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Glycosylated fibronectin in preeclampsia: a systematic review and meta-analysis

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Abstract

Background Preeclampsia (PE) is a complex multisystem disease, and its timely diagnosis and treatment impact the health of patients and perinatal infants. Studies have reported elevated levels of maternal serum glycosylated fibronectin (GlyFn) in patients with PE compared with pregnant women without PE (controls), suggesting its potential as a novel biomarker for screening and diagnosing PE. Therefore, this study aims to evaluate maternal serum GlyFn levels and their diagnostic accuracy in PE.

Methods A systematic literature search was conducted using PubMed, EMBASE, Web of Science, and the Cochrane Library up to January 15, 2024. The Newcastle-Ottawa Quality Assessment Scale and the Quality Assessment of Diagnostic Accuracy Studies-2 tool were used to evaluate study quality. Heterogeneity was assessed using I^2 statistics. In the meta-analysis comparing maternal serum GlyFn levels between PE and controls, standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated. Publication bias was detected, and sensitivity and subgroup analyses were conducted to verify the robustness of the results and identify potential sources of heterogeneity. For the meta-analysis of diagnostic, the accuracy of maternal serum GlyFn levels between PE and controls, sensitivity and specificity were pooled and the summary receiver operating characteristic curve and area under the curve were used as measures of overall accuracy. This review was registered in the International Prospective Register of Systematic Reviews (registration number: CRD42024512172).

Results A total of 11 studies were included, and the meta-analysis revealed that maternal serum GlyFn levels were significantly higher in the PE group than in the control group (SMD = 1.08, 95% CI = 0.72–1.43, $P < 0.001$). Heterogeneity may arise from differences in the detection method and research type. Overall, the combined sensitivity and specificity of maternal serum GlyFn levels in diagnosing PE were 0.81 (95% CI = 0.77–0.85, $P < 0.001$) and 0.80 (95% CI = 0.77–0.82, $P < 0.001$), respectively, with an area under the curve of 0.90.

Conclusions This meta-analysis confirmed that maternal serum GlyFn levels are significantly higher in patients with PE and exhibit high diagnostic accuracy for PE diagnosis, suggesting its potential as a biomarker for screening and diagnosing PE.

Keywords Preeclampsia, Glycosylated fibronectin, Diagnosis, Systematic review, Meta-analysis

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Background

Preeclampsia (PE) is a complex multisystem disease that affects 3–5% of pregnancies [1, 2]. Adverse outcomes of PE include progressive tissue damage and multiorgan lesions such as stroke, liver, and kidney failure [3, 4]. For perinatal infants, PE may lead to intrauterine growth retardation, as well as long-term neurodevelopmental disorders and metabolic diseases in adulthood [5, 6]. Currently, there is no effective treatment method; only placental delivery can alleviate symptoms [7, 8]. Therefore, exploring reliable methods for screening, diagnosing, and predicting PE is necessary for its proper management and mitigating adverse outcomes.

The current diagnosis of PE relies on clinical assessment, which demonstrates limitations in early prediction and diagnosis [1, 2, 9–11]. Existing predictive biomarkers include physical indicators (such as uterine artery pulsatility index) and biochemical indicators (such as soluble vascular endothelial growth factor receptor 1 (sFlt1), placental growth factor (PlGF)) [11–15]. The two-stage theory believes that PE arises from systemic endothelial dysfunction and multi-organ function damage, which are caused by shallow trophoblast invasion leading to impaired spiral artery remodeling [1, 2]. Uterine artery pulsatility index measured by uterine artery Doppler velocimetry effectively reflects the high-resistance blood flow characteristic of PE; however, this method relies on skilled ultrasound technicians and have a long measurement time [14, 15]. The sFlt-1/PlGF ratio, associated with angiogenesis, shows a sensitivity of 80% and a specificity of 92% for PE prediction [16]. In a follow-up cohort of 7554 singleton pregnant women, the AUC of PAPP-A combined with maternal factors for predicting PE was also low, at 0.66 [17]. The poor predictive accuracy of these biomarkers restricts their utility in clinical practice, highlighting the need for identifying and validating new biomarkers.

Table 1 Search strategy for PubMed

Step	search terms	
#1	"(fibronectin) AND (glycosylated)" OR "glycosylated fibronectin" OR "GlyFn"	
#2	MeSH terms	"hypertension, pregnancy induced" OR "pre eclampsia" OR "Eclampsia"
#3	Title/abstract	"hypertension pregnancy induced" OR "pregnancy induced hypertension" OR "gestational hypertension" OR "hypertension gestational" OR "transient hypertension pregnancy" OR "pregnancy transient hypertension" OR "pregnancy hypertension" OR "hypertension in pregnancy" OR "pre eclampsia" OR "Preeclampsia" OR "pregnancy toxemias" OR "pregnancy toxemia" OR "edema proteinuria hypertension gestosis"
#4	#2 AND #4	
#5	#1 AND #4	

Several research reports suggest that maternal serum glycosylated fibronectin (GlyFn) levels are elevated in patients with PE and may be a novel biomarker for screening, diagnosing, and monitoring PE [18–27]. Most fibronectin in serum or plasma, called plasma fibronectin, is produced and secreted by liver cells in soluble form, whereas the so-called cellular fibronectin is produced by many cell types, including fibroblasts, endothelial cells, and smooth muscle cells [18]. Both plasma and cellular fibronectin exhibit complex glycosylation patterns [18]. Impaired spiral artery remodeling induces systemic endothelial responses, leading to the release large amounts of fibronectin into the bloodstream, thereby elevating maternal serum GlyFn levels [28]. These changes in GlyFn may reflect impaired vascular function, offering potential early diagnostic clues. However, variability in serum GlyFn levels reported across studies has led to inconsistent cut-off values for its use in diagnosing PE [18–20, 22, 26].

The aim of this study is to conduct a systematic review and meta-analysis of published studies on the relationship between maternal serum GlyFn levels and PE. In addition, we investigated the accuracy of maternal serum GlyFn levels in PE diagnosis.

Methods

We conducted and reported this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [29]. The completed PRISMA checklist is available in Supplementary Table 1. This review was registered in the International Prospective Register of Systematic Reviews (registration number: CRD42024512172).

Search strategy

The records were searched on January 15, 2024, using the following databases: PubMed, EMBASE, Web of Science, and the Cochrane Library. The detailed search terms used in PubMed can be found in Table 1, and appropriate adjustments were made in other databases. No publication date restrictions were applied. After retrieval, duplicates were checked and references were managed using Endnote X9 library (Clarivate Analytics, Philadelphia, PA, USA).

Eligibility and quality assessment

Two reviewers (L. Liao and M. Liu) independently assessed eligibility. Titles and abstracts of all retrieved records were screened to identify potentially eligible studies, and all selected studies were analyzed in full text for conclusive evaluation. Eligible studies met the following criteria. Inclusion criteria were [1] Population: Pregnant women; [2] Intervention: Measurement of maternal serum GlyFn levels by methods such as enzyme-linked

immunosorbent assays (ELISA) and point-of-care (POC); [3] Comparison: PE diagnosis was made based on the American College of Obstetricians and Gynecologists criteria and the International Society for the Study of Hypertension in Pregnancy guidelines [1, 30]; and [4] Outcome: Serum GlyFn diagnostic sensitivity, specificity, and other indicators. Exclusion criteria were [1] studies that lacked data on maternal serum GlyFn levels or sensitivity and/or specificity of GlyFn; [2] case reports, commentaries, or reviews; and [3] studies published in non-English.

Two reviewers (Y. Yin and Q. Xu) independently assessed the quality of eligible studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) [31, 32]. Each study was scored for eight items of the NOS, and a study was considered low, moderate, or high quality if the score was ≤3, 4–6, or ≥7, respectively. Additionally, we evaluated the methodological quality of the studies included in the meta-analysis of diagnostic accuracy using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS2) tool [33]. Four domains were analyzed to assess the risk of bias: patient selection, index test, reference standard, and flow and timing. Applicability concerns were evaluated across three domains: patient selection, index test, and reference standard. Ratings for risk of bias and applicability concerns were categorized as low, high, or unclear if data were insufficient or inadequate for a conclusive judgment. In addition, the overall credibility of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach [34]. Any discrepancies between reviewers were resolved through discussion and consultation with a third reviewer (R. Zhou).

Data extraction

Two reviewers (L. Liao and M. Liu) independently performed data extraction. For each eligible study, the following data were recorded: first author, publication year, study region, research type, specimen type, detection method, classification of PE, control group category, maternal serum GlyFn levels (expressed as mean [standard deviation (SD)], median [interquartile range (IQR)], or median and range), cutoff, and number of true positives, true negatives, false positives, and false negatives. If only figures were provided, two reviewers (L. Yuan and S. Xie) independently used GetData Graph Digitizer 2.26 to extract data or contacted the author for availability. When median (quartiles) or median (range) of maternal serum GlyFn levels were reported, the data were transformed into mean (SD) as described in previous studies [35, 36]. Maternal serum GlyFn levels of preterm and term PE were combined into a single effect size following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, Version 6.3, and the formulae were as follows:

$$Mean = (N_1 M_1 + N_2 M_2)/(N_1 + N_2)$$

$$SD = \sqrt{\frac{(N_1 - 1)\,SD_1^2 + (N_2 - 1)\,SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}\,(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}}$$

where N = sample size and M = mean of the group [23]. Any discrepancies between reviewers were resolved through discussion and consultation with a third reviewer (R. Zhou).

Statistical analysis

Stata/SE 15.1 (StataCorp, College Station, TX, USA) was used for the meta-analysis. Statistical heterogeneity across the included studies was evaluated using the I^2 statistic, with $I^2 > 50\%$ indicating high heterogeneity. In cases where I^2 was >50%, a random-effects meta-analysis model was used to combine the studies; otherwise, a fixed-effect model was used. Continuous variables were analyzed using standard mean difference (SMD) and 95% confidence interval (CI). A two-sided $P < 0.05$ was considered statistically significant. Begg's funnel plot and Egger's test were employed to assess the risk of publication bias. If publication bias exists, the trim and fill method used to identify and correct funnel plot asymmetry caused by publication bias. Sensitivity analysis was performed using the leave-one-out method to verify the robustness of the results and identify potential sources of heterogeneity. Subgroup analyses were conducted based on the study region, research type, detection method, pregnancy stage at sample collection, and control group category to identify sources of heterogeneity. In the meta-analysis of diagnostic accuracy, Meta-DiSc 1.4 software (Unit of Clinical Biostatistics team, Hospital Universitario Ramony Cajal, Madrid, Spain) was used to assess threshold effect. Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated with their respective 95% CIs. Overall accuracy was assessed using a summary receiver-operating characteristic curve (SROC) and the area under the curve (AUC).

Results

Study selection

Figure 1 illustrates the detailed process of records selection. Initially, 43 records were retrieved based on the established selection criteria. After removing duplicates, the titles and abstracts of 22 records were screened, and 12 unqualified records were excluded. The list of studies excluded at records screening is available in Supplementary Table 2. Finally, full texts of the remaining records

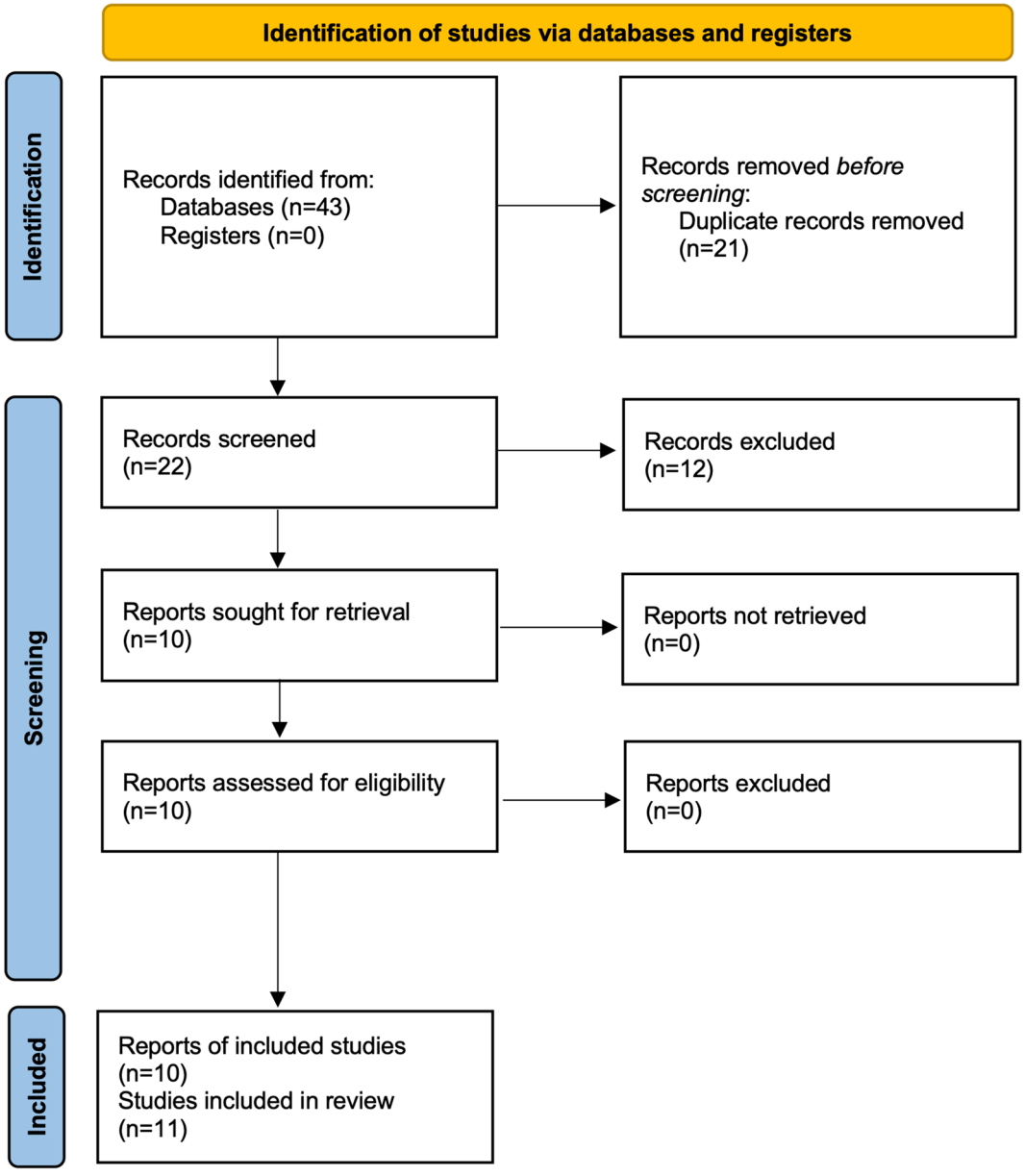

Fig. 1 Flow chart showing the study selection process

were screened, resulting in the inclusion of 11 studies from 10 reports in the meta-analysis [18–27]. Among these, 8 studies were included in the meta-analysis of continuous variables [18–27], and 6 were included in the meta-analysis of diagnostic accuracy [18–20, 22, 25, 26].

Study characteristics

Table 2 presents the general characteristics of the included studies. These studies were conducted in five countries, with six in Europe and four in Asia. Four studies were cohort studies, and six were case–control studies. Detection methods for maternal serum GlyFn levels included ELISA, POC platforms, and ELISA/POC. Serum collection occurred predominantly in the third trimester across seven studies, with one study in the first trimester, one in both the first and third trimesters, and one in the first, middle, and third trimesters. Six studies evaluated the accuracy of maternal serum GlyFn levels in distinguishing pregnancies with PE from controls. Among them, the diagnostic cutoff value was 510 μg/mL in 2 studies, and the values in the remaining 4 studies were all less than 510 μg/mL and different. All studies were considered high quality, scoring ≥ 7 on NOS; Supplementary Tables 3–4). Additionally, methodological quality assessment results using the QUADAS2 tool indicated a low risk of bias in most studies (Fig. 2). The GRADE approach indicated that the overall certainty of the evidence for this meta-analysis was very low due to

Table 2 Characteristics of the included studies

First author/First, third author	Published year	Study region	Research type	Sample size (Control)	Sample size (PE)	methods of detection of GlyFn	Category of control group	Pregnancy stage at sample collection	Gestational age at sample collection (Control)	Gestational age at sample collection (PE)	cut-off (μg/mL)	NOS
Rasanen(1)	2015	Finland	Case-control	24	11	ELISA/POC	Non single category	First trimester	9.7(6.4–13.0)[a]	9.3(7.3–11.0) [a]	176.4	7
				28	12			Second trimester	23.3(17.4–26.6) [a]	22.4(21.6–26.3) [a]		
				34	13			Third trimester	35.4(27.0-39.7) [a]	36.4(28.1–38.7) [a]		
Rasanen(2)	2015	Finland	Case-control	34	44	ELISA/POC	Non single category	Third trimester	34.8(27.0–39.0) [a]	35.0(27.0–39.0) [a]	176.4	7
Huhn	2020	Switzerland	Cohort	119	32	ELISA/POC	Non single category	Third trimester	29 (8.5)[b]	30 (7.3) [b]	315	8
Nagalla	2020	India	Case-control	469	135	POC	Non single category	Third trimester	28.76 (4.81)[c]	31.71 (3.79) [c]	263	7
Wang	2021	China	Cohort	147	49	ELISA	Non single category	Third trimester	29 (24–33)[d]	30 (25–32) [d]	NA	8
Kesireddy	2022	India	Case-control	16	35	POC	Gestational hypertension	Third trimester	NA	NA	350	7
Moungmaithong	2023	China	Case-control	1584	101	ELISA	Non single category	First trimester	12.3(12.1–12.7) [d]	12.4(12.1–12.7) [d]	NA	7
Sokratous, Sarli	2023	United Kingdom	Case-control	1000	200	POC	Non single category	First trimester	12.7 (12.4–13.1) [d]	12.7 (12.4–13.1) [d]	NA	7
Sokratous, Wright	2023	United Kingdom	Cohort	316	93	POC	Gestational hypertension	Third trimester	NA	NA	510	8
Sokratous, Syngelaki	2023	United Kingdom	Cohort	78	26	POC	Chronic hypertension	Third trimester	34.0 (31.5–35.4)d	34.1 (31.5–35.6)d	510	8
Sokratous, Syngelaki	2024	United Kingdom	Case-control	600	100	POC	Non single category	Third trimester	NA	NA	NA	7

ELISA, enzyme-linked immunosorbent assays; POC, point-of-care; NA, not available; NOS, Newcastle-Ottawa quality assessment scale; [a]median (range); [b]median (interquartile range); [c]mean (SD); [d]median (the first and third quartiles)

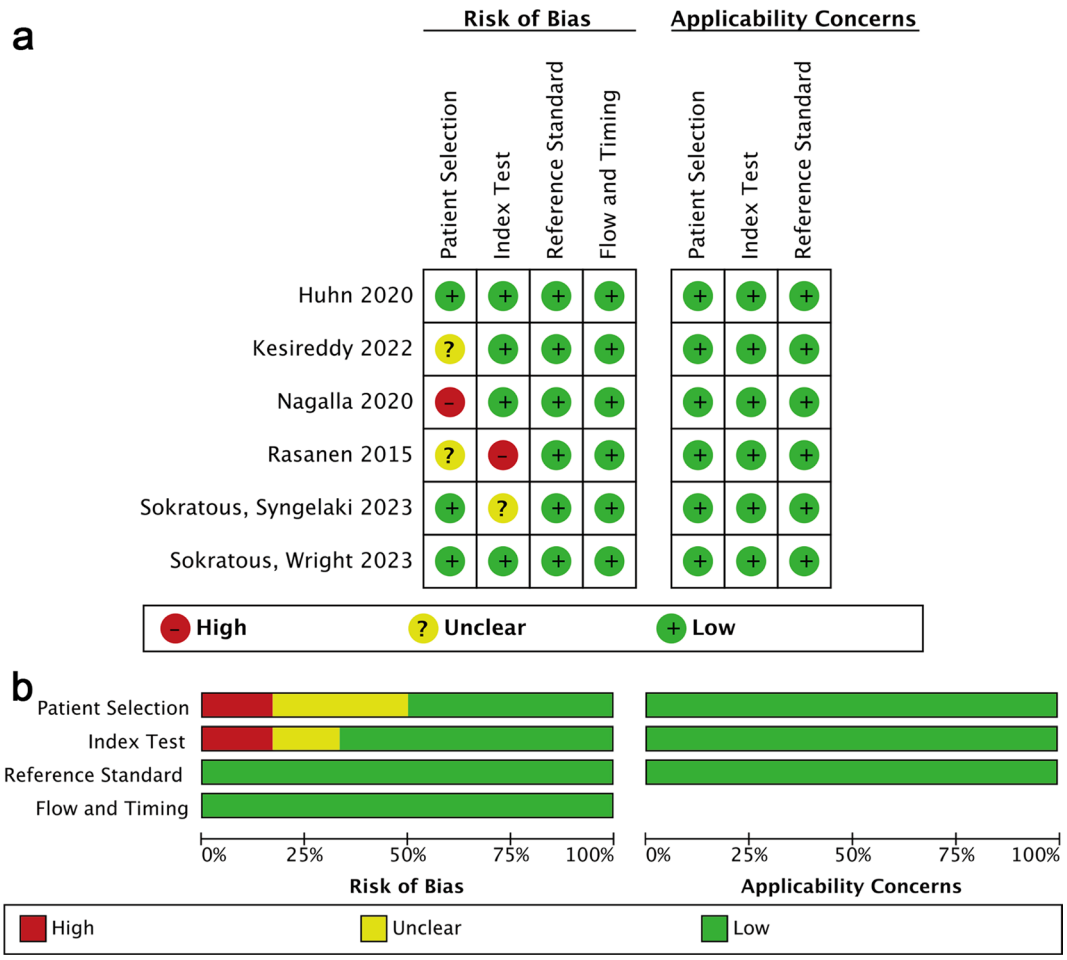

Fig. 2 Risk of bias and applicability concerns summary and graph. **a**, Risk of bias and applicability concerns graph; **b**, Risk of bias and applicability concerns summary

the inclusion of non-randomized studies, serious risk of bias, and serious inconsistency (Supplementary Table 5).

Differences in maternal serum GlyFn levels between PE and controls

Due to statistical heterogeneity across studies ($I^2 = 92.2\%$), a random-effects model was used for pooled meta-analysis. The results revealed that patients with PE exhibited elevated maternal serum GlyFn levels compared with controls (SMD = 1.08, 95% CI = 0.72–1.43, $P < 0.001$; Fig. 3).

In the publication bias test, the funnel plot displayed asymmetry (Fig. 4). However, Egger's test ($P = 0.079$) and Begg's test ($P = 0.083$) did not indicate the presence of publication bias. Sensitivity analysis using the leave-one-out method indicated that no single study significantly altered the association (Fig. 5), and no additional studies were imputed through the trim and fill method, suggesting the robustness of the research.

Subgroup analyses were conducted based on study region, research type, detection method, pregnancy stage at sample collection, and control group category (Table 3). In each of these subgroups, patients with PE had elevated maternal serum GlyFn levels compared with controls. Subgroup analysis indicated that different detection methods (ELISA/POC: $I^2 = 49.4\%$) and research types (Cohort: $I^2 = 53.1\%$) may have contributed to heterogeneity.

Diagnostic value of maternal serum GlyFn levels between PE and controls

Six studies were included in this analysis. Spearman correlation coefficient (coefficient: −0.714; $P = 0.111$) suggested no threshold effect. Overall, pooled sensitivity and specificity were 0.81 (95% CI = 0.77–0.85; $I^2 = 94.7\%$) and 0.80 (95% CI = 0.77–0.82; $I^2 = 96.6\%$; Fig. 6a–b). Combined PLR and NLR were 4.02 (95% CI = 1.45–11.10; $I^2 = 96.9\%$) and 0.19 (95% CI = 0.06–0.61; $I^2 = 95.5\%$; Fig. 6c–d), respectively. The DOR was 23.51 (95% CI = 3.22–171.46; $I^2 = 95.0\%$; Fig. 7a). The AUC for SROC was 0.90 (Fig. 7b), indicating high accuracy for PE diagnosis.

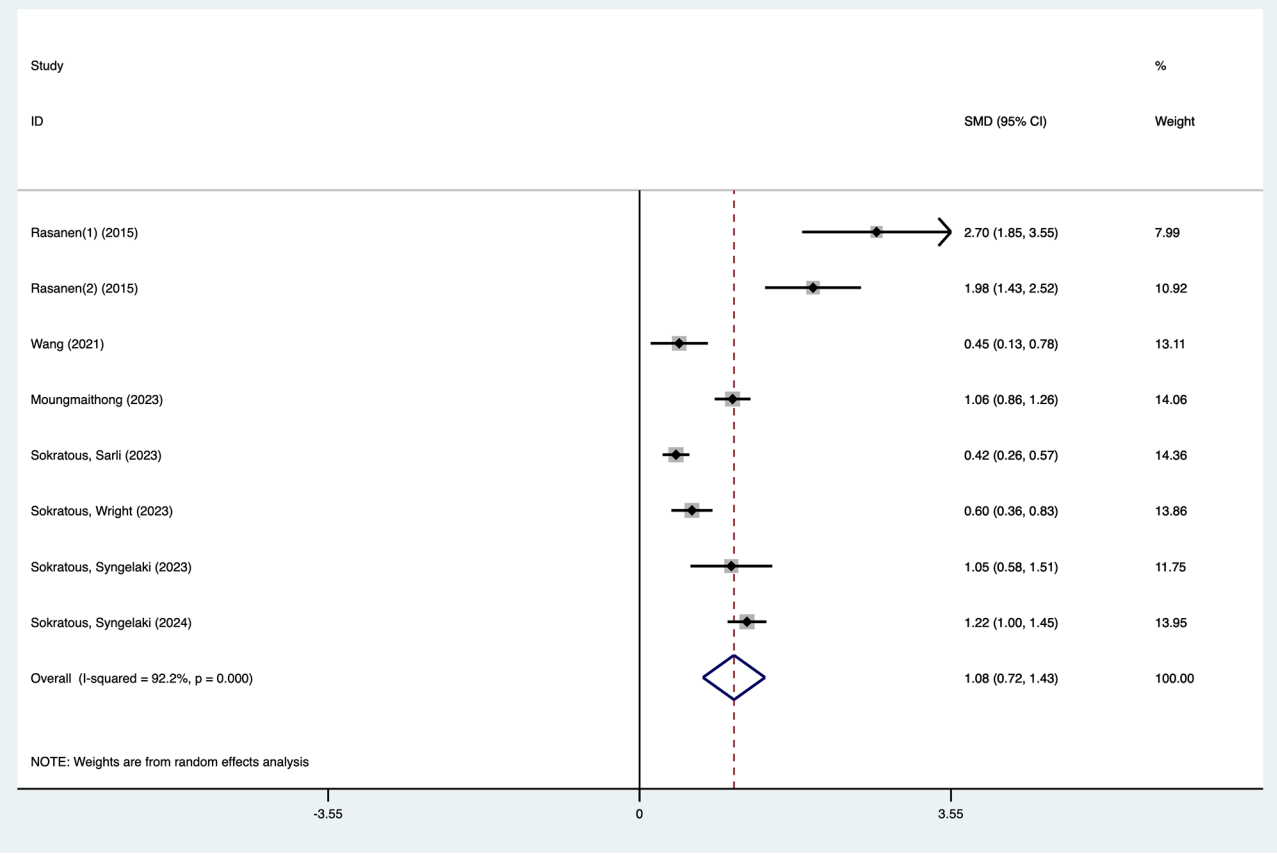

Fig. 3 Forest plot of maternal serum GlyFn levels in PE patients compared with controls

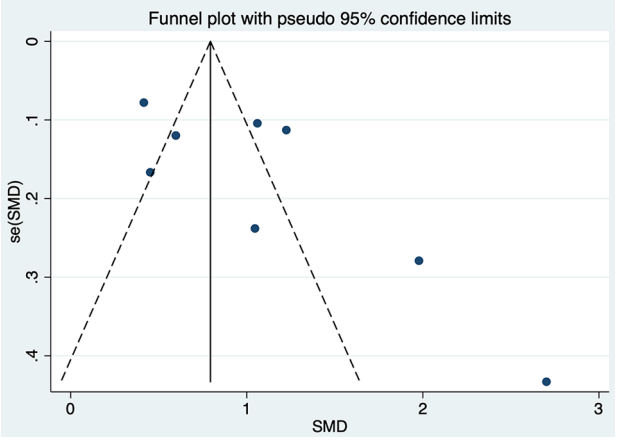

Fig. 4 Funnel plot of publication bias test

We further investigated the source of heterogeneity by conducting subgroup analyses, which revealed that detection method, category of control group and inconsistent cut-off values may have contributed to heterogeneity among included studies (Table 4). Test accuracy was found to have better sensitivity, specificity, PLR, NLR, DOR, and AUC in the ELISA/POC and non-single category control group, with low heterogeneity. In the group with cutoff values of 510 μg/mL, the heterogeneity decreased significantly, but the sensitivity and specificity decreased significantly.

Discussion

Our meta-analysis demonstrated that maternal serum GlyFn levels were significantly elevated in patients with PE, and maternal serum GlyFn levels exhibit high diagnostic accuracy in PE diagnosis, indicating its potential as a high-accuracy diagnostic marker for PE. This study represents the first systematic review and meta-analysis focusing on the expression levels of maternal serum GlyFn in PE and specifically assessing its diagnostic accuracy.

Although significant heterogeneity and publication bias were identified in the meta-analysis of differences in maternal serum GlyFn levels between PE and controls, sensitivity analysis and the trim and fill method both confirmed the stability of the results. Subgroup analysis indicated that the heterogeneity may stem from differences in detection methods. While the studies included in the meta-analysis used various methods such as POC platforms or ELISA, previous research has shown similar ranges in ROC curves generated by both methods [19, 23]. POC platforms offer rapid testing different from

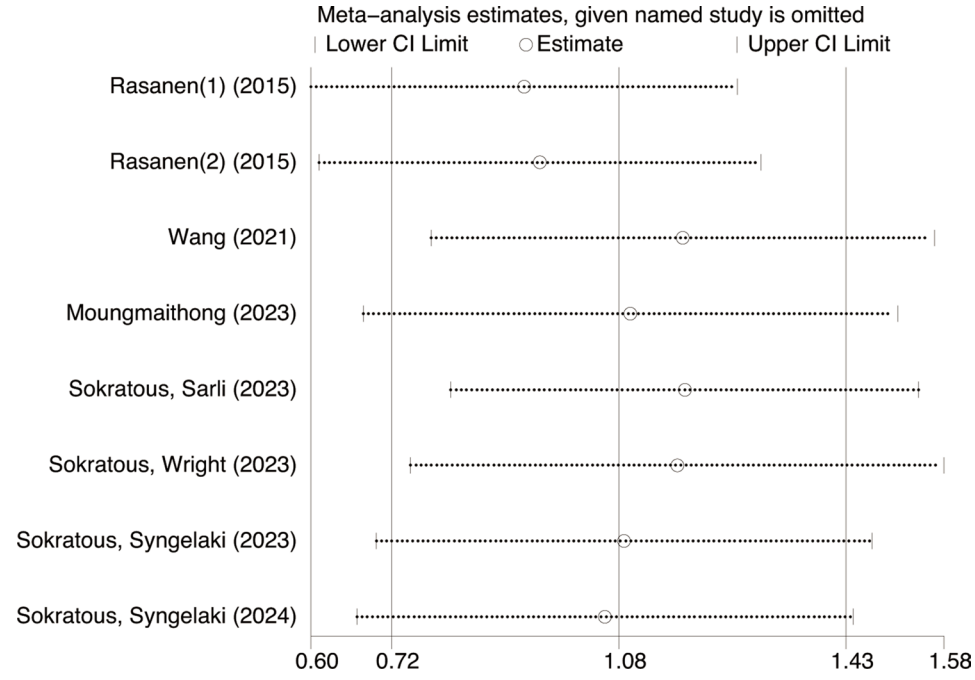

Fig. 5 Results of leave-one-out sensitivity analysis

Table 3 Subgroup analysis of the association between maternal serum GlyFn levels and PE

Subgroup	Included Studies	SMD	95% CI	I^2
Study region				
Europe	6	1.22	0.74–1.70	93.7
Asia	2	0.77	0.17–1.37	89.6
Research type				
Case-control	5	1.36	0.82–1.90	95.1
Cohort	3	0.65	0.37–0.93	53.1
Detection method				
ELISA/POC	2	2.26	1.57–2.96	49.4
ELISA	2	0.77	0.17–1.37	89.6
POC	4	0.81	0.39–1.22	92.0
Pregnancy stage at sample collection				
First trimester	2	0.73	0.10–1.37	95.9
Third trimester	6	1.23	0.76–1.71	90.7
Category of control group				
Gestational hypertension	1	0.60	0.36–0.83	-
Chronic hypertension	1	1.05	0.58–1.51	-
Non single category	6	1.91	0.73–1.66	94.2
Overall	8	1.08	0.72–1.43	92.2

ELISA, enzyme-linked immunosorbent assays; POC, point-of-care

traditional instruments such as ELISA and provides real-time results and care plans [37, 38], potentially expanding the scope of accurate, fast, and inexpensive prediction of PE [26].

The AUC, ranging from 0.5 to 1, reflects diagnostic accuracy [39]. Our data suggest that maternal serum GlyFn holds high diagnostic value and may be a potential useful biomarker, but heterogeneity remains significant. Our subgroup analysis revealed that heterogeneity may originate from differences in the detection method, category of control group and inconsistent cut-off values. A study of maternal serum GlyFn levels for predicting superimposed PE in pregnant women with chronic hypertension reported an AUC of 0.752 (95% CI = 0.647–0.856) [25]. Two studies focused on predicting PE in women with gestational hypertension suggested that maternal serum GlyFn levels had low diagnostic efficacy [22, 26]. The control group for the other three studies was of the non-single category, with significantly reduced heterogeneity and improved diagnostic efficiency [18–20]. However, whether the objective reasons for this difference are real or unknown remains unclear, and prospective studies are warranted to explore this aspect. In addition, among the included studies, only two studies had consistent cutoff values, which were also the highest [25, 26]. A high cut-off value can improve diagnostic accuracy but reduce the ability to make an early diagnosis [40]. Consistent with our results, sensitivity was significantly reduced in the group with a cut-off of 510 μg/mL. Therefore, more well-designed, large-sample, multicenter studies will be needed in the future to standardize the measurement and determine the optimal cutoff value.

In our meta-analysis, the sample collection of studies included occurred at different gestational weeks; however, this was not identified as a significant source of heterogeneity. Research suggests that screening for term PE at 36 weeks' gestation with any combination of biomarkers (MAP, PlGF, and GlyFn) may be more effective than screening with the same biomarkers at 12 weeks'

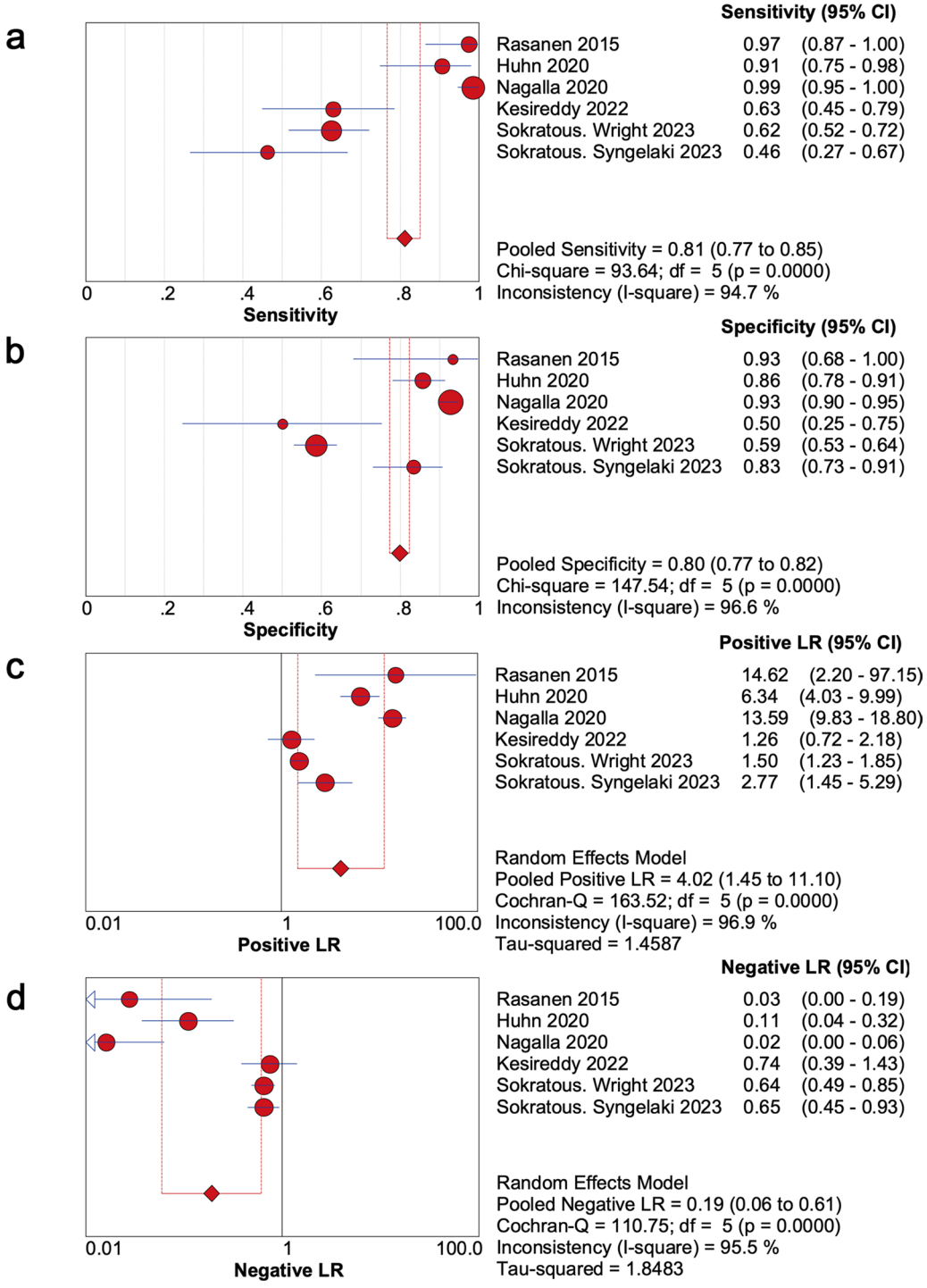

Fig. 6 Diagnostic value of maternal serum GlyFn levels between PE and controls. **a**, sensitivity; **b**, specificity; **c**, positive likelihood ratio; d negative likelihood ratio

gestation [27], suggesting that GlyFn may have better screening and diagnostic value in the third trimester. However, conflicting findings indicate that maternal serum GlyFn levels in the control group remained unchanged, whereas those in the PE group gradually increased with gestational age [18]. This raises the question of whether the observed differences are related to differences in the diagnostic cutoff value at different stages of pregnancy. This suggests that the gestational age should be considered when determining the diagnostic cutoff value in clinical practice and future research studies.

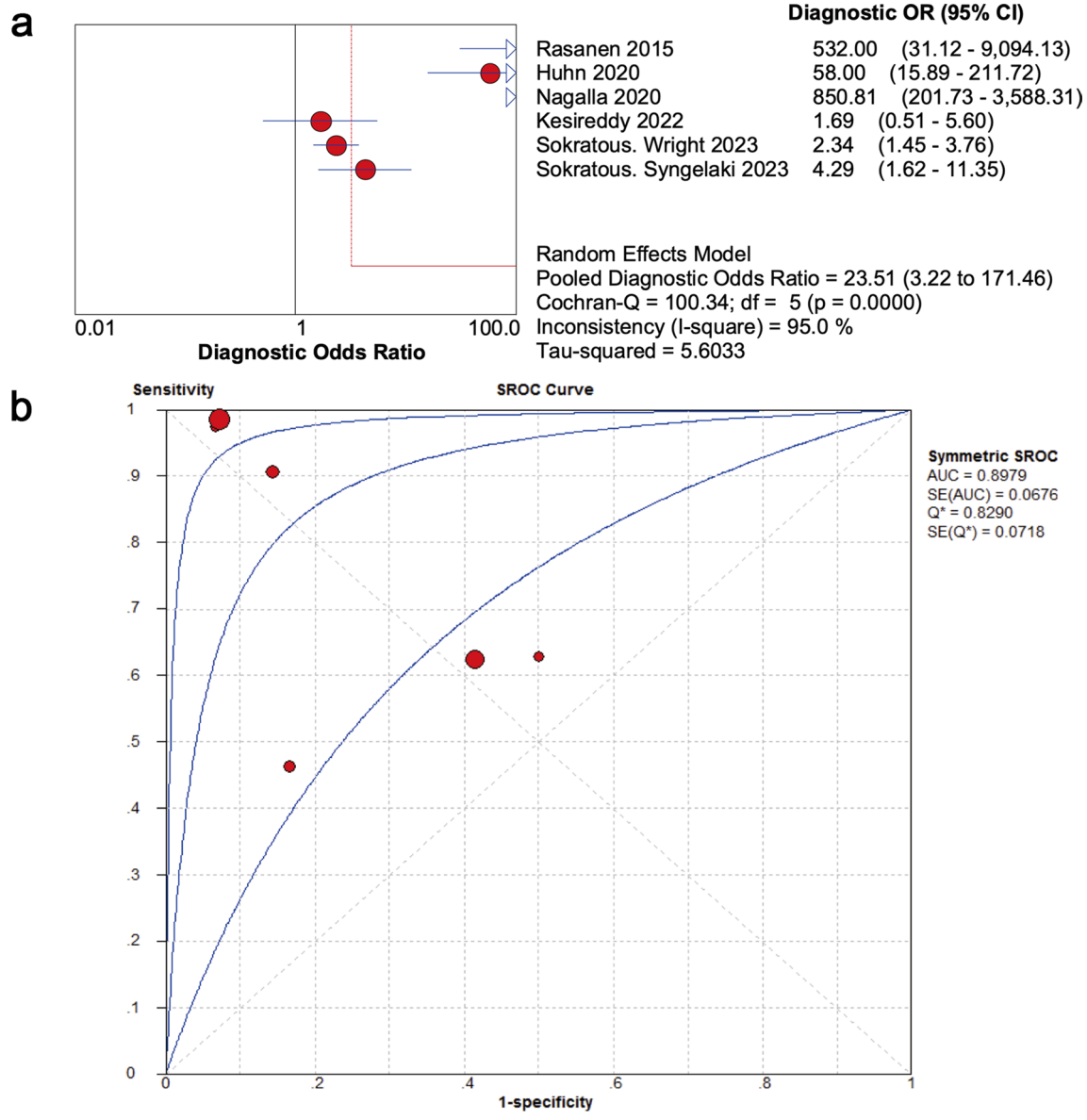

Fig. 7 Diagnostic value of maternal serum GlyFn levels between PE and controls. **a**, diagnostic odds ratio; **b**, receiver-operating characteristic curve

Various biomarkers, including sFlt1 and PlGF, have been proposed to complement clinical presentation for PE diagnosis [41, 42]. A meta-analysis of 15 studies demonstrated the efficacy of the sFlt-1/PlGF ratio in diagnosing PE, reporting that the ratio had a combined sensitivity of 80% and specificity of 92% for predicting PE in high- and low-risk patients [16]. In our meta-analysis results, the sensitivity of GlyFn was slightly higher than that of sFlt-1/PlGF, which is more conducive to the early detection of PE. A study of singleton pregnant women with new-onset hypertension at 24–41 weeks of gestation found that the predictive performance of PE delivery within 2 weeks of presenting with elevated maternal serum GlyFn was similar to that of PlGF and the sFlt-1/PlGF ratio [26]. In a study of women with chronic hypertension, the predictive performance of GlyFn was similar to that of PlGF and the sFlt-1/PlGF ratio for superimposed PE within 2 weeks of examination [25]. However, several studies have examined biomarkers such as sFlt1, PlGF, and GlyFn simultaneously and reported that GlyFn may offer superior predictive performance in PE diagnosis [18–20]. In third trimester, the AUCs of sFlt1 and PlGF for diagnosing PE were 0.96 and 0.94, respectively, which were lower than that of GlyFn (0.99) [18]. Furthermore, sFlt1 and PlGF are typically measured by ELISA, whereas the measurement of GlyFn can be performed using POC, which can greatly reduce costs. In addition, another biomarker, PAPPA, has significantly lower sensitivity and specificity for diagnosing PE than GlyFn [19]. Our meta-analysis showed that maternal

Table 4 Subgroup analysis of diagnostic value of maternal serum GlyFn levels between PE and controls

Subgroup	Included Studies	Sensitivity (95% CI), I^2 (%)	Specificity (95% CI), I^2 (%)	PLR (95% CI), I^2 (%)	NLR (95% CI), I^2 (%)	DOR (95% CI), I^2 (%)	AUC
Study region							
Europe	4	0.72(0.65–0.78), 91.8	0.69(0.65–0.73), 93.6	3.69(1.41–9.66),92.5	0.30(0.13–0.69), 88.0	16.17(2.66–98.35), 91.0	0.87
Asia	2	0.76(0.69–0.83), 92.7	0.67(0.62–0.71), 94.7	4.30(1.15–16.14), 94.9	0.15(0.02–1.06), 91.6	33.8(1.57-696.22), 94.0	0.92
Research type							
Case-control	3	0.92(0.88–0.96), 94.5	0.91(0.89–0.94), 89.9	5.88(0.86-40.009), 96.3	0.07(0.00-4.71), 97	85.77(0.78-9430.84), 95.9	0.96
Cohort	3	0.66(0.57–0.73), 87.1	0.69(0.64–0.73), 95.2	2.94(1.10–7.84), 94.0	0.45(0.23–0.87), 84.2	7.62(1.44–40.20), 90.6	0.80
Detection method							
ELISA/POC	2	0.94(0.86–0.98), 36.2	0.87(0.80–0.92), 0.0	6.98(3.58–13.65), 13.7	0.07(0.02–0.25), 33.4	120.80(15.63-933.91), 48.5	0.97
POC	4	0.78(0.73–0.83), 96.2	0.79(0.76–0.81), 97.9	2.92(0.79–10.82), 98.0	0.31(0.08–1.13), 96.5	10.38(0.95–113.60), 96.2	0.83
Pregnancy stage at sample collection							
Second and third trimester	1	0.97(0.87-1.00), -	0.93(0.68-1.00), -	14.62(2.20-97.15), -	0.03(0.00-0.19), -	532.00(31.12-9094.13), -	
Third trimester	5	0.79(0.74–0.83), 95.2	0.80(0.77-0,82), 97.2	3.41(1.17–9.95), 97.5	0.25(0.08–0.84), 95.9	14.50(1.82-115.62), 95.6	0.86
Category of Control group							
Gestational hypertension	2	0.63(0.54–0.71), 0	0.58(0.53–0.63), 0	1.47(1.21–1.78), 0	0.66(0.51–0.85), 0	2.24(1.44–3.48), 0	-
Chronic hypertension	1	0.46(0.27–0.51), -	0.83(0.73–0.91), -	2.77(1.45–5.29), -	0.65(0.45–0.93), -	4.29(1.62–11.35), -	0.75
Non single category	3	0.97(0.94–0.99), 52.7	0.91(0.89–0.93), 62.8	9.89(5.09–19.19), 73.8	0.04(0.01–0.16), 66.1	268.59(36.37-1982.56), 75.2	0.98
cut-off (μg/mL)							
510	2	0.59(0.49–0.68), 54.0	0.63(0.58–0.68), 94.5	1.89(1.05–3.38), 68.4	0.64(0.52–0.80), 0	2.71(1.63–4.51), 16.6	-
other	4	0.92(0.88–0.95), 91.8	0.90(0.88–0.93), 86.9	5.82(1.79–18.87), 94.6	0.08(0.01–1.07), 95.1	74.84(3.52-1593.11), 93.8	0.61
Overall	6	0.81(0.77–0.85), 94.7	0.80(0.77–0.82), 96.6	4.02(1.45–11.10), 96.9	0.19(0.06–0.61), 95.5	23.51(3.22-171.46), 95.0	0.90

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; CI, confidence interval; n, number of studies; ELISA, enzyme-linked immunosorbent assays; POC, point-of-care

serum GlyFn had a strong diagnostic effect with an AUC of 0.92, suggesting that it is highly likely to become an effective biomarker for the prediction and diagnosis of PE.

The underlying cause of elevated maternal serum GlyFn levels remains unclear, although a study suggested associations with inflammation and endothelial dysfunction [18], given fibronectin's involvement in these processes [43–45]. In addition, reduced GlyFn levels in the cord blood of infants born to preeclampsia patients [46] may help explain the effects of preeclampsia on the fetus. However, how GlyFn is involved in the molecular mechanism of PE pathogenesis requires more in-depth basic research.

The strengths of our meta-analysis are twofold. First, this is the first systematic review and meta-analysis focused on the expression levels of maternal serum GlyFn in PE, demonstrating that GlyFn is significantly elevated in PE. Second, by specifically assessing its diagnostic accuracy, our analysis highlights the potential of maternal serum GlyFn in predicting and diagnosing PE, providing a new experimental basis for improving PE prediction and diagnosis in the future. Despite the promising potential of maternal serum GlyFn as a biomarker for PE, several limitations exist. First, there was a high degree of heterogeneity among the included studies. Subgroup analyses suggested possible associations with different GlyFn detection methods (ELISA vs. POC), control group category, and inconsistent cut-off values. Additionally, most of the included studies had small sample sizes, with fewer than 1000 cases, which could introduce biases such as selection bias. While sensitivity analysis showed that our results are valid, further studies with larger sample sizes, more diverse populations, and more homogeneous data are warranted to strengthen our conclusions. Second, some studies included in the meta-analysis used

case–control designs to assess diagnostic accuracy. Thus, prospective cohort studies are needed to overcome the selection bias inherent in case–control studies, which may affect the accuracy estimates.

Conclusions

In conclusion, our study indicated that maternal serum GlyFn levels were significantly increased in PE and had a high diagnostic specificity of PE. Maternal serum GlyFn is expected to become a potential biomarker for the diagnosis of PE, providing a new direction for the early prediction and diagnosis of PE in a more accurate, fast, and cost-effective approach, which will have a beneficial effect on maternal and child health. However, further large-scale, longitudinal, and validated studies are needed to update our current conclusions, which are essential for evaluating screening performance and establishing optimal diagnostic thresholds for clinical practice.

Abbreviations

PE	Preeclampsia
sFlt1	Soluble Vascular Endothelial Growth Factor Receptor 1
PlGF	Placental Growth Factor
GlyFn	Glycosylated Fibronectin
NOS	Newcastle-Ottawa Quality Assessment Scale
QUADAS2	Quality Assessment of Diagnostic Accuracy Studies-2
SD	Standard Deviation
IQR	Interquartile Range
SMD	Standard Mean Difference
CI	Confidence Interval
PLR	Positive Likelihood Ratio
NLR	Negative Likelihood Ratio
DOR	Diagnostic Odds Ratio
SROC	Summary Receiver-Operating Characteristic Curve
AUC	Area Under the Curve
ELISA	Enzyme-Linked Immunosorbent Assays
POC	Point-Of-Care

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

LL, ML and RZ conceived and designed this study. LL and ML assessed eligibility and YY and QX assessed the quality of eligible studies. Any discrepancies between reviewers were resolved through discussion and consultation with RZ. LL and ML performed data extraction. LY and SX used GetData Graph Digitizer 2.26 to extract data and contacted the author for availability. LL and ML drafted the manuscript. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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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