

ORIGINAL RESEARCH

PERIOPERATIVE MEDICINE

Association of cathepsin D (CTSD) polymorphism and serum levels with myocardial infarction risk in type-2 diabetes mellitus

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ABSTRACT

Background & objective: Type 2 diabetes mellitus (T2DM) significantly increases the risk of cardiovascular disease, including myocardial infarction (MI). Cathepsin D (CTSD), which is involved in the metabolic and inflammatory pathways, may serve as a diagnostic biomarker. This study investigated the association between the CTSD polymorphism (rs928508030) and MI in patients with T2DM, and evaluated CTSD, adiponectin, and TNF- α as diagnostic biomarkers.

Methodology: This cross-sectional study enrolled 120 participants: 40 controls, 40 T2DM patients, and 40 T2DM patients with MI. The serum levels of CTSD, adiponectin, and TNF- α were measured using ELISA. Genotyping of CTSD rs928508030 SNP was performed using tetra-ARMS PCR. Statistical analyses included ANOVA, chi-square tests, ROC curve analysis, and Pearson correlations.

Results: T2DM and MI patients exhibited significantly higher CTSD (374 ± 118 ng/L) and TNF- α (160 ± 52.8 ng/L) and lower adiponectin (9.0 ± 1.7 mg/L) levels than the controls ($P < 0.001$). The A allele of rs928508030 was enriched in the T2DM (54%) and T2DM and MI (51%) groups compared to the controls (0%, $P < 0.001$). ROC analysis demonstrated high diagnostic accuracy for CTSD (AUC = 94%), adiponectin (AUC = 93%), and TNF- α (AUC = 93%) in MI detection. Positive correlations were found between CTSD and TNF- α ($r = 0.514$) and HbA1c ($r = 0.554$), whereas adiponectin was inversely correlated with metabolic inflammatory markers ($P < 0.05$).

Conclusion: CTSD rs928508030 A allele and elevated CTSD levels were associated with increased MI risk in T2DM patients. CTSD, along with adiponectin and TNF- α , exhibits strong diagnostic potential for MI in this population. These findings underscore the role of the genetic and inflammatory pathways in diabetic cardiovascular complications.

Abbreviations: CTSD: Cathepsin D, DM: diabetes mellitus, EDTA: ethylenediaminetetraacetic acid, T2DM: Type 2 diabetes mellitus, MI: myocardial infarction, SNP: single nucleotide polymorphisms, TNF- α : Tumor necrosis factor-alpha

Keywords: Cathepsin D; Cardiovascular Complications; Diabetes Mellitus; Myocardial Infarction; T2DM; TNF- α ; Adiponectin.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by elevated blood glucose levels owing to insulin resistance and/or relative insulin insufficiency. Unlike type 1 diabetes, which is caused by autoimmune destruction of pancreatic β -cells, T2DM develops gradually and is frequently associated with obesity, sedentary lifestyle, and hereditary vulnerability.¹ According to recent estimates, T2DM has become an epidemic that affects over 500 million people worldwide. Its prevalence is expected to continue to increase, particularly in low- and middle-income nations (International Diabetes Federation, 2019). Owing to its increasing prevalence and heavy impact on healthcare systems, this illness is a serious public health problem.² T2DM is associated with major long-term consequences, such as cardiovascular illnesses, nephropathy, retinopathy, and neuropathy, in addition to persistent hyperglycemia.³ Myocardial infarction (MI) continues to be among the most common causes of morbidity and death among individuals with diabetes.⁴ T2DM is a well-known risk factor for cardiovascular illnesses, including MI. Several biochemical indicators have been linked to the development of cardiovascular problems in individuals.⁵ Adipocytes produce the hormone adiponectin, which has anti-inflammatory and insulin-sensitizing properties. Lower circulating levels of adiponectin have been found in individuals with type 2 diabetes, and have been associated with an increased risk of MI, suggesting a protective function in vascular homeostasis.⁶ In contrast, TNF- α is a proinflammatory cytokine that increases insulin resistance and endothelial dysfunction. TNF- α levels are associated with T2DM and atherosclerosis and contribute to the inflammatory cascade that causes cardiovascular diseases in patients with diabetes.⁷

The Cathepsin D gene (CTSD) was precisely mapped to the short arm of chromosome 11 at position 15.5 (11p15.5). The gene spans approximately 11,173 bp on the complementary strand and comprises nine exons that undergo transcriptional and post-transcriptional regulation. This genomic organization facilitates the expression of multiple protein products through alternative splicing events, which ultimately contribute to the diversity of CTSD functions in various cellular compartments.⁸

Recent studies have identified several single-nucleotide polymorphisms (SNPs) within the CTSD gene that may influence CTSD expression and activity. Studies examining single nucleotide polymorphisms (SNPs) at the CTSD locus may modulate enzyme function and activity. These genetic variations appear to have substantial implications in both normal physiology and

pathological conditions.^{9,10} In addition to genetic disorders, alterations in CTSD expression and activity have been implicated in the pathogenesis of various conditions including breast cancer and cardiovascular disorders. In the context of T2DM, elevated CTSD levels may exacerbate insulin resistance and inflammatory pathways, potentially contributing to cellular damage and increased cardiovascular risk.^{11–13} CTSD is a protease enzyme from the acid protease family that is largely generated in lysosomes and destroys cellular proteins. CTSD plays a critical role in several fundamental cellular processes including apoptosis, autophagy, and cellular stress response control, making it an essential component of the biological balance of the immune system.¹⁴ Despite its critical role in these cellular activities, blood levels vary dramatically in chronic diseases such as type 2 diabetes and myocardial infarction.¹⁵

Higher CTSD levels in T2DM patients may aggravate insulin resistance and inflammatory indicators such as TNF- α , leading to cellular damage and a higher risk of cardiovascular disease¹⁰. Furthermore, other studies have found that excessive levels of CTSD may cause vascular tissue rupture and degeneration, reinforcing the link between this enzyme and myocardial infarction.¹⁶ Despite extensive research on the role of CTSD in metabolic and cardiovascular pathologies, existing studies have predominantly focused on its expression or activity in isolation, either in T2DM or MI. A notable gap persists in our understanding of the interplay between CTSD genetic polymorphisms and their dual associations with T2DM and MI. While prior investigations have linked CTSD to insulin resistance, inflammatory pathways, and cardiovascular complications, no comprehensive studies have directly examined the diagnostic potential of CTSD polymorphisms in MI among T2DM patients. This has limited the development of targeted biomarkers for early cardiovascular risk stratification in high-risk populations.

2. METHODOLOGY

The study was conducted between December 2023 and March 2024, in the Department of Clinical Biochemistry and Chemistry at Al-Qadisiyah University, College of Medicine, on 120 individuals, including 80 patients 40 with T2DM and 40 with T2DM and MI, from Al-Zahraa Teaching Hospital, Ibn Al-Bitar Hospital, and the Specialized Cardiac Center. This study included experiments at the Al-Amin Center for Advanced Biotechnology and Research in Najaf Governorate and the Clinical Biochemistry Unit of the Laboratory Department at the Al-Zahraa Teaching Hospital. The mean age of the diabetic patients was 52.3 ± 8.2 years,

Table 1: Demographic, metabolic, and inflammatory biomarker profiles of study participants

Characteristic		Control (n = 40)	DM (n = 40)	MI & DM (n = 40)	P-value
Age (years)		49 ± 5.8	52.3 ± 8.2	57.4 ± 6.9	0.16 ^{ONS}
Gender	Male	15 (37 %)	16 (40 %)	22 (55 %)	0.2 ^{CNS}
	Female	25 (63 %)	24 (60 %)	18 (45 %)	
BMI (kg/m ²)		25.3 ± 3.1	28.4 ± 0.84	28.9 ± 1.54	0.16 ^{ONS}
HbA1c (%)		5.1 ± 0.4 ^A	8.2 ± 2.0 ^B	9.1 ± 2.3 ^C	< 0.001 ^{ONS}
Adiponectin (mg/l)		13.8 ± 4.7 ^A	11.4 ± 3.2 ^B	9.0 ± 1.7 ^C	< 0.001 ^{ONS}
Cathepsin (ng/L)		233.6 ± 55.8 ^A	291 ± 41.6 ^B	374 ± 118 ^C	< 0.001 ^{ONS}
TNF-α (ng/L)		98.8 ± 31.4 ^A	126 ± 62 ^B	160 ± 52.8 ^C	< 0.001 ^{ONS}

C: Chi-square test; O: one-way ANOVA; ***: significant at P < 0.001. Statistical analysis was performed using one-way ANOVA variance with post-hoc Tukey's test for pairwise comparisons (denoted by superscript letters A, B, and C; different letters indicate significant intergroup differences).

Table 2: ROC curve analysis for diagnostic biomarkers in myocardial infarction group.

Variables	Cut-off value	Sens* %	Spec %	PPV*	NPV	Accuracy	AUC %	P-value (AUC = 0.05)
Adiponectin (mg/L)	≤ 10.46	95	90	90	95	85	93	< 0.0001**
Cathepsin (ng/L)	> 258.6	88	88	88	88	75	94	
Tumor necrosis factor-α (ng/L)	> 122.3	92	80	82	91	72	93	

Sens: Sensitivity; Spec: Specificity; PPV: positive predictive value; NPV: negative predictive value; accuracy [(Sensitivity + Specificity) - 1]; AUC: area under the curve

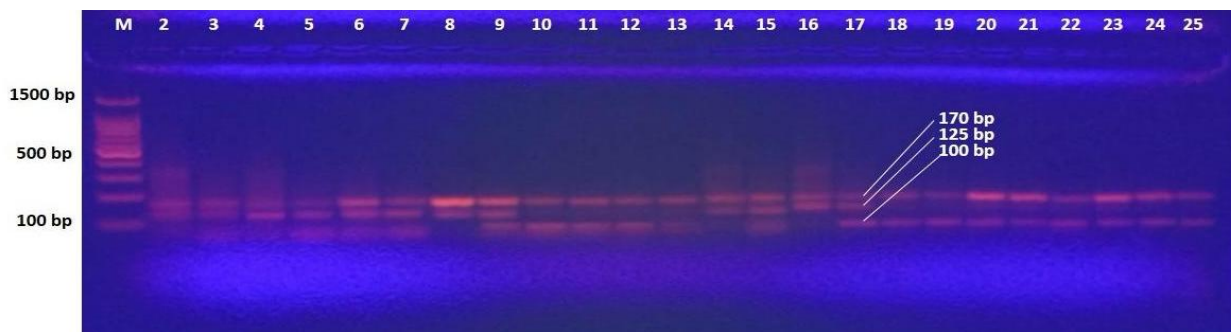


Figure 1: Representative electrophoreses the rs928508030 SNP variants within study subjects. in capturing the disparity of CTSD gene genotypes among a diverse array of samples

while the mean age of the type 2 diabetic patients with MI was 57.4 ± 6.9 years. The control group consisted of 40 healthy, unrelated volunteers from the general population, with a mean age of 49 ± 5.8 years. Informed consent was obtained from all participants and the study design was approved by the local ethics committee. Participants were asked to describe family and individual characteristics that increased their risk of coronary heart

disease as well as their lifestyle choices. Inclusion criteria: Diabetes diagnosed by a physician and with tests confirming diabetes and patients with MI diagnosed by a cardiologist. The exclusion criteria were as follows: kidney disease, thyroid disease, autoimmune disease, congenital heart disease, other ischemic heart diseases such as angina pectoris and unstable angina, type 1 diabetes, and patients receiving insulin therapy.

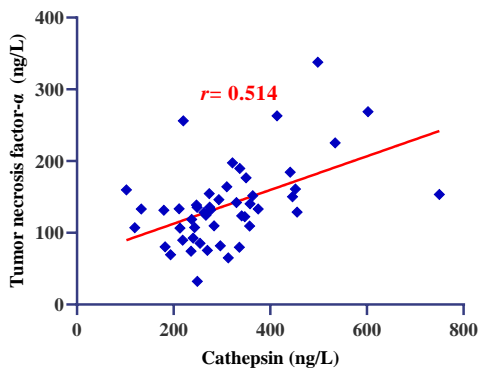
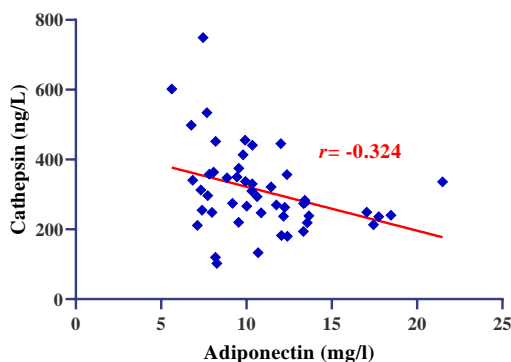
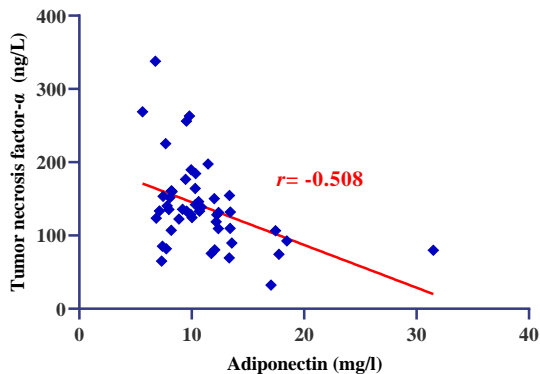


Figure 2: The different charts showing correlation between variable

2.1. Biochemical Analysis

Each patient had 5 ml of blood drawn from a vein and then separated into two test tubes: 2 ml with ethylenediaminetetraacetic acid (EDTA) for genetic study and 3 ml with a gel tube for biochemical analysis. The blood samples in the gel tubes were centrifuged at 3000-x g for ten minutes to obtain the serum. The serum was stored at -20°C until used.¹⁷ Serum levels of adiponectin: Catalog no. [E1550Hu], lot no. [202410010]; cathepsin D: catalog no. [E4668Hu], lot

no. [202410010], and TNF-α: Catalog No. [E0082Hu], lot no. [202410010] were measured using enzyme-linked immunosorbent assay (ELISA) kits. All assays were performed in the laboratory of Al-Zahraa Teaching Hospital in Kut, according to the manufacturer's protocol.

2.2. DNA Extraction

The genotyping of the CTSD gene polymorphism performed using the tetra amplification-refractory mutation system (TETRA-ARMS) technology and a specific set of primers. Genomic DNA was extracted from fresh human blood samples using the Wizard® Genomic DNA Purification Kit (Promega Corporation, USA; Cat. Nos. A1120, A1123, A1125, A1620; Lot No. 0000699929) following the manufacturer's protocol.

Tetra-ARM PCR was used to determine the genotype of CTSD. Four primers were designed (Forward Outer, Forward Inner, Reverse Inner, and Reverse Outer). The CTSD gene, specifically targeting the G/A SNP (rs928508030), utilized a nested primer system for amplification, and the outer primers included the forward primer 5'-TAGCAGGCAGAACAAGTTACAAACACAGA-3' and reverse primer 5'-TCAATTGAACTGAAATCTCCTTGTTGCT-3', generating a 170 bp product. Allele-specific inner primers included the forward primer 5'-GGGAGAAAAGAACAAGAGTACATCCG-3' (targeting the G allele) and reverse primer 5'-TAGCAGGCAGAACAAGTTACAAACACAGA-3' (targeting the A allele), which share sequence identity with the outer forward primer, but produce distinct smaller amplicons of 125 bp (G allele) and 100 bp (A allele) through nested PCR

2.3. Statistical analysis

Statistical analyses of the demographic and clinical characteristics of the individuals diagnosed with MI and DM were performed using GraphPad Prism® (version 9.3.1). Categorical variables were evaluated using the chi-square test. For datasets comprising more than two groups, one-way analysis of variance (ANOVA) was implemented, followed by Tukey's post-hoc test for specific pairwise comparisons. Linear relationships between variables were examined using the Pearson's correlation coefficient. A significance level of $P < 0.05$ was applied to all statistical inferences. Data are expressed as mean ± standard deviation (SD) for normally distributed continuous variables or as frequencies and percentages for categorical measures, consistent with their respective data types and distributional properties.

3. RESULTS

Table 1 summarizes the baseline demographic and clinical characteristics of the study cohort, including age, sex distribution, body mass index (BMI), and metabolic/inflammatory biomarkers (e.g., HbA1c, adiponectin, cathepsin, and TNF- α).

Significant intergroup differences (one-way ANOVA, $P < 0.001$) were observed in glycemic markers (HbA1c), insulin resistance, and inflammatory mediators (TNF- α), with MI and DM participants exhibiting the highest values. Post hoc analysis revealed distinct subgroup differences (denoted by superscripts A, B, and C).

This study evaluated the diagnostic performance of adiponectin, cathepsin, and TNF- α levels in patients with MI. All biomarkers showed high diagnostic accuracy, with AUC values $\geq 93\%$. Adiponectin showed the highest sensitivity and specificity, while TNF- α had the highest sensitivity, and cathepsin balanced sensitivity and specificity.

Pearson's correlations among metabolic and inflammatory biomarkers revealed significant interrelationships (all $P < 0.05$). Cathepsin was correlated with TNF- α ($r = 0.514$) and aligned with shared inflammatory pathways. Adiponectin is inversely associated with inflammatory mediators (e.g., $r = -0.508$ with TNF- α).

Table 3 details the genotype (GG, GA, AA) and allele (G, A) frequencies of the CTSD rs928508030 SNP across control ($n = 40$), DM ($n = 40$), and MI & DM ($n = 40$) cohorts. Genotype distributions and allele frequencies were analyzed using chi-square tests. The GG genotype was predominant in controls (100%), while GA and AA genotypes were significantly enriched in DM (40% GA, 28% AA) and MI & DM (50% GA, 23% AA) groups ($P < 0.001$). Similarly, the A allele frequency was markedly higher in DM (54%) and MI & DM (51%) compared to controls (0%, $P < 0.001$), suggesting a potential association between the A allele and metabolic-inflammatory pathologies in diabetes and cardiovascular disease.

4. DISCUSSION

In this study, demographic factors such as age, sex, and body mass index did not differ significantly between the control, T2DM, and T2DM groups with MI, indicating a

Table 3: Genotype and allele frequencies of the CTSD rs928508030 polymorphism across study groups.

CTSD		Control (n = 40)	DM (n = 40)	MI & DM (n = 40)	X2	P-Value
CTSD	GG	40 (100)	13 (32)	11 (27)	31.6	< 0.001***
	GA	0 (0)	16 (40)	20 (50)		
	AA	0 (0)	11 (28)	9 (23)		
Allele	G	80 (100)	37 (46)	39 (49)	34.8	< 0.001***
	A	0 (0)	43 (54)	41 (51)		

*Chi-square, N: Number, Fr: frequency, ***: significant at $p < 0.001$.*

balanced distribution of baseline characteristics and minimizing potential confounding effects on biomarker interpretation. This consistency enhances the credibility of the observed differences in the biomarkers. Transitioning to glycemic control markers, our results revealed a significant elevation in HbA1c levels among diabetic patients, particularly those with MI, compared to healthy controls. This elevation reflects poor glycemic control, which substantially increases the risk of cardiovascular complications. A study by Yang et al. (2020) demonstrated that even among non-diabetic individuals, higher HbA1c levels were associated with an increased risk of coronary heart disease; individuals with HbA1c levels between 6.0% and 6.5% had a 90% higher risk than those with levels between 5.0% and 5.5%.¹⁸ Similarly, According to Romera et al. (2025), individuals with T2DM who had HbA1c values $\geq 8.5\%$ had a considerably higher risk of myocardial infarction and stroke than those with HbA1c levels $< 7.0\%$.¹⁹ These findings underscore the role of elevated HbA1c level as a significant marker of poor glycemic management and heightened cardiovascular risk.

The current study revealed that blood adiponectin levels were significantly lower in both T2DM and T2DM with MI groups than in healthy controls, as shown in Table 1. This finding supports the concept that low adiponectin levels may contribute to the pathogenesis of diabetes and cardiovascular diseases given the role of adiponectin in enhancing insulin sensitivity and exerting anti-inflammatory effects under normal physiological conditions. Several studies have consistently demonstrated an inverse relationship between circulating adiponectin levels and risk of developing T2DM. A cross-sectional study by Hong et al. (2023) of 2,356 adults with metabolic comorbidities (obesity, dyslipidemia, and hypertension) found that those in the lowest tertile of adiponectin levels had a 2.3-fold higher risk of receiving a new diagnosis of T2DM than those in the highest tertile.²⁰ Similarly, Kim et al. (2025) of 12,540 diabetic individuals found that when adiponectin levels were 32% lower, the risk of death increases by 1.8

times.²¹ In addition to its metabolic effects, adiponectin plays a pivotal role in cardiovascular protection. Elevated adiponectin levels have been shown to preserve vascular integrity, inhibit the progression of atherosclerosis, and reduce plaque formation. Conversely, reduced adiponectin levels contribute to endothelial dysfunction and heightened risk of MI. Recent findings by Xiang et al. (2024) demonstrated significantly lower adiponectin levels in patients with coronary artery disease than in controls.²² Furthermore, adiponectin confers cardiovascular protection by modulating inflammatory pathways and enhancing endothelial function.²³

Patients with T2DM and MI exhibited significantly elevated levels of TNF- α compared to controls (Table 1). In this study, a significant negative correlation was observed between TNF- α and adiponectin levels, suggesting that increased systemic inflammation may suppress the anti-inflammatory and insulin-sensitizing effects of adiponectin. A 2024 cross-sectional research of 495 diabetic patients found that TNF- α -driven inflammation reduced the insulin-sensitizing actions of adiponectin. Elevated TNF- α levels were adversely correlated with adiponectin activity ($\beta = -0.18$, $P < 0.001$). TNF- α alters adiponectin signaling pathways, leading to increased insulin resistance and endothelial dysfunction.²⁴ Conversely, a positive correlation was observed between TNF- α and cathepsin D levels, implying that heightened inflammatory responses might upregulate lysosomal protease activity. Elevated CTSD levels driven by TNF- α could reflect enhanced cellular stress, apoptosis, and tissue remodeling observed in diabetic and cardiovascular pathologies.²⁵ This relationship supports the concept that persistent inflammation in T2DM fosters cellular damage through CTSD activation while simultaneously impairing metabolic regulation via adiponectin suppression.

Serum cathepsin D levels were significantly elevated in patients with T2DM compared with those in healthy controls (Table 1). Furthermore, CTSD levels were positively correlated with both BMI and HbA1c, suggesting their potential as biomarkers of insulin resistance and metabolic dysfunction. These findings align with those of a previous study by Liu et al. (2017), who demonstrated significantly higher CTSD concentrations in T2DM patients relative than in controls. They also reported positive associations between CTSD levels and metabolic parameters such as HOMA-IR, triglycerides, fasting blood glucose, and HbA1c, reinforcing its role in metabolic disturbance.¹⁰ Additionally, Wang et al. (2020) proposed that the pro-inflammatory environment associated with T2DM and cardiovascular disease could lead to increased CTSD expression as a compensatory mechanism aimed at resolving inflammation through apoptosis of activated

immune cells.²⁶ Moreover, CTSD has been implicated in the accumulation of advanced glycation end products (AGEs), which exacerbate vascular complications in diabetic patients.²⁷ Recent findings by Kobayashi *et al* (2023) further suggest that lysosomal dysfunction, a hallmark of diabetic cardiomyopathy, may result in cytoplasmic leakage of CTSD, activating apoptotic pathways in cardiomyocytes and promoting adverse cardiac remodeling and myocardial dysfunction.²⁸ Interestingly, a moderate inverse correlation between the CTSD and adiponectin levels was observed in this study. This suggests that increased CTSD may suppress adiponectin levels, linking inflammation and metabolic derangement. Supporting this, Molvin et al. (2020) indicated that combining adiponectin and CTSD measurements could enhance the prediction of cardiovascular risk in individuals with diabetes.²⁶

Research has demonstrated that myocardial CTSD upregulation following myocardial infarction serves a protective function against cardiac remodeling and dysfunction. This protection operates, at least partially, through promotion of myocardial autophagic flux. This suggests that CTSD plays an important role in heart response to ischemic injury.²⁹ Recent Mendelian randomization (MR) analyses have investigated causal relationships between various CTSD and cardiovascular diseases. These studies found that CTSD increased the risk of myocardial infarction.³⁰ Based on the available search results, there appears to be a gap in research that specifically examines the relationship between CTSD polymorphisms, myocardial infarction, and T2DM. While separate studies have established connections between CTSD and either cardiovascular conditions or diabetes, research directly investigating CTSD polymorphisms in relation to both conditions simultaneously is limited.

5. LIMITATIONS

The study highlights the strengths of a well-structured case-control design, rigorous genotyping, and comprehensive biomarker profiling of CTSD, TNF- α , and adiponectin. The rs928508030 A allele was strongly associated with T2DM and MI along with high diagnostic accuracy, underscoring the CTSD biomarker potential. However, the limitations of this study include its modest sample size, cross-sectional design, and geographical specificity. Future directions include longitudinal studies in larger, ethnically diverse cohorts; expanding genetic analyses to include additional CTSD SNPs and related genes; and conducting clinical trials to assess the therapeutic targeting of CTSD or its inflammatory partners.

6. CONCLUSION

This study revealed a significant association between CTSD rs928508030 polymorphism, elevated serum CTSD levels, and increased MI risk in patients with T2DM. The A allele of rs928508030 was exclusively prevalent in the T2DM, T2DM, and MI groups, correlating with higher CTSD, pro-inflammatory TNF- α , and reduced anti-inflammatory adiponectin levels. ROC analyses revealed high diagnostic accuracy for CTSD, adiponectin, and TNF- α in detecting MI, underscoring their combined utility as biomarkers. These findings highlight the role of CTSD in metabolic-inflammatory pathways and their potential for early MI risk stratification in diabetic populations.

7. Data availability

The numerical data generated during this research are available from the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

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10. Authors' contribution

The authors contributed equally to the conceptualization of the research, collected data, and participated in data analysis and write-up, editing, and review.

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