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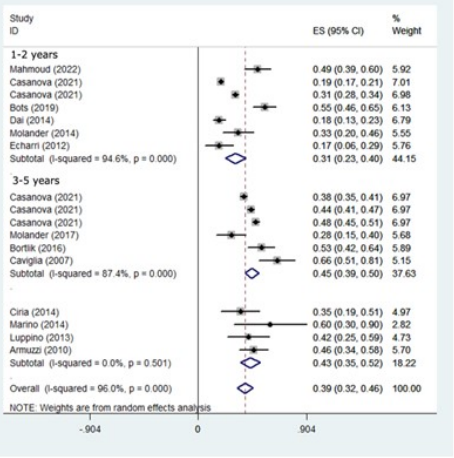

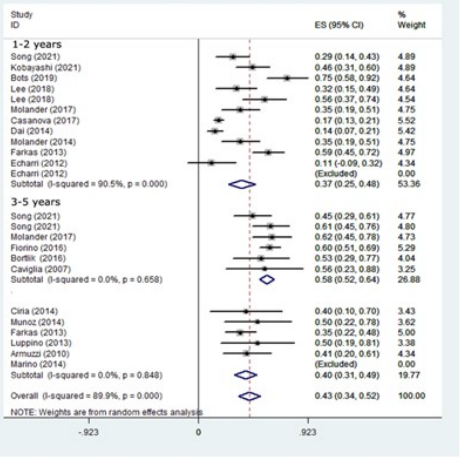

The overall risk of relapse after discontinuation of anti-TNF agent was 43% for UC and 43% for CD. In UC, the relapse rate was 37% at 1-2 year, 58% at 3-5 years. In CD, the relapse rate was 38% at 1-2 year, 53% at 3-5 years, 49% at more than 5 years.

When clinical remission was the only criterion for stopping anti-TNF agent, the relapse rate was 42% in UC and 45% in CD, which decreased to 40% in UC and 36% in CD when clinical remission and endoscopic healing were required.

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Long-term clinical outcomes after the discontinuation of anti-TNF agents in patients with inflammatory bowel disease: a meta-analysis

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ABSTRACT

Background: there are concerns regarding the risk of relapse after discontinuation of

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anti-tumor necrosis factor (anti-TNF) therapy in patients with inflammatory bowel disease (IBD). A systematic review and meta-analysis were performed to evaluate the risk of relapse after discontinuation of anti-TNF agent in patients, and the response to retreatment with the same anti-TNF agent.

Methods: electronic databases were searched to identify relevant studies. Primary outcomes were the pooled percentage of relapses after the withdrawal of anti-TNF agents. Secondary outcomes were the pooled percentage of the response to retreatment with the same anti-TNF agent after relapse.

Results: thirty-seven studies were included in this meta-analysis. The overall risk of relapse after discontinuation of anti-TNF agent was 43 % for ulcerative colitis (UC) and 43 % for Crohn's disease (CD). In UC, the relapse rate was 37 % at 1-2 year, and 58 % at 3-5 years. In CD, the relapse rate was 38 % at 1-2 year, 53 % at 3-5 years, and 49 % at more than five years. When clinical remission was the only criterion for stopping anti-TNF agent, the relapse rate was 42 % in UC and 45 % in CD, which decreased to 40 % in UC and 36 % in CD when clinical remission and endoscopic healing were required. Retreatment with the same anti-TNF agent induced remission again in 78 % of UC patients and 76 % of CD patients.

Conclusion: our meta-analysis showed that a high proportion of IBD patients will relapse after discontinuation of anti-TNF agent. The response to retreatment with the same anti-TNF agent is generally favorable in patients who relapse.

Keywords: Inflammatory bowel disease. Ulcerative colitis. Crohn's disease. Anti-TNF agents. Relapse.

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of the gastrointestinal tract (1). Anti-TNF agents including infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP), and golimumab (GOL) have demonstrated good efficacy such as clinical remission, endoscopic healing, and mucosal healing in patients with IBD (2). However, pivotal clinical trials and postmarketing surveillance studies have identified some drug-

related adverse events (2,3).

The issue of whether anti-TNF agents can be stopped in IBD patients in remission depends on some factors: a) the cost of the medications; b) the potential for serious side effects; and c) the possibility that the patient could maintain durable remission off treatment (4). A consensus expert panel convened by the European Crohn's and Colitis Organization (ECCO) reviewed the published literature and agreed a series of consensus practice points about anti-TNF withdrawal in IBD (5). The consensus points out that the risk of relapse after anti-TNF withdrawal is between 30-40 % at one year, and greater than 50 % beyond two years. Currently available data are insufficient to make recommendations on when anti-TNF agents can be stopped in patients with IBD. Therefore, the decision to discontinue anti-TNF agent is typically made on the basis of an individual judgment of benefits *vs* risks and cost effectiveness (6).

In this sense, to identify the right time and specific patients in which these drugs could be withdrawn is extremely relevant. A systematic review and meta-analysis showed that the risk of relapse after anti-TNF agent withdrawal in patients in clinical remission was 44 % in CD and 38 % in UC (7). Another systematic review and meta-analysis showed that the pooled one-year relapse rate after anti-TNF agent withdrawal in CD patients was 38 % (8). However, most of the included studies analyzed in two meta-analyses included a small number of patients and had a short follow-up time. Thus, the real long-term clinical outcomes of IBD patients after anti-TNF agent discontinuation are not well known. The aims of our meta-analysis were to evaluate the long-term risk of relapse after discontinuation of anti-TNF agent in IBD patients, and to assess the response to retreatment with the same anti-TNF agent after relapse.

METHODS

Search strategy

We systematically searched PubMed, Ovid Embase, Medline, Cochrane CENTRAL, and conference abstracts such as those of the ECCO, Digestive Diseases Week (DDW), and United European Gastroenterology (UEG) Week since an inception up to

October 2022. Search terms were “Anti-tumor necrosis factor”, “Anti-TNF”, “Infliximab”, “Adalimumab”, “Certolizumab pegol”, “Golimumab”, “IFX”, “ADA”, “CZP”, “GOL”, “Inflammatory bowel disease”, “IBD”, “Ulcerative colitis”, “UC”, “Crohn’s disease”, “CD”, “stop”, “stopped”, “discontinuation”, “discontinue”, “withdrawal” and “withdrawn”.

Inclusion criteria and exclusion criteria

Studies were included which met the criteria as follows: a) all randomized control trials (RCTs) or prospective studies or retrospective studies or cohort studies of IBD patients treated with anti-TNF agents; b) all studies describing the incidence of relapse and/or the effectiveness of retreatment with the same anti-TNF agent after discontinuation of anti-TNF in IBD patients with clinical remission or endoscopic healing; c) the anti-TNF agents were IFX, ADA, CZP, and GOL; and d) full text. The exclusion criteria were as follows: a) studies published as reviews, letters, case reports, editorials, comments, and conference abstracts; and b) studies that did not include any of the outcomes of the interest.

Data extraction

Information was extracted from each study, including baseline characteristics such as author name, year of publication, country, study type, sample size, anti-TNF agents, age, sex, type of anti-TNF (IFX, ADA, CZP, and GOL), criteria for stopping the anti-TNF agent and duration of follow-up. Primary outcomes were the pooled percentage of relapses after discontinuation of anti-TNF agents. Secondary outcomes were the pooled percentage of the response to retreatment with the same anti-TNF agent after relapse.

Statistical analysis

The data was analyzed by Stata SE 15.1; the proportion and 95 % confidence interval (CI) were used to calculate the percentage of relapses and the response to retreatment with the same anti-TNF agent. Forest plots were used to present data visually. Heterogeneity was evaluated using the Cochran’s Q test and I^2 statistics, and

p-value < 0.10 or I^2 > 50 % means the heterogeneity was significant. The random-effects model was used if heterogeneity was significant; otherwise, the fixed-effects model was adopted. Publication bias was assessed with funnel plots and Begg's test.

RESULTS

Study selection and baseline characteristics

We initially retrieved 233 unique citations from PubMed, Ovid Embase, Medline, Cochrane CENTRAL, and conference abstracts such as those of the ECCO, DDW and UEG week. One hundred and twenty-five studies were excluded in the first screening because of duplication. After reading the titles, abstracts and full-text of citations, 71 studies were excluded and 37 studies were included. The PRISMA Flow chart is shown in figure 1 and the details of the studies are shown in table 1 (7-34). A total of 18 studies focused on UC patients and 30 studies on CD patients. The anti-TNF agent was IFX in 37 studies and ADA and IFX in 13 studies. No studies assessed discontinuation of CZP and GOL. Immunosuppressors were widely used after discontinuation of anti-TNF agent. However, the dosage and duration of immunosuppressors in patients with discontinuation of anti-TNF agent were different in the included studies. Therefore, it was not possible to analyze the relapse rate in terms of whether or not immunosuppressants were administered. Nine studies evaluated the efficacy of retreatment with the same anti-TNF agent in IBD patients who relapsed after discontinuation of the drug.

Risk of relapse in IBD patients and subgroup analysis after discontinuation of anti-TNF agents

Thirteen studies evaluated relapse in 6,071 IBD patients after discontinuation of anti-TNF agents and reported a relapse rate of 39 % (95 % CI = 32-46 %; I^2 = 96 %) (Fig. 2). Eighteen studies evaluated relapse in 1,086 UC patients after discontinuation of anti-TNF agents and reported a relapse rate of 43 % (95 % CI = 34-52 %; I^2 = 89.9 %) (Fig. 3). Thirty studies evaluated relapse in 2,753 CD patients after discontinuation of anti-TNF agents and reported a relapse rate of 43 % (95 % CI = 37-50 %; I^2 = 91.1 %) (Fig. 4).

If only clinical remission was assessed, the incidence of relapse was 37 % (95 % CI = 28-46 %; I^2 = 98 %) in IBD patients. If only endoscopic healing was assessed, the incidence of relapse was 53 % (95 % CI = 42-64 %) in IBD patients. If clinical remission and endoscopic healing were assessed, the incidence of relapse was 40 % (95 % CI = 27-53 %; I^2 = 91.4 %) in IBD patients.

If only clinical remission was assessed, the incidence of relapse was 42 % (95 % CI = 22-62 %; I^2 = 95 %) in UC patients. If only endoscopic healing was assessed, the incidence of relapse was 46 % (95 % CI = 38-54 %) in UC patients. If clinical remission and endoscopic healing were assessed, the incidence of relapse was 40 % (95 % CI = 20-61 %; I^2 = 89.1 %) in UC patients.

If only clinical remission was assessed, the incidence of relapse was 45 % (95 % CI = 38-52 %; I^2 = 91.2 %) in CD patients. If clinical remission and endoscopic healing were assessed, the incidence of relapse was 36 % (95 % CI = 25-48 %; I^2 = 91.8 %) in CD patients.

Risk of relapse in IBD patients during the follow-up of 1-2 years after discontinuation of anti-TNF agents

Six studies evaluated relapse in 2,599 IBD patients during the follow-up of 1-2 years after discontinuation of anti-TNF agents and reported a relapse rate of 31 % (95 % CI = 23-40 %; I^2 = 94.6 %) (Fig. 2). Ten studies evaluated relapse in 732 UC patients during the follow-up of 1-2 years after discontinuation of anti-TNF agents and reported a relapse rate of 37 % (95 % CI = 25-48 %; I^2 = 90.5 %) (Fig. 3). Sixteen studies evaluated relapse in 1,735 CD patients during the follow-up of 1-2 years after discontinuation of anti-TNF agents and reported a relapse rate of 38 % (95 % CI = 31-45 %; I^2 = 88 %) (Fig. 4).

Risk of relapse in IBD patients during the follow-up of 3-5 years after discontinuation of anti-TNF agents

Four studies evaluated relapse in 3,332 IBD patients during the follow-up of 3-5 years after discontinuation of anti-TNF agents and reported a relapse rate of 45 % (95 % CI = 39-50 %; I^2 = 87.4 %) (Fig. 2). Five studies evaluated relapse in 247 UC

patients during the follow-up of 3-5 years after discontinuation of anti-TNF agents and reported a relapse rate of 58 % (95 % CI = 52-64 %; I^2 = 0 %) (Fig. 3). Eight studies evaluated relapse in 443 CD patients during the follow-up of 3-5 years after discontinuation of anti-TNF agents and reported a relapse rate of 53 % (95 % CI = 47-58 %; I^2 = 33.7 %) (Fig. 4).

Risk of relapse in IBD patients in the follow-up of more than five years after discontinuation of anti-TNF agents

Six studies evaluated relapse in 219 CD patients more than five years after discontinuation of anti-TNF agents and reported a relapse rate of 49 % (95 % CI = 27-70 %; I^2 = 90.9 %) (Fig. 4).

Efficacy of retreatment with the same anti-TNF agent after relapse

Retreatment with the same anti-TNF agent in IBD, UC, and CD patients who relapsed after discontinuation of anti-TNF agent induced remission in 85 % (95 % CI = 76-94 %; I^2 = 87.2 %; 420 patients) (Fig. 5), 78 % (95 % CI = 68-89 %; I^2 = 92.5 %; 840 patients), and 76 % (95 % CI = 67-84 %; I^2 = 95.3 %; 2,040 patients) of patients, respectively.

Publication bias

A funnel plot was performed to assess the publication bias. The Deeks' test revealed no evidence of publication bias (p = 0.202, p = 0.061, p = 0.127). The results did not significantly change when the analysis of robustness was performed.

DISCUSSION

In our study, the risk of relapse in IBD patients who discontinued anti-TNF agents after achieving clinical remission, endoscopic healing, and both clinical remission and endoscopic healing reached 37 %, 53 %, and 40 %, respectively. Consequently, even IBD patients in both clinical remission and endoscopic healing after discontinuing anti-TNF agents may relapse eventually. In this respect, it should be taken into account that IBD patients would be expected to experience flares, even with excellent disease control such as endoscopic healing.

In our meta-analysis of UC patients, the overall relapse rate after discontinuation of anti-TNF agent was 43 %; the relapse rate for CD patients was slightly lower (43 %). Some studies did not find evidence of a higher relapse rate in patients with fistulizing or luminal CD when both disease phenotypes were assessed in the same study (22-24). Some studies found that discontinuation of IFX was relatively successful in luminal CD, with a cumulative probability of being free of relapse of 70 % at one year in contrast with perianal disease (27). A study by Brooks AJ also found that 58 % of CD patients with luminal disease remained in steroid-free complete remission after discontinuation of IFX *vs* fistulas remained closed in only 35 % of CD patients (23). Larger sample controlled studies should be performed to conclude whether perianal and luminal CD are to be managed differently with respect to the discontinuation of anti-TNF agent.

Our meta-analysis also showed that when discontinuation of anti-TNF agent was based exclusively on the achievement of clinical remission, 42 % of UC patients relapsed during the follow-up. However, if patients discontinued anti-TNF agents after achieving both clinical remission and endoscopic healing, the relapse rate decreased to 40 %. Similar differences were observed for CD patients, and these differences were more significant. Therefore, endoscopic healing is probably a major factor that must be evaluated when considering discontinuation of anti-TNF agents. However, some studies were not able to demonstrate a correlation between endoscopic remission at discontinuation and the frequency of or the time to relapse, either in CD or in UC patients (20,34). Therefore, future prospective studies will need to clarify this issue.

There are some other factors which can affect the risk of relapse after discontinuation of anti-TNF agents. Clinical features such as smoking habit and biomarkers such as C-reactive protein, anti-*Saccharomyces cerevisiae* antibodies, fecal calprotectin and anti-TNF trough levels have been associated with a higher risk of relapse after discontinuation of anti-TNF agents (15). However, these factors could not be studied in our meta-analysis.

Our meta-analysis showed that retreatment with the same anti-TNF agent in IBD patients who relapsed after discontinuation was very effective, inducing remission in

85 % of IBD patients (78 % of UC patients and 76 % of CD patients). A possible explanation for this finding could be the fact that the high efficacy of retreatment with anti-TNF agents in patients who relapsed may reflect the fact that the patients treated with these drugs are a selected group that was previously identified as anti-TNF responders.

The strength of our study is that a large number of IBD patients who discontinue anti-TNF agents during long-term follow-up (> 5 years) were included in this meta-analysis. At the same time, there were limitations in our meta-analysis. First, the retrospective design of most of the included studies should be interpreted with caution. Furthermore, the meta-analysis is based on uncontrolled studies, as no randomized controlled studies have evaluated the treatment withdrawal strategy as a management option in patients with IBD. Second, the results of this meta-analysis were sometimes heterogeneous. Much of this heterogeneity disappeared in subgroup analyses based on some of these variables, although some remained unexplained. However, we cannot perform subgroup analysis according to the type of anti-TNF agents such as IFX and ADA. Third, given the limited information for the included studies, we were not able to assess the role of some biomarkers such as C-reactive protein, fecal calprotectin, and anti-TNF trough levels as risk factors for relapse after discontinuing anti-TNF agents.

In conclusion, our meta-analysis showed that a high proportion of IBD patients in remission with anti-TNF agents will relapse after discontinuation of the drug. At the same time, we found that response to retreatment with the same anti-TNF agent is generally favorable in patients who relapse. Therefore, discontinuation of anti-TNF agents cannot be considered as a globally advisable strategy for all IBD patients in routine clinical practice.

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Table 1. Characteristics of included studies

Author	Year	Country	Study type	Mean age	Female	Anti-TNF agents	Remission	Follow-up
Mahmoud	2022	Netherlands	A multicenter, prospective study	40.2 (29.7-53.1)	42 (51.9)	IFX, ADA	CR and EH	2.0 (1.6-2.1) years
Song	2021	Korea	A retrospective multicenter cohort study	26.0 (20.0-37.0)	36 (33.0)	IFX, ADA	EH for UC, CR for CD	5 years
Kobayashi	2021	Japan	A multicenter, open-label randomized controlled trial	NA	NA	IFX	EH for UC	48 weeks
Casanova	2021	Spain	An observational, retrospective, multicenter study	CD: 29 (6-76); UC: 35 (9-71)	CD: 382 (52.3); UC: 147 (45.4)	IFX, ADA	CR	34 months
Bots	2019	Netherlands	A single-center observational cohort study	CD: 43 (34-53); UC: 48 (33-57)	CD: 50 (65 %); UC: 16 (67 %)	IFX, ADA	CR and EH	2 years
Reenaers	2018	France and Belgium	A prospective multicenter cohort study	32 (25-39)	43 (42)	IFX	CR	7 years
Lee	2018	Korea	Retrospective study	UC: 39.7 + 15.7; CD: 25.3 + 7.9	UC: 19 (67.9); CD: 5 (29.4)	IFX	EH for UC, CR for CD	UC: 41 (8-109) months CD: 141 (66-262) months

Molander	2017	Finland	A prospective multicenter study	UC: 32 (13-58); CD: 33 (15-52)	24	IFX, ADA	EH for UC, CR for CD	36 (31-41) months
Casanova	2017	Spain	A retrospective, observational, multicenter study	42 (17-85)	529 (50.1)	IFX, ADA	CR	19 (6-176) months
Brooks	2017	UK	Prospective study	23 (8-70)	51	IFX, ADA	CR and EH	510 (365-2,160) days
Fiorino	2016	European countries	A multicenter retrospective cohort study	35.7 (28.1-46.5)	NA	IFX	CR	4.7 (1.9-7.4) years
Bortlik	2016	Czech Republic	A prospective observational study	UC: 38 (18-73); CD: 31 (16-65)	47	IFX, ADA	EH for UC, CR and EH for CD	30 (7-47) months
Annunziata	2014	NA	Retrospective study	NA	NA	IFX	CR and EH	NA
Chauvin	2014	France	Retrospective study	23 (19-33)	57 (62 %)	IFX	CR	NA
Ciria	2014	NA	Retrospective study	NA	NA	IFX, ADA	CR	NA
Dai	2014	China	Prospective study	UC: 31 (12-57); CD: 26 (14-63)	127	IFX	CR and EH	1 year
Dart	2014	UK	Retrospective study	32 (17-61)	33	IFX	CR and EH	25 (19-35) months

Felice	2014	NA	Retrospective study	NA	NA	IFX	NR	NA
Marino	2014	NA	Retrospective study	NA	NA	IFX	CR and EH	NA
Molander	2014	Finland	Prospective study	CD: 22 (13-42); UC: 26 (8-45)	24	IFX, ADA	CR and EH	12 months
Munoz	2014	NA	Prospective study	NA	NA	IFX	CR and EH	NA
Ramos	2014	NA	Retrospective study	NA	NA	IFX, ADA	CR	NA
Farkas	2013	Hungary	Prospective study	31 (17-60)	28	IFX	CR	12 months
Luppino	2013	NA	Retrospective study	NA	NA	IFX	CR and EH	NA
Molnar	2013	Hungary	Prospective study	25.4 (8-67)	64	IFX, ADA	CR	14 months
Echarri	2012	NA	Retrospective study	NA	NA	IFX, ADA	CR and EH	NA
Louis	2012	France	Prospective study	32 (26-39)	66 (57 %)	IFX	CR	28 + 2 months
Lu	2012	Canada	Retrospective study	30 (14-47)	6	IFX	CR	8.1 + 2.6 years
Steenholdt	2012	Denmark	Retrospective study	CD: 25 (21-33); UC: 26 (21-36)	36	IFX	CR	1,153 (0-2,312) days
Crombe	2011	France	Retrospective study	14.5 (12-16)	66 (55 %)	IFX	CR	120 months
Armuzzi	201	NA	Retrospective	NA	NA	IFX	CR	NA

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	2010		Retrospective study					
Nuti	2010	NA	Retrospective study	NA	NA	IFX	CR	NA
Waugh	2010	Canada	Retrospective study	25 + 1.4	26	IFX	CR	4.1 (0.5-6.7) years
Guidi	2008	Italy	Retrospective study	35 (25-57)	1	IFX	CR	28 + 16 years
Wynands	2008	France	Retrospective study	10.3 + 2.5	15	IFX	CR	12 months
Caviglia	2007	Italy	Retrospective study	47.7 + 15.6	27	IFX	CR and EH for UC, CR for CD	60 months
Domenech	2005	Spain	Retrospective study	28.8 (14-52)	14	IFX	CR	50 months

IFX: infliximab; ADA: adalimumab; CP: certolizumab pegol; GOL: golimumab; UC: ulcerative colitis; CD: Crohn's disease. Criteria of clinical remission (CR): UC: a total Mayo score of ≤ 2 points, with no individual subscore exceeding 1 point; CD: CDAI of ≤ 150 points. Criteria of endoscopic healing (EH): UC: Mayo < 2; CD: SES-CD < 5.

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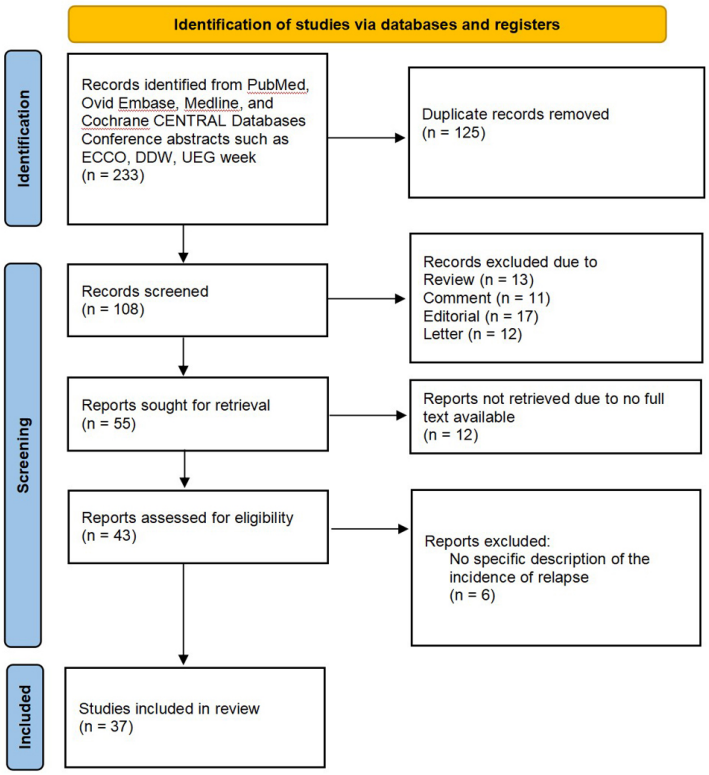

Fig. 1. A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.

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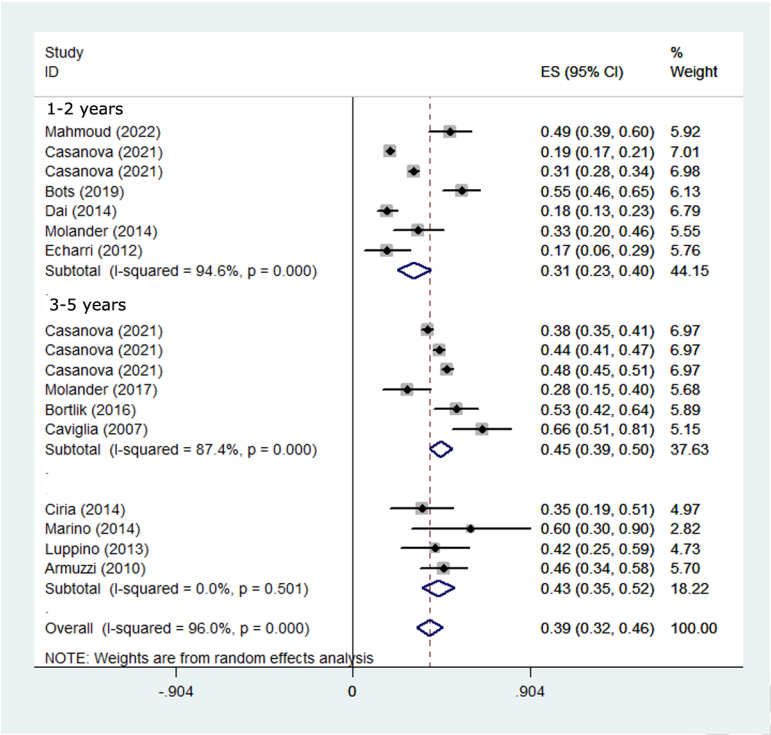

Fig. 2. Forest plot depicting the pooled relapse rate in IBD patients after discontinuation of anti-TNF agents.

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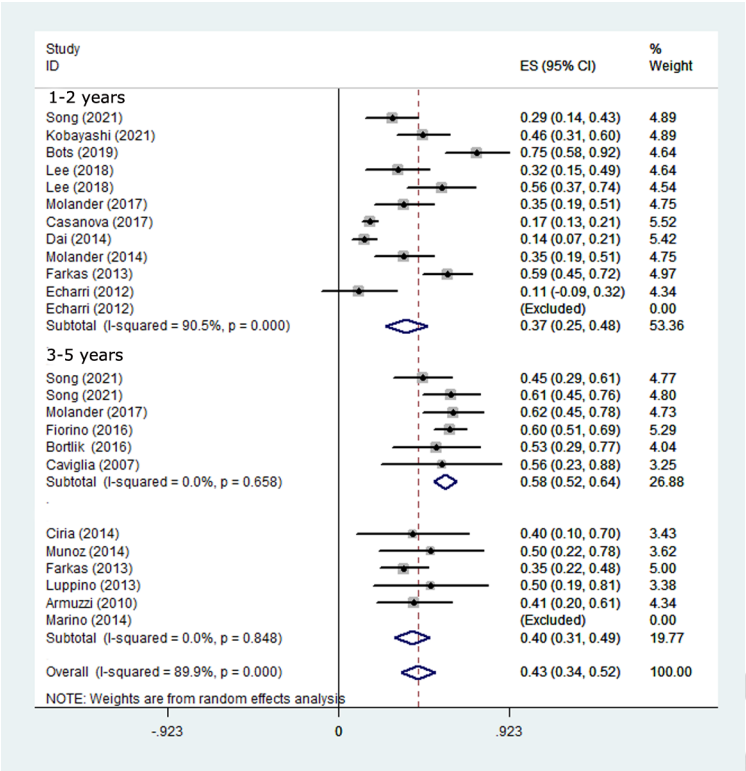

Fig. 3. Forest plot depicting the pooled relapse rate in UC patients after discontinuation of anti-TNF agents.

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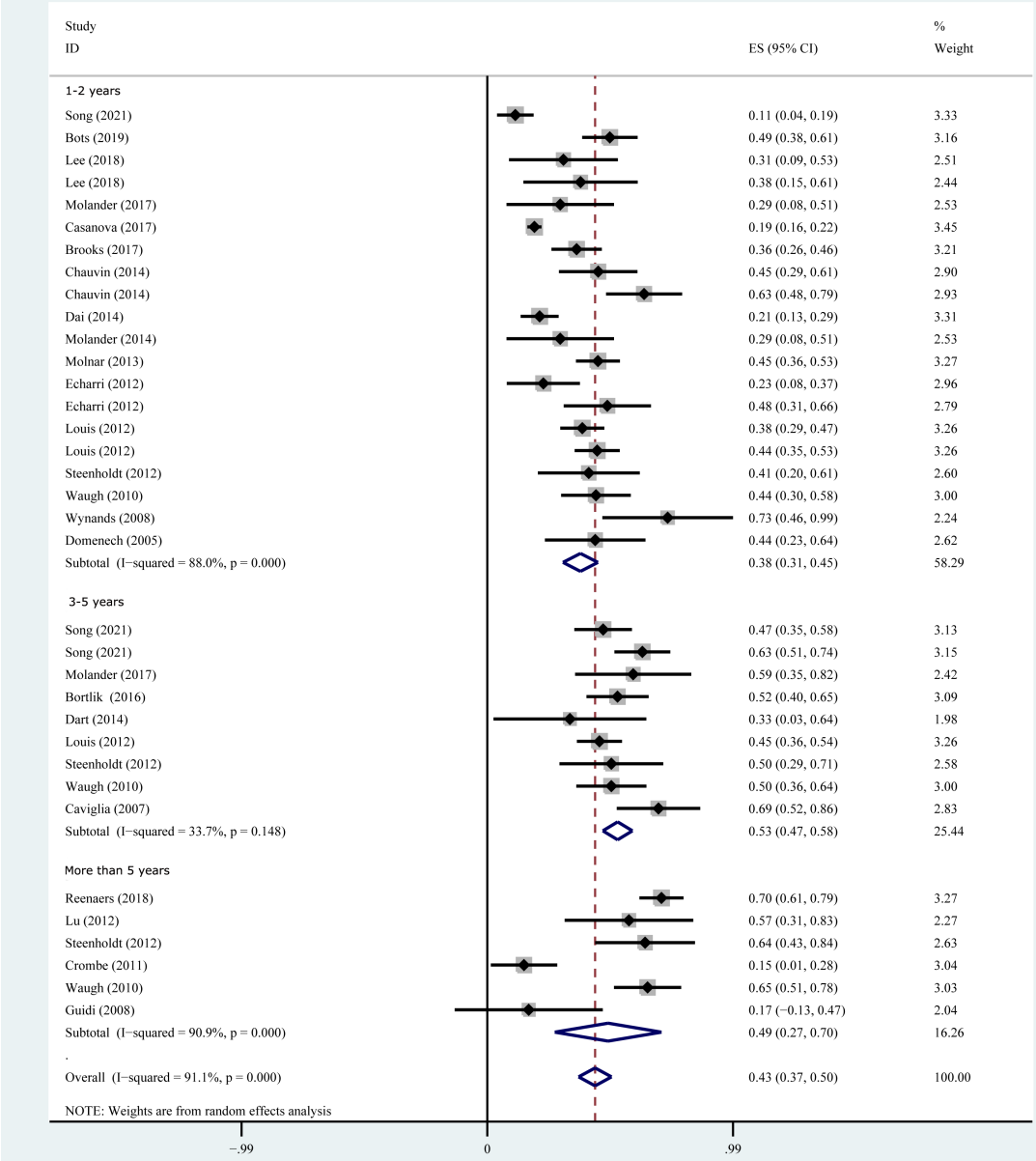

Fig. 4. Forest plot depicting the pooled relapse rate in CD patients after discontinuation of anti-TNF agents.

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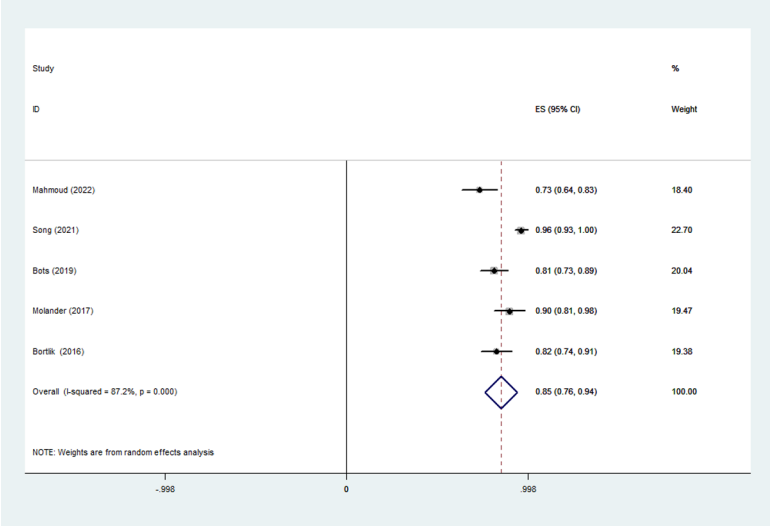

Fig. 5. Forest plot depicting the pooled remission rate in IBD patients who relapsed after discontinuation of anti-TNF agents.