

ASSOCIATION OF BNP GENE SNP rs198389 WITH NT-proBNP LEVELS IN HYPOTHYROID PATIENTS PRIOR TO TREATMENT

ALAA SALMAN

Ishtar Medical Technical Institute, Iraq;
e-mail: alaas3223@gmail.com

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Background. Cardiovascular system is particularly responsive to fluctuations in thyroid hormone levels and hypothyroid patients are at an increased risk of worse cardiovascular outcomes. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a recognised biomarker for heart failure. Several studies indicate that thyroid disorders may influence blood NT-proBNP level, nevertheless, a consensus has not been established. **Objective.** To investigate the impact of the single nucleotide polymorphism rs198389 in NT-proBNP gene on the NT-proBNP serum level in patients with untreated primary hypothyroidism. **Methods.** The study included 100 newly diagnosed hypothyroid patients and 100 healthy controls, with NT-proBNP level measured with enzyme-linked fluorescent assay and genetic analysis conducted via PCR. **Results.** Our findings indicated significantly elevated NT-proBNP level across all genotypes (CC, CT, TT) in hypothyroid patients compared to controls. This elevation correlated strongly with thyroid-stimulating hormone level. **Conclusions.** The study demonstrated that NT-proBNP can discriminate between hypothyroid patients and healthy controls, but further studies are needed to establish its role in cardiovascular risk prediction.

Key words: NT-proBNP, single nucleotide polymorphisms, thyroid-stimulating hormone, hypothyroidism, correlation analysis.

Primary hypothyroidism is a condition characterized by insufficient production of thyroid hormones. It is among the most prevalent endocrine disorders worldwide, impacting roughly 4-10% of the population [1]. This condition, which is more prevalent in women and older adults, leads to a myriad of systemic effects due to the critical role played by thyroid hormones in metabolism, growth, and development [2]. Deficiency of these hormones, primarily thyroxine (T4) and triiodothyronine (T3), results in various metabolic derangements and can significantly impact cardiovascular well-being [3].

The cardiovascular system is particularly responsive to fluctuations in thyroid hormone levels. Thyroid hormones modulate cardiac output, heart rate, systemic vascular resistance, and blood pressure through direct and indirect mechanisms. Hypothyroidism has been associated with increased systemic vascular resistance, diastolic dysfunction, and a higher prevalence of atherosclerosis, contributing to an elevated risk of cardiovascular diseases (CVD). Studies have shown that hypothyroid patients are at

an increased risk of heart failure, coronary artery disease, and myocardial infarction [4, 5].

NT-proBNP (N-terminal pro-B-type natriuretic peptide) is a recognized biomarker for heart failure. It is generated in reaction to ventricular volume expansion and pressure overload, conditions frequently observed in cardiac dysfunction. Elevated NT-proBNP levels have been linked to worse cardiovascular outcomes in various populations, including those with heart failure, acute coronary syndrome, and other cardiovascular diseases [6, 7]. In the context of hypothyroidism, the altered hemodynamic state and elevated systemic vascular resistance may lead to elevated NT-proBNP levels, indicating cardiac stress and potential heart failure [8].

Brain natriuretic peptide (BNP) is a neurohormone produced by the ventricles in response to pressure overload. BNP and the amino-terminal prohormone of brain natriuretic peptide (NT-proBNP) are two forms of natriuretic peptides derived from proBNP. In comparison to BNP, NT-proBNP exhibits greater stability and possesses a longer bio-

logical half-life. Consequently, NT-proBNP serves as a superior marker for the diagnosis or exclusion of heart failure [9]. NT-proBNP serves as an effective biomarker for evaluating the severity and prediction of this illness [10]. Several studies indicate that thyroid disorders may influence blood NT-proBNP levels; nevertheless, a consensus has not been established. Numerous studies [11, 12] indicated that patients with hypothyroidism exhibited markedly higher NT-proBNP levels in comparison to euthyroid patients; however, other investigations reported no association between the two [13, 14]. This study aims to examine the impact of untreated primary hypothyroidism on NT-proBNP levels.

Single nucleotide polymorphism (SNP) in a gene such as NPPB (encoding NT-proBNP) may influence the expression and function of this biomarker [15]. Understanding these genetic variations can help in identifying individuals at higher risk for cardiovascular complications and tailoring personalized treatment strategies.

This study aims to assess the biochemical and genetic variation of NT-proBNP in patients with untreated primary hypothyroidism. By focusing on serum concentrations and genetic polymorphism, we seek to provide comprehensive insights into the cardiovascular risks associated with this endocrine disorder. We will analyze the correlations between this biomarker and various clinical and demographic characteristics, including age and gender, to understand its impact on cardiovascular health in hypothyroid patients.

Materials and Methods

The study enrolled 200 participants: 100 patients diagnosed with primary hypothyroidism and 100 healthy controls. All hypothyroid patients were newly diagnosed by an endocrinologist and had not begun treatment. The inclusion criteria were a TSH level >10 mIU/l and free T4 levels below the normal reference range. Controls were age- and gender-matched individuals with normal thyroid function tests. All participants underwent fasting blood glucose testing; those with a history of diabetes or fasting glucose ≥ 126 mg/dl were excluded.

Ethics approval and consent to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) at the Ishtar Medical Institute (approval no. 107, dated October 19, 2024) and with the 1964 Helsinki Decla-

ration and its later amendments, or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

Any subjects with renal failure, cardiovascular diseases, diabetes mellitus, anemia, obesity (BMI ≥ 35), pregnancy, pulmonary disease (such as pneumonia and COPD), and stroke patients were excluded from this study.

Biochemical analysis. This investigation was carried out in the Clinical Biochemistry Department's labs, the specialized center for endocrinology and diabetes/ Baghdad. Blood samples were collected from all participants from December 1, 2024, to April 30, 2025. Serum concentration of NT-proBNP was measured using enzyme-linked fluorescent assay (ELFA).

Genetic analysis. Genomic DNA was isolated from blood samples utilizing an established protocol (FavorPrep™ Genomic DNA Extraction Mini Kit). The BNP gene was amplified using polymerase chain reaction (PCR). Amplification was conducted using a programmed thermal cycler with gradient PCR capabilities. The primer sequence: Forward: 5'-CTG TGA GTC ACC CCG TGC TC-3', Reverse: 5'-GGC AGG AAC GCG CTG GAG AC-3' was used according to Al-Ibrahimi et al [16].

Amplification conditions for the BNP gene (NPPB):

Step	Purpose	t, °C	Time, min	Cycles
1	Initial denaturation	95	5	
2	DNA denaturation	95	1	35
	Primer annealing	58	1	
	Template elongation	72	1:30	
3	Final elongation	72	5	
4	Incubation	8	–	Hold

The amplified products were subsequently separated via electrophoresis [17] using a 2% agarose gel stained blue. The length of the product was 186 base pairs. The product was processed using the restriction enzyme MspI, as described in the procedures for *Moraxella* species [18].

Statistical analysis. Data were analyzed using SPSS software. Normality of continuous variables was assessed using the Shapiro-Wilk test. All data

were normally distributed ($P > 0.05$), allowing parametric tests. Differences in biomarker levels between groups were assessed using t -tests. The ANOVA test is used for comparison within groups. Genotype distributions were analyzed using chi-square tests. Correlation coefficients were calculated. Multiple linear regression analysis was performed to identify independent predictors of NT-proBNP in the hypothyroid group, including age, sex, BMI, and TSH. ROC curve analysis was conducted to evaluate the ability of NT-proBNP to discriminate between hypothyroid patients and healthy controls.

Results

The presence of extracted DNA was determined by agarose gel electrophoresis [19]. The isolated DNA was colorless; hence, bromophenol blue dye was utilized to facilitate the loading phase of the electrophoresis (Fig. 1).

The products of amplification were separated by electrophoresis on a 2% agarose gel with blue stain. The PCR result was 186 bp [20] (Fig. 2).

Analysis of the BNP gene polymorphism. The amplification and digestion results of the BNP gene via PCR-RFLP assay revealed T and C alleles and

Table 1. Demographic and clinical attributes of the study participants

Characteristic	Hypothyroidism ($n = 100$)	Controls ($n = 100$)	P -value
Age, years	52.3 ± 11.4	51.7 ± 12.1	0.74
Gender, M/F	40/60	38/62	0.78
BMI, kg/m ²	27.4 ± 3.5	26.9 ± 3.3	0.44
TSH, mIU/l	16.5 ± 4.2	2.4 ± 0.6	<0.001
Free T4, pmol/l	9.8 ± 1.2	16.5 ± 2.1	<0.001

Table 2. Serum concentration of biomarker among study groups

Parameter	Hypothyroidism ($n = 100$)	Controls ($n = 100$)	P -value
NT-proBNP, pg/ml	290.5 ± 85.7	95.4 ± 30.2	<0.001

Table 3. Genotype distributions of SNPs

SNP	Genotype	Hypothyroidism ($n = 100$)	Controls ($n = 100$)	P -value
rs198389 (NPPB)	C allele	106	95	0.35
	T allele	94	105	0.35
	CC	28	20	0.12
	CT	50	55	0.54
	TT	22	25	0.67

Note. $\chi^2 = 1.67$, $P > 0.05$ (not significant), $df = 1$

Table 4. Comparative analysis of mean NT-proBNP across studied groups based on genotype

Parameter	Genotype	Groups		P -value
		Hypothyroidism ($n = 100$)	Control ($n = 100$)	
mean NT-proBNP	CC	310.2 ± 90.5	102.5 ± 32.8	< 0.001
	CT	295.7 ± 87.2	97.3 ± 31.5	< 0.001
	TT	270.8 ± 82.1	90.4 ± 29.7	< 0.001
	P -value	0.064	0.081	

Note. P -value in ANOVA test utilised for comparisons between and within groups

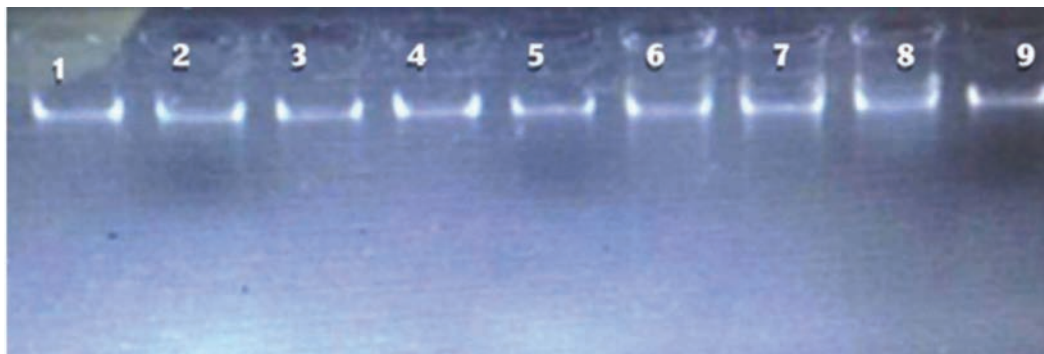


Fig. 1. Genomic DNA extracted from whole blood. From the left, lanes 1-4 contain DNA obtained from controls, while lanes 5-9 contain DNA obtained from patients, analyzed using a 1% agarose gel

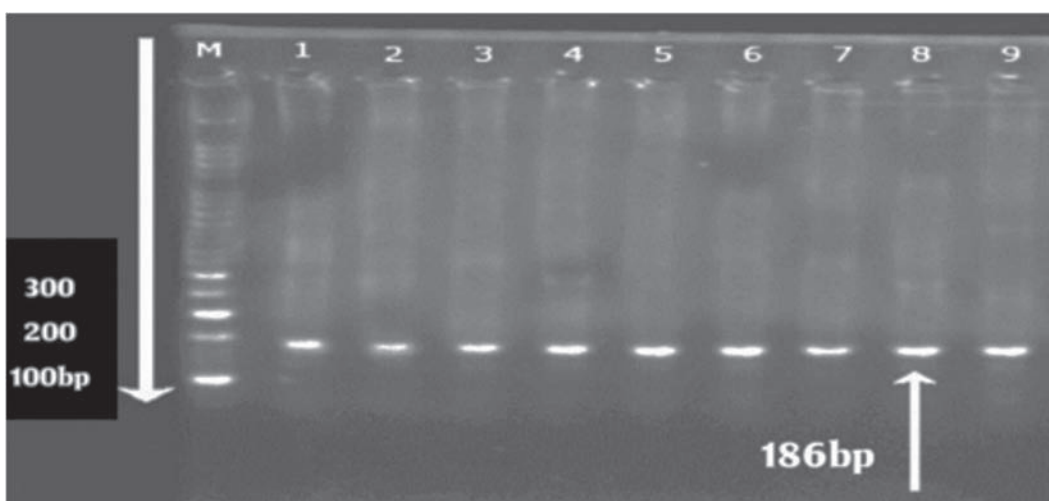


Fig. 2. Image of amplification and PCR product (186 bp) of the BNP gene on 2% agarose gel. Lane M, DNA ladder 100 bp; lanes 1-9, PCR products measuring 186 bp

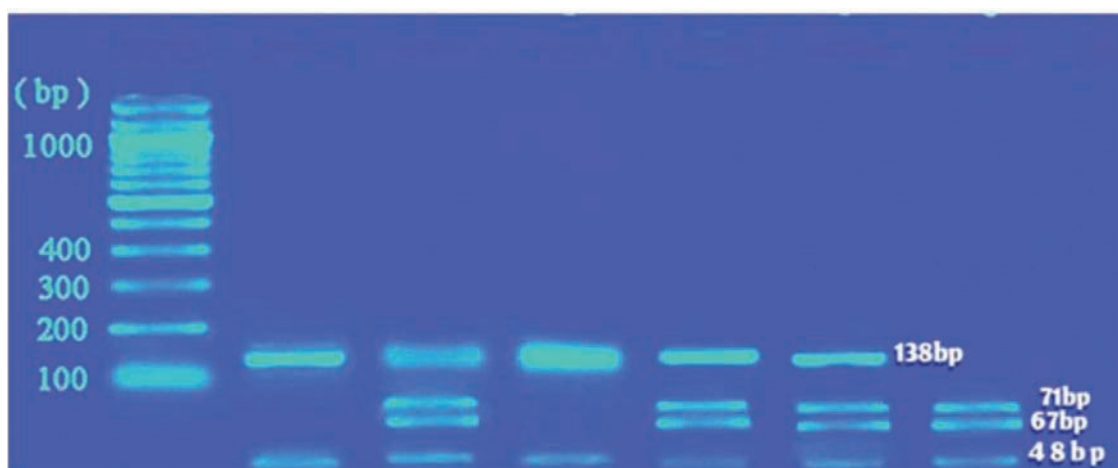


Fig. 3. The electrophoretic image illustrates the NT-proBNP genotyping on a 5% agarose gel. Lane M contains a 100 bp DNA ladder. Lanes 1 and 3 exhibit two bands at 48 and 138 bp, indicating the homozygous TT genotype. Lane 6 displays three bands at 48, 67, and 71 bp, signifying the homozygous CC allele. Lanes 2, 4, and 5 present four bands at 48, 67, 71, and 138 bp, representing the heterozygous TC genotype

three genotypes processed by the restriction enzyme MspI [16]: TT exhibited two bands at 48 and 138 bp, CC displayed three bands at 48, 67, and 71 bp, and TC presented four bands at 48, 67, 71, and 138 bp (Fig. 3).

The frequency distribution of genotypes and each allele within the analyzed group is presented in Table 3, indicating that no statistically significant differences were observed between the two groups concerning genotype frequencies or individual alleles ($P > 0.05$).

Table 4 illustrates the comparison of mean NT-proBNP levels between hypothyroidism patients and controls according to the different genotypes of SNP rs198389 in the NPPB gene. The mean NT-proBNP levels are significantly higher in hypothyroidism patients compared to controls across all genotypes (CC, CT, TT), with P -values < 0.001 , indicating strong statistical significance. Within each group (hypothyroidism and control), there are no statistically significant differences in NT-proBNP levels across genotypes, with P values of 0.064 and 0.081, respectively. This demonstrates that elevated NT-proBNP levels are consistently observed in hypothyroidism regardless of genotype, underscoring the impact of thyroid dysfunction on cardiac stress markers.

The correlation analysis in Table 5 reveals that age and TSH levels are significant predictors of NT-proBNP levels in patients with untreated primary hypothyroidism. Specifically, older age and higher TSH levels are associated with increased NT-proBNP levels, indicating greater cardiac stress. Gender and BMI, while showing positive correlations, are not statistically significant predictors of NT-proBNP levels in this study. This highlights the importance of monitoring TSH and considering age when assessing cardiovascular risk in hypothyroid patients.

The ROC curve analysis for NT-proBNP demonstrates good discriminative ability between hypothyroid patients and healthy controls (Table 7, Fig. 4). The area under the curve (AUC) is 0.89. At a cut-off value of 150 pg/ml, NT-proBNP achieves a sensitivity of 85% and a specificity of 80%. This indicates that NT-proBNP can effectively distinguish untreated hypothyroid patients from euthyroid individuals, but does not directly predict future cardiovascular events.

Discussion

The observed elevations in NT-proBNP levels among hypothyroid patients suggest a significant im-

Table 5. Correlation coefficients between biomarker and clinical parameters

Parameter	NT-proBNP, pg/ml
Age	$r = 0.24, P = 0.02$
Gender, M/F	$r = 0.18, P = 0.07$
BMI, kg/m ²	$r = 0.15, P = 0.10$
TSH, mIU/l	$r = 0.42, P < 0.001$
Free T4, pmol/l	$r = -0.38, P < 0.001$

Table 6. Multiple linear regression analysis for NT-proBNP in hypothyroid patients ($n = 100$)

Variable	Beta coefficient	95% CI	P -value
TSH, mIU/l	0.38	0.21–0.55	<0.001
Age, years	0.21	0.02–0.40	0.03
BMI, kg/m ²	0.09	-0.10–0.28	0.35
Sex, female vs male	0.12	-0.07–0.31	0.21

Table 7. ROC curve analysis for NT-proBNP

Biomarker	AUC	Sensitivity, %	Specificity, %	Cutoff value
NT-proBNP	0.89	85	80	150 pg/ml

impact of thyroid hormone deficiency on cardiac function. NT-proBNP, an indication of cardiac stress, was notably elevated in hypothyroid patients compared to controls [21], indicating increased ventricular strain and potential heart failure risk [22]. This aligns with previous findings that hypothyroidism can exacerbate heart failure symptoms through increased systemic vascular resistance and impaired diastolic function [23]. Pakula et al. [14] indicated that the opposing effects of hypothyroidism-induced hypometabolism and elevated cytokines and endothelins may explain the neutral effect of hypothyroidism on NT-proBNP.

The current genetic analysis identified no significant associations between the rs198389 SNP in the NPPB gene and elevated NT-proBNP levels within the hypothyroidism and control groups. This demonstrates that elevated NT-proBNP levels are consistently observed in hypothyroidism regardless of genotype. The current study does not align with studies that suggest individuals with certain

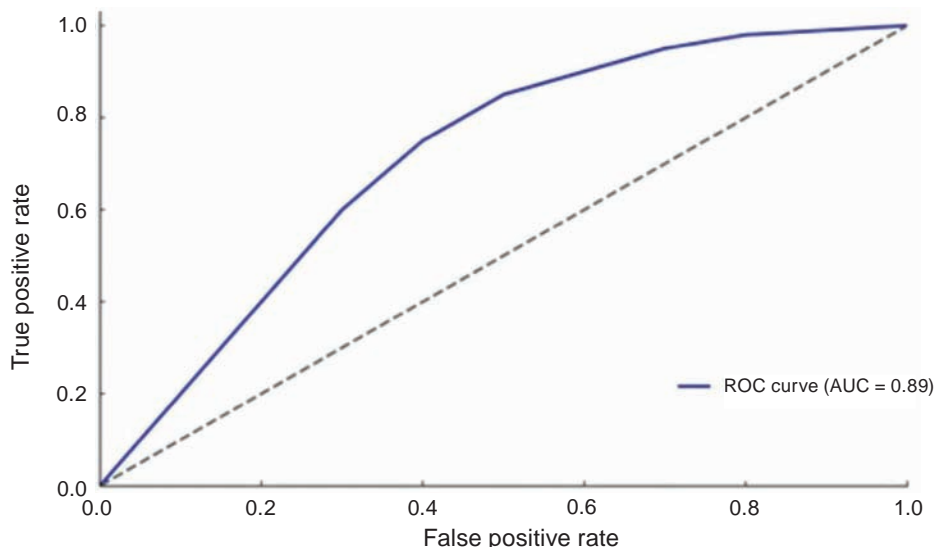


Fig. 4. Receiver operating characteristic (ROC) curve for NT-proBNP

genetic profiles may be at higher risk for cardiovascular complications in the context of hypothyroidism [24, 25]. The current genetic analysis identified no significant associations between the rs198389 SNP and NT-proBNP levels. However, the sample size ($n = 100$ per group) provides limited statistical power to detect small genetic effects. Therefore, we cannot entirely exclude a minor contribution of the rs198389 polymorphism to NT-proBNP variation. Larger multi-center studies are needed to confirm the absence of association.

Age and gender were also found to influence biomarker levels, albeit to a lesser extent. Our results align with previous studies showing that NT-proBNP is positively associated with age. Older patients exhibited higher NT-proBNP levels, consistent with the general age-related increase in cardiovascular risk [26]. Gender differences, while present, were less pronounced, suggesting that both male and female hypothyroid patients are at significant risk for cardiovascular complications [27]. These findings are consistent with previous studies that have shown age and gender to be important factors in cardiovascular risk assessment [28].

The ROC curve analysis demonstrated that NT-proBNP has good discriminative ability between hypothyroid patients and healthy controls. NT-proBNP showed high sensitivity and specificity for distinguishing untreated hypothyroidism. However, because our ROC analysis was based on case-control

status rather than hard cardiovascular endpoints, the findings should be interpreted as exploratory. Prospective studies with longitudinal follow-up are needed to determine whether NT-proBNP predicts actual cardiovascular events in hypothyroid patients.

The inclusion of some overweight and class I obese individuals (mean BMI 27.4) may have influenced NT-proBNP levels, although our multivariable analysis did not find BMI to be an independent predictor.

Conclusion. This study provides evidence of cardiovascular risks associated with untreated hypothyroidism as reflected by elevated NT-proBNP levels. Our data suggest that the rs198389 polymorphism does not significantly modulate NT-proBNP levels in this cohort, but this finding requires replication in larger studies. NT-proBNP shows good discriminative ability between hypothyroid patients and controls, supporting its potential use in clinical assessment of cardiac stress. However, its role as a predictor of future cardiovascular events remains to be validated.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ЗВ'ЯЗОК ПОЛІМОРФІЗМУ SNP rs198389 ГЕНУ BNP ТА РІВНЯМИ NT-PROBNP У ПАЦІЄНТІВ ІЗ ГІПОТИРЕОЗОМ ДО ЛІКУВАННЯ

Alaa Salman

Ishtar Medical Technical Institute, Iraq;
e-mail: alaas3223@gmail.com

Вступ. Серцево-судинна система особливо чутлива до коливань рівня тиреоїдних гормонів, і пацієнти з гіпотиреозом мають підвищений ризик розвитку серцево-судинних порушень. N-кінцевий про-B-тип натрійуретичний пептид (NT-proBNP) є визнаним біомаркером серцевої недостатності. Декілька досліджень показали, що порушення функції щитоподібної залози можуть впливати на рівень NT-proBNP у крові, хоча остаточного висновку з цього питання ще не зроблено. **Мета.** Дослідити вплив однонуклеотидного поліморфізму rs198389 у гені NT-proBNP на рівень NT-proBNP у сироватці крові пацієнтів із нелікованим первинним гіпотиреозом. **Методи.** До дослідження було залучено 100 пацієнтів з нещодавно діагностованим гіпотиреозом та 100 здорових осіб контрольної групи; рівень NT-proBNP вимірювали за допомогою флуоресцентного імуноензимного аналізу, а генетичний аналіз проводили методом ПЛР. **Результати.** Отримані результати показали значно підвищений рівень NT-proBNP у всіх генотипах (CC, CT, TT) у пацієнтів із гіпотиреозом порівняно з контрольною групою. Це підвищення чітко корелювало з рівнем тиреотропного гормону. **Висновки.** Дослідження продемонструвало, що NT-proBNP дозволяє розрізнити пацієнтів із гіпотиреозом та здорових осіб контрольної групи, але необхідні подальші дослідження для встановлення його ролі у прогнозуванні серцево-судинного ризику.

Ключові слова: NT-proBNP, однонуклеотидні поліморфізми, тиреотропний гормон, гіпотиреоз, кореляційний аналіз.

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