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Evaluation of Insulin-like Growth Factor Binding Protein 2 (IGFBP2) Efficacy in Classifying Risk Groups in Patients with Non-ST elevation Acute Coronary Syndrome (NSTE-ACS) According to the Reynolds Risk Score

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Abstract

Background: Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)as subtypes of non-ST elevation acute coronary syndrome (NSTE-ACS), with NSTEMI characterized by acute myocardial necrosis detectable through cardiac biomarkers. The Reynolds score is a predictive tool that assesses the likelihood of cardiovascular events over the next ten years based on various criteria. Insulin-like Growth Factor Binding Protein 2(IGFBP2), a member of the IGFBP family, interacts with IGFs in the circulatory system to regulate their activity.

Objectives: This study aimed to investigate the relationship between serum IGFBP2 levels and Reynolds scores in patients with NSTE-ACS. with the objective of classifying the risk into three categories: low, medium and high.to assist doctors in evaluating the level of risk based on clinical criteria.

Methods: case-control study included 90 individuals divided into three groups: NSTEMI patients, unstable angina patients, and a control group. The study collected clinical and demographic data, including age, sex, BMI, family history of coronary disease, medical history.

Result: patients with NSTE-ACS showed no significant differences in IGFBP2 levels(p=0.560). among patients categorized into low, medium, and high-risk groups based on the Reynolds score, there was no statistically significant variance in IGFBP2 levels(p=0.750).

Conclusion The study discovered that there were no significant variations in the level of IGFBP2 among the three risk categories defined by the Reynolds Score in individuals with NSTE-ACS. Therefore, it was not possible to classify individuals into Low, medium and high-risk categories using this biomarker.

تقييم فعالية عامل النمو الشبيه بالأنسولين 2 (IGFBP2) في تصنيف المجموعات المعرضة للخطر لدى المرضى الذين يعانون من متلازمة الشريان التاجي الحادة بدون ارتفاع ST (NSTE-ACS) وفقًا لدرجة مخاطر رينولدز

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الخلاصة

خلفية البحث: احتشـــاء عضـــلة القلب غير المرتبطة بارتفاعST(NSTEMI)والذبحة الصـــدرية غير المستقرة(UA) كأنواع فرعية من متلازمة الشريان التاجي الحادة غير المرتبطة بارتفاع (NSTE_ACS) ST.مع NSTEMI الذي يتميز بنخر عضلة القلب الحاد , يمكن اكتشافه من خلال المؤشرات الحيوية للقلب. يعتبر مؤشـــر رينولدز أداة تنبؤيه تقوم بتقييم احتمالية حدوث امراض القلب والأوعية الدموية على مدى الســـنوات العشـــر القادمة بناءً على معايير مختلفة. البروتين المرتبط بعامل النمو الشـــبيه بالأنســـولين 2(IGFBP2)، وهو أحد أفراد عائلة (البروتين المرتبط بعامل النمو الشبيه بالأنسولين)، يتفاعل مع (عوامل النمو الشبيهة بالأنسولين) في الدورة الدموية لتنظيم نشاطها.

الأهداف: هدفت هذه الدراســـة إلى البحث في العلاقة بين (IGFBP2)ونتائج رينولدز في المرضـــى الذين يعانون منNSTE-ACS. بهدف تصـــنيف المخاطر إلى ثلاث فئات: منخفضـــة ومتوســـطة وعالية وذلك لمساعدة الأطباء في تقييم مستوى المخاطر على أساس المعايير السريرية.

طرق البحث: شملت دراسة الحالات والشواهد 90 فرداً تم تقسيمهم إلى ثلاث مجموعات: مجموعة مرضـى) احتشـاء عضـلة القلب غير المرتبطة بارتفاعٍ ST) ومجموعة مرضـى (الذبحة الصـدرية غير المسـتقرة) و(مجموعة المراقبة)، اذ جمعت الدراســـة البيانات الســـريرية والديموغرافية للمرضـــى بما في ذلك العمر والجنس ومؤشر كتلة الجسم والتاريخ العائلي لمرض الشريان التاجي والتاريخ الطبي

النتيجة: المرضـى الذين يعانون NSTE_ACS لم يظهروا أي فروق ذات دلالة إحصـائية في(IGFBP2) (P=0.560)في المرضى الذين تم تصنيفهم إلى مجموعات (منخفضة ومتوسطة وعالية الخطورة) بناءً على درجة رينولدز لم يكن هناك تباين ذو دلالة إحصائية في مستوياتIGFBP2 (P=0.750).

الاســتنتاج: تبين في هذه الدراســة عدم وجود فروق ذات دلالة إحصــائية في مســتوى IGFBP2 بين الفئات الثلاثة المحددة بواســطة مؤشــر رينولدز لدى الأفراد المصــابين NSTE-ACS. ولذلك لم يكن من الممكن تصنيف الأفراد إلى فئات منخفضة ومتوسطة وعالية الخطورة باستخدام هذا المؤشر الحيوي.

1. Introduction

Cardiovascular disease is the primary global cause of mortality, with ischemic heart disease being the leading contributor (Neama and Shwaikh, 2023). Coronary artery disease (CAD) is a condition that occurs due to atherosclerosis, which causes the narrowing of the arteries and limits blood flow to the distant part of the heart muscle, resulting in ischemia (Jasim et al., 2023). Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) are both classified as non-ST elevation acute coronary syndrome (NSTEACS). These disorders exhibit commonalities in terms of their etiology and anticipated prognosis. Nevertheless, NSTEMI can be distinguished from UA based on the existence of acute myocardial necrosis (Puelacher et al., 2019). Cardiac biomarkers, like Troponin, are employed to distinguish between non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) in cases of acute coronary syndrome where no ST elevations are detected on the electrocardiogram (ECG). Positive biomarker results indicate NSTEMI, while negative biomarker results indicate UA (Evanchan, 2020).

Unstable angina and non-ST elevation myocardial infarction (NSTEMI) have a common etiology, but vary in terms of the extent of cardiac injury resulting from decreased blood supply. This disparity determines the quantities of identifiable indicators of cardiac damage (Piatek et al., 2020). Both UA and NSTEMI manifest symptoms and indications of diminished blood circulation to the cardiac muscle while at rest or engaging in minimal physical activity (Puelacher et al., 2019). Patients diagnosed with unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI) should promptly undergo risk assessment to determine the need for an early invasive intervention (Rahmani et al., 2020). The Reynolds score is a prognosis tool used to assess the likelihood of experiencing a heart attack, stroke, or other major cardiovascular event during the next ten years (Khandia et al., 2021).

The score comprises the subsequent variables. The variables of interest include sex, age, smoking habit, presence of diabetes, systolic blood pressure, total cholesterol levels, HDL cholesterol levels, high sensitivity CRP levels, and family history (Gaasch et al., 2020). The population was categorized into subgroups based on their level of risk, including low, moderate, and high risk groups.The three categories are defined as follows: RRS less than 5%, RRS ranging from 5% to 10%, and RRS equal to or over 10% (Klisić et al., 2018).

The insulin-like growth factor (IGF) family comprises polypeptide hormones (IGF-1 and 2) and their surface receptors, specifically Insulin-like growth factor receptors I and II (IGF-1R, IGF-2R), together with additional IGF-binding proteins (IGFBPs) (Vaezi et al., 2023). Insulin-like growth factors (IGFs) possess a comparable composition to insulin and are present in many tissues throughout the body. IGF-1 is found in both the circulation and arteries, Studies have demonstrated that IGF-1 has positive impacts on the heart in instances of atherosclerosis, The IGFBP family with six members regulates the presence of IGF(Wang et al., 2023). IGFBP2, a constituent of the IGFBP family, has the ability to modulate the function and activity of IGFs by interacting with them in the circulatory system. Additionally, it hinders the binding of IGFs to IGF receptors Moreover, it possesses the capability to bind to IGFs and elicit either a growth-inhibitory or growth-promoting effect, which is contingent upon the presence of IGFs in specific cell types (Wei et al., 2021).The liver is the main producer of IGFBP-2, which is the second most abundant IGFBP seen in the bloodstream (Rauzier et al., 2022). The current study aimed to investigate the association between serum IGFBP2 level and Reynolds score in patients with unstable angina \ Non-ST-Elevation Myocardial Infarction, with

the objective of stratifying the risk into low, moderate and high categories. to assist doctors in evaluating the level of risk based on clinical criteria

2. Materials and Methods

In the current case-control study, 90 samples total, ages ranging from 44 to 70 years, were split into three groups: 30 patients with unstable angina, 30 patients with nstemi, and 30 people in the control group. The study was conducted out at the Karbala Center for Cardiac Diseases and Surgery. The participants were gathered between October 2023 and January 2024. The study protocol received approval from the Ethical Committee of Karbala College of Medicine and the Karbala Health directorate, and agreement was acquired from the patients. Participants' five milliliters of venous blood were drawn, put in a simple gel tube, and allowed to coagulate for thirty to sixty minutes at room temperature. Following centrifugation, the samples were kept at -20 °C until analysis. Serum IGFBP2 levels were quantified using a sandwich ELISA method, while lipid profile, Hs-Troponin I, and Hs-CRP levels were assessed using an Auto analyzer chemical system. IGFBP2 was measured using a BT LAB system from China; GIESSE Diagnostics kit for lipid profile; bioMérieux system for Hs-troponin I test; Abbott system for Hs-CRP test.

The following equation was employed to calculate body mass index (BMI).

BMI (kg/m2) = weight / (height)2

The patients were categorized into three groups based on their body mass index (BMI): normal (BMI 18.5-24.9 kg/m2), overweight (BMI 25-29.9 kg/m2), and obese (BMI ≥ 30.0 kg/m2) (Donini et al., 2020).

2.1. Inclusion Criteria

Patients are diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI) and Unstable Angina by considering their medical history, physical examination, electrocardiogram (ECG), and serum Troponin test.

2.2. Exclusion Criteria

Individuals afflicted with both acute and chronic renal disease, together with cardiac insufficiency.

2.3. Statistical Analysis

The research utilised descriptive statistical methods to examine the data, utilising counts and percentages for categorical variables and a median (Min-Max) and interquartile range (IQR): Q1–Q3) for scale variables. The Shapiro-Wilk test was used to confirm that the data distribution was normal. Inferential statistical techniques were employed to examine aberrant distributions, including the Mann-Whitney Test and Kruskal-Wallis Test . The Spearman rank test was used to evaluate the association in the case study, and all hypothesis tests were deemed statisti cally significant if their p-value was less than 0.05.

3. Results

In the current study, the proportion of patients in the 40–50 year age group is 11.7%, in the 51–61 year age group is 48.3%, and in the 62 year and over age group is 40%. In the control group, the proportion of people aged 40–50 is 46.7%, the percentage of people aged 51–61 is 30%, and the percentage of people aged 62 and above is 23.3%. Half of the groups in study were male, while the other half were female. Patients' BMI categories show that 28.3% are considered to be in the normal range, 33.3% are overweight, and 38.3% are obese. Of the controls, 50% had a normal BMI, 26.7% were overweight, and 23.3% were obese. A questionnaire used to gather the patients' medical histories

revealed that roughly 20% of them smoked, 60% had diabetes, 73.3% had hypertension, and 21.7% had FH Premature CAD. 60% of those with known CAD engage in physical exercise. See Table 1.

Table 1: Demographics and Clinical Characteristics of The Study Participants.

Characteristics		Patient Group N=60	Control Group N=30	
Demographic	**Age** (40-50 year) (51-61 year) (≥62 year)	 7 (11.7 %) 29 (48.3%) 24 (40%)	 14 (46.7%) 9 (30%) 7 (23.3%)	
	Sex (male/female)	(30/30) (50%/50%)	(15/15) (50%/50%)	
	BMI Normal Overwight Obese	 17 (28.3%) 20 (33.3%) 23 (38.3%)	 15 (50%) 8 (26.7%) 7 (23.3%)	
Medical History	FH Premature CAD (Yes/ No)	(13 /47) (21.7%/78.3)	(6/24) (20%/80%)	
	Smoking (Yes/No)	(12/48) (20%/80%)	(4/26) (13.3%/86.7%)	
	DM (Yes/No)	(36/24) (60%/40%)	(4/26) (13.3%/86.7%)	
	HTN (Yes/No)	(44/16) (73.3% /26.7%)	(12/18) (40% /60%)	
	Physical activity (Yes /No)	(36 /24) (60% /40%)	(30/0) 100%	
	KnownCAD (Yes/No)	(37/23) (61.7% /38.3)	–	
		Median (Min-Max)	Median (Min-Max)	P value
Age		60 (44-70)	55 (44-70)	0.020
BMI		27.5 (19-39)	25.4 (23-35)	0.175

BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, FH Premature CAD: family history of premature Coronary artery disease, KnownCAD: Known Coronary artery disease

In general, individuals with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) did not exhibit a statistically significant difference in IGFBP2 levels (p=0.560) compared to the control group. the median (Min-Max), IQR where 124.5 (21.4- 728.8), 260.0 and 124.3 (38.0- 578.3),250.9 respectively. see Table 2.

Table 2: Comparison of IGFBP2 Level Between Patients With (NSTE-ACS) And Control.

Marker	Patient, N=60		Control, N=30		P value
	Median (Min-Max)	IQR	Median (Min-Max)	IQR	
IGFBP2	124.5 (21.4- 728.8)	260.0	124.3 (38.0- 578.3)	250.9	0.560
Mann-Whitney Test was, significant at $p \leq 0.05$; N: number; IQR: interquartile range, Min: Minimum, Max: Maximum					

The study showed that there was no statistically significant variation in the level of IGFBP2 (P=0.750) among patients who were classified into three risk categories: low-risk, medium-risk, and high-risk groups, based on the Reynolds score. the median (Min-Max), IQR of IGFBP2 where 141.8(21.4-728.8)383.8, 106.0(32.4-537.1) 112.0 and 121.9(35.1-606.0)175.5 respectively. See Table 3

Table 3: The Comparison of IGFBP2 Level with Reynolds Score in Patients With (NSTE-ACS)

Reynolds Score							
Marker	Low N=27		Medium N=15		High N=18		P value
	Median (Min-mix)	IQR	Median (Min-mix)	IQR	Median (Min-mix)	IQR	
IGFBP2	141.8 (21.4-728.8)	383.8	106.0 (32.4-537.1)	112.0	121.9 (35.1-606.0)	175.5	0.750
Kruskal-Wallis Test was, significant at $p \leq 0.05$; N: number; IQR: interquartile range,Min: Minimum, Max: Maximum							

The current study demonstrated a significant and positive association in patients with NSTE-ACS between IGFBP2, LDL, and HDL. However, there is a non-significant positive relationship between IGFBP2 and Total Cholesterol. On the other hand, Age, BMI, Troponin I, and TG with IGFBP2 exhibit a significant negative correlation. see Table 4.

Table 5: Correlations Between IGFBP2 and Laboratory Parameters in Patient With (NSTE-ACS)

parameters	IGFBP2	
	Correlation coefficient (r)	P value.
Age	-0.286*	0.027
BMI	-0.691**	0.000
Hs-Troponin I	-0.407**	0.001
Hs-CRP	-0.077	0.559
HDL	0.579**	0.000
TG	-0.821**	0.000
LDL	0.289**	0.025
Total Cholesterol	0.040	0.764
Spearman test was, *Correlation is significant at the 0.05 level, BMI: Body mass index; Hs-TroponinI: high- sensitivity TroponinI; Hs-CRP:High-sensitivity C-reactive protein TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol		

4. Discussion

The current study observed that a majority of patients with unstable angina / non-ST elevation myocardial infarction (NSTE-ACS) fell into the age range of 51-61 years (48.3%) and the age range of 62 years and over (40%) As stated in Table (1) . A study conducted by Benjamin in 2019 found that elderly adults have a much greater frequency of most cardiovascular disorders compared to other age groups (Benjamin et al., 2019).

The current study indicated that 40% of patients were classified as obese and 33.3% as overweight. Obesity was known to increase the morbidity of cardiovascular disease (CVD) both directly and indirectly (Koliaki et al., 2019).

In the present investigation, the proportion of males is equivalent to that of females, as indicated in Table (1) .A study conducted by Barton in 2023 revealed that Cardiovascular medicine,has historically been perceived as a predominantly male-oriented ailment. While men have a higher incidence of myocardial infarction (MI), women exhibit a higher mortality rate when accounting for age and other relevant factors that may impact the outcomes (Barton et al., 2023). Older women are more susceptible to coronary artery disease (CAD) due to the absence of oestrogen, which acts as a preventive factor for women before menopause (Al-Haidari et al., 2023)

Furthermore, 45% of the patients were diagnosed with type 2 diabetes, while hypertension was detected in 75% of them As stated in Table (1). Type 2 diabetes mellitus (DM) and hypertension (HTN) are widely recognised factors that elevate the likelihood of developing cardiovascular disease (CVD). In addition, individuals who have both diabetes mellitus (DM) and hypertension (HTN) are at an increased risk of cardiovascular mortality compared to those who have only one of these illnesses (Koliaki et al., 2019).

The findings of the present investigation indicate that there is no statistically significant disparity in the concentration of IGFBP2 between patients with NSTE-ACS and the control group, as illustrated in Table (2). In a study conducted by Wang, it was found that patients with acute myocardial infarction had higher levels of IGFBP-2 compared to healthy individuals. However, there is a lack of research examining the specific influence of IGFBP-2 levels on cardiovascular disease(Wang et al., 2023). Patients diagnosed with ACS showed a significant decrease in serum levels of (IGFBP-2) (Topf et al., 2022). Research on the role of insulin-like growth factor binding protein-2 (IGFBP-2) in atherosclerosis is scarce (Wang et al., 2024).

To the best of our knowledge, there is currently no study that has specifically investigated the correlation between IGFBP2 and patients with NSTE_ACS. However, the majority of previous studies conducted thus far have focused on Acute coronary syndrome (ACS) as a whole.

The findings of the current investigation suggest that there were no notable disparities in IGFBP2 levels among patients classified into three risk groups: low-risk, intermediate-risk, and high-risk, as assessed by the Reynolds score, as illustrated in Table (3). Due to the unique nature of our current study, it has been challenging to find previous research that directly relates to it. Our study takes a new approach by investigating the link between IGFBP2 and Reynolds score, a methodology that has not been found in the literature we have reviewed.

Our results are consistent with other research showing IGFBP-2 to be a metabolic syndrome marker with an inverse relationship to triglyceride and BMI levels (Wang et al., 2023). Lau 2021 demonstrated that negative metabolic risk markers, such as elevated body mass index, decreased insulin sensitivity, and unfavourable lipid profiles, are associated with lower levels of IGFBP2. As evidenced by recent clinical research, IGFBP-2 is one of the best

biomarkers that inversely correlates with metabolic syndrome(Lau et al., 2021). IGFBP-2 levels were positively correlated with high-density lipoprotein (HDL-cholesterol) and negatively correlated with plasma (TG). According to the results, there may be a correlation between the creation of chylomicrons with apoB-48 and the decreased clearance of VLDL and IDL particles with apoB-100. These two potential kinetic variables most likely have an impact on the unfavourable connection between TG levels and circulating IGFBP-2 circulation (Rauzier et al., 2022). The results of this study showed a non-significantly negative correlation between Hs-CRP and igfbp2. Dong's work shows a strong relationship between higher serum levels of CRP and IGFBP2(Dong et al., 2020).

5. Conclusion

This study highlights the significant role of age, obesity, type 2 diabetes, and hypertension as key risk factors for NSTE-ACS, with equal gender distribution emphasizing unique risks for women, especially postmenopausal.

While IGFBP2 is linked to metabolic syndrome, this study found no significant differences in its levels between NSTE-ACS patients and controls or across risk groups. These findings suggest a limited role for IGFBP2 in predicting or stratifying NSTE-ACS risk, warranting further research to clarify its clinical significance.

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