Am J Transl Res 2025;17(7):5036-5044
www.ajtr.org /ISSN:1943-8141/AJTR0160660

*Original Article*

# Association of D-dimer, platelet-activating factor, and soluble vascular endothelial growth factor receptor 1 levels with disease severity and prognosis in gestational hypertension

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Received September 22, 2024; Accepted June 9, 2025; Epub July 15, 2025; Published July 30, 2025

**Abstract:** Objective: To investigate the associations of D-dimer (D-D), platelet-activating factor (PAF), and soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels with disease severity and prognosis in hypertensive disorders complicating pregnancy (HDCP). Methods: A total of 138 HDCP patients were categorized as the gestational hypertension (GH, n = 62), preeclampsia (PE, n = 45), and severe preeclampsia (SPE, n = 31) groups. Fifty healthy pregnant women served as controls. Plasma D-D and serum PAF and sVEGFR-1 levels were measured and compared. ROC curves assessed their diagnostic and prognostic value. Based on neonatal Apgar score <7 or grade III amniotic fluid contamination, patients were divided into good (n = 73) and poor (n = 65) prognosis groups. Results: D-D, PAF, and sVEGFR-1 levels increased with disease severity (all P<0.05). The AUCs for diagnosing HDCP severity were 0.893 (D-D), 0.889 (PAF), 0.825 (sVEGFR-1), and 0.944 (combined). Multivariate logistic regression identified D-D, PAF, sVEGFR-1, and 24h RPO as independent prognostic factors (all P<0.05). Combined AUC for prognosis prediction was 0.883. Conclusion: Elevated D-D, PAF, and sVEGFR-1 levels are closely associated with HDCP severity and prognosis, offering high diagnostic and predictive value.

**Keywords:** Hypertensive disorders of pregnancy, D-dimer, platelet-activating factor, human soluble vascular endothelial growth factor receptor 1, disease condition, prognosis

## Introduction

Hypertensive disorders complicating pregnancy (HDCP) are multisystem syndromes unique to pregnancy and represent a leading cause of maternal and perinatal mortality worldwide [1]. According to the World Health Organization, the incidence of HDCP has been rising annually. In developing countries, HDCP accounts for up to 16% of maternal deaths, posing a significant public health challenge that endangers both maternal and neonatal health [2]. Clinically, HDCP is characterized by new-onset hypertension, proteinuria, and multi-organ dysfunction after 20 weeks of gestation. However, its pathogenesis remains incompletely understood. Current evidence suggests that HDCP involves multiple mechanisms, including vascular endothelial injury, oxidative stress, inflammatory cytokine release, and placental ischemia-hypoxia. In particular, small artery spasms, hemodynamic disturbances, and imbalance in the coagulation-fibrinolysis system contribute to impaired maternal organ perfusion and placental dysfunction [3-5].

Approximately 30% of HDCP cases progress to severe forms such as preeclampsia or eclampsia, often leading to serious complications including HELLP syndrome and placental abruption. These conditions are associated with perinatal mortality rates 5-8 times higher than in normotensive pregnancies [6, 7], highlighting the urgent need for early identification of high-risk patients and timely intervention.

Recent advances in molecular biology have spurred interest in identifying biomarkers that reflect HDCP pathophysiology and prognosis. D-dimer (D-D), a fibrin degradation product,

https://doi.org/10.62347/WGEX7482

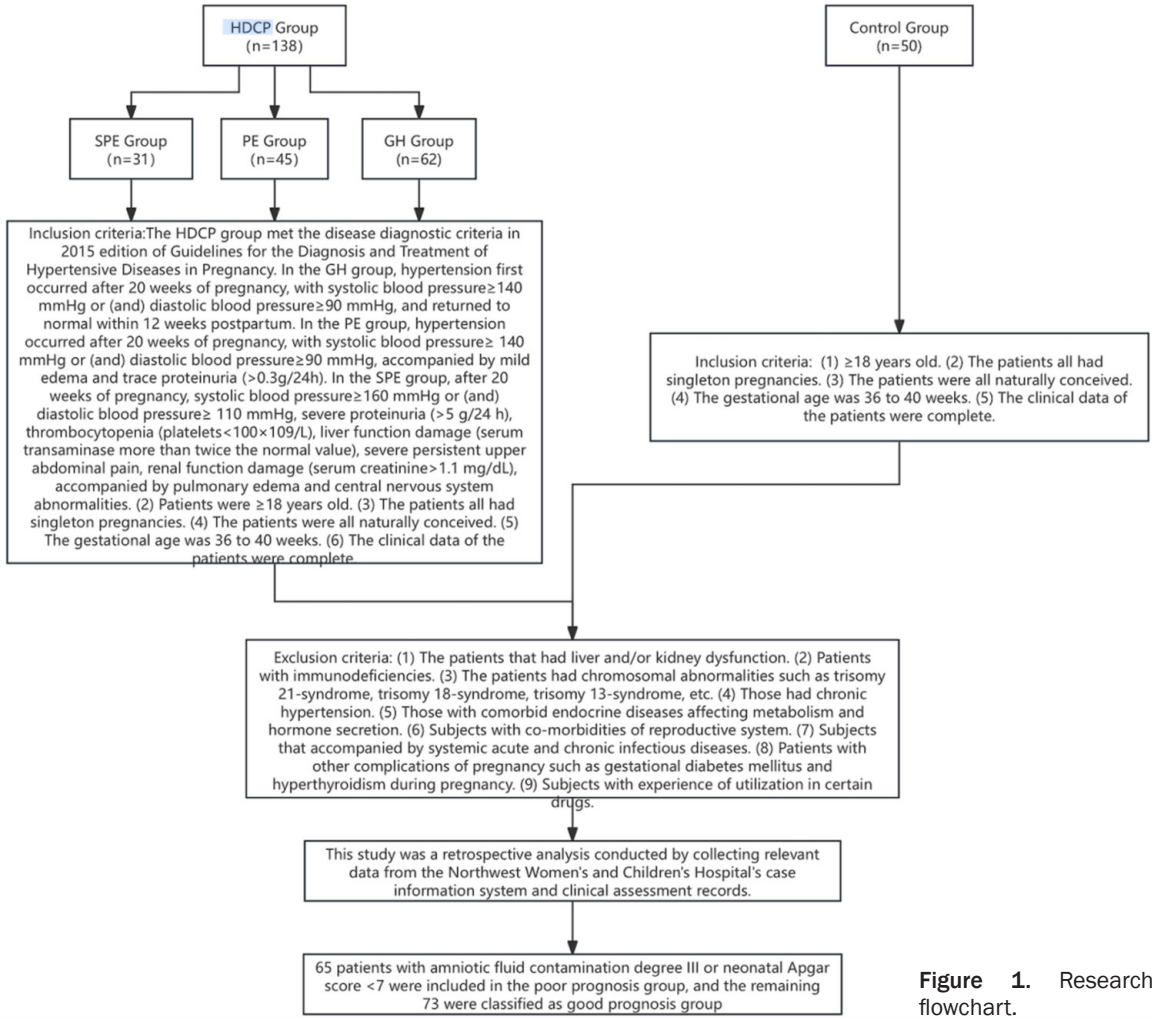


**Figure 1.** Research flowchart.

is associated with hyperfibrinolysis, placental microthrombosis, and defective spiral artery remodeling [8]. Platelet-activating factor (PAF), a potent procoagulant mediator, promotes vasoconstriction, increased vascular permeability, and trophoblast apoptosis, contributing to placental ischemia-reperfusion injury [9]. Soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), an anti-angiogenic factor, antagonizes VEGF and placental growth factor (PlGF) activity, impairs placental vascular development, and reduces uteroplacental perfusion [10].

This study innovatively investigates the combined detection of D-D, PAF, and sVEGFR-1, representing coagulation dysfunction, platelet activation, and angiogenic imbalance, respectively. By analyzing expression levels across HDCP severity groups, we explore the molecular interplay underlying disease progression and assess the utility of these markers for early risk stratification, organ damage evaluation, and outcome prediction. These findings provide new insight into the pathophysiological interaction of HDCP and offer a foundation for individualized monitoring and targeted therapy to improve maternal and fetal outcomes. The research flowchart is shown in **Figure 1**.

## Patients and methods

### *Patient selection*

A total of 138 patients diagnosed with HDCP admitted to Northwest Women's and Children's Hospital between April 2020 and April 2023 were included in this retrospective study. Ethical approval was obtained from the ethics committee of Northwest Women's and Children's Hospital. Based on disease severity,

patients were categorized into three subgroups: 31 with severe preeclampsia (SPE), 45 with preeclampsia (PE), and 62 with gestational hypertension (GH). An additional 50 healthy pregnant women admitted during the same period served as the control group.

Diagnostic criteria were as follows [11]: GH group: Hypertension onset after 20 weeks of gestation (systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg), resolving within 12 weeks postpartum. PE group: Hypertension as above, accompanied by mild edema and proteinuria >0.3 g/24 h. SPE group: SBP ≥160 mmHg and/or DBP ≥110 mmHg, with ≥5 g/24 h proteinuria, thrombocytopenia (platelets $<100\times10^9$/L), elevated liver enzymes (>2× normal), renal dysfunction (serum creatinine >1.1 mg/dL), persistent upper abdominal pain, pulmonary edema, or central nervous system involvement.

Inclusion criteria: (1) Diagnosis met the 2015 Guidelines for the Diagnosis and Treatment of Hypertensive Disorders in Pregnancy [12]; (2) Age ≥ 18 years; (3) Singleton pregnancy; (4) Natural conception; (5) Gestational age between 36 and 40 weeks; (6) Complete clinical data.

Exclusion criteria: (1) Liver or kidney dysfunction; (2) immunodeficiency; (3) fetal chromosomal abnormalities (e.g., trisomy 21/18/13); (4) chronic hypertension; (5) endocrine/metabolic disorders, reproductive system diseases, or systemic infections; (6) pregnancy complications (e.g., gestational diabetes, hyperthyroidism); (7) use of specific medications.

*Sample collection*

On the morning after admission, 5 mL of fasting venous blood was collected from each subject, divided into two anticoagulated tubes for plasma and serum separation. D-D levels were measured using an automated coagulation analyzer (Sysmex, Japan), with assay kits from Beijing Zhongsuijinqiao Biotech Co., Ltd. Serum PAF and sVEGFR-1 levels were measured using ELISA kits from the same supplier. Data were recorded including age, pre-pregnancy body weight, gestational weeks, parity, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, serum creatinine, albumin, systolic blood pressure, diastolic blood pressure, and 24-hour proteinuria (24h PRO).

*Data extraction*

The study extracted data from the hospital's medical records, including age, pre-pregnancy body mass index (BMI), gestational age, duration of gestation, and systolic/diastolic blood pressure.

*Outcome measures*

Patients were classified into poor prognosis (n=65) and good prognosis (n=73) groups based on amniotic fluid contamination (grade III) and neonatal Apgar score <7 [13].

*Statistical analysis*

The sample size was calculated based on a case-control study design using G*Power 3.1 software for an independent-samples t-test. Parameters were set for a two-tailed test with $\alpha = 0.05$ and power $(1-\beta) = 0.80$. Based on previous studies on hypertensive disorders in pregnancy, a medium effect size (Cohen's $d = 0.5$) was assumed for the intergroup difference in D-D levels [13]. The estimated minimum sample size was 128 participants. Considering the actual conditions of the hospital, a total of 188 subjects were ultimately enrolled.

Statistical analysis was performed using SPSS version 27.0. Continuous variables were tested for normality and expressed as mean ± standard deviation. For comparisons among three or more groups, one-way analysis of variance (ANOVA) was used, and the LSD-t post hoc test was adopted. For comparisons between two groups, independent-samples t-tests were applied. Categorical variables were expressed as frequencies and percentages; comparisons among multiple groups were conducted using the chi-square ($\chi^2$) test or Fisher's exact test as appropriate. A two-sided *P*-value <0.05 was considered significant.

## Results

*Comparison of clinical data*

No statistically significant differences were observed in age, pre-pregnancy BMI, gestational age, or parity among the groups (all P>0.05).

**Table 1.** Comparison of clinical data between groups ($\bar{x}\pm s$)

| Clinical data | Control Group (n = 50) | GH Group (n = 62) | PE Group (n = 45) | SPE Group (n = 31) | F | *P* |
|---|---|---|---|---|---|---|
| Age (years old, $\bar{x}\pm s$) | 30.24±3.15 | 29.64±3.74 | 30.51±2.98 | 30.10±3.97 | 0.602 | 0.603 |
| Prepregnancy body weight (kg, $\bar{x}\pm s$) | 58.06±7.04 | 59.09±6.97 | 58.30±7.42 | 59.62±8.93 | 0.377 | 0.770 |
| Gestational weeks (weeks, $\bar{x}\pm s$) | 38.78±2.01 | 38.41±2.71 | 38.36±2.94 | 38.01±2.16 | 1.308 | 0.273 |
| Number of births | | | | | | |
| Primigravida | 36 | 40 | 26 | 21 | 2.215 | 0.529 |
| Multipara | 14 | 22 | 19 | 10 | | |
| Systolic pressure (mmHg, $\bar{x}\pm s$) | 116.31±12.06 | 149.36±12.10 | 157.30±12.91 | 164.50±16.40 | 119.088 | <0.001 |
| Diastolic pressure (mmHg, $\bar{x}\pm s$) | 75.60±7.99 | 93.06±6.49 | 101.64±8.33 | 106.10±7.35 | 140.611 | <0.001 |

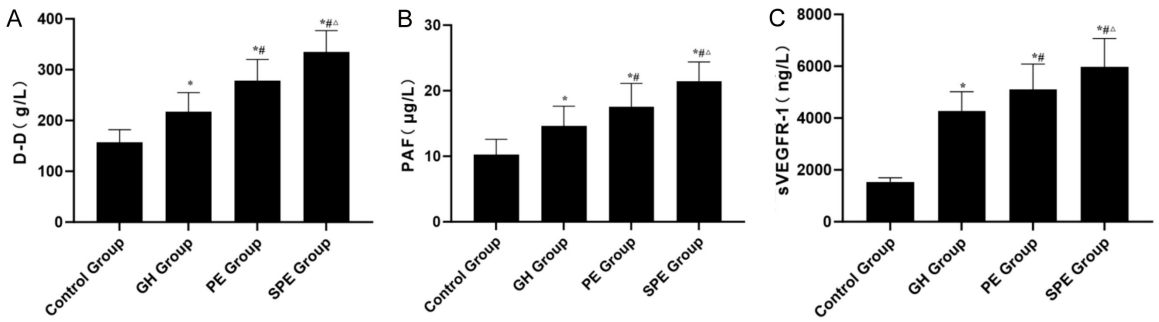


**Figure 2.** Comparison of plasma D-D, PAF, and sVEGFR-1 levels Note: A: D-D; B: PAF; C: sVEGFR-1. Compared to control group, *P<0.05; compared to GH group, #P<0.05; compared to PE group, △P<0.05. D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

However, significant differences were found in both SBP and DBP (both P<0.05), as shown in **Table 1**.

*Comparison of D-D, PAF and VEGFR-1 levels*

D-D, PAF and VEGFR-1 levels in the GH, PE, and SPE groups were significantly higher than those of the control group (all P<0.05). Among the three HDCP subgroups, D-D, PAF and VEGFR-1 levels were higher in the PE and SPE groups compared to the GH group (all P<0.05), with the highest levels observed in the SPE group (all P<0.05). See **Figure 2**.

*ROC curve analysis of biomarkers in assessing disease severity*

ROC curve analysis revealed that the areas under the curve (AUCs) for D-D, PAF, and sVEGFR-1 in evaluating disease severity were 0.893, 0.889, and 0.825, respectively. When combined, the AUC increased to 0.944, indicating excellent diagnostic performance (**Figure 3A**; **Table 2**).

*ROC curve analysis for prognostic prediction*

The predictive value of D-D, PAF, and sVEGFR-1 levels for HDCP prognosis was evaluated by ROC analysis. The AUCs were 0.701, 0.767, and 0.703, respectively, while the combined model achieved an AUC of 0.883, indicating superior predictive power (**Figure 3B**; **Table 3**).

*Comparison of prognostic indicators in HDCP patients*

We compared indicators between the good and poor prognosis groups among HDCP patients. There were no significant differences in age, pre-pregnancy BMI, gestational age, delivery time, TG, TC, HDL-C, LDL-C, hemoglobin, serum creatinine, or albumin (all P>0.05). However, DBP, 24h PRO, D-D, PAF, and sVEGFR-1 levels differed significantly between the two groups (all P<0.05), as detailed in **Table 4**.

*Multivariate logistic regression analysis*

Multivariate logistic regression identified 24h PRO, PAF, sVEGFR-1, D-D, SBP, and DBP as

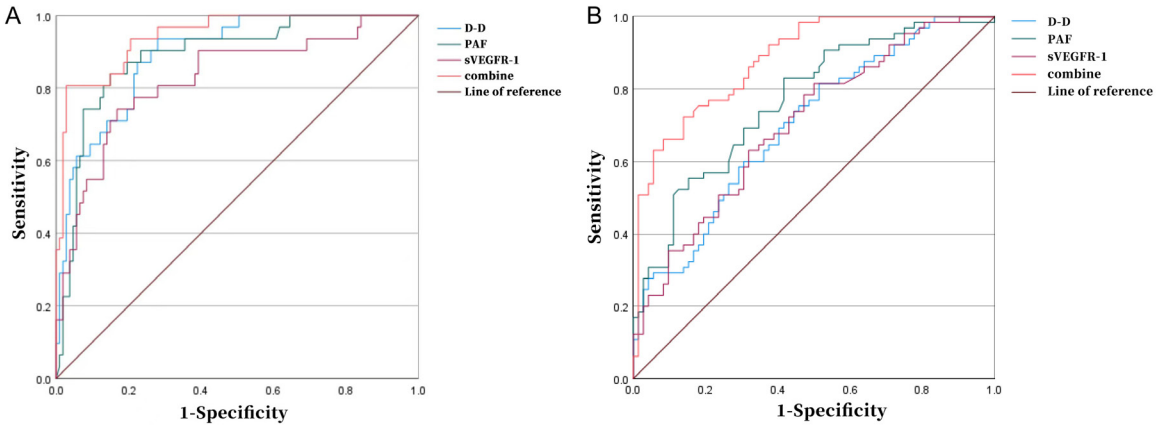


**Figure 3.** ROC curve. Note: A: ROC curveanalysis of the evaluation value of D-D, PAF, and sVEGFR-1 levels on the severity of HDCP; B: ROC curve analysis of the predictive value of D-D, PAF and sVEGFR-1 levels in HDCP gravidas. D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

**Table 2.** ROC curve parameters of the evaluation value of D-D, PAF, and sVEGFR-1 levels on the severity of HDCP

| Index | AUC | Truncation value | Sensitivity | Specificity | *P* | 95% CI |
|---|---|---|---|---|---|---|
| D-D | 0.893 | 265.33 g/L | 93.50 | 72.00 | <0.001 | 0.835~0.950 |
| PAF | 0.889 | 18.55 μg/L | 83.90 | 85.00 | <0.001 | 0.824~0.954 |
| sVEGFR-1 | 0.825 | 5542.465 ng/L | 74.20 | 83.20 | <0.001 | 0.736~0.914 |
| Combine | 0.944 | - | 80.60 | 97.20 | <0.001 | 0.903~0.985 |

Note: D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

**Table 3.** ROC curve parameters of D-D, PAF, and sVEGFR-1 levels for predicting the prognosis of HDCP gravidas

| Indicator | AUROC | Cut-off | Sensitivity | Specificity | *P* | 95% CI |
|---|---|---|---|---|---|---|
| D-D | 0.701 | 264.845 | 81.50 | 48.60 | <0.001 | 0.615~0.787 |
| PAF | 0.767 | 16.01 | 83.10 | 58.30 | <0.001 | 0.689~0.846 |
| sVEGFR-1 | 0.703 | 4909.975 | 81.50 | 50.00 | <0.001 | 0.617~0.789 |
| Combination of above indicators | 0.883 | - | 72.30 | 96.10 | <0.001 | 0.829~0.937 |

Note: D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

independent predictors of poor prognosis in HDCP (all P<0.05), as presented in **Table 5**.

*Nomogram model construction*

Based on the multivariate regression results, a nomogram model was constructed to predict HDCP prognosis, as shown in **Figure 4**.

## Discussion

HDCP is a set of serious conditions that pose significant threats to maternal and fetal health. Due to the unclear pathogenesis, effective preventive and therapeutic strategies remain lacking [13]. Mild cases may present with edema, hypertension, proteinuria, blurred vision, and headache, while severe cases can cause dysfunction of vital organs such as the heart, liver, and kidneys. Increasing evidence suggests that platelet activation plays a pivotal role in the onset and progression of HDCP [14, 15].

Pathologically, systemic smallartery spasms induce vascular endothelial injury and disturb the balance between coagulation and fibrinolysis systems, leading to a hypercoagulable state. This contributes to abnormal changes in coagulation-related biomarkers and increases the risk of thrombosis, thereby endangering both maternal and neonatal outcomes [16-18].

**Table 4.** Comparison of indicators with different prognoses of HDCP

| Indicator | Good prognosis group (n = 73) | Poor prognosis group (n = 65) | t/$X^2$ | P |
|---|---|---|---|---|
| Age (years, $\bar{x}$±s) | 29.82±3.55 | 30.25±3.59 | 0.701 | 0.481 |
| Pre-pregnancy body mass (kg, $\bar{x}$±s) | 58.04±8.14 | 59.98±6.75 | 1.510 | 0.133 |
| Gestational weeks (weeks, $\bar{x}$±s) | 38.24±2.80 | 37.90±2.64 | 0.725 | 0.470 |
| Number of births | | | | |
| Primigravida | 45 | 42 | 0.130 | 0.718 |
| Multipara | 28 | 23 | | |
| Systolic blood pressure (mmHg, $\bar{x}$±s) | 154.23±15.12 | 156.61±14.04 | 0.952 | 0.343 |
| Diastolic blood pressure (mmHg, $\bar{x}$±s) | 97.27±8.74 | 100.48±9.23 | 2.095 | 0.038 |
| TG (mmol/L, $\bar{x}$±s) | 1.58±0.43 | 1.63±0.39 | 0.712 | 0.478 |
| TC (mmol/L, $\bar{x}$±s) | 4.41±1.22 | 4.60±1.27 | 0.896 | 0.372 |
| HDL-C (mmol/L, $\bar{x}$±s) | 1.05±0.26 | 1.09±0.29 | 0.854 | 0.394 |
| LDL-C (mmol/L, $\bar{x}$±s) | 3.26±0.78 | 3.39±0.81 | 0.960 | 0.339 |
| Hemoglobin (g/L, $\bar{x}$±s) | 117.34±25.62 | 120.31±27.40 | 0.658 | 0.512 |
| Serum creatinine (μmol/L, $\bar{x}$±s) | 59.32±14.29 | 60.12±15.03 | 0.320 | 0.749 |
| Albumin (g/L, $\bar{x}$±s) | 37.95±7.34 | 38.47±6.93 | 0.427 | 0.670 |
| 24h PRO (g/24 h, $\bar{x}$±s) | 0.97±0.21 | 1.21±0.31 | 5.374 | <0.001 |
| D-D (g/L) | 241.06±53.33 | 285.28±57.74 | 4.676 | <0.001 |
| PAF (μg/L) | 15.33±3.48 | 19.13±3.92 | 6.024 | <0.001 |
| sVEGFR-1 (ng/L) | 4726.16±1086.95 | 5153.98±1131.94 | 2.263 | 0.025 |

Note: TG: Triglyceride; TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; 24h PRO: 24-Hour Urinary Protein; D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

**Table 5.** Multifactorial logistic regression analysis affecting prognosis of those with HDCP

| Factor | b | S.E | $X^2$ | P | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|---|
| 24h PRO | 1.773 | 0.516 | 11.806 | 0.001 | 5.888 | 2.142 | 16.189 |
| PAF | 1.642 | 0.567 | 8.386 | 0.004 | 5.165 | 1.700 | 15.695 |
| sVEGFR-1 | 1.492 | 0.612 | 5.943 | 0.015 | 4.446 | 1.340 | 14.754 |
| D-D | 1.487 | 0.634 | 5.501 | 0.019 | 4.424 | 1.277 | 15.327 |
| Diastolic blood pressure | 1.198 | 0.754 | 2.524 | 0.112 | 3.313 | 0.756 | 14.525 |

Note: 24h PRO: 24-Hour Urinary Protein; D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

D-D, a specific marker of secondary fibrinolysis, reflects both hypercoagulability, and hyperfibrinolysis. Its elevated levels are strongly associated with the coagulation status in HDCP patients [19, 20]. In this study, plasma D-D levels were significantly higher in the GH, PE, and SPE groups than in the control group and increased progressively with disease severity. These findings are consistent with prior studies [21, 22], supporting the notion that D-D is a sensitive marker for hemocoagulation abnormalities and thrombotic tendency in HDCP.

PAF, produced by vascular endothelial cells, is a potent platelet aggregator and inflammatory mediator. It is involved in the pathogenesis of thrombosis and vascular inflammation and may affect cardiac function [23-25]. PAF is also linked to endothelial damage and blood pressure regulation. It has thus been hypothesized to contribute to the development and progression of HDCP [25-28]. Our results showed significantly elevated PAF levels across all HDCP subgroups, with higher levels corresponding to greater disease severity, indicating its involvement in the prothrombotic state of HDCP.

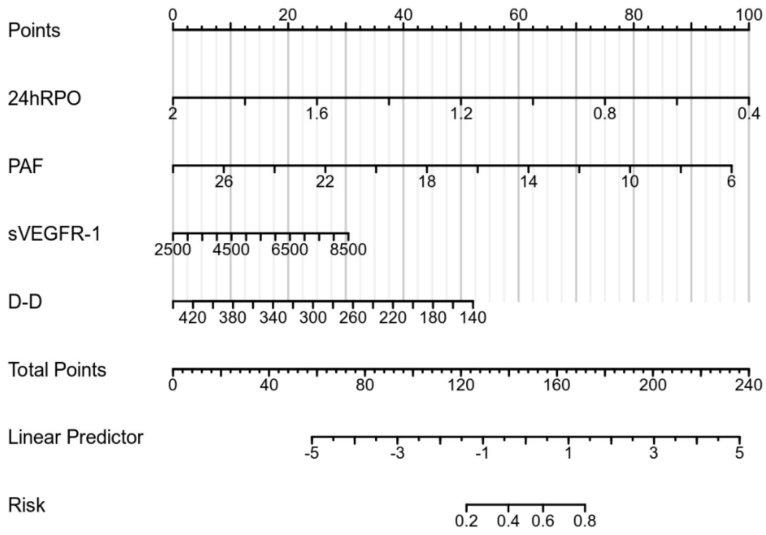


**Figure 4.** Construction of nomogram model. Note: D-D: D-dimer; PAF: platelet-activating factor; sVEGFR-1: soluble vascular endothelial growth factor receptor 1.

The placenta produces several angiogenic factors, including VEGF and placental growth factor. Vascular endothelial injury and impaired trophoblast function can hinder normal vascular remodeling, resulting in narrowed small arteries, reduced placental perfusion, and hypoxia within the chorionic villi [29-31]. This hypoxic environment stimulates VEGF-related pathways and promotes sVEGFR-1 overexpression [32, 33].

Our findings revealed progressively increased sVEGFR-1 levels from GH to SPE, supporting its association with disease progression and placental dysfunction.

Additionally, this study explored the prognostic implications of these biomarkers. Univariate and multivariate logistic regression analyses identified elevated levels of D-D, PAF, and sVEGFR-1 as independent predictors of poor prognosis. ROC curve analysis further confirmed that the combined use of these three markers yields high predictive value for HDCP prognosis.

However, because this was a single-center retrospective analysis including small sample size, the research results may have biases. In future studies, we will further expand the sample size and adopt a multi-center prospective study analysis to obtain more reliable research data.

In summary, levels of D-D, PAF, and sVEGFR-1 are significantly elevated in HDCP and are closely associated with disease severity and prognosis. These biomarkers may serve as valuable tools for risk stratification, monitoring, and clinical decision-making in patients with hypertensive disorders complicaitng pregnancy.

## Disclosure of conflict of interest

None.

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