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Original Article

Association of Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, and Mean Platelet Volume with Systemic Lupus Erythematosus Disease Activity: A Meta-analysis

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Objective. A series of common blood tests neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and mean platelet volume (MPV) could provide a measure of systemic lupus erythematosus (SLE) activity. **Methods.** We searched the Medline, Embase, and Cochrane databases and performed a meta-analysis comparing NLR, PLR, and MPV in patients with SLE to controls, and examined correlation coefficients between NLR, PLR, and MPV and SLE activity based on SLE Disease Activity Index (SLEDAI) using random-effects models. **Results.** Nine studies were included in this meta-analysis. Meta-analysis revealed that NLR was significantly higher in the SLE group than in the control group (standard mean difference [SMD] = 2.747, 95% confidence interval [CI] = 1.241 ~ 4.254, $p < 0.001$). PLR was also significantly higher in the SLE group (SMD = 1.564, 95% CI = 0.122 ~ 3.006, $p = 0.034$). Meta-analysis of correlation coefficients showed that both NLR and PLR were positively associated with SLEDAI (correlation coefficient = 0.404, 95% CI = 0.299 ~ 0.500, $p < 0.001$; correlation coefficient = 0.378, 95% CI = 0.234 ~ 0.505, $p < 0.001$). The pooled sensitivity and specificity of NLR for diagnosis of lupus nephritis were 75.1% (95% CI, 68.5 ~ 81.0) and 72.9% (95% CI, 64.9 ~ 80.0), respectively. The area under the curve of NLR were 0.794. However, meta-analysis indicated no elevated MPV in the SLE group and no correlation between MPV and SLE activity. **Conclusion.** This meta-analysis demonstrated that both NLR and PLR are higher in patients with SLE, a significantly positive correlation exists between NLR/PLR and SLE activity. **(J Rheum Dis 2017;24:279-286)**

Key Words. Blood cell count, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by aberrant immune regulation, activation of T cells and polyclonal B cells, and excessive production of autoantibodies and cytokines leading to intense inflammation and multiple organ damage [1]. Disrupted immune regulation caused by the deregulation of B- and T-cell activation and aberrant production of cytokines is considered to play a key role in the pathogenesis of SLE [2].

Recent studies have reported the numbers and ratios of complete blood cell (CBC) subgroups in rheumatic diseases [3,4]. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) have recently been investigated as new inflammatory markers for the assessment of inflammation in many inflammatory, cardiovascular, and malignant diseases [5,6]. NLR is calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes, and PLR is calculated as the absolute platelet count divided by the absolute lymphocyte count. As a novel marker for inflammation, NLR may be useful to estimate the activity of autoimmune and inflammatory diseases [7]. PLR is also used as an index for inflammatory status in diverse diseases [8]. The MPV is the volume of the average circulating platelets in femtoliters, and it is a marker of platelet activation known to be associated with

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inflammation [9]. NLR, PLR, and MPV are inexpensive and easily obtainable laboratory markers for systemic inflammation. However, their roles in SLE remain unclear.

Studies on NLR, PLR, and MPV in SLE patients compared to healthy controls, on the relationship between NLR, PLR, and MPV levels and SLE activity, and on the association of NLR with renal involvement in SLE have reported controversial results [3,10-17]. This may be because of the small sample sizes, low statistical power, and/or the presence of clinical heterogeneity. We performed the present meta-analysis to overcome the limitations of individual studies and resolve inconsistencies [18-20]. The aim of this meta-analysis was to systematically review the evidence concerning the relationship between hematologic indices and SLE, to establish a correlation between NLR, PLR, and MPV and SLE activity, and to evaluate the diagnostic value of NLR for differentiating renal involvement from SLE.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined NLR, PLR, or MPV in patients with SLE and healthy controls. The Medline, Embase, and Cochrane databases were searched to identify all available previous articles (until April 2017). The keywords and subject terms used in the search were "neutrophil to lymphocyte ratio," "mean platelet volume," "neutrophil to lymphocyte ratio," "platelet to lymphocyte ratio," and "systemic lupus erythematosus." All references cited in the identified articles were also reviewed to identify additional studies not covered by the abovementioned electronic databases. Studies were considered eligible if: (1) they were case-control, cross-sectional, or cohort studies; (2) they provided data on NLR, PLR, or MPV in SLE and controls; (4) they provided data on the correlation coefficient between NLR, MPV, or PLR and SLE activity based on SLE Disease Activity Index (SLEDAI); or (5) they included sufficient data to calculate the sensitivity and specificity of NLR for the diagnosis of lupus nephritis (LN). Studies were excluded if: (1) they contained overlapping or insufficient data; or (2) they were reviews or case reports. Data concerning methods and results were extracted from original studies by two independent reviewers. Discrepancies in findings between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [21]. The following information was extracted from each study: primary author, year of publication, country, number of participants, mean and standard deviation (SD) of NLR, PLR, or MPV, and correlation coefficients between NLR, PLR, or MPV and disease activity. Raw data on NLR were extracted from primary studies to fill four cell values (true positive, false positive, true negative, and false negative) in a diagnostic 2×2 table. When the data given were medians, interquartile ranges, or ranges, the mean and SD values were obtained using previously described formulae [22,23]. We scored the quality of each included study based on the Newcastle-Ottawa Scale [24]. The highest score was nine. Scores ranging from 6 to 9 were considered to indicate high methodological quality.

Evaluation of statistical associations

We performed a meta-analysis examining NLR, PLR, or MPV in patients with SLE and healthy controls; correlation coefficients between NLR, PLR, or MPV and SLEDAI; and the diagnostic accuracy of NLR for LN. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). We assessed within-study and between-study variations and heterogeneity using Cochran's Q test [25]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the significant Q statistic ($p<0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis [26]. When the significant Q statistic ($p<0.10$) did not indicate heterogeneity across studies, the fixed-effects model was used. The model assumed that all studies estimated the same underlying effect, and it considered within-study variations only [25]. We quantified the effect of heterogeneity using $I^2=100\%\times(Q-df)/Q$ [27], where I^2 measured the degree of inconsistency between studies and determined whether the percentage of total variation across studies was due to heterogeneity rather than chance. I^2 ranged from 0% to 100%; I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively [27]. We combined sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR), and diagnostic odds ratio estimates and analyzed summary receiver operating characteristic (SROC) curves for diagnosing LN. Area under the curve (AUC) (in this case, area under the SROC curve) provides an overall summary of test performance and shows the

trade-off between sensitivity and specificity [28]. Q* index is another useful global estimate of test accuracy for comparing SROC curves [28]. In the present meta-analysis, statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA) and Meta-DiSc version 1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain) [29].

Evaluation of publication bias

Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test [30], which measured funnel plot asymmetry using a natural logarithm scale of SMDs.

RESULTS

Studies included in the meta-analysis

We identified 75 studies using electronic and manual search methods (Supplementary data). Ten of the studies were selected for full-text review on the basis of their titles and abstracts. One of these was excluded because they included other diseases [31]. Thus, nine articles met the inclusion criteria [3,10-17] (Table 1, Figure 1). One report contained data on two different groups [12], so we analyzed these studies independently. There were five comparison studies on NLR in SLE and controls, three on PLR, five on MPV, two on correlation coefficients between NLR, PLR, or MPV and SLE, and three on the diagnosis of LN (Table 1). The quality assessment score of each study ranged between 6 and 8. The characteristic features of the studies included in the meta-analysis are summarized in Table 1.

Meta-analysis comparing NLR, PLR, and MPV in SLE patients and controls

The present meta-analysis revealed that NLR was significantly higher in the SLE group than that in the control group (SMD=2.747, 95% CI=1.241~4.254, p<0.001) (Table 2, Figure 2). PLR was significantly higher in the SLE group than that in the control group (SMD=1.564, 95% CI=0.122~3.006, p=0.034) (Table 2, Figure 2). However, the meta-analysis showed no evidence of elevated MPV in the SLE group (SMD=0.590, 95% CI=−0.157~1.337, p=0.121) (Table 2, Figure 2).

Table 1. Characteristics of the individual studies included in the meta-analysis

Study	Country	Group	Number		Data	Matched	Result			Study quality
			Case	Control			SMD	Magnitude*	p-value	
Yolbas, 2016 [3]	Turkey	NLR	51	55	Calculated	NA	1.330	Large	<0.001	6
Wu, 2016 [10]	China	NLR	116	136	Calculated	Age, sex	3.698	Large	<0.001	7
Qin, 2016 [11]	China	NLR	154	151	Original	Age, sex	5.174	Large	<0.001	8
Li-1, 2015 [12]	China	NLR	20	149	Original	Age, sex	2.424	Large	<0.001	8
Li-2, 2015 [12]	China	NLR	59	149	Original	Age, sex	1.127	Large	<0.001	8
Khan, 2017 [17]	Pakistan	MPV	50	NA	Original	Age, sex	NA	NA	NA	7
Yolbas, 2016 [3]	Turkey	MPV	51	55	Original	NA	0.438	Small	0.026	7
Qin, 2016 [11]	China	MPV	154	151	Original	Age, sex	0.460	Small	<0.001	8
El-Garf, 2016 [16]	Egypt	MPV	29	36	Original	Age, sex	1.675	Large	<0.001	8
Safak, 2014 [13]	Turkey	MPV	44	44	Original	Age, sex	−0.954	Large	<0.001	8
Yavuz, 2014 [14]	Turkey	MPV	20	30	Original	Age, sex	1.449	Large	<0.001	8
Yolbas, 2016 [3]	Turkey	PLR	51	55	Calculated	NA	1.530	Large	<0.001	6
Wu, 2016 [10]	China	PLR	116	136	Calculated	Age, sex	2.712	Large	<0.001	7
Qin, 2016 [11]	China	PLR	154	151	Original	Age, sex	0.461	Small	<0.001	8
Ayna, 2017 [15]	Turkey	NLR	78	30	Original	NA	83†	54‡	NA	7
Qin, 2016 [11]	China	NLR	99	55	Original	NA	70.7†	63.6‡	NA	7
Li, 2015 [12]	China	NLR	20	59	Original	NA	64.7†	91.6‡	NA	7

SMD: standardized mean difference, NLR: neutrophil to lymphocyte ratio, MPV: mean platelet volume, PLR: platelet to lymphocyte ratio, NA: not available. *Magnitude of Cohen's d effect size: 0.2~0.5, small effect; 0.5~0.8, medium effect; ≥0.8, large effect. †Sensitivity for diagnosis of lupus nephritis, ‡specificity for diagnosis of lupus nephritis.

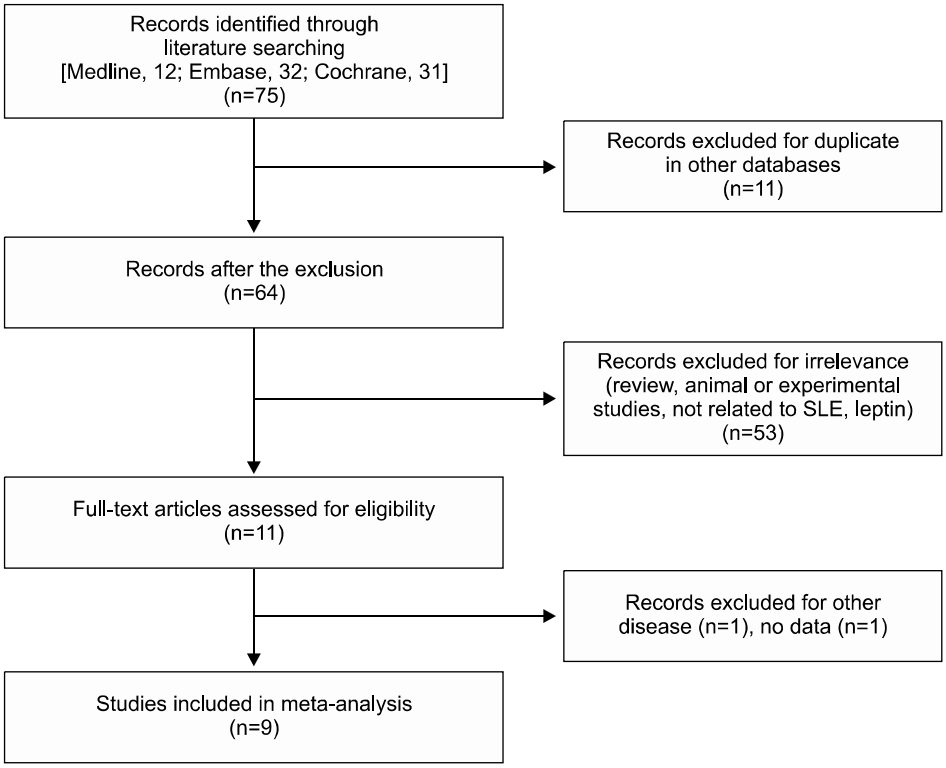

Figure 1. Flow diagram of the study selection process. SLE: systemic lupus erythematosus.

Table 2. Meta-analysis of the association between NLR, PLR, and MPV and SLE

Group	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD	95% CI	p-value	Model	p-value	I^2
NLR	Overall	5	2.747	1.241～4.254	<0.001	R	<0.001	98.4
PLR	Overall	3	1.564	0.122～3.006	<0.001	R	<0.001	98.2
MPV	Overall	5	0.590	−0.157～1.337	0.121	R	<0.001	93.9

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MPV: mean platelet volume, SLE: systemic lupus erythematosus, SMD: standard mean difference, CI: confidence interval, R: random effects model.

Meta-analysis of the relationship between NLR, PLR, and MPV and SLE activity

Meta-analysis of correlation coefficients identified that NLR was positively associated with SLE activity based on SLEDAI (correlation coefficient=0.404, 95% CI=0.299～0.500, p<0.001) (Table 3). PLR was positively associated with SLE activity (correlation coefficient=0.378, 95% CI=0.234～0.505, p<0.001) (Table 3). However, the meta-analysis showed no correlation between MPV and SLE activity (correlation coefficient=−0.665, 95% CI=−0.965～0.382, p=0.192) (Table 3).

Diagnostic accuracy of NLR for LN

The pooled sensitivity and specificity of NLR were 75.1% (95% CI, 68.5～81.0) and 72.9% (95% CI, 64.9～80.0), respectively (Table 3). The PLR and NLR were 2.575 (95% CI, 1.403～4.726) and 0.407, respectively (95% CI, 0.309～0.537) (Table 3). Figure 3 shows the performance of the NLR test in the form of SROC curves. The AUC and Q* index of NLR were 0.794 and 0.731, respectively (Table 3, Figure 3).

Heterogeneity and publication bias

Between-study heterogeneity was identified during the meta-analyses of NLR, PLR, and MPV in patients with SLE (Tables 2 and 3). However, all of the studies showed the same direction of the effect size, except for MPV. Publication bias results in a disproportionate number of positive studies, and poses a problem for meta-analyses. However, we found no evidence of publication bias in the meta-analysis performed in this study (Egger's regression test p-values>0.1), indicating low probability of pub-

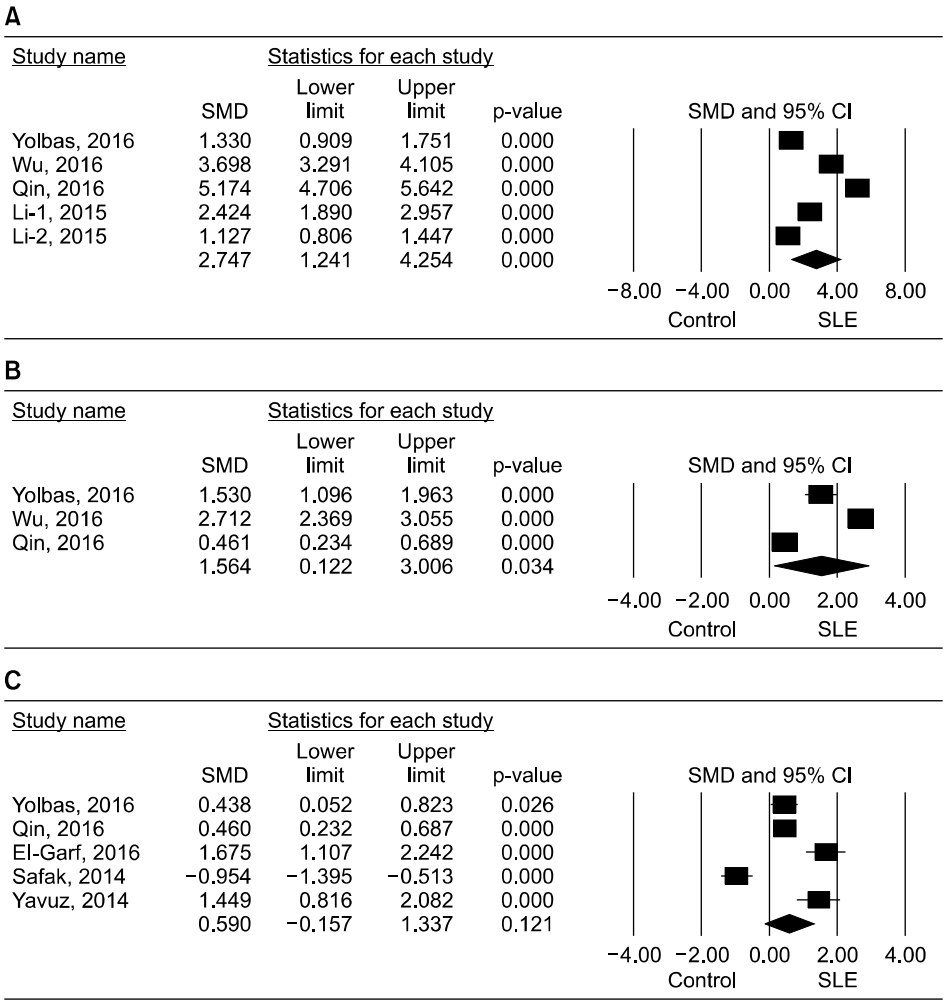

Figure 2. Meta-analysis of the relationship between NLR (A), PLR (B), and MPV (C) and SLE compared with control. NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MPV: mean platelet volume, SMD: standard mean difference, CI: confidence interval, SLE: systemic lupus erythematosus.

lication bias (Tables 2 and 3).

DISCUSSION

In this meta-analysis, we combined the evidence for NLR, PLR, and MPV in SLE, the correlation between NLR, PLR, and MPV and SLE activity, and diagnostic values of NLR for LN. The meta-analysis revealed that NLR and PLR were significantly higher in the SLE group than in the control group, and that NLR and PLR, were positively correlated with SLE activity measured by SLEDAI.

It is needed to be explained why NLR and PLR are high in SLE. The cause of increased NLR and PLR may be increased cytokines and the inflammatory processes associated with SLE. The inflammatory process in SLE involves inflammatory cells and molecules that cause changes in the number, shapes, and sizes of bone marrow cells and peripheral blood cells [2]. SLE is characterized by B-cell activation and resultant autoimmunity with the production of numerous cytokines [32]. Cytokines play a very important role in the pathogenesis of SLE [33]. Neutrophils and platelets are involved in the production of these cytokines, which contribute to the activation of neutrophils and platelets [34]. Leukocytes play a major role in inflammatory processes, and neutrophils are the most abundant type of leukocytes. Platelet activation is observed in patients with SLE [35]. Lymphocyte count is usually decreased in SLE, and platelet count is decreased in SLE patients very often [36]. High correlation may suggest that NLR and PLR would be conditional relations of cytokines or inflammatory products from high SLE activity.

ESR and CRP level are the most widely used markers for measuring acute-phase response to indicate inflammation in RA. ESR and CRP are influenced by several factors unrelated to inflammation such as age, sex, anemia, and renal failure [37]. However, NLR and PLR are not affected by age, gender, and hemoglobin level [38]. In addition,

Table 3. Meta-analysis of the correlation coefficients between NLR, PLR, and MPV and SLE activity (SLEDAI) (A) and of the diagnostic accuracy of NLR for lupus nephrtitis (B)

A.

Group	Population	No. of studies	Test of association			Test of heterogeneity		
			Correlation coefficient	95% CI	p-value	Model	p-value	I^2
NLR	Overall	2	0.404	0.299～0.500	<0.001	R	0.128	56.2
PLR	Overall	2	0.378	0.234～0.505	<0.001	R	0.191	41.5
MPV	Overall	2	−0.665	−0.965～0.382	0.192	R	<0.001	98.0

NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MPV: mean platelet volume, SLEDAI: systemic lupus erythematosus disease activity index, CI: confidence interval, R: random effects model.

B.

Population	No. of studies	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	AUC (SE)	Q* (SE)
Overall	3	0.751 (0.685～0.810)	0.729 (0.649～0.800)	2.575 (1.403～4.726)	0.407 (0.309～0.537)	0.794 (0.046)	0.731 (0.039)

CI: confidence interval, PLR: positive likelihood ratio, NLR: negative likelihood ratio, AUC: area under the curve, SE: standard error.

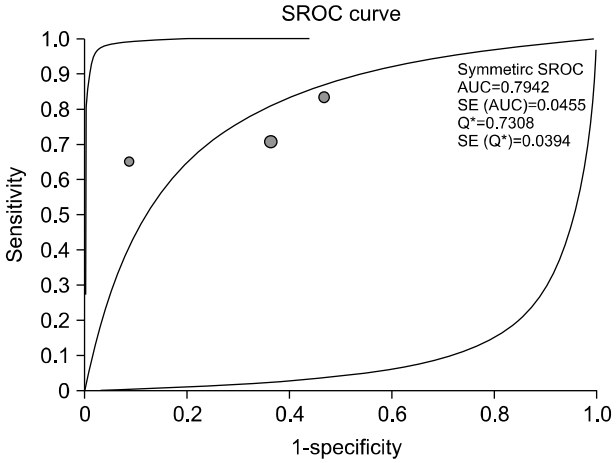

Figure 3. Summary receiver-operating characteristic curves for neutrophil to lymphocyte ratio for the diagnosis of lupus nephritis. Solid circles represent individual studies included in this meta-analysis. The curve shown is a regression line that summarizes the overall diagnostic accuracy. SE (AUC): standard error of the area under the curve, Q*: an index defined by the point on the S receiver operating characteristics curve where the sensitivity and specificity are equal, and SE (Q*): Q* index standard error. SROC: summary receiver operating characteristic, AUC: area under the curve, SE: standard error.

NLR and PLR are relatively stable compared to individual white blood cell parameters [11]. NLR and PLR are cost effective and easily obtained indicators from CBC tests. As easily measurable and available laboratory parameters, NLR and PLR could be considered as new biomarkers for inflammatory response or disease activity in SLE patients. MPV is another marker used in the assessment of inflammation. However, we failed to observe high or low levels of MPV in SLE or a correlation of MPV with disease activity. The association between MPV and SLE remains unclear.

The present study has certain shortcomings that should be considered. First, a small number of studies were included in this meta-analysis, most of the included studies had small sample sizes, and only a small number of studies evaluated the correlation coefficients between the hematological indices and SLE severity and their diagnostic value for LN. Thus, the meta-analysis may be underpowered. Second, the studies included patients with heterogeneous demographic characteristics and clinical features. NLR, PLR, and MPV values may be affected by multiple factors. Heterogeneity and confounding factors such as drugs used (e.g., immunosuppressive agents, hydroxychloroquine, and corticosteroids) may have affected the present results. For example, glucocorticoids may affect the count, size, and function of neutrophils, lymphocytes, and platelets. However, this meta-analysis also has strengths. First, to the best of our knowledge, this meta-analysis is the first study to combine evidence of NLR, MPV, and PLR in SLE according to disease activity. Second, compared with individual studies, this study should provide more reliable data on the relationship between NLR, PLR, and MPV and SLE by in-

creasing the level of statistical power and resolution through the pooling of the results of independent analyses.

CONCLUSION

The present meta-analysis demonstrated that NLR and PLR are higher in patients with SLE, and that a significantly positive correlation exists between NLR/PLR and SLE activity. These findings suggest that NLR and PLR may be useful indices for determining the extent of inflammation of SLE. Although there is high correlation between NLR, PLR and SLE activity, these ratios from CBC profile cannot totally replace SLE activity such as SLEDAI. Further studies are needed to elucidate whether NLR and PLR can serve as biomarkers for monitoring SLE activity.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at http://www.jrd.or.kr and at https://doi.org/10.4078/jrd.2017.24.5.279.

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