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Infliximab for patients with moderate to severely active ulcerative colitis: an updated meta-analysis of randomized controlled trials

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Abstract

Background and aims Ulcerative colitis (UC) is a serious inflammatory bowel disease with significant morbidity and mortality. Infliximab (IFX), a TNF-alpha antagonist, is recommended by the American Gastroenterological Association, but its clinical effectiveness and safety are based on limited studies. This meta-analysis of randomized controlled trials (RCTs) evaluates the efficacy and safety of IFX in moderate-to-severe active UC, providing evidence for its clinical application.

Methods A systematic search of major English (PubMed, MEDLINE, Web of Science, Embase, Cochrane Library) and Chinese databases (CNKI, SinoMed, Wanfang, VIP) was conducted up to September 25, 2023, to identify RCTs comparing IFX against placebo, aminosalicylates, corticosteroids, or immunosuppressants for moderate-to-severe UC. Pooled analyses assessed short- and long-term clinical response, clinical remission, endoscopic remission (mucosal healing), safety outcomes, and corresponding 95% confidence intervals. Subgroup analyses, heterogeneity assessment, sensitivity analyses, publication bias evaluation (funnel plots), and meta-regression were performed.

Results Twenty RCTs involving 2,350 patients (IFX: $n=1,300$; controls: $n=1,050$) were included. IFX demonstrated significant superior efficacy versus controls across all primary endpoints: short-term (RR = 1.38, $P<0.001$) and long-term clinical response (RR = 1.52, $P=0.007$); short-term (RR = 1.38, $P<0.001$) and long-term clinical remission (RR = 1.52, $P=0.022$); short-term (RR = 1.58, $P=0.001$) and long-term endoscopic remission (RR = 1.39, $P=0.010$). Adverse event rates did not differ significant between groups (RR = 1.00, $P=0.933$). Meta-regression suggested geographical region as a potential source of heterogeneity for short-term clinical response.

Conclusions IFX has a more positive effect on active UC than placebos, aminosalicylic acid preparations, steroids, or immunosuppressive drugs, but shows no superiority in terms of adverse responses.

Keywords Ulcerative colitis, Infliximab, TNF-alpha antagonists, Evidence-based practice, Meta-analysis

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Introduction

Ulcerative colitis (UC) is an inflammatory bowel illness with high morbidity and mortality rates worldwide [1, 2]. Globally, the total incidence and prevalence of UC are estimated to range from 1.2 to 20.3 per 10,000 and from 7.6 to 24.5 per 10,000 persons, respectively [3, 4]. The incidence of UC-related mortality is 15.9 per 1000 cases, which is 1.4 times higher than the death rate of the general population [5]. As awareness of the disease and medical treatment have improved in developed countries, the incidence of UC has continued to increase in the twenty-first century in many newly industrialized countries in South America, Asia, Africa, and the Middle East [6].

UC is usually characterized by recurrence and remission. At the onset of UC, patients usually present with typical symptoms such as diarrhea, bellyache, mucus, purulence and blood stool. In addition, the disease may be accompanied by extraintestinal manifestations, such as peripheral arthritis and hematological malignancy [7, 8]. It will be complicated by toxic megacolon, lower digestive tract massive bleeding, and intestinal perforation; furthermore, it may even cause colon cancer.

Tumor necrosis factor-alpha (TNF-α) plays a crucial part in the pathogenesis of UC by increasing the recruitment and adhesion of leukocytes to vascular endothelial cells, and overexpression can lead to intestinal inflammation and mucosal damage [9]. With the advent of biologic medications, particularly antitumor necrosis factor-α, the management of UC has greatly improved over the past few years. For those with moderate-to-severe active UC in adulthood, the American Gastroenterological Association (AGA) recommends treatment with TNF-alpha antagonists [10]. Infliximab (IFX) is a purified recombinant DNA-derived chimeric murine human IgG1k monoclonal antibody [9]. IFX can induce lamina propria T cell death by activating complement-dependent and antibody-dependent cells, which leads to Fc receptor-mediated leukocyte engagement and consequently target cell lysis. IFX also binds to membrane-bound TNF (mTNF) and Fcγ receptors [11–15]. The use of IFX in patients with active UC still presents a significant treatment gap, leading to ongoing debates about its effectiveness and safety. In clinical trials (ACT1 and ACT2), IFX demonstrated superiority over a placebo in achieving and maintaining clinical remission [16]. However, there are potential serious side effects associated with its application. Some UC patients may experience severe adverse events, including opportunistic infections, reactivation of latent tuberculosis, or infusion reactions [17]. In addition, the long-term efficacy of IFX for UC has only been documented in a small amount of research, most of which are non-prospective and non-RCTs [18]. Previous study [19] has evaluated IFX therapy in UC, results indicated the IFX did not suggest any difference between cyclosporine as rescue therapies for steroid-refractory UC in pooled analysis of RCTs. However, Guo C, et al. [20] revealed that IFX was significantly more effective in short-term response, long-term response and long-term remission. But there were no significant differences in the short-term remission. In addition, the methodology about sensitivity analysis, publication bias, assessment of the quality of evidence, were not comprehensively performed. Determining the appropriateness of IFX for treating UC is challenging. Therefore, our research aims to examine the efficacy and safety of IFX in moderate-to-severe active UC, and validate its widespread clinical application to treat UC.

Methods

Eligibility criteria

Inclusion criteria

The inclusion criteria were developed based on the PICOS principle and were as follows: (1) UC patients with a moderate-to-severe level of disease definitively diagnosed by colonoscopy, pathologic biopsy, and Mayo score; (2) the test group used IFX as an intervention, and the control group used other treatments, such as placebo, aminosalicylic acid preparations, steroids or immunosuppressive agents; (3) short-term (4–12 weeks) clinical response, clinical remission, and/or long-term (≥ 6 months) clinical response and clinical remission was reported; secondary outcome endpoints included short-term (4–12 weeks) or long-term (≥ 6 months) endoscopic mucosal healing, and incidence of adverse events; (4) the research was a randomized controlled trial (RCTs); (5) the country of the patient and course of disease were not restricted.

Exclusion criteria

The exclusion criteria were as follows: (1) lack of information or incomplete data in studies; (2) nonhuman research, including animal and in vitro research; (3) pregnant and lactating women and children; (4) retrospective studies, case reports, conference papers, meta-analyses, reviews; and (5) duplicate publications.

Search methodology

We systematically searched the PubMed, MEDLINE, Web of Science, Embase, Cochrane Library, China Biomedical Literature Service (SinoMed), China National Knowledge Infrastructure (CNKI), VIP and Wanfang electronic databases from the database's creation to September 25, 2023, to identify relevant studies. The search tactic was constructed by integrating titles, keywords, free words and subject headings using the following combinations of words: (Colitis, Ulcerative/ulcerative colitis/

UC/Moderate ulcerative colitis/Severe ulcerative colitis/Moderate to severely active ulcerative colitis) AND (Infliximab/anti-tumor necrosis factor/tumor necrosis factor/tumor necrosis factor antibody/MAb cA2/Monoclonal Antibody cA2/Antibody cA2, Monoclonal/cA2, Monoclonal Antibody/Infliximab-dyyb/Infliximab dyyb/Inflectra/Remicade/Infliximab-abda/Infliximab abda/Renflexis/IFX) AND (random/randomized/clinical trial/RCTs). Additionally, the citations of pertinent reviews and systematic reviews were manually searched.

Literature screening and data extraction

Two independent reviewers screened the original literature blindly depending on the criteria for inclusion and exclusion, extracted data using a data extraction table, and cross-checked their final results. Disagreements between the reviewers were settled by seeking advice from a third person. The information in the data extraction form includes: (1) general information about the contained literature, including the author's name, publication country, and publication date; (2) essential information about the study population, for instance, the totality of participants, age, course of disease, dose of intervention drugs, mode of administration, and each group's case count; (3) interventions and dosages; (4) relevant outcome indicators; and (5) key information needed for the risk of bias evaluation.

Research quality assessment

Selected studies were blindly evaluated by two reviewers using the Cochrane Risk of Bias Tool (RoB 2.0). Discrepancies were resolved through consensus or consultation with a third reviewer. Bias assessment was performed across the following domains: 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), Other potential sources of bias.. The items were presented as questions to elicit yes, no, or unclear. Each study was categorized as having low, unclear, or high risk of bias for each domain, with justifications provided for all judgments. The overall bias assessment was visualized using Review Manager (RevMan) 5.4, generating a standardized risk-of-bias graph and summary table.

Statistical analysis

Stata version 14.0 (Stata) was used to conduct the meta-analysis. The relevant outcome indicators observed in this study were binary data, which were used to calculate the 95% confidence intervals (CI) for the relative risk (RR). We evaluated heterogeneity among the literature using the Q test and the I^2 test. $I^2 \leq 25\%$ represents low heterogeneity, $25\% < I^2 \leq 50\%$ represents moderate heterogeneity, $I^2 > 50\%$ represents high heterogeneity. $I^2 > 50\%$ and $P < 0.1$ indicated heterogeneity between studies, and in such cases, a random effects model was employed. Conversely, when $I^2 \leq 50\%$ and $P \geq 0.1$, the studies had less heterogeneity, and a fixed effects model was employed. If heterogeneity existed between studies, sources of heterogeneity were further analyzed using subgroup analyses based on the dose of intervening medication in the incorporated studies. Sensitivity analysis was conducted to determine whether the combined results were stable. To identify publication bias, contour-enhanced funnel plots were made. Meta-regression analysis was carried out to examine the impact of potential mixing elements and their heterogeneous origins on the overall effect size.

Evidence quality grading

We used GRADEpro, proposed by the GRADE Working Group and developed by the Cochrane Collaboration network, to assess the quality of the evidence for seven outcomes (short-term clinical response, long-term clinical response, short-term clinical remission, long-term clinical remission, short-term endoscopic mucosal healing, long-term endoscopic mucosal healing, and incidence of adverse events).

Results

Results of article screening

We searched different databases according to the search strategy developed and initially obtained 3198 documents. All the literature was eliminated for duplicates by EndNote X9.1 to obtain 2311 documents. The titles and summaries of the remaining 2311 documents were filtered, and 1984 documents were excluded after removing reviews, case reports, conference abstracts, animal experiments, and uncorrelated articles. The full texts of 327 documents were further read, and 305 were eliminated due to non-RCTs, insufficient outcome data and no control group. 2 documents excluded due to full text not being available, eventually enrolling 20 studies. An illustration of the flowchart of literature screening is presented in Fig. 1.

Study features

A total of 2350 patients were involved in twenty studies, including 1300 patients treated with IFX and 1050 control patients. Among the included studies, 3 mg/kg IFX was given in one trial [21]. Three trials [22–24] applied 4 mg/kg IFX to patients. 16 trials [25–39] applied 5 mg/kg IFX. Three trials [25, 31] applied 10 mg/kg IFX, and one trial [31] applied 20 mg/kg IFX to patients. 5 mg/kg and 10 mg/kg IFX were parallelly applied in three trials. One

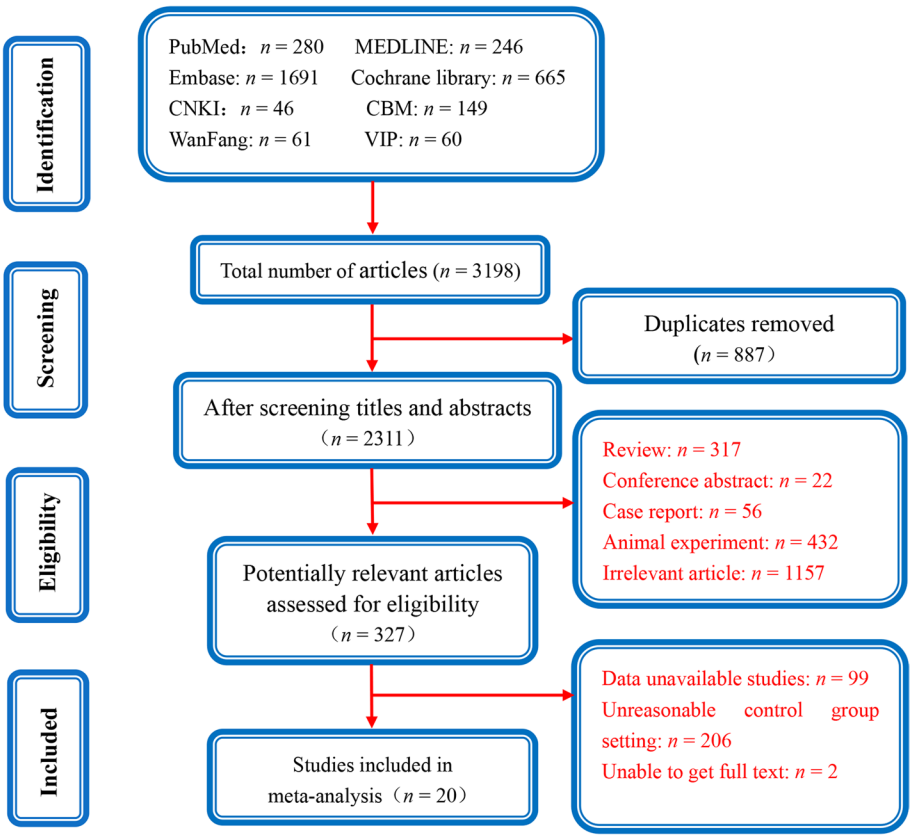

Fig. 1 PRISMA flowchart of the study selection process

trial [31] parallelly applied 5 mg/kg, 10 mg/kg and 20 mg/kg IFX to patients.

Short-term clinical response was reported in 17 studies [21–25, 27, 29, 30, 32–39], long-term clinical response was reported in 6 studies [25, 27, 29, 30, 39], short-term clinical remission was reported in 17 studies [21–26, 28, 29, 32–39], long-term clinical remission was reported in 7 studies [25–27, 29, 31, 39], short-term mucosal remission was reported in 6 studies [25, 29, 30, 32, 39], long-term mucosal remission was reported in 3 studies [29, 31, 39], and adverse reactions were reported in 13 studies [21–25, 29, 31–33, 36–38]. The study characteristics are listed in Supplementary Table 1.

Study quality assessment

Figure 2 illustrates an evaluation of the methodological quality of the contained literature. There was low bias risk with respect to randomized sequence generation in all of the enrolled studies. In most of the enrolled studies, there was low bias risk with respect to allocation concealment. Only a few of the included RCTs used blinding, and the remaining studies did not use blinding or did not mention the application of blinding; therefore, there was an unclear risk of performance bias and detection bias. No studies examined bias due to incomplete outcome data and selected reporting.

Meta-analysis results

Meta-analysis of primary outcome results

Effect of IFX on short/long-term clinical response in moderate-to-severe UC Sixteen studies (1845 patients) reported short-term clinical responses, while six studies (1059 patients) reported long-term clinical response. Before conducting pooled analyses of the outcome metrics, we examined the heterogeneity between these studies. The results suggested moderate statistical heterogeneity for both short-term clinical responses ($P = 0.003$, $I^2 = 55.8\%$) and long-term clinical responses ($P = 0.011$, $I^2 = 66.4\%$). Consequently, we employed a random effects model for the pooled analysis. The results revealed that the short-term clinical response rate (RR = 1.38, 95% CI: 1.27–1.51, $Z = 7.136$, $P = 0.000$; Fig. 3A) and long-term clinical response rate (RR = 1.52, 95% CI: 1.12–2.07, $Z = 2.696$, $P = 0.007$; Fig. 3B) were greater in the IFX group than in the control group.

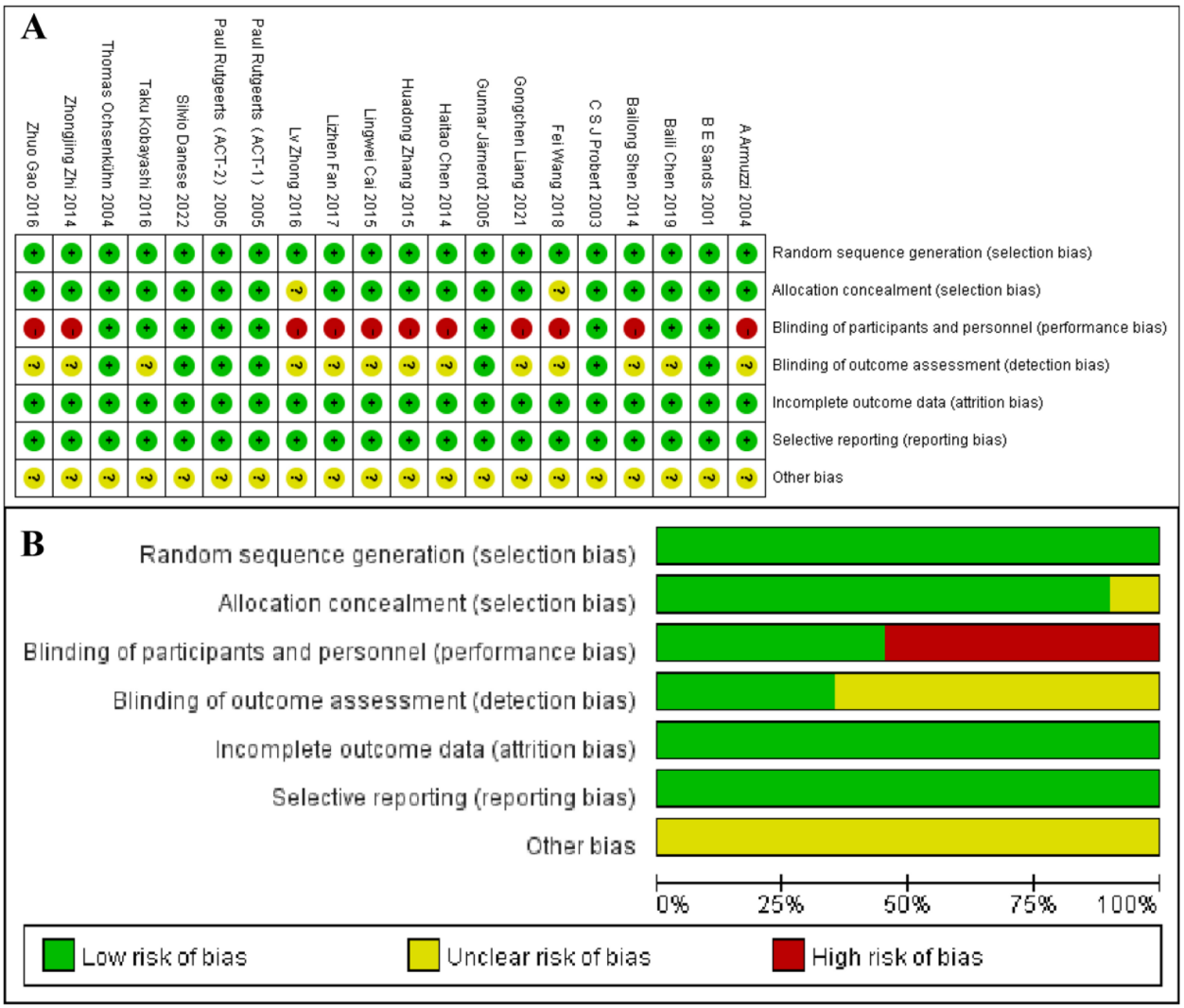

Fig. 2 Quality assessment of included studies

Effect of IFX on short/long-term clinical remission in moderate-to-severe UC Seventeen studies (1929 patients) reported short-term clinical remission, while seven studies (1463 patients) reported long-term clinical remission. Heterogeneity among these studies was investigated before performing pooled analysis of the outcome measures. The results indicated moderate statistical heterogeneity for both short-term clinical remission ($P<$ 0.000, $I^2=$ 62.4%) and long-term clinical remission ($P=$ 0.008, $I^2=$ 65.6%). Therefore, a random effects model was chosen for the pooled analysis. The results showed the short-term clinical remission rate (RR = 1.38, 95% CI: 1.25–1.54, $Z=$ 6.041, $P=$ 0.000; Fig. 3C) and long-term clinical remission rate (RR = 1.52, 95% CI: 1.12–2.07, $Z=$ 2.295, $P=$ 0.022; Fig. 3D) in the IFX group were greater than those in the control group.

Meta-analysis of secondary outcome results

Effect of IFX on short/long-term mucosal remission in moderate-to-severe UC Six studies (1184 patients) reported short-term endoscopic remission, and three studies (704 patients) reported long-term endoscopic remission. Heterogeneity between these studies was examined before performing pooled analyses. The results indicated significant heterogeneity for short-term endoscopic remission ($P<$ 0.000, $I^2=$ 75.8%); hence, a random effects model was employed. There was no heterogeneity in long-term endoscopic remissions ($P<$ 0.890, $I^2=$ 0%); hence, a fixed effects model was employed. Based on the meta-analysis, IFX led to significantly higher rates of short-term endoscopic remissions (RR = 1.58, 95% CI: 1.20–2.08, $Z=$ 3.278, $P=$ 0.001; Fig. 4A) and long-term

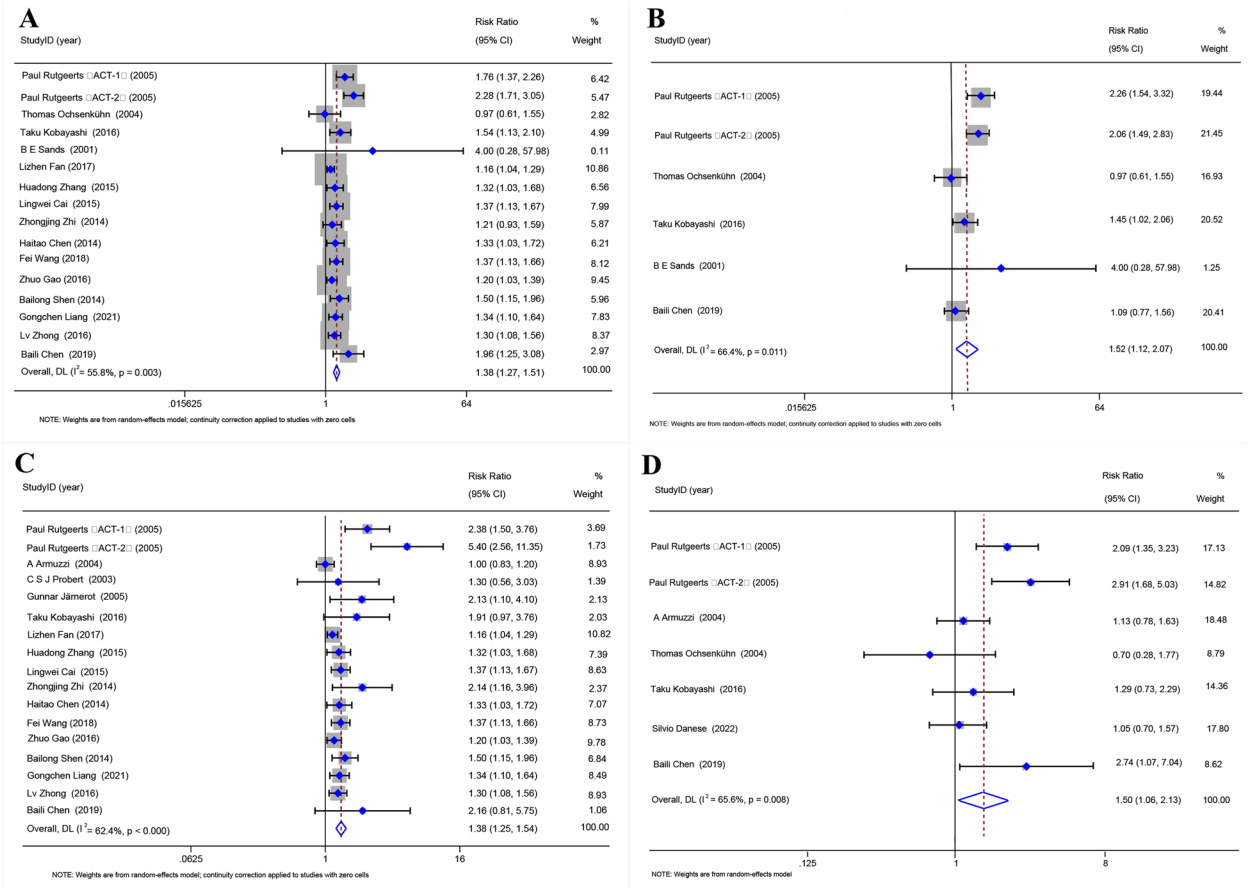

Fig. 3 Forest plots of the RR of short-term clinical response, long-term clinical response, short-term clinical remission, and long-term clinical remission show the following: **A** short-term clinical response; **B** long-term clinical response; **C** short-term clinical remission; and **D** long-term clinical remission. All meta-analyses used random effects models

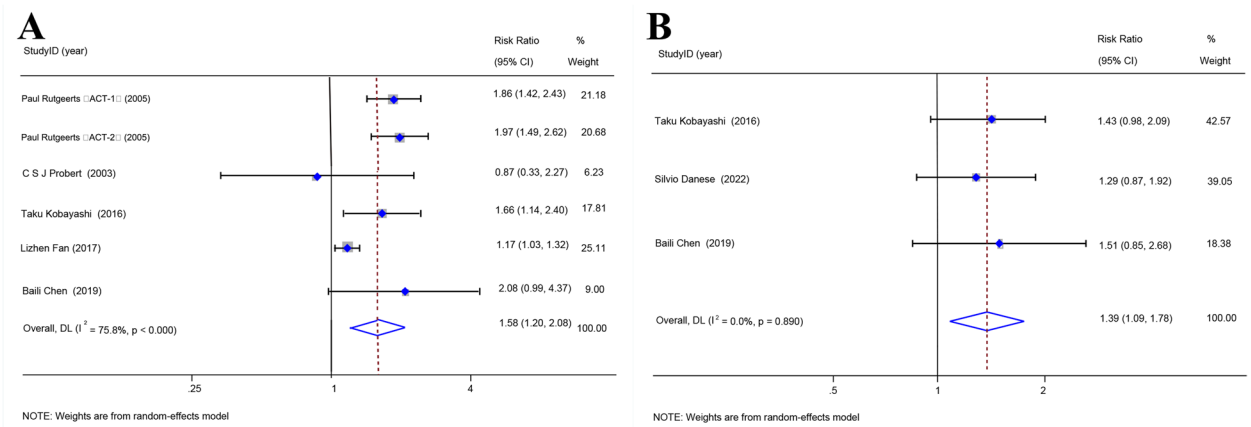

Fig. 4 Forest plot and RR for short/long-term endoscopic (mucosal) remission. **A**: Forest plot of short-term endoscopic remission. **B**: Long-term endoscopic remission

endoscopic remissions (RR = 1.39, 95% CI: 1.09–1.78, Z = 2.561, P = 0.010; Fig. 4B) than the control treatments.

Subgroup analysis

Further subgroup analyses were performed to account for differences in the dose of IFX used. These studies were divided into 5 subgroups according to the dose of IFX used: 3 mg/kg, 4 mg/kg, 5 mg/kg, 10 mg/kg, and 20 mg/kg. In the outcome measure of short-term clinical response, and long-term clinical response, the subgroup with a dose of 20 mg/kg did not achieve statistical significance (short-term clinical response: RR = 3.00, 95% CI: 0.17–53.17, Z = 0.746, P = 0.455, Fig. 5A; long-term clinical response: RR = 4.00, 95% CI: 0.26–61.76, Z = 0.993, P = 0.321, Fig. 5C). All outcomes were superior in the IFX group compared with the control group: short-term clinical response (RR = 1.44, 95% CI: 1.31–1.59, Z = 7.566, P = 0.000, Fig. 5A), short-term clinical remission (RR = 1.47, 95% CI: 1.27–1.73, Z = 6.366, P = 0.000, Fig. 5B), long-term clinical response (RR = 1.68, 95% CI: 1.33–2.13, Z = 4.310, P = 0.000, Fig. 5C), long-term clinical remission (RR = 1.45, 95% CI: 1.06–1.98, Z = 3.251, P = 0.001, Fig. 5D), short-term endoscopic remission (RR = 1.65, 95% CI: 1.33–2.05, Z = 4.519, P = 0.000, Fig. 5E). The highest rate of short-term clinical response (RR = 1.96, 95% CI: 1.48–2.61, Fig. 5A), short-term clinical remission (RR = 3.04, 95% CI: 1.39–6.68, Fig. 5B), long-term clinical response (RR = 2.28, 95% CI: 1.76–2.94, Fig. 5C), long-term clinical remission (RR = 2.59, 95% CI: 1.61–4.16, Fig. 5D), short-term endoscopic remission (RR = 1.86, 95% CI: 1.51–2.29, Fig. 5E) was seen in the subgroup with a dosage of 10 mg/kg.

Safety

A total of 13 studies reported adverse reactions during follow-up, mainly including gastrointestinal reactions, leukopenia, joint pain, and skin sensitization. Before performing pooled analysis, heterogeneity was routinely assessed, and the presence of moderate heterogeneity was observed (P = 0.015, I^2 = 51.9%). Therefore, we employed a random effects model. The pooled analysis indicated that IFX-treated patients had a similar rate of adverse reactions as control patients (RR = 1.00, 95% CI: 0.91–1.11, Z = 0.084, P = 0.933). The forest plot of the meta-analysis of security is shown in Fig. 6.

Sensitivity analysis and publication bias

Considering the significant heterogeneity of the included study samples ≥10 and to evaluate the stability of the study results (short-term clinical response, short-term clinical remission), we conducted the sensitivity analysis using case-by-case exclusion. After excluding the studies one by one, there was no significant change in the short-term clinical response and short-term clinical remission, suggesting that the pooled results have some stability and reliability (Fig. 7A, B). Furthermore, we assessed possible publication bias using contour-enhanced funnel plots, which allowed us to take into account the statistical significance of the study's estimates (P < 0.01, P < 0.05, P < 0.1, or P > 0.1), as well as the areas in which the study was considered to be missing. The results of the contour-enhanced funnel plots for short-term clinical response (Fig. 7C) and short-term clinical remission (Fig. 7D) showed that the majority of missing studies fell within the district of statistical significance (P < 0.01), suggesting that the asymmetry in the funnel plots was not due to publication bias. We reviewed the original studies and hypothesized that the asymmetry of the funnel plots might be caused by poor methodological quality of small-sample studies, different dosages of interventions, and missing blinding.

Meta-regression analysis

To estimate the influence of potential effect modification elements on the heterogeneity of the resulting variable, we performed meta-regression. We hypothesized that the following covariates were possible contributors to the heterogeneity of the outcome variables: (1) the dose of infliximab (3 mg/kg or 4 mg/kg or 5 mg/kg or 10 mg/kg or 20 mg/kg) and (2) region (multinational/Germany/Japan/USA/China/Italy/Sweden). A univariate analysis indicated that infliximab dose had no marked effect on the aggregate effect size of short-term clinical response (P = 0.10) and short-term clinical remission (P = 0.22; Table 1 and Figure S1). According to the results of multivariate analysis, dose and region had no strong association with the heterogeneity of the aggregate effect size of short-term clinical response. In contrast, short-term clinical response was affected by region (P = 0.00; Table 1 and Figure S1), suggesting that the source of heterogeneity may be different study regions.

Assessment of the quality of evidence

We used the Cochrane Collaboration Network GRADEpro to assess the quality of proof for outcome indicators. The results showed a low level of evidence for short-term clinical response, long-term clinical response, and short-term clinical remission, a very low level of evidence for long-term clinical remission and short-term endoscopic remission, and a moderate level of evidence for long-term endoscopic remission and adverse events, as shown in Fig. 8. We hypothesize that the downgrading of evidence is due to the following factors: (1) large deviations in randomization, blinding and allocation concealment in the included studies; (2) significant heterogeneity; (3) small sample size; and (4) a wider confidence interval.

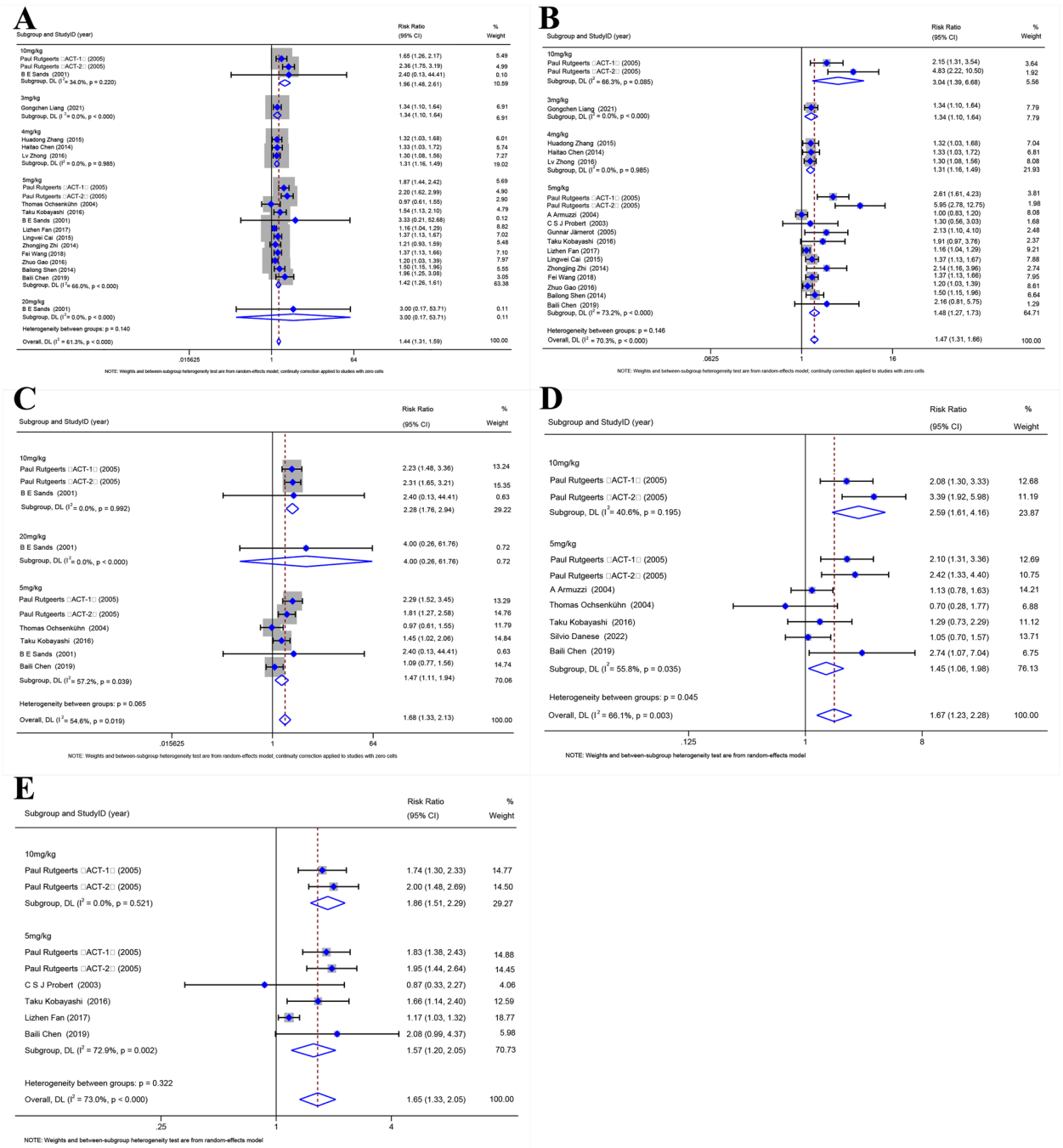

Fig. 5 Subgroup analysis of IFX dose. **A**: short-term clinical response; **B**: short-term clinical remission; **C**: long-term clinical response; **D**: long-term clinical remission. **E**: short-term endoscopic remission

Discussion

The pathogenesis of UC is complex and is related to genetic factors, infectious factors, dysbiosis of intestinal flora, vitamin D deficiency and abnormal immune response of intestinal mucosa [40–42], thus there is still a lack of specific therapeutic methods for UC. The emergence of biologics has been a major breakthrough in the treatment of UC [43]. Upadacitinib, a JAK1-selective inhibitor, received clinical remission rate and response rate 25.4% and 72.6%, in UC treatment [44]. However, it was not been applied as first-line therpy. To date, AGA has recommended the use of TNF-α antagonists to treat

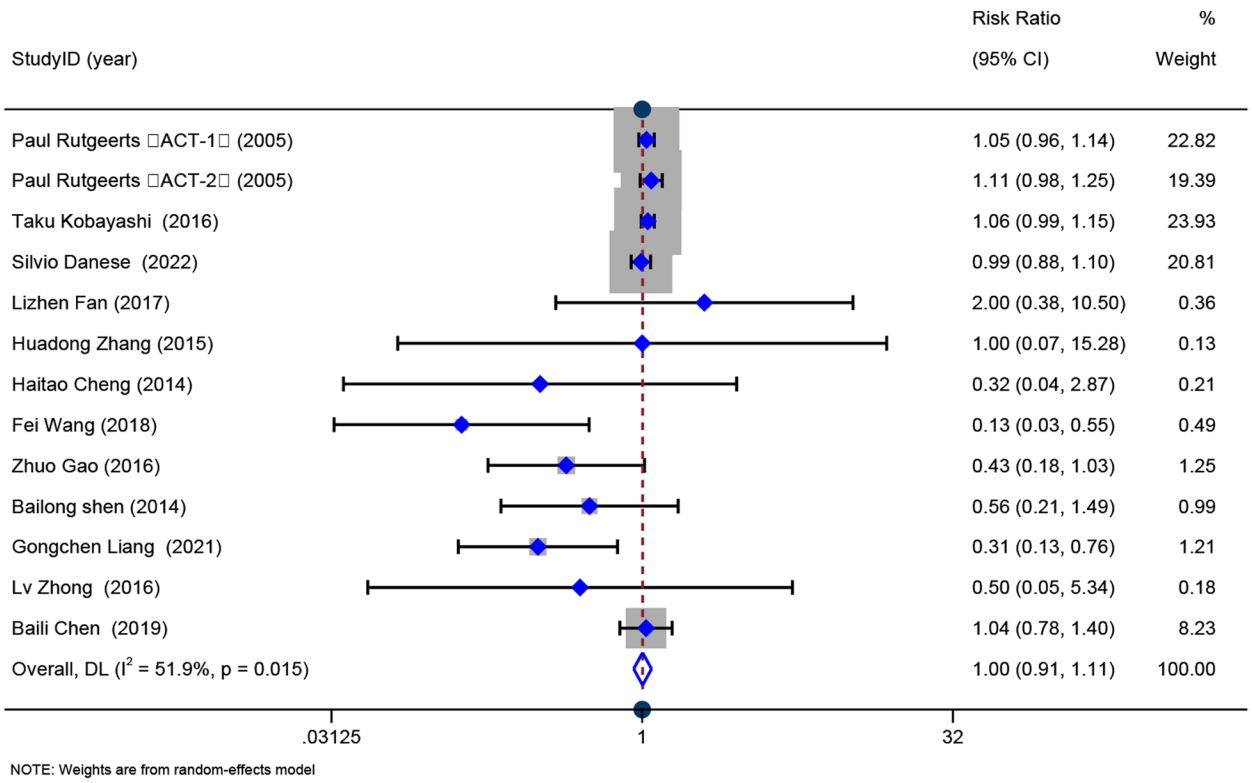

Fig. 6 Forest plot of the meta-analysis of adverse events in the two groups

moderate-to-severe active UC among adults [10]. The TNF-α inhibitor IFX was approved in 2005 as the first biologic to be formally used for the therapy of moderate-to-severe UC [43]. IFX is a human-mouse chimeric immunoglobulin G1 monoclonal antibody that achieves anti-inflammatory effects by binding to transmembrane and soluble TNF-α, blocking its binding receptors and thereby inhibiting its activity [9]. Infusion rate-induced infusion reaction adverse events are almost recognized as one of the adverse effects of IFX, including immediate infusion reaction and late infusion reaction often manifested as fever, rash, muscle or joint pain or even respiratory distress [45]. Therefore, IFX should be started at a small dose and then the infusion rate should be gradually and progressively increased until the full target rate is reached [46]. The mechanism of action of IFX is the inhibition of the production of TNF-α, which is involved in the normal inflammatory and immune responses, thereby increasing the incidence of infection. Studies have shown that IFX is an independent risk factor for serious infections and is associated with disease severity and combined use of analgesics or glucocorticoids [47]. In a Danish cohort study, it was found that 24% of patients with colitis required hospitalization due to infection during treatment and the incidence of secondary gastrointestinal infections was 16% [48]. However, one study showed that IFX, while increasing the risk of infection in patients, was associated with a reduction in mortality in patients with IBD [49]. For the development of malignancy, a systematic evaluation concluded that anti-TNF-α drugs were not associated with an increased risk of malignancy in patients with IBD [50]. Although immunogenicity-related adverse reactions are mild and easily controlled, they may lead to treatment interruption [51]. The potential adverse effects of IFX are high, but the available data suggest that the therapeutic index of IFX is advantageous for the treatment of moderate to severe IBD and that it is an effective and safe option [52]. A study by Paul Rutgeerts et al. [25] found that in the prevalence of adverse incidents, the number of worsening UC and anemia were more numerous in the placebo team than in the IFX team, whereas the number of serious infections, lupus-like reactions, and neurologic disorders was slightly higher in the IFX group than in the group receiving placebo. Therefore, regardless of the type of drug therapy, it is critical to assess the associated risks before treatment and to closely monitor the associated adverse event indicators during treatment.

In recent years, the goal of treatment for UC has evolved from clinical remission to the pursuit of

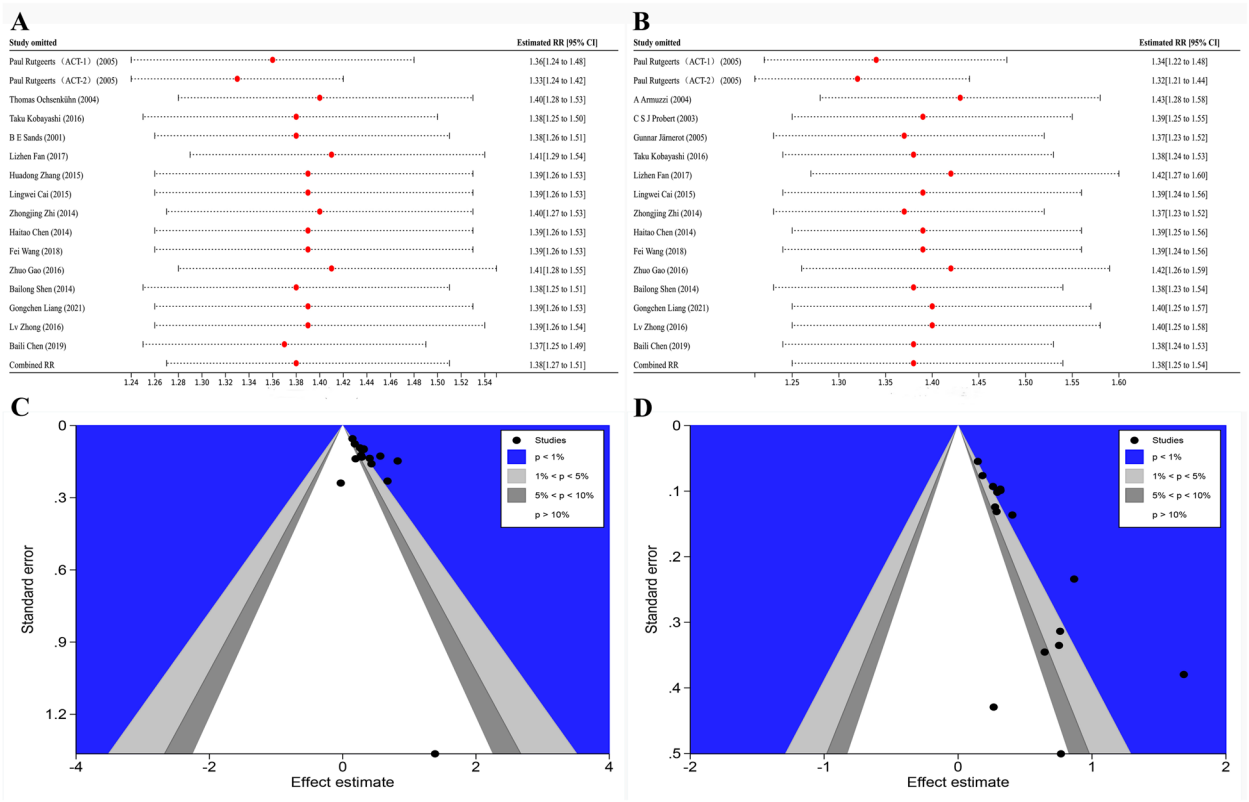

Fig. 7 Contour-enhanced funnel plot, and sensitivity analysis using the one-by-one elimination method. **A**: Sensitivity analysis of short-term clinical responses. **B**: Sensitivity analysis of short-term clinical remission. **C**: Contour-enhanced funnel plot of short-term clinical response. **D**: Contour-enhanced funnel plot of short-term clinical remission

Table 1 Results of meta-regression analysis

Covariates	Univariate analysis				Multivariate analysis		
	Exponentiated coefficient	95% CI	*P*	Tau^2	Exponentiated coefficient	95% CI	*P*
The dose of infliximab (3 mg/kg or 4 mg/kg or 5 mg/kg or 10 mg/kg or 20 mg/kg)							
short-term clinical response	−0.07	−0.14 to 0.01	0.10	0.02	−0.01	−0.08 to 0.16	0.67
short-term clinical remission	−0.01	−0.27 to 0.07	0.22	0.07	−0.1	−0.28 to 0.07	0.23
Region (multinational/Germany/Japan/USA/China/Italy/Sweden)							
short-term clinical response	0.17	0.09 to 0.26	***0.00***	0.00	0.16	0.06 to 0.26	***0.00***
short-term clinical remission	0.04	−0.08 to 0.16	0.49	0.09	0.04	−0.08 to 0.15	0.50

Significant results are shown in bold and italic

endoscopic mucosal healing up to further pathological histological remission [53]. Many clinical trials have focused on clinical response and clinical remission, and symptom presentation and inflammatory activity in patients with UC usually correlate with the extent of UC involvement [54], as the most valuable short-term goal in UC, and currently, we still decide on the treatment strategy of patients based on clinical symptoms [55]. Studies have shown that achieving endoscopic remission is strongly associated with lower recurrence rates, bowel resection rates, and cancer rates in UC [53]. A randomized controlled study showed that the degree of mucosal healing in UC treated with IFX was associated with improved clinical outcomes such as colectomy [56]. Thus endoscopic mucosal healing has become a major indicator of treatment outcome [57]. However, over the past decade, studies have found that clinical symptoms are not proportional to mucosal healing, and

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	The treatment group	The control group	Relative (95% CI)	Absolute (95% CI)		
Short-term clinical response												
16	randomised trials	serious[a]	serious[b]	not serious	not serious	none	798/1045 (76.4%)	433/800 (54.1%)	**RR 1.34** (1.15 to 1.55)	**184 more per 1,000** (from 81 more to 298 more)	⨁⨁◯◯ Low	IMPORTANT
Long-term clinical response												
6	randomised trials	not serious	serious[b]	not serious	serious[c]	none	324/652 (49.7%)	121/407 (29.7%)	**RR 1.25** (1.05 to 1.50)	**74 more per 1,000** (from 15 more to 149 more)	⨁⨁◯◯ Low	IMPORTANT
Short-term clinical remission												
17	randomised trials	serious[a]	serious[b]	not serious	not serious	none	606/1088 (55.7%)	350/841 (41.6%)	**RR 2.27** (1.82 to 2.84)	**529 more per 1,000** (from 341 more to 766 more)	⨁⨁◯◯ Low	IMPORTANT
Long-term clinical remission												
7	randomised trials	serious[a]	serious[b]	not serious	serious[c,d]	none	245/852 (28.8%)	105/611 (17.2%)	**RR 1.11** (1.04 to 1.20)	**19 more per 1,000** (from 7 more to 34 more)	⨁◯◯◯ Very low	IMPORTANT
Short-term mucosal remission												
6	randomised trials	serious[a]	serious[b]	not serious	serious[c,d]	none	421/709 (59.4%)	170/475 (35.8%)	**RR 1.05** (0.82 to 1.35)	**18 more per 1,000** (from 64 fewer to 125 more)	⨁◯◯◯ Very low	NOT IMPORTANT
Long-term mucosal remission												
3	randomised trials	not serious	not serious	not serious	serious[c]	none	108/352 (30.7%)	78/352 (22.2%)	**RR 1.15** (0.98 to 1.36)	**33 more per 1,000** (from 4 fewer to 80 more)	⨁⨁⨁◯ Moderate	NOT IMPORTANT
Adverse events												
13	randomised trials	serious[a]	not serious	not serious	not serious	none	721/1171 (61.6%)	534/930 (57.4%)	**RR 1.00** (0.91 to 1.11)	**0 fewer per 1,000** (from 52 fewer to 63 more)	⨁⨁⨁◯ Moderate	NOT IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Large biases in randomization, allocation concealment and blinding in the included studies.
b. Significant heterogeneity.
c. The sample size is small.
d. The confidence interval is wider.

Fig. 8 Outcome indicators evidence quality evaluation

some patients in clinical remission continue to have mucosal inflammation [58]. And a meta-analysis showed that the majority of patients with UC rectal bleeding and normal bowel frequency had achieved endoscopic remission, but many patients continued to have abnormal bowel frequency despite endoscopic remission [59]. There are several possible explanations for this discrepancy: 1) increased paracellular permeability due to insidious inflammation leads to irritable bowel syndrome-like symptoms in patients with remission-phase UC [60]. 2) colonic inflammation impairs the nervous system, leading to dysfunction of the colonic smooth muscle [61]. 3) activation of mast cells may lead to rectal hypersensitivity [62]. Thus, the inconsistency between clinical symptoms and endoscopic relief leads to the possibility of incomplete or overtreatment of UC. Furthermore, due to the mucosal characteristics of UC, histological healing becomes a long-term therapeutic goal for UC. However, it has been shown that approximately one-third of UC patients with endoscopic remission do not achieve histological remission because histological remission lags behind with endoscopic mucosal improvement [63]. And

the presence of histological inflammation in the presence of endoscopic mucosal remission may be an explanation for the persistence of symptoms [64].

Results from a study of the efficacy and safety of IFX monotherapy versus combination therapy versus azathioprine (AZA) monotherapy in the treatment of UC showed that the steroid-free remission rate at week 16 was 22%, 24%, and 40% in the IFX, AZA, and IFX/AZA groups, respectively. Week 8 clinical response rates were 88%, 66%, and 86% in the IFX, AZA, and IFX/AZA groups, respectively. The clinical response rates at week 16 were 69%, 50%, and 77% in the IFX, AZA, and IFX/AZA groups, respectively. The mucosal healing rates at week 16 were 55%, 37%, and 63%, respectively. For the incidence of adverse events, the IFX/AZA group was the lowest, followed by the IFX group, and the AZA group was the highest with 21.25%, 21.79%, and 34.18%, respectively. Based on the above findings, it was concluded that IFX treatment was more effective than the AZA group and the incidence of adverse events was lower than the AZA group. This is similar to the results of our study. But on the other hand, the efficacy of both IFX/AZA group was higher than IFX group and AZA group and the safety was also higher. Studies have shown that combination therapy some IBD patients are more effective [65]. A meta-analysis showed that the efficacy and safety of different combination therapies were comparable in patients with IBD. And IFX + AZA had the highest clinical remission rate and lowest adverse events [66]. Among the included studies, some studies reported longer duration of dosing, and it was found that the clinical response rate and clinical remission rate gradually decreased with the duration of dosing [25, 28, 30, 39]. And in Taku Kobayashi and Baili Chen's study, it was found that the incidence of adverse events gradually increased with the duration of treatment. In Taku Kobayashi's study, the incidence of adverse events in the IFX group was 81.7% at week 14 and 96.2% at the endpoint. A retrospective study in Japan showed that at week 12, 94.4% and 77.8% of the IFX group achieved clinical response and clinical remission, respectively, whereas at week 52, the clinical response rate and clinical remission rate in the IFX group were 76.5% and 70.6%, respectively [67]. This study is consistent with our results. However, one study reported a positive correlation between IFX concentrations and efficacy outcomes in patients with IBD [68]. Such results warrant further study.

This study focuses on the clinical benefits of IFX in patients with moderate-to-severe UC. However, the potential limitations of this meta-analysis should be noted. First, there are methodological limitations. Although all 20 included studies were RCTs, only a few were double-blind designs, and most of the rest were neither double-blind nor single-blind. In addition, the small sample size enrolled in the study may have led to selection bias and implementation bias. Additionally, no publication bias was found based on the contour-enhanced funnel plots, and we speculated that the asymmetry of the funnel plots might be due to the inferior methodological quality of the small-sample studies, the different intervention dosages, and the lack of blinding. Second, meta-regression analysis results found that the region of the original study was a potential synergistic variable, which led to significant heterogeneity of the aggregated results. The restriction to English and Chinese studies may introduce language bias, as relevant research published in other languages was excluded. This could limit the generalizability of the findings, particularly in regions where non-English or non-Chinese literature dominates the evidence base. Furthermore, the types and cases of adverse events covered in the enrolled studies were limited, and most studies reported the number of adverse incidents that occurred, so the number of patients with each specific undesirable reaction could not be extracted, which may have affected the safety evaluation of IFX. Meanwhile, the lack of individual patient data (IPD), which limits the ability to explore moderators of treatment effects. Finally, the studies did not use uniform efficacy evaluation criteria and included various comparators (placebo, steroids, 5-ASA, immunosuppressants) as control group, which led to clinical heterogeneity. All of these factors may have contributed to the instability of this analysis. Future studies on the efficacy and safety of IFX in UC treatment should involve larger cohorts and longer assessment periods to better evaluate the risk–benefit profile.

In summary, this meta-analysis, encompassing 2,350 patients from 20 studies, demonstrates that IFX has a definitive therapeutic effect in moderate-to-severe UC, with no significant increase in adverse events compared to control treatments. The findings provide evidence-based support for IFX's clinical application. However, due to inherent methodological limitations, such as variability in study designs, selection, language and reported biases, the results should be interpreted cautiously. Further validation through large-scale, multicenter, prospective RCTs with extended follow-up periods and comprehensive adverse event monitoring is warranted to strengthen these conclusions.

Abbreviations

UC	Ulcerative colitis
CI	Confidence intervals
TNF-α	Tumor necrosis factor-alpha
IFX	Infliximab
RCTs	Randomized controlled trials
RR	Relative risk
AGA	The American Gastroenterological Association

IBD Inflammatory bowel disease
AZA Azathioprine

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Not applicable.

Authors' contributions
MZ and MML performed the search and drafted the manuscript. YZO, QH and MML performed the data extraction. XDY and TY designed the study, drafted manuscript preparation and revision. YZO, QH and MML equally involved and equally contributed into the study conduction.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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