



Neutrophil-to-Lymphocyte Ratio in Asthmatic Patients and Healthy People: A Meta-analysis

Liping Lei¹, Jiangfa Li^{2,*}, Haihui Liu¹ and Biwen Mo^{1,**}

¹Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guilin Medical University, Guilin, China

²Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Guilin Medical University, Guilin, China

*Corresponding author: Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Guilin Medical University, Guilin, China. Email: 247546160@qq.com

**Corresponding author: Department of Respiratory and Critical Care Medicine, Affiliated Hospital of Guilin Medical University, Guilin, China. Email: mobiwen2002@sohu.com

Received 2020 November 21; Accepted 2021 April 18.

Abstract

Objectives: The purpose of this study was to investigate the differences in neutrophil-to-lymphocyte ratio (NLR) between asthmatic patients and healthy individuals.

Methods: PubMed, EMBASE, and Cochrane Library databases were searched for studies on NLR among asthmatic patients and healthy people. Review Manager (RevMan) software was used for statistical analysis.

Results: Six studies, including 1584 patients, were analyzed in this study. NLR was significantly different between asthmatic patients and healthy people.

Conclusions: NLR in the peripheral blood of asthmatic patients was higher than that of healthy people. This result has certain clinical value in distinguishing asthma patients from healthy people.

Keywords: Neutrophil-to-Lymphocyte Ratio, Asthma, Meta-analysis

1. Context

Asthma is a heterogeneous disease characterized by reversible airway obstruction and chronic inflammation. It has been estimated that about 300 million people suffer from chronic asthma worldwide (1). Inflammation is the primary pathological mechanism leading to hyperresponsiveness and airway remodeling in asthma patients; it also plays a vital role in the occurrence and development of asthma (2). In addition to chronic airway inflammation, systemic inflammatory mast cell activation occurs in patients with asthma, mediated by a variety of cell cytokines (e.g., eosinophilic neutrophils, macrophages, platelets, etc.) and a variety of mediators, which have been considered crucial in the development of clinical asthma (3, 4).

Research on neutrophil-to-lymphocyte ratio (NLR) has gained interest over recent years. Systemic inflammation measured by NLR has a significant association with prevalent chronic conditions (5, 6). In asthma patients, a high NLR is associated with an increased risk of severe exacerbation, and NLR has been suggested as a useful marker for asthma (7). Research has shown that NLR and PLR may be potential diagnostic indices for pediatric recurrent wheez-

ing (8). However, the role of NLR in the diagnosis and assessment of bronchial asthma remains unclear.

2. Objectives

The purpose of this meta-analysis was to explore the role and clinical significance of NLR in the diagnosis of bronchial asthma so as to provide a theoretical basis for the diagnosis of bronchial asthma.

3. Methods

3.1. Literature Search

A comprehensive search for studies on NLR that distinguished asthmatic patients from healthy people was conducted using EMBASE, PubMed, and Cochrane databases prior to 10 April 2020. The search strategy (Table 1) and query criteria were as follows: (((NLR[Title/Abstract]) OR ((neutrophil[Title/Abstract]) AND lymphocyte[Title/Abstract]))) AND ((asthma[Title/Abstract]) OR "Asthma"[Mesh]). This is a meta-analysis, and ethical approval was not required.

Table 1. Literature Search Strategy^a

Step No.	Query
#1	"neutrophil" [Title/Abstract]
#2	"lymphocyte" [Title/Abstract]
#3	"NLR" [Title/Abstract]
#4	"asthma" [Title/Abstract]
#5	"asthma" [Mesh]
#6	#1 AND #2
#7	#3 OR #6
#8	#4 OR #5
#9	#7 AND #8

Abbreviation: MeSH, medical subject headings.

^a This table provides details on how the literature was searched in various databases.

3.2. Study Selection

Criteria for the inclusion of articles were the following: (1) evaluating asthmatic patients and healthy controls; (2) addressing NLR; and (3) studying mild or stable asthma. The exclusion criteria comprised of: (1) being reviews; conference abstracts, non-human research, comments, and letters; and (2) not including a control group.

3.3. Data Extraction

The two researchers independently read the literature and extracted the data according to the inclusion and exclusion criteria. The following data were extracted: (1) the first author, (2) the country, (3) the year, (4) the number of patients, (5) the mean age, (6) the gender ratio, and (7) the NLR.

3.4. Quality Assessment

A modification of the Newcastle-Ottawa scale (NOW) was used for the quality evaluation of the literature (9). This scale consists of the following three parts: (1) patient selection, (2) comparability between the two groups, and (3) the evaluation of outcomes of interest. The total score is nine, and an article with a score of six or more is of high quality (Table 2).

3.5. Statistical Analysis

The forest plots were established using the random model in the new methodology, and heterogeneity testing was also conducted in this study. Review Manager (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) was used for data analysis.

3.6. Grouping Description

The overall analysis included six studies. Subgroup 1 included four studies performed among adults, and subgroup 2 included children as cases. Subgroups 3 and 4 included two subgroups with no obvious heterogeneity, which were generated by excluding each study one by one in order to analyze the heterogeneity of the overall analysis group.

4. Results

According to the search criteria, we retrieved 138 articles, 24 of which were duplicates. One hundred and five articles were excluded by scanning the titles and abstracts. Finally, six articles (10-15) were included in this study. The selection process of the literature is presented in Figure 1.

4.1. Study Characteristics

Demographic characteristics are shown in Table 2.

4.2. Heterogeneity Test

The heterogeneity of the overall analysis and subgroups 1 and 2 were high, $I^2 = 89\%$, $I^2 = 91\%$, and $I^2 = 89\%$, respectively. We used the random model for analysis. There was no obvious heterogeneity in subgroups 3 and 4, $I^2 = 0\%$ and $I^2 = 26\%$, respectively.

4.3. The Mean Difference

This study showed that the comprehensive mean differences between the two groups in overall and subgroups 1 and 2 were 0.69, 0.73, 0.60, 0.3, 1.04, respectively, which was statistically significant ($P < 0.05$; Figure 2). The comprehensive mean difference of asthmatic groups was higher than that of healthy groups.

4.4. Publication Bias

A funnel plot was used to evaluate possible publication bias (Figure 3).

5. Discussion

Neutrophils participate in airway inflammation and are activated in inflammatory pulmonary diseases such as asthma (16). NLR is likely to be a biomarker for airway and systemic inflammation (5), and it may be different in asthmatic patients and healthy people. Four studies (11-13, 15) showed that the ratio of neutrophils to lymphocytes was significantly different between control groups and asthma groups. In contrast, two studies (10, 14) showed no significant difference between asthma and healthy groups.

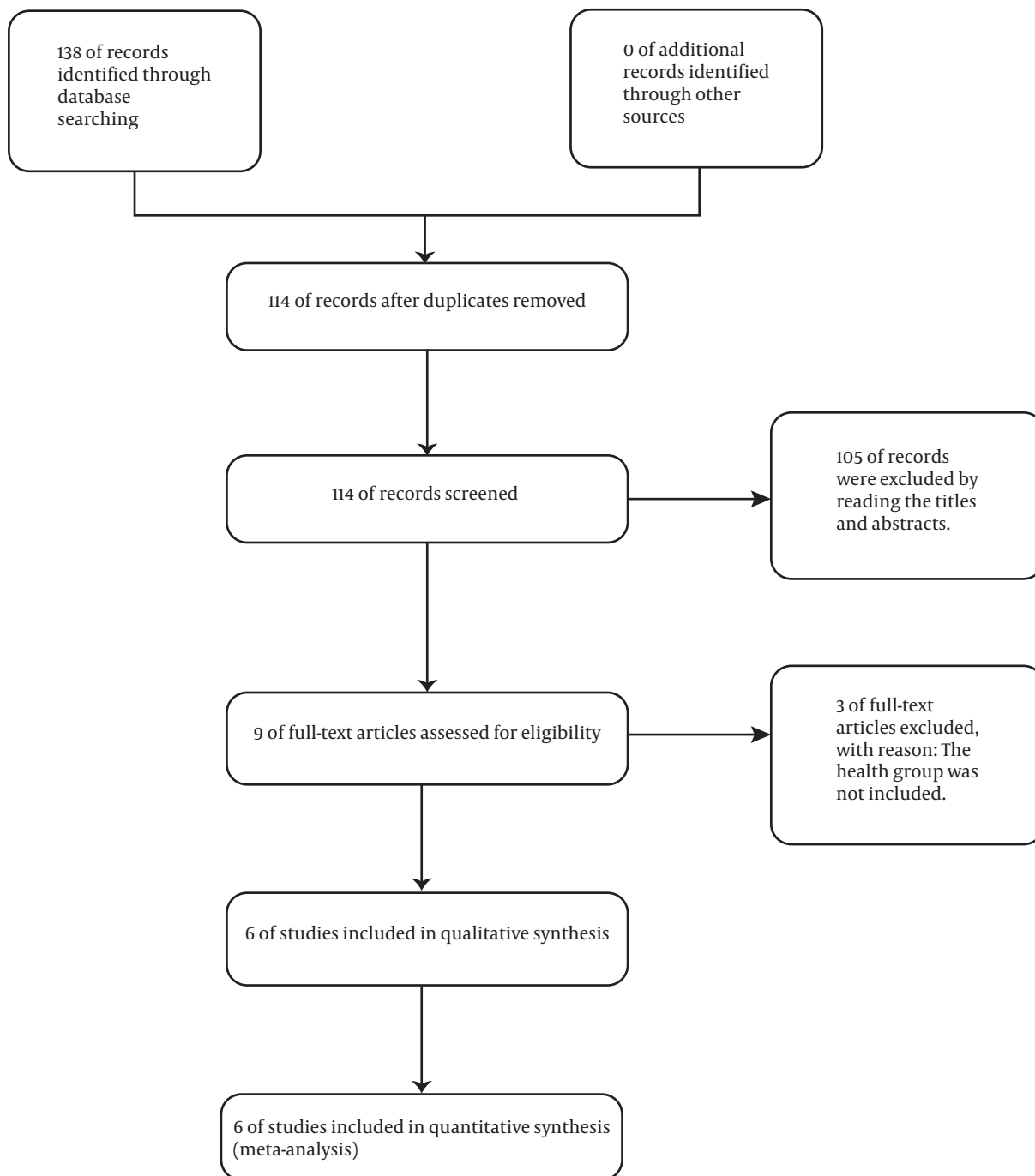


Figure 1. The process of study selection

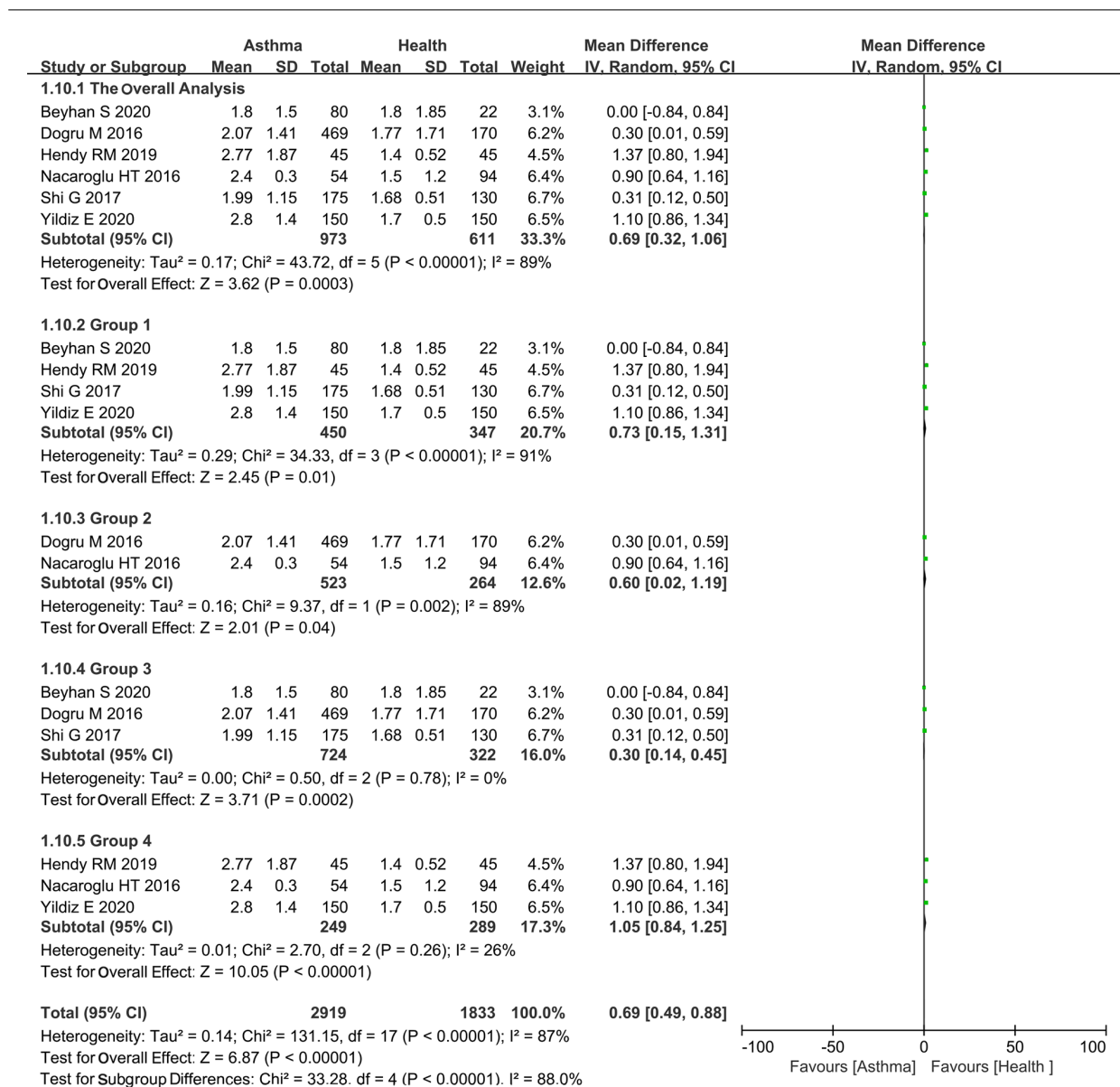


Figure 2. Forest plots showing the mean difference with corresponding 95%. Confidence intervals (CIs) for NLR in asthma and healthy group in each study. Overall analysis, including six articles. Subgroup 1 included four studies with included adults cases, and subgroup 2 included children as cases. Subgroups 3 and 4 included two subgroups with no obvious heterogeneity, which were generated by excluding each study one by one in order to analyze the heterogeneity of the overall analysis group.

Table 2. Characteristics of the Included Studies^a

Author	Year	Nation	NOWS Score	Total Number		Gender Ratio (M:F)		Age (y)		NLR	
				Asthma Group	Healthy Group	Asthma Group	Healthy Group	Asthma Group	Healthy Group	Asthma Group	Healthy Group
Beyhan S. (10)	2020	Turkey	8	80	22	57:23	7:15	41.5 ± 11.6	42.0 ± 10.5	1.8 ± 1.5	1.8 ± 1.85
Dogru M. (11)	2016	Turkey	6	469	170	266:203	90:80	8.58 ± 3.25	8.71 ± 3.03	2.07 ± 1.41	1.77 ± 1.71
Hendy R. M. (12)	2019	Egypt	8	45	45	20:25	16:29	37.82 ± 14.54	33.07 ± 10.89	2.77 ± 1.87	1.4 ± 0.52
Nacaroglu H. T. (13)	2016	Turkey	7	54	94	27:27	47:47	10 ± 3	NA	2.4 ± 0.3	1.5 ± 1.2
Shi G. (14)	2017	Chinese	6	175	130	60:115	40:90	47.94 ± 12.63	49.51 ± 13.58	1.99 ± 1.15	1.68 ± 0.51
Yildiz E. (15)	2020	Turkey	6	150	150	80:70	78:72	35 ± 3.1	38 ± 2.5	2.8 ± 1.4	1.7 ± 0.5

Abbreviations: NOW score, the score of Newcastle-Ottawa Scale; NLR, neutrophil-to-lymphocyte ratio; NA, not applicable.
^a Values are expressed as mean ± SD unless otherwise indicated.

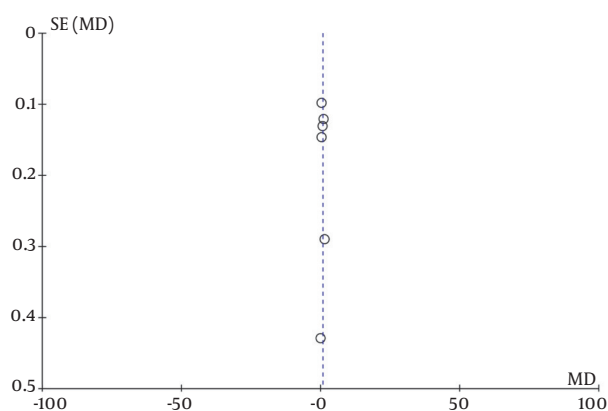


Figure 3. The funnel plot

In sum, our results suggested that NLR in asthmatic patients was significantly higher than that in healthy individuals, both among adults and children. NLR can be used to distinguish asthmatic patients from healthy people, and increased NLR has a certain clinical value in distinguishing asthma patients from healthy people (14). Because the heterogeneity of the overall analysis was very high, heterogeneity analysis was performed to identify the possible causes of heterogeneity. We found that no obvious heterogeneity in subgroups 3 and 4 through the one-by-one elimination method. In addition to these two subgroups, there was high heterogeneity in any combination of three or more studies.

Some limitations in the present study need to be pointed out. First, only a few studies were included. Second, the included studies were all non-randomized controlled and retrospective studies. More prospective multicenter studies are needed to further verify our findings.

6. Conclusions

The ratio of neutrophils to lymphocytes in the peripheral blood of asthmatic patients is higher than that in healthy individuals. This result has certain clinical value in distinguishing asthma patients from healthy people.

Footnotes

Authors' Contribution: Liping Lei and Jiangfa Li searched the literature, reviewed the literature, and performed statistical analysis. Liping Lei and Haihui Liu wrote the first draft. Biwen Mo reviewed the final draft.

Conflict of Interests: The authors of this manuscript declare no relationship with any companies whose products or services may be related to the subject matter of the article.

Funding/Support: This study was supported by the National Natural Science Foundation of China (81760008 and 81460005), the Guangxi Natural Science Foundation Program (2018GXNSFDA281041), the High Level of Innovation Team and Outstanding Scholars Program in Colleges and Universities in Guangxi, and Self-funded Project of Guangxi Zhuang Autonomous Region Health Commission (No. Z20200261).

References

- Rogliani P, Calzetta L, Matera MG, Laitano R, Ritondo BL, Hanania NA, et al. Severe asthma and biological therapy: When, which, and for whom. *Pulm Ther.* 2020;**6**(1):47–66. doi: 10.1007/s41030-019-00109-1. [PubMed: 32048241]. [PubMed Central: PMC7229123].
- Locksley RM. Asthma and allergic inflammation. *Cell.* 2010;**140**(6):777–83. doi: 10.1016/j.cell.2010.03.004. [PubMed: 20303868]. [PubMed Central: PMC3134388].
- Lemanske R. Inflammatory events in asthma: An expanding equation. *J Allergy Clin Immunol.* 2000;**105**(6 Pt 2):S633–6. doi: 10.1067/mai.2000.106155. [PubMed: 10856170].

4. Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic inflammation in older adults with asthma-COPD overlap syndrome. *Allergy Asthma Immunol Res.* 2014;**6**(4):316–24. doi: [10.4168/aaair.2014.6.4.316](https://doi.org/10.4168/aaair.2014.6.4.316). [PubMed: [24991455](https://pubmed.ncbi.nlm.nih.gov/24991455/)]. [PubMed Central: [PMC4077958](https://pubmed.ncbi.nlm.nih.gov/PMC4077958/)].
5. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med.* 2012;**5**(1):2. doi: [10.1186/1755-7682-5-2](https://doi.org/10.1186/1755-7682-5-2). [PubMed: [22281066](https://pubmed.ncbi.nlm.nih.gov/22281066/)]. [PubMed Central: [PMC3277482](https://pubmed.ncbi.nlm.nih.gov/PMC3277482/)].
6. Sunbul M, Sunbul EA, Kanar B, Yanartas O, Aydin S, Bacak A, et al. The association of neutrophil to lymphocyte ratio with presence and severity of obstructive sleep apnea. *Bratisl Lek Listy.* 2015;**116**(11):654–8. doi: [10.4149/bll_2015_125](https://doi.org/10.4149/bll_2015_125). [PubMed: [26621161](https://pubmed.ncbi.nlm.nih.gov/26621161/)].
7. Mochimaru T, Ueda S, Suzuki Y, Asano K, Fukunaga K. Neutrophil-to-lymphocyte ratio as a novel independent predictor of severe exacerbation in patients with asthma. *Ann Allergy Asthma Immunol.* 2019;**122**(3):337–339. doi: [10.1016/j.anai.2018.11.029](https://doi.org/10.1016/j.anai.2018.11.029). [PubMed: [30508585](https://pubmed.ncbi.nlm.nih.gov/30508585/)].
8. Jiang C, Yu H, Zhu W, Xu J, Lou B, Sun Q, et al. Neutrophil-lymphocyte ratio in children with recurrent wheezing. *Pediatr Allergy Immunol.* 2017;**30**(4):227–31. doi: [10.1089/ped.2017.0801](https://doi.org/10.1089/ped.2017.0801).
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;**25**(9):603–5. doi: [10.1007/s10654-010-9491-z](https://doi.org/10.1007/s10654-010-9491-z). [PubMed: [20652370](https://pubmed.ncbi.nlm.nih.gov/20652370/)].
10. Beyhan Sagmen S, Kiral N. The evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in asthma control. *Rev Fr Allergol.* 2020;**60**(1):20–3. doi: [10.1016/j.reval.2019.09.001](https://doi.org/10.1016/j.reval.2019.09.001).
11. Dogru M, Yesiltepe Mutlu RG. The evaluation of neutrophil-lymphocyte ratio in children with asthma. *Allergol Immunopathol.* 2016;**44**(4):292–6. doi: [10.1016/j.aller.2015.09.005](https://doi.org/10.1016/j.aller.2015.09.005). [PubMed: [26777420](https://pubmed.ncbi.nlm.nih.gov/26777420/)].
12. Hendy RM, Elawady MA, Mansour AI. Assessment of neutrophil/lymphocyte percentage in bronchial asthma. *Egypt J Chest Dis Tuberc.* 2019;**68**(1):74.
13. Nacaroglu HT, İsgüder R, Bent S, Erdem Bahceci S, Ceylan G, Korkmaz HA, et al. Can neutrophil/lymphocyte ratio be a novel biomarker of inflammation in children with asthma? *Eur J Inflamm.* 2016;**14**(2):109–12. doi: [10.1177/1721727x16660558](https://doi.org/10.1177/1721727x16660558).
14. Shi G, Zhao JW, Ming L. [Clinical significance of peripheral blood neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with asthma]. *Nan Fang Yi Ke Da Xue Xue Bao.* 2017;**37**(1):84–8. Chinese. [PubMed: [28109104](https://pubmed.ncbi.nlm.nih.gov/28109104/)]. [PubMed Central: [PMC6765764](https://pubmed.ncbi.nlm.nih.gov/PMC6765764/)].
15. Yildiz E, Alaşan F, Kuzu S, Koca B. Eosinophil to lymphocyte and neutrophil to lymphocyte ratio as a new predictive and prognostic factor at the both asthma and allergic rhinitis. *Acta Med Mediterr.* 2020;**36**:329–33. doi: [10.31923/pooltext-preprint-3365-0093-0026](https://doi.org/10.31923/pooltext-preprint-3365-0093-0026).
16. Lokwani R, Wark PAB, Baines KJ, Barker D, Simpson JL. Hypersegmented airway neutrophils and its association with reduced lung function in adults with obstructive airway disease: an exploratory study. *BMJ Open.* 2019;**9**(1). e024330. doi: [10.1136/bmjopen-2018-024330](https://doi.org/10.1136/bmjopen-2018-024330). [PubMed: [30696679](https://pubmed.ncbi.nlm.nih.gov/30696679/)]. [PubMed Central: [PMC6352776](https://pubmed.ncbi.nlm.nih.gov/PMC6352776/)].