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Original Research Paper

Serum Levels of Interleukin-18 and Monocyte Chemoattractant Protein-1 in Patients with Acute Coronary Syndrome

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Abstract: : Acute coronary syndrome (ACS) is a kind of coronary artery disease emergency and has the characteristics of rapid appear, rapid disease change, with high morbidity and mortality rates, which puts ACS as a major public health problem. Inflammatory cells in plaque and its inflammatory products can trigger ACS by inducing plaque instability and rupture. **Objective:** The present study aims to investigate the association between ACS and the two proinflammatory cytokines; interleukin-18 (IL-18) and monocyte chemoattractant protein-1 (MCP-1). **Materials and Methods:** A case-control study was conducted involving 90 patients with ACS [ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (USA) and 60 participants with non-ACS [stable angina (SA) and healthy controls]. The IL-18 and MCP-1 levels were assessed by enzyme-linked immunosorbent assay (ELISA) for all the participants. **Results:** The results showed that ACS patients had significantly higher levels of IL-18 compared with non-ACS patients ($p<0.001$), but MCP-1 had a non-significant difference between these two groups (0.863). **Conclusion**: The result suggests a significant association of IL-18 but not MCP-1 with ACS.

Keywords: Interleukin-18; Monocyte chemoattractant Protein-1; Acute coronary syndrome.

1. Introduction

Acute coronary syndrome (ACS) is one of the most prevalent presentations of coronary artery disease (CAD) [1]. It represents a spectrum of clinical manifestations resulting from a sudden reduction in blood flow to the heart, leading to myocardial injury [2].

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 [3]. 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 [4].

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 [5].

Therefore, identification of novel biomarkers may facilitate the diagnosis of ACS. IL-18, a proinflammatory cytokine, and its receptor subunits are both expressed within atherosclerotic lesions, suggesting a potential role in plaque development and progression [6]. In addition, IL-18 has been associated with the development of subclinical atherosclerosis [7].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) [8].

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Monocyte chemoattractant protein-1 (MCP-1) is one of the most important cytokines related to the pathogenesis of atherosclerosis, which plays a main role in the recruitment of monocytes into the vascular wall [9]. Furthermore, MCP-1 blood levels have been associated with increased incidence of acute ischemic events in patients with CAD [10]. The present study aims to investigate the association of IL_18 and MCP-1 with ACS.

2. 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 150 participiiant classified into 5 groups (Group STEMI 30, Group NSTEMI 30, Group USA 30, Group SA 30 and Group control 30 as healthy). The patients with UA and the healthy individuals form the non-ACS group. Age of participants ranged between 28 and 65 years.

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 TnI I, triglyceride, IL-18 and MCP-1. Troponin I levels were assessed using a fluorescence immunoassay, while triglyceride were determined using enzymatic colorimetric methods. Levels of IL-18, and MCP-1 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 the distribution of the data was examined as Kamenkroff- Simonoff in order to determine the use of the appropriate type of test (t test or Maan Whitney. ANOVA or Kruskal. Adjustment for multiple comparisons or potential confounding factors.

3. Results and discussion

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: Frequency Distribution of 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		

ACS = Acute Coronary Syndrome, Non-ACS = Non Acute Coronary Syndrome %= percentage, N. = number, SD = standard deviation; X2 =Chi-square; df = degree of freedom, P = probability value. S=Significant at(P < 0.05), NS= Non Significant at (P > 0.05), #=

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Indepandent t test.

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 (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 ACS group is lower than that of the non- 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).

Thee 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: Frequency Distribution of 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/m^2		(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 51.11%	30 50%		
Hypertension (N,%)	Non Hypertensive	41 45.56%	41 68.33%	7.5 (1)	0.006 (HS)
	Hypertensive	49 54.44%	19 31.67%		
Total (N)		90	60		

ACS = Acute Coronary Syndrome, Non-ACS = Non Acute Coronary Syndrome, %= percentage, N. = number, SD = standard deviation; X2 =Chi-square; df = degree of freedom, P = probability value. S=Significant at (P < 0.05), NS= Non Significant at (P > 0.05), #= Independent t test.

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

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value (72.32) and p-value (<0.001) suggest a significant relationship between lipid levels and cardiovascular conditions.

Table 3: Frequency Distribution of Troponin I and Dyslipidemia for ACS, and Non-ACS Groups

Clinical Data		**ACS**	**Non -ACS**	**X^2 (df)**	**P-value (Sig.)**
Troponin I (N,%) OR=0	**Negative**	30 33.33%	60 100%	66.6 (2)	**<0.001 (HS)**
	Positive	60 66.67%	0 0%		
TG (Mean ± SD) mg/dl		211.16 ±91.4	169.78 ±90.7	2.72#	**0.007 (HS)**
Dyslipidemia (N,%) OR=0.32	**No**	10 11.11%	17 28.33%	7.23 (1)	**0.007 (HS)**
	Yes	80 88.89%	43 71.67%		

ACS = Acute Coronary Syndrome, Non-ACS = Non Acute Coronary Syndrome, %= percentage, N. = number, SD = standard deviation; X2 =Chi-square; df = degree of freedom, P = probability value. S=Significant at (P < 0.05), NS= Non Significant at (P > 0.05), #= Independent t test, OR=Odd ratio.

Table 4 shows the median levels of the inflammatory biomarkers (IL-18, MCP-1) 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, MCP-1 levels did not differ significantly between the two groups (p = 0.863), see figures 1 and 2.

Bio-marker	Groups				Mann-Whitney U test	P-value (Sig.)
	ACS (N=90)		Non -ACS (N=60)			
	Median	IQR	Median	IQR		
IL-18	26.77	16.	18.61	5.4	1093	<0.0
(ng/L)		98		8		01 (HS)
MCP-1 (ng/L)	265.96	92.69	275.93	70.01	2655	0.863 (NS)

ACS = Acute Coronary Syndrome, Non-ACS = Non Acute Coronary Syndrome, IQR=Interquartile range, M-W= data were analyzed by using the Mann-Whitney U test; P = probability value. S=Significant at (P < 0.05), NS= Non Significant at (P > 0.05).

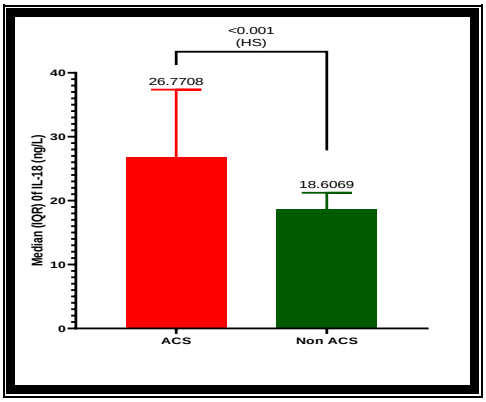

Fig 1: Bar Chart of IL-18 between ACS and Non-ACS

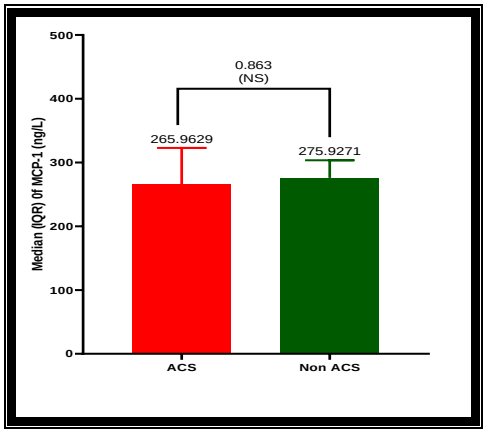

Fig 2: Bar Chart of MCP-1 between ACS and Non – ACS

The finding of the present study is in line with Allami, who reported a mean age of 56.2 years in Iraqi patients with ACS [11]. 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 [12]. This contrasts

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with Western populations, indicates that ACS in these populations tends to present a decade later, typically around the age of 65–70 [13]. 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 [14]. This interpretation of the contrast in the results is supported by what was reported by Hussain & Lafta, 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[15].

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 [16]. 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 [17].

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 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[18].

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 [19]. 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 [11].

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 [20,19] Estrogen has vasodilatory, anti-inflammatory, and anti-atherosclerotic properties, which may account for reduced coronary risk in premenopausal women [20]. Additionally, social and systemic factors, such as underdiagnosis and undertreatment, may contribute to the lower representation of women in acute presentations [21]. 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 [22].

Therefore, the presentation of women with atypical symptoms can lead to under-diagnosis and misclassification into non-ACS categories. Importantly, research by Joseph 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[23].

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 [24, 25]. 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 [26, 27].

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 and Demirci , who reported that patients with ACS often present with less severe obesity than those with stable angina or chronic disease, highlighting the

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complexity of BMI as a cardiovascular risk factor[28,29].

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 [30]. Chronic hyperglycemia contributes to endothelial dysfunction, inflammation, and accelerated atherosclerosis, thereby increasing the likelihood of acute events [31]. This highlights the necessity for diabetes-focused primary prevention in CAD management, especially in populations with high baseline insulin resistance [32].

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 [33].

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 [34].

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 [35].High-sensitivity troponin assays have revolutionized ACS diagnostics by enabling the early identification of myocardial necrosis even before overt ECG changes [36]. 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, 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 [37].

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 , who emphasized lipid accumulation and inflammatory processes as critical mediators of plaque instability leading to ACS [38]. 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 [39].

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 [40]. The results of the current study agrees with Xiong 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 [41]. 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 [42].

The present study's finding is corroborated by Opstad 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 [43]. The elevated IL-18 levels

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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 [44]. Differences in study populations, genetic backgrounds, and timing of sample collection could account for minor variations in absolute levels [44].

Additionally, Zhang linked high IL-18 concentrations to the angiographic severity of coronary artery obstruction, reinforcing its prognostic and diagnostic utility in acute coronary presentations [45]. 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 [45].

For MCP-1; unlike IL-18, MCP-1 levels did not differ significantly between ACS and Non-ACS groups. This is a notable finding, as MCP-1 is conventionally understood to be a chemokine involved in monocyte recruitment to inflamed endothelium, a precursor to foam cell formation and plaque development, and the lack of statistical significance contrasts with some reports indicating elevated MCP-1 levels in ACS patients. For example, He observed significantly higher MCP-1 levels in STEMI patients compared to stable angina and healthy controls, attributing this to MCP-1's role in monocyte recruitment and plaque instability [46].

However, the present result consistent with a study of Ma who found no significant difference in MCP-1 levels between ACS and stable CAD, suggesting that MCP-1 may not consistently differentiate between disease states and with a study indicating that MCP-1 may be more reflective of chronic low-grade inflammation rather than acute plaque instability [47]. This finding diverges from studies suggesting MCP-1 as a chemokine that mediates monocyte recruitment to inflamed endothelium and promotes atherogenesis [48]. A study by Hernández-Presa emphasized that MCP-1 expression is sensitive to hemodynamic forces and oxidative stress, which may vary across patient populations. Additionally, the absence of association might reflect the fact that MCP-1 levels are more elevated during chronic stages of atherosclerosis or in subclinical inflammation rather than during acute events[49].

However, the lack of difference in this study might be attributable to many factors such as the sample size, population heterogeneity or timing of biomarker sampling. Additionally, variability in assay sensitivity could affect MCP-1 detectability. Furthermore, MCP-1 levels may not exhibit rapid fluctuation in response to acute events, as opposed to IL-18, which are more directly involved in the acute inflammatory response and tissue remodeling. Moreover, MCP-1 may plateau in both ACS and stable CAD patients due to chronic atherosclerotic activity, thus limiting its discriminatory power in acute settings. This interpretation is supported by Qintar *et al*. (2017), who noted that MCP-1 levels were not consistently predictive of short-term outcomes post-myocardial infarction, despite being elevated in cardiovascular disease. Therefore, while MCP-1 has been implicated in atherogenesis, its utility as a reliable biomarker that discriminate ACS from non-ACS remains uncertain and warrants further investigation [50].

Conclusion

The findings of this study showed that ACS patients had significantly higher levels of IL-18 but not MCP-1 compared with non-ACS patients, which support the role of IL-18 in the pathogenesis of ACS, and suggested the need for more studies to evaluate the diagnostic values of IL-18 and in distinguishing ACS from non-ACS

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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.

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