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Efficacy and prognosis of adalimumab for Crohn's disease at different disease locations: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: For over ten years, adalimumab (ADA) has been approved for treating active moderate to severe Crohn's disease (CD), showing irreplaceable efficacy. However, the difference in efficacy and prognosis when the disease pathology occurs in different locations of the body is still unclear. This study used systematic meta-analysis to assess the efficacy of ADA and prognosis in CD in different locations of disease pathology.

MATERIALS AND METHODS: We used "Adalimumab OR ADA OR HUMIRA OR IgG1 monoclonal antibody" AND "Crohn disease OR Crohn's disease OR CD OR IBD OR inflammatory bowel disease" as search strategies for searching electronic databases in the Embase, PubMed and CNKI databases. A systematic meta-analysis of proportions was performed to analyze the data.

RESULTS: A total of 1,253 patients in 15 articles were included in our study. The results showed that treatment with ADA led to overall remission rates that were elevated (70%, 95% CI: 58%-79%) but a nonnegligible overall relapse rate (28%, 95% CI: 12%-53%) in patients with CD. More importantly, we indicated that the use of ADA in patients with colon only (L2), ileum and colon (L3) and upper gastrointestinal tract (L4) CD led to significantly lower clinical remission rates. The use of ADA in patients with L2 led to significantly higher relapse rates, but the use of ADA in patients with ileum only (L1) and L3 CD led to significantly lower relapse rates.

CONCLUSIONS: Our findings clarify different remission and relapse rates depending on the location of the disease pathology and may be useful for clinicians' choice of treatment strategies.

Key Words:
Adalimumab, Crohn's disease, Disease locations, Systematic review, Meta-analysis.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract, and its etiology might be a complex interaction of genetic susceptibility loci, environmental risk factors, and changes in the gut microbiome, eventually leading to a maladjusted innate and adaptive immune response[1-3]. The incidence rate of CD has been increasing in both developing and first world countries in recent decades[4]. As a debilitating and expensive disease, CD often diminishes the quality of life for patients and may cause serious psychological burden and economic pressure on patients and their families[5]. Previous studies[6,7] confirm that during relapse and remittance of chronic intestinal inflammation as symptoms of CD, patients' lives are significantly affected in that quality of life for them decreases. Thus, it is necessary to evaluate the clinical agent-related efficacy and prognosis of CD more accurately.

For over 10 years, adalimumab (ADA), as an IgG1 monoclonal antibody that targets tumor necrosis factor (TNF) α, has been approved by the Food and Drug Administration (FDA) for treating active moderate to severe CD[8,9]. As a first-line biological agent for CD, ADA has rapid onset, long efficacy, relative safety and tolerability and may even induce clinical remission in CD patients who have failed to respond to or are intolerant to infliximab (INX). Furthermore, previous studies[10,11] demonstrated that ADA was an effective treatment for inducing and maintaining long-term clinical remission and response for a faction of the CD population. Thus, it is of great importance to identify the CD patient population with potentially optimal

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efficacy and prognosis for ADA use in order to improve the quality of life of patients.

The disease location of CD includes the ileum only (L1), colon only (L2), ileum and colon (L3), and upper gastrointestinal tract (L4), which are crucial factors affecting the efficacy and prognosis of patients. Our previous study[12] confirmed that the different remission rates of INX depended on the location of the disease. However, there is still a lack of systematic analysis to clarify the differences in the efficacy and prognosis of patients who suffer from CD in different locations of pathology and are treated by ADA. This study aims to fill this gap through a systematic review and meta-analysis. This study will provide a more accurate reference for the clinical usage of ADA and encourage further research and development of new agents for patients with specific disease locations that have poor efficacy or prognosis.

Materials and Methods

Search Strategy

The systematic meta-analysis articles of the efficacy and prognosis of ADA in CD with different disease locations were searched first. When no related articles were found, we constructed a systematic review and meta-analysis of clinical trials involving CD patients treated with ADA based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses **(checklist)**. "Adalimumab OR ADA OR HUMIRA OR IgG1 monoclonal antibody" AND "Crohn disease OR Crohn's disease OR CD OR IBD OR inflammatory bowel disease" were used as search strategies for searching studies in the Embase, PubMed and CNKI databases, with no language limitations, and all included keywords used "ALL Fields" as index terms. Two of the authors (W.Y. and Z.H.) finished the review process for the reference lists of the included studies[12-14]. The last search was finished on July 15th, 2021.

Selection Criteria for Studies in this Review

All patients in the included studies suffered from CD and agreed to participate in the experimental or retrospective study regarding ADA treatment. The following studies were excluded by two authors: (1) those without clinical research; (2) those without outcomes or without detailed outcomes of patients; (3) those without specific information of the exact location of disease pathology of CD; (4) multiple articles that counted patients from the same study; (5) those that served as graduation theses, editorials, letters and only abstract[12-14].

Initial Review of Studies

First, the initial database was compiled by EndNote (version X9.3.1), and all duplicate articles were eliminated. Second, we screened these citations depending on the title and abstract, which met the inclusion criteria of the relevant studies[12]. After the full-text articles were assessed by the two authors (W.Y. and Z.H.), the final selections that met the inclusion criteria, were included in the review. Any disagreement was resolved through mutual discussion and consensus of the two authors[12-14].

Data Extraction

The data of the initial review were recorded in a standard form of data extraction by the two authors (W.Y. and Z.H.) independently. The following detailed information was collected: name of the author, publication years, number of patients, sex, age, disease location, Crohn's Disease Activity Index (CDAI), dose, concomitant medications/therapies, follow-up time, and clinical outcomes[12-14].

Assessment of Study Quality and Risk of Bias

The authors (W.Y. and Z.H.) used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the quality of the studies[15,16] (relative to risk and bias). Based on the user guide of QUADAS-2, eight items were addressed in this meta-analysis. In domain 1 (Patient selection), the item "Was a case-control design avoided?" was omitted because this study is a meta-analysis of proportions. In domain 2 (index test), the items "Were the index test results interpreted without knowledge of the results of the reference standard?" and "If a threshold was used, was it prespecified?" were replaced by "Did the method part describe the criteria of outcomes and prognosis after administration?" because CD is a systemically determined disease. In domain 3 (reference standard), the item "Were the reference standard results interpreted without knowledge of the results of the index test?" was omitted. In domain 4 (Flow and timing), the item "Was there an appropriate interval between index test and reference standard?" was omitted. High risk of bias (No), low risk of bias (Yes), and uncertainty

(Unclear) were used as rating scales to assess the included research data[12,17].

Statistical Analysis

The meta package (version 4.9-2) of R software (version 4.0.5) was used to perform the systematic meta-analysis and funnel plot for the proportions (including close to 0 or 100%). Tests for homogeneity were processed by Cochran's Q test and Higgins' I^2 statistics. The data were calculated by the random-effect model when values were considered significant heterogeneity ($p \leq 0.1$ and/or $I^2 \geq 50\%$), and the data were calculated by the fixed-effect model when values were considered *to have* significant homogeneity[12,17] ($p > 0.1$ and/or $I^2 < 50\%$). The presence of publication bias was assessed using a funnel plot.

Results

Research Results and Quality Assessment

After removal of duplicates, a total of 14,270 potentially relevant articles were preliminarily included. Second, 10,830 non-research articles, 3,289 other topic articles and 3 articles with no full text were excluded. Then, 133 articles with insufficient results were removed. The detailed process of the article search is shown in Figure 1. Ultimately, 15 articles[18-32] involving 1,253 patients were included in the study. The quality assessment is shown in Table I. The clinical characteristics of the patients are shown in Table II. All included studies[18-32] described the disease location and clinical response of patients. Five articles[19,21,23,26,30] included the relapse rate of patients (Table III).

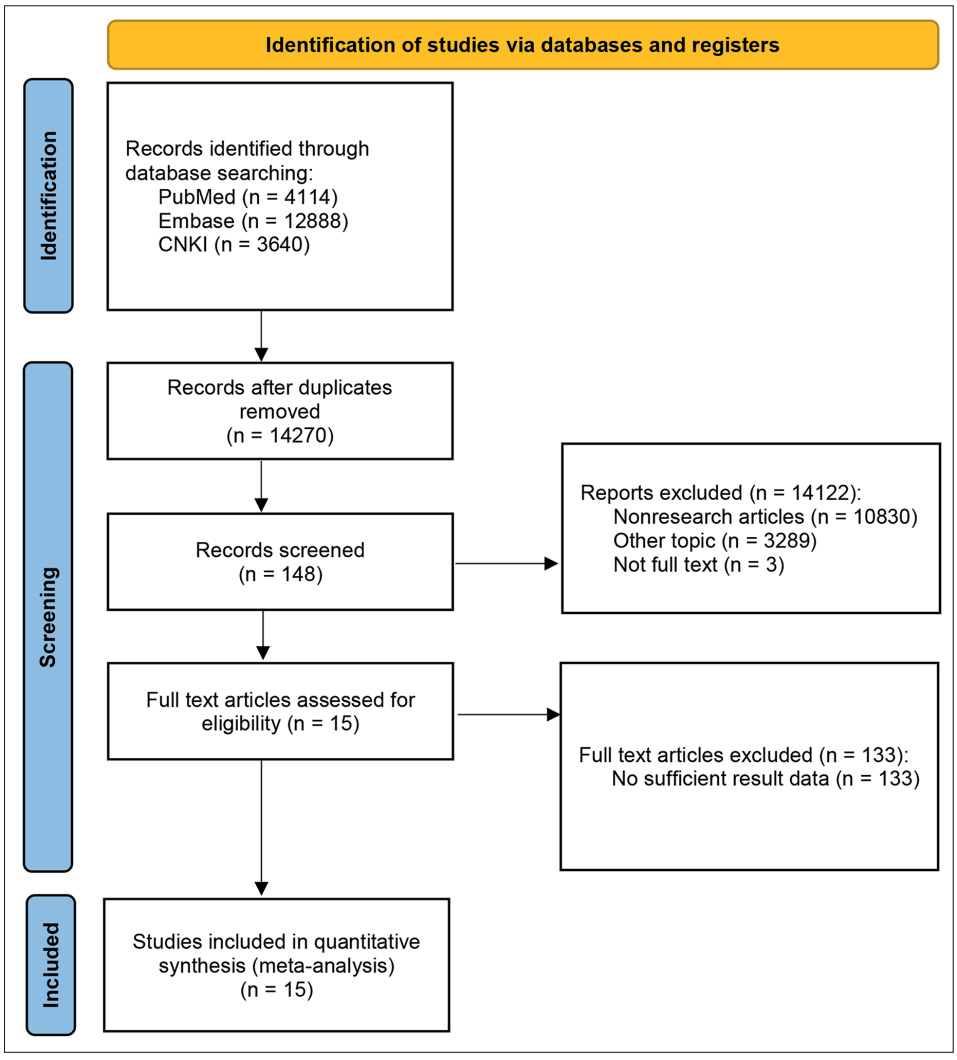

Figure 1. Flow diagram of the literature selection process.

Table I. The results of methodological quality assessment based on the QUADAS-2 tool.

Author, year	QUDAS					
	1	2	3	4	5	6
Kotze et al[18] 2014	Yes	Yes	Yes	Yes	Yes	Yes
Papamichael et al[19] 2012	Yes	Unclear	Yes	Yes	Yes	Yes
Seiderer et al[20] 2007	Yes	Yes	Yes	Yes	Yes	Yes
Savarino et al[21] 2013	Yes	Yes	Yes	Yes	Yes	No
Matsumoto et al[22] 2016	Yes	Yes	Yes	Yes	Yes	No
López-Sanromán et al[23] 2017	Yes	Yes	Yes	Yes	Yes	No
Colombel et al[24] 2017	Yes	Yes	Yes	Yes	Yes	Yes
Tonelli et al[25] 2012	Unclear	Yes	Yes	Yes	Yes	Yes
Cordero Ruiz et al[26] 2011	Yes	Unclear	No	Unclear	Unclear	Yes
Plevris et al[27] 2018	Yes	Yes	No	Unclear	Unclear	Yes
Hanauer et al[28] 2006	Yes	Yes	Yes	Yes	Yes	No
Ward et al[29] 2017	Yes	Unclear	No	Unclear	Unclear	No
Asada et al[30] 2018	Yes	Yes	Yes	Yes	Yes	Yes
Assa et al[31] 2019	Yes	Yes	Yes	Yes	Yes	No
Rismo et al[32] 2012	Yes	Yes	Yes	Yes	Yes	No

Note: Items of the modified QUADAS-2 tool used in this study: (1) Was a consecutive or random sample of patients enrolled? (2) Did the study avoid inappropriate exclusions? (3) Did the method part describe the criteria of outcomes and prognosis after administration? (4) Is the reference standard likely to correctly classify the target condition? (5) Did all patients receive the same reference standard? (6) Were all patients included in the analysis? According to the QUADAS-2 manual, each item was assessed as "yes", "no" or "unclear".

Meta-Analysis of the Clinical Remission Rate of ADA in CD Patients with Different Disease Locations

Fourteen studies[18-32] involving 1,253 patients were included in the analysis of clinical remission rates. The analysis of the overall estimate of the clinical remission rate had significant heterogeneity ($I^2 = 92\%$, $p < 0.01$); thus, the random-effect model was chosen for all subgroup analyses, and the overall estimate of the clinical remission rate was 70% (95% CI: 58%-79%, Figures 2-5). The results showed that the CD population with L1 CD, comprising more than 30% of the total CD population, had similar clinical remission rates to the CD population with L1 CD, which comprised less than 30% of the total CD population ($p = 0.8147$) (Table IV). However, CD populations with L2 CD, which comprise less than 25% (77%, 95% CI: 65%-85%), L3 CD, less than 50% (74%, 95% CI: 57%-86%), and L4 CD, less than 10% (73%, 95% CI: 62%-82%), had significantly higher clinical remission rates compared to the CD population with L2 CD, more than 25% (64%, 95% CI: 48%-77%, $p < 0.0001$), L3 CD, more than 50% (64%, 95% CI: 46%-79%, $p = 0.0014$), and L4 CD, more than 10% of the total CD population (59%, 95% CI: 29%-84%, $p < 0.0001$) (Figure 3-5, Table IV). These results indicate that the efficacy of ADA varies significantly in different disease pathology locations.

Meta-analysis of the Relapse Rate of ADA in CD patients with Different Disease Locations

Five articles[19,21,23,26,30] involving 135 patients were included in the analysis of relapse rates. The overall estimate of relapse rate was 28% (95% CI: 12%-53%, Figures 6-9), with significant heterogeneity ($I^2 = 83\%$, $p < 0.01$). Thus, the subsequent subgroup analysis was performed using a random-effect model. The results showed that CD populations with L1 CD made up more than 50% (23%, 95% CI: 2%-53%), those with L2 CD made up less than 40% (16%, 95% CI: 8%-29%), and those with L3 CD more than 40% of total CD populations (25%, 95% CI: 9%-54%) had significantly lower relapse rates compared to the CD population with L1 CD made up less than 50% (29%, 95% CI: 7%-68%, $p = 0.0029$), those with L2 CD made up more than 40% (42%, 95% CI: 18%-71%, $p < 0.0001$), and those with L3 CD made up less than 40% of the total CD population (29%, 95% CI: 2%-91%, $p = 0.0132$) (Figures 6-8, Table IV). However, the CD population with L4 CD comprising more than 0% of the total CD population had relapse rates similar to those of the CD

Table II. Clinical characteristics of patients.

Number of patients	Sex (M/F)	Age (years)†	CDAI†	Concomitant medications or/and therapy method	ADA dosages	Follow-up time	Ref
50	27/23	29.0 ± 13.1	NI	AZA (42), CS (21)	160 at 0 and 2 weeks, followed by 40 mg every 2 weeks	12 months	18
23	13/10	34.3 (17-58)	NI	AZA (10), INX (3), 5-ASA (2)	160 at 0 and 2 weeks, followed by 40 mg every 2 weeks	6 months	19
16	8/8	39.1	290	AZA (4), MP (2), 6-TG (1), MTX (1)	160 at 0 and 2 weeks, followed by 80 mg every 2 weeks	At least 6 months	20
16	8/8	45 (22-66)	268 (163- 430)	Surgery (16)	160/80 mg at 0 and 2 weeks, followed by 40 mg every 2 weeks	24 months	21
176	126/50	30.6	270.3	Elemental diet (88), 5-ASA (123), steroid use (18)	160 at 0, 80 at 2 weeks, followed by 40 mg every 2 weeks	12 months	22
45	19/26	35 (30-40)	Less than 200 (29), more than 200 (13)	Surgery (45), glucocorticoids (42), immunosuppressants (35), anti-TNFα (28)	160 at 0, 80 at 2 weeks, followed by 40 mg every 2 weeks	52 weeks	23
244	103/141	31.6	270.5	Surgeries (20), prednisone (244), AZA (244)	160 at 0, 80 at 2 weeks, followed by 40 mg every 2 weeks	48 weeks	24
12	3/9	43.5 (27-59)	NI	CS plus 5-ASA (3), 5-ASA only (5), CS only (3)	20 mg	4 weeks	25
25	10/15	38.3	208.1	Corticoids (15), AZA (11), MTX (2)	160 at 0, 80 at 2 weeks, followed by 40 mg every 2 weeks	48 weeks	26
152	80/72	36 (28-50)	NI	Immunosuppression (66)	40 mg	12 weeks	27
225	100/125	38.7	302.2	CS (98), systemic CS (60), budesonide (38)	40 mg/20 mg, 80 mg/40 mg, 160 mg/80 mg	4 weeks	28
95	52/43	37 (31-47)	NI	Immunomodulation (75)	40 mg	26 weeks	29
26	19/7	33 (19-57)	159 (74–307)	5-ASA (22), CS (2), immunosuppressant (8), INX (10), bowel resection (16), stricture plasty (4)	160/80 mg at 0 and 2 weeks, followed by 40 mg every 2 weeks	2 years	30
78	55/23	14.3 (6-18)	17.9 (10.0-27.5)	6-TG (27), MTX (7)	40 mg, 25 mg/m^2	72 weeks	31
70	38/39	36.9 (16-71)	259.6 (121-492)	CS (18), AZA/MTX (23), 5-ASA (9)	40 mg	52 weeks	32

Abbreviations: CDAI, Crohn's Disease Activity Index; NI, no information; CS, corticosteroids; ADA, adalimumab; AZA, azathioprine; INX, infliximab; 5-ASA, 5-amino salicylic acid; MP, 6-mercaptopurine; 6-TG, 6-thioguanine; MTX, methotrexate. †, Median and range.

Table III. Disease pathology locations and the response of patients.

Ref	Disease location	Clinical response	Prognosis
18	L1 (11), L2 (10), L3 (29)	44 clinical remission	NI
19	L1 (10), L2 (13)	17 clinical remission	15 relapse
20	L1 (0), L2 (3), L3 (8), L4 (5)	10 clinical remission	NI
21	L1 (9), L2 (7)	15 clinical remission	1 relapse
22	L1 (34), L2 (114), L3 (28)	114 clinical remission	NI
23	L1 (26), L3 (19), L4 (2)	38 clinical remission	22 relapse
24	L1 (35), L2 (71), L3 (129), L4 (9)	93 clinical remission	NI
25	L1 (1), L3 (6), L4 (5)	12 clinical remission	NI
26	L1 (3), L2 (8), L3 (14)	15 clinical remission	3 relapse
27	L1 (45), L2 (29), L3 (78)	105 clinical remission	NI
28	L1 (132), L2 (62), L3 (19), L4 (38)	58 clinical remission	NI
29	L1 (11), L2 (28), L3 (56)	58 clinical remission	NI
30	L1 (8), L2 (3), L3 (13), L4 (2)	24 clinical remission	5 relapse
31	L1 (42), L2 (4), L3 (32), L4 (29)	50 clinical remission	NI
32	L1 (19), L2 (24), L3 (32)	54 clinical remission	NI

Abbreviations: NI: no information.

population with no L4 CD of the total CD population. ($p = 0.6443$), respectively (Figure 9, Table IV). The above results showed that significant prognostic differences also existed in patients with different disease pathology locations after administration of ADA.

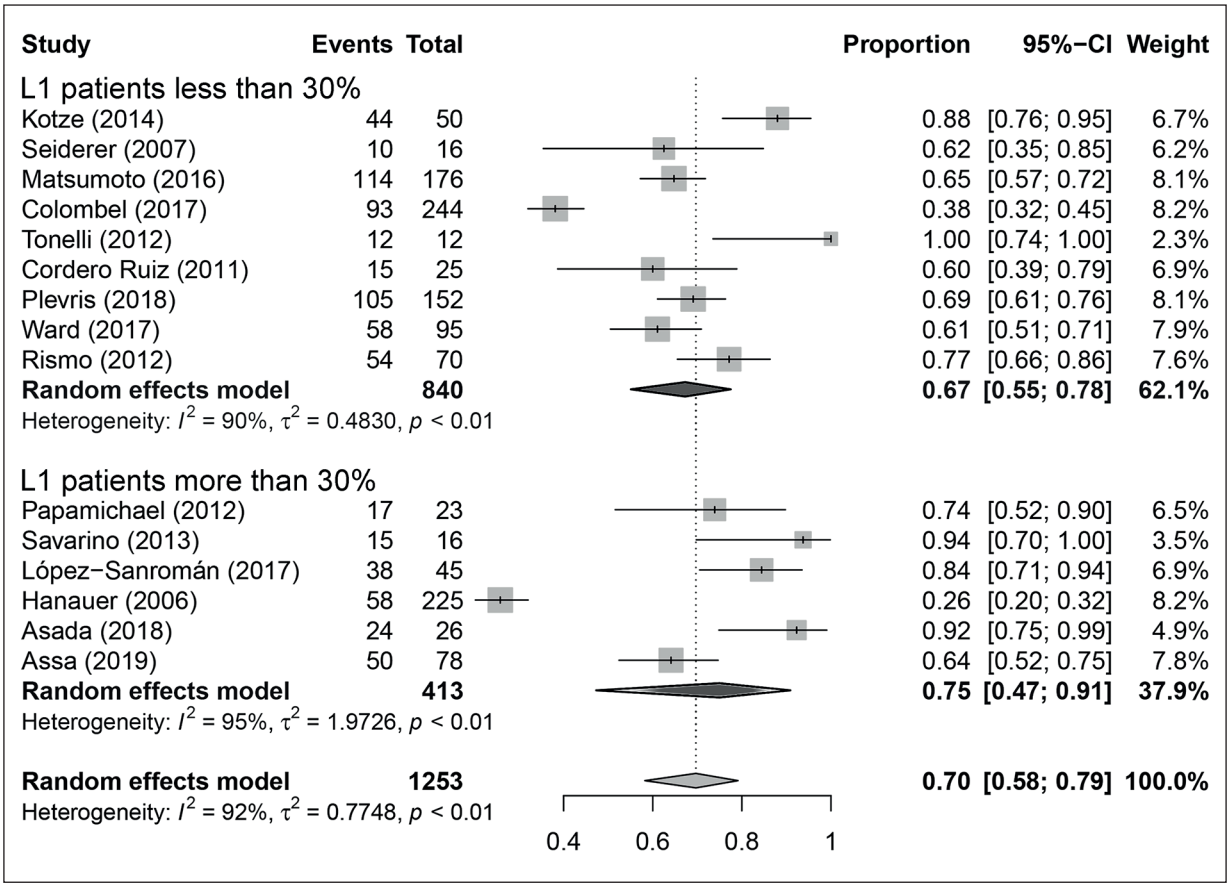

Figure 2. Forest plot of clinical remission rate and confidence intervals in groups with more than 30% and less than 30% L1 CD patients.

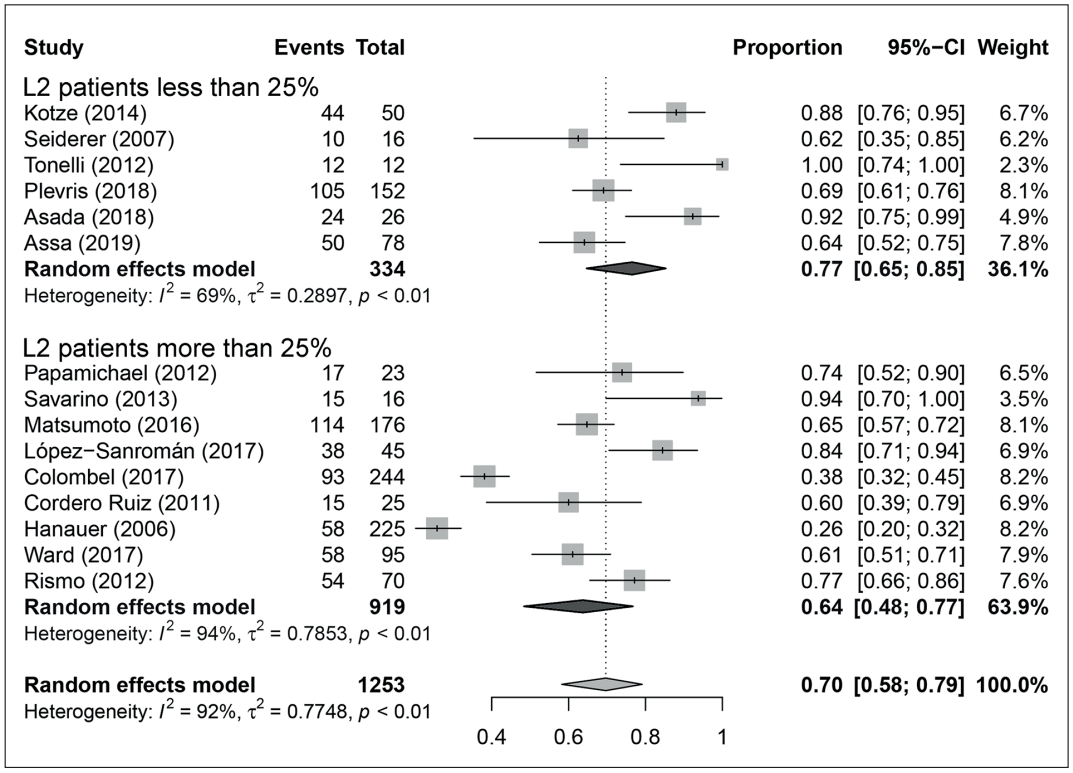

Figure 3. Forest plot of clinical remission rate and confidence intervals in groups with more than 25% and less than 25% L2 CD patients.

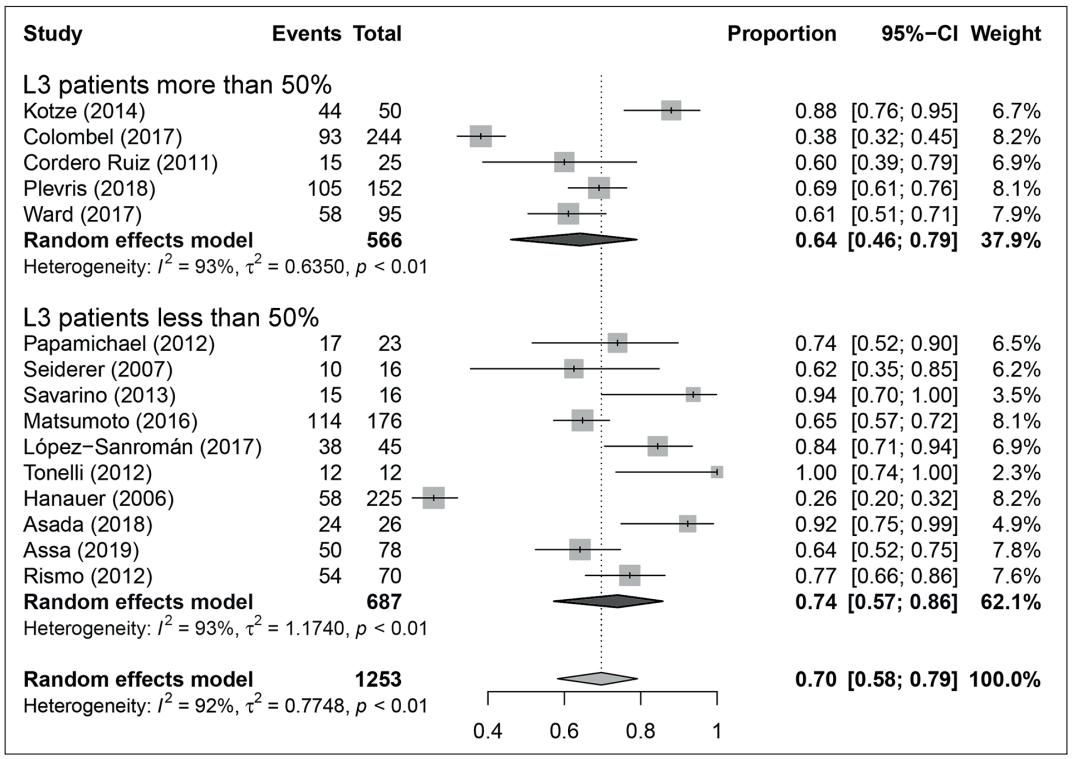

Figure 4. Forest plot of clinical remission rate and confidence intervals in groups with more than 50% and less than 50% L3 CD patients.

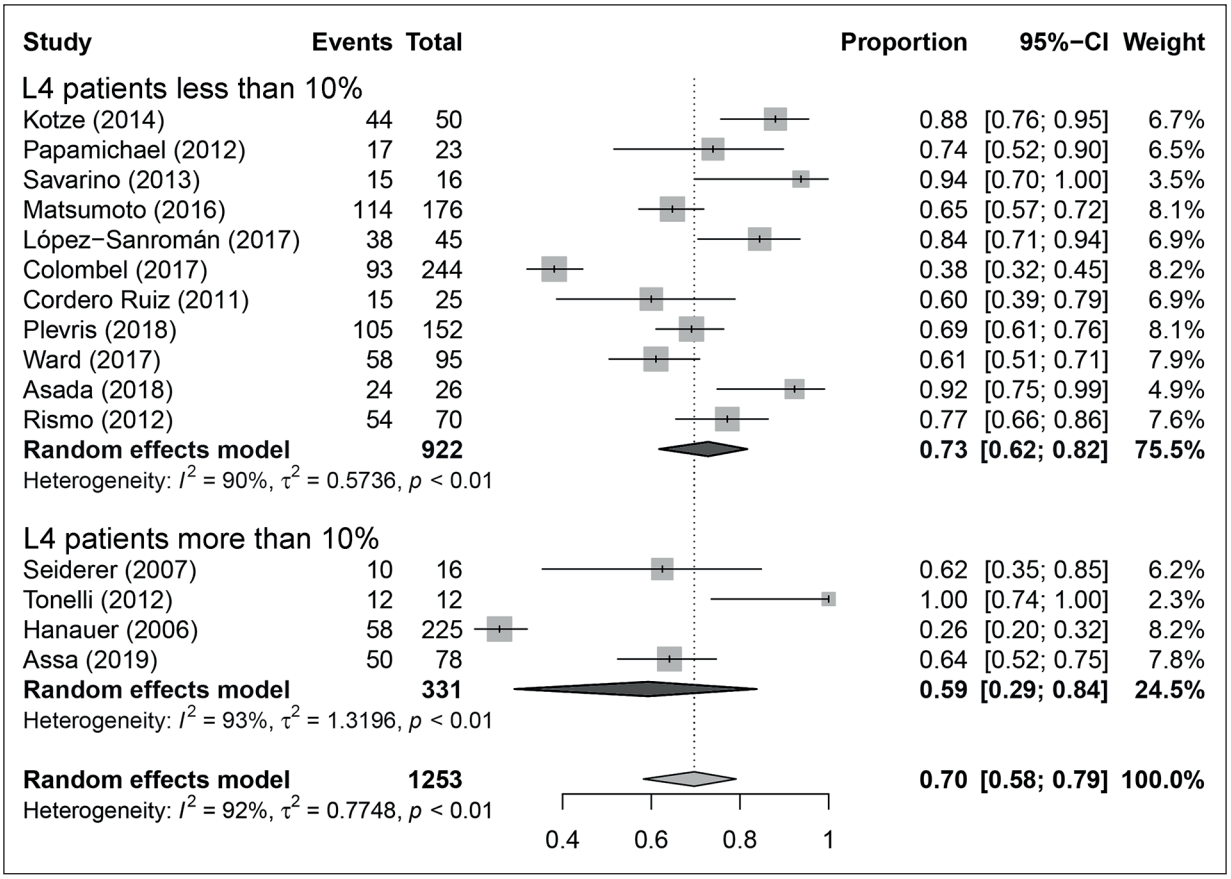

Figure 5. Forest plot of clinical remission rate and confidence intervals in groups with more than 10% and less than 10% L4 CD patients.

Publication Bias

The publication bias of the meta-analysis is revealed in funnel plots (Figure 10). In the funnel plots, the gray circle indicates the articles included in the meta-analysis, including the meta-analysis of clinical remission and relapse rates. The two dashed lines represent the 95% CI, and the two vertical dashed lines in the middle represent the total proportion.

Table IV. The results of meta-regression analysis.

Disease location	Clinical remission rete	Relapse rate	
L1	0.8147	0.0029	*p*
L2	< 0.0001	< 0.0001	
L3	0.0014	0.0132	
L4	< 0.0001	0.6443	

Discussion

CD is a recurrent chronic inflammatory gastrointestinal disease that often leads to a severe decline in quality of life and causes tremendous psychological and economic pressure on patients and their families[6,7]. This study used a systematic meta-analysis to clarify the influence of CD patients' disease locations on the clinical remission and relapse rates of ADA. The main findings of this study include that the groups with a higher proportion of L1 and L3 CD patients had lower relapse rates than the groups with a lower proportion of L1 and L3 CD patients. However, for groups with a higher proportion of L2, patients had higher relapse rates than the groups with a lower proportion of L2 patients. The groups with a higher proportion of L2, L3 and L4 CD patients had lower clinical remission rates than the groups with a lower proportion of L2, L3 and L4 CD patients.

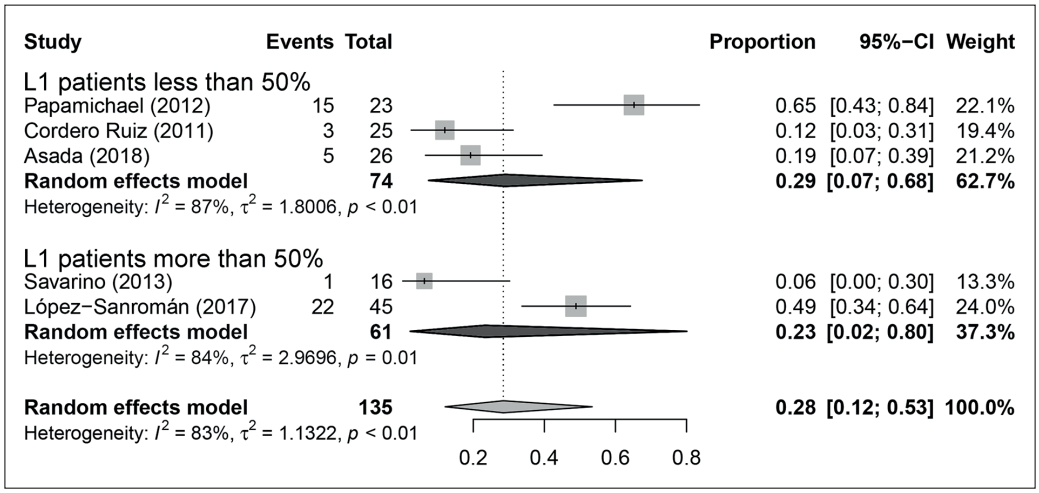

Figure 6. Forest plot of relapse rate and confidence intervals in groups with more than 50% and less than 50% L1 CD patients.

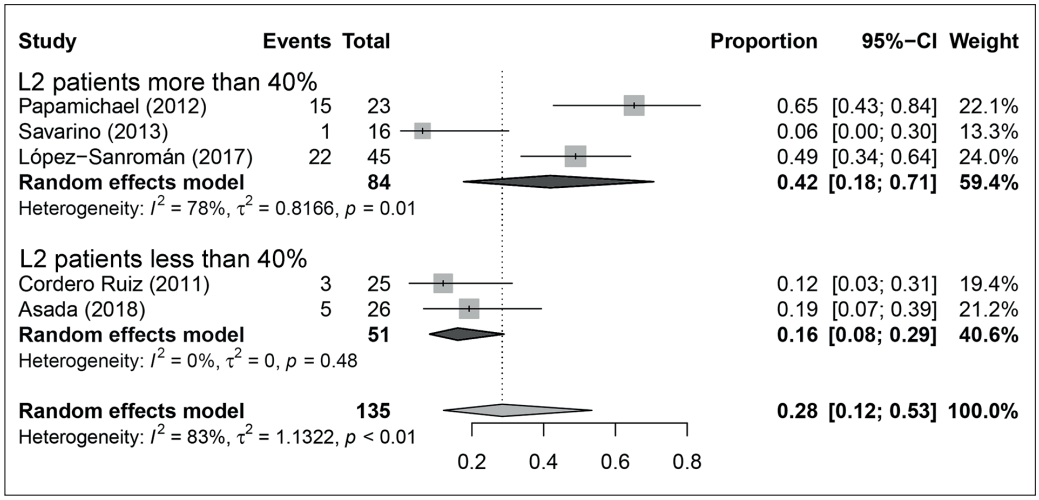

Figure 7. Forest plot of relapse rate and confidence intervals in groups with more than 40% and less than 40% L2 CD patients.

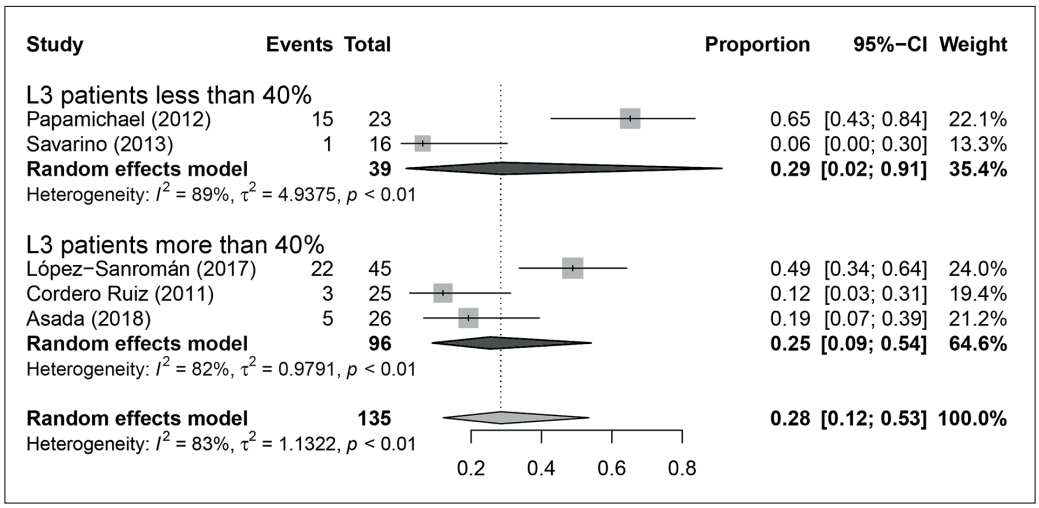

Figure 8. Forest plot of relapse rate and confidence intervals in groups with more than 40% and less than 40% L3 CD patients.

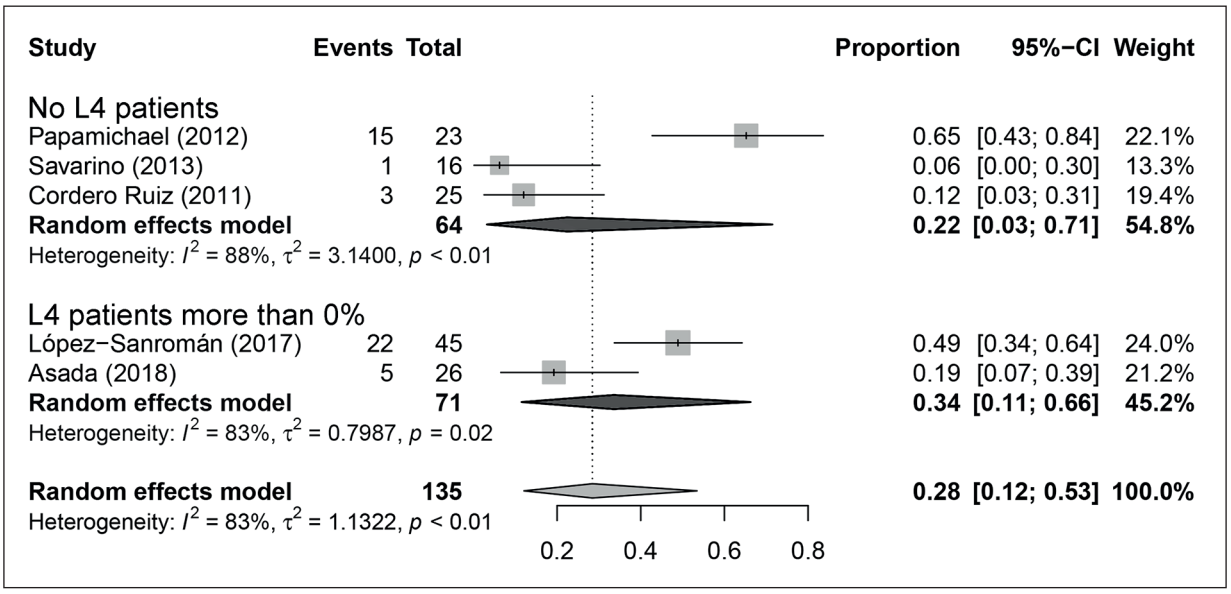

Figure 9. Forest plot of relapse rate and confidence intervals in groups with more than 0% and no L4 CD patients.

Since ADA was approved by the FDA, it has quickly become the first-line drug for CD patients because of its characteristics of fast onset, long efficacy, high safety and good tolerance. ADA has been proven to have the effect of maintaining long-term remission in CD patients[10]. However, the difference in clinical efficacy and prognosis caused by different disease locations in CD patients is still an important factor affecting drug efficacy[12]. The results of this study suggest that ADA is effective in patients with CD, but caution should be exercised as related to disease locations. L1 CD patients receiving ADA can achieve a lower relapse rate without a difference in efficacy, so they have the highest clinical benefit. In contrast, L2 CD patients have the lowest clinical benefit from ADA treatment.

L2 CD patients had poorer efficacy after administration of INX[12]. This study confirmed that L2 CD patients not only had poorer efficacy but also had poor prognosis after treatment with ADA. Therefore, drug selection for L2 CD patients should be more cautious, and the development of new anti-L2 CD agents should be encouraged. Moreover, the groups containing higher rates of L3 and L4 CD patients had poorer clinical remission rates than the groups containing lower rates of L3 and L4 CD patients after administration of ADA. However, there was no significant efficacy difference in INX treatment

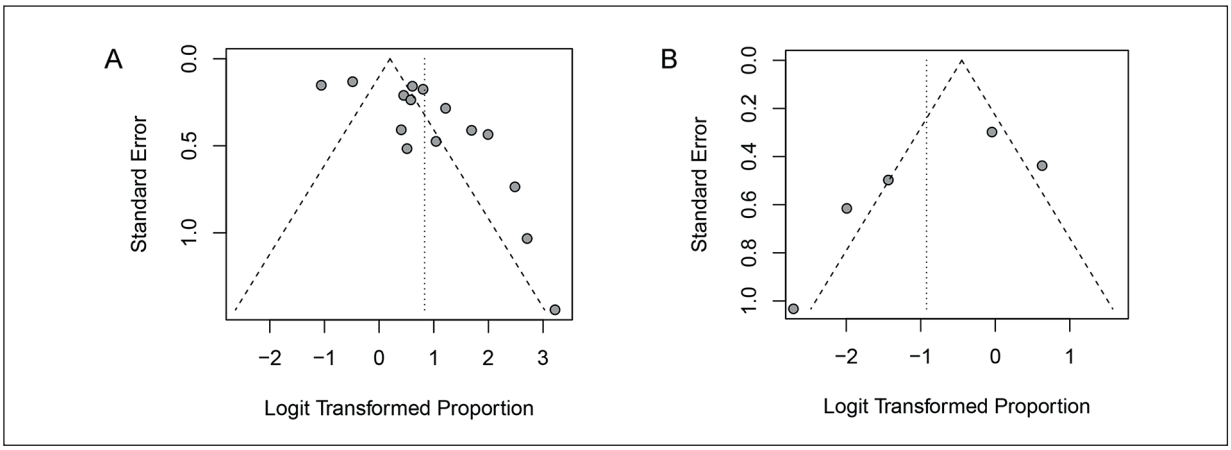

Figure 10. Funnel plots for publication bias. **A,** Overall estimate of the clinical remission rate. **B,** Overall estimate of relapse rate.

of CD between the groups with higher and lower ratios of L3 and L4 CD patients[12]. Thus, it is recommended that other drugs (including INX), combination therapy, or both be used as much as possible to improve the probability of clinical remission for L3 and L4 CD patients.

L3 CD patients often have a poorer prognosis because of the wide range of lesions. However, our results suggested that patients treated with ADA had lower relapse rates in L3 CD patients. Therefore, L3 CD patients could be recommended to be treated with ADA with comprehensive consideration. The above results provide guiding significance for the clinical administration of ADA and the prevention of relapse.

Of course, there were still some limitations in this study. First, because CD is a systemic inflammatory disease, it is inevitable that patients often have difficulty unifying the duration of disease. Although ADA is mostly used as an alternative drug for INX, whether patients use ADA in the early stage of onset may be an important factor affecting the clinical remission and relapse rates. Second, due to the differences in race, country and medical conditions of patients included in this study, there may be differences in the judgment of doctors in the process of clinical treatment, including the choice of combination therapy. Third, the usage of an elemental diet may be one of the crucial factors causing the difference in clinical remission rates and relapse rates. However, in this analysis, there is no article to clarify the usage of elemental diet.

Conclusions

We have highlighted the influence of the CD's location on the efficacy and relapse rate of ADA in CD patients. Our results may help physicians provide more personalized treatment strategy choices based on the disease location of CD patients. Our research also stimulates the development of new agents with prognoses related to disease location.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethical Statement

Ethics statement was not required since the research is a systemic review and meta-analysis of previously published studies.

Acknowledgements

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Data Availability Statement

All data generated or analyzed during this study are included in this article.

Authors' Contribution

Wenliang Yu designed the study. Wenliang Yu and Zichun Hua searched and collected the data. Wenliang Yu and Zichun Hua analyzed the results. Wenliang Yu and Zichun Hua drafted the manuscript.

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