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Expression and clinical significance of lncRNA non-coding RNA activated by DNA damage (NORAD) in patients with gestational hypertension

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ABSTRACT

Objectives: Gestational hypertension (GH), the most common type of hypertensive disorders in pregnancy, often occurs in women during pregnancy. The purpose of this study was to investigate the expression and clinical significance of lncRNA NORAD in gestational hypertension, and to discuss the possibility of lncRNA NORAD as a diagnostic marker of gestational hypertension.

Material and methods: A total of 219 participants were involved in the study. Basic clinical information of all participants was collected, and the expression of NORAD in serum was detected by RT-qPCR. ROC curves were drawn to evaluate the diagnostic value of NORAD expression for gestational hypertension. Multiple linear regression analysis was done to explore the relationship between NORAD and clinical variables. Logistic regression analysis was conducted to analyze the independent influence of different variables on the development of gestational hypertension into preeclampsia.

Results: The expression level of NORAD in gestational hypertension was higher than that of healthy individuals, and the expression level of NORAD in preeclampsia was higher than that of gestational hypertension and healthy individuals. The ROC curve suggested that the expression of NORAD has a higher diagnostic value for gestational hypertension. Multiple linear regression analysis showed that systolic blood pressure (SBP) and diastolic blood pressure (DBP) were correlated with the expression of NORAD. SBP, DBP and NORAD were all factors that affect the development of gestational hypertension to preeclampsia, which were known by logistic regression analysis.

Conclusions: LncRNA NORAD may be used as a biomarker for gestational hypertension diagnosis and can influence its progression into preeclampsia.

Key words: lncRNA NORAD; gestational hypertension; preeclampsia; diagnostic

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INTRODUCTION

Hypertensive disorders in pregnancy are common obstetric diseases, accounting for 5~10% of all pregnancies [1, 2], and the resulting maternal deaths account for about 10~16% of the total number of pregnancy-related deaths, while the second leading cause of maternal deaths [3, 4]. At present, there are clear and widely accepted standards for the classification and diagnosis of hypertensive disorders in pregnancy at home and abroad. According to the basis of disease and the degree of organ damage, hypertensive disorders in pregnancy are divided into five categories, namely, gestational hypertension (GH), preeclampsia, eclampsia, chronic hypertension with preeclampsia, and chronic hypertension [5]. Based on current understanding, the causes of hypertensive disorders in pregnancy may involve a variety of factors such as maternal, placenta, and fetus, including abnormal immune regulation, genetic factors, and nutritional factors [1]. However, the etiology and mechanism of the disease cannot be clearly explained at present [6–8]. Therefore, in order to ensure the health and improve the prognosis of mothers and infants, clinical diagnosis and prevention of the condition of pregnant women should not be neglected.

RNA molecules that are longer than 200 nucleotides and have no coding ability are called long non-coding RNA (lncRNA) [9, 10]. It has been confirmed that lncRNA plays an important role in epigenetic regulation, cell cycle regulation, and cell differentiation regulation [11], which has been

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regarded as a biomarker for diagnosis or prognosis in terms of molecular regulation, providing more possibilities for the treatment of a variety of diseases [12, 13]. Song et al. [14] have confirmed that some lncRNAs may participate in the pathogenesis of preeclampsia through methylation and signaling pathways. Sun et al. [15] also studied the effect of the lncRNA-HEIPP expression on the pathogenesis of preeclampsia. These findings suggested that lncRNA may play a role in hypertensive disorders in pregnancy.

Non-coding RNA Activated by DNA damage (NORAD) is highly conserved and expressed in large quantities. In humans, the NORAD gene is located at CHR20Q11.23 with a transcription length of 5.3 kb [16, 17]. NORAD is involved in the maintenance of genomic stability and regular mitosis, and can specifically bind to a variety of proteins in the nucleus [18]. Studies have shown that NORAD may be involved in the occurrence and development of cancer in the body and has an impact on the proliferation, invasion, and apoptosis of cancer cells [19, 20]. NORAD has been proven to inhibit cell senescence, apoptosis, and atherosclerosis [20]. Silencing NORAD has been verified by reducing KLF5 to inhibit the formation of atherosclerotic plaque [21]. It is known that high blood pressure is a key risk factor for atherosclerosis, which influences each other and acts as a cause and effect for each other. Based on this speculation, NORAD may affect the process of gestational hypertension.

In conclusion, this study aims to explore the expression and clinical significance of serum lncRNA NORAD in patients with gestational hypertension and to understand its potential as a biomarker for the diagnosis of gestational hypertension.

MATERIAL AND METHODS

Sample of clinical participants

Participants (n = 219) from Anhui No.2 Provincial People's Hospital were selected as clinical samples, which included healthy individuals (n = 73), gestational hypertension (n = 74), and preeclampsia (n = 72). Diagnostic criteria for gestational hypertension: in the third trimester of pregnancy (> 20 weeks), the SBP increases to 140 mmHg or the DBP increases to 90 mmHg or more, or both. Diagnostic criteria for preeclampsia: hypertension (blood pressure ≥ 140/90 mmHg) and proteinuria (urinary protein ≥ 0.3 g within 24 h) in pregnant women at the end of pregnancy (> 20 weeks). All participants underwent auxiliary routine examinations such as blood routine and urine routine and excluded the history of multiple pregnancies and trauma. All the included participants recorded and analyzed maternal data such as maternal medical and obstetric data, fetal conditions, and the collected experimental blood samples were stored in a –80°C refrigerator for subsequent research. Without surgery or other treatment, participants should sign informed consent as required under the approval of the scientific research ethics committee of Anhui No.2 Provincial People's Hospital.

Real-time quantitative PCR assay

Total RNA was extracted from serum by TRIzol reagent (Invitrogen, USA). RNA was reverse transcribed into cDNA using the SuperScript II Reverse Transcriptase Kit (Invitrogen, USA). The reaction system was then formulated according to the requirements of the SYBR®Green PCR Kit (TaKaRa, Japan) and detected in a 7500 Real-time PCR system (Applied Biosystems, USA). Finally, with Glyceraldehyde phosphate dehydrogenase (GAPDH) as an internal reference, the NORAD level was calculated by the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

The experimental data were analyzed using SPSS 20.0 and GraphPad Prism 7.0 software. The data conforming to the normal distribution were represented by n or mean ± standard deviation. Student *t*-test was taken to compare the differences between the two groups. Multiple linear regression analysis was done to explore the relationship between NORAD and clinical variables. Logistic regression was used to analyze the relationship between different variables and the development of gestational hypertension into preeclampsia. The diagnostic value of NORAD was evaluated by the ROC curve. $P < 0.05$ is considered statistically significant.

RESULTS

Basic information of participants

The relevant clinical information of the participants is shown in Table 1. All participants (n = 219) were divided into healthy individuals (n = 73), gestational hypertension (n = 74) and preeclampsia (n = 72). According to the statistical results, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the participants in gestational hypertension and preeclampsia groups were higher than those in the healthy individuals ($p < 0.001$), while the participants' age, gestation period, body mass index (BMI), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were not statistically significant ($p > 0.05$).

The expression of NORAD and its clinical relevance

The expression detection of lncRNA NORAD is shown in Figure 1. In the serum of gestational hypertension and preeclampsia, the expression of NORAD was increased compared with healthy individuals. Among them, the expression of NORAD in gestational hypertension was higher than that in healthy individuals, and the expression of NORAD in

Table 1. Basic clinical information of the participants

Indicators	Participants (n = 219)			p value
	Healthy individuals (n = 73)	Gestational hypertension (n = 74)	Preeclampsia (n = 72)	
Age [years]	27.99 ± 2.47	28.46 ± 2.73	28.83 ± 2.74	0.158
Pregnancy [week]	37.08 ± 1.85	36.64 ± 1.89	36.75 ± 1.87	0.326
BMI [kg/m^2]	23.74 ± 3.63	24.75 ± 3.29	24.44 ± 3.99	0.230
TG [mmol/L]	1.25 ± 0.27	1.26 ± 0.36	1.32 ± 0.31	0.350
HDL-C [mmol/L]	1.20 ± 0.20	1.18 ± 0.17	1.15 ± 0.13	0.223
LDL-C [mmol/L]	2.12 ± 0.41	2.10 ± 0.36	2.18 ± 0.47	0.506
SBP [mmHg]	113.73 ± 7.81	143.88 ± 12.26	153.14 ± 19.06	< 0.001
DBP [mmHg]	73.37 ± 4.23	92.95 ± 2.00	95.38 ± 3.42	< 0.001

BMI — body mass index; TG — triacylglycerol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; SBP — systolic blood pressure; DBP — diastolic blood pressure; Data are expressed as n or mean ± standard deviation

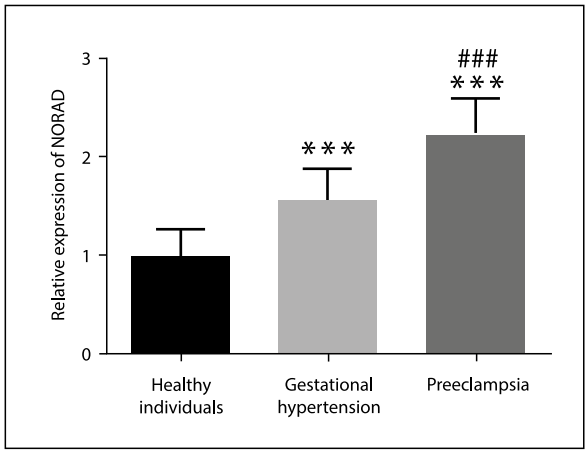

Figure 1. The relative expression of non-coding RNA Activated by DNA damage (NORAD) in gestational hypertension and preeclampsia was markedly increased compared with healthy individuals; ***p < 0.001, compared with healthy individuals; ###p < 0.001, compared with the gestational hypertension group

preeclampsia was significantly up regulated compared with gestational hypertension and healthy individuals. In Table 2, the multiple linear regression analysis of NORAD-related variables showed that SBP and DBP were related to the expression of NORAD (p < 0.001).

The diagnostic value of NORAD and logistic regression analysis

The diagnostic value of NORAD for gestational hypertension was evaluated by the ROC curve. As shown in Figure 2, the area under the curve (AUC) was 0.909, the sensitivity was 85.1%, and the specificity was 89.0%, indicating that the expression of NORAD has a high diagnostic value for gestational hypertension. That is, NORAD may be chosen to diagnose gestational hypertension. The data in Table 3 suggested the relationship between different variables and the development of preeclampsia from gestational hypertension according to logistic regression analysis. Among the many characteristics, SBP (OR = 3.074, 95% CI = 1.332–7.093, p = 0.009), DBP (OR = 3.097, 95% CI = 1.361–7.047, p = 0.007) and NORAD (OR = 8.143, 95% CI = 3.573–18.561, p < 0.001) had an impact on the progression of gestational hypertension to preeclampsia, which means that NORAD may be considered as a reference factor to affect the health of pregnant women.

DISCUSSION

Hypertensive disorders in pregnancy are one of the main causes of morbidity and death in pregnant women and fetuses. Although the etiology of hypertension in pregnancy is currently unclear, obesity in pregnant women, atherosclerosis, hypertension, and other cardiovascular diseases, gestational diabetes is known to be risk factors [22, 23]. The clinical significance of gestational hypertension, one of the categories of clinical disorders in pregnancy, was explored in this study. Gestational hypertension is generally the first hypertensive disorder that occurs during pregnancy, with systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg, or both [24–26]. Pregnant women have negative urine protein, and a small number of patients may have upper abdominal discomfort or thrombocytopenia. And the most common complication of gestational hypertension is the development of preeclampsia, in which pregnant women have hypertension greater than 140/90 mmHg and proteinuria with urine protein ≥ 0.3 g (24 h) [27]. At the present stage, more conservative treatment methods are generally adopted for the treatment of gestational hypertension. The basic principle is to take rest and calm treatment to control the drop in blood pressure of pregnant women, extend the pregnancy period as much as possible, and protect the safety of mother and child. Atenolol, metoprolol, methyldopa, and other drugs are often used to control blood

Table 2. Multiple linear regression analysis on variables associated with lncRNA NORAD

Characteristics	Coefficient	Standard error	t	p value
Age [years]	–0.004	0.010	–0.396	0.693
Pregnancy [week]	0.005	0.014	0.380	0.704
BMI [kg/m^2]	0.006	0.008	0.768	0.444
TG [mmol/L]	0.146	0.079	1.839	0.068
HDL-C [mmol/L]	–0.026	0.173	–0.151	0.880
LDL-C [mmol/L]	0.049	0.064	0.769	0.443
SBP [mmHg]	0.010	0.003	3.872	< 0.001
DBP [mmHg]	0.076	0.014	5.660	< 0.001

BMI — body mass index; TG — triacylglycerol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; SBP — systolic blood pressure; DBP — diastolic blood

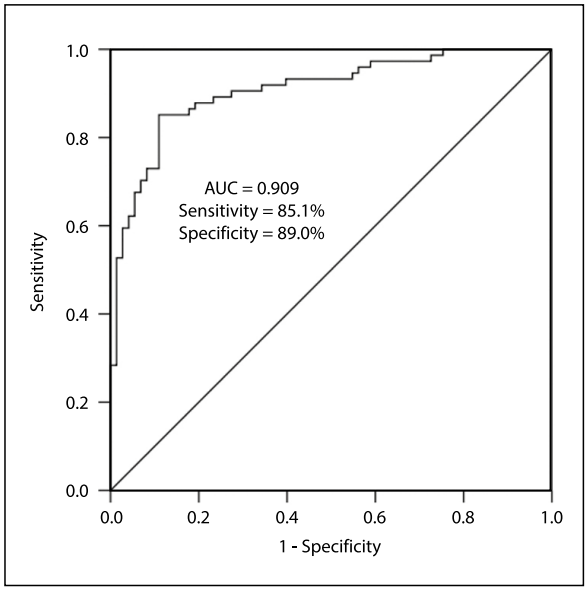

Figure 2. The receiver operating characteristic curve of non-coding RNA Activated by DNA damage (NORAD) was drawn to analyze the diagnostic significance in gestational hypertension, which shows that the area under the curve (AUC) is 0.909, the sensitivity is 85.1%, and the specificity is 89.0%

pressure, but the impact of drug side effects on pregnant women should be minimized [28, 29]. Therefore, to ensure the health of pregnant women and infants, and reduce morbidity and mortality, it is necessary to prevent and diagnose gestational hypertension in advance.

In this study, the expression level of NORAD in serum of healthy individuals, gestational hypertension, and preeclampsia was compared. It is concluded that NORAD was highly expressed in gestational hypertension. Group analysis found that the expression of NORAD in gestational hypertension was higher than that of healthy individuals, and the expression of NORAD in preeclampsia was higher than that of gestational hypertension and healthy individuals. Similarly, Dai et al. [30] detected the increased expression of lncRNA in patients with pregnancy-induced hypertension (including gestational hypertension and preeclampsia) through RT-qPCR. Fu et al. [21] found that inhibition of NORAD inhibited inflammation, oxidative stress, and lipid levels of the atherosclerotic aorta in mice. Exploring the clinical information of the participants further confirmed that the SBP and DBP of patients with gestational hypertension and preeclampsia were higher than those of healthy people, and the NORAD level positively correlated with SBP and DBP. The above results illustrated that the expression of NORAD may affect patients with gestational hypertension and participate in the process of hypertension. A large number of reports indicated that as a regulatory RNA, lncRNA NORAD was widely used in pathological processes such as diabetic nephropathy, atherosclerosis, tumors, and cancer [20, 31–33]. Studies have confirmed that lncRNA NORAD upregulated TLR4 by targeting miR-520h to promote cell proliferation, inhibit cell apoptosis, and aggravate the progression of diabetic nephropathy [34]. In addition, existing research results have shown that knockdown of NORAD under hypoxic conditions inhibits the angiogenesis-related ability of HUVECs, suggesting that angiogenesis is reduced [35]. Based on the above research, it is speculated that NORAD may be used as a regulatory gene to accelerate the disease of patients with diabetes. Therefore, the study of NORAD in gestational hypertension has a certain clinical value.

Gestational hypertension is defined as a hypertensive disease that occurs after 20 weeks of pregnancy with symptoms such as headache and blurred vision [36]. Among them, 5%~7% of patients can develop preeclampsia, a severe form of gestational hypertension, accompanied by symptoms such as severe headache, chest tightness, and proteinuria [37]. According to the ROC curve, the expression of NORAD has a high diagnostic value for gestational hypertension. Meanwhile, logistic regression analysis confirmed that NORAD is a reference factor for the development of

Table 3 Relationship between different variables and the development of gestational hypertension into preeclampsia

Characteristics	OR	95% CI	p value
Age [years]	1.056	0.476–2.342	0.894
Pregnancy [week]	1.483	0.645–3.408	0.353
BMI [kg/m^2]	1.113	0.492–2.516	0.797
TG [mmol/L]	1.220	0.536–2.777	0.636
HDL-C [mmol/L]	1.443	0.653–3.189	0.365
LDL-C [mmol/L]	1.088	0.478–2.477	0.840
SBP [mmHg]	3.074	1.332–7.093	0.009
DBP [mmHg]	3.097	1.361–7.047	0.007
LncRNA NORAD	8.143	3.573–18.561	< 0.001

OR — odds ratio; CI — confidence interval; BMI — body mass index; TG — triacylglycerol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; SBP — systolic blood pressure; DBP — diastolic blood pressure

gestational hypertension to preeclampsia. In other words, NORAD can be recognized as having the potential to diagnose gestational hypertension.

As far as existing screening methods are concerned, it has not been possible to accurately determine that pregnant women are at risk of gestational hypertension or preeclampsia in the first three months of pregnancy [38]. Therefore, with the gradual deepening of research on hypertension in pregnancy, the diagnosis of lncRNA has also become a research hotspot and focus. This study confirmed that the expression of NORAD has a certain regulatory effect on patients with hypertension in pregnancy and provides the corresponding theoretical basis. Further studies on the regulation of the disease and NORAD are needed if it is to be applied in clinical and follow-up treatment.

CONCLUSIONS

In summary, this study clarified that the expression of lncRNA NORAD in serum of gestational hypertension and preeclampsia was significantly increased. It was speculated that lncRNA NORAD may be used as a biomarker for gestational hypertension diagnosis.

Conflict of interest

All authors declare no conflict of interest.

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