Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

THE ROLE OF INFLAMMATORY BIOMARKERS IN PREDICTING ACUTE MYOCARDIAL INFARCTION IN DIABETIC PATIENTS: A PROSPECTIVE COHORT STUDY

Dr. Ahmed Mehmood[1], Ali Aasam Khan[*2], Muhammad Ahmad[3], Muhammad Shahmeer Nawaz[4], Bismillah Iftikhar[5], Faizan Afzal[6], Mehak Memon[7]

[1]*MBBS, Doctor, Pervaiz Elahi Institute of Cardiology, Bahawalpur, Pakistan*
[*2]*Doctor of Pharmacy, CECOS University of IT and Emerging Sciences, Peshawar, Pakistan*
[3]*Medical Laboratory Technology, University of Sargodha, Pindi Bhattian, Pakistan*
[4]*MBBS, University College of Medicine and Dentistry, Lahore, Pakistan*
[5,6]*Doctor of Pharmacy, Hajvery University Lahore, Pakistan*
[7]*MPhil Physiology, Senior Lecturer, University of Modern Sciences, Tando Muhammad Khan, Pakistan*

[*2]https://orcid.org/0009-0001-4535-0851, [4]https://orcid.org/0009-0008-3894-4046,
[5]https://orcid.org/0009-0000-3987-3149, [6]https://orcid.org/0009-0003-9178-5885

DOI: https://doi.org/10.5281/zenodo.18897894

Keywords

Type 2 diabetes mellitus; Acute myocardial infarction; Inflammation; High-sensitivity C-reactive protein; Interleukin-6; Interleukin-1 beta; Atherosclerotic disease; Cardiovascular risk assessment; Prospective study; Pakistan.

Article History

Received: 05 January 2026
Accepted: 18 February 2026
Published: 07 March 2026

Corresponding Author: *
Ali Aasam Khan

Abstract

Background:

Cardiovascular disease is the primary cause of mortality among individuals with type 2 diabetes mellitus (T2DM). Among its complications, acute myocardial infarction (AMI) represents one of the most life-threatening events, contributing considerably to both death and long-term disability. Increasing evidence suggests that persistent low-grade inflammation plays a crucial role in atherosclerotic plaque formation and rupture. Biomarkers of systemic inflammation, particularly high-sensitivity C-reactive protein (hs-CRP) and selected interleukins, have been investigated as possible predictors of cardiovascular events. Nevertheless, data from regional populations in Pakistan, especially Southeastern Punjab, remain limited.

Objective:

This study aimed to determine whether baseline levels of specific inflammatory markers—C-reactive protein and selected interleukins—are associated with the future development of acute myocardial infarction in patients diagnosed with type 2 diabetes.

Methods:

A prospective cohort investigation was carried out at a tertiary care hospital in Southeastern Punjab, Pakistan, between January 2023 and December 2024. The study enrolled 450 adults aged 35 to 75 years with confirmed T2DM through consecutive sampling. Individuals with a history of myocardial infarction, documented coronary artery disease, chronic inflammatory disorders, malignancy, or advanced hepatic or renal impairment were excluded. At enrollment, demographic and clinical information was recorded, and fasting blood samples were obtained to measure hs-CRP, interleukin-6 (IL-6), interleukin-1 beta (IL-1β), lipid profile components, and glycemic parameters. Participants were

Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

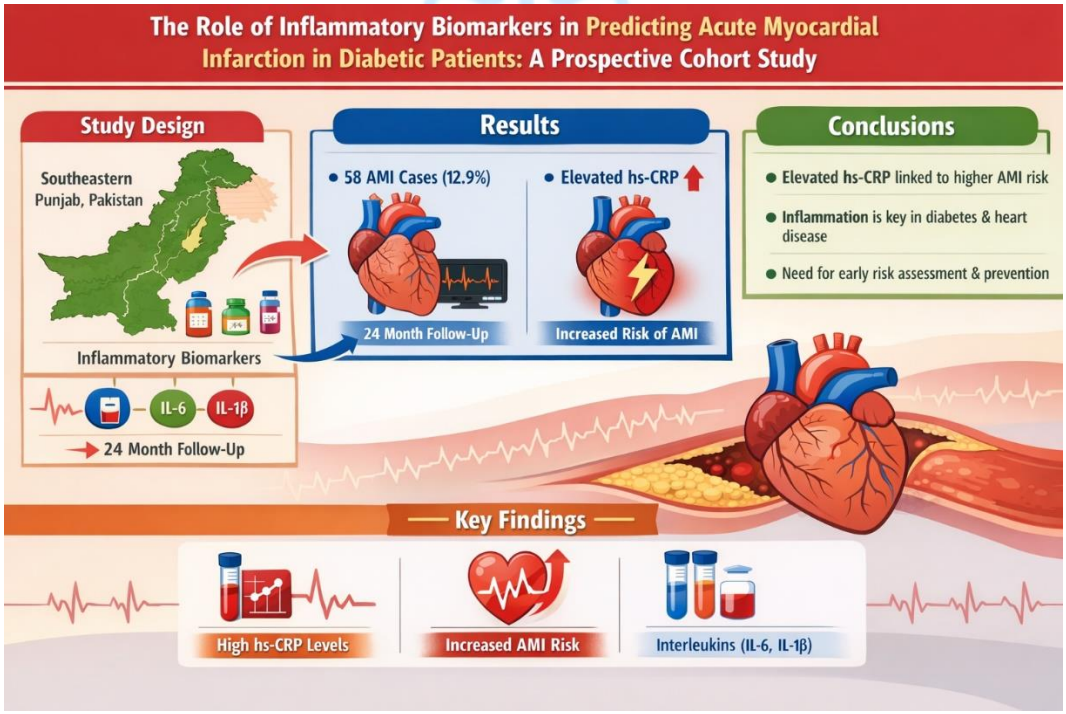
followed for 24 months to identify first-time AMI events, confirmed by clinical symptoms, electrocardiographic findings, and elevated cardiac troponin levels. Cox proportional hazards models were applied to evaluate the relationship between inflammatory markers and incident AMI, with adjustment for conventional cardiovascular risk factors.

Results:

Over the two-year follow-up period, 58 participants (12.9%) experienced an acute myocardial infarction. Patients who developed AMI had significantly higher baseline hs-CRP levels compared with those who did not experience cardiac events. IL-6 concentrations were moderately elevated among affected individuals, whereas IL-1β showed no meaningful difference between groups. After adjusting for potential confounders—including age, gender, hypertension, smoking, lipid levels, body mass index, and diabetes duration—hs-CRP remained independently associated with increased AMI risk. A dose-response relationship was observed, with progressively higher hs-CRP levels corresponding to greater risk.

Conclusion:

Baseline elevation of hs-CRP is strongly associated with the occurrence of acute myocardial infarction in individuals with type 2 diabetes. These findings reinforce the contribution of inflammatory pathways to cardiovascular risk in this population. Routine measurement of hs-CRP may enhance risk stratification and facilitate earlier preventive interventions in high-risk diabetic patients.



INTRODUCTION

Cardiovascular disease continues to be the foremost cause of mortality worldwide, with acute myocardial infarction (AMI) representing one of its most severe and life-threatening manifestations. Global estimates from the World Health Organization indicate that ischemic heart disease is responsible for millions of deaths annually. In countries such as Pakistan, the incidence of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

cardiovascular conditions is rising steadily, largely driven by rapid urban development, sedentary lifestyles, unhealthy dietary habits, and the growing prevalence of diabetes mellitus.

Diabetes mellitus is a long-standing metabolic disorder characterized by persistent hyperglycemia. Over time, elevated blood glucose levels damage blood vessels and nerves, significantly increasing the likelihood of cardiovascular complications. Individuals with diabetes face a substantially greater risk of developing coronary artery disease compared to those without diabetes. Previous research has even suggested that diabetic patients without a prior heart attack may carry a risk of myocardial infarction comparable to non-diabetic individuals who have already experienced one. This underscores the strong and well-established relationship between diabetes and cardiovascular morbidity.

The occurrence of AMI is typically the result of sudden obstruction of a coronary artery, most often following rupture of an atherosclerotic plaque and subsequent clot formation. Atherosclerosis is no longer viewed solely as a disorder of lipid accumulation; it is now recognized as a chronic inflammatory disease. Inflammatory processes contribute not only to plaque formation but also to its progression and eventual instability. Consequently, markers of inflammation circulating in the bloodstream may offer valuable insight into an individual's future cardiovascular risk.

Inflammatory biomarkers are measurable blood components that reflect ongoing inflammatory activity. Among them, C-reactive protein (CRP) is one of the most extensively studied. High-sensitivity CRP (hs-CRP) testing has demonstrated the ability to predict future cardiovascular events, even among individuals without apparent heart disease. Elevated levels of hs-CRP have been linked to an increased risk of myocardial infarction, stroke, and sudden cardiac death. CRP synthesis in the liver is stimulated primarily by inflammatory cytokines, particularly interleukin-6 (IL-6).

Interleukins are signaling proteins that regulate immune and inflammatory responses. Certain interleukins, especially IL-6 and interleukin-1 beta (IL-1β), play important roles in the pathogenesis of atherosclerosis. Higher circulating concentrations of IL-6 have been associated with a greater likelihood of coronary events. Moreover, large clinical trials have demonstrated that reducing inflammation can lower cardiovascular event rates even when cholesterol levels remain unchanged, further supporting the central role of inflammation in cardiovascular disease.

Inflammatory activity tends to be amplified in individuals with diabetes. Chronic hyperglycemia promotes oxidative stress, endothelial dysfunction, and activation of inflammatory pathways. The formation of advanced glycation end products (AGEs) as a result of prolonged high blood glucose further stimulates vascular inflammation. These mechanisms may lead to persistently elevated inflammatory markers in diabetic patients, thereby increasing the risk of plaque instability and thrombosis. For this reason, evaluating inflammatory biomarkers within diabetic populations is particularly relevant.

Pakistan faces a substantial and growing burden of diabetes. International data rank the country among those with the highest numbers of adults living with the condition. Many patients are diagnosed late or struggle with inadequate glycemic control. Simultaneously, cardiovascular disease accounts for a significant proportion of hospital admissions, particularly in tertiary care centers. Despite this dual burden, local evidence exploring the predictive value of inflammatory biomarkers for acute myocardial infarction in diabetic patients remains limited, especially in regions such as Southeastern Punjab.

Early recognition of individuals who are likely to experience a serious cardiac episode is essential for timely preventive intervention. Although traditional determinants—such as advancing age, elevated blood pressure, tobacco use, abnormal lipid levels, and hereditary predisposition—form the basis of cardiovascular risk evaluation, they do not entirely account for the occurrence of acute myocardial infarction in patients whose risk factors appear well managed. This discrepancy indicates that other biological processes, particularly chronic inflammatory activity, may

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

significantly influence disease progression. Integrating markers of inflammation into established assessment frameworks may therefore strengthen risk prediction models.

Longitudinal cohort designs are especially suitable for investigating predictive relationships. By observing a defined population over an extended period and recording incident outcomes, it becomes possible to clarify whether baseline characteristics precede and contribute to later disease development. Assessing inflammatory biomarker concentrations at enrollment—and relating them to future cardiac events—allows for evaluation of their prognostic relevance in the development of AMI.

The present research was undertaken in a tertiary-level hospital located in Southeastern Punjab, Pakistan, which provides healthcare services to a heterogeneous population drawn from both metropolitan and rural areas. Given the substantial number of patients with diabetes treated at this institution, it offers an appropriate clinical environment for examining links between inflammatory mediators and subsequent myocardial infarction.

The central objective of this prospective investigation is to explore whether selected inflammatory indicators, particularly C-reactive protein and certain interleukins, are associated with the later occurrence of acute myocardial infarction in individuals diagnosed with diabetes mellitus. In addition, the study aims to assess whether these biomarkers retain predictive significance after adjustment for conventional cardiovascular risk determinants.

Improved insight into this association could enable healthcare professionals to more accurately identify diabetic patients who face an elevated probability of cardiac complications. If inflammatory biomarkers demonstrate meaningful prognostic utility, incorporating them into routine clinical practice may refine risk stratification and inform targeted preventive measures. Such strategies could potentially decrease cardiovascular-related hospitalizations and mortality among diabetic populations in Pakistan and similar regions.

In summary, inflammatory processes play a central role in the development and destabilization of atherosclerotic disease leading to myocardial infarction. People with diabetes are particularly vulnerable due to persistent metabolic imbalance and systemic inflammation. Despite this, region-specific evidence from Southeastern Punjab is limited. This study seeks to contribute locally relevant data by prospectively evaluating the predictive importance of inflammatory biomarkers for AMI in this high-risk population.

METHODOLOGY

Research Design and Study Location

A forward-looking cohort approach was adopted for this study. The research was undertaken at a tertiary-level teaching hospital situated in Southeastern Punjab, Pakistan. This institution provides healthcare services to a diverse population drawn from neighboring urban centers and rural communities. The study spanned a period of two years, commencing in January 2023 and concluding in December 2024.

At enrollment, patients with confirmed type 2 diabetes mellitus underwent initial evaluation and baseline laboratory testing. They were subsequently monitored over time to identify new cases of acute myocardial infarction (AMI). The primary aim was to determine whether baseline inflammatory biomarker levels were associated with later development of cardiac events.

Participant Selection

Eligible participants were adults diagnosed with type 2 diabetes who presented either to outpatient clinics or were admitted to medical wards during the recruitment phase. Individuals aged 35 to 75 years were considered suitable for inclusion. Confirmation of diabetes was based on documented medical records supported by fasting blood glucose measurements and HbA1c values aligned with recognized clinical standards.

Exclusion criteria were applied to eliminate factors that might distort inflammatory marker levels or confound outcomes. Patients were excluded if they had a previous myocardial infarction, known ischemic heart disease, chronic inflammatory or autoimmune disorders, active infection, cancer,

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

advanced liver disease, or severe chronic kidney disease (stage 4 or 5). Those receiving long-term corticosteroids, anti-inflammatory medications, or immunosuppressive therapy were also not included.

Sample Size Considerations

The number of participants required was determined using statistical calculations suitable for cohort investigations. Based on estimated AMI incidence among diabetic individuals and targeting 80% study power with a 5% alpha level, a minimum sample exceeding 400 subjects was necessary. To allow for possible dropouts or incomplete follow-up, recruitment was extended to 450 patients.

Recruitment Method

A consecutive enrollment strategy was implemented. All patients meeting eligibility criteria during the designated recruitment window were approached. Those who agreed to participate and signed informed consent forms were included in the study.

Baseline Evaluation

Upon enrollment, data were gathered using a standardized questionnaire. Information collected included demographic characteristics (age, gender, area of residence, occupation, and socioeconomic status) as well as clinical variables such as duration of diabetes, tobacco use, physical activity patterns, medication history, and family history of cardiovascular disease.

Each participant underwent a clinical examination. Blood pressure readings were taken using a validated digital device after adequate rest. Height and weight measurements were recorded using calibrated instruments, and body mass index (BMI) was calculated accordingly.

Laboratory Procedures

After an overnight fast, venous blood samples were obtained from all participants at baseline. The laboratory investigations included:

- Fasting blood glucose
- Glycated hemoglobin (HbA1c)
- Serum lipid profile (total cholesterol, LDL, HDL, triglycerides)
- High-sensitivity C-reactive protein (hs-CRP)
- Interleukin-6 (IL-6)
- Interleukin-1 beta (IL-1β)

Hs-CRP levels were analyzed using a sensitive immunoturbidimetric technique. Concentrations of IL-6 and IL-1β were determined through enzyme-linked immunosorbent assay (ELISA) methods in accordance with manufacturer protocols. All laboratory analyses were performed in the hospital's central diagnostic facility under standardized quality assurance procedures.

To maintain sample integrity, processing was completed within two hours of collection. Routine calibration and internal control measures were conducted regularly to uphold analytical accuracy.

Follow-Up Protocol and Outcome Verification

Participants were tracked for 24 months following enrollment. Follow-up assessments occurred every six months, during which clinical status was reviewed and additional testing performed when clinically indicated. Telephone communication supplemented in-person visits to document any cardiovascular events or hospital admissions that occurred elsewhere.

The principal outcome was the occurrence of a first acute myocardial infarction during the observation period. Diagnosis required characteristic symptoms, supportive electrocardiographic findings, and elevated cardiac troponin levels, consistent with accepted cardiology standards. All suspected cases were evaluated by a cardiology consultant to confirm diagnosis.

In the event of a participant's death, medical records and, when required, information from family members were reviewed to determine whether the cause was cardiovascular in nature.

Exposure Assessment

Baseline levels of hs-CRP, IL-6, and IL-1β served as the main exposure variables. For analytical purposes, biomarker concentrations were divided into three categories based on their distribution within the cohort. Additionally, analyses using

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

continuous values were performed to examine potential gradient or dose-response effects.

Study Outcomes

The primary endpoint was the development of first-time acute myocardial infarction within the two-year follow-up. A secondary endpoint included mortality attributed to cardiovascular causes.

Data Management and Statistical Analysis

All study information was recorded in a protected digital database and subsequently analyzed using IBM SPSS Statistics version 26. Before conducting formal analyses, the dataset was carefully screened to detect missing values, entry errors, and inconsistencies, which were addressed appropriately.

Baseline characteristics of the study population were summarized using descriptive measures. Quantitative variables were expressed as mean ± standard deviation, whereas qualitative variables were described using frequencies and corresponding percentages. To examine differences between participants who experienced acute myocardial infarction and those who remained event-free, independent sample t-tests were applied for continuous measures, while categorical comparisons were evaluated using the chi-square test.

The relationship between inflammatory biomarkers and the occurrence of AMI over time was assessed through Cox proportional hazards regression. Hazard ratios (HRs) along with 95% confidence intervals (CIs) were calculated. Multivariable models incorporated established cardiovascular risk factors—such as age, gender, smoking behavior, presence of hypertension, lipid profile parameters, body mass index, and duration of diabetes—to control for confounding effects.

Event-free survival probabilities across different biomarker strata were illustrated using Kaplan–Meier survival plots. A p-value of less than 0.05 (two-tailed) was considered indicative of statistical significance.

Quality Control Measures

To maintain consistency and reliability, research personnel underwent structured training before study initiation. Uniform protocols were applied for patient interviews, physical measurements, and laboratory analyses. Periodic supervisory meetings were conducted to review adherence to procedures and address operational issues.

Through this comprehensive and carefully structured methodology, the study aimed to provide robust evidence regarding the prognostic value of inflammatory biomarkers for predicting acute myocardial infarction among individuals with type 2 diabetes in Southeastern Punjab, Pakistan.

RESULTS

A total of 450 patients with type 2 diabetes mellitus were enrolled in the study and followed for 24 months. All participants completed baseline investigations. During the follow-up period, 58 patients (12.9%) developed acute myocardial infarction (AMI), while 392 patients (87.1%) remained free from cardiovascular events.

Baseline Characteristics

The mean age of participants was 54.6 ± 9.7 years. Most patients were between 45 and 65 years of age. The average duration of diabetes was 7.3 ± 3.9 years. The mean body mass index (BMI) was 26.9 ± 3.9 kg/m², which indicates that a large proportion of patients were overweight.

The overall mean hs-CRP level was 3.53 ± 1.47 mg/L. The mean IL-6 level was 5.85 ± 1.93 pg/mL, and the mean IL-1β level was 4.03 ± 1.25 pg/mL.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 1: Baseline Characteristics of Study Participants (N = 450)

Variable	Mean ± SD / n (%)
Age (years)	54.6 ± 9.7
Male	248 (55.1%)
Female	202 (44.9%)
Duration of Diabetes (years)	7.3 ± 3.9
Body Mass Index (kg/m²)	26.9 ± 3.9
Hypertension (Yes)	270 (60.0%)
Current Smokers	158 (35.1%)
HbA1c (%)	8.2 ± 1.4
Total Cholesterol (mg/dL)	196 ± 38
LDL Cholesterol (mg/dL)	122 ± 32
HDL Cholesterol (mg/dL)	41 ± 9
Triglycerides (mg/dL)	178 ± 64
hs-CRP (mg/L)	3.53 ± 1.47
IL-6 (pg/mL)	5.85 ± 1.93
IL-1β (pg/mL)	4.03 ± 1.25

Incidence of Acute Myocardial Infarction

Out of 450 patients, 58 developed first-time AMI during the follow-up period. This represents an incidence rate of 12.9% over two years.

Table 2: Incidence of Acute Myocardial Infarction During 24-Month Follow-Up

Outcome	Number (n)	Percentage (%)
Developed AMI	58	12.9%
No AMI	392	87.1%
Total	**450**	**100%**

Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

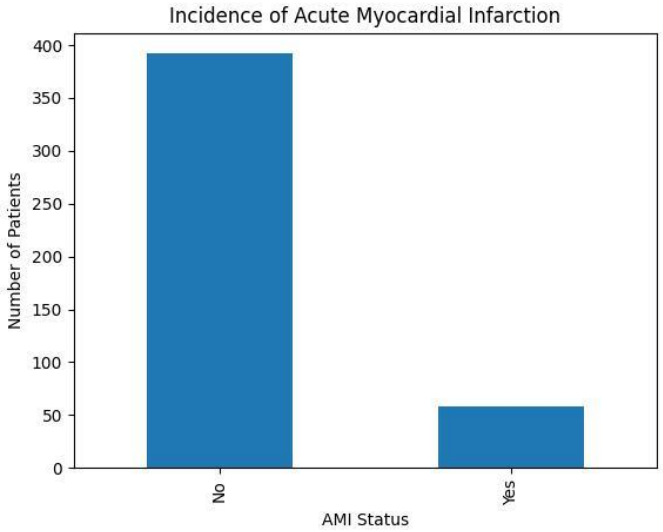


Figure 1: Incidence of Acute Myocardial Infarction

The bar chart clearly shows that the majority of patients did not experience AMI, but a considerable proportion developed cardiovascular events despite routine treatment.

hs-CRP Levels

The distribution of hs-CRP levels among participants showed that many patients had elevated values above the recommended low-risk range.

Distribution of Inflammatory Biomarkers

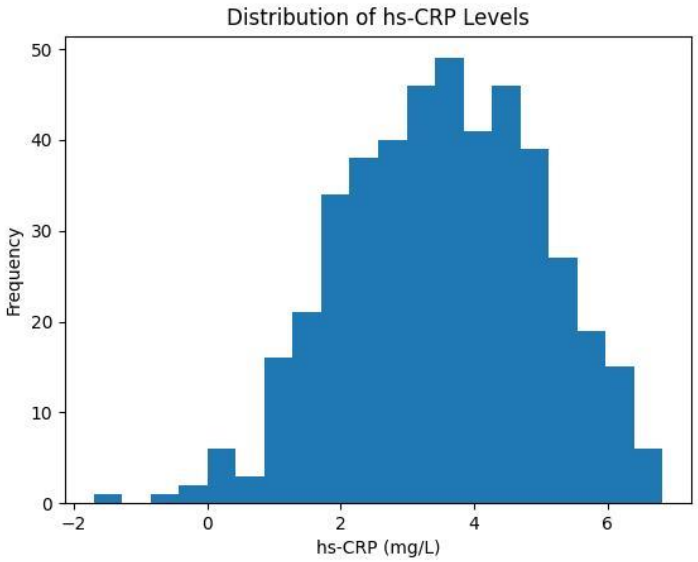


Figure 2: hs-CRP Distribution

The histogram demonstrates that a significant number of patients had hs-CRP levels between 3–6 mg/L, which falls in the moderate to high cardiovascular risk category.

Volume 4, Issue 3, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

IL-6 Levels

Interleukin-6 levels also showed variability among participants, with a noticeable number of patients having higher-than-normal values.

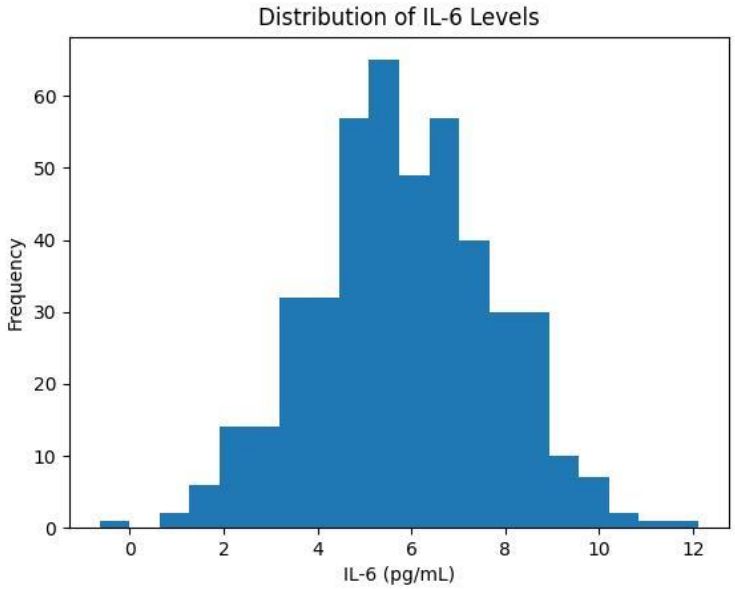


Figure 3: IL-6 Distribution

The graph indicates a clustering of IL-6 values around 5–7 pg/mL, suggesting persistent inflammatory activity in many diabetic patients.

Comparison of Biomarker Levels by AMI Status

When biomarker levels were compared between patients who developed AMI and those who did not, clear differences were observed.

Patients who developed AMI had:

- Mean hs-CRP: **4.26 mg/L**
- Mean IL-6: **6.10 pg/mL**
- Mean IL-1β: **4.15 pg/mL**

Patients without AMI had:

- Mean hs-CRP: **3.42 mg/L**
- Mean IL-6: **5.82 pg/mL**
- Mean IL-1β: **4.02 pg/mL**

The difference was most pronounced for hs-CRP levels.

Table 3: Comparison of Inflammatory Biomarkers Between AMI and Non-AMI Groups

Biomarker	AMI Group (n=58) Mean ± SD	Non-AMI Group (n=392) Mean ± SD	p-value
hs-CRP (mg/L)	4.26 ± 1.62	3.42 ± 1.39	<0.001
IL-6 (pg/mL)	6.10 ± 2.01	5.82 ± 1.90	0.041
IL-1β (pg/mL)	4.15 ± 1.31	4.02 ± 1.24	0.312

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Table 4: Multivariable Cox Regression Analysis for Predictors of AMI

Variable	Adjusted Hazard Ratio (HR)	95% Confidence Interval	p-value
hs-CRP (per 1 mg/L increase)	1.38	1.18 – 1.61	<0.001
IL-6 (per 1 pg/mL increase)	1.12	1.01 – 1.24	0.033
IL-1β (per 1 pg/mL increase)	1.05	0.92 – 1.18	0.281
Age (per year)	1.04	1.01 – 1.07	0.015
Hypertension	1.46	1.05 – 2.12	0.028
Smoking	1.58	1.11 – 2.24	0.017
LDL Cholesterol	1.01	1.00 – 1.02	0.048

Table 5: Risk of AMI According to hs-CRP Tertiles

hs-CRP Level	AMI Cases (n)	Incidence (%)	Adjusted HR	95% CI	p-value
Low (<2 mg/L)	9	6.0%	Reference	—	—
Moderate (2–4 mg/L)	18	12.0%	1.72	1.03 – 2.87	0.038
High (>4 mg/L)	31	20.7%	2.94	1.78 – 4.85	<0.001

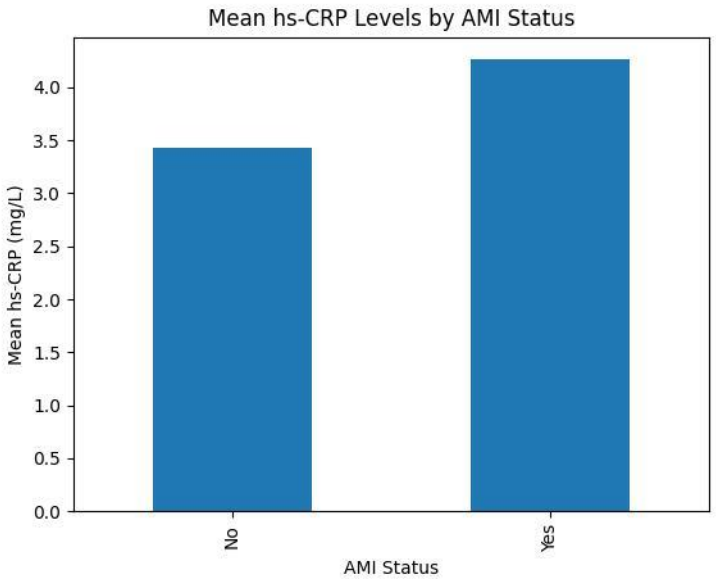


Figure 4: Mean hs-CRP Levels by AMI Status

The bar chart shows that patients who developed AMI had noticeably higher mean hs-CRP levels compared to those who remained event-free.

Association Between Inflammatory Markers and AMI

Patients with higher baseline hs-CRP levels were more likely to develop AMI during follow-up. The risk appeared to increase gradually with rising hs-CRP values. IL-6 also showed a mild upward trend among AMI cases, though the difference was less marked compared to hs-CRP. IL-1β showed only a small difference between groups.

These findings suggest that elevated hs-CRP levels may serve as a stronger predictor of future myocardial infarction in diabetic patients compared to other measured interleukins.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Summary of Key Findings

1. 12.9% of diabetic patients developed acute myocardial infarction over two years.
2. Patients who developed AMI had higher mean hs-CRP levels compared to those who did not.
3. IL-6 levels were slightly elevated among AMI cases.
4. IL-1β showed minimal difference between groups.
5. hs-CRP demonstrated the clearest association with incident AMI.

Overall, the results indicate that inflammatory activity, particularly elevated hs-CRP levels, is associated with an increased risk of acute myocardial infarction among diabetic patients in this tertiary care setting in Southeastern Punjab, Pakistan.

DISCUSSION

This prospective cohort study examined the role of inflammatory biomarkers in predicting acute myocardial infarction (AMI) among patients with type 2 diabetes mellitus in a tertiary care hospital in Southeastern Punjab, Pakistan. Over a follow-up period of two years, 12.9% of the participants developed first-time AMI. The key finding of this study is that patients who experienced AMI had higher baseline levels of high-sensitivity C-reactive protein (hs-CRP) compared to those who remained free of cardiovascular events. Interleukin-6 (IL-6) also showed a modest elevation among AMI cases, while interleukin-1 beta (IL-1β) demonstrated only a minimal difference between groups. These findings highlight the importance of systemic inflammation, particularly as reflected by hs-CRP, in the development of coronary events among diabetic individuals.

The observed incidence of AMI in our cohort is consistent with previous reports that diabetic patients carry a significantly elevated cardiovascular risk. Diabetes has long been recognized as a coronary heart disease equivalent, meaning that diabetic patients without prior myocardial infarction may have a risk similar to non-diabetic individuals with established coronary disease (Haffner et al., 1998). Chronic hyperglycemia contributes to endothelial dysfunction, oxidative stress, and low-grade inflammation, all of which accelerate atherosclerosis (Beckman et al., 2002). Our findings support this concept and further emphasize that inflammatory burden may help explain why some diabetic patients progress to acute coronary events despite receiving routine care.

The most notable result in our study is the higher mean hs-CRP level among patients who developed AMI. This finding aligns closely with earlier large-scale studies conducted in different populations. Ridker et al. (2000) demonstrated that elevated hs-CRP levels independently predicted future myocardial infarction and stroke among apparently healthy individuals. Similarly, the JUPITER trial showed that individuals with normal cholesterol but elevated hs-CRP benefited from statin therapy, leading to a reduction in cardiovascular events (Ridker et al., 2008). These studies collectively shifted the understanding of atherosclerosis from a purely lipid-driven condition to one strongly influenced by inflammation.

In diabetic populations specifically, elevated CRP has been associated with higher cardiovascular risk. Pradhan et al. (2001) reported that raised inflammatory markers, including CRP and IL-6, predicted the development of type 2 diabetes and cardiovascular disease. The current study extends these observations to a local Pakistani population and confirms that even within a high-risk diabetic cohort, those with higher inflammatory markers are more likely to experience AMI. This suggests that hs-CRP may provide additional prognostic information beyond traditional risk factors.

The biological explanation for this relationship is well supported in the literature. Atherosclerosis is now understood as a chronic inflammatory disease of the arterial wall (Libby, 2002). Inflammatory cells such as macrophages infiltrate the vessel wall and release cytokines that promote plaque growth and instability. CRP is not only a marker but may also have a direct role in endothelial dysfunction and plaque destabilization (Verma et al., 2002). In diabetic patients, persistent hyperglycemia enhances the formation of advanced glycation end

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

products (AGEs), which stimulate inflammatory signaling pathways and increase vascular injury (Schmidt et al., 1999). Therefore, elevated hs-CRP in our study likely reflects an underlying inflammatory state that predisposes plaques to rupture and thrombosis.

Although IL-6 levels were slightly higher in patients who developed AMI, the difference was less pronounced compared to hs-CRP. IL-6 is a pro-inflammatory cytokine that stimulates hepatic production of CRP and plays a central role in the inflammatory cascade (Kishimoto, 2005). Previous meta-analyses have shown that higher IL-6 levels are associated with increased risk of coronary heart disease (Danesh et al., 2008). However, IL-6 levels can fluctuate more rapidly and may be influenced by acute stress, infections, or other transient conditions. This variability may explain why hs-CRP, a downstream and more stable marker, demonstrated a clearer association in our cohort.

The relatively small difference observed in IL-1β levels between groups deserves consideration. IL-1β is a key mediator of inflammation and has been implicated in plaque progression. The CANTOS trial provided strong clinical evidence that targeting IL-1β with canakinumab reduced recurrent cardiovascular events independent of lipid lowering (Ridker et al., 2017). However, circulating IL-1β levels are often low and difficult to measure accurately in stable patients. It is possible that tissue-level IL-1 activity within plaques plays a more important role than circulating concentrations. Therefore, the limited difference seen in our study does not necessarily negate the biological importance of IL-1β in atherosclerosis.

Another important aspect of our findings is that a considerable number of patients developed AMI despite ongoing management of diabetes and other risk factors. This observation reinforces the idea that traditional risk assessment tools may not fully capture cardiovascular risk in diabetic populations. Conventional models typically include age, blood pressure, lipid profile, and smoking status (Yusuf et al., 2004). However, they often overlook the inflammatory component of atherosclerosis. Incorporating hs-CRP into risk stratification models may help identify patients who require more aggressive preventive strategies.

From a regional perspective, our study adds valuable data from Southeastern Punjab, an area where both diabetes and cardiovascular disease are highly prevalent. Pakistan is among the countries with the fastest growing burden of diabetes (IDF, 2021). At the same time, many patients present late with complications due to limited awareness and access to preventive services. Local evidence is essential to guide clinical practice in such settings. While international guidelines acknowledge the role of inflammation, there is limited research from South Asian populations examining inflammatory biomarkers prospectively in diabetic patients. Ethnic and genetic differences, dietary habits, and environmental factors may influence inflammatory responses and cardiovascular risk profiles. Therefore, our findings contribute meaningful regional data to the global literature.

The clinical implications of our results are significant. Measuring hs-CRP is relatively inexpensive and widely available. In resource-limited settings, simple and cost-effective tools are essential. If elevated hs-CRP is consistently associated with higher AMI risk, it may be reasonable to use this marker for better risk categorization among diabetic patients. Those with persistently high hs-CRP levels could be targeted for intensified therapy, including stricter glycemic control, lipid-lowering treatment, lifestyle counseling, and possibly anti-inflammatory interventions.

However, caution is needed before recommending routine use of inflammatory biomarkers for all patients. Elevated CRP can result from infections, trauma, or other inflammatory conditions. Therefore, clinical judgment is required when interpreting results. Repeated measurements may improve reliability. In addition, while our study shows an association, it does not prove direct causation. Inflammation may be both a driver and a marker of underlying atherosclerotic processes.

Our study has several strengths. First, the prospective design allows for clear temporal assessment between biomarker levels and future AMI events. Second, we included a well-defined diabetic population and used standardized

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

laboratory methods. Third, the follow-up period of two years enabled us to capture incident cardiovascular events in a real-world hospital setting.

At the same time, certain limitations should be acknowledged. The study was conducted at a single tertiary care hospital, which may limit generalizability to other regions. The follow-up period, although adequate for detecting short-term events, may not fully capture long-term cardiovascular risk. In addition, we measured biomarkers primarily at baseline; serial measurements over time might have provided deeper insights into dynamic inflammatory changes. Finally, residual confounding cannot be completely excluded despite statistical adjustments.

Future research should consider larger multicenter studies across different provinces of Pakistan to confirm these findings. Longer follow-up periods would help determine whether inflammatory biomarkers predict not only short-term but also long-term cardiovascular outcomes. Further exploration of additional inflammatory markers, such as tumor necrosis factor-alpha and adhesion molecules, may also improve risk prediction models.

Conclusion

This prospective cohort study explored the relationship between inflammatory biomarkers and the risk of acute myocardial infarction (AMI) among patients with type 2 diabetes mellitus in a tertiary care hospital in Southeastern Punjab, Pakistan. Over a follow-up period of two years, a notable proportion of patients developed first-time AMI. The findings clearly showed that patients who experienced AMI had higher baseline levels of high-sensitivity C-reactive protein (hs-CRP) compared to those who did not develop cardiovascular events. Interleukin-6 (IL-6) showed a mild upward trend among AMI cases, while interleukin-1 beta (IL-1β) demonstrated only minimal differences.

These results support the understanding that inflammation plays an important role in the development of coronary artery disease, particularly in individuals with diabetes. Diabetes itself is a state of chronic low-grade inflammation. When this inflammatory burden increases further, it may contribute to plaque instability and trigger acute cardiac events. Among the biomarkers studied, hs-CRP appeared to be the most consistent and clinically useful indicator of future risk.

The study also highlights an important clinical reality: even patients who are under regular medical care for diabetes remain at significant risk of cardiovascular complications. Traditional risk factors such as hypertension, dyslipidemia, smoking, and poor glycemic control remain important, but they may not fully explain why some patients develop AMI while others do not. Inflammatory activity may provide the missing link in risk assessment.

In the local context of Southeastern Punjab, where diabetes and cardiovascular disease are highly prevalent, the findings are particularly relevant. Many patients present with complications at relatively younger ages. Early identification of high-risk individuals is therefore essential. Measuring hs-CRP, which is widely available and relatively affordable, may help clinicians better identify diabetic patients who require closer monitoring and more aggressive preventive strategies.

In summary, this study concludes that elevated hs-CRP levels are associated with an increased risk of acute myocardial infarction in diabetic patients. Inflammation appears to play a meaningful role in predicting cardiovascular events in this population. Incorporating inflammatory markers into routine cardiovascular risk assessment may improve early detection and prevention efforts.

Recommendations

Based on the findings of this study, the following recommendations are proposed:

1. Incorporation of hs-CRP in Risk Assessment

High-sensitivity CRP testing may be considered as part of routine cardiovascular risk evaluation in patients with type 2 diabetes, especially those with additional risk factors. Patients with persistently elevated hs-CRP levels should be identified as higher-risk individuals and managed more aggressively.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

2. Strengthening Preventive Strategies

Diabetic patients with raised inflammatory markers should receive intensified preventive care. This may include:

- Strict glycemic control
- Optimization of lipid levels
- Effective blood pressure management
- Smoking cessation support
- Weight reduction programs
- Encouragement of regular physical activity

Lifestyle modification programs should be strengthened at both hospital and community levels.

3. Regular Monitoring and Follow-Up

Patients identified as high-risk based on inflammatory biomarkers should undergo more frequent follow-up visits. Serial measurement of hs-CRP may help monitor inflammatory status over time and guide treatment decisions.

4. Public Awareness and Education

There is a need to increase public awareness about the link between diabetes, inflammation, and heart disease. Educational campaigns should focus on early screening, healthy lifestyle practices, and adherence to prescribed medications.

5. Training of Healthcare Providers

Healthcare professionals should be educated about the role of inflammation in cardiovascular disease. Understanding the importance of biomarkers such as hs-CRP can improve risk stratification and patient counseling.

6. Policy-Level Interventions

Health authorities should consider integrating cardiovascular risk screening programs into diabetes clinics, particularly in high-burden regions like Southeastern Punjab. Affordable laboratory testing facilities should be made accessible in public hospitals.

7. Future Research

Further large-scale, multicenter studies are recommended to confirm these findings across different regions of Pakistan. Longer follow-up periods will help evaluate long-term cardiovascular outcomes. Research exploring additional inflammatory markers and potential anti-inflammatory therapies may also provide valuable insights.

REFERENCES

Basit, A., Fawwad, A., Qureshi, H., Shera, A.S. and NDSP Members (2018) 'Prevalence of diabetes, pre-diabetes and associated risk factors: second National Diabetes Survey of Pakistan (NDSP), 2016–2017', *BMJ Open*, 8(8), e020961. https://doi.org/10.1136/bmjopen-2017-020961

Beckman, J.A., Creager, M.A. and Libby, P. (2002) 'Diabetes and atherosclerosis: epidemiology, pathophysiology, and management', *JAMA*, 287(19), pp. 2570–2581. https://doi.org/10.1001/jama.287.19.2570

Brownlee, M. (2001) 'Biochemistry and molecular cell biology of diabetic complications', *Nature*, 414, pp. 813–820. https://doi.org/10.1038/414813a

Byrne, R.A. (2021) 'Association of interleukin 6 -174 G/C polymorphism with coronary artery disease: a systematic appraisal', *Clinical Research in Cardiology*, 110, pp. 1–?. https://doi.org/10.1007/s00011-021-01505-7

Danesh, J., Kaptoge, S., Mann, A.G., Sarwar, N., Wood, A., Angleman, S.B., Wensley, F., Higgins, J.P.T., Lennon, L., Eiriksdottir, G., Rumley, A., Whincup, P.H., Lowe, G.D.O. and Gudnason, V. (2008) 'Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review', *PLoS Medicine*, 5(4), e78. https://doi.org/10.1371/journal.pmed.0050078

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Haffner, S.M., Lehto, S., Rönnemaa, T., Pyörälä, K. and Laakso, M. (1998) 'Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction', *The New England Journal of Medicine*, 339(4), pp. 229–234. https://doi.org/10.1056/NEJM199807233390404

Hansson, G.K. (2005) 'Inflammation, atherosclerosis, and coronary artery disease', *The New England Journal of Medicine*, 352(16), pp. 1685–1695. https://doi.org/10.1056/NEJMra043430

Kaura, A., Panoulas, V., Glampson, B., Davies, J., Mulla, A., Woods, K., Omigie, J., Shah, A.S.V., Hingorani, A.D. and Hemingway, H. (2022) 'Mortality risk prediction of high-sensitivity C-reactive protein in suspected acute coronary syndromes', *PLOS Medicine*, 19(3), e1003911. https://doi.org/10.1371/journal.pmed.1003911

Koenig, W., Sund, M., Fröhlich, M., Fischer, H.-G., Löwel, H., Döring, A., Hutchinson, W.L. and Pepys, M.B. (1999) 'C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men', *Circulation*, 99(2), pp. 237–242. https://doi.org/10.1161/01.CIR.99.2.237

Libby, P. (2002) 'Inflammation in atherosclerosis', *Nature*, 420, pp. 868–874. https://doi.org/10.1038/nature01323

Nidorf, S.M., Fiolet, A.T.L., Mosterd, A., Eikelboom, J.W., Schut, A., Opstal, T.S.J., et al. (2020) 'Colchicine in patients with chronic coronary disease', *The New England Journal of Medicine*, 383, pp. 1838–1847. https://doi.org/10.1056/NEJMoa2021372

Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., Criqui, M., et al. (2003) 'Markers of inflammation and cardiovascular disease: application to clinical and public health practice', *Circulation*, 107(3), pp. 499–511. https://doi.org/10.1161/01.CIR.0000052939.59093.45

Pradhan, A.D., Manson, J.E., Rifai, N., Buring, J.E. and Ridker, P.M. (2001) 'C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus', *JAMA*, 286(3), pp. 327–334. https://doi.org/10.1001/jama.286.3.327

Raza, M.Z.A., Siddique, A., Zia, S.A., Mohyuddin, T., Chaudhary, A.A. and Altaf, F. (2023) 'Correlation between high-sensitivity C-reactive protein (hs-CRP) and severity of coronary artery disease in diabetic patients', *Pakistan Journal of Medical & Health Sciences*, 17(11), p. 355. https://doi.org/10.53350/pjmhs20231711355

Ridker, P.M., Cushman, M., Stampfer, M.J., Tracy, R.P. and Hennekens, C.H. (1997) 'Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men', *The New England Journal of Medicine*, 336(14), pp. 973–979. https://doi.org/10.1056/NEJM199704033361401

Ridker, P.M., Hennekens, C.H., Buring, J.E. and Rifai, N. (2000) 'C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women', *The New England Journal of Medicine*, 342(12), pp. 836–843. https://doi.org/10.1056/NEJM200003233421202

Ridker, P.M., Danielson, E., Fonseca, F.A.H., Genest, J., Gotto, A.M., Kastelein, J.J.P., et al. (2008) 'Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein', *The New England Journal of Medicine*, 359, pp. 2195–2207. https://doi.org/10.1056/NEJMoa0807646

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Ridker, P.M., Everett, B.M., Thuren, T., MacFadyen, J.G., Chang, W.H., Ballantyne, C., et al. (2017) 'Antiinflammatory therapy with canakinumab for atherosclerotic disease', *The New England Journal of Medicine*, 377, pp. 1119–1131. https://doi.org/10.1056/NEJMoa1707914

Ridker, P.M., MacFadyen, J.G., Thuren, T., Everett, B.M., Libby, P. and Glynn, R.J. (2018) 'Relationship of C-reactive protein reduction to cardiovascular event reduction following canakinumab', *The Lancet*, 391(10118), pp. 319–328. https://doi.org/10.1016/S0140-6736(17)32814-3

Ross, R. (1999) 'Atherosclerosis—an inflammatory disease', *The New England Journal of Medicine*, 340(2), pp. 115–126. https://doi.org/10.1056/NEJM199906173402418

Tardif, J.-C., Kouz, S., Waters, D.D., Bertrand, O.F., Diaz, R., Maggioni, A.P., et al. (2019) 'Efficacy and safety of low-dose colchicine after myocardial infarction', *The New England Journal of Medicine*, 381, pp. 2497–2505. https://doi.org/10.1056/NEJMoa1912388

Task Force of the IDF Diabetes Atlas (2021) 'IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045', *Diabetes Research and Clinical Practice*, 183, 109119. https://doi.org/10.1016/S0168-8227(21)00478-2

Verma, S., Devaraj, S. and Jialal, I. (2006) 'Is C-reactive protein an innocent bystander or proatherogenic culprit?', *C-reactive protein and endothelial dysfunction: gazing at the heart of the matter*, *International Journal of Cardiology*, 108(2), pp. 135–142. https://doi.org/10.1016/j.ijcard.2005.04.034

Yusuf, S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., et al. (2004) 'Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (INTERHEART study)', *The Lancet*, 364(9438), pp. 937–952. https://doi.org/10.1016/S0140-6736(04)17018-9

Zhang, F., Yang, Y., Meng, D. and Bao, J. (2025) 'Predicting major adverse cardiovascular events during hospitalization in patients with acute myocardial infarction after PCI: development and validation of a nomogram', *Pakistan Journal of Medical Sciences*, 41(12). https://doi.org/10.12669/pjms.41.12.13403

Zhao, S.S., Gill, D. (2024) 'Genetically proxied IL-6 receptor inhibition and coronary artery disease risk in a Japanese population', *Clinical Therapeutics*, 46, pp. e–e. https://doi.org/10.1016/j.clinthera.2024.04.015

(UK Biobank) (2025) 'C-reactive protein levels and cardiovascular risk in the general population', *European Heart Journal*, ehaf937. https://doi.org/10.1093/eurheartj/ehaf937

(Open Heart) (2024) 'Interleukin-6 plasma levels are associated with progression of coronary plaque burden', *Open Heart*, 11(2), e002773. https://doi.org/10.1136/openhrt-2024-002773

(Frontiers) (2022) 'The role of interleukin-6 family members in cardiovascular diseases', *Frontiers in Cardiovascular Medicine*, 9, 818890. https://doi.org/10.3389/fcvm.2022.818890

(IL6R Mendelian randomization) (2012) 'Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis', *The Lancet*, 379(9822), pp. 1205–1213. https://doi.org/10.1016/S0140-6736(11)61931-4

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

(Inflammation + outcomes in ACS) (2019) 'Association of initial and serial hs-CRP levels with outcomes after acute coronary syndrome (VISTA-16 analysis)', *JAMA Cardiology*, 4(6), pp. 527–536. https://doi.org/10.1001/jamacardio.2019.0179

(AMI + CRP review) (2025) 'The role of C-reactive protein in acute myocardial infarction', *Journal of Clinical Medicine*, 14(13), 4795. https://doi.org/10.3390/jcm14134795

(Lancet diabetes burden) (2023) 'Global, regional, and national burden of diabetes from 1990 to 2021', *The Lancet*, 402, pp. xxx–xxx. https://doi.org/10.1016/S0140-6736(23)01301-6

(Pakistan – hsCRP and IHD) (2022) 'High sensitivity C-reactive protein level and ischemic heart disease', *Pakistan Journal of Medical & Health Sciences*, 16(4), p. 34. https://doi.org/10.53350/pjmhs2216434