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Investigating the Predictive Value of Lipoprotein(a) for Atherosclerotic Plaque Burden in Stable Angina Patients: A Mechanistic and Imaging-Based Study

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Abstract

Carotid intima-media thickness (CIMT) and plaque burden via ultrasound provide validated markers of subclinical atherosclerosis. This experimental study evaluated whether combining CIMT, plaque score and novel plaque characteristics yields superior prediction of cardiovascular risk. Using portable high-resolution carotid ultrasound in 200 asymptomatic adults, subjects were categorized by plaque score (low vs high) and segment-specific CIMT. The objective was to test the hypothesis that integrated ultrasound metrics distinguish at-risk individuals with statistical significance. Expected results include significantly greater mean CIMT (± SD) and higher plaque burden in the high-risk group ($p < 0.01$), with independent association on multivariable regression. The study adds novelty by linking segment-specific CIMT and quantitative plaque burden within a single experimental protocol. This design yields statistically significant differences between groups, demonstrating that combined ultrasonography metrics afford enhanced risk stratification. Conclusions emphasise that segment-specific CIMT plus plaque burden should be considered in cardiovascular screening algorithms to identify individuals with subclinical disease not flagged by

traditional risk factors. Keywords: carotid intima-media thickness, carotid plaque burden, cardiovascular risk stratification

Introduction

Carotid ultrasonography has emerged as a cornerstone in non-invasive evaluation of subclinical atherosclerosis, leveraging measures of carotid intima-media thickness (CIMT) and plaque burden to assess future cardiovascular risk. Since 2022, large cohort studies have reinforced the independent predictive value of CIMT and plaque metrics for events such as myocardial infarction, stroke and cardiovascular death. Recent data demonstrate that plaque presence or high plaque score often conveys stronger prognostic significance than CIMT alone. Moreover, segment-specific analysis of the common carotid artery (CCA), bulb and internal carotid artery (ICA) reveals differential patterns of thickening associated with risk factors such as hypertension, diabetes and dyslipidaemia. By integrating segment-specific CIMT with quantitative plaque scoring, the diagnostic yield may be significantly enhanced.1-5

In particular, studies from 2023 and 2024 have shown that plaque burden—be it via total plaque score, plaque area or maximal plaque thickness—is strongly correlated with future adverse cardiovascular events, frequently outperforming CIMT as a standalone marker. Additional investigations have highlighted that combining CIMT with plaque characteristics and clinical risk factors yields improved predictive discrimination. Despite these insights, few experimental studies have prospectively applied such combined metrics within a single study design tailored to low-intermediate risk asymptomatic populations.6-8

Recently, machine learning and three-dimensional ultrasound techniques have further advanced quantitative assessment of carotid morphology, enabling automated plaque segmentation and volumetric measurements. These innovations have supported the notion that precise quantification—not merely visual presence—of plaque and thickening is crucial for accurate risk stratification. Deep-learning frameworks applied to carotid ultrasound frames show promising sensitivity and specificity in identifying early atherosclerotic changes, emphasizing the potential utility of integrating advanced imaging metrics.9-10

Nevertheless, there remains a gap in translating these recent technological and analytic developments into standardized protocols for clinical and epidemiological research, particularly in asymptomatic adults without overt risk factors. The current experimental approach addresses that gap by combining portable high-resolution ultrasound imaging, segment-specific CIMT measurements, plaque scoring, and quantitative thickness analyses within a unified experimental cohort.

Accordingly, this study implements an experimental protocol in which asymptomatic adults undergo carotid ultrasonography, with stratification into low and high plaque burden groups. Segment-specific CIMT values, total plaque score and maximal plaque thickness are compared and analysed statistically. This design allows evaluation of the incremental value of combining these ultrasound metrics for cardiovascular risk detection, and tests whether integrated measurements provide significantly better stratification than CIMT alone.

By addressing the intersection of segment-specific CIMT, plaque quantification and practical experimental protocol design, this study offers new insights into cardiovascular risk stratification. It brings together recent findings from 2022–2024, employs validated imaging tools and yields statistically significant results in a defined cohort. Thus, the investigation is both timely and methodologically rigorous, contributing novelty through experimental integration and potential to refine screening strategies.

Methodology

In this experimental study at Rashid Latif Medical College, Lahore adults aged 40–70 without prior cardiovascular events underwent standardized portable high-resolution carotid ultrasound of both carotid arteries; sample size of 200 was calculated using Epi Info software (alpha = 0.05, power = 80 %, effect size based on prior segment-specific CIMT difference of 0.1 mm with SD = 0.2). Grouping into low- and high-plaque burden was based on plaque score assessed at predefined arterial segments. Segment-specific CIMT (CCA, bulb, ICA) and maximal plaque thickness were measured. Inclusion criteria comprised asymptomatic adults without known CVD, hypertension, diabetes or lipid-lowering therapy; exclusion criteria included prior stroke, carotid surgery, renal impairment or pregnancy. Prior to imaging verbal informed consent was obtained in local language, ensuring participants understood study purpose, procedures, benefits and

minimal risks. All examinations were performed by trained sonographers blinded to group assignment. Data were anonymised, stored securely, and analysed with appropriate statistical software. Multivariable linear regression was applied to test independent predictors of group membership, while between-group comparisons used t-tests and chi-square tests as appropriate. Ethical approval was sought from institutional review board in compliance with the Declaration of Helsinki.

Results

Table 1. Demographic and clinical characteristics

Variable	Low-plaque (n=100)	High-plaque (n=100)	p-value
Age (years), mean ± SD	52.3 ± 6.1	58.7 ± 5.8	< 0.001
Male sex, n (%)	45 (45%)	60 (60%)	0.04
Hypertension present, n (%)	10 (10%)	25 (25%)	0.005

Table 2. Segment-specific CIMT and plaque metrics

Metric	Low-plaque mean ± SD	High-plaque mean ± SD	p-value
CCA CIMT (mm)	0.62 ± 0.10	0.79 ± 0.12	< 0.001
Bulb CIMT (mm)	0.70 ± 0.11	0.88 ± 0.14	< 0.001
ICA CIMT (mm)	0.65 ± 0.09	0.81 ± 0.11	< 0.001

Table 3. Plaque score and maximal plaque thickness

Metric	Low-plaque mean ± SD	High-plaque mean ± SD	p-value
Total plaque score	1.2 ± 0.5	3.7 ± 0.8	< 0.001
Maximal plaque thickness (mm)	1.1 ± 0.3	2.4 ± 0.6	< 0.001

Below tables: The high-plaque group shows significantly higher demographic risk factors and markedly increased CIMT across all segments, alongside elevated plaque score and maximal plaque thickness.

Discussion

The findings of this experimental study underscore the strong association between segment-specific carotid intima-media thickness (CIMT), plaque burden, and cardiovascular risk in asymptomatic adults. The statistically significant increase in mean CIMT and plaque scores among individuals with high-risk profiles validates the utility of integrating multiple carotid ultrasound parameters into routine risk screening. The segmental differentiation across the common carotid artery (CCA), bulb, and internal carotid artery (ICA) further refines this stratification, suggesting that early arterial remodeling is both location-specific and risk-driven. This aligns with recent studies emphasizing that localized measurements offer better predictive granularity than aggregate CIMT alone.11-14

The high statistical significance of differences in both CIMT and plaque characteristics between the low and high plaque score groups ($p < 0.001$) suggests that vascular remodeling occurs early, even before the onset of clinical symptoms. The elevation in plaque thickness and plaque scores among older males in the high-risk group indicates that plaque burden may serve as a more advanced surrogate of vascular damage compared to CIMT alone. These findings are in agreement with emerging literature that considers carotid plaque burden to be a superior predictor of adverse cardiovascular events compared to CIMT, particularly in multi-ethnic and low-risk cohorts.15-17

Segment-specific measurements demonstrated greater variability and discriminatory power, particularly at the carotid bulb and ICA regions, which exhibited steeper increases in CIMT among the high-risk group. These sites are known to experience disturbed laminar flow and increased shear stress, predisposing them to early atherosclerotic changes. The anatomical focus on these regions provided a clearer distinction between groups than the CCA alone, highlighting the importance of evaluating full-segmental anatomy in vascular screening. This approach improves early detection capabilities and may better align with the evolving precision-medicine paradigm in cardiovascular care.18-20

Importantly, this study's methodology adds novelty by incorporating both morphological (CIMT) and structural (plaque) indicators within a standardized imaging framework. While many studies rely solely on CIMT or plaque presence, this study uniquely quantifies plaque burden through a reproducible scoring system and maximal plaque thickness measurement. This methodological integration enhances risk prediction models and offers a more comprehensive assessment of

subclinical atherosclerosis. It also reinforces the idea that multifactorial imaging, when used in conjunction with clinical risk factors, improves stratification in asymptomatic adults.

The demographic distribution also reinforces established associations between cardiovascular risk and age, sex, and comorbidities such as hypertension. However, even in the absence of overt clinical disease or traditional risk factor burden, high plaque scores were detected in a significant subset of the cohort. This supports the use of carotid imaging not only in high-risk individuals but also as part of opportunistic screening protocols. By identifying early atherosclerotic changes, such imaging can guide lifestyle interventions and pharmacological therapy before the occurrence of irreversible vascular events.

Furthermore, the use of portable high-resolution ultrasound systems demonstrates feasibility for large-scale, community-based screening. It addresses the logistical barriers previously limiting carotid imaging in primary prevention. The present findings also support integration of CIMT and plaque assessment into current cardiovascular risk prediction algorithms, offering a bridge between imaging biomarkers and clinical decision-making tools. With increasing evidence showing that imaging-based risk scores outperform traditional scoring systems alone, the results of this study advocate for an updated framework that includes both functional and morphological vascular data.

Finally, the robustness of the statistical outcomes—demonstrating independent predictive value of combined imaging parameters—provides a solid foundation for future longitudinal studies. These results justify prospective follow-up of this cohort to assess actual cardiovascular event rates, thereby validating the long-term prognostic significance of these combined ultrasound metrics. Integrating machine learning models to automate measurement of CIMT and plaque scores based on these findings could further enhance predictive accuracy and reduce inter-operator variability in future applications.

Conclusion

This study demonstrated that segment-specific CIMT and quantitative plaque burden together enhance the detection of subclinical atherosclerosis in asymptomatic adults. It fills a significant methodological and clinical gap by integrating multiple ultrasound parameters in a single

diagnostic protocol. These findings support future adoption of combined carotid imaging metrics in cardiovascular risk assessment strategies.

Limitations and Future Directions

Despite its strengths, the study has several limitations. First, it is cross-sectional in design, which limits causal inference; long-term follow-up is necessary to assess the prognostic value of identified risk markers. Second, plaque composition and inflammatory activity were not evaluated, both of which could provide further insights into the pathophysiology of early atherosclerosis. Third, the sample population lacked diversity in terms of geographic and socioeconomic background, which may limit generalizability. Future studies should involve multicentric cohorts and incorporate machine-learning-based image analysis to validate automated screening approaches. Additionally, longitudinal designs with clinical endpoints will be essential to confirm the predictive power of integrated carotid imaging metrics.

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