ORIGINAL ARTICLE

AL-ANBAR MEDICAL JOURNAL
Anb. Med. J. 20(2): 144–150, 2024

# Predictive Value of Resistin in Acute Coronary Syndrome Patients with and without Type 2 Diabetes Mellitus

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(Received : 4 April 2024; Accepted : 25 June 2024; First published online: 13 July 2024)

## ABSTRACT

**Background:** Resistin in humans is classified as an adipokine and has been proposed as an inflammatory marker, associated with the development of atherosclerosis and coronary artery disease.
**Objectives:** To evaluate serum resistin levels in patients with acute coronary syndrome (ACS) with and without type 2 diabetes mellitus (T2DM). In addition, correlating serum resistin with clinical and biochemical parameters was another objective.
**Materials and methods:** This study included 60 patients with ACS diagnoses. The participants were categorized into two groups: 30 patients with both ACS and T2DM and 30 patients with ACS but without T2DM. The control group comprised 30 healthy individuals who matched the patient groups regarding sex and age. Levels of serum lipids, fasting blood glucose (FBG), Hemoglobin A1c (HbA1c), C-reactive protein (CRP), troponin I, and resistin, were estimated for each participant.
**Results:** The levels of resistin in the serum were significantly higher in ACS with T2DM or ACS without T2DM patients compared to healthy individuals (1.184 ± 0.271 ng/mL and 1.249 ± 0.358 *vs.* 0.601 ± 0.141 ng/mL, respectively, P-value = 0.001). The analysis of the data exhibited a significant positive correlation between serum resistin and CRP levels in the ACS with T2DM (r = 0.412; P-value = 0.018) and the ACS without T2DM (r = 0.467; P-value = 0.01). There was no significant correlation between serum resistin levels and other variables in these two groups. The receiver operating characteristic (ROC) analysis in ACS with T2DM exhibited that serum resistin level larger than 0.896 ng/mL was correlated with an elevated incidence of ACS (Area Under the Curve = 0.988, sensitivity = 93.33%, specificity = 93.33%, and likelihood ratio = 14). In contrast, ROC analysis in ACS without T2DM exhibited that a serum resistin level greater than 0.830 ng/mL was correlated with an elevated incidence of ACS (Area Under the Curve = 0.978, sensitivity = 90%, specificity = 90%, and likelihood ratio = 9).
**Conclusion:** Serum resistin can be used to predict ACS in patients with or without T2DM. Also, resistin is an effector molecule of the inflammatory response that contributes to ACS.
**Keywords:** Resistin; Acute coronary syndrome; Type 2 diabetes mellitus.

**DOI:** 10.33091/amj.2024.148512.1654


## INTRODUCTION

Acute coronary syndrome (ACS) is defined as a sudden decrease in blood flow to the cardiac muscle and includes unstable angina (UA), ST-elevation myocardial infarction (STEMI), and non-ST-elevation myocardial infarction (NSTEMI). ACS impacts more than 7 million individuals annually and is the primary cause of mortality worldwide [1]. The underlying mechanisms of ACS include atherosclerotic plaque instability and rupture, platelet aggregation, and blood clot formation. Coronary plaque instability results in the development of stable coronary artery disease (CAD) in ACS [2].

The relationship between diabetes mellitus (DM) and cardiovascular illness is widely acknowledged, and CAD is a prevalent macrovascular complication commonly associated

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http://doi.org/10.33091/amj.2024.148512.1654

with diabetes [3]. CAD and DM share numerous risk factors, including obesity, dyslipidemia, stress, and a sedentary lifestyle, among others. Patients diagnosed with type 2 diabetes mellitus (T2DM) have a two to threefold increased incidence of ACS compared to the general population [4].

Patients with ACS and DM are at a greater risk for adverse short-term and long-term outcomes than non-diabetic individuals [5]. In comparison to those without DM, diabetic patients exhibit a higher plaque burden, a greater quantity of necrotic core, and a higher frequency of thin-cap fibroatheromas. Coronary thrombotic complications frequently arise due to the perturbation of these precarious plaques. Moreover, microvascular dysfunction in diabetic patients may serve as an independent predictor of future cardiovascular events [6].

Adipose tissue acts as an endocrine organ, and it produces and secretes bioactive adipokines that have both pro- and anti-inflammatory effects. These adipokines can be the ones that are responsible for the inflammatory activation observed in ACS [7]. The Mitchell Lazar Group initially discovered Resistin, a pro-inflammatory cytokine, as a link between diabetes and obesity in 2001. The discovery that it mediated insulin resistance led to the term "resistin" [8]. Resistin is a peptide hormone that belongs to the resistin-like molecule family which contains cysteine-rich secreted proteins [9]. It consists of 108 amino acids, and its molecular mass is 12.5 kDa [8]. The resistin gene in human beings is located on chromosome 19, with resistin being of great significance in the inflammation process, where macrophages are responsible for its secretion [9].

Recently, there has been considerable interest in the relationship between atherosclerosis and adipocyte biology and the responses of inflammatory pathways [10]. Resistin is gaining increasing attention in cardiovascular research due to its varied activities in endothelial damage, inflammatory response, and the buildup of lipids [9]. Furthermore, various perspectives indicate that resistin exacerbates the susceptibility of atherosclerotic plaque, promotes plaque rupture, and influences the remodeling of the heart following myocardial infarction [11–13]. The activity of human endothelial cells can be boosted by resistin. This is done by increasing the expression of monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1. Reports indicate that macrophages infiltrating atheromas secrete resistin, which stimulates the migration of vascular smooth muscle cells and influences endothelial function [14–16]. Patients diagnosed with ACS exhibited coronary plaques characterized by larger regions rich in macrophages, in contrast to those diagnosed with chronic stable angina, which served as the main source of resistin. The secretion of resistin was stimulated by inflammatory responses [17], and resistin can also stimulate the synthesis of pro-inflammatory mediators, including tumor necrosis factor-a (TNF-a), interleukin-12 (IL-12), and IL-6, thereby exacerbating the pro-inflammatory response. Furthermore, resistin has the potential to impact the functionality of vascular cells by activating endothelial cells, increasing the expression of ET-1, chemokines, and adhesion molecules, as well as inducing the expression of matrix metalloproteinases [18], increasing the signaling of CD40 ligands through the down-regulation of TNF receptor-associated factor-3. The involvement of these pro-inflammatory mediators in plaque destabilization has already been shown. Moreover, resistin can potentially stimulate lipid accumulation within macrophages [19]. The data provided above collectively indicate that resistin potentially plays a role in expediting the progression of atherosclerosis and functions as a destabilizing factor that contributes to the development of ACS.

Several researches have documented an association between resistin and ACS. However, because ROC analysis wasn't done in previous studies, the cut-off value of resistin for predicting ACS in patients with and without T2DM hasn't been looked at. Furthermore, no study has examined the serum resistin levels in ACS patients in Iraq. It is important to note that the findings from studies conducted on other ethnic groups may not necessarily apply to the results in our study population. As a result, our research aimed to assess serum resistin levels in ACS patients, both with and without T2DM, and determine whether it is possible to rely on resistin for ACS prediction. The second goal was to correlate serum resistin with clinical and biochemical parameters.

## MATERIALS AND METHODS

### Study population

The study was conducted from November 2023 to February 2024 at Al-Ramadi Teaching Hospital, Ramadi City, Anbar, Iraq, namely in the Emergency and Coronary Care Unit (CCU). This study comprised a group of 60 patients who had been diagnosed with ACS, with ages spanning from 35 to 65 years. The participants were categorized into two cohorts: 30 patients with both ACS and T2DM and 30 patients with ACS but without T2DM. The control group comprised 30 healthy individuals who matched the patient groups regarding sex and age. None of the control group had previous histories of cardiovascular disease, which includes all forms of coronary heart disease and stroke.

The exclusion criteria encompassed patients with heart failure, valvular heart disease, renal or hepatic dysfunction, prediabetes, chronic inflammatory disorders (such as inflammatory bowel disease, osteoarthritis, and rheumatoid arthritis), proof of active infective or neoplastic conditions, and those who had undergone major surgery or trauma. Twenty-seven out of 87 patients were excluded (12 with chronic kidney disease, one with hepatitis B, five with prediabetes, three with heart failure, and six were not fasting). The remaining 60 ACS patients were categorized into two groups, as above.

Demographic data, body mass index (BMI), history of risk factors, smoking habit, and family history of cardiovascular disease in first-degree relatives were documented. The calculation of BMI involves the division of weight, measured in kilograms, by the square of height, measured in meters. All study participants underwent standard clinical examinations. This study was approved by the Ethical Approval Committee of the University of Anbar (Reference Number 52, Dated 1-11-2023). Informed consent was obtained from all participants (patients and controls).

The sample size was calculated with the Kish and Leslie formula [ $N = Z^2\ p\ (p–1)\ /\ d^2$ ], where N = sample size, Z = Z-score for the desired confidence level (1.96 for 95% confidence), p = assumed true population prevalence of ACS patients, and d = margin of error (0.05). The prevalence of ACS was 6% in Saudi Arabia [20]. However, no previous study has examined the prevalence of ACS in Iraq. Thus, if we assume that the prevalence of ACS in Iraq is comparable to that in Saudi Arabia, the sample size will be 87 patients based on the equation above. However, the study only included 60 patients since there was a scarcity of ACS patients who did

not have T2DM, as it is a major risk factor for developing this disease. Moreover, the small sample size was a result of the numerous exclusionary criteria.

### Sampling

After obtaining consent from all participants and following stringent aseptic procedures, seven milliliters of fasting venous blood were collected from each participant, including patients with ACS within 24 hours of symptom onset, as well as controls.

Two milliliters of venous blood were carefully placed into a tube containing ethylenediaminetetraacetic acid (EDTA) to conduct a hemoglobin A1c (HbA1c) analysis. The residual venous blood was gradually transferred into a gel tube and left to coagulate for 15 min at room temperature. Then, we centrifuged it for 10 minutes at 4000 rpm. The serum was divided into portions and stored at −20°C until analysis.

### Measurement

Commercial kits (SUNLONG BIOTECH, China) used enzyme-linked immunosorbent assays to quantify fasting serum resistin levels, with a measurement interval of 0.3–3.6 ng/mL. The measurement of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and routine blood tests were performed using colorimetric and turbidimetric methods by commercial kits (Abbott, USA). C-reactive protein (CRP) was evaluated using an electro-chemiluminescence immunoassay by commercial kits (Roche, Switzerland). Cardiac Troponin I (cTnI), and HbA1c were assessed using electro-chemiluminescence immunoassay and HPLC, respectively, by commercial kits (Nipigon, Canada).

### Statistical analysis

The statistical analysis was conducted utilizing version 22 of the IBM Statistical Package for Social Sciences (SPSS) Statistics software (IBM Corp., Armonk, NY, USA). To summarize the numerical variables, descriptive statistics were utilized. This involved performing calculations to determine means, standard deviations, and standard errors. Frequencies and percentages of categorical variables were acquired. To assess the significance of mean differences among the three groups (ACS with T2DM, ACS without T2DM, and a control group), a one-way analysis of variance (ANOVA) was performed. By employing analysis of variance (ANOVA) tables and the Fisher's LSD (Least Significant Difference) test, statistically significant differences among the three groups for the numerical parameters were identified. To evaluate the intensity and direction of linear relationships between pairs of numerical variables within each group, Pearson's correlation coefficients (r) were calculated. Correlation analysis quantifies the degree of association between two variables using coefficients ranging from -1 (indicating perfect negative correlation) to 1 (indicating perfect positive correlation). Two-tailed tests were used to determine the significance of the correlation coefficients, assessing the likelihood of observing the obtained correlations under the null hypothesis of no correlation. To determine statistical significance, a P-value $<$ 0.05 was used in all analyses. The Receiver Operating Characteristic (ROC) curve technique was employed to assess the diagnostic or screening potential of parameters for disease detection. It also helped define the optimal cut-off value that balances sensitivity and specificity for accurate disease diagnosis.

## RESULTS

Table 1 displays the clinical and laboratory features of the subjects. In the ACS with T2DM group, 10 cases (33%) had STEMI, 16 cases (54%) had NSTEMI, and 4 cases (13%) had UA. In the ACS without T2DM group, 9 cases (30%) had STEMI, 14 cases (47%) had NSTEMI, and 7 cases (23%) had UA. The three studied groups did not exhibit any significant differences in age, sex, BMI, T. cholesterol, and LDL-C. The ACS with T2DM group had significantly higher levels of FBG, HbA1c, TG, and VLDL-C than the control group or the ACS without T2DM group (P-value = 0.001). To compare with the control group, the ACS with T2DM group had significantly higher levels of troponin I and CRP but lower levels of HDL-C (P-value = 0.01). The ACS without T2DM group, on the other hand, only had significantly higher levels of troponin I and CRP (P-value = 0.01).

The amount of resistin in the blood was much higher in people with ACS and T2DM compared to healthy people (1.184 ± 0.271 ng/mL and 1.249 ± 0.358 ng/mL *vs.* 0.601 ± 0.141 ng/mL, respectively; P-value = 0.001). Although mean fasting serum resistin levels were lower in ACS with T2DM patients compared to ACS without T2DM, the disparity between the two groups wasn't significantly different (P-value = 0.360), as shown in Figure 1.

A strong positive relationship was found between serum resistin and CRP levels in both the ACS with T2DM (r = 0.412; P-value = 0.018) and the ACS without T2DM (r = 0.467; P-value = 0.01). In these two groups, there was no significant correlation between serum resistin levels and other variables, i.e., age, sex, FSG, T. cholesterol, TG, HDL, LDL, VLDL, HbA1c, and troponin I (Table 2).

The receiver operating characteristic (ROC) curve was employed to assist in the discrimination of ACS from the healthy control group based on levels of resistin. The area under the curve (AUC) illustrates how levels of resistin can serve as a prognostic indicator of ACS. Every point on the ROC curve further demonstrates the specificity and sensitivity of this parameter in ACS prediction. The ROC analysis yields two major outcomes: the optimal cut-off point (maximum specificity and sensitivity) value for the test and the test's diagnostic role. The test values are dichotomized by cut-off points, which provide the diagnosis, of whether it is diseased or not. Determining the cut-off point value necessitates a concurrent evaluation of specificity and sensitivity [21]. A ROC analysis in ACS with T2DM revealed a correlation between an elevated incidence of ACS and a serum resistin level greater than 0.896 ng/mL (AUC = 0.988, sensitivity = 93.33%, specificity = 93.33%, likelihood ratio = 14). In contrast, ROC analysis in ACS without T2DM exhibited that a serum resistin level greater than 0.830 ng/mL was correlated with an elevated incidence of ACS (AUC = 0.978, sensitivity = 90%, specificity = 90%, likelihood ratio = 9), as shown in Figure 2.

## DISCUSSION

ACS encompasses three diseases that are associated with atherosclerosis in the coronary arteries, including UA, NSTEMI, and STEMI. Many plasma or serum biomarkers can serve as suitable diagnostic tools for this specific disease. It is known that inflammation and endothelial dysfunction


http://doi.org/10.33091/amj.2024.148512.1654

**Table** 1. The demographic, clinical, and biochemical characteristics of the research subjects.[*†‡§]

| Variables | Control Mean ± SD | ACS with T2DM Mean ± SD | ACS without T2DM Mean ± SD | P-value |
|---|---|---|---|---|
| Age (years) | 54.23 ± 8.56 | 55.67 ± 8.15 | 55.87 ± 7.73 | 0.700 |
| Male/Female, n | 21/9 | 22/8 | 20/10 | 0.858 |
| Smoking, n (%) | 3 (10%) | 8 (27%)[*,‡] | 17 (57%)[†] | 0.001 |
| BMI (kg/m$^2$) | 28.22 ± 2.02 | 28.93 ± 1.62 | 27.87 ± 2.38 | 0.126 |
| FBG (mg/mL) | 91.40 ± 9.72 | 245.67 ± 60[*,‡] | 100.37 ± 17.94 | 0.001 |
| HbA1c (%) | 5.04 ± 0.351 | 9.18 ± 2.14[*,‡] | 5.38 ± 0.223 | 0.001 |
| T.C (mg/dL) | 166.87 ± 25.01 | 179.47 ± 47.79 | 180.27 ± 48.64 | 0.386 |
| TG (mg/dL) | 117.07 ± 32.62 | 186 ± 39.14[*,‡] | 144.53 ± 42.65[†] | 0.001 |
| HDL (mg/dL) | 46.63 ± 10.79 | 37.57 ± 11.80[*] | 42.07 ± 11.58 | 0.011 |
| LDL (mg/dL) | 96.82 ± 23.38 | 102.92 ± 39.59 | 109.29 ± 34.12 | 0.348 |
| VLDL (mg/dL) | 23.41 ± 6.52 | 38.97 ± 21.98[*,‡] | 28.90 ± 20.40[†] | 0.001 |
| Troponin I (ng/mL) median (range) | 0.013 (0.009-0.024) | 0.950[*] (0.021-42) | 0.231[†] (0.016-29.79) | 0.007 |
| CRP (mg/L) median (range) | 1.35 (0.35-5.20) | 12.33[*] (0.89-57) | 5.66[†] (1.71-65) | 0.001 |

[*] P-value < 0.05, ACS with T2DM compared to the control group.
[†] P-value < 0.05, ACS without T2DM compared to the control group.
[‡] P-value < 0.05, ACS with T2DM compared to ACS without T2DM.
[§] ACS with T2DM: Acute coronary syndrome with type 2 diabetes mellitus; ACS without T2DM: Acute coronary syndrome without type 2 diabetes mellitus; BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; VLDL: Very low-density lipoprotein cholesterol; CRP: C-reactive protein.

**Table** 2. Correlation between serum resistin and other variables.[*†]

| Variables | ACS with T2DM Resistin | | ACS without T2DM Resistin | |
|---|---|---|---|---|
| | r | P-value | r | P-value |
| Age (years) | 0.009 | 0.946 | -0.124 | 0.345 |
| BMI (kg/m$^2$) | -0.157 | 0.409 | 0.02 | 0.92 |
| FBG (mg/mL) | 0.01 | 0.97 | -0.07 | 0.71 |
| HbA1c (%) | 0.29 | 0.12 | -0.25 | 0.18 |
| T.C (mg/dL) | 0.11 | 0.56 | 0.19 | 0.31 |
| TG (mg/dL) | -0.17 | 0.38 | -0.09 | 0.63 |
| HDL (mg/dL) | -0.17 | 0.37 | 0.09 | 0.62 |
| LDL (mg/dL) | 0.17 | 0.37 | 0.22 | 0.24 |
| VLDL (mg/dL) | -0.07 | 0.70 | -0.12 | 0.54 |
| Troponin I (ng/mL) | 0.05 | 0.80 | -0.04 | 0.82 |
| CRP (mg/L) | 0.412[*] | 0.018 | 0.467[*] | 0.01 |

[*] Significant (P-value < 0.05).
[†] ACS with T2DM: Acute coronary syndrome with type 2 diabetes mellitus; ACS without T2DM: Acute coronary syndrome without type 2 diabetes mellitus; BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; VLDL: Very low-density lipoprotein cholesterol; CRP: C-reactive protein.

play a critical role in plaque destabilization and vulnerability. Research suggests that resistin may influence systemic inflammation to mediate some of its pro-atherosclerotic properties. Resistin contributes to atherosclerosis partly by modulating endothelial function and inciting endothelial activation [1, 13]. The present study established the cut-off point for resistin as a predictor of ACS, which is crucial in the medical field for assessing the performance of diagnostic methods since no previous study has identified it. We demonstrated that resistin in serum at the cut-offs of 0.896 ng/mL and 0.830 ng/mL resulted in very high sensitivity, specificity, and excellent accuracy in predicting the incidence of ACS, with and without T2DM, respectively. We can use these results to accurately predict ACS before it occurs, as resistin accelerates the development of atherosclerosis and reduces stability, both of which contribute to the development of ACS. Therefore, this parameter has significant importance, especially in asymptomatic individuals with a family history of premature

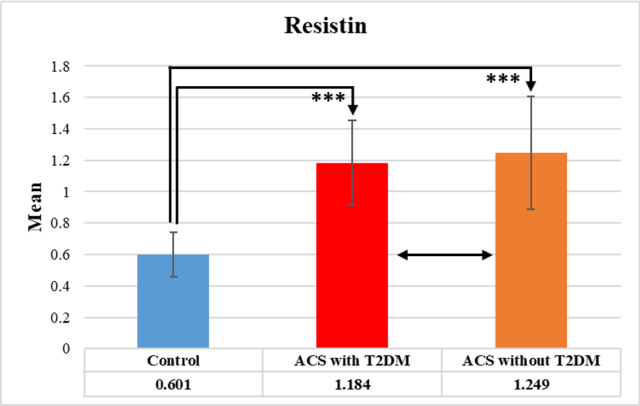


**Figure** 1. Mean resistin level (ng/ml) ± Standard Deviation in acute coronary syndrome (ACS) patients with and without type 2 diabetes mellitus (T2DM), and healthy control Group; *** indicates P-value $< 0.001$, no asterisks indicate P-value $\geq 0.05$ (non-significant); Sample sizes: ACS with T2DM n = 30, ACS without T2DM n = 30, and controls n = 30.

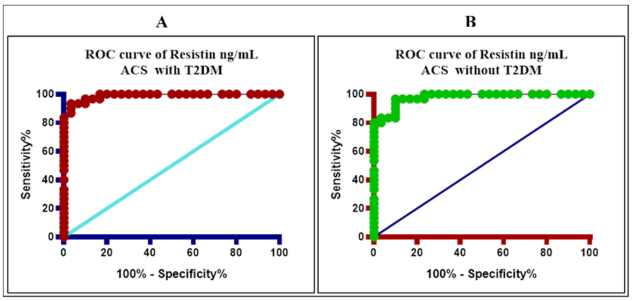


**Figure** 2. The receiver operating characteristic (ROC) curve of serum resistin (ng/mL) for predicting (A) acute coronary syndrome (ACS) patients with type 2 diabetes mellitus (T2DM), and (B) ACS patients without T2DM. The cut-off value of 0.896 ng/mL for resistin in serum yielded a sensitivity of 93.33% and a specificity of 93.33% in the prediction of the incidence of ACS with type T2DM. The cut-off value of 0.830 ng/mL for resistin in serum yielded a sensitivity of 90% and a specificity of 90% in the predicting the incidence of ACS without T2DM.

CAD. Measuring resistin levels in this population may help identify individuals at the highest risk, for whom aggressive preventive risk management would be most beneficial.

In comparison to the control group, we observed significantly higher serum levels of resistin in patients with ACS, which is consistent with previous studies [22–25]. An inflammatory process in mononuclear cells preceding myocardial necrosis could potentially explain the elevation in resistin levels in ACS. Researchers reported significantly higher resistin levels in human inflammatory cells compared to human adipocytes. These findings may additionally support the hypothesis that in the conditions of the ACS, resistin might represent inflammatory rather than metabolic processes [23].

In the present study, we found no significant correlation between serum resistin levels and metabolic parameters such as BMI, blood glucose, and lipid profile, and this aligns with the results of prior studies [22, 25]. Further research is necessary to elucidate the impacts of resistin on the human metabolic syndrome. Moreover, Chu and Qiao's findings, which reported a positive correlation between serum resistin level and cTnI [23, 25], differ from ours. The rationale behind this is that the study population is comparatively small and only shows a few correlations.

Regarding CRP, we found a significant positive correlation between serum resistin and CRP levels in the ACS with T2DM and the ACS without T2DM. The obtained results bear resemblance to the findings of Qiao, Wang, and Pourmoghaddas [23, 24, 26], yet they diverge from Chu's findings, which revealed no correlation between serum resistin level and CRP [25]. This suggests that CRP and resistin have a complicated relationship, which may include inflammatory processes, since ACS is a condition that gets worse quickly. This data suggests a potential cause-and-effect relationship between CRP and resistin in ACS patients. Nevertheless, further research is necessary to establish this correlation and elucidate its metabolic pathways.

Recent studies have demonstrated a significant increase in serum resistin levels in T2DM patients compared to the control group [27–30]. Therefore, we expected the ACS with T2DM to have higher resistin levels than the group without T2DM, but our study revealed the opposite. While ACS patients with T2DM had lower mean serum resistin levels than ACS patients without T2DM, the difference wasn't statistically significant. This is because most patients with T2DM, upon arrival at the emergency department, exhibit elevated glucose levels as a stress response. Consequently, we administer soluble insulin as an immediate intervention to regulate their blood glucose levels until their condition stabilizes. Insulin, widely recognized as the primary inhibitor of resistin [31], demonstrates lower or nearly equivalent levels of resistin in ACS patients with T2DM compared to those without T2DM.

There are several limitations to the current study: First, the study population is relatively small and only showed some correlations (a lack of statistical power due to the small sample size). For this reason, we advise investigators to carry out comparable studies with larger sample sizes to obtain more precise findings. Second, the study did not consider the various ACS therapy methods, nor did it examine obesity-related characteristics such as body fat distribution and composition. Third, this study only included Iraqi participants, which may limit the applicability of the results to participants from other ethnicities.

## CONCLUSION

The high serum level of resistin in patients with ACS indicates the presence of an inflammatory process that precedes myocardial necrosis, which can predict the occurrence of ACS. The study's clinical implications include the following: First, serum resistin is a biomarker for predicting ACS in patients with and without T2DM. Second, resistin participates in ACS as an inflammatory reaction effector molecule.

## ETHICAL DECLARATIONS

### Acknowledgments

None.


http://doi.org/10.33091/amj.2024.148512.1654

### Ethics Approval and Consent to Participate

The Ethical Approval Committee of the University of Anbar approved the study (Reference Number 52, Dated 1-11-2023). Informed consent was obtained from all participants, both patients and controls.

### Consent for Publication

Not applicable (no individual personal data included).

### Availability of Data and Material

None.

### Competing Interests

The authors declare that there is no conflict of interest.

### Funding

No funding.

### Authors' Contributions

All authors have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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http://doi.org/10.33091/amj.2024.148512.1654