Systematic Review and Meta-Analysis on Role of Adiponectin to Leptin Ratio in Women with Polycystic Ovarian Syndrome

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ABSTRACT

Objective: PCOS or Polycystic Ovarian Syndrome, a multifaceted disorder marked by disruptions in endocrine and metabolic processes, influences reproductive age women. The most commonly used criteria for diagnosing this condition are the Rotterdam 2003 and the National Institutes of Health Consensus 1990 guidelines. Recent studies are currently focusing on novel biomarkers, such as adiponectin and leptin to gain deeper insights on the intricate pathophysiology of PCOS. Therefore, this review aimed to consolidate the importance of the A:L (adiponectin to leptin) ratio as a potential and promising biomarker for PCOS.

Materials and Methods: The method followed the PRISMA 2020 guidelines. Furthermore, MEDLINE, Proquest, and EBSCOhost databases were used to obtain eligible studies published up to February 2023. This study was registered in PROSPERO on April 2, 2023 with registration number CRD42023411754. ESHRE/ASRM or Rotterdam Guideline was used as the diagnosis criteria for women with PCOS. To examine the studies' heterogeneity, the I^2 statistic and Cochran's Q test were utilized. Meanwhile, the evaluation on publication bias visually employed a funnel plot and was confirmed through Egger's test and rank correlation test. Data analysis was conducted with JASP 0.17.1, and statistical significance was characterized as a p-value below 0.05.

Results: In the systematic review, a total of nine studies were incorporated, and seven studies were used in the subsequent meta-analysis. Each paper showcased a reduced A:L ratio in women with PCOS, with a standardized mean difference (SMD) among PCOS and control groups of 0.49 (CI: 0.37 - 0.61). The residual heterogeneity test yielded a p-value of 0.069, and no publication bias indication both pre and post intervention (p=0.002).

Conclusion: Referring to the findings, the A:L ratio was notably lower in PCOS patients. Consequently, the A:L ratio holds promise as a novel and potential biomarker for PCOS.

Keywords: Polycystic ovarian syndrome; adiponectin to leptin ratio; biomarker (Siriraj Med J 2023; 75: 838-850)

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) stands as a familiar and diverse endocrine disruption that impacts reproductive age women. This condition significantly impacts the endocrine, reproductive, and metabolic systems.[1] In numerous studies, the occurrence differs based on the particular used criteria for diagnosis. The worldwide prevalence can vary, spanning from 4% to 21% when considering the Rotterdam 2003 criteria and the National Institutes of Health Consensus 1990 criteria.[2] Over the years, PCOS has shown a rapidly increasing trend and is frequently associated with abdominal adiposity, infertility, obstetrical problems, and cardiovascular disease, leading to a deprived life quality.[3]

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https://doi.org/10.33192/smj.v75i12.265452

Recent analysis revealed that this disease is linked to a range of metabolic disorders, emphasizing the need for further in-depth investigation to explore the relationship between the two entities.[4] This field of study aims to uncover novel biomarkers to provide enhanced comprehension of the intricate pathophysiological mechanisms at play in PCOS, including factors like adiponectin (A) and leptin (L).[5] These adipokines have been associated to a variety of metabolic disorders, such as obesity, insulin resistance, hyperandrogenism, as well as dyslipidemia.[6]

Leptin, originating from adipose tissue, serves as an indicator of body fat levels and plays role in energy homeostasis and insulin resistance.[7] Adiponectin is additionally generated by adipocytes, controlling lipid metabolism and glucose uptake. Furthermore, it functions by increasing hepatic glycolysis and fatty acid oxidation, as well as decreasing gluconeogenesis.[8] Numerous investigations have documented the connection between leptin and adiponectin and their relevance to cardiometabolic conditions, suggesting that the A:L ratio could act as a predictor of metabolic risk factors.[9] A:L ratio also has better diagnostic accuracy in identifying the risk of insulin resistance compared to these adipokines alone.[10] In PCOS patients, it has shown potential as a promising biomarker for diagnosis, as PCOS shares several common metabolic disturbances.[11] Despite previous reports have investigated the connection between the A:L ratio and PCOS, a better understanding of these adipokines in the course of disease is still needed. Findings also show fewer studies on the significance of the A:L ratio as a biomarker, thus we performed a meta-analysis to synthesize its magnitude and obtain the effect size (ES). Therefore, this article summarizes the final results of the A:L ratio as a promising reliable biomarker for PCOS.

MATERIALS AND METHODS

The design was planned and executed as the guideline in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 protocol.[12]

Variable of interest and aim of the study

This study examines the differences in the A:L ratio between PCOS and non-PCOS groups as a novel diagnosis biomarker.

Eligibility criteria

This article encompassed all previously published observational studies that examined the A:L ratio's role in marking inflammation and insulin resistance in PCOS cases.

All articles published dating up to 2023 were also included. Furthermore, the 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM or Rotterdam Guideline)[13,14] were used as diagnosis criteria for women with PCOS. Studies falling under categories, such as review, case reports, case series, conference abstracts, book sections, commentaries/editorials, and studies consisting of non-human subjects were omitted. Articles lacking complete text and those unrelated to the relevant subject matter were also disregarded.

Literature search and information sources

The PRISMA 2020 guidelines were used during the literature search. MEDLINE, Proquest, and EBSCOhost search engines were used to find relevant cases, dating up to February 2023. All studies obtained were screened for duplicates, while the titles and abstracts were independently reviewed by the authors. Furthermore, the studies were omitted from consideration if the titles and/or abstracts did not align with the focus of this review. The full text was read by three authors and the eligible papers were included in this review. Conflicts were solved by consensus and the opinion of all reviewers.

Data collection process

Six reviewers individually carried out the process of data extraction. Any disagreements that arose were resolved through common consent among the reviewers and, when necessary, by seeking the input of the sixth reviewer. Comprehensive data was documented concerning the name of the primary author, study year, the country, the study's type, demographic characteristic of the patients (number of participants and their age), PCOS diagnosis criteria, population matching, adjusted confounding factors/exclusion criteria, and their outcome of interest. For bivariate data extraction, yielded studies were further classified based on the L:A or A:L ratio from each group (PCOS and non-PCOS). This primary outcome was measured by mean difference (MD) as the parameter of ES.

Data and outcome measures

Adiponectin and leptin serum level was presented as μg/L or ng/mL, consecutively. Values were displayed as mean ± standard deviation (SD) for normally distributed data, or as median (interquartile range) for not normally distributed data. A:L ratio was reported or calculated by dividing the amount of adiponectin by the amount of leptin, leading to a single numerical value of ratio. When the study reported the L:A ratio, the value was reversed to obtain the A:L ratio.

Synthesis of result and summary measures

The main outcomes were tabulated in univariate and bivariate results. Data regarding the number of participants and patient's age were included as demographic characteristics in each study. The types of study, PCOS diagnosis criteria, population matching, and other possible outcome biases were also presented in an univariate table. These baseline characteristics were further discussed to elaborate on the confounding factors that could interfere with the results of the A:L ratio. The bivariate table presents the A:L ratio for each group, and also a *p-value* and 95% Confidence Interval (CI).

Quality assessment

Each article underwent evaluation utilizing the Newcastle-Ottawa Scale (NOS) for case-control studies, and an adjusted version of NOS was employed for cross-sectional studies.[15,16] These tools consisted of three main domains, namely (a) Selection, (b) Comparability, (c) Outcome/exposure. According to the NOS for case-control studies, the quality was classified as follows: (1) Good (3-4 stars in the selection domain, 1-2 stars in comparability, and 2-3 stars in exposure), (2) Fair (2 stars in selection, 1-2 stars in comparability, and 2-3 stars in exposure), and (3) Poor (0-1 star in selection or 0 stars in comparability or 0-1 stars in exposure). In relation to the modified NOS for cross-sectional studies, the categorization of study quality was conducted as outlined below: (1) Very good (9-10 stars), (2) Good (7-8), (3) Satisfactory (5-6), (4) Unsatisfactory (0-4). Each study was independently assessed by two authors. Any discrepancies were resolved through deliberation among all the authors until an unanimous agreement was achieved. The findings of the assessment of study quality are displayed in Table 1.

Data synthesis and statistical analysis

The standardized mean difference (SMD) and the 95% CI of the A:L ratio in participants of all included studies was calculated using the "Meta-Analysis Effect Size Calculator".[17] The standard error (SE) was obtained by dividing the length of the CI by 3.92. The ES and SE were then entered into a Microsoft Excel spreadsheet and used to perform meta-analysis. I^2 statistic and Cochran's Q test were employed to examine the heterogeneity among articles. In cases where heterogeneity was identified ($p < 0.10$ or $I^2 > 75\%$)[18,19], It was used the random effects model for the analysis, and generated a forest plot to illustrate the combined effect size. Subsequently, a visual assessment on the publication bias was performed through a funnel plot. The statistical confirmation was accomplished by conducting a rank correlation and Egger's tests. The trim and fill method[16] was employed to correct the bias found. However, it was unable to ascertain the presence of publication bias when the total number of included studies was fewer than 10. All analyses were conducted using JASP 0.17.1 and p <0,05 was assumed as statistically significant.

RESULTS

Literature search

Fig 1 presents a flowchart summarizing the study selection process and its outcomes. Furthermore, the searches strategy yielded 561 potentially relevant studies. Following the specified criteria for selection, a total of 12 studies were pinpointed for a more thorough full-text evaluation, one was considered not suitable, and another two had no control group for comparison. In total, nine papers were involved in systematic review and seven studies eligible for data extraction were used in meta-analysis. The PCOS groups exhibited sample sizes that spanned from 31 to 241, while the control groups had sample sizes ranging from 22 to 216.

Characteristics of included studies

A total of nine studies, consisting of 1,598 women (865 PCOS and 733 non-PCOS) met the inclusion criteria. The characteristics, including the number of participants (N), age (years), population matching, exclusion criteria, and area under the curve (AUC) represented the sensitivity and specificity of A:L ratio were extracted from each study and reported in Table 1. Furthermore, six of them were case-control studies[5,20–24] and the other three were cross-sectional studies.[11,25,26] All the papers used the Rotterdam ESHRE/ASRM 2003 criteria for diagnosing PCOS. The mean ages of PCOS and non-PCOS populations ranged from 23.4 ± 6.1 to 32.85 ± 4.25 years and 23.9 ± 3.6 to 32.5 ± 4.9 years, respectively. The results showed that only five studies[5,11,20,22,26] had carried out age population matching and two studies[11,26] had performed BMI-matching population. Among the nine studies, two came from India[5,11], one from Bangladesh[24], one from Ghana[21], two from Bahrain[22,23], one from Australia[25], one from Italy[26] and one from Brazil.[20]

Quality Assessment

Quality assessment for obtained studies were performed using the NOS for case-control (Table 2A) and cross-sectional studies (Table 2B). A total of three, five, and one papers were in the very good,[11,25,26] good,[5,20–23] and fair quality categories, respectively.[24]

In the nine studies included in the qualitative

TABLE 1. Study Characteristics.

Author, Year, Country	Types of Study	N		Age (Mean ± SD)		Population matching	Exclusion Criteria	Sensitivity/ Specificity of A:L ratio AUC*
		PCOS	Non PCOS	PCOS	Non PCOS			
Mishra et al., 2022, India[11]	Cross-Sectional Study	60	60	27.5 ± 2.83	27.83 ± 3.03	Age and BMI	Pregnant, liver disease, lactating and women with diabetes, glucocorticoids, Cushing syndrome, late onset of CAH or other serious medical condition, history of intake of oral contraceptives in the last 3 months, antiandrogens, antidiabetic, ovulation induction agents, antipsychotic, or antihypertensive or hormone replacement therapy.	0.7873 (cut off ≤0.1154)
Mohana et al., 2021, Bangladesh[24]	Case-Control Study	20	20	27.30 ± 1.29	26.45 ± 0.91	N/A	N/A	0.868* (cut off 4.35); P<0.001
Obirikorang et al., 2019, Ghana[21]	Case Control Study	BMI <30: 54 BMI ≥30: 50	52	32.85 ± 4.25	31.63 ± 4.88	N/A	Women with Cushing syndrome, androgen-producing tumors, hyperprolactinemia, non-classic adrenal hyperplasia, diabetes, and active thyroid disease.	0.83
Sarray et al., 2015, Bahrain[22]	Case-Control Study	241	216	28.6 ± 6.1	27.5 ± 7	Age and Ethnic	Androgen-producing tumors, nonclassic adrenal hyperplasia, 21-hydroxylase deficiency, hyperprolactinemia, Cushing disease, and active thyroid disease.	0.650 Cut-off 0.039 P<.001
Shorakae et al., 2018, Australia[25]	Cross-Sectional Study	46	22	30 ± 6	29 ± 8	N/A	Pregnancy, use of any medication that could interfere with SNS activity, diabetes, insulin resistance within 3 months before recruitment, history of secondary hypertension, cardiovascular, cerebrovascular, renal, liver, thyroid, or lung disease, or severe mental illness.	N/A

TABLE 1. Study Characteristics. (Continue)

Author, Year, Country	Types of Study	N		Age (Mean ± SD)		Population matching	Exclusion Criteria	Sensitivity/ Specificity of A:L ratio
		PCOS	Non PCOS	PCOS	Non PCOS			AUC*
Gupta et al., 2017, India[5]	Case-Control Study	223	216	25 ± 10	25 ± 10	Age	Pregnant, lactating, and women with any kind of gynecological or obstetrical problems, women on medication including hormone replacement therapy, with any viral, bacterial, allergy, and inflammatory disease.	N/A
Golbahar et al., 2012, Bahrain[23]	Case-Control Study	50	50	29.5 ± 2.9	28.5 ± 5.9	N/A	History of insulin resistance, ovarian failure, or any other endocrine or major organ disorders.	0.861 (95%CI 0.786 –0.936)
Savastano et al., 2011, Italy[26]	Cross-Sectional Study	BMI <25: 42 BMI ≥25: 48	BMI <25: 20 BMI ≥25: 20	BMI <25: 24.1 ± 4.6 BMI ≥25: 24.8 ± 4.0	BMI <25: 23.9 ± 3.6 BMI ≥25: 25.4 ± 4.6	Age and BMI	The presence of T2DM or abnormal glucose tolerance was excluded by the oral glucose tolerance test (OGTT), Smoking or alcohol consumption, pregnancy, hypothyroidism, hyperprolactinemia, Cushing's disease, non-classical congenital adrenal hyperplasia; previous (within the last 6 months) use of oral contraceptives, glucocorticoids, anti-androgens, ovulation induction agents, anti-obesity drugs, or other hormonal drugs.	N/A
Lecke et al., 2011, Brazil[20]	Case-Control Study	BMI <25: 8 BMI ≥25: 23	BMI <25: 19 BMI ≥25: 38	BMI <25: 25.4 ± 5.3 BMI ≥25: 23.4 ± 6.1	BMI <25 :29.3 ± 5.9 BMI ≥25: 32.5 ± 4.9	Age	Pregnant women with diabetes, thyroid dysfunction, liver or renal disease, and have received drugs known to interfere with hormonal levels for at least 3 months.	N/A

*Area Under the Curve

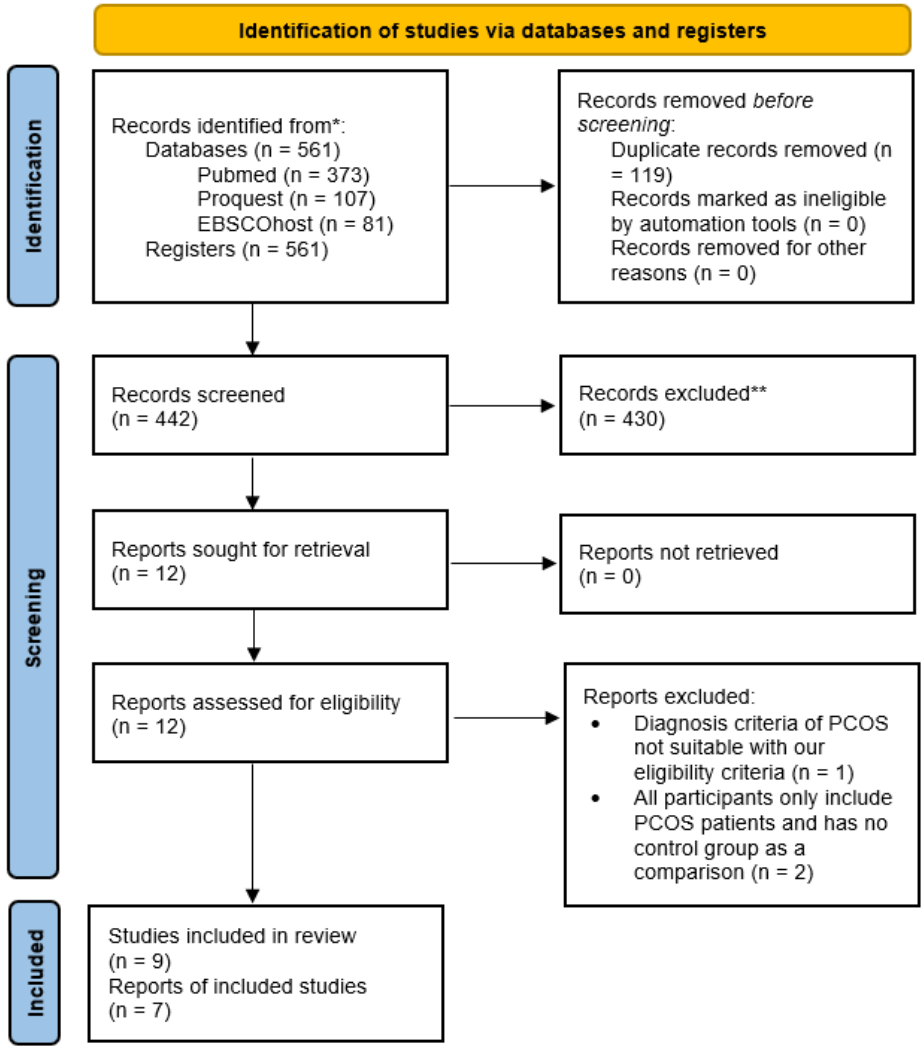

Fig 1. PRISMA flow diagram of involved studies.

TABLE 2A. Risk of bias assessment for case-control studies.

Author, year	Selection				Comparability	Exposure			Conclusion
	S1	S2	S3	S4	C1	E1	E2	E3	
Lecke et al., 2011	☆	☆	☆	☆	☆	☆	☆	☆	Good
Golbahar et al., 2012	☆	☆	☆	☆	☆	☆	☆	☆	Good
Sarray et al., 2015	☆	☆	☆	☆	☆☆	☆	☆	☆	Good
Gupta et al., 2017	☆	☆	-	☆	☆	☆	☆	☆	Good
Obirikorang et al., 2019	☆	☆	-	☆	☆	☆	☆	☆	Good
Mohana et al., 2021	☆	-	-	☆	☆☆	☆	☆	☆	Fair

Note: S1: adequate case definition, S2: case representativeness, S3: control selection, S4: control definition, C1: Comparability, E1: Exposure Ascertainment, E2: identical method of ascertainment for cases and controls, and E3: non-Response Rate.

TABLE 2B. Bias assessment risk for cross-sectional studies.

Author, year	Selection				Comparability	Outcome		Conclusion
	S1	S2	S3	S4	C1	O1	O2	
Savastano et al., 2011	☆	☆	☆	☆	☆☆	☆☆	☆	Very Good
Shorakae et al., 2018	☆	☆	☆	☆☆	☆☆	☆☆	☆	Very Good
Mishra et al., 2022	☆	☆	☆	☆☆	☆☆	☆☆	☆	Very Good

Note: S1: sample representativeness, S2: sample size, S3: non-respondents, S4: exposure ascertainment, C1: comparability, O1: assessment of outcome, and O2: statistical test.

synthesis, the A:L ratio exhibited a significant decrease in PCOS patients, with p-values of <0.0001 to 0.05. The meta-analysis findings from the seven incorporated studies were visualized in both forest and funnel plots (Figs 2A and 2B). The accumulation diagrams of forest plots showed the SMD in each study and the ultimate ES derived from the amalgamation of all the studies. As displayed by the figure, the ultimate weighting of the combined value was depicted in the form of a rhombus shape, while a square shape indicated a weight for each study. The dimensions of each square were determined based on the study's weight in the meta-analysis and calculated referring to the population samples.

Sarray et al.,[22] constituted the larger proportion of samples (N= 457) and Mohana et al.,[24] accounted for the smallest proportion (N=40). All studies had an ES favoring PCOS groups, which was marked by the positive ES on the right side of the plot. A study by Shorakae et al.,[25] had a 95% CI border coinciding with the vertical axis on the left. Based on meta-analysis results, SMD between PCOS and non-PCOS groups was 0.49 (CI: 0.37 - 0.61). Table 5 showed the model for meta-analysis with each Q-statistics and their p-values.

The test results of residual heterogeneity showed a p-value of 0.069. This indicated that the heterogeneity for all studies was not statistically affecting the result, leading to the selection of the fixed effect model. When heterogeneity was attributed to random variation, the random effects model was employed, and it could not be explained because the model presupposed that the

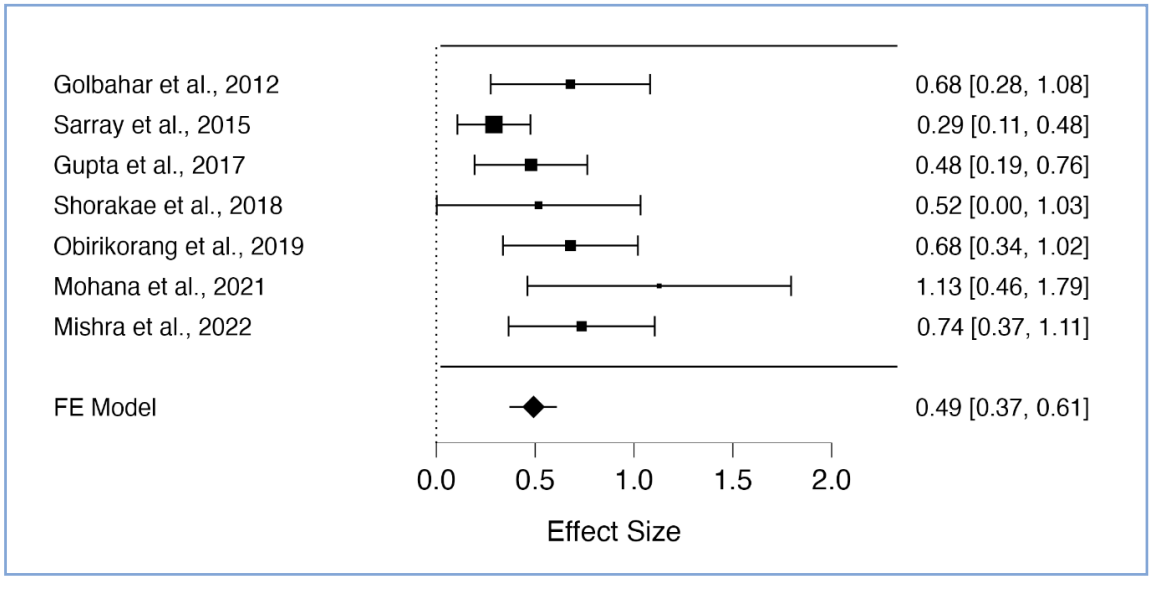

Fig 2A. Meta-analysis results for A:L Ratio (Forest Plot)

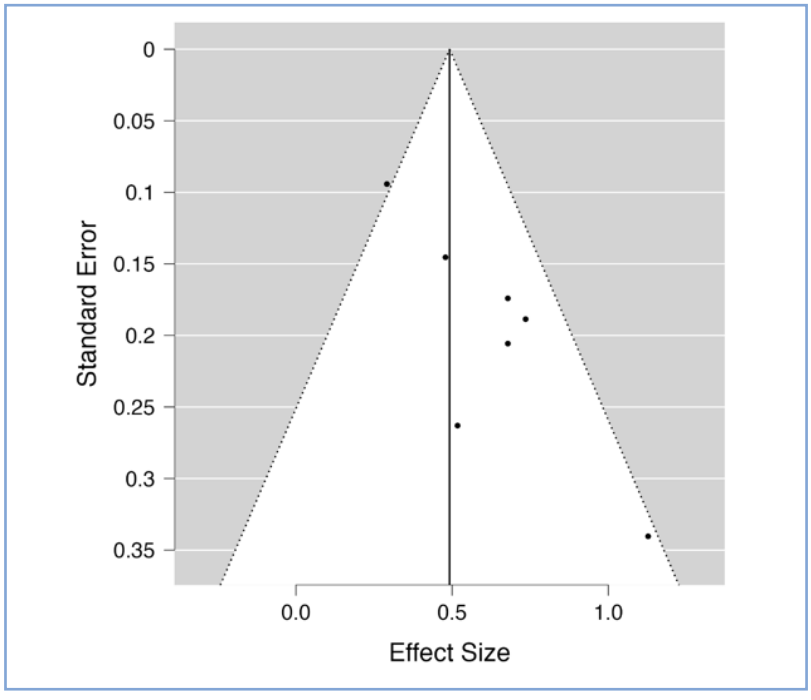

Fig 2B. Meta-analysis results for A:L Ratio (Funnel Plot).

TABLE 3. Results of studies in meta-analysis.

No	Author, Year	Adiponectin/Leptin Ratio				
	PCOS*	PCOS	Non PCOS*	p-value**	SE	SMD
1.	Golbahar et al., 2012[23]	0.25 ± 0.08	0.50 ± 0.15	< 0.001	0.2057	0.6785
2.	Sarray et al., 2015[22]	2.6 (0.2–99.0)	4.8 (0.4–116.9)	0.002	0.0942	0.2912
3.	Gupta et al., 2017[5]	0.53 ± 0.625	0.66 ± 0.68	0.012	0.1454	0.4789
4.	Shorakae et al., 2018[25]	0.07 (0.1)	0.13 (0.1)	0.05	0.2630	0.5175
5.	Obirikorang et al., 2019[21]	0.60 (0.35–0.88)	1.19 (0.92–1.37)	< 0.0001	0.1741	0.6785
6.	Mohana et al., 2021[24]	0.17 (0.12, 0.22)	0.47 (0.29, 0.74)	<0.001	1.1276	0.3404
7.	Mishra et al., 2022[11]	0.15±0.24	3.03±15.04	< 0.0001	0.1886	0.7354

treatment impact was distributed over certain populations and gave each study a more equal weighting. Furthermore, these effects were varying but connected to each other. The results of the I^2 test showed an estimate of 46.287% (<75%), indicating that the random effect model was not considerable.

Results for the Omnibus test of Model Coefficients showed a p-value of <0.001, and the association of the A:L ratio was considered significant. Furthermore, significant results were observed between SMD in PCOS and non-PCOS groups (with intercept result of p<0.001), as shown in Table 4B.

The Egger test was used to assess the bias observed and the results showed no publication bias before and after the intervention (p=0.002). Regarding the correlation test for detecting asymmetry in the funnel plot, Kendall's T value was 0.524, but this correlation did not reach statistical significance (p = 0.136), as detailed in Table 4C.

TABLE 4A. Test for fixed and random effects model.

Test	Q	Df	p-value
Omnibus test of Model Coefficients	64.839	1	<0.001
Residual Heterogeneity Test	11.683	6	0.069

TABLE 4B. Coefficient and residual heterogeneity estimates.

Test	Estimate	95% CI		SE	p-value
		Lower	Upper		
Intercept	0.492	0.372	0.612	0.061	< 0.001

TABLE 4C. Rank correlation test and regression test for funnel plot asymmetry (Egger's test).

Test	Kendall's T / z	p-value
Rank test	0.524	0.136
sei	3.034	0.002

Calculation on SE for both groups from all included studies was performed employing the formula below: SE = (upper CI limit – lower CI limit) / 3.92, or by calculating the square root of the calculated error variance (v). A total of six studies were inside the 95% confidence triangle, with five being located near the vertical axis with 0.49 as the symmetrical line, and one located far from the triangle at the right side of the bottom. Furthermore, only one study was located outside the triangle area. The funnels plot diagram showed that the distribution of studies was asymmetry, with 1 study lying outside the triangle area with SE between 0.05 to 0.1. Others were plotted inside the triangle area, with three studies having an SE between 0.1 to 0.2, two had values between 0.2 to 0.3, and one was between 0.3 to 0.35. The higher the SE, the lower the position of the papers in the inverted funnel, indicating low power compared to others. Accompanying the plot was the 'Rank Correlation Test' for assessing funnel plot asymmetry, and the results showed non-significance with a p-value of 0.136.

DISCUSSION

Meta-analysis results suggested that PCOS patients had a lower A:L ratio, with a statistically significant ES (MD=0.49, 95%CI: 0.37 -0.61, p<0.001). Similarly, Lin et al.,[27] found that in patients with PCOS, adiponectin levels fell statistically significant, but leptin levels rose significantly. Leptin was a hormone derived from adipocytes and encoded by the human obese (ob) gene, which regulated glucose homeostasis. Several studies had recognized its role in several metabolic and endocrine disorders, including PCOS. Prolonged elevation of circulating leptin levels in obese individuals can lead to the development of resistance and decreased receptor sensitivity to leptin.[28] Decreased leptin sensitivity could lead to excessive triglyceride accumulation in multiple

organs and impaired insulin sensitivity.[29] Moreover, the expression of leptin receptors had also been documented in granulosa cells, indicating that it had direct regulatory action in maintaining ovarian folliculogenesis. Leptin resistance could alter the process and this explained the contribution of leptin in PCOS pathophysiology.[30]

Based on two previous meta-analyses,[31,32] increased concentrations of leptin were linked with an increased probability of developing PCOS compared to control participants. According to previous studies, higher levels were also linked to an increased risk of insulin resistance, metabolic disturbance, and cardiovascular disease, all of which could contribute to the development of PCOS. Leptin was assumed to have a stimulatory impact on LH secretion while exerting an inhibitory influence on the actions of FSH and insulin-like growth factor (IGF)-1.[33] Moreover, hyperleptinemia conditions can inhibit ovarian response to gonadotropin stimulation. Based on these findings, raised leptin levels could potentially disrupt hormonal balance and ovarian function in women, elucidating its contribution to PCOS pathophysiology.[34] As analyzed by Zheng et al.,[32] hormone levels were somewhat elevated in non-obese PCOS patients than controls with matching BMI, but this difference was not statistically significant. Hence, leptin levels were elevated in individuals with PCOS, regardless of their BMI.

Adiponectin hormone released by adipose tissue contributes to mitigating atherogenic harm and insulin resistance, and it also has an effect on other tissues. Given adiponectin's insulin-sensitizing properties, its reduced levels in obesity, and the capacity of testosterone to diminish adiponectin levels,[34] one could hypothesize that women with PCOS might have lower concentrations.[34] Among non-PCOS women, the levels exhibited a decline as BMI increased.[36] Meanwhile, in women with PCOS, there was an independent impact on insulin sensitivity, which was not associated with obesity and had been observed in lean individuals as well (BMI < 25 kg/m^2).[37] Adiponectin receptor 1 (adipoR1) and adiponectin receptor 2 (adipoR2) have been discovered as the membrane receptors responsible for mediating its glucose-lowering and anti-inflammatory actions. Previous research indicated that the expression of these receptors was diminished in individuals with obesity. Nevertheless, in women with PCOS, there was an upregulation observed in both visceral fat and subcutaneous tissue.[35]

According to meta-analysis by Toulis et al.,[38] adiponectin was reduced in PCOS women in contrast with control group with a comparable BMI. The levels were descending in obese individuals with PCOS than those without. Also, it was related to insulin sensitivity, where patients with higher insulin resistance had more inferior amounts of the hormone.

The A:L ratio has been considered as an indication of adipose tissue malfunction and a potentially valuable biomarker for metabolic disorders.[39] Insulin resistance (IR) had been associated with a decrease in A:L ratio. Even though IR is considered an intrinsic feature to PCOS, yet it is not included in most established diagnostic criteria. Therefore, A/L ratio come up as a promising novel biomarker for IR in PCOS patients, regarding their independent association with PCOS. Besides, it might help to identify PCOS women who are at risk of developing IR, which marked by an alteration in the A:L ratio and subsequently be used as a screening tools for the risk factor of IR in PCOS.[11]

Several studies showed that A:L ratio considered as the best predictor of IR in PCOS, compared to other adipokines (adiponectin (A) alone, leptin (L) alone, resistin (R) alone, or L:R ratio).[22,39,40] Supported by its AUC values in the ROC curve, the A:L ratio exhibited superior sensitivity and specificity in five studies (with AUC values of 0.787[11], 0.868,[24] 0.830[21], 0.861,[23] and 0.650[22]). An AUC between 0.8 and 0.9 as reported in three of the studies[21,23,24] indicated a good diagnostic performance.[41] The ROC curve was unaffected by disease prevalence since it depended on the sensitivity and specificity. Therefore, samples could be calculated independent of the incidence of disease among the general population.[42]

For decades, IR is considered as a major factor for the development of the metabolic syndrome.[43] With the purpose to prevent further metabolic and cardiovascular complications, A:L ratio emerge as a propitious biomarker of IR, thus generate a requirement of an accurate and personalized clinical assessment. Treatment plans should be customized for each PCOS woman based on her risk profile for metabolic disease, as well as any complaints she may have regarding infertility, hirsutism, or menstruation disturbances.[44]

Heterogeneity and publication bias analysis

The I^2 test for heterogeneity showed a value of 46.287%, which could be classified as *"represent moderate heterogeneity"*.[45] Considering the low to moderate heterogeneity of this result, further subgroup analyses were not necessary. The heterogeneity of the result could be observed from clinical, methodological, or statistical perspectives. From a clinical perspective, the differences in participants or outcomes could lead to high levels. This study involved 40 to 457 women as participants. The larger the sample, the more likely or unlikely the ES could occur. From a methodological

perspective, the differences in study design and population matching could lead to high heterogeneity. Apart from the matching effort, all studies excluded those with pregnancy, diabetes, liver disease, renal dysfunction, history of oral contraceptives, hormonal imbalance (Cushing syndrome, androgen deficiency), and all medical history encompassing the use of medications such as hormone replacement therapy, as well as any history of viral, bacterial, allergic, or inflammatory conditions. Considering the possibility of controlling the confounding factors at the beginning of the study, heterogeneity from methodological perspectives was unlikely. Ultimately, from a statistical perspective, variation in intervention effects or results contributed to increased heterogeneity. In this systematic review, three studies reported the L/A ratio and four other studies reported the A:L ratio. Four studies reported ratio in median and interquartile range values,[21,22,25] and three other papers reported in mean and SD values. Despite the various reporting results, all studies were calculated using SMD in meta-analysis, thus minimizing the statistical heterogeneity.

The source of potential bias in this study included publication bias, where there was a tendency among authors and publishers to predominantly release papers that showcased significant results. In this systematic review, results for the A:L ratio driven from all papers were reportedly significant. Other sources of bias included data variances among methodological designs, where two and five studies had cross-sectional and case-control designs.

Strengths and limitations of the study

Our review had several strengths, including being the first meta-analysis that investigated the potential role of the A:L ratio in determining the presence of inflammation in PCOS. This review also included all studies that either reported an A:L ratio or an inverted L:A ratio. All studies were considered to have good quality, implying more reliable conclusions. The results varied based on the difference in the A:L ratio in PCOS and non-PCOS groups, with several papers being reported in mean and median. These varying results could be solved by normalizing the data distributions to obtain more parametric findings. Several confounding variables, particularly insulin resistance and BMI could not be adjusted. This condition could potentially influence the outcome and exposure relationship, leading to a discrepancy in the summary ES.

Future directions

A threshold for A:L ratio had been proposed, with values of >1.0, 0.5-1, and <0.5 being deemed normal, moderately increased risk, and severe increase in cardiometabolic risk, respectively.[39] Furthermore, there was no established cut-off value for the A:L ratio as a biomarker for PCOS. Future studies with larger populations and interventional study designs are advised to depict the appropriate values of the A:L ratio limit in PCOS patients.

CONCLUSION

The findings revealed a significant reduction in the A:L ratio among PCOS patients than non-PCOS individuals. Consequently, the A:L ratio holds promise as a potential novel biomarker for PCOS in the forthcoming.

ACKNOWLEDGEMENTS

Acknowledgments are delivered to all partners from Atma Jaya Catholic University of Indonesia for the support and contributions provided.

Conflict of interest

No conflict of interest in this study.

Funding

There was no specific grant or funding from any institutions or sponsors.

Registration of review protocol

This review was registered in PROSPERO on April 2nd, 2023 with the registration number CRD42023411754.

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