ORIGINAL ARTICLE

EXPLORING THE ROLE OF NON-HDL CHOLESTEROL IN ACUTE CORONARY SYNDROME: A CASE-CONTROL STUDY

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Objectives: This case-control study aimed to investigate the association between non-high-density lipoprotein (non-HDL) cholesterol levels and acute coronary syndrome (ACS) among individuals not recently treated with statins.

Methodology: A total of 100 participants with ACS, who had not received recent statin therapy, were selected from the Coronary Care Unit (CCU) at Al-Kadhimiyah Hospital in Baghdad, Iraq. Controls, matching the eligibility criteria of cases except for ACS symptoms, were randomly chosen from the same hospital. Both groups met criteria including age over 40, and a history of diabetes mellitus, hypertension, smoking, and obesity. Statistical significance was set at $p < 0.05$.

Results: The study found a significant independent association between elevated non-HDL cholesterol levels and ACS, with an average non-HDL level of 154.2 mg/dl (normal: 130 mg/dl) among ACS cases ($p < 0.001$), compared to 120 mg/dl in controls. Elevated non-HDL levels were also correlated with increased BMI ($p = 0.01$, $r = 0.3$) and various lipid markers ($p < 0.05$), except HDL.

Conclusion: Elevated non-HDL cholesterol levels upon admission may serve as a potential indicator of ACS risk. These findings underscore the importance of non-HDL cholesterol assessment in ACS risk stratification and management.

Keywords: Non-HDL; Dyslipidemia; Acute Coronary Syndrome; Association

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INTRODUCTION

Acute coronary syndrome (ACS) encompasses myocardial infarction and unstable angina, manifesting as newly developing or rapidly worsening angina, exertional angina, or angina at rest without evident myocardial ischemia.[1] Established risk factors for coronary or peripheral artery disease include age, sex, family history, smoking, hypertension, hypercholesterolemia, and diabetes.[2] Atherosclerosis, characterized by arterial thickening or hardening due to plaque accumulation in the artery walls, is a pivotal pathology underlying cardiovascular diseases.[3] Dyslipidemia, particularly hyperlipidemia, has been consistently implicated as a risk factor for atherosclerosis.[4] Accordingly, reducing low-density lipoprotein cholesterol (LDL-C) has been prioritized in lipid-lowering therapy for patients with coronary artery diseases (CAD), as endorsed by the American Heart Association (AHA) guidelines.[5]

Despite successful reductions in LDL-C levels in CAD patients, the prevalence of coronary heart disease (CHD) remains high.[6] Non-HDL cholesterol (Non-HDL-C), encompassing total cholesterol in lipoproteins excluding high-density lipoprotein cholesterol (HDL-C), has emerged as a significant independent predictor of cardiovascular disease (CVD) risk.[7] Patients with CAD or high cardiovascular risk are advised to consider Non-HDL-C as a secondary target for lipid-lowering therapy.[8] Recent discussions have centered around the non-HDL to HDL-C ratio and its relevance to metabolic syndrome, reflecting a shift towards recognizing the distinct contributions of different lipoproteins to CHD risk. The National Institute of Health Care Excellence (NICE) in the United Kingdom has updated its recommendations, favoring Non-HDL-C over LDL-C as the primary target for lipid-lowering treatment in individuals with diabetes, albeit differing from other international guidelines.[9]

However, existing literature suffers from limitations such as inadequate acknowledgment and underutilization of Non-HDL-C testing in clinical assessments of atherosclerotic cardiovascular disease (ASCVD). Notably, several studies have underscored the association between Non-HDL-C and the severity of coronary artery lesions, underscoring its role as an independent predictor of severe coronary artery disease.[10-13] Given the scarcity of studies addressing these issues in the Iraqi population, this study aimed to explore the relationship between Non-HDL hyperlipidemia and acute coronary syndrome. By gathering local data on patient-centered dyslipidemia management, this research may contribute to a better understanding of the potential benefits of maintaining lower serum cholesterol levels, particularly Non-HDL-C, in mitigating the risk of ASCVD. This is particularly pertinent for patients with type 2 diabetes, where Non-HDL cholesterol has been identified as a robust indicator of cardiovascular disease risk. Therefore, this study addresses a critical gap in knowledge and holds implications for tailored cardiovascular risk management strategies in the Iraqi population, ultimately aiming to improve patient outcomes and inform clinical practice.

METHODOLOGY

Study Design: A retrospective case-control study was conducted at Coronary Care Unit (CCU) in Baghdad, Iraq, spanning from July 1, 2021, to July 1, 2022.

Setting: The study was conducted at Al-Kadhimiyah Teaching Hospital, specifically within its CCU, which provided a suitable environment for the observation and treatment of acute coronary syndrome (ACS) cases.

Participants: A total of 200 individuals were enrolled in the study. The case group comprised 100 individuals who were conveniently selected from the CCU before initiating statin therapy or any other treatment. The control group also consisted of 100 individuals, conveniently selected from the same hospital, meeting eligibility criteria similar to the cases but without presenting symptoms of chest pain or dyspnea and not admitted to the CCU.

Variables: The variables considered in the study included age, sex, smoking status, lipid profile, ACS location (if ST-elevation myocardial infarction [STEMI] or unstable angina), echocardiography (ECHO) findings, and outcome measures.

Data Sources/Measurement: Data were collected through patient history, electrocardiogram (ECG) evaluations, echocardiography, blood tests (including troponin levels), and clinical observations. Ethical approvals were obtained from the relevant authorities, and verbal consent was secured from all participants.

Bias: Efforts were made to minimize bias by employing strict eligibility criteria, obtaining ethical approvals, and ensuring uniform data collection procedures for both case and control groups. However, inherent biases associated with the retrospective nature of the study and the convenience sampling method cannot be entirely ruled out.

Study Size: A total of 200 participants (100 cases and 100 controls) were included in the study, which was deemed adequate for the analysis of the selected variables and outcomes.

Quantitative Variables: Continuous data were presented as means with standard deviations (SD), while categorical variables were expressed as percentages. Analysis of variance (ANOVA) and t-tests were employed for comparing means between groups, and Fisher's exact test or the chi-square test was utilized for assessing differences in categorical variables.

Statistical Methods: Normality of data distribution was verified using graphical methods. Statistical significance was defined as a P-value less than 0.05. Pearson's correlation analysis was conducted to explore relationships between lipid profile measures. Additionally, multivariable logistic regression analysis was performed to examine the association between non-HDL and different types of ACS. Data management and statistical analyses were carried out using R software and associated statistical packages (R version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants: The study included 100 cases and 100 controls. Among the ACS group, there were 64 men and 36 women, while smoking and comorbidities like hypertension and diabetes were present in 49%, 69%, and 52% of cases, respectively. The mean age of the cases and controls was 56.9 ± 11.4 and 56.5 ± 9.7 years, respectively. Baseline characteristics between cases and controls were comparable, with no statistically significant differences observed in age, gender distribution, smoking status, or comorbidities ($p > 0.05$).

Descriptive Data: Table 1 presents the baseline characteristics and lipid profile of patients and controls. Statistically significantly higher lipid profile values, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very-low-

density lipoprotein (VLDL), and non-high-density lipoprotein (Non-HDL), were observed in the case group compared to controls ($p < 0.001$).

Outcome Data: Regarding the association between lipid profile characteristics and different types of ACS (STEMI, non-STEMI, unstable angina), no significant differences were observed in lipid profiles among the three ACS subtypes ($p > 0.05$). However, there were significant associations between demographic factors and comorbidities with ACS subtypes. For instance, age ($p = 0.04$), smoking status ($p = 0.04$), and diabetes ($p = 0.002$) showed significant associations with different ACS types, Table 2.

Table 1: Baseline characteristics of patients and controls and the statistical difference between them

	Cases	Control	P-value*
Total (N)	**100**	**100**	**-**
Age, years	56.9 ± 11.4	56.5 ± 9.7	0.800
Male Female	64 (64%) 36 (36%)	51 (51%) 49 (49%)	0.400
Current Smoking	49 (49%)	27 (27%)	0.200
BMI (kg/m^2)	27.0 ± 2.6	27.0± 1.5	0.800
Co-morbidities			
Hypertension	69 (69%)	71 (71%)	0.800
Diabetes	52 (52%)	44 (44%)	> 0.90
Lipid Profile			
Total Cholesterol	187.6 ± 43.1	165.8 ± 25.6	< 0.001
Triglyceride	173.5 ± 65.0	140.4 ± 27.6	< 0.001
LDL	117.1 ± 34.9	104.2 ± 19.9	0.001
VLDL	35.3 ± 10.9	27.7 ± 4.3	< 0.001
HDL	33.6 ± 7.1	45.2 ± 7.4	< 0.001
Non-HDL	154.2 ± 41.8	120.6 ± 27.4	< 0.001

**Welch Two Sample t-test; Pearson's Chi-squared test with Yates' continuity correction*

Main Results: Multivariable logistic regression analysis was conducted to explore the relationship between non-HDL dyslipidemia and ACS subtypes, adjusting for age, gender, smoking, hypertension, and diabetes. The analysis revealed that non-HDL was not a standalone risk factor for STEMI ($p = 0.2$), non-STEMI ($p = 0.3$), or unstable angina ($p = 0.8$), Table 3.

Table 3: multivariable logistic regression analysis between non-HDL dyslipidaemia and ACS types

Outcome	OR	95% CI	P-value
STEMI	0.52	0.17 - 1.50	0.2
Non-STEMI	1.76	0.61 - 5.46	0.3
Unstable Angina	1.26	0.27 - 9.05	0.8

**Adjusted for age, gender, smoking, hypertension, and diabetes*
OR = Odds Ratio, CI = Confidence Interval, STEMI = ST elevation myocardial infarction

The patients presented with a wide range of symptoms: transient LOC (227; 45.8%), dizziness (171; 34.5%), vertigo (56; 11.3%), blackouts (graying of vision) (48; 9.7%), falls (40; 8.1%), palpitations (37; 7.5%), nausea and vomiting (27; 5.4%), diaphoresis (25; 5%), and generalized weakness (16; 3.2%). The HUTT test was positive in 298 patients (60.1%). The most common diagnosis based on the HUTT test result was vasovagal syncope (158; 79.8%), orthostatic hypotension (23; 11.6%), autonomic dysfunction (12; 6.1%) and POTS (5; 2.5%). Patients with vasovagal syncope were divided into mixed type (130; 82.3%), vasodepressor type (23; 14.6%), and cardioinhibitory type (5; 3.2%). The correlation between age, gender, and presenting symptoms with HUTT results is shown in Tables 1 and 2. It is imperative to mention here that only vertigo, dizziness, blackouts, and LOC were statistically significant when compared to the diagnostic yield of HUTT testing. No significant correlation (p-value>0.05) was found between the presenting symptoms, age, gender, and specific diagnosis on HUTT testing.

Table 2: Association between demographics, co-morbidities, lipid profile and the different ACS types

	STEMI	Non-STEMI	Unstable Angina	*P-value
Total (N)	**52**	**38**	**10**	**-**
Age, years	54.2 ± 10.4	60.2 ± 12.3	58.2 ± 10.2	0.04
Smoking	31 (60%)	16 (42%)	2 (20%)	0.04
Diabetes	18 (35%)	27 (71%)	7 (70%)	0.002
Hypertension	38 (73%)	24 (63%)	7 (70%)	0.6
Heart failure	18 (35%)	11 (29%)	2 (20%)	0.7
BMI (kg/m^2)	26.5 ± 2.6	27.2 ± 2.7	27.3 ± 1.8	0.4
Lipid Profile				
Total Cholesterol, mg/dL	189.0 ± 50.0	184.8 ± 34.7	190.5 ± 34.9	0.9
Triglyceride, mg/dL	165.9 ± 58.8	172.3 ± 68.3	217.7 ± 72.8	0.068
LDL, mg/dL	115.0 ± 38.7	120.4 ± 31.0	116.1 ± 28.8	0.8
VLDL, mg/dL	34.5 ± 10.2	35.2 ± 11.1	39.8 ± 13.6	0.4
HDL, mg/dL	34.3 ± 7.0	33.2 ± 7.0	31.2 ± 8.3	0.4
Non-HDL, mg/dL	154.9 ± 47.3	152.0 ± 35.1	158.9 ± 36.2	0.9

**One-way ANOVA; Fisher's exact test; Kruskal-Wallis's rank sum test*
BMI = body mass index, STEMI = ST elevation myocardial infarction

DISCUSSION

Our study aimed to explore the relationship between newly diagnosed acute coronary syndrome (ACS), specifically myocardial infarction and unstable angina, and serum lipid measures, focusing on low-density lipoprotein (LDL) and non-high-density lipoprotein cholesterol (non-HDL). Our findings revealed a robust association between non-HDL levels and ACS ($p = 0.001$), aligning with previous research such as the Lipid Research Clinics Program Follow-up Study, which emphasized the superior correlation of non-HDL with ACS risk compared to LDL. These results underscore the potential clinical significance of non-HDL as a predictive marker for ACS risk assessment and management.

Moreover, our study observed a positive correlation between non-HDL levels and body mass index (BMI), indicative of an increased ACS risk associated with higher BMI values. While the correlation between BMI and lipid parameters, except HDL, was consistent with our findings, discrepancies were noted in a study by Babikr WG et al. conducted at Najran University Hospital (Najran, Saudi Arabia), emphasizing the complexity of these relationships across different populations and settings.[15]

Comparisons with studies such as that conducted by Shahid SU et al. at the Department of Microbiology and Molecular Genetics, University of the Punjab, Lahore, further highlight the association between dyslipidemia and ACS risk.[16] While our study demonstrated higher lipid profiles in ACS cases compared to controls, the observed disparities in risk factors like diabetes mellitus (DM), hypertension (HT), and smoking underscore the multifactorial nature of ACS etiology and the interplay of various contributing factors.

Consistent with prior research by Amusat S et al.[17] our study identified significant positive correlations between non-HDL and other lipid profiles, emphasizing the utility of non-HDL as a comprehensive marker of cardiovascular risk. These findings support the notion that individuals with elevated non-HDL levels may face an increased risk of atherosclerosis and subsequent cardiovascular diseases.

LIMITATION

Our study has several limitations that warrant consideration. The lack of assessment of non-HDL ratios in different ACS subtypes, particularly between unstable angina and acute coronary syndrome, hampers the comprehensive evaluation of non-HDL's prognostic significance across various clinical manifestations of coronary artery disease. Additionally, the single-site nature of the study limits the generalizability of findings to broader demographic and geographic contexts, necessitating caution in extrapolating results to diverse populations. Furthermore, the limited sample size may compromise the statistical robustness of results and limit their applicability to larger patient cohorts.

CONCLUSION

In conclusion, our study emphasizes the importance of addressing secondary lipid targets, particularly elevated non-high-density lipoprotein cholesterol (non-HDL-C) and low high-density lipoprotein cholesterol (HDL-C) levels, in preventing cardiovascular diseases (CVD) and atherosclerosis. The significant association between high non-HDL-C levels and acute coronary syndrome (ACS) underscores the need to prioritize non-HDL-C reduction alongside traditional low-density lipoprotein cholesterol (LDL-C) lowering strategies. Incorporating interventions targeting HDL-C elevation and optimal non-HDL-C levels into clinical practice guidelines can enhance risk stratification and optimize preventive strategies, ultimately reducing the burden of CVD and improving patient outcomes.

AUTHORS' CONTRIBUTION

MKMM and RBA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MKMM, RBA, and AKKAG: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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