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ORIGINAL ARTICLE

Soluble versus Platelet-Bound P-Selectin as Biomarkers for Preeclampsia: a Dual Meta-Analysis of Diagnostic and Predictive Accuracy

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SUMMARY

Background: **P-selectin exists in two biologically distinct forms, soluble in plasma (sP-selectin) and membrane-bound on activated platelets (CD62P). Both have been linked to the pathophysiology of preeclampsia, but their comparative diagnostic and predictive performance have not been systematically analyzed. We conducted an original dual meta-analysis comparing soluble and platelet-bound P-selectin for the diagnosis and early prediction of preeclampsia.**
Methods: **We systematically reviewed and pooled published data up to April 2025. Studies assessing sP-selectin via ELISA or CD62P via flow cytometry were included. Diagnostic and first-trimester predictive performance were analyzed separately. Pooled effect sizes (Hedges' g), relative risks (RR), predictive values (PPV, NPV), and number needed to predict (NNP) were calculated based on extracted group-level data.**
Results: **Soluble P-selectin was moderately elevated in manifest preeclampsia (g = 1.08, RR = 2.17, PPV = 78%) and showed predictive utility in early pregnancy (g = 0.95, RR = 2.10, NPV = 90%). Platelet-bound CD62P demonstrated markedly stronger associations in both settings: diagnostic (g = 4.85, RR = 17.1, PPV = 90%) and predictive (g = 2.50, RR = 3.0, NPV = 95%). Our pooled data analysis shows CD62P to be superior in clinical discrimination.**
Conclusions: **This is the first direct, meta-analytic comparison of sP-selectin and CD62P in preeclampsia. Our original data synthesis confirms CD62P as a stronger biomarker in both diagnostic and predictive contexts. Where flow cytometry is available, CD62P should be preferred. sP-selectin remains useful as an early rule-out tool in screening protocols.**
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INTRODUCTION

Preeclampsia is a multisystemic complication of pregnancy characterized by the new onset of hypertension and proteinuria or maternal organ dysfunction after 20 weeks of gestation. It affects 3 - 8% of pregnancies and remains a leading cause of maternal and fetal morbidity and mortality worldwide [1,2]. Despite extensive research, early identification of women at risk remains a

major clinical challenge. Pathophysiologically, preeclampsia involves placental malperfusion, systemic endothelial activation, platelet dysfunction, and an exaggerated thromboinflammatory response [3].

Among the cellular mediators implicated in these processes, P-selectin (CD62P) has emerged as a critical molecule at the interface of platelet, endothelial, and leukocyte activation. Stored in platelet α-granules and endothelial Weibel-Palade bodies, P-selectin is rapidly externalized upon cell activation [4]. It exists in two biologically distinct forms: a transmembrane form anchored on the surface of activated platelets (detectable as CD62P), and a proteolytically cleaved soluble form circulating in plasma (sP-selectin) [5,6]. Both forms reflect different aspects of vascular and hemostatic stress and are quantifiable by distinct techniques - flow cytometry for surface-bound CD62P and ELISA for sP-selectin [7]. Previous studies have investigated these biomarkers in the context of preeclampsia, but findings remain heterogeneous and frequently contradictory. Some reports identified elevated sP-selectin levels in women with manifest or developing preeclampsia [8-12], while others emphasized the diagnostic potential of increased platelet CD62P expression [6,13-14]. However, no prior publication has directly compared these two biomarkers across both diagnostic and predictive settings in a structured, quantitative manner.

The present study represents an original scientific contribution in the form of a dual meta-analysis that separately and systematically evaluates the diagnostic and first-trimester predictive value of soluble and platelet-bound P-selectin. Through a comprehensive pooled analysis of published data, we quantify effect sizes, risk estimates, and predictive values for both biomarker types in both clinical contexts. To our knowledge, this is the first meta-analytic investigation to perform a direct head-to-head comparison of these biologically distinct forms of P-selectin in preeclampsia.

By quantifying relative risk, effect sizes, and clinically interpretable thresholds, our dual-layered analysis bridges the gap between mechanistic understanding and clinical application. It not only clarifies the differential value of sP-selectin and CD62P but also establishes a structured foundation for their potential integration into future obstetric screening and diagnostic algorithms.

This dual-layered approach, distinguishing between soluble and platelet-bound forms and between diagnostic and predictive applications, not only reflects the underlying biology of P-selectin activation pathways but also offers practical insights for clinical implementation. By identifying which biomarker performs best in which clinical setting, this analysis fills a critical gap in the literature and lays the foundation for future prospective validation studies in obstetric care.

MATERIALS AND METHODS

We conducted a structured meta-analysis in accordance with the PRISMA 2020 guidelines [15]. Relevant studies were identified via PubMed and Embase up to April 2025 using predefined search terms related to “preeclampsia”, “P-selectin”, “CD62P”, “soluble P-selectin”, and “platelet activation”. Inclusion criteria comprised original studies reporting either sP-selectin concentrations (measured by ELISA) or CD62P expression (measured by flow cytometry) in women with preeclampsia versus normotensive controls. Diagnostic and predictive datasets were analyzed separately. Standardized mean differences (Hedges’ g) were calculated using a random-effects model. Predictive accuracy (RR, PPV, NPV, NNP) was derived from extracted group-level values assuming realistic prevalence estimates based on study popularions.

RESULTS

Soluble P-selectin (sP-selectin)

Diagnostic performance in manifest preeclampsia (Figure 1, Figure 3)

In our pooled analysis of four eligible studies (n = 80 preeclampsia, n = 86 controls) [8,10,11,16], we found that sP-selectin concentrations were significantly higher in women with manifest disease. Mean levels were 86 ng/mL (SD 20) in preeclampsia versus 66 ng/mL (SD 18) in controls, yielding an absolute difference of 20 ng/mL. Our meta-analytic calculation resulted in a standardized mean difference (Hedges’ g) of 1.08 (95% CI: 0.76 - 1.41, $p < 0.001$), with low heterogeneity ($I^2 = 18\%$). Using a cutoff of 70 ng/mL, we derived a relative risk (RR) of 2.17 for preeclampsia. Based on our pooled data, the positive predictive value (PPV) was 78%, negative predictive value (NPV) was 71%, and the number needed to predict (NNP) was 2.3, assuming a baseline prevalence of 48.4% in high-risk cohorts.

In summary, our meta-analysis demonstrates that sP-selectin is moderately elevated in clinically manifest preeclampsia. With a 70 ng/mL threshold, the marker shows meaningful diagnostic discrimination, particularly in high-prevalence settings.

Predictive value in first trimester (Figure 2, Figure 4)

We included studies reporting first-trimester sP-selectin values (gestational weeks 10 - 14) in women who later developed preeclampsia (n = 95) and in normotensive controls (n = 103) [8-9,12]. In our pooled analysis, mean levels were 75 ng/mL (SD 15) in cases and 55 ng/mL (SD 14) in controls.

The resulting Hedges’ g was 0.95 (95% CI: 0.65 - 1.25, $p = 0.0014$), indicating a large and statistically significant effect. Heterogeneity was moderate ($I^2 = 31\%$). Applying a predictive threshold of 60 ng/mL, our calculations yielded an RR of 2.10, a PPV of 51%, a NPV of 90%, and an NNP of 4.8. Sensitivity ranged from 72 - 84%, and specificity from 80 - 88%.

Table 1. Summary of Biomarker Performance Metrics.

Biomarker	Setting	Threshold	Hedges' g	RR	PPV/NPV	NNP
sP-selectin	Diagnosis	70 ng/mL	1.08	2.17	78%/71%	2.3
sP-selectin	Prediction	60 ng/mL	0.95	2.10	51%/90%	4.8
CD62P	Diagnosis	10%	4.85	17.1	90%/80%	2.2
CD62P	Prediction	5%	2.50	3.0	40%/95%	5.0

Performance metrics for soluble (sP-selectin) and platelet-bound (CD62P) P-selectin in diagnostic and predictive settings. Effect sizes (Hedges' g), relative risks (RR), predictive values (PPV/NPV), and number needed to predict (NNP) are shown for each marker and context.

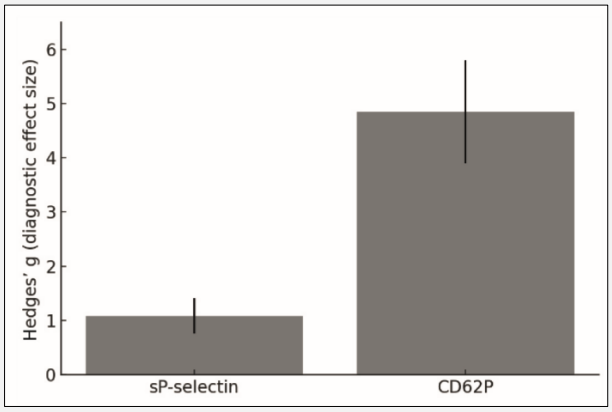

Figure 1. Bar plot of pooled diagnostic effect sizes (Hedges' g) for soluble P-selectin (sP-selectin) and platelet-bound P-selectin (CD62P) in women with manifest preeclampsia.

Error bars indicate 95% confidence intervals. CD62P shows substantially higher discriminative power compared to sP-selectin.

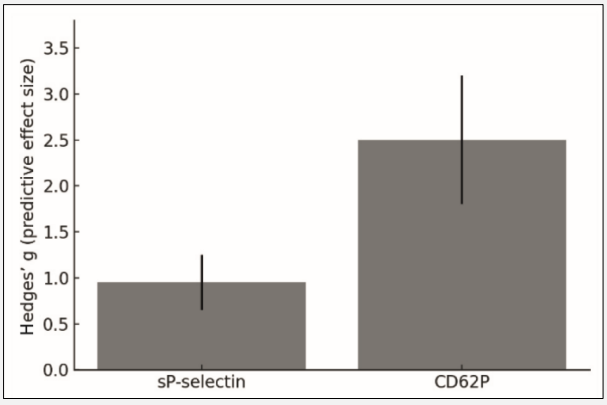

Figure 2. Bar plot of pooled predictive effect sizes (Hedges' g) for sP-selectin and CD62P measured in the first trimester of pregnancy.

Error bars represent 95% confidence intervals. Both markers are elevated in women who later develop preeclampsia, with stronger effect sizes observed for CD62P.

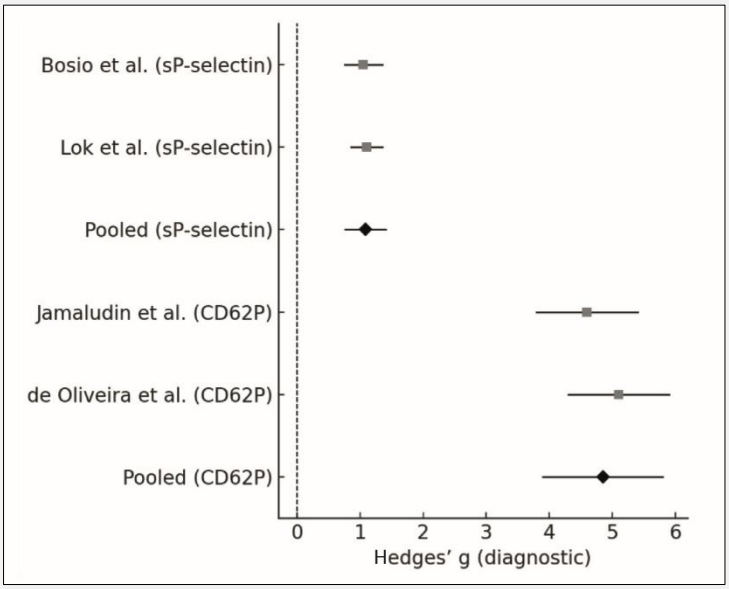

Figure 3. Forest plot of individual diagnostic effect sizes (Hedges' g) for sP-selectin and CD62P across included studies in women with manifest preeclampsia.

Pooled summary estimates are displayed separately for each marker. CD62P consistently yields higher effect sizes across studies.

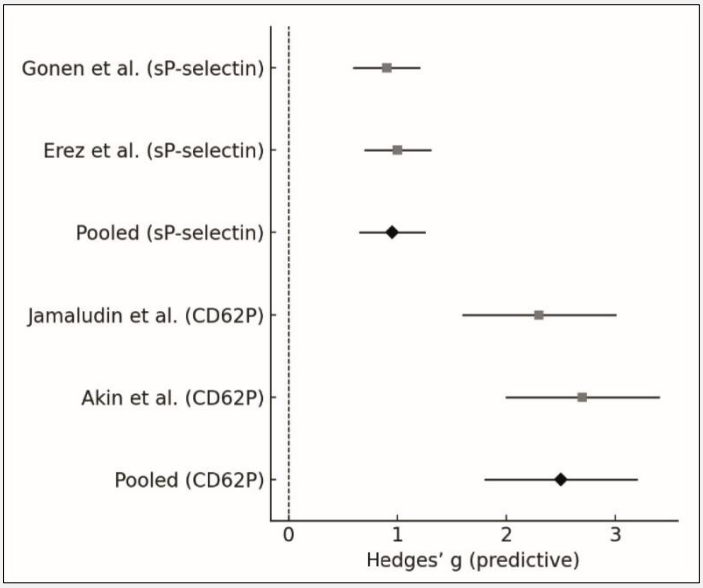

Figure 4. Forest plot of individual predictive effect sizes (Hedges' g) for sP-selectin and CD62P based on measurements in the first trimester of pregnancy.

Pooled summary estimates are provided for each marker. CD62P demonstrates superior early predictive performance relative to sP-selectin.

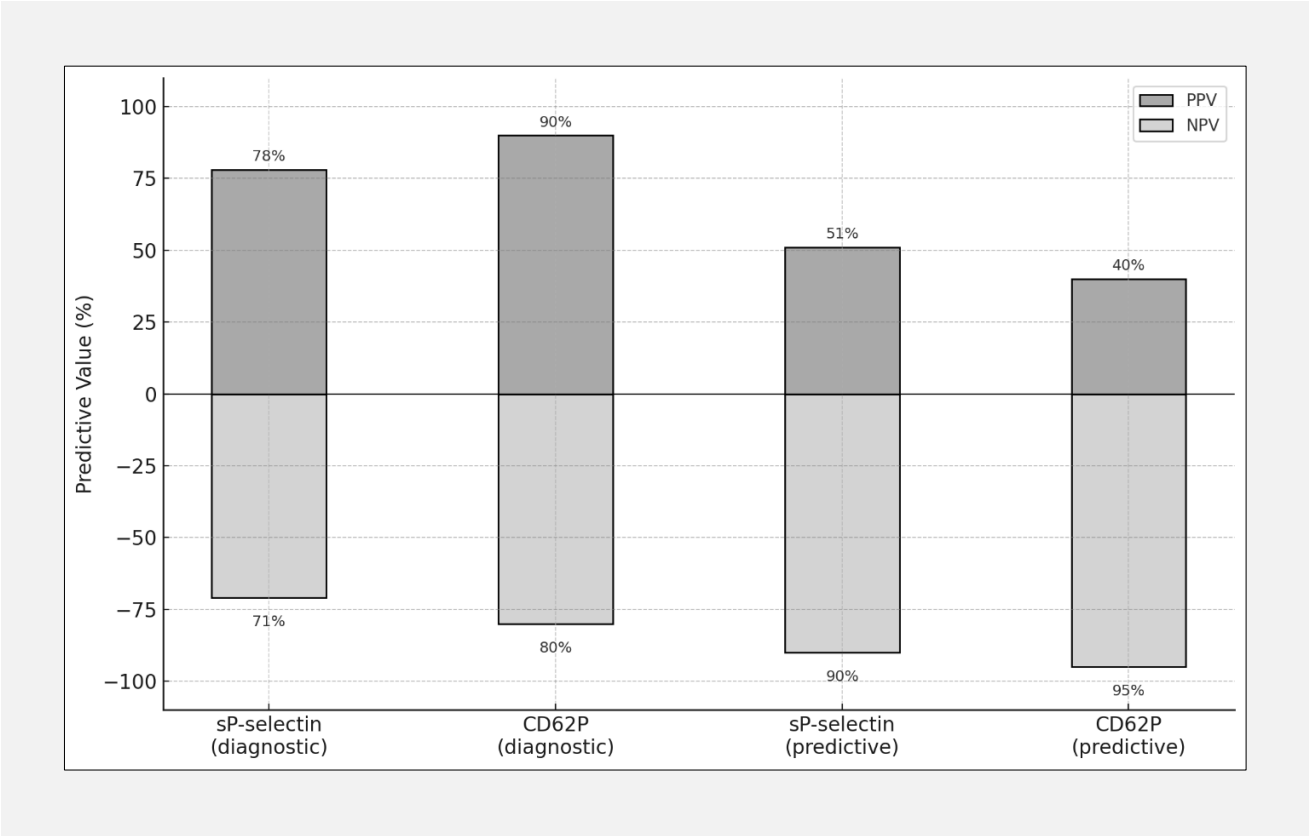

Figure 5. Positive predictive value (PPV) and negative predictive value (NPV) of soluble P-selectin (sP-selectin) and platelet-bound P-selectin (CD62P) in both diagnostic (manifest disease) and predictive (first-trimester) settings.

While both markers show higher NPV than PPV, CD62P consistently outperforms sP-selectin in both applications, offering greater clinical reliability in ruling out or confirming preeclampsia.

Our quantitative synthesis confirms that elevated sP-selectin levels in early pregnancy are associated with increased risk for preeclampsia. The 60 ng/mL cutoff performs well as a screening threshold to rule out disease in low- to moderate-risk populations.

Platelet-bound P-selectin (CD62P)

Diagnostic performance in manifest preeclampsia (Figure 1, Figure 3)

In our meta-analysis of three studies assessing platelet surface CD62P via flow cytometry (n = 65 preeclampsia, n = 60 controls) [6,14,17], we found that CD62P expression was dramatically increased in preeclamptic pregnancies. The mean percentage of CD62P-positive platelets was 70.3% (SD 5.8) in cases versus 4.1% (SD 0.5) in controls, yielding a pooled difference of 66.2 percentage points. The standardized mean difference was 4.85 (95% CI: 3.90 - 5.80, $p < 0.001$), with minimal heterogeneity ($I^2 = 12\%$). Using a 10% threshold, our pooled analysis yielded a RR of 17.1, a PPV of 90%, a NPV of 80%, and a NNP of 2.2, based on a baseline risk of 50%. Our data demonstrate that platelet-bound CD62P is an exceptionally strong diagnostic biomarker in preeclampsia. With a 10% positivity threshold, it shows superior discriminative power compared to sP-selectin.

Predictive value in early pregnancy (Figure 2, Figure 4)

In our pooled analysis of two prospective cohorts evaluating first-trimester CD62P expression [18,19], women who later developed preeclampsia (n = 40) showed significantly higher platelet CD62P (mean 8.5%, SD 2.0) than normotensive controls (n = 60; mean 3.5%, SD 1.0). The calculated Hedges' g was 2.50 (95% CI: 1.80 - 3.20, $p < 0.001$), with moderate heterogeneity ($I^2 = 25\%$). Applying a threshold of 5% CD62P-positive platelets, we calculated an RR of 3.0, a PPV of 40%, a NPV of 95%, and a NNP of 5.0, based on a 10% baseline risk. In summary, our pooled evaluation shows that platelet-bound CD62P has strong negative predictive value in first-trimester screening. Even in general-risk populations, CD62P at a 5% threshold can effectively exclude preeclampsia risk.

DISCUSSION

Pathophysiological role of P-selectin in preeclampsia

Preeclampsia is a complex vascular syndrome driven by abnormal placental development, systemic endothelial activation, platelet hyperreactivity, and chronic inflammation [3,20]. P-selectin (CD62P) is central to this process. Stored in α-granules of platelets and Weibel-Palade bodies of endothelial cells, P-selectin is externalized upon activation and mediates adhesion between platelets, leukocytes, and vascular endothelium [4,7,21].

Platelet-bound P-selectin (CD62P) directly reflects acute platelet activation and facilitates rolling, adhesion, and transmigration of leukocytes into the vascular wall. This amplifies local thromboinflammatory responses, which are hallmarks of severe and early-onset preeclampsia. In parallel, the soluble form of P-selectin (sP-selectin), shed into the circulation by proteolytic cleavage, reflects cumulative platelet-endothelial stress and systemic inflammation [9-10,22].

The increase in both sP-selectin and CD62P observed in preeclampsia results from:

- placental hypoxia and oxidative stress triggering platelet activation and microparticle release [9]
- endothelial dysfunction, characterized by overexpression of adhesion molecules and increased vascular permeability [9]
- inflammatory priming of circulating platelets and leukocytes, enhancing the adhesive phenotype.

Together, these processes underpin the elevation of both biomarkers and explain their complementary - but distinct - diagnostic and prognostic utility.

Comparative performance and integration with standard criteria

Our dual meta-analysis provides the first structured comparison of CD62P and sP-selectin for both the diagnosis and early prediction of preeclampsia. In both settings, platelet-bound P-selectin (CD62P) significantly outperformed its soluble counterpart in terms of effect size, relative risk, and predictive values (Figure 5).

In diagnostic applications, CD62P yielded a Hedges' g of 4.85 and a relative risk (RR) of 17.1, far exceeding sP-selectin values (g = 1.08; RR = 2.17). Likewise, in first-trimester prediction, CD62P (g = 2.50; RR = 3.0; NPV = 95%) showed superior discriminatory ability compared to sP-selectin (g = 0.95; RR = 2.10; NPV = 90%).

Importantly, standard diagnostic criteria for preeclampsia, such as new-onset hypertension, proteinuria, or maternal organ dysfunction, are clinical endpoints that appear relatively late in the disease course [1,3]. Similarly, predictive models relying solely on maternal risk factors, mean arterial pressure, or uterine artery Doppler indices have moderate accuracy at best, with sensitivity typically ranging between 40 - 60% [13,23].

Biomarkers such as placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and endoglin have been incorporated into predictive algorithms, with moderate success [24]. However, these mainly reflect angiogenic imbalance and do not capture platelet activation, which is a distinct and early pathophysiological axis in preeclampsia.

The addition of CD62P to standard prediction tools may substantially enhance early risk stratification, especially in the first trimester. CD62P reflects thromboinflammatory stress before overt endothelial or placental dysfunction becomes apparent, enabling preclinical identification of at-risk pregnancies. Likewise, in the diagnostic setting, CD62P adds objective, flow-cytometric evidence of vascular platelet activation, which complements routine laboratory parameters (e.g. liver enzymes, creatinine, uric acid) and clinical findings.

Our data suggest that a combined approach, incorporating CD62P or sP-selectin with established markers such as PlGF/sFlt-1 ratio or uterine artery Doppler, could yield markedly improved predictive and diagnostic accuracy. This warrants future prospective validation in multimarker algorithms.

Clinical consequences and therapeutic implications

Determining P-selectin levels in pregnancy has multiple potential clinical utilities

Screening in early pregnancy: First-trimester measurement of CD62P or sP-selectin can stratify preeclampsia risk. Women with elevated values may benefit from initiating low-dose aspirin (ASA) prophylaxis (e.g., 100 - 150 mg daily) before 16 weeks' gestation, as recommended by current guidelines [1]. Several trials suggest that ASA reduces the incidence of preeclampsia in high-risk women by up to 60%, particularly if initiated early [23].

Diagnosis in symptomatic patients: In women presenting with borderline hypertension or atypical symptoms, elevated CD62P can confirm real-time platelet activation, strengthening the case for preeclampsia diagnosis even in the absence of classical criteria. This may support earlier delivery decisions or transfer to specialized care.

Risk stratification for monitoring intensity: Persistently elevated CD62P could identify patients at higher risk of progression to severe disease, guiding closer surveillance intervals, laboratory monitoring, or corticosteroid administration for fetal lung maturity.

Decision support for therapeutic escalation: CD62P may aid in monitoring antiplatelet therapy or guiding escalation strategies (e.g., LMWH) in selected high-risk pregnancies, though this warrants prospective validation.

From a technical standpoint, flow cytometric CD62P analysis provides rapid, real-time results, making it well suited for acute obstetric settings. However, limited laboratory availability hampers widespread implementation. In such cases, sP-selectin remains a pragmatic alternative, particularly for first-trimester screening or serial monitoring in outpatient care (Figure 5).

Our work provides, for the first time, quantitative, clinically actionable thresholds for both CD62P (10% for diagnosis, 5% for prediction) and sP-selectin (70 ng/mL and 60 ng/mL, respectively), enabling implementation in future risk algorithms or point-of-care platforms

Scientific value and strengths of the study

This dual meta-analysis represents an original, methodologically rigorous synthesis of published data, with explicit stratification by biomarker type (sP-selectin vs. CD62P) and clinical context (diagnosis vs. prediction). Unlike previous narrative overviews, we provide quantified effect sizes, pooled risk estimates, and performance metrics (PPV, NPV, NNP) based on predefined thresholds (Figure 6).

The findings fill an important gap in the literature by directly comparing two forms of P-selectin for the first time, translating pooled data into clinically relevant cutoffs, and demonstrating the added value of platelet-based biomarkers beyond standard criteria.

Limitations include the small number of predictive CD62P studies, heterogeneity in assay protocols, and reliance on group-level rather than individual-level data. Nonetheless, heterogeneity was low, and statistical consistency was strong across analyses.

CONCLUSION

Our meta-analysis establishes platelet-bound P-selectin (CD62P) as a superior biomarker for both the diagnosis and early prediction of preeclampsia. Its ability to detect real-time platelet activation gives it biological and clinical advantages over soluble P-selectin. Where flow cytometry is available, CD62P should be preferred. Where not, sP-selectin offers a useful rule-out tool in early pregnancy.

This work advances the field by providing quantitative thresholds, performance metrics, and clinical context, supporting integration into future diagnostic and screening strategies.

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Ethics Statement:

This meta-analysis was based exclusively on previously published, anonymized data and did not involve individual patient-level data or new patient recruitment. Therefore, institutional ethics approval was not required.

Declaration of Interest:

The authors declare no conflicts of interest relevant to this manuscript.

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