European Review for Medical and Pharmacological Sciences 2020; 24: 11719-11728

The neutrophil to lymphocyte ratio as a novel predictor of asthma and its exacerbation: a systematic review and meta-analysis

W.-J. HUANG[1], G.-T. HUANG[2], Q.-M. ZHAN[1], J.-L. CHEN[1], W.-T. LUO[1], L.-H. WU[1], L.-Y. WU[1], Z.-N. LU[1], Y.-F. SUN[1]

[1]Affiliated Liutie Central Hospital of Guangxi Medical University, Liuzhou, Guangxi, China
[2]Guilin University of Technology, Guilin, Guangxi, China

Abstract. – OBJECTIVE: It is widely known that the main white blood cell populations, and neutrophil to lymphocyte ratio (NLR), are involved in systemic inflammation. The usefulness of NLR measurements has been reported in patients with asthma. We performed a systematic review and meta-analysis of studies to investigate the relationship between the NLR and asthma and its exacerbations.

MATERIALS AND METHODS: We systematically searched PubMed and Embase databases for studies (published between Jan 1, 1950 and Jan 2, 2020; no language restrictions) comparing the NLR values in patients with stable asthma or asthma exacerbations to healthy controls. We assessed pooled data by use of a random-effects model.

RESULTS: Of 260 identified studies, 6 were eligible and were included in our analysis (N = 2418 participants). Compared with 439 healthy controls, 743 stable asthma patients in four studies showed significantly greater NLR values (standardized mean difference, SMD, 0.567, 95% CI 0.212-0.922; $p = 0.002$). Furthermore, compared with 1063 stable asthma patients, 402 asthma exacerbation patients yielded significantly greater NLR values (random effects SMD 1.335, 95% CI 0.429-2.241; $p < 0.001$).

CONCLUSIONS: Our meta-analysis showed that the NLR values are a reasonable and easy-to-use marker for asthma and its exacerbations. Further studies, with larger sample sizes and more phenotypes, are required to establish its use as a predictive parameter in asthma.

Key Words:
Asthma, Exacerbation, Meta-analysis, Neutrophil-to-lymphocyte ratio.

Introduction

Asthma is a common chronic health problem, placing a great burden on families and society[1]. The immuno-histopathologic features of asthma involve granulocytic and lymphocytic infiltration, epithelial cell injury and mast cell activation[2,3]. Although available anti-inflammatory treatments have not been shown to reliably alter this natural history of the disorders, morbidity is reduced during treatment[4,5]. Research related to early diagnostic markers in patients affected by asthma is thus a priority for public health.

The blood neutrophil to lymphocyte ratio (NLR), a marker of chronic inflammation, is known as a simple, widely available and inexpensive index measured from complete blood counts. In various recent studies, the NLR has been evaluated as a probable predictor of inflammation periods in chronic diseases[6-8] and many other diseases[9-11]. Elevated NLR value predicted a poor overall survival rate in bladder cancer patients[12] and indicated a severe exacerbation in patients with chronic obstructive pulmonary disease (COPD)[13]. In the pathogenesis of asthma, cytokines cause an increase in neutrophils[14], and lymphocytes have a central role as a conductor of the immune orchestra that contributes to asthma[15].

Several studies have investigated NLR in patients with asthma. Because individual studies might not be able to provide sufficient evidence or power on their own to provide validated results or to affect practice, we decided to assess objectively the potential role of the NLR to distinguish between healthy subjects and patients with stable asthma, and between patients with stable asthma and asthma exacerbations. Therefore, we did a systematic review and meta-analysis to establish the effect of the NLR to distinguish healthy controls from those with stable asthma or asthma exacerbation.

Corresponding Author: Yifan Sun, MD; e-mail: sunyifan@gxmu.edu.cn

Materials and Methods

Search and Selection

We selected relevant studies published between Jan 1, 1950, and Jan 2, 2020, by searching the PubMed and Embase databases with the following query: ["NLR ratio" OR "neutrophils-to-lymphocyte ratio"] AND [asthma OR wheeze OR wheezing OR bronchiolitis OR bronchitis]. We searched for the terms in titles and abstracts and used MeSH terms.

Titles and abstracts were independently scanned by three authors (W.H, G.H and Y.S), and the studies were retrieved for full-text assessment when they satisfied the inclusion criteria. We obtained full texts from interlibrary loans, from electronic databases, or by emailing the authors. After screening, the reviewers compared their results and resolved discrepancies.

We included fully reported original studies that assessed both blood neutrophil-to-lymphocyte ratio during the stable phase of asthma or at the time of hospital admission for asthma exacerbations. Subjects with or without asthma were compared, and those with stable asthma were compared to those with exacerbations of asthma (case-control design). We excluded duplicate articles, studies in the form of abstracts and conference proceedings, and studies not published in full text. We included studies in which asthma was diagnosed by physicians or from medical reports; parental reports of current wheezing (≥1 episode in the past years); parental reports of treatment for asthma or asthma exacerbations; and parental reports of doctor diagnosis of asthma. We excluded studies that did not distinguish between asthma/wheezing conditions and other atopic conditions (e.g., "history of asthma or other allergies," "history of wheezing or bronchitis"). We also excluded studies that analyzed "wheeze ever" as an outcome only.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of each study[16]. This scale consists of 3 parts: 1) selection of the cohort, 2) comparability of cohorts on the basis of the design or analysis and 3) how outcomes of interest were assessed, and exposure ascertained. Studies in which at least six factors were present were considered high quality.

Data Extraction

Three authors (Q.Z., W.L. and J.C.) extracted the following data from each selected study: the year of publication, the total number of participants, age (mean [SD]), gender, and NLR values (mean [SD]). We used medians and ranges to obtain the means and standard deviations of NLR values for each study[17]. Three independent reviewers (L.W., L.W. and Z.L.) assessed risk for bias according to the PRISMA recommendations.

Statistical Analysis

We performed separate meta-analyses for main outcome, first to evaluate the differences of NLR values between healthy and stable asthma subjects, and then to evaluate the NLR of stable asthma patients versus those with exacerbations. We used standardized mean differences (SMD) and 95% confidence intervals (CIs) to construct forest plots of continuous data. $p < 0.05$ was considered statistically significant. We used the Q statistic (significance level at $p < 0.10$) to assess heterogeneity of SMD between studies. We also did I^2 testing to assess the magnitude of the heterogeneity between studies, with values less than 25% representing no heterogeneity, and values greater than 50% regarded as indicative of moderate-to-extreme heterogeneity[18]. We calculated the pooled SMD and corresponding 95% confidence intervals using a random-effects model. The correlation between study size and magnitude of effect was assessed by using Begg and Mazumdar rank correlation tests and Egger tests to evaluate the potential for publication bias and defined significant publication bias as $p < 0.10$[19]. We assessed the influence of an individual study on overall risk estimate by sensitivity analysis[20]. The trim-and-fill computation was used to further estimate the effect of publication bias on the interpretation of the results[21]. We used Stata (version 12.0) for all statistical analyses.

Results

Our search identified 260 studies. Figure 1 presents the search and selection process. We screened 247 titles, of which 41 were retained after using the reference management program EndNote (Thomson Reuters Corp., New York, NY, USA) to exclude some of the duplicate titles automatically. After reading full texts, 6 articles (with data for 2418 participants) were included in our analysis (Figure 1)[22-27].

NLR in Controls and Stable Asthma

Table I details the characteristics of the four studies investigating the NLR in controls *vs.* subjects with asthma. Most were retrospective

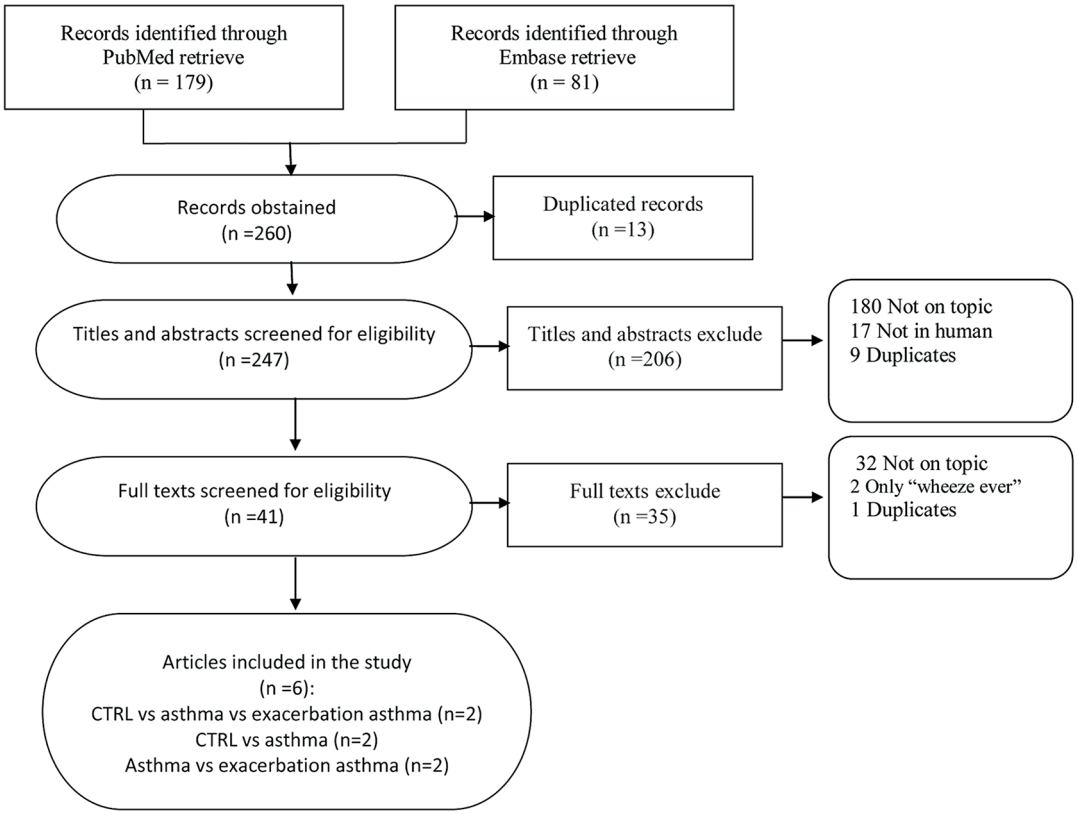

Figure 1. Flow chart showing the literatures search and selection.

studies, which comprised a total of 743 asthma patients (370 females and 373 males) and 439 healthy controls (246 females and 193 males) (22-25). The mean NLR values were 1.58 ± 0.98 and 2.30 ± 1.18 in healthy and asthma patients, respectively, a 45% greater NLR in asthma patients.

The asthma patients showed a greater mean increase in the NLR than the controls when analyzed by forest plots (Figure 2). The random-effects model was employed due to substantial heterogeneity between studies (I2 = 85.8%, $p <$ 0.001). Pooled analysis showed that the NLR was significantly higher in patients with asthma (SMD 0.567, 95% CI 0.212-0.922; $p = 0.002$). The sensitivity analysis showed that the meta-analysis was stable (Figure 3). Egger tests showed significant publication bias ($c = 0.083$). Moreover, further analysis with trim-and-fill tests indicated that one potential missing study was required on the left side of the funnel plot to ensure symmetry (Figure 4). The adjusted SMD was reduced significantly (0.415, 95% CI 0.058-0.772; $p = 0.023$).

NLR in Stable Asthma vs. Asthma Exacerbations

The characteristics of the four studies investigating NLR values in stable asthma and asthma exacerbations are presented in Table II. Three studies were retrospective[23,24,27] whereas one was prospective[27]. They comprised a total of 1063 stable asthma patients (494 females and 569 males) and 402 asthma exacerbation patients (205 females and 197 males). The mean NLR was 2.02 ± 0.68 and 4.81 ± 4.87 in asthma and asthma exacerbation patients respectively, a 138% greater NLR in asthma exacerbation patients (Figure 5).

The forest plot demonstrated greater mean NLR values in patients with asthma exacerbations when compared with patients with stable asthma, with a statistically significant between-study heterogeneity ($I^2 = 97.4\%$, $p < 0.001$). Pooling the data of these investigations showed that the NLR was significantly higher in patients with asthma exacerbations (random effects SMD 1.335, 95% CI 0.429-2.241; $p <$ 0.001). The sensitivity analysis

Table I. Real Time-PCR primers.

			Control group				Asthma group		
First author, year, country	study design	NOS (stars)	n	Age (Years)	Gender (F/M)	NLR Mean ± SD	n	Age (Years)	Gender (F/M)	NLR mean ±SD
Dogru (2015) Turkey	R	7	170	8.71±3.03	80/90	1.77±1.71	469	8.58±3.25	203/266	2.07±1.41
Nacaroglu (2016) Turkey	R	6	94	14.08±3.33	47/47	1.5±1.2	54	10±3	27/27	2.4±0.3
Shi (2017) China	R	7	130	49.51±13.58	90/40	1.68±0.15	175	49±14	115/60	1.99±1.15
Hendy (2018) Egypt	P	7	45	33.07±10.89	29/16	1.4±0.52	45	37.82±14.54	25/20	2.77±1.87

Table II. Characteristics of include studies.

			Asthma group				Asthma exacerbation group		
First author, year, country	study design	NOS (stars)	n	Age (Years)	Gender (F/M)	NLR Mean ± SD	n	Age (Years)	Gender (F/M)	NLR mean ±SD
Nacaroglu (2016) Turkey	R	7	54	10±3	27/27	2.4±0.3	54	10±3	27/27	4.9±8.1
Mochimaru (2018) Japan	P	6	58	60.33±14.31	32/26	2.07±0.13	46	60.33±14.31	25/21	2.48±0.14
Shi (2017) China	R	7	175	49±14	115/60	1.99±1.15	87	49.51±13.58	48/39	9.69±9.84
Cag (2019) Turkey	R	7	776	7.5±1.19a	320/456	1.65±1.16	215	7.5±1.19	105/110	2.18±1.41

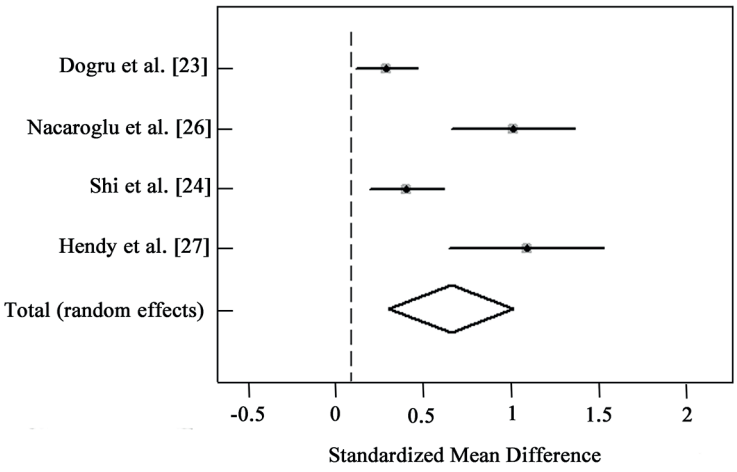

Figure 2. Forest plots of studies examining NLR and asthma. Cochran's Q = 21.19 (df = 3), $p < 0.0001$; I^2 (variation in SMD attributable to heterogeneity) = 85.8%.

comparing subjects with stable asthma to those with asthma exacerbations indicated no substantial alteration when single studies were removed, indicating that the results of the meta-analysis were stable (Figure 6). There was no significant publication bias in this analysis ($p = 0.621$).

Discussion

Our results show that, compared with healthy controls, blood NLR values are significantly greater in patients with stable asthma, but the difference was reduced after trim and fill adjustments were made. Furthermore, compared with patients with stable asthma, patients with asthma exacerbations show higher blood NLR values, with no difference before and after trim and fill. These data lend support to the idea that the NLR can be used as a diagnostic parameter for asthma.

To diagnose a subject as having asthma, he/she should have a methacholine test, a pre-bronchodilator airflow obstruction and reversibility test, or a pre- but not post-bronchodilator airflow obstruction test[28]. In recent years, there has been an increasing interest in the investigation of easily acquired biomarkers for the diagnosis of asthma[29]. The induced sputum cell count is currently the most valid, specific and discriminative method for evaluating airway inflammation in asthmatic patients[30]. However, because this method is difficult to administer in routine practice, it is unlikely to serve as a routine test for diagnosis or monitoring of asthma. Other biomarkers like

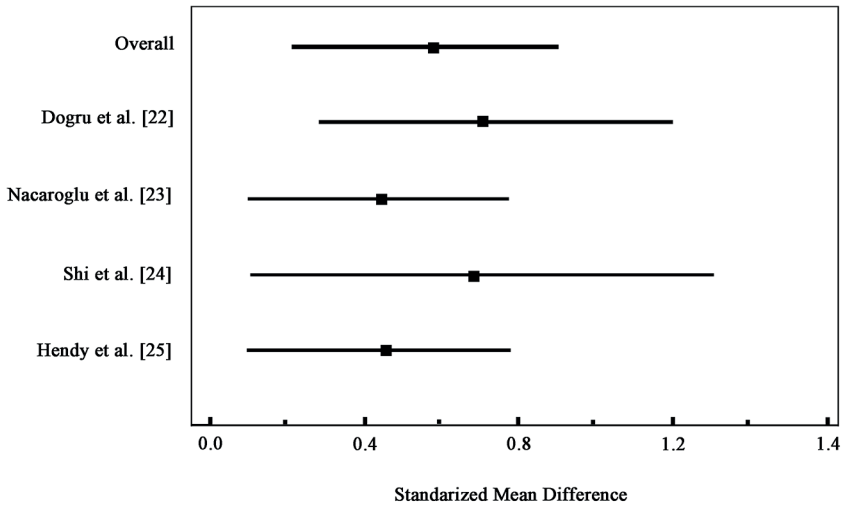

Figure 3. Sensitivity analysis of the association between NLR ratio and asthma. The influence of individual studies on the overall standardized mean difference (SMD) is shown. Solid squares represent the pooled SMD when remaining study is omitted from the meta-analysis. Two ends of each straight line represent 95% CI.

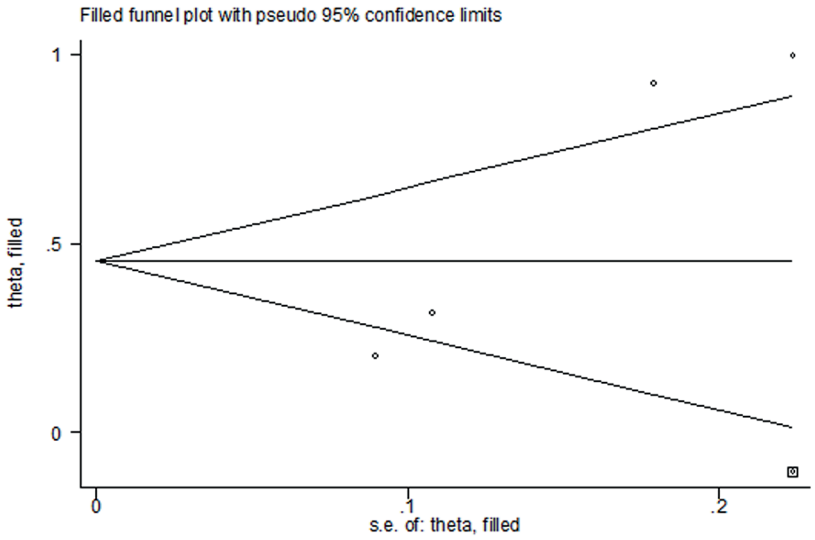

Figure 4. Funnel plot studies showing healthy controls and patients with stable asthma trimming and filling. Enclosed circles and free circles represent dummy studies and genuine studies, respectively.

peripheral blood cell counts and fractional nitric oxide of exhaled air etc., are currently being reported[31-33].

Neutrophils, as the first line of defense against fungal and bacterial infections, play an essential role in the immune system. The numbers and activation levels of neutrophils are higher in patients with symptomatic asthma compared to the absence of symptoms or after treatment of, and recovery from the allergic process[34]. However, other authors found a similar number of neutrophils in induced sputum or bronchoalveolar lavage (BAL) from control subjects compared with patients with slight to moderate asthma[35,36]. This implies that the number or percentage of neutrophils alone as an index of asthma is unreliable. Nevertheless, neutrophils have been found to be involved in synthesis of metalloproteinases MMP-9[37], elastase[38,39], myeloperoxidase[40], lipid mediators[41] and reactive oxygen species[42], which are increased in asthma patients compared to controls. Thus, neu-

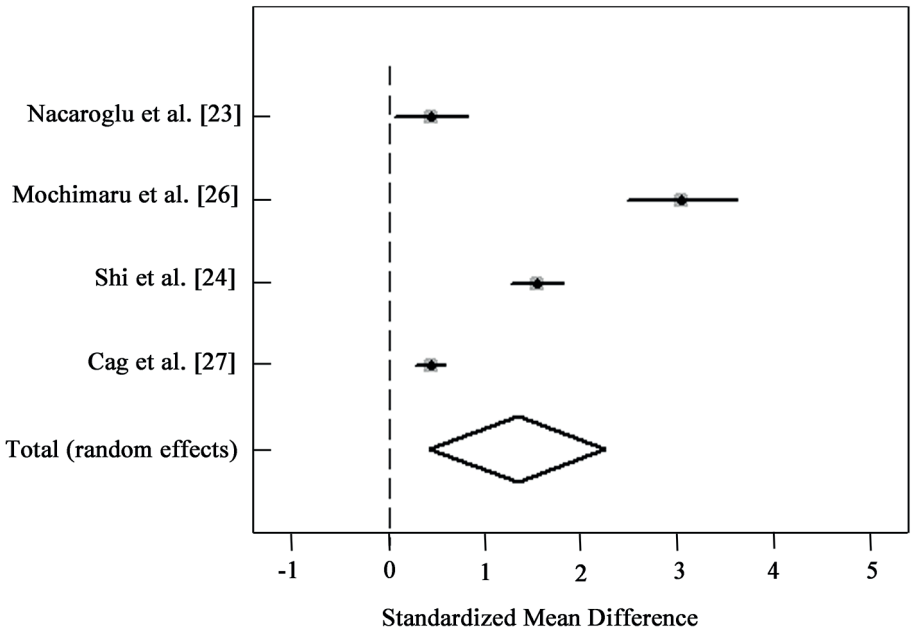

Figure 5. Forest plots of studies examining asthma and exacerbation asthma. Cochran's Q = 114.56 (df = 3), $p < 0.0001$; I^2 (variation in SMD attributable to heterogeneity) = 97.4%.

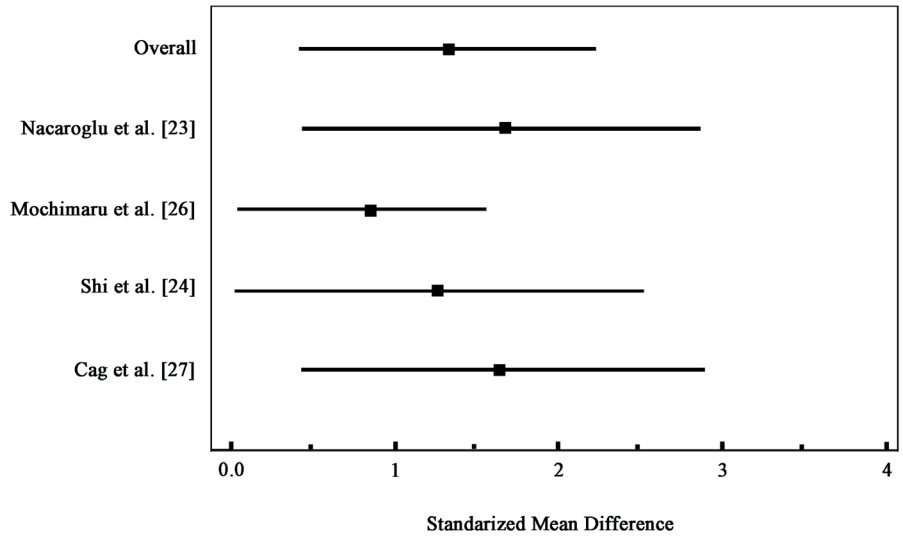

Figure 6. Sensitivity analysis of the association between NLR and exacerbation asthma. The effect of individual studies on the overall standardized mean difference is shown.

trophils can contribute to early and late asthma responses indirectly by producing these other factors.

Lymphocytes are thought to be associated with the clinical manifestation of asthma[43,44]. The number of activated $CD4^+$ lymphocytes in BAL fluid has been shown to be related to the exacerbation of asthma[43], and $CD4^+$ lymphocytes in peripheral blood have been shown to inversely correlate with clinical improvement during acute asthma[44]. In contrast to these findings, Oosterhoff et al[45] reported that the day-to-night changes of lymphocyte number in peripheral blood and BAL fluid were not associated with increased nocturnal airway obstruction in asthma, and there were no differences in lymphocyte number between nocturnal asthma or control groups[46,47]. Therefore, using only the number of lymphocytes in peripheral blood as a biomarker for asthma is controversial, and may not be accurate.

The NLR initially was utilized as a marker for the general immune response to various stress stimuli[48]. However, there is a propensity recently to take the NLR as a predictor of the onset, progression, and prognosis of most cancers[49-52]. In the latest meta-analysis conducted by Panagiotis et al[8], NLR values were significantly higher during COPD exacerbation compared with both the asymptomatic period and the control group. Despite several potential physiological advantages of the NLR, there is no clear evidence of efficacy for the NLR as biomarker related to respiratory symptoms.

In this context, we postulated the NLR as a marker of chronic inflammation that can be acquired easily by routine blood examination. Findings from this meta-analysis show a clinical value of the NLR for the diagnosis of asthma. This value was noted despite the fact that the NLR has been shown to associate with several chronic inflammatory disease states that could have blunted its overall diagnostic value for asthma. Moreover, larger NLR values were associated with more severe asthma. These findings show the potential value of the NLR for monitoring asthma and suggest that the NLR should be considered an indicator of effective treatment in patients with asthma exacerbations. Most importantly, these data support a rapid, inexpensive and technologically simple method for the diagnosis of asthma.

A limitation of this analysis is that the number of enrolled studies was small. Investigations with larger sample sizes should be performed to increase reliability. Second, most of the studies included were retrospective. The experimental details of different retrospective studies vary; potential heterogeneities among them can influence the final results. Biases in patient selection and data analysis were unavoidable. Finally, most of these studies only evaluated the NLR at one point-time,

and we do not know whether the fractions of neutrophils and lymphocytes change over time.

Conclusions

Briefly, although further studies are needed to establish the optimal approach to establish its use as a predictive parameter for asthma, our findings clearly lend support to the use of the NLR for the diagnosis of asthma.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgments

Funding: This study was supported by the Youth Science Fund Project of Guangxi Medical University (Grant No. GXMUYSF201939)..

References

1) Huang Y. Chronic Respiratory Disease, Asthma. Springer US, 2015.
2) Gelfand EW, Joetham A, Wang M, Takeda K, Schedel M. Spectrum of T-lymphocyte activities regulating allergic lung inflammation. Immunol Rev 2017; 278: 63-86.
3) Amin K. The role of mast cells in allergic inflammation. Respir Med 2012; 106: 9-14.
4) Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, Miller DP, Bleecker ER, Simons FER, Szefler SJ. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol 2012; 130: 332-342. e310.
5) Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. Allergy & Asthma Proceedings, 2012.
6) Ahsen A, Ulu MS, Yuksel S, Demir K, Uysal M, Erdogan M, Acarturk G. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. Inflammation 2013; 36: 1357-1362.
7) Yang Z, Zhang Z, Lin F, Ren Y, Liu D, Zhong R, Liang Y. Comparisons of neutrophil-, monocyte-, eosinophil-, and basophil-lymphocyte ratios among various systemic autoimmune rheumatic diseases. APMIS 2017; 125: 863-871.
8) Paliogiannis P, Fois AG, Sotgia S, Mangoni AA, Zinellu E, Pirina P, Carru C, Zinellu A. The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: a systematic review and meta-analysis. Eur J Clin Invest 2018; 48: e12984.
9) Wilar R. Diagnostic value of eosinopenia and neutrophil to lymphocyte ratio on early onset neonatal sepsis. Korean J Pediatr 2019; 62: 217-223.
10) OĐelea MR, Andrei N, Moise LG. The significance of the neutrophil to lymphocyte ratio in silicosis. Journal of Contemporary Clinical Practice 2018; 4: 53-59.
11) Chen N, Liu S, Huang L, Li W, Yang W, Cong T, Ding L, Qiu M. Prognostic significance of neutrophil-to-lymphocyte ratio in patients with malignant pleural mesothelioma: a meta-analysis. Oncotarget 2017; 8: 57460-57460.
12) Bhindi B, Hermanns T, Wei Y, Yu J, Richard PO, Wettstein MS, Templeton A, Li K, Sridhar SS, Jewett MA. Identification of the best complete blood count-based predictors for bladder cancer outcomes in patients undergoing radical cystectomy. Br J Cancer 2016; 114: 207-212.
13) Günay E, Ulaşli SS, Akar O, Ahsen A, Günay S, Koyuncu T, Ünlü M. Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: a retrospective study. Inflammation 2014; 37: 374-380.
14) Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic inflammation in older adults with asthma-COPD overlap syndrome. Allergy Asthma Immunol Res 2014; 6: 316-324.
15) Holgate ST. Innate and adaptive immune responses in asthma. Nat Med 2012; 18: 673-673.
16) Wells GA, Tugwell P, O'Connell D, Welch V, Peterson J, Shea B, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses, 2015.
17) Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
18) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
19) Eng G, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. The Lancet 2014; 384: 2228-2234.
20) Xuan C, Tian QW, Li H, Zhang BB, He GW, Lun LM. Levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, and risk of coronary artery disease: A meta-analysis based on 4713 participants. Eur J Prev Cardiol 2016; 23: 502-510.
21) Duval S, Tweedie R. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455-463.
22) Dogru M, Yesiltepe Mutlu RG. The evaluation of neutrophil–lymphocyte ratio in children with asthma. Allergol Immunopathol (Madr) 2016; 44: 292-296.

23) Nacaroglu HT, Isgüder R, Bent S, Erdem Bahceci S, Ceylan G, Korkmaz HA, Karaman S, Unsal Karklner CS, Can D. Can neutrophil/lymphocyte ratio be a novel biomarker of inflammation in children with asthma? Eur J Inflamm 2016; 14: 109-112.

24) 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: 84-88.

25) Hendy RM, Elawady MA, Mansour AI. Assessment of neutrophil/lymphocyte percentage in bronchial asthma. Egypt J Chest Dis Tuberc 2019; 68: 74-79.

26) Mochimaru T, Fukunaga K, Kuwae M, Watanabe R, Okuzumi S, Baba R, Kamatani T, Tanosaki T, Matsusaka M, Ueda S, Betsuyaku T. Neutrophil to lymphocyte ratio is a novel predictor of severe exacerbation in asthma patients. Am J Respir Crit Care Med 2018; 122: 337-339.

27) Cag Y, Pacal Y, Gunduz M, Isik S, Kertmen BA, Toprak N, Ozaydin SE, Ozcetin M, Kut A. The effect of peripheral blood eosinophilia on inflammatory markers in asthmatic patients with lower respiratory tract infections. J Int Med Res 2019; 47: 2452-2460.

28) Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J 1993; 6 Suppl 16: 5-40.

29) Louis R, Lau LC, Bron AO, Roldaan AC, Radermecker M, Djukanovic R. The relationship between airways inflammation and asthma severity. Am J Respir Crit Care Med 2000; 161: 9-16.

30) Nair P, Hargreave FE. Measuring bronchitis in airway diseases: clinical implementation and application: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010; 138: 38S-43S.

31) Tran TN, Khatry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. Ann Allergy Asthma Immunol 2014; 113: 19-24.

32) Gelb AF, Taylor CF, Shinar CM, Gutierrez C, Zamel N. Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics. Chest 2006; 129: 1492-1499.

33) Calciano L, Portas L, Corsico AG, Olivieri M, Degan P, Ferrari M, Fois A, Pasini AMF, Pasini A, Zanolin ME, de Marco R, Accordini S. Biomarkers related to respiratory symptoms and lung function in adults with asthma. J Breath Res 2018; 12: 026012-206012.

34) Radeau T, Chavis C, Damon M, Michel F, De Paulet AC, Godard P. Enhanced arachidonic acid metabolism and human neutrophil migration in asthma. Prostaglandins Leukot Essent Fatty Acids 1990; 41: 131-138.

35) Taha RA, Laberge S, Hamid Q, Olivenstein R. Increased expression of the chemoattractant cytokines eotaxin, monocyte chemotactic protein-4, and interleukin-16 in induced sputum in asthmatic patients. Chest 2001; 120: 595-601.

36) Boulet L-P, Turcotte H, Boutet M, Montminy L, Laviolette M. Influence of natural antigenic exposure on expiratory flows, methacholine responsiveness, and airway inflammation in mild allergic asthma. J Allergy Clin Immunol 1993; 91: 883-893.

37) Cundall M, Sun Y, Miranda C, Trudeau JB, Barnes S, Wenzel SE. Neutrophil-derived matrix metalloproteinase-9 is increased in severe asthma and poorly inhibited by glucocorticoids. J Allergy Clin Immunol 2003; 112: 1064-1071.

38) Nadel J. Role of enzymes from inflammatory cells on airway submucosal gland secretion. Respiration 1991; 58: 3-5.

39) Monteseirín J, Bonilla I, Camacho MJ, Chacón P, Vega A, Chaparro A, Conde J, Sobrino F. Specific allergens enhance elastase release in stimulated neutrophils from asthmatic patients. Int Arch Allergy Immunol 2003; 131: 174-181.

40) Hood PP, Cotter TP, Costello JF, Sampson AP. Effect of intravenous corticosteroid on ex vivo leukotriene generation by blood leucocytes of normal and asthmatic patients. Thorax 1999; 54: 1075-1082.

41) Maloney CG, Kutchera WA, Albertine KH, McIntyre TM, Prescott SM, Zimmerman GA. Inflammatory agonists induce cyclooxygenase type 2 expression by human neutrophils. J Immunol 1998; 160: 1402-1410.

42) Kato M, Nakano M, Morikawa A, Kimura H, Shigeta M, Kuroume T. Ability of polymorphonuclear leukocytes to generate active oxygen species in children with bronchial asthma. Int Arch Allergy Immunol 1991; 95: 17-22.

43) Walker C, Kaegi MK, Braun P, Blaser K. Activated T cells and eosinophilia in bronchoalveolar lavages from subjects with asthma correlated with disease severity. J Allergy Clin Immunol 1991; 88: 935-942.

44) Corrigan C, Hartnell A, Kay A. T lymphocyte activation in acute severe asthma. The Lancet 1988; 331: 1129-1132.

45) Oosterhoff Y, Hoogsteden HC, Rutgers B, Kauffman HF, Postma DS. Lymphocyte and macrophage activation in bronchoalveolar lavage fluid in nocturnal asthma. Am J Respir Crit Care Med 1995; 151: 75-81.

46) Mackay TW, Wallace W, Howie S, Brown PH, Greening A, Church M, Douglas N. Role of inflammation in nocturnal asthma. Thorax 1994; 49: 257-262.

47) Jarjour NN, Busse WW, Calhoun WJ. Enhanced production of oxygen radicals in nocturnal Asthma1-3. Am Rev Respir Dis 1992; 148: 905-911.

48) Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001; 102: 5-14.

49) Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P, Wang Q, Yang W. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev 2017; 58: 1-13.

50) Goh BK, Chok A-Y, Allen Jr JC, Quek R, Teo MC, Chow PK, Chung AY, Ong H-S, Wong W-K. Blood neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios are independent prognostic factors for surgically resected gastrointestinal stromal tumors. Surgery 2016; 159: 1146-1156.

51) Murray NP, Fuentealba C, Reyes E, Lopez MA, Salazar A, Minzer S, Munoz L, Orrego S, Guzman E, Arzeno L. Predictive Value of Neutrophil to Lymphocyte Ratio in the Diagnosis of Significant Prostate Cancer at Initial Biopsy: A Comparison with Free Percent Prostate Specific Antigen, Prostate Specific Antigen Density and Primary Circulating Prostate Cells. Asian Pac J Cancer Prev 2019; 20: 3385-3389.

52) Chan JY, Zhang Z, Chew W, Tan GF, Lim CL, Zhou L, Goh WL, Poon E, Somasundaram N, Selvarajan S. Biological significance and prognostic relevance of peripheral blood neutrophil-to-lymphocyte ratio in soft tissue sarcoma. Sci Rep 2018; 8: 1-9.