Archives of Clinical Obstetrics and Gynecology Research

Systematic Review

Predictive Performance of sFlt-1, PlGF and the sFlt-1/PlGF Ratio for Preeclampsia: A Systematic Review and Meta-Analysis

Luhan Zhang[1,2,*], Ying Feng[1,2], Wenjing Li[1,2], Qi Sun[3], Yuanyuan Li[3], Weiwei Xing[3], Guifeng Ding[1,2,#]

[1]*Urumqi Maternal and child Health Hospital, Urumqi, 830000, Xinjiang, China*

[2]*Xinjiang Clinical Research Center for Perinatal Diseases, Urumqi, 830000, Xinjiang, China*

[3]*Medical Research Design and Data Analysis Center of Traditional Chinese Medical Hospital of Xinjiang Uygur Autonomous Region, Urumqi, 830000, Xinjiang, China*

Correspondence

Guifeng Ding

NO.344 Jiefang South Road, Tianshan District, Urumqi, 830000, Xinjiang, China.

E-mail: dingguifeng123@126.com

- Received Date: 07 Sep 2023
- Accepted Date: 12 Mar 2025
- Publication Date: 10 May 2025

Keywords: Attitude, oocyte cryopreservation, female academic staff, Universities

Abstract

Background: *It is difficult to evaluate whether monitoring serum sFlt-1, PlGF, or sFlt-1/PlGF in pregnant women who are suspected of having PE can significantly shorten the PE diagnosis time.*

Objectives: *To estimate the accuracy of sFlt-1, PlGF and sFlt-1/PlGF in preeclampsia prediction.*

Search Strategy*: Databases including PubMed, Web of Science, Medline, CNKI, SinoMed, VIP Journal, and Wanfang Data were searched for eligible studies published until October 7, 2022.*

Selection Criteria: *The research subjects were pregnant women with or without PE. The research types were case-control studies and cohort studies. This was an original study involving the detection of at least one of the following in the blood, serum or plasma: sFlt-1, PlGF, and sFlt-1/PlGF.*

Data Collection and Analysis: *Meta-Disc 1.4 was employed, using the Sen, Spe, PLR, NLR, and DOR to plot SROC, and subgroup analysis and meta-regression were conducted.*

Main Results: *Meta-analysis showed that for sFlt, PlGF and sFlt-1/PlGF, the Sen was 0.811 (95% CI: 0.783-0.837), 0.735 (95% CI: 0.713–0.757), and 0.779 (95% CI: 0.763–0.795), respectively; the Spe was 0.786 (95% CI: 0.769-0.802), 0.731 (95% CI: 0.721-0.741), and 0.885 (95% CI: 0.881-0.889), respectively. It was found to be attributable to study design, literature quality, sample size, disease subtypes, and cut-off values by using subgroup analysis and meta-regression.*

Conclusions: *The sFlt-1/PlGF ratio showed better predictive performance for preeclampsia than sFlt-1 or PlGF alone. However, the predictive value of the latter two cannot be ignored.*

Introduction

Preeclampsia (PE) is a multiorgan disease that is common in pregnancy after 20 weeks of gestation and mainly presents as signs and symptoms of newly developed hypertension with proteinuria or other end-organ dysfunction [1]. Worldwide, approximately 3%~5% of pregnancies are complicated with PE [2]; PE is associated with high morbidity and mortality, accounting for 5%~7% of all pregnant women's deaths [3], and it mainly occurs in low- and middle-income countries [4]. The fetuses and newborns of pregnant women with PE may experience growth restriction [5], respiratory distress, eclampsia, HELLP syndrome, renal failure, death, or other adverse outcomes [6]. PE is often complicated with other conditions, such as renal insufficiency [7], impaired liver function [8], and neurological disorders [9], and patients with PE are also at risk of postpartum recurrence and developing cardiovascular and cerebrovascular diseases [10], diabetes [11], end-stage renal disease [12], dementia [13], and others.

At present, the biggest problem in clinical practice is failure to identify patients with preeclampsia early. Patients are already in the middle or late stages of the disease when treated, often have multiple concurrent organ complications, and need referral to a tertiary care center or multidisciplinary treatment[14]. Fortunately, if we can detect and identify high-risk PE patients early and instruct them to take a small dose of aspirin in the first trimester to extend the gestational age, we may be able to reduce the incidence of PE and prevent the occurrence of maternal and infant complications [15]. Due to the complex

Citation: Zhang L, Feng Y, Li W, et al. Predictive Performance of sFlt-1, PlGF and the sFlt-1/PlGF Ratio for Preeclampsia: A Systematic Review and Meta-Analysis. Arch Clin Obs Gyn Res. 2024;4(1):1-13.

pathophysiological characteristics and clinical unpredictability of PE and the limited evidence for the detective performance of different diagnostic methods, there has been no accurate and reliable diagnostic method for predicting PE to date [16,17].

The etiology of PE has not been fully elucidated. There is evidence that maternal endothelial dysfunction due to placental factors plays a significant role in the pathogenesis of PE [18,19]. Soluble fms-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic factor secreted by the placenta, binds to vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in the maternal circulation. In the bound form, sFlt-1 interacts with membranous tyrosine kinase, which is critical to the biological activity of sFlt-1. High concentrations of antiangiogenic factors (e.g., sFlt-1) and low concentrations of proangiogenic factors (e.g., VEGF and PlGF) can produce an antiangiogenic state, leading to general maternal vascular dysfunction [20,21] and eventually to hypertension, proteinuria, and other clinical manifestations of PE [22].

The study population, gestational age, cut-off value, detection and analysis platform, and disease subtypes such as early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE) were included in studies from different countries [23,24] are diverse, and the observed diagnostic sensitivity and specificity are still highly variable and controversial. This lack of consistency makes it difficult to evaluate whether monitoring serum sFlt-1, PlGF, or sFlt-1/PlGF in pregnant women who are suspected of having PE can significantly shorten the PE diagnosis time. An increasing number of large-scale, multicenter studies about the detection of sFlt-1, PlGF, and sFlt-1/PlGF concentrations in predicting PE have been published, which has prompted us to conduct this systematic review and meta-analysis to determine whether sFlt-1, PlGF or sFlt-1/PlGF can better predict PE than existing clinical indicators, enabling early screening and timely intervention, avoiding further disease progression, and improving maternal and infant morbidity and mortality.

Methods

A systematic review and meta-analysis were performed according to the PRISMA-DTA statement [25]. The meta-analysis was registered in Prospero (CRD42021218579).

Information sources and search strategy

Two researchers, Luhan Zhang and Yuanyuan Li, independently searched English (PubMed, Web of Science, and Medline) and Chinese (China National Knowledge Infrastructure (CNKI), Wanfang Data, Weipu Journal Resources, and Chinese Biomedical Literature) databases. The databases were searched from inception to October 7, 2022, for journal articles that were publicly published. At the same time, the references listed in the obtained documents were manually searched to ensure that no documents had been omitted in the electronic search. The English keywords used for retrieval were preeclampsia and soluble fms-like tyrosine kinase-1, preeclampsia and sFlt-1, preeclampsia and placental growth factor, and preeclampsia and PlGF. The Chinese keywords used for retrieval were 'zixianqianqi' and sFlt-1, 'zixianqianqi' and soluble fms-like tyrosine kinase 1, 'zixianqianqi' and PlGF, 'zixianqianqi' and placental growth factor..

Eligibility criteria

The inclusion criteria were as follows: 1) The research subjects were pregnant women with or without PE; 2) The research types were case-control studies and cohort studies; 3) The studies showed results for the diagnostic standard for PE; 4) The research was an original study involving the detection of at least one of the following in the blood, serum or plasma: sFlt-1, PlGF, and sFlt-1/PlGF; 5) The research data were valid and reliable, and the 2×2 table (true positive number, false positive number, false negative number, and true negative number) could be extracted completely or could be calculated from existing data; and 6) There were exact cut-off values for sFlt-1, PlGF, and sFlt-1/PlGF in blood, serum, or plasma for PE prediction.

The exclusion criteria included the following: 1) abstracts, reviews, duplicate publications, and repeated literature studies were excluded; and 2) studies on nonsingleton pregnancies, pregnancies resulting in death, or other complications were excluded.

Study selection

All the documents were manually and independently screened by two researchers, Luhan Zhang and Yuanyuan Li, and then reviewed according to the preset literature inclusion and exclusion criteria. The full texts of the obtained studies were reviewed in depth to determine whether the studies should be included or excluded. Disagreement was resolved by discussion and negotiation or a definitive opinion given by a third authoritative expert, Qi Sun, or the author was contacted to obtain original information.

Data extraction

According to a preset extraction table, the data from documents that met the inclusion criteria, including the first author, publication year, study design type, study population characteristics, number of cases and controls, gestational age at the time of sampling, cut-off value, disease subtypes (early-onset and late-onset disease), assay used, number of true positives, number of false positives, number of false negatives, number of true negatives, sensitivity, and specificity, were extracted independently by Luhan Zhang. Controversial data encountered during the data extraction process were addressed in conjunction with a second researcher, Wenjing Li, through discussion and negotiation. If no consensus was reached, the problem was left to a third authoritative expert, Ying Feng, for resolution.

Assessment of risk of bias

The methodological quality of the included studies was examined by two independent reviewers, Luhan Zhang and Weiwei Xing, by using the Cochrane Collaboration Diagnostic Test Methodology Quality Assessment Guide and Quality Review of Diagnostic Accuracy Studies-2 (QUADAS-2) [26] to assess the deviation risk. A third researcher, Yuanyuan Li, gave the final opinion on disagreements during the screening process. The risk of deviation was mainly applied in the following five aspects: case selection, trials to be evaluated, diagnostic standard, case flow and progression. The first three aspects also judged the clinical applicability of the method to be tested.

Diagnostic accuracy evaluation

The number of true positives, true negatives, false positives, and false negatives from all studies were extracted, and the combined sensitivity (Sen), specificity (Spe), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) and their 95% confidence intervals (CIs) were calculated. The Sen and Spe of the included studies were used to construct symmetric receiver operating characteristic (SROC) curves and to calculate the area under the curve (AUC) for each variable. The combined effect was determined based on each study.

Data synthesis

A meta-analysis was performed on all data using Review Manager 5 (Version 5.0 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Meta-Disc 1.4 (XI Cochrane um, Barcelona, Spain). First, the receiver operating characteristic (ROC) curve was drawn, and whether the figure was "shoulder-arm-shaped" was observed. Then, the Spearman correlation coefficient of the sensitivity logarithm and (1-specificity) logarithm was calculated to determine whether there was a threshold effect. The Cochran Q test and I2 statistic were used to assess heterogeneity. When there was significant heterogeneity among studies, a random effects model (P<0.05 or I2>50%) was used. Otherwise, the fixed-effects model for data pooling was applied. Subgroup analysis was conducted based on presets, and meta-regression was also used to explore the source of statistical heterogeneity. All statistical tests were two-sided, and P<0.05 was considered statistically significant.

Results

Study selection

Figure 1 summarizes the literature search and selection process. A total of 1,716 articles were identified; among them, 563 duplicate articles were excluded, leaving 1,153 articles that potentially met the criteria. After reviewing the titles and abstracts of the articles, 1,024 articles were excluded; the full texts of the remaining 129 articles were read, 71 did not meet the inclusion criteria (for reasons including poor outcome prediction, insufficient information in the 2×2 table, lack of a control group, and poor quality of literature), and 58 studies were finally included in the study.

Study characteristics

All 58 studies, 39 in English and 19 in Chinese, were published between 2001 and 2020 and came from different parts of the world. A total of 33,558 patients were enrolled, including 3,661 cases in the case group (all were PE patients according to the diagnostic standard) and 29,897 in the control group (all were non-PE patients). It was known from the included literature that the case group included all singleton PE patients without other hypertensive disorder complications; the control group included pregnant women with singleton pregnancies and normal prenatal examinations during the same period. Among them, 19 studies were prospective studies, and the other 39 studies were retrospective studies. The included studies were mostly case-control studies and a few cohort studies. The gestational age measured by each test index were not the same, so the cut-off values used were different. There were 16 studies that determined the concentration of sFlt-1 to predict PE, 28 that determined the PlGF concentration to predict PE, and 41 that determined the sFlt-1/PlGF ratio to predict PE. There were 3 reports of sFlt-1 alone predicting EO-PE, 5 of PlGF that alone predicting EO-PE, 2 of sFlt-1 alone predicting LO-PE, 12 of sFlt-1/PlGF alone predicting EO-PE, and 7 of PlGF alone predicting LO-PE. When the same article had different cut-off values, the concentration of each index was measured and included in the subsequent meta-analysis (Table 1).

Risk of bias of included studies

The 58 included studies were evaluated and scored according to the following three criteria: “Yes”, “No” and “Unclear”. Among the quality items, there were 3 studies at high risk of deviation in the 1st item, which addressed the disease spectrum; in the 3rd item, on the acceptableness of the test interval, there was 1 study at high risk of deviation; in the 8th item, the standard diagnostic blinding method, there was 1 study at high risk of deviation; in the 9th item, addressing relevant clinical information, there were 13 studies at high risk of deviation; and in the 10th item, whether to explain the unexplainable/intermediate result report, there were 14 studies at high risk of deviation. Figure 2 summarizes the quality assessment of these studies. In most studies, there were great reports, including a full description of the selection criteria, patient profiles, tests, and use of appropriate reference standards (Figure 2).

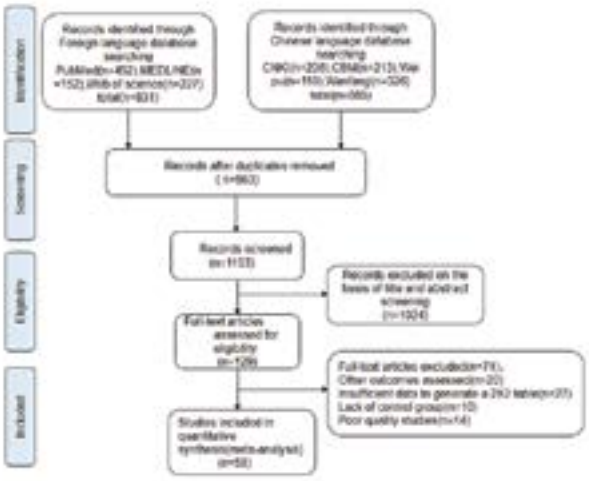

Figure 1. *PRISMA flowchart outlining study selection.*

Table 1.*Characteristics of the Included Studies*

No.	The first author	Published year	Study design	Characteristics:				PE Definition	GA(wk)	measurements	assay used
				Study Population	Cases (n)	Control Population	Control(n)				
1	Andersen[50]	2016	Prospective cohort study	PE	137	Non-PE	1732	ACOG	20-34	PLGF□sFlt-1/PLGF	KRYPTOR
2	Andersen[50]	2016	Prospective cohort study	EO-PE	18	Non-PE	1732	ACOG	20-34	PLGF□sFlt-1/PLGF	KRYPTOR
3	Andersen[50]	2016	Prospective cohort study	LO-PE	119	Non-PE	1732	ACOG	20-34	PLGF□sFlt-1/PLGF	KRYPTOR
4	Bahlmann[31]	2016	Prospective cohort study	PE	194	Non-PE	390	ISSHP	average 37	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics

No.	The first author	Published year	Study design	Characteristics:				PE Definition	GA(wk)	measurements	assay used
				Study Population	Cases (n)	Control Population	Control(n)				
5	Bian[64]	2019	Case control study	PE	101	Non-PE	599	BJOG2014	20-36	sFlt-1/PLGF	Roche Diagnostics
6	Cai L[56]	2018	cohort study	PE	34	Non-PE	348	Obstetrics and Gynecology (8th edition)	14-18	sFlt-1/PLGF	Roche Diagnostics
7	Chen YM[27]	2018	Case control study	PE	35	Non-PE	41	Gestation gestation Guidelines for the Diagnosis and Treatment of Hypertension (2015)	9-13	sFlt-1□PLGF□sFlt-1/PLGF	Rayto
8	Chen YQ[57]	2018	Case control study	high risk PE	11	Non-PE	260	Obstetrics and Gynecology (8th edition)	28-34	sFlt-1/PLGF	Roche Diagnostics
9	Chuah[65]	2018	prospective case-control study	EO-PE	24	Non-PE	18	Have	20-33+6	sFlt-1/PLGF	Roche Diagnostics
10	Chuah[65]	2018	prospective case-control study	EO-PE	24	Non-PE	18	Have	20-33+6	sFlt-1/PLGF	Roche Diagnostics
11	Chuah[65]	2018	prospective case-control study	LO-PE	23	Non-PE	12	Have	34-delivery	sFlt-1/PLGF	Roche Diagnostics
12	Chuah[65]	2018	prospective case-control study	LO-PE	23	Non-PE	12	Have	34-delivery	sFlt-1/PLGF	Roche Diagnostics
13	De Vivo[32]	2008	prospective case-control study	PE	52	Non-PE	52	Have	24-28	sFlt-1□PLGF□sFlt-1/PLGF	R&D Systems
14	Diab[33]	2008	Prospective cohort study	PE	33	Non-PE	66	ACOG	23	sFlt-1□PLGF□sFlt-1/PLGF	R&D Systems
15	Diab[33]	2008	Prospective cohort study	EO-PE	8	Non-PE	66	ACOG	23	sFlt-1□PLGF□sFlt-1/PLGF	R&D Systems
16	Ding[34]	2018	Case control study	PE	136	Non-PE	350	ACOG2002	□20	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
17	Doherty[66]	2014	Prospective cohort study	serve PE	6	Non-PE	14	Have	24	sFlt-1/PLGF	R&D Systems
18	Dragan[67]	2017	Prospective cohort study	PE	14	Non-PE	12291	ISSHP	30-37	sFlt-1/PLGF	Roche Diagnostics
19	Forest[68]	2014	Prospective nested case-control study	PE	180	Non-PE	338	Canadian College of Obstetricians and Gynecologists	20-32	sFlt-1/PLGF	R&D Systems
20	Gao J[68]	2014	Case control study	PE	41	Non-PE	88	Obstetrics and Gynecology (5th edition)	15-20 □24-28	sFlt-1□PLGF	Roche Diagnostics
21	Ghosh[51]	2012	Prospective cohort study	PE	43	Non-PE	467	ISSHP	20-22	PLGF	Manufactured in Marburg, Germany
22	Hanita[69]	2014	Prospective cohort study	high risk PE	12	Non-PE	72	ASSHP	29–36	sFlt-1/PLGF	Roche Diagnostics
23	Hassan[35]	2013	Nested case-control studies	PE	83	Non-PE	250	ACOG	16-20	sFlt-1□PLGF□sFlt-1/PLGF	R&D Systems
24	Huang R[43]	2018	prospective case-control study	PE	60	Non-PE	30	Gestation gestation Guidelines for the Diagnosis and Treatment of Hypertension (2015)	11-14	PLGF	Shanghai Biotechnology Company
25	Huang X[44]	2017	Prospective cohort study	PE	12	Non-PE	620	Obstetrics and Gynecology (8th edition)	11-14	PLGF	-
26	Huhn[81]	2018	Case control study	EO-PE	34	Non-PE	64	The “traditional” criteria for PE	15-42	sFlt-1/PLGF	Roche Diagnostics
27	Huhn[81]	2018	Case control study	LO-PE	25	Non-PE	45	The “traditional” criteria for PE	15-42	sFlt-1/PLGF	Roche Diagnostics
28	Jia D[45]	2018	Case control study	PE	138	Non-PE	58	Obstetrics and Gynecology (8th edition)	average 37	PLGF	Shanghai Biotechnology Company
29	Jiang F[46]	2019	Case control study	PE	123	Non-PE	105	Obstetrics and Gynecology (8th edition)	Before hospital delivery	PLGF	Triage Meterpro terpro
30	Ke W[58]	2019	Case control study	PE	98	Non-PE	452	Have	20-36	sFlt-1/PLGF	Roche Diagnostics
31	Kim[70]	2007	Case control study	PE	46	Non-PE	100	Have	14-23	sFlt-1/PLGF	R&D Systems
32	Kusanovic [52]	2009	Case control study	PE	62	Non-PE	1560	ACOG	20-25	PLGF	R&D Systems
33	Lafuente-Ganuza[71]	2019	Case control study	PE	51	Non-PE	258	ACOG	24-33	sFlt-1/PLGF	Roche Diagnostics
34	Lafuente-Ganuza[71]	2019	Case control study	PE	51	Non-PE	258	ACOG	24-33	sFlt-1/PLGF	Roche Diagnostics
35	Lehnen[72]	2013	Case control study	PE	63	Non-PE	72	Have	2 to 4 weeks before delivery	sFlt-1/PLGF	Roche Diagnostics
36	Madazli[53]	2005	Case control study	serve PE	14	Non-PE	108	Have	21-26	PLGF	R&D Systems

No.	The first author	Published year	Study design	Characteristics:				PE Definition	GA(wk)	measurements	assay used
				Study Population	Cases (n)	Control Population	Control(n)				
37	Mayer-Pickel [73]	2019	Case control study	PE	38	Non-PE	84	Have	12-40	sFlt-1/PLGF	Roche Diagnostics
38	Nguye[36]	2018	Case control study	high risk PE	30	Non-PE	67	Have	24-28	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
39	Nikuei[82]	2020	Case control study	PE	38	Non-PE	20	Have	-	sFlt-1/PLGF	-
40	Nikuei[82]	2020	Case control study	PE	38	Non-PE	20	Have	-	sFlt-1/PLGF	-
41	Ohkuchi[74]	2013	Case control study	PE	6	Non-PE	792	Have	26–31	sFlt-1/PLGF	Roche Diagnostics
42	Park[75]	2014	Case control study	low risk PE	8	Non-PE	254	ACOG	24–27	sFlt-1/PLGF	Roche Diagnostics
43	Phupong[37]	2020	Case control study	elderly gravida with PE	14	Non-PE	286	ACOG	16-18	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
44	Phupong[37]	2020	Case control study	EO-PE	5	Non-PE	286	ACOG	16-18	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
45	Sabria[76]	2017	Case control study	PE	65	Non-PE	130	ISSHP	24-36	sFlt-1/PLGF	Roche Diagnostics
46	Saleh[77]	2016	Case control study	PE	62	Non-PE	45	Have	After delivery	sFlt-1/PLGF	Roche Diagnostics
47	Schmidt[54]	2009	Case control study	PE	7	Non-PE	54	ISSHP	15-18	PLGF	DRG, Marburg, Germany
48	Shokry[38]	2010	Nested cohort study	PE	27	Non-PE	213	Have	13-16	sFlt-1□PLGF	-
49	Sovio[78]	2017	Prospective cohort study	PE	132	Non-PE	3751	ACOG	20-36	sFlt-1/PLGF	Roche Diagnostics
50	Stepan[55]	2016	Case control study	EO-PE	83	Non-PE	174	ISSHP	When PE was diagnosed	PLGF□sFlt-1/PLGF	Roche Diagnostics
51	Stepan[55]	2016	Case control study	LO-PE	95	Non-PE	271	ISSHP	When PE was diagnosed	PLGF□sFlt-1/PLGF	Roche Diagnostics
52	Stubert[39]	2014	Case control study	PE	12	Non-PE	50	ACOG	19-26	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
53	Stubert[39]	2014	Case control study	EO-PE	9	Non-PE	50	ACOG	19-26	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
54	Sun W[59]	2020	Case control study	PE	33	Non-PE	132	Have	20-26	sFlt-1/PLGF	R&D Systems
55	Tarase-viciene[40]	2016	prospective case-control study	PE	72	Non-PE	72	ACOG2002	25-34	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
56	Tardif[41]	2017	Nested case-control studies	PE	8	Non-PE	59	Have	20-37	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
57	Tidwell[81]	2001	Case control study	PE	14	Non-PE	25	ACOG	16-20	PLGF	R&D Systems
58	Verlohren[79]	2014	Case control study	PE	234	Non-PE	468	ISSHP	20-33	sFlt-1/PLGF	Roche Diagnostics
59	Verlohren[79]	2014	Case control study	EO-PE	100	Non-PE	200	ISSHP	20-33	sFlt-1/PLGF	Roche Diagnostics
60	Verlohren[79]	2014	Case control study	EO-PE	100	Non-PE	200	ISSHP	20-33	sFlt-1/PLGF	Roche Diagnostics
61	Verlohren[79]	2014	Case control study	LO-PE	134	Non-PE	268	ISSHP	20-33	sFlt-1/PLGF	Roche Diagnostics
62	Verlohren[79]	2014	Case control study	LO-PE	134	Non-PE	268	ISSHP	20-33	sFlt-1/PLGF	Roche Diagnostics
63	Ye Y[29]	2006	Case control study	PE	16	Non-PE	156	Obstetrics and Gynecology (6th edition)	26-28	sFlt-1□PLGF	-
64	You C[47]	2018	Case control study	PE	40	Non-PE	40	Obstetrics and Gynecology (8th edition)	11-14	PLGF	-
65	Yu[42]	2019	Case control study	PE	48	Non-PE	134	Have	12-36	sFlt-1□sFlt-1/PLGF	Roche Diagnostics
66	Yuan X[61]	2010	Case control study	PE	57	Non-PE	200	Obstetrics and Gynecology (7th edition)	20-24	sFlt-1/PLGF	R&D Systems
67	Yuan X[60]	2013	Case control study	PE	122	Non-PE	230	Obstetrics and Gynecology (7th edition)	16-20	sFlt-1/PLGF	R&D Systems
68	Zeisler[80]	2016	Case control study	PE	101	Non-PE	399	ISSHP	24-36	sFlt-1/PLGF	Roche Diagnostics
69	Zhang L[48]	2018	Case control study	PE	36	Non-PE	58	Obstetrics and Gynecology (8th edition)	21-29	PLGF	-
70	Zhao S[62]	2020	cohort study	PE	39	Non-PE	340	Have	24-36	sFlt-1/PLGF	Roche Diagnostics
71	Zhong Y[30]	2019	Prospective nested case-control study	PE	48	Non-PE	134	Obstetrics and Gynecology (8th edition)	12-36	sFlt-1□PLGF□sFlt-1/PLGF	Roche Diagnostics
72	Zhou W[63]	2017	Case control study	PE	61	Non-PE	115	Obstetrics and Gynecology (7th edition)	16-20	sFlt-1/PLGF	Shanghai Biotechnology Company
73	Zhou X[49]	2017	Case control study	PE	84	Non-PE	84	Obstetrics and Gynecology (8th edition)	11-13	PLGF	R&D Systems
74	Zhu X[83]	2020	Case control study	EO-PE	30	Non-PE	100	Obstetrics and Gynecology (8th edition)	sFlt-1/PLGF	-	
75	Zhu X[83]	2020	Case control study	EO-PE	116	Non-PE	100	Obstetrics and Gynecology (8th edition)	sFlt-1/PLGF	-	

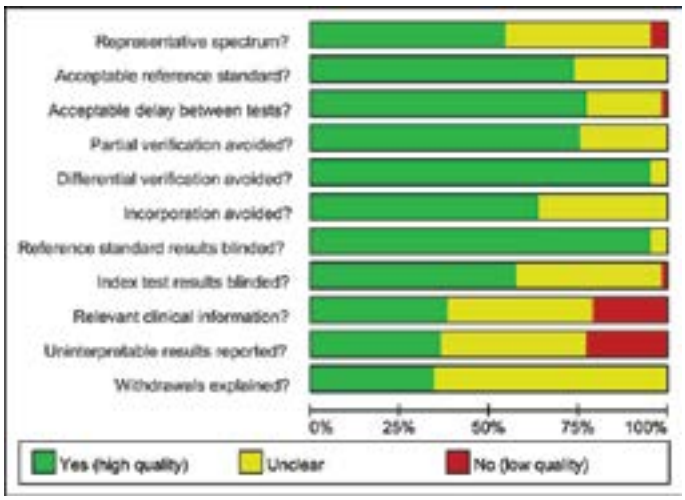

Figure 2. *Quality of the studies.*

Synthesis of results

Diagnostic accuracy evaluation

The results from the Meta-Disc 1.4 software showed that in the 16 [27-42], 28 [27-32,34-41,43-55], and 41 [27,30-33,35-37,39-42,50,55-83] studies using sFlt-1, PlGF, and the sFlt-1/PlGF ratio, respectively, to predict PE, the Spearman correlation coefficients were -0.222, -0.171, and -0.118, respectively, and the P values were 0.408, 0.384, and 0.464, respectively, indicating that there was no threshold effect. The results for the heterogeneity tests showed P<0.001 and I2>75%, indicating that the heterogeneity among different studies was great. A random effects model was used for the meta-analysis, and the results showed that the overall combined Sen was 0.811 (95% CI: 0.783-0.837), 0.735 (95% CI: 0.713–0.757), and 0.779 (95% CI: 0.763–0.795), respectively; Spe was 0.786 (95% CI: 0.769-0.802), 0.731 (95% CI: 0.721-0.741), and 0.885 (95% CI: 0.881-0.889), respectively; the PLR was 5.097 (95% CI: 3.498-7.426), 4.053 (95% CI: 3.150-5.214), and 6.385 (95% CI: 4.847-8.410), respectively; the NLR was 0.265 (95% CI: 0.164-0.430), 0.341 (95% CI: 0.275-0.423), and 0.241 (95% CI: 0.192-0.303), respectively; the DOR was 21.092 (95% CI: 10.857-40.976), 14.150 (95% CI: 8.972-22.315), and 31.431 (95% CI: 19.681-50.197), respectively; and the AUC was 0.9005, 0.8582, and 0.9065, respectively (Figures 3, 5-7).

Subgroup analysis and metaregression

The forest plot of the combined DOR for sFlt-1 was obtained by Meta-Disc 1.4 software. The DORs of each study and the combined DOR were not distributed along the same straight line. Meanwhile, Cochran's Q=99.16, P<0.001, indicating that there was heterogeneity caused by non-threshold effects. A subgroup analysis of 16 articles was conducted according to study design (prospective or retrospective), sample size (≥50 or <50), and literature quality ("Unclear"≤4 or "Unclear"> 4), and 3 articles [31, 32, 40] were left. The overall combined Sen was 0.826 (95% CI: 0.780-0.866), I2=51.3%; the combined Spe was 0.691 (95% CI: 0.649-0.730), I2=52.9%; the combined PLR was 2.661 (95% CI: 2.316_3.056), I2=0.0%; the combined NLR was 0.256 (95% CI: 0.199-0.329), I2=3.10%; and the combined DOR was 11.251 (95% CI: 7.872-16.081). The chi-squared for heterogeneity was 0.11, P=0.947, I2=0.0%, indicating that there was no heterogeneity among the studies, and thus, a fixed-effects model was used to combine the study results. The AUC

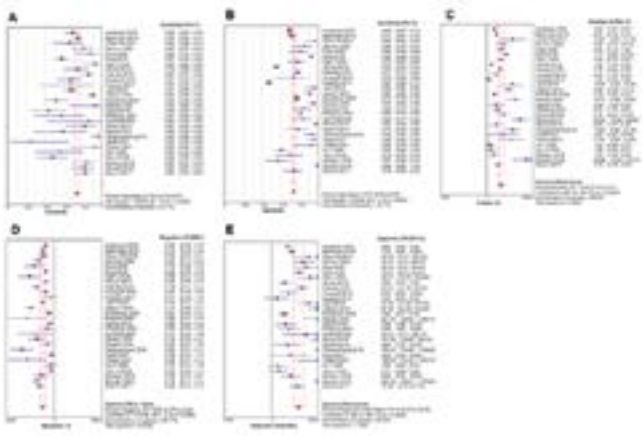

Figure 3. *Forest plot of PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of preeclampsia..*

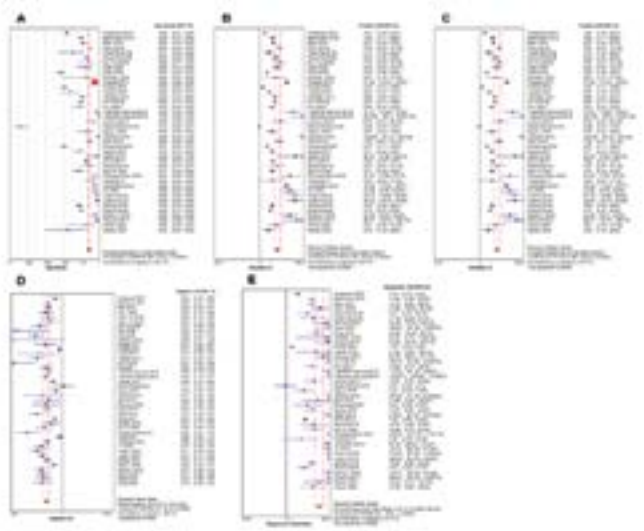

Figure 4. *Forest plot of sFlt-1/PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of preeclampsia.*

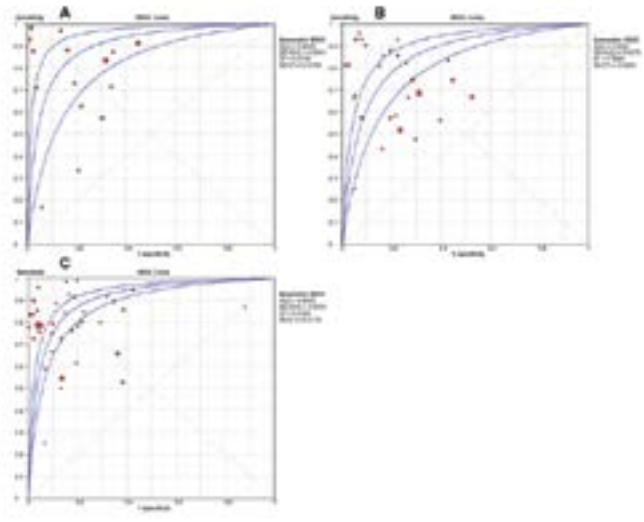

Figure 5. *Summary receiver operator characteristic curve of sFlt-1 (a), PlGF (c) and sFlt-1/PlGF (c).*

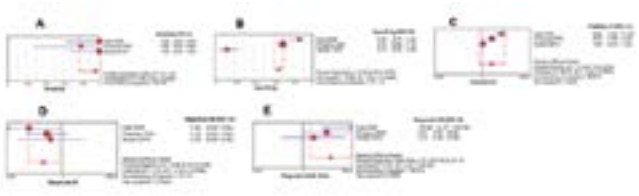

***Figure 6**. Forest plot of sFlt-1 predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of EO-PE.*

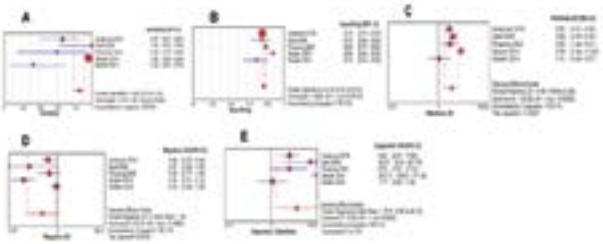

***Figure 7**. Forest plot of PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of EO-PE.*

was 0.8366. The combined DOR, the results, and the forest plot are shown in Figure 4 and Table 2.

In the forest plot of the combined DOR for PlGF and sFlt-1/PlGF, the DORs of each study and the combined DOR were not distributed along the same straight line. At the same time, Cochran'sQ=247.74, P<0.001, and Cochran-Q=632.89, P<0.001, respectively, demonstrating that there was heterogeneity elicited by non-threshold effects. Meta-regressions of 29 and 43 data points were conducted separately according to study design (prospective or retrospective), sample size (≥30 or <30), literature quality ("Unclear"≤4 or "Unclear">4), PlGF cut-off value (≥100 or <100), detected gestational week (≤14 w or >14 w to parturition), sFlt-1/PlGF cut-off value (≥30 or <30), and detected gestational week (≤20 w or >20 w to parturition). The heterogeneity might be related to the sample size and cut-off values (Table 2).

According to the data for the EO-PE and LO-PE classification in the literature, the two entities were divided into subgroups. There were 3 reports of EO-PE detected by sFlt-1 alone [33,37,39], the combined DOR was 13.160 (95% CI: 1.952-88.713), and the AUC was 0.9217. There were 5 reports of PlGF alone predicting EO-PE [33,37,39,50,55], the combined DOR was 13.108 (95% CI: 1.865-92.146), and the AUC was 0.8754. There were two reports of PlGF alone predicting LO-PE [50,55], the combined DOR was 8.572 (95% CI: 2.254-32.603). sFlt-1/PlGF alone predicted EO-PE in 12 cases [33,37,50,55,65,79,81,83], the combined DOR was 230.24 (95% CI: 63.956-828.82), and the AUC was 0.9806. There were seven data points that predicted LO-PE [50,55,65,79,81], the

***Table 2.** Summary of meta analysis results*

Indicator	Index	Merger value	95% CI	I2(%)	Cochran-Q	P
sFlt-1	Sen	0.811	0.783–0.837	86.6	111.71	<0.001
	Spe	0.786	0.769–0.802	96.1	388.12	<0.001
	PLR	5.097	3.498–7.426	92.5	199.92	<0.001
	NLR	0.265	0.164–0.430	92.5	199.81	<0.001
	DOR	21.092	10.857–40.976	84.9	99.16	<0.001
subgroup	Sen	0.826	0.780-0.866	51.3	4.11	0.128
	Spe	0.691	0.649-0.730	52.9	4.25	0.119
	PLR	2.661	2.316-3.056	0.0	1.64	0.440
	NLR	0.256	0.199-0.329	3.1	2.07	0.356
	DOR	11.251	7.872-16.081	0.0	0.11	0.947
PLGF	Sen	0.735	0.713–0.757	83.1	159.78	<0.001
	Spe	0.731	0.721–0.741	96.1	693.94	<0.001
	PLR	4.053	3.150–5.214	90.6	287.00	<0.001
	NLR	0.341	0.275–0.423	83.1	159.84	<0.001
	DOR	14.150	8.972–22.315	86.2	195.03	<0.001
sFlt-1/PLGF	Sen	0.779	0.763–0.795	86.4	295.18	<0.001
	Spe	0.885	0.881–0.889	98.6	2855.25	<0.001
	PLR	6.385	4.847–8.410	96.5	1136.54	<0.001
	NLR	0.241	0.192–0.303	88.4	345.59	<0.001
	DOR	31.431	19.681-50.197	91.5	470.98	<0.001

Sen: sensitivity;Spe:specificity;PLR:positive likelihood ratio;NLR:negative likehood ratio;DOR:diagnostic odds ratio;95%CI:95% confidence interval.

Table 3. *Summary of EO-PE and LO-PE meta analysis results*

Indicator	Index	Merger value	95% CI	I2(%)	Cochran-Q	P
sFlt-1 (EO-PE,n=3)	Sen	0.955	0.772-0.999	36.1	3.13	0.209
	Spe	0.652	0.603-0.698	97.5	78.98	<0.001
	PLR	2.615	0.735-9.304	96.6	59.1	<0.001
	NLR	0.217	0.059-0.798	0	1.23	0.54
	DOR	13.16	1.952-88.713	34.8	3.07	0.216
PlGF (EO-PE,n=5)	Sen	0.862	0.788-0.917	87.5	31.91	<0.001
	Spe	0.776	0.758-0.793	78.3	18.43	0.001
	PLR	3.401	1.844-6.275	85.9	28.28	<0.001
	NLR	0.259	0.058-1.160	92.8	55.58	<0.001
	DOR	13.108	1.865-92.146	88	33.42	<0.001
PlGF (LO-PE,n=2)	Sen	0.776	0.714-0.830	94.4	17.73	<0.001
	Spe	0.682	0.662-0.703	47.9	1.92	0.166
	PLR	2.331	1.974-2.752	54.5	2.2	0.138
	NLR	0.273	0.082-0.911	92.1	12.61	<0.001
	DOR	8.572	2.254-32.603	90.4	10.37	0.001
sFlt-1/PlGF (EO-PE,n=12)	Sen	0.944	0.921-0.961	69.1	35.64	<0.001
	Spe	0.805	0.790-0.819	96.5	317.71	<0.001
	PLR	13.751	4.948-38.216	96.9	358.78	<0.001
	NLR	0.084	0.048-0.147	55	24.44	0.011
	DOR	230.24	63.956-828.82	79.2	52.93	<0.001
sFlt-1/PlGF (LO-PE,n=7)	Sen	0.72	0.680-0.757	91.6	71.8	<0.001
	Spe	0.72	0.702-0.737	97.9	280.66	<0.001
	PLR	6.148	2.717-13.912	96.2	156.43	<0.001
	NLR	0.318	0.194-0.522	92.7	81.89	<0.001
	DOR	20.997	5.947-74.132	93.7	95.25	<0.001

EO-PE:early onset preeclampsia;LO-PE:late onset preeclampsia;Sen: sensitivity;Spe:specificity;PLR:positive likelihood ratio;NLR:negative likelihood ratio;DOR:diagnostic odds ratio;95%CI:95% confidence interval.

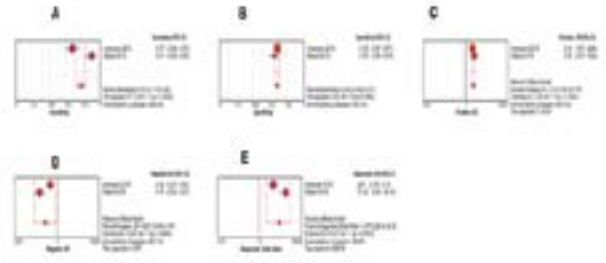

Figure 8: *Forest plot of PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of LO-PE.*

combined DOR was 20.997 (95% CI: 5.947-74.132), and the AUC was 0.8877. The results are shown in Figures 8-11 and Table 3.

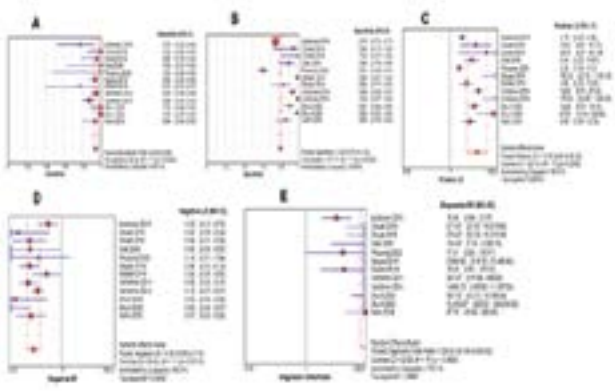

Figure 9: *Forest plot of sFlt-1/PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of EO-PE..*

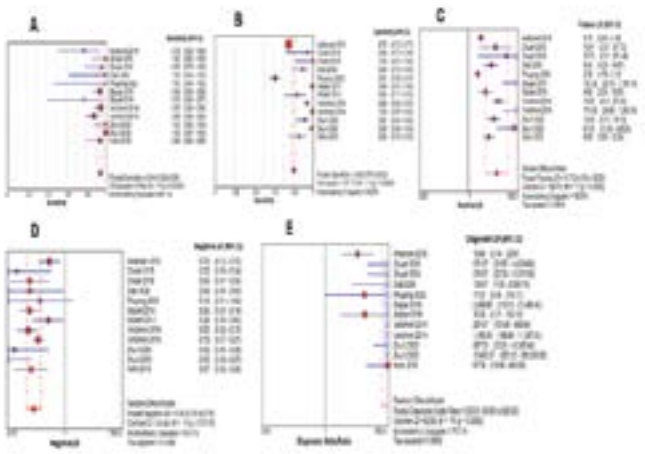

Figure 10: *Forest plot of sFlt-1/PlGF predicting summary sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and diagnostic odds ratio (e) of LO-PE.*

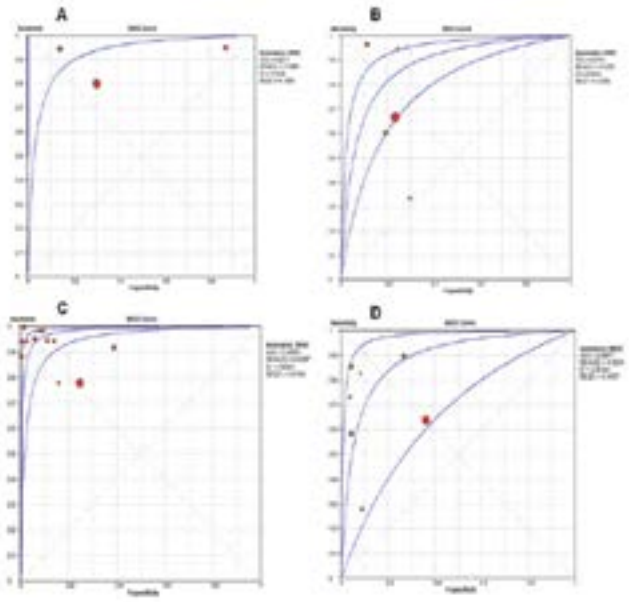

Figure 11: *Symmetric receiver operator characteristic curve of sFlt-1 predicting EO-PE (a), PlGF predicting EO-PE (b), sFlt-1/PlGF predicting EO-PE (c) and sFlt-1/PlGF predicting LO-PE (d)..*

Comment

Main findings

A total of 58 articles were included in this systematic review and meta-analysis. Although the test indicators reported in the articles were different, the standard used was the diagnostic criteria for PE recommended by international guidelines. Meta-analysis showed that the combined Sen of sFlt, PlGF and sFlt-1/PlGF was 0.811 (95% CI: 0.783-0.837), 0.735 (95% CI: 0.713–0.757), and 0.779 (95% CI: 0.763–0.795), respectively; the Spe was 0.786 (95% CI: 0.769-0.802), 0.731 (95% CI: 0.721-0.741), and 0.885 (95% CI: 0.881-0.889), respectively; and the AUC was 0.9005, 0.8582, and 0.9065, respectively. From the individual Sen, Spe, and AUC, we determined that the sFlt-1/PlGF ratio was more effective in PE prediction than sFlt-1 or PlGF alone, which may be due to the sFlt-1/PlGF ratio eliminating the detection error. The efficacy of sFlt-1 alone for predicting PE was similar to that of PlGF alone, and the efficacy of sFlt-1 was slightly better than that of PlGF; however, the heterogeneity of the pooled statistics for each variable was relatively high.

The results from the subgroup analysis showed that the reasons for sFlt-1-related heterogeneity might be the quality of the literature, the size of the sample, or the study design (prospective or retrospective). The high-quality, prospective and large-sample-size references included in the subgroup analysis confirmed that sFlt-1 concentration detection is indeed helpful in predicting PE. Meta-regression analysis including study design, sample size, cut-off value, detected gestational age, and literature quality found that the heterogeneity in PlGF detection might be associated with sample size. We also divided EO-PE and LO-PE into two subgroups. Only EO-PE was detected by sFlt-1, and the combined odds ratio of EO-PE detected by PlGF and sFlt-1/PlGF was higher than the combined odds ratio of LO-PE, indicating that PlGF and sFlt-1/PlGF had better screening performance for EO-PE.

Meta-regression analysis by study design, sample size, cut-off value, detected gestational age, and study quality showed that sFlt-1/ PlGF-related heterogeneity might be associated with the cut-off value.

Strengths and limitations

It is undeniable that our study also has some limitations. First, in terms of study inclusion, although the literature screening was carried out independently by two researchers according to the preset criteria, there was still a certain selection bias. In addition, since the information needed by the 2×2 table could not be directly extracted in most of the studies, there was a slight discrepancy between the results we obtained after calculation and those given in the literature; this might have resulted from the different ways of recording decimal places in the data by the researchers. Second, in terms of the interaction level of the included studies, the heterogeneity of each of the pooled detection indicators was high, the examined range of gestational weeks in some studies was wide, and the distribution of cut-off values was scattered. Some studies have shown that the concentration of each detection indicator changes with gestational age, so many studies use cut-off values related to gestational age, thus resulting in greater heterogeneity. Third, regarding the level of system evaluation, due to language limitations, documents in languages other than Chinese and English were not retrieved, and only foreign articles with English versions were searched.

Comparison with existing literature

The subgroup analysis results from a systematic review and meta-analysis on detecting PlGF alone in PE prediction, published by Swati Agrawal [84], showed that the accuracy of prediction gradually increased after 19 weeks of pregnancy. This is also in line with the evidence that the concentration of PlGF changes in PE patients during pregnancy [85]: PlGF increased before 30 weeks of pregnancy and decreased after

34 weeks. When the cut-off value was 80-120 pg/mL, the Sen of PlGF in predicting PE was the highest (0.78); however, the lack of uniform standards for cut-off value division have limited its clinical applicability. We have included original research literature that was published from 2018 to 2021. The difference between our study and the previous meta-analysis lies in what we found through subgroup analysis, i.e., that PlGF concentration detection might be more accurate in PE prediction when considering larger sample sizes. The articles with large sample sizes were mostly multicenter studies with diverse populations, which can better account for differences in genetic, behavioral, and race-related factors, and thus, it can better illustrate that the detection of PlGF can predict PE. This is also a reminder to researchers that high-quality research programs should be designed in the future.

A meta-analysis conducted by Swati Agrawal [86] divided patients into high-risk and low-risk groups for a subgroup analysis, which showed that the Spe of sFlt-1/PlGF was high (0.80) in high-risk patients. No significant differences were found in other evaluation indicators. One study [80] pointed out that it is necessary to consider the effective period the cut-off value in predicting PE, and different cut-off ranges can exclude PE within one week and predict PE within 4 weeks. Another study [87] proposed that for early-onset or late-onset PE, sFlt-1/PlGF cut-off values were used to predict the disease. As preeclampsia is a highly heterogeneous disease, it can be seen that PlGF and sFlt-1/PlGF predict a higher DOR for EO-PE than for LO-PE, indicating that PlGF and sFlt-1/PlGF have better performance in screening EO-PE. It may be that preeclampsia (usually in its early stages) has two stages, the first of which is incomplete remodeling of the spiral arteries and the second of which involves uterine placental perfusion disorders and oxidative stress of the placenta. Oxidatively stressed syncytiotrophoblastic cells (STB) secrete proteins that disrupt the balance of angiogenesis in pregnant women and are biomarkers for preeclampsia [88]. Oxidative stress occurs in the late stage, but the gestational ages in most of the included studies are concentrated in the early and middle stages of pregnancy, so the prediction effect for the late stage is not as good as that for the early stage. Since the time interval between the test results and the onset of preeclampsia is not reported in the literature, we cannot analyze this. The research subjects included in our study were not strictly divided according to basic conditions (age, race, pregnancy times, conception method, weight, etc.). In addition, the detection reagents, platforms and methods, and gestational weeks of each study were different. All these factors may have caused differences in the cut-off values. Due to the large differences in the cut-off values among studies, previous meta-analyses have not provided an exact cut-off level. State-of-the-art prediction models for the disease rely on prior risk for disease determined by maternal characteristics and changes in the biomarker data after transformation into the multiple of the median for gestational age and maternal characteristics; however, classification with the cutoff value obtained from this study was not easy, so we did not include these studies. The specificity in our research was also very high, indicating effective identification of non-PE patients, which relieves the anxiety of low-risk patients and prevents unnecessary expenses incurred by hospitalization monitoring and treatment due to misdiagnosis and other reasons [89].

Conclusions and Implications

In summary, the sFlt-1/PlGF ratio is more effective than sFlt-1 or PlGF alone in PE prediction. However, the effectiveness of the latter two cannot be ignored, since both tests are beneficial in the early diagnosis of PE, helping to identify high-risk patients and improve adverse outcomes in these patients and their infants. In the future, more prospective multicenter studies will be required to further refine the population, disease subtypes, detected gestational age, testing platforms, and cut-off values. In this way, we can conduct more detailed subgroup analysis to explore the sources of heterogeneity among studies and provide a reference for clinical decision-making.

Author contributions

Guifeng Ding and Qi Sun conceived and designed the analysis. Luhan Zhang and Yuanyuan Li screened studies. Luhan Zhang and Weiwei Xing assessed the studies. Qi Sun and Ying Feng were the third party for the screening and quality assessment of the literature. Luhan Zhang and Wenjing Li extracted and collected data. Luhan Zhang and Yuanyuan Li jointly analyzed the data and reported the results. All authors participated in the manuscript writing and revision.

Declaration of Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest..

Funding

Xinjiang Uygur Autonomous Region "Tianshan Innovation Team Plan"(2020D14010); National Natural Science Foundation of China(81960285).

References

1. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237-e260.
2. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013;347:f6564.
3. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019;124(7):1094-1112.
4. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. Lancet. 2016;387(10022):999-1011.
5. McKinney D, Boyd H, Langager A, Oswald M, Pfister A, Warshak CR. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. Am J Obstet Gynecol. 2016;214(3):395.e1-395.e3957.
6. van Oostwaard MF, van Eerden L, de Laat MW, et al. Maternal and neonatal outcomes in women with severe early onset pre-eclampsia before 26 weeks of gestation, a case series. BJOG. 2017;124(9):1440-1447.
7. Conti-Ramsden FI, Nathan HL, De Greeff A, et al. Pregnancy-Related Acute Kidney Injury in Preeclampsia: Risk Factors and Renal Outcomes. Hypertension. 2019;74(5):1144-1151.
8. Alese MO, Moodley J, Naicker T. Preeclampsia and HELLP syndrome, the role of the liver. J Matern Fetal Neonatal Med. 2021;34(1):117-123.
9. Logue OC, George EM, Bidwell GL 3rd. Preeclampsia and the brain: neural control of cardiovascular changes during pregnancy and neurological outcomes of preeclampsia. Clin Sci (Lond). 2016;130(16):1417-1434.
10. Brouwers L, van der Meiden-van Roest AJ, Savelkoul C, et al.

Recurrence of pre-eclampsia and the risk of future hypertension and cardiovascular disease: a systematic review and meta-analysis. BJOG. 2018;125(13):1642-1654.

11. Engeland A, Bjørge T, Daltveit AK, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. Eur J Epidemiol. 2011;26(2):157-163.
12. Wang IK, Muo CH, Chang YC, et al. Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. CMAJ. 2013;185(3):207-213.
13. Basit S, Wohlfahrt J, Boyd HA. Pre-eclampsia and risk of dementia later in life: nationwide cohort study. BMJ. 2018;363:k4109.
14. [14] Guidelines for the Diagnosis and treatment of hypertensive disorders during pregnancy (2020). Chinese Journal of Obstetrics and Gynecology. (04) (2020) 227-228-229-230-231-232-233-234-235-236-237-238.
15. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017;377(7):613-622.
16. Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia Screening: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2017;317(16):1668-1683.
17. Committee Opinion No. 638: First-Trimester Risk Assessment for Early-Onset Preeclampsia. Obstet Gynecol. 2015;126(3):e25-e27.
18. Tomimatsu T, Mimura K, Matsuzaki S, Endo M, Kumasawa K, Kimura T. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. Int J Mol Sci. 2019;20(17):4246.
19. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol. 2019;15(5):275-289.
20. Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. Am J Obstet Gynecol. 2022;226(2S):S1019-S1034.
21. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(14):1690-1702.
22. Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
23. Rana S, Sannon H. Angiogenic Proteins: Can These Biomarkers Help to Prevent Maternal Deaths Related to Preeclampsia?. Hypertension. 2017;69(3):401-403.
24. Wise J. Two new blood tests will help doctors rule out pre-eclampsia, says NICE. BMJ. 2016;353:i2690.
25. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018;319(4):388-396..
26. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-536.
27. Chen YM, Lu S, Gu LY, et al. Serum SFLT-1 and PIGF levels during early pregnancy and their correlation with preeclampsia. Modern Practical Medicine. 2018;30(11):1493-1496.
28. Gao J, Shen J, Jiang Y, et al. The value of serum sFLT-1 and PLGF in predicting the occurrence of preeclampsia during the second trimester of pregnancy. Zhonghua Fu Chan Ke Za Zhi. 2014;49(1):22-25.
29. Ye YH, Liu L, Zhan Y, Peng W. Predictive value of serum soluble fms-like tyrosine kinase 1 concentration in preeclampsia at second trimester. Zhonghua Fu Chan Ke Za Zhi. 2006;41(7):433-435.
30. Zhong YL, Zhou WJ, Su L, Yu F. The role of soluble FMS-like tyrosine kinase-1 and placental growth factor in the prediction of preeclampsia. Chinese Journal of Maternal and Child Health. 2019; 34(02): 270-272.
31. Bahlmann F, Al Naimi A. Using the angiogenic factors sFlt-1 and PlGF with Doppler ultrasound of the uterine artery for confirming preeclampsia. Arch Gynecol Obstet. 2016;294(6):1133-1139.
32. De Vivo A, Baviera G, Giordano D, Todarello G, Corrado F, D'anna R. Endoglin, PlGF and sFlt-1 as markers for predicting pre-eclampsia. Acta Obstet Gynecol Scand. 2008;87(8):837-842.
33. Diab AE, El-Behery MM, Ebrahiem MA, Shehata AE. Angiogenic factors for the prediction of pre-eclampsia in women with abnormal midtrimester uterine artery Doppler velocimetry. Int J Gynaecol Obstet. 2008;102(2):146-151.
34. Ding G, Liping L, Moli D, et al. A study of the association between the sFlt-1/PIGF ratio and preeclampsia in Xinjiang Uygur Autonomous Region of China. Artif Cells Nanomed Biotechnol. 2018;46(sup3):S281-S286.
35. Hassan MF, Rund NM, Salama AH. An Elevated Maternal Plasma Soluble fms-Like Tyrosine Kinase-1 to Placental Growth Factor Ratio at Midtrimester Is a Useful Predictor for Preeclampsia. Obstet Gynecol Int. 2013;2013:202346.
36. Nguyen TH, Bui TC, Vo TM, Tran QM, Luu LT, Nguyen TD. Predictive value of the sFlt-1 and PlGF in women at risk for preeclampsia in the south of Vietnam. Pregnancy Hypertens. 2018;14:37-42.
37. Phupong V, Areeruk W, Tantbirojn P, Lertkhachonsuk R. Soluble fms-like tyrosine kinase 1 and placental growth factor ratio for predicting preeclampsia in elderly gravida. Hypertens Pregnancy. 2020;39(2):139-144.
38. Shokry M, Bedaiwy MA, Fathalla MM, Alsemary A, Elwakil S, Murphy A. Maternal serum placental growth factor and soluble fms-like tyrosine kinase 1 as early predictors of preeclampsia. Acta Obstet Gynecol Scand. 2010;89(1):143-146.
39. Stubert J, Ullmann S, Bolz M, et al. Prediction of preeclampsia and induced delivery at <34 weeks gestation by sFLT-1 and PlGF in patients with abnormal midtrimester uterine Doppler velocimetry: a prospective cohort analysis. BMC Pregnancy Childbirth. 2014;14:292.
40. Tarasevičienė V, Grybauskienė R, Mačiulevičienė R. sFlt-1, PlGF, sFlt-1/PlGF ratio and uterine artery Doppler for preeclampsia diagnostics. Medicina (Kaunas). 2016;52(6):349-353.
41. Tardif C, Dumontet E, Caillon H, et al. Angiogenic factors sFlt-1 and PlGF in preeclampsia: Prediction of risk and prognosis in a high-risk obstetric population. J Gynecol Obstet Hum Reprod. 2018;47(1):17-21.
42. Yu F, Bai Q, Zhang S, Jiang Y. Predictive value of soluble fms-like tyrosine kinase-1 against placental growth factor for preeclampsia in a Chinese pregnant women population. J Clin Lab Anal. 2019;33(5):e22861.
43. Huang R, Wang Y, Lai F, et al. The value of serum placental growth factor in predicting the occurrence of preeclampsia during the first trimester. Chinese Journal of Medical Sciences. 2018;8(14):71-74.
44. Xiaoling H, Shaoyu Z, Chunxia R, Yuping H. Placental Protein 13, Pregnancy Associated Plasma Protein-A, and Placental Growth Factor in Predicting Preeclampsia, Chin J Med. 2017;39(04):97-99.
45. Jia D, Fang L, Si X. The role of serum platelet-derived growth factor-B, placental growth factor and soluble FMS-like tyrosine kinase 1 in predicting the occurrence of preeclampsia. Anhui Medical Journal. 2018;22(04):685-688.
46. Fengli J, Yanan M, Li W. The clinical value of placental growth factor in the early diagnosis of preeclampsia. Medical

Information. 2019;32(16):160-162.

47. Chunhua Y. Preeclampsia, Papp-A and PLGF expression in preeclampsia in early pregnancy: A clinical analysis. Journal of Clinical Medicine. 2018;38(02):66-67.
48. Lifang Z. Serum placental growth factor in the prediction of early onset preeclampsia. Journal of Taitang Medical College. 2018;39(04):462-463.
49. Xiangmin Z. The value of placental protein 13 combined with placental growth factor for early screening of preeclampsia. Chinese general medicine. 2017;20(S2):114-116.
50. Andersen LB, Dechend R, Jørgensen JS, et al. Prediction of preeclampsia with angiogenic biomarkers. Results from the prospective Odense Child Cohort. Hypertens Pregnancy. 2016;35(3):405-419.
51. Ghosh SK, Raheja S, Tuli A, Raghunandan C, Agarwal S. Combination of uterine artery Doppler velocimetry and maternal serum placental growth factor estimation in predicting occurrence of pre-eclampsia in early second trimester pregnancy: a prospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2012;161(2):144-151.
52. Kusanovic JP, Romero R, Chaiworapongsa T, et al. A prospective cohort study of the value of maternal plasma concentrations of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. J Matern Fetal Neonatal Med. 2009;22(11):1021-1038.
53. Madazli R, Kuseyrioglu B, Uzun H, Uludag S, Ocak V. Prediction of preeclampsia with maternal mid-trimester placental growth factor, activin A, fibronectin and uterine artery Doppler velocimetry. Int J Gynaecol Obstet. 2005;89(3):251-257.
54. Schmidt M, Dogan C, Birdir C, et al. Placental growth factor: a predictive marker for preeclampsia?. Gynakol Geburtshilfliche Rundsch. 2009;49(2):94-99.
55. Stepan H, Hund M, Gencay M, et al. A comparison of the diagnostic utility of the sFlt-1/PlGF ratio versus PlGF alone for the detection of preeclampsia/HELLP syndrome. Hypertens Pregnancy. 2016;35(3):295-305.
56. Lina C, Jianbo L, Shubiao W, Baoju Z. The clinical value of soluble vascular endothelial growth factor receptor-1 / placental growth factor combined with uterine arterial pulse index in predicting preeclampsia. Chinese Journal of General Medicine. 2018;21(07): 827-830.
57. Yunqi C, Ting L. The significance of sFLT-1 and PLGF in predicting preeclampsia in high-risk pregnant women. Chinese Journal of Maternal and Child Health. 2018;33(23):5372-5375.
58. Weilin K, Weihua Z, Qing L. SFLT-1 / PLGF ratio in predicting preeclampsia. Journal of Binzhou Medical College. 2019;42(04):275-277.
59. Sun WY, Ma LJ, Wu SY, Jia KK, Li SF, Wang Y. The predictive value of serum sFLT-1, pigF and complement-system activation factors in the second trimester of preeclampsia in pregnant women with preeclampsia risk factors. Chinese Journal of Obstetrics and Gynecology. 2020;21(05):489-491.
60. Yuan X, Wei Z, Jiang L, Zhang Y. The value of soluble vascular endothelial growth factor receptor 1 to placental growth factor ratio in predicting preeclampsia. Jiangsu Medical. 2013;39(14):1641-1643.
61. Yuan XS, Zhang YM, Jiang YQ, Jiang LX. The value of serum soluble vascular endothelial growth factor receptor 1/ placental growth factor ratio as a predictor of preeclampsia risk. Journal of Laboratory Medicine. 2010;25(10):784-786.
62. Zhao S, Liu X, Wang J, Gao L. The significance of serum soluble vascular endothelial growth factor receptor-1 / placental growth factor ratio in predicting preeclampsia in pregnant women. Chinese Journal of Clinicians. 2020;48(09):1086-1088.
63. Zhou W, Huang Y, Zhong Z, Luo M, Wang T, Huang J. Correlation and predictive value of serum sFLT-1 /PLGF ratio with severe preeclampsia. Chinese Journal of Maternal and Child Health. 2018;33(23):5394-5396.
64. Bian X, Biswas A, Huang X, et al. Short-Term Prediction of Adverse Outcomes Using the sFlt-1 (Soluble fms-Like Tyrosine Kinase 1)/PlGF (Placental Growth Factor) Ratio in Asian Women With Suspected Preeclampsia. Hypertension. 2019;74(1):164-172.
65. Chuah TT, Tey WS, Ng MJ, Tan ETH, Chern B, Tan KH. Serum sFlt-1/PlGF ratio has better diagnostic ability in early- compared to late-onset pre-eclampsia. J Perinat Med. 2018;47(1):35-40.
66. Doherty A, Carvalho JC, Drewlo S, et al. Altered hemodynamics and hyperuricemia accompany an elevated sFlt-1/PlGF ratio before the onset of early severe preeclampsia. J Obstet Gynaecol Can. 2014;36(8):692-700.
67. Dragan I, Georgiou T, Prodan N, Akolekar R, Nicolaides KH. Screening for pre-eclampsia using sFlt-1/PlGF ratio cut-off of 38 at 30-37 weeks' gestation. Ultrasound Obstet Gynecol. 2017;49(1):73-77.
68. Forest JC, Thériault S, Massé J, Bujold E, Giguère Y. Soluble Fms-like tyrosine kinase-1 to placental growth factor ratio in mid-pregnancy as a predictor of preterm preeclampsia in asymptomatic pregnant women. Clin Chem Lab Med. 2014;52(8):1169-1178.
69. Hanita O, Alia NN, Zaleha AM, Nor Azlin MI. Serum soluble FMS-like tyrosine kinase 1 and placental growth factor concentration as predictors of preeclampsia in high risk pregnant women. Malays J Pathol. 2014;36(1):19-26.
70. Kim SY, Ryu HM, Yang JH, et al. Increased sFlt-1 to PlGF ratio in women who subsequently develop preeclampsia. J Korean Med Sci. 2007;22(5):873-877.
71. Lafuente-Ganuza P, Lequerica-Fernandez P, Carretero F, et al. A more accurate prediction to rule in and rule out pre-eclampsia using the sFlt-1/PlGF ratio and NT-proBNP as biomarkers. Clin Chem Lab Med. 2020;58(3):399-407.
72. Lehnen H, Mosblech N, Reineke T, et al. Prenatal Clinical Assessment of sFlt-1 (Soluble fms-like Tyrosine Kinase-1)/PlGF (Placental Growth Factor) Ratio as a Diagnostic Tool for Preeclampsia, Pregnancy-induced Hypertension, and Proteinuria. Geburtshilfe Frauenheilkd. 2013;73(5):440-445.
73. Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M. Comparison of mean platelet volume (MPV) and sFlt-1/PlGF ratio as predictive markers for preeclampsia. J Matern Fetal Neonatal Med. 2021;34(9):1407-1414..
74. Ohkuchi A, Hirashima C, Suzuki H, et al. Evaluation of a new and automated electrochemiluminescence immunoassay for plasma sFlt-1 and PlGF levels in women with preeclampsia. Hypertens Res. 2010;33(5):422-427.
75. Park HJ, Kim SH, Jung YW, et al. Screening models using multiple markers for early detection of late-onset preeclampsia in low-risk pregnancy. BMC Pregnancy Childbirth. 2014;14:35.
76. Sabrià E, Lequerica-Fernández P, Ganuza PL, et al. Use of the sFlt-1/PlGF ratio to rule out preeclampsia requiring delivery in women with suspected disease. Is the evidence reproducible?. Clin Chem Lab Med. 2018;56(2):303-311.
77. Saleh L, Verdonk K, Jan Danser AH, et al. The sFlt-1/PlGF ratio associates with prolongation and adverse outcome of pregnancy in women with (suspected) preeclampsia: analysis of a high-risk cohort. Eur J Obstet Gynecol Reprod Biol. 2016;199:121-126.
78. Sovio U, Gaccioli F, Cook E, Hund M, Charnock-Jones DS, Smith GC. Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women.

Hypertension. 2017;69(4):731-738.

79. Verlohren S, Herraiz I, Lapaire O, et al. New gestational phase-specific cutoff values for the use of the soluble fms-like tyrosine kinase-1/placental growth factor ratio as a diagnostic test for preeclampsia. Hypertension. 2014;63(2):346-352.
80. Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016;374(1):13-22.
81. Huhn EA, Kreienbühl A, Hoffmann I, et al. Diagnostic Accuracy of Different Soluble fms-Like Tyrosine Kinase 1 and Placental Growth Factor Cut-Off Values in the Assessment of Preterm and Term Preeclampsia: A Gestational Age Matched Case-Control Study. Front Med (Lausanne). 2018;5:325.
82. Nikuei P, Rajaei M, Roozbeh N, et al. Diagnostic accuracy of sFlt1/PlGF ratio as a marker for preeclampsia. BMC Pregnancy Childbirth. 2020;20(1):80.
83. Zhu X, Chen L, Li R. Values of serum sFlt-1, PLGF levels, and sFlt-1/PLGF ratio in diagnosis and prognosis evaluation of preeclamptic patients. Clin Exp Hypertens. 2020;42(7):601-607.
84. Agrawal S, Shinar S, Cerdeira AS, Redman C, Vatish M. Predictive Performance of PlGF (Placental Growth Factor) for Screening Preeclampsia in Asymptomatic Women: A Systematic Review and Meta-Analysis. Hypertension. 2019;74(5):1124-1135.
85. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. Lancet. 2019;393(10183):1807-1818.
86. Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study. Hypertension. 2018;71(2):306-316.
87. Zhao M, Zhu Z, Liu C, Zhang Z. Dual-cutoff of sFlt-1/PlGF ratio in the stratification of preeclampsia: a systematic review and meta-analysis. Arch Gynecol Obstet. 2017;295(5):1079-1087.
88. Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia - two placental causes of preeclampsia?. Placenta. 2014;35 Suppl:S20-S25.
89. Fox A, McHugh S, Browne J, et al. Estimating the Cost of Preeclampsia in the Healthcare System: Cross-Sectional Study Using Data From SCOPE Study (Screening for Pregnancy End Points). Hypertension. 2017;70(6):1243-1249.