enteritis; Crohn's

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Author contributions: GL conceived of and designed the study. YYX collected and analyzed the data and wrote the first draft of the paper. LY collected and analyzed the data. PA and BZ supervised the data collection process and assisted in writing the paper. All authors contributed to article revision and approved the final version.

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Abbreviations: IFX, Infliximab; CD, Crohn's disease; OR, odds ratio; CI, confidence interval; TNF-α, Tumor necrosis factor alpha; SSIs, surgical site infections; UC, ulcerative colitis; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; AZA, Azathioprine; MTX, Methotrexate; CsA, Cyclosporin A; NA, not available.

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Disease; Inflammatory Bowel Disease 1; Granulomatous Enteritis; Ileocolitis; Granulomatous Colitis; Terminal Ileitis; Regional Ileitis. Postoperative Complications: Complication, Postoperative; Complications, Postoperative; Postoperative Complication. Infliximab: mAb cA2; Monoclonal Antibody cA2; cA2, Monoclonal Antibody; Remicade) to retrieve studies from the PubMed, EMBASE, and Cochrane Library databases from inception of each database until March 2018.

Inclusion criteria for this study consisted of the following points: 1) all trials recorded postoperative complications of CD patients who underwent abdominal surgery and received preoperative IFX; 2) papers were written in English; and 3) complete data could be obtained. Exclusion criteria consisted of the following points: 1) studies were specifically for pediatric, elderly, or pregnant populations; 2) studies were published as an abstract or at a conference; 3) papers were published as a case study or case series; and 4) clinical trial information was incomplete.

After removing duplicate literature, the preliminary screening was carried out using titles and abstracts. Studies remaining eligible based on the inclusion criteria were further screened by reading the full text. Meta-analysis was performed on the studies that passed screening for both inclusion and exclusion criteria.

Data Extraction

The following variables were extracted: age at diagnosis, gender, publication year, duration of disease, preoperative concomitant medication, type of surgery, type and quantity of postoperative complications, and other clinical information. All data extraction was performed by 2 investigators simultaneously. Any divergence between the 2 investigators was resolved by discussion or by a third investigator.

Major complications were defined as complications resulting in surgical or percutaneous intervention or being cared for in an intensive care or intermediate care unit (level I or II care)[10] for complications such as anastomotic leak, intra-abdominal abscess, bleeding, pneumonia, death, or other complications. Minor complications which typically did not require surgical intervention could be minor for grade I or II or major for grade III or IV complications, according to the Clavien-Dindo classification of surgical complications.[11] Infectious complications included anastomotic leak, intra-abdominal abscess, surgical site infections (SSIs), and other infectious complications. Data were classified according to the definitions of complications.

Statistical Analysis

All statistical analyses were performed using Review Manager 5.3 software. The Mantel-Haenszel analysis method was applied with Z test. The odds ratio (OR) and 95% confidence interval (CI) were estimated using the random effects model for each study and shown in a forest plot. The Cochran Q test and quantity I^2 were used to evaluate heterogeneity across studies. For the Cochran Q test, $P > 0.1$ was defined as no heterogeneity, and $P < 0.1$ was defined as with heterogeneity. Similarly, $I^2 \leq 50\%$ was defined as acceptable heterogeneity. Subgroup analysis and sensitivity analysis were used to detect the source of heterogeneity, while funnel plot was used to identify publication bias. $P < 0.05$ was considered to be statistically significant.

RESULTS

Literature Search Results

The retrieval process and results are shown in Figure 1. One thousand, one hundred eighty-three studies were retrieved from 3 electronic databases; 124 of them were deleted due to duplication. Browsing titles and abstracts revealed 1004 studies that described "ulcerative colitis," "review and meta," "case and letter," "recurrence," or another term that would require exclusion. These studies were excluded. Thirty-seven of the remaining 55 studies were excluded after reading the full text. Studies were excluded if they were "unable to distinguish UC and CD from IBD after contacting the corresponding authors" or if "IFX cannot be separated from other biological agents." Finally, a total of 18 studies[6,7,10,12–26] were identified from 2004 to 2018. These studies had a total of 6032 patients; 1407 of these patients received IFX, and 4589 patients did not. The cumulative overall, major, minor, infectious, noninfectious, surgical, and medical complications could be assessed in 16,[6,7,10,12–17,19–23,25,26] 12,[6,7,12,14–18,20–23] 11,[6,7,12,14–18,20,22,23] 14,[6,7,12,14–17,19–25] 12,[6,7,12,14,16,17,19–23,25] 12,[6,7,12,14–17,19–23] and 11[6,7,12,14–17,20–23] studies, respectively. While reoperation, readmission, and mortality could be assessed in 8,[6,7,12,14,16,19,21,23] 5,[6,7,15,16,23] and 7[6,7,14,17,20,21,23] studies, respectively.

Characteristics of Included Studies and Patients

The demographic and clinical characteristics are shown in Table S1. Most of the studies were performed in the United States. Other research countries included Brazil, Japan, Italy, Denmark, Germany, Belgium, and the United Kingdom. Fourteen studies were retrospective, 3 were prospective, and 1 was a randomized, controlled trial. The duration of IFX exposure was 7 days to 3 months due to the half-life and clearance of IFX.[27,28] The dosages of IFX were from 5 mg/kg to 10 mg/kg every 8 weeks,[24] 5 mg/kg every 8 weeks,[12] and 5 mg/kg (1-time dosing).[17,18] Concomitant medications including steroids, immunomodulators, 5-aminosalicylic acid (5-ASA), 6-mercaptopurine (6-MP), azathioprine (AZA), methotrexate (MTX), corticoids, antibiotics, and cyclosporine A (CsA) were recorded. Follow-up in most studies was 30 days postoperative except for the studies by Kasparek et al[14] (not available [NA]), Regueiro et al[22] (1 year), Marchal et al[17] (10 days or 3 months), Myrelid et al[19] (30 days or during the postoperative hospital stay), and Nørgård et al[21] (30 or 60 days). Details of surgery type and postoperative complications are shown in Table S1.

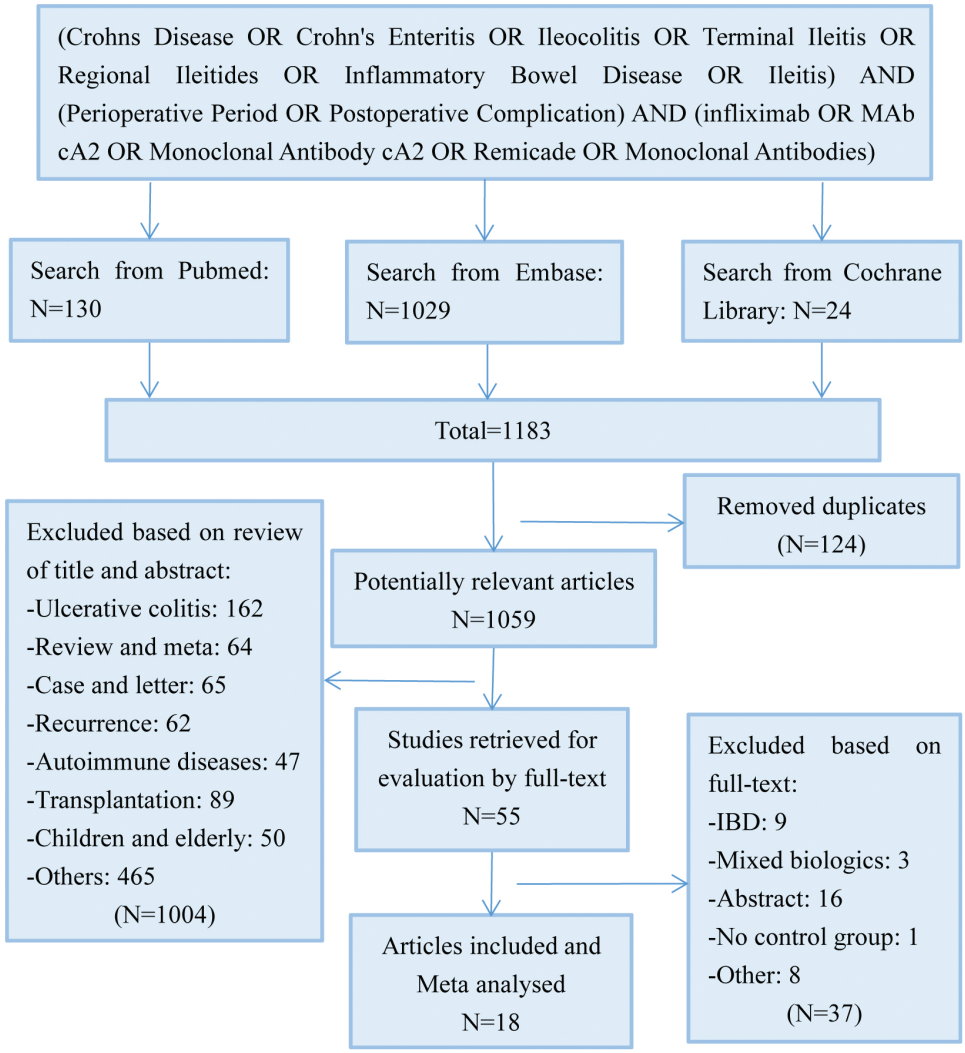

FIGURE 1. Flow chart for study selection.

Bias of Included Studies

Risk of bias was evaluated from the following aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias (Fig. 2). As shown in the figure, most studies represent high risk (red) of selection bias,[6,7,10,12,13,15–21,25,26] which was 77.78% for random sequence generation and 66.67% for allocation concealment. The second highest risk was attrition bias,[10,13,18,26] for which the proportion was 22.22%. All of the articles had low risk (green) for performance bias. Unclear risk of bias (yellow) was most common for blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Cumulative Overall Complications

Incidence of cumulative overall complications were recorded in a total of 16 studies that included 5498 patients. Postoperative cumulative overall complications were reported for 619 out of 1309 patients in the IFX group and 1064 out of 4189 patients in the control group. There was no significant difference in the incidence of cumulative overall complications between the IFX and control groups (OR = 1.17, 95% CI, 0.82–1.66, P = 0.39, Fig. 3A). Heterogeneity was significantly high among the studies (P < 0.0001, I^2 = 73%). Sensitivity analysis showed that removing the study by El-Hussuna et al[13] significantly decreased heterogeneity (OR = 0.95, 95% CI, 0.80–1.14, P = 0.24, I^2 = 21%, Table S2). No publication bias was detected based on the symmetry of the funnel plot (Fig. 3B).

Major and Minor Complications

Twelve studies (4352 patients) recorded major complications, and 11 studies (2059 patients) recorded minor complications. Major complications were reported by 365 out of 977 patients in the IFX group and 688 out of 3375 patients in the control group. Minor complications were reported in 126 out

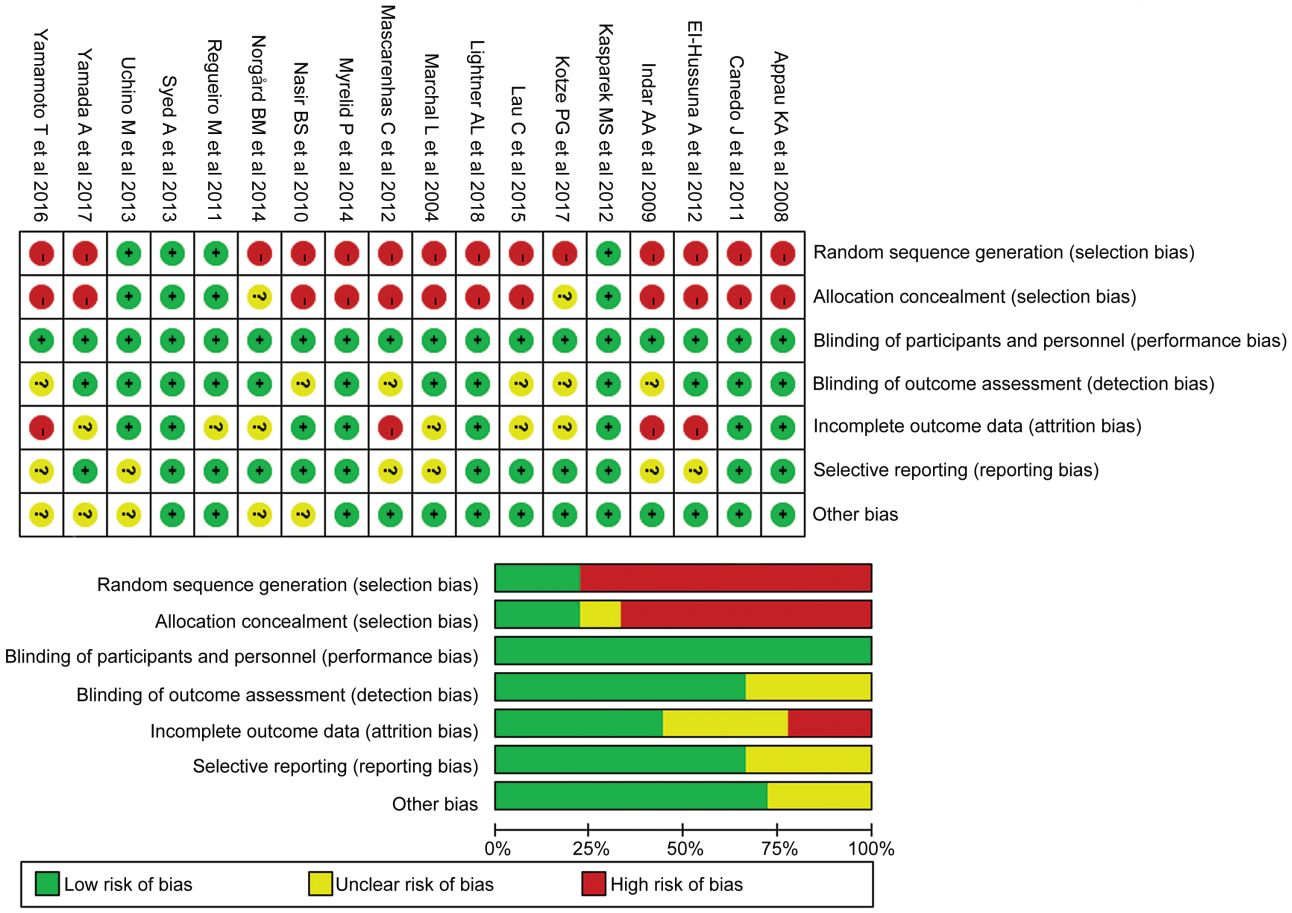

FIGURE 2. Risk of bias graph: Judgements about each risk of bias item for each included study (top) and judgements about each risk of bias item presented as percentages across all included studies (bottom). Low, unclear or high risk of bias were indicated by green, yellow, and red, respectively.

of 763 patients in the IFX group and 151 out of 1296 patients in the control group. There were no significant differences in the incidence of either major (OR = 1.41, 95% CI, 0.85–2.34, P = 0.19, Fig. 4A) or minor (OR = 1.14, 95% CI, 0.81–1.61, P = 0.46, Fig. 4C) complications between the IFX and control groups. Publication bias was not significant based on the symmetry of the funnel plots (Fig. 4B, D). The heterogeneity of minor complications was low (P = 0.16, I^2 = 30%), while that of major complications was significantly high (P < 0.00001, I^2 = 77%). Sensitivity analysis showed that leaving out any

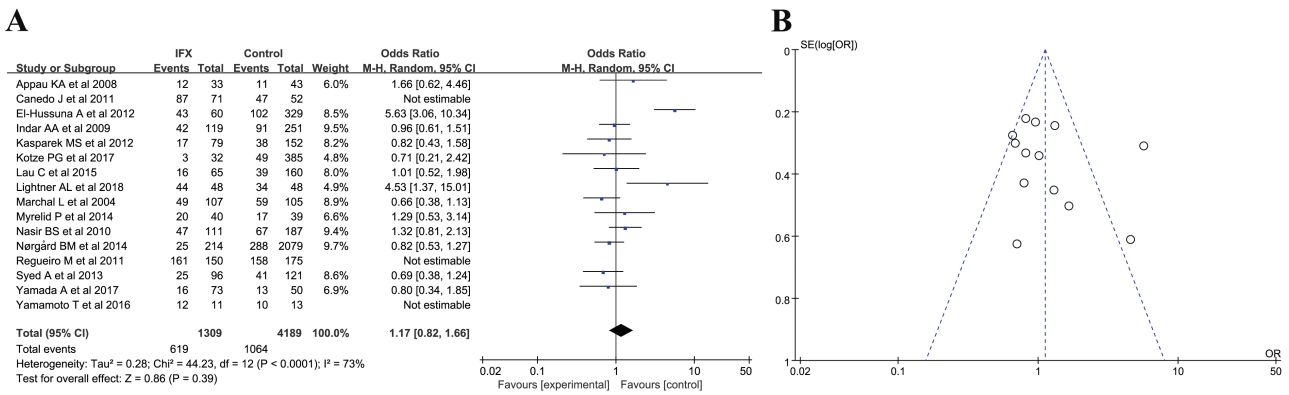

FIGURE 3. Cumulative overall complications in IFX and control groups: A, Forest plot for overall complications. B, Funnel plot for overall complications.

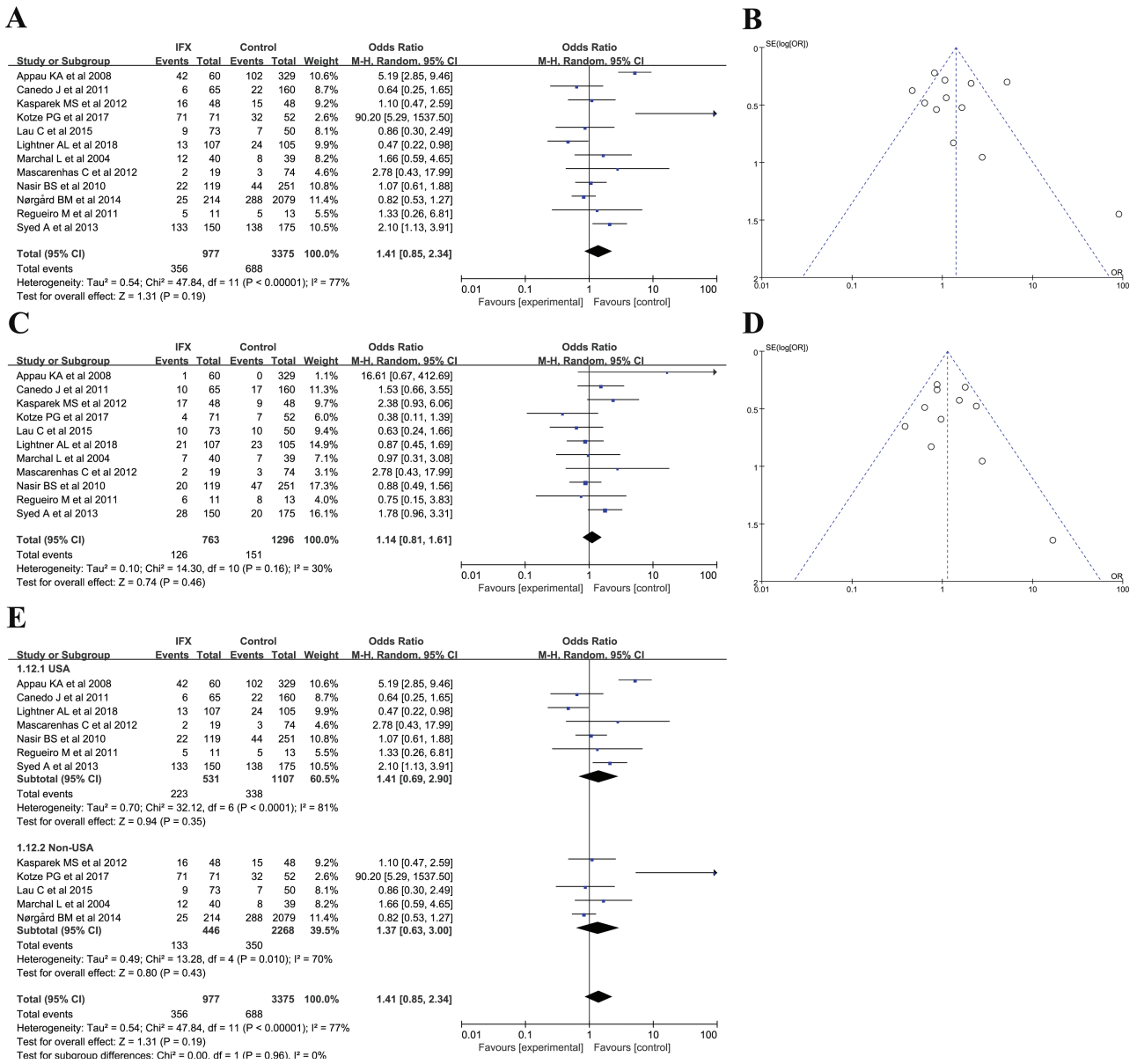

FIGURE 4. Major and minor complications in IFX and control groups: A, Forest plot for major complications. B, Funnel plot for major complications. C, Forest plot for minor complications. D, Funnel plot for minor complications. E, Subgroup analysis of major complications according to the country of the research center (USA and non-USA).

one of the included studies would not significantly impact the results for major complications (Table S2). Further subgroup analysis suggested that there was no significant correlation between major complications and the country of the research center (USA and non-USA, Fig. 4E).

Infectious and Noninfectious Complications

Fourteen studies (5179 patients) recorded infectious complications; 301 out of 1244 patients in the IFX group and 485 out of 3935 in the control group reported infectious complications. Twelve studies (4651 patients) recorded noninfectious complications; 262 out of 1092 patients in the IFX group and 555 out of 3559 in the control group reported noninfectious complications. There were no significant differences in either the infectious (OR = 1.23, 95% CI, 0.87–1.74, $P = 0.24$, Fig. 5A) or noninfectious (OR = 1.06, 95% CI, 0.88, 1.28, $P = 0.54$, Fig. 5B) complications between the IFX and control groups. Publication bias was not significant based on the symmetry of the funnel plots (Fig. 5C, D). Heterogeneity was significantly high for both infectious ($P = 0.0006$, $I^2 = 64\%$) and noninfectious ($P = 0.004$, $I^2 = 60\%$) complications. Sensitivity analysis (Table S2) found that the heterogeneity of infectious

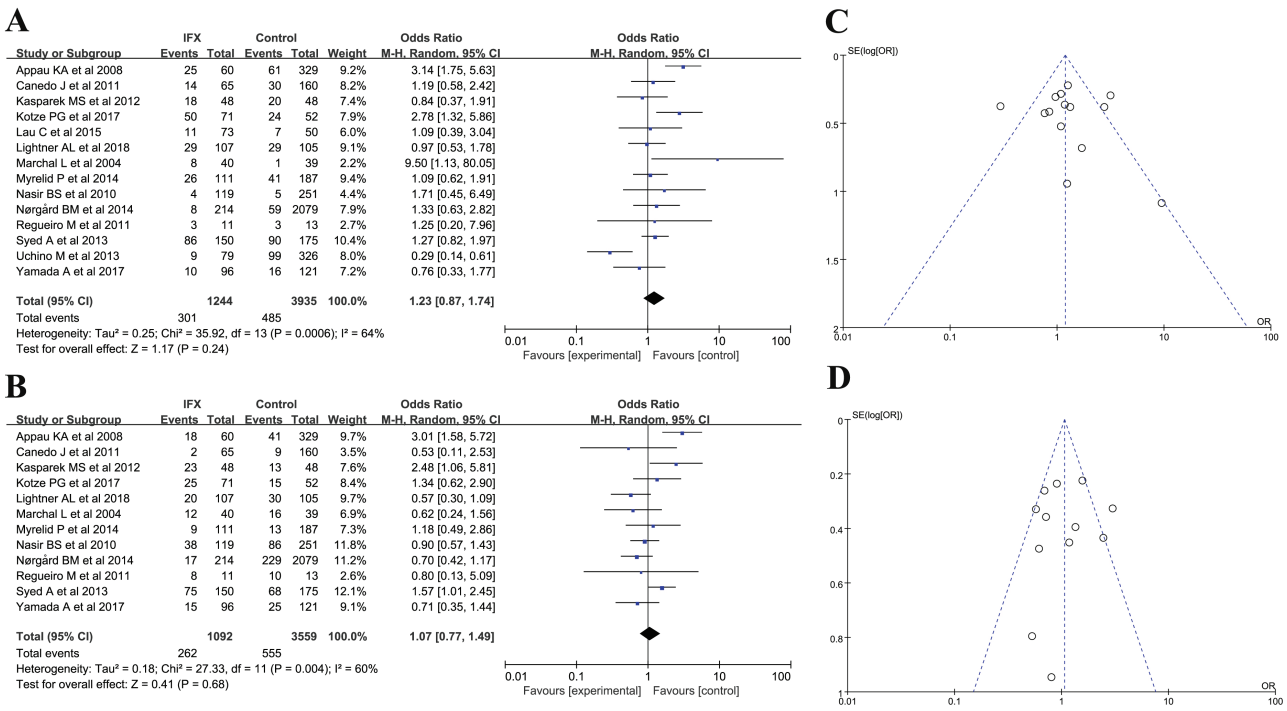

FIGURE 5. Infectious and noninfectious complications in IFX and control groups: A, Forest plot for infectious complications. B, Forest plot for noninfectious complications. C, Funnel plot for infectious complications. D, Funnel plot for noninfectious complications.

complications may originate from Uchino et al[24] (OR = 1.37, 95% CI, 1.13–1.68, P = 0.07, I^2 = 40%) and heterogeneity of noninfectious complications may originate from Appau et al[6] (OR = 0.97, 95% CI, 0.80–1.19, P = 0.08, I^2 = 40%).

Surgical and Medical Complications

Twelve studies (4557 patients) recorded surgical complications, and 11 studies (4259 patients) recorded medical complications. Surgical complications were reported for 365 of the 977 patients in the IFX group and 688 of the 3375 patients in the control group. Medical complications were reported for 126 of the 763 patients in the IFX group and 151 of the 1296 patients in the control group. There were no significant differences in either the surgical (OR = 1.14, 95% CI, 0.82–1.58, P = 0.43, Fig. 6A) or medical (OR = 1.32, 95% CI, 0.98–1.78, P = 0.07, Fig. 6B) complications between the IFX and control groups. Publication bias was not significant based on the symmetry of the funnel plot (Fig. 6C, D). Heterogeneity was significantly high for surgical complications (P = 0.002, I^2 = 62%). Sensitivity analysis (Table S2) found that heterogeneity of surgical complications may originate from Appau et al[6] (OR = 1.03, 95% CI, 0.84–1.25, P = 0.18, I^2 = 28%).

Reoperation, Readmission and Mortality

Reoperation, readmission, and mortality could be assessed in 8, 5, and 7 studies, respectively. Reoperation was reported in 83 of 826 patients in the IFX group and 260 of 3135 patients in the control group. Readmission was reported in 63 of 461 patients in the IFX group and 72 of 711 patients in the control group. Mortality was reported for 7 of 702 patients in the IFX group and 58 of 2973 patients in the control group. A forest plot showed no statistically significant difference between the IFX and control groups in reoperation (OR = 1.06, 95% CI, 0.78–1.45, P = 0.70, Fig. 7A), readmission (OR = 1.46, 95% CI, 0.80–2.66, P = 0.22, Fig. 7B), or mortality (OR = 1.12, 95% CI, 0.31–3.98, P = 0.86, Fig. 7C). Publication bias was not significant based on the symmetry of the funnel plots for each complication (Fig. 7D, E, F). Heterogeneity of reoperation was low (P = 0.39, I^2 = 5%), while that of readmission (P = 0.10, I^2 = 49%) and mortality (P = 0.19, I^2 = 32%) were relatively high. Sensitivity analysis showed that leaving out the study by Lightner et al[16] (OR = 1.83, 95% CI, 1.20–2.79, P = 0.40, I^2 = 0%) for readmission and the studies by Appau et al[6] (OR = 0.53, 95% CI, 0.21–1.32, P = 0.42, I^2 = 0%) or Nørgård et al[21] (OR = 1.78, 95% CI, 0.59–5.35, P = 0.54, I^2 = 0%, Table S2) for mortality significantly decreased heterogeneity.

DISCUSSION

The present meta-analysis investigated the relationship between various postoperative complications and preoperative IFX usage in CD patients. The results were consistent with most previously reported meta-analysis studies,[9,29] suggesting that preoperative IFX does not increase the risk of postoperative complications of CD, including cumulative overall, major,

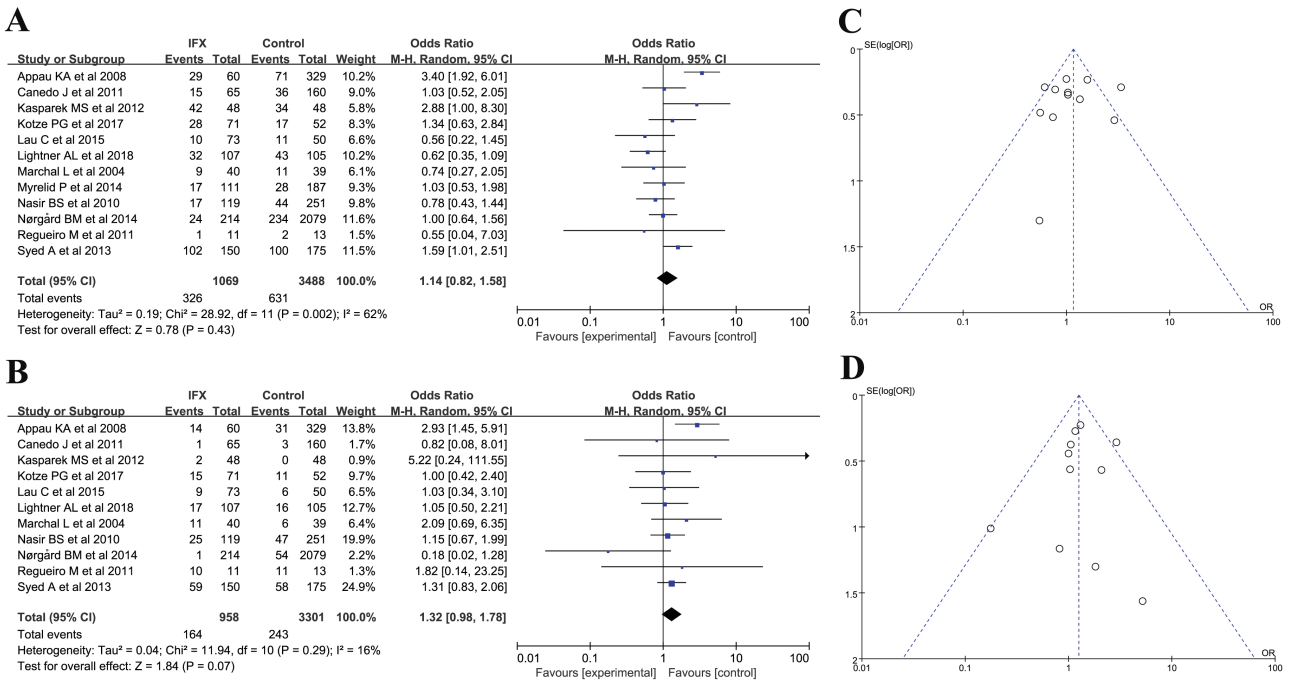

FIGURE 6. Surgical and medical complications in IFX and control groups: A, Forest plot for surgical complications. B, Forest plot for medical complications. C, Funnel plot for surgical complications. D, Funnel plot for medical complications.

minor, infectious, noninfectious, surgical, and medical complications, as well as reoperation, readmission, and mortality. On the contrary, other studies reported that IFX is associated with postoperative complications.[8,30–33]

The results of previously published related meta-analysis reported conflicting findings. Ehteshami-Afshar et al[29] suggested that although IFX did not decrease the rate of surgery, it did not increase most postoperative side effects. Rosenfeld et al[9] reported that IFX may be safe to continue in the preoperative period without increasing the risk of postoperative complications for CD patients undergoing abdominal surgery. Our results are in accordance with the latter findings. On the contrary, Narula et al[30] showed that anti-TNF-α therapies appear to increase the risk of postoperative complications. El-Hussuna et al[31] reported that anti-TNF-α agents increased the risk of anastomotic complications in CD patients. Billioud et al[32] and Yang et al[33] reported that preoperative anti-TNF-α use slightly increases the occurrence of postoperative complications in IBD, particularly for infectious complications in CD patients. These conclusions are contrary to our findings. This collection of conflicting reports indicates that well-controlled trials should be performed to fully understand the true efficacy of IFX in CD patients.

Obvious heterogeneity was observed for cumulative overall, major, infectious, noninfectious, and surgical complications. Heterogeneity was significantly decreased when the study by El-Hussuna et al[13] was removed from analysis of cumulative overall complications. He reported that preoperative biologic treatment had no influence on anastomotic complications. One patient in this study used adalimumab, and the authors did not classify complications in detail; therefore, this study may have been the main source of heterogeneity. Neither sensitivity nor subgroup analysis of countries could identify a source of heterogeneity for major complications. Only when the study by Appau et al[6] was removed did the heterogeneity slightly decrease; however, it was still at a very high level. Appau et al found that presurgical treatment with IFX in patients with CD was associated with increased postoperative sepsis, abscess, and readmission. Heterogeneity of noninfectious and surgical complications is also linked to this study.[6] Uchino M et al[24] showed that administration of preoperative IFX was not a risk factor for surgical site infection; however, only surgical site infections were analyzed, which may be the reason heterogeneity was observed for infectious complications.

We evaluated the risk of bias by selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The inclusion of many retrospective studies (not randomized, controlled studies) increased selection bias. Incomplete outcome data in 4 studies[10,13,18,26] increased attrition bias. In addition, there was also bias caused by limited sample size[7,10,14,15,17,18,22] and single center research.[6,10,12,14–18,20,22–24] Fortunately, despite some heterogeneity in our meta-analysis, no significant publication bias was found based on funnel plot analysis. The funnel plot is based on the fact that precision in estimating the underlying treatment effect will increase as the sample size of component studies increases.[29] Therefore, the accuracy of funnel plots may be affected by fewer studies that included reoperation (8), readmission, (5) and mortality (7).

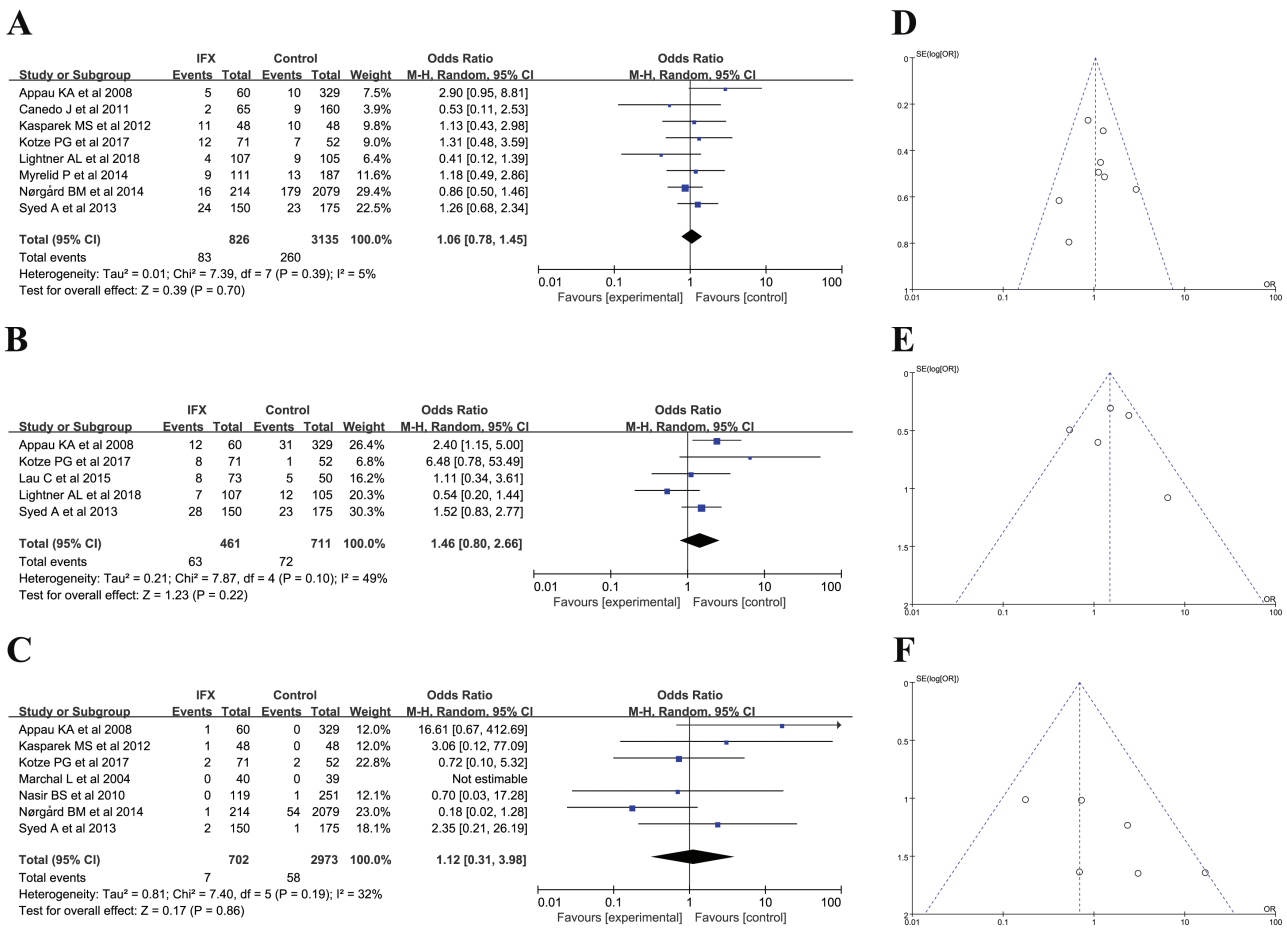

FIGURE 7. Reoperation, readmission and mortality in IFX and control groups: A, Forest plot for reoperation. B, Forest plot for readmission. C, Forest plot for mortality. D, Funnel plot for reoperation. E, Funnel plot for readmission. F, Funnel plot for mortality.

Limitations in this meta-analysis are inevitable. First, most of the studies included in the analysis were retrospective. Only 3 prospective studies[14,23,24] and 1 randomized controlled study[22] were included. The deficiency or absence of information extraction from retrospective studies may lead to distortion of conclusions. For example, duration of disease, dosage of IFX, time since last IFX treatment, age of onset, concomitant medication, type of surgery, surgical approach, and timing of surgery will all have an effect on the postoperative recovery. This type of information is only partially recorded and cannot be further analyzed (Table S1). Second, publication bias assessed by funnel plot is too subjective, and the conclusion may vary from person to person. Abstracts or conference-reported studies[34–36] were not included and may affect the outcome of the present meta-analysis, considering that we contacted corresponding authors of related studies without receiving a reply. Third, different studies use different definitions for the classification of complications; this will affect the accuracy of data extraction. Finally, the study by Kasparek et al[14] failed to record the postoperative follow-up time. While the majority of studies reported a 30-day follow-up, follow-up times of 1 year,[22] 10 days and 3 months,[17] and 60 day[21] were also reported. Late sepsis is mainly caused by recurrent CD, which is not a surgical complication.[37]

In conclusion, the present meta-analysis showed no evidence that the preoperative use of IFX increased postoperative complications in CD patients. Compared with other meta-analyses, we included more recently published manuscripts.[7,16,25] Our results indicate that patients with CD who need surgery do not need to have IFX withdrawn before the operation. However, the safety of IFX still needs to be verified by long-term observational studies with larger sample sizes.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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