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Investigating the association of albuminuria with the incidence of preeclampsia and its predictive capabilities: a systematic review and meta-analysis

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Abstract

Background Preeclampsia (PE) is a severe hypertensive disorder affecting approximately 6.7% of pregnancies worldwide. Identifying reliable biomarkers for early prediction could significantly reduce the incidence of PE and facilitate closer monitoring and timely management. This study aims to investigate the association between albuminuria in early pregnancy and the subsequent development of PE, and to explore its predictive abilities.

Methods A systematic search was conducted across PubMed, Embase, and Web of Science on July 15, 2024, for studies published between January 1, 1990, and June 30, 2024. Quality assessments were performed using the Joanna Briggs Institute Critical Appraisal and Risk of Bias in Non-randomized Studies - of Exposures Checklists. Random-effects models in STATA were used to conduct meta-analyses comparing urine albumin and albumin-to-creatinine ratio levels in patients who later developed PE versus those who did not. The incidence of PE was also compared between patients with and without albuminuria in early pregnancy. The predictive ability of albuminuria for PE was assessed using META-DISC software.

Results A total of 26 studies comprising 7,640 pregnant women were systematically reviewed. Of these, 17 studies met the quality criteria for inclusion in the meta-analyses. Our findings indicate that urine albumin (Hedges's g = 0.48 [95% confidence interval (CI): 0.16–0.80]; *p-value* < 0.001) and albumin-to-creatinine ratio (Hedges's g = 0.48 [95% CI: 0.16–0.80]; *p-value* = 0.003) were significantly higher in the early stages of pregnancy in patients who later developed PE compared to those who did not. The incidence of PE was higher in patients with early-diagnosed albuminuria (log odds ratio = 2.56 [95% CI: 1.75–3.38]; *p-value* < 0.001). The pooled sensitivity and specificity for albuminuria in predicting PE were 56% [95% CI: 48-64%] and 87% [95% CI: 85-89%], respectively.

Conclusions Elevated maternal urine albumin and albumin-to-creatinine ratio in early pregnancy are associated with a higher risk of developing PE. While these biomarkers show promise for early identification of at-risk patients, the

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relatively low sensitivity suggests that albuminuria alone may not be a robust predictor of PE, which underscores the need for future research in this regard.

Trial registration Review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42024575772.

Keywords Albuminuria, Prediction, Preeclampsia, Pregnancy, Urine analysis

Introduction

Preeclampsia (PE) is a severe hypertensive disorder of pregnancy, characterized by new-onset hypertension and proteinuria occurring after 20 weeks of gestation [1, 2]. Affecting approximately 6.7% of pregnancies globally, it represents a significant cause of maternal and fetal morbidity and mortality [3–5]. The condition can lead to severe complications, including eclampsia, hemolysis, elevated liver enzymes, and low platelet count syndrome (HELLP), as well as preterm birth and intrauterine growth restriction [1]. PE can impact multiple maternal organ systems, such as renal, hepatic, ocular, hematological, or neurological systems [6, 7]. Despite significant advances in obstetric care, the precise pathophysiology of PE remains unclear, and effective early prediction and preventive measures are still limited [2, 8–10]. Identifying reliable biomarkers for the early prediction of at-risk women could significantly reduce the incidence of PE and facilitate closer monitoring and timely management [8, 10].

Recent studies have investigated the association between albuminuria in early pregnancy and the subsequent development of PE, and observed that pregnant women with PE exhibit distinct alterations in their urinary albumin profiles compared to normal pregnant counterparts [11–13]. Albuminuria is a pathological condition characterized by the abnormal presence of albumin in the urine, serving as a key indicator of renal dysfunction and endothelial injury, both of which are integral components of the pathophysiology of PE [14, 15]. Endothelial dysfunction leads to increased vascular permeability, resulting in the leakage of albumin and other proteins from the bloodstream into the urine [14, 16]. This systemic endothelial damage indicates broader vascular health issues that precede the clinical manifestations of PE [17]. Furthermore, impaired renal function, as evidenced by albuminuria, suggests compromised glomerular filtration, a significant component of the renal pathology associated with PE [18, 19].

Previous studies have explored the long-term renal function and albuminuria following PE [19–21]. Additionally, some research has investigated the correlation between early proteinuria and the development of PE [22, 23]. Notably, albuminuria exhibits lower inter-laboratory bias than proteinuria in hypertensive pregnancy [24], and several clinical guidelines recommend albuminuria for assessing chronic kidney disease and glomerular damage [25, 26]. To the best of our knowledge, this is the first systematic review and meta-analysis aimed at assessing the relationship between albuminuria in early pregnancy and the subsequent development of PE, as well as evaluating its potential as a predictive biomarker for PE. This synthesis of existing evidence aims to improve our understanding of the utility of albuminuria in identifying high-risk pregnant women and to inform future clinical applications.

Materials and methods

This study aims to evaluate the role of albuminuria as a predictor of subsequent PE. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [27], to ensure transparency and rigor. Also, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [28] was followed for conducting the meta-analysis. Furthermore, the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration code CRD42024575772.

Search strategy

Our research question was formulated by following the Patient, Intervention, Comparison, and Outcome (PECO) framework [29] as follows:

Patient Pregnant women.

Exposure Albuminuria.

Comparator Pregnant women without albuminuria.

Outcome PE.

We conducted a systematic search on 15 July 2024, across three electronic databases, including PubMed, Embase, and Web of Science, for studies published in English from 1 January 1990 to 30 June 2024. The search syntax employed variations of keywords related to (1) Albuminuria, and (2) PE. Supplementary Materials 1 provides a comprehensive description of the keywords and filters utilized in each database. Additionally, the reference lists of included studies and the Google Scholar database were manually searched to identify additional relevant articles.

Eligibility criteria

All peer-reviewed articles investigating the role of albuminuria in early pregnancy as a predictor of subsequent PE (early or late) were considered for inclusion. Studies that assessed the prediction of PE by albuminuria, the Urine Albumin-to-Creatinine Ratio (UACR), or the number of patients with micro- or macro-albuminuria were included.

The exclusion criteria were as follows: (1) studies that did not assess our primary outcome or lacked essential information; (2) animal studies; (3) articles that were not available in English full-text; and (4) review articles, case reports, case series, brief reports, meeting abstracts, book chapters, letters, editorials, commentaries, correspondence, and study protocols.

Study selection

Two independent reviewers (PR, MP) screened the identified studies based on the title and abstract, and selected the studies for further eligibility assessment. Subsequently, the same two reviewers (PR and MP) independently assessed the full texts of the remaining studies against the inclusion criteria. Any disagreements were resolved via discussion, and if needed, the third reviewer (SH) was consulted to reach the final decision.

Data collection

Two individual reviewers performed data extraction independently (PR, MP). Disagreements between the reviewers were resolved by double-checking the extracted data and discussing it with a third reviewer (SH). Data from each included article were systematically compiled across four key categories: general information (first author, publication year, country of origin, and study design), participant characteristics (sample size, mean age), measurement of albuminuria (urine albumin levels in women with and without PE, UACR in women with and without PE, and the number of patients with and without albuminuria who developed and did not develop PE) and laboratory data (type of urine samples, measurement methods for albumin and creatinine, gestational age at the time of sampling, and utilized cut-offs, for albuminuria).

Quality assessment

Two researchers (MP, PR) independently evaluated the methodological quality of each reviewed study based on the Joanna Briggs Institute (JBI) Clinical Appraisal Checklists for case-control and cohort studies (Supplementary Materials 2) [30]. The case-control and cohort checklists comprised 10 and 11 items examining the methodological quality of the articles, respectively. Each item was answered with either "Yes", "No", "Unclear", or "Not applicable". Studies that successfully satisfied at least 70% of the items (i.e., answered by "Yes") were considered to be included in the meta-analysis.

Furthermore, the two reviewers independently validated the results of their initial risk of bias assessment using the Risk of Bias in Non-randomized Studies - of Exposures (ROBINS-E) tool [31]. This tool evaluates the risk of bias in non-randomized follow-up studies examining exposure effects by assessing methodological quality across seven domains: confounding factors, exposure measurement, participant selection, post-exposure interventions, missing data, outcome measurement, and selection of reported results. For each domain, the risk of bias is categorized as "Low," "Moderate," "Serious," or "Critical." Based on these domain-specific judgments, an overall risk of bias assessment is determined for each study.

Meta-analysis

Initially, means and standard deviations for continuous data, along with counts for categorical data, were extracted into a Microsoft Excel spreadsheet. For studies that reported median and range (or interquartile range) values instead of means and standard deviations, these were converted to means and standard deviations using established formulas from prior literature [32, 33].

Meta-analyses were performed using STATA version 18.0 (Stata Corp. LLC, TX, USA). A random-effects model with a restricted maximum likelihood (REML) method was employed to pool the data. REML assumes that random effects (study-level deviations) and residuals (within-study errors) follow a normal distribution and are independent of each other. These assumptions ensure unbiased and efficient estimates of heterogeneity, which is particularly important given the small to moderate number of studies in our analysis [34]. Heterogeneity across studies was assessed using Cochran's Q and I^2 statistics, where an I^2 value greater than 50% indicated high heterogeneity, and an I^2 value of 50% or less indicated low heterogeneity.

To estimate the effect size for comparing means between two groups for continuous variables, Hedges's g was calculated with 95% confidence intervals (CIs). Hedges's g was chosen over Cohen's d to correct for bias in effect size estimation, particularly due to the inclusion of studies with small sample sizes in this meta-analysis [35]. For categorical data, the log odds ratio with 95% CIs was used to estimate the effect size of group differences. Pooled effect sizes (Hedges's g and log odds ratio) were interpreted as follows: A Hedges's g value above 0.8 generally indicates a large effect size, between 0.5 and 0.8 indicates a medium effect, and below 0.2 indicates a small effect. If both the pooled effect size and its 95% CI were above 0, it indicated significantly higher values, if both were below 0, it indicated significantly lower values, and

if the 95% CI crossed 0, it indicated no significant differences between the groups [36]. Statistical significance was determined with a theta *p-value* < 0.05 considered significant for overall between-group differences. Forest plots were also created to visually represent the effect sizes of individual studies and the overall effect size.

To assess the potential presence of publication bias among the analyzed studies, funnel plots were interpreted by visually assessing the symmetry of the distribution of effect sizes plotted against their precision (standard error), with a substantial asymmetry suggesting the potential presence of publication bias. Additionally, statistical evaluations were conducted using Begg's test (a nonparametric rank correlation test) [37] and Egger's test (a regression-based test for small-study effects) [38] were utilized. A *p-value* < 0.05 in either test suggested the presence of publication bias. When publication bias was detected, the nonparametric trim-and-fill method was applied to adjust the effect size by imputing missing studies on either the right side (R0: the side with the larger effect sizes) or the left side (L0: the side with the smaller effect sizes) [39].

Additionally, a separate meta-analysis was conducted to evaluate the diagnostic accuracy of albuminuria in the early stages of pregnancy for predicting the subsequent development of PE. For this analysis, the META-DISC 1.4 software (Cochrane Colloquium) was employed [40], a tool whose utility has been demonstrated in prior studies [41]. A bivariate random-effects regression model was applied to estimate pooled values for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR), each with corresponding 95% CIs. The summary receiver operating characteristics (sROC) curve was generated, and the area under the curve (AUC) was calculated for each included study. Also, to assess the degree of heterogeneity among the studies, the I^2 statistic and *p-values* were computed for each forest plot.

Results

Search results

Our systematic search yielded 1,197 records. After removing 364 duplicates, 833 records remained for title and abstract screening. Upon screening, 711 were excluded based on predefined criteria. The full texts of the remaining 122 records were assessed for eligibility, resulting in 18 articles meeting the inclusion criteria. Additionally, manual screening of the reference lists of included studies and the Google Scholar database identified eight more eligible articles, culminating in a total of 26 studies included in this systematic review [42–67]. The screening process is visually represented in the PRISMA 2020 flow chart, depicted in Fig. 1.

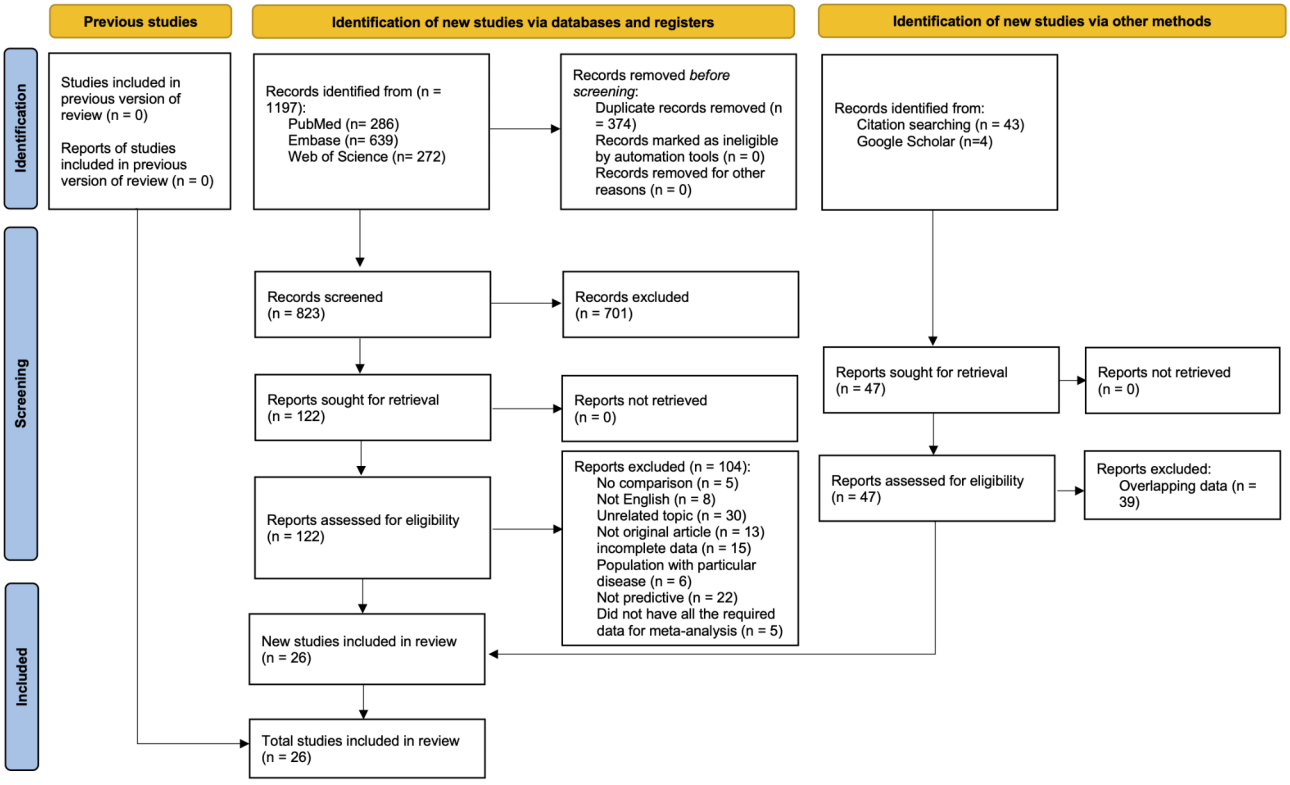


Fig. 1 PRISMA 2020 flow chart

Study characteristics

A total of 26 studies, with sample sizes ranging from 50 to 2,464, were included, culminating in a total sample size of 7,640 women. The publication years ranged from 1992 to 2024, with eight studies published before 2010 [42–46, 48, 49, 67], and the remaining 18 were published after 2010 [47, 50–66]. Geographically, 18 studies (69.2%) were conducted in Asia, with India being the most prominent country, represented by 14 studies. Additionally, four studies were conducted in Europe, two in Africa, one in North America, and one in Australia. Except for three studies that employed a case-control design [56, 61, 63], the remaining 23 studies utilized a prospective cohort design.

The data were classified into three groups for the prediction of PE: (1) Seven studies examined urine albumin levels in patients who subsequently developed PE versus those who did not [42–47, 67]; (2) Sixteen studies included data on the UACR values in patients who developed and did not develop PE [42, 43, 45, 47, 51, 55, 58–67], and (3) Thirteen studies compared the number of participants with and without albuminuria who developed and did not develop PE [48–60]. Detailed characteristics and findings of the included studies are provided in Tables 1 and 2.

Quality assessment

Based on the designs of the studies, the JBI Clinical Appraisal Checklist for case-control ($n = 3$) [56, 61, 63] and cohort ($n = 23$) [42–55, 57–60, 62, 64–67] studies were used for the quality assessment. Based on our assessment, a total of 17 studies met at least 70% of the JBI Clinical Appraisal Checklists criteria and were considered suitable for inclusion in our meta-analyses [42–46, 48, 50–54, 56, 61–63, 66, 67]. In contrast, the remaining nine studies were excluded due to insufficient methodological quality [47, 49, 55, 57–60, 64, 65] (Tables 1 and 2). Detailed information regarding the quality assessment of the reviewed studies is provided in Supplementary Materials 3.

The results of our quality assessment validation using the ROBINS-E checklist indicated that, among the 17 studies included in our meta-analysis, six demonstrated an overall low risk of bias, while 11 were assessed as having an overall moderate risk of bias. Additionally, of the nine studies excluded from the meta-analysis due to insufficient quality, seven were judged to have an overall serious risk of bias, and two were classified as having an overall critical risk of bias (Supplementary Materials 3).

Meta-analysis

Comparison of urine albumin levels and UACR in pregnant women who subsequently developed PE versus those who did not

By pooling data from six studies [42–46, 67] which included a total of 4,674 pregnant women, and applying a random-effects model (I^2 = 21.72%), we found significantly higher pooled urine albumin levels in patients who subsequently developed PE compared to those who did not (Hedges's g = 0.41 [95% CI: 0.24–0.58]; *p-value* < 0.001) (Fig. 2**(a)**). A leave-one-out sensitivity analysis confirmed the consistency of these findings, with *p-values* remaining below 0.05 upon omission of each study (Fig. 2**(b)**). Furthermore, the *p-values* from Begg's and Egger's tests were 1.000 and 0.573, respectively, indicating no significant publication bias across the analyzed studies. The funnel plot for the publication bias assessment is provided in Supplementary Material 4.

To further analyze UACR levels in patients who subsequently developed PE versus those who did not, we pooled data from nine studies [42, 43, 45, 51, 61–63, 66, 67], encompassing 5,258 pregnant women, using a random-effects model (I^2 = 79.55%). The meta-analysis revealed that women who later developed PE demonstrated significantly higher UACR levels than those who did not (Hedges's g = 0.48 [95% CI: 0.16–0.80]; *p-value* = 0.003) (Fig. 3**(a)**). However, a high level of heterogeneity (I^2 = 79.55%) was observed in our analysis, which may be attributed to variations in UACR measurement methods, differences in study endpoints, and methodological diversity across the included studies. To address this issue, we performed a leave-one-out sensitivity analysis, which indicated that the effect size remained statistically significant (*p-values* < 0.05) even when each of the nine studies was omitted in turn (Fig. 3**(b)**). Moreover, Begg's and Egger's tests yielded *p-values* of 0.251 and 0.159, respectively, suggesting no significant publication bias among the analyzed studies (Supplementary Material 4).

Assessing the utility of early-pregnancy albuminuria in predicting the development of PE

After pooling data from seven studies [48, 50–54, 56] comprising a total of 1,301 pregnant women using a random-effects model (I^2 = 68.21%), we observed a significantly higher incidence of PE in patients previously identified with albuminuria compared to those who did not (log odds ratio = 2.56 [95% CI: 1.75–3.38]; *p-value* < 0.001) (Fig. 4**(a)**). The leave-one-out analysis confirmed the consistency of this finding, with *p-values* remaining below 0.05 even after omitting each study individually (Fig. 4**(b)**). An evaluation of publication bias across the analyzed studies resulted in *p-values* of 0.071 and 0.015 for Begg's and Egger's tests, respectively. The

Table 1 Characteristics and findings of the studies examining the urine albumin and UACR levels in patients with and without further PE diagnosis

1. Urine albumin

Study	Country	Design	Age; y	Non-PE patient	PE patient	Non-PE patient's Alb; mg/L	PE patient's Alb; mg/L	U/A sample	U/A assessment timeline; gestational weeks	Alb measurement methods	Cr measurement methods	Overall appraisal (JBI)
Konstantin-Hansen et al. (1992) [42]	Denmark	PC	18–44	193	14	4.5 ± 3.5	5.1 ± 3.5	Clean-catch	20	Radioimmunoassay	Jaffe	Include
Masse et al. (1993) [43]	Canada	PC	N/A	1116	109	5.9 ± 7.2	9.3 ± 24.8	Clean-catch	15–24	Nephelometry	N/A	Include
Phuapradit et al. (1993) [44]	Thailand	PC	25.5 ± 0.6	177	13	10.7 ± 6.6	11.9 ± 2.5	Clean-catch	28–32	dipstick	colorimetric	Include
Baker et al. (1994) [45]	UK	PC	N/A	487	13	4.0 ± 1.0	4.6 ± 2.5	Clean-catch	18–19	Immunoturbidimetry	Jaffe	Include
Soltan et al. (1996) [46]	Egypt	PC	20.3 ± 2.6	71	17	7.7 ± 2.3	8.4 ± 2.0	Clean-catch	14–24	Immunodiffusion	N/A	Include
Poon et al. (2008) [67]	UK	PC	32.6 ± 6.9	2413	51	5.0 ± 7.0	9.8 ± 16.7*	Clean-catch	11–14	Immunoturbidimetry	colorimetric	Include
Hymavathi et al. (2023) [47]	India	PC	24.0 ± 4.5	45	7	11.0 ± 7.0	40.5 ± 31.8*	N/A	11–13	Immunoturbidimetry	Modified Jaffe	Seek further info

2. UACR

Study	Country	Design	Age; y	Non-PE patient	PE patient	Non-PE patient's UACR; mg/mmol	PE patient's UACR; mg/mmol	U/A sample	U/A assessment timeline; gestational weeks	Alb measurement methods	Cr measurement methods	Overall appraisal (JBI)
Konstantin-Hansen et al. (1992) [42]	Denmark	PC	(18–44)	193	14	0.5 ± 0.2	0.7 ± 0.5	Clean-catch	20	Radioimmunoassay	Jaffe	Include
Masse et al. (1993) [43]	Canada	PC	N/A	1116	109	0.6 ± 0.6	0.8 ± 1.5	Clean-catch	15–24	Nephelometry	N/A	Include
Baker et al. (1994) [45]	UK	PC	N/A	487	13	0.5 ± 0.1	0.5 ± 0.2	Clean-catch	18–19	Immunoturbidimetry	Jaffe	Include
Poon et al. (2008) [67]	UK	PC	32.6 ± 6.9	2413	51	0.4 ± 0.6	0.8 ± 1.3*	Clean-catch	11–14	Immunoturbidimetry	colorimetric	Include
Kuromoto et al. (2010) [61]	Japan	CC	31.1 ± 3.9	172	25	1.1 ± 1.0	1.5 ± 1.2	Clean-catch	1–14	N/A	N/A	Include
Baweja et al. (2011) [62]	Australia	PC	29.5 ± 4.8	259	6	29.8 ± 22.4	58.8 ± 54.3*	Clean-catch	17–20	HPLC	Modified Jaffe	Include
Fatema et al. (2011) [51]	Bangladesh	PC	25.1 ± 4.1	109	10	5.3 ± 7.8	5.1 ± 3.3	Clean-catch	10–14	Immunoturbidimetry	colorimetric	Include
Kronborg et al. (2011) [63]	Denmark	CC	32.2 ± 4.1	127	24	0.7 ± 3.1	0.5 ± 0.3	Clean-catch	1–19	Fluoroimmunoassay	Colorimetric	Include

Table 1 (continued)

1. Urine albumin												
Study	**Country**	**Design**	**Age; y**	**Non-PE patient**	**PE patient**	**Non-PE patient's Alb; mg/L**	**PE patient's Alb; mg/L**	**U/A sample**	**U/A assessment timeline; gestational weeks**	**Alb measurement methods**	**Cr measurement methods**	**Overall appraisal (JBI)**
Gupta et al. (2017) [64]	India	PC	25.1 ± 1.5	225	6	0.6 ± 0.6	5.2 ± 8.9*	Clean-catch	17–20	Immunoturbidimetry	Modified Jaffe	Exclude
Mishra et al. (2017) [55]	India	PC	27.8 ± 4.8	54	8	19.3 ± 8.0	51.9 ± 18.8*	Clean-catch	20–28	Immunoturbidimetry	Modified Jaffe	Seek further info
Rajeshwari et al. (2019) [58]	India	PC	20.1 ± 4.9	42	8	21.8 ± 12.9	53.2 ± 19.6*	Clean-catch	18–28	Immunoturbidimetry	Modified Jaffe	Exclude
Agarwal et al. (2022) [59]	India	PC	25.6 ± 3.2	132	24	11.3 ± 15.8	31.6 ± 50.8*	Clean-catch	20–24	Biuret	Modified Jaffe	Exclude
Hymavathi et al. (2023) [47]	India	PC	24.0 ± 4.5	45	7	1.4 ± 0.6	3.1 ± 1.3*	N/A	11–13	Immunoturbidimetry	Modified Jaffe	Seek further info
Latha et al. (2023) [65]	India	PC	N/A	57	6	2.1	25.4*	Clean-catch	17–24	Immunoturbidimetry	Modified Jaffe	Exclude
Singh et al. (2023) [66]	India	PC	26.3 ± 4.8	123	7	2.0 ± 1.2	4.2 ± 3.6*	Clean-catch	14–28	N/A	N/A	Include
Kumari et al. (2024) [60]	India	PC	28.4 ± 3.9	91	9	16.3 ± 5.5	47.5 ± 20.2*	Clean-catch	17–20	Immunoturbidimetry	Modified Jaffe	Exclude

Abbreviations: Alb = albumin, CC = case-control, Cr = creatinine, HLPC = High-Performance Liquid Chromatography, JBI = Joanna Briggs Institute, N/A = not available, PC = prospective cohort, PE = preeclampsia, U/A = urine analysis, UACR = urine albumin-to-creatinine ratio

* A statistically significant difference (*p-value* < 0.05) was observed in between the groups

Table 2 Characteristics and findings of the studies examining further PE incidence between the patients with and without albuminuria

Study	Country	Design	Age; y	Patients with albuminuria		Patients without albuminuria		U/A sample	U/A assessment timeline (gestational weeks)	Albuminuria definition	Alb measurement methods	Cr measurement methods	Overall appraisal (JBI)
				Non-PE	PE	Non-PE	PE						
Das et al. (1996) [48]	India	PC	N/A	9	13*	102	6	Clean-catch	24–34	Alb = 20 mg/L	Immunochemical	N/A	Include
Salako et al. (2003) [49]	Nigeria	PC	N/A	28	8*	56	1	24-hour	N/A	Alb = 30 mg/day	Turbidimetry	N/A	Seek further info
Bahasadri et al. (2011) [50]	Iran	PC	25.0 ± 2.9	19	8*	53	1	Clean-catch	24–29	UACR = 0.3 mg/mmol	N/A	Jaffe	Include
Fatema et al. (2011) [51]	Bangladesh	PC	25.1 ± 4.1	55	14*	150	12	Clean-catch	24–28	UACR = 3.6 mg/mmol	Immunoturbidimetry	colorimetric	Include
Sheela et al. (2011) [52]	India	PC	25.6 ± 3.9	24	19*	413	39	Clean-catch	20–24	Alb = 30 mg/L	immunometric assay	Jaffe	Include
Singh et al. (2013) [53]	India	PC	25.4 ± 3.5	21	15*	112	9	24-hour	17–20	UACR = 3.9 mg/mmol	Immunoturbidimetry	Modified Jaffe	Include
Singh et al. (2015) [54]	India	PC	N/A	9	12*	110	1	Clean-catch	24–34	Alb = 30 mg/L	N/A	Jaffe	Include
Mishra et al. (2017) [55]	India	PC	27.8 ± 4.8	2	4*	55	1	Clean-catch	N/A	UACR = 33.5 mg/mmol	Immunoturbidimetry	Modified Jaffe	Seek further info
Chawla and Malik (2018) [56]	India	CC	N/A	16	7*	52	1	Clean-catch	24–29	Alb = 30 mg/L	Immunochemical	N/A	Include
Upadhyay et al. (2018) [57]	India	PC	N/A	18	14*	27	3	Clean-catch	20–24	UACR = 0.2 mg/mmol	Bromocresol green assay	Modified Jaffe	Seek further info
Rajeshwari et al. (2019) [58]	India	PC	20.0 ± 4.2	2	12*	156	4	Clean-catch	24–28	UACR = 33.5 mg/mmol	Immunoturbidimetry	Modified Jaffe	Exclude

Table 2 (continued)

Study	Country	Design	Age; y	Patients with albuminuria		Patients without albuminuria		U/A sample	U/A assessment timeline (gestational weeks)	Albuminuria definition	Alb measurement methods	Cr measurement methods	Overall appraisal (JBI)
				Non-PE	PE	Non-PE	PE						
Agarwal et al. (2022) [59]	India	PC	25.6 ± 3.2	20	8*	54	2	Clean-catch	20–28	UACR = 0.2 mg/mmol	Biuret	Modified Jaffe	Exclude
Kumari et al. (2024) [60]	India	PC	23.8 ± 3.9	2	7*	89	2	Clean-catch	20–28	UACR = 33.5 mg/mmol	Immunoturbidimetry	Modified Jaffe	Exclude

Abbreviations: CC = case-control, Cr = creatinine, JBI = Joanna Briggs Institute, N/A = not available, PC = prospective cohort, PE = preeclampsia, U/A = urine analysis, UACR = urine albumin-to-creatinine ratio.

* A statistically significant difference (*p-value* < 0.05) was observed in the PE incidence between the patients with and without albuminuria.

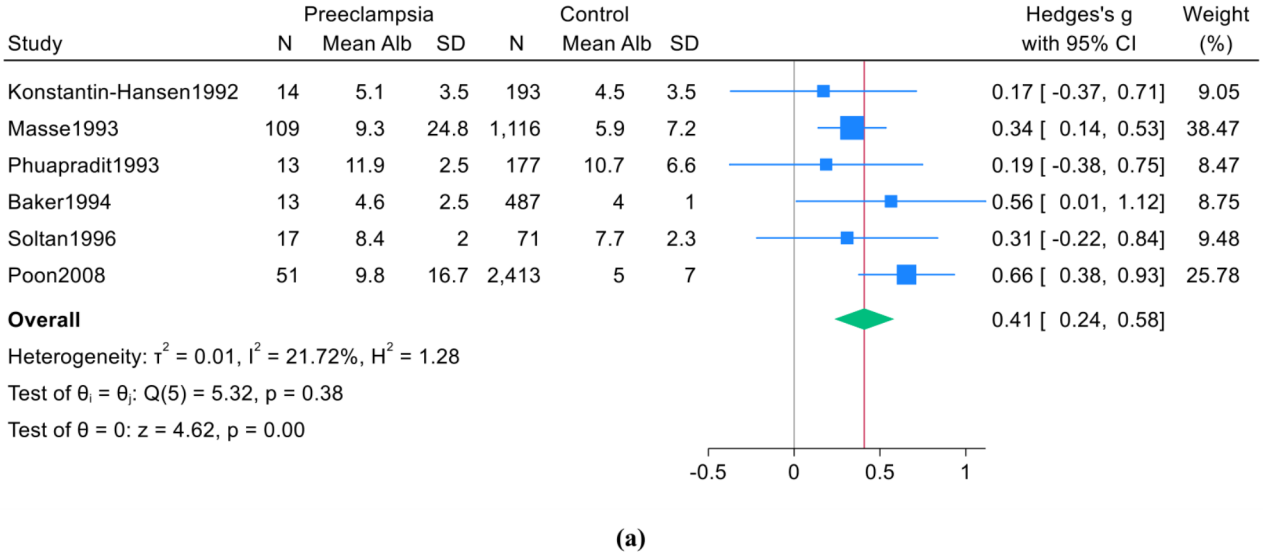
results of Egger's test suggest potential bias across the studies. To address this, we conducted a non-parametric trim-and-fill analysis using the L0 option. Our findings indicated that no studies were imputed on the right side, while three missing studies were imputed on the left side, resulting in a smaller estimated effect size for the difference between the study groups (Hedges's g = 1.99 [95% CI: 1.08–2.91]) (Supplementary Material 4).

Furthermore, using META-DISC 1.4 software, we analyzed the accuracy of albuminuria in predicting the occurrence of PE in later stages of pregnancy. By pooling data from the same seven studies [48, 50–54, 56], encompassing a total of 1,301 pregnant women, we obtained a pooled sensitivity of 56% [95% CI: 48-64%] and a specificity of 87% [95% CI: 85-89%]. The moderate sensitivity suggests that albuminuria testing may miss nearly half of pregnant women at risk for PE, highlighting the need for complementary diagnostic tools. However, the high specificity indicates that when albuminuria is detected, it is a reliable indicator of PE, reducing the likelihood of false-positive diagnoses. Additionally, a pooled PLR of 4.67 [95% CI: 3.02–7.23] suggests that a positive albuminuria test result increases the probability of PE, supporting its utility in confirming the diagnosis. Conversely, a pooled NLR of 0.43 [95% CI: 0.27–0.68] indicates that a negative result moderately reduces the probability of PE, though not conclusively. The pooled DOR of 12.62 [95% CI: 5.87–27.16] and AUC of 0.877 further highlights the overall promising diagnostic accuracy of albuminuria for PE. The forest plots for these analyses are provided in Supplementary Materials 5.

Discussion

This study offers valuable insights into the potential utility of maternal urine albumin levels in early pregnancy as a predictor for the development of PE later in pregnancy. Our meta-analyses indicate that both urine albumin and UACR levels are significantly higher in pregnant women who are subsequently diagnosed with PE. Additionally, we consistently observed a higher incidence of PE in women who had albuminuria detected in the earlier stages of pregnancy. These findings suggest that analyzing maternal urine samples for albumin levels could help identify patients at increased risk of developing PE as pregnancy progresses.

Early identification of PE enables clinicians to perform more targeted follow-up examinations and assessments for high-risk patients, potentially facilitating earlier intervention. Timely detection and management of PE can mitigate its adverse effects on both mothers and fetuses, thereby enhancing overall pregnancy outcomes [68]. In this regard, extensive research has investigated various predictive factors in the early stages of pregnancy for PE. Notably, uterine artery Doppler studies and several



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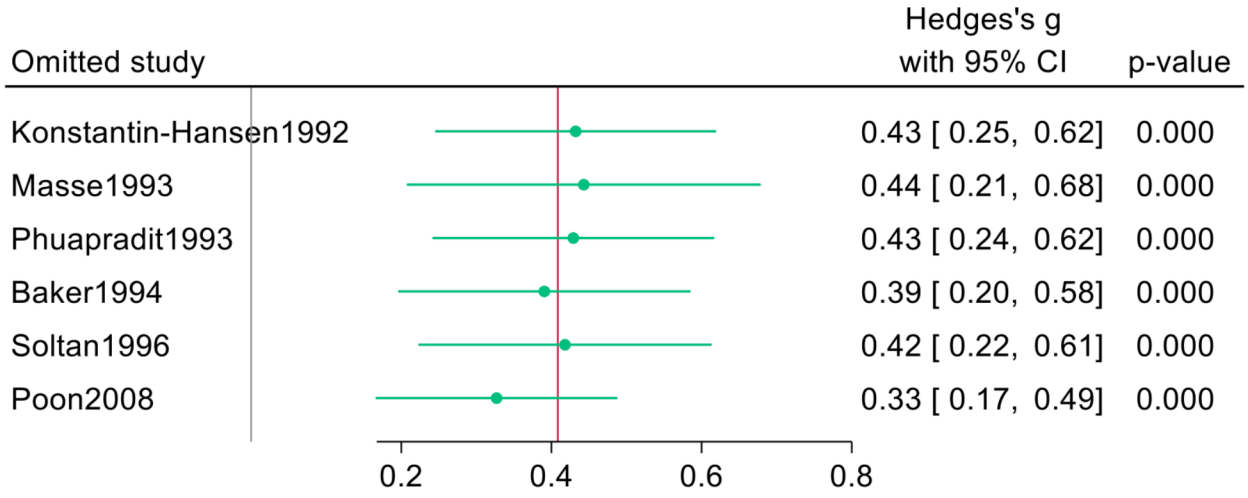
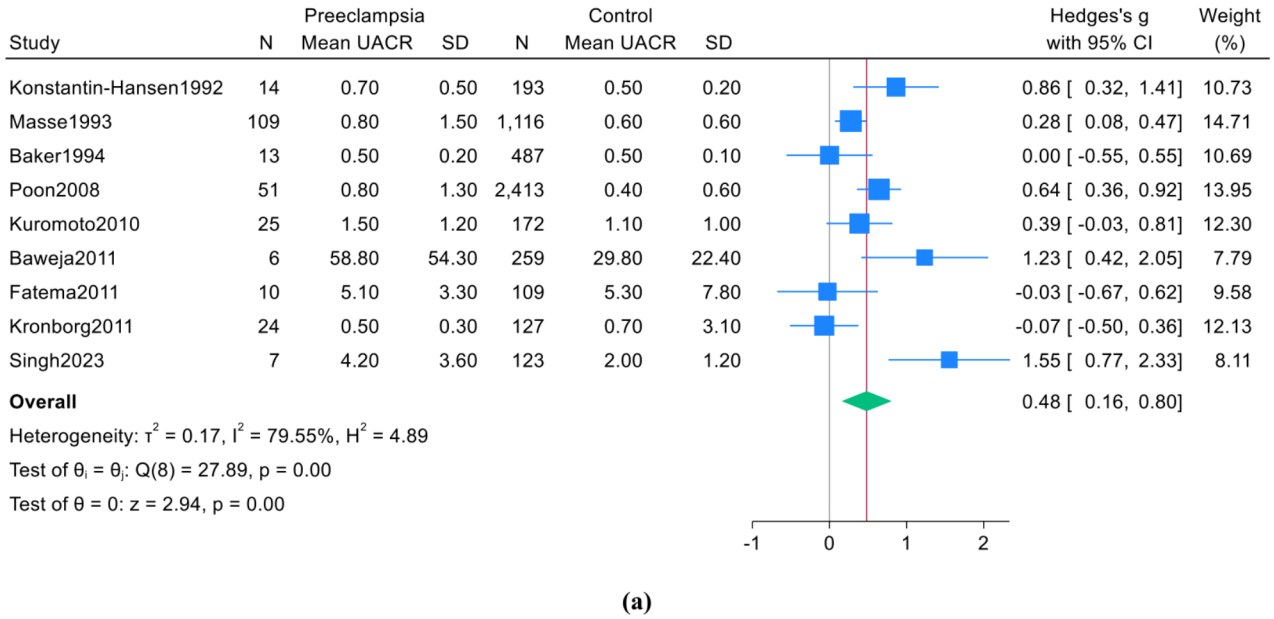


(b)

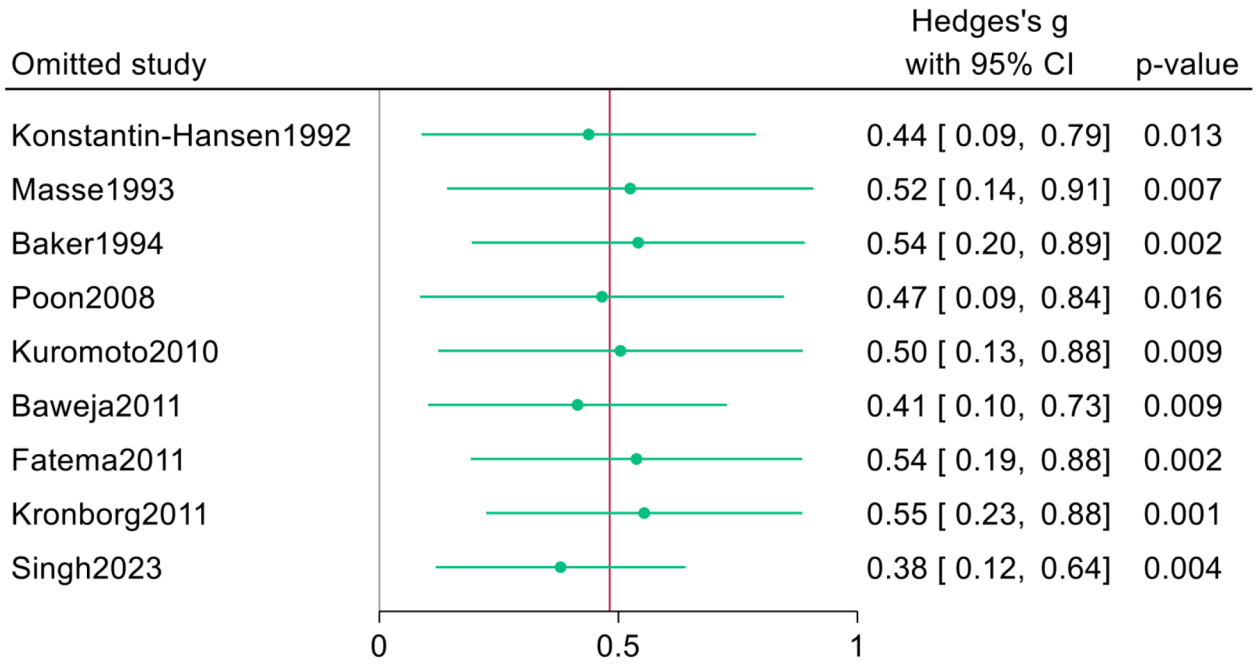
Fig. 2 Comparison of urine albumin levels in pregnant women who subsequently developed PE versus those who did not: (**a**) forest plot, (**b**) leave-one-out sensitivity analysis

plasma biomarkers—such as vitamin D, the soluble fms-like tyrosine kinase 1/placental growth factor ratio, and soluble endoglin—have shown promising results [69, 70]. Additionally, predictive models for PE have been developed, emphasizing factors such as maternal body mass index, the first-trimester uterine artery resistance index, and the placental growth factor [71]. Despite these advancements, no single marker has demonstrated adequate performance for routine clinical use [70, 71]. This underscores the need for a reliable, practical marker for predicting PE that can be easily integrated into clinical practice.

In the pursuit of reliable and feasible early pregnancy biomarkers for predicting PE, we thoroughly investigated the utility of maternal urine albumin and UACR. This study builds on prior research that explored the potential predictive capabilities of these measures [11, 12, 67, 72]. Our findings suggest that elevated urine albumin levels, the presence of microalbuminuria, and increased UACR levels may serve as potential indicators for the subsequent development of PE. We found a pooled AUC of 0.877, indicating a favorable overall predictive ability of albuminuria for PE. However, the pooled sensitivity was 56%, while the specificity was a favorable 87%. This indicates that negative results for albuminuria can reliably predict a lower risk of PE development. However, positive results are weaker predictors of subsequent PE development, highlighting the greater value of negative



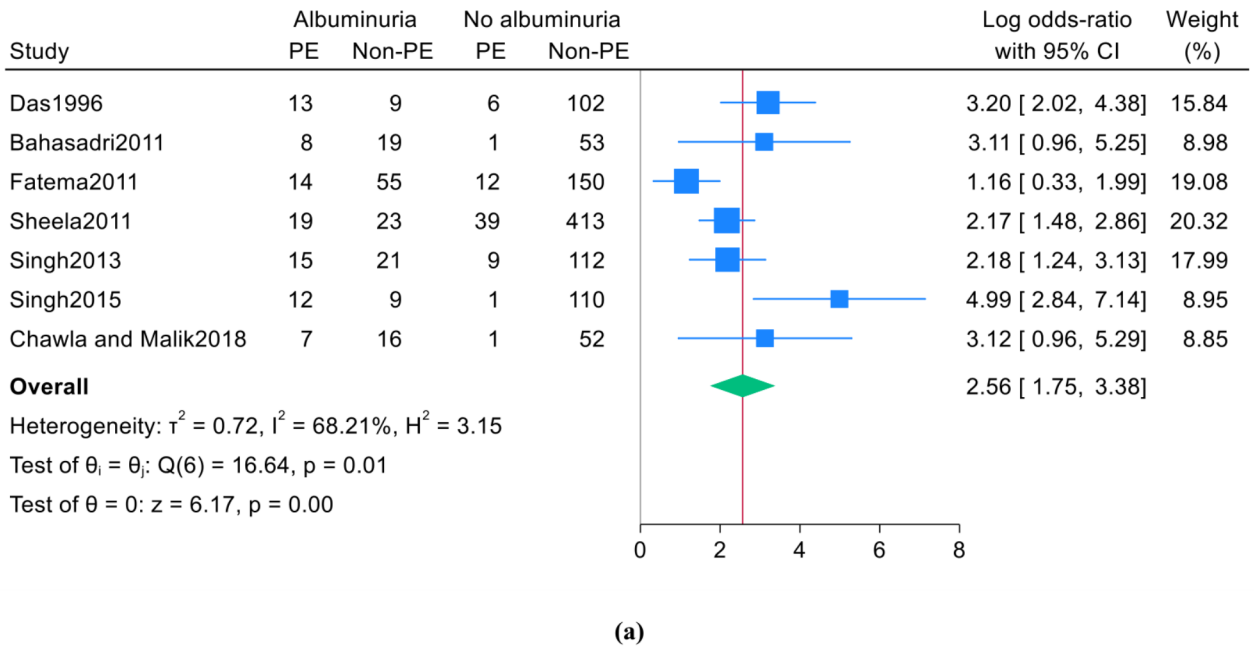
(a)



(b)

Fig. 3 Comparison of UACR in pregnant women who subsequently developed PE versus those who did not: (**a**) forest plot, (**b**) leave-one-out sensitivity analysis

results. This finding aligns with previous studies [11, 72]. The limited sensitivity of albuminuria as a predictor of PE can be attributed to several factors. Variability in diagnostic criteria across studies, including differences in the thresholds for albuminuria or UACR levels, may affect the accuracy of detection. Additionally, discrepancies in test methodologies, variations in hydration status, and the presence of coexisting conditions among the study populations may have contributed to false-negative results. Moreover, as albuminuria primarily reflects renal dysfunction, it may not comprehensively capture the multi-organ involvement characteristic of PE [6, 15], thereby limiting its effectiveness as a standalone predictive marker. Therefore, while it is established that



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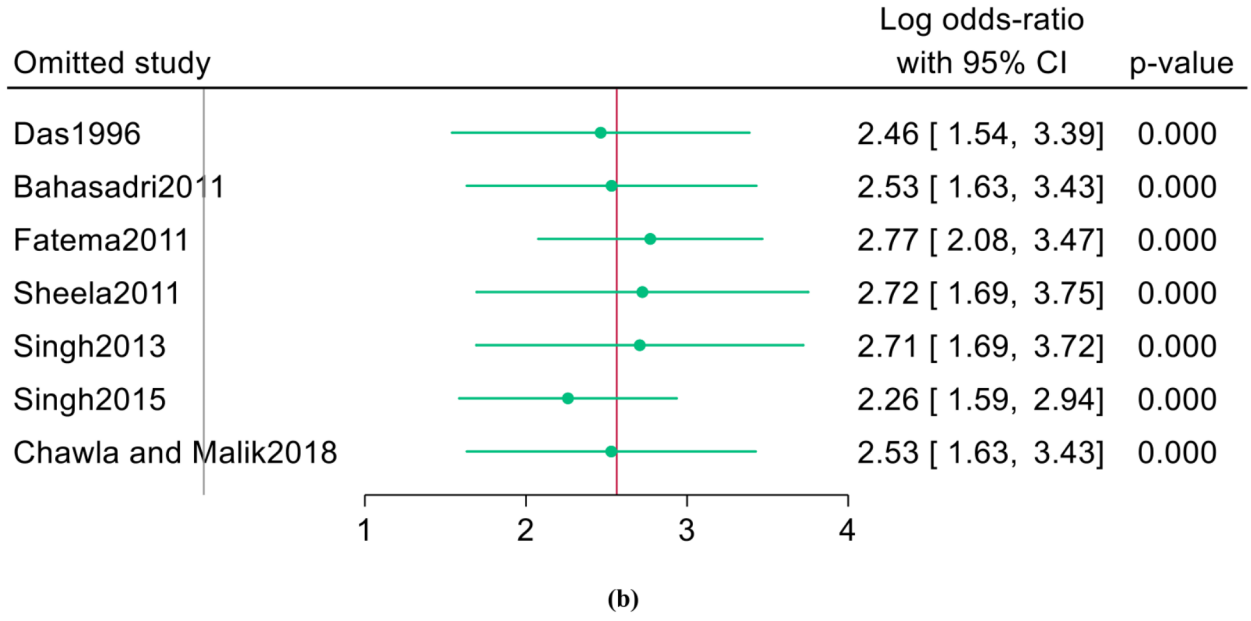

(b)

Fig. 4 Comparison of PE development in patients with and without albuminuria: (**a**) forest plot, (**b**) leave-one-out sensitivity analysis

urine albumin and UACR levels are significantly higher in patients who develop PE compared to those who do not, there remains uncertainty regarding the positive predictive power of this biomarker. It may not be a robust standalone predictor of PE, and its potential inclusion in combined predictive models warrants further investigation. Nevertheless, these results suggest that routine urine analysis for albumin and creatinine levels could provide valuable insights into the risk of PE later in pregnancy. Specifically, diagnosing patients as free of albuminuria may allow for a significantly lower estimated risk of subsequent PE development.

The mechanism by which early pregnancy albuminuria predicts PE is fundamentally associated with endothelial dysfunction and renal pathology [73, 74]. Albuminuria signifies a compromise in the integrity of the glomerular filtration barrier, which is critically dependent on the selective permeability of the endothelium [75, 76]. The presence of albuminuria during early pregnancy indicates that endothelial cells are compromised, resulting in increased permeability and the leakage of albumin from

the bloodstream into the urine [73]. This endothelial dysfunction is systemic, reflecting broader vascular health issues. Systemic endothelial dysfunction is a known precursor to PE, directly affecting placental development and function, leading to inadequate placental perfusion and subsequent pregnancy complications [74].

The link between early pregnancy albuminuria and PE can be further elucidated through the cascade of pathophysiological events following endothelial dysfunction [74]. Impaired endothelial function hampers proper trophoblastic invasion and spiral artery remodeling, critical processes for establishing adequate uteroplacental blood flow [77]. Poor placentation results in placental hypoxia and the release of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 and soluble endoglin, into the maternal circulation, exacerbating systemic endothelial injury and contributing to hypertension and proteinuria, hallmark features of PE [78–80]. Additionally, these vascular and renal alterations induce inflammatory responses and oxidative stress, further destabilizing maternal hemodynamics [81–83]. Thus, early detection of albuminuria serves as an early warning signal for these underlying dysfunctions, providing a predictive marker for the development of PE, and underscoring the importance of vigilant monitoring and intervention in affected pregnancies.

The identification of albuminuria as an early predictor of PE contains several significant clinical implications. Firstly, it underscores the potential for routine screening of albuminuria in early pregnancy as an integral part of standard prenatal care [84]. Utilizing albuminuria as a screening tool could facilitate the implementation of prophylactic measures, such as low-dose aspirin, which has been demonstrated to reduce the incidence of PE in high-risk populations [85]. In 2022, Wang et al. conducted a systematic review and meta-analysis of 39 randomized controlled studies encompassing 39,044 participants to assess the prophylactic efficacy of aspirin during pregnancy. Their analysis demonstrated that aspirin administration significantly reduces the risk of preeclampsia when initiated between 12 and 16 weeks of gestation [86]. However, some trials did not support the protective effect of aspirin [87], indicating that the effectiveness of aspirin for preeclampsia prevention still requires further verification. Moreover, the use of low-dose aspirin for PE prevention is associated with potential risks, including a possibly increased but inconclusive risk of placental abruption [88] and bleeding complications such as postpartum hemorrhage [89]. Additional concerns include gastrointestinal side effects [90], gaps in knowledge regarding aspirin use, challenges related to adherence [91], uncertainty regarding the optimal dosage, and economic constraints that may hinder its widespread implementation [92]. Furthermore, a recent study analyzing 17 clinical practice guidelines on aspirin use for PE prevention found that, although all guidelines endorse its use, they differ in recommendations regarding initiation criteria, dosage, and gestational age for administration. This variability underscores the necessity of an individualized risk-benefit assessments in clinical decision-making [93]. Major guidelines, such as those from the American College of Obstetricians and Gynecologists (ACOG), the National Institute for Health and Care Excellence (NICE), and the European Society of Cardiology (ESC), recommend aspirin prophylaxis for pregnant individuals with established risk factors for PE. However, these guidelines do not currently include early pregnancy albuminuria as a criterion for stratifying PE risk [1, 94, 95].

Moreover, identifying women with albuminuria allows healthcare providers to tailor management strategies to include more frequent monitoring of blood pressure, renal function, and fetal growth, thereby enabling early identification and treatment of complications [2]. Also, recognizing the role of albuminuria in predicting PE can also inform the development of novel therapeutic strategies targeting endothelial function. Interventions aimed at improving endothelial health, such as antioxidant therapy or agents that enhance nitric oxide bioavailability, could potentially reduce the risk of PE in women identified with albuminuria in early pregnancy [96–98]. Albumin in urine has traditionally been measured through various quantitative immunochemical methods or semiquantitative dipstick tests. The cost and availability of albuminuria testing can vary significantly across healthcare settings, with resource-limited regions often facing financial constraints [99]. In these contexts, cost-effective alternatives, such as urine dipstick tests, provide a feasible screening option despite their lower sensitivity and specificity compared to more quantitative laboratory-based assays. Although test strips offer rapid and inexpensive screening, quantitative analysis may be more suitable in well-equipped healthcare facilities due to its greater accuracy [100].

This study has several strengths. Firstly, by conducting a thorough search, we were able to include all eligible studies published within the specified timeframe, providing a comprehensive overview of the utility of albuminuria in predicting PE. Additionally, we applied strict criteria for quality assessment, allowing us to include only studies with satisfactory methodological quality in our meta-analysis, thus ensuring the reliability of our findings. Lastly, we performed various sets of meta-analyses to evaluate the utility of different urine albumin indicators in predicting PE. This was complemented by a diagnostic accuracy meta-analysis, which provided pooled sensitivity and specificity estimates for albuminuria in predicting PE, offering a precise and comprehensive evaluation.

However, this study has certain limitations that require cautious interpretation of its findings. Firstly, there was significant heterogeneity in the populations of the reviewed studies, which may limit the generalizability of our results. Secondly, a considerable proportion of the studies were conducted in India, further limiting the geographic generalizability of our findings. Thirdly, although we observed relatively good predictive abilities for albuminuria in predicting PE, the heterogeneity for all outcomes was high ($I^2 > 50\%$), potentially due to varying diagnostic criteria for albuminuria across the analyzed studies. Therefore, future larger studies with well-established and more homogeneous designs are needed to achieve a precise understanding of the predictive ability of albuminuria for PE. Fourthly, the sensitivity of METADISC software to the small number of studies included in this meta-analysis may have introduced additional variability, affecting the robustness and generalizability of the results [101]. Additionally, a large proportion of the included studies were published over ten years ago. This raises concerns regarding potential advancements in urinary protein quantification techniques that may affect the accuracy and comparability of finding. Future studies should consider these methodological differences when interpreting results and focus on evaluating the predictive performance of albuminuria using the latest quantification methods. Finally, it is important to note that albuminuria alone is a limited predictor of PE, as it primarily reflects kidney dysfunction and does not capture the broader, multi-organ nature of the disease [6, 15]. PE involves systemic endothelial dysfunction affecting multiple organs [6], and relying solely on albuminuria may overlook critical mechanisms, underscoring the need for more comprehensive biomarkers and predictive models to better address PE's systemic pathophysiology. Moreover, future research should focus on establishing standardized cut-off values for albuminuria to optimize both sensitivity and specificity, thereby enhancing its clinical utility as a predictive marker.

Conclusion

To conclude, our findings suggest that patients who are diagnosed with PE during pregnancy tend to have significantly higher albumin and UACR values in the earlier stages of pregnancy. This indicates that maternal urine albumin levels may serve as a potential predictive biomarker for PE, allowing the identification of high-risk patients early on. Early identification could enable clinicians to implement closer monitoring and timely preventive and treatment interventions, potentially improving pregnancy outcomes. Our analysis of predictive accuracy demonstrated a favorable specificity, but relatively low sensitivity for albuminuria in predicting PE, indicating that negative results may be more informative than positive results. Thus, while albuminuria may not yet be a robust independent predictor of PE suitable for routine clinical practice, we believe that incorporating this biomarker into predictive models could enhance their predictive abilities. Despite the variability among the studies reviewed and the noted limitations, there is a critical need for future research involving larger sample sizes and more rigorous methodologies to gain a clearer understanding of the utility of urine albumin as a predictor of PE.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AUC	Area Under the Curve
ESC	European Society of Cardiology
DOR	Diagnostic Odds Ratio
CI	Confidence Interval
HELLP	Hemolysis, Elevated Liver enzymes, and Low Platelet count
JBI	Joanna Briggs Institute
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
NICE	National Institute for Health and Care Excellence
NLR	Negative Likelihood Ratio
PE	Preeclampsia
PECO	Patient, Intervention, Comparison, and Outcome
PLR	Positive Likelihood Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
REML	Restricted Maximum Likelihood
sROC	summary Receiver Operating Characteristics
UACR	Urine Albumin-to-Creatinine Ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07444-z.

Supplementary Material 1: Title of data: Utilized keywords and filters in each online dataset. Description of data: Utilized keywords and filters in each online dataset.

Supplementary Material 2: Title of data: Joanna Briggs Institute Clinical Appraisal Checklists for case-control and cohort studies. Description of data: Joanna Briggs Institute Clinical Appraisal Checklists for case-control and cohort studies.

Supplementary Material 3: Title of data: Table S1-3. Description of data: finding of Quality Assessments based on Joanna Briggs Institute and Risk of Bias in Non-randomized Studies - of Exposures Checklists.

Supplementary Material 4: Title of data: Figure S1-4. Description of data: Funnel plots illustrating the assessment of publication bias, along with the adjusted funnel plot following the trim-and-fill analysis.

Supplementary Material 5: Title of data: Figure S5. Description of data: Forest plots for the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and summary receiver operating characteristics for preeclampsia prediction using the albuminuria.

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Author contributions

P.R.: Conceptualization, Project administration, Methodology, Investigation, Data curation, Writing– original draft.M.P.: Investigation, Data curation, Formal analysis, Software, Writing– original draft.S.H.: Conceptualization, Project administration, Investigation, Data curation, Writing– review and editing.B.H.: Conceptualization, Project administration, Writing– review and editing.All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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