

Review Article

Association of circulatory chemerin levels with the severity of pre-eclampsia: A systematic review and bootstrapped meta-analysis

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ABSTRACT

Introduction: This study presents a systematic review and meta-analysis to investigate the association between circulating chemerin levels and the severity of preeclampsia (PE).

Material and Methods: A thorough search was conducted across multiple databases, including PubMed/MEDLINE, SCOPUS, and the Cochrane Library, up to March 31, 2024, focusing on observational studies that compared chemerin levels in patients with severe versus mild PE. Two independent reviewers extracted mean and standard deviation (SD) values of chemerin levels from these studies. The quality and risk of bias of the included studies were assessed using the Newcastle–Ottawa Scale. Standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated to evaluate the difference in chemerin levels between severe and mild PE groups. Sensitivity analyses were performed to address heterogeneity and ensure the reliability of the findings. Additionally, a bootstrapped meta-analysis with 1,000 and 10,000 simulations was conducted to further validate the results.

Results: Six observational studies were included in the analysis. The findings revealed that patients with severe PE had significantly higher chemerin levels compared to those with mild PE (SMD 1.55, 95% CI 0.67–2.43, $p < 0.0001$). The bootstrapped meta-analysis supported the accuracy of these findings (SMD = 1.54, CI = 0.74–2.38). No publication bias was identified using Begg's and Egger's tests, and the sensitivity analysis confirmed the robustness of the results.

Conclusion: This meta-analysis provides compelling evidence that chemerin levels are significantly elevated in patients with severe PE compared to those with mild PE. Further research is warranted to investigate the potential of circulating chemerin as a diagnostic marker for PE severity.

Keywords: Adipokine; Chemerin; Pre-eclampsia; Systematic review; Meta-analysis

INTRODUCTION

Complications related to pregnancy significantly increase mortality risk, especially in developing countries. Preeclampsia (PE), characterized by hypertension and proteinuria after 20 weeks of gestation, can manifest as either mild or severe. While mild PE includes symptoms like chest pain, vomiting, and high blood pressure, severe PE involves more serious conditions like abdominal pain, kidney failure, and blurred vision. PE is associated with liver and kidney dysfunction, pulmonary edema, thrombocytopenia, and a higher risk for diabetes and cardiovascular diseases. According to the World Health Organization, the global incidence of PE ranges from 2 to 10% of pregnancies, with a related mortality rate of 12%.^{1,2}

The exact pathophysiology of PE is not fully understood, but it is believed to involve placental hypoxia, oxidative stress, and immune modulation, leading to the production of proinflammatory cytokines. Adipokines, such as chemerin, are gaining attention as potential early biomarkers for PE. Chemerin is involved in processes like adipogenesis, energy metabolism, and inflammation. Recent studies have suggested a link between chemerin levels and PE, but there is limited direct evidence on whether these levels correlate with PE severity.^{3–5}

This systematic review and meta-analysis aim to provide precise information on the association between circulating chemerin levels and PE severity by comparing severe and mild PE groups. Sensitivity and bootstrapped meta-

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analyses were also conducted to ensure robust and precise outcomes.

MATERIAL AND METHODS

This review followed the PRISMA (Preferred Reporting Items For Systematic Reviews And Meta-Analysis) guidelines and was registered with PROSPERO (CRD42024526676).

Search strategy

We conducted a comprehensive literature search up to March 31, 2024, using PubMed, Cochrane Library, Scopus, and other databases. The search terms included “Chemerin” and “preeclampsia” without any time or language restrictions. Additional articles were identified through manual searches of bibliographies and contacting authors for unpublished data. Three researchers independently performed the literature searches. Any differences in their findings were resolved through discussions with other authors. Additionally, efforts were made to acquire any unpublished data. When necessary, the corresponding authors of the respective articles were contacted for further information.

Study selection criteria

To be included, studies had to be observational, focused on circulating chemerin levels in preeclampsia (PE), and compared levels between severe and mild PE groups. Participants needed to be human, with PE diagnosis criteria defined according to guidelines⁶ from the ‘American College of Obstetricians and Gynecologists (ACOG) or the International Society for the Study of Hypertension in Pregnancy (ISSHP). The studies also had to be written in English. Exclusion criteria included studies that did not specify whether PE was severe or mild, studies that only compared chemerin levels between PE and control groups, studies focusing on diseases other than PE, duplicate reports, reviews, experimental animal studies, letters to the editor, and commentaries.

Data extraction and quality assessment

After applying the inclusion criteria, the following details were extracted from each included study: first author names, country and year of publication, number of participants in severe and mild PE groups, PE diagnosis criteria, means, and standard deviations (SD) for age, anthropometric data, and circulating chemerin levels, as well as the chemerin measurement method and units. If data were reported in quartiles or as medians and ranges, conversions were performed to make them suitable for meta-analysis.^{7,8} Study quality was assessed using the Newcastle–Ottawa Scale

(NOS) for observational studies, which scores studies from 0 to 9 based on selection, comparability, and exposure criteria.⁹

Statistical analysis

The meta-analysis aimed to compare chemerin levels between severe and mild preeclampsia (PE) groups using standardized mean difference (SMD) with a 95% confidence interval (CI) as the outcome measure. A random-effects model was applied to the data. Heterogeneity was assessed using the DerSimonian-Laird estimator, Q-test, and I² statistic. If heterogeneity ($\tau^2 > 0$) was detected, a prediction interval for true outcomes was calculated. Potential outliers and influential studies were identified through studentized residuals and Cook’s distances, with outliers defined using Bonferroni correction and influential studies identified if Cook’s distance exceeded the median plus six times the interquartile range.

Funnel plot asymmetry was examined using the rank correlation and regression tests, with the ‘trim-and-fill method’ applied to adjust for significant publication bias. The robustness of the meta-analysis was evaluated through a one-study leave-out sensitivity analysis. All analyses were two-tailed, with a significance threshold of $p < 0.05$. The primary analyses were performed using Review Manager (version 5.4), Jamovi (version 2.3), and OpenMeta(Analyst), while the bootstrapped meta-analysis was conducted using OpenMEE software.

RESULTS

Search results and study characteristics

The literature search identified 27 articles on chemerin levels in PCOS. After removing duplicates, reviews, and commentaries, 11 studies were selected for full-text review. Of these, five did not report chemerin levels between severe and mild PE patient groups, leaving six studies for the final analysis.¹⁰⁻¹⁵ The PRISMA flow diagram is shown in Figure 1.

Study characteristics and Newcastle–Ottawa Scale quality scores are detailed in Supplementary Material [Table 1], with scores ranging from 6 to 8, indicating medium to high quality. All six studies measured serum chemerin using the ELISA method. PE diagnosis followed ACOG guidelines, with criteria including gestational blood pressure >140 mmHg systolic or >90 mmHg diastolic and proteinuria in previously normotensive patients before 20 weeks of gestation. Maternal age averaged between 25 and 34 years. Gestational age was reported in three studies as being in the third trimester,^{10,12,14} and in two studies as either second or third trimester,^{11,13} while one study sampled in the first trimester before PE diagnosis.¹⁵ The studies had either cross-sectional¹⁰⁻¹⁴ or prospective cohort designs.¹⁵

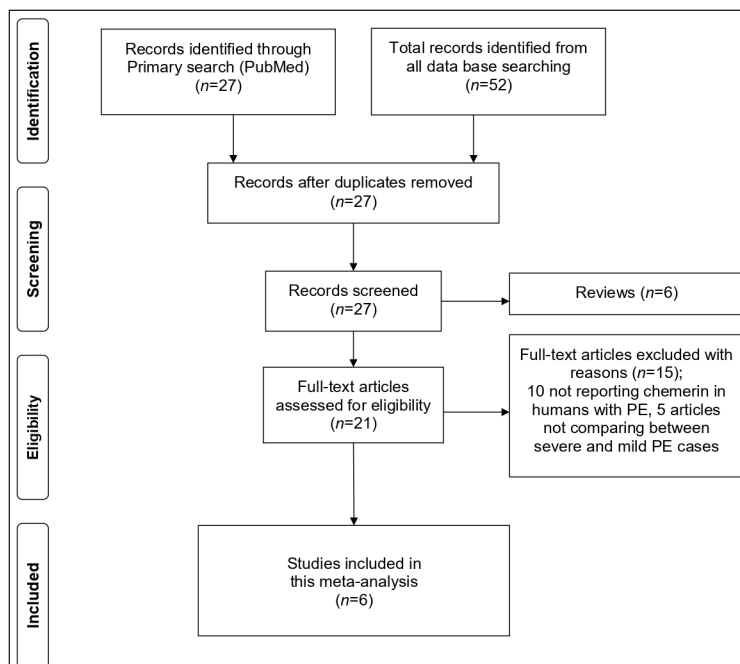


Figure 1: The study flowchart.

Table 1: Characteristics of included studies comparing the circulating chemerin between severe and mild PE patients.

Study, Year, Country	Severe PE						Mild PE						Sample, Method, Units	Confounder adjustment	NOS score
	n	Mean age	Mean GA	Mean BMI	Chemerin (Mean)	Chemerin (SD)	n	Mean age	Mean GA	Mean BMI	Chemerin (Mean)	Chemerin (SD)			
Al-Refai AA. ¹⁰ (2012), Saudi Arabia	10	34.37	32.68	30.46	479	158.56	19	34.37	32.68	30.46	281.95	144.54	Serum, ELISA, ng/mL	Age, BMI, GA	8
Cetin O et al. ¹¹ , (2017), Turkey	43	27.65	NA	26.10	394.72	100.01	45	28.11	NA	26.86	322.11	37.6	Serum, ELISA, ng/mL	Age, GA	7
Duan DM et al. ¹² , (2012), China	23	29.19	35.83	23.34	289.6	74.43	49	29.19	35.83	23.24	228.1	87.99	Serum, ELISA, ng/mL	Age, GA	7
Murad AM et al. ¹³ , (2020), Iraq	33	24.45	NA	28.43	435.06	55.4	33	25.00	NA	26.61	227.49	57.4	Serum, ELISA, ng/mL	Age, BMI, GA	8
Wang L et al. ¹⁴ , (2015), China	30	28.5	37.4	28.65	493.83	105.23	30	27.9	38.5	27.49	330.23	56.22	Serum, ELISA, ng/mL	Age, GA	7
Xu QL et al. ¹⁵ , (2014), China	18	27.2	10.67	25.4	365.5	116.5	23	27.2	10.67	25.4	270.3	91.8	Serum, ELISA, ng/mL	Age, GA	7

BMI: Body mass index, GA: Gestational age, PE: Preeclampsia, NA: Not applicable, NOS: Newcastle-ottawa Scale, ELISA: Enzyme-linked immunoassay, SD: Standard deviation.

Circulating chemerin between severe and mild PE patients

Six studies comparing chemerin levels between 157 severe PE and 199 mild PE patients were included.¹⁰⁻¹⁵ The meta-analysis using a random-effects model estimated an average standardized mean difference of 1.55 (95% CI: 0.67–2.43),

showing significantly higher chemerin levels in severe PE [$z = 3.46$, $p = 0.0005$, Figure 2]. The Q-test indicated heterogeneity among true outcomes ($Q(5) = 46.38$, $p < 0.0001$, $\tau^2 = 1.0891$, $I^2 = 91\%$). A 95% prediction interval for true outcomes ranged from -0.67 to 3.77 , suggesting that while the average outcome is positive, some studies might report negative outcomes. One

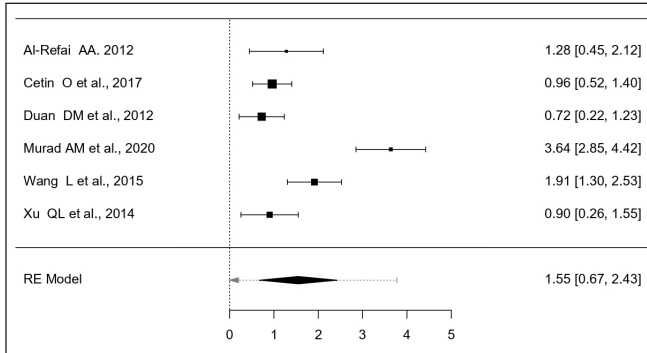


Figure 2: The forest plot comparing serum chemerin between severe and mild PE patients. PE: Preeclampsia.

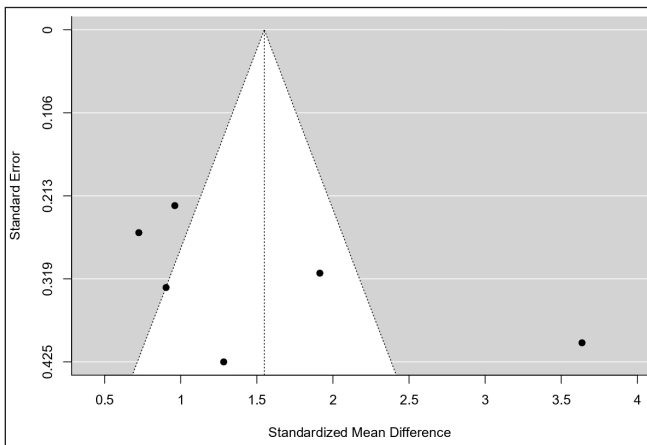


Figure 3: The funnel plot for publication bias.

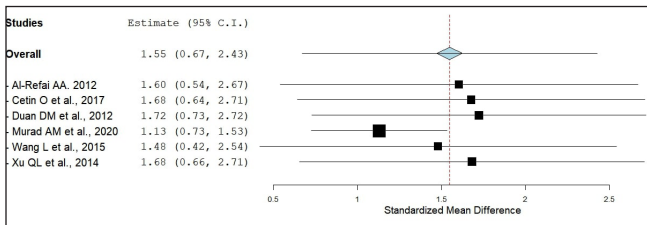


Figure 4: The results of sensitivity analysis.

study¹³ was identified as a potential outlier with a studentized residual larger than ± 2.63 and was also considered overly influential according to Cook's distances.

Publication bias and sensitivity analysis

As shown in Figure 3, there was no evidence of funnel plot asymmetry. Both the rank correlation and regression tests indicated no asymmetry ($p = 0.27$ and $p = 0.18$, respectively). A one-study leave-out sensitivity analysis confirmed the stability of the results, indicating consistently higher chemerin levels in severe PE regardless of which study was omitted [Figure 4].

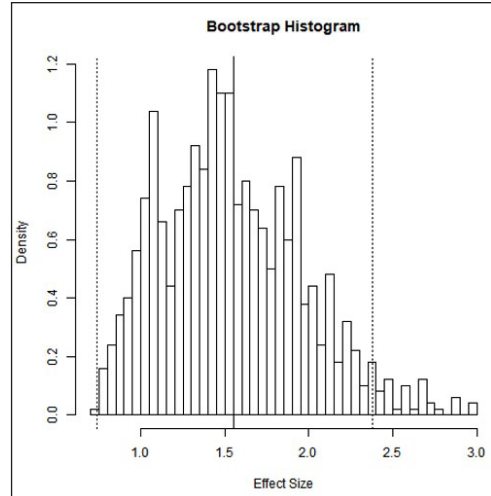


Figure 5: The histogram of bootstrap analysis using 1000 replicates.

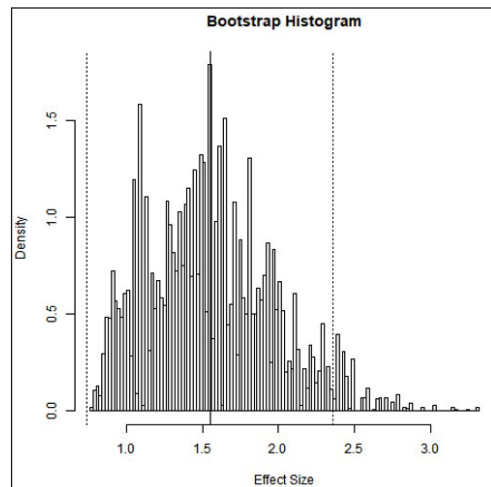


Figure 6: The histogram of bootstrap analysis using 10,000 replicates.

Bootstrapped meta-analysis

A bootstrapped meta-analysis with 1000 and 10,000 replicates [Figures 5 and 6] supported the accuracy of the original meta-analysis. The mean SMD over 1000 replicates was 1.54 (95% CI, 0.74–2.38), and over 10,000 replicates was 1.55 (95% CI, 0.74–2.36), as shown in Table 2. Bootstrapping is particularly valuable when dealing with a small sample size, an unknown population distribution, or a complex or non-standard statistics. It also helps assess the stability of results by repeatedly resampling from the original data to calculate confidence levels and other accuracy measures.

DISCUSSION

This meta-analysis reveals that chemerin levels are significantly higher in severe preeclampsia (PE) patients compared to

Table 2: The results of a bootstrapped meta-analysis.

Description	Observed effect size (SMD)	95% CI	Figure
Meta-analysis (9 studies)	1.55	0.67:2.42	Fig. 2
Bootstrapped meta-analysis	Mean over the replicates	95% CI	
Bootstrap replicates: 1000	1.54	0.74:2.38	Fig. 5A
Bootstrap replicates: 10000	1.55	0.74:2.36	Fig. 5B

CI: Confidence interval, SMD: Standardized mean differences.

those with mild PE ($p < 0.0001$). This finding underscores the association between elevated circulating chemerin levels and PE severity. However, substantial heterogeneity (91%) was observed [Figure 2]. Sensitivity analysis identified the study by Murad *et al.* (2020) as a potential source of this heterogeneity.¹³ Excluding this study reduced heterogeneity to 59%, while the significant association between higher chemerin levels and severe PE persisted (SMD = 1.13, 95% CI: 0.72 to 1.54, $p < 0.0001$). This indicates that although the study by Murad *et al.*¹³ (2020) contributes to heterogeneity, it does not alter the overall conclusion of increased chemerin levels in severe PE.

The heterogeneity could stem from the younger maternal age and gestational stage (second or third trimester) in the Murad *et al.*¹³ (2020) study. Elevated circulating chemerin in severe PE is likely due to increased proinflammatory adipokine synthesis from the placenta during pregnancy.^{16,17} While the precise mechanisms linking chemerin to PE are not fully understood, recent studies suggest that elevated placental chemerin disrupts normal placental development, contributing to PE onset.¹⁸ Chemerin inhibits trophoblast migration, invasion, and tube formation, affecting trophoblast lipid metabolism and promoting pyroptosis and inflammation, thereby playing a role in PE development.¹⁹⁻²¹

PE is associated with altered body mass index (BMI), insulin resistance, and glucose and lipid metabolic abnormalities, which may contribute to heterogeneity. However, the limited number of studies precluded a meta-regression analysis of these covariates. Nonetheless, recent evidence indicates that chemerin's association with PE is independent of BMI and obesity status.^{4,5} The included studies in this meta-analysis reported comparable maternal age, gestational age, and BMI for PE patients. Sensitivity analysis [Figure 4] confirmed the robustness of the finding of elevated chemerin in severe PE, with no single study overly influencing the outcome. Additionally, no significant publication bias was detected [Figure 3]. Despite the limited number of studies, further

research on chemerin's role as a marker for PE detection and severity progression is needed. The accuracy of our meta-analysis was validated through bootstrapped meta-analyses with 1000 and 10,000 replicates, confirming the association of higher chemerin levels with severe PE [Table 2].

Strengths and limitations of this meta-analysis should be noted. Limitations are inherent to the observational study designs included, and heterogeneity may arise from methodological and clinical variations across studies in design, setting, participant selection, and demographic, hormonal, and metabolic parameters. We addressed this through random effects meta-analysis and sensitivity analyses. The quality assessment of individual studies indicated medium to high quality. Due to the limited number of studies available for comparison (only six), it was not feasible to conduct a separate subgroup analysis. Nevertheless, the overall meta-analysis results were robust and stable, as confirmed by sensitivity and bootstrapped analyses. Consequently, this meta-analysis supports the association of higher circulating chemerin levels with PE severity. Further well-controlled studies with larger sample sizes are warranted to evaluate chemerin's utility for PE diagnosis and disease progression monitoring.

CONCLUSION

This is the first bootstrapping meta-analysis to assess the association of circulating chemerin with PE severity. The results indicate significantly higher serum chemerin levels in severe PE patients compared to mild PE patients, supporting chemerin measurement as a potential method for identifying severe PE. The findings' validity, robustness, and accuracy are confirmed through sensitivity and bootstrapped meta-analyses. However, further research is needed to explore the diagnostic accuracy of serum chemerin for PE diagnosis and monitoring severity progression.

Authors' contributions

SRV, MM, SS: Conceptualization; SRV, AA, KG, JJ, AR, AK, BK: Data curation, analysis, methodology and software; MT, SS: Supervision, validation; SRV, MM, AA, KG, JJ: Writing-original draft; BK, MT, SS: Writing-review and editing. All authors approved the final manuscript.

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Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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