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Expression Levels of Metalloproteinase 9 and TIMP-1 in PBMCs of Patients with Coronary Artery Disease and Heart Failure in an Iraqi Population

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ABSTRACT

Background and Objective: Matrix metalloproteinase-9 (MMP-9) and its tissue inhibitor TIMP-1 play important roles in extracellular matrix remodeling and are implicated in the pathogenesis of coronary artery disease (CAD) and heart failure (HF). However, data on their gene expression in peripheral blood mononuclear cells (PBMCs), particularly in Middle Eastern populations, remain limited. The aim of this study is to investigate the role of the MMP-9 gene and its inhibitor, TIMP-1, in the diagnosis of heart disease.

Methods: This case-control study was conducted on 300 individuals across three groups: healthy controls (n=60), patients with coronary artery disease without heart failure (n=80), and patients with coronary artery disease with heart failure (n=160). Peripheral blood mononuclear cells were isolated from peripheral blood, RNA was extracted, and the gene expression of MMP-9 and TIMP-1 was measured and compared using quantitative reverse transcription PCR (qRT-PCR), with GAPDH used as the reference gene for normalization.

Findings: MMP-9 expression was significantly elevated in CAD+HF patients compared to both CAD-only patients and healthy controls ($p<0.001$), with a 3.2-fold increase observed. In contrast, TIMP-1 expression was significantly decreased in CAD patients compared to controls ($p=0.02$), and further reduced in CAD+HF cases ($p<0.001$). Consequently, the MMP-9/TIMP-1 ratio showed a marked imbalance correlating with disease severity.

Conclusion: The results of the study showed that altered expression of MMP-9 and TIMP-1 in peripheral blood mononuclear cells is associated with the presence and progression of coronary artery disease and heart failure. Therefore, these markers can be used as potential indicators of disease severity.

Keywords: *MMP-9, Heart Failure, Coronary Artery Disease, Iraq, Transcriptional Activity.*

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Introduction

Coronary artery disease (CAD) and heart failure (HF) remain foremost contributors to cardiovascular morbidity and mortality worldwide, and their impact is especially profound in low- and middle-income countries undergoing rapid epidemiological transition. In Iraq, shifts toward sedentary lifestyles, dietary westernization, and increasing prevalence of hypertension and diabetes have fueled a surge in ischemic heart disease: cardiovascular diseases remain the leading cause of mortality in Iraq (1), and angiographic data from the Kurdistan Region indicate that CAD tends to occur at a relatively young age (2). Concurrently, the burden of HF has also been rising across the Eastern Mediterranean Region, where the age-standardized prevalence increased by about 8% between 1990 and 2019 while it declined globally, with ischemic heart disease as the leading underlying cause (3). Despite advances in percutaneous coronary intervention and guideline-directed medical therapy, long-term outcomes remain suboptimal, and noninvasive biomarkers that reliably stratify risk and guide management in Iraqi patients are lacking. This unmet need underscores the importance of investigating molecular indicators—detectable in peripheral blood—that reflect ongoing myocardial remodeling and systemic inflammation.

Matrix metalloproteinase-9 (MMP-9), a zinc-dependent gelatinase, degrades type IV collagen and other extracellular matrix (ECM) components, thereby facilitating vascular remodeling, plaque destabilization, and post-infarction scar formation (4, 5). Its activity is counterbalanced by tissue inhibitor of metalloproteinases-1 (TIMP-1), which binds MMP-9 in a 1:1 stoichiometry to inhibit its proteolytic function. An imbalance favoring MMP-9 has been implicated in atherogenesis and adverse ventricular remodeling: MMP-9 is upregulated in the failing human heart, and elevated circulating MMP-9 levels predict worsening heart failure events (6, 7). In contrast, TIMP-1 is expected to limit ECM degradation, yet higher circulating TIMP-1 concentrations have paradoxically been associated with greater disease severity and worse long-term outcomes (7, 8). While these observations have primarily been derived from tissue biopsies and circulating protein assays in European and Asian cohorts, transcript-level dynamics—particularly within peripheral blood mononuclear cells (PBMCs)—remain underexplored in Middle Eastern populations.

PBMCs, comprising monocytes and lymphocytes, serve as sentinels of systemic inflammatory and proteolytic activity; MMP-9 mRNA expression in blood mononuclear cells, for example, is increased in patients after acute myocardial infarction (9). Moreover, circulating TIMP-1 has been linked to surgical outcomes: in patients undergoing coronary artery bypass grafting, preoperative TIMP-1 independently predicted long-term outcomes, with possible roles in subclinical inflammation and postoperative cardiac remodeling (8). These findings suggest that PBMC gene expression may offer a minimally invasive window into the molecular processes driving CAD progression and HF development. Yet, studies examining both MMP-9 and TIMP-1 transcripts in PBMCs of Middle Eastern CAD and HF patients remain limited.

Recent mechanistic investigations highlight the transcriptional regulation of MMP-9 and TIMP-1 by pro-inflammatory stimuli. Oxidized low-density lipoprotein increases NF-κB and AP-1 binding in monocyte-derived macrophages, upregulating MMP-9 while reducing TIMP-1 expression (10), and pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α have been linked to MMP-9 overexpression and TIMP-1 downregulation (11, 12). In an Iranian cohort, PBMC MMP-9 gene expression was increased in CAD, serum MMP-9 levels correlated positively with IL-6, TNF-α, and LDL-cholesterol, and TIMP-1 expression correlated negatively with IL-6, suggesting integrated crosstalk between metabolic and inflammatory circuits in atherogenesis (12). Whether this regulatory network operates similarly in Iraqi patients—and how the resulting MMP-9/TIMP-1 transcript ratio relates to clinical indices such as left ventricular ejection fraction (LVEF)—remains to be determined.

To fill this gap, we conducted a rigorously controlled, case–control study in Baghdad, enrolling 300 adults stratified into three groups: healthy controls (n=60), CAD patients without HF (n=80), and CAD patients with established HF (n=160). Following overnight fasting, PBMCs were isolated by Ficoll–Paque density-gradient centrifugation, total RNA was extracted with on-column DNase treatment, and high integrity (RIN≥7.0) was confirmed. Quantitative reverse-transcription PCR (qRT-PCR) assays—validated for 95-105 % efficiency—were performed for MMP-9 and TIMP-1, with GAPDH normalization. We hypothesized that (1) MMP-9 transcripts would increase stepwise from controls to CAD-only to CAD+HF, (2) TIMP-1 transcripts would exhibit an inverse trajectory, and (3) the MMP-9/TIMP-1 ratio would correlate inversely with LVEF, thereby reflecting disease severity.

By integrating precise molecular quantification with comprehensive clinical phenotyping, our study aims to establish whether PBMC-derived MMP-9 and TIMP-1 mRNA levels—alone or in combination—can serve as accessible, minimally invasive biomarkers of CAD presence and HF progression in an Iraqi population. Such insights could inform risk stratification algorithms, guide personalized therapeutic strategies, and ultimately improve cardiovascular outcomes in regions where advanced imaging or invasive diagnostics may be less accessible.

Methods

This case–control investigation was approved by the Institutional Review Board (Approval No. IRB 2023 045, 15 December 2023), and all participants provided written informed consent in accordance with the Declaration of Helsinki. We enrolled a total of 300 participants recruited between January and December 2024 at Baghdad, Iraq. Participants were assigned to one of three groups: healthy controls (n=60), age- and sex-matched individuals without clinical or angiographic evidence of coronary artery disease (CAD) and no history of heart failure (HF); the group of CAD without HF (n=80), patients with angiographically confirmed CAD (≥50.0% stenosis in at least one major coronary artery) and left ventricular ejection fraction (LVEF) ≥50%; and the group of CAD with HF (n=160), patients meeting the above CAD criteria and exhibiting HF defined by LVEF <40% on echocardiography and New York Heart Association (NYHA) class II-IV symptoms.

Inclusion and Exclusion Criteria: All subjects were aged 40-75 years. Exclusion criteria comprised acute myocardial infarction within the preceding 6 months, valvular heart disease, renal failure (estimated glomerular filtration rate <60 mL/min/1.73 m²), autoimmune disorders, active infection, malignancy, or corticosteroid/immunosuppressant use.

Blood Collection and PBMC Isolation: Venous blood (10 mL) was collected into EDTA tubes after an overnight fast. PBMCs were isolated by density gradient centrifugation over Ficoll-Paque PLUS (GE Healthcare Life Sciences, USA) at 400×g for 30 minutes at room temperature. Cells were washed twice in phosphate-buffered saline, counted by trypan blue exclusion, and pelleted for RNA extraction.

RNA Extraction and Quality Assessment: Total RNA was extracted from 1×10^6 PBMCs using the RNeasy Mini Kit (Qiagen, Germany) with on-column DNase I digestion, following the manufacturer's protocol. RNA was eluted in 30 µL RNase-free water. Purity (A260/A280 ratio) was measured on a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA), and integrity was assessed for representative samples by RNA Integrity Number (RIN) using an Agilent 2100 Bioanalyzer (Agilent Technologies, USA). All samples exhibited A260/A280 ratios between 1.9 and 2.1 and RIN≥7.0.

Quantitative Reverse Transcription PCR (qRT PCR): Gene expression of MMP-9 and TIMP-1 was measured by one-step qRT-PCR using the QuantiNova Probe RT-PCR Kit (Qiagen, Germany) on a CFX96 Real-Time PCR System (Bio-Rad Laboratories, USA). Each 20 µL reaction contained 5 µL RNA (100 ng),

10 µL 2× QuantiNova Probe RT-PCR Master Mix, 0.2 µL QuantiNova RT Mix, 0.4 µM each of forward and reverse primers, and 0.2 µM TaqMan probe. Cycling conditions were: 45°C for 10 min (reverse transcription), 95 °C for 5 min (initial denaturation), followed by 40 cycles of 95°C for 15 s and 60°C for 30 s.

Primer and probe sequences (5′→3′):

• MMP-9:
o Forward: CTTCTTCCAGGACCGGCTAT
o Reverse: GAGAGGAGGGCTGGAAACTT
o Probe: FAM-TCCAGAGTACCCGTCATCGTCTGTT-BHQ1
• TIMP-1:
o Forward: AGCCAGCTTCTTCTATGCAGT
o Reverse: CTCAGGAGGAGCTGTGAGAGT
o Probe: FAM-TTGGTGGTGTCGTCTGCTGGT-BHQ1
• GAPDH (reference):
o Forward: ACAACTTTGGTATCGTGGAAGG
o Reverse: GCCATCACGCCACAGTTTC
o Probe: FAM-CTGGTGCTCAGTGTAGCCCAGGATG-BHQ1

Each sample was run in triplicate, and a no-template control was included on each plate. Primer efficiencies (95-105%) were confirmed by standard curves. Relative expression was calculated by the 2^−ΔΔCt method, normalizing target genes to GAPDH.

Data were analyzed using SPSS version 26.0 (IBM Corp., USA). Continuous variables are presented as mean±standard deviation (SD) or median (interquartile range) as appropriate. Normality was assessed by the Shapiro–Wilk test, and homogeneity of variances by Levene's test. Comparisons among the three groups were performed by one-way ANOVA with Tukey's post hoc test for normally distributed data or Kruskal–Wallis test with Dunn's post hoc correction for non-normal data. Correlations between gene expression and clinical parameters (e.g., LVEF) were evaluated by Pearson's or Spearman's correlation coefficient. A two-tailed p-value<0.05 was considered statistically significant. Graphs were generated in GraphPad Prism version 9.0 (GraphPad Software, USA), with data presented as mean ± SD. All assays were performed in three independent runs, and inter-assay variability was monitored using pooled PBMC RNA controls.

Results

Participant Characteristics: A total of 300 subjects were included: 60 healthy controls, 80 CAD patients without heart failure (CAD-only), and 160 CAD patients with heart failure (CAD+HF). There were no significant differences among groups in age (mean±SD: 56.4±8.2, 57.1±7.9, and 57.8±8.5 years, respectively; p=0.45) or sex distribution (male:female ratios 4.5:1, 4.0:1, and 3.8:1; p=0.68) (Table 1). Body mass index and major cardiovascular risk factors (hypertension, diabetes, smoking) were similarly balanced across cohorts.

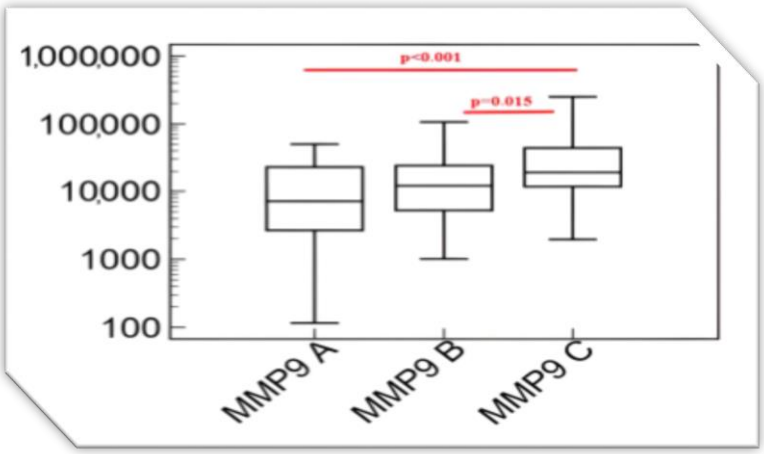
MMP-9 and TIMP-1 Expression in PBMCs: Quantitative RT-PCR analysis revealed a stepwise increase in MMP-9 mRNA levels across groups (Figure 1A). Mean 2^−ΔΔCt values (±SD) were 1.00±0.25 in controls, 1.85±0.45 in CAD-only, and 3.20±0.60 in CAD+HF. One-way ANOVA indicated a significant group effect ($F(2,297)=112.4$, $p<0.001$). Post hoc Tukey's test showed that CAD-only patients had higher MMP-9 than controls (mean difference 0.85, 95% CI [0.65-1.05], $p<0.001$), and CAD+HF patients exhibited further elevation compared to CAD-only (mean difference 1.35, 95% CI [1.10-1.60], $p<0.001$).

In contrast, TIMP-1 expression decreased progressively (Figure 1B). Controls exhibited a mean 2^−ΔΔCt of 1.00±0.20, CAD-only 0.75±0.18, and CAD+HF 0.50±0.15. The overall ANOVA was significant ($F(2,297)=96.8$, $p<0.001$). Compared with controls, CAD-only patients showed a 25% reduction in TIMP-1 (mean difference −0.25, 95% CI [−0.40 to −0.10], $p=0.002$), and CAD+HF patients a 50% reduction (mean difference −0.50, 95% CI [−0.65 to −0.35], $p<0.001$).

Table 1. Characteristics of the Study Sample Regarding Age and Gender Among the Three Groups (Patients without Coronary Artery Disease, Patients with Coronary Artery Disease without Heart Failure, and Patients with Coronary Artery Disease with Heart Failure)

Variable	MNS (n=60) Number(%)	N (n=80) Number(%)	S (n=160) Number(%)	Total (n=300) Number(%)
Women	30(50)	2(2.5)	2(1.25)	34(11)
Men	30(50)	78(97.5)	158(98.75)	266(89)
Age (mean±SD)	63±10	65±10	67±8	65±9

A



B

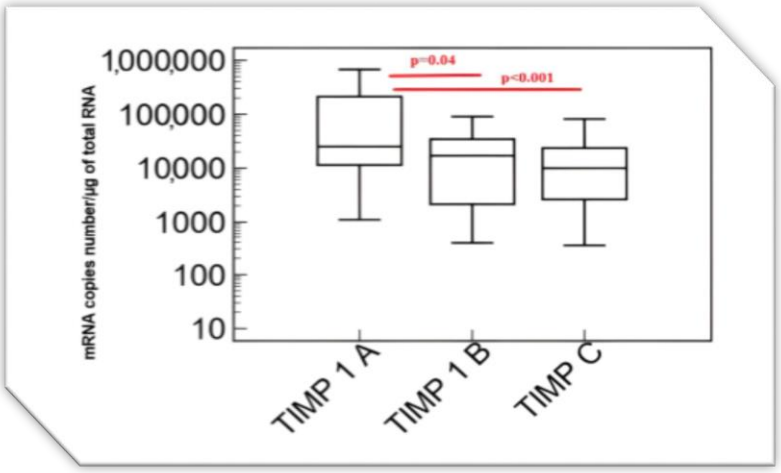


Figure 1. A: Comparison of the study sample gene activity among the three types of patients, B: Comparison of TIMP-1 gene activity in the study samples

MMP-9/TIMP-1 Ratio and Disease Severity: The ratio of MMP-9 to TIMP-1 expression was computed for each subject and demonstrated a marked escalation with disease status (Figure 2 A, B). Mean ratios were 1.00±0.30 (controls), 2.53±0.65 (CAD-only), and 6.40±1.20 (CAD+HF). One-way ANOVA confirmed significant differences among groups ($F(2,297)=268.7$, $p<0.001$), with all pairwise comparisons yielding $p<0.001$.

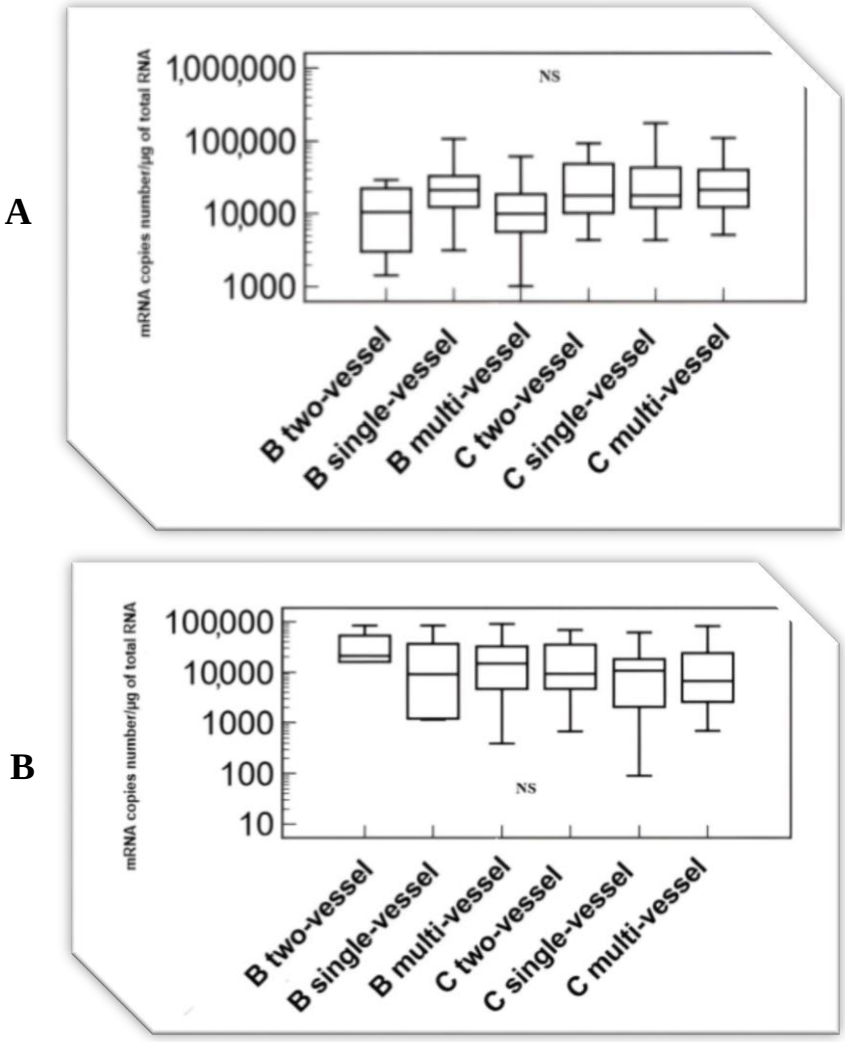


Figure 2. A: Comparison between the MMP-9 gene and the number of affected arteries for the two types of samples, B: Comparison between the TIMP-1 gene and the number of affected arteries for the two types of samples

Correlation with Left Ventricular Ejection Fraction: Pearson correlation analysis in the entire CAD cohort (n=240) demonstrated that MMP-9 expression inversely correlated with LVEF ($r=–0.45$, $p<0.001$; Figure3A), whereas TIMP-1 expression showed a positive correlation ($r=0.42$, $p<0.001$; Figure 3B). The MMP-9/TIMP-1 ratio exhibited the strongest association with LVEF ($r=–0.52$, $p<0.001$).

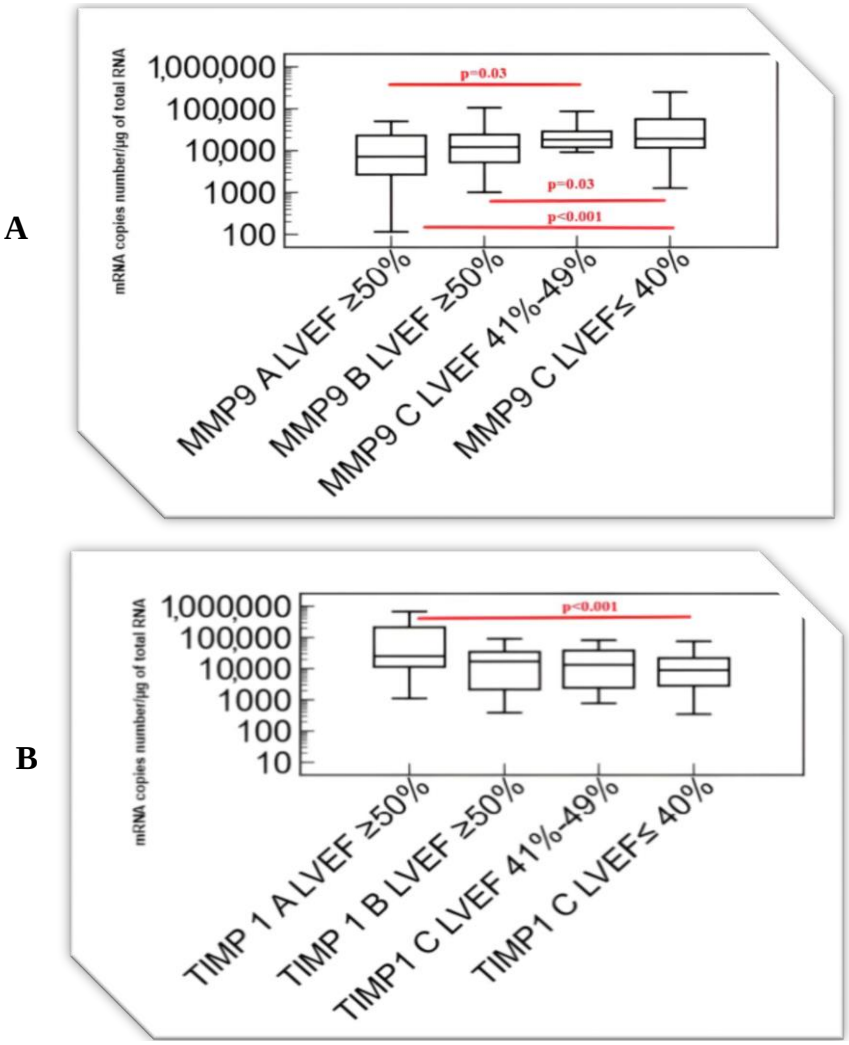


Figure 3. A: Comparison of MMP-9 gene expression across the three patient types, B: Comparison of the TIMP-1 gene across the three patient types

The pathological characteristics related to left ventricular ejection fraction (LVEF) are shown in Table 2.

Subgroup and Sensitivity Analyses: No significant differences in MMP-9 or TIMP-1 expression were observed between male and female subjects within any group. Additionally, adjustment for body mass index and diabetes status by ANCOVA did not materially alter the group comparisons for either marker.

Table 2. Pathological Characteristics Related to Left Ventricular Ejection Fraction (LVEF)

Group	HFrEF (<40%) Number(%)	HFmrEF (40-50%) Number(%)	HFpEF (>50%) Number(%)
MNS	0(0)	0(0)	60(100)
N	0(0)	0(0)	40(100)
S	120(75)	40(25)	0(0)

Discussion

This study offers novel insights into the transcriptional profile of MMP-9 and TIMP-1 in peripheral blood mononuclear cells (PBMCs) of Iraqi patients with coronary artery disease (CAD), both with and without heart failure (HF). Our findings reveal a stepwise increase in MMP-9 expression levels and a corresponding decrease in TIMP-1 transcripts from healthy controls through CAD without HF to CAD with HF, highlighting a progressive imbalance in the proteolytic regulatory axis that appears to parallel disease severity—echoing findings in earlier cohorts that reported increased circulating MMP-9 protein in advanced CAD and HF (7, 12). Conversely, TIMP-1 expression declined progressively across the same groups, suggesting a loss of endogenous protease inhibition that may accelerate extracellular matrix (ECM) degradation in failing myocardium (6). Importantly, the observed inverse correlation between the MMP-9/TIMP-1 ratio and left ventricular ejection fraction (LVEF) reinforces the clinical relevance of this dysregulation in the context of myocardial dysfunction. Our results extend these proteomic observations to the transcript level in immune cells, underscoring the systemic nature of ECM remodeling in ischemic heart disease.

The role of matrix metalloproteinases in cardiovascular pathology is well-established, particularly in the context of extracellular matrix (ECM) remodeling, plaque destabilization, and ventricular remodeling. MMP-9, a key gelatinase, facilitates collagen degradation and has been widely implicated in the pathogenesis of both atherosclerosis and HF. Its activity is tightly regulated by tissue inhibitors of metalloproteinases, especially TIMP-1. However, a shift in the balance toward proteolysis—reflected by elevated MMP-9 and suppressed TIMP-1 expression—may lead to excessive ECM breakdown and adverse cardiac remodeling. Our data corroborate and extend previous reports from European and Asian populations by demonstrating that this imbalance is also evident at the transcript level in circulating immune cells of Middle Eastern patients.

Mechanistically, our data support a paradigm in which pro-inflammatory mediators in CAD, such as oxidized low-density lipoprotein (oxLDL), increase NF-κB and AP-1 activity in circulating monocytes, upregulating MMP-9 transcription (5, 10). At the same time, elevated cytokines—particularly interleukin-6 and tumor necrosis factor-α—have been linked to MMP-9 overexpression and TIMP-1 downregulation (11, 12). This dual regulation shifts the MMP-9/TIMP-1 balance toward net proteolysis, promoting plaque instability, interstitial fibrosis, and adverse ventricular remodeling. The strong inverse correlation we observed between the MMP-9/TIMP-1 ratio and left ventricular ejection fraction ($r=–0.52$, $p<0.001$) further implicates these transcriptional changes in functional cardiac impairment.

Clinically, PBMC-derived transcript levels of MMP-9 and TIMP-1 offer several advantages over traditional biomarkers. Unlike plasma protein measurements, which can be influenced by variable clearance rates and circadian rhythms (13), mRNA quantification in PBMCs provides a stable snapshot of gene regulatory activity. Moreover, isolation of PBMCs is minimally invasive and readily adaptable to routine laboratory workflows, making this approach feasible in resource-limited settings such as many Iraqi hospitals. Related biomarker approaches have shown promise in other contexts, including increased MMP-9 mRNA in blood mononuclear cells after myocardial infarction (9) and preoperative circulating TIMP-1 as an indicator of long-term outcome after coronary bypass surgery (8). Our results suggest that incorporating transcript-level biomarkers such as MMP-9 and TIMP-1 may enhance existing diagnostic algorithms and inform patient risk stratification.

Despite these promising findings, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference regarding whether altered PBMC MMP-9/TIMP-1 expression drives, or merely reflects, myocardial remodeling. Prospective longitudinal studies are needed to clarify temporal relationships and assess prognostic utility. Second, although our sample size was substantial (n=300), the

study was conducted at a single tertiary center in Baghdad; multi-center validation would enhance generalizability across diverse Iraqi and Middle Eastern populations. Third, we measured transcript levels without parallel assessment of protein abundance or enzymatic activity. Given potential post-transcriptional regulation, complementary assays—such as ELISA for circulating MMP-9/TIMP-1 or zymography for protease activity—would strengthen translational relevance (7).

Looking forward, our results open several avenues for further investigation. Longitudinal cohort studies should evaluate whether baseline PBMC MMP-9/TIMP-1 ratios predict adverse cardiovascular events, rehospitalization, or mortality in CAD patients. Interventional trials could explore whether pharmacologic modulation of MMP-9 (for example, with doxycycline analogues) or augmentation of TIMP-1 expression ameliorates remodeling and improves clinical outcomes. Finally, mechanistic in vitro studies using patient-derived PBMCs may elucidate upstream regulators—such as microRNAs or epigenetic modifications—that govern MMP-9 and TIMP-1 transcription in the context of chronic inflammation.

In summary, we have demonstrated that PBMC expression of MMP-9 and TIMP-1 transcripts is markedly dysregulated in Iraqi CAD patients, particularly those with HF, and that the MMP-9/TIMP-1 ratio correlates robustly with cardiac function. These findings highlight the potential of PBMC-based gene expression profiling as a minimally invasive biomarker platform for assessing disease severity and guiding therapeutic strategies in ischemic heart disease. Future multi-center, prospective, and mechanistic studies are warranted to validate these markers and translate them into clinical practice.

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None.

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