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Systematic Review

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Risk Stratification in Preeclampsia Using Serum Uric Acid, Calcium, and C-Reactive Protein: A Systematic Review

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ABSTRACT

Background: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide, necessitating reliable biomarkers for early detection and clinical risk stratification. This systematic review evaluated the role of serum uric acid (SUA), serum calcium, and C-reactive protein (CRP) as metabolic and inflammatory biomarkers in preeclampsia.

Methods: This review was conducted according to the PRISMA 2020 guidelines and search of PubMed/MEDLINE, Scopus, Web of Science, EMBASE, EBSCOhost, CINAHL, CENTRAL, Google Scholar, and grey literature sources was performed. Of 1,252 records identified, eight observational studies involving over 58,000 pregnant women met the inclusion criteria.

Results: Serum uric acid was consistently elevated in women with established preeclampsia and was associated with disease severity, fetal growth restriction, preterm birth, and adverse maternal outcomes. While earlier studies questioned its predictive value, recent large cohort studies demonstrated dose-dependent associations between elevated first-trimester SUA concentrations and subsequent development of preeclampsia. CRP levels were consistently higher in women with preeclampsia, and high-sensitivity CRP showed superior performance over SUA in differentiating severe from non-severe disease. Evidence regarding serum calcium was limited and inconclusive.

Conclusions: Current evidence identifies serum uric acid as the most consistent biomarker for risk stratification in preeclampsia, while CRP provides complementary information on inflammatory activity and disease severity. The evidence supporting serum calcium remains insufficient. Further large, prospective multicentre studies are needed to validate combined biomarker models and establish standardized clinical thresholds.

Key-words: Preeclampsia; Serum uric acid; C-reactive protein; Serum calcium; Biomarkers; Risk stratification; Systematic review

INTRODUCTION

Preeclampsia is a multisystem hypertensive disorder of pregnancy characterized by new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or evidence of maternal end-organ dysfunction. [1,2] It affects approximately 2–8% of pregnancies worldwide and remains one of the leading causes of maternal and perinatal morbidity and mortality, particularly in low- and middle-income countries.

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Women with preeclampsia are at increased risk of eclampsia, HELLP syndrome, acute kidney injury, stroke, and long-term cardiovascular disease, while affected pregnancies are associated with preterm birth, fetal growth restriction, low birth weight, and perinatal mortality. [1-4] Despite advances in antenatal care, early identification of women at risk remains a significant clinical challenge.

The pathogenesis of preeclampsia is complex and multifactorial, involving abnormal trophoblastic invasion, impaired remodeling of the spiral arteries, placental ischemia, oxidative stress, endothelial dysfunction, immune dysregulation, and exaggerated systemic inflammation. [3,4] These interconnected mechanisms culminate in widespread maternal vascular injury and multiorgan dysfunction. Consequently, there has been

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growing interest in identifying biochemical biomarkers that reflect these underlying pathological processes and may facilitate earlier diagnosis, assessment of disease severity, and individualized risk stratification. [3,4]

Among the proposed biomarkers, SUA has emerged as one of the most extensively investigated. Traditionally considered a consequence of reduced renal clearance in preeclampsia, accumulating evidence suggests that hyperuricemia may also contribute to endothelial dysfunction, oxidative stress, inflammation, and impaired placental angiogenesis. [5] Several observational studies have consistently demonstrated significantly elevated SUA concentrations in women with established preeclampsia, with higher levels correlating with disease severity, fetal growth restriction, preterm birth, and adverse maternal outcomes. [5-12] However, whether elevated SUA is merely a consequence of the disease or an early predictor of its development remains controversial. While earlier investigations found no significant differences in first- or second-trimester SUA concentrations among women who subsequently developed preeclampsia [5], more recent large multicentre cohort studies have reported dose-dependent associations between elevated early-pregnancy SUA levels and subsequent disease development, suggesting a potential role in early risk prediction. [8,11,12]

Systemic inflammation also plays a pivotal role in the development and progression of preeclampsia. C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to inflammatory cytokines, has been widely investigated as a marker of maternal inflammatory activity. Elevated CRP concentrations have consistently been reported in women with preeclampsia and have been associated with increasing disease severity and adverse pregnancy outcomes. [6,10] Furthermore, recent evidence indicates that high-sensitivity CRP (hs-CRP) may outperform SUA in distinguishing severe from non-severe preeclampsia, highlighting its potential value as a complementary biomarker for prognostic assessment. [10]

Serum calcium has also been implicated in the pathophysiology of hypertensive disorders of pregnancy because of its role in vascular smooth muscle contraction, endothelial function, intracellular signalling, and blood pressure regulation. Altered calcium homeostasis may contribute to increased vascular resistance and endothelial dysfunction, thereby promoting the development of preeclampsia. Nevertheless, studies evaluating serum calcium have reported inconsistent findings, and its clinical utility as an independent biomarker remains uncertain because of variations in study populations, laboratory methodologies, and outcome definitions. [13,14]

Although serum uric acid, CRP, and serum calcium have each been investigated individually, few reviews have examined these biomarkers collectively within the context of metabolic and inflammatory risk stratification. Considering that preeclampsia results from multiple interacting biological pathways, integrating biomarkers that reflect metabolic dysfunction, inflammation, oxidative stress, and vascular injury may provide a more comprehensive assessment of disease risk than reliance on a single laboratory parameter. Moreover, several recent large-scale cohort studies have substantially expanded the evidence regarding the predictive utility of serum uric acid, warranting an updated synthesis of the available literature.

Therefore, this systematic review aimed to comprehensively evaluate the available evidence regarding the role of serum uric acid, serum calcium, and C-reactive protein as metabolic and inflammatory biomarkers for risk stratification in preeclampsia. Specifically, we sought to synthesize evidence on their associations with disease occurrence, severity, maternal and fetal outcomes, and their potential clinical utility in prediction, diagnosis, and prognostic assessment.

MATERIALS AND METHODS

Study Design and Protocol Registration- This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261461804**.** The review aimed to evaluate the available evidence regarding the role of SUA, serum calcium, and CRP as metabolic and inflammatory biomarkers for risk stratification in preeclampsia.

Search Strategy- A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, EMBASE, EBSCOhost, CINAHL, CENTRAL, and

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Google Scholar from January 2000 to July 2026. Grey literature was searched through OpenGrey, ClinicalTrials.gov, WHO ICTRP, PROSPERO, WorldCat, and ISRCTN Registry. Additional studies were identified through manual reference screening and citation tracking.

The search strategy combined controlled vocabulary (MeSH and Emtree terms) with free-text keywords related to preeclampsia, serum uric acid, hyperuricemia, serum calcium, hypocalcaemia, C-reactive protein, hs-CRP, biomarkers, prediction, diagnosis, severity, and risk stratification.

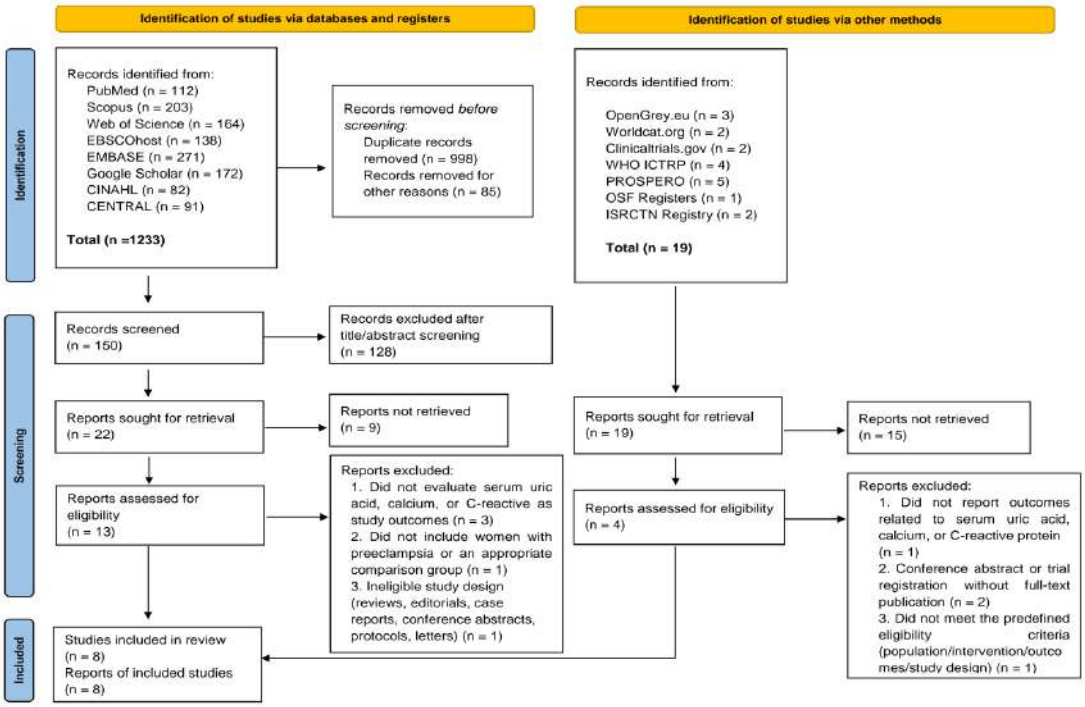

Fig. 1: PRISMA 2020 flow diagram illustrating the study selection process

Eligibility Criteria- Original observational studies and clinical trials evaluating serum uric acid, serum calcium, and/or C-reactive protein among pregnant women with preeclampsia were eligible. Studies reporting biomarker concentrations, diagnostic accuracy, prediction of disease, severity assessment, maternal outcomes, or fetal outcomes were included.

Narrative reviews, systematic reviews, meta-analyses, editorials, conference abstracts without full text, protocols, letters, case reports, animal studies, duplicate publications, and studies not reporting the biomarkers of interest were excluded.

Study Selection- Two reviewers independently screened titles and abstracts followed by full-text assessment according to predefined eligibility criteria. Disagreements were resolved through discussion until consensus was reached.

Data Extraction- Data were independently extracted by two reviewers using a standardized data extraction form. The extracted information included the author(s) and year of publication, country, study design, sample size, gestational age at biomarker measurement, serum uric acid, serum calcium and/or C-reactive protein (CRP) levels, maternal and fetal outcomes, and the major findings of each included study.

Data Synthesis- Substantial heterogeneity existed regarding study design, population characteristics, timing of biomarker assessment, laboratory methods, and outcome reporting. Consequently, quantitative meta-analysis was considered inappropriate. Therefore, findings were synthesized qualitatively using a narrative approach.

The study selection process is presented in Fig. 1. A total of 1,252 records were identified through database searching and other sources, including 1,233 records from electronic databases and 19 records from additional sources. After removal of 998 duplicate records and 85 records removed before screening, 150 studies underwent title and abstract screening.

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Following screening, 128 studies were excluded and 22 reports were sought for full-text retrieval from database searches. Nine full-text articles were unavailable, leaving 13 articles for eligibility assessment. Four additional reports identified through other methods underwent full-text assessment after retrieval. Nine full-text articles were subsequently excluded because they either did not evaluate serum uric acid, calcium, or CRP, included an ineligible study population, represented conference abstracts or trial registrations without complete publications, or did not satisfy the predefined eligibility criteria. Ultimately, eight studies fulfilled the inclusion criteria and were included in the qualitative synthesis. [5-12]

RESULTS

Eight observational studies published between 2015 and 2026 were included in the qualitative synthesis as summarized in Table 1. The studies were conducted in China (n = 4), India (n = 3), and the United States (n = 1) and collectively included over 58,000 pregnant women. [5-12]

Most investigations evaluated serum uric acid, whereas two studies additionally assessed C-reactive protein, and limited evidence was available regarding serum calcium. Biomarker assessment ranged from the first trimester to the time of diagnosis of preeclampsia. Outcomes included disease prediction, disease severity, maternal complications, fetal growth restriction, preterm birth, and neonatal outcomes.

Table 1: Summary of Included Studies

Study	Biomarker(s)	Major Findings	Clinical Interpretation
Chen *et al*. [5]	SUA	Elevated only after clinical disease; not predictive during first or second trimester	Marker of disease severity rather than early prediction
Kaur *et al*. [6]	SUA, CRP	Both biomarkers significantly increased in preeclampsia; correlated with blood pressure and neonatal morbidity	Combined metabolic and inflammatory markers may improve prediction
Li *et al*. [7]	SUA	SUA independently associated with severe preeclampsia and mediated inflammatory pathways	Useful severity biomarker
Yue *et al*. [8]	SUA	Elevated first-trimester SUA predicted subsequent preeclampsia in a dose-dependent manner	Early pregnancy risk stratification
Singh *et al*. [9]	SUA	SUA progressively increased from gestational hypertension to eclampsia	Reflects disease severity
Biswas *et al*. [10]	SUA, hs-CRP	hs-CRP demonstrated superior discrimination of severe preeclampsia compared with SUA	CRP complements SUA in prognostic assessment
Zhang *et al*. [11]	SUA/Creatinine ratio	Higher ratio independently predicted preeclampsia among women of advanced maternal age	Modified SUA indices may improve prediction
Zhao *et al*. [12]	SUA	Elevated SUA before 20 weeks independently increased preeclampsia risk in >44,000 pregnancies	Strong evidence supporting early SUA screening

Overall, serum uric acid was consistently elevated in women with established preeclampsia and demonstrated significant associations with disease severity, fetal growth restriction, preterm birth, and adverse maternal outcomes. Although early studies suggested that serum uric acid lacked predictive value before clinical onset, more recent large multicentre cohort studies demonstrated dose-dependent associations between elevated first-trimester serum uric acid concentrations and subsequent development of preeclampsia. Similarly, C-reactive protein was consistently elevated among women with preeclampsia. The available evidence suggests that inflammatory activity increases with disease severity, and high-sensitivity CRP may outperform serum uric acid in distinguishing severe from non-severe disease.

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Evidence regarding serum calcium was comparatively limited because relatively few eligible studies evaluated this biomarker. Consequently, its independent clinical utility remains uncertain.

Collectively, the available evidence indicates that serum uric acid represents the most consistent biochemical marker for risk stratification, whereas CRP provides complementary information regarding systemic inflammation and disease severity. Future well-designed prospective multicentre studies are needed to validate multimarker prediction models incorporating serum uric acid, CRP, and serum calcium for routine clinical use.

DISCUSSION

This systematic review synthesized the available evidence regarding the role of SUA, serum calcium, and CRP as metabolic and inflammatory biomarkers for risk stratification in preeclampsia. Eight observational studies involving more than 58,000 pregnant women were included. Overall, the findings demonstrate that SUA is consistently elevated in women with established preeclampsia and correlates with disease severity, while CRP reflects the inflammatory burden of the disease and may provide additional prognostic value. In contrast, the evidence supporting serum calcium remains limited and insufficient to establish its independent clinical utility. These findings suggest that combining metabolic and inflammatory biomarkers may improve clinical risk stratification compared with reliance on individual laboratory parameters.

Among the evaluated biomarkers, serum uric acid demonstrated the strongest and most consistent association with preeclampsia. All included studies reported significantly higher SUA concentrations among women with preeclampsia compared with normotensive pregnancies, with progressively increasing levels observed in severe disease and eclampsia. [5-12] Elevated SUA was also associated with adverse maternal and fetal outcomes, including preterm birth, fetal growth restriction, lower birth weight, and maternal intensive care admission. [5,8,9,12] These observations are biologically plausible because hyperuricemia reflects impaired renal clearance secondary to glomerular endotheliosis while simultaneously contributing to oxidative stress, endothelial dysfunction, inflammation, and reduced nitric oxide bioavailability, all of which are central mechanisms in the pathogenesis of preeclampsia. [3,4]

One of the most important findings of this review is the evolving evidence regarding the predictive role of SUA during early pregnancy. Chen *et al.* reported that first- and second-trimester SUA concentrations did not differ significantly between women who subsequently developed preeclampsia and those with uncomplicated pregnancies, suggesting that hyperuricemia was primarily a consequence of established disease. [5] However, this conclusion contrasts with more recent evidence. Yue *et al.* demonstrated a dose-dependent association between elevated first-trimester SUA and subsequent development of preeclampsia, particularly when measured between 8 and 12 weeks' gestation. [8] Similarly, Zhang *et al.* showed that the serum uric acid-to-creatinine ratio independently predicted preeclampsia among women of advanced maternal age [11] while Zhao *et al*. in the largest multicentre cohort included in this review, identified a nonlinear relationship between SUA concentrations measured before 20 weeks and subsequent disease risk, with an apparent threshold of approximately 240 µmol/L. [12] Collectively, these studies suggest that the predictive value of SUA may depend on gestational timing, study population, and analytical methodology. Improvements in study design, larger sample sizes, and more robust statistical adjustment in recent investigations likely explain the shift toward supporting SUA as an early biomarker for risk stratification.

Systemic inflammation represents another hallmark of preeclampsia, and the findings of this review support the clinical relevance of C-reactive protein. Both studies evaluating CRP demonstrated significantly higher concentrations in women with preeclampsia than in normotensive controls. [6,10] Furthermore, CRP showed positive correlations with blood pressure, maternal disease severity, and adverse neonatal outcomes [6]. Particularly noteworthy was the prospective study by Biswas et al., which demonstrated that high-sensitivity CRP (hs-CRP) outperformed SUA in distinguishing severe from non-severe preeclampsia. [10] These findings suggest that CRP reflects ongoing systemic inflammatory activation rather than simply renal dysfunction and may therefore provide complementary prognostic information when used alongside SUA. Considering that CRP measurement is inexpensive, standardized, and

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widely available, its incorporation into multimarker risk assessment strategies may have practical clinical utility.

Compared with SUA and CRP, the evidence regarding serum calcium was considerably more limited. Although altered calcium homeostasis has been implicated in vascular smooth muscle contraction, endothelial dysfunction, and abnormal placental vascular development, few studies fulfilling the eligibility criteria specifically evaluated serum calcium in relation to preeclampsia. [13,14] Consequently, the current review was unable to establish consistent evidence supporting its independent diagnostic or prognostic value. [13, 14] Nevertheless, existing physiological evidence suggests that disturbances in calcium metabolism may contribute to disease development, indicating that further well-designed prospective studies are warranted before definitive conclusions can be drawn. [13,14]

An important implication of the present review is that preeclampsia cannot be adequately characterized by a single biochemical marker. The disorder results from complex interactions among placental dysfunction, endothelial injury, oxidative stress, inflammation, immune dysregulation, and altered maternal cardiovascular adaptation. [13,14] Accordingly, biomarkers reflecting different biological pathways are likely to provide complementary information. SUA predominantly reflects metabolic and renal dysfunction, whereas CRP reflects systemic inflammation, and serum calcium may reflect vascular and endothelial homeostasis. [13, 14] Integrating these biomarkers with established clinical risk factors and imaging modalities, such as uterine artery Doppler assessment, may improve early identification of women at high risk and facilitate personalized antenatal surveillance.

Despite promising findings, clinical implementation is limited by substantial heterogeneity in diagnostic criteria, biomarker timing, assay methods, study populations, and reported thresholds. This variability limits direct comparison and quantitative synthesis, while validated cut-offs for SUA and CRP remain uncertain. Future multicentre prospective studies using standardized methods are needed to establish reliable thresholds and validate multimarker prediction models.

STRENGTHS

This review has several strengths. It followed PRISMA 2020 guidelines and was prospectively registered in PROSPERO, ensuring methodological transparency. A comprehensive search across multiple databases and grey literature sources helped minimize publication bias. The review also incorporated recent evidence, including large multicentre cohort studies from 2023–2026, providing an updated perspective on serum uric acid in early pregnancy. Finally, its multimarker approach evaluated metabolic and inflammatory biomarkers together for clinical risk stratification.

LIMITATIONS

Several limitations should be noted. Only eight studies met the eligibility criteria, limiting the strength of evidence. Considerable heterogeneity in study design, populations, laboratory methods, biomarker timing, and outcomes prevented quantitative meta-analysis. Evidence was predominantly based on serum uric acid, with limited data on CRP and serum calcium. All studies were observational, limiting causal inference, and restricting inclusion to English-language publications may have introduced language bias.

CONCLUSIONS

Current evidence suggests that serum uric acid is the most consistently associated biochemical marker for the occurrence and severity of preeclampsia, with emerging evidence supporting its role in early pregnancy risk stratification. CRP provides complementary information regarding systemic inflammation and disease severity, whereas the evidence supporting serum calcium remains limited and inconclusive. Collectively, these findings indicate that integrating metabolic and inflammatory biomarkers may enhance the identification and risk stratification of women with preeclampsia compared with the use of individual biomarkers alone. However, the available evidence is predominantly derived from observational studies and is limited by methodological heterogeneity. Well-designed, large-scale prospective multicentre studies are required to validate combined biomarker models, establish standardized diagnostic thresholds, and determine their clinical utility in routine obstetric practice.

CONTRIBUTION OF AUTHORS

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Critical review- Anu Kumari Baitha, Waqas Alauddin
Article editing- Anu Kumari Baitha, Waqas Alauddin
Final approval- Anu Kumari Baitha, Waqas Alauddin

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