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Original Article

Analysis of serological risk factors for preeclampsia and the predictive role of high homocysteine levels

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Abstract: Objectives: To investigate the serological risk factors for preeclampsia, focusing on homocysteine level and its predictive role in the condition. Methods: A retrospective analysis was conducted on 242 pregnant women (121 preeclampsia cases and 121 healthy controls) admitted from January 2022 to June 2023. Serological markers, including homocysteine, fasting blood glucose (FBG), triglycerides (TG), and inflammatory indicators, were compared between the two groups. Statistical analyses, including multivariate logistic regression and receiver operating characteristic (ROC) analysis, were performed to identify significant predictors. Results: Elevated homocysteine levels were strongly associated with preeclampsia, showing a high area under the curve (AUC) of 0.978 in ROC analysis, with a sensitivity of 93.4% and a specificity of 95.0% at a 9.230 μmol/L threshold. TG and FBG were also associated with increased preeclampsia risk, though the latter's significance diminished in multivariate analysis. In terms of inflammatory markers, Interleukin-6 (IL-6) levels were elevated, whereas C-reactive protein (CRP) levels were unexpectedly lower in preeclampsia cases. Lower Vitamin C level was correlated with the presence of preeclampsia. Conclusion: Elevated homocysteine level was a significant predictor of preeclampsia, alongside dyslipidemia and altered inflammatory responses.

Keywords: Preeclampsia, homocysteine, biomarkers, hypertension, inflammation, pregnancy

Introduction

Preeclampsia, a complex hypertensive disorder in pregnancy characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, remains a leading cause of maternal and perinatal morbidity and mortality globally [1, 2]. Despite substantial research efforts, its pathophysiological mechanisms remain incompletely understood, leaving a significant knowledge gap in effective prevention and management strategies [3]. This has fueled an ongoing quest to identify reliable serological markers that could facilitate early prediction and intervention [4].

Over the years, numerous potential biomarkers have been evaluated in the context of preeclampsia, such as placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and endoglin [5, 6]. However, the clinical utility of these markers remains limited due to variable sensitivity and specificity [7]. More recently, elevated homocysteine levels have attracted attention as a possible contributor to the development of preeclampsia [8]. Homocysteine, a sulfur-containing amino acid, is an intermediary product formed during the conversion of methionine to cysteine [9]. Hyperhomocysteinemia is a known factor associated with endothelial dysfunction, oxidative stress, and coagulation abnormalities, which are hallmarks of the preeclamptic state [10].

The association between hyperhomocysteinemia and preeclampsia has been suggested in several studies, but the findings have been inconsistent, potentially due to differences in study design, population characteristics, and diagnostic criteria for preeclampsia [11, 12]. Despite these inconsistencies, it has been hypothesized that elevated homocysteine may contribute to abnormal placental vasculature development and reduced perfusion, central

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events in the pathogenesis of preeclampsia [13].

Furthermore, the impact of genetic and nutritional factors on homocysteine metabolism must be considered [14]. Polymorphisms in genes encoding enzymes such as methylenetetrahydrofolate reductase (MTHFR) can lead to aberrant homocysteine levels [15].

Given these complexities and the systemic nature of preeclampsia, it is crucial to analyze serological factors within a broader context that accounts for genetic predispositions, nutritional status, and other risk modifiers. A comprehensive analysis that considers these components will enhance our understanding of the disease and refine strategies for risk stratification and intervention. This study aims to elucidate the relationship between high homocysteine levels and the development of preeclampsia through a multifactorial approach.

Materials and methods

Case selection

A retrospective analysis was conducted on 242 pregnant women either hospitalized or who underwent health check-ups at our hospital between January 2022 and June 2023. Among them, 121 patients with a diagnosis of preeclampsia were categorized into the "Preeclampsia Group", while the resting 121 healthy pregnant women were included in the "Non-Preeclampsia Group". This study was approved by the Ethics Committee of the International Peace Maternal and Child Health Hospital Affiliated to Shanghai Jiao Tong University, China (GKLW2017-102).

Inclusion criteria: ① Aged 18 years or older; ② Singleton pregnancy; ③ Complete medical records, including prenatal care documents.

Exclusion criteria: ① Severe pregnancy-related complications such as placental abruption, preterm birth, or intrauterine growth restriction; ② History of failed Down syndrome screening or refusal to undergo screening; ③ Chronic diseases that could affect serological indicators, including but not limited to chronic kidney disease, diabetes, cardiovascular disease, liver disease, and autoimmune diseases; ④ Active infections during pregnancy or within the first three months; ⑤ Use of medications known to affect serological indices in the year prior to pregnancy, such as corticosteroids, chemotherapy, radiotherapy, or immunosuppressants; ⑥ History of threatened abortion or major fetal abnormalities detected during routine prenatal ultrasounds; ⑦ Participation in another clinical trial involving drug interventions.

Data collection

Data was collected for both groups via the medical record system, including demographic details, blood test results, and indicators for monitoring maternal and fetal health, along with vitamin and inflammatory levels. Demographic data was collected upon admission, whereas all other test results were obtained during the mid-trimester of pregnancy.

Outcome measurements

During the mid-trimester of pregnancy, fasting venous blood samples (10 mL) were collected from these women in the morning. Hemoglobin (Hb), neutrophil, and lymphocyte levels were analyzed using an automated hematology analyzer (BC-6900, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China) from a portion of the whole blood sample. The remaining samples were centrifuged at 3500 r/min for 10 minutes with a low-temperature (TLD 12A, Hunan Xiangxi Scientific Instrument Factory, China), and the separated serum was then stored at -80°C for further analysis.

Subsequently, levels of albumin, fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), C-reactive protein (CRP), homocysteine (Hcy), and vitamin C were measured using a biochemical analyzer (BS-860, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). Additionally, pregnancy-associated plasma protein-A (PAPP-A), sFlt-1, PlGF, and 25-hydroxyvitamin D levels were determined using a chemiluminescent immunoassay analyzer (Architect i2000SR, Abbott Laboratories, USA). The multiple of median (MoM) for PAPP-A and the sFlt-1/PLGF ratio were also calculated. Finally, levels of vitamins A and E were assessed using high-performance liquid chromatography (1260 Infinity II, Agilent Technologies, Inc., USA).

Statistical methods

The data were analyzed using SPSS statistical software version 29.0 (SPSS Inc., Chicago, IL,

Table 1. Comparison of demographic characteristics between the preeclampsia and non-preeclampsia groups

Parameters	Non-preeclampsia Group (n = 121)	Preeclampsia Group (n = 121)	t/χ^2	P
Age (years)	28.25 ± 3.37	28.36 ± 3.51	0.257	0.797
BMI (kg/m^2)	25.42 ± 1.56	25.74 ± 1.62	1.605	0.110
Ethnicity (Han/Other) [n (%)]	117 (96.69%)/4 (3.31%)	114 (94.21%)/7 (5.79%)	0.857	0.355
Smoking status [n (%)]			0.213	0.899
Never smoker	95 (78.51%)	92 (76.03%)		
Smoked prior to pregnancy	16 (13.22%)	18 (14.88%)		
Current smoker	10 (8.26%)	11 (9.09%)		
Gestational diabetes mellitus [n (%)]	8 (6.61%)	10 (8.26%)	0.240	0.624
Gestational hypertension [n (%)]	1 (0.83%)	5 (4.13%)	1.538	0.215
Maternal education (years)	12.62 ± 2.22	12.19 ± 2.34	1.448	0.149
Primipara [n (%)]	106 (87.6%)	104 (85.95%)	0.144	0.704
Abortion history [n (%)]	29 (23.97%)	32 (26.45%)	0.197	0.657

BMI: Body Mass Index.

Table 2. Comparison of inflammatory markers between the preeclampsia and non-preeclampsia groups

Parameters	Non-preeclampsia Group (n = 121)	Preeclampsia Group (n = 121)	t	P
IL-6 (pg/ml)	9.54 ± 1.54	10.02 ± 1.94	2.160	0.032
CRP (mg/L)	10.53 ± 2.32	9.67 ± 1.96	3.124	0.002
Neutrophil (10^9/L)	7.84 ± 2.17	8.23 ± 2.83	1.210	0.228
Lymphocyte (10^9/L)	2.25 ± 1.07	2.41 ± 0.94	1.221	0.223

IL-6: Interleukin-6; CRP: C-reactive Protein.

USA). Categorical variables were presented as frequencies and percentages [n (%)] and compared using chi-square tests. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Variables that followed a normal distribution were reported as means ± standard deviations (M ± SD), while those that did not conform to a normal distribution were presented as medians with interquartile ranges (IQR). A *p*-value of less than 0.05 was considered indicative of statistical significance.

For correlation analysis, Pearson's method was used for normally distributed continuous variables, whereas Spearman's rank correlation was applied to non-parametric or categorical data. Further analyses included univariate and multivariate analyses, as well as receiver operating characteristic (ROC) analysis, specifically targeting serological factors associated with preeclampsia. These comprehensive analyses aimed to identify significant predictors and evaluate their performance in diagnosing preeclampsia. This approach ensures thorough and accurate evaluation of the data, providing robust insights into the serological risk factors for preeclampsia.

Results

Basic data

Demographic characteristics such as age, body mass index (BMI), ethnicity, smoking status, maternal education level, parity, and history of abortion were comparable between the non-preeclampsia and preeclampsia groups ($P > 0.05$, **Table 1**).

Blood proteins, blood glucose, and lipids

No significant differences were found in hemoglobin or albumin levels between the groups. However, FBG and TG were significantly higher in the preeclampsia group compared to the non-preeclampsia group (both $P < 0.05$). TC levels did not differ significantly between the groups. Detailed data are presented in **Table 2** and **Figure 1**.

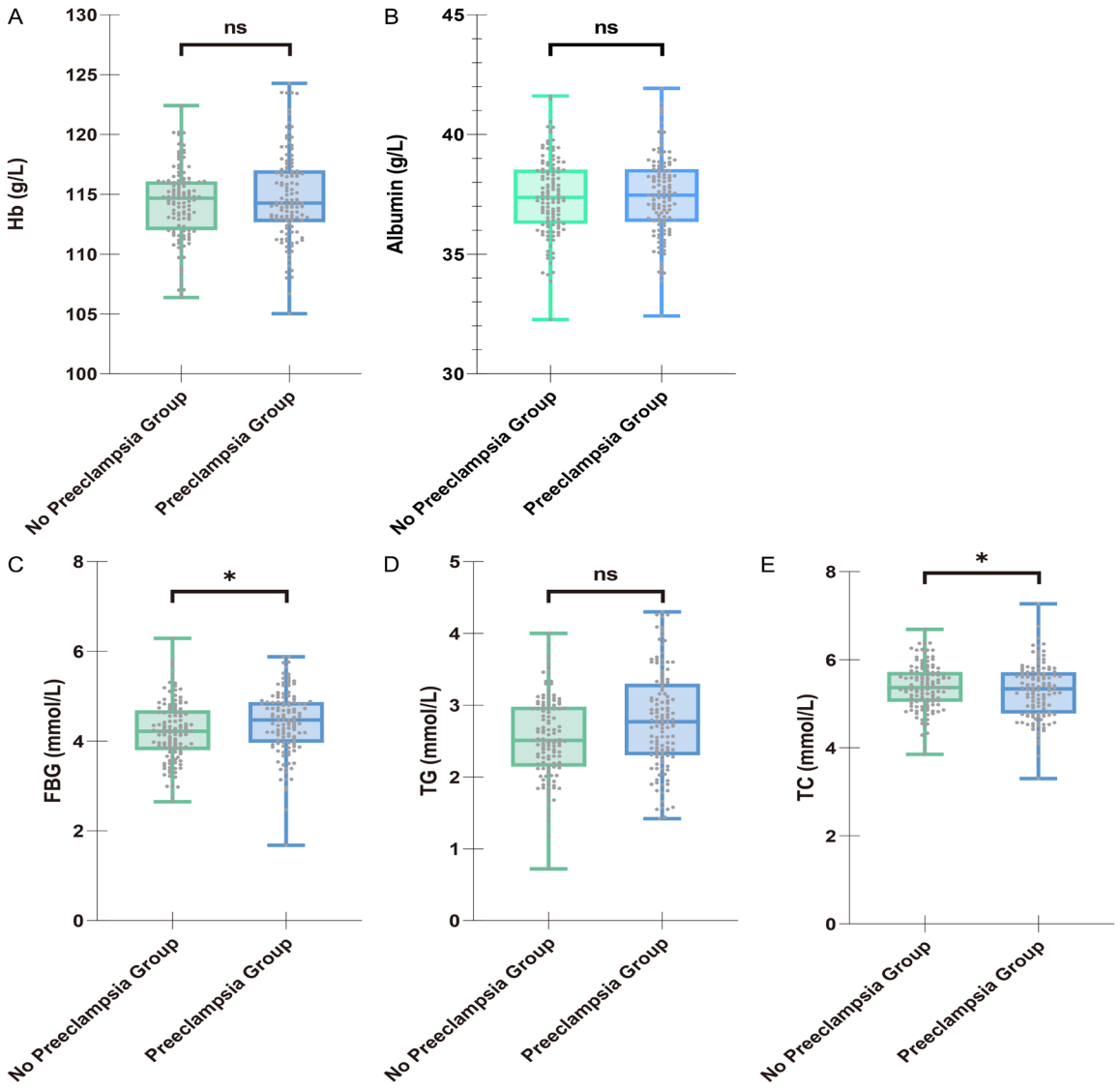

Figure 1. Comparison of serum proteins, blood glucose, and lipids between the preeclampsia and non-preeclampsia groups. A: Hb (g/L); B: Albumin (g/L); C: FBG (mmol/L); D: TG (mmol/L); E: TC (mmol/L). Hb: Hemoglobin; FBG: Fasting Blood Glucose; TG: Triglycerides; TC: Total Cholesterol. Ns: $P > 0.05$; *: $P < 0.05$; **: $P < 0.01$.

Maternal and fetal health monitoring indicators

In the comparison of maternal and fetal health monitoring indicators between the two groups, all examined parameters exhibited significant differences (**Figure 2**). Levels of PAPP-A (MOM), sFlt-1/PLGF ratio, and Hcy levels were all significantly higher in the preeclampsia group compared to the non-preeclampsia group ($P < 0.05$ or $P < 0.001$).

Vitamins

Vitamin C levels were significantly lower in the preeclampsia group compared to the non-preeclampsia group ($t = 2.549$, $P = 0.011$). No significant differences were observed in Vitamin A ($t = 1.574$, $P = 0.117$), Vitamin E ($t = 1.062$, $P = 0.289$), and 25-hydroxyvitamin D ($t = 0.599$, $P = 0.550$) levels between the two groups (**Figure 3**).

Inflammatory indicators

The IL-6 levels were significantly elevated in the preeclampsia group ($t = 2.160$, $P = 0.032$; **Table 2**). Conversely, CRP levels were significantly lower in the preeclampsia group ($t = 3.124$, $P = 0.002$). No significant differences were observed in neutrophil ($t = 1.210$, $P =$

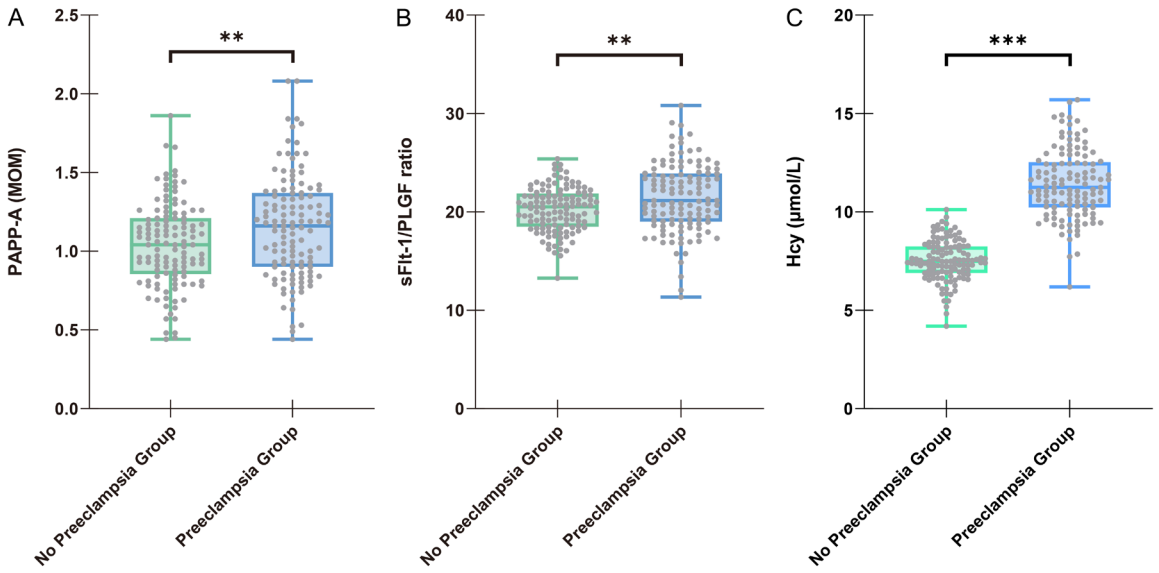

Figure 2. Comparison of maternal and fetal health monitoring indicators between the preeclampsia and non-preeclampsia groups. A: PAPP-A (MOM); B: sFlt-1/PLGF ratio; C: Hcy (μmol/L). PAPP-A: Pregnancy-associated Plasma Protein A; MOM: Multiple of the Median; sFlt1: Soluble Fms-like Tyrosine Kinase 1; PLGF: Placental Growth Factor; Hcy: Homocysteine. Ns: **: P < 0.01; ***: P < 0.001.

0.228) and lymphocyte counts (t = 1.221, P = 0.223) between the two groups. These findings indicate a potential role of IL-6 in the pathophysiology of preeclampsia and suggest an altered inflammatory response, as evidenced by the differential CRP levels.

Serological risk factors analysis of preeclampsia

The correlation analysis of serological factors in preeclampsia patients highlighted several significant associations (**Table 3**). FBG levels showed a positive correlation with preeclampsia (r = 0.165, P = 0.010), indicating that higher glucose levels were associated with the condition. TG also demonstrated a positive correlation (r = 0.168, P = 0.009), as did Pregnancy-associated Plasma Protein A (PAPP-A) with a correlation coefficient of 0.169 (P = 0.008). The sFlt-1/PLGF ratio was significantly correlated with preeclampsia (r = 0.188, P = 0.003), suggesting its potential role in the disease's progression. A strong positive correlation was observed with homocysteine (Hcy) levels (r = 0.829, P < 0.001), supporting its predictive role in preeclampsia. Conversely, Vitamin C levels exhibited a negative correlation (r = -0.156, P = 0.015), indicating lower levels in individuals with preeclampsia. Interleukin-6 (IL-6) showed a modest positive correlation (r = 0.132, P = 0.041) with preeclampsia. Interestingly, CRP levels were negatively correlated (r = -0.198, P = 0.002), suggesting a complex relationship between inflammation and preeclampsia. These correlations underscore the multifactorial nature of serological contributions to preeclampsia and highlight potential markers for its prediction and monitoring.

The univariate logistic regression analysis of serological factors in preeclampsia identified several significant predictors (**Table 4**). FBG was associated with an increased risk of preeclampsia, with a coefficient of 0.401 and an odds ratio (OR) of 1.493 (P = 0.035). TG also significantly predicted preeclampsia, with a coefficient of 0.619 and an OR of 1.858 (P = 0.003). PAPP-A demonstrated a strong association with preeclampsia, showing a coefficient of 1.266 and an OR of 3.548 (P = 0.005). The sFlt-1/PLGF ratio was another significant predictor, with a coefficient of 0.138 and an OR of 1.148 (P = 0.003). Hcy levels demonstrated the highest predictive value, with a coefficient of 2.317 and an OR of 10.148 (P < 0.001), highlighting its strong predictive role in preeclampsia. Vitamin C showed a protective association, with a coefficient of -0.015 and an OR of 0.985 (P = 0.013). IL-6 had a positive association, with a coefficient of 0.160 and an OR of 1.173 (P = 0.033). Additionally, CRP demonstrated a protective role, with a coefficient of -0.189 and

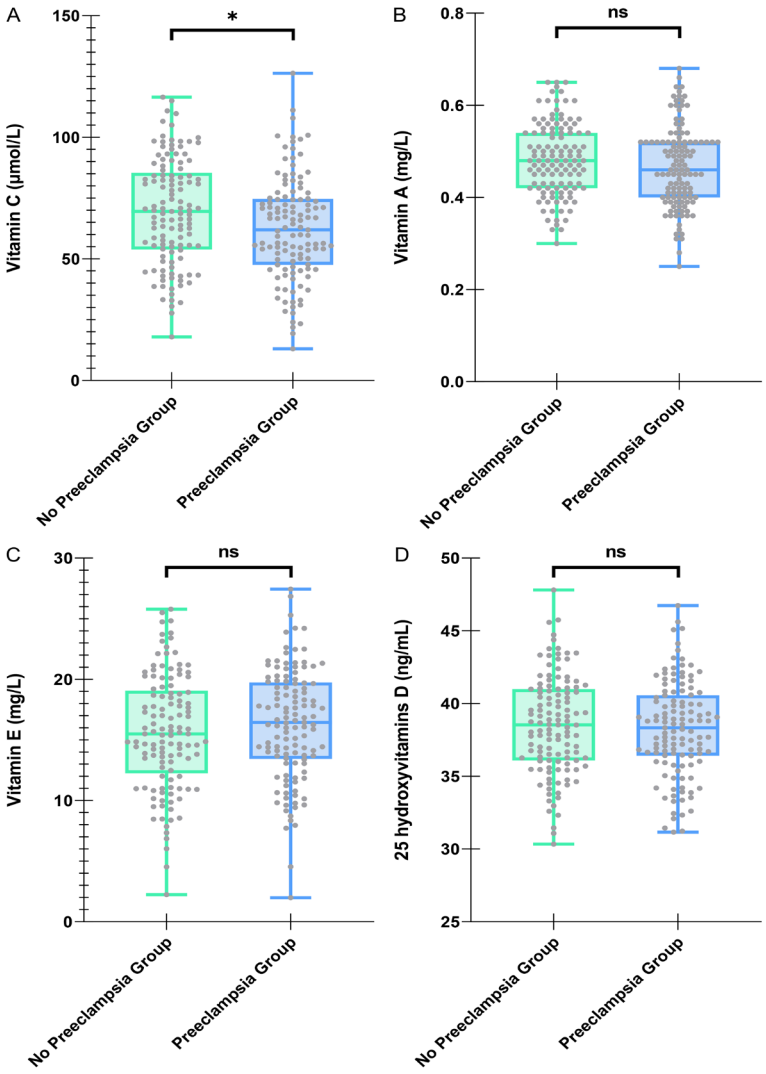

Figure 3. Comparison of vitamin levels between the preeclampsia and non-preeclampsia groups. A: Vitamin C (μmol/L); B: Vitamin A (mg/L); C: Vitamin E (mg/L); D: 25 hydroxyvitamins D (ng/mL). Ns: P > 0.05; *: P < 0.05.

Table 3. Correlation analysis of serological factors with preeclampsia

Parameters	r	P
FBG (mmol/L)	0.165	0.010
TG (mmol/L)	0.168	0.009
PAPP-A (MOM)	0.169	0.008
sFlt-1/PLGF ratio	0.188	0.003
Hcy (μmol/L)	0.829	*P* < 0.001
Vitamin C (μmol/L)	-0.156	0.015
IL-6 (pg/ml)	0.132	0.041
CRP (mg/L)	-0.198	0.002

FBG: Fasting Blood Glucose; TG: Triglycerides; PAPP-A: Pregnancy-associated Plasma Protein A; MOM: Multiple of the Median; sFlt-1: Soluble Fms-like Tyrosine Kinase 1; PLGF: Placental Growth Factor; Hcy: Homocysteine; IL-6: Interleukin-6; CRP: C-reactive Protein.

an OR of 0.828 (*P* = 0.003). These findings underscore the multifaceted nature of serological factors in predicting preeclampsia and highlight key markers like Hcy for further investigation.

The multivariate logistic regression analysis of serological factors in preeclampsia identified Hcy as a significant predictor of the condition, while other factors showed varying levels of association (**Table 5**). Hcy exhibited a significant association with preeclampsia, with a coefficient of 2.245 and an OR of 9.438 (*P* < 0.001), indicating its robust predictive value. TG also emerged as a significant factor with a coefficient of 1.182 and an OR of 3.260 (*P* = 0.032), suggesting an elevated risk of preeclampsia with higher TG levels. In contrast, other factors such as FBG (a coefficient of 0.115 (*OR* = 1.122, *P* = 0.806)), PAPP-A (a coefficient of 0.260 (*OR* = 1.297, *P* = 0.819)), sFlt-1/PLGF ratio (a coefficient of 0.058 (*OR* = 1.060, *P* = 0.581)), Vitamin C (a coefficient of -0.017 (OR = 0.983, P = 0.262)), IL-6 (a coefficient of 0.100 (*OR* = 1.105, *P* = 0.603)), and CRP (a coefficient of -0.179 (*OR* = 0.836, *P* = 0.229)) did not show significant associations in the multivariate model. These results highlight the critical role of Hcy as a serological risk factor in preeclampsia, while the impact of other factors may be less prominent in a multivariable context.

Predictive role of high Hcy levels in preeclampsia

The ROC analysis of serological factors for preeclampsia identified Hcy as the most effective predictor, with an AUC of 0.978 (**Table 6**). Other factors demonstrated varying degrees of diagnostic utility, specifically, sFlt-1/PLGF ratio (AUC = 0.609), CRP (AUC = 0.614), FBG (AUC = 0.576), TG (AUC = 0.614), PAPP-A (AUC = 0.592),

Table 4. Univariate logistic regression analysis of serological factors in preeclampsia

Parameters	Coefficient	Std Error	Wald	P	OR	95% CI
FBG (mmol/L)	0.401	0.190	2.112	0.035	1.493	1.035-2.185
TG (mmol/L)	0.619	0.211	2.941	0.003	1.858	1.239-2.838
PAPP-A (MOM)	1.266	0.447	2.831	0.005	3.548	1.503-8.736
sFlt-1/PLGF ratio	0.138	0.046	3.013	0.003	1.148	1.052-1.260
Hcy (μmol/L)	2.317	0.345	6.719	< 0.001	10.148	5.641-22.192
Vitamin C (μmol/L)	-0.015	0.006	2.498	0.013	0.985	0.973-0.997
IL-6 (pg/ml)	0.160	0.075	2.127	0.033	1.173	1.015-1.364
CRP (mg/L)	-0.189	0.063	3.015	0.003	0.828	0.730-0.934

Std: Standard; OR: Odds Ratio; CI: Confidence Interval; FBG: Fasting Blood Glucose; TG: Triglycerides; PAPP-A: Pregnancy-associated Plasma Protein A; MOM: Multiple of the Median; sFlt-1: Soluble Fms-like Tyrosine Kinase 1; PLGF: Placental Growth Factor; Hcy: Homocysteine; IL-6: Interleukin-6; CRP: C-reactive Protein.

Table 5. Multivariate logistic regression analysis of serological factors in preeclampsia

Parameters	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
FBG (mmol/L)	0.115	0.468	0.245	0.806	1.122	0.448	2.808
TG (mmol/L)	1.182	0.552	2.140	0.032	3.260	1.105	9.620
PAPP-A (MOM)	0.260	1.136	0.229	0.819	1.297	0.140	12.025
sFlt-1/PLGF ratio	0.058	0.106	0.552	0.581	1.060	0.862	1.304
Hcy (μmol/L)	2.245	0.366	6.134	< 0.001	9.438	4.607	19.335
Vitamin C (μmol/L)	-0.017	0.015	-1.122	0.262	0.983	0.954	1.013
IL-6 (pg/ml)	0.100	0.191	0.520	0.603	1.105	0.759	1.608
CRP (mg/L)	-0.179	0.149	-1.204	0.229	0.836	0.624	1.119

FBG: Fasting Blood Glucose; TG: Triglycerides; PAPP-A: Pregnancy-associated Plasma Protein A; MOM: Multiple of the Median; sFlt-1: Soluble Fms-like Tyrosine Kinase 1; PLGF: Placental Growth Factor; Hcy: Homocysteine; IL-6: Interleukin-6; CRP: C-reactive Protein.

Table 6. ROC analysis of serological factors for predicting preeclampsia

Parameters	Best threshold	Sensitivity	Specificity	AUC	Youden index	F1 score
FBG (mmol/L)	4.385	0.545	0.645	0.596	0.190	0.574
TG (mmol/L)	3.150	0.570	0.612	0.597	0.182	0.414
PAPP-A (MOM)	1.175	0.496	0.711	0.598	0.207	0.556
sFlt-1/PLGF ratio	22.915	0.380	0.893	0.609	0.273	0.511
Hcy (μmol/L)	9.230	0.934	0.950	0.978	0.884	0.942
Vitamin C (μmol/L)	77.925	0.802	0.397	0.590	0.199	0.249
IL-6 (pg/ml)	10.875	0.380	0.810	0.576	0.190	0.456
CRP (mg/L)	10.595	0.702	0.521	0.614	0.223	0.327

ROC: Receiver Operating Characteristic; AUC: Area Under the Curve.

Vitamin C (AUC = 0.585), and IL-6 (AUC = 0.601). These findings underscore the critical role of Hcy in preeclampsia prediction and highlight its potential utility as a focused target for diagnostic interventions.

Discussion

This study investigated serological risk factors for preeclampsia and their predictive role, especially elevated homocysteine levels, shedding light on the multifactorial nature of this condition. Preeclampsia, a complex hypertensive disorder of pregnancy, remains a significant cause of maternal and fetal morbidity and mortality worldwide [16]. Understanding its pathophysiology and identifying reliable biomarkers for its prediction are crucial for early intervention and management.

One of the standout findings from our study was the strong association between elevated homocysteine (Hcy) levels and preeclampsia. The robust predictive value of Hcy was underscored by its high AUC from the ROC analysis, indicating its potential as a reliable biomarker. Elevated Hcy levels have been implicated in endothelial dysfunction through oxidative stress, contributing to the pathogenesis of preeclampsia [17, 18]. This amino acid can injure the vascular endothelium, promoting thrombosis and inflammation, which processes central to the development of conditions like preeclampsia [19]. Moreover, Hcy may interfere with nitric oxide (NO) availability, further impairing vascular relaxation and promoting hypertension [20].

TG also emerged as a significant factor associated with preeclampsia risk. Elevated TG levels reflect altered lipid metabolism, a common feature in preeclampsia, contributing to endothelial cell dysfunction [21, 22]. Hypertriglyceridemia can enhance oxidative stress and inflammatory responses, exacerbating vascular injury and hypertension [23]. The liver's increased production of very-low-density lipoproteins (VLDL) in response to insulin resistance might partially explain these elevated levels during pregnancy complicated by preeclampsia [24, 25]. Insulin resistance, commonly observed in preeclamptic pregnancies, can further promote triglyceride storage and limited clearance, exacerbating this condition [26].

FBG level was correlated with preeclampsia, though its significance diminished in multivariate analyses. This observation reflects the common metabolic disturbances occurring in affected pregnancies and possibly points to a link between preeclampsia and GDM, as insulin resistance can unify these conditions [27, 28]. Hyperglycemia's role in oxidative stress and endothelial dysfunction is well-documented, though its contribution may not be as independent or strong as homocysteine or TG in this context [29, 30].

Albumin and hemoglobin levels did not show significant differences between groups, which may suggest that traditional markers of anemia or hypoalbuminemia might not be directly predictive or could be secondary to other metabolic disturbances. The proteinuria typically seen in preeclampsia was not directly reflected by serum albumin levels, indicating a more complex interaction at the renal level, possibly involving glomerular filtration barrier disturbances that do not manifest merely as systemic hypoalbuminemia [31].

The role of inflammation in preeclampsia was also highlighted in our study. Elevated IL-6 levels in the preeclamptic group suggest an activated inflammatory response. IL-6 is a cytokine with both pro-inflammatory and anti-inflammatory roles, and its elevation may reflect systemic inflammation contributing to endothelial dysfunction [32, 33]. Meanwhile, the observed decrease in CRP levels in the preeclampsia group was intriguing, given CRP's usual role as a marker of inflammation [34]. This paradoxical finding could suggest a dysregulated inflammatory response or differences in the timing of CRP elevation relative to IL-6, warranting further investigation into the temporal dynamics of these markers in preeclampsia.

The role of vitamins, particularly Vitamin C, emerged as significant in our study, with lower levels associated with preeclampsia. Vitamin C, an antioxidant, may protect against oxidative stress, a key component in preeclampsia's pathogenesis [35]. Its deficiency could exacerbate the oxidative injury to endothelial cells, suggesting potential therapeutic implications [36]. However, other vitamins like A, E, and D did not demonstrate significant differences, which may indicate that their roles might be less direct or were modulated by other nutritional and metabolic factors in pregnancy.

The complex interaction between placental factors and systemic health was also evident in the sFlt-1/PLGF ratio, which was elevated in preeclampsia. This imbalance reflects increased anti-angiogenic factors and decreased pro-angiogenic factors, disrupting placental development and function, ultimately contributing to the symptomatic presentation of preeclampsia [36]. This ratio underscores the importance of the placenta in mediating systemic effects in preeclampsia and highlights potential targets for therapeutic intervention or early prediction.

This study, while providing valuable insights into the serological factors associated with preeclampsia, has several limitations that should be acknowledged. The retrospective nature of the study may introduce biases related to data

collection and the variability in diagnostic criteria or laboratory methodologies over the study period. Additionally, as a single-center study, the findings might not be entirely generalizable to broader populations with different genetic, environmental, or lifestyle factors. Furthermore, the study focused on specific biomarkers which, while significant, do not capture the full complexity of preeclampsia's pathophysiology. Future prospective, multicentric studies are needed to validate these findings and explore additional factors that could further elucidate preeclampsia's multifactorial nature.

Conclusion

In conclusion, our study reinforces the multifactorial pathophysiology of preeclampsia, marked by endothelial dysfunction, oxidative stress, dyslipidemia, and inflammatory imbalances. The synergistic interplay of these factors highlights the need for an integrated approach to prediction and management, wherein lifestyle interventions, nutritional supplementation, and targeted therapies might collectively mitigate risk and improve maternal-fetal outcomes in preeclampsia. Further research, especially prospective and multicentric in nature, is necessary to build upon these findings, validate potential biomarkers, and translate them into clinical practice for timely preeclampsia management.

Disclosure of conflict of interest

None.

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