


# Correlation Analysis of NAMPT rs61330082 Polymorphism in Type 2 Diabetes Mellitus Combined with Hypertension

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**Introduction:** This study aimed to investigate the association of Nicotinamide phosphoribosyl transferase (NAMPT) rs61330082 polymorphism with co-morbid hypertension (HTN) and the progression of hypertension in Chinese patients with type 2 diabetes mellitus (T2DM).

**Methods:** A total of 453 T2DM patients were genotyped for the polymorphism of rs61330082 using SNP-scan high-throughput technology. These patients were divided into T2DM group (261 patients) and T2DM combined with hypertension group (T2MH, 192 patients). The T2MH group was further categorized into Grade I, Grade II, and Grade III based on the results of the Hypertension Grade Score. Peripheral blood plasma urea, plasma creatinine, renin-angiotensin system (RAS) indexes, and lipid biochemistry indexes were measured in patients and analyzed in relation to NAMPT polymorphisms.

**Results:** We found that the presence of the NAMPT rs61330082-AA genotype was associated with a significantly increased risk of developing higher-grade hypertension in patients with T2MH. In addition, the A allele of the NAMPT rs61330082 gene displayed more associated in developing a higher grade of hypertension compared to the G allele. Also, the level of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) increased with hypertension grade in the NAMPT rs61330082-GG genotype.

**Conclusion:** NAMPT rs61330082 polymorphism was significantly associated with the progression of hypertension grade in T2MH patients and also affected plasma creatinine and LDL-c levels.

**Keywords:** NAMPT, polymorphism, T2DM, hypertension classification

## Introduction

Globally, the number of people with diabetes has increased exponentially over the past three decades and 90% of them have type 2 diabetes (T2DM).<sup>1</sup> The prevalence of diabetes mellitus in China increased from 10.9% to 12.4% between 2013 and 2018,<sup>2</sup> with approximately 60% of T2DM patients having comorbid hypertension,<sup>3</sup> and the combination of diabetes mellitus and hypertension produces a synergistic effect that significantly increases the risk of occurrence and progression of macrovascular and microvascular complications.<sup>4</sup> The prevalence is increasing in all age groups, but the trend is more severe in the younger age groups and there is substantial evidence of a strong correlation between morbidity and mortality from complications such as hypertension and cardiovascular disease.<sup>5,6</sup> Insulin resistance is a common pathway in the development of T2DM and hypertensive disease.<sup>7</sup> Nicotinamide phosphoribosyl transferase (NAMPT), an adipokine secreted primarily by macrophages and adipocytes, also known as visfatin and pre-B cell colony-enhancing factor, is considered to be an insulin mimetic factor and a potential regulator in inflammatory and immune processes,<sup>8,9</sup> and contributed to the onset of insulin resistance, a typical characteristic of T2DM.<sup>10</sup> Then, the

NAMPT gene is located between human chromosome 7q22.2 and q31.33 and contains 10 introns and 11 exons,<sup>11</sup> which was found to be associated with insulin resistance syndrome-related phenotypes in nondiabetic Mexican-Americans.<sup>12</sup>

Many studies have reported the association between NAMPT gene polymorphisms and hypertension<sup>13,14</sup> and its resulting cardiovascular diseases<sup>15,16</sup> and diabetes,<sup>17,18</sup> however, the conclusions are inconsistent. There are also no studies analyzing its association with T2DM combined with hypertension. Therefore, we explored the association of NAMPT gene polymorphisms with Chinese patients with T2DM combined with hypertension and their hypertension grading and analyzed its relationship with lipids.

## Materials and Methods

### Study Subjects

All subjects were 453 patients with T2DM diagnosed between September 2021 and January 2022 at Guilin Medical University Hospital. Patients included in the study were consecutive. Exclusion criteria included severe cardiovascular diseases such as severe heart failure, stroke all types of embolism, and other diabetic complications. Special conditions such as type 1 diabetes mellitus, abnormal liver and renal function, malignant tumors, autoimmune diseases, and pregnancy in women were also excluded. All subjects did not take any medication 12h prior to participation in the experiment. There were no statistically significant differences in age and gender between the T2DM and T2MH groups ( $p > 0.05$ ). All subjects were independent individuals without any genetic relationship. The study protocol was reviewed and approved by the Medical Ethics Committee (2023QTLL-37) of our institution and is in accordance with the Declaration of Helsinki. In addition, the diagnosis of type 2 diabetes mellitus in the included study population was based on American Diabetes Association (ADA) criteria of fasting glucose (FPG)  $\geq 126$  mg/dL (7.0 mmol/L) or 2-hour blood glucose (2-hour PG)  $\geq 200$  mg/dL (11.1 mmol/L) or Hemoglobin A1C (HbA1C)  $\geq 6.5\%$  (48 mmol/mol),<sup>19</sup> and the diagnosis of hypertension was based on the report of the Subcommittee of Professional and Public Education of the American Heart Association Council with a systolic blood pressure (SBP)  $\geq 130$  mmHg and/or diastolic blood pressure (DBP)  $\geq 80$  mmHg.<sup>20</sup> Hypertension grading criteria were based on the Eighth Joint National Committee's evidence-based management guidelines.<sup>21</sup> To determine the grading of high blood pressure without taking antihypertensive medication. Measurements need to be taken 2–3 times at 1–4 week intervals to determine elevated blood pressure and its grading. Grade I is SBP 140–159 mmHg and/or DBP 90–99 mmHg; Grade II is SBP 160–179 mmHg and/or DBP 100–109 mmHg; Grade III is SBP  $\geq 180$  mmHg and/or DBP  $\geq 110$  mmHg. The final hypertension classification was 144 patients due to missing data on blood pressure levels in some T2MH patients.

### Testing Indicators

Baseline information was collected from the clinical medical records of all participants, including data on age, sex, weight, blood pressure, blood glucose, plasma creatinine, plasma urea, lipids, adrenocorticotrophic hormone (ACTH), and RAS biochemical indices. Blood biochemical tests were performed in the Laboratory Department of Guilin Medical University Hospital (ISO15189 NO.ML00036). The biochemical indices of ACTH and RAS were gauged using the AutoLumo A6000 automatic chemiluminescence immunoassay analyzer, while the remaining indices were assessed with the Cobas 8000 biochemical analyzer. The levels of glycosylated hemoglobin were measured using automated ion exchange chromatography, with a reference range of 4.0–6.0% (Bio-Rad, CA). For HbA1c, the variation coefficient (CV) for both inter-assay and intra-assay instances was less than or equal to 3.1%, with values below 6.5%. The Friedewald equation was employed to calculate low-density lipoprotein cholesterol (LDL-C).<sup>22</sup>

### NAMPT Gene Polymorphism Analysis

The reagents and methods used for DNA isolation, primer design and genotyping were consistent with our previous studies. The PCR primer sequence information is as follows: NAMPT rs61330082 A/G (Forward: 5'-TTGTAAGTGTACTAG TATTACTACATT GGTGAGTTCC-3', Reverse: 5'-TTTTGTAAGTGTACTAGTATTACTACATTGGT GAGTCCT-3').

## Statistical Analysis

All statistical assessments were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Independent samples *t*-test and Mann–Whitney *U*-test were selected based on whether continuous variables conformed to a normal distribution. Three or more measurements were compared using the Kruskal–Wallis test or one-way ANOVA. Categorical variables and Hardy-Weinberg genetic balance were tested using the  $\chi^2$  test. Logistic regression analysis was used to assess the effects of known or potential risk factors on the emergence of T2MH and the analysis of interactions. P-values of less than 0.05 were considered statistically significant differences.

## Results

### Comparison of Clinical and Biochemical Characteristics

Patients with T2DM combined with hypertension had higher levels of Postprandial Blood Glucose (PBG) ( $P=0.028$ ), ACTH ( $P=0.009$ ), and blood pressure levels (SBP<0.001, DBP=0.055) than patients with T2DM. At the same time we performed binary regression analysis of the indicators with significant differences showing that SBP was an independent risk factor ( $P=0.002$ ) whereas PBG, ACTH and DBP ( $P>0.05$ ) were not. The rest of the clinical characteristics and biochemical indices were not statistically different, proving that our selected cohort was comparable (Table 1).

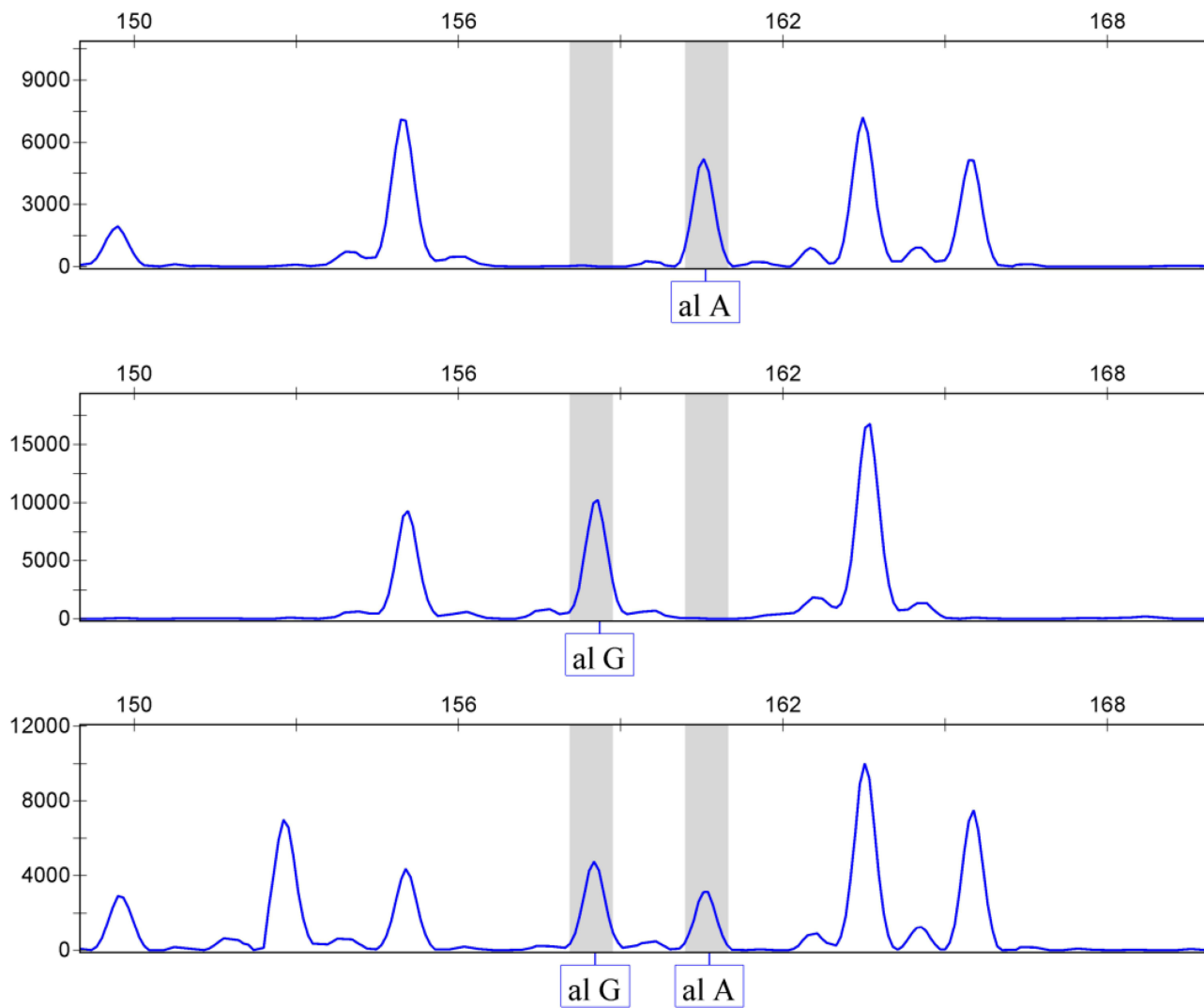
### The Relation Between NAMPT Gene Polymorphisms and T2MH

All genotypes and allele frequencies conformed to Hardy-Weinberg equilibrium (all  $P>0.05$ ). The genotype and allele distributions of NAMPT rs61330082 are shown in Figure 1, Tables 2 and 3. The results showed that the distribution of genotypes of NAMPT was not significant between the T2DM group and the comorbidity group but differed significantly among the different hypertension classifications of T2MH ( $\chi^2=10.675$ ,  $P=0.030$ ), with the AA genotype frequency being lowest in the Grade I group and the GG genotype frequency being lowest in the Grade III group. There was also a significant difference in A and G allele frequencies between the two groups ( $\chi^2=7.110$ ,  $P=0.029$ ), with the Grade III group having a higher A allele frequency than the Grade I and II group.

**Table 1** Clinical Characteristics of the Study Subjects

Variables	Total	T2DM Sufferers	T2MH Sufferers	P value
N	453	261	192	–
Age (years)	61.00(52.00–68.00)	61.00(52.00–67.00)	62.50(53.00–70.00)	0.061
M:F	273/180	159/102	114/78	0.740*
Weight (kg)	65.00(56.00–72.00)	65.00(55.00–70.00)	65.00(56.00–73.00)	0.518
SBP (mmHg)	136.00(124.00–154.00)	130.00(120.00–145.00)	143.00(127.50–157.50)	<0.001
DBP (mmHg)	85.00(78.00–95.00)	84.50(77.75–92.25)	87.00(79.00–97.50)	0.055
HbA1c (%)	8.30(6.80–10.20)	8.20(6.85–10.30)	8.40(6.70–10.20)	0.979
PBG (mmol/L)	8.32(6.12–12.76)	7.87(6.12–11.66)	9.54(6.07–13.93)	0.028
Plasma creatinine ( $\mu$ mol/L)	5.40(4.30–6.96)	5.39(4.33–6.69)	5.50(4.21–7.70)	0.441
Plasma urea (mmol/L)	74.00(62.00–91.00)	73.00(62.25–88.75)	77.00(61.00–101.00)	0.130
TG (mmol/L)	1.70(1.08–2.72)	1.68(1.05–2.70)	1.73(1.12–2.83)	0.414
TC (mmol/L)	4.60 $\pm$ 1.31	4.58 $\pm$ 1.30	4.63 $\pm$ 1.32	0.680**
HDL-c (mmol/L)	1.00(0.85–1.22)	1.01(0.85–1.21)	1.00(0.84–1.22)	0.651
LDL-c (mmol/L)	2.81 $\pm$ 1.00	2.86 $\pm$ 0.99	2.80 $\pm$ 1.22	0.508
ACTH (pg/mL)	15.03(5.89–29.40)	13.04(4.01–28.21)	19.44(7.40–33.40)	0.009
Angiotensin II (pg/mL)	117.02(101.42–159.44)	114.47(101.11–159.67)	121.20(102.41–165.57)	0.399
ALD (pg/mL)	15.79(8.36–31.46)	15.23(8.31–29.76)	17.15(8.45–32.08)	0.572
Ren (pg/mL)	135.67(106.38–186.39)	137.29(109.17–185.10)	135.68(102.70–191.44)	0.427
ALD/Ren	8.56(4.75–15.78)	9.41(5.40–15.86)	7.44(4.07–15.31)	0.198

**Notes:** All variables were calculated by Kolmogorov–Smirnov test, data with normal distribution was indicated by mean  $\pm$  standard deviation (SD), otherwise, it was presented by median (inter-quartile range, P25–P75). The P values were calculated by \*Pearson chi-square test, \*\*Independent-sample *t*-test and blank Mann–Whitney *U*-test, separately.



**Figure 1** Capillary electrophoresis peak map of rs61330082.

Considering confounding risk factors such as age, sex, and dyslipidemia, binary logistic regression analyses were used to estimate the dominance odds ratios (ORs) for the prevalence of hypertension in diabetic patients, and ordered logistic regression analyses were used to estimate the ORs for the progression of hypertension grading in patients with T2MH. The results of the binary and ordered logistic regression analyses (expressed as [T2DM vs T2MH]) as dependent variables, and blood pressure,

**Table 2** NAMPT Gene Polymorphism Relating in Chinese Patients with Type 2 Diabetes

Genotype and Allele		Total	T2DM	T2MH	Comparison	$\chi^2$	P value
NAMPTrs61330082	AA	205	70(26.8)	56(29.2)	AA vs GA+GG	0.303	0.528
	GA	211	124(47.5)	86(44.8)	GA vs AA+GG	0.329	0.566
	GG	41	67(25.7)	50(26.0)	GG vs AA+AG	0.008	0.929
	Total	453	261(100)	192(100)	AA vs GA vs GG	0.401	0.818
	A	462	264(50.6)	198(51.6)	A vs G	0.086	0.769
	G	444	258(49.4)	186(48.4)			

**Notes:** Data are shown as n(percent). The P values were calculated by chi-square test.

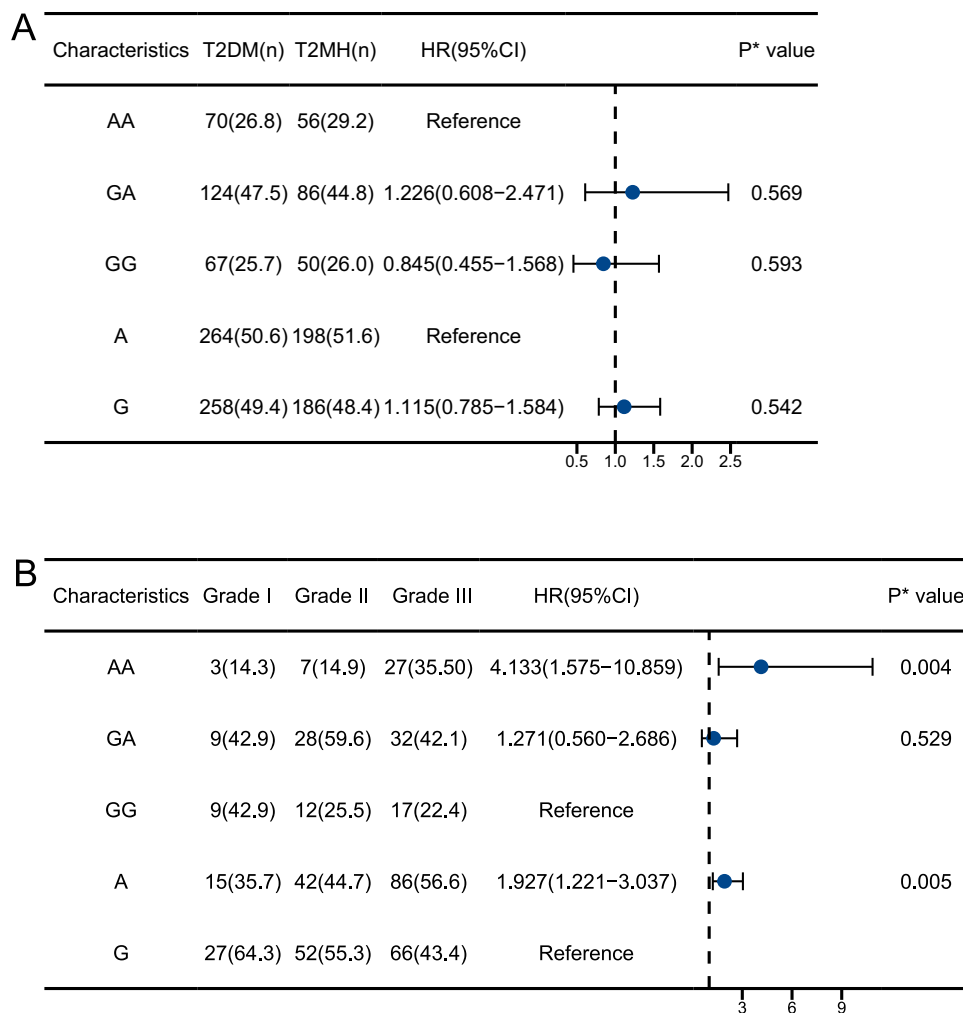
**Abbreviations:** NAMPT, nicotinamide phosphoribosyl-transferase; T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension.

**Table 3** NAMPT Gene Polymorphism Relating to Hypertension Classification in Chinese Patients with Type 2 Diabetes

Genotype and Allele		Total	Grade I	Grade II	Grade III	$\chi^2$	P value	HR (95% CI)	P* value
NAMPT rs61330082	AA	37	3(14.3)	7(14.9)	27(35.50)	10.675	0.030	3.149(1.051–6.347)	0.001
	GA	69	9(42.9)	28(59.6)	32(42.1)				
	GG	38	9(42.9)	12(25.5)	17(22.4)				
	Total	144	21(100)	47(100)	76(100)				
	A	143	15(35.7)	42(44.7)	86(56.6)	7.110	0.029	1.834(1.171–2.845)	0.008
	G	145	27(64.3)	52(55.3)	66(43.4)			Reference	
	Total	288	42(100)	94(100)	152(100)				

**Notes:** Data are shown as n(percent). The P values were calculated by chi-square test. The P\* values were calculated by logistic test.  
**Abbreviations:** NAMPT, nicotinamide phosphoribosyl-transferase; T2DM, type 2 diabetes mellitus; T2MH, type 2 diabetes mellitus with hypertension; HR, hazard ratio; CI, confidence interval.

FBG, ACTH and NAMPT genotype as covariates, respectively; and [Grade I vs Grade II vs Grade III] as dependent variables, and age, plasma creatinine and NAMPT genotype as covariates) showed that after adjusting for confounders, NAMPT gene polymorphisms and diabetes mellitus combined with hypertension were not significantly correlation (Figure 2A) but significant correlation with the progression of hypertension grading in T2MH patients (Figure 2B). The risk of graded progression of



**Figure 2** Analysis of regression. (A) T2DM vs T2MH, P\* Value was adjusted by blood pressure, FBG and ACTH as covariates (B) Grade I vs Grade II vs Grade III, P\* Value was adjusted by age and plasma creatinine as covariates.

hypertension was 3.609 times higher in the AA genotype than in the GG genotype (95% CI: 1.099, 11.857;  $P=0.034$ ). The risk of graded progression of hypertension was 1.903 times higher in the A allele than in the G allele (95% CI, 1.063, 3.404;  $P=0.030$ ). The risk of graded progression of hypertension was 1.903 times higher in the G genotype (95% CI, 1.063, 3.404;  $P=0.030$ ).

## The Relation Between Levels of Lipid Metabolism Indexes, ACTH, and NAMPT Gene Polymorphism in the T2DM Population

The results in Table 4 showed that all ACTH in the T2MH group was higher than that in the T2DM group, in which the difference in expression of GA genotype was statistically significant ( $P=0.008$ ). However, the differences in other lipid metabolism indexes (TG, TC, HDL-c, LDL-c) between the two were not statistically significant.

## Comparison of Baseline Data Between Different Hypertension Class Groups in the T2MH Group

Table 5 summarises the clinical and biochemical characteristics of T2DM patients with different hypertensive grades (21 Grade I, 47 Grade II, 76 Grade III). The differences in gender, body weight, blood glucose index, lipid metabolism index, TG, TC, ACTH, and RAAS system index were not statistically significant ( $P>0.05$ ). The mean age of the Grade I group was less than that of the Grade II and III groups ( $P=0.017$ ). We also found that the level of plasma creatinine Grade I < Grade II < Grade III ( $P=0.021$ ). The difference in blood pressure levels, although not statistically significant, also showed a stepwise increase (SBP,  $P=0.379$ ; DBP,  $P=0.241$ ).

## Association of NAMPT Gene Polymorphisms with Serum TG, TC, and Lipid Levels in T2DM Patients with Different Hypertension Grades

Table 6 demonstrates the comparison of NAMPT gene polymorphisms with serum TG, TC, and lipid levels in T2DM patients with different hypertension classifications. Both plasma creatinine and LDL-c showed an increase with increasing grade in T2MH patients expressing the GG genotype ( $P=0.014$ ;  $P=0.018$ ). This finding was absent in T2MH patients expressing AA and GA genotypes. Plasma urea, TG, TC, and HDL-c were not statistically significant in all three genotypes of T2MH patients with different hypertension grades ( $P>0.05$ ).

**Table 4** Association Between NAMPT (rs61330082) Polymorphism and Lipid Metabolism Index and ACTH

Variables	Groups	NAMPT rs61330082		
		AA	GA	GG
TG	T2MH	1.60(1.11–2.73)	1.80(1.10–3.00)	1.74(1.04–2.97)
	T2DM	1.72(1.07–2.32)	1.80(1.08–2.87)	1.49(0.84–2.63)
	P value	0.547	0.868	0.213
TC	T2MH	4.68±1.30	4.54±1.23	4.95±1.62
	T2DM	4.62±1.24	4.54±1.37	4.62±1.29
	P value	0.841	0.789	0.27
LDL-c	T2MH	2.72±0.90	2.73±1.04	3.08±1.26
	T2DM	2.87±0.95	2.80±0.92	2.86±1.01
	P value	0.177	0.505	0.385
HDL-c	T2MH	1.07(0.93–1.27)	0.96(0.85–1.17)	1.01(0.84–1.23)
	T2DM	1.05(0.92–1.22)	1.01(0.87–1.20)	0.99(0.83–1.28)
	P value	0.938	0.426	0.702
ACTH	T2MH	16.32(7.37–31.25)	21.89(8.50–39.11)	15.62(3.54–26.62)
	T2DM	12.09(6.48–22.43)	11.80(3.25–31.43)	14.11(4.10–28.15)
	P value	0.459	0.008	0.848

**Notes:** Data with normal distribution was indicated by mean ± standard deviation (SD), otherwise, it was presented by median (inter-quartile range, P25–P75). The p values were calculated by Mann–Whitney U-test.

**Table 5** Clinical Characteristics of the T2MH Patients

Variables	Total	Grade I	Grade II	Grade III	P value
N	144	21	47	76	–
Age (years)	64.00(55.00–71.00)	57.00(53.00–64.00)	68.00(58.00–72.00)	68.00(58.00–72.00)	0.017
M:F	85/59	13/8	30/17	42/34	0.617*
Weight (kg)	64.00(53.50–72.00)	59.00(56.00–68.00)	62.25(53.13–74.75)	66.00(56.00–72.5)	0.723
SBP (mmHg)	145.00(129.00–159.50)	145.00(117.00–153.50)	146.00(127.50–156.50)	145.00(131.00–165.00)	0.379
DBP (mmHg)	87.00(78.50–97.00)	78.00(70.50–97.00)	88.00(78.00–97.00)	87.00(81.00–98.00)	0.241
HbA1c (%)	8.30(6.70–10.20)	8.80(7.10–11.50)	8.40(6.68–10.30)	8.05(6.70–10.00)	0.461
PBG (mmol/L)	9.32(5.85–12.74)	9.85(5.70–19.10)	8.53(6.04–11.96)	9.32(5.57–13.03)	0.732
Plasma creatinine (μmol/L)	5.70(4.30–8.50)	4.36(3.87–6.13)	5.70(4.50–8.70)	6.20(4.55–8.68)	0.021
Plasma urea (mmol/L)	79.00(65.00–105.00)	70.00(59.75–92.50)	77.00(64.00–105.00)	85.00(66.25–108.75)	0.413
TG (mmol/L)	1.68(1.09–2.46)	2.16(1.61–3.82)	1.38(1.03–2.51)	1.38(1.03–2.51)	0.103
TC (mmol/L)	4.52±1.11	4.65±0.75	4.46±1.24	4.52±1.11	0.720 <sup>^</sup>
HDL-c (mmol/L)	1.00(0.85–1.22)	0.98(0.73–1.32)	0.99(0.82–1.13)	1.01(0.85–1.23)	0.599
LDL-c (mmol/L)	2.66(2.07–3.26)	2.72(2.22–3.23)	2.65(1.85–3.36)	2.61(2.05–3.26)	0.921
ACTH (pg/mL)	20.99(8.20–36.68)	19.02(8.82–37.43)	24.75(9.47–44.73)	19.24(7.06–29.33)	0.289
Angiotensin II (pg/mL)	123.58(104.45–166.69)	120.42(103.49–217.56)	124.07(104.99–167.78)	128.30(103.19–165.78)	0.966
ALD (pg/mL)	15.17(8.34–31.15)	15.98(5.20–73.34)	17.15(8.67–35.95)	14.60(8.26–34.67)	0.864
Ren (pg/mL)	138.80(102.48–193.63)	125.71(102.51–187.95)	142.96(101.45–208.36)	138.60(102.56–177.80)	0.744
ALD/Ren	7.89(4.05–15.81)	8.34(3.62–26.54)	7.43(3.92–19.20)	8.14(4.07–14.42)	0.910

**Notes:** All variables were calculated by Kolmogorov–Smirnov test, data with normal distribution was indicated by mean ± standard deviation (SD), otherwise, it was presented by median (inter-quartile range, P25–P75). The P values were calculated by \*Pearson chi-square test, <sup>^</sup>One-way ANOVA test and blank Kruskal–Wallis test.

**Table 6** Association Between NAMPT (rs61330082) Polymorphism and Lipid Metabolism Index in Different Grades T2MH Patients

Variables	Groups	AA	P value	GA	P value	GG	P value	P* value
Plasma creatinine	Grade I	4.12(4.02–4.21)	0.228	5.40(4.41–7.94)	0.856	4.00(3.50–4.50)	0.014	0.420
	Grade II	6.17(5.99–9.75)		5.65(4.60–8.60)		4.60(4.30–7.90)		
	Grade III	6.20(4.26–8.55)		5.75(4.65–8.40)		6.40(5.10–9.10)		
Plasma urea	Grade I	73.50(70.00–77.00)	0.689	70.00(58.00–91.00)	0.926	67.00(58.00–91.00)	0.247	0.094
	Grade II	93.00(72.50–107.00)		79.00(61.00–111.50)		74.00(65.00–83.00)		
	Grade III	81.00(62.00–105.00)		83.50(66.50–110.00)		88.00(68.00–100.00)		
TG	Grade I	2.97(2.24–3.70)	0.228	2.06(1.80–3.86)	0.188	2.07(1.04–2.92)	0.189	0.400
	Grade II	1.08(0.90–2.32)		1.57(1.14–2.90)		1.12(0.94–1.92)		
	Grade III	1.54(1.14–2.13)		1.59(1.09–2.23)		1.84(1.38–2.39)		
TC	Grade I	4.39(3.95–4.83)	0.943	4.80(4.41–5.25)	0.496	4.38(4.20–5.06)	0.824	0.880
	Grade II	4.60(3.83–4.76)		4.31(3.66–5.09)		4.90(3.87–5.54)		
	Grade III	4.16(3.76–5.33)		4.38(3.50–5.09)		4.69(4.43–5.44)		
HDL-c	Grade I	0.80(0.74–0.85)	0.164	0.98(0.88–1.35)	0.814	1.01(0.88–1.35)	0.763	0.111
	Grade II	1.01(0.79–1.17)		0.95(0.87–1.12)		1.06(0.83–1.32)		
	Grade III	1.10(0.91–1.30)		1.01(0.84–1.20)		0.98(0.85–1.19)		
LDL-c	Grade I	2.63(2.09–3.17)	0.906	2.86(2.68–3.38)	0.409	2.50(2.35–5.79)	0.018	0.086
	Grade II	2.20(1.96–2.83)		2.73(1.86–3.41)		2.92(2.03–3.44)		
	Grade III	2.34(2.05–3.00)		2.28(1.88–3.22)		3.15(2.91–4.24)		

**Notes:** Data are shown as median (inter-quartile range, P25–P75). The p values were calculated by Kruskal–Wallis test. The p\* values were calculated by regression analysis of interaction.

## Discussion

To the best of our knowledge, this is the first epidemiological study to investigate the association of NAMPT gene polymorphisms with susceptibility and hypertension grade in Chinese patients with type 2 diabetes and hypertension. We

found no statistically significant association between NAMPT gene polymorphisms and T2DM combined hypertension, but a significant correlation with its hypertension grade progression.

T2DM is a multifactorial metabolic disease characterized by insulin resistance and progressive decline in islet cell function. T2DM and HTN are related to each other, and their coexistence is linked to various diabetes-associated complications.<sup>23</sup> Although the underlying pathophysiological mechanisms remain elusive, genetic susceptibility as a key to T2DM and diabetes-related diseases is increasingly recognized. NAMPT as a nicotinamide adenine dinucleotide biosynthetic enzyme impacts multiple metabolic and stress responses and also plays a major role in regulating insulin secretion in pancreatic  $\beta$ -cells. Several NAMPT gene polymorphisms are related to T2DM and lipid profiles in different ethnic groups.<sup>24–27</sup> Therefore, it is crucial to investigate the link of NAMPT rs61330082 polymorphism with susceptibility to T2DM, HTN complication, and lipid profile in the Chinese population as it has never been evaluated and reported yet.

In the present study, we reported that NAMPT-rs61330082 genotype and allele frequencies were not significantly different between T2DM and controls but were significantly different in T2MH patients with different grades. The NAMPT rs61330082 polymorphism was also found to be unrelated to hypertension susceptibility in T2DM patients but associated with hypertension grade in T2MH patients, in which the AA genotype and the A allele were significant risk factors for the progression of hypertension grade. Although there are no previous studies on the correlation of NAMPT gene polymorphisms with T2MH and its hypertensive grade, some studies are showing its association with the progression of the risk of hypertension and related diseases. S Q<sup>28</sup> and Delicia<sup>29</sup> found that rs61330082 led to elevated triglyceride levels, severe systolic blood pressure, and severe hypertension in obese children. In patients with gestational hypertension, Marcel<sup>14,30</sup> found that rs61330082 affected circulating levels of visfatin while reducing the effectiveness of antihypertensive therapy. Meanwhile, NAMPT gene polymorphisms have been associated with susceptibility to other complications in patients with T2DM. Tarek's<sup>18</sup> study showed that the NAMPT-948G/T polymorphism was associated with a predisposition to cardiovascular disease (CVD) in patients with T2DM, and Pedro<sup>15</sup> showed that the NAMPT-rs9770242 polymorphism may increase the risk of coronary artery disease (CAD) in patients with T2DM. Therefore, we hypothesized that the potential mechanism by which rs61330082, located in the promoter region of the NAMPT gene, is associated with susceptibility to hypertension grade progression in patients with T2MH may be that the AA genotype or A allele of rs61330082 results in altered transcriptional activity, which affects the structure, function, or expression of NAMPT, and that this SNP may be a useful biomarker for assessing the progression of hypertension grades in T2MH in national populations.

Serum creatinine levels are strongly associated with T2DM<sup>31</sup> and hypertension.<sup>32</sup> We found that plasma creatinine levels were significantly different and increased with hypertension grade in patients with different grades of T2MH. Meanwhile, we found the same results in T2MH expressing the GG genotype. Therefore, we suspected that the NAMPT-GG genotype might contribute to the increase in hypertension grade by affecting plasma creatinine. Meanwhile, Jia<sup>33</sup> found in a previous study that genetic variants of NAMPT may affect lipid parameters in Chinese patients with T2DM, and Tokunaga<sup>34</sup> found that the NAMPT-1535 C/T polymorphism affected certain lipid levels in patients with T2DM, including reduced HDL-c levels and increased TG levels in patients with the TT genotype. Our study also found significant differences in LDL-c levels in the T2MH population expressing the GG genotype and rising with blood pressure class.

There are some limitations of our study and analyses that need to be pointed out. First, our research concentrated on the NAMPT polymorphic site, and future investigations should delve deeper into NAMPT's mechanisms in NOD mice and its impact on patients suffering from T2DM and hypertension. Additionally, the count of instances for certain indicators decreased owing to the absence of foundational clinical data. Thirdly, additional collection and analysis will be conducted on environmental risk elements linked to NAMPT gene variations.

## Conclusion

NAMPT rs61330082 polymorphism was significantly associated with the progression of hypertension grade in T2MH patients and also affected plasma creatinine and LDL-c levels.

## Data Sharing Statement

Data are available by the corresponding author upon reasonable request.



## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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