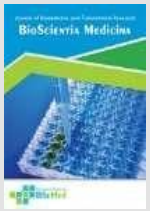
eISSN (Online): 2598-0580



**Bioscientia Medicina: Journal of Biomedicine & Translational Research**

Journal Homepage: www.bioscmed.com

# Beyond Cholesterol: The Independent Roles of Inflammation and Renal Dysfunction in Carotid Atherosclerosis Among Indonesian Elders

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**ARTICLE INFO**

**Keywords:**
Atherosclerosis
Dyslipidemia
Elderly
hsCRP
Renal Dysfunction

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All authors have reviewed and approved the final version of the manuscript.

*https://doi.org/10.37275/bsm.v9i9.1386*

**A B S T R A C T**

**Background:** Atherosclerosis remains a leading cause of mortality in aging populations, driven by a complex interplay of metabolic and inflammatory factors. While dyslipidemia is a cornerstone of risk, the contributions of systemic inflammation, marked by high-sensitivity C-reactive protein (hsCRP), and declining renal function are increasingly recognized. This study aimed to elucidate the independent associations of hsCRP, dyslipidemia, and renal function with the presence of carotid atherosclerosis in an understudied elderly Indonesian population. **Methods:** We conducted a single-center, case-control study at a tertiary hospital in Palembang, Indonesia, from January to June 2024. One hundred participants aged ≥60 years were enrolled from the geriatric outpatient clinic. Cases were defined by the presence of carotid plaque, identified via B-mode Doppler ultrasound, and defined according to international consensus criteria. Controls had no evidence of plaque. We performed multivariate logistic regression to identify independent predictors of atherosclerosis, including hsCRP, lipid parameters, and estimated glomerular filtration rate (eGFR). **Results:** After multivariable adjustment, three factors emerged as significant, independent predictors of carotid atherosclerosis. High total cholesterol (≥200 mg/dL) was the most powerful predictor, associated with a more than seven-fold increased odds of plaque (Adjusted Odds Ratio [aOR]: 7.38; 95% Confidence Interval [CI]: 2.87–18.94; p<0.001). Elevated hsCRP (≥2 mg/L) (aOR: 3.38; 95% CI: 1.33–8.59; p=0.005) and abnormal eGFR (≤90 mL/min/1.73m$^2$) (aOR: 3.36; 95% CI: 1.10–10.22; p<0.001) were also robustly associated with atherosclerosis, each conferring over a three-fold increase in odds. **Conclusion:** In this elderly Indonesian study, dyslipidemia remains a dominant risk factor for carotid atherosclerosis. However, systemic inflammation (high hsCRP) and mild renal dysfunction (abnormal eGFR) are also powerful, independent contributors. These findings highlight the multifactorial nature of atherosclerosis and underscore the importance of a comprehensive risk assessment that extends beyond traditional lipid profiling to include markers of inflammation and renal health.

## 1. Introduction

The global demographic shift towards an older population has brought the challenges of age-related diseases to the forefront of public health.[1] Among these, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide. The aging process itself is a potent, non-modifiable risk factor for ASCVD, intrinsically linked to progressive, deleterious changes in cardiovascular structure and function, such as increased arterial

stiffness and profound endothelial dysfunction.[2] These age-related phenomena create a pro-atherogenic vascular environment, paving the way for the development and progression of atherosclerosis. Pathophysiologically, atherosclerosis is no longer considered a simple plumbing issue of lipid accumulation within the arterial wall.[3] It is now unequivocally recognized as a chronic, low-grade inflammatory disease. This paradigm, often termed "inflammageing," posits that a persistent, systemic inflammatory state contributes directly to all stages of atherogenesis—from initial leukocyte recruitment and endothelial activation to plaque maturation, instability, and eventual rupture. A key mediator and highly sensitive biomarker of this systemic inflammation is high-sensitivity C-reactive protein (hsCRP), an acute-phase reactant synthesized by the liver. A vast body of evidence has firmly established that elevated hsCRP levels are a powerful predictor of future cardiovascular events, such as myocardial infarction and stroke, even among individuals with seemingly normal lipid profiles.[4] The protein is not merely a bystander; it may actively participate in the disease process by promoting the expression of adhesion molecules, inducing endothelial dysfunction, and activating the complement system within the vascular wall.[5]

While the association between hsCRP and atherosclerosis is well-documented in many Western populations, there is a conspicuous lack of data from specific ethnic groups and geographic regions, particularly in Southeast Asia.[6] The genetic background, dietary habits, and environmental exposures of populations such as those in Indonesia can significantly modulate disease risk and the utility of specific biomarkers.[7] Understanding these relationships within a local context is paramount for developing tailored and effective public health strategies. Furthermore, the risk of atherosclerosis in the elderly is seldom attributable to a single factor. It is the result of a complex interplay between traditional risk factors (dyslipidemia, hypertension), emerging inflammatory pathways, and the functional decline of other organ systems, most notably the kidneys. Mild renal dysfunction, a common finding in the elderly, is itself a potent and independent risk factor for ASCVD, creating a vicious cycle often referred to as the cardio-renal syndrome.[8] The novelty of this investigation lies in its integrated approach to risk factor assessment within a specific, under-represented demographic. While many studies have examined single risk factors in isolation, this is one of the first in an elderly Indonesian population to concurrently analyze the independent and relative contributions of the three core pillars of modern atherogenesis: metabolic derangement (dyslipidemia), systemic inflammation (hsCRP), and end-organ dysfunction (renal decline). By evaluating this triad of risk within a single model, our study moves beyond simplistic associations to uncover the complex interplay of these pathways. This provides a unique and nuanced perspective on cardiovascular risk in a non-Western population, offering data that can inform region-specific clinical guidelines and highlight the universal importance of a multifactorial approach to prevention.[9,10] The primary aim of this study was to determine the independent association between elevated high-sensitivity C-reactive protein (hsCRP) levels and the presence of carotid atherosclerotic plaque in an elderly Indonesian population.

## 2. Methods

This study was conducted as an analytical observational study employing a case-control design. All study procedures were performed in strict accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Dr. Mohammad Hoesin General Hospital Palembang. All participants were provided with a detailed explanation of the study's objectives and procedures, and all provided written informed consent prior to their inclusion. Participants were recruited from the Geriatric Outpatient Clinic at Dr. Mohammad Hoesin General Hospital, a tertiary referral hospital in Palembang, South Sumatra, Indonesia, between

January and June 2024. We employed a consecutive sampling strategy to minimize selection bias. Patients attending the clinic for routine medical evaluation were screened for eligibility. Inclusion criteria were individuals of either gender aged 60 years or older who were willing and able to provide informed consent. We implemented specific exclusion criteria to avoid confounding by conditions known to acutely influence inflammatory markers or atherosclerosis. These included patients with acute or chronic infectious diseases, known autoimmune or rheumatological diseases (rheumatoid arthritis, systemic lupus erythematosus), a history of malignancy, or those who had undergone major surgery within the preceding three months.

The primary outcome of this study was the presence of subclinical carotid atherosclerosis, defined by the identification of one or more atherosclerotic plaques via B-mode Doppler ultrasonography. All ultrasound examinations were performed by a single experienced cardiologist blinded to the participants' clinical and laboratory data to ensure consistency and minimize operator bias. The ultrasound protocol involved a comprehensive B-mode scan of both the right and left common carotid arteries (CCA), the carotid bifurcations, and the proximal internal carotid arteries (ICA). An atherosclerotic plaque was defined according to the internationally recognized Mannheim Carotid Intima-Media Thickness and Plaque Consensus criteria. Specifically, a plaque was identified as a focal structure that protrudes into the vessel lumen by at least 0.5 mm or is 50% greater than the surrounding Carotid Intima-Media Thickness (CIMT) value, OR any region with a focal thickness greater than 1.5 mm. Cases (Plaque Positive): Participants with one or more identifiable atherosclerotic plaques in any of the examined carotid segments. Controls (Plaque Negative): Participants with no evidence of focal plaque in any examined carotid segment.

Upon enrollment, a standardized case report form was used to collect comprehensive data for each participant. This included demographic information (age, gender, education level), lifestyle factors (smoking history, regular physical activity), and a detailed medical history focusing on comorbidities such as hypertension and type 2 diabetes mellitus (T2DM). Anthropometric measurements, including height and weight, were taken to calculate Body Mass Index (BMI). After an overnight fast, venous blood samples were collected from all participants. Plasma hsCRP levels were quantified using a high-sensitivity immunoturbidimetric assay on an automated clinical chemistry analyzer. Based on established guidelines for cardiovascular risk stratification, hsCRP levels were categorized as low (<2 mg/L) or elevated (≥2 mg/L). Serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using standard enzymatic colorimetric methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula, provided that triglycerides were <400 mg/dL. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Serum creatinine was measured, and the estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. For analysis, eGFR was categorized as normal (>90 mL/min/1.73m²) or abnormal (≤90 mL/min/1.73m²) to identify even mild renal impairment. Serum albumin and calcium were also measured.

The sample size was determined based on the primary objective of detecting a significant association between elevated hsCRP and atherosclerosis. Using an alpha of 0.05 and a desired statistical power of 80%, and assuming an odds ratio of at least 2.8 for the association, with a prevalence of elevated hsCRP in the control group of approximately 35-40%, a minimum sample size of 48 cases and 48 controls was required. To account for potential dropouts or incomplete data, we aimed to recruit 100 participants (50 cases and 50 controls). All collected data were entered into a database and analyzed using SPSS for Windows (Version 25.0). The statistical analysis was conducted in three stages. First, descriptive and univariate

analyses were performed to characterize the study population. Categorical variables were presented as frequencies and percentages. Continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD), while non-normally distributed (skewed) data were reported as median and interquartile range (IQR) or range (minimum–maximum). Second, bivariate analyses were conducted to assess the unadjusted associations between independent variables and the presence of atherosclerotic plaque (case vs. control status). The Chi-square test (or Fisher's exact test where appropriate) was used to compare categorical variables. For continuous variables, the Independent T-Test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate the magnitude of these associations. A p-value of $<0.05$ was considered statistically significant. Third, a multivariate logistic regression analysis was performed to identify the independent predictors of atherosclerotic plaque. All variables that demonstrated a potential association with the outcome in the bivariate analysis (defined by a p-value $< 0.25$) were considered for inclusion in the initial model. A backward stepwise elimination method was used to derive the most parsimonious final model, retaining only those variables that remained statistically significant ($p<0.05$). Due to significant multicollinearity among the lipid parameters (total cholesterol, LDL cholesterol, non-HDL cholesterol), only one representative variable—total cholesterol—was retained in the final model to ensure stable estimates. The results of the multivariate analysis were presented as adjusted odds ratios (aOR) with their corresponding 95% CIs. The overall performance of the final model was assessed using the Nagelkerke $R^2$ statistic to estimate the proportion of variance explained, and its calibration was checked using the Hosmer-Lemeshow goodness-of-fit test.

**3. Results**

Figure 1 showed a detailed demographic and lifestyle profile of the 100 elderly study participants from the Geriatric Clinic at Dr. Mohammad Hoesin General Hospital. The initial analysis provides a clear snapshot of the population, revealing a balanced age distribution with a slight majority (56%) in the 60-69 year age bracket and the remainder (44%) in the 70-79 year range. A notable characteristic of the sample is a significant gender predominance, with females constituting two-thirds (66%) of the participants, compared to 34% males. The most compelling insights emerge from the comparative analysis of lifestyle factors stratified by the presence or absence of atherosclerotic plaque. A sedentary lifestyle was strikingly more common among individuals with atherosclerosis. In the group with plaque (n=54), a vast majority of 91% did not engage in regular exercise. In stark contrast, the group without plaque (n=46) exhibited a healthier activity profile, with 20% of individuals exercising regularly—a rate more than double that of the plaque-present group (9%). As highlighted by the key finding, this dramatic difference in physical activity was statistically significant ($p=0.023$), suggesting a powerful protective association of exercise against the development of subclinical atherosclerosis in this population. Furthermore, the data on smoking history reinforces established cardiovascular risk paradigms. The prevalence of smoking was more than twice as high in the group with atherosclerotic plaque, with 24% identifying as smokers, compared to just 11% in the plaque-absent group. Although not highlighted as a statistically significant finding in the figure's summary, this strong trend provides complementary evidence linking adverse lifestyle choices to vascular disease. Figure 1 effectively illustrates that within this specific elderly Indonesian population, while demographic factors characterize the sample, it is the modifiable lifestyle behaviors that sharply differentiate between those with and without subclinical atherosclerosis. The visual data compellingly supports the statistical conclusion that physical inactivity, in

particular, is a significant correlate of atherosclerotic plaque burden.

Figure 2 showed a compelling visual comparison of the prevalence of three major clinical comorbidities—dyslipidemia, hypertension, and diabetes mellitus—between the study groups with and without atherosclerotic plaque. The data clearly illustrates the distinct risk profiles associated with each condition. The most striking finding, visually and statistically, was the profound disparity in the prevalence of dyslipidemia. Among individuals with carotid plaque, a substantial majority, 77.8%, had dyslipidemia. This was nearly double the prevalence in the plaque-absent group, where only 41.3% of individuals were diagnosed with the condition. As highlighted by the p-value of < 0.001, this difference was highly statistically significant, underscoring dyslipidemia's powerful association with the presence of atherosclerosis in this population. In contrast, the other major comorbidities did not show a statistically significant difference between the two groups. Hypertension was highly prevalent overall but was almost identically distributed, affecting 66.7% of the plaque-present group and 67.4% of the plaque-absent group (p=0.942). This suggests that while hypertension is a common condition in this elderly sample, it did not distinguish between those with and without plaque. Similarly, the prevalence of Diabetes Mellitus was comparable between the groups. It was present in 38.9% of individuals with plaque and 34.8% of those without, a difference that was not statistically significant (p=0.337). Figure 2 effectively demonstrates that while hypertension and diabetes are common health issues in this elderly population, dyslipidemia is the single comorbidity that shows a dramatic and statistically significant association with the presence of carotid plaque.

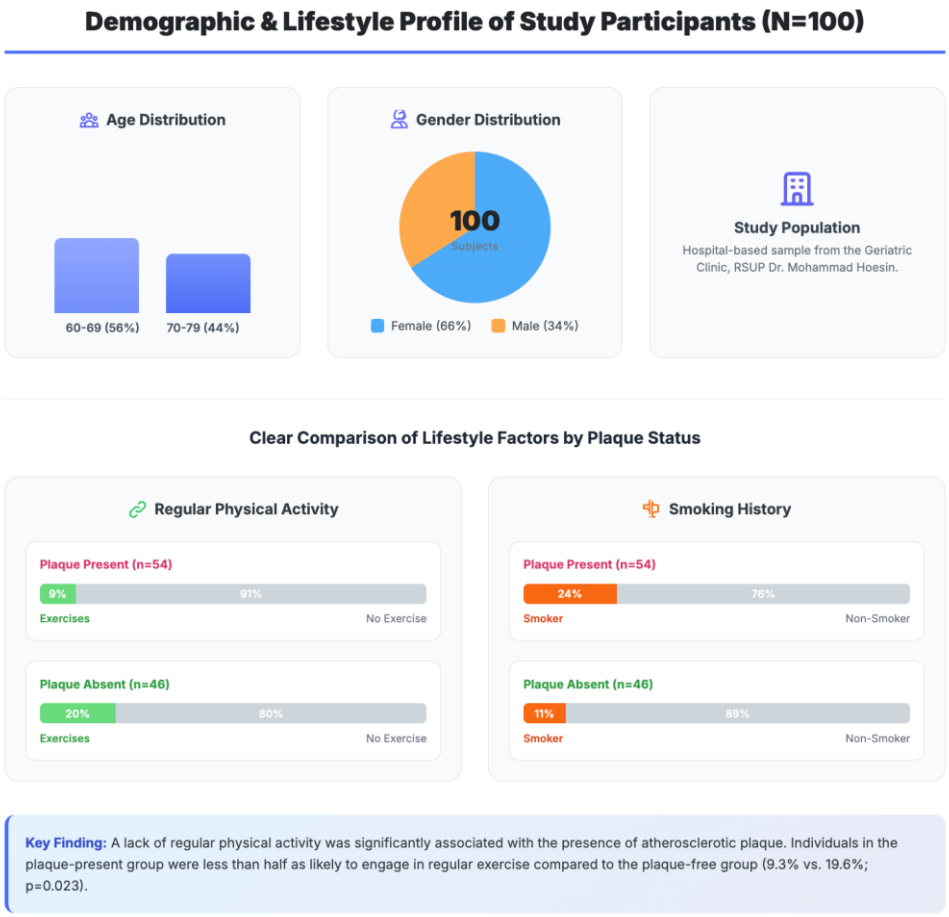


Figure 1. Demographic and lifestyle profile of study participants.

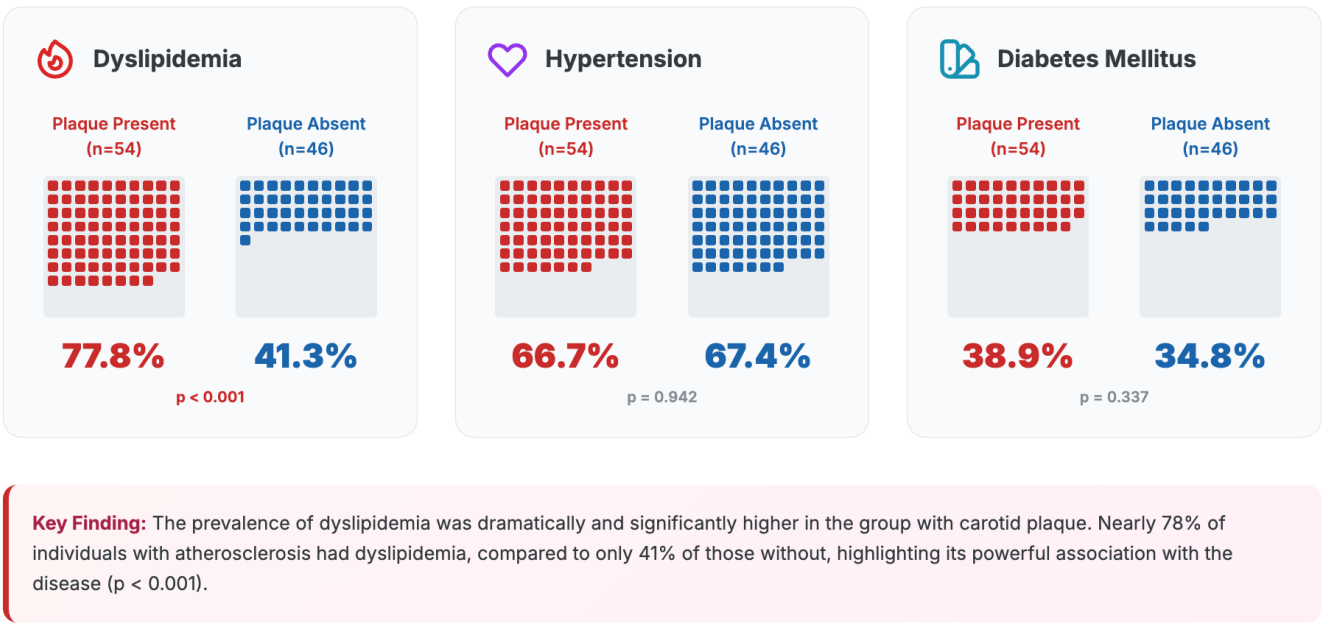


Figure 2. Prevalence of clinical comorbidities by plaque status.

Figure 3 showed a clear and compelling comparison of key laboratory markers between elderly participants with and without carotid atherosclerotic plaque, revealing a distinctly pro-atherogenic profile in the group with disease. The analysis of inflammatory status indicated that individuals with plaque had significantly higher levels of systemic inflammation. The median hsCRP level in the plaque-present group was 2.7 mg/L, a value nearly double the median of 1.4 mg/L observed in the plaque-absent group. This substantial difference was statistically significant ($p = 0.002$), highlighting a strong association between inflammation and the presence of atherosclerosis. The most dramatic differences were observed across the lipid profiles. All measures of atherogenic cholesterol were significantly elevated in the plaque-present group: Total Cholesterol was markedly higher, with a mean of 229.1 mg/dL compared to 186.7 mg/dL in the control group ($p < 0.001$). LDL Cholesterol, the primary target of lipid-lowering therapy, showed a substantial elevation, with a median of 156.1 mg/dL versus 106.9 mg/dL ($p < 0.001$). Non-HDL Cholesterol, which represents all cholesterol-containing atherogenic lipoproteins, was also significantly higher at 185.5 mg/dL compared to 112.0 mg/dL ($p < 0.001$). Finally, the comparison of renal function, measured by eGFR, showed a trend towards lower function in the group with plaque. The mean eGFR was 94.0 mL/min/1.73m² in the plaque-present group versus 105.0 mL/min/1.73m² in the plaque-absent group. However, this difference did not reach the threshold for statistical significance ($p = 0.060$) in this particular comparison. Figure 3 provides robust evidence that individuals with carotid plaque exhibit a multi-faceted adverse laboratory profile characterized by both significantly heightened systemic inflammation and a dramatically more atherogenic lipid status.

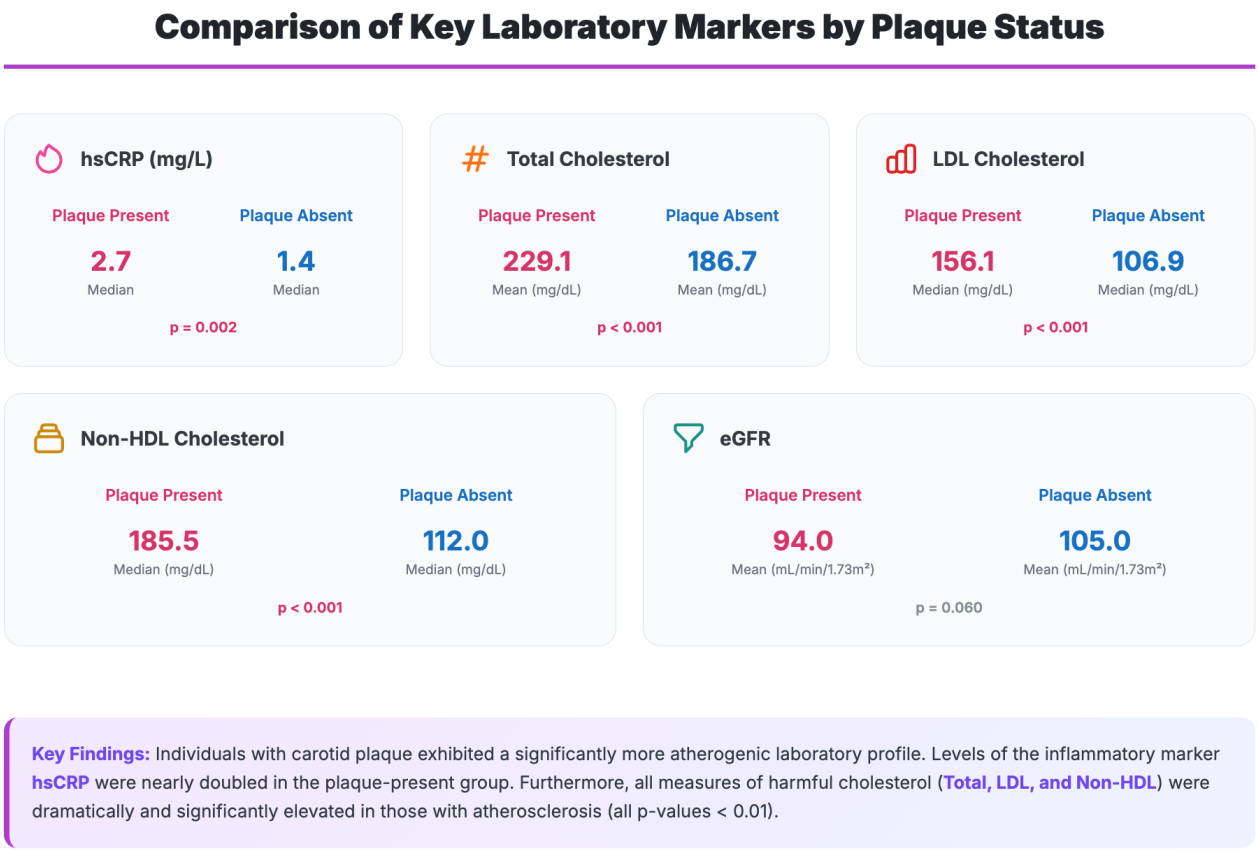


Figure 3. Comparison of key laboratory markers by plaque status.

Figure 4 showed a forest plot illustrating the bivariate (unadjusted) association between several categorized risk factors and the presence of carotid plaque. The analysis powerfully demonstrates the relative strength of each factor in predicting the outcome. The most striking associations were observed with measures of atherogenic dyslipidemia. High LDL Cholesterol (≥130 mg/dL) emerged as the most potent predictor, increasing the odds of having carotid plaque by a staggering 7.76-fold (95% CI: 3.13 – 19.23). Similarly, High Total Cholesterol (≥200 mg/dL) conferred a 7.00-fold increase in odds (95% CI: 2.86 – 17.11). The composite measure of High Non-HDL Cholesterol (≥130 mg/dL) was also strongly and significantly associated with a nearly 4-fold increased risk (OR 3.99, 95% CI: 1.61 – 9.71). Beyond lipid metabolism, systemic inflammation, as measured by Elevated hsCRP (≥2 mg/L), was also a significant predictor. It was associated with a more than 3-fold increase in the odds of having plaque (OR 3.12, 95% CI: 1.37 – 7.11).

In contrast, several other factors showed trends toward increased risk but did not reach statistical significance, as their 95% confidence intervals crossed the line of no effect (OR=1.0). These included Abnormal eGFR (OR 2.20) and High Triglycerides (OR 1.83). Lastly, Low HDL Cholesterol did not demonstrate a statistically significant protective association in this analysis (OR 0.64, 95% CI: 0.20 – 1.48). The figure clearly visualizes that in an unadjusted analysis, elevated levels of atherogenic lipoproteins (LDL, Total, and Non-HDL cholesterol) are the most powerful predictors of carotid plaque, with systemic inflammation also playing a significant role.

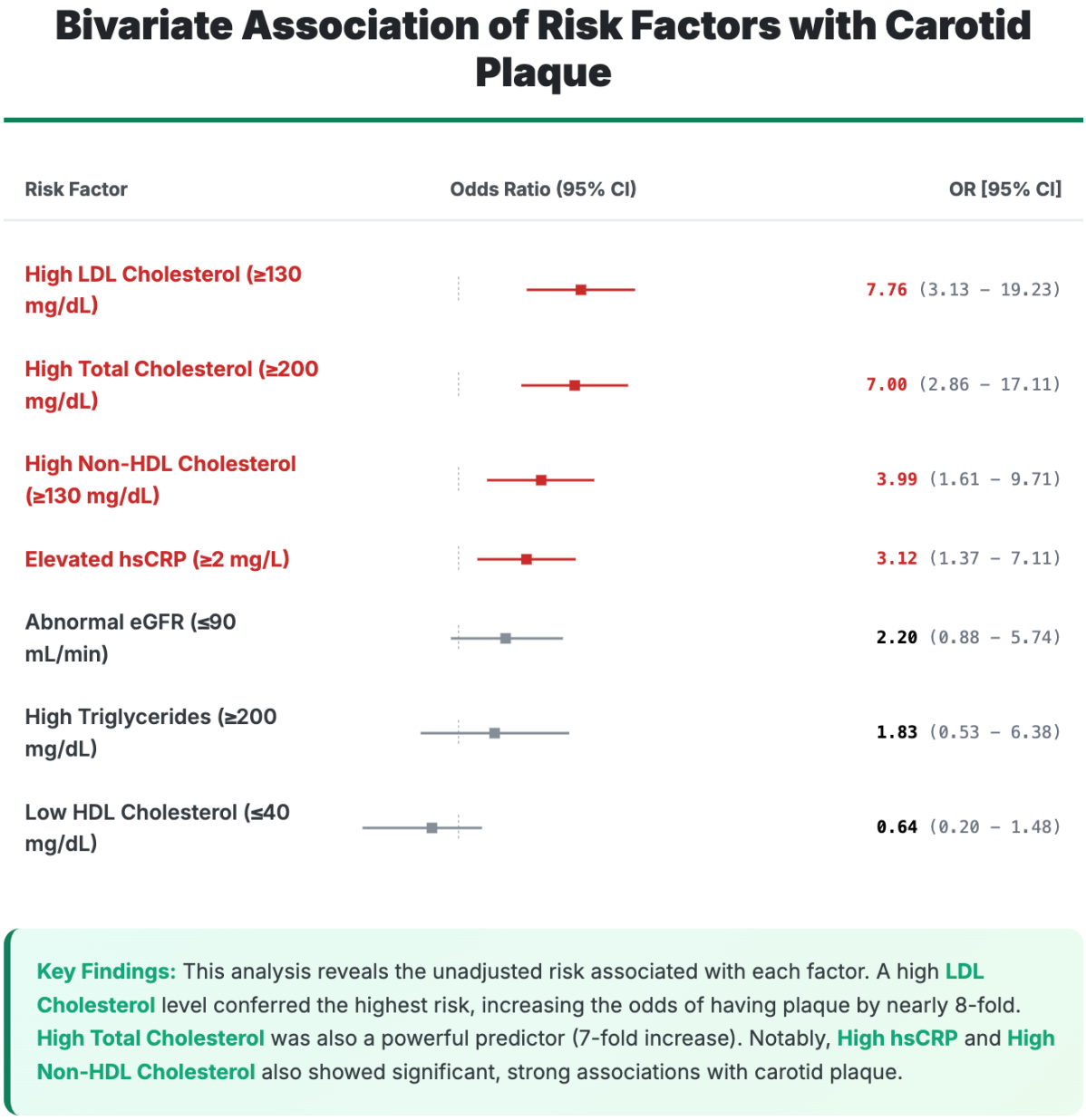


Figure 4. Bivariate association of risk factors with carotid plaque.

Figure 5 showed the final, most impactful results of the study, presenting the three factors that emerged as powerful, independent predictors of carotid plaque after a multivariate logistic regression analysis. This advanced statistical analysis adjusted for the influence of other variables, isolating the most critical drivers of the disease. The most dominant risk factor identified was High Total Cholesterol. Even after accounting for inflammation and renal function, individuals with high cholesterol had a staggering 7.38-fold increase in the odds of having atherosclerotic plaque compared to those with normal cholesterol levels (95% CI: 2.87 – 18.94). The high statistical significance of this finding ($p < 0.001$) underscores that dyslipidemia is a foundational pillar in the development of atherosclerosis. Beyond the powerful metabolic risk, the figure compellingly illustrates that other biological pathways also play a

crucial, independent role. Systemic inflammation, indicated by Elevated hsCRP, was significantly associated with a 3.38-fold increase in the odds of having plaque (95% CI: 1.33 – 8.59; p = 0.005). In parallel, renal dysfunction, marked by an Abnormal eGFR, conferred a nearly identical and significant risk, increasing the odds of atherosclerosis by 3.36 times (95% CI: 1.10 – 10.22; p < 0.001). The significance of these two findings is their independence, demonstrating that both inflammation and poor kidney function are not merely byproducts of high cholesterol but are distinct processes that contribute substantially to the disease. Figure 5 presents a clear triad of risk. It confirms that while high cholesterol is the leading predictor, a comprehensive understanding of atherosclerotic risk requires consideration of the independent and significant contributions from both systemic inflammation and renal dysfunction.

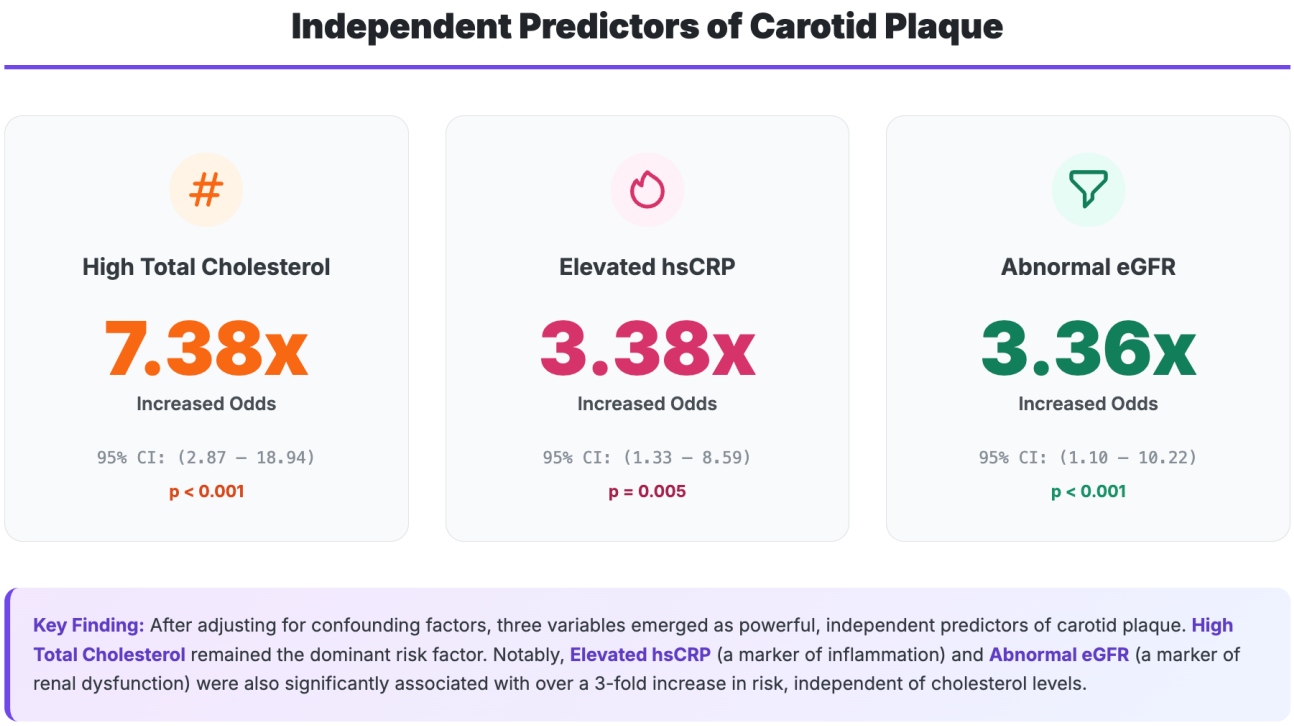


Figure 5. Independent predictors of carotid plaque.

**4. Discussion**

This study, conducted in an elderly Indonesian population, sought to dissect the complex interplay of factors contributing to subclinical atherosclerosis.[9] Our investigation moves beyond a simple inventory of risk factors to reveal a hierarchical and synergistic relationship between metabolic derangement, systemic inflammation, and organ-system decline. The results paint a vivid picture of atherogenesis as a multifactorial process, identifying a powerful and independent triad of risk: dyslipidemia, inflammation (marked by hsCRP), and renal dysfunction (marked by reduced eGFR).[10] The most emphatic finding of our analysis was the colossal, independent association between high total cholesterol and the presence of carotid plaque, with an adjusted odds ratio exceeding seven. This result is not merely a statistical observation; it is a profound biological statement that reaffirms the "response-to-retention" hypothesis as the central, initiating doctrine of atherosclerosis.[11] This hypothesis posits that the entire atherosclerotic cascade begins with one critical event: the infiltration

and retention of apolipoprotein B-containing lipoproteins, primarily LDL, within the subendothelial space of the arterial wall. In a healthy state, the endothelium acts as a selective barrier, regulating the passage of molecules.[12] However, in the presence of hypercholesterolemia, this barrier becomes overwhelmed. LDL particles traverse the endothelial layer and become trapped in the extracellular matrix, bound by proteoglycans. This sequestration is the point of no return. Once retained, these LDL particles undergo a series of destructive chemical modifications. They are oxidized by reactive oxygen species generated by local vascular cells (endothelial cells, smooth muscle cells) and become glycated in the presence of hyperglycemia. This modified LDL is no longer recognized by the native LDL receptor. Instead, it becomes a potent, pro-inflammatory signal—a molecular beacon of distress.[12]

This modified LDL triggers the first wave of the inflammatory response. The overlying endothelial cells, sensing danger, upregulate the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1).[13] These molecules act as sticky landing pads for circulating monocytes. These monocytes adhere to the endothelium, squeeze through the cell junctions in a process called diapedesis, and enter the intima, where they differentiate into macrophages. These macrophages are the key actors in the next phase. They express a variety of scavenger receptors (such as SR-A and CD36) that avidly bind and internalize the modified LDL. Unlike the native LDL receptor, these scavenger receptors are not downregulated by intracellular cholesterol content.[13] This leads to a relentless, unregulated uptake of lipids, causing the macrophages to become engorged with cholesterol esters. These lipid-laden macrophages, known as "foam cells," are the pathognomonic hallmark of the early atherosclerotic lesion, or fatty streak. The accumulation of these dying and dead foam cells forms the necrotic lipid core of a mature atherosclerotic plaque. The immense odds ratio of over 7.0 observed in our study is a direct clinical reflection of this powerful, foundational biological process. It signifies that the presence of excess circulating cholesterol is not just a risk factor; it is the essential substrate without which the atherosclerotic plaque cannot efficiently form. While inflammation and other factors are critical amplifiers and propagators of the disease, the process is fundamentally initiated and fueled by lipid deposition. This finding powerfully reinforces the rationale for aggressive lipid-lowering therapy as the non-negotiable cornerstone of ASCVD prevention.[14]

While dyslipidemia provides the fuel, inflammation is the fire that ignites and sustains the atherosclerotic process. Our study robustly demonstrates that an elevated hsCRP level is not merely a reflection of this fire but an independent risk factor, tripling the odds of having carotid plaque even after accounting for the powerful effect of cholesterol.[15] This supports the critical concept of "residual inflammatory risk"—the danger that persists even when cholesterol levels are controlled. The pathophysiological role of hsCRP extends far beyond that of a passive bystander; it is an active participant in vascular injury. hsCRP is a pentameric protein whose structure allows it to act as a versatile molecular scaffold.[15] In the presence of tissue damage, it can dissociate into its monomeric form (mCRP), which exhibits potent pro-inflammatory activities. One of its key functions is to recognize and bind to phosphocholine, a molecule exposed on the surface of damaged or apoptotic cells, including the foam cells within an atherosclerotic plaque. This binding action serves as a tag, marking the cells for clearance by activating the classical complement pathway. While this is a protective clean-up mechanism, chronic activation of complement within the vessel wall can lead to collateral damage, perpetuating inflammation and tissue injury.[16] Furthermore, hsCRP directly targets the endothelium, the critical gatekeeper of vascular health. It has been shown to suppress the expression and activity of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing nitric oxide (NO). NO is arguably the most important anti-atherosclerotic

molecule produced by the body; it is a potent vasodilator, it inhibits platelet aggregation, and it suppresses the expression of pro-inflammatory adhesion molecules. By reducing NO bioavailability, hsCRP shifts the endothelial balance towards a state of dysfunction, characterized by vasoconstriction, platelet activation, and increased leukocyte adhesion—a perfect storm for atherogenesis.

hsCRP also directly promotes the expression of ICAM-1 and VCAM-1 on endothelial cells, amplifying the recruitment of monocytes into the vessel wall. It stimulates macrophages already within the plaque to produce more pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), creating a vicious self-amplifying cycle of inflammation.[16] Finally, it can induce a pro-thrombotic state by increasing the expression of plasminogen activator inhibitor-1 (PAI-1), which inhibits fibrinolysis and promotes clot stability on the surface of a ruptured plaque. The independent odds ratio of over 3.0 for hsCRP in our multivariate model is the clinical signature of these potent, lipid-independent biological actions. It signifies that the intensity of the systemic inflammatory response is a distinct dimension of cardiovascular risk. A patient with a high hsCRP has an activated, dysfunctional endothelium and a vascular bed that is primed for plaque development, regardless of their cholesterol level. This finding provides a compelling rationale for measuring hsCRP to unmask this "residual inflammatory risk" and to identify high-risk individuals who may require more intensive therapeutic strategies.[17]

One of the most profound findings of our investigation was the emergence of even mild renal dysfunction (eGFR ≤90 mL/min/1.73m²) as a powerful and independent predictor of atherosclerosis, carrying a risk magnitude equivalent to that of high-level inflammation. This unmasks the insidious and often underappreciated role of the cardio-renal-atherosclerotic axis, where declining kidney function actively poisons the vasculature through multiple, synergistic mechanisms that are distinct from traditional risk pathways. The kidneys are the body's master purifiers. When their function declines, a host of waste products that are normally cleared accumulate in the bloodstream.[17] This goes far beyond simple urea and creatinine. A class of protein-bound solutes, known as "uremic toxins," builds up. Key among these are indoxyl sulfate and p-cresyl sulfate. These toxins are not inert; they are biologically active and directly pathogenic to the endothelium. They generate massive oxidative stress by stimulating NADPH oxidase in vascular cells, leading to the production of superoxide and other reactive oxygen species.[18] This oxidative stress, in turn, reduces NO bioavailability, promotes inflammation, and accelerates endothelial cell senescence—a state of irreversible growth arrest where cells become pro-inflammatory and pro-thrombotic. Beyond toxic solutes, renal decline disrupts the body's fundamental homeostatic systems. The activation of the Renin-Angiotensin-Aldosterone System (RAAS) becomes a central feature, leading to increased angiotensin II and aldosterone levels. These hormones exert direct, damaging effects on the vasculature, promoting vasoconstriction, fibrosis, inflammation, and sodium retention, which collectively contribute to hypertension and arterial stiffness.[18]

Furthermore, chronic kidney disease leads to a profound dysregulation of mineral and bone metabolism. As GFR falls, the kidneys fail to excrete phosphate effectively, leading to hyperphosphatemia. They also fail to produce calcitriol (active vitamin D), leading to hypocalcemia. This stimulates the parathyroid glands to produce parathyroid hormone (PTH) and the bone to produce fibroblast growth factor 23 (FGF-23). This complex hormonal milieu, particularly high phosphate and high FGF-23, has a devastating effect on blood vessels. It actively promotes the transformation of vascular smooth muscle cells into osteoblast-like cells, which then deposit calcium into the vessel wall. This process of vascular calcification turns flexible arteries into rigid, pipe-like tubes, dramatically increasing the risk of plaque rupture and cardiovascular events. The

independent odds ratio of over 3.0 for abnormal eGFR in our study is the clinical manifestation of this multifaceted vascular assault.[18] It demonstrates that the health of the kidneys is inextricably linked to the health of the arteries. A decline in GFR is not just a marker of kidney damage; it is a systemic alarm bell indicating the presence of a highly pro-atherogenic, pro-inflammatory, and pro-calcific state that dramatically accelerates vascular disease, independent of a patient's cholesterol level.[19]

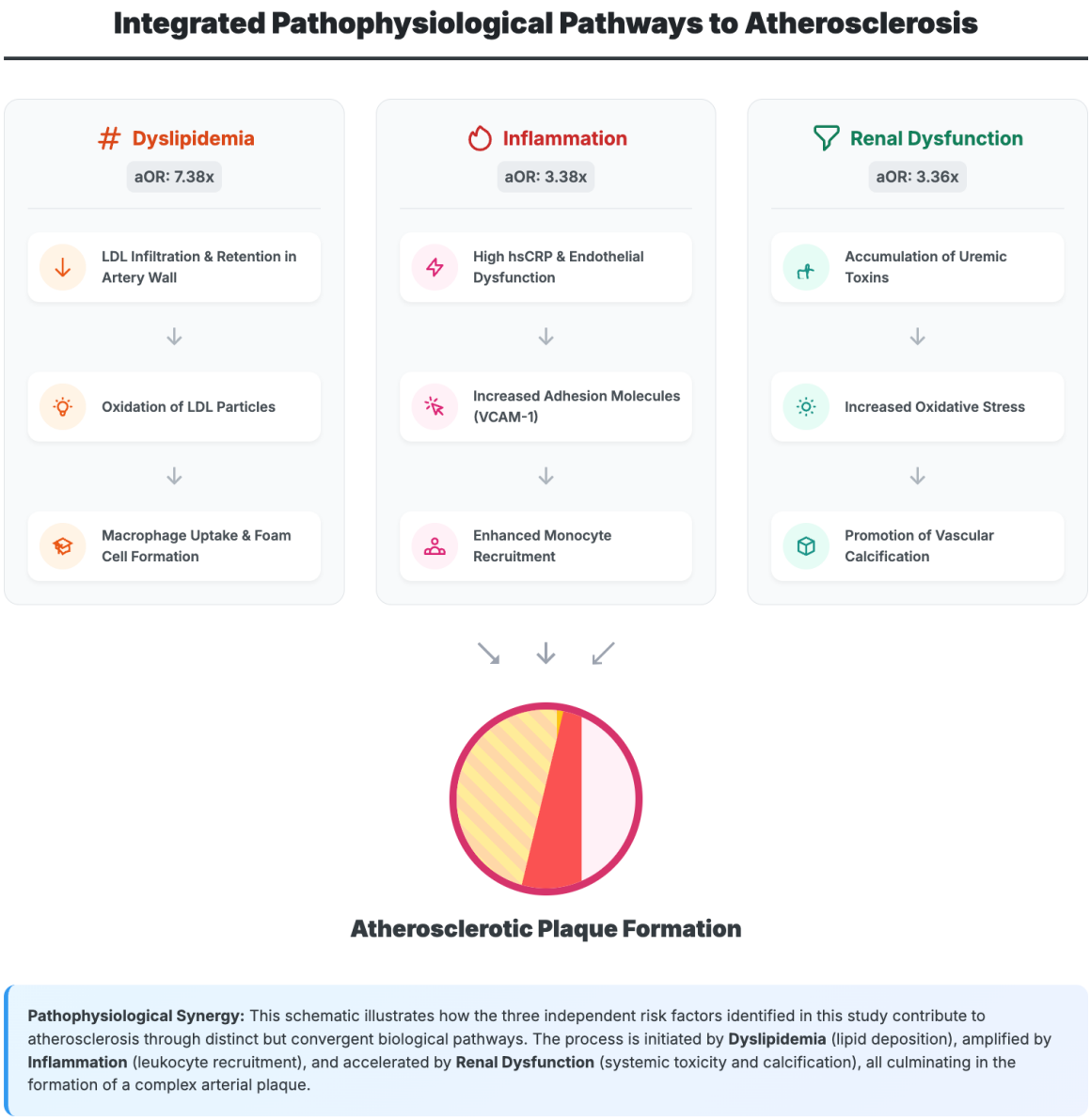


Figure 6. Integrated pathophysiological pathways to atherosclerosis.

Figure 6 showed a powerful and elegant schematic that synthesizes the study's statistical findings into a cohesive biological narrative, illustrating the integrated pathophysiological pathways leading to atherosclerosis. The diagram masterfully depicts how the three statistically significant, independent predictors—dyslipidemia, inflammation, and renal dysfunction—are not isolated phenomena but rather

distinct yet convergent contributors to the ultimate formation of an atherosclerotic plaque. Each pathway, headed by its adjusted odds ratio from the multivariate analysis, outlines a step-by-step progression from systemic risk factor to localized vascular pathology. The schematic correctly positions dyslipidemia as the foundational pathway, underscored by its dominant adjusted odds ratio of 7.38x. This signifies that the metabolic derangement of lipids is the primary and most powerful initiating force in the journey towards atherosclerosis. The process begins with LDL Infiltration & Retention in the Artery Wall. In a state of hypercholesterolemia, the endothelium, the single-cell layer lining the arteries, becomes overwhelmed. Low-density lipoprotein (LDL) particles, the primary carriers of cholesterol, cross the endothelial barrier and enter the subendothelial space, known as the intima. Here, they become trapped by binding to extracellular matrix molecules like proteoglycans. This sequestration is the critical first step, as it increases the residence time of the LDL particles, exposing them to the local oxidative environment of the vessel wall. Oxidation of LDL Particles. Once retained, the trapped LDL is attacked by reactive oxygen species (ROS) generated by local vascular cells. This chemical modification transforms native LDL into oxidized LDL (ox-LDL), a highly pathogenic and immunogenic form. ox-LDL is no longer recognized by the normal LDL receptor, and it acts as a potent "danger signal" that triggers a defensive, yet ultimately maladaptive, inflammatory response from the arterial wall. Macrophage Uptake & Foam Cell Formation. The presence of ox-LDL stimulates the overlying endothelium to express adhesion molecules that recruit circulating monocytes. These monocytes migrate into the intima and differentiate into macrophages. These macrophages express scavenger receptors, such as CD36 and SR-A, which recognize and avidly internalize the ox-LDL particles. Unlike the native LDL receptor, these scavenger receptors are not downregulated by high intracellular cholesterol levels. This leads to a relentless and unregulated accumulation of cholesterol within the macrophage, causing it to transform into a lipid-engorged "foam cell." The accumulation of these foam cells forms the fatty streak, the earliest visible lesion of atherosclerosis, and their subsequent death contributes to the formation of the necrotic, lipid-rich core of a mature plaque. This entire cascade, initiated by high cholesterol, provides a clear biological basis for its commanding odds ratio. Figure 6 illustrates inflammation as a crucial amplifier of the atherosclerotic process, backed by a significant adjusted odds ratio of 3.38x. This pathway highlights that the inflammatory response is not just a consequence of lipid deposition but an independent force that dramatically fuels the disease. The process is characterized first by High hsCRP & Endothelial Dysfunction. High-sensitivity C-reactive protein (hsCRP) is more than a passive marker; it actively participates in vascular damage. It suppresses the production of nitric oxide (NO), a critical molecule that maintains endothelial health by promoting vasodilation and inhibiting inflammation and thrombosis. The loss of NO bioavailability is a hallmark of endothelial dysfunction, creating a pro-atherosclerotic environment. Increased Adhesion Molecules (VCAM-1). Stimulated by hsCRP and other inflammatory cytokines, endothelial cells begin to express adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), on their surface. These molecules function like molecular Velcro, catching circulating inflammatory cells, particularly monocytes. Enhanced Monocyte Recruitment. The monocytes adhere to the activated endothelium and migrate into the subendothelial space. Once inside the intima, they mature into the very macrophages that consume oxidized LDL, thus directly linking the inflammatory cascade with the dyslipidemia pathway.[19] This demonstrates a vicious cycle: lipids trigger inflammation, and inflammation enhances the cellular response to lipids, creating a self-perpetuating cycle of plaque growth. The third pathway, Renal Dysfunction, is shown to be an equally potent independent risk factor, with an adjusted odds ratio of

3.36x. This pathway introduces unique mechanisms that accelerate and intensify the atherosclerotic process. It begins with the accumulation of uremic toxins. When kidney function declines, waste products that are normally filtered from the blood accumulate. These include protein-bound uremic toxins like indoxyl sulfate, which are directly toxic to endothelial cells, promoting dysfunction and a pro-inflammatory state. Increased oxidative stress. Uremic toxins stimulate the production of ROS throughout the body, creating a state of systemic oxidative stress. This not only damages vascular cells directly but also accelerates the oxidation of LDL particles, thus amplifying a key step in the dyslipidemia pathway. Promotion of vascular calcification, a distinct and dangerous feature of atherosclerosis in this context. Impaired kidneys disrupt mineral metabolism, leading to high phosphate levels and hormonal imbalances. This pathological environment induces vascular smooth muscle cells within the artery wall to transform into bone-like cells, which then deposit calcium into the plaque. This process turns flexible arteries into brittle, rigid tubes, increasing plaque instability and the risk of rupture.[20] This powerful visual synthesis illustrates that the plaque is not a simple structure but a complex amalgamation of the inputs from each pathway. It contains a lipid core derived from dyslipidemia, an inflammatory infiltrate of macrophages driven by the inflammation pathway, and is often hardened by calcium deposits promoted by renal dysfunction. The synergy of these processes—initiated by lipids, amplified by inflammation, and accelerated by renal dysfunction—explains how three distinct clinical conditions can work in concert to create a single, life-threatening vascular lesion.[20]

## 5. Conclusion

In this comprehensive investigation of an elderly Indonesian study, we have moved beyond a simple list of risk factors to reveal a synergistic and hierarchical triad of risk for carotid atherosclerosis. Our findings confirm that dyslipidemia remains the foundational pillar of the disease, providing the essential substrate for plaque formation with overwhelming predictive power. However, our work critically establishes that systemic inflammation, indexed by hsCRP, and mild renal dysfunction, indexed by eGFR, are not mere bystanders. They are potent and independent forces, each more than tripling the odds of disease. These factors represent distinct biological pathways—vascular inflammation and cardio-renal toxicity—that significantly amplify risk on top of the underlying lipid burden. This study champions a necessary evolution in clinical practice: a shift towards an integrated, multifactorial risk assessment that quantifies not only the metabolic fuel but also the inflammatory fire and the systemic organ-system stress that collectively drive atherosclerosis in our aging global population.

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