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Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with systemic lupus erythematosus and their correlation with activity: A meta-analysis

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ABSTRACT

Objective: The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been suggested to be potential biomarkers for systemic lupus erythematosus (SLE). We thus performed this meta-analysis to investigate the relationship between NLR and PLR and SLE.

Methods: A literature review was conducted by searching the Pubmed, Embase, Cochrane and Wanfang online databases from inception to 1 June 2019. Studies were pooled and the standard mean difference (SMD) with 95% confidence interval (CI) was calculated using a random-effect or fixed-effect model.

Results: A total of fourteen studies were eventually included in the meta-analysis, of which nine (1246 SLE patients and 976 healthy controls) reported the NLR of SLE patients and healthy controls, six (646 SLE patients, 524 healthy controls) reported the PLR of SLE patients and healthy controls, nine (1128 SLE patients) reported the correlation coefficients between the NLR and SLE disease activity index (SLEDAI) in SLE patients, and six (715 SLE patients) reported correlation coefficients between PLR and SLEDAI in SLE patients. The NLR and PLR in SLE patients were significantly higher than in healthy controls (SMD = 1.004, 95%CI = 0.781–1.227, $P < 0.001$, SMD = 0.709, 95%CI = 0.58–0.838, $P < 0.001$), and were both positively correlated with SLEDAI (correlation coefficient = 0.429, 95%CI = 0.288–0.552, $P < 0.001$, correlation coefficient = 0.309, 95%CI = 0.091–0.498, $P < 0.001$, respectively).

Conclusion: NLR and PLR were significantly higher in SLE patients compared with healthy controls, and were positively correlated with SLEDAI, suggesting that NLR and PLR are useful biomarkers in the management of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a very common autoimmune disease that causes various clinical manifestations that range from minor cutaneous and skeletal muscle symptoms to lupus nephritis, mental abnormalities and lethal thrombosis [1]. Although the pathogenesis of SLE remains unclear, the occurrence and development of SLE are closely related to a dysfunctional immune system, especially in the presence of anti-DNA antibodies [2].

Despite improvements in the recognition of SLE, challenges remain in diagnosing and monitoring SLE due to the complexity of its pathogenesis. Multiple serum markers, such as anti-Smith, anti-dsDNA, antphospholipid and antinuclear antibodies, were extensively used in the diagnosis and evaluation of SLE inflammatory status [3]. However, these tests were expensive and inconvenient. It is therefore urgent to develop less costly and more convenient biomarkers for facilitating the management of SLE.

The NLR and PLR have recently been used in combination with other biomarkers to estimate the prognosis of a large number of rheumatic diseases and malignancies [4–6]. Hao X et al. had previously reported a relationship between NLR and PLR and SLE [7]. However, the included number of studies was relatively small. We therefore aim to summarize the relationship between NLR and PLR and SLE, and correlate NLR and PLR and SLE disease activity index (SLEDAI) in a larger number of studies.

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2. Materials and Methods

2.1. Search strategy

A systematic search of all relevant publications in the Pubmed, Embase, Wanfang and Cochrane online databases, was performed by two independent investigators (Lisha Ma and Renfang Zhou). The search keywords were as follows: “neutrophil to lymphocyte ratio”, “neutrophil-to-lymphocyte ratio”, “neutrophil lymphocyte ratio”, “NLR”, “platelet to lymphocyte ratio”, “platelet-to-lymphocyte ratio”, “platelet lymphocyte ratio”, “PLR”, “systemic lupus erythematosus”, “lupus nephritis” and “lupus”. Studies were included if they met any of the following criteria: (1) they were cross-sectional or case-control studies with SLE patients diagnosed according to the 1982 ACR, 1987 ACR, 1997 ACR or 2010 ACR/EULAR classification criteria; (2) they provided data regarding NLR or/and PLR in case and/or control groups; (3) they provided data regarding the correlation coefficient between NLR and PLR and SLEDAI. No language restriction was applied. Exclusion criteria: (1) duplicate reports or insufficient data; (2) reviews, conference abstracts or case reports; (3) the object of the study was not human. Discrepancies between the reviewers were resolved by a third investigator.

2.2. Literature quality and data extraction

The quality of the methodologies of all of the included publications was evaluated with the Newcastle-Ottawa quality assessment scale (NOS). Information extracted from each study was as follows: first author, publication year, study region, sample type, the number of participants, criteria for diseases, mean with standard deviation (SD) of the NLR and PLR, and correlation coefficients between the NLR and PLR and disease activity. Data presented as a median and range was converted to mean with SD using a previously described formula [8]. If the original important data was unavailable, further details were obtained by contacting the corresponding author through e-mail. The meta-analysis was performed in accordance with PRISMA guidelines [9].

2.3. Evaluation of statistical associations

This study conducted a meta-analysis that compared the NLR and PLR of SLE patients and healthy controls, and the correlation coefficients between the NLR and PLR and the SLEDAI. Results were written as standardized mean differences (SMDs) with 95% confidence intervals (CIs). The SMD magnitude was defined as follows: 0.2–0.5 was identified as a small effect; 0.5–0.8 was identified as a medium effect; ≥0.8 was identified as a large effect. Cochran’s Q-statistics was used to evaluate within and between-study variations and heterogeneities. When a significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies, a random-effects model was selected for meta-analysis. Otherwise, a fixed-effects model was used. I^2 statistics were used to measure inconsistency. A value of 25% − 50% indicated a low degree of heterogeneity; 50%–75% indicated a moderate degree of heterogeneity; > 75% indicated a high degree of heterogeneity. Statistical manipulations were performed with Comprehensive Meta Analysis V2 (Biostat, Englewood, NJ, USA).

2.4. Evaluation of heterogeneity, sensitivity and publication bias

A meta-regression analysis was used to identify the source of any heterogeneity utilizing publication year, ethnicity, sample size and study quality. A sensitivity analysis was conducted to assess the influence of each individual study on the pooled SMD by deleting each study individually. Publication bias was detected using a funnel plot and Egger’s regression test.

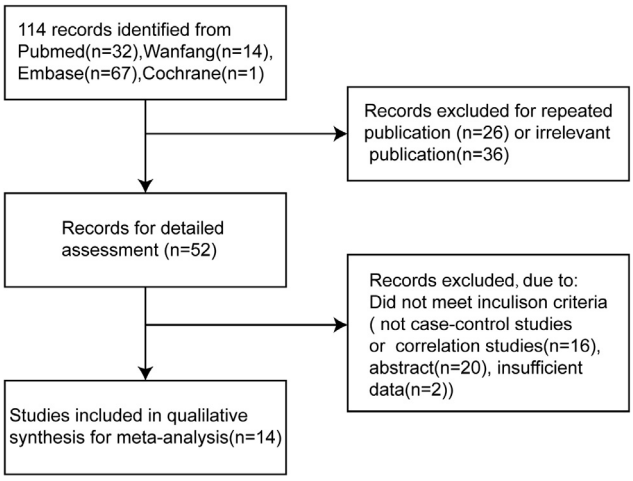


Fig. 1. Flow chart of the study selection process.

3. Results

3.1. Search results and study characteristics

A total of 114 articles were initially acquired, of which 32 were obtained from Pubmed, 67 from Embase, 1 from Cochrane and 14 from Wanfang. We finally excluded 98 articles because they were either duplicate publications, had an unmatched purpose, were a review or conference abstract, or were of a low quality or had insufficient data. Fourteen studies [10–23] ultimately met the inclusion criteria (shown in Fig. 1), and their characteristics are presented in Table 1. Of these, nine reported the NLR in SLE patients and healthy controls, nine reported the correlation coefficients between NLR and SLEDAI in SLE patients, six reported the PLR of SLE patients and healthy controls, and six reported correlation coefficients between PLR and SLEDAI in SLE patients.

3.2. Meta-analysis of NLR in SLE compared with HC

Eleven studies comprising 1246 SLE patients and 976 healthy controls explored the role of NLR in SLE. Considerable heterogeneity ($I^2 = 82.222$) was noted between these studies and a random-effects model was therefore used. As compared with healthy controls, SLE patients had a significantly higher NLR. (SMD = 1.004, 95%CI = 0.781–1.227, $P < 0.001$, shown in Fig. 2. and Table 2.)

Sensitivity analysis showed that the pooled SMD was not materially changed when each study was sequentially excluded. The meta-regression analysis revealed that study quality ($P = 0.002$) and sample size ($P = 0.012$), not ethnicity ($P = 0.602$) or publication year ($P = 0.467$), significantly impacted heterogeneity. The funnel plot was symmetric (shown in Fig. 3.), with Egger’s regression analysis ($P = 0.201$) showing an absence of publication bias.

3.3. Meta-analysis of PLR in SLE compared with HC

Six studies, which included 646 SLE patients and 524 healthy controls, were ultimately involved in the meta-analysis. Data were pooled using a random-effect model due to the high heterogeneity ($I^2 = 98.142$) of the data, which showed that SLE patients had a higher PLR than healthy controls (SMD = 0.709, 95%CI = 0.580–0.838, $P < 0.001$, shown in Fig. 4 and Table 2).

The sensitivity analysis showed that the pooled SMD value was not essentially altered when each study was sequentially removed, indicating that the results are stabile. The meta-regression analysis revealed that publication year ($P < 0.001$), not study quality ($P = 0.173$), ethnicity ($P = 0.204$) or sample size ($P = 0.288$) had a

Table 1
The characteristics of SLE-related studies in this meta-analysis.

First Author, year, country	Number of patients		NLR		Correlation coefficient of SLEDAI		PLR		Correlation coefficient of SLEDAI		Criteria for disease	NOS
	SLE (M/F)	HC (M/F)	SLE	HC			SLE	HC				
Weilin, 2019 [9], China	155(24/131)	135(30/105)	2.66 ± 1.54	1.69 ± 0.64	0.264		/	/	/		1997 ACR	7
Jianlin Yu, 2018 [10], China	189(20/169)	/	/	/	0.281		/	/	/		2012SLICC	7
HATTAO YU, 2018 [11], China	212 (23/189)	201 (20/181)	/	/	0.211		/	/	/		1982 ACR	6
Siyan Xie, 2018 [12], China	105(12/93)	105(13/92)	/	/	/		155.[1] ± 92.57	110.28 ± 26.56	− 0.159		2010 ACR/EULAR	7
Wafaa M. Soliman, 2018 [13], Egypt	120(18/102)	30(9/21)	3.60 ± 2.22	1.06 ± 0.30	0.525		290.15 ± 128.52	158.86 ± 25.19	0.512		ACR	8
Fengxian Tan, 2018 [14], China	100(46/54)	47(22/25)	4.94 ± 2.11	1.47 ± 1.01	0.779		181.71 ± 6.55	90.23 ± 3.39	0.542		1997 ACR	8
Zaixing Yang, 2017 [15], China	344	170	3.38 ± 2.7	1.78 ± 0.75	/		/	/	/		2012SLICC	9
Yinxia Zhao, 2017 [16], China	62(3/59)	/	/	/	0.587		/	/	/		1982 ACR	6
Hyoun-Ah Kim, 2017 [17], Korea	120(9/121)	/	/	/	0.282		/	/	0.117		/	6
Yunxiu Wu, 2016 [18], China	116(19/97)	136(25/111)	2.87 ± 1.7	1.67 ± 0.57	0.312		148.58 ± 95.08	100.43 ± 25.25	0.298		1997 ACR	8
Servet Yolbas, 2016 [19], Turkey	51(4/47)	55(4/35)	6.06 ± 12.30	2.4 ± 3.33	/		395.9 ± 735.7	150.97 ± 190.52	/		2010 ACR/EULAR	9
Xiaoqing Liu, 2016 [20], China	127(14/113)	103(16/87)	3.08 ± 2.46	1.63 ± 0.5	/		/	/	/		1982 ACR	8
Baodong Qin, 2015 [21], China	154(17/137)	151(20/131)	3.61 ± 2.04	1.82 ± 0.49	0.471		155.64 ± 91.69	123.01 ± 39.07	0.44		1982 ACR	7
Lixiu Li, 2015 [22], China	79(6/73)	149(17/132)	5.00 ± 4.35	2.00 ± 0.76	/		/	/	/		/	7

SLE: systemic lupus erythematosus; HC: healthy control; NLR: neutrophil to lymphocyte ratio; DAS: disease activity score; NA: not available.

significant effect on heterogeneity. Funnel plot analysis and Egger's regression test ($P = 0.015$) indicated a publication bias in this meta-analysis. By checking the funnel plot, we found that the graph symmetry (shown in Fig. 5.) was influenced by the study written by Tan F et al [15]. After removing this study the estimated level was SMD = 0.556, 95%CI = 0.428–0.685, $P = 0.365$, $I^2 = 54.87$ (shown in Fig. 6.), and the publication bias was eliminated (Egger's test $P = 0.335$).

3.4. Meta-analysis of the correlation between NLR and SLEDAI

The meta-analysis of nine studies including 1128 SLE patients showed that NLR was positively correlated with SLEDAI (correlation coefficient = 0.429, 95%CI = 0.288–0.552, $P < 0.001$, shown in Fig. 6. and Table 3). The sensitivity analysis showed that no individual study influenced the pooled SMD, which illustrates the result's stability. Heterogeneity was very large in this meta-analysis ($I^2 = 87.545\%$). A meta-regression analysis revealed that study quality ($P < 0.001$) and sample size ($P < 0.001$), not ethnicity ($P = 0.683$) or publication year ($P = 0.262$), influenced heterogeneity. A funnel plot (shown in Fig. 7) and Egger's regression analysis ($P = 0.058$) demonstrated no publication bias in this meta-analysis.

3.5. Meta-analysis of the correlation between PLR and SLEDAI

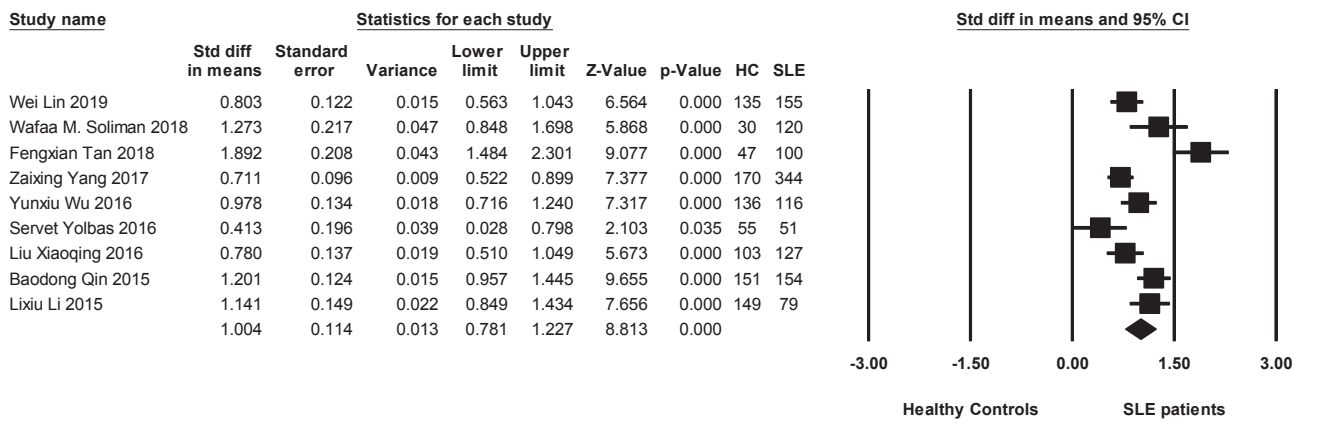
Six studies containing 715 SLE patients provided the correlation coefficient between PLR and SLEDAI. The pooled data showed that PLR had an obviously positive correlation with SLEDAI (correlation coefficient = 0.309, 95%CI = 0.091–0.498, $P < 0.001$, shown in Fig. 8 and Table 3).

To evaluate the stability of the result, a sensitivity analysis was performed by sequentially omitting each study, which showed that no single study rendered the SMD non-significant. The meta-regression analysis demonstrated that ethnicity ($P < 0.001$) and sample size ($P = 0.049$), not study quality ($P = 0.845$) or publication year ($P = 0.257$), had a significant effect on heterogeneity. Neither funnel plot (shown in Fig. 9) nor Egger's regression analysis ($P = 0.605$) showed a significant publication bias.

4. Discussion

Neutrophils, lymphocytes and platelets have important roles in the occurrence and development of SLE. Neutrophils demonstrate several facets of dysfunction, which include reduced phagocytic and lysosomal activity, the production of reactive oxygen species (ROS), increased adhesion molecules and cellular aggregation and intracellular activation, which exacerbate the disease. Lymphocytes are also abnormally activated [2], and exhibit abnormal mitochondrial hyperpolarization, an exhausted supply of intracellular glutathione, and reduced ATP biosynthesis, which results in spontaneous apoptosis [24,25]. T lymphocytes are considered to be central to the pathogenesis of SLE because of their association with MHC proteins. Platelets, primarily recognized for their critical role in normal haemostasis, were also involved in the progression of SLE. The activated platelets in patients with SLE upregulate the circulatory autoantigenic load through the release of microparticles. Prior studies have proposed that the complex pathophysiology of neutrophils, lymphocytes and platelets is closely related to the pathogenetic, immune-mediated mechanisms of disease [26]. Thus, NLR and PLR were constantly studied to elucidate the inflammation state of SLE, which has garnered the attention of several physicians.

NLR and PLR are readily available, inexpensive, and less sensitive to multiple physiological and pathological conditions compared with independent neutrophils, lymphocytes, and total white blood cell count. NLR and PLR therefore have the potential to be novel inflammatory biomarkers.



Meta Analysis

Fig. 2. Forest plot of studies examining NLR and SLE.

Table 2
Meta-analysis of NLR and PLR in SLE compared to that in HC.

	No. of studies	No. of patients		Test of association			Test of heterogeneity		
		SLE	Control	SMD	95%CI	*P*	Model	*P*	I^2
NLR	9	1246	976	1.004	0.781–1.227	< 0.001	R	< 0.001	82.222
PLR	6	646	524	0.709	0.580–0.838	< 0.001	R	< 0.001	98.142

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; CI, confidence interval; R, random effects model; SMD, standard mean difference.

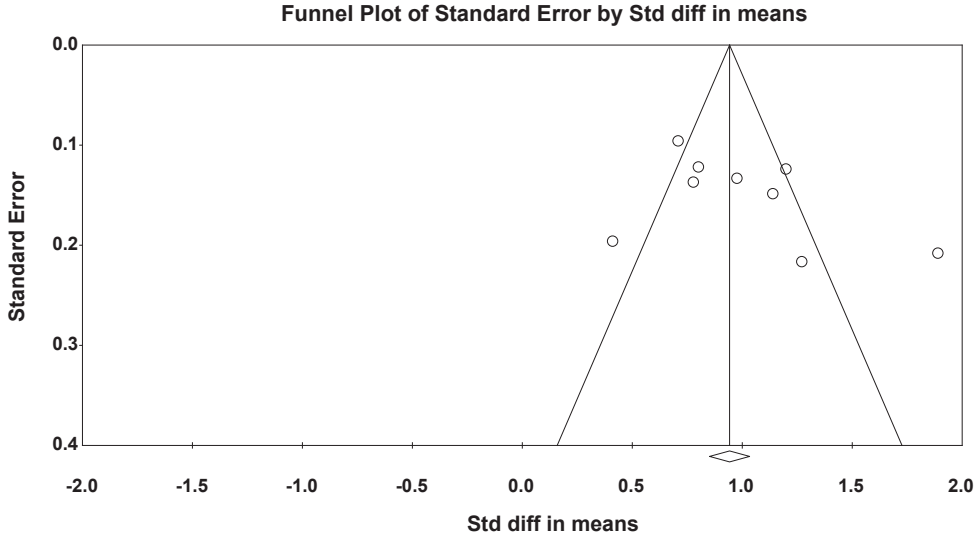
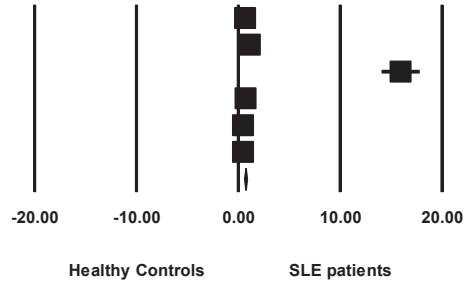


Fig. 3. Funnel plot of studies examining the relationship between NLR and SLE.

In this study we conducted a meta-analysis to detect the relationship between NLR and NLR and SLE. Our results showed that SLE patients have a significantly higher NLR and PLR than healthy controls. All of the included studies reported that both NLR and PLR were significantly higher in SLE patients. These consistent results strengthen the reliability of our results. However, the relatively small samples used require further studies. Although our results are consistent with those of a previous meta-analysis performed by Hao et al, we performed an up-to-date meta-analysis with a larger number of studies. Further, a meta-analysist that included correlations was performed. What is different in this work from a meta-analysis of the levels of NLR and PLR is that there remains disputes among prior studies regarding this correlation, even if their results showed that NLR and PLR were positively correlated with SLEDAI, which suggesting that NLR and PLR are useful biomarkers for inspecting the disease activity of SLE. By analyzing these studies, we did not find the reason behind these different reSults, AND study quality, ethnicity, sample size, publish years were not special.

Combined with previous reports, we can speculate that NLR and PLR are effective at evaluating the severity of SLE, or the prognosis of other inflammatory diseases. However, the studies included in this meta-analysis of the correlation of NLR and SLE activity were only nine and six, respectively. Attention should therefore be paid to the interpretation of the result of this meta-analysis, as it might have been underpowered.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	HC	SLE
Siyan Xie 2018	0.667	0.142	0.020	0.389	0.945	4.703	0.000	105	105
Wafaa M. Soliman 2018	1.134	0.214	0.046	0.714	1.554	5.290	0.000	30	120
Fengxian Tan 2018	15.940	0.946	0.895	14.085	17.794	16.844	0.000	47	100
Yunxiu Wu 2016	0.718	0.130	0.017	0.462	0.973	5.504	0.000	136	116
Servet Yolbas 2016	0.464	0.197	0.039	0.078	0.850	2.354	0.019	55	51
Baodong Qin 2015	0.461	0.116	0.013	0.234	0.689	3.976	0.000	151	154
	0.709	0.066	0.004	0.580	0.838	10.784	0.000		



Meta Analysis

Fig. 4. Forest plot of studies examining PLR and SLE.

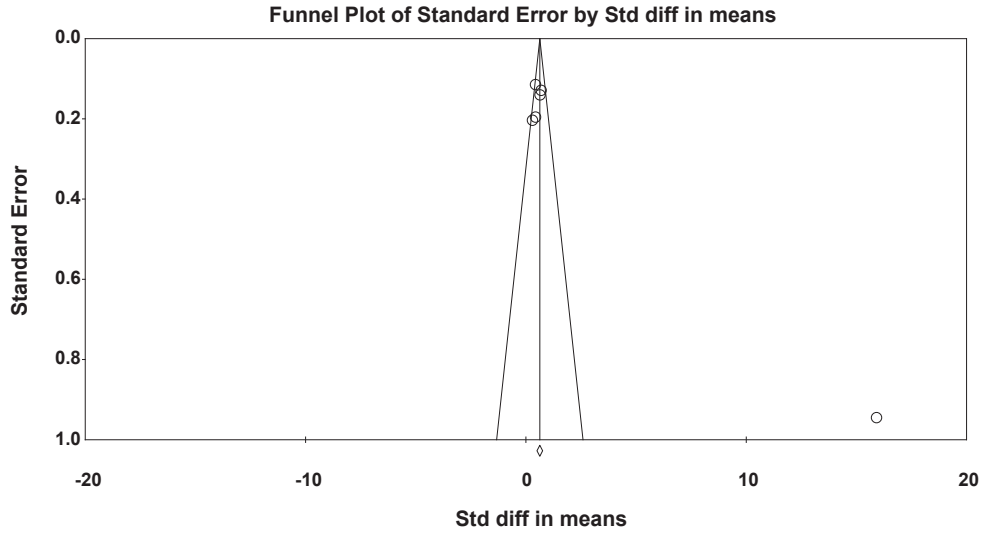
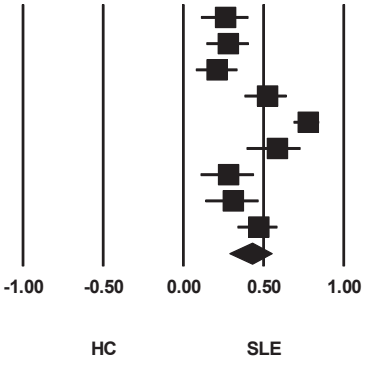


Fig. 5. Funnel plot of studies examining the relationship between PLR and SLE.

Study name	Correlation	Lower limit	Upper limit	Z-Value	p-Value
Wei Lin 2019	0.264	0.111	0.405	3.334	0.001
Jianlin Yu 2018	0.281	0.144	0.407	3.938	0.000
Haitao Yu 2018	0.211	0.078	0.336	3.097	0.002
Wafaa M. Soliman 2018	0.525	0.382	0.644	6.308	0.000
Fengxian Tan 2018	0.779	0.688	0.846	10.271	0.000
Zhao Yinxia 2017	0.587	0.395	0.730	5.170	0.000
Hyoun-Ah Kim 2017	0.282	0.108	0.439	3.135	0.002
Yunxiu Wu 2016	0.312	0.138	0.468	3.431	0.001
Baodong Qin 2015	0.471	0.338	0.586	6.284	0.000
	0.429	0.288	0.552	5.536	0.000



Meta Analysis

Fig. 6. Meta-analysis of the correlation coefficient between NLR and SLEDAI.

Table 3
Meta-analysis of the correlation coefficient between NLR and PLR and SLEDAI.

	No. of studies	No. of patients	Test of association			Test of heterogeneity		
			Correlation coefficient	95%CI	*P*	Model	*P*	I^2
NLR	9	1128	0.429	0.288–0.552	< 0.001	R	0.795	87.545
PLR	6	715	0.309	0.091–0.498	< 0.001	R	0.003	89.326

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; CI, confidence interval; R, random effects model; SMD, standard mean difference.

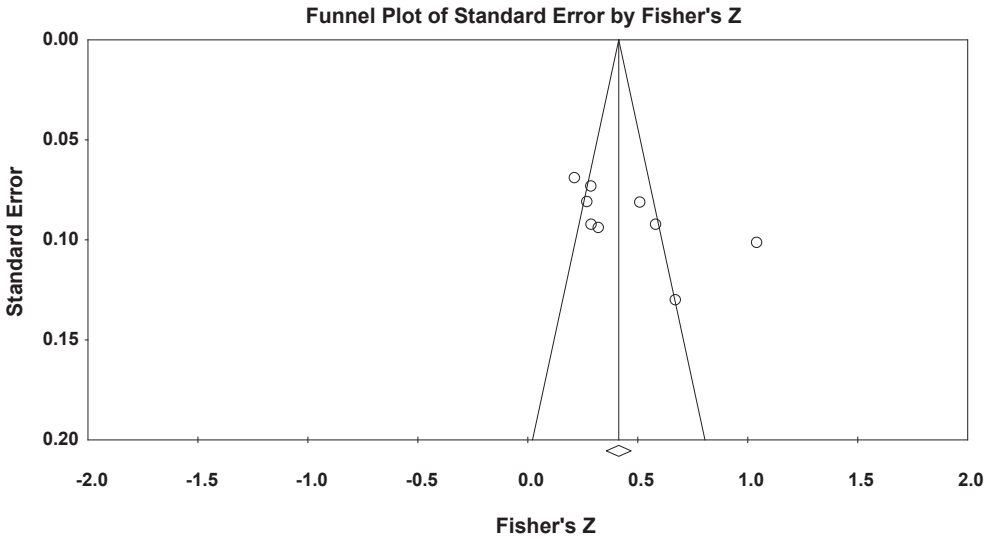


Fig. 7. Funnel plot of studies examining the correlation coefficient between NLR and SLEDAI.

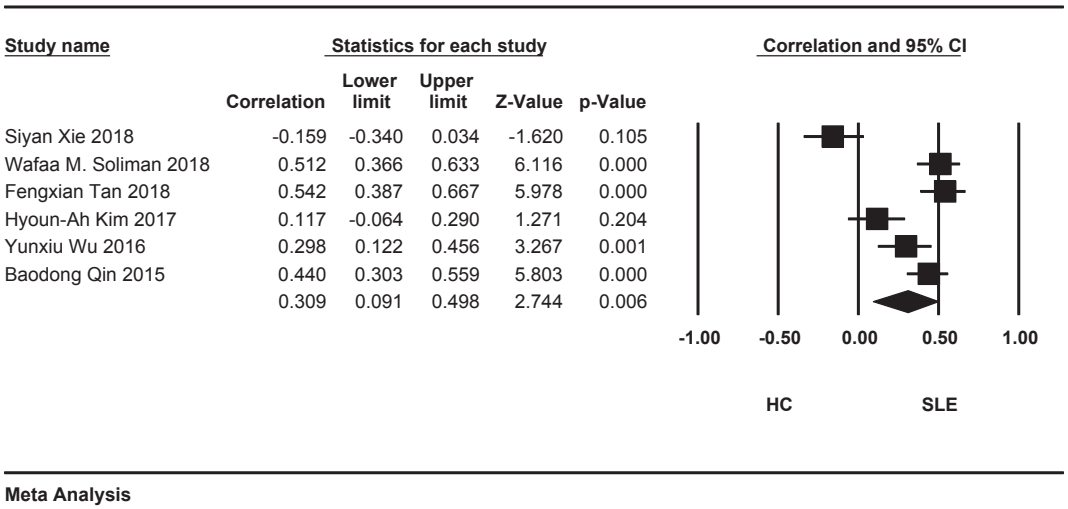


Fig. 8. Meta-analysis of the correlation coefficient between PLR and SLEDAI.

To detect the source of the heterogeneity between NLR studies, we had attempted to conduct a subgroup analysis divided into China and other country groups. The heterogeneity was still high. According to the forest and funnel plots, one PLR study was identified as an outlier due to its relatively low SD values compared with those of other studies. After removing this study from the analysis, the heterogeneity became low (I^2 = 54.87), indicating that the excluded study was the source of heterogeneity.

Although a meta-analysis generally strengthens the quality of available evidence, several shortages should be considered in this meta-analysis. Firstly, there were only a few of included studies and the number of participants is relatively small, which might affect the conclusions discussed in this work. Secondly, in this study complicated autoimmune diseases, such as RA patients with liver or cardiovascular complications, were not excluded due to the limited number of those who could be included. Thirdly, although we had identified the source of high heterogeneity, confounding factors such as basic metabolism index, smoking and drugs may have affected our results. Further analysis had not been done due to the limited data provided by the included studies. Finally, the machine model of the blood analyzer instrument and its reference ranges were not mentioned in the included studies, which may have impacted our results.

In summary, our meta-analysis revealed that NLR and PLR were significantly higher in SLE patients, and were positively correlated with

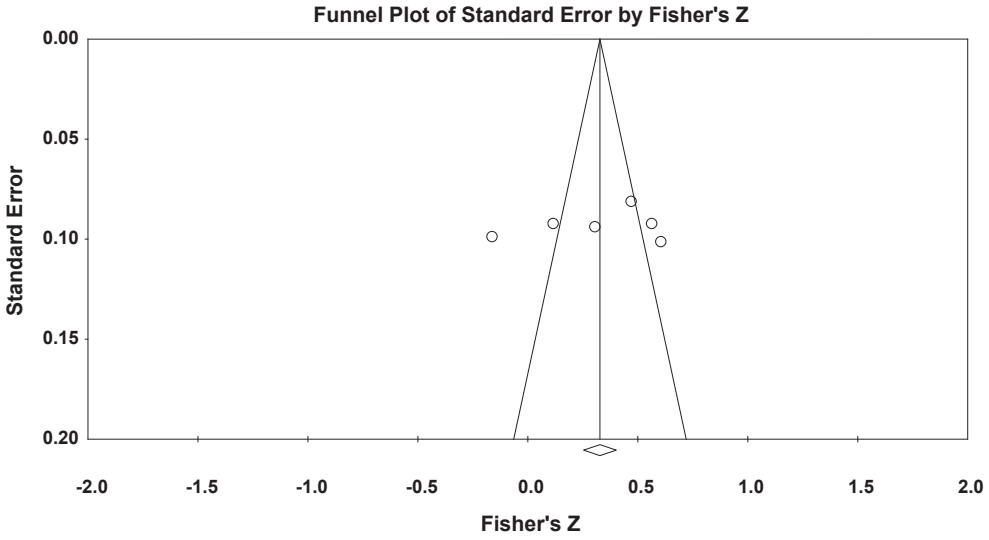


Fig. 9. Funnel plot of studies examining the correlation coefficient between PLR and SLEDAI.

SLEDAI, which suggests that NLR and PLR could be useful biomarkers in the management of SLE.

Declaration of Competing Interest

The authors disclosed no conflict to this publication.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105949.

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