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The relationship between FABP And GDF-15 levels in evaluation with syntax score to predict the complexity of coronary artery lesion

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ABSTRACT: The complexity of coronary artery disease (CAD) lesions significantly influences patient outcomes and determines the choice of treatment approaches. For that reason, several classifications were established to grade these lesions and predict clinical outcomes effectively, which led to the discovery of the SYNTAX scores. Growth differentiation factor-15 (GDF-15) is a transforming growth factor that showed to increase significantly in various pathological conditions, including cardiovascular disease. Fatty acid-binding protein (FABP), a protein involved in lipid metabolism, has been implicated as a potential biomarker for CAD. So, the current study aimed to assess the levels of FABP and GDF-15 in association with the SYNTAX score to predict lesion complexity in CAD in a prospective comparative study that was conducted on 120 patients with CAD categorized according to SYNTAX score into low, intermediate, and high scores who were subjected to an assessment of the demographic factors, lipid profile, FABP and GDF-15 and compared with each other with an assessment of the association of the measured markers with the SYNTAX score. The results of the present work showed that as the syntax score went up, the levels of FABP and GDF-15 went up significantly, and the ROC curve results showed that the levels of GDF-15 have excellent discrimination ability in differentiating between patients with a high syntax score and patients with a low score with a sensitivity and specificity of 92% and 98%, whereas FABP showed a good discrimination ability which leads to the conclusion that levels of FABP and GDF-15 may be used in association as a predictor for the complexity of coronary artery lesions in parallel with SYNTAX score.

KEYWORDS: Coronary artery disease; SYNTAX score; growth differentiation factor-15; fatty acid-binding protein.

1. INTRODUCTION

In the field of cardiology, accurately predicting the complexity of coronary artery lesions is crucial for treatment decisions and patient management. The Syntax Score 2 is a valuable tool for assessing the complexity of coronary artery lesions in patients with coronary artery disease (CAD). Estimating the complexity of coronary artery lesions is essential for guiding treatment decisions and predicting patient outcomes. However, accurately assessing the complexity of coronary artery lesions can be challenging due to the multifactorial nature of the disease [1]. Additionally, the Syntax Score 2 takes into account not only anatomical characteristics of the coronary vasculature but also clinical factors, providing a comprehensive assessment of lesion complexity [2]. Fatty acid-binding protein (FABP), a protein involved in lipid metabolism, has been implicated as a potential biomarker for CAD. It was hypothesized that elevated FABP levels would be associated with higher syntax scores and increased lesion complexity [3-8]. FABP, GDF-15 levels were measured using enzyme-linked immunosorbent assays [(ELISA), and syntax scores were calculated based on angiographic findings. The complexity of coronary artery lesions was categorized into low, intermediate, and high groups. Our results showed a significant positive correlation between FABP, GDF-15 levels and syntax scores, indicating that higher FABP, GDF-15 levels were associated with more complex lesions. Furthermore, FABP, GDF-15 levels were found to be independently predictive of lesion complexity, even after adjusting for traditional risk factors [8-12]. These findings suggest that FABP, GDF-15

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may be a valuable biomarker for risk stratification and guiding treatment decisions in patients with CAD [12-16]. In the last years, biomarkers such as GDF-15 and FABP have gained attention due to their potential to offer deeper insights into the pathophysiological mechanisms underlying CAD. GDF-15, part of the transforming growth factor-beta (TGF-β) superfamily, is a stress-responsive cytokine expressed during cellular stress, inflammation, and tissue injury. Elevated levels of GDF-15 are linked to adverse cardiovascular outcomes, highlighting its role in regulating inflammation and apoptosis within the cardiovascular system [17-20].

Similarly, FABP, particularly the heart-type (H-FABP), is a small intracellular protein crucial for the uptake, transport, and metabolism of long-chain fatty acids. H-FABP is released into the bloodstream upon myocardial injury, serving as a valuable biomarker for detecting acute myocardial infarction and ongoing cardiac injury. Elevated H-FABP levels indicate poor outcomes in CAD patients, correlating with the extent of myocardial damage. Additionally, the lipid profile, encompassing total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-c), is a well-established set of biomarkers reflecting lipid metabolism and cardiovascular risk. Dyslipidemia, characterized by elevated levels of TC, TG, LDL-C, and low levels of HDL-c, is a major risk factor for atherosclerosis and CAD progression. The Syntax Score, developed during the SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) trial, is a robust tool for assessing the anatomical complexity of coronary artery lesions based on coronary angiography [21-23]. By evaluating lesion location, number, extent of stenosis, and anatomical complexities, the Syntax Score provides a quantitative measure of disease severity, guiding treatment decisions and predicting patient outcomes. Despite the individual significance of GDF-15, FABP, and lipid profiles, their combined use with the Syntax Score to predict coronary artery lesion complexity. Understanding the relationship between these biomarkers and the Syntax Score could enhance risk stratification and management of CAD patients by integrating biochemical and anatomical markers of disease severity [24-27].

The current study aimed to assess the relationship between FABP and GDF-15 in association with the SYNTAX score to predict lesion complexity in CAD patients in parallel with other CAD risk factors such as hypertension, diabetes mellitus, and high lipid indicis.

2. RESULTS AND DISCUSSION

2.1. Categorization of syntax score

According to the results obtained in the current study and in alignment with the previous studies, the syntax score was categorized into three categories: low (1-22.5), intermediate (23–31), and high (>31) [23]. The majority of patients subjected to the current study (n = 63, 52.5%) had a low syntax score, 44 patients (36.67%) had an intermediate score, and 13 patients (10.83%) had a high score (Figure 1).

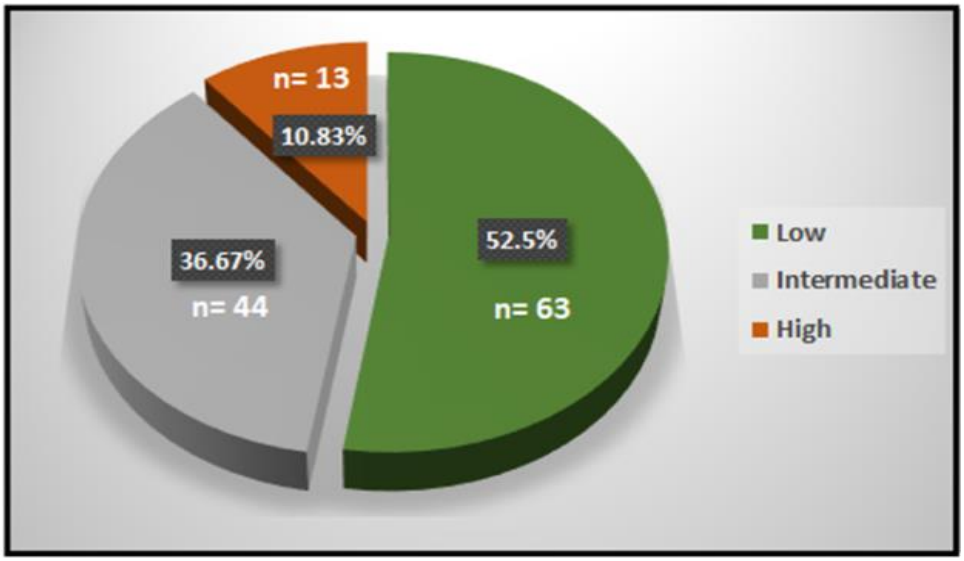

Figure 1. Distribution of patients according to SSII score

2.2. Association of FABP and GDF-15 with syntax score

Table 1 shows the association of FABP and GDF-15 with syntax score. Patients with high syntax score had higher level of FABP and GDF-15 (1.6±0.2 mg/dl and 410.36±90.22 mg/dl, respectively) than those with intermediate score (1.39±0.29 mg/dl and 298.32±72.46 mg/dl, respectively) or patients with low score (1.4±0.22 mg/dl and 212.22±57.44 mg/dl, respectively) with significant difference. Results also showed a significant difference in the levels of GDF-15 between patients with low and intermediate syntax score. On the other hand, the levels or FABP in patients with intermediate score were non significantly differ from those of patients with low score (Figure 2 and 3). These findings may indicate the significance of using GDF-15 and FABP in assessing the coronary artery lesions especially between patients with high score against those with intermediate and low SYNTAX score. Furthermore, the levels of GDF-15 showed more predictive ability as it showed to be significantly increased in patients with intermediate score comparing with those of patients with low SYNTAX score.

In accordance with the results obtained in the present study Several studies were conducted previously to explore the correlation between the syntax score and the levels of GDF-15 and their role in predicting the complexity of coronary artery lesions. These studies provide valuable insights into the potential role of GDF-15 as a biomarker in this context and demonstrate the predictive value of GDF-15 in patients with stable CAD undergoing elective percutaneous coronary intervention (PCI). They found that higher baseline GDF-15 levels were independently associated with an increased risk of major adverse cardiovascular events (MACE), defined as death, nonfatal heart attack, or cardiac revascularization, over a follow-up period of 3.7 years [28]. Importantly, adding the GDF-15 to a model including traditional risk factors and the syntax score significantly improved the predictive value of MACE [29–32].

Moreover, regarding FABP correlation with cardiac score, previous study demonstrated that there is a relationship between H-FABP and cardiac risk scores and showed that it can be used to evaluate the diagnosis and prognosis of patients with ACS. The main pathophysiological mechanism is the reduction of coronary flow due to thrombus formation on the plaque in ACS. Plaque erosion is responsible for 25% of patients [33]. Another study also revealed that H-FABP was a useful biomarker for worse outcomes due to its capability of predicting adverse clinical events in patients with stable CAD, suggesting that H-FABP might help to risk assessment in stable CAD [34].

Table 1. Association of FABP and GDF-15 with syntax score

Variables	Low (n= 63)	Intermediate (n=44)	High (n=13)	p-value
FABP				
Mean±SD	1.4±0.22[a]	1.39±0.29[a]	1.6±0.2[b]	0.026
Range	0.78-1.81	0.78-2.02	1.28-2.02	
GDF-15				
Mean±SD	212.22±57.44[a]	298.32±72.46[b]	410.36±90.22[c]	<0.001
Range	109.4-377.3	165.2-586.1	271.9-586.1	

Levels with the different letters in the same raw are significantly different

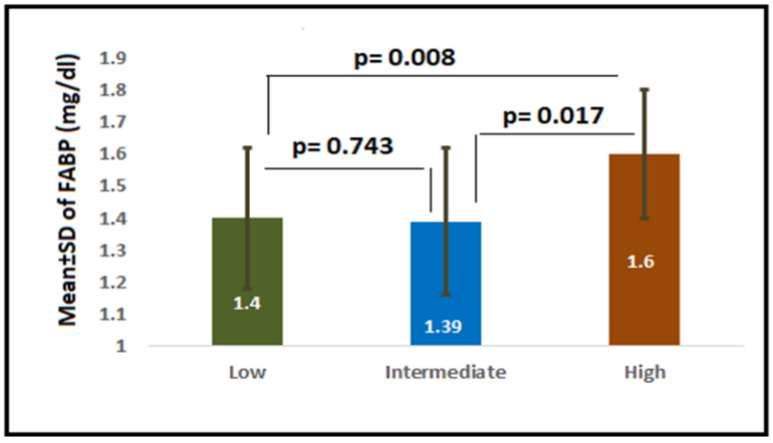

Figure 2. Mean serum level of FABP according to syntax score in patients with CHD

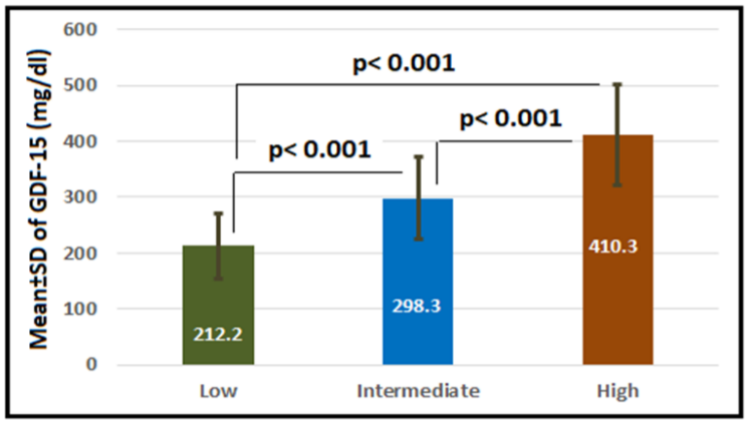

Figure 3. Mean serum level of GDF-15 according to syntax score in patients with CHD

2.3. The context of discrimination between high and intermediate syntax score

As a conformation to results presented above, ROC curve analysis was performed and showed that for GDF-15, the AUC was 0.863, 95%CI= 0.756-0.969, p<0.001. The best cut of value was 345 mg/dl. At this cut off value the sensitivity and specificity of the test was 85% and 75%, respectively. For FABP, the AUC was 0.684, 95%CI= 0.543-0.824, p=0.046. The best cut of value was 1.6 mg/dl. At this cut off value the sensitivity and specificity of the test was 62% and 66%, respectively (Figure 4). These results may show that the discrimination efficiency of GDF-15 was higher than that of FABP which is in agreement with previous study which reported that there was a significant elevated levels of GDF-15 in stable CAD patients versus a healthy control group which might be used for the discrimination between patients at high risk versus those on low risk of cardiovascular problems [35], and also agreed with that postulated by Zeren et al who demonstrated that H-FABP is a useful marker for the diagnosis and risk evaluation of patients with non-ST elevation ACS but it is insufficient in evaluating the severity of CAD [36].

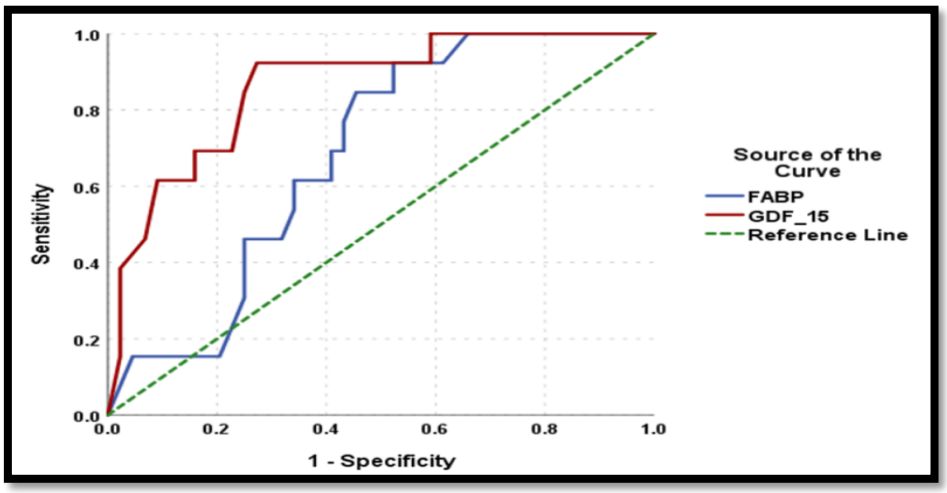

Figure 4. Receiver operating characteristic curve for GDF-15 in the context of discrimination between intermediate and high syntax score

2.4. The context of discrimination between high and low syntax score

For GDF-15, the AUC was 0.981, 95%CI= 0.950-1.00, p<0.001. The best cut of value was 321 mg/dl. At this cut off value the sensitivity and specificity of the test was 92% and 98%, respectively. For FABP, the AUC was 0.744, 95%CI= 0.604-0.883, p=0.046. The best cut of value was 1.57 mg/dl. At this cut off value the sensitivity and specificity of the test was 62% and 76%, respectively (Figure 5). In a pattern similar to that mentioned before, GDF-15 levels showed excellent efficiency in discriminating between patients with high SYNTAX scores and those with low scores, whereas FABP showed a fair efficiency to discriminate patients with high scores from those with low scores.

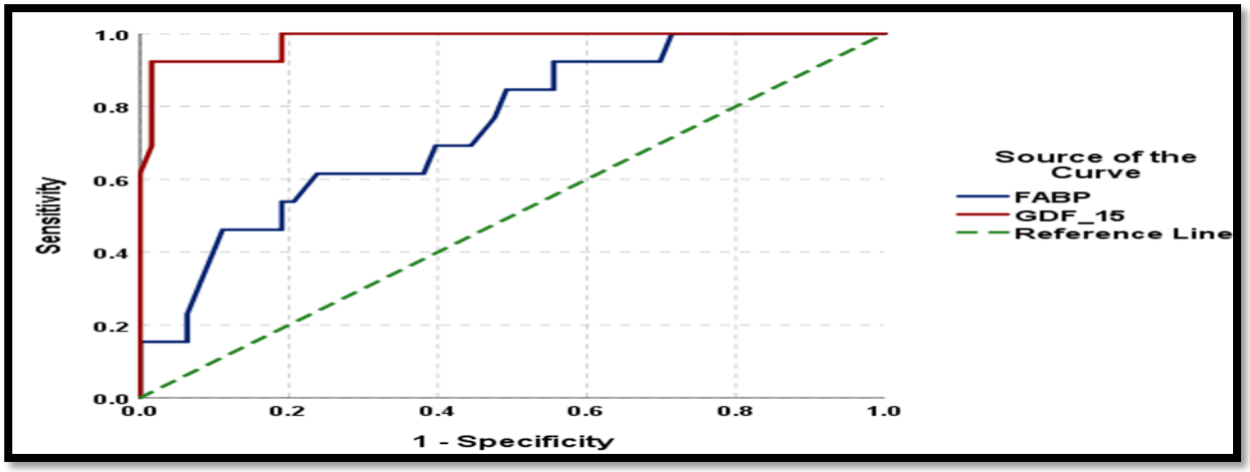

Figure 5. Receiver operating characteristic curve for GDF-15 in the context of discrimination between intermediate and high syntax score

The greater levels of FABP and GDF-15 in patients with higher Syntax scores with the good results that obtained from the ROC curve analysis indicate that these biomarkers may represent the severity and complexity of CAD. Higher FABP levels in patients with severe CAD may indicate more extensive heart damage and ongoing inflammatory processes. The considerable difference in FABP levels amongst Syntax score groups highlight its potential usefulness in determining CAD complexity. This is consistent with prior research, which has highlighted FABP's significance in acute coronary syndromes and its predictive relevance in CAD patients [37-40].

GDF-15 is known for its function in inflammation, cell proliferation, and apoptosis, and greater levels in individuals with high Syntax scores imply it may be involved in advanced atherosclerotic disease. GDF-15's capacity to reflect both inflammatory and oxidative stress pathways may account for its substantial relationship with more complex and extensive coronary lesions. These findings are consistent with previous research that has identified GDF-15 as a predictor of unfavorable cardiovascular outcomes and its link with disease severity [41-44].

2.5. Correlation of syntax score, FABP and GDF-15 with lipid profile, age and BMI

Pearson's correlation was used to explore the possible correlation of syntax score FABP and GDF-15 with lipid profile, age and BMI. The results are shown in Table 2. Syntax score displayed a significant positive correlation with each of age (r= 0.252, p= 0.005), BMI (r= 0.317, p< 0.001), TC (r= 0.211, p= 0.008), TG (r= 0.263, p= 0.004), FABP (r= 0.199, p= 0.029) and GDF-15 (r= 0.723, p<0.001), whereas syntax score had a significant negative correlation with HDL-C (r= -0.197, p= 0.031).

On the other hand, GDF-15 demonstrated a significant positive correlation with each of BMI (r= 0.415, p<0.001), TC (r= 0.551, p<0.001), TG (r= 0.439, p< 0.001), LDL-C (r= 0.401, p<0.001) and very low-density lipoprotein cholesterol (VLDL-C) (r= 0.448, p<0.001).

Finally, FABP displayed a significant positive correlation with GDF-15 (r= 0.303, p= 0.001).

High HDL levels minimize the chance of developing atherosclerosis. HDL particles may prevent atherosclerosis by promoting reverse cholesterol transfer and inhibiting inflammation, thrombosis, and oxidation [45,46]. The current study supports the previous findings which demonstrated that CHD patients have considerably reduced levels of HDL cholesterol [47].

VLDL, a kind of bad cholesterol heavy in triglycerides, accumulates in the arteries. VLDL levels were lower than in other groups and significantly different from those in the control group. Because TG in the control group was higher than TG.

The significant correlations between elevated levels of total cholesterol (TC), triglycerides (TG), LDL-C, and VLDL-C with higher Syntax scores underscore the critical role of lipedema in the development of coronary artery disease (CAD). Increased levels of LDL-C and VLDL-C contribute to the formation and progression of atherosclerotic plaques, leading to more complex and severe coronary artery lesions, as evidenced by higher Syntax scores. Similarly, elevated TG levels are linked to a higher residual risk of cardiovascular events, likely due to their role in creating small, dense LDL particles that are highly thermogenic [48-50]

The lack of a significant association between HDL-C and the Syntax score may be attributed to several factors. Although HDL-C is known for its protective effects against atherosclerosis through reverse cholesterol transport, its levels alone may not fully capture its functionality or the complex interactions between various lipid components and other risk factors that influence CAD severity [51,52].

Table 2. Pearson's correlation of syntax score, FABP and GDF-15 with lipid profile, age and BMI

Variables		Syntax	FABP	GDF-15
Age	r	0.252	-0.042	0.131
	p	0.005	0.645	0.155
BMI	r	0.317	0.057	0.415
	p	<0.001	0.540	<0.001
TC	r	0.241	0.142	0.551
	p	0.008	0.122	<0.001
TG	r	0.407	0.099	0.439
	p	<0.001	0.280	<0.001
HDL-c	r	-0.197	0.048	-0.070
	p	0.031	0.603	0.447
LDL-C	r	0.328	0.084	0.401
	p	<0.001	0.367	<0.001
VLDL-C	r	0.263	0.107	0.448
	p	0.004	0.246	<0.001
FABP	r	0.199		
	p	0.029		
GDF15	r	0.723	0.303	
	p	<0.001	0.001	

3. CONCLUSION

The study's findings show that specific biomarkers have strong relationships with the Syntax score, a well-established measure of coronary artery disease (CAD) complexity. In particular, patients with high Syntax scores had considerably higher levels of FABP (Fatty Acid-Binding Protein) and GDF-15 (Growth Differentiation Factor-15) than those with intermediate or low scores.

4. MATERIALS AND METHODS

4.1. Study protocol

The study was conducted at Al Naharin University's Department of Chemistry and Biochemistry, College of Medicine. The research involved participants from the Coronary Care Unit at Al-Imamian Al-Kadhimiyain Medical City, Ibn Al-Bitar Cardiac Center in Baghdad, and the Karbala Cardiac Center in Karbala, Iraq. They were patients diagnosed with acute coronary syndrome (ACS) by cardiologists. During the study period, from April to November 2023, 120 patients aged 40 years or older were selected as ACS cases from 356 admitted patients, with 236 excluded due to specific criteria. Diagnosis for ACS, including unstable angina, non-ST-segment, and ST-segment elevation myocardial infarction, was determined using clinical presentation, ECG changes, and, when necessary, cardiac enzyme levels. Blood samples and cardiac enzyme measurements, such as AST, were taken upon admission to the CCU.

Electrocardiogram assessments were carried out using equipment from BIOMED Company, USA, with skilled nurses conducting the recordings and a specialist cardiologist supervising. For control subjects, fasting for 8–14 hours were required prior to blood sample collection. Patient data were gathered via a questionnaire upon CCU admission, probing onset time of chest pain, medical history including CHD, hypertension, diabetes, and lifestyle factors such as smoking, statin use, and alcohol consumption.

Calculations of Body Mass Index were based on the formula:

BMI (kg/m2) = Weight in kilograms / [height (m)]^2

4.2. Exclusion criteria

Patients meeting any of the following criteria were not included in the study:

1.Admission to the hospital occurring more than 36 hours after the onset of chest pain.

2.Presence of renal failure as per diagnostic criteria (absolute increase in serum creatinine of 0.3 mg/dl or a percentage increase of 50%, or patients already undergoing dialysis).
3.History of stroke, skeletal muscle injury, or trauma.
4.Use of statins or any other hypolipidemic drugs.
5.Age less than 30 years.
6.Abdominal enlargement due to causes other than central obesity.
7.Patients of non-Iraqi nationality.
8.Previous participation in the current study.
9.Known history of thyroid, hepatic, or malignant disease.
10.Anemia (Hemoglobin <9g/dl for males and <8g/dl for females).
11.History of drug abuse or alcohol consumption.
12.Presence of concurrent infectious diseases.
13.Valvular heart disease.
14.Inability to determine the onset or cessation time of symptoms (if pain was not persistent at presentation).

Additionally, individuals were categorized as smokers if they were current smokers or had smoked within the past 30 days. A never-smoker was defined as someone who had never smoked or had not been a daily smoker and had consumed less than 100 cigarettes (or an equivalent amount of tobacco) in their lifetime.

Family history of coronary heart disease (CHD) was established as a history of CHD in first-degree male relatives before age 55 years or female relatives before age 65 years (including parents, siblings, and offspring) who experienced angina, myocardial infarction, or sudden cardiac death without an obvious cause at that age or younger.

4.3. Inclusion Criteria

The study encompassed adult individuals presenting with chest pain or typical symptoms indicative of Acute Coronary Syndrome (ACS) at the emergency department. Patients aged 18 years and above, diagnosed by a physician, were included in the analysis.

All participants in the control and patient group were required to fast for 8 to 14 hours prior to blood specimen collection. Consent was obtained from all control group subjects after explaining the purpose of the study.

The study has approved by the Institutional Review Board (IRB) of the College of Medicine, University of Al-Nahrain, Baghdad, Iraq. In addition, an informed written consent for participation in the study was signed by investigated subjects according to the Helsinki principles (Number 2/3/340 in 23/02/2023).

4.4. Specimen collection

Five milliliter venous blood sample were drawn from each patient, following the same procedure for the control group. These blood samples were then placed in clean tubes and allowed to clot at room temperature for a maximum of thirty minutes. Subsequently, the clotted samples underwent centrifugation to obtain serum, which was divided into five portions:

1. Another portion of serum was transferred to a 0.5 ml Eppendorf tube to measure growth differentiation factor -15., also stored at -20°C until analysis using ELISA technique according to manufacturer instructions.
2. Another portion of serum was placed into a 0.5 ml Eppendorf tube for the evaluation of Heart type fatty acid binding protein kept at -20°C until analysis of FABP using ELISA technique according to manufacturer instructions.

4.5. Statistical Analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were presented as mean and standard deviation, and analyzed with analysis of variance (ANOVA). Least significant difference (LSD) was used as a post hoc analysis. Categorical variables were analyzed with Chi square. Receiver operating characteristic curve (ROC) was used to evaluate the discriminative value of FABP and GDF-15 in the context of discrimination between low, intermediate and high syntax score. Pearson's correlation test was used to explore the possible correlation FABP and GDF-15

with lipid profile, age and BMI. A p- value less than 0.05 was considered to indicate a statistically significant difference [53,54].

Author contributions: Concept – R.A.; Design – R.A., M.H.; Supervision – R.A., M.H.; Resources – R.T.; Materials – R.T.; Data Collection and/or Processing – R.T., M.H.; Analysis and/or Interpretation – R.T., M.H.; Literature Search – R.T.; Writing – R.T.; Critical Reviews – R.A., M.H.

Conflict of interest statement: "The authors declared no conflict of interest" in the manuscript.

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