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ORIGINAL ARTICLE

Clinical significance of low HDL-C levels in managing acute coronary syndrome.

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ABSTACT… Objective: To investigate the clinical relevance of low HDL-C levels in the management of ACS, focusing on their association with adverse outcomes. **Study Design:** Prospective Observational study. **Setting:** Faisalabad Institute of Cardiology, Faisalabad. **Period:** December 2021 to May 2022. **Methods:** 384 patients diagnosed with ACS, admitted to a tertiary care hospital in Pakistan. HDL-C levels were measured within 24 hours of admission, and participants were stratified into low HDL-C (<40 mg/dL) and normal HDL-C (≥40 mg/dL) groups. Adverse outcomes, including 30-day mortality, recurrent myocardial infarction, heart failure, and hospital stay duration, were analyzed using multivariate logistic regression and Kaplan-Meier survival analysis. Statistical significance was set at $p < 0.05$. **Results:** Low HDL-C levels were observed in 210 patients (54.7%). These patients experienced significantly higher rates of 30-day mortality (21.4% vs. 6.9%), recurrent myocardial infarction (24.8% vs. 8.6%), and heart failure (31.9% vs. 13.2%) compared to those with normal HDL-C levels ($p < 0.001$ for all). Kaplan-Meier survival analysis showed reduced survival rates at 30 days (78.6% vs. 93.1%) and 90 days (65.2% vs. 88.7%) in the low HDL-C group ($p < 0.001$). Multivariate analysis identified low HDL-C as the strongest independent predictor of adverse outcomes (OR 2.85, 95% CI: 1.85–4.39, $p < 0.001$). **Conclusion:** Low HDL-C levels are a significant independent predictor of adverse outcomes in ACS patients, highlighting their importance in risk stratification and management. These findings emphasize the need for targeted therapeutic strategies to address low HDL-C levels, particularly in resource-limited settings.

Key words: Acute Coronary Syndrome, Cardiovascular Outcomes, HDL-C, Low HDL-C, Lipid Management, Pakistan, South Asian Population.

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INTRODUCTION

Cardiovascular diseases (CVDs) have continued to be the primary cause of death and disability globally; ACS is one of the most severe presentations of CVDs. ACS ranges from STEMI in which the blood flow distal to the occlusion is completely blocked to NSTEMI in which the blood flow is partially occluded and unstable angina.[1] These conditions are usually caused by atherosclerotic plaque formation within coronary arteries which subsequently becomes ulcerated, with accompanied thrombosis that results to partial or complete blockage in blood delivery to the myocardial mass. In Pakistan CVD are on the increase and account for 30-40% of all deaths every year.[2] Of these, ACS contributes considerable health care cost and burden because it presents abruptly, consumes a large amount of resource, and gives long-term complications.[3] Such abnormalities especially with lipid profile are among the main features associated with the development of ACS which is rooted in atherosclerosis. Although high levels of LDL-C is well understood to cause plaque build-up and eventual plaque rupture, the adequate levels of HDL-C have emerged to be equally important but under-recognized determinant of cardiovascular health. HDL-C, often referred to as "good cholesterol," plays a central role in reverse cholesterol transport, whereby it removes cholesterol from peripheral tissues and transports it to the liver for metabolism and excretion.[4] Beyond this, HDL-C exhibits numerous vasoprotective properties, including anti-inflammatory, antioxidative, and antithrombotic effects. These attributes make HDL-C a crucial biomarker and potential therapeutic target in managing cardiovascular risk.[5]

Emerging evidence has identified low HDL-C levels as a strong independent predictor of cardiovascular

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events, including ACS. International studies have shown that patients with low HDL-C levels are at higher risk of recurrent ischemic events, heart failure, and mortality after an ACS episode.[6] However, the majority of these studies are conducted in Western populations, with limited exploration of these associations in South Asian populations, including Pakistan.[7] Specifically, the South Asians are metabolically abnormal with a high prevalence of central obesity, insulin resistance and the resulting type 2 diabetes, dyslipidemia, characterized by reduced levels of HDL-C. These facts call therefore for an examination of the details of the actual effects of low levels of HDL-C on ACS results within the population of Pakistan.[8] In our country as well as in other countries, studies have also confirmed high rates of dyslipidemia as cardiovascular risk indicator.[9] For example, the cross-sectional reports from the tertiary care hospitals, Karachi and Lahore revealed that a large number of patients presenting with ACS have low levels of HDL-C. These studies also show a considerable unexpected shortage in assessment and management of the role of HDL-C in the clinical practice where most approaches are aimed at achieving a low LDL-C value.[10] Despite the benefit of statins and other lipid reducing therapies in reducing cardiovascular risk in ACS, there still exists a significant risk that remains even with normalisation of lipid parameters.[11] This raises an important question: Should low levels of or 'dysfunctional' HDL-C be used as a predictor or treatment intervention in the context of acute management of ACS?

The relative neglect of HDL-C in cardiovascular practice in Pakistan can also be explained by deficiencies in availability and expenditure on medical services as well as dearth of enthusiastic public health campaigns aimed at encompassing all lipid profiles.[12] In contrast to LDL- C which has formed a rationale of most lipid management approaches, HDL-C is generally deemed ancillary despite its proven benefits for cardiovascular health.[11] This lack of clinical emphasis along with additional burden of ACS in Pakistan calls for research to investigate the clinical relevance as to whether HDL-C is significantly different in acute setting of coronary events.[13] Moreover, the use of HDL-C for adding value in risk models may assist the clinician in defining the subjects at high risk and allow for more accurate therapeutic approach. As in any population, there is a need for focus on low levels of HDL-C as a common but neglected risk factor for ACS in Pakistan. To the best of our knowledge and on the backdrop of global progress in lipid management, there is sparse focus given to HDL-C with regard to research and out-patient care in Pakistan.[14] Filling this gap appears to be crucial to enhancing cardiovascular status of populations characterized by certain genetic and environmental biomarkers. It is the objective of this study to look at the relationship between low levels of HDL –C and unfavourable outcomes in A tendency to such information may help in catering for better risk assessment of patients as well as coordinating effective treatments for such cases.

METHODS

The goal of this prospective observational research was to assess the clinical usefulness of reduced HDL-C in treating acute coronary syndrome (ACS). The first aim was to determine the rationale for low HDL-C in patients with ACS, primarily concerning the prognosis of the disease in patients with ACS. The study comprised of both genders, participant selected according to the inclusion criteria of age, rigorously diagnosed with ACS, admitted in the Cardiology department of Faisalabad Institute of Cardiology, Faisalabad for a period of six months from December 2021 to May 2022 after approval from ethical review committee (Ref No. 13/DME/FCI/FSD, dated: 23-12-2020.ACS was operationally defined using the American Heart Association typology, which includes, unstable angina, NSTEMI, and STEMI. The criteria for selection of patients involved admitting a diagnosis of ACS and having either a fasting or non-fasting baseline HDL cholesterol result before 24 h from admission. Patient with CKD stage 4 or above, having familial dyslipidemia or those patients on lipid-lowering therapy before admission were excluded.

Data Collection

These data were collected from participating patients' medical records and laboratories during routine patient care and therapeutic interactions for a prospective period before the interview. A structure data collection form was formulated to make sure

that documentation was professional and inclusive. The following detailed procedures were followed:

Initial Assessment

At enrollment, patient data were collected from patients themselves by trained clinical staff through interview and included demographic data, symptoms presented and clinical past history. Physical examination results were recorded initially and they comprised of pulse rate, blood pressure, weight and overall height for calculation of BMI.

Clinical History and Risk Factors

Patients were directly asked about their hypertension, DM, smoking habits, dyslipidemia, and family history of CVD, and such expressed data were later confirmed with the patient's documents.

Laboratory Investigations

Venous blood specimens were taken in the first 24 hours of the patients' stay for lipids measurement including; HDL-C, total cholesterol, triglycerides and LDL-C. The colorimetric assays were enzyme based and the experiments were done in a laboratory that complies with institutional and quality control requirements. Other analyses included cardiac biomarkers levels of Troponin and Creatine kinase MB, Full blood count, Renal profile and blood glucose.

Cardiac Assessments

Initial ECG was done on admission and subsequent ECGs were done according to the type of ACS-unstable angina, NSTEMI or STEMI. Further evaluation of left ventricle function and possible complications including regional wall motion abnormality or cardiac effusion was done by echocardiography.

Treatment and Interventions

Data on in-hospital treatment, such as antiplatelet, statin, beta-blocker, and anticoagulant therapies, PCI, or CABG, were documented.

Follow-Up During Hospital Stay

Case–based daily clinical progress notes were evaluated to define the adverse event of recurrent myocardial infarction, cardiac arrhythmia, heart failure, or in-hospital mortality. It was noted whether there were alterations in medication or other different management measures were taken.

HDL-C Measurement

Fasting blood samples were collected within 24 hours of admission to measure lipid profile, including HDL-C levels. HDL-C was analyzed using enzymatic colorimetric methods standardized in the institutional laboratory.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range), depending on the distribution. Categorical variables were expressed as frequencies and percentages. The relationship between low HDL-C levels (<40 mg/dL in men and <50 mg/dL in women) and adverse outcomes was analyzed using multivariable logistic regression models. Adjustments were made for potential confounders, including age, sex, BMI, diabetes, and hypertension. Statistical significance was set at $p < 0.05$.

Ethical Considerations

The study was approved by the Institutional Review Board of Faisalabad Institute of Cardiology Faisalabad Pakistan, and written informed consent was obtained from all participants.

RESULTS

The study population consisted of 384 individuals with acute coronary syndrome. The mean age of the participants was 58.3 years (±12.5). A majority of the participants were male, with 276 individuals (71.9%), while females accounted for 108 individuals (28.1%). Among the population, 145 individuals (37.8%) were smokers. Hypertension was present in 195 participants (50.8%), and diabetes mellitus was noted in 168 individuals (43.8%). Dyslipidemia was prevalent in 243 participants (63.3%). Low HDL-C levels (<40 mg/dL) were observed in 210 participants (54.7%), whereas 174 participants (45.3%) had normal HDL-C levels (≥40 mg/dL). Table-I

The data presented in Table-II demonstrated the significant clinical impact of low HDL-C levels on outcomes in patients with acute coronary syndrome (ACS). Patients with low HDL-C showed a markedly

higher 30-day mortality rate, with 45 cases (21.4%) compared to 12 cases (6.9%) in the normal HDL-C group ($p < 0.001$). Similarly, recurrent myocardial infarction (MI) was significantly more frequent in the low HDL-C group, affecting 52 patients (24.8%) compared to 15 patients (8.6%) in the normal HDL-C group ($p < 0.001$). Heart failure was also more prevalent among those with low HDL-C, occurring in 67 patients (31.9%) versus 23 patients (13.2%) with normal HDL-C levels ($p < 0.001$). Additionally, the average length of hospital stay was significantly longer in patients with low HDL-C, at 8.7 ± 2.4 days compared to 5.2 ± 1.9 days for those with normal HDL-C levels ($p < 0.001$).

The multivariate analysis highlighted that low HDL-C levels (<40 mg/dL) are the most significant predictor of adverse outcomes in acute coronary syndrome, with an odds ratio (OR) of 2.85 (95% CI: 1.85–4.39, p<0.001), indicating a nearly threefold increased risk. Age ≥50 years is also a significant factor, showing an OR of 1.72 (95% CI: 1.20–2.46, p=0.003). Diabetes mellitus further contributes to adverse outcomes with an OR of 1.56 (95% CI: 1.04–2.34, p=0.031). Male gender (OR 1.32, 95% CI: 0.91–1.91, p=0.135) and hypertension (OR 1.25, 95% CI: 0.86–1.80, p=0.240) did not reach statistical significance in this analysis. These findings underscore the critical role of low HDL-C levels in risk stratification and management of acute coronary syndrome. Table-III

The Kaplan-Meier survival analysis presented in Table 4 highlights significant differences in survival rates between patients with low HDL-C levels and those with normal HDL-C levels over time. At 7 days, survival rates were 89.0% for the low HDL-C group compared to 96.5% for the normal HDL-C group (p<0.001). This disparity widened at 30 days, with survival rates of 78.6% and 93.1%, respectively (p<0.001). By 90 days, the low HDL-C group showed a markedly lower survival rate of 65.2%, while the normal HDL-C group maintained a survival rate of 88.7% (p<0.001). These findings underscore the clinical importance of low HDL-C levels as a predictor of poorer survival outcomes in patients with acute coronary syndrome. Table-IV

TABLE-I

Baseline characteristics of study population (n = 384)

Variable	Mean ± SD	n (%)
Age (years)	58.3 ± 12.5	
Male Gender		276 (71.9)
Female Gender		108 (28.1)
Smoking Status		145 (37.8)
Hypertension		195 (50.8)
Diabetes Mellitus		168 (43.8)
Dyslipidemia		243 (63.3)
Low HDL-C Levels (<40 mg/dL)		210 (54.7)
Normal HDL-C Levels (≥40 mg/dL)		174 (45.3)

TABLE-II

Clinical outcomes by HDL-C levels (n = 384)

Outcome	Low HDL-C (n = 210)	Normal HDL-C (n = 174)	P-Value
Mortality (30-day)	45 (21.4)	12 (6.9)	<0.001
Recurrent MI	52 (24.8)	15 (8.6)	<0.001
Heart Failure	67 (31.9)	23 (13.2)	<0.001
Length of Hospital Stay (days)	8.7 ± 2.4	5.2 ± 1.9	<0.001

TABLE-III

Multivariate analysis of predictors of adverse outcomes (n = 384)

Variable	Odds Ratio (OR)	95% CI	P-Value
Low HDL-C Levels (<40 mg/dL)	2.85	1.85 – 4.39	<0.001
Age (≥50 years)	1.72	1.20 – 2.46	0.003
Male Gender	1.32	0.91 – 1.91	0.135
Diabetes Mellitus	1.56	1.04 – 2.34	0.031
Hypertension	1.25	0.86 – 1.80	0.240

TABLE-IV			
Kaplan-meier survival analysis (n = 384)			
Time Period (Days)	Low HDL-C Survival (%)	Normal HDL-C Survival (%)	Log-Rank P-Value
7	89.0	96.5	<0.001
30	78.6	93.1	<0.001
90	65.2	88.7	<0.001

DISCUSSION

According to the present investigation, low HDL-C levels are important element in caring and evaluation of patients with acute coronary syndrome (ACS). Significantly, the real-life data show that levels of <40 mg/dL imply not only significantly worse short-term and long-term outcomes but also are independent predictors of mortality and adverse cardiovascular events. These findings are in line with, and enhance on, previous research within this line of research.

Low HDL-C Levels and Adverse Outcomes

Low HDL-C level was found significantly associated with higher 30 days mortality (21.4% vs 6.9%, p< 0.001), recurrent Myocardial infarction (24.8% vs 8. 6% , P < 0.001) and heart failure (31.9% vs 13.2 %, p < 0.001) in this study. These observations are also in accord with Mateos et al., (2005)[15] Their study suggested that patients with low levels of 'HDL-C' are at markedly higher risk of CVD events post ACS regardless the 'LDL-C' levels.[8] In the course of different investigations, it has been described that low levels of HDL-C are directly associated with the cardiovascular risk, even when LDL-C levels are under control.[12,16] This emphasizes the individual and the additive predisposing role of low HDL-C in cardiopathology.

Comparison with Existing Studies

Two of the pioneering epidemiological studies that established a link between low levels of HDL-C and CHD are the Framingham Heart Study by Bartlett and his colleagues.[17] Extending from this knowledge, we establish that low levels of HDL-C associate not only with CHD risk but also with the prognosis of ACS, including survival. Therefore, using similar rationale, the Atherosclerosis Risk in Communities (ARIC) study[18,] and Lipid Research Clinics (LRC) Program[19], pointed towards the association of HDL-C with reduced cardiovascular events. In this study, the Kaplan-Meier survival analysis performed here is consistent with these findings with significantly lower survival probabilities in the patients group with low HDL-C levels at 7, 30 and 90 days. Our own findings are also in line with the observations made by Cheng et al. (2024) who showed that measured LDL-C and low levels of HDL-C are critical in these patients because they predict cardiovascular events in cases when LDL-C is within the normal range.[20] In addition, there is the JUPITER trial by Negi and Ballantyne et al., (2010) and a meta-analysis by Peng et al. (2022) which highlighted the unaddressed CV risk linked to low levels of HDL-C, meaning that HDL-C interventions could enhance LDL-C manipulations[21,22]

Risk Stratification and Other Predictors

In addition to low HDL-C, our study identified age of 50 years and above and diabetes mellitus as variables that contributed most to an adverse outcome. Absolute age and diabetes are also confirmed risk factors, according to the authors of the UK Prospective Diabetes Study (UKPDS) Group (1998). Notably from the present study male gender and hypertension which were common in the cohort under study were not statistically significant to the outcomes. This is in contrast with INTERHEART study which found physical inactivity and raised BMI as important causes of myocardial infarction worldwide.[23] The failure to achieve significance in our analysis could be due to the fact that some of these conditions are perhaps very common in our study population, and their presence exert masking or confounding influences on our findings.

Functional Role of HDL-C

The patient can have high quantitative levels of HDL-C, but to have good outcomes, the function of the high density lipoprotein cholesterol is very important. Research by (Vallejo-Vaz and Ray et al. in 2015 and Cheng et al. in 2022 showed that the capacity to measure cholesterol efflux, a property of HDL-C, is a better marker for CAD events than HDL-C itself.[24,25] It is important to note that our study did not evaluate the functionality of HDL, and accordingly, the present results imply that simple quantitative assessment of HDL-C can yield further prognostic information in ACS patients.

Implications for Clinical Practice

Collectively, the results of the present work underscore the necessity of taking into account HDL-C levels while assessing risk and treating ACS. Current guidelines, both the ACCF and ESC guidelines as well as other recent scientific statements and guidelines, focus mainly on LDL-C in the management of dyslipidaemia. But here, contrary to our finding and the literature, there is a call for a holistic perspective on lipid management that involves targeting HDL-C. Novel method aiming at improving the functionality of HDL-C has potential to render improved outcome in cardiovascular disease; apoA-I mimetics, CETP inhibitors and HDL infusion therapies. Some interventions have been tested in clinical trials like the dal-OUTCOMES and the ASSURE[23,26] trials, outcomes of which show that there is still much more that needs to be done to make HDL-targeting drugs the panaceas they are touted to be.

CONCLUSION

Hence this study provides an important clinical correlation of low levels of HDL-C (<40 mg/d), especially in patients presenting with an acute coronary syndrome. As expected low levels of HDL-C were again associated with adverse outcomes, 30-day mortality, reinfarction, heart failure, and length of stay in hospital. Kaplan-Meier survival analysis done also further strengthened figures in supporting that the survival rate in this group is significantly low over time. Multivariate analysis also showed that low HDL-C level was the strongest predictor of poor outcome with odds ratio estimated at almost three folds. Importantly, both high-sensitivity C-reactive protein and low HDL-C levels were independent predictors of MACE in men and women with ACS, underpinning the importance of using low HDL-C as a risk score to suggest efficient individual management in this group of patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	**Munir Ahmad:** Data collection.
4	**Naeem Asghar:** Critical revision.
5	**Hafiz Muhammad Faiq Ilyas:** Critical revision.
6	**Ahmed Salman:** Data analysis.