International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 15s,2025
https://theaspd.com/index.php

# Serum Levels Of Matrix Metalloproteinase-9 And Interleukin-18 In Patients With Acute Coronary Syndrome

**Falah Hasan Hadi[1], Prof. Dr. Wasan Sami Hameed[2]**
[1]Department of Medical Microbiology, Faculty of Medicine, University of Kufa, falahh.hamada@student.uokufa.edu.iq
[2]Department of Medical Microbiology, Faculty of Medicine, University of Kufa , wasansh.shukur@uokufa.edu.iq

***Abstract***
*Acute coronary syndrome (ACS) is a kind of coronary artery disease emergency and has the characteristics of rapid onset and rapid disease change, with high morbidity and mortality rates, which puts ACS as a major public health problem. The present study aims to investigate the association of Matrix metalloproteinase-9 (MMP-9)and interleukin-18 (IL-18), with ACS. The study involved 90 patients with ACS (STEMI, NSTEMI, and unstable angina) and 60 participants with non-ACS (stable angina and healthy control). The study was conducted as a case-control design. MMP-9 and IL-18 were assessed by enzyme-linked immunosorbent assay (ELISA). The results showed that ACS patients had a significantly higher levels of IL-18 compared with non-ACS patients and MMP-9 had a -significant difference between these two groups, and these results suggest a significant association of MMP-9 and IL- 18 with ACS.*
***Keywords:*** *microRNA ;Interleukin-18; Matrix metalloproteinase-9; Acute coronary syndrome.*

## INTRODUCTION

Acute coronary syndrome (ACS) is one of the most prevalent presentations of coronary artery disease (CAD) (Omidi *et al.*, 2020). It represents a spectrum of clinical manifestations resulting from a sudden reduction in blood flow to the heart, leading to myocardial injury (Tajbakhsh *et al.*, 2021). Acute coronary syndrome is defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP) (Yang & Zhang, 2022). ACS continue to be a leading cause of illness and death throughout the world and early diagnosis and therapeutic approach are of paramount importance for better outcome (Beza *et al.*, 2021).

The clinical recognition of ACS also depends on evaluation of symptoms, ischemia changes in electrocardiogram (ECG), and changes in troponin I (TnI) (Bouzid *et al.*, 2023). Electrocardiogram (ECG) and biomarkers such as troponin I (TnI), which are commonly used to diagnose ACS, play key roles in the early identification of ACS, but each comes with significant limitations that can hinder diagnostic accuracy (Nadendla *et al.*, 2024). Troponin I levels may not rise immediately following the onset of ACS symptoms, which can lead to false-negative results in the condition's early stages (Banerjee *et al.*, 2019). Furthermore, elevated TnI levels are not exclusive to ACS and can be seen in a range of conditions, including chronic kidney disease, pulmonary embolism, and heart failure, all of which can complicate diagnosis (Kulkarni *et al.*, 2024).

In addition, ECG may not show significant changes, or the changes may be non-specific, such as ST-segment depression or T-wave inversions, which can also be seen in other conditions like pericarditis, electrolyte imbalances, or left ventricular hypertrophy (Sudhir & Brady, 2023). Furthermore, in elderly individuals and patients with diabetes, typical symptoms are not always observed (Sciacqua *et al.*, 2021). Therefore, identification of novel biomarkers may facilitate the diagnosis of ACS .

Matrix metalloproteinase-9 (MMP-9), also known as gelatinase B, has numerous substrates and is involved in a wide range of physiological functions, including protease and cytokine activity

regulation. In addition, MMP-9 plays a role in elastin degradation, which promotes the breakdown of plaques' thin, fibrous caps (Mondal *et al.,* 2020). One study has demonstrated that MMP-9 levels were significantly higher in patients with vulnerable atherosclerotic plaques than in patients without vulnerable atherosclerotic plaques, indicating that MMP-9 levels are closely associated with vulnerable atherosclerotic plaques (Cabral-Pacheco *et al.,* 2020).
Interleukin-18 (IL-18) is a proinflammatory cytokine. It has been shown that IL-18 receptor subunits as well as IL-18 are expressed in atherosclerotic lesions (Bhat & Dhawan, 2015). In addition, IL-18 has been associated with the development of subclinical atherosclerosis (Danese and Montagnana, 2016). Furthermore, elevated IL-18 levels and the genetic variation of the IL-18 have been linked with acute coronary events and cardiovascular mortality among patients with coronary artery disease (CAD) (Bahrami *et al.*, 2021).

## METHODOLOGY

The study was conducted as a case-control design at Al-Najaf Center for Cardiovascular Surgery and Cardiac Catheterization in Najaf city – Iraq, from November 2023 to July 2024. It involved 120 patients with coronary artery disease (CAD), including 90 patients with ACS [30 patients with ST-elevation myocardial infarction (STEMI), 30 patients with non-ST-elevation myocardial infarction (NSTEMI), and 30 patients with unstable angina (UA)], and an additional 30 patients with stable angina (SA). A further 30 healthy individuals were participated in this study. The patients with SA and the healthy individuals form the non-ACS group .
Patients were selected based on the American College of Cardiology and American Heart Association (ACC/AHA) diagnostic criteria. Exclusion criteria included patients aged ≤ 27 years and those with severe renal or liver disease, malignancy, mental illness, or heart failure. Ethical approval was obtained from the College of Medicine at the University of Kufa, and informed consent was collected from all participants.

Data collection was carried out through a questionnaire capturing demographic and clinical information, along with measurement of the body mass index (BMI) and the blood samples were collected via venipuncture, 3 mL to gel tubes for serum analyses , including Troponin I , triglyceride, MMP-9 and IL-18. while Troponin I levels were assessed using a fluorescence immunoassay, triglyceride were determined using enzymatic colorimetric methods and levels of MMP-9 and IL-18 were measured by ELISA assays .

Data analysis was conducted using SPSS software, with results presented as medians and interquartile ranges. Group comparisons were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate, ROC, correlation

## RESULTS

Table (1) shows the frequency distribution between the ACS group (STEMI, NSTEMI and USA) and non-ACS group (SA and control) by their demographic data. This table explains that there is a non-significant difference between ACS and non- ACS groups regarding the age mean (p-value=0.716). Most of the patients in the ACS and non-ACS are those in the age group 56 years old and more. In addition, statistically, there is a non-significant difference between ACS and non-ACS groups regarding the age groups when analyzed by Chi-square test, (p-value=0.896). Furthermore, the table shows that most participants were males. Statistically, there is a high significant difference between ACS and non-ACS groups regarding the sex when analyzed by Chi-square test, (p-value=0.002).

Table (1): Demographic Characteristics for ACS and Non-ACS Groups

| Demographic Characteristics | ACS | Non-ACS | Statistics X2 (df) | P-value (Sig.) |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| **Age (Mean ± SD) year** | | (55.5±6.8) | (55.0±7.3) | .364 # | .716 (NS) |
| **Age Groups (N,%)** | **< 50 y** | 17 18.89% | 13 21.67% | .220 (2) | 0.896 (NS) |
| | **50 – 55 y** | 25 27.78% | 17 28.33% | | |
| | **56 y and More** | 48 53.33% | 30 50% | | |
| **Sex (N,%)** | **Males** | 83 92.22% | 44 73.33% | 9.89 (1) | **0.002 (HS)** |
| | **Females** | 7 7.78% | 16 26.67% | | |
| **Total (N)** | | **90** | **60** | | |

Table (2) shows the frequency distribution between ACS group (STEMI, NSTEMI and USA) and non- ACS group (SA and control) by their BMI and clinical characteristics. This table explains that the mean of BMI of the non-ACS group is higher than that of the ACS group. In addition, most of the patients with ACS had overweight, while those in the non-ACS group were mostly obese . Statistically, there is a high significant difference between the ACS and non-ACS groups regarding BMI and BMI classifications (p-values were < 0.001 for both BMI and BMI classifications).

The table shows that there is a highly significant difference between the two groups regarding the diabetic status (p-values were =0.002) with a higher percentages of diabetes in the ACS group. The participants in the ACS and non-ACS groups were mostly smoker with a non-significant difference between the two groups (p-values were < 0.987). Moreover, those in the ACS group had higher percentage of hypertension than that of the non-ACS group with a highly significant difference between ACS and non-ACS groups when analyzed by Chi-square test, (p-values were =0.006).

Table (2): BMI and Clinical Characteristics for ACS and Non-ACS Groups

| **Clinical Characteristics** | | **ACS** | **Non - ACS** | $X^2$ **(df)** | **P-value (Sig.)** |
|---|---|---|---|---|---|
| **BMI (Mean ± SD) kg/m²** | | (28±2.99) | (31±6.19) | 3.92# | **0.001 (HS)** |
| **BMI classification (N,%)** | **Underweight** | 0 0% | 0 0% | 13.58 (2) | **0.001 (HS)** |
| | **Healthy Weight** | 14 15.56% | 7 11.67% | | |
| | **Overweight** | 53 58.89% | 20 33.33% | | |
| | **Obese** | 23 25.56% | 33 55% | | |
| **Diabetes (N,%)** | **Non-Diabetic** | 40 44.44% | 42 70% | 9.48 (1) | **0.002 (HS)** |
| | **Diabetic** | 50 55.56% | 18 30% | | |
| **Smoking (N,%)** | **Non-Smoker** | 44 48.89% | 30 50% | 0.018 (1) | 0.894 (NS) |

| | | | | | |
|---|---|---|---|---|---|
| | **smoker** | 46<br>51.11% | 30<br>50% | | |
| **Hypertension (N,%)** | **Non Hypertensive** | 41<br>45.56% | 41<br>68.33% | 7.5<br>(1) | **0.006 (HS)** |
| | **Hypertensive** | 49<br>54.44% | 19<br>31.67% | | |
| **Total (N)** | | **90** | **60** | | |

Table (3) presents a frequency distribution of troponin I positivity and dyslipidemia with the levels of serum triglyceride in the ACS and non-ACS groups. For Troponin I, most ACS patients tested positive for troponin I, while all those in the non-ACS group tested negative. The chi-square value (66.6) and p-value (<0.001) indicate a highly significant difference between the two groups.

The mean level of TG in the ASC group is higher (211.16 mg/dl) than that of the non-ASC group (169.78 mg/dl) with a highly significant difference (p-value<0.001). For dyslipidemia, the ACS group shows a significantly higher percentage of dyslipidemia (88.89%) compared to the non-ACS group (71.67). The chi-square value (72.32) and p-value (<0.001) suggest a significant relationship between lipid levels and cardiovascular conditions.

Table (3): Troponin I and Dyslipidemia for ACS, and Non-ACS Groups

| **Clinical Data** | | **ACS** | **Non -ACS** | $X^2$ **(df)** | **P-value (Sig.)** |
|---|---|---|---|---|---|
| **Troponin I (N,%)** | **Negative** | 30<br>33.33% | 60<br>100% | 66.6 (2) | **<0.001 (HS)** |
| | **Positive** | 60<br>66.67% | 0<br>0% | | |
| **TG (Mean ± SD) mg/dl** | | 211.16 ±91.4 | 169.78 ±90.7 | 2.72# | **0.007 (HS)** |
| **Dyslipidemia (N,%)** | **No** | 10<br>11.11% | 17<br>28.33% | 7.23 (1) | **0.007 (HS)** |
| | **Yes** | 80<br>88.89% | 43<br>71.67% | | |

Table (4) shows the median levels of the inflammatory biomarkers (MMP-9, IL-18) between ACS and non-ACS groups using the Mann-Whitney U test. The results show that IL-18 levels were significantly higher in ACS patients ($p < 0.001$), suggesting a strong association between these biomarker and acute coronary events. In contrast, MMP-9 levels did not differ significantly between the two groups ($p = 0.863$), see figures 2 and 3.

| **Bio-marker** | **Groups** | | | | **Mann-Whitney U test** | **P-value (Sig.)** |
|---|---|---|---|---|---|---|
| | **ACS (N=90)** | | **Non -ACS (N=60)** | | | |
| | **Median** | **IQR** | **Median** | **IQR** | | |
| **IL-18 (ng/L)** | 26.77 | 16.98 | 18.61 | 5.48 | 1093 | **<0.001 (HS)** |
| **MMP-9 (ng/L)** | 1705.45 | 1418.10 | 1440.24 | 508.74 | 1810 | **0.001 (HS)** |

International Journal of Environmental Sciences
ISSN: 2229-7359
Vol. 11 No. 15s,2025
https://theaspd.com/index.php

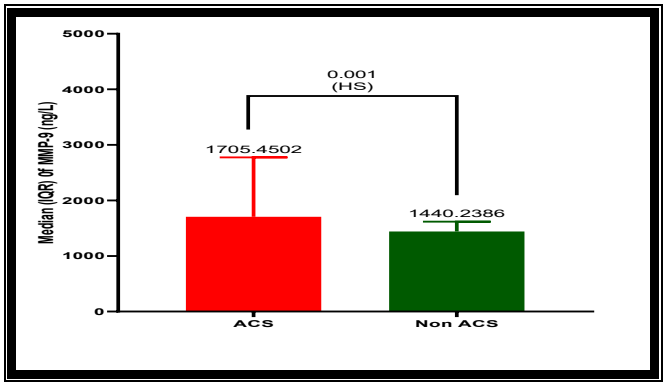


Figure (1): Bar Chart of MMP-9 between ACS and Non -ACS

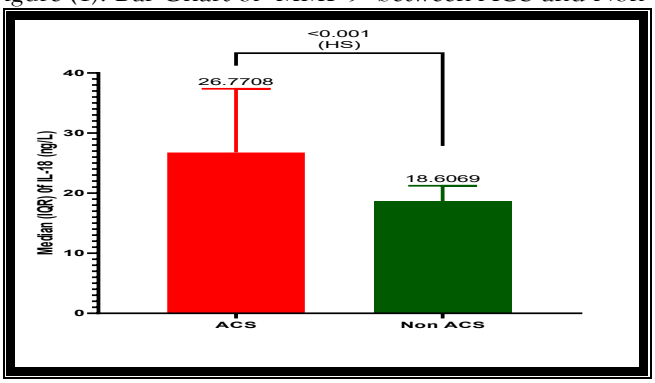


Figure (2): Bar Chart of IL-18 between ACS and Non-ACS

Table (5) provides Receiver Operating Characteristic (ROC) curve statistics for MMP-9, IL-18 in distinguishing between ACS and Non-ACS groups. For IL-18, AUC was 0.798, Sensitivity= 100%, and Specificity= 96%. For MMP-9, AUC was 0.665 , Sensitivity= 97%, and Specificity= 100%.

Table (5): ROC Curve Statistics of IL-18, MMP-9 and miRNA-941 between ACS and Non-ACS Groups

| Bio-marker | Area | SE | 95% CI | Cut off | Sensitivity | Specificity | P-value (Sig.) |
|---|---|---|---|---|---|---|---|
| IL-18 (ng/L) | 0.798 | 0.035 | 0.729-0.866 | 10.78 | 100 | 96 | <0.0001 (HS) |
| MMP-9 (ng/L) | 0.665 | 0.044 | 0.578-0.751 | 648.91 | 97 | 100 | 0.001 (HS) |

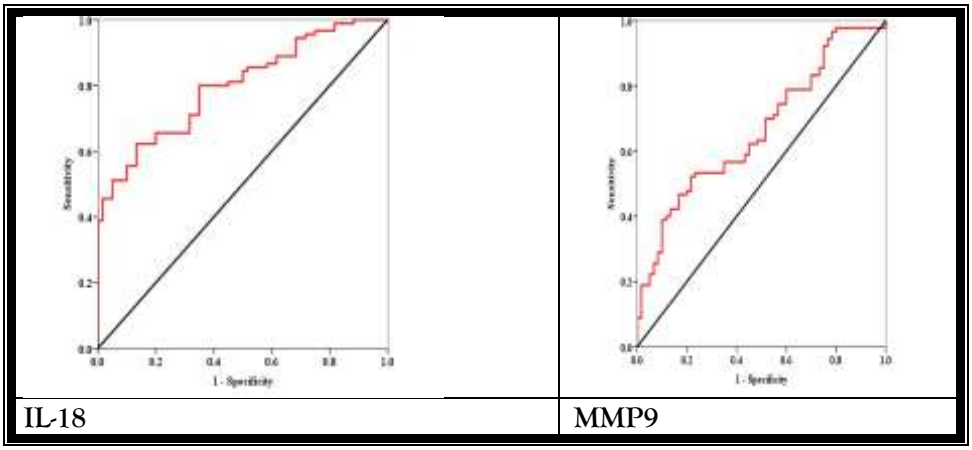


Figure (3): ROC Curve Showing the AUROC, Cutoff, Sensitivity, Specificity and p-value of MMP-9and IL-18 between ACS and Non-ACS Groups

## DISCUSSION

According to age, there was no statistically significant difference in the mean age (about 55 years) between ACS and non-ACS groups, with both groups showing a majority in individuals aged 56 years and older .

The finding of the present study is in line with Allami *et al.* (2024), who reported a mean age of 56.2 years in Iraqi patients with ACS. In contrast, the mean age of the current study is substantially younger than that of the Western populations, where the average age at first myocardial infarction often exceeds 65 years (Timmis *et al.*, 2023). This contrasts with Western populations, indicates that ACS in these populations tends to present a decade later, typically around the age of 65–70 (Nowbar *et al.*, 2019). Such regional differences may be attributable to the earlier onset of cardiovascular risk factors in Middle Eastern populations, including hypertension, diabetes, and smoking, as well as to dietary and lifestyle factors (Turk-Adawi *et al.*, 2018). This interpretation of the contrast in the results is supported by what was reported by Hussain & Lafta (2019), who found a higher regional prevalence of modifiable risk factors such as diabetes mellitus, hypertension, smoking, and dyslipidemia, as extensively documented in post-war Iraq .

Notably, this earlier disease manifestation corresponds with data from other low- and middle-income countries in the Middle East and South Asia, where the epidemiological transition is accelerating due to rapid urbanization and lifestyle changes (Yusuf *et al.*, 2001). These results suggest an urgent need for national screening programs targeting individuals in their late forties or early fifties, particularly in regions where cardiovascular risk factor control remains suboptimal (Mohammad *et al.*, 2021).

According to sex, an important finding of this study was the predominance of males in the ACS group. This result is consistent with global and regional literature, which identifies male as a strong independent predictor of ACS, particularly in younger and middle-aged adults. Marzà-Florensa *et al.* (2025) reported that men under 55 years of age had nearly double the incidence of ACS compared to female, while female were more frequently represented in non-obstructive and atypical forms of coronary artery disease .

Sex-related differences, particularly during the premenopausal period, are primarily attributed to the estrogen-dependent modulation of endothelial mediators, including nitric oxide, prostaglandins, and endothelium-derived hyperpolarizing factors (Haider *et al.*, 2020). Additionally, women typically possess smaller epicardial coronary artery diameters and exhibit higher baseline myocardial blood flow, both of which contribute to increased endothelial shear stress. Elevated shear stress may play a pivotal role in the observed sex-based disparities in acute coronary syndrome (ACS) susceptibility, as low shear stress has been hypothesized to promote focal lipid accumulation, pathological vascular remodeling, and plaque instability (Allami, 2024). The disparity may be partially explained by biological mechanisms (biological differences), particularly the cardioprotective role of estrogen in premenopausal women, which are frequently cited as contributing factors to delayed the onset of atherosclerosis in women (Mehta *et al.*, 2016; Haider *et al.*, 2020). Estrogen has vasodilatory, anti-inflammatory, and anti-atherosclerotic properties, which may account for reduced coronary risk in premenopausal women (Mehta *et al.*, 2016).

Additionally, social and systemic factors, such as underdiagnosis and undertreatment, may contribute to the lower representation of women in acute presentations (Bosomworth & Khan, 2023). It has also been suggested that women are more likely to experience non-obstructive coronary syndromes or atypical symptoms, which could lead to delayed diagnosis or misclassification as non-ACS, thereby explaining their increased presence in the SA group (Amsterdam *et al.*, 2014; DeFilippis *et al.*, 2019).

Therefore, the presentation of women with atypical symptoms can lead to under-diagnosis and misclassification into non-ACS categories. Importantly, research by Joseph *et al.* (2021) emphasizes that even when women do experience ACS, they are less likely to be referred

for invasive testing or receive guideline-directed therapies, potentially contributing to observed differences in subgroup representation .

For BMI, the current study found that the mean BMI was significantly higher in the non-ACS group compared to the ACS group. Furthermore, while overweight was more common in the ACS patients, obesity was prevalent in the non-ACS group of this study. These findings resonate with the controversial phenomenon where overweight and moderately obese individuals with cardiovascular disease may exhibit better short-term outcomes than those with normal weight (Romero-Corral *et al.*, 2006; Flegal *et al.*, 2013). Several studies have hypothesized that increased nutritional reserves, metabolic profiles, and cardioprotective adipokines in overweight individuals could play a protective role during acute cardiac events (Oreopoulos *et al.*, 2008; Kalantar-Zadeh *et al.*, 2010).

Furthermore, the obesity may contribute to the development of stable coronary artery disease (e.g. SA), it is not necessarily a predictor of acute plaque rupture or myocardial infarction, Which supported by Lopez-Jimenez *et al.* (2004) and Demirci *et al.* (2022), who reported that patients with ACS often present with less severe obesity than those with stable angina or chronic disease, highlighting the complexity of BMI as a cardiovascular risk factor.

For diabetes, the analysis showed that diabetes was significantly more prevalent in ACS patients than in non-ACS patients. This finding is well-agreement with existing research, as diabetes mellitus is a well-established independent risk factor for both the development and severity of CAD, particularly in the context of ACS (Ahmed *et al.*, 2017). Chronic hyperglycemia contributes to endothelial dysfunction, inflammation, and accelerated atherosclerosis, thereby increasing the likelihood of acute events (Juricic *et al.*, 2025). This highlights the necessity for diabetes-focused primary prevention in CAD management, especially in populations with high baseline insulin resistance (Siam *et al.*, 2024).

For Smoking, The study reported no significant difference in smoking prevalence between ACS and non-ACS groups. Although smoking is a well-documented major modifiable risk factor for coronary artery disease and ACS, the lack of significant difference in the current dataset may be attributed to the high baseline prevalence of smoking across the study population, which is supported by the high percentage of smoker in the control group of this study, possibly reflecting regional smoking trends rather than disease-specific associations (Peto *et al.*, 2010).

For Hypertension, a statistically significant difference was found in the prevalence of hypertension between ACS group and non-ACS group. This result supports extensive evidence that hypertension is a critical risk factor for both the initiation and progression of atherosclerosis, contributing to endothelial injury and increased arterial stiffness (Whelton *et al.*, 2014).

For troponin I, the finding of this study illustrates the presence of a statistically significant difference of troponin I positivity between ACS group and non-ACS group, through a strong association between troponin I positivity and ACS compared to absence of troponin I positivity in the non-ACS group. This finding agrees with contemporary literature emphasizing the diagnostic specificity of cardiac troponin I (cTnI) for myocardial injury, particularly in ACS (Raber *et al.*, 2021). High-sensitivity troponin assays have revolutionized ACS diagnostics by enabling the early identification of myocardial necrosis even before overt ECG changes (Maayah *et al.*, 2024). The complete absence of troponin positivity among non-ACS patients further reinforces the biomarker's utility in ruling out ACS in differential diagnosis scenarios. This finding also corroborates results from Patel *et al.* (2023), who reported an elevated cTnI in over 80% of patients with confirmed ACS in a high-risk population. The absence of false positives in the non-ACS cohort of this study strengthens its diagnostic validity, though differences in timing of sample collection post-symptom onset or lab assay sensitivity may explain minor variations in other studies.

For dyslipidemia, the finding of this study illustrates the presence of a statistically significant higher level of TG in ACS patients than in non-ACS patients

This study agrees with the pathophysiological model proposed by Yuan *et al.* (2023), who emphasized lipid accumulation and inflammatory processes as critical mediators of plaque instability leading to ACS. The particularly elevated TG in NSTEMI patients could be attributed to a higher burden of metabolic syndrome or undiagnosed insulin resistance, both known drivers of atherogenic dyslipidemia (Sadeq *et al.*, 2022).

**For MMP-9**, this study also demonstrated significantly higher MMP-9 levels in the ACS group compared to the non-ACS group. suggesting a strong link between MMP-9 expression and acute coronary pathology. These findings are consistent with prior study implicating MMP-9 in extracellular matrix remodeling and plaque rupture (Olejarz *et al.*, 2020). Angelini *et al.* (2018) demonstrated that MMP-9 levels are elevated in non-ST-elevation ACS, suggesting a role in adaptive immunity and plaque destabilization. Furthermore, Wang *et al.* (2020) reported that high MMP-9 levels correlate with plaque rupture risk in STEMI patients, emphasizing its clinical relevance.

MMP-9, a matrix metalloproteinase involved in extracellular matrix degradation, plays a pivotal role in plaque rupture and vascular remodeling, critical processes in the development of ACS (Angelini *et al.*, 2018; Santana & Tanus-Santos, 2018). The elevated MMP-9 levels in both STEMI and USA groups consistent with the biomarker's established role in promoting plaque rupture through degradation of the extracellular matrix (Theofilis *et al.*, 2022). The notably high levels in USA might reflect the subclinical plaque vulnerability that characterizes this subgroup.

Fernandez *et al.* (2016) found that increased MMP-9 levels were significantly correlated with emotional stress and plaque instability in ACS patients. Similarly, Guo *et al.* (2014) established a positive correlation between MMP-9 levels and the severity of coronary artery lesions, supporting its value not only as a biomarker but potentially as a therapeutic target in ACS management. The elevation of MMP-9 in this study supports its role as a key effector in plaque destabilization and myocardial matrix breakdown, both of which precipitate acute ischemic episodes.

For IL-18, the findings in the present study revealed that IL-18 levels were significantly higher in the ACS patients compared to the non-ACS group. Thus, these data suggested that IL-18 may have applications as a biomarker of ACS, with the ability to distinguish ACS from non-ACS .These results are agreement with literature highlighting IL-18 as a key pro-inflammatory cytokine involved in plaque instability, endothelial dysfunction, and myocardial injury (Ma *et al.*, 2018). In addition, Akerblom *et al.* 2019 study also highlighting the role of IL-18 as a pro-inflammatory cytokine in ACS .

The results of the current study agrees with Xiong *et al.* (2025) who reported that IL-18 levels were significantly higher in STEMI and NSTEMI patients compared to those with stable CAD, supporting its involvement in plaque destabilization and rupture. Interlukin-18 amplifies inflammatory cascades by inducing IFN-γ production, promoting the recruitment of monocytes and macrophages, and enhancing the expression of adhesion molecules within atherosclerotic lesions (Zhou *et al.*, 2014).

The present study's finding is corroborated by Opstad *et al.* (2016), who found that elevated levels of IL-18 were independently associated with adverse cardiovascular outcomes and increased risk of cardiovascular events in patients with coronary artery disease, underscoring its prognostic significance. The elevated IL-18 levels in ACS patients may reflect a heightened systemic inflammatory response and plaque vulnerability, which is consistent with its role as a biomarker of plaque instability (Angelini *et al.*, 2018). Differences in study populations, genetic backgrounds, and timing of sample collection could account for minor variations in absolute levels (Subramanian 2019).

Additionally, Zhang *et al.* (2017) linked high IL-18 concentrations to the angiographic severity of coronary artery obstruction, reinforcing its prognostic and diagnostic utility in acute coronary presentations. The biological plausibility of this association is well-supported: IL-18

promotes the destabilization of atherosclerotic plaques through its effects on inflammatory signaling pathways and smooth muscle cell apoptosis, processes intimately connected with the pathophysiology of ACS.

These results supported by the previously mentioned results of the present study which revealed a significantly higher expression of IL-18 in the ACS group compared to the non-ACS group, and the gradually upregulation of IL-18 as the degree of coronary artery stenosis and myocardial injury increased and strengthen by the results of previous studies that indicate the correlation of IL-18 with ACS and typically elevated in ACS and ACS subtypes as the studies of Zhou *et al.* (2014) and Opstad *et al.* (2016).

These findings are partially consistent with prior study that reported an associated of IL-18 with ACS severity (Xiong *et al.,* 2024). For instance, Zhou *et al.* (2014) reported a significant correlation between IL-18 levels and the GRACE score in ACS patients, highlighting IL-18's potential as a severity marker rather than a primary discriminator between ACS subtypes. Additionally, Opstad *et al.* (2016) found elevated IL-18 levels to be predictive of adverse cardiac events in coronary artery disease (CAD) patients .

IL-18 is a pro-inflammatory cytokine known to promote atherogenesis through activation of interferon-gamma (IFN-γ) and enhancement of endothelial dysfunction (Bhat & Dhawan, 2015). Previous studies have consistently linked IL-18 to acute coronary events. However, its role in the stable angina has been less emphasized (Zhang & Dhalla, 2024). Zhou *et al.* (2014) found elevated IL-18 levels in patients with higher Global Registry of Acute Coronary Events (GRACE) scores, underscoring its inflammatory relevance even in less acute conditions .

Similarly, Opstad *et al.* (2016) reported that chronically elevated IL-18 may signal ongoing subclinical inflammation contributing to plaque progression in coronary artery disease. The relatively modest specificity in this result may be due to IL-18's expression in other systemic inflammatory conditions, which reduces its ability to exclude non-CAD individuals. Additionally, individual variability in cytokine levels, circadian rhythm, and comorbid inflammatory diseases (e.g., diabetes, autoimmune disorders).

The ROC analysis showed excellent diagnostic performance for MMP-9 in distinguishing ACS from Non ACS with a statistical significance. Therefore, the exceptional sensitivity in this study positions MMP-9 as a potentially indispensable biomarker for early ACS diagnosis.

This divergent pattern likely reflects MMP-9's role in plaque rupture and thrombus formation, which are hallmark features of ACS. Supporting evidence from Santana and Tanus-Santos (2018) and Angelini *et al.* (2018) highlights that MMP-9 is significantly elevated in patients with ruptured plaques and acute thrombotic events.

## CONCLUSION

This study elucidates the potential of IL-18 as a valuable biomarker in the context of ACS, while also highlighting the complex interplay of demographic and clinical factors that contribute to its manifestation. The results showed that ACS patients had a significantly higher levels of IL-18 compared with non-ACS patients and MMP-9 had a -significant difference between these two groups, and these results suggest a significant association of MMP-9 and IL- 18 with ACS. Future research should focus on longitudinal studies to assess the prognostic value MMP-9 and IL-18 with ACS and other inflammatory markers in diverse populations, as well as the development of comprehensive strategies for the early identification and management of patients at risk for acute coronary events. The integration of such biomarkers into clinical practice may ultimately enhance patient outcomes and inform targeted therapeutic interventions.

**Acknowledgement:** The authors would like to sincerely thank all individuals who have willingly participated in this study. Additionally, we would like to acknowledge the diligent efforts of the Al-Najaf Cardiac Center staff, particularly in the laboratorty section.

**Funding Information:**No external funding was provided for this study

**Ethics:** The College of Medicine, University of Kufa's ethical committee approved the study. Consent was obtained from all participants. Parents provided verbal and written consent, and

agreement was obtained from both participants and researchers for publication.

**REFERENCES**

1. Omidi, N., Sadeghian, S., Salarifar, M., Jalali, A., Abbasi, S. H., Yavari, N., ... & Poorhosseini, H. (2020). Relationship between the severity of coronary artery disease and cardiovascular risk factors in acute coronary syndrome: based on Tehran Heart Center's Data Registry. *The Journal of Tehran University Heart Center*, *15*(4), 165.
2. Tajbakhsh, A., Gheibi Hayat, S. M., Taghizadeh, H., Akbari, A., Inabadi, M., Savardashtaki, A., ... & Sahebkar, A. (2021). COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. *Expert review of anti-infective therapy*, *19*(3), 345-357.
3. Nadendla, R. R., Narayanan, H., Murgod, R., Alboloi, K. S., Savira, M., & Muthuprasanna, P. (2024). Current and Prospective Biochemical Markers for the Identification of Acute Coronary Syndrome-A Review. *Biomedical and Pharmacology Journal*, *17*(4), 2071-2085.
4. Bhat, O., & Dhawan, V. (2015). Role of IL-18 and its signaling in atherosclerosis. *Inflammation and cell Signaling*, *2*(1).
5. Allami, M. (2024). A Cross-Sectional Study on the Epidemiology and Risk Factors of Acute Coronary Syndrome in Northern Iraq. *Cureus*, *16*(6).
6. Mehta, L. S., Beckie, T. M., DeVon, H. A., Grines, C. L., Krumholz, H. M., Johnson, M. N., ... & Wenger, N. K. (2016). Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*, *133*(9), 916-947.
7. Nowbar, A. N., Gitto, M., Howard, J. P., Francis, D. P., & Al-Lamee, R. (2019). Mortality from ischemic heart disease: Analysis of data from the World Health Organization and coronary artery disease risk factors From NCD Risk Factor Collaboration. *Circulation: cardiovascular quality and outcomes*, *12*(6), e005375.
8. Amsterdam, E. A., Wenger, N. K., Brindis, R. G., Casey, D. E., Ganiats, T. G., Holmes, D. R., ... & Zieman, S. J. (2014). 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American college of cardiology*, *64*(24), e139-e228.
9. Haider, A., Bengs, S., Luu, J., Osto, E., Siller-Matula, J. M., Muka, T., & Gebhard, C. (2020). Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *European heart journal*, *41*(13), 1328-1336.
10. Hochman, J. S., Tamis, J. E., Thompson, T. D., Weaver, W. D., White, H. D., Van de Werf, F., ... & Califf, R. M. (1999). Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *New England Journal of Medicine*, *341*(4), 226-232.
11. Hussain, A. M., & Lafta, R. K. (2019). Burden of non-communicable diseases in Iraq after the 2003 war. *Saudi medical journal*, *40*(1), 72.
12. Mohammad, A. M., Rashad, H. H., Habeeb, Q. S., Rashad, B. H., & Saeed, S. Y. (2021). Demographic, clinical and angiographic profile of coronary artery disease in kurdistan region of Iraq. *American Journal of Cardiovascular Disease*, *11*(1), 39.
13. Timmis, A., Kazakiewicz, D., Townsend, N., Huculeci, R., Aboyans, V., & Vardas, P. (2023). Global epidemiology of acute coronary syndromes. *Nature Reviews Cardiology*, *20*(11), 778-788.
14. Yusuf, S., Reddy, S., Ôunpuu, S., & Anand, S. (2001). Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*, *104*(22), 2746-2753.
15. Ahmed, M. H., Awadalla, H., Elmadhoun, W. M., Osman, M., Noor, S. K., & Almobarak, A. O. (2017). Prevalence and risk factors for acute coronary syndrome among Sudanese individuals with diabetes: a population-based study. *Cardiology research*, *8*(5), 184.
16. Flegal, K. M., Kit, B. K., Orpana, H., & Graubard, B. I. (2013). Association of all-cause

mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *Jama*, *309*(1), 71-82.
17. Kalantar-Zadeh, K., Streja, E., Kovesdy, C. P., Oreopoulos, A., Noori, N., Jing, J., ... & Anker, S. D. (2010, November). The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. In *Mayo Clinic Proceedings* (Vol. 85, No. 11, pp. 991-1001). Elsevier.
18. Lopez-Jimenez, F., Jacobsen, S. J., Reeder, G. S., Weston, S. A., Meverden, R. A., & Roger, V. L. (2004). Prevalence and secular trends of excess body weight and impact on outcomes after myocardial infarction in the community. *Chest*, *125*(4), 1205-1212.
19. Oreopoulos, A., Padwal, R., Norris, C. M., Mullen, J. C., Pretorius, V., & Kalantar-Zadeh, K. (2008). Effect of obesity on short-and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity*, *16*(2), 442-450.
20. Peto, R., Whitlock, G., & Jha, P. (2010). Effects of obesity and smoking on US life expectancy. *The New England journal of medicine*, *362*(9), 855-6.
21. Raber, I., McCarthy, C. P., & Januzzi Jr, J. L. (2021). A test in context: interpretation of high-sensitivity cardiac troponin assays in different clinical settings. *Journal of the American College of Cardiology*, *77*(10), 1357-1367.
22. Bhat, O., & Dhawan, V. (2015). Role of IL-18 and its signaling in atherosclerosis. *Inflammation and cell Signaling*, *2*(1).
23. Popovic, B., Varlot, J., Humbertjean, L., Sellal, J. M., Pace, N., Hammache, N., ... & Camenzind, E. (2024). Coronary Embolism Among Patients With ST-Segment–Elevation Myocardial Infarction and Atrial Fibrillation: An Underrecognized But Deadly Association. *Journal of the American Heart Association*, *13*(10), e032199.
24. Yuan, D., Chu, J., Qian, J., Lin, H., Zhu, G., Chen, F., & Liu, X. (2023). New concepts on the pathophysiology of acute coronary syndrome. *Reviews in Cardiovascular Medicine*, *24*(4), 112.
25. Sadeq, A., Al Saffar, H., & Alabdali, S. (2022). Inflammatory markers in patients who presented with acute coronary syndrome and history of COVID-19 infection: a cross-sectional study. *F1000Research*, *11*, 987.
26. Turk-Adawi, K., Sarrafzadegan, N., Fadhil, I., Taubert, K., Sadeghi, M., Wenger, N. K., ... & Grace, S. L. (2018). Cardiovascular disease in the Eastern Mediterranean region: epidemiology and risk factor burden. *Nature Reviews Cardiology*, *15*(2), 106-119.
27. DeFilippis, A. P., Chapman, A. R., Mills, N. L., De Lemos, J. A., Arbab-Zadeh, A., Newby, L. K., & Morrow, D. A. (2019). Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. *Circulation*, *140*(20), 1661-1678.
28. Romero-Corral, A., Montori, V. M., Somers, V. K., Korinek, J., Thomas, R. J., Allison, T. G., ... & Lopez-Jimenez, F. (2006). Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *The Lancet*, *368*(9536), 666-678.
29. Congress, S. H. (2018). Abstracts: SA Heart Congress 2018. *SA Heart Journal*, *15*(4), 270-312.
30. Dong, L., Mintz, G. S., Witzenbichler, B., Metzger, D. C., Rinaldi, M. J., Duffy, P. L., ... & Maehara, A. (2015). Comparison of plaque characteristics in narrowings with ST-elevation myocardial infarction (STEMI), non-STEMI/unstable angina pectoris and stable coronary artery disease (from the ADAPT-DES IVUS Substudy). *The American journal of cardiology*, *115*(7), 860-866.
31. Zhou, J., Deng, G., Yang, T., Ma, Q., & Luo, X. (2014). Association between interleukin-18 and Global Registry of Acute Coronary Events score in patients with acute coronary syndrome. *Journal of Central South University (Medical Sciences)*, 570-576.
32. Ma, C. Y., Xu, Z. Y., Wang, S. P., Peng, H. Y., Liu, F., Liu, J. H., & Ren, F. X. (2018). Change of inflammatory factors in patients with acute coronary syndrome. *Chinese Medical*

*Journal*, *131*(12), 1444-1449.
33. Qintar, M., Sharma, P. P., Pokharel, Y., et al. (2017). Prevalence and predictors of elevated high-sensitivity C-reactive protein in post–myocardial infarction patients. *Clinical Cardiology, 40*(12), 1205–1211.
34. Patel, B., Omeh, J., Tackling, G., Gupta, R., Sahadeo, T., Villcant, V., ... & Makaryus, A. N. (2023). The clinical association between carbon monoxide poisoning and myocardial injury as measured by elevated troponin I levels. *Journal of clinical medicine*, *12*(17), 5529.
35. Angelini, G., Flego, D., Vinci, R., Pedicino, D., Trotta, F., Ruggio, A., ... & Crea, F. (2018). Matrix metalloproteinase-9 might affect adaptive immunity in non-ST segment elevation acute coronary syndromes by increasing CD31 cleavage on CD4+ T-cells. *European Heart Journal*, *39*(13), 1089-1097.
36. Subramanian, A. (2019). Association of Cytokines IL6, IL10, IL18, TNFα in acute coronary syndrome. *J Cardio Vasc Med*, *5*, 1-9.
37. Opstad, T. B., Arnesen, H., Pettersen, A. Å., & Seljeflot, I. (2016). Combined elevated levels of the proinflammatory cytokines IL-18 and IL-12 are associated with clinical events in patients with coronary artery disease: an observational study. *Metabolic syndrome and related disorders*, *14*(5), 242-248.
38. Zhang, C., Liu, P., Xia, K., Fang, H., Jiang, M., Xie, Q., ... & Yang, T. (2017). Association of serum prealbumin with angiographic severity in patients with acute coronary syndrome. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, *23*, 4041.
39. Tuñón, J., Blanco-Colio, L., Cristóbal, C., Tarín, N., Higueras, J., Huelmos, A., ... & López-Bescós, L. (2014). Usefulness of a combination of monocyte chemoattractant protein-1, galectin-3, and N-terminal probrain natriuretic peptide to predict cardiovascular events in patients with coronary artery disease. *The American journal of cardiology*, *113*(3), 434-440.
40. Whelton, S. P., Narla, V., Blaha, M. J., Nasir, K., Blumenthal, R. S., Jenny, N. S., ... & Michos, E. D. (2014). Association between resting heart rate and inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin-6, and fibrinogen)(from the Multi-Ethnic Study of Atherosclerosis). *The American journal of cardiology*, *113*(4), 644-649.
41. Hernandez-Presa, M., Bustos, C., Ortego, M., Tunon, J., Renedo, G., Ruiz-Ortega, M., & Egido, J. (1997). Angiotensin-converting enzyme inhibition prevents arterial nuclear factor-κB activation, monocyte chemoattractant protein-1 expression, and macrophage infiltration in a rabbit model of early accelerated atherosclerosis. *Circulation*, *95*(6), 1532-1541.
42. Åkerblom, A., James, S. K., Lakic, T. G., Becker, R. C., Cannon, C. P., Steg, P. G., ... & PLATO Investigators. (2019). Interleukin-18 in patients with acute coronary syndromes. *Clinical cardiology*, *42*(12), 1202-1209.
43. Banerjee, D., Perrett, C., & Banerjee, A. (2019). Troponins, Acute Coronary Syndrome and Renal Disease: From Acute Kidney Injury Through End-stage Kidney Disease. *European Cardiology Review*, *14*(3), 187–190.
44. Kulkarni, S. M., Roongta, R., & Sankar, S. (2024). Clinical profile of patients and sensitivity of troponin I in patients with and without acute coronary syndrome: An observational study. The National Medical Journal of India, 36(5), 305–309.
45. Sudhir, A., & Brady, W. J. (2023). Electrocardiographic differential diagnosis of st segment depression. The Electrocardiogram in Emergency and Acute Care, 184-190.
46. Sciacqua, A., Succurro, E., Armentaro, G., Miceli, S., Pastori, D., Rengo, G., & Sesti, G. (2021). Pharmacological treatment of type 2 diabetes in elderly patients with heart failure: randomized trials and beyond. *Heart failure reviews*, 1-15.
47. Bahrami, A., Sathyapalan, T., & Sahebkar, A. (2021). The role of interleukin-18 in the development and progression of atherosclerosis. *Current Medicinal Chemistry, 28*(9), 1757-1774.
48. Danese E. and Montagnana M. (2016). An historical approach to the diagnostic biomarkers of acute coronary syndrome. *Annals of Translational Medicine, 4* (10):194.

49. Mondal, S., Adhikari, N., Banerjee, S., Amin, S. A., & Jha, T. (2020). Matrix metalloproteinase-9 (MMP-9) and its inhibitors in cancer: A minireview. *European journal of medicinal chemistry*, *194*, 112260.
50. Cabral-Pacheco, G. A., Garza-Veloz, I., Castruita-De la Rosa, C., Ramirez-Acuña, J. M., Perez-Romero, B. A., Guerrero-Rodriguez, J. F., ... & Martinez-Fierro, M. L. (2020). The roles of matrix metalloproteinases and their inhibitors in human diseases. *International journal of molecular sciences*, *21*(24), 9739.
51. Bianconi, V., Sahebkar, A., Atkin, S. L., & Pirro, M. (2018). The regulation and importance of monocyte chemoattractant protein-1. *Current opinion in hematology*, *25*(1), 44-51.
52. Bosomworth, J., & Khan, Z. (2023). Analysis of gender-based inequality in cardiovascular health: an umbrella review. Cureus, 15(8).
53. Joseph, N. M., Ramamoorthy, L., & Satheesh, S. (2021). Atypical manifestations of women presenting with myocardial infarction at tertiary health care center: an analytical study. Journal of mid-life health, 12(3), 219-224.
54. Marzà-Florensa, A., Kiss, P., Youssef, D. M., Jalali-Farahani, S., Lanas, F., di Cesare, M., ... & Peters, S. A. (2025). Sex Differences in Acute Coronary Syndromes: A Scoping Review Across the Care Continuum. Global heart, 20(1), 26.
55. Demirci, D., Demirci, D. E., & Chi, G. (2022). Association between obesity grade and the age of the first acute coronary syndrome: Prospective observational study. International Journal of Cardiology, 351, 93-99.
56. Maayah, M., Grubman, S., Allen, S., Ye, Z., Park, D. Y., Vemmou, E., ... & Hu, J. R. (2024). Clinical interpretation of serum troponin in the era of high-sensitivity testing. *Diagnostics*, *14*(5), 503.
57. Siam, N. H., Snigdha, N. N., Tabasumma, N., & Parvin, I. (2024). Diabetes Mellitus and Cardiovascular Disease: exploring epidemiology, pathophysiology, and treatment strategies. *Reviews in Cardiovascular Medicine*, *25*(12), 436.
58. Juricic, S., Klac, J., Stojkovic, S., Tesic, M., Jovanovic, I., Aleksandric, S., ... & Beleslin, B. (2025). Molecular and Pathophysiological Mechanisms Leading to Ischemic Heart Disease in Patients with Diabetes Mellitus. International Journal of Molecular Sciences, 26(9), 3924.
59. Xiong, C., Yu, Q., Gao, F., Liu, S., Zhang, J., Ma, T., & Liu, S. (2024). Prognostic significance of IL-18 in acute coronary syndrome patients. Clinical Cardiology, 47(2), e24229.
60. Bouzid, Z., Faramand, Z., Martin-Gill, C., Sereika, S. M., Callaway, C. W., Saba, S., ... & Al-Zaiti, S. S. (2023). Incorporation of serial 12-lead electrocardiogram with machine learning to augment the out-of-hospital diagnosis of non-ST elevation acute coronary syndrome. *Annals of Emergency Medicine*, *81*(1), 57-69.
61. Beza, L., Leslie, S. L., Alemayehu, B., & Gary, R. (2021). Acute coronary syndrome treatment delay in low to middle-income countries: a systematic review. *IJC Heart & Vasculature*, *35*, 100823.
62. Yang, Y., Li, G., & Zhang, R. (2022). [Retracted] Correlation Analysis of Acute Coronary Syndrome with Serum IL-18, MMP-9, hs-CRP, and Plasma FIB. *BioMed Research International*, *2022*(1), 5984184.