Systematic Review and Meta-Analysis

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Association between neutrophil-to-lymphocyte ratio and polycystic ovary syndrome

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) has been suggested to be a potential biomarker for assessing the systemic inflammatory response in polycystic ovary syndrome (PCOS). This meta-analysis is aimed at evaluating whether PCOS patients present with a higher NLR and whether obesity, metabolic, and hormonal indices have effects on the states.

Methods: We performed a literature search on PubMed, Embase and Web of Science (last update: August 2, 2022). Pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated by applying random-effects models. Meta-regression analyses were used to explore the sources of heterogeneity and assess the relationship between NLR and several clinical parameters. Sensitivity analysis and publication bias were also assessed.

Results: Thirteen studies involving 826 PCOS patients and 780 healthy controls were eligible for the present meta-analysis. Generally, NLR significantly increased in PCOS women versus healthy women (SMD = 0.81, 95% CI = 0.30–1.33, $P = .002$). NLR disparity was subsequently investigated in obese and non-obese cohorts. Obese PCOS women exhibited a higher NLR than obese controls (SMD = 0.56, 95% CI = 0.24–0.87, $P = .001$), and a similar difference was shown between non-obese PCOS and non-obese controls (SMD = 0.36, 95% CI = 0.02–0.71, $P = .038$). No significant NLR disparity was observed between obese versus non-obese PCOS women (SMD = 0.50, 95% CI = –0.37 to 1.38, $P = .259$). Meta-regression analysis revealed that NLR was significantly positively associated with fasting blood glucose ($P = .006$) and total cholesterol levels ($P = .021$), but not correlated with body mass index and other parameters in PCOS patients. Sensitivity analysis indicated that no individual study significantly affected the overall pooled result, and no publishing bias was observed.

Conclusion: PCOS women typically present with an increased NLR. Such an increase is independent of obesity and may be associated with glycolipid metabolic disorders.

Abbreviations: BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, CVD = cardiovascular disease, FBG = fasting blood glucose, FSH = follicle-stimulating hormone, HOMA-IR = homeostasis model assessment of insulin resistance, LH = luteinizing hormone, NLR = neutrophil-to-lymphocyte ratio, PCOS = polycystic ovary syndrome, SMD = standardized mean differences, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride.

Keywords: glucose and lipid metabolism, meta-analysis, neutrophil-to-lymphocyte ratio, obesity, polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders afflicting 5% to 10% of reproductive-age women.[1] Characterized by irregular menstruation, hyperandrogenism, polycystic ovarian morphology, and infertility,[2] this syndrome drives several metabolic disorders such as insulin resistance, abnormal glucose, and lipid metabolism. PCOS women with metabolic disturbances are at higher risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD).[3] Although it is possible to confirm low-grade chronic inflammation as an essential player in PCOS, we are near nowhere an accurate answer to the puzzles of metabolic-inflammatory pathogenesis of this disease.[4]

Low-grade chronic inflammation describes a state characterized by increases in several indicators such as C-reactive

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protein (CRP), tumor necrosis factor-α, interleukin-6, and neutrophil-to-lymphocyte ratio (NLR).[4] A recent meta-analysis demonstrated that PCOS women had significantly increased CRP and interleukin-6 levels and borderline increased tumor necrosis factor-α levels when compared with non-PCOS women[5] NLR is a recently introduced marker of systemic inflammation, which is highly sensitive, readily available, and reasonably inexpensive.[6,7] Recent studies have revealed that elevated NLR is associated with multiple chronic diseases, such as T2DM, thyroid diseases, and novel coronavirus infections.[8–10] NLR may be a better predictor of disease progression in common endocrine diseases than CRP. Previous research displayed that NLR, but not CRP, was significantly related to liver fibrosis and disease activity score in patients with nonalcoholic steatohepatitis.[11] Another recent study demonstrated that NLR was significantly negatively correlated with bone mineral density after adjusting for other risk factors in postmenopausal women; however, the correlation was not observed between CRP and bone mineral density.[12] Moreover, combined CRP and NLR were recently claimed to be the best-advanced detection in the diagnosis of inflammatory or autoimmune diseases.[13,14] Therefore, NLR and CRP may play complementary roles in the diagnosis of some diseases, but superior is NLR for prognosis assessment in specific diseases.

Over the past few years, growing studies have been seen assessing correlations between NLR and PCOS and the relevant metabolic parameters. But inconsistent findings have been obtained. The present meta-analysis was conducted on all eligible studies to confirm whether PCOS women present with an increased NLR and whether obesity has implications for the inflammatory condition.

2. Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines which contain a 27-item checklist[15] (see Supplemental Appendix 1, Supplemental Digital Content 1, http://links.lww.com/MD/H321: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist), and this study protocol followed the guidelines. Since this is a systematic review and meta-analysis, ethical approval was not required.

2.1. Search strategy

We searched subject headings and keywords from PubMed, EMBASE, and Web of Science (last update: August 2, 2022). The search strategy consisted of these headings and keywords (polycystic ovary syndrome, PCOS, neutrophil-to-lymphocyte ratio, neutrophil-lymphocyte ratio, and NLR). Taking PubMed as an example, the detailed retrieval strategy can be found in Supplemental Appendix 2, Supplemental Digital Content 2, http://links.lww.com/MD/H322. The relevant bibliography of candidate articles was manually searched to identify additional studies.

2.2. Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: studies comparing NLR between PCOS women and healthy women; PCOS and control subjects did not suffer from other types of endocrine disease, such as T2DM, hypertension, hyperprolactinemia, or thyroid diseases; and they did not take any drugs in the last 6 months. Studies were ruled out if they were non-human studies, no healthy women as a control group, review articles, conference abstracts, letters to the editor, or case reports, or non-English language literature.

2.3. Data extraction and quality assessment

Two investigators independently reviewed eligible studies and extracted data on study characteristics, NLR records, and metabolic and hormonal indicators. The information for basic features of literature was extracted: the first author's surname, year of publication, study design, study location, the diagnostic criteria for PCOS, and sample size. If the means and standard deviations of NLR cannot be directly obtained from the selected studies (e.g., studies only provided interquartile ranges instead of standard deviations), the necessary conversion was performed according to previously reported methods.[16,17] Anthropometric and metabolic data records alongside age were summarized, consisting of body mass index (BMI), fasting blood glucose (FBG), homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol (TC), and triglyceride (TG). Hormonal indices, including follicle-stimulating hormone (FSH), and luteinizing hormone (LH), were also recorded. Any disagreement was solved by a third reviewer.

The quality of the individual studies included in the present meta-analysis was assessed using a modified criterion under the Newcastle-Ottawa Quality Assessment Scale .[18] Studies were scored on a scale from 0 to 9. A study with a score of 0 to 3 was rated as low-quality, and that with a score of 7 to 9 was viewed as high-quality.

2.4. Statistical analysis

All data were analyzed with STATA version 15 (StataCorp LP, College Station, TX). The individual effect size (i.e., the mean difference in NLR between PCOS versus healthy controls) was calculated as standardized mean difference (SMD) and 95% confidence interval (CI) by employing a random-effects model, which is more conservative than a fixed-effects model.[19] Between-study heterogeneity was estimated by the chi-square-based Q test with the significance level set at $P < .10$. An I^2 of >50% indicated significant heterogeneity. We performed meta-regression analysis in which the dependent variable was the pooled effect size, and the independent variables were predefined as sample size of case group and metabolic and hormonal indices in PCOS (i.e., age, BMI, FBG, HOMA-IR, FSH, LH, TC, and TG). Sensitivity analysis was conducted by sequentially omitting one study at a time. Publication bias was assessed visually by the funnel plot and statistically evaluated by Egger test.

$P < .05$ was regarded to be statistically different unless otherwise noted.

3. Results

3.1. Study selection

The initial search yielded 92 relevant citations. After removing duplicates (n = 54), 38 records remained. Fifteen articles were excluded because they were reviews, conference review, conference abstracts, letter and non-human studies. Among the remaining 23 articles selected for full-text reading, 10 were further excluded for no healthy controls and insufficient data (detailed in Supplemental Appendix 3, Supplemental Digital Content 3, http://links.lww.com/MD/H323). Finally, 13 studies met all eligibility criteria and were included in our meta-analysis.[20–32] More information about the study selection process was illustrated in Figure 1.

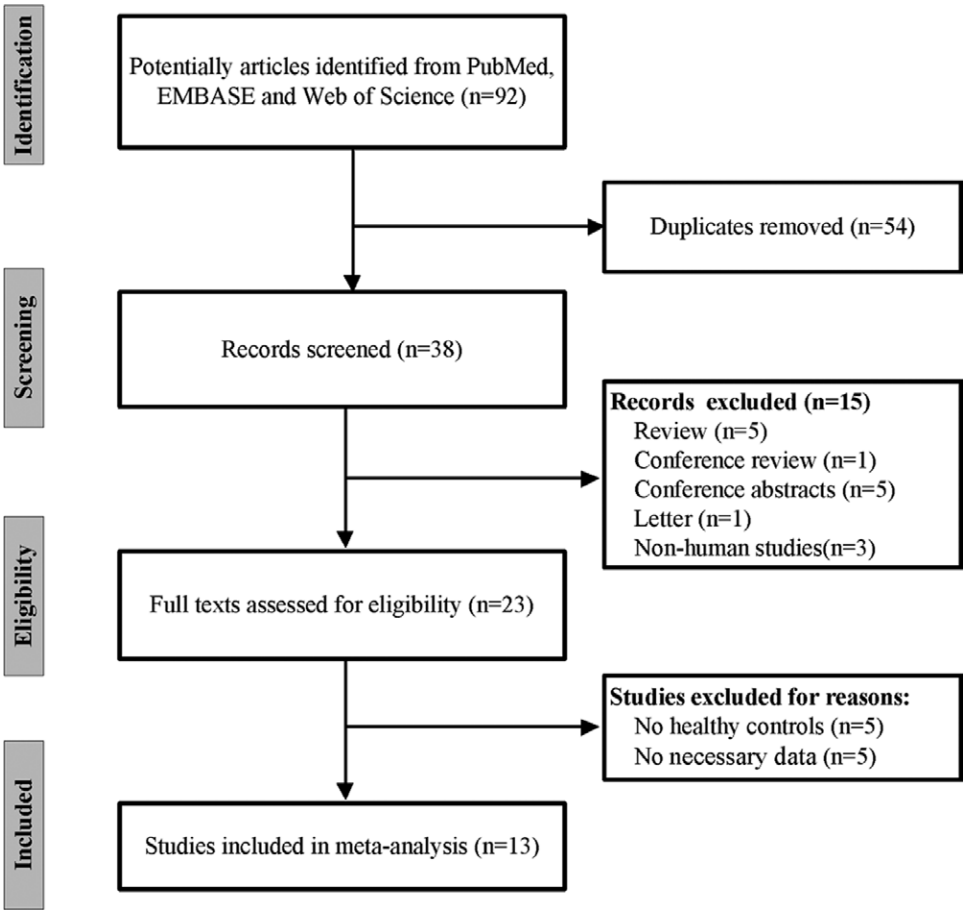

Figure 1. The flow chart of the study selection process.

3.2. Study characteristics and quality assessment

The main characteristics of the 13 studies were listed in Table 1. These studies were published from 2014 to 2022, representing 826 PCOS women and 780 healthy controls. The age of PCOS women ranged from 18.3 to 32.2 years, and BMI ranged from 23.1 to 29.3 km/m^2, based on data from the thirteen studies. Nine studies were conducted in Turkey, and the other four in Saudi, China, Chipre and Iraq, respectively. Nine were cross-sectional in design, and four was case-control studies. Rotterdam criteria were applied for the definition of PCOS in all included studies except one[29] which did not report clearly the criteria. Nine studies provided information on FBG, HOMA-IR, FSH and LH levels. TC and TG levels were reported in eight studies. The Newcastle-Ottawa Quality Assessment Scale quality scores varied from 4 to 9, with 5 studies of high-quality and 8 of moderate-quality. None of the studies obtained a low-quality rating.

3.3. NLR in PCOS and healthy controls

The number of included subjects in the PCOS group and the healthy control group varied from 30 to 112 and 24 to 135, respectively; and the corresponding NLR ranging from 1.8 to 9.0 in PCOS patients and 0.77 to 3.30 in healthy women, respectively. Subjects in six studies were stratified into obese and non-obese cohorts.[15,17–19,23] Detailed results are displayed in Table 2.

3.4. Meta-analysis

Comparisons of NLR disparity were conducted across four cohorts: overall PCOS women versus healthy controls, Obese PCOS group versus obese control group, non-obese PCOS group versus non-obese control group, and Obese PCOS group versus non-obese PCOS group. As revealed in Figure 2, NLR was generally higher in PCOS women than healthy controls (SMD = 0.81, 95% CI = 0.30–1.33, P = .002). As shown in Figure 3, obese PCOS patients had a higher NLR than obese controls (SMD = 0.56, 95% CI = 0.24–0.87, P = .001, Fig. 3A); similarly, non-obese PCOS women also had a higher NLR than non-obese controls (SMD = 0.36, 95% CI = 0.02–0.71, P = .038, Fig. 3B); however, obese PCOS women did not significantly differ from non-obese PCOS women (SMD = 0.50, 95% CI = –0.37 to 1.38, P = .259, Fig. 3C). Heterogeneity between studies was observed in all the four comparisons with I^2 ranging from 50.2% to 95.6%.

3.5. Meta-regression analysis

We performed meta-regression analysis with NLR as the dependent variable, and age, BMI, sample sizes, FBG, HOMA-IR, FSH, LH, TC, and TG as independent variables. As shown in Table 3, NLR was positively correlated with FBG (P = .006), and TC (P = .021) in PCOS women. No significant associations were identified between NLR and other independent variables (all P > .05).

Table 1

Demographic and clinical data of PCOS patients included in this meta-analysis.

References	Region	Study design	Age (yr)	BMI (kg/m^2)	FBG (mg/dL)	HOMA-IR	FSH (IU/L)	LH (IU/L)	TC (mg/dL)	TG (mg/dL)	Quality score
Keskin, 2014[20]	Turkey	Case-control	32.2 ± 4.1	27.3 ± 5.9	104.8 ± 14.0	2.6 ± 1.2	6.0 ± 1.7	11.9 ± 2.3	204.9 ± 30.9	119.9 ± 57.6	9
Yuksel, 2015[21]	Turkey	Cross-sectional	22.9 ± 4.4	24.3 ± 0.93	NA	3.6 ± 5.4	4.6 ± 1.7	8.3 ± 4.8	NA	NA	5
Agacayak, 2015[22]	Turkey	Cross-sectional	26.2 ± 4.0	24.0 ± 4.0	104.0 ± 18.0	NA	NA	NA	192.0 ± 51.1	135.6 ± 54.1	6
Yilmaz, 2016[23]	Turkey	Cross-sectional	23.8 ± 4.7	29.0 ± 7.4	88.3 ± 8.8	3.1 ± 1.8	5.4 ± 1.5	10.7 ± 6.5	NA	NA	6
Tola, 2017[24]	Turkey	Cross-sectional	18.4 ± 2.5	23.3 ± 2.1	89.2 ± 5.24	3.3 ± 2.4	6.9 ± 2.0	8.6 ± 5.9	148.6 ± 27.2	84.6 ± 29.3	6
Kösem, 2019[25]	Turkey	Cross-sectional	19.4 ± 2.6	23.1 ± 3.9	88.8 ± 3.4	1.8 ± 0.6	7.2 ± 2.2	8.9 ± 5.1	160.5 ± 31.6	83.0 ± 36.7	7
Aydın, 2020[26]	Turkey	Cross-sectional	26.8 ± 4.7	28.2 ± 5.6	89.7 ± 10.0	NA	4.7 ± 1.4	5.6 ± 3.5	177.1 ± 32.9	101.4 ± 42.4	6
Can, 2020[27]	Turkey	Cross-sectional	24.0 ± 4.5	27.6 ± 6.3	89.0 ± 11.8	3.2 ± 5.5	NA	NA	NA	NA	5
Özay, 2021[28]	Chipre	Cross-sectional	22.0 ± 3.3	23.4 ± 6.1	NA	1.8 ± 1.2	NA	NA	179.5 ± 42.3	90.5 ± 46.5	7
Al-Dahhan, 2021[29]	Iraq	Cross-sectional	23.4 ± 2.8	29.3 ± 3.6	NA	NA	5.2 ± 2.2	10.3 ± 2.1	NA	NA	5
Almaeen, 2022[30]	Saudi	Case-control	21.1 ± 0.3	26.4 ± 1.02	NA	NA	7.4 ± 2.6	14.9 ± 4.8	184.0 ± 42.6	143.6 ± 41.9	6
Taşkömür, 2022[31]	Turkey	Case-control	18.3 ± 1.3	23.8 ± 2.3	86.2 ± 12.7	2.4 ± 0.6	6.2 ± 1.7	15.1 ± 6.5	165.7 ± 34.3	120.2 ± 54.6	8
Liu, 2022[32]	China	Case-control	26.1 ± 4.8	26.5 ± 3.4	89.3 ± 14.4	3.1 ± 2.4	5.8 ± 1.8	11.3 ± 7.5	NA	NA	8

BMI = body mass index, FBG = fasting blood glucose, FSH = follicle-stimulating hormone, HOMA-IR = homoeostasis model assessment of insulin resistance, LH = luteinizing hormone, NA = not accessed, PCOS = polycystic ovary syndrome, TC = total cholesterol, TG = triglyceride.

3.6. Sensitivity analysis

Sensitivity analysis indicated that the overall pooled estimate was not excessively influenced by any particular study (Fig. 4).

3.7. Publication bias

No publication bias was evidenced by a symmetry funnel plot (Fig. 5). The Egger test subsequently supported this result ($P = .315$).

4. Discussion

Our meta-analysis demonstrated that NLR was significantly increased in PCOS women compared with healthy women. When we examine the impact of obesity on NLR results, we found that both obese and non-obese PCOS women had higher NLR as compared to the corresponding obese and non-obese controls; however, no pronounced NLR difference was observed between obese versus non-obese PCOS patients. Another important finding was that NLR was positively correlated with FBG and TC, other than BMI and other metabolic and hormonal indices in PCOS women. These results suggest that NLR increases are obesity-independent, which may be associated with disorders of glucose and lipid metabolism in PCOS. To the best of our knowledge, this is the first meta-analysis evaluating the association between NLR and PCOS.

Neutrophils and lymphocytes are two of the most abundant subtypes of leukocytes. For far too long, neutrophils have been considered the most significant player during the systemic inflammatory response. An increased neutrophil count often predicts severe systemic inflammation; in contrast, immunoregulatory lymphocytes are suppressed in inflammatory and stress response.[6,7] Therefore, NLR that reveals the interaction between the two subtypes in systemic inflammation has served as a combined marker, surpassing CRP in predicting inflammation state.[13,14] This efficacy has been proven in risk prediction of CVD in a recent meta-analysis, reporting a significant association between an increased NLR and higher CVD risk.[33] More shreds of medicine-based evidence ascertained a significant correlation between PCOS and CVD.[34–36] Whether neutrophils and lymphocytes play a part in the PCOS-CVD association is worth careful investigations, and a full view of this issue is outside the breath of the present work. Of course, insulin resistance is involved in the metabolic pathogenesis of PCOS and a significant contributor to the link between PCOS and CVD.[37–39] However, this contribution was not observed, as indicated by a nonsignificant NLR-HOMA-IR relationship in our analysis. Possible reasons were the relatively small number of studies and the high degree of heterogeneity across studies included. In addition, although a meta-analysis of ankylosing spondylitis studies reported a good correlation between NLR and CRP,[40] this association was not pronounced in our meta-regression as a limited number of CRP studies were included. No evidence supported associations between NLR and FSH, and LH. For relationships with other hormonal parameters such as prolactin and testosterone, a small number of studies remove a major opportunity for a meta-analysis. It is likely that associations among NLR, CRP, and the metabolic and hormonal parameters in PCOS will be investigated by interested researchers, so deeper comprehension of the relationships will be uncovered using a combined NLR and CRP assay.

The current meta-analysis has several limitations. First, considerable heterogeneity in NLR disparity was observed in the initially pooled analysis. The significant associations of NLR with FBG, and TC in the meta-regression analysis suggest that these two parameters fluctuations could partly

Table 2

Results of neutrophil to lymphocyte ratio in PCOS patients and healthy controls.

	PCOS patients			Healthy controls		
References	Sample size (N)	Mean	Standard deviation	Sample size (N)	Mean	Standard deviation
Keskin, 2014[20]	62 (OB: 32, non-OB: 30)	2.61 (OB: 2.80, non-OB: 2.40)	1.38 (OB: 1.60, non-OB: 1.10)	60 (OB: 30, non-OB: 30)	1.45 (OB: 1.40, non-OB: 1.50)	0.41 (OB: 0.30, non-OB: 0.50)
Yuksel, 2015[21]	35	2.04	0.87	27	2.28	0.72
Agacayak, 2015[22]	30 (OB: 15, non-OB: 15)	9.00 (OB: 7.30, non-OB: 10.30)	9.40 (OB: 8.0, non-OB: 11.0)	30 (OB: 15, non-OB: 15)	3.30 (OB: 2.20, non-OB: 4.50)	5.60 (OB: 1.00, non-OB: 8.30)
Yilmaz, 2016[23]	41 (OB: 25, non-OB: 16)	2.08 (OB: 2.17, non-OB: 1.94)	0.74 (OB: 0.83, non-OB: 0.57)	30 (OB: 16, non-OB: 14)	1.74 (OB: 1.91, non-OB: 1.59)	0.63 (OB: 0.84, non-OB: 0.32)
Tola, 2017[24]	34	2.42	1.14	33	2.05	0.62
Kösem, 2019[25]	41	2.00	0.74	41	1.90	0.67
Aydın, 2020[26]	36	2.30	1.57	24	3.08	3.02
Can, 2020[27]	56 (OB: 31, non-OB: 25)	2.01 (OB: 2.08, non-OB: 1.93)	0.71 (OB: 0.91, non-OB: 0.63)	48 (OB: 23, non-OB: 25)	1.97 (OB: 1.94, non-OB: 2.01)	1.07 (OB: 0.67, non-OB: 1.32)
Özay, 2021[28]	110	2.31	0.83	135	1.86	0.65
Al-Dahhan, 2021[29]	92	6.82	0.97	46	1.81	0.22
Almaeen, 2022[30]	88	1.80	0.95	118	0.77	0.26
Taşkömür, 2022[31]	89 (OB: 26, non-OB: 63)	2.28 (OB: 1.97, non-OB: 2.41)	5.06 (OB: 1.31, non-OB: 5.97)	98 (OB: 27, non-OB: 71)	1.74 (OB: 1.73, non-OB: 1.75)	1.54 (OB: 0.82, non-OB: 1.76)
Liu, 2022[32]	112 (OB: 68, non-OB: 44)	1.94 (OB: 2.61, non-OB: 0.90)	1.06 (OB: 0.75, non-OB: 0.47)	90 (OB: 47, non-OB: 43)	1.54 (OB: 2.13, non-OB: 0.88)	0.92 (OB: 0.76, non-OB: 0.55)

OB = obese, PCOS = polycystic ovary syndrome.

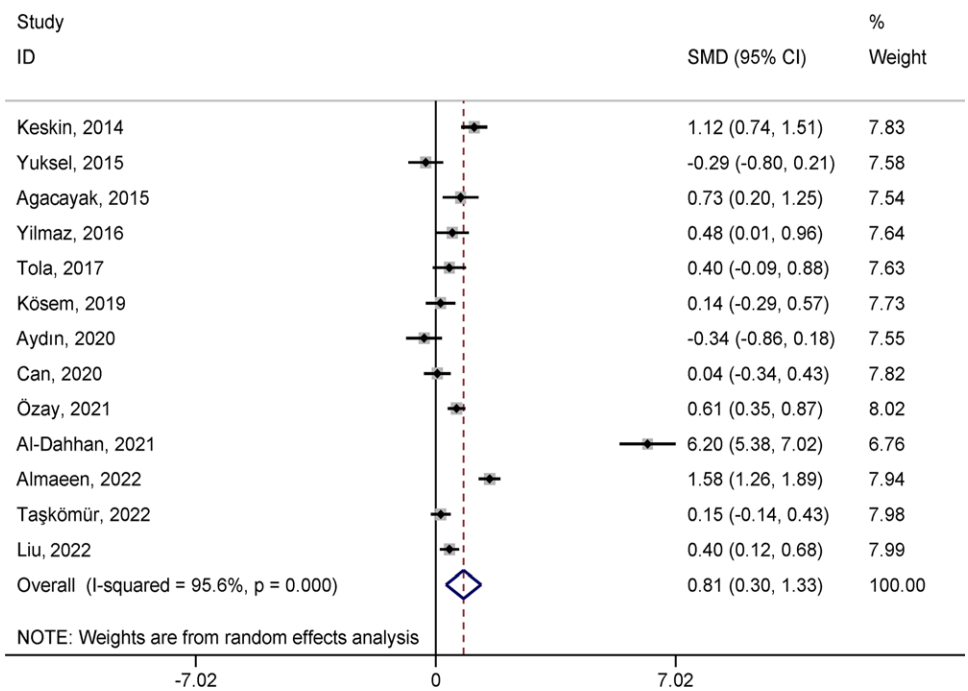

Figure 2. Forest plot for the comparison of overall neutrophil-to-lymphocyte ratio between polycystic ovary syndrome women and healthy women. CI = confidence interval, SMD = standardized mean differences.

explain the source of heterogeneity. Second, the majority of included studies in our meta-analysis were from Turkey (9 out of 13); therefore, the present findings may not be robust and generalizable. However, our sensitivity analysis revealed that no single study substantially influenced the pooled results. Third, although this meta-analysis included 13 studies, the combined sample size was still relatively small in both PCOS and control groups, especially in separate obese

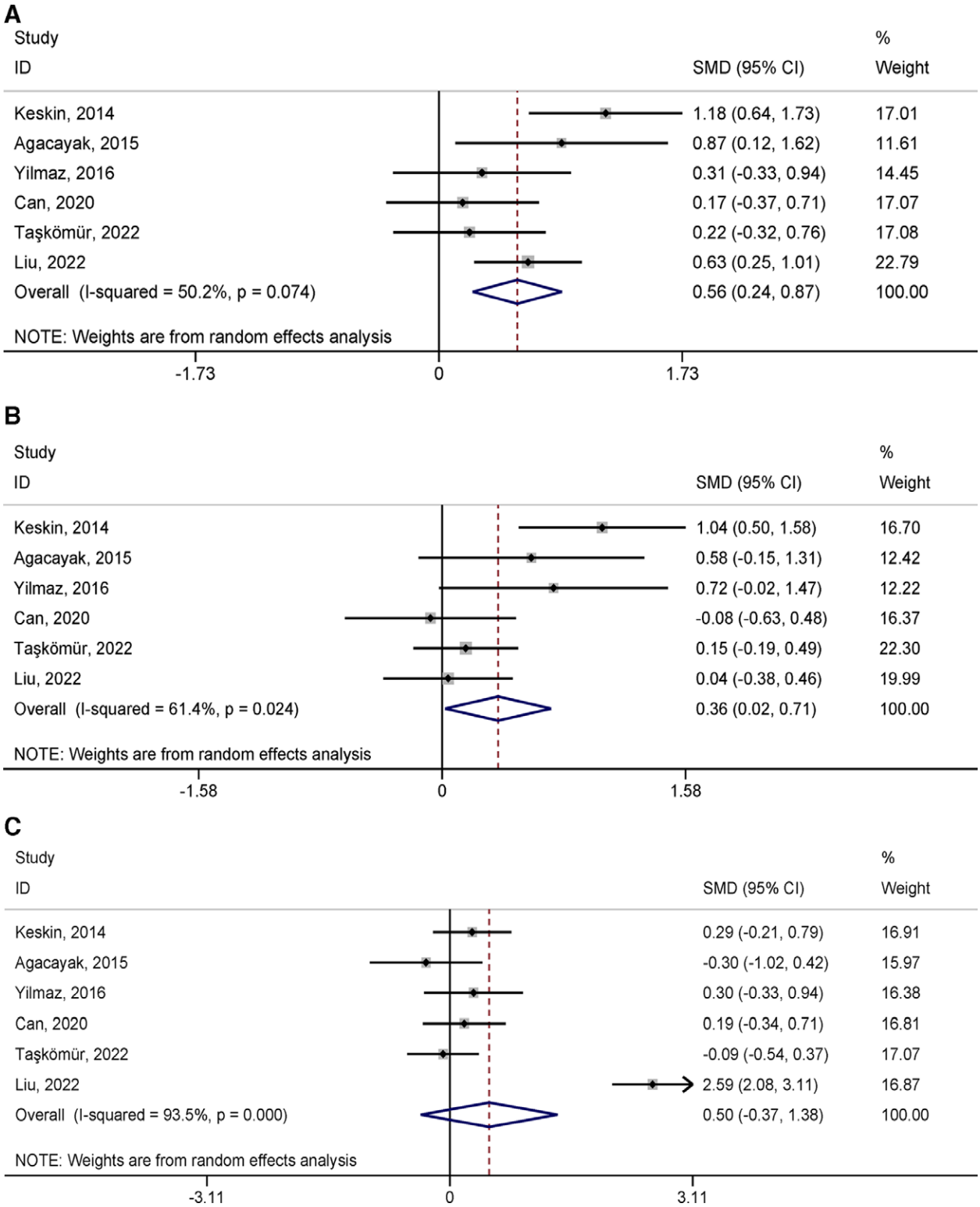

Figure 3. Forest plot for the comparison of neutrophil-to-lymphocyte ratio between obese PCOS women and obese controls (A); between non-obese PCOS women and non-obese controls (B); and between obese PCOS women and non-obese PCOS women (C). CI = confidence interval, PCOS = polycystic ovary syndrome, SMD = standardized mean differences.

or non-obese cohorts. Further research would be needed to confirm the relationship in a larger, more diverse population. Finally, only articles published in English were included, which could have introduced the publication bias and selection bias, although our funnel plot and Egger test showed no significant bias.

5. Conclusion

PCOS patients present with a higher NLR than healthy women, suggesting that NLR may serve as a readily obtained biomarker for evaluating the systemic inflammatory states in PCOS. Improved knowledge of the obesity-independent

Table 3

Meta-regression analysis with neutrophil-to-lymphocyte ratio as the dependent variable.

Variables	Exp(B)	*t*	95% confidence interval	*P*
Sample sizes	1.020	1.31	0.987–1.055	.215
Age	1.023	1.32	0.770–1.359	.866
Body mass index	1.372	1.61	0.891–2.112	.135
Fasting blood glucose	1.047	3.66	1.017–1.078	**.006**
HOMA-IR	0.836	–0.89	0.525–1.330	.399
Follicle-stimulating hormone	0.914	–0.13	0.193–4.318	.897
Luteinizing hormone	1.126	0.53	0.672–1.886	.611
Total cholesterol	1.018	3.11	1.004–1.033	**.021**
Triglyceride	1.016	1.98	0.996–1.037	.096

Bold *P*-value denotes statistical significance.

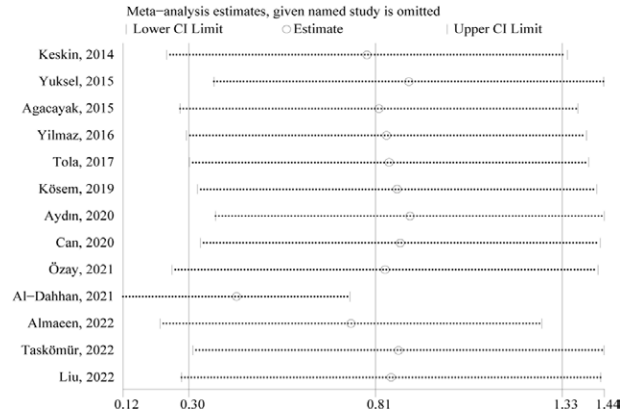

Figure 4. Sensitivity analysis for assessing the impact of every study on the overall pooled estimate. CI = confidence interval.

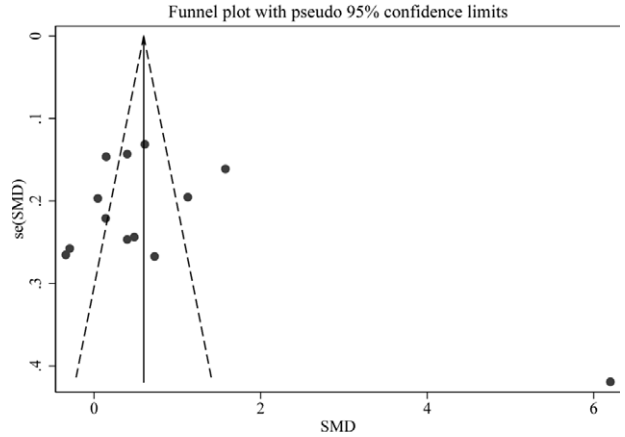

Figure 5. Visual inspection of funnel plots evaluating potential publication bias of the included studies. se = standard error, SMD = standardized mean differences.

property of NLR and the possible associations of NLR with glucose and lipid metabolism in PCOS should encourage researchers to be committed to studies with a larger and more diverse sample.

Author contributions

Conceptualization: Zhongwei Zhou.
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Writing – original draft: Li Li, Jianxiu Yu.
Writing – review & editing: Zhongwei Zhou.

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