Application of the neutrophil to lymphocyte ratio in the diagnosis and activity determination of ulcerative colitis

A meta-analysis and systematic review

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Abstract

Background: The neutrophil to lymphocyte ratio (NLR) may be a potential biomarker to evaluate the condition of ulcerative colitis (UC), but whether it can determine the activity of UC is still controversial. So we conducted this meta-analysis to study the relationship between them.

Methods: We searched the databases of Pubmed, Embase, Cochrane, Wanfang, and CNKI to collect qualified articles. Random effect or fixed effect model is used to calculate the standard mean difference (SMD) with 95% confidence interval (CI).

Results: A total of 11 articles (including 1741 participants) were included in this meta-analysis. The results showed that the level of NLR in peripheral blood of patients with UC was significantly higher than that of control group (SMD = 1.04, 95% CI = 0.71-1.36). The NLR value of active patients was significantly higher than that of inactive patients (SMD = 1.35, 95% CI = 0.87-1.83).

Conclusion: NLR may be a useful index to determine the severity and activity of UC, and it is expected to be widely used in clinical practice in the future.

Abbreviations: CI = confidence interval, NLR = neutrophil to lymphocyte ratio, SMD = standard mean difference, UC = ulcerative colitis.

Keywords: activity, meta-analysis, neutrophil to lymphocyte ratio, ulcerative colitis

1. Introduction

Ulcerative colitis (UC) is a chronic, recurrent, and idiopathic inflammatory bowel disease of unknown etiology, which is characterized by persistent inflammation of the rectal and colonic mucosa.[1,2] Early evaluation of the activity of ulcerative colitis

can determine the treatment of patients and reduce the rate of operation and mortality.[3] Endoscopy combined with pathological biopsy is a reliable method to evaluate UC, but its invasive and expensive characteristics and the related complications of invasive operation limit its application and is difficult to be used as continuous monitoring.[4] Although the specificity and sensitivity of fecal calprotectin and lactoferrin in noninvasive determination are higher than ESR and C-reactive protein, they have not been widely used in clinical practice due to their high cost and inconvenience.[5,6] Therefore, it is very important to find a cost-effective, convenient and accurate method to measure the activity of UC.

The neutrophil to lymphocyte ratio (NLR) in peripheral blood is easy to obtain and the cost is low. Recent studies have shown that NLR of peripheral blood has a certain significance in the prognosis of patients with acute heart failure and colorectal cancer, bladder cancer, breast cancer, and reflects systemic inflammation to a certain extent.[7–10] Some scholars have studied the relationship between NLR and the activity of UC, but the results are still controversial. Therefore, our aim is to explore the relationship between NLR and UC's activity in combination with published clinical studies.

2. Methods

2.1. Literature search

We conducted a literature search on the NLR of patients with UC and the control group. Two investigators (Ma and Pang)

searched the relevant articles of Pubmed, Embase, Cochrane, Wanfang, and CNKI from the establishment of the database to April 2020, and any inconsistent judgments were resolved through joint discussions. We searched "Ulcerative Colitis" and "Neutrophil to Lymphocyte Ratio" by combining key words with free words, and reviewed the references included in the literature in order to increase the comprehensiveness of the search results. Only English and Chinese articles are included.

2.2. Study selection

The studies included in this meta-analysis meet the following inclusion criteria: case-control studies; the evaluation criteria of ulcerative colitis activity are Trueloveand Witts criteria[11] or Mayo score[12]; the relationship between UC and its activity with NLR was evaluated; the study only analyzed adults. The exclusion criteria are as follows: repeated reports or articles

with insufficient information; Summaries, letters or meta-analysis; articles whose data can not be extracted. First of all, the abstract and title were screened, and the repetitive literature and those that obviously do not meet the standard were excluded. By examining the full text, the eligibility of the research that temporarily meets the eligibility criteria was further evaluated. A flow-chart of the process used for selection of the studies is presented in Figure 1. The process was independently reviewed and discussed by Ma and Pang.

2.3. Literature quality and data extraction materials

The following information was extracted from each study: first author, year of publication, country, number of participants, average and standard deviation of NLR, and criteria for judging UC activity, as shown in Table 1. Two investigators (Ma and Pang) independently extracted data from eligible articles and
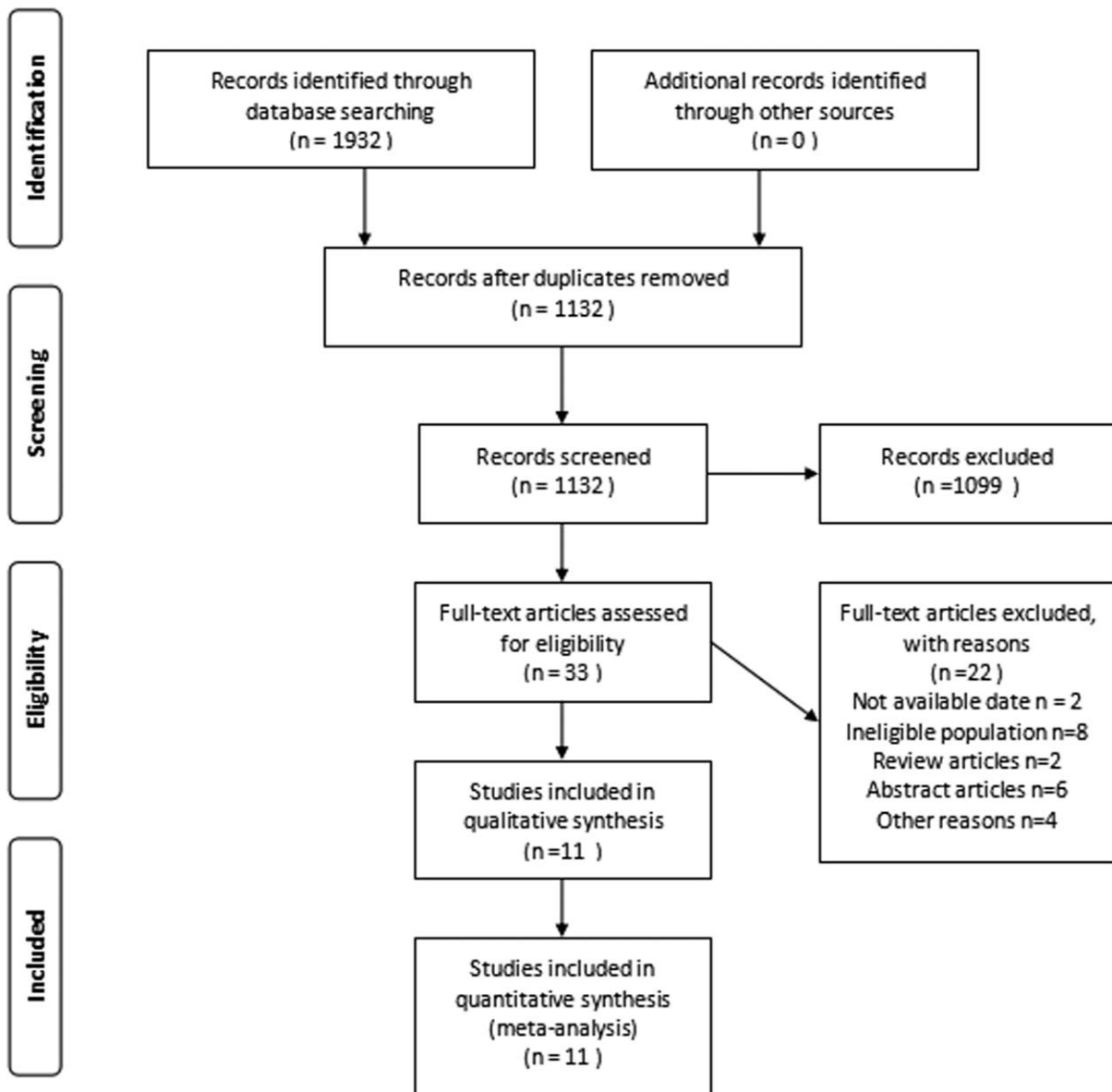

Figure 1. The process of study identification.

Table 1

General characteristics of included studies.

Author	Year	Country	Number (M/F)		NLR		Diagnostic criteria of active	Location of UC	Age of patients with UC
			UC	HC	UC	Control			
Torun et al	2012	Turkey	196 (125/71)	59 (34/25)	2.67 ± 1.29	2.01 ± 0.64	TWS	R + L + Pan	43.3 ± 13.5
Celikbilek et al	2013	Turkey	26 (18/8)	28 (10/18)	2.79 ± 1.48	1.77 ± 0.68	TWS	–	44.88 ± 13.23
Xiao et al	2014	China	80 (35/45)	60 (28/32)	3.03 ± 1.72	1.77 ± 0.66	TWS	–	47.14 ± 16.41
Acarturk et al	2015	Turkey	42 (28/14)	41 (14/27)	2.84 ± 1.66	1.68 ± 0.59	TWS	–	39.40 ± 11.15
Demir et al	2015	Turkey	71 (47/24)	140 (84/56)	2.31 ± 1.31	1.98 ± 0.85	TWS	–	46.0 ± 16.7
Jiang et al	2016	China	121 (56/65)	122 (54/68)	3.51 ± 2.51	1.58 ± 0.73	Mayo	–	53.94 ± 15.66
Hanafy et al	2018	Egypt	168 (100/68)		4.00 ± 2.38		TWS	L + Pan + P	–
Okba et al	2019	Egypt	80 (34/46)	40 (28/12)	2.13 ± 0.61	1.44 ± 0.19	Mayo	L + Pan + P	34.0 ± 9.45
Rong et al	2019	China	95 (58/37)	100 (59/41)	3.95 ± 1.83	1.54 ± 0.75	Mayo	–	48.19 ± 6.37
Tian et al	2019	China	148 (91/57)	42 (20/22)	2.73 ± 0.39	2.10 ± 0.41	Mayo	L + Pan + P	48.19 ± 14.77
Xu et al	2019	China	55 (29/26)		4.94 ± 5.41		TWS	–	43.3 ± 9.167

HC = healthy control, L = left sided, M/F = male/female, Mayo = mayo score, NLR = neutrophile to lymphocyte ratio, P = proctosigmoid, Pan = pancolitis, R = right sided, TWS = Truelove and Witts' classification, UC = ulcerative colitis.

discussed any inconsistent results. When the data of the selected article cannot be obtained, we try to send an email to consult the corresponding author. The quality of the included literature was evaluated according to the Newcastle-Ottawa scales for cross-sectional studies. High-quality studies score at least 6. This meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All analyses in the present study were based on previous published studies, thus no ethical approval and patient consent are required.[13]

2.4. Statistical analysis

We conducted a meta-analysis to explore the relationship between NLR and ulcerative colitis. In addition, we discussed whether NLR is related to the activity of ulcerative colitis. When using the TAW standard to assess UC activity, patients are classified as mild, moderate, and severe according to the number of bloody stools per day, heart rate, hemoglobin, erythrocyte sedimentation rate and body temperature. Patients with moderate or severe UC are considered to be in the active phase, while patients in the mild group are considered to be in remission. When the Mayo UC score is used to evaluate the disease activity of UC, if the score is greater than 2, the disease activity is considered; if the score = 0 to 1, the disease is considered inactive. The results are reflected in the form of standard mean difference (SMD) and 95% confidence interval (CI). We used the I^2 statistic to evaluate intra-and inter-study heterogeneity.[14] When $I^2 > 50\%$ means there was obvious heterogeneity, the random effect model was used, otherwise, we chose the fixed effect model. In order to explore the source of heterogeneity, we used age for subgroup analysis. A sensitivity analysis was conducted to delete each study to assess its impact on the stability of the results. The interpretation of funnel chart is greatly influenced by subjective judgment, so we chose Egger test to evaluate publication bias.[15] We used Stata12 software for statistical analysis. $P < .05$ was considered to be statistically significant.

3. Results

3.1. Study selection

According to our retrieval strategy, 1923 articles that may meet the criteria were initially retrieved, of which 791 articles were deleted because of repetition. After reading the titles and abstracts

of the remaining 1132 articles, 1099 unrelated articles were excluded. Among them, 33 articles have been evaluated in detail. After excluding insufficient data, conference summaries, non-activity criteria and other articles, 11 articles were finally included in our meta-analysis.[16–26] The flow chart of the screening process is shown in Figure 1.

3.2. Study characteristics

Our meta-analysis included 11 studies investigating the relationship between NLR and the activity of UC, involving 1741 patients. The 11 studies were conducted in China, Turkey, and Egypt, including 5 in China, 4 in Turkey and 2 in Egypt. We use the Newcastle-Ottawa scale to evaluate the quality of the included literature. As shown in Table 2, all the articles have a score of not less than 6, indicating good quality.

3.3. Meta-analysis of NLR in UC compared with control group

The meta-analysis included 9 studies involving 859 patients with UC and 632 patients in the healthy group. The results showed that the level of NLR in peripheral blood of patients with UC was significantly higher than that of healthy group (SMD = 1.04, 95% CI = 0.71-1.36). Because of its high heterogeneity ($I^2 = 87.1\%$), we chose the random effect model for data analysis. According to

Table 2

Assessment of study quality using the Newcastle-Ottawa scale for cohort studies.

Author	NOS selection	NOS comparability	NOS exposure	Total (max 9)
Torun et al	***	**	**	7
Celikbilek et al	***	**	**	7
Xiao et al	***	**	***	8
Acarturk et al	***	**	**	7
Demir et al	***	**	**	7
Jiang et al	***	*	**	6
Hanafy et al	****	**	**	8
Okba et al	***	**	**	7
Rong et al	***	**	**	7
Tian et al	***	**	*	6
Xu et al	***	**	***	8

the subgroup analysis of whether the age was over 40 years old, the results showed that the heterogeneity of the subgroup under 40 years old decreased significantly (SMD = 1.15, 95% CI = 0.73-1.56, I^2 = 45.0%). However, there was no decrease in heterogeneity in the subgroup older than 40 years old (SMD = 1.01, 95% CI = 0.61-1.40, I^2 = 89.8%). We conducted a sensitivity analysis, removing each study in turn, the results did not change significantly, which proved that the results were robust. In the meta-analysis conducted in this study, there was no published bias (Egger regression test P = .442). The forest plots are presented in Figures 2 and 3.

3.4. Meta-analysis of NLR in active UC patients and inactive UC patients

A total of 11 studies included meta-analysis of 745 active patients and 476 inactive patients. The results showed that the NLR value of active patients was significantly higher than that of inactive patients (SMD = 1.35, 95% CI = 0.87-1.83). Because of its high heterogeneity (I^2 = 92.2%), we chose the random effect model for data analysis. According to the subgroup analysis of whether the age was over 40 years old, the heterogeneity did not decrease in the subgroups under 40 years old (SMD = 2.10, 95% CI = 0.99-3.21, I^2 = 92.3%). There was no decrease in heterogeneity in the subgroup older than 40 years old (SMD = 1.08, 95% CI = 0.57-1.59, I^2 = 91.4%). We conducted a sensitivity analysis, excluding each study in turn, the results did not change significantly, which proved that the results were robust. In the meta analysis

conducted in this study, there was no published bias (Egger regression test P = .234). The forest plots are presented in Figures 4 and 5.

4. Discussion

UC is a chronic gastrointestinal disease characterized by persistent and diffuse inflammation of colorectal mucosa with unknown etiology. The pathogenesis of the disease may be related to immune factors, genetic factors, and so on. Determining the degree of inflammatory activity in patients with UC is of great significance in assessing the severity of the disease and making active and effective treatment plans for patients.

According to the Truelove and Witts criteria score, clinical remission is defined as having 1 to 2 stools without blood, no fever or tachycardia, normal or "return to normal" hemoglobin, normal or "return to normal" erythrocyte sedimentation rate, and weight gain. The number of intestinal motility, body temperature, tachycardia, and anemia are widely used in clinic. But the inaccuracy of these indicators lies in that the chief complaint of the patient does not always correspond to the severity of the disease. At present, colonoscopy combined with pathological biopsy is still the gold standard for judging the activity of ulcerative colitis.[27] However, colonoscopy may cause injury caused by the operation and is a contraindication to severe UC. In addition, colonoscopy does not help predict the recurrence of disease in remission patients. Therefore, it is very important to find a suitable noninvasive measurement method to avoid
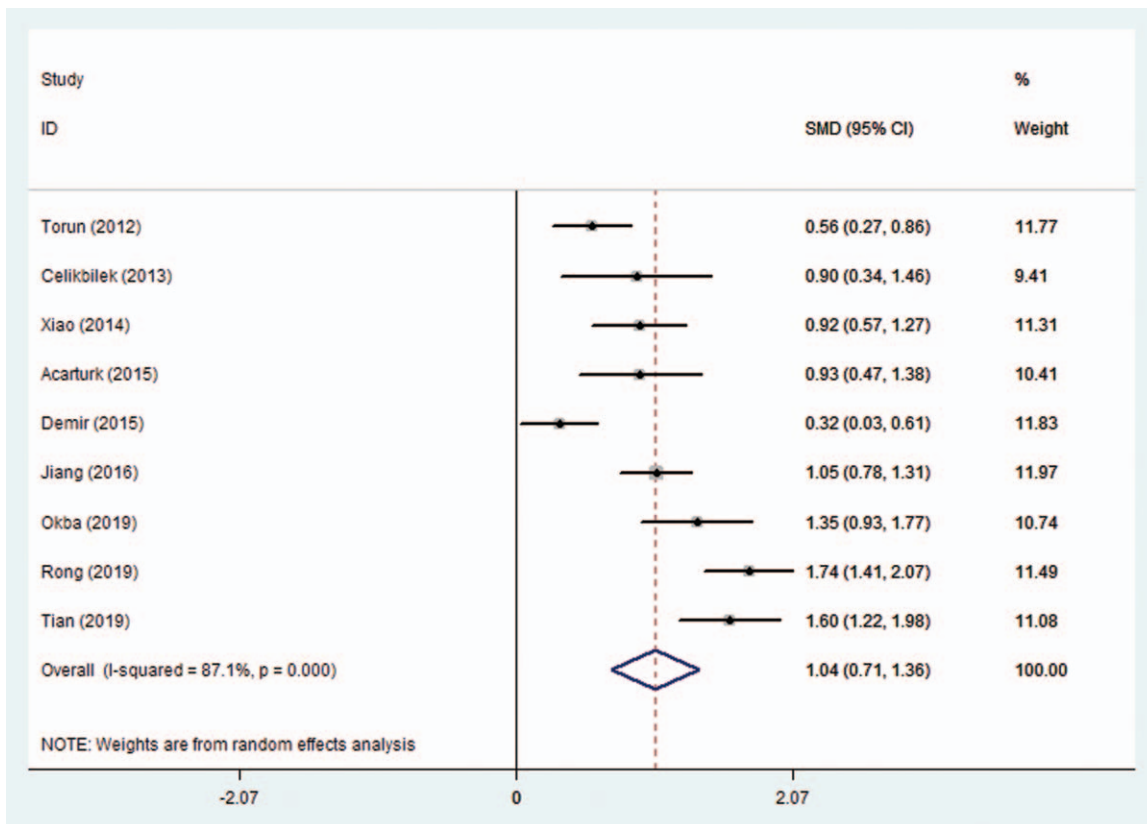

Figure 2. Meta-analysis of NLR ratio between UC patients and control group. NLR = neutrophil to lymphocyte ratio, SMD = standard mean difference, UC = ulcerative colitis.

Figure 3. Subgroup analysis of NLR ratio between UC patients and control group. NLR = neutrophil to lymphocyte ratio, SMD = standard mean difference, UC = ulcerative colitis.
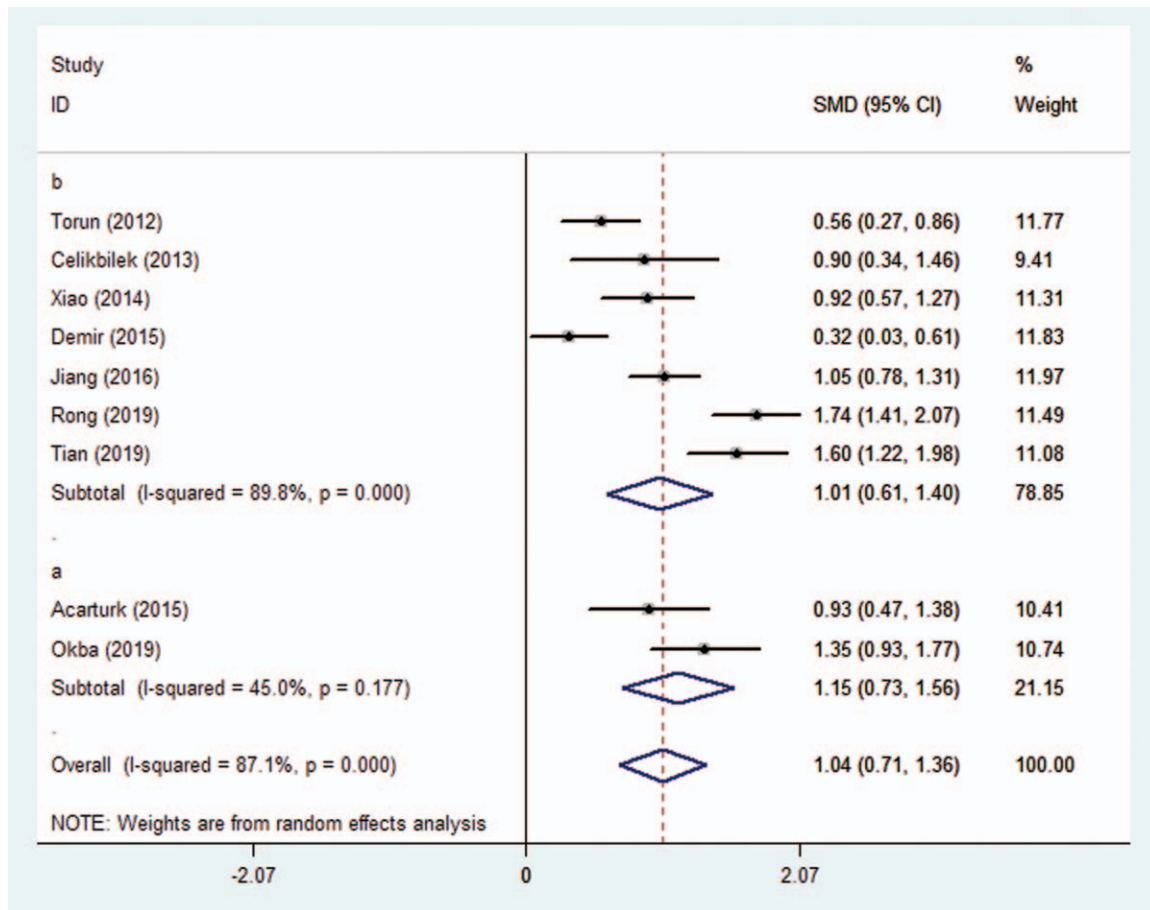
complications. There are 2 main types of noninvasive indicators commonly used in clinical practice. Among them, the traditional serological indicators (CPR, ESR, white blood cell count, etc) are most commonly used in clinic, and they can reflect the activity of inflammation. However, when there are tissue necrosis, infection, and other factors, CPR and ESR will also increase rapidly. Therefore, it is not enough to use it alone as an index to evaluate activity.[28,29] Vermeire et al[30] believe that these serological indicators should be used as a supplement to endoscopy and other examination methods, so as to play the greatest role, rather than an alternative method. In addition, fecal markers (fecal calprotectin and lactoferrin) have high sensitivity and specificity in judging the activity of UC, which is an ideal noninvasive biomarker of UC activity in clinic. However, due to its high cost, long sample processing time and inconvenient sample collection, its clinical application is limited.[31]

NLR is a simple and economical indicator of systemic inflammatory load. It is widely used in the prognosis evaluation of many kinds of tumors, such as colorectal cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, and so on.[32–35] In addition, in the study of Celikbilek et al,[17] it was also found that NLR is related to the activation of ulcerative colitis. Recent studies have shown that NLR is significantly increased in patients with active ulcerative colitis.[36] Some

studies have shown that not only the average NLR of patients with ulcerative colitis is significantly higher than that of the healthy group, but also the NLR of patients with active UC is significantly higher than that of patients with inactive UC.[18,25] On the contrary, some studies hold different views. In a retrospective case-control study of Cherfane, NLR can effectively distinguish active UC from the control group, but not inactive UC.[37] We carried out this meta analysis, according to the existing disputes, This meta-analysis shows that NLR is a reliable inflammatory marker to reflect the disease status and evaluate the activity of UC. Our results showed that the NLR of UC patients was significantly higher than that of the control group, and the NLR of active UC patients was also significantly higher than that of inactive UC patients. All the included literatures reported a significant increase in NLR in patients with UC, which increased the credibility of our results. The results we have obtained can be explained. Neutrophils play an important role in the occurrence and development of ulcerative colitis and are important intestinal mucosal infiltrating cells.[38] The role of neutrophils in the pathogenesis of ulcerative colitis is twofold. On the one hand, neutrophils are the main cells involved in active nonspecific response to inflammation. Ulcerative colitis occurs neutrophil aggregation and abscess formation on the apical epithelial surface of the intestinal recess, which is the main pathological feature of
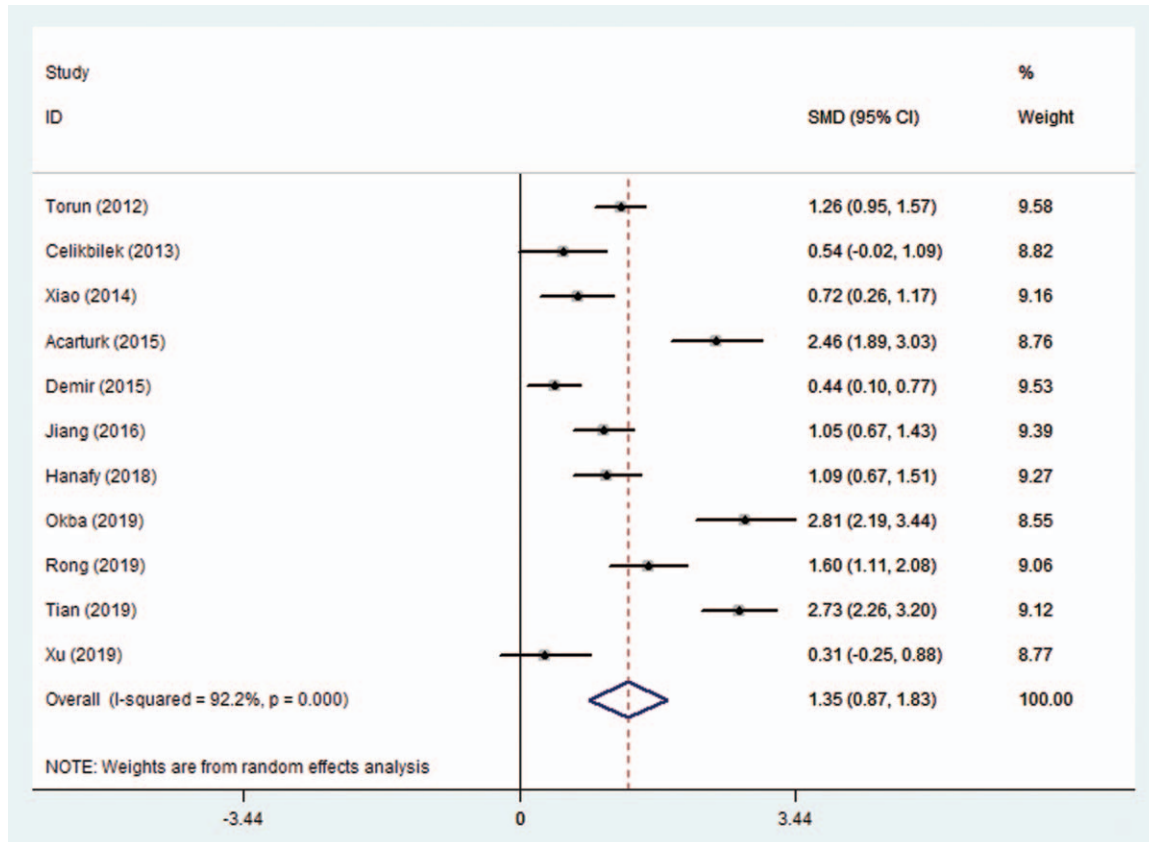
Figure 4. Meta-analysis of NLR in active UC group and inactive UC group. NLR = neutrophil to lymphocyte ratio, SMD = standard mean difference, UC = ulcerative colitis.

ulcerative colitis. This is related to direct epithelial injury and clinical activity. In addition, interleukin-1, interleukin-6, myeloperoxidase, tumor necrosis factor-α, and elastase secreted by them can lead to further damage of intestinal mucosa.[39] On the other hand, the infiltration of neutrophils as phagocytes in the mucous membrane helps to remove bacteria and cell fragments that contaminate the wound. In addition, as early as Nixon et al, it has been confirmed that neutrophils help to promote the repair of intestinal mucosa by inducing the synthesis of proteins and lipid mediators.[38] Macdonald et al[40] pointed out that neutrophils release defensins and actinomycin to stimulate the formation of epithelial cells and increase the production of protective mucin, thus actively maintaining the homeostasis of the tissue environment. The dual effect of neutrophils on intestinal mucosa has also been confirmed by WARO et al[41] The count of lymphocytes can reflect the ability of the body's immune system to respond to inflammation. In recent studies, it has been proved that the DNA of lymphocytes in patients with ulcerative colitis is impaired and their responsiveness to mitogen hemagglutinin is decreased, resulting in a decrease in lymphocyte response in both peripheral blood and intestinal mucosa.[16,42] NLR provides information about the persistent inflammation of neutrophils and the lymphocytes involved in the regulatory pathway. Therefore, NLR can be used as a measure of persistent inflammation and explain the reason for the increase of NLR in ulcerative colitis, especially in its active stage. According to the literature we included, the best cut-off point for the NLR ratio of UC during the active period ranges from 1.91 to 3.10. This can help us make timely judgments about the changes in UC, and take further necessary examinations and treatments.

As far as we know, our meta-analysis is the first report on this subject. By combining the results of independent analysis, increased statistical power and resolution enable our work to better understand the relationship between NLR and the activity of UC. We conducted a sensitivity analysis of all studies and showed that our conclusion is stable. No significant publication bias was observed in Egger test. However, there are still some inadequacies in our study. First of all, only 11 articles were included in the meta analysis, including 1741 participants, and the number of participants in each study was relatively small, which may affect the conclusion of the article. Second, in order to standardize our research, we only include studies based on Truelove and Witts criteria or Mayo score as evaluation criteria, which may be a potential limitation of our research. Third, the heterogeneity of the conclusion is high, although we conducted a subgroup analysis based on whether it is over 40 years old, but did not solve all the sources of heterogeneity. The cause of heterogeneity may be related to the fact that NLR is affected by factors in different characteristic populations. In addition, other confounding factors may also lead to heterogeneity, such as whether the population is using glucocorticoids. Because some reports suggest that glucocorticoids may affect the number and
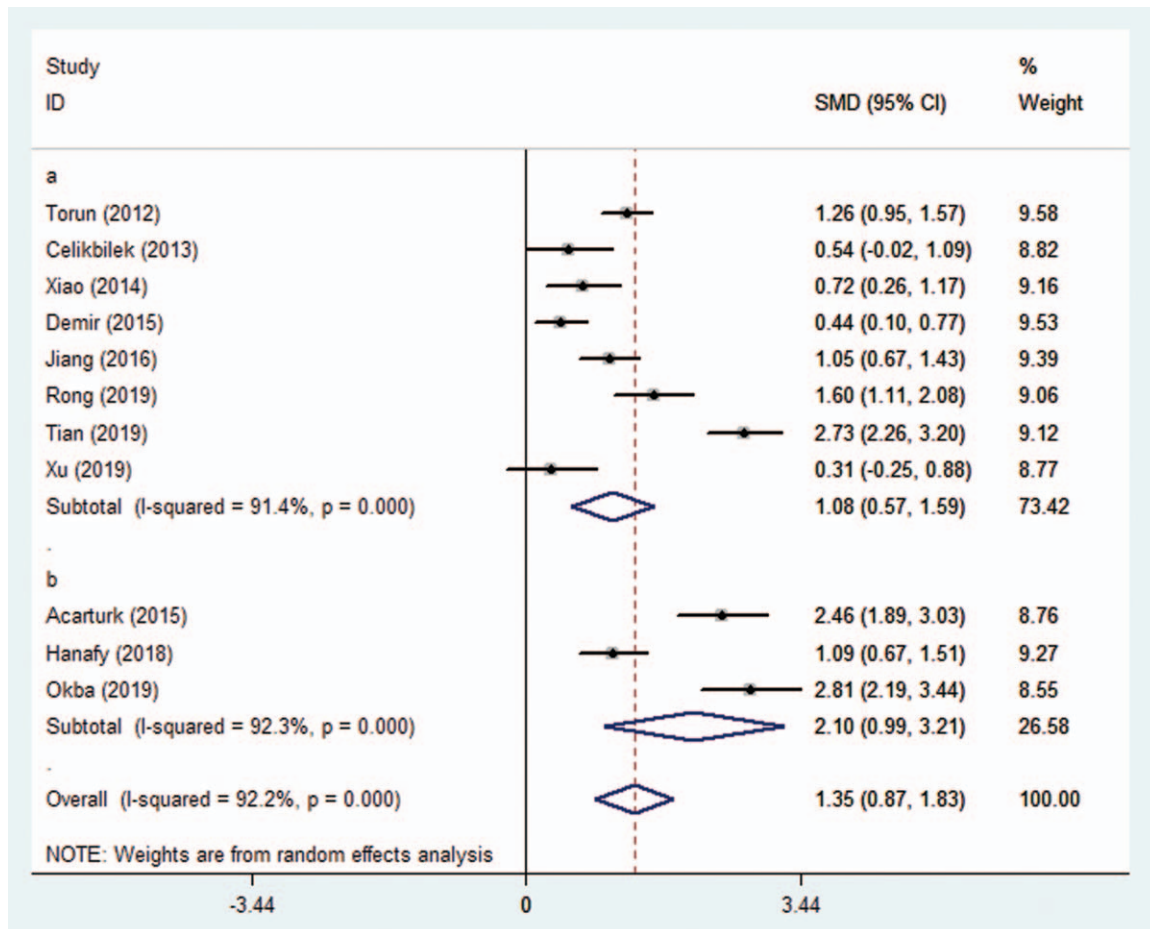
Figure 5. Subgroup analysis of NLR in active UC group and inactive UC group. NLR = neutrophil to lymphocyte ratio, SMD = standard mean difference, UC = ulcerative colitis.

function of neutrophils and lymphocytes.[43] Fourth, the lack of research in European and American populations limits the universality of the population, and more relevant studies that meet the conditions need to be included in the future.

5. Conclusion

All in all, the meta-analysis showed that the NLR of UC patients was significantly higher than that of non-UC controls, and the NLR of active UC patients was significantly higher than that of UC patients in remission stage. It is suggested that NLR may be a useful index to judge the severity and activity of UC. And because of its easy to obtain and characteristics, it is expected to be used in clinical practice after more verification, so as to provide a convenient and reliable method to assist in determining the condition of UC.

Author contributions

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