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The role of growth differentiation factor -15 (GDF-15) levels in association with syntax score in predicting 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 SYNergy between percutaneous coronary intervention (PCI) with TAXUS™ and cardiac surgery (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. So, the current study aimed to assess the levels of 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 categorised according to SYNTAX score into low, intermediate, and high scores who were subjected to an assessment of the demographic factors, lipid profile, 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 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%, which leads to the conclusion that levels of GDF-15 may be used as a predictor for the complexity of coronary artery lesions in parallel with SYNTAX score.

KEYWORDS: Coronary artery disease; growth differentiation factor-15; lipid profile; SYNTAX score.

1. INTRODUCTION

Diabetes mellitus, hypertension, overweight, high cholesterol levels, and tobacco use are critical factors contributing to the onset and advancement of coronary artery disease (CAD). These elements are extensively supported by research for their role in CAD risk [1]. High blood pressure damages the inner lining of arteries, leading to the dangerous plaque formation that underlies CAD, with substantial research confirming its role in increasing the likelihood of heart attacks and strokes [2]. Elevated levels of "bad" LDL cholesterol and reduced levels of "good" HDL cholesterol are known to escalate CAD risk [3]. People with diabetes face a significantly higher risk of developing CAD, partly due to the harmful effects of high blood sugar on blood vessels and the prevalence of other risks like high blood pressure and abnormal lipid profiles [4]. Carrying excess weight, particularly around the midsection, can independently elevate the risk for CAD as a result of adipose tissue accumulation [4,5]. Smoking cigarettes is a major preventable risk factor for CAD, as it causes direct damage to blood vessel walls, contributes to systemic inflammation, decreases good HDL cholesterol levels, and fosters clot formation within the arteries [6–8].

The SYNergy between Percutaneous Coronary Intervention (PCI) with TAXUS™ and Cardiac Surgery (SYNTAX) score evaluates the complexity of coronary blockages by reviewing angiographic data, counting the number and positioning of blockages, and their severities, to calculate a score reflecting the overall condition's gravity. It is seen as a reliable predictor due to its meticulous inclusion of all significant stenoses, anatomical detail-oriented approach, ability to direct revascularization strategy, and predictive power in gauging cardiovascular risks [9, 10]. This makes the SYNTAX score an essential tool for risk

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stratification and guiding treatment in complex CAD cases, enhancing prognostication and patient management. The SYNTAX score differs from traditional methods by providing a more detailed and systematic evaluation of the anatomical complexities of the coronary vasculature, and the key points of differentiation include angiographic detail, quantitative scoring, a focus on lesion complexity, standardization, and procedural planning. In summary, the SYNTAX score offers a granular, angiography-based approach to CAD assessment, enhancing treatment planning accuracy [11–14].

Growth differentiation factor-15 (GDF-15), which is considered one of the transforming growth factor beta cytokine family members [15, 16]. It is expressed at low levels in most normal tissues but can be significantly elevated in various pathological conditions, including cardiovascular disease [7, 8]. GDF-15 is involved in a wide range of biological processes, such as inflammation, oxidative stress, and cardiovascular remodelling, which makes it a promising biomarker of CAD complexity [9, 10]. Several studies have linked the increments in GDF-15 levels with adverse cardiovascular events and poor prognosis in patients with stable CAD and acute coronary syndromes [17–19]. In addition, GDF-15 showed to provide prognostic information that may surpass that provided by traditional risk factors and biomarkers, such as high-sensitivity C-reactive protein (hs-CRP) and bovine B-type natriuretic peptide (NT-pro BNP) [20, 21]. Despite this growing body of evidence, the specific role of GDF-15 in CAD is still not fully known, especially in the context of complex coronary artery lesions [22].

The current study aimed to assess the levels of 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).

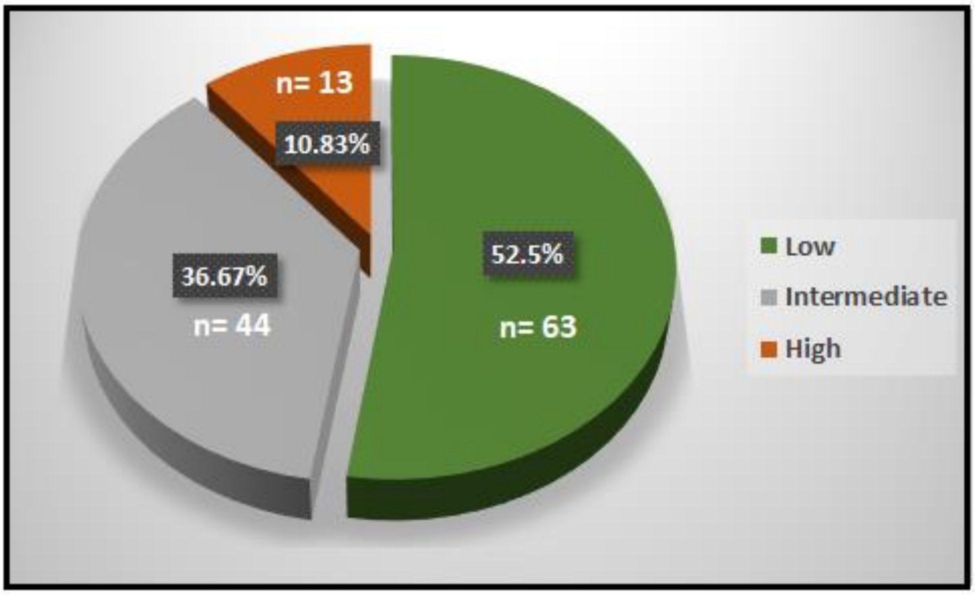

Figure 1. Distribution of patients according to SSII score

2.2 Association of demographic factors with syntax score

Results illustrated in Table 1 illustrated that patients with a high syntax score showed a mean age of 68.31±6.72 years, which is significantly higher (p<0.05) than the mean age of patients who have an intermediate score (62.91±9.1 years) or those with a low score (60.4±9.33 years), and these results agreed with previously published research that reported that ageing is considered an independent risk factor that has a significant effect on the complexity of CAD and high syntax score results. So, patients with old age are expected to have a more complicated CAD than younger patients, which is due to the fact that vascular endothelium functions become dimenshed with ageing, which is also accompanied by a progression in arterial sclerosis [24], which was also confirmed by another study that concluded that for the two-year mortality there is a significant interaction between age and SYNTAX-score [25].

Likewise, the mean body mass index (BMI) in patients with a high syntax score was 35.79±5.04 k/m2, which was significantly higher than that of patients with an intermediate score (32.76±3.85 k/m2) and those with a low score (31.52±3.94 k/m2), with a significant difference. These results disagree with those obtained previously by Al Kersh et al., who stated that BMI cannot be considered an independent risk factor for CAD complexity according to their results [24], but this study was conducted on a small number of CAD patients (52) which made their result not fully reliable, whereas another study conducted on 600 patients showed a result that agreed with the results of the current study in that the highest BMI was obtained with patients having the highest syntax score [26], which is caused by the obesity effects on cardiovascular risk factors and also due to the fact that obese patients showed a higher prevalence of CAD [27].

Results regarding other CAD risk factors revealed that the frequency of hypertension and T2DM was more common among patients with a high syntax score (92.31% and 84.62%, respectively) than those with an intermediate score (63.64% and 68.19%, respectively) or those with a low score (51.47% and 50.79%, respectively), with significant differences among these subgroups. These results are completely consistent with those obtained by Saha and his colleagues, who demonstrated that hypertensive patients showed a significantly higher syntax score than that of normo-tensive patients, and they also demonstrated that the syntax score increased with an increase in the fasting blood sugar and glycosylated hemoglobin levels. The explanation of these results was obtained from the previously reported article, which stated that the infarct-related artery in diabetic patients showed a significantly smaller minimal lumen diameter in comparison with that in non-diabetics, so diabetics suffer from a higher prevalence of diffuse and extensive coronary atherosclerosis [26]. Several studies link hypertension with the high syntax score [24–28] and attribute that to the pathophysiological process of blood pressure that exerts a mechanical force that affects atherosclerotic plaque growth, as well as the correlation between arterial stiffness, pulsating hemodynamics, and coronary perfusion [28, 29].

Results illustrated in Table 1 showed that despite smoking being more common among patients with a high syntax score (69.23%) than either patients with an intermediate score (50%) or a low score (30.1%), the difference was not significant among the studied groups, which is similar to a previous study which stated that there is no significant difference in syntax score between smoking and non-smoking patients with ischemic heart disease [26]. On the other hand, the results also showed a significant difference in smoking habit between patients with a high score in comparison with low score patients, which is consistent with several previous studies which reported that smoking was considered a significant independent risk factor for CAD complexity and high syntax score results, which are caused by the smoking effect that results in atherogenesis, vasomotor dysfunction, and thrombosis in multiple vascular beds [24,28,30]

Table 1. Association of demographic factors with syntax score

Variables		Low (n= 63)	Intermediate (n=44)	High (n=13)	p-value
Age, years	**Mean±SD**	60.4±9.33a	62.91±9.1a	68.31±6.72b	0.014
	Range	42-79	48-79	57-78	
Gender	**Male**	46(73.02%)	26(59.0(%)	11(84.62%)	0.136
	Female	17(26.98%)	18(40.91%)	2(15.38%)	
BMI, kg/m2	**Mean±SD**	31.52±3.94a	32.76±3.85a	35.79±5.04b	0.008
	Range	22.53-44.96	25.43-43.93	29.4-45.67	
Risk factors	**HTN**	35(51.47%)	28(63.64%)	12(92.31%)	0.044
	DM	32(50.79%)	30(68.19%)	11(84.62%)	0.034
	Ex/current smoking	24(30.1%) a	22(50%) ab	9(69.23%) b	0.096

2.3. Association of lipid profile parameters with syntax score

With the exception of HDL-C, all components of the lipid profile were significantly associated with the syntax score. The TG and TC in patients with high syntax score were 214.31±49.77 mg/dl and 218.34±11.91 mg/dl, respectively, which was significantly ($p<0.05$) higher than that of patients with intermediate score (170.26±37.5 mg/dl and 203.0±31.2 mg/dl, respectively) or those with low score

(163.6±51.81 mg/dl and 181.85±33.14 mg/dl, respectively). Similarly, patients with a high syntax score had a higher level of LDL-C and VLDL-C (142.94±18.4 mg/dl and 42.81±9.88 mg/dl, respectively) than those with an intermediate score (138.0±31.14 mg/dl and 34.06±7.5 mg/dl, respectively) or patients with a low score (118.23±36.76 mg/dl and 32.47±9.96 mg/dl, respectively) with a significant difference (Table 2). Several studies demonstrated similar results, but with differences in the significant results obtained. For instance, Mohammed et al. demonstrated that LDL levels increased significantly in patients with high syntax scores, which was accompanied by a significant decrease in the HDL level [28], which was already concluded in previous work which demonstrated that dyslipidaemia has been linked to more severe forms of CAD [24].

Table 2. Association of lipid profile parameters with syntax score

Variables		Low (n= 63)	Intermediate (n=44)	High (n=13)	p-value
TG	Mean ± SD	163.6±51.81a	170.26±37.5b	214.31±49.77b	0.002
	Range	83.13-283.9	99.89-283.13	148.97-295	
TC	Mean ± SD	181.85±33.14a	203.0±31.2b	218.34±11.91c	<0.001
	Range	115.83-260.6	142.86-316.6	202.78±239.8	
HDL	Mean ± SD	33.34.78±10.15	31.58±9.31	29.5±4.54	0.122
	Range	15.48-64.39	21.3-58.64	25-39.18	
LDL, mg/dl	Mean ± SD	118.23±36.76a	138.0±31.14b	142.94±18.4c	0.004
	Range	29.98-195.29	80.28-235.31	120.67-175.51	
VLDL	Mean ± SD	32.47±9.96a	34.06±7.5a	42.81±9.88b	0.001
	Range	16.63-56.79	19.98-56.63	29.79-58.93	

2.4. Association of GDF-15 levels with syntax score

The results of the present work, illustrated in Figure 2, show that as the syntax score went up, the levels of GDF-15 went up significantly (p<0.05), which is evident in the significant elevation in GDF-15 levels in patients with high scores compared to those with intermediate scores, which in turn showed significantly higher GDF-15 levels than those in patients with low syntax scores.

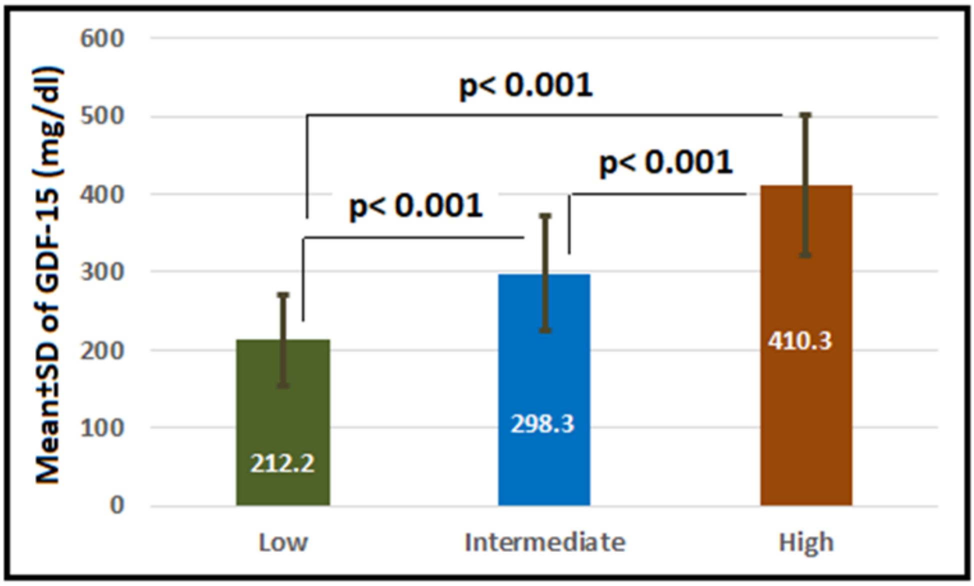

Figure 2. Mean serum level of GDF-15 according to syntax score in patients with coronary heart disease (CHD)

These significant increases in GDP-15 levels were confirmed by the receiver operating characteristic (ROC) curve results illustrated in Figure 3, which showed that the area under the curve (AUC) of GDF-15 was 0.829, 95% CI = 0.754–0.905, p<0.001. The best cut-off value was 254 mg/dl. At this cut-off value, the sensitivity and specificity of the test were 75% for each in the discrimination between patients with intermediate and low syntax scores that were considered good discriminating factors.

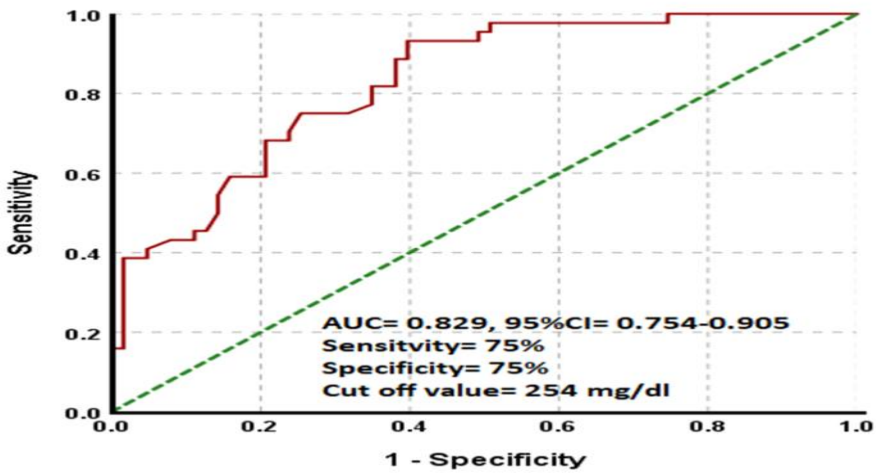

Figure 3. ROC curve for GDF-15 levels in patients with intermediate syntax score comparing with low score patients.

Moreover, in a discrimination between patients of high and intermediate syntax score, GDF-15 levels showed an AUC of 0.863, 95%CI= 0.756-0.969, p<0.001 with a best cut of value of 345 mg/dl at which the sensitivity and specificity of the test was 85% and 75%, respectively which indicate that this marker can be considered as discriminator marker with a very good sensitivity and good specificity as illustrated in Figure 4.

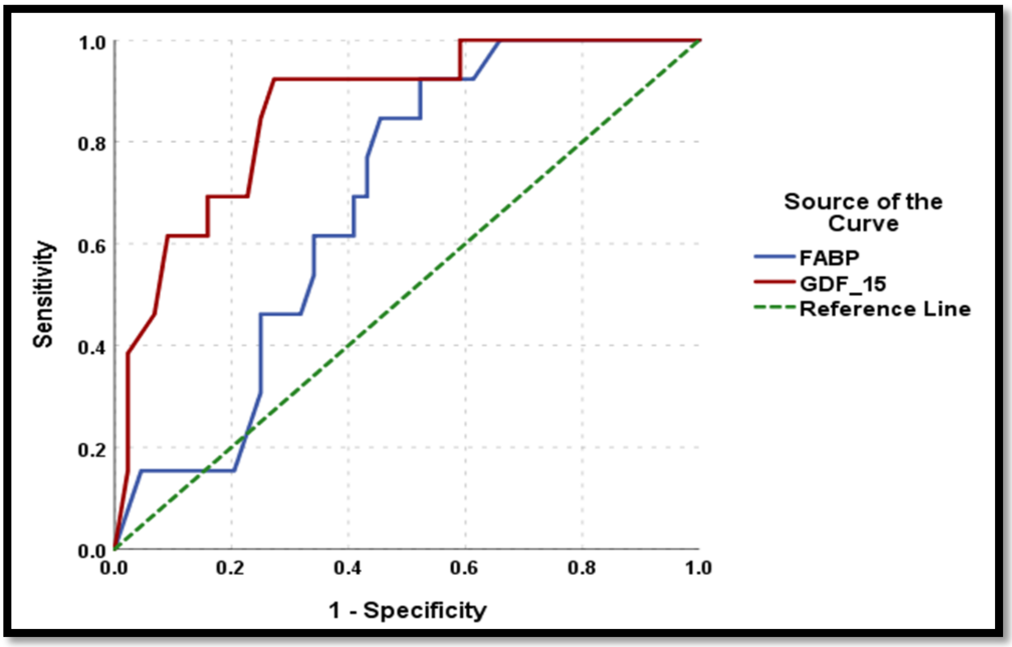

Figure 4. ROC curve for GDF-15 levels in patients with intermediate syntax score comparing with high score patients.

In addition to the above ROC curve results, the levels of GDF-15 showed excellent discrimination ability in differentiating between patients with a high syntax score and patients with a low score, as demonstrated clearly in figure 5, which showed that the AUC for GDF-15 was 0.981, 95%CI= 0.950-1.00, p<0.001 with a best cut of value of 321 mg/dl, at which the sensitivity and specificity of the test were 92% and 98%, respectively. Finally, the Roc curve results demonstrate that GDF-15 can be considered a powerful marker for CAD complexity because it has the ability to discriminate between the three categories of syntax scores.

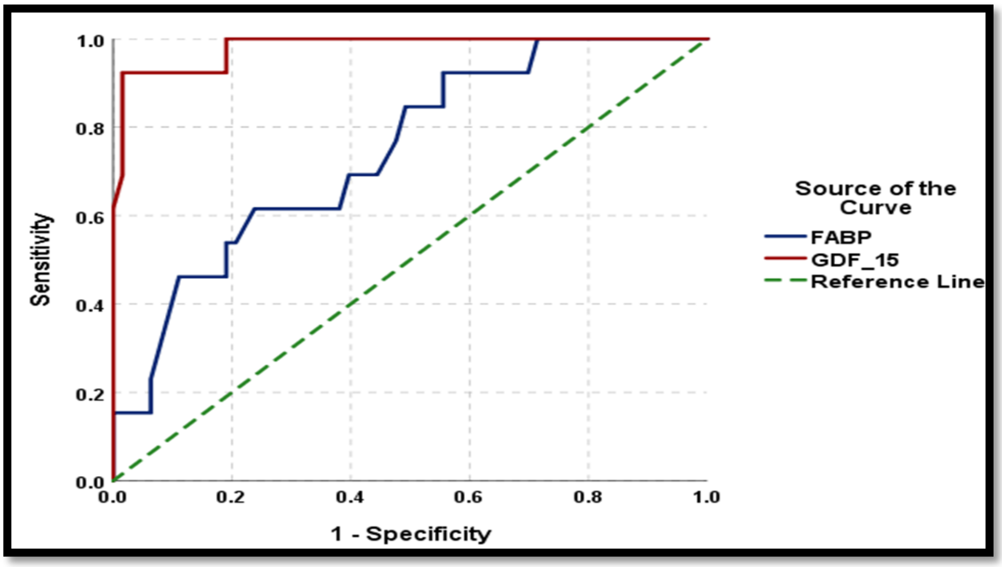

Figure 5. ROC curve for GDF-15 levels in patients with high syntax score comparing with low score patients.

In the current study, possible correlations of syntax score and GDF-15 with lipid profile, age, and BMI were evaluated by Pearson's correlation test, which is illustrated in Table 3, which revealed that positive (direct) significant correlations were obtained between syntax score with both age (r = 0.252, p = 0.005) and BMI (r = 0.317, p< 0.001) and also showed to correlate directly and significantly with the levels of GDF-15 (r = 0.723, p<0.001), TC (r = 0.211, p = 0.008), and TG (r = 0.263, p = 0.004). On the contrary, the levels of HDL-C were negatively (inversely) and significantly correlated (r = -0.197, p = 0.031) with the syntax score. Additionally, levels of GDF-15 were correlated positively and significantly with each of BMI (r = 0.415, p<0.001) and the levels of TC (r = 0.551, p<0.001), TG (r = 0.439, p<0.001), LDL-c (r = 0.401, p<0.001), and VLDL-C (r = 0.448, p<0.001).

Table 3. Pearson's correlation of syntax score, GDF-15 with lipid profile, age and BMI

Variables		Syntax	GDF-15
Age	r	0.252	0.131
	p	0.005	0.155
BMI	r	0.317	0.415
	p	<0.001	<0.001
TC	r	0.241	0.551
	p	0.008	<0.001
TG	r	0.407	0.439
	p	<0.001	<0.001
HDL-c	r	-0.197	-0.070
	p	0.031	0.447
LDL-c	r	0.328	0.401
	p	<0.001	<0.001
vLDL-c	r	0.263	0.448
	p	0.004	<0.001
GDF15	r	0.723	
	p	<0.001	

Collectively, the present study enlisted 120 patients with established CAD. On the basis of baseline characteristics such as demographic information, medical history, and cardiovascular risk factors, coronary angiography was then performed, and syntax scores were computed to gauge the complexity of coronary artery lesions. We observed a substantial positive correlation between Growth Differentiation Factor-15 levels and Syntax scores, with a correlation coefficient (r) of 0.72 indicating a strong positive relationship and a highly significant p-value (< 0.001), underscoring the robustness of this association. Specifically, patients presenting with elevated GDF-15 concentrations were found to have a higher likelihood of possessing complex coronary artery lesions, as indicated by increased Syntax scores. This was further bolstered by the observation that high GDF-15 levels were predictive of a heightened risk of adverse cardiovascular events.

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 [31] 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. Importantly, adding the GDF-15 to a model including traditional risk factors and the syntax score significantly improved the predictive value of MACE [32–35]. Similarly, Sabirzyanova et al. investigated the association between GDF-15 and adverse outcomes in patients with triple-vessel disease or CAD of the left main artery undergoing coronary artery bypass graft surgery (CABG) or PCI. They reported that high GDF-15 levels before the procedure were associated with an increased risk of MACE, defined as death, heart attack, or stroke, during a follow-up period of 3.4 years [36].

The strong correlation between GDF-15 levels and increased Syntax scores suggests that GDF-15 may serve as a useful indicator of lesion severity and could be instrumental in risk stratification for CAD patients. This association is of clinical relevance, as patients with complicated coronary artery lesions, as denoted by higher Syntax scores, are often subject to a greater risk of negative procedural outcomes and may require more intensive management strategies. Thus, GDF-15 could play an essential role in the management and therapeutic planning of such patients.As reported before by Nar et al. [35] and Kożuch et al. [37], GDF-15 levels were independently associated with the presence and extent of coronary artery disease, as determined by the syntax score, in a group of patients undergoing elective cardiac catheterization [38]. Previous literature regarding GDF-15 identified a significant elevated levels in stable CAD patients versus a healthy control group. High GDF-15 was also linked to a heightened risk of cardiovascular events like death and heart attacks over the course of two years. In a comparable vein, several studies have suggested that GDF-15 is considerably increased in individuals with notable CAD, as evidenced by major artery stenosis [39–45].The possible explanation for this association between GDF-15 and syntax score is due to the fact that GDF-15 has been thoroughly studied in connection with the progression of atrial fibrillation, CHD, myocardial infarction, and heart failure. Studies have shown a positive correlation between serum norepinephrine levels, the thickness of the posterior wall, and left ventricular mass in cases of hypertensive heart disease or ventricular hypertrophy. These higher levels of GDF-15 indicate potential cytoprotective actions of GDF-15 [46].

3. CONCLUSION

Results obtained in the current study revealed that there is a strong link between the levels of GDF-15 and coronary lesion complexity and cardiovascular risk. Additionally, the evaluation of GDF-15 alongside other biomarkers could enhance our understanding of cardiovascular pathophysiology and aid in the development of composite risk assessment models. It's also imperative to consider the implementation of these findings in routine clinical practice, which entails evaluating

4. MATERIALS AND METHODS

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 was 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

Additionally, socio-demographic information such as age, gender, place of residence, education level, and marital status were recorded, along with measurements of weight and height for BMI computation. Levels of GDF-15 were measured using a sandwich ELISA according to manufacturer instructions.

4.1. Exclusion criteria

1. Patients who are admitted to the hospital more than 36 hours after the start of chest pain.
2. Patients with renal failure
3. History of stroke, skeletal muscle injury, or trauma.
4. Anemia.
5. Use of statins or any other hypolipidemic drugs.
6. Presence of concurrent infectious diseases.
7. Age less than 30 years.
8. Abdominal enlargement due to causes other than central obesity.
9. Patients of non-Iraqi nationality.
10. Previous participation in the current study.
11. Valvular heart disease.
12. Known history of thyroid, hepatic, or malignant disease.
13. History of drug abuse or alcohol consumption.
14. Inability to determine the onset or cessation time of symptoms (if pain was not persistent at presentation).

4.2. Inclusion Criteria:

The study encompassed adult individuals presenting with chest pain or typical symptoms indicative of ACS at the emergency department. Patients aged 18 years and older, diagnosed by a physician, were included in the analysis. All participants in the control and patient groups 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 purpose of the ELISA kit mentioned in the article is to measure the concentration of human GDF15 using the sandwich-ELISA technique. The kit provides a pre-coated micro-ELISA plate and specific antibodies to detect human GDF15 levels in samples through color changes, aiding in quantifying the protein's concentration.

4.3. Statistical Analysis

The statistical analyses were conducted using SPSS software version 25.0. The numerical data were reported as the mean and standard deviation and were analyzed using the analysis of variance (ANOVA) test and the post hoc analysis using the least significant difference (LSD) method. The analysis of categorical variables was conducted using the Chi-square test. The discriminative value of GDF-15 in distinguishing between low, moderate, and high syntax scores was assessed using ROC curve analysis. The Pearson's correlation test was employed to investigate the potential link between GDF-15 and lipid profile, age, and BMI. A p-value below 0.05 is considered statistically significant [47, 48].

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