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Article

Diagnostic Performance of Selected Inflammatory and Glycemic Biomarkers in Chronic Cardiovascular Disease

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Abstract: Background: Cardiovascular disease (CVD) remains the leading cause of mortality worldwide and is closely associated with chronic inflammation and glycemic dysregulation. Biomarkers reflecting these pathological processes may improve the early identification and risk assessment of patients with chronic CVD. Objective: This study aimed to evaluate the inflammatory and glycemic profiles of patients with CVD by assessing high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and glycated hemoglobin (HbA1c), and to determine their diagnostic and predictive value. Methods: A case-control study was conducted involving 100 participants, including 60 patients with CVD (ischemic heart disease, heart failure, or stroke) and 40 apparently healthy controls. hs-CRP, IL-6, and TNF-α were measured in serum samples, whereas HbA1c was measured in whole blood. Comparisons between groups were performed using the independent-samples t-test. Multivariable logistic regression analysis was used to identify independent predictors of CVD, while receiver operating characteristic (ROC) curve analysis evaluated the diagnostic performance of each biomarker. Results: hs-CRP, IL-6, TNF-α, and HbA1c levels were significantly higher in patients with CVD than in healthy controls (all $p < 0.001$). Logistic regression analysis identified HbA1c, IL-6, and TNF-α as independent predictors of CVD, with HbA1c demonstrating the strongest association. ROC analysis showed that hs-CRP had the highest diagnostic accuracy (AUC = 0.921), followed by HbA1c (AUC = 0.918), whereas IL-6 and TNF-α demonstrated moderate discriminative performance. Conclusion: Inflammatory and glycemic biomarkers are significantly associated with CVD. hs-CRP exhibited excellent diagnostic performance, while HbA1c, IL-6, and TNF-α independently predicted CVD. Combined assessment of inflammatory and glycemic biomarkers may improve cardiovascular risk stratification and support earlier identification of high-risk patients.

Keywords: Cardiovascular Disease (CVD), High-Sensitivity C-Reactive Protein (Hs-CRP), Interleukin-6 (IL6), Tumor Necrosis Factor-Alpha (TNF-A), Glycated Hemoglobin (HbA1c).

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1. Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 18 million deaths annually and imposing a substantial burden on healthcare systems and societies [1], [2]. CVD encompasses a heterogeneous group of disorders affecting the heart and blood vessels, among which ischemic heart disease (IHD), heart failure (HF), and stroke are the most clinically significant because they contribute substantially to [premature mortality, disability, and recurrent hospitalization [2], [3], [4].

Chronic inflammation and glycemic dysregulation are closely interconnected mechanisms that contribute to cardiovascular injury. Persistent inflammatory activation promotes endothelial dysfunction, leukocyte recruitment, plaque formation, and plaque

instability, whereas insulin resistance and chronic hyperglycemia accelerate vascular damage through oxidative stress, endothelial injury, and metabolic abnormalities [1], [3], [5]. These processes contribute to the development and progression of major cardiovascular disorders, including IHD, HF, and stroke.

Among inflammatory biomarkers, hs-CRP is the most widely used clinical indicator of low-grade systemic inflammation and has consistently been associated with cardiovascular risk and adverse outcomes [6], [7]. IL-6, an upstream inflammatory cytokine, plays an important role in endothelial dysfunction, plaque progression, and cardiovascular events, while TNF-α contributes to vascular inflammation, oxidative stress, myocardial remodeling, and heart failure progression [6], [8], [9]. Together, these biomarkers reflect different stages of the inflammatory cascade involved in chronic CVD pathogenesis.

Glycated hemoglobin (HbA1c), a marker of long-term glycemic exposure, has also emerged as an important indicator of cardiovascular risk. Elevated HbA1c has been associated with ischemic heart disease, stroke, heart failure, cardiovascular mortality, and adverse clinical outcomes, even among some individuals without diagnosed diabetes [10], [11]. Chronic hyperglycemia promotes endothelial dysfunction, inflammation, and accelerated atherosclerosis, highlighting the close interaction between metabolic and inflammatory pathways in CVD [3].

Although numerous studies have evaluated inflammatory biomarkers or glycemic markers individually, relatively few have investigated these biomarkers simultaneously, particularly in Middle Eastern populations where diabetes, hypertension, and CVD are highly prevalent. Furthermore, integrated evaluation of hs-CRP, IL-6, TNF-α, and HbA1c across patients with IHD, HF, and stroke remains limited [8], [12].

Therefore, the present study aimed to evaluate the inflammatory and glycemic profiles of patients with CVD, including IHD, HF, and stroke, by assessing hs-CRP, IL-6, TNF-α, and HbA1c, and to investigate their diagnostic and predictive value in distinguishing patients with CVD from healthy controls.

2. Materials and Methods

2.1 Study Design and Participants

This case-control study was conducted in Basra, Iraq, between 29 September 2025 and 16 April 2026. A total of 100 participants were enrolled, including 60 patients with established CVD and 40 apparently healthy controls. Participants were aged between 35 and 75 years, and healthy controls were selected to achieve comparable age and sex distributions with the patient group. Patients were recruited from the Cardiac Intensive Care Units of Al-Fayhaa Teaching Hospital and Basra General Hospital. The CVD group included patients with previously confirmed IHD, HF, or stroke, based on medical records and physician diagnosis. Control subjects were recruited from the general community and had no known history of CVD or other chronic systemic illnesses. Demographic and clinical information, including age, sex, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), medication history, and smoking status, was obtained using a structured questionnaire.

2.2 Inclusion and Exclusion Criteria

Eligible participants were men and women aged 35–75 years. Patients were required to have a confirmed diagnosis of chronic CVD (IHD, HF, or stroke) and to have undergone an overnight fast of approximately 8 hours before blood collection. Healthy controls had no history of cardiovascular or chronic systemic disease. Participants were excluded if they had chronic kidney or liver disease, acute infection, inflammatory or autoimmune disorders, malignancy, or current smoking.

2.3 Blood Sample Collection and Laboratory Analysis

Following an overnight fast of approximately 8 hours, venous blood samples were collected from all participants. Approximately 4–5 mL of blood was collected into gel tubes for serum preparation. Samples were centrifuged at 3000 rpm for 15 minutes, and serum aliquots were stored at −18°C until inflammatory and immunological analyses were performed. An additional 2 mL of blood was collected into EDTA tubes for HbA1c measurement. Serum concentrations of IL-6 and TNF-α were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits following the manufacturers' protocols. HbA1c and hs-CRP were measured using the i-CHROMA™II fluorescence immunoassay analyzer, according to the manufacturer's instructions.

2.4 Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were tested for normality using the Shapiro–Wilk test and are presented as mean ± standard deviation (SD), while categorical variables are expressed as frequencies and percentages. Comparisons between CVD patients and healthy controls were performed using the independent-samples t-test for continuous variables and the chi-square test for categorical variables. To identify independent predictors of CVD, a multivariable binary logistic regression model was constructed with CVD status (case = 1, control = 0) as the dependent variable. Independent variables included HbA1c, IL-6, TNF-α, age, sex, and body mass index (BMI). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The diagnostic performance of hs-CRP, HbA1c, IL-6, and TNF-α was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was used to assess discriminative ability, and the optimal cutoff value for each biomarker was determined by maximizing the Youden index. A p-value < 0.05 was considered statistically significant.

3. Results

Table 1. Baseline Demographics Characteristics of Study Participants.

Variable	Control (n=40)	CVD (n=60)	Total (n=100)	P value
Age (years)	56.1 ± 10.2	59.2 ± 9.0	57.9 ± 9.5	0.12
Gender				0.379
Male, n (%)	13 (32.5%)	26 (43.3%)	39 (39.0%)	
Female, n (%)	27 (67.5%)	34 (56.7%)	61 (61.0%)	
BMI (kg/m²)	29.4 ± 5.8	30.1 ± 5.7	29.8 ± 5.7	0.502

Data are mean ± SD for continuous variables and n (%) for categorical variables. Independent samples t-test; Chi-square test for gender. $p < 0.05$.

Table 1 shows the baseline demographic characteristics of the study participants. There were no statistically significant differences between patients with chronic CVD and healthy controls in terms of age (p = 0.12), sex distribution (p = 0.379), or body mass index (BMI) (p = 0.502).

Table 2. Distribution of DM and HTN Among Patients with CVD (n = 60).

Clinical Group	n	%
DM + HTN	37	61.7%
DM only	4	6.7%
HTN only	12	20.0%
Neither DM nor HTN	7	11.7%
Total	60	100%

DM = diabetes mellitus; HTN = hypertension. Data represent absolute frequency and percentage within the CVD group only.

Among the 60 patients with CVD, 37 (61.7%) had both DM and HTN, 4 (6.7%) had DM only, 12 (20.0%) had HTN only, and 7 (11.7%) had neither DM nor HTN.

Table 3. Comparison of Inflammatory and Glycemic Biomarkers Between Control Subjects and Patients with Cardiovascular Disease.

Marker	Control (n=40) Mean ± SD	CVD (n=60) Mean ± SD	P value
hs-CRP (mg/L)	0.80 ± 2.65	6.70 ± 3.98	<0.001
IL-6 (pg/mL)	68.11 ± 39.74	167.49 ± 112.45	<0.001
TNF-α (pg/mL)	56.52 ± 34.21	123.77 ± 79.33	<0.001
HbA1c (%)	4.48 ± 0.52	7.14 ± 2.22	<0.001

Data are presented as mean ± SD. P values were calculated using the independent-samples t-test.

Table 3 shows the comparison of inflammatory and glycemic biomarkers between the study groups. Serum hs-CRP, IL-6, TNF-α, and HbA1c levels were all significantly higher in patients with CVD than in healthy controls (all $p < 0.001$), indicating enhanced systemic inflammation and chronic glycemic dysregulation in the CVD group.

Table 1. Multivariable Logistic Regression Analysis of Independent Predictors of Cardiovascular Disease.

Variable	Adjusted OR	95% CI	P value	Interpretation
IL-6	1.027	1.009 – 1.045	0.003	Independent predictor
TNF-α	1.032	1.010 – 1.055	0.004	Independent predictor
HbA1c	17.969	3.145 – 102.658	0.001	Independent predictor

OR = odds ratio; CI = confidence interval.

Multivariable logistic regression analysis identified HbA1c, IL-6, and TNF-α as independent predictors of CVD after adjustment for age, sex, and BMI. HbA1c showed the strongest association with CVD (adjusted OR = 17.97, 95% CI: 3.15–102.66, $p = 0.001$), while IL-6 (OR = 1.027, $p = 0.003$) and TNF-α (OR = 1.032, $p = 0.004$) were also significantly associated with increased odds of CVD.

Table 2. Diagnostic Performance of Inflammatory and Glycemic Biomarkers for Cardiovascular Disease.

Marker	AUC	95% CI	Optimal Cutoff	Sensitivity	Specificity
IL-6	0.772	0.690 – 0.854	120.36 pg/mL	66.7%	90.0%
TNF-α	0.757	0.673 – 0.841	95.17 pg/mL	65.0%	90.0%
hs-CRP	0.921	0.868 – 0.974	0.15 mg/L	95.0%	92.5%
HbA1c	0.918	0.864 – 0.972	5.20%	83.3%	90.0%

AUC = area under the ROC curve. 95% CI based on standard error approximation. Optimal cut-off by maximum Youden index (sensitivity + specificity − 1).

Receiver operating characteristic (ROC) analysis demonstrated that hs-CRP showed the highest diagnostic performance for distinguishing patients with CVD from healthy controls (AUC = 0.921), followed closely by HbA1c (AUC = 0.918). IL-6 and TNF-α showed moderate diagnostic accuracy, with AUC values of 0.772 and 0.757, respectively. These findings indicate that hs-CRP and HbA1c provide superior discrimination of CVD compared with the evaluated inflammatory cytokines.

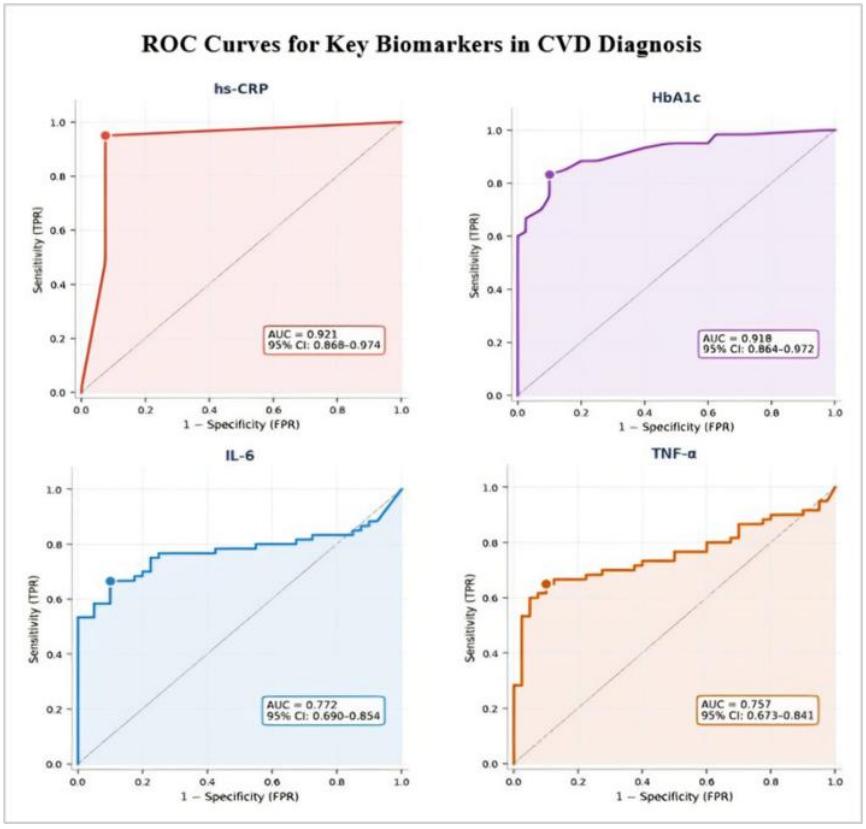

Figure 1. Receiver Operating Characteristic (ROC) Curves of hs-CRP, HbA1c, IL-6, and TNF-α for the Diagnosis of Cardiovascular Disease.

ROC curves comparing the diagnostic performance of hs-CRP, HbA1c, IL-6, and TNF-α for distinguishing patients with cardiovascular disease from healthy controls. The diagonal dashed line represents an AUC of 0.50 (no discriminative ability).

4. Discussion

The present study investigated the inflammatory and glycemic profiles of patients with chronic CVD, including IHD, HF, and stroke, and evaluated the diagnostic and predictive value of hs-CRP, IL-6, TNF-α, and HbA1c. The principal findings demonstrated that all four biomarkers were significantly elevated in patients with chronic CVD compared with healthy controls. Furthermore, hs-CRP showed the highest diagnostic accuracy, followed by HbA1c, while IL-6 and TNF-α exhibited moderate discriminative performance. Multivariable logistic regression analysis identified HbA1c, IL-6, and TNF-α as independent predictors of CVD, highlighting the combined contribution of chronic inflammation and glycemic dysregulation to CVD.

The significantly elevated hs-CRP levels observed in the present study indicate enhanced systemic and vascular inflammation in patients with CVD, supporting the established role of inflammation in endothelial dysfunction, atherosclerotic progression, plaque instability, and subsequent cardiovascular events. As an acute-phase protein

primarily induced by the IL-6 signaling pathway, hs-CRP reflects low-grade inflammatory activity and has been closely associated with vascular injury and thrombotic plaque remodeling. Emerging evidence also suggests that CRP, particularly its monomeric form, may actively participate in vascular damage rather than acting solely as a passive inflammatory marker [13], [14], [15], [16].

The excellent diagnostic performance of hs-CRP observed in the present study (AUC = 0.921) agrees with recent international studies demonstrating strong associations between elevated hs-CRP, coronary artery disease severity, cardiovascular risk, and adverse clinical outcomes [17], [18], [19]. Although hs-CRP is a nonspecific inflammatory marker and its concentration may be influenced by concurrent inflammatory conditions, previous studies have suggested that it remains one of the most practical and clinically accessible biomarkers for cardiovascular risk assessment [20], [21].

Consistent with the elevated hs-CRP levels observed in the present study, serum IL-6 concentrations were also significantly increased in patients with CVD and remained an independent predictor after multivariable adjustment. These findings further support the central role of IL-6 in cardiovascular pathophysiology. As a key upstream inflammatory cytokine, IL-6 promotes endothelial dysfunction, vascular inflammation, monocyte recruitment, smooth muscle cell activation, and acute-phase signaling, thereby accelerating atherosclerosis and contributing to plaque destabilization, ischemic heart disease progression, adverse cardiac remodeling in heart failure, and poor outcomes after stroke [9], [22], [23].

The persistence of IL-6 as an independent predictor in the present study is biologically plausible because IL-6 reflects a more proximal inflammatory pathway than downstream biomarkers such as hs-CRP and has been closely linked to atherothrombosis and cardiovascular progression [24], [25]. Similar findings have been reported in recent studies, where elevated IL-6 independently predicted long-term cardiovascular events, stroke, and major adverse cardiovascular outcomes in patients with coronary artery disease and other high-risk populations [23], [26], [28]. Although some authors have noted that differences in assay methods and population characteristics may influence IL-6 cutoff values, these factors are unlikely to alter the consistent association between elevated IL-6 and CVD [24].

Consistent with the findings for IL-6, the present study demonstrated significantly elevated serum TNF-α levels in patients with CVD, and TNF-α remained an independent predictor after multivariable analysis. TNF-α is a key pro-inflammatory cytokine that contributes to endothelial dysfunction, oxidative stress, leukocyte adhesion, plaque progression, and myocardial remodeling, thereby linking vascular inflammation with both atherosclerotic disease and HF [29], [30], [31].

The independent association of TNF-α observed in the present study is consistent with previous international studies reporting significant relationships between elevated TNF-α levels, coronary artery disease severity, and adverse cardiovascular outcomes [14], [32], [33]. Although the biological effects of TNF-α may vary according to disease stage and receptor-specific signaling pathways, current evidence consistently supports its role as an important mediator of chronic vascular inflammation [2], [34].

Consistent with the inflammatory biomarker findings, the present study demonstrated significantly elevated HbA1c levels in patients with CVD. HbA1c also showed excellent diagnostic performance, second only to hs-CRP, and emerged as the strongest independent predictor of CVD in the multivariable analysis. These findings highlight the important contribution of chronic glycemic dysregulation to cardiovascular disease. HbA1c reflects long-term glycemic exposure and contributes to endothelial dysfunction, oxidative stress, advanced glycation end-product (AGE) formation, and vascular inflammation, thereby promoting atherosclerosis and cardiovascular injury [35],

[36], [37]. Chronic hyperglycemia also contributes to myocardial remodeling and impaired cardiac function, providing a mechanistic link to IHD, HF, and stroke [38], [39].

The strong association between HbA1c and CVD observed in the present study agrees with previous studies demonstrating that elevated HbA1c is independently associated with coronary artery disease, ischemic stroke, heart failure, and major adverse cardiovascular events [40], [41], [42]. Although Olesen et al. (2023) reported significant associations mainly in patients with established coronary artery disease, differences in study populations and disease severity may explain this discrepancy [43].

Multivariable logistic regression identified HbA1c, IL-6, and TNF-α as independent predictors of CVD, with HbA1c demonstrating the strongest association. Unlike simple group comparisons, multivariable analysis identifies biomarkers that remain significantly associated with disease after adjustment for potential confounding factors, providing stronger evidence of their clinical relevance. These findings agree with previous studies reporting independent associations of HbA1c with coronary artery disease and major cardiovascular events [44], [45]. While IL-6 and TNF-α have likewise been recognized as independent predictors of adverse cardiovascular outcomes [46], [47].

Receiver Operating Characteristic(ROC) analysis demonstrated that hs-CRP had the highest diagnostic accuracy, followed closely by HbA1c, whereas IL-6 and TNF-α showed moderate discriminative performance. These findings are consistent with previous studies reporting the high diagnostic performance of hs-CRP in ischemic heart disease and acute coronary syndrome [48], [49]. Similarly, previous investigations have highlighted the diagnostic value of HbA1c for cardiovascular risk stratification and prediction of adverse cardiovascular outcomes [50], [51]. Although IL-6 and TNF-α remained independent predictors in the logistic regression analysis, their relatively lower AUC values suggest that they may be more useful as complementary inflammatory biomarkers rather than standalone diagnostic markers [52]. Overall, these findings indicate that the combined assessment of inflammatory and glycemic biomarkers may improve the diagnostic evaluation and risk stratification of patients with chronic cardiovascular disease.

5. Conclusion

The present study demonstrated that patients with chronic CVD exhibit significantly elevated inflammatory and glycemic biomarkers compared with healthy controls, indicating the important contribution of chronic inflammation and glycemic dysregulation to CVD. Among the evaluated biomarkers, hs-CRP showed the highest diagnostic performance for distinguishing patients with CVD from healthy controls, whereas HbA1c, IL-6, and TNF-α were identified as independent predictors of CVD in multivariable logistic regression analysis. These findings suggest that the combined assessment of inflammatory and glycemic biomarkers may improve cardiovascular risk stratification and support the early identification of individuals at increased cardiovascular risk. Further large-scale prospective studies are recommended to validate these findings and determine their prognostic value in different cardiovascular populations.

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