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Correlation between N-terminal pro-atrial natriuretic peptide, corin, and target organ damage in hypertensive disorders of pregnancy

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Abstract

The objective was to evaluate the correlation between N-terminal pro-atrial natriuretic peptide (NT-proANP), corin and the severity of target organ injury in hypertensive disorders of pregnancy. A total of 78 women with hypertensive disorders of pregnancy and 49 normotensive pregnancies were enrolled. The clinical characteristics, laboratory index and echocardiogram results were collected. NT-proANP, corin, sFlt-1 and PlGF levels were measured. A receiver's operating characteristics (ROC) curve was performed to evaluate the efficacy of predicting target organ injury in the HDP group. The NT-proANP, corin, and sFlt-1/PlGF ratio were increased in the HDP group ($p < .05$). The area under the curve (AUC) predicted by NT-proANP and corin were larger than sFlt-1/PlGF ratio (0.779, 0.867, and 0.766, respectively). The creatinine and urine protein were significantly increased, while the estimated glomerular filtration rate (eGFR) was dramatically decreased in the HDP group ($p < .05$ each). The left atrial diameter (LAD), left atrial volume index (LAVI), left ventricular posterior wall thickness (LVPWT), and left ventricular septal thickness (LVST) were larger in the HDP group ($p < .001$ each). The NT-proANP/corin levels were positively correlated with LAD, creatinine, and urine protein, and negatively correlated with eGFR in HDP group ($p < .05$ each). Multiple regressions demonstrated that NT-proANP was an independent risk factor of LAD and urine protein, and corin was an independent risk factor of creatinine and eGFR in HDP group. NT-proANP and corin may be reliable biomarkers for evaluating the severity of target organ damage in the hypertensive disorders of pregnant patients.

KEYWORDS
corin, hypertensive disorders of pregnancy, N-terminal pro-atrial natriuretic peptide, placental growth factor, soluble FMS-like tyrosine kinase

1 | INTRODUCTION

Hypertensive disorders of pregnancy are common pregnancy complications related to some severe adverse events, such as placental abruption, HELLP syndrome, heart failure, stroke, and disseminated intravascular coagulation.[1] Early evaluation of hypertensive disorders of pregnancy can effectively reduce the occurrence of adverse events. However, there is still a lack of valuable biomarkers to monitor the severity of hypertensive disorders of pregnancy.

Atrial natriuretic peptide (ANP) which contains a 28-amino acid peptide, belongs to the natriuretic peptide family and is synthesized and stored in atrial myocytes.[2] The signal peptide in the endoplasmic reticulum removes the 25 amino acid sequence in the pre-pro-atrial natriuretic peptide and converts it into pro-atrial natriuretic peptide.[2] When the heart pressure and volume load increase, the pro-atrial natriuretic peptide released from atrial myocytes is cleaved by corin to generate active ANP and inactive N-terminal pro-atrial natriuretic peptide (NT-proANP).[2,3] The effect of ANP in regulating water-salt balance and blood pressure is exerted by increasing the glomerular filtration rate, promoting the excretion of renal sodium and water, and inhibiting sodium reabsorption.[2]

Corin is a membrane-bound convertase that is highly expressed in the heart. It is a key enzyme that cleaves proANP into active ANP.[4] Recently, some scholars found that corin was also expressed in the uterus of pregnant mice. The lack of corin and ANP in the uterus damaged the remodeling of spiral arteries, which in turn led to hypertension and proteinuria during pregnancy.[5] Uterine corinmRNA reduction and corin mutations have been reported in patients with preeclampsia,[5,6] while our previous study demonstrated that circulating corin and NT-proANP levels in pregnant women with hypertensive disorders of pregnancy were increased,[7] which has suggested that corin and NT-proANP may be potential predictors for hypertensive disorders of pregnancy.

Vascular endothelial growth factor (VEGF) can promote angiogenesis by binding to FMS-like tyrosine kinase 1 (Flt-1). Flt-1 is selectively expressed on the surface of vascular endothelial cells.[8] However, sFlt-1 in plasma is a truncated form of Flt-1, which exerts an antiangiogenic effect because it cannot bind to VEGF.[9] Placental growth factor (PlGF) belongs to the VEGF family and is mainly expressed in the placenta.[8] The levels of sFlt-1 and PlGF show an opposite trend at the end of pregnancy. Furthermore, the sFlt-1/PlGF ratio has been used as a biomarker for the early diagnosis and prediction of preeclampsia.[10] However, the sensitivity in patients with pregnancy-induced hypertension is low.[8] Moreover, it is not yet clear whether it is applicable to other types of hypertensive disorders of pregnancy, such as pre-existing hypertension and antenatally unclassifiable hypertension. The purpose of this study was to evaluate whether NT-proANP and corin can be used as a predictor of the severity of target organ damage in women with hypertensive disorders of pregnancy, and furthermore, to compare the sensitivity of NT-proANP/corin and the sFlt-1/PlGF ratio in hypertensive disorders of pregnancy.

2 | METHODS

2.1 | Study design

Pregnant women were enrolled in Dalian Maternity Hospital and First Affiliated Hospital of Dalian Medical University (Dalian, China) from April 2018 to April 2019. Patients who met the diagnostic criteria for hypertensive disorders of pregnancy were enrolled in the HDP group. Normotensive women who had a gestational age of more than 20 weeks were enrolled in the control group. At the same time, the control group patients not suffering from the following diseases: (1) persons younger than 20 years old or older than 45 years old; (2) combined with other underlying heart diseases (rheumatic heart disease, coronary atherosclerotic heart disease, congenital heart disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, atrial fibrillation, heart failure, etc.); (3) malignant tumors and immune system diseases; (4) acute or chronic kidney disease, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2; and (5) patients who were clearly diagnosed with secondary hypertension, severe liver insufficiency (value more than three times the upper limitation of normal), or patients who had a diagnosis of diabetes. The research details are shown in the Figure 1. All procedures followed the Declaration of Helsinki. This clinical study was registered at www.chictr.org.cn/enindex.aspx, and the registration number is ChiCTR-RCH-10000748.

2.2 | Clinical definitions and study participants

The diagnostic criteria of hypertensive disorders of pregnancy referred to the guidelines issued by the European Society of Cardiology in 2018,[11] including gestational hypertension, preeclampsia or eclampsia, chronic hypertension, and chronic hypertension complicated with preeclampsia or eclampsia. Hypertension was defined as a systolic blood pressure (SBP) $\geq$ 140 mm Hg or diastolic blood pressure (DBP) $\geq$ 90 mm Hg.[11] A total of 127 pregnant women with a gestational age of $>$ 20 weeks were included in this study. The percentages of the control group and HDP group were 38.6% ($n = 49$) and 61.4% ($n = 78$), respectively. In the HDP group, 10 (12.8%) patients occurred gestational hypertension, 36 (46.2%) patients occurred preeclampsia or eclampsia, eight (10.3%) patients occurred chronic hypertension, and 24 (30.7%) patients occurred chronic hypertension complicated with preeclampsia or eclampsia.

2.3 | Clinical data collection

Blood samples were collected before delivery. Clinical data including age, height, weight, blood pressure, blood glucose, creatinine, urine protein, eGFR, and echocardiography results were collected. Because some patients have records of taking antihypertensive drugs, the highest blood pressure recorded during the follow-up period was selected. Low-density lipoprotein-cholesterol (LDL-c), total cholesterol

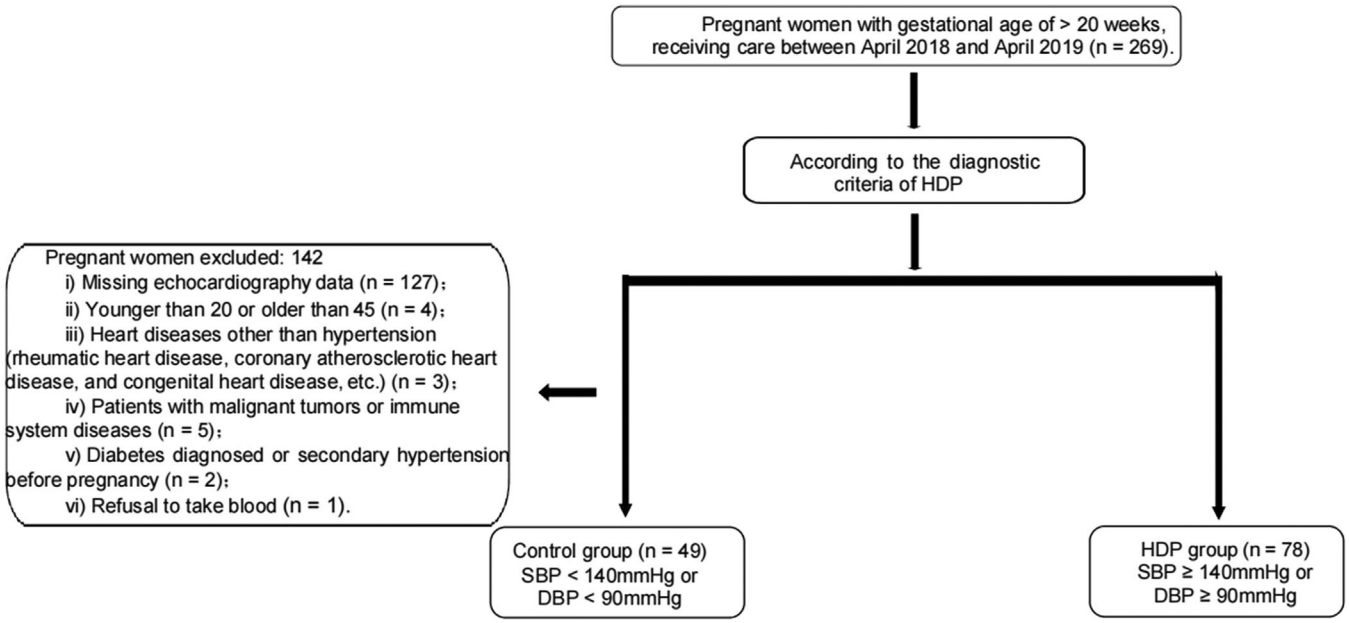

FIGURE 1 Flow chart of the study protocol. HDP, Hypertensive disorders of pregnancy; SBP, systolic blood pressure; DBP, diastolic blood pressure

(TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-c) were measured by a Hitachi 7170 automatic biochemical analyzer (WEI RIKANG Bioengineering Co. Ltd., China). Urine protein was measured and classified by the UC 3500 Fully Automatic Urine Analyzer (Sysmex Corporation, Japan) using the dry chemical method.

According to the recommendations of the American Society of Echocardiography and the European Society of Cardiovascular Imaging,[12] the left atrial volume index (LAVI) = the left atrial volume (LAV)/body surface area (BSA), where LAV = $\pi/6 \times$ Left atrial diameter (LAD) × Lx × Sx. LAD, Lx, and Sx are the anteroposterior diameter of the left atrium, the upper and lower diameters of the left atrium, and the transverse diameter of the left atrium, respectively, and BSA = 0.0061 × height + 0.0128 × weight - 0.1529. Body mass index (BMI) = weight (kg) / height^2 (m^2). eGFR (ml/min/1.73m^2) = $141 \times \min(\text{Scr}/0.7, 1)^{-0.329} \times \max(\text{Scr}/0.7, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \times 1.159$ according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

2.4 | Laboratory index measurement

The plasma levels of the NT-proANP, corin (R&D Systems, Minneapolis, USA), PlGF, and sFlt-1 (Signalway Antibody, TX, USA) were measured by enzyme-linked immunosorbent assay (ELISA) kits, and the sFlt-1/PlGF ratio of each sample was calculated.

2.5 | Statistical analysis

All data were analyzed by SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as the mean ± standard deviation. Non-normally distributed data were represented by the median (interquartile range). Qualitative information expressed as a percentage (%). The Student's t-test or the Mann–Whitney nonparametric test were used to assess the average difference between groups if the data were continuous variables. And the chi-square test was selected if the data were categorical variables. The Pearson or Spearman correlation analysis was used to determine the correlation between the two variables, and stepwise multiple linear regression analysis was selected to evaluate the relationship between NT-proANP, corin, sFlt-1/PlGF ratio, and target organ function. Logistic regression was used to identify significant predictors of urine protein. $p < .05$ was considered to be statistically different.

3 | RESULTS

3.1 | Demographic characteristics and comparison of renal, heart function between the HDP and control groups

There were no significant differences in age, height, weight, BMI, and fast blood glucose between the control group and the HDP group (all $p > .05$). Both the SBP and the DBP of the HDP group were significantly higher than those of the control group ($p < .001$ each). The LDL-c, TC, and TG levels of the HDP group were increased, but the HDL-c level was lower ($p < .05$). The creatinine and urine protein levels were significantly increased in the HDP group, while the eGFR level in the HDP group was lower than that in the control group ($p < .05$ each). Regarding the results of the echocardiography, compared with the control group, the HDP group showed larger LAD, LAVI, left ventricular

TABLE 1 Characteristics of the study population and comparison of renal, cardiac function between the HDP and control group

Parameter	Control group	HDP group	*p*-value
Age (year)	31.31 ± 4.037	30.90 ± 3.982	.577
Height (cm)	162.8 ± 4.829	162.3 ± 5.048	.556
Weight (kg)	66.93 ± 9.841	69.53 ± 14.65	.275
BMI (kg/m^2)	25.30 ± 3.850	26.33 ± 5.047	.229
SBP (mm Hg)	115.6 ± 8.010	161.4 ± 22.27	< .001*
DBP (mm Hg)	74.8 ± 7.458	102.9 ± 14.72	< .001*
Glu (mmol/L)	4.37 ± 0.814	4.50 ± 0.829	.379
TC (mmol/L)	6.103 ± 0.898	6.782 ± 1.833	.017*
TG (mmol/L)	3.237 ± 1.238	3.755 ± 1.864	.093
LDL-C (mmol/L)	3.05 (2.64, 3.43)	3.815 (3.018, 4.563)	< .001*
HDL-C (mmol/L)	1.880 (1.625, 2.210)	1.690 (1.400, 2.010)	.041*
Creatinine (mmol/L)	45.82 ± 8.671	55.15 ± 12.15	< .001*
eGFR (ml/min/1.73m^2)	128.9 ± 9.848	118.8 ± 14.33	< .001*
Urine protein (*n*, %)	– (30, 61.2%)	– (0, 0)	< .001*
	–/+ (5, 10.2%)	–/+ (8, 10.3%)	
	+ (13, 26.5%)	+ (26, 33.3%)	
	++ (1, 2.1%)	++ (20, 25.6%)	
	+++ (0, 0)	+++ (22, 28.2%)	
	++++ (0, 0)	++++ (2, 2.6%)	
LAD (mm)	33.43 ± 3.279	35.73 ± 3.670	< .001*
LVEDD (mm)	44.04 ± 3.764	45.19 ± 5.152	.178
LVST (mm)	9.347 ± 1.128	10.24 ± 1.175	< .001*
LVPWT (mm)	9.224 ± 1.046	10.0 ± 1.128	< .001*
LAVI (ml/m^2)	17.60 ± 4.537	21.58 ± 7.058	< .001*
LVEF (%)	57.18 ± 2.108	56.95 ± 2.643	.600

Abbreviations: BMI, body mass index; HDP, hypertensive disorders of pregnancy; SBP, systolic blood pressure; DBP, diastolic blood pressure; Glu, glucose; TC, total cholesterol; TG, total triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter; LVST, left ventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.
*$p < .05$, compared with the control group.
Values are means ± SDs.

posterior wall thickness (LVPWT), and left ventricular septal thickness (LVST) ($p < .001$ each). There were no significant differences in the left ventricular end diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) ($p > .05$ each) (Table 1).

3.2 | Comparison of plasma NT-proANP, corin, and sFlt-1/PlGF ratio between the two groups

The NT-proANP and corin in the HDP group were significantly increased compared with the control group (2.364 ± 0.887 vs. 1.489 ± 1.213 nmol/L, $p = .001$; 2379 ± 786.531 vs. 1341 ± 560.132 pg/ml $p < .001$). The sFlt-1/PlGF ratio of the HDP group was significantly increased than that of the control group (1.355 [0.865–2.126] vs. 0.765 [0.577–1.103], $p < .001$) (Figure 2).

3.3 | Correlation of NT-proANP, corin, and sFlt-1/PlGF ratio with target organ dysfunction

In the HDP group, the corin levels were positively correlated with creatinine ($r = 0.353$, $p = .020$), while negatively correlated with eGFR ($r = -0.394$, $p = .009$). The NT-proANP levels were significantly positively correlated with urine protein ($r = 0.337$, $p = .036$), and positively correlated with LAD ($r = 0.387$, $p = .010$). There was no significant correlation between the sFlt-1/PlGF ratio and eGFR, urine protein, creatinine, and LAD (all $p > .05$) (Table 2). In the control group, the NT-proANP, corin levels and sFlt-1/PlGF ratio were not significantly correlated with creatinine, urine protein, eGFR and LAD (all $p > .05$) (Table S1).

Stepwise multiple linear regression was used for analysis in the HDP group with creatinine, eGFR, LAD, LVEDD, LVST, LVPWT, LVEF, and LAVI as dependent variables, meanwhile age, height, weight, SBP, DBP,

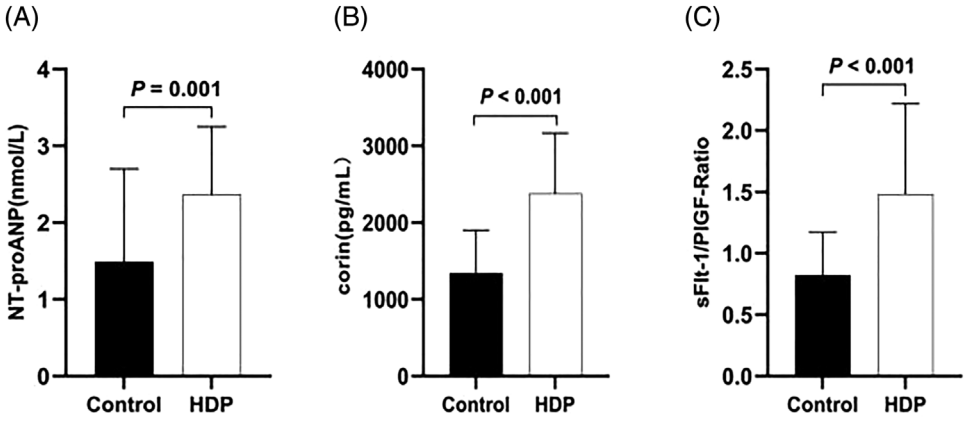

FIGURE 2 Comparison of the plasma NT-proANP, corin, and sFlt-1/PlGF ratio between the two groups. (A) Plasma concentration of NT-proANP. (B) Plasma concentration of corin. (C) Plasma concentration of sFlt-1/PlGF-Ratio. HDP, hypertensive disorders of pregnancy; NT-proANP, N-terminal pro-atrial natriuretic peptide; sFlt-1/PlGF, serum soluble tyrosine kinase-1/placental growth factor

TABLE 2 Correlation of NT-proANP, corin, and sFlt-1/PlGF ratio with creatinine, urine protein, eGFR and LAD in the HDP group

	NT-proANP (nmol/L)		Corin (pg/ml)		sFlt-1/PlGF ratio	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Creatinine (mmol/L)	0.124	.430	0.353	.020*	−0.151	.334
Urine protein	0.337	.036*	0.131	.426	−0.248	.128
eGFR (ml/min/1.73m^2)	−0.160	.307	−0.394	.009*	0.201	.197
LAD (mm)	0.387	.010*	0.280	.069	0.064	.684

Abbreviations: NT-proANP, N-terminal pro-atrial natriuretic peptide; sFlt-1/PlGF, serum soluble tyrosine kinase-1/placental growth factor; LAD, left atrial diameter; eGFR, estimated glomerular filtration rate.
*$P < 0.05$.

fast blood glucose, TC, TG, LDL-c, HDL-c, NT-proANP, corin, and sFlt-1/PlGF ratio as independent variables. Stepwise multiple linear regression showed that Corin was an independent predictor for creatinine and eGFR in the HDP group. NT-proANP was an independent predictor for LAD (Table 3). Logistic regression analysis of urine protein in hypertensive disorders of pregnancy patients with age, height, weight, SBP, DBP, fast blood glucose, TC, TG, LDL-c, HDL-c, NT-proANP, corin, and sFlt-1/PlGF ratio were used as independent variables. Multivariate logistic regression analysis showed that NT-proANP was a significant predictor of urine protein (OR: 5.474, 95% CI: 1.147-26.119, $p = .033$) (Table S2).

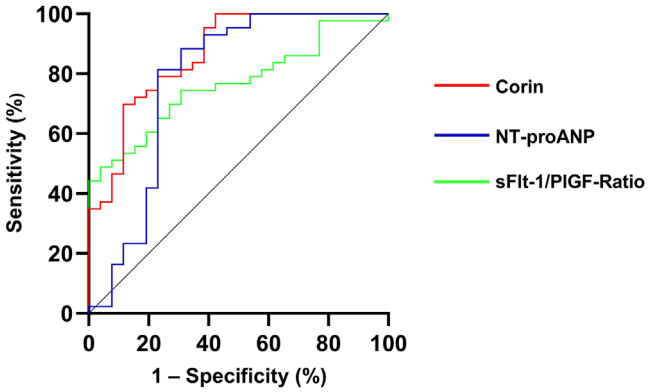

FIGURE 3 ROC curves for predicting the severity of pregnant women with or without hypertension. Blue line: NT-proANP; Red line: Corin; Green line: sFlt-1/PLGF ratio; NT-proANP, N-terminal pro-atrial natriuretic peptide; sFlt-1/PlGF, serum soluble tyrosine kinase-1/placental growth factor

3.4 | Comparison of ROC curves of NT-proANP, corin, and sFlt-1/PlGF ratio in pregnancy with or without hypertension

The sensitivity and specificity of NT-proANP at a cut-off value of 151.1 nmol/L were 81.4% and 76.9%, with an AUC of 0.779 (95% CI, 0.644–0.914). The sensitivity and specificity of corin at a cut-off value of 1891.8 pg/ml were 69.8% and 88.5%, with an AUC of 0.867 (95% CI, 0.778–0.955). The sensitivity and specificity of sFlt-1/PlGF ratio at a cut-off value of 138.6 were 48.8% and 96.2%, with an AUC of 0.766 (95% CI, 0.656–0.875) (Figure 3 and Table 4). The corin showed better predictive ability compared with the sFlt-1/PlGF ratio ($p < .001$), however, there was no statistical significant difference between NT-proANP and sFlt-1/PlGF ratio ($p = .660$).

TABLE 3 Stepwise multiple linear regression analysis of creatinine, eGFR, LAD, LVEDD, LVST, LVPWT, LVEF, and LAVI in HDP patients

	Independent variables	β-coefficient	t-value	p value
Creatinine	Corin	0.353	2.414	.020
eGFR	Age	−0.472	−3.744	.001
	Corin	−0.334	−2.646	.012
LAD	SBP	−0.346	−2.506	.016
	NT-proANP	0.321	2.321	.025
LVEDD	SBP	0.538	4.088	< .001
LVST	SBP	0.699	6.260	< .001
LVPWT	SBP	0.500	3.695	.001
LVEF (%)	SBP	−0.463	−3.345	.002
LAVI	Height	−0.420	−3.023	.004
	Weight	−0.318	−2.285	.028
	DBP	0.394	3.090	.004

Abbreviations: eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter; LVST, left ventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; NT-proANP, N-terminal pro-atrial natriuretic peptide.

TABLE 4 Comparison of ROC curve in the HDP and control group

	AUC (95%-CI)	Threshold	Sensitivity (%)	Specificity (%)	p-value
NT-proANP	0.779 (0.644–0.914)	151.1	81.4	76.9	< .001
Corin	0.867 (0.778–0.955)	1891.8	69.8	88.5	< .001
sFlt-1/PlGF-Ratio	0.766 (0.656–0.875)	138.6	48.8	96.2	< .001

Abbreviations: AUC, Area under the curve; CI, Confidence interval; NT-proANP, N-terminal pro-atrial natriuretic peptide; sFlt-1/PlGF, serum soluble tyrosine kinase-1/placental growth factor.

4 | DISCUSSION

Our results showed that the plasma levels of the NT-proANP and corin in the HDP group were significantly increased in the population of Northeast China. Consistent with the findings by Thompson that corin and NT-proANP levels were significantly increased in preeclampsia patients in the United States, other studies showed that patients with higher levels of plasma corin were more likely to develop eclampsia in the mid-pregnancy early stage in the Japanese population.[13,14] In a prospective study, it was demonstrated that the corin levels of hypertensive disorders of pregnancy patients during late pregnancy were higher than those in normal-tensive pregnant women. Moreover, the increment in corin content was directly related to the increased blood pressure in late pregnancy.[15]

ANP, cleaved by corin from proANP in the heart, plays an important role in blood pressure regulation and sodium homeostasis. A study showed that corin and ANP in the pregnant uterus promote trophoblast invasion and spiral artery remodeling, and that a defect in corin and ANP may contribute to pre-eclampsia.[5] Meanwhile, Finn–Sell and coworkers reported that ANP nonspecific knockout mice did not show hypertension and proteinuria before or during pregnancy.[16] However, a recent study showed that corin knockout mice exhibit pregnancy-associated hypertension.[17] Scholars found that mice lacking corin and ANP in the uterus were prone to develop hypertension and proteinuria during pregnancy,[5] characteristics of preeclampsia. The intrauterine defection of corin and ANP leads to hypertensive disorders of pregnancy, while elevated blood pressure leads to additional corin and ANP secreting by atrial released into the plasma. Therefore, the high level of plasma corin and ANP was cardiac in origin. But, some scholars have found that the high level of plasma corin in preeclampsia may be placental in origin.[18] The mechanisms of corin and ANP in the pathophysiology of hypertensive disorders of pregnancy still need to be further explored.

Our previous study reported that the plasma levels of NT-proANP and corin were associated with neonatal adverse events in hypertensive disorders of pregnant patients.[7] In this study, we found that plasma NT-proANP was an independent risk factor for LAD and urine protein, and corin was an independent risk factor for creatine and eGFR in hypertensive disorders of pregnancy patients, whereas there was no significant correlation in pregnant women with normal blood pressure. A study of the population of a community discovered that elevated NT-proANP was an independent predictor of cardiovascular events and mortality.[19] Another study revealed that patient mortality increased after a stroke and acute myocardial infarction with elevated plasma NT-proANP levels.[20] Previously, a study confirmed that elevated ANP in the elderly was associated with chronic kidney disease regardless of

heart disease.[21] All this evidence demonstrates that ANP may be an evaluated marker for cardiovascular disease. For the first time, we have found that ANP and corin are independent risk factors for cardio and renal functions in hypertensive disorders of pregnancy, which suggests they may be predictors in evaluating heart and renal target organ damage in hypertensive disorders of pregnancy.

The sFlt-1/PlGF ratio was reported as a sensitive predictor for preeclampsia.[8,22,23] Studies have found that preeclampsia is characterized by the conversion of angiogenesis and antiangiogenic factors to inappropriate placental circulation.[8,24] Hypoxia caused by placental defects is an important link in the development of preeclampsia.[24] Under hypoxic conditions, the level of PlGF in the circulation decreases, while the level of sFlt-1 increases, and the expression of sFlt-1, mRNA and protein in the placenta also increases significantly.[25] We also found that the sFlt-1/PlGF ratio increased in the HDP group. Previous studies demonstrated that the sFlt-1/PlGF ratio can be used to predict preeclampsia within 1 week during the middle and late stages of pregnancy.[10] Lehnen and coworkers[8] found that the sFlt-1/PlGF ratio had high specificity but low sensitivity for preeclampsia and was less sensitive for other types of hypertensive disorders of pregnancy. Furthermore, sFlt-1/PlGF ratio was not correlated with heart and renal function in hypertensive disorders of pregnancy. Therefore, sFlt-1/PlGF ratio could not be used as a reliable biomarker for evaluating hypertensive disorders of pregnancy. The results of our study showed that the AUC for NT-proANP and corin was larger and the sensitivity was higher than the sFlt-1/PlGF ratio. Therefore, NT-proANP and corin were more valuable than the sFlt-1/PlGF ratio in hypertensive disorders of pregnancy.

In summary, the plasma levels of NT-proANP and corin were significantly increased in hypertensive disorders of pregnancy patients and were related to the target organ function. The NT-proANP and corin were more predictive than the sFlt-1/PlGF ratio. Thus, NT-proANP and corin are expected to be reliable biomarkers for evaluating the severity of target organ damage in hypertensive disorders of pregnant patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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