P- ISSN 1991-8941 E-ISSN 2706-6703
2024,(18), (02):154 – 162

Journal of University of Anbar for Pure Science (JUAPS)

Open Access

Prospective randomized controlled trial of liver function tests in unstable angina risk prediction

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ARTICLE INFO

Received: 04 / 05 /2024
Accepted: 04/ 07 /2024
Available online: 28/12 /2024

10.37652/juaps.2024.149368.1248

Keywords:
Acute coronary syndrome; Unstable angina; Liver function tests; Cardiac troponin I; High-sensitivity C-reactive protein

ABSTRACT

Cardiovascular diseases continue to be the leading cause of morbidity and mortality in developed nations. Elevated liver function levels have recently been implicated as possible risk factors for cardiovascular diseases in the adult population. This study aims to assess the correlation of hepatic function tests with cardiac troponin I (cTnI) and high-sensitivity C-reactive protein (hs-CRP) in adult males with unstable angina and to explore the potential of these biomarkers as predictive tools. Conducted at AL-Ramadi Teaching Hospital, Iraq from October 2023 to January 2024, this study included 90 male adult participants (60 healthy individuals and 30 patients with unstable angina). Sociodemographic and biochemical variables were collected using a systematic questionnaire and standardized measurement procedures. The average values for body mass index, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein cholesterol, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transferase, cTnI, and hs-CRP were significantly higher ($P<0.05$) in the patients with unstable angina compared with those in the control group. Furthermore, bilirubin, GGT, and AST levels showed a significant correlation with cTnI and hs-CRP levels in the patients with unstable angina. Our data indicated that bilirubin, GGT, and AST have the best predictive value for the risk of unstable angina. Continued monitoring of these biomarkers in patients suffering from liver function disorders will help identify early signs of unstable angina and improve the prevention and treatment of this disease.

Introduction

Cardiovascular diseases (CVDs) remain the world's top cause of morbidity and mortality and represent one of the most serious issues faced by global health systems [1]. Acute coronary syndrome (ACS) and other coronary artery disorders are among the most prevalent cardiovascular conditions [2]. Unstable angina is an issue in which the heart receives inadequate blood and oxygen, triggering chest discomfort or agony. It represents a type of ACS that may lead to a myocardial infarction [3]. Multiple causative factors, such as dyslipidemia, hypertension, smoking, male gender, advanced age, obesity, diabetes, and lifestyle with less or no physical activity may increase an individual's susceptibility to atherosclerosis and other CVDs [4].

Despite efforts to identify, mitigate, and manage risk factors, the overall death rate for coronary artery disorders is still rising [5].

Liver markers, such as bilirubin, alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), have been used in the diagnosis of nonalcoholic fatty liver disease and hepatic dysfunction [6]. Some studies have recently unveiled the role of liver enzymes in CVD development [7, 8]. Although several researchers have focused on the correlations between liver markers and risk factors for heart diseases, the connections appear to be inconsistent [9]. A previous study reported the existing relationship between GGT activity and the prevalence of CVDS, including but not limited to coronary heart disease, stroke, arterial hypertension, heart failure, cardiac arrhythmias, and all-cause and cardiovascular mortality [10]. Li *et al*. [11] revealed the correlation between high levels of ALT and

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increased risk of in-hospital mortality in patients with acute myocardial infarction. By contrast, a previous investigation did not reveal any sign of a connection between ALT or AST and CVDs [12]. Kunutsor *et al*. [13] indicated that adding total bilirubin to the existing risk factors panel does not significantly enhance the ability to predict the risk of CVDs.

Cardiac troponin I (cTnI) and C-reactive protein (CRP) measurements provide excellent diagnostic and prognostic accuracy in patients with acute myocardial infarction [14]. However, the correlation between liver markers and unstable angina in Anbar Governorate in Iraq has never been explored. This study aimed to assess the contribution of liver function tests, hs-CRP, and cTnI to the advancement of unstable angina in adult males from Ramadi City, Iraq.

Subjects and Methods

Study Design and Participants

This study comprised a sample of 90 adult males aged 40–73 years from the Ramadi district in Iraq. Among the participants, 30 were newly diagnosed with unstable angina at AL-Ramadi Teaching Hospital between October 2023 and January 2024. Sixty individuals without any health issues were included as a control group.

Ethical Considerations

The research ethics committee of the University of Anbar approved this study protocol following the World Medical Association's Declaration of Helsinki (license number: 147-24-12-2023). All the participants in this study gave their informed consent for its publication.

Inclusion and Exclusion Criteria

This investigation included patients with unstable angina who did not have a history of acute illness or terminal disease. Alcoholism, malignancy, chronic renal disease, liver disease, or drug-induced steatosis were among the medical conditions that disqualified applicants.

Collecting Data and Sampling

A well-established questionnaire platform was utilized to gather demographic data, lifestyle-related risk factors, medical history, and prescribed medications for currently diagnosed or previously diagnosed underlying disorders. Blood samples were collected within 24 hours of the patient receiving a diagnosis of unstable angina. In brief, 5 mL of whole blood was collected, transferred to gel tubes, and centrifuged at 400×g for 10 minutes. The serum was then stored in Eppendorf tubes until use at 20 °C.

Body Mass Index (BMI) and Blood Pressure

The BMI was determined by dividing the weight of the body in kilograms by the square of the height in meters. Following a 10-minute interval of rest, the blood pressure of each arm was monitored on two occasions with a minimum time interval of 1 minute between each pair of measurements. Average values from the two measurements were computed for each arm. The highest reading was used to determine the mean diastolic (DBP) and systolic blood pressure (SBP) of both arms. High blood pressure was indicated by a SBP of 130 mmHg and a DBP of 80 mmHg [15].

Diagnostic Criteria and Measurement of Biochemical Biomarkers

The patients with unstable angina were diagnosed by cardiologists using cTnI and ECG tests in accordance with the following diagnostic reference standards: total cholesterol (T.C) ≥ 200 mg/dL, triacylglycerol (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥ 110 mg/dL, ALP > 126 U/L, AST > 59 U/L, GGT > 40 U/L, bilirubin 0.3–1.0 mg/dL, and high-sensitivity C-reactive protein (hs-CRP) ≥ 2 mg/L. Serum liver enzymes, bilirubin, lipid profile, and hs-CRP were analyzed by enzyme colorimetric assay using a fully automated Mindray-BS240 autoanalyzer following the manufacturer's recommendation [16, 17]. cTnI concentration was quantified using an electrochemiluminescence immunoassay system, specifically the NIPIGON Robot R1, Ontario, Canada. Two monoclonal antibodies specific to cTnI were used to quantify its level I. Fluorescence was measured at 350 nm [18].

Statistical Analysis

The data were analyzed using version 8.0.1 of Graph Pad Prism. The mean and standard deviation were computed to provide clarity to the data. A t-test on independent samples was utilized to identify any significant differences between means. The degree of relationship between continuous variables was ascertained by utilizing Pearson's correlation coefficient (r). Statistical significance was determined at a probability threshold of 0.05. Version 22.021 of the MedCalc software was utilized to compute the area under the receiver operating curve (ROC curve), cut-off value, sensitivity, and specificity of liver biomarkers.

Results

This study comprised 30 male patients diagnosed with unstable angina. The age of the patients ranged from 40 years to 73 years, with an average age of 60.13 ± 9.63 years. The control group consisted of 60 healthy men whose average age was 56.77 ± 8.33 years. The BMI, SBP, DBP, TG, total cholesterol, LDL, AST, GGT, bilirubin, cTnI, and hs-CRP levels in the patients with unstable angina were significantly greater than those in the control group ($p<0.05$). No notable differences in ALP level were observed between the two groups ($P>0.05$). The HDL in the patients was lower than that in the control group ($P>0.05$) (Table 1).

In the patients with unstable angina, Pearson correlation and linear regression analyses revealed the significant positive correlation ($p<0.05$) of serum cTnI with age, SBP, triglyceride, and total cholesterol. Furthermore, an examination of cTnI levels revealed no correlation with BMI, DBP, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) as presented in Table 2. A significant positive correlation ($p<0.05$) with serum cTnI concentration was observed for the levels of bilirubin, AST, and GGT in the patients with unstable angina (Table 2, Figure 1). According to the Pearson correlation coefficient values (Table 2, Figure 1D), the strongest correlation ($r = 0.503$, $p<0.05$) was observed between cTnI and bilirubin. AST, SBP, and GGT were also found to have a moderate correlation with cTnI.

Table 1. Characteristics (including demographic and clinical aspects) of the groups being studied.

Variables	Patient group		Control group		p-value
	Mean	±SD	Mean	±SD	
Age (year)	60.13	9.63	56.77	8.33	0.0900
BMI (kg/m^2)	27.36	1.59	26.41	2.22	0.0410
SBP (mmHg)	137.0	12.29	121.3	5.88	<0.0001
DBP (mmHg)	85.50	16.47	80.75	4.20	0.0376
TG (mg/dL)	169.2	44.36	135.4	23.19	<0.0001
T.C. (mg/dL)	197.0	39.88	173.8	28.49	0.0024
HDL (mg/dL)	35.93	6.84	38.54	6.93	0.1035
LDL (mg/dL)	130.6	34.84	117.3	23.49	0.0455
ALP (U/L)	95.39	22.75	92.44	20.51	0.5399
AST (U/L)	24.55	6.03	16.82	6.73	0.0223
GGT (U/L)	24.73	7.16	21.17	7.09	0.0436
Bilirubin (mg/dL)	0.448	0.128	0.185	0.084	<0.0001
cTnI (ng/mL)	0.031	0.007	0.013	0.001	<0.0001
hs-CRP (ng/L)	8.636	3.124	2.444	1.718	<0.0001

Data are presented as mean ± standard deviation (SD). Utilizing the Student's t-test to distinguish unstable angina patients from the control group. BMI- body mass index, SBP- systolic blood pressure, DBP- diastolic blood pressure, TG- triglyceride, T.C.- total cholesterol, HDL- high-density lipoprotein, LDL- low-density lipoprotein, ALP- alkaline phosphatase, AST- aspartate transaminase, GGT- gamma-glutamyl transferase, TcnI- troponin I, hs-CRP- high-sensitivity C-reactive protein. $P\leq0.05$ was considered a statistically significant difference.

Table 2. Serum cTnI concentration levels with studied variables.

Variable 1	Variable 2	r*	p-value
cTnI (ng/mL)	Age (year)	0.3468	0.0008
	BMI (kg/m^2)	0.1961	0.0654
	SBP (mm Hg)	0.4751	<0.0001
	DBP (mm Hg)	0.0829	0.4372
	TG (mg/ dL)	0.3561	0.0006
	T.C. (mg/ dL)	0.2730	0.0101
	HDL (mg /dL)	-0.0104	0.9221
	LDL (mg/ dL)	0.1531	0.1645
	ALP (U/ L)	0.0990	0.3585
	AST (U/ L)	0.4778	<0.0001
	GGT (U/ L)	0.3137	0.0052
	Bilirubin (mg/dL)	0.5036	<0.0001

cTnI- troponin I, BMI- body mass index, SBP- systolic blood pressure, DBP- diastolic blood pressure, TG- triglyceride, T.C.- total cholesterol, HDL- high-density lipoprotein, LDL- low-density lipoprotein, ALP- alkaline phosphatase, AST- aspartate transaminase, GGT- gamma-glutamyl transferase.
*r- Pearson's coefficient correlation of parameters.

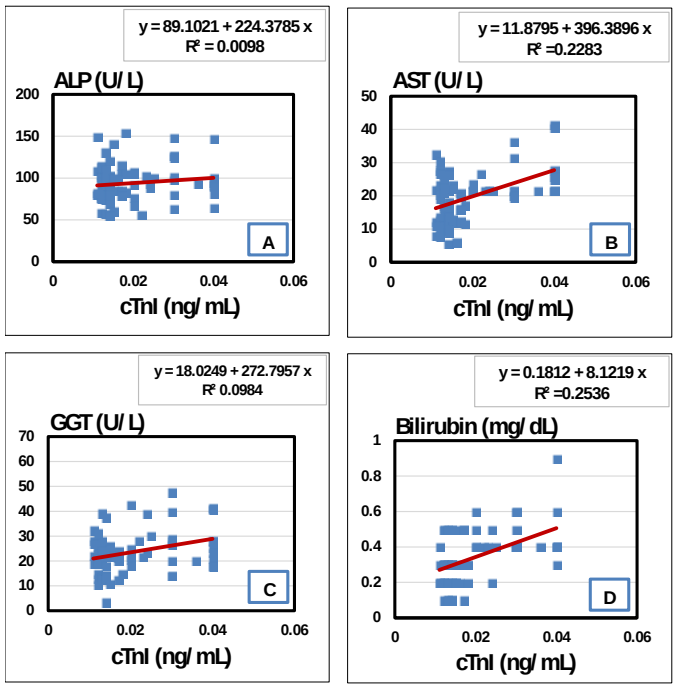

Figure 1. Correlations between troponin I and hepatic markers. A: correlation with alkaline phosphatase (ALP), B: correlation with aspartate transaminase (AST), C: correlation with γ-glutamyl transferase (GGT), D: correlation with bilirubin.

Statistical analysis revealed the positive correlation (Table 3) of hs-CRP levels with age, SBP, DBP, TG, total cholesterol, and LDL in the patients with unstable angina. Furthermore, cTnI was found to be inversely associated with HDL ($P > 0.05$). Among the liver functions studied, a significant positive correlation with serum hs-CRP levels was observed for AST ($r = 0.52$, $p<0.05$) and GGT ($r = 0.50$, $p<0.05$) (Figure 2).

Table 3. Correlations of serum hs-CRP levels with studied variables.
hs-CRP- high-sensitivity C-reactive protein.
*r- Pearson's coefficient correlation of parameters.

Variable 1	Variable 2	r*	p-value
hs-CRP (ng/L)	Age (year)	0.2655	0.0196
	BMI (kg/m^2)	0.1386	0.2324
	SBP (mm Hg)	0.5258	<0.0001
	DBP (mm Hg)	0.2506	0.0276
	TG (mg/ dL)	0.3811	0.0006
	T.C. (mg/ dL)	0.2407	0.0350
	HDL (mg/ dL)	-0.1841	0.1090
	LDL (mg/ dL)	0.3300	0.0044
	ALP (U/ L)	0.2234	0.0557
	AST (U/ L)	0.5252	<0.0001
	GGT (U/ L)	0.5061	<0.0001
	Bilirubin (mg/dL)	0.3669	0.0013

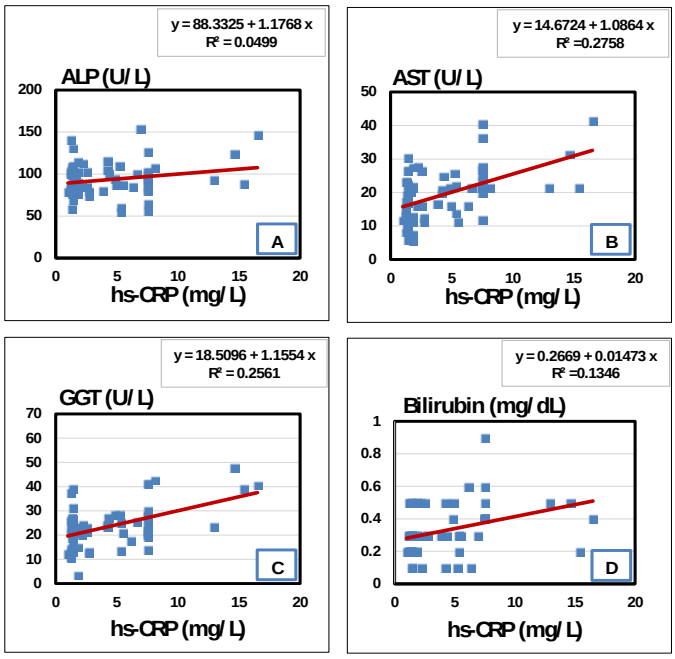

Figure 2. Correlations between high-sensitivity C-reactive protein and liver function tests. A: correlation with alkaline phosphatase (ALP), B: correlation with aspartate transaminase (AST), C: correlation with γ-glutamyl transferase (GGT), D: correlation with bilirubin.

The best cutoff value for GGT was 27.3 for the patients with unstable angina. This threshold had a sensitivity of 43.3% and a specificity of 87.5%. The AUC was 0.671, with a 95% CI ranging from 0.555 to 0.773. The most optimal cutoff value for bilirubin was determined to be 0.3, with a sensitivity of 92.6% and a specificity of 83.3%. The AUC was 0.844 with a 95% CI of 0.751 to 0.913 as presented in Table 4 and Figure 3.

Table 4. ROC (area under the receiver operating characteristic curve) of hepatic markers in patients with unstable angina.

Cardiac markers	AUC	Std. Error	95% Confidence interval	p-value
ALP (U/L)	0.552	0.0682	0.443 to 0.658	0.4432
AST (U/L)	0.788	0.0492	0.686 to 0.870	<0.0001
GGT (U/L)	0.671	0.0640	0.555 to 0.773	0.0076
Bilirubin (mg/dL)	0.844	0.0447	0.751 to 0.913	<0.0001

AUC- area under the curve, ALP- alkaline phosphatase, AST- aspartate transaminase, GGT- gamma-glutamyl transferase. P≤0.05 was considered a statistically significant difference.

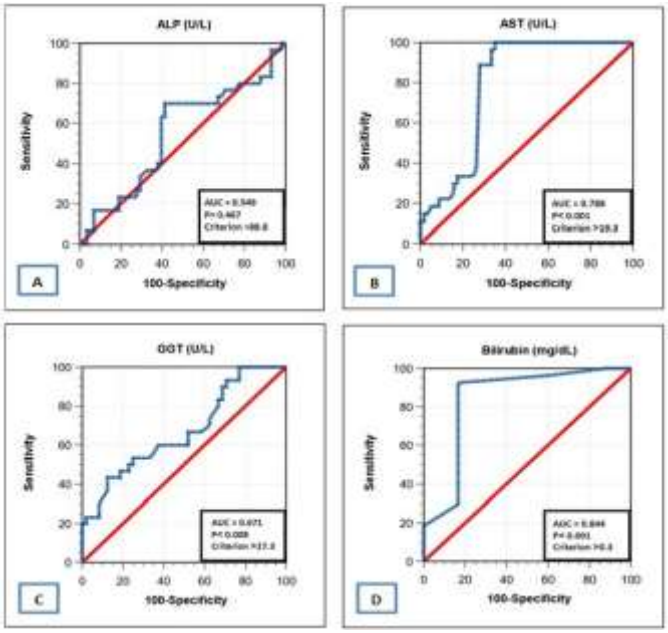

Figure 3. Receiver operating characteristic curves of hepatic function tests in patients with unstable angina. A: ROC curve of alkaline phosphatase (ALP), B: ROC curve of aspartate transaminase (AST), C: ROC curve of γ-glutamyl transferase (GGT), D: ROC curve of bilirubin.

Discussion

Unstable angina is a prevalent condition frequently seen in the emergency room. Approximately 10% of individuals diagnosed with ACSs have unstable angina, which is a clinical condition characterized by myocardial ischemia occurring at rest or during modest activity without immediate myocardial necrosis or damage [19].

This research comprised male patients who experienced unstable angina within 24 hours following an injury. Their BMI and levels of blood triglycerides, total cholesterol, and LDL were elevated. Conversely, their serum HDL levels were low. Dyslipidemia is a common risk factor found in individuals with ACSs, with a higher prevalence in males than in females [20]. A death rate of 13.5% was recorded among individuals with CVD who have a high BMI [21]. Our findings were consistent with a previous investigation on patients in a hospital in Ukraine [4]. The study's data indicated that individuals with unstable angina exhibited disruptions in fat metabolism compared with the control group, signifying a reduction in HDL and an increase in total cholesterol, triglycerides, and LDL [4]. Ketelhuth *et al*. [22] discovered that patients with unstable angina had higher levels of total cholesterol, TG, and LDL than the control group but found no significant difference in HDL levels between them.

Studies on individuals with ACS have demonstrated significant variability in the predictive significance of abnormalities seen in the biochemical markers of liver function tests. Thus, the present research sought to determine the hepatic indicators of males within 24 hours after being admitted for unstable angina. According to this investigation, individuals with unstable angina often had increased levels of liver enzymes and bilirubin. The results of our study did not align with the prior data, which suggested that AST, ALT, ALP, and bilirubin levels are within the normal range for most patients with unstable angina [10]. Nevertheless, a recent investigation has verified that elevated levels of typical indicators of liver damage (GGT, ALT, AST, ALP, and bilirubin) are linked to a high likelihood of developing CVDs [23].

The liver has a high level of metabolic activity. Therefore, any change in blood flow to the liver during a sudden heart attack directly or indirectly affects the circulation and structure of the liver, leading to increased ALT and AST levels. In addition, liver congestion can result in a sudden dysfunction of the right ventricle, causing increased levels of hepatic transaminases. The leading causes implicated in this case were venous congestion, impaired hepatocyte oxygen extraction capacity, and reperfusion injury [11]. Heart failure is a condition when the heart is unable to pump enough blood to fulfill the body's metabolic needs. It is often caused by a malfunctioning heart and can sometimes show indications of a noncardiac problem, including liver diseases. Elevated liver enzymes and direct and indirect serum bilirubin might result from passive hepatic congestion caused by increased central venous pressure. Acute hepatocellular necrosis accompanied by significant increases in serum aminotransferases may be inherent in compromised perfusion resulting from reduced cardiac output [24].

The timely identification of people at high risk and accurate prediction of prognosis is equally important as

validating the diagnosis of unstable angina. The predictive significance of liver biomarkers in individuals with unstable angina remains uncertain. Only a few studies have evaluated the correlation between cardiac biomarkers and liver function. Therefore, we investigated the correlation of cTnI and hs-CRP levels with liver function tests in patients with early-stage unstable angina, intending to use this connection as a prognostic indicator. The findings of our study demonstrated a good link between cTnI levels and AST and bilirubin levels. Although a considerable connection was found between cTnI and GGT, no statistically significant link was observed between cTnI and ALP within 24 hours following unstable angina.

Concerning hs-CRP, our findings demonstrated its excellent association with AST and GGT, a moderate correlation with bilirubin, and a poor correlation with ALP. Jasiewicz *et al.* [25] found a favorable correlation between the amount of cTnI in the blood and the levels of ALT and AST in patients with ACS precisely 12 hours after admission. In addition, Demirelli *et al*. [26] observed a significant correlation between gamma-glutamyl transferase activity and troponin. Another investigation demonstrated a statistically significant but weak correlation between the highest levels of cTnI and ALP in plasma (correlation coefficient: 0.21, P = 0.003) [27]. Previous research has shown a favorable correlation between hs-CRP and elevated blood GGT levels. This difference was also found to be significant in individuals with acute myocardial infarction [28].

The current ROC results indicated that liver function biomarkers, particularly AST, GGT, and bilirubin, may help predict the risk of unstable angina. Predicted outcomes for patients undergoing acute myocardial infarction can be ascertained using liver indicators as indicated by prior research. Increased levels of liver enzymes are associated with a heightened CVD risk. They can be attributed to heart failure and have a strong correlation with mortality [29]. Furthermore, the results of the present investigation aligned with the conclusion drawn by Xu *et al.* [30], who determined that increased levels of bilirubin may be used to predict significant adverse cardiac events in individuals with ACS.

Conclusions

This study found that elevated liver function levels were linked to a high likelihood of developing CVDs. High concentrations of bilirubin, GGT, and AST were also found to be correlated with a high likelihood of developing unstable angina. The findings indicated that liver enzymes, bilirubin, cTnI levels, and hs-CRP can be utilized for the early identification of unstable angina.

Acknowledgments

The authors are highly thankful to the patients and healthy controls who have participated in this research and the medical staff in the Cardiac Resuscitation Unit at Ramadi Teaching Hospital for their valuable support in facilitating the collection of blood samples from STEMI patients.

Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2024,(18), (02):154 – 162

دراسة تجريبية عشوائية محكومة محتملة لاختبارات وظائف الكبد في التنبؤ بخطر الذبحة الصدرية غير المستقرة

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الخلاصة:

لا تزال أمراض القلب والأوعية الدموية هي السبب الرئيسي للمراضة والوفيات في الدول المتقدمة. تم مؤخرًا اعتبار المستويات المرتفعة من وظائف الكبد متورطة كعوامل خطر محتملة للإصابة بأمراض القلب والأوعية الدموية لدى البالغين. تهدف هذه الدراسة إلى تقييم العلاقة بين اختبارات وظائف الكبد وكل من التروبونين القلبي I (cTn I) والبروتين التفاعلي C عالي الحساسية (hs-CRP) لدى الذكور البالغين المصابين بالذبحة الصدرية غير المستقرة. بالإضافة إلى ذلك، لاستكشاف إمكانات هذه المؤشرات الحيوية كعلامات تنبؤية. أُجري المشروع في مستشفى الرمادي التعليمي بالعراق في الفترة من أكتوبر 2023 إلى يناير 2024. وتضمنت الدراسة 90 مشارك بالغ من الذكور، و60 شخص كمجموعة مراقبة صحية و30 مريض يعانون من مرض الذبحة الصدرية غير المستقرة. تم جمع المتغيرات الاجتماعية والديموغرافية والكيميائية الحيوية باستخدام استبيان منهجي وإجراءات قياس موحدة. كانت القيم المتوسطة لمؤشر كتلة الجسم، وضغط الدم الانقباضي، وضغط الدم الانبساطي، والدهون الثلاثية، والكوليسترول الكلي، وكوليسترول البروتين الدهني منخفض الكثافة، والفوسفاتيز القلوي، وناقلة أمين الأسبارتات، وناقلة جاما كلوتاميل، وcTn I، وhs-CRP أعلى بشكل ملحوظ ($P < 0.05$) في مرضى الذبحة الصدرية غير المستقرة مقارنة بمجموعة السيطرة. وعلاوة على ذلك، تم الكشف عن وجود علاقة كبيرة بين مستويات البيليروبين، GGT، وAST وكلا من مستويات cTnI وhs-CRP في مرضى الذبحة الصدرية غير المستقرة. في الختام، تشير بياناتنا إلى أن البيليروبين، GGT، وAST تمتلك أفضل قيمة تنبؤية لخطر الذبحة الصدرية غير المستقرة بالمقارنة مع اختبارات الكبد الأخرى. ونتيجة لذلك، فإن المراقبة المستمرة لهذه المؤشرات الحيوية لدى المرضى الذين يعانون من اضطرابات وظائف الكبد لن تحدد العلامات المبكرة لمرض الذبحة الصدرية غير المستقرة فحسب، بل ستحسن أيضًا الوقاية من المرض وعلاجه.

الكلمات المفتاحية: متلازمة الشريان التاجي الحادة. الذبحة الصدرية غير المستقرة. اختبارات وظائف الكبد؛ تروبونين القلب الأول. بروتين سي التفاعلي عالي الحساسية.