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Endothelial Dysfunction, Microalbuminuria, and Cardiac Biomarkers as Predictors of Preeclampsia in Gestational Arterial Hypertension

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Abstract

Background: Gestational arterial hypertension (GAH) affects 6–10% of pregnancies and may progress to preeclampsia (PE) in up to 46% of cases. Early identification of patients at risk for this transformation remains a critical clinical challenge. This study aimed to identify independent clinical, laboratory, and hemodynamic predictors of PE development in women with GAH.
Methods and Results: This study enrolled 160 pregnant women after 20 weeks of gestation: 54 healthy controls and 106 with GAH. Among GAH patients, 46 (43.4%) subsequently developed PE. All participants underwent assessment of flow-mediated dilation (FMD), microalbuminuria (MAU), NT-proBNP, echocardiography, and 24-hour ambulatory blood pressure monitoring (ABPM) at the initial visit. Multivariate logistic regression identified five independent predictors: FMD <10% (aOR=7.15; 95% CI 1.84–27.78; P=0.005), BMI ≥30 kg/m² (aOR=4.52; 95% CI 1.36–15.03; P=0.014), MAU >30 mg/day (aOR=4.28; 95% CI 1.08–16.97; P=0.038), non-dipper profile (aOR=3.95; 95% CI 1.05–14.86; P=0.042), and NT-proBNP >125 pg/mL (aOR=3.67; 95% CI 1.01–13.35; P=0.049). ROC analysis demonstrated the highest discriminative ability for FMD (AUC=0.849) and MAU (AUC=0.821).
Conclusion: FMD, MAU, NT-proBNP, BMI, and non-dipper profile are independent predictors of PE in GAH patients. Integration of these biomarkers may enable early risk stratification and timely intervention.(**International Journal of Biomedicine. 2026;16(3):333-338.**)

Keywords: flow-mediated dilation • NT-proBNP • non-dipper • body mass index

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Abbreviations

ABPM, ambulatory blood pressure monitoring; **AUC**, area under the curve; **BMI**, body mass index; **CI**, confidence interval; **DI SBP**, dipping index of systolic blood pressure; **FMD**, flow-mediated dilation; **GAH**, gestational arterial hypertension; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **MAU**, microalbuminuria; **MS**, morning surge; **NT-proBNP**, N-terminal pro-brain natriuretic peptide; **OR**, odds ratio; **aOR**, adjusted odds ratio; **PE**, preeclampsia; **ROC**, receiver operating characteristic; **SBP**, systolic blood pressure; **TI SBP**, time index of systolic blood pressure; **TG**, triglycerides.

Introduction

Hypertensive disorders of pregnancy (HDP) remain a leading cause of maternal morbidity and mortality, accounting for approximately 14% of all maternal deaths worldwide.[1] According to global estimates by Abalos et al., the incidence of PE ranges from 2% to 8% of pregnancies, with substantially higher rates in low- and middle-income countries.[2] The Lancet Series on Preeclampsia (2021) emphasized that PE is a leading cause of iatrogenic preterm delivery and is associated with significant maternal and perinatal morbidity.[3]

Gestational arterial hypertension (GAH), defined as new-onset hypertension after 20 weeks of gestation without proteinuria, affects 6–10% of pregnancies.[4] Prospective

studies have demonstrated that 15–46% of women with GAH subsequently develop PE, with the highest risk in those presenting before 34 weeks.[5] Reliably predicting which GAH patients will progress to PE remains one of the most important unresolved challenges in obstetric medicine.[6]

The pathophysiology of PE is understood through the two-stage model: defective spiral artery remodeling and placental ischemia (Stage 1) trigger the release of anti-angiogenic factors—primarily soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin—into the maternal circulation, causing systemic endothelial dysfunction and multi-organ damage (Stage 2).[7,17] Flow-mediated dilation (FMD) of the brachial artery is a validated non-invasive marker of endothelial function.[8] A meta-analysis by Weissgerber et al. (2016), encompassing 37 studies, demonstrated that FMD is significantly impaired before (SMD=−0.84), during (SMD=−1.41), and after (SMD=−0.90) preeclamptic pregnancies, establishing that endothelial dysfunction precedes, accompanies, and outlasts PE.[9]

Microalbuminuria (MAU), reflecting glomerular endothelial injury, predicts PE before overt proteinuria develops.[10] A 2025 systematic review and meta-analysis confirmed the association of albuminuria with increased risk of PE and its predictive value.[11] N-terminal pro-brain natriuretic peptide (NT-proBNP) has emerged as a cardiovascular stress marker in pregnancy: a 2025 meta-analysis of 31 studies (n=3,915) showed NT-proBNP levels are significantly elevated in PE, with a mean difference of 206.19 pg/mL (P≤0.001).[12] A multicenter longitudinal study demonstrated that adding NT-proBNP to the sFlt-1/PlGF ratio significantly improved short-term prediction of PE requiring delivery within one week.[13]

Ambulatory blood pressure monitoring (ABPM) has demonstrated superiority over office measurements in predicting adverse pregnancy outcomes.[14] The non-dipper pattern (nocturnal SBP reduction <10%) increases PE risk (OR=2.8; 95% CI 1.4–5.6).[15] Obesity (BMI ≥30 kg/m²) doubles PE risk according to a meta-analysis of 25 million pregnancies (pooled OR=2.8; 95% CI 2.6–3.1).[6,16]

Despite growing evidence on individual predictors, studies evaluating the combined predictive value of FMD, MAU, NT-proBNP, and ABPM parameters in women with GAH remain scarce, particularly in Central Asian populations. This study aimed to identify independent predictors of PE in GAH patients, evaluate their discriminative ability, and explore inter-relationships through correlation analysis.

Material and Methods

This study was conducted at the Republican Specialized Scientific and Practical Medical Center of Cardiology (Tashkent, Uzbekistan) between 2022 and 2025. A total of 160 pregnant women were enrolled after 20 weeks of gestation: 54 healthy controls and 106 with GAH diagnosed according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria(4)–systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg first occurring after 20 weeks in a previously normotensive woman, without proteinuria or PE features at enrollment. During follow-up, 46 of 106 GAH patients (43.4%) developed PE. Exclusion criteria were chronic hypertension, secondary hypertension, pre-gestational diabetes mellitus, chronic kidney disease, autoimmune disorders, multiple pregnancy, and congenital fetal anomalies.

At the initial visit, all participants underwent clinical evaluation including anthropometric measurements (BMI) and office blood pressure measurement per ESC/ESH 2018 guidelines.[18] Laboratory investigations included serum creatinine, uric acid, fasting glucose, lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C, atherogenic index), NT-proBNP (electrochemiluminescence immunoassay), and 24-hour microalbuminuria (enzymatic analysis). Standard echocardiography was performed using a Philips Affiniti 30 system. Brachial artery FMD was assessed per international guidelines(8) using a 7.5 MHz linear transducer; FMD <10% was considered indicative of endothelial dysfunction. Twenty-four-hour ABPM was performed using the Cardiospy recorder (LABTech LTD, Hungary) with measurements every 15 minutes (day) and 30 minutes (night). Parameters included dipping index of SBP (DI SBP), time index of SBP load (TI SBP), and morning surge (MS); non-dipper was defined as DI SBP <10%.

Statistical analysis was performed using R (version 4.3.0). Continuous variables were expressed as mean±SD or median [IQR]. Between-group comparisons used Student's t-test, Mann-Whitney U test, chi-square, or Fisher's exact test as appropriate. Univariate logistic regression was performed to screen potential predictors; variables with P<0.20 were subsequently entered into a multivariate logistic regression model to identify independent predictors. ROC analysis determined optimal cut-off values (Youden index). Spearman correlation analysis evaluated inter-variable relationships. P<0.05 was considered significant.

Results

Baseline clinical and laboratory characteristics are presented in Table 1. Women with GAH had significantly higher BMI (28.83±4.87 vs. 25.40±3.72 kg/m², P<0.001), office SBP (148.51±11.12 vs. 112.61±8.26 mmHg, P<0.001), and lower FMD (8.10±3.09% vs. 13.50±2.73%, P<0.001) compared to controls. The non-dipper prevalence was 59.4% vs. 9.3% (P<0.001).

The comparison of GAH subgroups at Visit 1 is shown in Table 2. Women who subsequently developed PE were older (31.65±6.31 vs. 28.02±4.71 years, P<0.001), had higher BMI (31.99 [28.33; 33.30] vs. 26.82 [25.10; 29.97] kg/m², P<0.001), elevated MAU (74.71 [56.96; 83.92] vs. 26.20 [13.25; 68.46] mg/day, P<0.001), higher NT-proBNP (174.53 [117.65; 209.53] vs. 105.09 [76.68; 165.89] pg/mL, P<0.001), and lower FMD (7.20 [6.47; 7.56] vs. 7.70 [7.09; 8.30]%, P<0.001). ABPM showed lower DI SBP (6.97 [6.37; 7.42] vs. 7.65 [6.73; 8.42]%, P=0.002) and higher TI SBP (44.56±13.25 vs. 34.82±8.48%, P<0.001) in the PE subgroup.

Univariate logistic regression and ROC analysis results are presented in Table 3. In univariate analysis, 11 potential predictors were evaluated, of which 9 demonstrated statistical significance (P<0.05). ROC analysis showed the highest AUC for FMD (0.849; cut-off ≤7.70%; sensitivity 82.6%; specificity

75.0%) and MAU (0.821; cut-off ≥55.60 mg/day; sensitivity 69.6%; specificity 98.3%). Multivariate logistic regression (Figure 1) identified five independent predictors: FMD <10% (aOR=7.15; 95% CI 1.84–27.78; P=0.005), BMI ≥30 kg/m² (aOR=4.52; 95% CI 1.36–15.03; P=0.014), MAU >30 mg/day (aOR=4.28; 95% CI 1.08–16.97; P=0.038), non-dipper profile (aOR=3.95; 95% CI 1.05–14.86; P=0.042), and NT-proBNP >125 pg/mL (aOR=3.67; 95% CI 1.01–13.35; P=0.049).

Table 1.

Clinical characteristics of the study participants.

Variable	Healthy (n=54)	GAH (n=106)	P
Age, years	28.87±5.25	29.64±5.61	0.514
Gestational age, weeks	24.54±3.80	23.93±3.34	0.338
BMI, kg/m²	25.40±3.80	28.83±5.21	<0.001
Office SBP, mmHg	101.22±10.53	147.41±11.22	<0.001
Office DBP, mmHg	64.20±6.12	86.21±10.04	<0.001
Office MBP, mmHg	76.53±7.16	106.51±10.02	<0.001
MAU, mg/day	12.01±5.11	46.73±38.96	<0.001
NT-proBNP, pg/mL	55.03±25.32	137.12±83.97	<0.001
Creatinine, μmol/L	44.20±10.20	64.75±15.36	<0.001
Fasting glucose, mmol/L	4.27±0.43	4.75±0.71	<0.001
Uric acid, mg/dL	4.70±0.45	5.43±1.03	<0.001
Triglycerides, mg/dL	175.00±45.78	259.76±67.99	<0.001
HDL-C, mg/dL	65.00±10.70	54.96±10.27	<0.001
Atherogenic index	2.77±0.88	3.57±0.96	<0.001
DI SBP, %	11.80±4.20	4.90±3.02	<0.001
TI SBP, %	7.91±6.58	37.81±11.28	<0.001
Morning surge, mmHg	18.20±17.80	42.64±7.85	<0.001
FMD, %	13.50±2.73	8.10±3.09	<0.001

Data presented as mean±SD. P-values from Mann-Whitney U test. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; MAU, microalbuminuria; DI SBP, dipping index of SBP; TI SBP, time index of SBP; FMD, flow-mediated dilation.

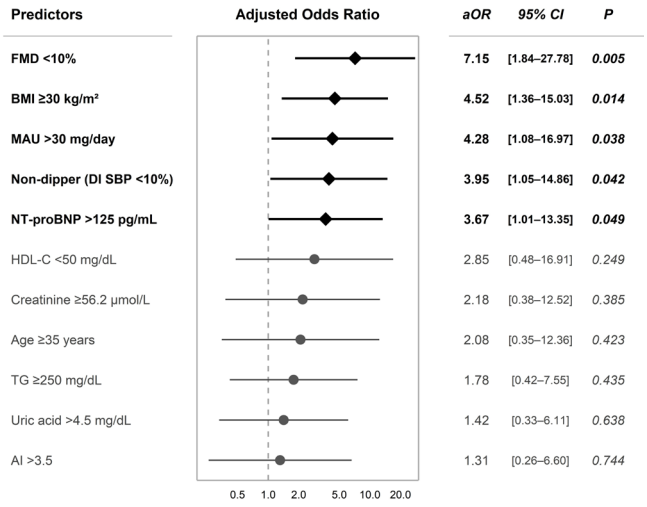

Figure 1. *Forest plot of adjusted odds ratios (aOR) from multivariate logistic regression analysis for predictors of preeclampsia in pregnant women with gestational hypertension (n=106). Diamond markers with bold labels indicate statistically significant independent predictors (P<0.05); circle markers indicate non-significant predictors. Horizontal lines represent 95% confidence intervals. The dashed vertical line denotes aOR=1.0.*

Table 2.

Baseline comparison of GAH and PE subgroups at Visit 1.

Variable	GAH (n=60)	PE (n=46)	P-value
Age, years	28.03±4.62	31.46±6.38	0.005
Gestational age, weeks	24.12±3.28	23.43±3.06	0.141
BMI, kg/m²	26.98±3.45	31.65±3.65	<0.001
Office SBP, mmHg	143.35±9.38	151.74±10.84	<0.001
Office DBP, mmHg	85.98±9.28	92.83±10.13	<0.001
Office MBP, mmHg	103.00±8.39	111.10±10.20	<0.001
MAU, mg/day	20.05±36.77	57.70±24.88	<0.001
NT-proBNP, pg/mL	103.25±82.22	176.88±79.41	<0.001
Creatinine, μmol/L	55.16±8.79	64.86±13.92	<0.001
Fasting glucose, mmol/L	4.74±0.60	5.13±0.78	0.009
Uric acid, mg/dL	5.25±0.82	5.70±1.21	0.069
Triglycerides, mg/dL	239.44±71.95	279.27±58.51	0.004
HDL-C, mg/dL	57.39±8.45	51.15±14.70	0.011
Atherogenic index	3.31±0.72	3.77±1.01	0.014
DI SBP, %	4.70±2.45	5.68±4.81	0.581
TI SBP, %	34.83±8.48	44.55±13.25	<0.001
Morning surge, mmHg	41.48±7.47	44.16±8.16	0.089
FMD, %	9.69±2.46	6.02±2.56	<0.001

Data presented as mean±SD. P-values from Mann-Whitney U test. GAH, gestational arterial hypertension; PE, preeclampsia. Other abbreviations as in Table 1.

Table 3.

Univariate logistic regression analysis and ROC characteristics for potential predictors of preeclampsia.

Predictor	OR (95% CI)	P	AUC	Cut-off (Se; Sp)
FMD <10%	**8.42 (3.12–22.73)**	**<0.001**	0.849	≤7.70% (82.6; 75.0)
BMI ≥30 kg/m²	**5.86 (2.38–14.43)**	**<0.001**	0.748	≥29.2 (71.7; 70.0)
MAU >30 mg/day	**4.30 (1.92–9.63)**	**<0.001**	0.821	≥55.6 (69.6; 98.3)
Non-dipper (DI SBP <10%)	**5.32 (2.17–13.04)**	**<0.001**	0.742	≤7.50% (73.9; 68.3)
NT-proBNP >125 pg/mL	**3.89 (1.68–9.01)**	**0.002**	0.780	≥154.6 (69.6; 85.0)
HDL-C <50 mg/dL	4.30 (1.63–11.34)	0.003	—	—
Creatinine ≥56.2 μmol/L	3.52 (1.52–8.15)	0.003	0.638	≥56.2 (63.0; 41.7)
Age ≥35 years	2.73 (1.10–6.78)	0.031	—	—
TG ≥250 mg/dL	2.48 (1.10–5.59)	0.029	—	—
Uric acid >4.5 mg/dL	1.74 (0.73–4.14)	0.211	—	—
AI >3.5	1.74 (0.79–3.83)	0.170	—	—

Bold indicates predictors that were significant in univariate analysis (P<0.05) and subsequently identified as independent predictors in multivariate analysis (Figure 1). OR, odds ratio; CI, confidence interval; AUC, area under the ROC curve; Se, sensitivity (%); Sp, specificity (%). Cut-off values determined by Youden index.

ROC analysis (Figure 2) demonstrated the highest discriminative ability for FMD (AUC=0.849; cut-off ≤7.70%; sensitivity 82.6%; specificity 75.0%), followed by MAU (AUC=0.821; cut-off ≥55.60 mg/day; sensitivity 69.6%; specificity 98.3%), NT-proBNP (AUC=0.780; cut-off ≥154.6 pg/mL; sensitivity 69.6%; specificity 85.0%), BMI (AUC=0.748; cut-off ≥29.2 kg/m²; sensitivity 71.7%; specificity 70.0%), and DI SBP (AUC=0.742; cut-off ≤7.50%; sensitivity 73.9%; specificity 68.3%).

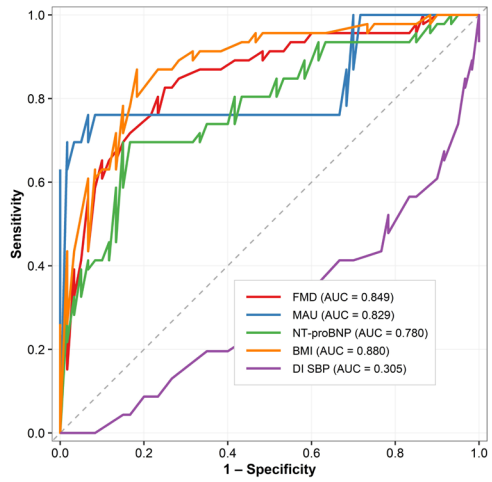

Figure 2. *Receiver operating characteristic (ROC) curves for continuous predictors of preeclampsia (n=106). Each curve represents the discriminative ability of a predictor, with the area under the curve (AUC) shown in the legend. The dashed diagonal line represents AUC=0.50.*

Table 4.

Significant Spearman correlation coefficients in women with gestational arterial hypertension (n=106).

Variable pair	Spearman r	Pathophysiological axis
FMD — NT-proBNP	−0.40***	Endothelial–cardiac
FMD — MAU	−0.33***	Endothelial–renal
MAU — Creatinine	+0.37***	Renal
MAU — TI SBP	+0.37***	Renal–hemodynamic
MAU — NT-proBNP	+0.35***	Renal–cardiac
DI SBP — TI SBP	−0.42***	Hemodynamic
IMT — HDL-C	−0.30**	Metabolic–lipid
IMT — Glucose	+0.30**	Metabolic
IMT — Creatinine	+0.29**	Metabolic–renal
HDL-C — TI SBP	−0.29**	Lipid–hemodynamic
MAU — BMI	+0.28**	Renal–metabolic
FMD — BMI	−0.27**	Endothelial–metabolic
Creatinine — HDL-C	−0.26**	Renal–lipid
FMD — HDL-C	+0.25**	Endothelial–lipid
NT-proBNP — HDL-C	−0.25**	Cardiac–lipid
NT-proBNP — BMI	+0.23*	Cardiac–metabolic
FMD — DI SBP	+0.22*	Endothelial–hemodynamic

**P<0.05; **P<0.01; ***P<0.001.*
FMD, flow-mediated dilation; MAU, microalbuminuria; BMI, body mass index; DI SBP, dipping index of systolic blood pressure; TI SBP, time index of systolic blood pressure; HDL-C, high-density lipoprotein cholesterol.

Spearman correlation analysis (Table 4) revealed distinct patterns in the GAH cohort (n=106). FMD demonstrated significant inverse correlations with NT-proBNP (r=−0.40, P<0.001), MAU (r=−0.33, P<0.001), and BMI (r=−0.27, P=0.005), and a positive correlation with HDL-C (r=+0.25, P=0.009). MAU was positively correlated with creatinine (r=+0.37, P<0.001), TI SBP (r=+0.37, P<0.001), NT-proBNP (r=+0.35, P<0.001), and BMI (r=+0.28, P=0.004). A strong inverse correlation was observed between DI SBP and TI SBP (r=−0.42, P<0.001). The endothelial-renal-cardiac triad (FMD–MAU–NT-proBNP) and the FMD–BMI relationship are illustrated in Figure 3A–D.

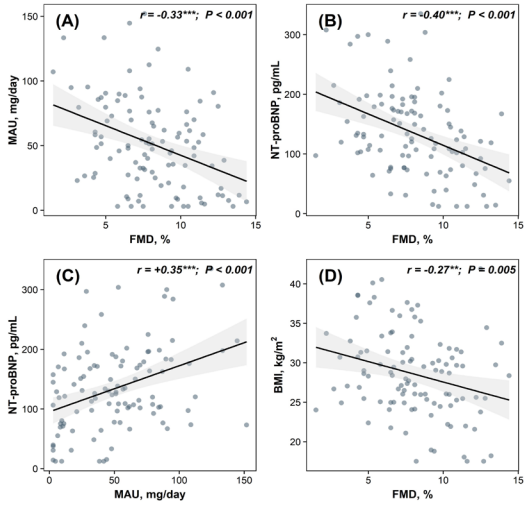

Figure 3. *Scatter plots of significant Spearman correlations in women with gestational arterial hypertension (n=106). (A) FMD versus MAU (r=−0.33, P<0.001). (B) FMD versus NT-proBNP (r=−0.40, P<0.001). (C) MAU versus NT-proBNP (r=+0.35, P<0.001). (D) FMD versus BMI (r=−0.27, P=0.005). Solid lines represent linear regression with 95% confidence intervals. **P<0.01; ***P<0.001.*

Discussion

This study identified five independent predictors of PE in women with GAH, with FMD demonstrating both the strongest predictive value (aOR=7.15) and the highest discriminative ability (AUC=0.849). These findings position endothelial function assessment as the cornerstone of PE risk stratification in GAH patients.

The primacy of FMD aligns with the two-stage model of PE, in which systemic endothelial dysfunction is the central pathogenic mechanism.[7] Our findings are supported by Weissgerber et al. (2016), who demonstrated significantly impaired FMD before PE onset (SMD=−0.84) across 37 studies,[9] and by Doganay et al. (2022), who confirmed impaired FMD in PE through a systematic review and meta-analysis.[19] The AUC of 0.849 in our study exceeds the 0.80 threshold considered excellent for diagnostic tests.

MAU emerged as the second-strongest predictor (aOR=4.28) with a remarkably high specificity of 98.3% at the optimal cut-off (55.60 mg/day), suggesting that elevated MAU in GAH is highly specific for subsequent PE. This

extends earlier observations[10] to a Central Asian population and is consistent with a 2025 systematic review confirming the predictive value of albuminuria for PE.[11] NT-proBNP as an independent predictor (aOR=3.67, AUC=0.780) is supported by the 2025 meta-analysis of 31 studies (n=3,915) confirming significantly elevated NT-proBNP in PE (mean difference 206.19 pg/mL, P≤0.001).[12] Our optimal cut-off (154.6 pg/mL) is consistent with the findings of Sabria et al. (2018), who demonstrated that NT-proBNP combined with the sFlt-1/PlGF ratio significantly improved prediction of PE requiring delivery within one week.[13] The non-dipper profile (aOR=3.95) underscores circadian blood pressure dysregulation in PE pathogenesis, consistent with Salazar et al. (2022), who reported an OR of 2.8 for nocturnal hypertension and PE risk.[15] In our study, non-dipper prevalence was 80.4% in the PE subgroup versus 43.3% in GAH (P<0.001). Obesity as a predictor (aOR=4.52) is consistent with the meta-analysis by Bartsch et al. (2016) of 25 million pregnancies (pooled OR=2.8).[16]

Importantly, correlation analysis in the total GAH cohort demonstrated an activated endothelial-renal-cardiac axis, with FMD occupying a central hub position (MAU: r=−0.33; NT-proBNP: r=−0.40). The inverse FMD–BMI correlation (r=−0.27, P=0.005) confirms that higher BMI is associated with greater endothelial impairment in GAH patients, consistent with evidence that obesity exacerbates endothelial dysfunction through chronic inflammation, oxidative stress, and reduced nitric oxide bioavailability.[20] MAU showed strong associations with creatinine (r=+0.37) and TI SBP (r=+0.37), linking renal injury to pressure overload. The inverse correlation between DI SBP and TI SBP (r=−0.42) confirms the hemodynamic significance of the non-dipper profile. Several univariate predictors (HDL-C, creatinine, atherogenic index) lost significance in multivariate analysis due to collinearity–creatinine in particular demonstrated low specificity (41.7%) and the lowest AUC (0.638), reflecting substantial renal functional reserve.

This study has limitations, including a relatively small sample size (n=106 GAH patients), a single-center design, and the absence of angiogenic biomarkers (sFlt-1/PlGF ratio). Recent predictive models combining NT-proBNP with angiogenic markers have demonstrated improved accuracy for PE prediction,[22,23] and PlGF-based testing has been validated in large multicenter trials.[25] However, FMD and MAU demonstrated comparable discriminative ability (AUC=0.849 and 0.821). The glomerular endotheliosis underlying MAU elevation in PE is well characterized,[21] and PE is associated with increased long-term cardiovascular risk,[24] reinforcing the importance of early identification. Future multicenter studies with larger cohorts incorporating angiogenic markers are warranted.

In conclusion, the present study demonstrates that endothelial dysfunction assessed by brachial artery FMD is the strongest independent predictor of PE in women with GAH (aOR=7.15; AUC=0.849), followed by BMI ≥30 kg/m² (aOR=4.52), MAU >30 mg/day (aOR=4.28), non-dipper blood pressure profile (aOR=3.95), and NT-proBNP >125 pg/mL (aOR=3.67). These five predictors represent distinct pathophysiological domains–endothelial function, metabolic risk, renal injury, circadian hemodynamics, and cardiac stress–providing a comprehensive multi-marker assessment of PE risk.

Integrating FMD, MAU, and NT-proBNP with ABPM-derived parameters into routine antenatal surveillance of GAH patients may substantially improve early risk stratification. This multimodal approach enables clinicians to identify those at highest risk before the clinical onset of PE, facilitating timely initiation of evidence-based preventive strategies including low-dose aspirin therapy, intensified surveillance protocols, and appropriate delivery planning. Further validation of this predictive panel in multicenter studies with diverse populations is warranted to confirm its clinical utility and cost-effectiveness.

Ethical Considerations

The study protocol was approved by the Ethics Committee of the Republican Specialized Scientific and Practical Medical Center of Cardiology. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Competing Interests

The authors declare that they have no competing interests.

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