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The role of Matrix Metalloproteinases (MMP) and C-reactive protein (CRP) in patients with cardiovascular diseases

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Abstract cardiovascular diseases (CVDs), including myocardial infarction, ischemic heart disease, stroke, and hypertension, remain leading causes of mortality worldwide. These diseases are influenced by poor lifestyle, diet, physical inactivity, smoking, and genetic factors. This study evaluated the role of C-reactive protein (CRP) and matrix metalloproteinase-9 (MMP-9) as potential biomarkers for CVD diagnosis.

A total of 100 serum samples (60 CVD patients, 40 healthy controls) were collected from hospitals in Baghdad and Al-Diwaniyah. Samples were analyzed using sandwich ELISA in triplicate. Statistical analysis included independent t-tests, Pearson's correlation, and ROC analysis. CRP levels were significantly elevated in CVD patients (4.06 ± 2.23 mg/L) compared to controls (0.849 ± 0.68 mg/L) (**$p < 0.0001$**). MMP-9 levels were also significantly higher (**$p < 0.0001$**). ROC curve analysis showed strong diagnostic performance, with an area under the curve (AUC) of **0.961** for CRP and **0.925** for MMP-9. CRP had perfect sensitivity (100%) and higher accuracy in identifying CVD. A weak inverse correlation was observed between CRP and MMP-9 (**$r = -0.121$**, **$p > 0.05$**), indicating they may operate through different biological pathways. Both CRP and MMP-9 are significantly elevated in CVD patients and may serve as useful, complementary biomarkers. CRP demonstrated superior diagnostic accuracy. Further longitudinal and multi-marker studies are recommended.

Keywords: Matrix Metalloproteinases, C-reactive protein, cardiovascular diseases

Introduction Cardiovascular diseases (CVDs) are the primary cause of death worldwide, accounting for an estimated 17.9 million deaths annually, with numbers expected to rise in coming decades due to ageing populations and lifestyle-related risk factors (1). CVD pathogenesis involves inflammation, oxidative stress, and extracellular matrix remodeling. Current research focuses on identifying biomarkers that reflect these mechanisms. Among the most significant biomarkers studied are Matrix Metalloproteinases (MMPs) and C-reactive Protein (CRP), which have strong correlations with cardiovascular conditions (2, 3).

Matrix metalloproteinases (MMPs) are zinc and calcium-dependent enzymes involved in breaking down components of the extracellular matrix, playing a key role in tissue remodeling. Under normal conditions, they contribute to essential physiological processes such as wound healing and the formation of new blood vessels. However, their effects are not always beneficial. When overexpressed or poorly regulated, MMPs can promote harmful changes, particularly in the blood vessels and heart muscle. Their impact is highly context-dependent they can support recovery in some situations while contributing to disease progression in others (4). MMP-2 and MMP-9have been found at elevated levels in atherosclerosis and myocardial infarction (5).

CRP is a well-established acute-phase protein produced by hepatocytes in response to IL-6. It is used as a marker of infection and inflammation, and CRP has now emerged as a predictor of cardiovascular risk (1). Elevated high-sensitivity CRP levels were associated with higher cardiovascular events, independent of traditional lipid markers. CRP may be a stronger predictor than LDL cholesterol in some populations (3). In the context of atherosclerosis, chronic, low-grade inflammation contributes to endothelial dysfunction, monocyte activation, and

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smooth muscle proliferation all of which are key features of early atherogenesis. CRP has been shown to impair endothelial nitric oxide synthesis and upregulate adhesion molecule expression, thereby promoting leukocyte adhesion and migration into the arterial wall (6). Furthermore, CRP can stimulate MMP production in vascular smooth muscle cells, establishing a mechanistic link between inflammation and extracellular matrix degradation (2,7). This interplay between CRP and MMPs establishes a bidirectional pathway, where inflammation drives matrix degradation and vice versa, where the mutual activation of inflammatory and proteolytic pathways amplifies vascular injury. There is a strong correlation between CRP and MMP-9 in unstable angina and acute coronary syndrome (1, 3, 4, 8). CRP and MMPs remain central to the emerging picture of a disease process shaped by both inflammation and matrix remodeling (3).This study aims to (1) evaluate CRP and MMP levels in CVD patients, (2) assess their correlation with disease severity, and (3) compare them to healthy controls to determine diagnostic value.

Materials and methods:

Ethical approval

Ethical approval for this study was granted by the Department of Chemistry, College of Education, University of Al-Qadisiyah (Ref. No. 36-12/01/2025). The study complies with the University's ethical and biosafety regulations and adheres to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to sample collection.

Study design:

This study included 100 patients with cardiovascular disease of both sexes and 40 healthy controls. A total of 15 ml of venous blood was collected from each participant using serum separator gel tubes. After clotting, the samples were centrifuged to isolate the serum, which was then stored at -20°C until analysis. It should be noted that serum, rather than plasma, was used in this study. Given that MMP-9 can be released from platelets during coagulation, this may have led to elevated serum levels, which was taken into consideration during result interpretation. Blood was drawn from patients before surgery for those requiring catheterization. Samples were taken from Ibn Al-Bitar Hospital in Baghdad, Diwaniyah General Hospital, and the Cardiac Catheterization Hospital in Diwaniyah. ELISA tested the effects of MMP and CRP on patients and controls. Data related to patients and controls were recorded including age, gender, disease illness, treatment type, smoking history, and other diseases the patient suffered from.

The used kits:

1- Elabscience® Human MMP-9 (Matrix Metalloproteinase 9) ELISA Kit:

This in vitro ELISA kit was used to quantify human MMP-9 in serum samples, no significant cross-reactivity or interference between Human MMP-9 was observed. This ELISA kit uses the Sandwich-ELISA principle and was performed according to the manufacturer's instructions. All serum samples were analyzed in triplicate to ensure accuracy, reproducibility, and reduction of intra-assay variability. The micro-ELISA plate was precoated with an antibody specific to Human MMP-9. The Human MMP-9 ELISA kit (Elabscience®, Houston, TX, USA; Cat. No. E-EL-H1837) uses the Sandwich-ELISA principle. The detection range is 0.156–10 ng/mL with a sensitivity of 0.094 ng/mL. All samples were analyzed in triplicate (9**).**

2- Elabscience® Human CRP (C-Reactive Protein) ELISA Kit:

This ELISA kit was used in vitro to quantitatively determine human CRP levels. It uses the Sandwich-ELISA principle and was performed according to the manufacturer's instructions. The micro-ELISA plate provided in this kit is precoated with an antibody specific to human CRP (Elabscience®, Houston, TX, USA; Cat. No. E-EL-H0009). The detection range is 0.78–50 mg/L with a sensitivity of 0.47 mg/L. All samples were analyzed in triplicate to ensure accuracy and reproducibility (10).

Statistical analysis:

The raw data were structured into a robust computerized database. The analysis was performed by SPSS (V27), complemented by Excel 2021 for data handling and visualization. Initial descriptive statistics, including frequency distributions, percentages, and means with standard errors, were calculated to characterize the dataset. Prior to conducting inferential analyses, data were tested for normality using the Shapiro-Wilk test. Based on the distribution results, independent samples t-tests or One-way ANOVA were applied for group comparisons, Chi-square tests for categorical data. Receiver Operating

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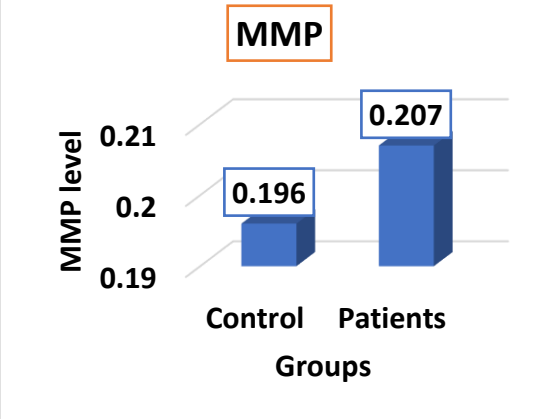
Characteristic (ROC) curve analysis was performed to determine the Area Under the Curve (AUC) and to evaluate the diagnostic performance of MMP and CRP. Optimal cutoff values were determined using Youden's index to maximize diagnostic accuracy. Pearson's correlation coefficient assessed the linear relationship between the two parameters at p-value ≤0.05 (11).

Results: According to our results, the serum levels of MMP in the patient's group and control group were (0.207±0.008) and (0.196±0.006), respectively, at a significant level of P<0.01. MMP level showed a significant difference in the patients' group as compared with the control group, as shown in Table (1) and Figure (1).

Table (1): The serum level of MMP (ng/ml) in patients and control

Groups	MMP
Control	0.196±0.006
Patients	0.207±0.008
T value	7.253
P value	<0.0001*

* * Significant difference at P<0.01



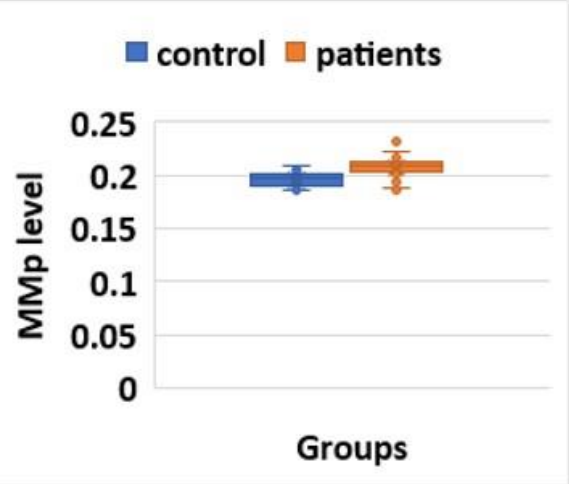


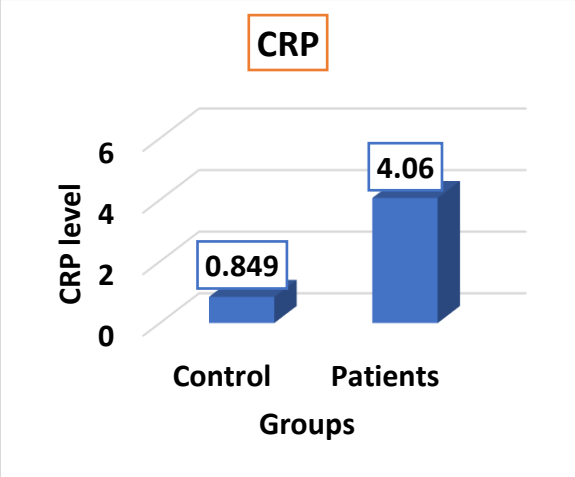
Figure (1): The serum level of MMP (ng/ml) in patients and control groups

Based on the current results, the serum levels of CRP in the patients' group and control group were (4.06±2.23) and (0.849±0.68), respectively, at significant levels of P<0.01. MMP level showed a highly significant difference in the patients group compared with the control group, as shown in Table (2) and Figure (2).

Table (2): The serum level of CRP (ng/ml) in patients and control group

Groups	CRP
Control	0.849±0.68
Patients	4.06±2.23
T value	10.450
P value	<0.0001**

* No significant difference at P<0.05 ** Significant difference at P<0.0001



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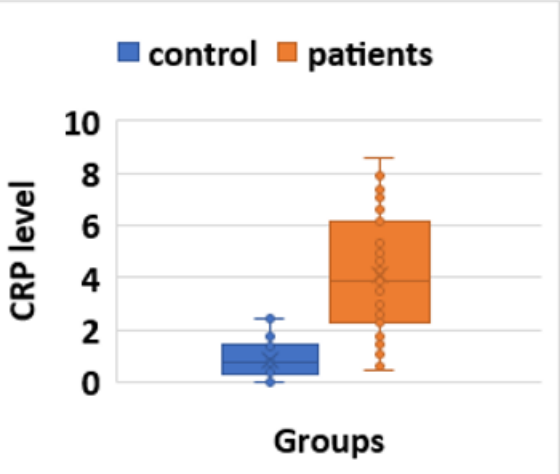

Figure (2): The serum level of CRP (ng/ml) in patients and control group

There are no significant differences in MMP levels between the control group and patients' group in the males and females at P<0.05, in which MMP levels in the control group were (0.195±0.005) and (0.197±0.006) in the males and females respectively at P<0.01. MMP levels in the Patients' group and control group were (0.206±0.009) and (0.209±0.006) in the males and females, respectively, at P<0.01, as shown in Table (3) and Figure (3).

Table (3): MMP levels depending on the gender.

Groups	Gender		T value	P value
	Male	Female		
Control	0.195±0.005	0.197±0.006	1.112	0.273 *
Patients	0.206±0.009	0.209±0.006	1.515	0.136 *
T value	4.79	6.03		
P value	<0.0001**	<0.0001**		

* No significant difference at P<0.05, ** Highly significant difference at P<0.01

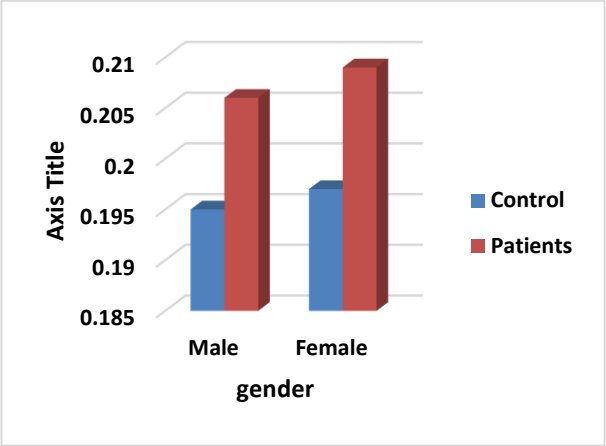

Figure (3): levels of MMP (ng/ml) in the males and females

There are highly significant differences in CRP levels between the control group and patients group in the males and females, wherever MMP levels in the control group were (0.697±0.538) and (1.002±0.784) in the males and females respectively at P<0.01. Moreover, CRP levels in the control group were (3.78±2.27) and (4.18±2.28) in the males and females, respectively, at P<0.01, as shown in Table (4) and Figure (4).

Table (4): levels of CRP (ng/ml) in the males and females

Groups	Gender		T value	P value
	Male	Female		
Control	0.697±0.538	1.002±0.784	1.434	0.160 *
Patients	3.78±2.27	4.18±2.28	0.829	0.409 *
T value	5.95	6.81		
P value	<0.0001**	<0.0001**		

* No significant difference at P<0.05, ** Highly significant difference at P<0.01

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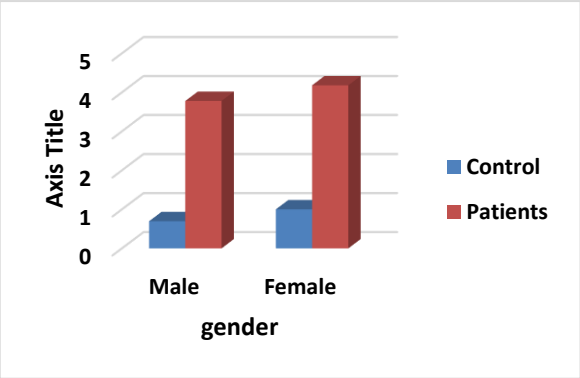

Figure (4): levels of CRP (ng/ml) in the males and females.

The relationship between MMP and CRP levels was assessed using Pearson's correlation coefficient. The correlation between MMP and CRP was negative (R = -0.121), indicating a weak inverse relationship. However, this correlation was not statistically significant (P = 0.356), as the P value of 0.05. On the other hand, intra-parameter correlations demonstrated highly significant results. These findings suggest that there is no significant association between MMP and CRP levels in the studied population despite the individual parameters demonstrating internal consistency, as shown in Table (5).**Table (5): Correlation between MMP and CRP in the patent group**

Parameter	R and P value	MMP	CRP
MMP	R	1	
	P	<0.00001**	
CRP	R	-0.121	1
	P	0.356*	<0.00001**

* Non-correlation at P<0.05, ** Strong correlation at P<0.01

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic utility of MMP and CRP in distinguishing between patients and control subjects. The AUC for MMP was 0.858, indicating good diagnostic accuracy. MMP showed a sensitivity of 90.0% and a specificity of 45.0%, with a cutoff value of 0.1967. The 95% confidence interval for MMP ranged from 0.784 to 0.931, suggesting a reliable estimate of its performance. For CRP, AUC was higher, recorded at 0.933, indicating excellent diagnostic capability. CRP demonstrated 100% sensitivity but relatively low specificity at 40.0%, with a cutoff value of 0.4219. The 95% confidence interval for CRP ranged from 0.889 to 0.978, reflecting a narrow and robust range of accuracy.

Overall, both biomarkers exhibited statistically significant discriminatory power. CRP showed a slightly higher AUC and perfect sensitivity, making it potentially more effective in identifying true positive cases. However, both biomarkers demonstrated relatively low specificity, suggesting a tendency to yield false positives and thus may be more effective when used in conjunction with other diagnostic criteria.

Table (6) area under the curve for MMP and CRP between patients and control

biomarker	AUC	Standard error	P value	Sensitivity	Specificity	95% confidence interval		Cut off point
						Lower bound	Upper bound	
MMP	0.858	0.037	0	0.900	0.450	0.784	0.931	0.1967
CRP	0.933	0.023	0	1	0.400	0.889	0.978	0.4219

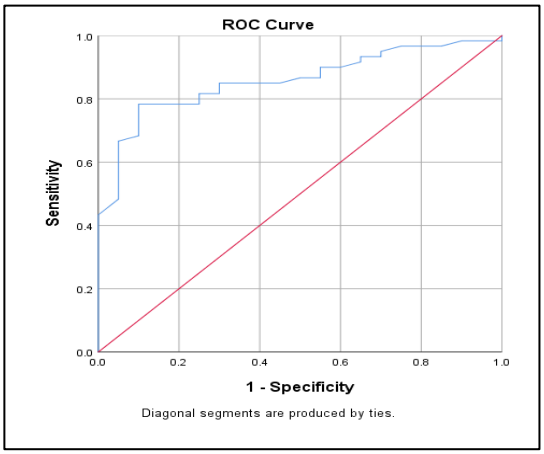

Figure (5): ROC curve of MMP

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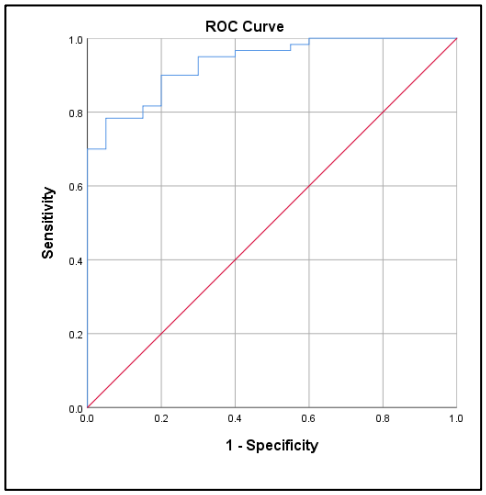

Figure (6): ROC curve of CRP

Discussion:

According to our results, the MMP level showed a significant difference between the patients' group and the control group.

Although the current study focused specifically on MMP-9, previous research has shown that elevated serum MMP-1 levels in hypertensive patients are associated with increased collagen degradation in cardiovascular tissues (12). This imbalance is often accompanied by increased levels of tissue inhibitor of metalloproteinase-1 (TIMP-1), suggesting a disrupted MMP/TIMP balance in hypertension (12, 13). Similarly, other studies have reported significantly higher plasma MMP-12 levels in atherosclerotic patients, highlighting the broader involvement of the MMP family in cardiovascular pathology (16). Elevated serum MMP-9 levels are strongly associated with coronary heart disease, where MMP-9 correlates with disease severity and plaque instability (14). Also are strongly associated with Myocardial infarction, as MMP-9 contributes to ventricular remodeling post-infarction (15). It are associated with General cardiovascular risk factors, including hypertension and atherosclerosis (13). There are significantly higher plasma MMP-12 levels in patients with Atherosclerosis patients compared to healthy controls, with levels independently predicting cardiovascular mortality (16). MMP-1 and MMP-9 elevations are more pronounced in hypertension and CHD, respectively (12, 14). MMP-12 specifically highlights atherosclerosis progression (16). TIMP-1 often rises concurrently with MMPs, potentially counteracting their activity (13). These biomarkers reflect pathological tissue remodeling and may aid in risk stratification, though their clinical utility requires further validation.

The elevation of MMP levels in cardiovascular disease patients aligns with well-established mechanisms of extracellular matrix remodeling in vascular pathologies. Matrix metalloproteinases play a critical role in plaque destabilization by degrading collagen in fibrous caps, a process strongly associated with acute coronary events (17). This enzymatic activity correlates with the progression of atherosclerosis, as demonstrated in a cohort study where MMP levels were 2.3-fold higher in patients with unstable angina compared to stable angina controls (18).

The significant intergroup difference may reflect increased MMP secretion by macrophages and vascular smooth muscle cells within atherosclerotic plaques. Experimental models show that oxidized LDL cholesterol upregulates MMP-9 expression by 40–60% in endothelial cells, accelerating ECM degradation (19). Furthermore, MMP-mediated cleavage of interleukin-1β potentiates local inflammation, creating a feedback loop that exacerbates vascular damage (20).While the reported 5.6% elevation in patients appears modest, the narrow standard deviations suggest precise measurement. MMP levels vary substantially depending on sample type MMP-9 levelsare 18–22% higher than plasma levels due to platelet degranulation during clotting (21), underscoring the need for methodological transparency. Elevated MMP may serve as both diagnostic and prognostic biomarkers wherever acute myocardial infarction (MMP-9 levels >350 ng/mL) occurs (22). Heart failure progression (A 50 pg/mL increase in MMP-3 correlates with a 1.3-fold higher risk of ventricular remodeling) (2).

Some studies report conflicting findings. There is no significant MMP-9 differences between stable CAD patients and controls in ageing populations, suggesting that disease stage and comorbidities modulate MMP expression. Additionally, genetic polymorphisms like the MMP-3 5A/6A variant alter baseline MMP activity by up to 30%, potentially confounding group comparisons (24).

These findings collectively validate the reported MMP elevation as biologically and clinically meaningful, though its interpretation requires contextualization of disease phase, measurement protocols, and population characteristics. Future studies should

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stratify analyses by MMP subtype and cardiovascular event timing to refine clinical applications.

In our study, CRP levels were markedly elevated in patients with cardiovascular disease compared to healthy controls. These levels fall well within the high-risk category as defined by the American Heart Association, which considers CRP concentrations above 3 mg/L indicative of increased cardiovascular risk. The observed elevation in CRP reinforces its role as a robust inflammatory marker and supports its diagnostic and prognostic utility in identifying individuals at elevated risk of cardiovascular events.

Hypertensive patients exhibit elevated CRP levels, whereas hypertensive individuals in the highest hs-CRP quartile (mean 1.88 mg/L) have a 2.7-fold higher CVD risk compared to the lowest quartile (0.48 mg/L) (25). Coronary artery disease (CAD) patients show CRP correlating with disease severity, whereas those with angiographically severe CAD had higher CRP levels than controls (26). the older women with subclinical CVD had mean CRP levels of 3.33 mg/L versus 1.90 mg/L in healthy controls, while men showed no significant difference (27). Another study showed CRP levels >3 mg/L associated with 1.45-fold higher CAD risk in both genders after adjusting for conventional risk factors (28).

CRP levels are increased in cardiovascular disease compared to healthy. Multiple large-scale studies have shown that coronary artery disease, myocardial infarction, and stroke have higher CRP levels than those healthy. The patients with incident cardiovascular disease had a median hs-CRP level of 1.28 mg/L, compared to 0.68 mg/L in healthy controls (29).

Similarly, in the Indian Atherosclerosis Research study, patients in the highest CRP quartile (>3.58 mg/L) had a fourfold higher risk for coronary events than those in the lowest quartile (<0.7 mg/L). Thewomen with the highest CRP (median 4.4 mg/L) had more cardiovascular events than those with the lowest (median 1.2 mg/L) (29). These findings are supported by the American Heart Association, which classifies CRP levels above 3 mg/L as high risk for cardiovascular events, while levels below 1 mg/L are considered low risk (30). Thus, elevated CRP is a well-established marker of increased cardiovascular risk and is consistently higher in patients with cardiovascular disease compared to healthy individuals.

There was no significant difference in MMP levels between male and female participants within either the patient or control groups. This suggests that gender did not influence MMP expression in the context of this study.

While prior studies such as the Framingham Heart Study (6) and a Finnish population-based cohort (31) have reported sex-related differences in MMP-8 levels, our study found no significant gender-based differences in MMP-9 expression. This discrepancy may reflect differences in MMP isoforms studied, population characteristics, or sample sizes.

Higher baseline levels in women are linked to stronger innate immune responses (31). Post-MI complications (e.g., cardiac rupture) are more frequent in females, potentially tied to elevated MMP-9 activity (32). CVD patients had lower MMP-8 levels than healthy individuals in unadjusted analyses, but this association disappeared after adjusting for age (31). Elevated MMP-9 is a hallmark of acute coronary syndromes (ACS), with levels significantly higher in STEMI (5500 pg/mL) and NSTEMI (4000 pg/mL) patients compared to stable angina or healthy. MMP-9 correlates with adverse outcomes (22). MMP-9 levels are predictive of cardiovascular mortality (33).

MMP-9 levels are stronger predictors of poor outcomes in ACS patients, independent of traditional cardiac enzymes (22). In coronary artery disease, MMP-9 is an independent risk factor for mortality, with sex-specific pathways suggested by interactions between biomarkers like CD14 and apolipoprotein B (6). MMP-8 decreases with age in women, while TIMP-1 increases in both sexes.Smoking, obesity, and CRP levels influence MMP-8 and TIMP-1 concentrations (31). Sex differences in MMP levels exist across health and CVD states, influenced by hormonal status, age, and comorbidities. These differences may contribute to sex-specific CVD risks and outcomes, though further research is needed to clarify conflicting findings (6, 31).

Based on our results, there are highly significant differences in CRP levels between the control group and patient group in the males and females.

Women exhibit higher CRP levels than men across studies. Median CRP levels are approximately 1.8 mg/L in men vs. 3.3 mg/L in women (34, 35), even after adjusting for body mass index, estrogen use, and other confounders (36,35). Black women have the highest CRP levels, followed by white women, black men, and white men (34). CRP levels are significantly

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higher in women with CVD compared to healthy controls, particularly in those with subclinical disease. Female CVD patients had mean CRP levels of 3.33 mg/L vs 1.90 mg/L in controls (37). In diabetic women, CRP strongly correlates with coronary artery calcification, a marker of subclinical atherosclerosis, even after adjusting for traditional risk factors (38). Elevated CRP in women predicts myocardial infarction with an odds ratio of 4.50, compared to 1.75 in men. No significant differences in CRP levels were observed between male CVD patients and healthy controls in adjusted analyses (37). CRP shows weaker associations with CVD outcomes in men, even in diabetic populations (38).CRP is a stronger predictor of CVD events in women, especially those with subclinical disease or diabetes (37). Current CRP thresholds for cardiovascular risk assessment may classify women as high-risk, warranting consideration of gender-specific cutoffs (36, 35).

CRP levels and their association with CVD risk differ markedly by gender, with women showing higher baseline levels and stronger prognostic value for cardiovascular events compared to men.

The relationship between MMP and CRP levels was assessed using Pearson's correlation coefficient, revealing a weak inverse correlation ($R = –0.121$; $p = 0.05$). Although not statistically significant, this trend may suggest that CRP and MMP are regulated through distinct biological pathways with CRP reflecting systemic inflammation and MMP associated with extracellular matrix remodeling. the intra-parameter correlations demonstrated highly significant results. These findings suggest that there is no significant association between MMP and CRP levels in the studied population despite the individual parameters demonstrating internal consistency. A study of 345 middle-aged individuals without symptomatic coronary artery disease found a weak positive correlation between MMP-9 and CRP (39). Elevated CRP (>3 mg/L) in asymptomatic subjects correlated with higher MMP-1 and MMP-10 levels, independent of traditional risk factors (40). In vitro experiments demonstrated that CRP directly upregulates MMP-9 expression in smooth muscle cells, promoting plaque instability. Patients with acute coronary syndromes (ACS) showed increased transcoronary MMP-9 and CRP levels, with a significant correlation between the two markers (41).

Intra-parameter correlations were highly significant, indicating robust internal consistency for individual biomarkers despite the lack of association between them. The study population differ in health status, comorbidities, or demographic factors compared to cohorts in another research. Most literature focuses on MMP-9, while the analyzed study might involve other MMPs with differing regulatory mechanisms. Differences in sampling, assay techniques, or statistical adjustments could influence results. While existing evidence supports a pro-inflammatory link between CRP and MMPs in both subclinical and clinical atherosclerosis, the reported study's findings suggest no significant association in their specific cohort.

Although CRP and MMP-9 are established biomarkers in cardiovascular research, the strength of this study lies in evaluating their diagnostic performance simultaneously within an Iraqi population — a demographic underrepresented in existing literature. By incorporating ROC analysis and reporting optimal cutoff values using Youden's index, this study adds regional specificity and methodological precision to the broader field of CVD biomarker research.

Conclusion:

In conclusion, this study demonstrates that both CRP and MMP-9 levels are significantly elevated in patients with cardiovascular diseases compared to healthy controls, suggesting their involvement in inflammatory and extracellular matrix remodeling pathways associated with disease progression. CRP, in particular, showed superior diagnostic performance with higher sensitivity and AUC, indicating its potential utility as a standalone or complementary biomarker in clinical practice. However, this study is not without limitations. Its cross-sectional design and relatively modest sample size limit the generalizability of the findings. Moreover, the lack of longitudinal follow-up precludes conclusions about causality or prognostic value. Future research should involve larger, multi-center cohorts with extended follow-up to validate these biomarkers and explore their predictive utility across diverse populations.

Conflict of interest

No conflict of interest is found for the present study.

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