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Original article

ASSOCIATION OF EDN1 rs10478694 POLYMORPHISM AND SERUM LEVELS OF ET-1 WITH CARDIOVASCULAR DISEASE IN THE DUHOK POPULATION

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ABSTRACT

This study investigated the association of the Endothelin-1 (EDN1) rs10478694 polymorphism and serum ET-1 levels with coronary artery disease (CAD) and hypertension in the Duhok Province population. Cardiovascular diseases (CVDs) represent a significant global health burden, and understanding their genetic predispositions is critical for targeted interventions. The endothelin system, particularly ET-1, is integral in vascular tone regulation and frequently implicated in various cardiovascular conditions. We conducted a case-control study involving 202 individuals, categorized into control, CAD, hypertension, and combined CAD/hypertension groups. Genotyping for EDN1 rs10478694 was performed via PCR-RFLP, and serum ET-1 levels were quantified by ELISA. Our findings revealed statistically significant associations: the 'rr' genotype and 'r' allele exhibited higher prevalence in all patient groups compared to controls (CAD: genotype p=0.021, allele p=0.022; Hypertension: genotype p=0.022, allele p=0.015; CAD with Hypertension: genotype p=0.021, allele p=0.012). This outcome suggests an elevated genetic susceptibility associated with the 'r' allele. Furthermore, a weak positive correlation between the 'r' allele/rr genotype and serum ET-1 levels substantiated a plausible biological mechanism affecting ET-1 expression and subsequent CVD risk. These results significantly enhance our understanding of CVD genetic architecture in this distinct population, thereby facilitating improved risk stratification and personalized prevention strategies.

KEYWORDS: Endothelin-1rs10478694 polymorphism, Coronary Artery Disease, Hypertension.

1. INTRODUCTION

Cardiovascular diseases (CVDs), including coronary artery disease (CAD) and hypertension, remain the leading global cause of death, responsible for an estimated 17.9 million deaths annually (World Health Organization, 2024; Roth *et al*., 2023). These conditions are multifactorial, arising from a complex interplay of genetic and environmental influences. Identifying genetic contributors is essential for risk prediction, early intervention, and the development of targeted therapies (Ahlqvist & Ballin, 2023; Ford *et al*., 2020), particularly in genetically distinct populations such as those in Duhok Province.

Among key molecular players in CVD pathophysiology is the endothelin system, which regulates vascular tone, blood pressure, and cardiac function (Anfinogenova & Turovskaya, 2022). Endothelin-1 (ET-1), a potent 21-amino acid vasoconstrictor produced by endothelial cells, acts through ETA and ETB receptors to mediate vascular reactivity (Barton & Ruschitzka, 2011; Maguire & Davenport, 2015). Dysregulation of ET-1 has been implicated in hypertension, atherosclerosis, and heart failure, making the EDN1 gene a strong candidate in cardiovascular genetic studies (Ford *et al*., 2020).

Genetic variation in EDN1 can influence ET-1 expression or activity. Of particular interest is the rs10478694 polymorphism (also known as 3A/4A or −134delA), located in the 5′-untranslated region (5′-UTR). This adenine insertion/deletion variant has been shown to affect mRNA stability and ET-1 protein levels (Popowski *et al*., 2004; Zintzaras *et al*., 2010). The 4A (insertion) allele has been linked in some studies to elevated ET-1 expression and increased cardiovascular risk (Thye *et al*., 2009).

However, studies examining the association between rs10478694 and CVDs have produced inconsistent results across populations (Brvar *et al*., 2022; Ebrahimi *et al*., 2019; Yildirim *et al*., 2016). These discrepancies underscore the need for population-specific investigations, given the impact of ethnic and environmental variability

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on genetic susceptibility (Mälarstig *et al*., 2008; Zintzaras *et al*., 2010).

Despite increasing interest in genetic risk factors for CVD, there is a lack of data on this variant in the Duhok Province population. Considering the functional implications of rs10478694 and its potential contribution to ET-1–mediated vascular dysfunction, its role in CAD and Hypertension warrants investigation in this specific demographic.

Therefore, the aim of this study is to investigate the association between the EDN1 rs10478694 polymorphism and serum ET-1 levels in relation to CAD and Hypertension among individuals in Duhok Province. By assessing both genetic and biochemical parameters, this study seeks to provide deeper insights into the role of EDN1 in cardiovascular risk and support personalized approaches to prevention and management.

2. MATERIALS AND METHODS

Study Design and Participants:

This case-control study included 202 individuals aged >35 years, recruited from Zakho General Hospital (Duhok Province, Iraq). Participants were classified into four groups: healthy controls, CAD patients without hypertension, hypertensive patients without CAD, and those with both CAD and hypertension. CAD was confirmed by coronary angiography. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg or current use of antihypertensive medication (Williams *et al*., 2018). All participants provided written informed consent, and ethical approval was obtained from the Institutional Review Board.

Inclusion and Exclusion Criteria:

Inclusion criteria comprised adults (>35 years) with complete clinical and laboratory data. Individuals with diabetes mellitus, chronic kidney disease, inflammatory disorders, or those on lipid-lowering or ET-1–modulating medications were excluded.

Sample Collection and Biochemical Assays:

Sample collection was conducted between October 2024 and January 2025. During this period, 4 mL of venous blood was drawn from each participant. Two millilitres were placed in EDTA tubes for DNA extraction, and 2 mL in plain tubes for serum collection. After clotting (30 minutes), samples were centrifuged at 10,000 rpm for 10 minutes. Serum was separated and stored at −20°C until use (CLSI, 2024). Serum glucose, lipid profile (cholesterol, triglycerides, HDL, LDL), and kidney function tests (urea, creatinine) were measured using an automated analyzer (Roche Cobas 6000 analyzer, High-Tech, Japan).

Body Mass Index (BMI) and Blood Pressure:

Height and weight were measured using a standard stadiometer and digital scale, and BMI was calculated as weight (kg) divided by height squared (m²) [WHO, 2000].

Systolic and diastolic blood pressures were measured with an automatic sphygmomanometer (Omron HEM-7120, Japan) in a seated position after 5 minutes of rest. Two readings were averaged for analysis [Kim *et al*., 2023].

DNA Extraction and Genotyping:

Genomic DNA was extracted using the GDSBio Quick Blood DNA Extraction Kit (N1132) and quantified via Nanodrop spectrophotometry (Thermo Fisher Scientific, USA). The EDN1 rs10478694 polymorphism was genotyped using PCR-RFLP. PCR was performed with primers adapted from Popowski *et al*. (2004). Cycling conditions were: 95°C for 5 min; 35 cycles of 95°C for 30s, 54°C for 30s, 72°C for 30s; followed by 72°C for 5 min. The 210 bp amplicon was digested with DraI (Jena Bioscience, Cat. No. EN-2145-01) at 37°C and resolved by 2.5% agarose gel electrophoresis (Abbas *et al*., 2023). Genotypes were identified as follows: RR (210 bp), rr (187 bp), and Rr (210 and 187 bp).

Quantification of Serum ET-1:

Serum ET-1 was measured using a commercial ELISA kit (Sunlong Biotech, REF: SL0651Hu) according to the manufacturer's protocol. Absorbance at 450 nm was recorded with a microplate reader, and ET-1 concentrations (pg/mL) were calculated using a standard curve ($Y = 0.00188X + 0.0611$, $R^2 = 0.995$). All samples were run in duplicate.

Statistical Analysis:

Data were analyzed using SPSS version 26. Genotype and allele frequencies were assessed by the chi-square test. A one-way ANOVA was used to compare group differences of serum ET-1 levels. Pearson correlation tested associations between continuous variables. ROC curve analysis (GraphPad Prism v9.3.1) was used to evaluate the diagnostic value of clinical and biochemical parameters. A P-value <0.05 was considered statistically significant.

3. RESULTS

Baseline Characteristics of Participants:

Table 1 presents the demographic, clinical, and biochemical characteristics of the study population stratified by group: controls, CAD, hypertension, and CAD with hypertension. The mean age progressively increased across groups, from 45 ± 7 years in controls to 59 ± 10 years in the combined group. Males were predominant in the CAD group (68%), while females constituted the majority in the hypertension group (60%).

Body mass index (BMI) was the highest in the hypertension group (31.1 ± 4.84 kg/m²). Random blood sugar (RBS), cholesterol, and triglyceride levels were elevated in all patient groups compared to controls. Systolic and diastolic blood pressures were significantly higher in hypertensive groups, with the highest values observed in the CAD with hypertension group. Serum ET-1 concentrations were markedly elevated in patient groups, reaching the highest level in the combined group (29.50 ± 13.74 pg/mL) and the lowest in controls (13.16 ± 11.29 pg/mL).

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Regarding coronary angiography, all controls had normal results, while multivessel disease was more frequent in the CAD with hypertension group. Cigarette smoking was more prevalent among CAD patients (48%), in contrast to the control group (20%).

Table (1): Summarizes the baseline characteristics of study participants by clinical group.

Biomarker	control (N (%)), 45 (22.28%)	CAD (N (%)), 50 (24.75%)	Hypertension (N (%)), 60 (29.70%)	Hypertension and CAD (N (%)), 47 (23.27%)
Male	23 (51.11%)	34 (68%)	24 (40%)	22 (46.81%)
Female	22 (48.89%)	16 (32%)	36 (60%)	25 (53.19%)
age(year)	45±7	54±9	53±10	59±10
Weight(kg)	77.5±9.6	80.7±12	82.5±11.4	80.6±11.7
Height(cm)	167.1±9.4	167.8±9.4	163.3±8.1	165.7±8.8
BMI [Kg/M2]	27.96±4.5	28.7±4.29	31.1±4.84	29.51±.98
RBS [mg/dL]	121.24±32.64	179.66±93.01	146.28±60.21	207.83±117.92
Cholesterol [mg/dL]	180.62±30.79	195.06±33.16	198.22±28.79	202.3±30.37
TG [mg/dL]	175.42±72.15	197.84±83.93	222.02±75.44	223.7±93.64
HDL [mg/dL]	52.6±8.94	52.5±12.56	53.78±9.47	52.43±8.66
LDL [mg/dL]	101.49±27.96	113.56±34.93	109.13±31.77	125.23±28.62
Urea [mg/dL]	24.30±3.92	30.96±8.33	26.80±5.00	34.25±10.00
Creatinine [mg/dL]	0.73±0.14	0.88±0.23	0.81±0.18	0.89±0.20
SBP [Mm Hg]	124±12.86	118.20±13.95	167.17±11.95	169.79±23.17
DBP [Mm Hg]	81.33±6.25	77±11.29	93.67±7.36	97.02±8.32
Coronary Angiography Information	N = 45, % = 100.00%	N = 23, % = 46.00%	N = 60, % = 100.00%	N = 13, % = 27.66%
-None	no	N = 13, % = 26.00%	No	N = 15, % = 31.91%
-1 vessel				
-2 or more vessels	no	N = 14, % = 28.00%	No	N = 19, % = 40.43%
Addiction (cigarette)	N = 36, % = 80.00%	N = 26, % = 52.00%	N = 49, % = 81.67%	N = 33, % = 70.21%
-NO				
-Yes	N = 9, % =20.00%	N = 24, % =48.00%	N = 11, % =18.33%	N = 14, % =29.79%
ET-1[pg ml]	13.164 ± 11.285	21.276 ± 16.368	20.790 ± 11.867	29.498 ± 13.735

Note: BMI for body mass index [Kg/M2]; TG for serum Triglyceride [mg/dL]; LDL for serum low density lipoprotein [mg/dL]; HDL for serum high density lipoprotein [mg/dL]; SBP for systolic blood pressure; DBP for diastolic blood pressure [Mm Hg]; and ET-1 for serum Endothelin-1 [pg ml].

Serum Endothelin-1 Levels:

Serum ET-1 levels were measured by ELISA in all participants. The assay demonstrated excellent linearity, with a standard curve equation of $Y = 0.00188X + 0.0611$ and an R^2 of 0.995 (Figure 1), confirming the reliability of quantification.

Mean ET-1 concentrations (pg/mL) varied significantly across the study groups. The highest levels were observed in the CAD with hypertension group (29.50 ± 13.74), followed by the CAD group (21.28 ± 16.37) and the hypertension group (20.79 ± 11.87). The lowest levels were found in the control group (13.16 ± 11.29), indicating a possible association between elevated ET-1 levels and cardiovascular pathology.

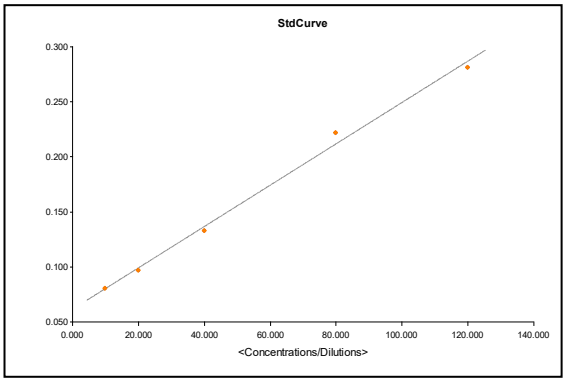

Figure 1: Standard curve for ELISA-based ET-1 quantification, demonstrating a strong linear correlation ($R^2 = 0.995$) between absorbance at 450 nm and ET-1 concentration.

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Genotyping of EDN1 rs10478694 Polymorphism:

All 202 participants were successfully genotyped for the EDN1 rs10478694 polymorphism using the PCR-RFLP method. Amplification produced a clear 210 bp product, which was digested with the DraI restriction enzyme to differentiate genotypes based on fragment sizes.

discrimination among genotypes in the study cohort (Figure 2).

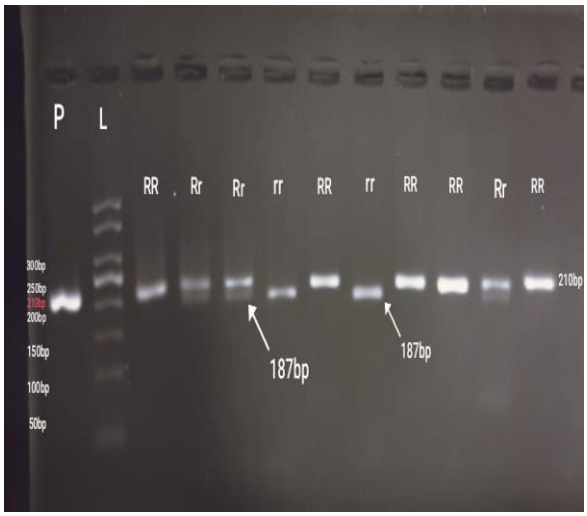

Figure 2: Representative gel electrophoresis showing EDN1 rs10478694 genotypes. Lanes: L, 50 bp DNA ladder; P, undigested PCR product (210 bp); RR, wild-type homozygote (210 bp); Rr, heterozygote (210 and 187 bp); rr, mutant homozygote (187 bp).

RR genotype (wild-type homozygous) produced a single undigested band at 210 bp, rr genotype (mutant homozygous) yielded a digested fragment at 187 bp (the 23 bp fragment was too small to visualize) and Rr genotype (heterozygous) displayed both 210 bp and 187 bp bands. These banding patterns allowed clear

Genotype and Allele Frequencies of EDN1 rs10478694 Polymorphism:

Genotyping of the EDN1 rs10478694 polymorphism was successfully performed in all 202 participants. The genotype and allele frequencies for the control and patient groups are summarized in Table 2.

In the control group (N = 45), the genotype distribution was 73.33% RR, 26.67% Rr, and 0.0% rr, with allele frequencies of 86.67% R and 13.33% r.

Compared to controls, all patient groups exhibited significant differences in genotype and allele frequencies. Specifically, the CAD group (N = 48) showed significant associations for genotype (p= 0.021) and allele (p = 0.022) frequencies. Similarly, the hypertension group (N = 60) displayed significant genotype (p = 0.022) and allele (p = 0.015) associations. The combined CAD and hypertension group (N = 47) also demonstrated significant differences in genotype (p = 0.021) and allele (p = 0.012) frequencies.

Notably, the rr genotype and r allele were more prevalent in all disease cohorts compared to controls, suggesting a potential role for the r allele in susceptibility to CAD and hypertension.

Table 2: Genotype and Allele Frequencies of EDN1 rs10478694 Polymorphism in Study Groups.

Study Groups	Sample Number	Genotypic Frequencies	Allele Frequencies	P-value (Genotype)	Significance (Genotype)	P-value (Allele)	Significance (Allele)
Control	45	RR: 73.33% Rr: 26.67% rr: 0.0%	R: 86.67% r: 13.33%	-	-	-	-
CAD	48	RR: 46.0% Rr: 52.0% rr: 2.0%	R: 72.0% r: 28.0%	0.021	*	0.022	*
Hypertension	60	RR: 58.33% Rr: 26.67% rr: 15.0%	R: 71.67% r: 28.33%	0.022	*	0.015	*
CAD and Hypertension	47	RR: 48.94% Rr: 42.55% rr: 8.51%	R: 70.21% r: 29.79%	0.021	*	0.012	*

Correlation of EDN1 rs10478694 Genotypes and Alleles with Serum ET-1 Levels:

Pearson correlation analysis was performed to assess the relationship between EDN1 rs10478694 genotypes and alleles and serum endothelin-1 (ET-1) levels. The results, presented in Table 3, indicate weak correlations across all comparisons.

The RR genotype (r = -0.1504) and the R allele (r = -0.1583) demonstrated slight negative correlations with serum ET-1 levels. In contrast, the heterozygous Rr genotype (r = 0.1106), the homozygous rr genotype (r = 0.0915), and the minor r allele (r = 0.1583) showed weak positive correlations with serum ET-1 concentrations.

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Table 3: Pearson Correlation Coefficients (r) between EDN1 rs10478694 Genotypes/Alleles and Serum ET-1 Levels.

Comparison Category	Genotype/Allele	Pearson Correlation Coefficient (r)
Genotype	RR	-0.1504
	Rr	0.1106
	rr	0.0915
Allele	R	-0.1583
	r	0.1583

Diagnostic Value of Clinical and Biochemical Parameters:

Receiver Operating Characteristic (ROC) curve analysis was employed to assess the diagnostic performance of various clinical and biochemical parameters in distinguishing hypertensive and atherosclerotic patients from healthy controls.

Among all biomarkers, systolic blood pressure (cut-off ≥ 140 mmHg; AUC = 0.7874) and age (cut-off ≥ 50 years; AUC = 0.7819) demonstrated the highest diagnostic value, with excellent sensitivity and specificity.

Table 4: ROC Analysis of Clinical and Biochemical Parameters for Differentiating Hypertensive and Atherosclerotic Patients from Controls.

Biomarker	Cut-off Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	P-value	DOR
Age	≥ 50.00	66.88	77.78	40.23	59.77	0.7819 (0.7085–0.8552)	< 0.0001 ****	1.4466
BMI	≥ 27.49	70.06	57.78	85.27	35.62	0.6286 (0.5334–0.7238)	0.0086 *	3.2027
RBS	≥ 148.00	41.40	88.89	92.86	30.30	0.6950 (0.6153–0.7747)	< 0.0001 ****	5.6522
Cholesterol	≥ 179.00	76.43	48.89	37.29	62.71	0.6550 (0.5640–0.7460)	0.0017 **	3.1022
TG	≥ 152.00	75.16	55.56	85.51	39.06	0.6525 (0.5575–0.7476)	0.0020 *	3.7821
HDL	≥ 62.00	21.66	86.67	85.00	24.07	0.5045 (0.4089–0.6001)	0.9276 ns	1.7967
LDL	≥ 118.00	50.96	73.33	86.96	30.00	0.6257 (0.5369–0.7145)	0.0109 *	2.8571
Urea	≥ 25.80	63.83	97.78	96.77	72.13	0.7568 (0.6856–0.8280)	< 0.0001 ****	5.6585
Creatinine	≥ 0.81	57.96	77.78	90.10	34.65	0.6931 (0.6136–0.7726)	< 0.0001 ****	4.8258
Systolic Pressure	≥ 140.00	67.52	95.56	98.15	45.74	0.7874 (0.7261–0.8488)	< 0.0001 ****	44.6863
Diastolic Pressure	≥ 90.00	73.25	73.33	90.55	44.00	0.7458 (0.6756–0.8160)	< 0.0001 ****	7.5298

AUC: Area Under the Curve; PPV: Positive Predictive Value; NPV: Negative Predictive Value; DOR: Diagnostic Odds Ratio

Significance levels: ns non-significant p > o.o5, * p< 0.05, ** p < 0.01, **** p < 0.0001.

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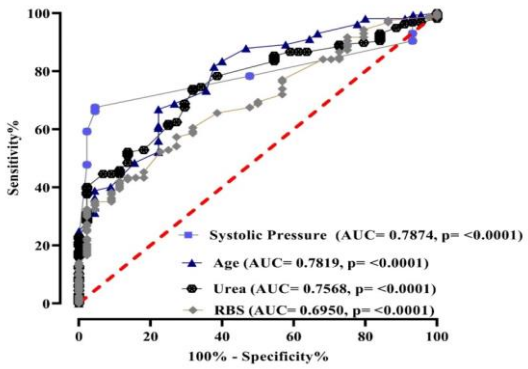

Figure 3: ROC Curves for Systolic Pressure, Age, Urea, and RBS.

4. DISCUSSION

This study investigated the association of the EDN1 rs10478694 polymorphism with CAD and Hypertension, as well as its correlation with serum ET-1 levels in a cohort from Duhok Province, Iraq. Our findings demonstrate a significant association between the rs10478694 variant and an increased risk of CVD. Specifically, the 'r' allele and the homozygous 'rr' genotype were found to be more prevalent in patients with CAD, hypertension, and their comorbidity when compared to healthy controls. This observation suggests that individuals with the 'r' allele, particularly in its homozygous form, may have an elevated genetic susceptibility to these conditions within the studied population.

This observation is consistent with previous studies implicating EDN1 polymorphisms in cardiovascular disease pathogenesis (Oo & Khine, 2018). Although the impact of rs10478694 varies across populations, previous research has identified the 4A insertion allele (corresponding to the 'r' allele) as a risk factor for essential hypertension and other vascular disorders (Thye *et al*., 2009). Our data align with these findings, supporting the notion that the 4A allele may contribute to increased disease susceptibility through regulatory effects on gene expression. The shift in genotype distribution toward Rr and rr genotypes in the patient groups reinforces the role of this variant in cardiovascular risk. A recent meta-analysis further supports this by demonstrating a significant association between the rs10478694 polymorphism and a higher risk of hypertension, particularly among Asian populations (Cheng *et al*., 2021).

Correlation analysis between genotypes and serum ET-1 levels revealed only weak associations, but their directionality supports a biologically plausible mechanism. The r allele and rr genotype were associated with slightly elevated ET-1 concentrations, while the R allele and RR genotype correlated with lower levels. Although modest in strength, these correlations align with the proposed functional effects of the rs10478694 polymorphism. Located in the 5′-untranslated region of the EDN1 gene, this variant has been suggested to influence mRNA stability and translation efficiency (Popowski *et al*., 2004; Zintzaras *et al*., 2010). Studies have shown that the 4A allele may enhance ET-1 production, contributing to endothelial dysfunction, vasoconstriction, inflammation, and vascular remodelling key processes in the development of both hypertension and atherosclerosis (Cheng *et al*., 2021; Khasawneh *et al*., 2022).

The population-specific context of this study adds value to the existing literature. The Duhok Province population represents a unique ethnic and genetic background that may harbour distinct risk profiles for complex diseases. Our findings contribute novel data on the genetic architecture of cardiovascular disease in this region, which is often underrepresented in genomic research. Such localized studies are essential for building equitable and population-specific models of disease risk.

Several strengths support the robustness of this study, including its case-control design, use of angiographic confirmation for CAD diagnosis, and incorporation of both genotypic and biochemical data. However, limitations must also be considered. The sample size, while sufficient to detect significant associations, may limit statistical power for detecting smaller effects or interactions. The low frequency of the rr genotype in the control group may also affect the generalizability of the results. Additionally, the cross-sectional nature of the study precludes causal interpretation.

CONCLUSION

This study found a significant association between the Endothelin-1 (EDN1) rs10478694 variant and an elevated risk for cardiovascular disease in the Duhok Province population. The 'r' allele and 'rr' genotype were more prevalent in patients with CAD and hypertension, suggesting this variant confers an increased genetic susceptibility. This is supported by a weak but biologically plausible correlation between the 'r' allele and higher serum ET-1 levels. Our findings provide novel, population-specific data that underscore the importance of the rs10478694 variant as a potential risk factor. While acknowledging the study's limitations, these results warrant future investigations into the mechanistic role of this variant in disease pathogenesis.

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Finally, we are deeply grateful to all participants who took part in this research.

Ethical Statement:

The study protocol was approved by the Zakho Health Directorate (Approval No. 2374). Written informed consent was obtained from all participants before sample collection.

Author Contributions:

Omer A. Mohammed Ameen: Conceptualization, Methodology, Data Curation, Formal Analysis, Investigation, Writing – Original Draft Preparation.
Awat Mustafa Abbas: Supervision, Project Administration, Validation, Writing – Review & Editing.

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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