The predictive performance of PlGF for screening preeclampsia in asymptomatic women: A systematic review and meta-analysis.

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ABSTRACT:

Preeclampsia (PE) is a systemic syndrome that appears to originate from the placenta and is associated with an imbalance between angiogenic factors in the maternal circulation. One of the well-studied and widely used factors is placental growth factor (PlGF), the levels of which drop in women destined to develop PE. This drop is known to precede the development of actual signs and symptoms of PE, thus proving to be a useful screening tool in predicting the disease. The literature varies widely in terms of the clinical usefulness of the test. We conducted a meta-analysis to study the predictive accuracy of PlGF in asymptomatic women. Our analysis included 40 studies with 3,189 cases of PE and 89,498 controls. The overall predictive odds ratio (POR) of the test was 9 [6-13]. Subgroup analysis evaluating various PlGF thresholds demonstrated that the predictive values were highest for PlGF levels between 80-120 pg/mL with a high POR of 25 [7-88], a sensitivity of 0.78 (95% CI 0.67-0.86], a specificity of 0.88 (95% CI 0.75-0.95), a positive likelihood ratio of 6.3 (95% CI 2.7-14.7), and a negative likelihood ratio of 0.26 (95% CI 0.16-0.42). Additionally, the accuracy was higher when the test was performed after 14 weeks of gestation (OR 10 [7-15]) and for prediction of early onset PE (OR 18 [9-37]). We conclude that PlGF is a useful screening tool to predict PE. Nonetheless, its utility should be judged with caution and randomized controlled trials are warranted to explore if its implementation improves perinatal outcomes in asymptomatic women.

Keywords:
Preeclampsia, Placental growth factor, PlGF, angiogenic factors, prediction, biomarker

INTRODUCTION:

Preeclampsia (PE) affects approximately 2-10% of all pregnancies and is a significant cause of maternal and perinatal morbidity and mortality.[1] The etiology of PE remains unclear, though recent advances in its understanding have elucidated critical biological roles for placentally derived angiogenic factors. There is growing evidence that an imbalance in these factors released from the placenta and maternal endothelium, including placental growth factor (PlGF), soluble Fms-like tyrosine kinase 1 (sFlt-1) and soluble Endoglin (sEng) are associated with the onset of the disorder.[2–4] PlGF is thought to induce non-branching angiogenesis leading to a low-resistance placental vascular network. In a healthy pregnancy, it increases with gestation in maternal circulation, with concentrations peaking at 26 to 30 weeks and declining towards term.[5] In pregnancies complicated by PE, limited angiogenesis early in pregnancy with shallow vascular

invasion of maternal spiral arteries leads to subsequent placental hypoperfusion. The angiogenic imbalance between PlGF and sFlt-1 has a pivotal role in the pathogenesis the disease, and their ratio is, thus, a useful tool in its prediction.[6] PlGF is abnormally low in women with PE as compared to their gestational age-matched controls. The decrease in PlGF level is evident as early as the beginning of the second trimester of pregnancy, prior to the development of signs and symptoms of the disease.[5] Although, the literature is split about its utility as a predictive biomarker. Various studies exploring PlGF as a predictor of PE report a wide variation in its diagnostic accuracy, which ranges between 45-95%. This disparity can be explained by the mixed patient population, varied cut-offs used, different analysis platforms, lack of distinction between early onset (EO) and late onset (LO) disease or PE with or without severe features, in most studies. This lack of uniformity, resulting in difficulty in clinical interpretation of the existing data, prompted us to perform this current meta-analysis. We aimed to investigate the accuracy of PlGF in predicting PE in asymptomatic women, as well as analyze the various cut-offs of PlGF, its potential across different gestational ages and its accuracy for the prediction of EO and LO-PE in low-risk and high-risk populations.

MATERIALS AND METHODS:

Data, analytic methods and study material are detailed below, and further details are available upon request.

Identification of studies

We performed a comprehensive systematic manual and electronic search according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) on MEDLINE, EMBASE and Web of Science from data inception to May 23rd, 2018 (Figure 1A). The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. The search strategy consisted of MeSH (medical subject heading) terms, Emtree terms, and keywords related to the disease (PE) combined with PlGF. Details of the search strategy are available in Appendix S1. Language restrictions were not applied. An all-inclusive database of relevant articles was constructed. The meta-analysis was registered in Prospero (CRD42019122756).

Study selection

The first stage of study selection involved scrutinizing the database by two independent investigators (SA and SS) to identify articles from the title and abstract review based on keywords for PlGF and PE. In the second stage, the titles and abstracts of all the identified citations were independently screened to identify studies that fulfilled the study inclusion criteria. Discrepancies were settled by discussion and consensus. In the final stage of study selection, the full texts of identified articles were obtained, and final inclusion or exclusion decisions were made after an independent, in-depth examination of the papers by the two investigators (SA and SS) to confirm study eligibility.

Data extraction and study quality assessment

The data from the eligible studies were extracted individually by two reviewers (SA and SS) using a standard protocol. Any discrepancies were settled by consensus and matters on which an agreement could not be made were resolved by a third reviewer. The data on the first author, publication year, country where the study was conducted, type of study design, characteristics of the population studied, number of cases and controls, gestational age at sampling, high-risk or low-risk population, PlGF cut-offs used, end-point of disease (EO or LO-PE), test kits used and the data required to make a 2x 2 table were collected. The authors were contacted by email in cases of missing information.

Acceptable reference standards for PE were either compatible with the previous definition, prior to 2013, or the new definition of the disease as defined by The American College of Obstetrics and Gynecology (ACOG) in 2013 or The International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2014.

Quality assessment

The methodological quality of all the included manuscripts was assessed by one of the reviewers (SA) using the quality assessment tool for Cochrane diagnostic accuracy review[7] (Figure 1B). The risk of bias was judged in four main domains, namely, patient sampling, index test, reference standard, flow of patients in the study and timing of the index test and the reference standard. Concerns regarding the applicability of the test in clinics were also judged in the first three domains.

Inclusion criteria for the studies:

1. Original research on pregnant women studying PlGF in blood, serum or plasma for the prediction of PE
2. Observational studies including cross-sectional, case-control, or cohort studies
3. Studies including singleton pregnancies only
4. Pregnant women with no signs or symptoms of PE at the time of PlGF testing
5. Blood drawn for analysis at any gestational age
6. Published until 22 May 2018
7. Data available to construct a 2×2 table for calculating the diagnostic values of the test.

Exclusion criteria for the studies:

1. Diagnostic accuracy of PlGF reported in combination with other markers and not individually
2. Only mean values of PlGF calculated in the two groups
3. Data presented did not allow pooling (missing data or correlation analysis)
4. Signs or symptoms of PE present at the time of blood sample collection
5. Accuracy determined for adverse perinatal outcomes and not for PE
6. Multiple or non-viable pregnancies included
7. Inadequate study design
8. PlGF used to diagnose rather than predict PE

Data synthesis and analysis

The data on the number of pregnant women with a true-positive, true-negative, false-positive and false-negative test results were extracted from all studies and a 2 x 2 diagnostic table was constructed by calculating the measures of accuracy, the prevalence of the disease and the sample size reported in the study. From the 2×2 tables, sensitivity (true positive rate), specificity (true negative rate) and likelihood ratios (LR) were derived with their 95% confidence intervals for individual studies. As a conventional correction, 0.5 was added to all zero counts in the table. As sensitivity and specificity are interdependent parameters, a combined indicator, predictive odds ratio (POR), was used, which represents the odds of a positive test in patients destined to develop PE as compared to the odds of a positive test in patients without the disease. The POR remains reasonably constant despite the change in thresholds in the various studies. The higher the odds

ratio, the closer is the ROC (receiver operator characteristic) curve to the upper left-hand corner of the plot and better is the performance of the test. HSROC (hierarchical summary receiver operator characteristic) model was used for hierarchical modeling to provide equivalent summary estimates, considering variability both between studies (heterogeneity) and within studies (random sampling error). The estimate of random effects was based on the Der Simonian-Laird method. The accuracy data from all the included studies were plotted on an HSROC curve with sensitivity on the x-axis and specificity on the y-axis and the area under the HSROC curve was calculated. This corresponds to the summary predictive odds ratio, which expresses the strength of association between the test and the disease.

Statistical heterogeneity among the studies was evaluated using the Q test, and the degree was estimated using I2 statistic. An exploration of the reasons for heterogeneity, rather than the computation of a single summary measure, is an essential goal of meta-analysis.[8] We investigated heterogeneity using stratified (subgroup) analyses.[9] The factors specified a priori as potential sources of heterogeneity included the patient population studied (high-risk, low-risk or general population, i.e., all women attending the antenatal clinic), end-point of the disease (EO-PE or LO-PE), gestational age at the time of testing, various thresholds used, and the platform used for the analysis. The measures of predictive accuracies were computed for all subgroups to assess their impact. To ease clinical interpretation of AUC and POR, we calculated sensitivity, specificity and likelihood ratios for the subgroup analyses as our measures of diagnostic accuracy. Publication bias was assessed by Deeks funnel plot constructed using log natural of the POR (predictive odds ratio) and reciprocal of the square root of the sample size on the x-axis and y-axis, respectively.

All data were statistically analyzed using StataMP 15.0 (StataCorp, College Station, TX, USA) and Review Manager 5.3 (RevMan, Version 5.3 for Windows, Nordic Cochrane Centre, Copenhagen, 2005).

RESULTS:

Literature identification and study quality

Figure 1A summarizes the process of literature identification and selection. Overall, 1,757 primary articles met our inclusion criteria. We retrieved 155 potentially eligible primary studies for detailed evaluation and inclusion in the systematic review, including 14 potentially eligible publications

from the reference lists of included studies. A thorough assessment led to the exclusion of 115 papers that did not meet our selection criteria. Overall, 40 studies fulfilled the criteria and were included in the systematic review. The quality assessment of these studies is summarized in Figure 1B. In the majority of the studies (n=24), there was good reporting with a prospective design, consecutive recruitment, adequate description of the selection criteria, patient spectrum, test and use of appropriate reference standard.

Study characteristics

The study characteristics are summarized in Table I and II. All 40 studies were published between 2001 and 2018 and originated from different parts of the world, the majority of which were developed countries (Table II). Statistical analysis was performed for all the studies together and individually for the following subgroups identified:

1. Gestational age at the time of screening (<14 weeks, ≥ 14 weeks to term, ≥ 19 weeks to term)
2. Study design (prospective and retrospective)
3. PlGF cut-off used to predict PE (50-150 and 80-120)
4. Study population (high-risk and low-risk)
5. Type of PE (EO and LO-PE)

In manuscripts involving the same patient population, published more than once, only the manuscript with the maximal number of patients was included. In studies evaluating more than one relevant outcome, e.g., total PE and EO and LO-PE, only the group with the highest patient population was considered for the overall analysis to avoid any duplication. The other end-points were considered for subgroup analysis. In studies with more than one PlGF threshold, only one set of values with a cut-off closer to a hundred was chosen.

Gestational age at the time of screening was <14 weeks in 15/40 studies and ≥ 14 weeks in the remaining studies (25/40), in 18 of which, it was ≥19 weeks. Twenty-four studies were prospective and 16 were retrospective. In all the studies, the chosen PlGF cut-off was not pre-determined, rather it was calculated based on the ROC curve with maximal accuracy. In 17/40 studies, the cut-off used was not provided. Of the remaining 23, the optimal cut off values were given as a discrete number (n=19), which was between 41-382 pg/mL or in MoMs (n=4). The high-risk population was defined differently in the studies, considering well-established risk factors for PE or their

combination as detailed in Table II. Low-risk pregnancies were singleton, uncomplicated pregnancies with no identifiable risk factors for PE. The baseline risk for PE in the population studied was high in seven studies, low in another seven and equal to the baseline risk in the general population attending the antenatal clinic in the remaining 26 studies. EO-PE was the end-point in 13 studies, defined as PE onset or diagnosis at <34 weeks (n=7), delivery at <34 weeks (n=5), or PE diagnosis at <32 weeks (n=1). LO-PE was the end-point in eight studies, defined as PE onset ≥34 weeks (n=4) or delivery ≥34 weeks (n=4). Different assays were used for the measurement of PlGF levels. The study characteristics are summarized in Tables I and II. The accuracy of the test in the various studies is tabulated in Supplement S2.

Data analysis

In the current meta-analysis, 40 studies were included with a total number of 92,687 women, of whom 3,189 developed PE and 89,498 did not. There was considerable heterogeneity in the strata. The sensitivities and specificities ranged widely from 7%[37] to 93%[12] and from 51%[14] to 97%[22], respectively. The optimal cut off values for PlGF ranged from 41.84 pg/mL[15] to 382.5 pg/mL.[17]

The global summary ROC curve and forest plot for all 40 studies included are shown in Figure 2A,B. The overall POR of PlGF for prediction of PE was 9[6-13]. The AUC for SROC was 0.83[0.80-0.86] (Figure 2B). The likelihood ratio of a positive test result was 4.1[3.3-5.1], and that of a negative test result was 0.45[0.37-0.55]. The unconditional negative predictive value was 0.67 [0.65-0.70] and the positive predictive value was 0.79[0.75-0.82]. The summary performance estimates are summarized in Table III. Due to clinical and methodological diversity, the heterogeneity was substantial (I2=99[99-100]) and, therefore, a "random effects" model was chosen (DerSimonian and Laird, 1986; Ades, Lu and Higgins, 2005). We explored the various reasons for heterogeneity using subgroup analysis. The overall risk of bias was high due to the different PlGF cut-offs chosen across different gestational ages. The overall HSROC curve showed a ROC type of trade-off between sensitivity and specificity, further indicating a threshold effect (Figure 2B). The proportion of heterogeneity likely caused due to the threshold effect was 0.10. The publication bias was minimal on a funnel plot (p-value=0.08).

We performed various subgroup analyses to explore the predictive value of PlGF. Firstly, we compared the predictive value of PlGF before 14 weeks (n=15), ≥ 14 weeks to term (n=25) and ≥19 weeks to term (n=18) (Figure 2C,D,E). POR was 8[4-14] before 14 weeks, increased to 10[7-

15] at ≥ 14 weeks and further increased to 11[7-20] at ≥ 19 weeks. The sensitivity was highest at ≥ 19 weeks (0.72[0.64-0.79]), while the specificity was highest before 14 weeks (0.89 [0.85-0.91]). Secondly, we analyzed the different cut-offs used for defining an abnormally low value of PlGF. Among the different studies, despite the non-arbitrary cut-offs, the variation was vast, with cut-offs ranging from 41.84 to 382.5. To eliminate the threshold effect, we did a subgroup analysis to include only studies with cut-offs between 50 and 150 (12 studies) and then between 80 and 120 (n=6). For the former, the POR was 16[7-33] and for the latter, the POR increased to 25[7-88]. The sensitivity and specificity were also higher in the latter at 0.78[0.67-0.86] and 0.88[0.75-0.95], respectively (Figure 3). For EO-PE, the POR increased to 18[9-37], while for LO-PE, it fell to 7[4-11]. The summary performance estimates were high for EO-PE, with an estimated sensitivity of 0.71[0.57-0.82] and a specificity of 0.88[0.82-0.93] (Figure 3).

DISCUSSION

This meta-analysis provides an overview of the discriminatory performance and predictive capacity of the pro-angiogenic marker PlGF for predicting PE in asymptomatic pregnant women. Forty-two studies met inclusion criteria and were subjected to quality testing using QUADAS-2 tool. Our results demonstrated good overall test accuracy in disease prediction. The diagnostic accuracies in the various subgroups further highlight the importance of PlGF in PE.

While treatment of PE should be based on signs and symptoms and not on test results, this test is clinically valuable in pinpointing asymptomatic women likely to develop PE as pregnancy advances, who will, therefore, gain from close surveillance. Women with normal PlGF levels are not likely to develop PE, and, thus, do not warrant close observation for this indication.

PlGF levels vary with gestational age

Across gestational ages, we found that the POR increased significantly when the test was performed at or after 14 weeks as compared to earlier in pregnancy. Its sensitivity significantly increased (51% to 67%), without a remarkable decrease in specificity (89% to 83%) (Figure 2C,D) with increasing gestational age. When the test was done at or beyond 19 weeks, its accuracy further increased (Figure 2E).

The available literature is inclined towards conducting the test in the second trimester of pregnancy, suggesting that the most appropriate timing for PE prediction is after 14 weeks. This practice is supported by the physiology of healthy low-risk pregnancies, where PlGF rises until 30

weeks of pregnancy and then declines towards term. It is also consistent with the model of placental angiogenesis proposed by Kingdom et al., whereby non-branching angiogenesis associated with high placental production of PlGF, is predominant in the latter half of pregnancy.[52] In patients with PE, the rise in PlGF is abolished and remains low until term.[5] Moreover, since PlGF levels start rising in the second half of pregnancy, the diagnosis of PE may be missed, if the prediction is based on levels obtained in the late first trimester, along with aneuploidy screening.[53] Of note, for all the studies on PlGF later in the pregnancy, the time intervals from PlGF testing to disease diagnosis are not provided and may range from a day to many weeks. This variable is unaccounted for and may, potentially, introduce bias.

Varying cut-offs and confounders

PlGF cut-offs were distributed widely across the studies, but restricting the analysis to ranges of 50 and 150 increased the predictive accuracy substantially (POR increased from 9[7-13] to 16[7-33], with a sensitivity of 76%, a specificity of 85%, and an AUC of 0.86), indicating a threshold effect (Figure 3). Further restriction to studies with a narrower cut-off range of 80 to 120, increased the POR to 25[7-88]. This highlights the importance of a standard cut-off for interpretation of PlGF results. When utilizing these narrow cut-offs, PlGF can serve as a valuable test for PE prediction in asymptomatic women. However, the threshold variability in the literature indicates a lack of standardization, limiting clinical applicability of the test. Interestingly, in all the included studies, the PlGF cut-off was not arbitrary, but instead, was extrapolated from ROC curves with the best predictive values. The disparity could be due to different platforms used for the analysis, the lack of distinction between EO and LO disease, or PE with and without severe features, and differing patient characteristics (age, ethnicity, method of conception, parity, body mass index, smoking and comorbidities).[54-56] The results emphasize the need for a standardized cut-off and warrant further trials to explore the levels of PlGF and whether gestational age-specific[5] and population-specific threshold will increase the predictive capacity of PlGF. A model which includes maternal characteristics along with levels of several biomarkers, including PlGF, may have a higher prediction accuracy than individual biomarkers in a single patient population.[35,57,58]

Type of PE (EO or LO)

EO-PE originates from placental malperfusion secondary to poor placentation, a process that begins very early at the time of implantation. LO-PE also originates secondary to placental

malperfusion, but later when the placenta outgrows the uterine capacity to sustain it.[59,60] It is the early onset disease that contributes most to perinatal morbidity and mortality and long-term maternal complications, and therefore, its recognition is of immense importance.[61] Our study shows that the POR in EO-PE is superior to POR in LO-PE, indicating better screening performance of PlGF for early-onset disease (Figure 3). Since the time interval between the test result and PE onset was not reported in the studies, we could not account for it in our analysis.

Strengths and weaknesses of the review

Following an extensive review of the literature, we believe that this is the first meta-analysis that comprehensively analyzes the ability of PlGF to predict PE in asymptomatic women. An important strength of our study is its comprehensive search strategy. Screening and study selection were made independently and reproducibly by two reviewers. Eight authors were contacted for missing data and five of them responded. Additionally, heterogeneity was explored and minimized through subgroup analyses. Potential publication bias was considered in accordance with published guidelines. Lastly, we used POR as a single measure of test performance for the overall analysis. This is because a meta-analysis of sensitivities and specificities alone would have been inappropriate for varying or unreported positivity thresholds, as it would have ignored threshold differences and underestimated diagnostic performance.

Our meta-analysis has several limitations. Firstly, the heterogeneity was high between studies. To overcome this, we performed various subgroup analyses and explored the different causes of heterogeneity, thus finding better accuracy values in the sub-analyses. Though both prospective and retrospective studies were included in the study, a subgroup analysis was performed to investigate this potential bias. Secondly, we could not stratify for the time interval between the test result and the clinical diagnosis of PE, as this was not provided in the studies. Lastly, although we maintained high-quality standards for the conduct of this systematic review and meta-analysis, we realize that the results and their implications are only as good as the source of the data. In the absence of a sufficient number of well-designed marker evaluation studies, we had to include studies that differed in the various methodological aspects.

Perspectives

In summary, among the various biochemical players, PlGF has emerged as one of the key biomarkers to predict PE. Our meta-analysis sheds light on the critical aspects of PlGF testing in asymptomatic women. The high POR indicates that it is a useful test to screen for the disease. A cut-off between 80-120 pg/mL has a very high specificity and is thus more useful to rule in PE. Hence, patients with low PlGF levels have a high likelihood of developing PE and warrant intensive surveillance to enable its prompt and early recognition and timely intervention. Patients with high PlGF levels are unlikely to develop PE, though the benefit of repeat testing and the ideal time frame for it in these patients remain unknown.

It is important to remember that the implementation of a biomarker in clinical practice is beneficial only when the added knowledge gained from it has the potential to influence medical decision making and change management. A recent randomized controlled trial looking at the clinical diagnostic utility of PlGF in women with suspected PE shows that the test shortens the time to diagnosis.[62] To date, no such trials have been conducted in asymptomatic women. Thus, despite the promising results of our meta-analysis, until such studies are undertaken, any utilization of PlGF testing in clinical practice should be regarded with caution. While the current diagnostics discussed in this manuscript will assist in the current management of preeclampsia, there is a need for the development of accurate and reliable test in diagnostics. This would be a step forward in the development of stratified medicine in obstetrics where targeted therapy could be applied.

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Novelty and Significance

What Is New?

This is the first meta-analysis comprehensively analyzing the accuracy of PlGF in the prediction of preeclampsia in asymptomatic women. The various subgroup analyses provide further insight into the multiple aspects of PlGF screening.

What Is Relevant?

PlGF has potential in predicting preeclampsia, although future studies are required to establish an optimum gestational age and threshold for prediction. Additionally, stratified studies in various patient populations using a common platform for analysis is imperative.

Summary

This study provides insight into the accuracies with which preeclampsia can be predicted in asymptomatic women using PlGF as a screening tool. This has the potential to decrease health care costs and improve maternal and neonatal outcomes.

Figure legends

Figure 1. A) Search strategy and study selection as per PRISMA-P guidelines. B) Quality analysis of included studies

Figure 2. A) Forest Plot and B) HSROC curve for all included studies C) <14 weeks D) ≥14 weeks E) ≥19 weeks

Figure 3. HSROC curve for A) Studies with a cut-off of 50-150 pg/mL B) Studies with a cut-off of 80-120 pg/mL C) EO-PE D) LO-PE

Tables

Table I. Broad overview of included studies

Study Characteristics	**Number of studies (n= 40)**
Gestational age	
<14 weeks	15
≥ 14 weeks to term	25
≥ 19 weeks to term	18

Type of PE	
EO-PE only	10
LO-PE only	4
Both EO-PE and LO-PE	3
The type of PE not distinguished	23
Patient population	
High-risk	7
Low-risk	7
General population	25
Study Design	
Prospective	24
Retrospective	16
Sample Type	
Serum	29
Plasma	11
Assay used	
R&D Systems, Minneapolis	13
DELFIA Kits (Perkin Elmer Life and Analytical Sciences)	7

R & D Systems Europe Ltd, Abingdon, UK	2
Elecsys (Roche)	4
DRG, Marburg, Germany	3
Kryptor	2
Beckman Coulter	1
Triage (Alere, San Diego, CA, USA)	1
Other	5
Not given	2

General population was defined as all patients attending an antenatal care clinic.

Table II. Characteristics of the included studies

No	Study	Country	Study design	Characteristics: Study population (developed PE)	Characteristics: Control population (no PE)	PE definition	Disease end-point	GA (wks)	Cases (n)	Controls (n)
1	Su et al, 2001[10]	Taiwan	Retrospective	Low risk	Same	Old	PE	14-19	27	227

2	Tidwell et al, 2001[11]	Taiwan	Retrospective	Primiparous low risk	Same	Old	PE	16-20	14	25
3	Madazil et al, 2005[12]	Turkey	Prospective	Low risk	Same	Old	PE	21-26	14	108
4	Stepan et al, 2007[13]	Germany	Prospective	Abnormal UADV	Same	Old	PE	19-24	12	51
5	Espinoza et al, 2007[14]	USA	Prospective	Low risk	Same	Old	All PE EO-PE	22-26	110	2988
6	Schmidt et al,, 2008[15]	Germany	Prospective	Low risk undergoing amniocentesis	Same	Old	PE	15-18	7	54
7	Sibai et al, 2008[16]	Brazil	Prospective	Previous PE/ chronic HTN	Same	Old	Preterm PE< 37 weeks	24-28	65	589
8	De Vivo et al, 2008[17]	Italy	Retrospective	Low risk	Same	Old	PE	24-28	52	52
9	Diab et al, 2008[19]	Egypt	Prospective	Abnormal UADV	Same	Old	All PE EO-PE	23	33	75
10	Kusanovic et	Chile	Prospective	Low risk	Same	Old	All PE	20-25	62	1560

	al, 2009[20]						EO-PE			
11	Audibert et al, 2010[21]	Canada	Prospective	Nulliparous low risk	Same	Old	All PE EO-PE	11-13	22	509
12	Shokry et al, 2010[22]	Saudi Arabia	Prospective	All patients in ANC	Same	Old	PE	13-16	27	213
13	Wortelboer et al, 2010[23]	Netherlands	Retrospective	All patients in ANC	Same	Old	EO-PE	8-13+6	88	480
14	Foidart et al, 2010 [24]	UK	Retrospective	All patients in ANC	Same	Old	EO-PE	11-13+6	30	150
15	Ghosh et al, 2012[25]	India	Prospective	All patients in ANC	Same	Old	PE	20-22	58	1046
16	Yu et al, 2011[27]	China	Retrospective	All patients in ANC	Same	Old	PE	12-16	31	93
17	Yousseff et al, 2011 [28]	Italy	Prospective	Developed late onset PE	All patients in ANC	Old	LO-PE	11-13+6	13	515
18	Dover et al, 2013[29]	Turkey	Prospective	Previous PE/ previous GHTN/ chronic HTN	Primiparous low risk	Old	PE	16-19	13	135
19	Myatt et al, 2012[30]	USA	Retrospective	All patients in ANC	Same	Old	PE	9-12+6	174	509

20	Ghosh et al, 2013[31]	India	Prospective	All patients in ANC	Same	Old	EO-PE	22-24	19	1187
21	Kuc et al, 2013[32]	Netherlands	Retrospective	All patients in ANC	Same	Old	EO-PE LO-PE	9-13+6	59	482
22	Boucoiran et al, 2013[33]	Canada	Prospective	All patients in ANC	Same	Old	PE	24-26	29	569
23	Myers et al, 2013[34]	Multicenter (UK, Australia, New Zealand)	Retrospective	Primiparous with PE requiring delivery <37 weeks	No preterm PE	Old	Preterm PE at <37 weeks	14-16	47	188
24	Akolekar et al, 2013[35]	UK	Retrospective	All patients in ANC	Same	Old	All PE EO-PE	11-13+6	1426	57458
25	Hassan et al, 2013[36]	Saudi Arabia, Egypt	Retrospective	All patients in ANC	Same	Old	PE	15-20	83	250
26	Schneuer et al, 2013[37]	Australia	Prospective	All patients in ANC	Same	Old	PE	10-14	68	2613
27	Moore Simas et al, 2014[38]	USA	Prospective	High risk	Same	Old	EO-PE	23-27+6	6	134

28	Stubert et al, 2014[39]	Germany	Prospective	Bilateral abnormal UADV	Same	Old	PE	19-26+6	12	38
29	Park et al, 2014[40]	Seoul, Korea	Prospective	All patients in ANC	Same	Old	LO-PE	24-27	8	254
30	Lai et al, 2014[41]	UK	Prospective	All patients in ANC	Same	Old	PE	30-33	118	3734
31	Moore et al 2015[42]	USA	Retrospective cohort	All patients in ANC	Same	New ACOG	LO-PE	13-16+6	16	56
32	Skrastad et al, 2014[43]	Norway	Prospective	Nulliparous / previous PE or GHTN	Same	Norwegian Assoc for O & G	PE	11-13	26	553
33	Crovetto er al, 2015[44]	Spain	Retrospective cohort	All patients in ANC	Same	Old	EO-PE LO-PE	8-13+6	57	9159
34	Anderson et al, 2016[45]	Denmark	Prospective	Nulliparous women	Same	Old	PE EO-PE LO-PE	20-34	117	1443
35	Chaiworapongs	USA	Prospective	Suspected SGA fetus	Same	Old	PE	24-33+6	29	291

	a et al, 2016[46]									
36	Salem et al, 2017[47]	Egypt	Prospective	All patients in ANC	Same	Old	PE	11-13	30	270
37	Erez et al, 2017[48]	USA	Retrospective	All patients in ANC	Same	Old	LO-PE	32-36	70	39
38	Agarwal et al 2017[49]	India	Retrospective	Primigravida <40 years	All patients in ANC	Old	PE	11-14	17	35
39	Benovska et al, 2018[50]	Czeck Republic	Retrospective	All patients in ANC	Same	New ACOG	All PE EO-PE	16-20	39	81
40	Birdir et al, 2018[51]	Germany	Prospective	All patients in ANC	Same	Old	PE	32-37	32	676

PE Preeclampsia; GA gestational age; Old PE definition prior to 2013; New PE definition after 2013; UADV uterine artery Doppler velocities; GHTN gestational hypertension; ANC antenatal clinic; SGA small for gestational age

Table III. POR and predictive accuracies of all the subgroup analyses.

	POR Estimate [95% CI]	**Sensitivity Estimate [95% CI]**	**Specificity Estimate [95% CI]**	**PLR Estimate [95% CI]**	**NLR Estimate [95% CI]**
All studies (n=40)	9[6-13]	0.61[0.53-0.69]	0.85[0.82-0.88]	4.1[3.3-5.1]	0.45[0.37-0.55]
<14 weeks (n=15)	8[4-14]	0.50[0.36-0.64]	0.89[0.85-0.91]	4.4[3.1-6.2]	0.57 [0.43-0.75]

≥14 weeks (n=25)	10[7-15]	0.68[0.60-0.75]	0.83[0.78-0.87]	3.9[3.0-5.1]	0.39[0.31-0.49]
≥ 19 weeks (n=18)	11[7-20]	0.72[0.64-0.79]	0.82[0.75-0.87]	3.9[2.8-5.5]	0.35[0.26-0.46]
Cut-off 50-150 (n=12)	16[7-33]	0.74[0.64-0.82]	0.85[0.78-0.90]	4.8[3.1-7.6]	0.31[0.21-0.45]
Cut-off 80-120 (n=6)	25[7-88]	0.78[0.67-0.86]	0.88[0.75-0.95]	6.3[2.7-14.7]	0.26[0.16-0.42]
EO-PE (n=13)	18[9-37]	0.71[0.57-0.82]	0.88[0.82-0.93]	6.0[3.9-9.4]	0.33[0.22-0.50]
LO-PE (n=7)	7[4-11]	0.45[0.29-0.63]	0.89[0.82-0.93]	4.1[2.9-5.8]	0.62[0.46-0.82]
High-risk (n=7)	6[3-11]	0.57[0.40-0.72]	0.82[0.71-0.89]	3.1[2.1-4.8]	0.53[0.38-0.73]
Low-risk (n=7)	10[5-19]	0.71[0.66-0.76]	0.80[0.67-0.89]	3.5[2.1-6.0]	0.36[0.29-0.45]
Prospective (n=24)	11[7-19]	0.66[0.55-0.76]	0.85[0.80-0.89]	4.4[3.3-6.0]	0.4[0.3-0.53]
Retrospective (n=16)	7[4-11]	0.55[0.44-0.65]	0.85[0.81-0.89]	3.7[2.8-4.9]	0.53[0.42-0.67]

POR Predictive odds ratio; CI confidence interval; EO-PE early onset pre-eclampsia; LO-PE late onset pre-eclampsia; PLR positive likelihood ratio; NLR negative likelihood ratio

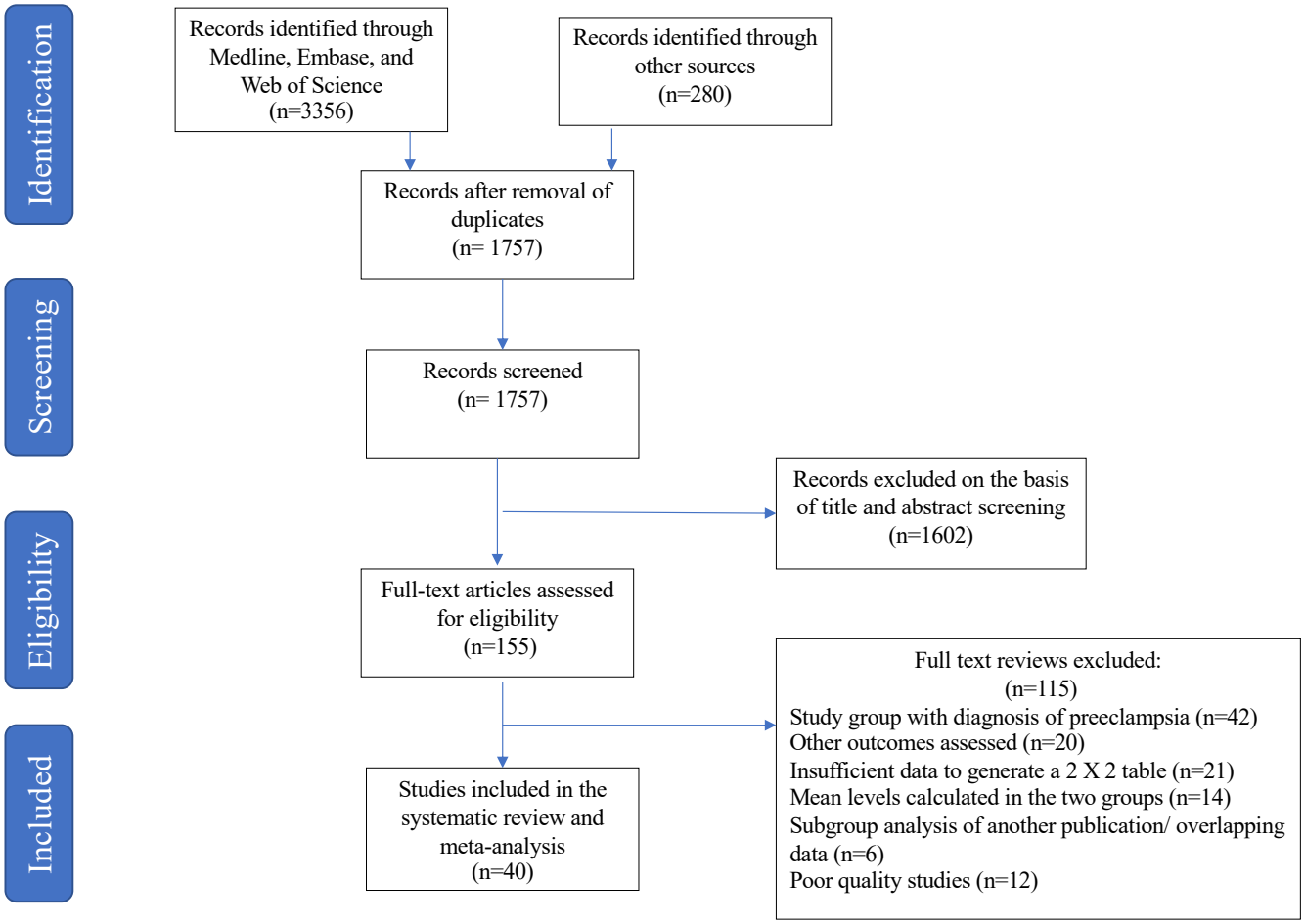


Figure 1A. Search strategy and study selection as per PRISMA-P guidelines.

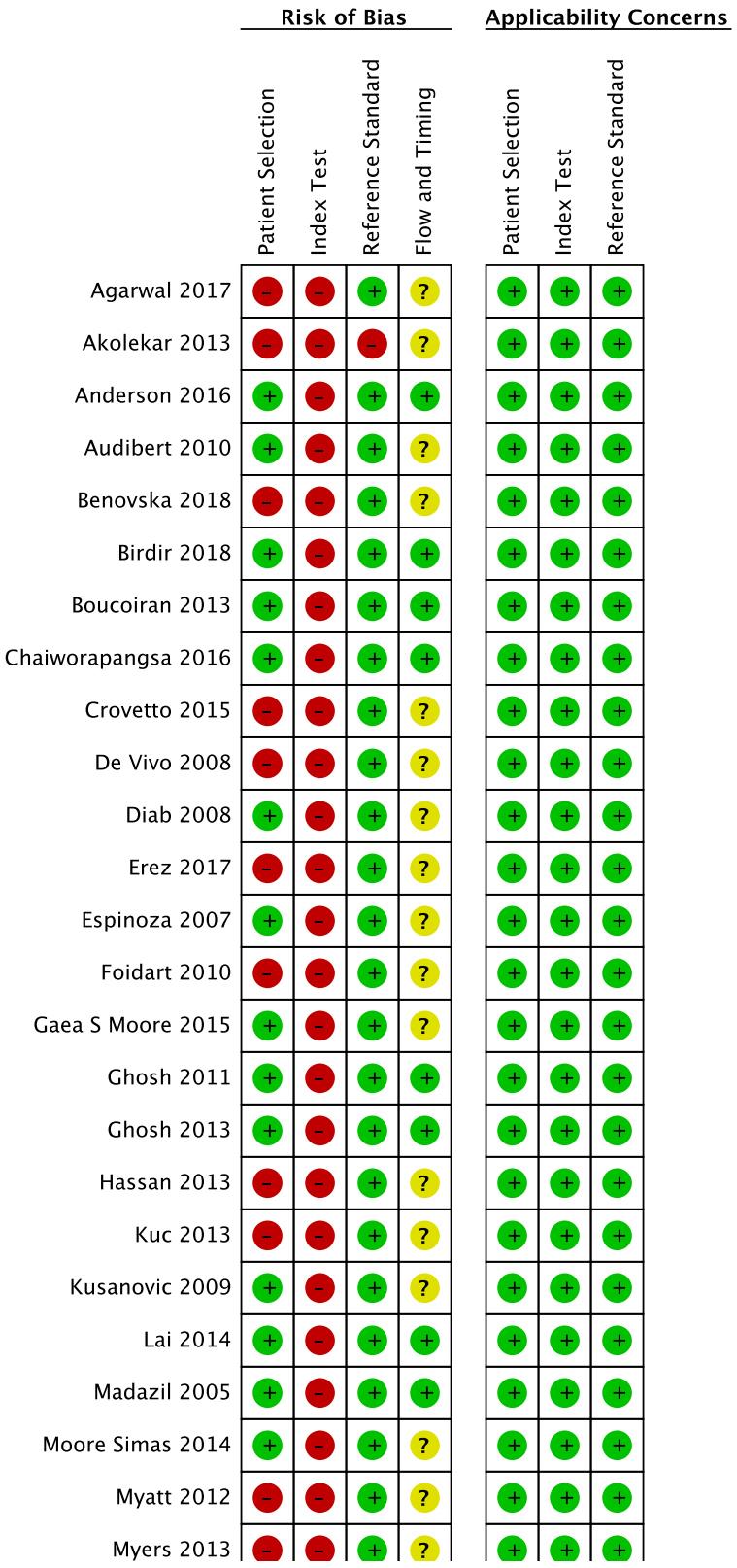


Figure 1B. Quality analysis of included studies

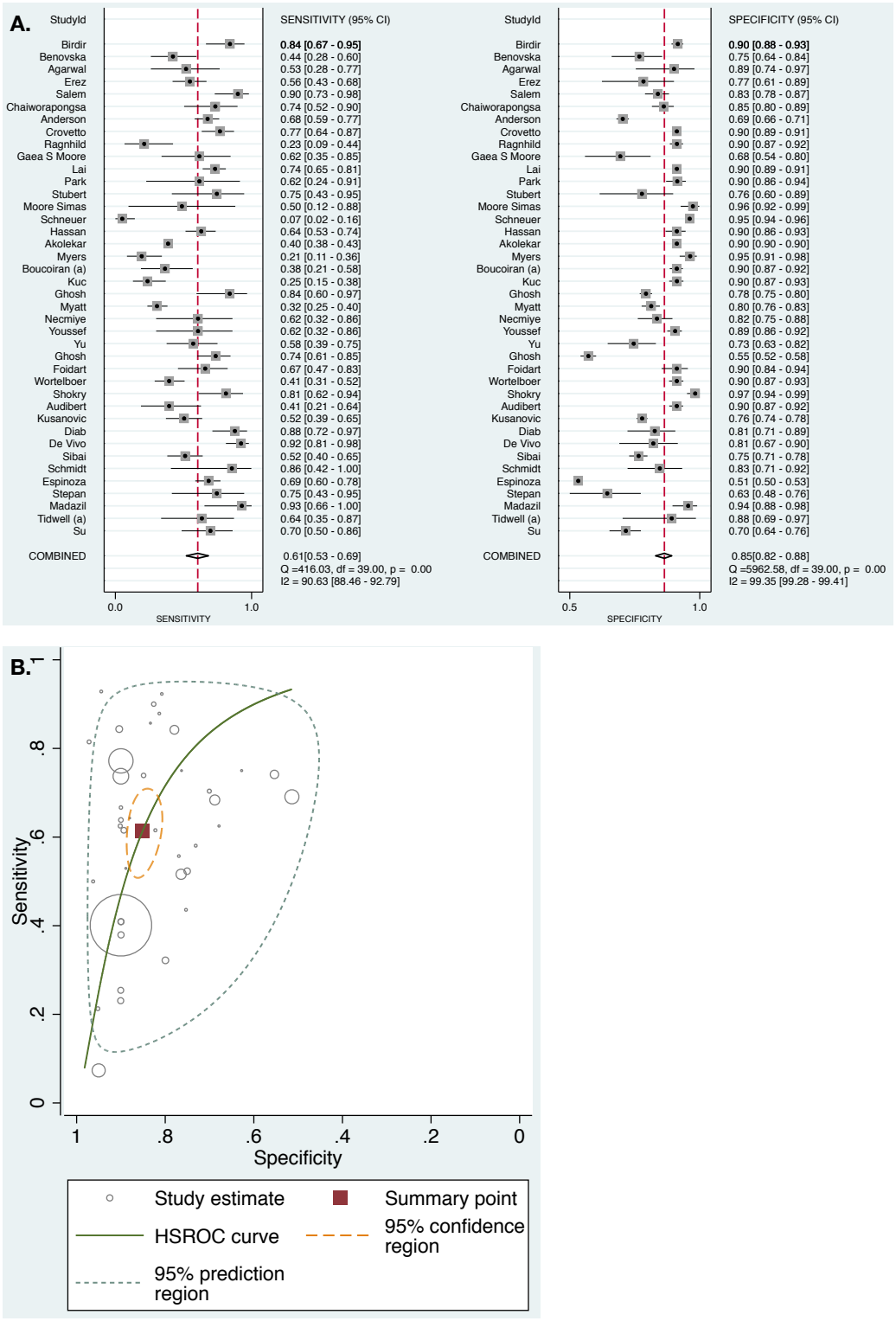
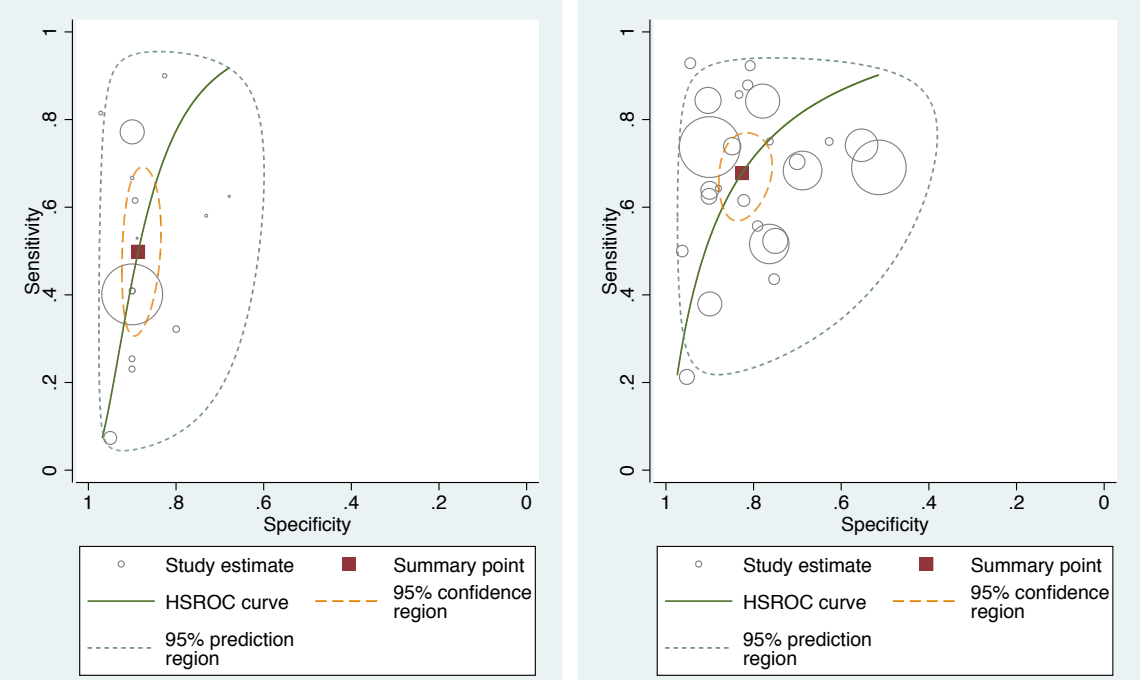


Figure 2. A) Forest Plot and B) HSROC curve for all included studies.



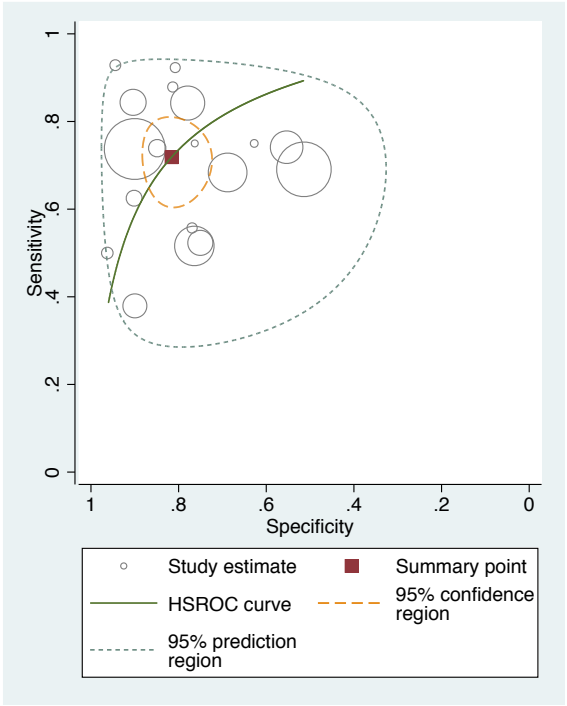


Figure 2. HSROC curve for studies C) <14 weeks D) ≥14 weeks E) ≥19 weeks

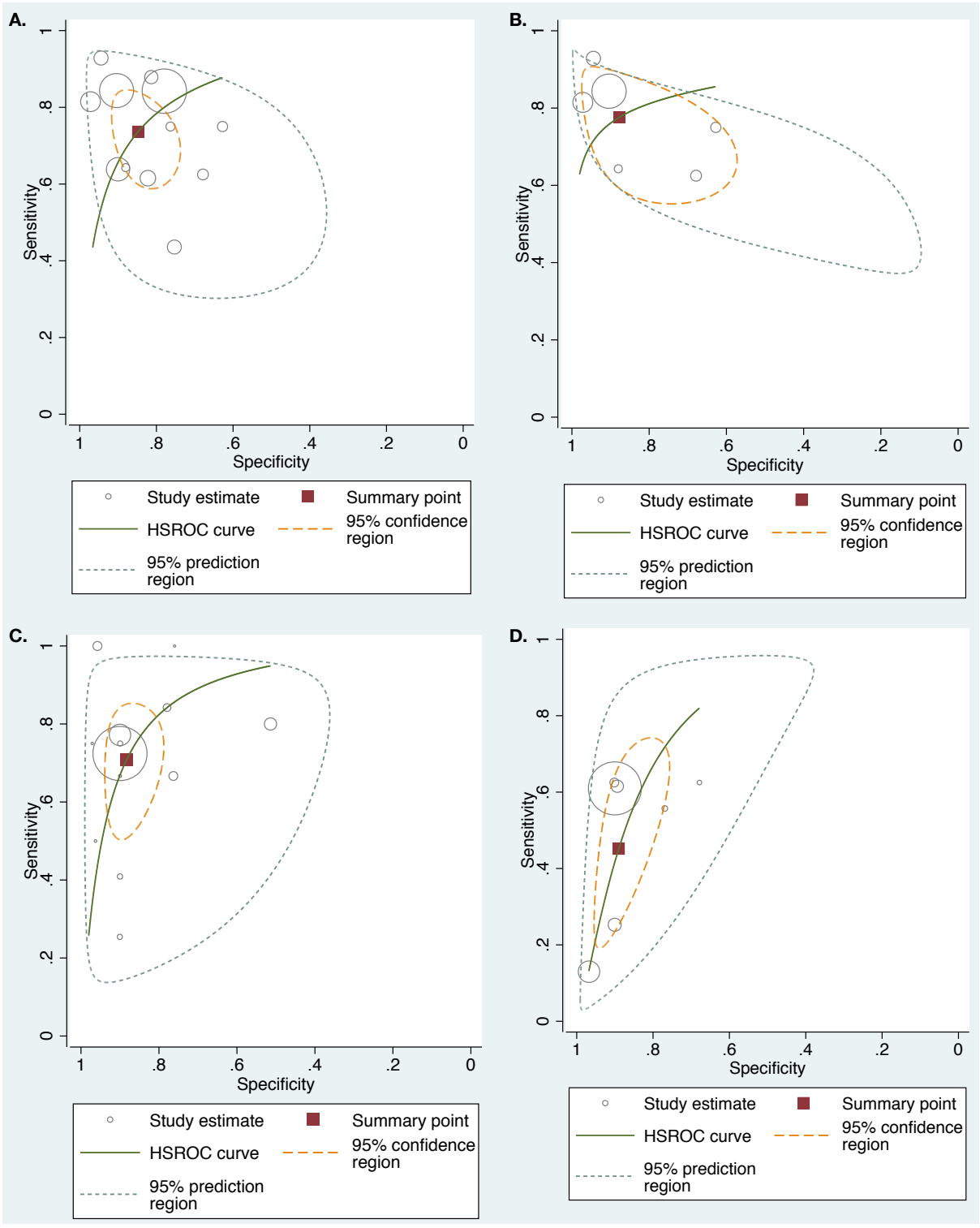


Figure 3. HSROC curve for A) Studies with a cut-off of 50-150 pg/mL B) Studies with a cut-off of 80-120 pg/mL C) EO-PE D) LO-PE