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Evaluating Liver Function Tests as Diagnostic and Discrimination Tools for Cardiovascular Diseases: Heart Disease and Ischemic Stroke

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Abstract:

Background: Cardiovascular diseases (CVD) encompass a range of disorders affecting the heart and blood vessels and are leading contributors to sudden death. This article investigates the role of liver function tests (LFTs) as diagnostic and discriminatory tools for CVD, particularly heart disease and ischemic stroke. **Method:** A cohort of sixty-two individuals aged 48 to 68, including patients with heart disease (HD), ischemic stroke (IS), and healthy (control), was studied. Thirteen biochemical indicators from the LFT panel were measured. **Results:** Our results revealed significant differences ($p < 0.05$) in five indicators: total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), total biliary acid (TBAc) and the aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT) among CVD patients. Notably, TBIL, DBIL, IBIL, and TBAc levels were significantly lower in heart disease and ischemic stroke patients compared to controls. Additionally, the AST/ALT ratio was significantly elevated in heart disease patients versus controls, while differences between ischemic stroke and control groups were less pronounced. **Conclusion:** These findings indicate that LFTs could enhance early diagnosis and risk stratification in cardiovascular assessments, advocating for further research to develop standardized guidelines for their clinical use in diagnosis and management of cardiovascular diseases.

Keywords: Cardiovascular Diseases (CVD), Liver Function Tests (LFTs), Heart Disease (HD), Ischemic Stroke (IS), Bilirubin, Biliary Acid and AST/ALT ratio.

تقييم اختبارات وظائف الكبد كأدوات تشخيص وتمييز لأمراض القلب والأوعية الدموية: أمراض القلب والسكتة الدماغية الإقفارية

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الملخص:

الخلفية: أمراض القلب والأوعية الدموية تشمل مجموعة من الاضطرابات التي تؤثر على القلب والأوعية الدموية وتعتبر من الأسباب الرئيسية للوفاة المفاجئة. هذه المقالة صممت لتقييم دور اختبارات وظائف الكبد كأدوات تشخيص وتمييز لأمراض القلب والأوعية الدموية، وخاصة أمراض القلب والسكتة الدماغية الإقفارية. الطريقة: تمت دراسة مجموعة من اثنين وستين فردًا تتراوح أعمارهم بين 48 و68 عامًا، بما في ذلك مرضى القلب والسكتة الدماغية الإقفارية والأصحاء كمجموعة قياسية. تم قياس ثلاثة عشر مؤشرًا من موشرات الكيموحيوية من اختبارات وظائف الكبد. النتائج: كشفت النتائج عن اختلافات كبيرة ($p < 0.05$) في خمسة مؤشرات كيموحيوية تضمنت (البيليروبين الكلي (TBIL)، والبيليروبين المباشر (DBIL)، والبيليروبين غير المباشر (IBIL)، وحمض الصفراء الكلي (TBAc) ونسبة أسبارتات أمينوترانسفيراز/ألانين أمينوترانسفيراز (AST/ALT)) بين مرضى أمراض القلب والأوعية الدموية. والجدير بالذكر أن مستويات TBIL وDBIL وIBIL وTBAc كانت أقل بشكل ملحوظ في مرضى أمراض القلب والسكتة الدماغية الإقفارية مقارنة بالاصحاء. بالإضافة إلى ذلك، كانت نسبة AST/ALT مرتفعة بشكل ملحوظ في مرضى أمراض القلب مقارنة بالاصحاء ، في حين كانت الاختلافات بين السكتة الدماغية الإقفارية ومجموعات الاصحاء أقل وضوحًا. الخلاصة: تشير هذه النتائج إلى أن اختبارات وظائف الكبد يمكن أن تعزز التشخيص المبكر وتقييم المخاطر نتيجة أمراض القلب والأوعية الدموية، مما يدعو إلى إجراء المزيد من البحوث لتطوير إرشادات موحدة لاستخدامها السريري في تشخيص وإدارة أمراض القلب والأوعية الدموية.

الكلمات المفتاحية: أمراض القلب والأوعية الدموية (CVD)، اختبارات وظائف الكبد (LFTs)، أمراض القلب (HD)، السكتة الدماغية الإقفارية (IS)، البيليروبين، حمض الصفراء ونسبة AST / ALT

Introduction:

Cardiovascular disease (CVD) encompasses ischemic and hemorrhagic conditions affecting the heart, brain, and other tissues. The World Health Organization (WHO) has indicated that cardiovascular diseases are the primary cause of death followed by diabetes. CVDs can be caused by five global risk factors contributing to CVD-related deaths include arteriosclerosis, high blood pressure, hyperlipidaemia, diabetes mellitus and obesity **[1].** The range of conditions classified under this term is broad and includes heart disease (HD), strokes, and various other conditions.

According to the Global Burden of Disease, the prevalence of CVD rose from 271 million in 1990 to 523 million in 2019, while deaths related to CVD increased from 12.1 million to 18.6 million during that time frame **[2]**. This refer to that the difficulties in diagnosing and treating cardiovascular disease (CVD), despite years of significant advancements and clinical initiatives, remain substantial. Numerous studies indicate that a range of early damaging events, including oxidative stress, inflammatory responses, ion imbalances, and metabolic disruptions occur in the body during the onset and progression of

cardiovascular disease **[3]**. These disturbances harm endothelial cells, neurons, and glial cells, significantly impacting the circulatory and nervous systems, leading to alterations in many DNA, protein, and metabolite molecules **[4]**.

On the other hand, previous studies concluded that there are relationship between liver functions and cardiovascular disease **[5-7]**. One of these studies believed that albumin has a notable connection with cardiac dynamics and inflammation, sharing several traits with the risk factors that exacerbate cardiovascular disease. It found that serum albumin levels could predict cardiovascular disease (CVD) deaths in individuals aged 55 to 85 year **[7]**. Another study reported that higher serum albumin levels, even within normal ranges, were linked to a lower risk of developing CVD within three years, while all-cause mortality showed no correlation. Chronic low serum albumin was not connected to mortality or new cases of CVD. However, a decrease in serum albumin could serve as an early warning sign for CVD, even when levels remain normal. Additionally, serum bilirubin seems to be associated with CVD events, including myocardial infarction and death, in patients without liver disease **[6]**. Also, the correlation of liver enzymes, aspartate aminotransferase and alanine aminotransferase (AST and ALT), with CVD was suggested by Adibi and his colleagues. Their study reported that the AST/ALT ratios were linked to coronary atherosclerosis in patients assessed through coronary angiography, and this relationship was found to be independently significant from other predictors in metabolic syndrome and C-reactive protein (CRP) levels **[5]**.

Liver function tests (LFTs) are routinely conducted even in normal conditions, but elevated levels may indicates to pathological conditions and can lead to complicated clinical interventions. Meanwhile, some patients may have critical liver disease that was previously undetected. Since some studies have assumed that LFTs may be correlated with a higher risk of coronary artery disease (CAD), this study aims highlighting a LFTs to determine its relationship with CVD. Thus, it may be feasible to identify these substances as potential biomarkers for researching, diagnosing and discrimination between cardiovascular diseases, particularly heart diseases (HD) and ischemic stroke (IS).

2. Materials and methods

2-1- Study design and participants:

A case-control study was conducted to explore the biochemistry changes for liver function tests associated with heart disease (HD) and ischemic stroke (IS). The study included patients who visited Al - Nasiriyah Teaching Hospital, Thi-Qar Province where it was performed during four months from February to May, 2024. Based on diagnostic evaluations by healthcare professionals, sixty-two individuals, aged (48 to 68 year), gave their informed consent to participate in this study as volunteers. The subjects were categorized into three groups as HD, IS and control groups. Firstly, the patients with Heart Disease, HD group, consisting of 20 patients included seven coronary heart disease (CHD), five bradycardia, three heart failure (HF) and five acute myocardial infarction (AMI). Secondly, Ischemic Stroke patients, IS group, comprising 17 patients and thirdly a control group comprising 25 individuals without any observable symptoms or history of cardiovascular disease (CVD). Demographic data as shown in table 1, including sex and age, were collected, and each participant underwent a clinical chemistry test to exclude the patients with other diseases.

Table 1: *Demographic information for participated subjects in groups of study based on sex and age.*

Clinical		Control	HD	IS
Demographic information				
Sex	Male	13	11	10
	Female	12	9	7
Age (years)		52 ± 4	64 ± 5	63 ± 5

2.2. Blood specimens and sample preparation

The venous blood samples (5 ml), after an overnight fast, from each participant were collected into dry vacutainer tubes as well as 5 mL vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). At the same day, collected blood samples were centrifuged at 1500 r/min and 4 °C for 15 minutes to obtain serum for chemistry assays using an automatic biochemical analyzer (Cobas-311, Switzerland). Plasma also was collected and stored at –80 °C for future analysis.

3. Results and Discussion

The clinical characteristics of participants in three study groups (control, HD, and IS groups) are outlined in Table 1 including liver function test parameters (Total protein, Albumin, Globulin, Prealbumin, Total bilirubin, direct bilirubin, Indirect bilirubin, Total biliary acid, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), AST/ALT, Albumin/globulin) as biochemical indicators. Despite the limited number of subjects, which is a common issue in population-based disease studies, the chi-square test and ANOVA revealed significant differences ($p<0.05$) in five out of thirteen tests. These traits included total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), Total biliary acid (TBAc) and aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT).

The results presented in Table 2, following statistical analysis, showed strong performance on both the calibration and validation sets. The accuracy, sensitivity, and AUC values were sufficient to distinguish between the HD and IS groups, as well as between CVD and non-CVD groups. A univariate statistical analysis, including paired t-tests (p-values) and fold changes (ratios), was conducted to compare all study groups. The p-values and fold changes for clinical traits were calculated using the Benjamini–Hochberg procedure, which establishes a significance threshold of 0.05 for p-values **[8, 9]**. The four substances associated with bilirubin metabolism and bile production (TBIL, DBIL, IBIL and TBAc) exhibited low significantly changed in HD and IS patients compared to the control groups.

The four clinical parameters in the HD, IS, and control groups revealed significant differences in their levels. It is well established, in aging, that liver dysfunction is one of risk factors for various physiological processes, contributing to a higher prevalence of cardiovascular disease (CVD).

Table 2: *A univariate statistical analysis, including paired t-tests (p-values) and fold changes (ratios) for biochemical indicators which were expressed as mean ± standard deviation. The p-values and fold changes were calculated using the Benjamin–Hochberg procedure, a significant difference was established based on significance threshold ($p < 0.05$).*

Clinical traits	Control	HD	IS	Fold change	*p*-value
Biochemical indicators					

Total protein	63.4±9.0	63.1±7.7	65.8±7.2	0.41	0.664
Albumin	39.1 ±7.4	38.4±5.4	39.5±5.4	0.58	0.564
Globulin	24.3±1.6	24.7±2.7	25.8±1.8	0.52	0.599
Albumin/globulin	1.5±0.3	1.6±0.3	1.6±0.2	0.42	0.521
Prealbumin	199.4±108.8	203.8±68.6	259.0±57.8	1.67	0.204
Total bilirubin	24.3±21.1	14.1±3.4	7.9±3.7	4.14	0.025*
Direct bilirubin	12.0±13.0	4.5±1.8	2.8±1.3	4.1	0.026*
Indirect bilirubin	12.3±8.1	9.6±2.6	5.1±2.4	4.41	0.020*
Total biliary acid	14.0±2.5	12.2±3.9	10.4±2.9	4.45	0.018*
Alkaline phosphatase	130.8±18.3	85.2±7.5	73.7±8.5	2.09	0.14
Alanine aminotransferase (ALT)	35.7±15.1	13.9±5.3	15.9±4.0	2.25	0.122
Aspartate aminotransferase (AST)	57.3±20.4	38.8±15.4	19.5±5.0	1.66	0.206
AST/ALT	1.5±0.8	2.7±0.5	1.2±0.6	5.1	0.012*

The total bilirubin in the blood is the combination of both direct (conjugated), the part of total bilirubin that is conjugated with glucose and making it water-soluble, and indirect (unconjugated), the unconjugated portion which is not water-soluble and originates from the breakdown of hemoglobin. Bilirubin, especially unconjugated bilirubin, possesses antioxidant properties. Research indicates that elevated levels of indirect bilirubin may be linked to a lower risk of cardiovascular diseases, attributable to its capacity to counteract oxidative stress **[10]**. DBIL levels serve as a marker for liver function. When liver function is compromised, direct bilirubin levels may rise, potentially correlating with cardiovascular risk factors like inflammation and metabolic syndrome. Both forms of bilirubin can indicate underlying inflammatory processes, and chronic inflammation is a recognized factor in the development of heart diseases. Bilirubin may offer protective benefits against heart disease. Additionally, bilirubin (TBIL, DBIL and IDBIL) levels can contribute to a

comprehensive evaluation of risk factors associated with heart disease. Also, biliary acids are intricately linked to cardiovascular risk through their roles in metabolism, inflammation, cholesterol regulation, and gut health. Understanding these relationships can help in assessing and managing cardiovascular risk more effectively. The relationship between total biliary acid levels and cardiovascular risk is complex, with high levels indicating metabolic dysfunction and specific profiles potentially offering protective effects. Several studies have indicated that altered total biliary acid levels may serve as biomarkers for cardiovascular risk. High levels of biliary acids can reflect metabolic dysfunction, while specific bile acid profiles may have protective effects against cardiovascular diseases **[11-14]**. Additionally, the role of TBAc in the context of ischemic stroke was noted. It is intricately linked to the mechanisms underlying ischemic stroke through their effects on cholesterol metabolism, inflammation, endothelial function, gut health, and overall metabolic regulation. Understanding these relationships can provide insights into potential preventive strategies and therapeutic targets for reducing ischemic stroke risk. Cholesterol metabolism and excretion is affected by dysregulation of bile acid levels which can lead to increased cholesterol accumulation in blood vessels, contributing to atherosclerosis, which is a significant risk factor for ischemic stroke. Some studies suggest that altered bile acid profiles may be predictive of ischemic stroke risk. These researches indicated that high levels of certain bile acids can signal increased cardiovascular risk, while specific bile acid compositions might be associated with better outcomes for patients **[12, 15-17]**. Conversely, certain bile acid compositions may offer protective effects, improving metabolic health and reducing inflammation, which could lead to more favourable outcomes for at-risk patients. This connection between bile acid levels and ischemic stroke risk indicates the potential utility of bile acid profiles as biomarkers in clinical practice. Monitoring these levels could facilitate the identification of individuals at higher risk and inform preventive strategies, emphasizing the importance of bile acids in cardiovascular disease management. The interplay between bile acid levels and ischemic stroke risk underscores the importance of understanding bile acid metabolism in cardiovascular health.

We can conclude from the above that there is an inverse relationship between levels of substances related to bilirubin metabolism and bile production and cardiovascular risk. Thus, the result of this study were similar with previous

studies and confirmed the low significantly value of bilirubin levels between CVD and control groups.

On the other hand, AST/ALT ratio has emerged as a significant biomarker in the context of cardiovascular diseases (CVD). Traditionally associated with liver function, this ratio is increasingly recognized for its potential implications in cardiovascular health, particularly in assessing risk and predicting outcomes in heart disease. Previous research found a significant link between elevated AST/ALT ratios and cardiovascular risk factors. A study reported that higher ratios are associated with an increased risk of cardiovascular events, especially in men, suggesting the ratio offers additional prognostic information beyond conventional risk factors**[18].** Furthermore, the AST/ALT ratio correlates with metabolic conditions like non-alcoholic fatty liver disease (NAFLD), which is a notable risk factor for cardiovascular disease. Elevated liver enzymes in NAFLD patients imply that the ratio may reflect broader metabolic issues contributing to cardiovascular risk **[19].** This ratio can be influenced by many factors, such as age, sex, and the presence of liver disease, which can distort its interpretation in the context of cardiovascular disease. For example, although elevated AST levels may indicate myocardial damage, they may also result from liver disease, complicating the clinical picture. Some studies suggest that the AST/ALT ratio may improve risk prediction models, while other studies suggest that it does not significantly improve the discriminatory power of cardiovascular risk assessment tools **[20]**. Thus, highlighting on this ratio needs to more research to clarify the role of the AST/ALT ratio in cardiovascular risk stratification. Although there are no significant changes in the values of Aspartate aminotransferase to Alanine aminotransferase ratio among all groups, our results show the high significant AST/ALT ratio between HD and control groups unlike its low value between IS and control groups. This result may be used as effective indicator for discrimination between HD and IS based on high or low AST/ALT than its normal level

In conclusion, the AST/ALT ratio presents a promising biomarker for assessing cardiovascular health. Its association with various cardiovascular risk factors and outcomes suggests that it may serve as a valuable adjunct in the evaluation of patients at risk for heart disease. However, further studies are essential to validate its clinical utility and elucidate the mechanisms connecting liver function to cardiovascular disease. Investigating AST/ALT ratio in different conditions and its interaction with other biomarkers of cardiovascular disease

may enhance its clinical utility. Furthermore, investigating the underlying mechanisms associated with liver function and cardiovascular pathology may provide insights into potential therapeutic targets for reducing cardiovascular risk.

References:

1. Muhsen Ali, A., et al., *Metabolomic Profiling of Submaximal Exercise at a Standardised Relative Intensity in Healthy Adults.* Metabolites, 2016. **6**(1).
2. Roth, G.A., et al., *Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study.* J Am Coll Cardiol, 2020. **76**(25): p. 2982-3021.
3. Xu, M., P.P. Liu, and H. Li, *Innate Immune Signaling and Its Role in Metabolic and Cardiovascular Diseases.* Physiol Rev, 2019. **99**(1): p. 893-948.
4. Severino, P., et al., *Ischemic Heart Disease Pathophysiology Paradigms Overview: From Plaque Activation to Microvascular Dysfunction.* International Journal of Molecular Sciences, 2020. **21**(21): p. 8118.
5. Adibi, P., et al., *Prediction of coronary atherosclerotic disease with liver transaminase level.* Liver Int, 2007. **27**(7): p. 895-900.
6. Horsfall, L.J., I. Nazareth, and I. Petersen, *Cardiovascular events as a function of serum bilirubin levels in a large, statin-treated cohort.* Circulation, 2012. **126**(22): p. 2556-64.
7. Schalk, B.W., et al., *Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam.* Am J Epidemiol, 2006. **164**(10): p. 969-77.
8. Ali, A.M., et al., *LC/MS-based discrimination between plasma and urine metabolomic changes following exposure to ultraviolet radiation by using data modelling.* Metabolomics, 2023. **19**(2): p. 13.
9. Benjamini, Y. and Y. Hochberg, *Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing.* Journal of the Royal Statistical Society: Series B (Methodological), 1995. **57**(1): p. 289-300.
10. Ziberna, L., et al., *Bilirubin is an Endogenous Antioxidant in Human Vascular Endothelial Cells.* Sci Rep, 2016. **6**: p. 29240.

11. Luo, L., et al., *Assessment of serum bile acid profiles as biomarkers of liver injury and liver disease in humans.* PLoS One, 2018. **13**(3): p. e0193824.
12. Punzo, A., et al., *Bile Acids and Bilirubin Role in Oxidative Stress and Inflammation in Cardiovascular Diseases.* Diseases, 2024. **12**(5).
13. Zhang, B.C., et al., *Increased serum bile acid level is associated with high-risk coronary artery plaques in an asymptomatic population detected by coronary computed tomography angiography.* J Thorac Dis, 2019. **11**(12): p. 5063-5070.
14. Zhang, S., et al., *The Role of Bile Acids in Cardiovascular Diseases: from Mechanisms to Clinical Implications.* Aging Dis, 2023. **14**(2): p. 261-282.
15. Charach, G., et al., *The association of bile acid excretion and atherosclerotic coronary artery disease.* Therap Adv Gastroenterol, 2011. **4**(2): p. 95-101.
16. Chong Nguyen, C., et al., *Circulating bile acids concentration is predictive of coronary artery disease in human.* Scientific Reports, 2021. **11**(1): p. 22661.
17. Mateu-Fabregat, J., et al., *Bile Acids and Risk of Adverse Cardiovascular Events and All-Cause Mortality in Patients with Acute Coronary Syndrome.* Nutrients, 2024. **16**(7): p. 1062.
18. Weng, S.F., et al., *The value of aspartate aminotransferase and alanine aminotransferase in cardiovascular disease risk assessment.* Open Heart, 2015. **2**(1): p. e000272.
19. Shen, J., et al., *Correlation of serum alanine aminotransferase and aspartate aminotransferase with coronary heart disease.* Int J Clin Exp Med, 2015. **8**(3): p. 4399-404.
20. Bian, Y., et al., *Association between aspartate aminotransferase to alanine aminotransferase ratio and mortality in critically ill patients with congestive heart failure.* Scientific Reports, 2024. **14**(1): p. 26317.