The rs243865 Polymorphism In Matrix Metalloproteinase-2 And Its Association With Target Organ Damage In Resistant Hypertension Patients: A cross-sectional Study

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Abstract

Background: Resistant hypertension presents significant clinical challenges, often precipitating a spectrum of cardiovascular complications. Particular attention recently has focused on the role of Matrix metalloproteinase-2 (MMP-2) gene polymorphisms, implicated in hypertensive target organ damage. Despite growing interest, the specific contribution of MMP-2 polymorphisms to such damage in resistant hypertension remains inadequately defined.

Objective: This study is the first to examine the rs243865 (-1306C>T) polymorphism in the MMP-2 gene in the Vietnamese population and in patients with resistant hypertension (RH), underscoring its critical role as a genetic determinant of target organ damage (TOD).

Methods: A cross-sectional study with both descriptive and analytical components, in 78 patients with resistant hypertension at the Can Tho Central General Hospital and Can Tho University of Medicine and Pharmacy Hospital from July 2023 to February 2024.

Results: More than three-quarters of RH patients had carotid-femoral PWV >10 m/s and microalbuminuria at prevalence of 79.5% and 75.6%, respectively. And more than half of RH patients had LVMI, relative wall thickness and carotid artery stenosis with the prevalence of 56.4%, 55.1% and 52.6%, respectively. Of 78 studied resistent hypertension patients, the presence of genotype CC was 76.9%, genotype CT accounted for 20.5% and 2.6% of genotype TT. The percentage of SNP rs243865(-1306C>T) carring allele T was 23.1%. The MMP-2 gene polymorphism 1306C/T (rs243865) was significantly associated with EF and carotid artery stenosis with OR (95%CI) of 8.1(1.3-51.4); p=0.026 and 4.5(1.1-20.1); p=0.048 respectively. The allele T was found to be significantly associated with arterial stiffness including Brachial-ankle PWV and Carotid-Femoral PWV with the correlation coefficient (95%CI) of 2.2 (0.6-3.8) and 1.8 (0.5-3.2) respectively.

Conclusions: The MMP-2 gene polymorphism rs243865 (-1306C>T) may have an association with measurable target organ damage in resistant hypertension.

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The Rs243865 Polymorphism In Matrix Metalloproteinase-2 And Its Association With Target Organ Damage In Resistant Hypertension Patients: A cross-sectional Study

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Abstract

Background: Resistant hypertension (RH) presents significant clinical challenges, often precipitating a spectrum of cardiovascular complications. Particular attention recently has focused on the role of Matrix metalloproteinase-2 (MMP-2) gene polymorphisms, implicated in hypertensive target organ damage. Despite growing interest, the specific contribution of MMP-2 polymorphisms to such damage in resistant hypertension remains inadequately defined
Objective: This study is the first to examine the rs243865 (-1306C>T) polymorphism in the MMP-2 gene in the Vietnamese population and in patients with RH, underscoring its critical role as a genetic determinant of target organ damage.
Methods: A cross-sectional study with both descriptive and analytical components, in 78 patients with resistant hypertension at the Can Tho Central General Hospital and Can Tho University of Medicine and Pharmacy Hospital from July 2023 to February 2024.
Results: More than three-quarters of RH patients had carotid-femoral pulse wave velocity (PWV) >10 m/s and microalbuminuria at prevalence of 79.5% and 75.6%, respectively. And more than half of RH patients had left ventricular mass index (LVMI), relative wall thickness and carotid artery stenosis with the prevalence of 56.4%, 55.1% and 52.6%, respectively. Of 78 studied resistent hypertension patients, the presence of genotype CC was 76.9%, genotype CT accounted for 20.5% and 2.6% of genotype TT. The percentage of SNP rs243865(-1306C>T) with allele T was 23.1%. The MMP-2 gene polymorphism 1306C/T (rs243865) was significantly associated with EF and carotid artery stenosis with OR (95%CI) of 8.1(1.3-51.4); p=0.026 and 4.5(1.1-20.1); p=0.048 respectively. The allele T was found to be significantly associated with arterial stiffness including Brachial-ankle PWV and Carotid-Femoral PWV with the correlation coefficient (95%CI) of 2.2 (0.6-3.8) and 1.8 (0.5-3.2) respectively.
Conclusions: The MMP-2 gene polymorphism rs243865 (-1306C>T) may have an association with measurable target organ damage in resistant hypertension.

Keywords: Resistant hypertension; matrix metalloproteinase-2; gene polymorphism; target organ damage; arterial stiffness.

Introduction

Resistant hypertension (RH) is characterized by the inability to achieve optimal blood pressure (BP) control despite the administration of maximum tolerated doses of antihypertensive medications, including a diuretic. This condition presents a significant clinical challenge, as it is influenced by a multitude of genetic, environmental, and pathophysiological factors that contribute to persistent hypertension. RH is closely associated with severe target organ damage (TOD), which includes damage to the heart, kidneys, and vasculature, significantly increasing the risk of cardiovascular events and mortality. Despite advancements in antihypertensive therapies, approximately 70% of patients with hypertension fail to achieve recommended BP targets, underscoring the complexity of this condition. [1]

Among the molecular mechanisms contributing to RH, matrix metalloproteinases (MMPs), particularly the gelatinase family (MMP-2, MMP-9), have garnered considerable attention. These enzymes play a critical role in extracellular matrix remodeling, a process essential to the pathogenesis of several cardiovascular diseases such as coronary artery disease (CAD), arteriosclerosis, and systemic hypertension [2]. MMP-2, in particular, has been implicated in the remodeling of cardiovascular tissues, contributing to vascular stiffness and fibrosis, both of which are key contributors to RH and TOD [3]. Recent studies have focused on the genetic variants of the MMP-2 gene, especially single nucleotide polymorphisms (SNPs), and their potential role in the development and progression of cardiovascular diseases[4-6]. These genetic polymorphisms are believed to modulate MMP-2 expression and activity, thereby influencing the extent of cardiovascular remodeling and associated TOD. Given the growing evidence linking MMP-2 activity with hypertension-related TOD, understanding the genetic underpinnings of MMP-2 in RH could offer new insights into disease mechanisms and therapeutic targets. The objectives of this study are: (1)To investigate the clinical characteristics and extent of target organ damage in patients with resistant hypertension; (2) To determine the polymorphisms of the MMP-2 gene and assess their association with target organ damage in patients with resistant hypertension.

Methods

Study Population

This study focused on hypertensive patients admitted to Can Tho Central General Hospital and Can Tho University of Medicine and Pharmacy Hospital from July 2023 to February 2024. The study population was divided into two groups: patients with resistant hypertension (RHT) and patients with well-controlled hypertension (HT). The protocol is present in the study diagram (figure 1). The diagnosis of resistant hypertension followed the 2021 guidelines of the Vietnam Hypertension Society [7].

Sample Size:

To achieve the objective: "Determining the polymorphism of rs243865 and its association with target organ damage in patients with resistant hypertension", we employed the formula for estimating a single proportion. The sample size was estimated using the following formula

$$n = Z^2_{1-\alpha/2}\frac{p(1-p)}{d^2}$$

- **n**: Required sample size.
- **Z**: Z-score corresponding to a 95% confidence interval, Z = 1.96.
- **d**: Desired margin of error (chosen as d = 0.1).
- **p**: Proportion of patients carrying the minor allele T in the resistant hypertension group,

estimated at 25%.

Applying the values to the formula yielded a required sample size of **72 patients** with resistant hypertension. In practice, **78 patients** were enrolled.

Inclusion Criteria

Adults aged 18 years or older diagnosed with resistant hypertension, defined as the failure to achieve target blood pressure (systolic <140 mmHg and/or diastolic <90 mmHg) despite the use of optimal or best-tolerated doses of three or more antihypertensive medications, including a diuretic, with blood pressure inadequately controlled as confirmed through home or ambulatory blood pressure monitoring (ABPM), and without secondary causes of hypertension or evidence of pseudoresistant hypertension.

Exclusion Criteria

Patients were excluded from the study if they had any of the following conditions: acute medical emergencies, active autoimmune diseases or ongoing immunosuppressive therapies, cancer or other malignant conditions, secondary hypertension confirmed by clinical and laboratory examinations, pregnancy or chronic kidney disease, or if they refused to participate or demonstrated non-adherence to the medication regimen.

Methodological Approach

Design Framework

The study employed a cross-sectional, descriptive-analytic design to investigate the association between the single nucleotide polymorphism (SNP) rs243865 (-1306C>T) in the matrix metalloproteinase-2 (MMP-2) gene and resistant hypertension (RH) versus non-resistant hypertension. Patients were recruited from two hospitals from July 2023 to February 2024. Patients were classified into resistant and non-resistant hypertension groups according to the ESC criteria for resistant hypertension.

Sampling Strategy

Non-probability convenience sampling method was employed**.** Patients meeting inclusion criteria were recruited consecutively upon admission to the cardiology and internal medicine departments. Trained research assistants approached patients daily, explained the study objectives, and obtained informed consent prior to enrollment. Convenience sampling was selected due to logistical feasibility and time constraints.

Research Protocol and Variables

Demographic and Risk Factors

Data were systematically collected regarding the following risk factors and comorbid conditions, clearly defined based on standard clinical criteria:
-Diabetes mellitus: Defined as having a documented diagnosis of diabetes, or current use of antidiabetic medications, or fasting plasma glucose ≥126 mg/dL, or HbA1c ≥6.5%.
-Overweight or obesity: Defined according to BMI classification, with overweight as BMI ≥25 kg/m² and obesity as BMI ≥30 kg/m², calculated from measured height and weight.
-Smoking status: Categorized as smoker (currently smoking ≥1 cigarette/day or having ceased smoking for at least 6 months prior to enrollment), or non-smoker (no lifetime smoking).
-History of heavy drinking: Defined according to the National Institute on Alcohol Abuse and

Alcoholism (NIAAA) guidelines as consumption of ≥14 drinks/week for males or ≥7 drinks/week for females, or a documented history of alcohol use disorder.
These data were obtained through structured patient interviews and cross-verified by medical records to ensure accuracy and consistency.

Clinical and Hemodynamic Parameters

Blood pressure and pulse pressure were measured using the BOSO ABI-100 system in all patients to minimize errors, with measurements taken at least twice in a seated position after 5 minutes of rest; pulse pressure was calculated as the difference between systolic and diastolic blood pressure. [8] A 24-hour ambulatory blood pressure monitoring (ABPM) device was utilized to assess mean systolic and diastolic blood pressure, nocturnal dipping, and early morning blood pressure surge. Resting heart rate was measured manually or with a digital monitor. Blood samples were collected to determine serum levels of urea, creatinine, and electrolytes, including sodium, potassium, and chloride.Target organ damage (TOD) was evaluated across several key organs, with specific diagnostic criteria used to define damage in each organ system.

Cardiac Damage

Left Ventricular Hypertrophy (LVH): LVH was assessed using echocardiography, with the left ventricular mass index (LVMI) calculated. According to the European Society of Cardiology (ESC) guidelines, LVH was defined as LVMI > 95 g/m² for women and LVMI > 115 g/m² for men. Electrocardiogram (ECG) criteria for LVH, such as the Sokolow-Lyon and Cornell voltage criteria, were also used as secondary diagnostic tools [1].
Ejection Fraction (EF): Left ventricular ejection fraction, a key indicator of cardiac function, was measured via echocardiography. Ejection fraction was classified as normal (≥50%), mildly reduced (41-49%), moderately reduced (30-40%), or severely reduced (<30%). All the echocardiography is made via Siemens Acuson X300 ultrasound machine.

Brain Damage

Brain damage was assessed through imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI). The presence of any of the following conditions was considered indicative of brain damage: White matter lesions, Cerebral microbleeds, Lacunar infarctions, Dilated perivascular spaces.
A history of stroke or transient ischemic attack (TIA) was also considered as evidence of brain damage.

Renal Damage

Renal damage was assessed using the urinary albumin-to-creatinine ratio (ACR). This method evaluates kidney function by measuring albumin excretion in the urine.
Renal damage was defined as an ACR of: Normal to mildly increased: <30 mg/g; Moderately increased: 30-300 mg/g; Severely increased: >300 mg/g.
Patients with a history of chronic kidney disease (CKD) stage 4 or 5, or renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m²), were excluded from the study to avoid confounding factors related to advanced renal failure.

Vascular Damage

Vascular stiffness was assessed using pulse wave velocity (PWV), defined as the speed at which arterial pressure waves move along the vessel wall, with a PWV > 10 m/s being indicative of vascular damage via the BOSO ABI-100 system. The ankle-brachial index (ABI) was also measured using the BOSO ABI-100 system. ABI is defined as the ratio of the systolic blood pressure measured

at the ankle to the systolic blood pressure measured at the brachial artery. An ABI ≤ 0.9 was indicative of peripheral arterial disease and thus considered a sign of vascular damage.

Carotid Stenosis: Carotid artery damage was assessed using ultrasound to measure carotid intima-media thickness (CIMT). Carotid stenosis was defined as the presence of plaques that caused a ≥50% reduction in the arterial lumen or if the intima-media thickness was ≥0.9 mm. Significant stenosis was confirmed through Doppler ultrasound via Siemens Acuson X300 ultrasound machine.

MMP-2 Gene Polymorphism Analysis

Sequencing (SEQ) Technique: A 4 ml blood sample was collected into EDTA-coated tubes and stored at 2°C until used for DNA extraction and analysis. The SNP genotype was determined using two direct sequencing methods.
Principle: The sequencing technique was carried out using an automated sequencer based on a modified Sanger method. In this method, the ddNTPs are not radioactively labeled but are tagged with different fluorescent dyes for each type of ddNTP. The automated sequencer comprises key components such as a capillary system, a laser illumination system, and a signal detection and processing system. The capillary electrophoresis bands emit light as they pass through a laser beam, and the color detection system records and encodes the nucleotides as A, T, C, or G.
Main Steps in Sequencing: DNA extraction using the Qiagen extraction kit. PCR amplification of the targeted SNP gene. Electrophoresis and purification of the PCR product using the Qiagen purification kit. PCR sequencing. Capillary electrophoresis for sequence determination: performed on the Beckman Coulter CEQ8000 sequencer, with the sequence further analyzed using the ABI 3500® sequencer and processed with SeqScape® v2.7 software. Results were analyzed by comparing the SNP location data with the reference sequence on NCBI.
Method: Sequencing was performed using the Beckman Coulter CEQ8000 sequencer

Statistical Analysis

The dataset underwent statistical treatment utilizing Stata version 15.1 and was articulated through frequency distribution (for qualitative variables), and mean ± standard deviation (for quantitative measures). Comparison for qualitative data was made by chi-square test, for quantitative data by Student's t test. A significance level of 0.05 was used for all tests to establish statistical significance. Stepwise multiple regression analysis with inclusion at the .01 level was used to evaluate the influence of gen rs243865(-1306C>T on targeted organ damage adjusted by clinical and sub-clinical characteristics. To estimate the relationship between MMP-2 gene single nucleotide polymorphisms and TOD, odds ratio (OR) and its 95% confidence interval (95%CI) were calculated for binary TOD variables including Echocardiogram EF and carotid artery stenosis. Regression coeffcients (ß reg. coef.) and its 95% confidence interval (95%CI) were calculated for continuous TOD variables including Brachial-ankle PWV (m/s) and Carotid-femoral PWV (m/s). The squared correlation coefficient (R^2) was calculated for proportion of variance explained by the model.

Ethical considerations

The study had been approved by the Ethics Council in Biomedical Research, Can Tho University of Medicine and Pharmacy through the Research Ethics Approval Form No. 23.006.NCS/HĐĐĐ dated on 15/06/2023, before data collection. The study had also been licensed to be conducted at Can Tho Central General Hospital and Can Tho University of Medicine and Pharmacy Hospital. The study was conducted with the consent of the participants through the consent form. The process of interview and the implementation of testing techniques were conducted conveniently and comfortably for the participants, not related to private issues that may affect the health or psychology

of the participants. The personal information of the participants was kept confidential. This study aimed to protect and improve public health and has no other purpose.

Results

In our analysis of 78 resistant hypertension (RH) patients, a significant proportion were female (62.8%), with an average age of 66.7 years, The majority of patients (65.4%) were over the age of 60, highlighting the predominance of an older cohort. Notably, 68% of the patients had a history of hypertension extending beyond 10 years, reflecting the chronic nature of RH, which complicates blood pressure (BP) control. (Table 1)

Table 1. Clinical Characteristics of RH patients (n=78)

Clinical Characteristics		n(%)
Sex	Male / female	29 (37.2) / 49 (62.8)
Age (years)	≤ 60 / > 60	27 (34.6) / 51 (65.4)
	(Mean ± SD)	66.7 ± 14.4
Duration of Hypertension (years)	≤ 10 / > 10	53 (68.0) / 25 (32.0)
	(Mean ± SD)	10.3 ± 5.6
Blood pressure level	Grade 1&2 / Grade 3	53 (67.9) / 25 (32.1)
Diabetes	Yes / No	22 (28.2) / 56 (71.8)
Overweight or obesity	Yes / No	20 (25.6) / 58 (74.4)
Smoking (curent or past history)	Yes / No	24 (30.7) / 54 (69.3)
History of heavy drinking	Yes / No	25 (32.1) /53 (67.9)
Triglycerid (mmol/l)	≥ 2.26 / <2.26	38 (48,7) /40 (51.3)
	(Mean ± SD)	2.85 ± 2.42
LDL (mmol/l)	≥ 3.36 / < 3.36	24 (30.8) /54 (69.2)
	(Mean ± SD)	2.95 ± 1.28
Blood lipid disorders	Yes / No	49 (62.8) / 29 (37.2)

*LDL: low-density lipoprotein, SD: Standard deviation*Despite treatment adherence, mean systolic and diastolic BP levels were persistently elevated, averaging 162.5 ± 29.6 mmHg and 92.7 ± 15.9 mmHg, respectively. This underscores the therapeutic challenges posed by RH. Common comorbidities included diabetes (28.2%) and obesity (25.6%). Additionally, dyslipidemia was prevalent, with high serum triglycerides (48.7%) and LDL cholesterol (30.8%). The prevalence of target organ damage (TOD) was striking, with 79.5% of patients demonstrating carotid-femoral pulse wave velocity (cfPWV) >10 m/s, an indicator of increased arterial stiffness. Microalbuminuria, found in 75.6% of patients, suggests significant renal impairment, while over half of the cohort showed elevated left ventricular mass index (LVMI) and increased relative wall thickness, both markers of adverse cardiac remodeling driven by chronic hypertension. (Table 2).

Table 2: Characteristics of TOD indicators of RH patients

Characteristics (n=78)	Mean ± SD
Echocardiographic left ventricular mass index (g/ m^2)	116.2 ± 47.3
Echocardiogram Ejection Fraction (EF) (%)	60.2 ± 15.1
Blood pressure (mmHg) Systolic/Diastolic	162.5 ± 29.6 / 92.7 ± 15.9
Pulse pressure (mmHg)	71.2 ± 20.6
ABI	0.9 ± 0.1
Brachial-ankle PWV (m/s)	17.8 ± 3.6
Carotid-femoral PWV (m/s)	12.5 ± 3.0
eGFR (ml/min/1.73m^2)	72.6 ± 31.2

Urinary ACR (µg/mg)	138.2 ± 147.5

ABI:ankle-brachial index, ACR: albumin-to-creatinine ratio, PWV: pulse wave velocity

The MMP-2 gene polymorphism rs243865 (-1306C>T) was investigated, revealing that 76.9% of patients carried the CC genotype, while 20.5% carried the CT genotype, and 2.6% the TT genotype (Table 3). The T allele frequency was 23.1%, potentially highlighting a genetic predisposition for more severe vascular outcomes in RH.

Table 3. Distribution of MMP2 gene polymorphisms rs243865 (-1306C>T) in RH patients

MMP2 gene polymorphisms rs243865 (-1306C>T)		n (%)
Genotye (n=78)	CC	60 (76.9)
	CT	16 (20.5)
	TT	2 (2.6)
Allele (n=78)	T carrier	18 (23.1)
	CC	60 (76.9)

MMP-2: Matrix metalloproteinase-2

Significant relationships were identified between the T allele and specific TOD markers, particularly reduced ejection fraction (EF) and increased cfPWV. T allele carriers exhibited a lower mean EF (53.8 ± 20.3%) compared to non-carriers (62.1 ± 12.7%), with a statistically significant difference (p=0.0421). Additionally, T allele carriers had higher brachial-ankle PWV and cfPWV values, nearing statistical significance (p=0.071 and p=0.074), suggestive of enhanced arterial stiffness (Table 4).

Table 4. The comparison mean of target organ damage indicators between MMP2 carrying polymorphisms nucleotide at rs243865 (-1306C>T) with and without allele T

Indicators of target organ damage	T Carrier (n=18)	CC (n=60)	*P* value
Left ventricular mass index (g/m^2) (mean ± sd)	120.1 ± 55.9	114.9± 44.9	.6899
EF in Echocardiogram	53.8 ± 20.3	62.1 ± 12.7	.0421
Blood pressure difference	70.3 ± 15.5	71.4 ± 22.1	.8417
ABI	0.98 ± 0.15	0.99 ± 0.2	.7588
Brachial-ankle PWV(m/s)	19.1 ± 3.5	17.4 ± 3.5	.071
Carotid-femoral PWV (m/s)	13.6 ± 2.9	12.2 ± 2.9	.0741
eGFR(mean ± sd)	66.6 ± 27.2	74.4 ± 32.3	.3562
ACR (mean ± sd)	130.2± 147.7	140.5±182.9	.843

ABI: ankle-brachial index, ACR: albumin-to-creatinine ratio, eGFR: estimated glomerular filtration rate, *PWV: pulse wave velocity, P* value: Indepentdent Samples T-test

The association between the T allele and carotid artery stenosis was also notable, with 72.2% of T allele carriers exhibiting stenosis compared to 46.7% of non-carriers, approaching statistical significance (p=0.057) (Table 5). T allele carriers exhibited a higher prevalence of ejection fraction (EF) < 40% and carotid artery stenosis compared to non-carriers (Table 6). Specifically, 22.2% of T allele carriers had an EF < 40%, compared to only 6.7% of non-carriers, approaching statistical significance (p=0.056). Similarly, carotid artery stenosis was present in 72.2% of T allele carriers versus 46.7% of non-carriers (p=0.057), indicating a potential role of the T allele in exacerbating arterial remodeling and stenosis (Table 5). After adjusting for age and serum potassium levels, the T allele remained significantly associated with EF < 40% (Table 6). After adjusting for age, hypertension duration, and sodium levels, T allele carriers had a significantly higher risk of carotid artery stenosis (Table 7).

Table 5. The comparison of percentage of hypertension-mediate organ damage between MMP-2 polymorphisms nucleotide at rs243865 (-1306C>T) with and without allele T

Symptoms of Target organ damage	T Carrier	CC	*P*

	(n=18)	(n=60)	value
History of stroke/ TIA	4 (22.2)	14 (23.3)	.922
ECG ischemia	9 (50.0)	18 (30.0)	.118
ECG left ventricular hypertrophy	4 (22.2)	13 (21.6)	.96
Echocardiogram EF < 40%	4 (22.2)	4 (6.7)	.056
Echocardiogram with regional hypokinesis	6 (33.3)	22 (37.7)	.796
Echocardiographic left ventricular mass index (>95 wonem and >115 men)	9 (50.0)	35 (58.3)	.532
Echocardiographic relative wall thickness ≥0.43	10 (55.7)	33 (55.0)	.967
Carotid artery stenosis	13 (72.2)	28 (46.7)	.057
Ankle-banchial index <0.9	3 (16.7)	11 (18.3)	.872
Carotid-femoral pulse wave velocity >10 m/s n(%)	16 (88.9)	45 (75.0)	.211
eGFR <60 ml/min/1.73m^2	7 (38.9)	17 (28.3)	.395
Albuminuria (Urine Albumin/Creatinine Ratio >30 µg/g)	14 (77.8)	45 (75.0)	.81

TIA: transient ischemic attack, eGFR: estimated glomerular filtration rate, P value : Chi-squared test

Table 6. Association of MMP2 Gene Polymorphism rs243865 (-1306C>T) and Echocardiogram EF in resistant hypertension (n=78)

		EF <40% n(%)	EF ≥ 40% N(%)	Univariate logistic regression		Multivariate logistic regression (*)	
				OR (95%CI)	*P* value	OR(95%CI)	*P* value
Rs243865(-1306C>T)	T Carrier	4 (22.2)	14(77.8)	4.0 (0.9-18.0)	.057	8.1(1.3-51.4)	.026
	CC	4 (6.7)	56(93.3)	-		-	
Age group	≤ 60 years	5 (18.5)	22(81.5)	-		-	-
	≥ 61 years	3(5.9)	48(94.1)	0.3(0.06-1.3)	.09	0.2(0.03-1.1)	.063
Potassium serum concentration	Mean±SD	3.3±0.3	3.6±0.4	0.13(0.14-1.2)	.06	0.1(0.01-1.3)	.075

EF: Ejection fraction, OR: Odd ratio, SD: Standard deviation, (*) The three-factor model R^2 = 0.2306

Table 7. Association of MMP2 Gene Polymorphism rs243865 (-1306C>T) and Carotid artery stenosis in resistant hypertension (n=78)

		Carotid artery	Univariate	Multivariate logistic

		stenosis		logistic regression		regression (*)	
		Yes	No	OR (95%CI)	*P* value	OR(95%CI)	*P* value
Rs243865(-1306C>T)	T Carrier	13(72.2)	5(27.8)	3.0 (1.0-9.4)	.057	4.5(1.1-20.1)	.048
	CC	28(46.7)	32(53.3)	-		-	
Age group	≤ 60 years	7 (25.9)	20(74.1)	-		-	
	≥ 61 years	34(66.7)	17(33.3)	5.7(2.1-16.1)	.001	3.7(1.1-12.1)	.03
Duration of Hypertension	≤ 10 years	21(39.6)	32(60.4)	-		-	
	≥ 11 years	20(80.0)	5(20.0)	6.1(2.0-18.7)	.002	3.6(1.0-12.7)	.050
Sodium serum concentration	Mean±SD)	139±3.6	136±3.0	1.3 (1.1-1.5)	.001	1.3(1.1-1.6)	.005

OR: Odd ratio, SD: Standard deviation, (*)The four-factor model $R^2 = 0.2857$

The T allele was also associated with higher carotid-femoral PWV, a marker of arterial stiffness and predictor of cardiovascular events (Table 8). The multivariate regression model showed a significant correlation between the T allele and increased PWV (β = 1.8, 95% CI 0.5-3.2, p=0.008). This highlights the potential role of the rs243865 polymorphism in promoting arterial stiffness.

Table 8. Association of MMP2 Gene Polymorphism rs243865 (-1306C>T) with Carotid-Femoral PWV in Resistant Hypertension (n=78)

		n	Mean±SD	Univariate linear regression		Multivariate linear regression (*)	
				ß reg. coef. (95%CI)	p-value	ß reg. coef. (95%CI)	*P* value
rs243865(-1306C>T)	T Carrier	18	13.6±2.9	1.4	.074	1.8	**.008**
	CC	60	12.1±2.9	(-0.1-3.0)		(0.5-3.2)	
Sex	Male	29	11.6±2.8	-1.42	.04	-1.1	.074
	Femal	49	13.0±2.9	(-2.7)-(-0.06)		(-2.2)-3.2	
Age group	≤ 60 yrs	27	10.9±2.9	-		-	
	≥ 61 yrs	51	13.3±2.7	2.3 (1.01-3.6)	.001	1.5(0.3-2.7)	.021
Duration of Hypertension	≤10 years	53	12.1±2.8	-		0.8	
	≥11 years	25	13.5±3.1	1.4 (0.04-2.8)	.049	(-0.5)-2.0	.213
Hypertension Level	Grade 1&2	53	11.6±2.6	-			
	Grade 3	25	14.3±2.8	2.7(1.3-3.9)	.001	2.7(1.6-3.9)	.001
Diabetes	Yes	22	13.4±3.1	1.3	.08	0.3	
	No	56	12.1±2.8	(-0.2)-2.7		(-0.9)-1.5	.657

OR: Odd ratio, SD: Standard deviation, (*) The six-factor model $R^2 = 0.3507$

Discussion

Principal Findings

In this study, we selected patients with true resistant hypertension (RH), excluding those with advanced-stage chronic kidney disease (CKD) and secondary hypertension. This ensured that the target organ damage (TOD) observed was specific to patients with primary hypertension, a population that typically receives inadequate screening for TOD. Our patient cohort, representing the healthcare setting of a developing country, included a predominantly lower-income population. These patients often exhibit limited concern for their health and lack access to regular check-ups compared to those in high-income countries. Our findings, which were largely anticipated, emphasize several critical characteristics and clinical implications of RH. These include the difficulty in controlling blood pressure (BP), its association with comorbidities, and the significant burden of TOD, consistent with prior studies over the past five years.

Comparison to Prior Work

Demographic and Clinical Characteristics

The predominance of females (62.8%) and older patients (65.4% over the age of 60) is consistent with previous research showing that RH is more prevalent among older adults and females [9, 10]. A history of hypertension exceeding 10 years in 68% of patients reflects the chronic nature of the condition, which not only complicates BP management but also elevates the risk of TOD [11]

Despite adherence to treatment, mean systolic and diastolic BP levels remained high (162.5 ± 29.6 mmHg and 92.7 ± 15.9 mmHg, respectively). This highlights the challenges of achieving BP targets in RH, which may be attributed to inflammatory mechanisms and hyperactivity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) [1].

The high prevalence of diabetes (28.2%) and obesity (25.6%) in this cohort aligns with well-established risk factors for RH. These conditions not only contribute to endothelial dysfunction but also exacerbate arterial stiffness, worsening hypertension [12, 13]. Dyslipidemia, characterized by elevated triglycerides (48.7%) and LDL cholesterol (30.8%), further increases cardiovascular risk and TOD [14]. Although diabetes and obesity are not considered primary causes of secondary hypertension, effective management of weight and glucose levels can improve BP control and overall prognosis in RH patients.

Target Organ Damage

The burden of TOD in RH patients was substantial. A high proportion of patients (79.5%) demonstrated elevated carotid-femoral pulse wave velocity (cfPWV >10 m/s), indicating significant arterial stiffness—a critical marker of vascular aging and cardiovascular risk [15]. While cfPWV is predominantly used in research settings rather than routine clinical practice, it remains a robust prognostic indicator independent of brachial BP. Interestingly, we observed that cfPWV does not always correlate with BP levels, suggesting that relying solely on BP measurements may overlook high-risk patients with significant arterial stiffness. The high prevalence of elevated cfPWV in our study could be both a consequence of prolonged hypertension and a contributing factor to RH.

Microalbuminuria was observed in 75.6% of patients, indicating early renal dysfunction and its central role in RH pathophysiology via sodium retention and RAAS activation [11, 16] . While most clinicians rely on creatinine levels and estimated glomerular filtration rate (eGFR) to assess renal damage, our findings reveal a concerning rate of early kidney damage even in patients without advanced CKD, warranting greater clinical attention.

Left ventricular hypertrophy (LVH) and increased relative wall thickness were observed in over half of the patients, consistent with previous studies highlighting the importance of echocardiography in accurately assessing cardiac TOD. Compared to electrocardiograms (ECG), echocardiography has

significantly higher sensitivity in detecting LVH [16-18].
Furthermore, RH has been shown to substantially increase the risk of severe cardiovascular events, including heart failure, myocardial infarction, and stroke, particularly in ambulatory resistant hypertension (ARH) cases [14].

Association of SNP with target organ damage

Our analysis demonstrates a strong association between the rs243865 (-1306C>T) polymorphism in the MMP-2 gene and target organ damage (TOD) in patients with resistant hypertension (RH). The results emphasize that the T allele (the minor allele) significantly increases the risk of arterial stiffness, carotid artery stenosis, and reduced ejection fraction (EF). Previous studies have shown that rs243865 enhances the transcriptional activity of MMP-2, leading to excessive extracellular matrix (ECM) degradation, which contributes to vascular and cardiac fibrosis [19, 20].
In this study, carotid-femoral pulse wave velocity (cfPWV), a key indicator of arterial stiffness, was on average 1.8 m/s higher in the T allele group compared to the CC genotype group. This aligns with previous finding [21], which highlighted the critical role of MMP-2 in promoting arterial fibrosis, particularly in older individuals. Other studies, also indicated that MMP-2 polymorphisms are associated with increased arterial stiffness in hypertensive populations [22, 23]. Furthermore, inflammation and oxidative stress interact with MMP-2 activity, exacerbating arterial stiffness in RH patients [24]. Evidence from multiple studies indicates that arterial stiffness is independently linked to genetic factors, irrespective of blood pressure control, paving the way for its potential as a predictive marker for resistance to antihypertensive therapy.[3, 21, 24]
The prevalence of carotid artery stenosis was significantly higher in the T allele group, underscoring its critical role in vascular remodeling. Our findings are consistent with previous studies, which demonstrated that rs243865 upregulates MMP-2, promoting the development of atherosclerotic plaques and narrowing the arterial lumen [19, 25],. Additionally, ECM remodeling mediated by MMP-2 reduces arterial elasticity and contributes to carotid artery stenosis [26]. However, prior studies emphasized that beyond rs243865, other genetic and environmental factors play a critical role, reflecting the multifactorial nature of this pathology [27].
Patients carrying the T allele exhibited significantly lower ejection fraction (EF), with an average reduction of approximately 8% compared to the CC genotype group, indicating impaired cardiac function and an increased risk of heart failure. Previous studies have reported that haplotypes in the MMP-2 gene are associated with left ventricular hypertrophy, myocardial infarction and impaired cardiac function. [28, 29] The enhanced activity of MMP-2 driven by rs243865 leads to extracellular matrix (ECM) degradation, destabilizing cardiac structure and triggering compensatory fibrosis. This finding presents a potential therapeutic application, as the inhibition of MMP-2 has been shown to improve cardiac function in preclinical models [30]. From a broader perspective on causality, reduced EF often originates from pressure overload and vascular remodeling. The influence of the MMP-2 gene on vascular structure, leading to arterial stiffness, may impair cardiac function by increasing afterload. [21]

The Role of Genetics in Target Organ Damage

Our study, align with previous study, highlights the significant role of the rs243865 (-1306C>T) polymorphism in the MMP-2 gene in the risk of target organ damage (TOD) [31]. This genetic variant not only exerts its effects independently but also interacts intricately with other factors such as inflammation and environmental influences. Specifically, this polymorphism increases the risks of arterial stiffness, carotid artery stenosis, and impaired cardiac function in patients with resistant hypertension (RH). Genetic variants within the MMP-2 gene can significantly alter the risk of cardiovascular diseases [5, 23]. These variants play a pivotal role in vascular remodeling, leading to severe outcomes such as left ventricular hypertrophy (LVH) and reduced cardiac pumping capacity. The rs243865 polymorphism, through enhanced MMP-2 activity, disrupts extracellular matrix

(ECM) integrity, thereby contributing to the structural weakening of the vasculature and heart. [32]. Furthermore, rs243865 has been implicated in other vascular diseases beyond hypertension, including ischemic stroke and aneurysms. This underscores its potential as a critical risk factor in systemic vascular conditions. The overactivation of MMP-2 associated with rs243865 leads to excessive ECM degradation, weakening vascular structures and promoting the development and progression of vascular lesions. [4, 33]. Recently, intermediate factors, such as obesity and insufficient physical activity, proved that capable to amplify the effects of rs243865 on blood pressure and TOD [6]. Obesity, through mechanisms of chronic inflammation and endocrine disruption, exacerbates MMP-2 activity, while sedentary lifestyles further contribute to vascular dysfunction [27]. Synthesizing all these findings, rs243865 emerges as not only a key genetic determinant of TOD but also a nexus of complex interactions with other factors, including inflammation, oxidative stress, lifestyle, and environmental influences. This highlights its potential as a target for personalized treatment strategies aimed at regulating MMP-2 activity and mitigating its associated impacts in the management of resistant hypertension.

Limitations

This study is limited by its small sample size, cross-sectional design, and focus on a single ethnic population, which may affect the generalizability of the findings. Additionally, unmeasured confounding factors, such as inflammation and interactions with other genetic polymorphisms, were not assessed. Further longitudinal and multi-ethnic studies are needed to validate these results and explore the broader implications of rs243865 and target organ damage in resistant hypertension. First, our study utilized a relatively small sample size (n=78), which may limit the generalizability and statistical power of our findings. To mitigate this, we calculated the sample size based on a statistically valid estimation formula to ensure adequate representation; however, larger multicenter studies would enhance statistical power. Second, the cross-sectional design of our study prevents us from establishing a causal relationship between the rs243865 polymorphism and target organ damage. While this design enabled identification of associations, longitudinal studies would be necessary to clarify causality and the temporal sequence of events. Third, although this is the first study about rs243865 in Vietnamese people, the focus on a single ethnic group limits the external validity of the findings, potentially restricting applicability to other populations. To address this, future research should include diverse ethnic groups to assess whether these genetic associations hold across different populations. Finally, due to limited data availability, we were unable to compare the genotype distribution of rs243865 in our resistant hypertension patients with that in the general Vietnamese population. This limitation should be addressed in future population-based studies to provide a more comprehensive interpretation of the genetic findings.

Future Directions

Future research could expand the scope by exploring additional genetic polymorphisms within the MMP-2 gene and their combined impact with rs243865 on resistant hypertension and associated target organ damage. Translating findings from genetic associations into clinical practice represents a significant opportunity. Genetic screening for MMP-2 polymorphisms could facilitate personalized medicine approaches by identifying patients at higher risk for resistant hypertension and severe TOD, allowing clinicians to initiate more aggressive or targeted interventions earlier in the treatment course. Additionally, therapeutic strategies targeting MMP-2 activity, such as the use of specific inhibitors, may offer new avenues for managing and mitigating vascular and cardiac complications in resistant hypertension patients and cardiovascular patients as our prior study [34].

Conclusions

This study underscores the critical role of the rs243865 (-1306C>T) polymorphism in the MMP-2 gene as a significant genetic determinant of target organ damage (TOD) in patients with resistant hypertension (RH). Our findings highlight the multifaceted impact of this polymorphism, including its association with increased arterial stiffness, carotid artery stenosis, and reduced ejection fraction. Importantly, the influence of rs243865 extends beyond its direct genetic effects, interacting with inflammation, oxidative stress, and modifiable factors such as obesity and physical activity. The high prevalence of TOD in our patient population underscores the urgent need for comprehensive screening and management strategies, particularly in resource-limited settings where access to advanced diagnostic tools remains a challenge.

The study provides compelling evidence for considering rs243865 as a potential biomarker for risk stratification and a target for therapeutic intervention. Future research should focus on validating these findings in larger and more diverse populations, exploring the mechanistic pathways linking MMP-2 activity to TOD, and evaluating the clinical efficacy of MMP-2 inhibitors in reducing vascular and cardiac complications in RH patients. Moreover, integrating genetic testing for rs243865 into clinical practice could pave the way for personalized treatment approaches, allowing for more targeted and effective management strategies.

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Conflicts of Interest

None declared.

Data Availability Statement

Data is presented in the main manuscript.

Author Contributions

Author Contributions AT-H contributed to conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, and writing—original draft. HQ-C contributed to data curation, formal analysis, genetic sequencing, investigation, methodology, software, validation. HA-V participated in resources, validation, genetic sequencing, and supervision. HAT contributed to investigation, methodology, validation, and writing—review & editing. VAV-T contributed to project administration, conceptualization, supervision, validation, visualization, and writing—review & editing.

Abbreviations

ABPM: ambulatory blood pressure monitoring
ABI: abnormal ankle-brachial index
ACR: albumin-to-creatinine ratio
BMI: Body mass index
BP: Blood pressure
CAD: coronary artery disease

CI: confidence interval
CT: computed tomography
CKD: chronic kidney disease
CIMT: carotid intima-media thickness
EF: Ejection fraction
eGFR: estimated glomerular filtration rate
TIA: transient ischemic attack
ECG: Electrocardiogram
OR: Odd ratio
MMP: matrix metalloproteinases
MMP-2: Matrix metalloproteinase-2
MMP-9: Matrix metalloproteinase-9
SNPs: single nucleotide polymorphisms
SD: Standard deviation
LVH: Left Ventricular Hypertrophy
LVMI: left ventricular mass index
PWV: pulse wave velocity
RH: resistant hypertension
TOD: target organ damage
JMIR: Journal of Medical Internet Research
RCT: randomized controlled trial

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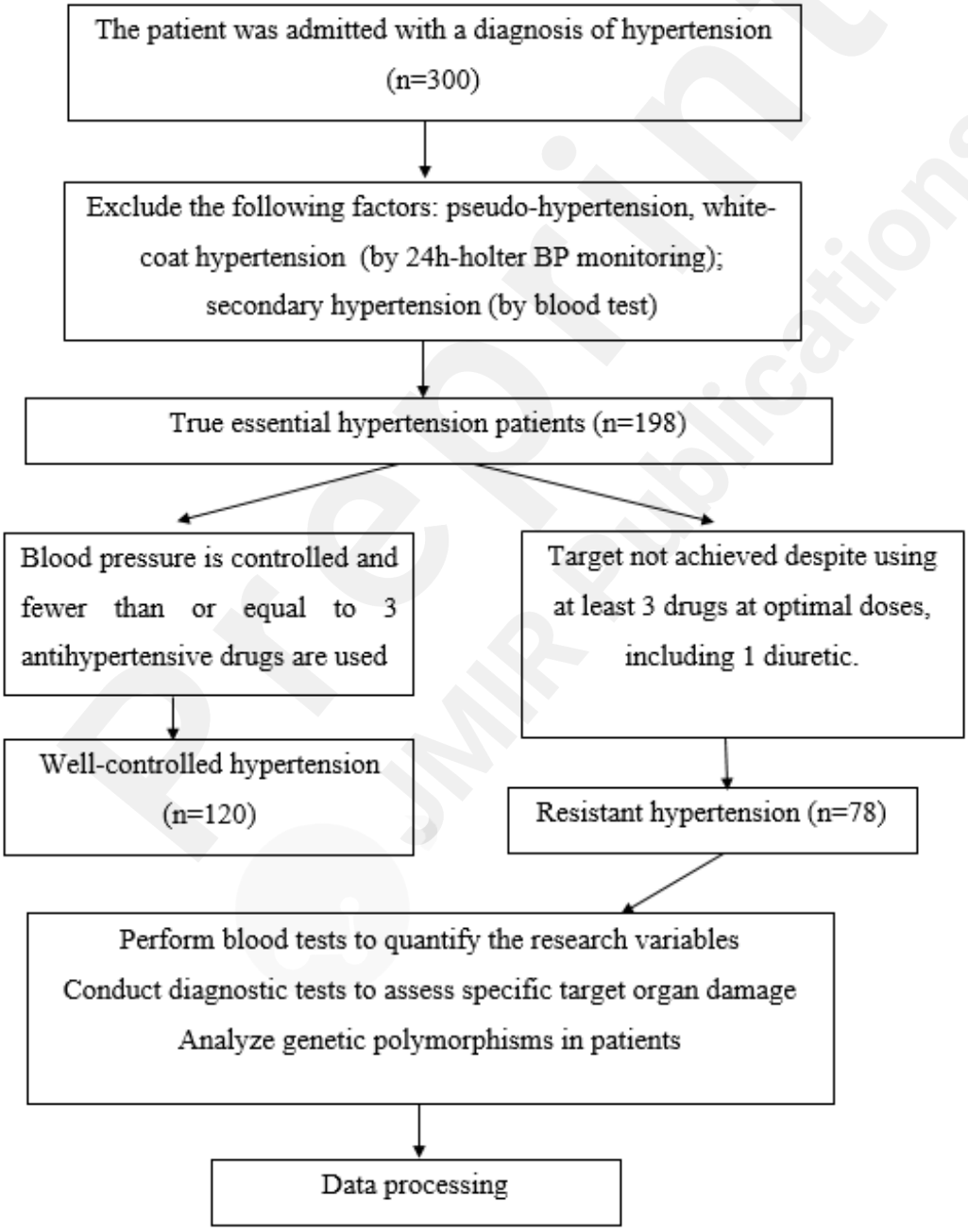

Figure 1

Supplementary Files

Figures

Study Protocol.