



## Diagnostic Significance of Neutrophil to Lymphocyte Ratio in Recurrent Aphthous Stomatitis: A Systematic Review and Meta-Analysis

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**ABSTRACT** **Introduction:** Recurrent aphthous stomatitis (RAS) is a prevalent ulcerative condition affecting oral mucosa.

**Objectives:** A systematic review and meta-analysis was performed to compare the level of neutrophil to lymphocyte ratio (NLR) between individuals with RAS and those who are healthy.

**Methods:** A systematic search for relevant publications before June 21, 2022, was conducted using Web of Science, PubMed, and Scopus. The results were presented as the standardized mean difference (SMD) with a 95% confidence interval (CI), and a random-effects model was used to calculate pooled effects due to the presence of significant heterogeneity. Quality assessment was performed using the Newcastle-Ottawa scale.

**Results:** Overall, 13 articles were included in the analysis. NLR was higher among patients with RAS compared to healthy controls (SMD = 0.50, 95% CI = -0.20 to 0.79, P = 0.001, I<sup>2</sup> = 91.5%). In the subgroup analysis based on the study design, it was found that retrospective studies showed higher levels of NLR in patients with RAS compared to healthy controls (SMD = 0.62, 95% CI = 0.16 to 1.08, P < 0.01), but these results were not applied to prospective studies (SMD = 0.35, 95% CI = -0.03 to 0.74, P < 0.07).

**Conclusion:** Elevated neutrophil to lymphocyte ratio revealed crosstalk between systematic inflammation and RAS.

## Introduction

Recurrent aphthous stomatitis (RAS) is a prevalent ulcerative condition affecting oral mucosa. It is characterized by painful, recurrent ulcerative lesions most commonly found on non-keratinized surfaces of the buccal mucosa, lips, tongue and floor of mouth [1]. They may be single or multiple in number and are described as well-demarcated, round or ovoid, and superficial [1]. RAS is estimated to affect approximately 20% population, most often arising in the second decade of life [2,3]. It has important impacts on quality of life, causing significant pain and difficulties with speech and mastication [4,5].

There are three primary categories of RAS, including minor RAS, major RAS and herpetiform RAS [1]. Minor RAS is the most common form, accounting for greater than 70% of cases and is considered the least severe presentation [1]. It is limited to the lips, tongue, and buccal mucosa; they are superficial, <10mm in diameter and resolve within two weeks. Major RAS is more severe, extending into the soft palate and pharynx, averaging >10mm and lasting up to six weeks [1]. Finally, herpetiform RAS consists of deeper ulcers, that are numerous in number, which will coalesce and resolve within 30 days [1].

Despite its wide prevalence, the pathophysiology of RAS remains elusive [3]. Histopathologically, the ulcers of RAS patients are characterized by substantial cell-mediated inflammation, including infiltration of neutrophils, monocytes, and T-cells [6,7]. Such evidence suggests an immunologic role in disease pathogenesis, specifically cell-mediated immunity. It is currently hypothesized that underlying genetic and immunologic factors may predispose an individual to RAS [3,8]. In the setting of triggers, such individual may develop a dysregulated immune response directed toward localized areas of the oral mucosa. Suggested triggers include mechanical injury, systemic disease, viral or bacterial infections, and food allergies - among others [3].

In this context, much research has attempted to characterize the immune response in these patients to better understand, treat and predict prognosis of disease. Several

inflammatory markers and cells have been the subject of investigations thus far. Such studies reveal elevations of proinflammatory cytokines, Th1 responses and neutrophil hyperactivity [9-12]. More recently, researchers have also looked to evaluate neutrophil-to-lymphocyte (NLR) values in this patient population. NLR is an emerging marker of chronic inflammation which has demonstrated strong prognostic utility in a variety of inflammatory and chronic disease states. NLR values have been shown to reflect severity of systemic inflammation and predict disease outcomes in a variety of malignancies, acute infections and chronic diseases [13]. It can be readily obtained from a standard hemogram and is of minimal cost to patient and provider.

## Objectives

To date, studies evaluating NLR in RAS patients have suggested that such a measure is elevated in this patient cohort; however, results are mixed and overall association remains inconclusive. As a result, a systematic review and meta-analysis of the current literature is warranted. In this study, we aim to evaluate the current literature to clarify this important association. The results of this study can help to validate NLR as a marker of RAS, further elucidating disease pathogenesis and shaping clinical management.

## Methods

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. Two independent investigators conducted the study selection, data extraction, and quality evaluation. Any disagreements were resolved through discussion.

## Literature Search

The search was systematically conducted on PubMed, Scopus, and Web of Science databases until June 21, 2022, using specific terms adjusted accordingly for each database: ((“neutrophil”[All Fields] AND “lymphocyte”[All Fields] AND “ratio”[All Fields]) OR “Neutrophil-to-lymphocyte

ratio"[All Fields] OR "NLR"[All Fields]) AND ("recurrent"[All Fields] ) AND (("aphthous"[All Fields] AND "stomatitis"[All Fields]) OR "stomatitis, aphthous"[MeSH Terms]). To exclude irrelevant research to the greatest extent possible, we required the specified keywords mentioned earlier to appear in the title or abstract. Additionally, we searched the references of the included studies to incorporate as many relevant studies as possible. Any references that did not provide appropriate information were excluded. Our search was not limited by date or language.

### **Inclusion and Exclusion Criteria**

This meta-analysis included studies that met the following criteria: (1) a comparative design with a case group and a control group. The control group consisted of healthy individuals matched to the case group, which included patients with RAS; (2) data on NLR levels in the study must be available, including mean and standard deviation; (3) the test samples must be taken from blood. Studies were excluded if they met the following criteria: (1) duplicated a previous publication; (2) included other conditions that may affect NLR levels; (3) were animal experiments.

### **Data Extraction and Conversion**

Two reviewers extracted data independently from all the studies that met the inclusion criteria. Basic information was extracted from each study, including publication year, the name of the first author, language, study design, RAS type, and NLR level.

### **Quality Assessment and Study Stratification**

Numerous methods exist for evaluating observational studies, but the most efficient one is the Newcastle-Ottawa Scale (NOS); hence, this scale was used to evaluate the included studies. NOS comprises of three components: selection, comparability, and exposure, with each having eight entries. This is a semi-quantitative scale, and a score ranging from 0-9 stars is assigned to each study.

### **Statistical Analysis**

To compare the two groups, Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) were used. Statistical heterogeneity was assessed through the Chi-squared test, and  $P < 0.10$  was considered significant. Quantitative estimation of heterogeneity was based on  $I^2$ , which ranged from 0% to 100%, where  $I^2 = 0-25\%$  indicated no or mild heterogeneity;  $I^2 = 25-50\%$  indicated moderate heterogeneity;  $I^2 = 50-75\%$  indicated large heterogeneity, and  $I^2 = 75-100\%$  indicated extreme heterogeneity. If  $I^2$  exceeded 50%, a random effects model was used, and if it was less than 50%, a fixed effect model was used.

Given the significant heterogeneity among studies, a sensitivity analysis was conducted. Additionally, subgroup analysis was conducted based on the study design, and publication bias was assessed using a funnel plot and an asymmetry test. The Egger test was used to identify the presence of publication bias by analyzing the value of  $p$ . STATA 12.0 was used for all analyses, and statistical significance was considered at  $P < 0.05$ , unless provided otherwise.

### **Certainty of Evidence**

We utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) technique to evaluate the certainty of the evidence for the outcome that was studied in our review [15].

## **Results**

### **Search Results and Included Studies**

After conducting a database search and a manual search of the article citation list, we identified a total of 210 results. Eventually, we included 13 papers [16-28] in our systematic review and meta-analysis, after eliminating duplicates and irrelevant records. The detailed process of inclusion and exclusion is presented in Figure 1, which shows the PRISMA flow diagram.

### **Characteristics of the Population and Quality Assessment**

In total, 13 articles, including 1239 patients with RAS and 1167 healthy controls, were included in the analysis [16-28]. Eleven of them were written in English [16,17,19-27], one in Arabic [28] and one in Turkish [18]. There were seven retrospective studies [16-18,21,25-27] and six prospective studies [19,20,22-24,28]. All of them were conducted in Turkey except for one study which was conducted in Syria [28]. Table 1 shows the overall characteristics of the included articles. The quality assessment revealed that all the studies were of moderate to high quality based on the NOS scale (Table 1).

### **Differences in NLR Level Between Patients With RAS and Healthy Controls**

A random-effect model revealed that NLR was higher among patients with RAS compared to healthy controls (Figure 2). However, the GRADE approach determined that the certainty of this summary estimate of effect was very low (Table 2).

Our subgroup analysis, based on study design, revealed that patients with RAS had a higher NLR compared to healthy controls in retrospective studies, but not in prospective studies, as shown in Figure 2. In our second subgroup analysis, based on the NOS score, we found that studies with

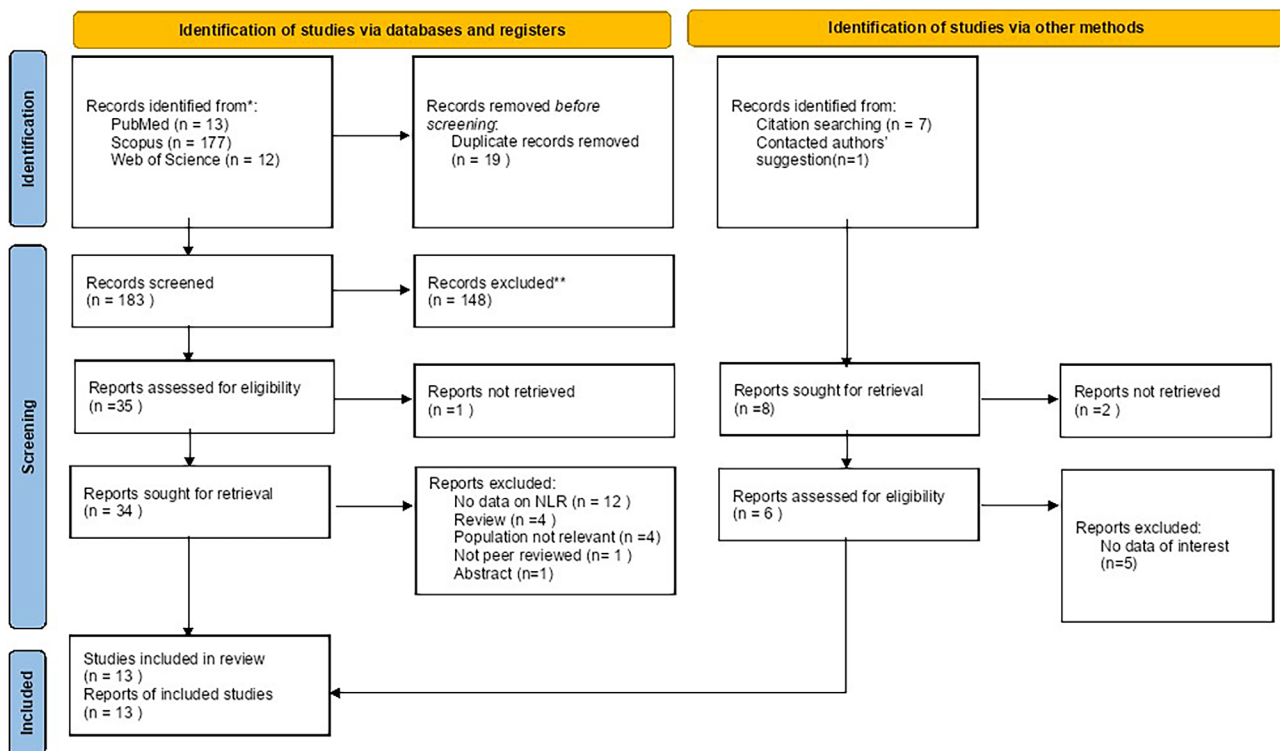


Figure 1. PRISMA 2020 flow diagram for new systematic reviews which includes searches of databases, registers and other sources.

Table 1. General characteristics of included studies.

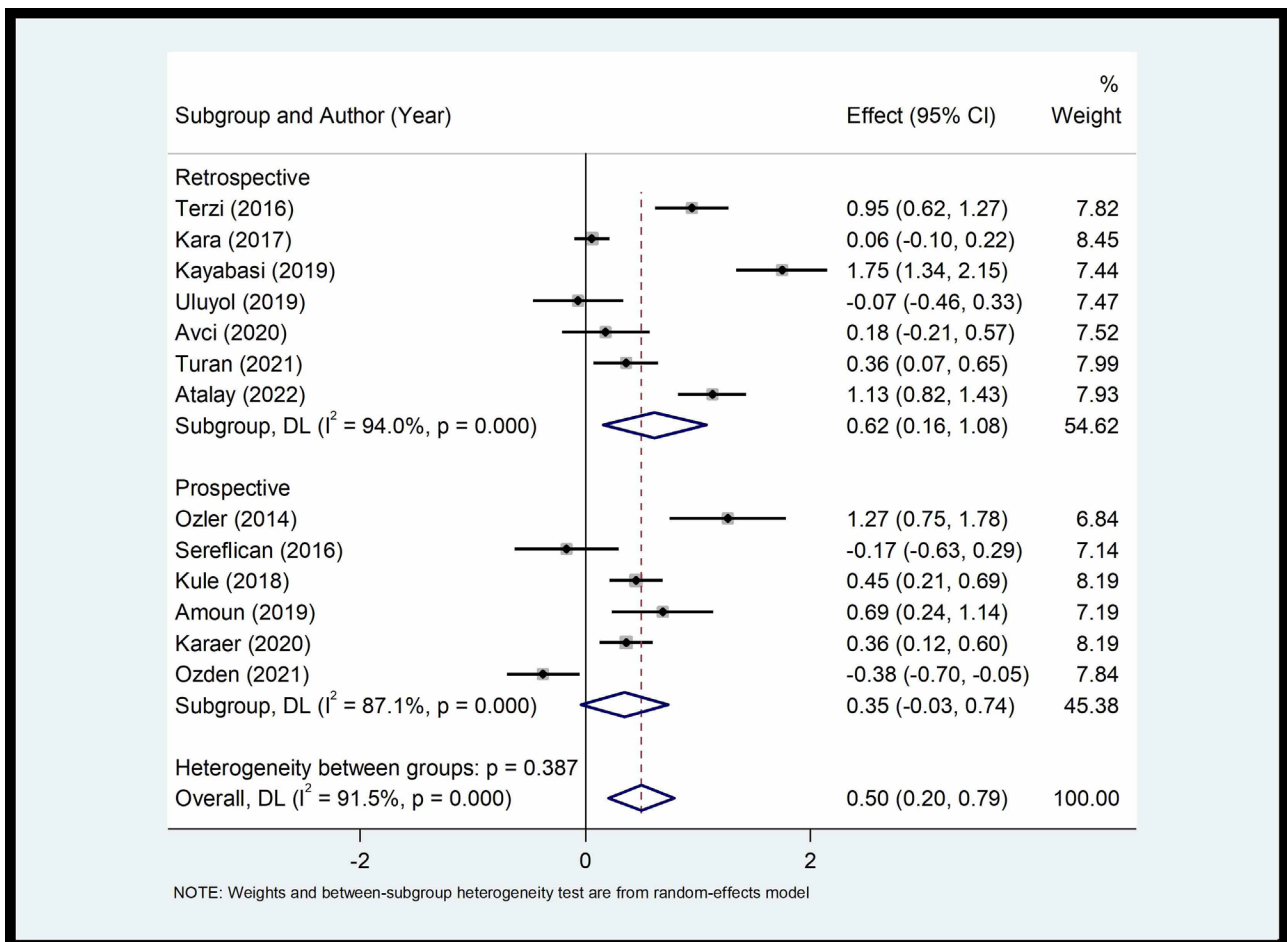
First author	Year	Country	Design	Timing of exposure-outcome measurement	Language	Type of RAS	RAS group		Healthy controls		NOS score
							N	NLR	N	NLR	
Ozler <sup>23</sup>	2014	Turkey	Prospective	Simultaneously	English	ND	35	2.05±0.63	35	1.34±0.48	7
Sereflican <sup>24</sup>	2016	Turkey	Prospective	Simultaneously	English	ND	39	2.12±0.65	34	2.26±1.02	7
Terzi <sup>25</sup>	2016	Turkey	Retrospective	Simultaneously	English	ND	80	3.37±1.74	80	1.95±1.21	6
Kara <sup>18</sup>	2017	Turkey	Retrospective	Simultaneously	Turkish	ND	306	1.88±1.00	300	1.83±0.73	8
Kule <sup>22</sup>	2018	Turkey	Prospective	Simultaneously	English	minor	143	2.25±1.07	134	1.85±0.64	8
Amoun <sup>28</sup>	2019	Syria	Prospective	Simultaneously	Arabic	ND	40	2.18±0.66	40	1.80±0.42	7
Kayabasi <sup>21</sup>	2019	Turkey	Retrospective	Simultaneously	English	ND	72	2.60±0.48	60	1.80±0.43	7
Uluyol <sup>27</sup>	2019	Turkey	Retrospective	Simultaneously	English	Minor or major	61	2.61±1.57	40	2.70±0.96	6
Avci <sup>17</sup>	2020	Turkey	Retrospective	Simultaneously	English	Minor or major	51	1.94±0.74	51	1.80±0.80	7
Karaer <sup>19</sup>	2020	Turkey	Prospective	Simultaneously	English	Minor	137	1.90±0.82	137	1.63±0.67	8
Ozden <sup>20</sup>	2021	Turkey	Prospective	Simultaneously	English	Minor, major, or herpetiform	81	1.95±1.03	69	2.38±1.27	8
Turan <sup>26</sup>	2021	Turkey	Retrospective	Simultaneously	English	ND	97	1.96±0.73	90	1.71±0.65	7
Atalay <sup>16</sup>	2022	Turkey	Retrospective	simultaneously	English	ND	97	2.66±1.10	97	1.70±0.49	7

ND = not declared; NLR = neutrophil to lymphocyte ratio; NOS = Newcastle-Ottawa scale; RAS = recurrent aphthous stomatitis;

a score of seven had higher NLR among patients with RAS compared to healthy controls, but studies with a score of six or eight did not show such a difference, as depicted in Figure 3.

Then, we analyzed the data of studies with minor RAS and mixed RAS, separately. The difference was not significant in either subgroup (Figure 4).

Our fourth subgroup analysis, based on sample size, showed that studies with a large sample size found higher NLR among patients with RAS in comparison to healthy controls, while studies with a small sample size did not show a significant difference, as illustrated in Figure 5. Lastly, in the final subgroup analysis based on article language, we observed that NLR was higher among patients with RAS



**Figure 2.** Meta-analysis of differences in neutrophil to lymphocyte ratio level between patients with recurrent aphthous stomatitis and healthy controls.

**Table 2. GRADE Evidence Profile for Studies on the Role of lymphocyte ratio level in recurrent aphthous stomatitis.**

No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Participants, N	Cases, N		
13	observational studies	not serious	very serious	not serious	not serious	very serious	2406	1239	⊕○○○	CRITICAL
									Very low	

compared to healthy controls in studies published in English, but not in studies published in other languages, as indicated in Figure 6.

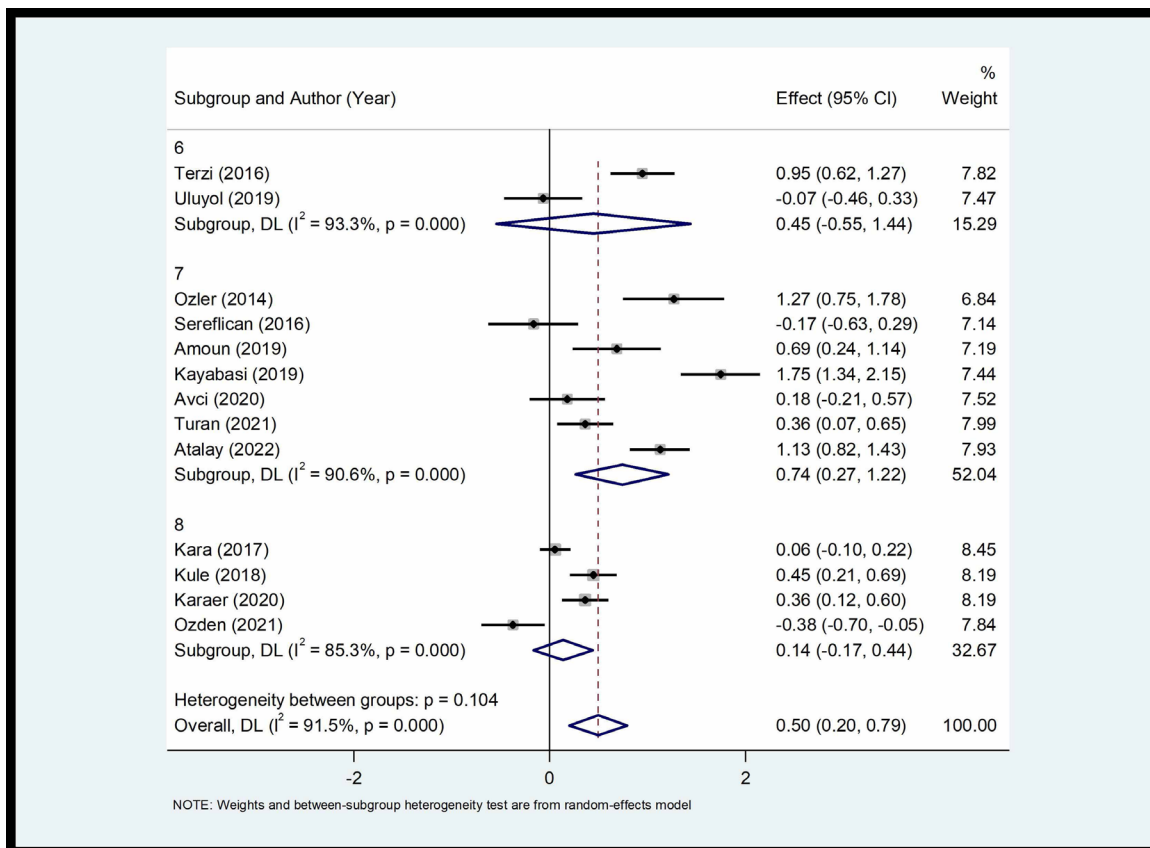
### Publication Bias

As depicted in Figure 7, our analysis did not reveal any significant publication bias among the studies that were included (with an Egger test P-value of 0.37 and a Begg test P-value of 0.58).

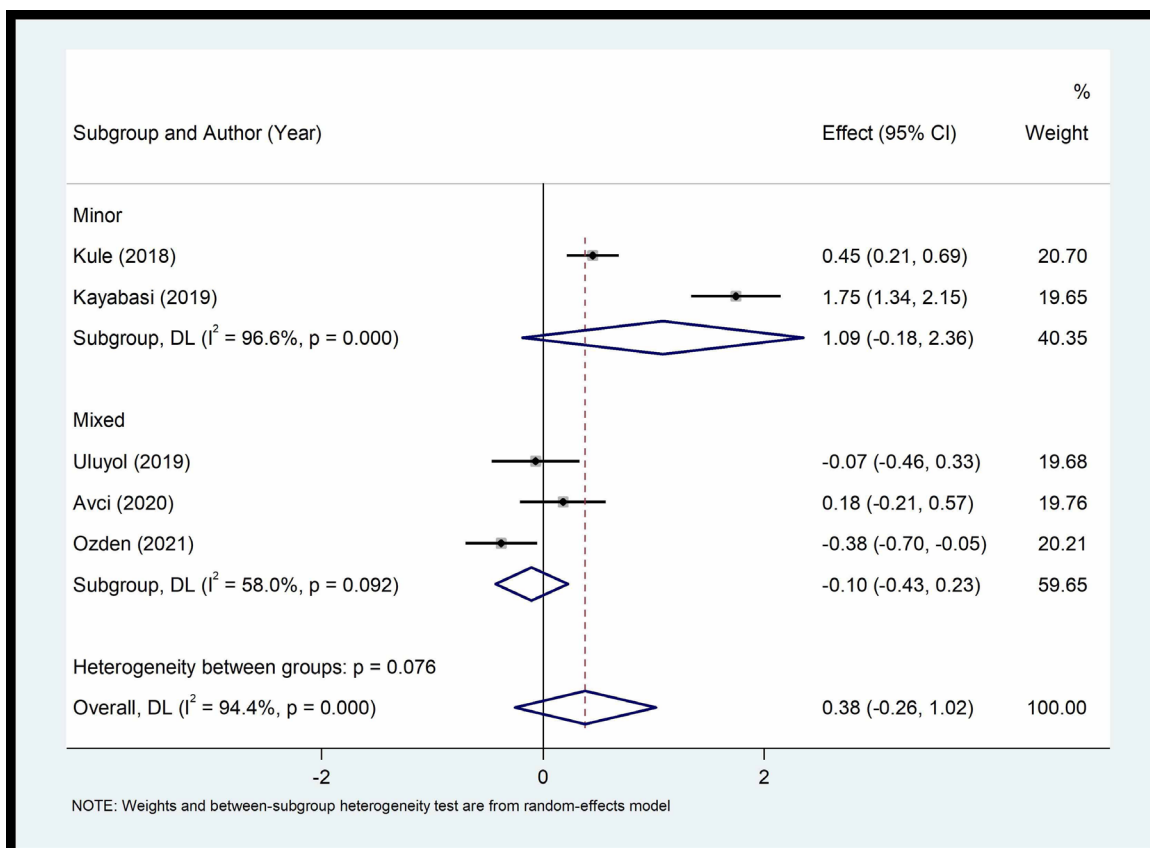
### Conclusions

The NLR, a measure of the ratio between neutrophils and lymphocytes, is a marker for inflammation and stress that

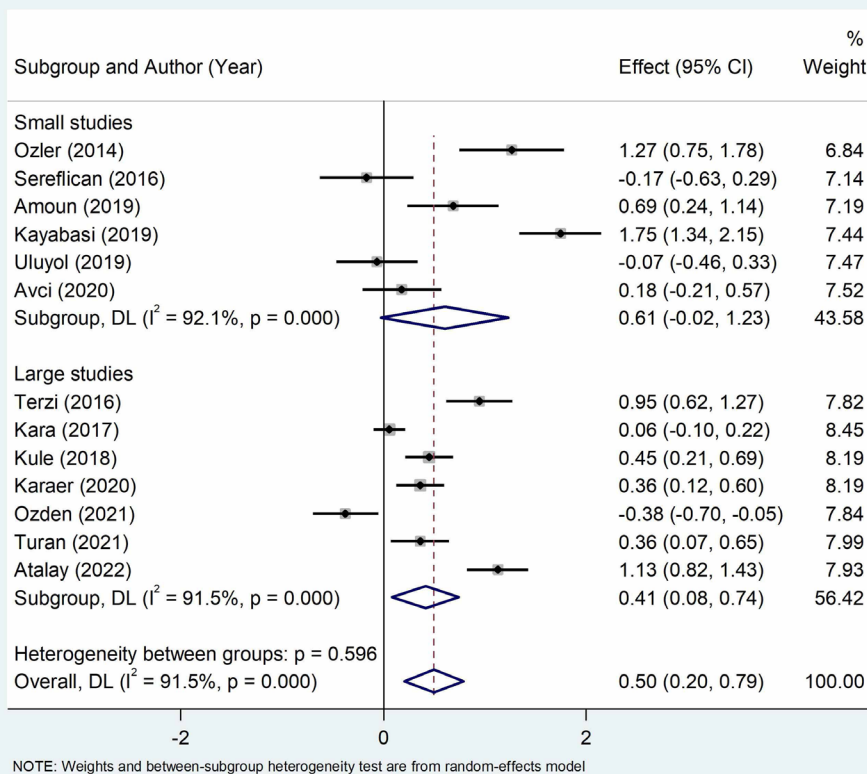
provides insight into the interplay between the innate and adaptive immune responses. Neutrophils are primary components of the innate immune system which forms the basis of pro-inflammatory processes [29] and lymphocytes are central to the adaptive immune system, serving a predominantly regulatory function [30]. The NLR thus provides insight into the balance between the innate and adaptive immune system. Higher NLR values are thought to indicate a more severe inflammatory state and suggest worse prognosis in a variety of pathologic states, including those related to inflammation, injury, surgery, and cancer [13]. Applying these concepts to recurrent aphthous stomatitis (RAS), the NLR may suggest that there is a subclinical inflammatory process present in these patients.



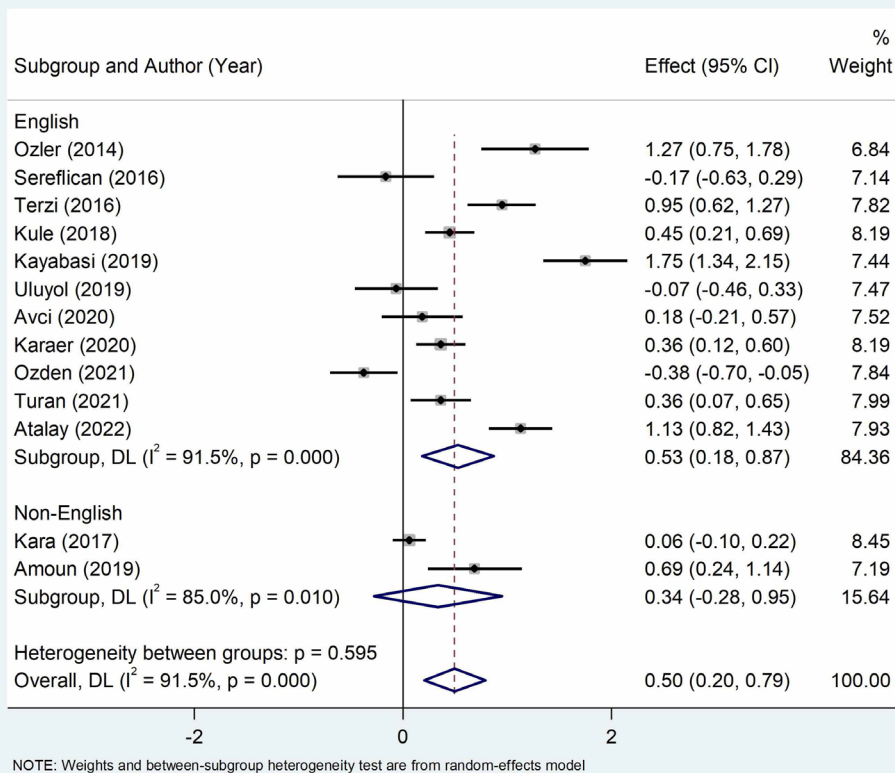
**Figure 3.** Subgroup analysis of the differences in neutrophil to lymphocyte ratio level between patients with recurrent aphthous stomatitis and healthy controls, according to Newcastle-Ottawa Scale score.



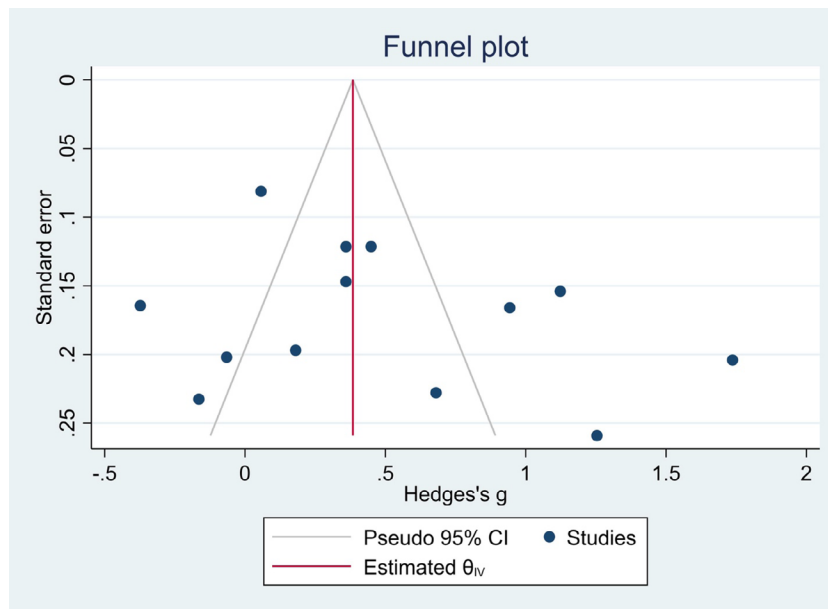
**Figure 4.** Subgroup analysis of the differences in neutrophil to lymphocyte ratio level between patients with recurrent aphthous stomatitis (RAS) and healthy controls, according to the type of RAS.



**Figure 5.** Subgroup analysis of the differences in neutrophil to lymphocyte ratio level between patients with recurrent aphthous stomatitis and healthy controls, according to sample size.



**Figure 6.** Subgroup analysis of the differences in neutrophil to lymphocyte ratio level between patients with recurrent aphthous stomatitis and healthy controls, according to the article language.



**Figure 7.** Funnel plot assessing publication bias.

Although the etiology of RAS is not fully elucidated in the literature, immunologic mechanisms are thought to play a central role in its pathologic cascade, making the NLR a useful tool in helping to understand and decipher the role of different immunologic elements in the disease process [3,31]. Strong evidence for immunologic underpinnings of the disease is based on histopathologic findings showing that aphthous ulcers of RAS patients are characterized by cell-mediated inflammation, largely neutrophilic, monocytic and T cell infiltration [6,7]. The neutrophilic cells in RAS patients have been shown to have increased production of reactive oxidative species, demonstrating a dysregulated immune response in these patients. This is further supported by the association of RAS with systemic inflammatory diseases such as inflammatory bowel disease, HIV and Behçet disease. Systemically, RAS patients exhibit a heightened pro-inflammatory state, with elevations in cytokines and altered leukocyte activities – for example, reduced activity of regulatory and anti-inflammatory mediators [32].

Keeping in mind these major principles from the literature, our study evaluated the diagnostic utility of NLR by measuring the difference in NLR values between those who were diagnosed with RAS versus those who were not. Our study included a total of 1239 patients with RAS and 1167 healthy controls across a total of 13 studies. The results of the meta-analysis demonstrate a higher NLR in patients with RAS as compared to those without RAS, indicated by a SMD of 0.50. The SMD of 0.50 is a standardized measure of the mean difference of NLR values between individuals with RAS as compared to those without and equates to a moderate effect size. Altogether, our results suggest that patients with RAS have elevated NLR values and such findings may

portend diagnostic significance, as well as further elucidate pathophysiology of disease. These findings contribute positively to the literature in that they help to discern the immunologic elements at play for patients with RAS, and taking into account the diseases relationship to other systemic inflammatory diseases, it may play a role in further delineating pathologic immune mechanisms of some devastating disease states previously referenced. Furthermore, our results indicate that there may be a relative neutrophilia present in patients with RAS compared to controls, allowing for us to pinpoint further disturbances in the immunologic mechanism of this disease process. With further investigation, this could present numerous applications in the future from a multitude of standpoints including genetics, immunology, pharmacology, cellular and molecular biology, etc.

Nonetheless, it is important to note that additional factors may be contributing to our findings. An example of this would be the known association between psychological stressors and RAS [33-35]. RAS patients who experience anxiety exhibit increased mean salivary cortisol levels [36]. Elevated cortisol leads to both neutrophilia and lymphopenia and may artificially elevate NLR values found in these patients. Ultimately, such immunologic perturbations may precipitate RAS flares [37,38]. Another example of factors contributing to our findings could be the presence of other inflammatory diseases in patients with RAS. There have been numerous studies and reports of comorbid systemic inflammatory diseases in patients with RAS and such inflammatory conditions may inherently produce elevated or altered NLR values. With a sample size of more than 1200 patients, this could present a variable influencing our results, especially given that patients who have evidence of RAS have a higher

incidence of inflammatory diseases. Other factors that could be influencing our results include laboratory error, inadequate samples, and inconsistencies amongst the included studies, as will be discussed in our limitations. There is a plethora of factors within each of the individual studies that could be contributing to our overall result, and the limitations of each study are not to be ignored when considering the utility of our results. Future studies that control for the presence of stress and anxiety when evaluating NLR values in RAS patients, and studies that focus on eliminating other confounding variables are necessary for gaining a better understanding of our results in the setting of RAS. Finally, across the studies in our meta-analysis, hematologic values and RAS diagnosis were obtained simultaneously. Thus, we cannot delineate cause and effect but, rather, can only state the presence of a correlation between the presence of RAS and elevated NLR values. As such, we cannot determine if elevated NLR values precipitate disease or, alternatively, are an end-result of the disease process. Future studies evaluating NLR values before and after RAS flares could help to answer this important question.

Another important implication of our findings lies in the diagnostic significance of our results. Currently, the diagnosis of RAS is largely clinical without an objective quantitative measure. A quantitative diagnostic value, as an adjunct to clinical presentation, may enable more efficient diagnosis of new and recurrent disease. Further, and perhaps of greater significance, NLR values may also serve to characterize disease severity in these patients to ultimately guide therapeutic management. To explain, currently, treatment of RAS involves a stepwise approach, with choice of anti-inflammatory agents escalated based on symptom severity and therapeutic response. However, many commonly used agents are not effective for all patients and targeted treatment remains a challenge. In this context, two prior studies have found that NLR measurements correlate with disease severity. Thus, NLR values may help to define severity of disease to guide selection of more appropriate anti-inflammatory agents while early in disease course. However, there remains inconsistencies in the literature in regard to NLR correlation with RAS severity. For example, a study by Kayabasi and colleagues found no significant differences in NLR values among RAS patients with active and inactive disease, suggesting absence of correlation with disease severity [39]. Therefore, further studies are needed to clarify this important correlation in order to more confidently determine the role of NLR in guiding treatment decisions. Nonetheless, the potential diagnostic significance of NLR values remains. In summary, NLR is a readily available and affordable hematologic value that may serve as an objective adjunctive tool to better diagnose disease.

Our study has both strengths and limitations. Foremost, this meta-analysis was conducted using a methodical

search process ensuring thorough review of the literature. Furthermore, based on the Begg and Egger test, assessment of publication bias showed no significant bias, further strengthening validity of our results. However, our results yielded significant heterogeneity for the overall pooled results with an overall  $I^2$  value of 91.5%, thus limiting generalizability of our findings. We speculated that study design could be contributing to heterogeneity and to further explore this, subgroup analysis was completed. However, such stratification did not appear to explain heterogeneity. Thus, we speculated additional factors contributing to heterogeneity may include variations in RAS diagnosis, study populations, and geographic location of studies. For example, baseline NLR values appear to vary by geographic location and race [13,40]. Such variations may suggest inherent differences in the degree to which NLR responds to pathologic insults among different populations and could introduce further heterogeneity.

Moreover, on subgroup analysis by study design, there was a loss of effect size for prospective studies. The reason for this is not clear and should be investigated further. In particular, retrospective studies are subject to a greater risk of bias, and it is unclear if the retained effect size in retrospective studies is a result of such. Therefore, additional prospective studies, perhaps with standardized protocols, will be needed to better characterize the associations of NLR values with RAS, and to clarify prognostic utility. In addition, the protocol of our systematic review had not been pre-registered (eg in PROSPERO). This is a concern as it introduces potential bias to the review and does not align with Cochrane guidance. Finally, the sample size ( $N = 13$ ) for our study is relatively small and may further limit greater generalization of results. As additional studies are published on the matter, future meta-analysis with greater sample sizes and power will be useful to confirm the findings of our study.

RAS is a highly prevalent disorder with a poorly understood pathogenesis, an imprecise method of treatment, and a measurable impact on patient quality of life. Despite unclear etiology, much research has supported a role of immune dysregulation in disease pathogenesis. In this systematic review and meta-analysis, we found NLR values to be significantly greater in patients with RAS as compared to those without, further supporting an immunologic mechanism of disease. In addition, our results suggest diagnostic utility of NLR values in RAS patients. Further, reports of correlations between elevated NLR values and disease activity support potential prognostic utility of NLR. However, due to small sample size and lack of effect size when stratifying by study design, further prospective studies will be needed to clarify associations found in this study and to further explore prognostic utility. Nonetheless, based on the results of our study, NLR is a practical marker of inflammation which shows an

association with RAS and holds potential to further elucidate pathophysiology and guide clinical management in these patients.

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