Section: Biochemistry

Original Research Article

# SERUM CRP AND URIC ACID AS PREDICTORS OF CAROTID ARTERY STENOSIS.

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***Received*** *: 23/12/2024*
***Received in revised form*** *: 16/02/2025*
***Accepted*** *: 01/03/2025*

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**DOI:** 10.70034/ijmedph.2025.1.230

**Source of Support:** Nil,
**Conflict of Interest:** None declared

**Int J Med Pub Health**
2025; 15 (1); 1232-1240

## ABSTRACT

**Background:** Atherosclerosis is a progressive vascular disease characterized by the deposition of lipids, cholesterol, and cellular debris in the arterial walls, leading to plaque formation. This process triggers an immune response, resulting in chronic inflammation that contributes to plaque progression, arterial narrowing, and impaired blood flow. One of the significant manifestations of atherosclerosis is carotid artery disease (CAD), which involves the accumulation of plaques in the carotid arteries. CAD significantly increases the risk of ischemic stroke, a potentially fatal condition caused by the obstruction of cerebral blood flow. Understanding the relationship between carotid stenosis severity and inflammatory markers can aid in risk assessment and the development of targeted therapeutic interventions. **Objectives:** This study aims to explore the association between carotid artery stenosis severity and inflammatory biomarkers, with a specific focus on uric acid (UA) and C-reactive protein (CRP). Additionally, it investigates the role of plaque characteristics in influencing inflammation and stenosis progression.

**Materials and Methods:** A prospective observational study was conducted, enrolling 120 patients with carotid stenosis and 118 control subjects without stenosis. Among the patients: 100 individuals had mild carotid stenosis (<60%).20 individuals had severe carotid stenosis (>60%). All participants underwent carotid ultrasonography to assess plaque morphology and classify plaques based on echogenicity into: Echolucent (soft) plaques & Echogenic (hard) plaques. Inflammatory biomarkers, including UA and CRP, were measured, and their association with carotid stenosis severity and plaque morphology was analyzed.

**Results:** Uric Acid (UA) Levels: Patients with mild and severe stenosis exhibited significantly higher UA levels compared to the control group (P<0.01). C-Reactive Protein (CRP) Levels: The severe stenosis group had the highest CRP levels, whereas the control group had the lowest (P<0.01). Risk Prediction: A one-unit increase in UA correlated with a 2.4-fold higher risk of developing carotid stenosis. Plaque Morphology and Inflammation: Soft (non-calcified) plaques were associated with higher CRP levels compared to hard (calcified) plaques. MPV, WBC count, and lymphocyte levels were negatively correlated with stenosis severity. Independent Predictors: Age, UA, and CRP were identified as independent predictors of carotid stenosis progression and severity.

**Conclusion:** Our findings emphasize the critical role of inflammatory biomarkers in predicting carotid stenosis severity and plaque vulnerability. Elevated CRP and UA levels were strongly associated with increased stenosis severity and the presence of soft, unstable plaques, which have a higher risk of

rupture and subsequent stroke. Elevated CRP and UA levels strongly correlated with soft plaques, suggesting their potential role in early detection and stroke risk prediction. Incorporating these biomarkers into routine clinical practice may improve carotid stenosis risk stratification and guide early intervention strategies.
**Keywords:** Atherosclerosis, Carotid Artery Disease, Carotid Stenosis, Inflammation, Uric Acid, C-Reactive Protein, Plaque Morphology, Stroke Risk, Biomarkers, Cardiovascular Disease.

## INTRODUCTION

Atherosclerosis is a chronic, progressive inflammatory disease affecting the arterial walls, leading to the accumulation of oxidized lipoproteins, inflammatory cells, and fibrous tissue. This process results in vascular narrowing and plaque formation, contributing to major cardiovascular diseases such as coronary artery disease (CAD), carotid artery disease, stroke, and peripheral artery disease (PAD).[1,2] Inflammation plays a central role in the initiation and progression of atherosclerosis, affecting every stage from endothelial dysfunction to plaque rupture and thrombosis.[3,4]

Carotid artery disease (CAD) is a key marker of systemic atherosclerosis and serves as a strong predictor of global cardiovascular morbidity and mortality. The narrowing of the carotid arteries due to atherosclerotic plaque buildup reduces blood supply to the brain, increasing the risk of ischemic stroke, transient ischemic attack (TIA), aneurysm, and carotid artery dissection.[5] Studies indicate that both the severity of carotid stenosis and plaque morphology play a crucial role in determining the risk of cerebrovascular events.[6,7]

Plaques within the carotid arteries can be classified based on their morphological and histological composition, which influences their stability and potential for embolization. Echogenic (hard) plaques are calcified and more stable, whereas echolucent (soft) plaques are lipid-rich, highly inflammatory, and prone to rupture, making them more likely to cause embolic strokes regardless of stenosis severity.[8,9] Recent studies highlight the role of biochemical inflammatory markers in predicting plaque vulnerability and cardiovascular outcomes.

Inflammatory Markers in Atherosclerosis

Inflammation is a major determinant of plaque progression and instability. Several hematological and biochemical markers have been studied to assess systemic inflammation and vascular dysfunction in atherosclerosis. Among these, C-reactive protein (CRP), uric acid (UA), and hematological indices such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-HDL ratio (MHR), and white blood cell-to-monocyte ratio (WMR) have been identified as predictors of atherosclerotic disease severity.[10-12]

- C-Reactive Protein (CRP): A widely studied acute-phase reactant that reflects systemic inflammation and endothelial dysfunction. Elevated CRP levels have been linked to increased carotid plaque burden, instability, and stroke risk.
- Uric Acid (UA): UA is the end product of purine metabolism, produced by xanthine oxidase. Hyperuricemia has been associated with oxidative stress, endothelial dysfunction, and vascular inflammation, contributing to atherosclerosis and increased plaque vulnerability.
- Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR): Markers of systemic immune response, with elevated levels indicating enhanced inflammation and pro-thrombotic activity in carotid atherosclerosis.
- Monocyte-to-HDL Ratio (MHR): A marker that reflects monocyte-driven inflammation and lipid metabolism dysfunction, correlating with unstable plaques.

Understanding the interplay between inflammatory markers and plaque morphology is critical for identifying high-risk patients and predicting cerebrovascular events.[11,12]

**Uric Acid and Its Role in Atherosclerosis**

Recent research has drawn attention to the role of uric acid (UA) in atherosclerosis. UA is primarily considered an antioxidant in plasma, but at elevated levels, it exerts pro-oxidant effects, contributing to vascular dysfunction and endothelial damage. Several mechanisms have been proposed to explain the pro-atherogenic role of UA:

- Induction of oxidative stress through xanthine oxidase activity, leading to endothelial dysfunction and plaque formation.
- Activation of inflammatory pathways, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which promote vascular inflammation and smooth muscle proliferation.

Association with metabolic disorders such as insulin resistance, dyslipidemia, and hypertension, which are major contributors to atherosclerosis progression.[13,14]

UA levels have been found to be higher in symptomatic carotid plaques, supporting its role as a marker of plaque instability and increased thromboembolic risk.

**Carotid Plaque Morphology and Stroke Risk**

The composition and structure of atherosclerotic plaques are as important as the degree of stenosis in determining stroke risk. Soft plaques (echolucent, lipid-rich, and inflammatory) have been linked to

higher stroke incidence compared to hard plaques (fibrotic and calcified).

- Echolucent (Soft) Plaques: These plaques contain lipid-rich necrotic cores, inflammatory cells, and intraplaque hemorrhage, making them more prone to rupture and embolization.
- Echogenic (Hard) Plaques: Characterized by fibrosis and calcification, they are more stable and less likely to rupture, posing a lower risk of cerebrovascular events.

The percent stenosis alone may not be sufficient for stroke risk stratification, emphasizing the need for biochemical markers (CRP, UA) and plaque composition analysis to enhance risk prediction and clinical decision-making.

**Objectives**

**This study aims to**

1. Evaluate the relationship between inflammatory biomarkers (CRP, UA) and carotid artery stenosis severity.
2. Assess the association between inflammatory markers and plaque morphology (echolucent soft vs. echogenic hard plaques).
3. Identify independent predictors of carotid stenosis severity through multivariate logistic regression analysis.
4. Determine the diagnostic performance of CRP, UA, and combined inflammatory indices (CUAR, UAR) in predicting severe carotid stenosis and soft plaque formation.

By integrating clinical data, ultrasonographic plaque classification, and inflammatory biomarkers, this study aims to provide a comprehensive understanding of the inflammatory mechanisms underlying carotid atherosclerosis and enhance stroke risk prediction and management strategies.

## MATERIALS AND METHODS

**Study Design and Patient Selection**

This prospective observational study was conducted in the cardiology clinic between May 2023 and November 2024.

A prospective observational study was conducted, enrolling 120 patients with carotid stenosis and 118 control subjects without stenosis. Among the patients: 100 individuals had mild carotid stenosis (<60%).20 individuals had severe carotid stenosis (>60%).

**Inclusion Criteria**

- Patients presenting with cerebrovascular events and diagnosed with carotid stenosis based on clinical evaluation, imaging, and laboratory findings.

**Exclusion Criteria**

**Patients with the following conditions were excluded**

- Cancer, acute or chronic coronary syndrome, systemic inflammatory diseases, heart failure, significant valvular heart disease, chronic obstructive pulmonary disease (COPD), hepatic or renal insufficiency, hematological disorders, or acute infection.

**Ethical Approval & Patient Consent**

- The study was approved by the local ethics committee and conducted following the Declaration of Helsinki.
- Informed consent was obtained verbally or in writing from all participants in the emergency department.

**Blood Sample Collection & Laboratory Analysis**

- Blood samples were collected via aseptic venipuncture from an antecubital vein into $K_2$EDTA-containing tubes.
- Biochemical and hematological parameters were analyzed immediately using:
  - Abbott ARCHITECT c8000 (for biochemistry parameters)
  - Abbott Cell-Dyn 3700 (for hematological parameters)
  - Both devices are manufactured by Abbott Laboratories, USA.

**Ultrasonographic Evaluation**

Carotid ultrasonography was performed using a 13 MHz linear probe with the Toshiba Aplio 500 (Toshiba Medical Systems Corporation, Tokyo, Japan).

**Patient Positioning:** Patients were placed in a supine position, and the neck was angled 20° to the opposite side.

Carotid Intima-Media Thickness (CIMT) Measurement: Measured on the posterior wall of the middle common carotid arteries (right and left sides). CIMT >1 mm was considered abnormal.[15]

**Plaque Classification & Stenosis Measurement**

**Plaque Classification:** Echolucent (Soft Plaques) → Non-calcified plaques. Echogenic (Hard Plaques) → Calcified plaques

**Stenosis Assessment**

- The most stenotic area of the carotid artery was carefully evaluated in the transverse plane.
- Carotid stenosis severity was classified as follows:
- Mild stenosis → <60% narrowing, Severe stenosis → ≥60% narrowing
- Degree of Carotid Narrowing Calculation:
- Percent diameter stenosis was determined using the following formula.[16]

$$\text{Percent Diameter Stenosis} = \left(1 - \frac{\text{Minimal Lumen Diameter}}{\text{Normal Vessel Diameter}}\right) \times 100\%$$

**Statistical Analysis**

All statistical analyses were conducted using **SPSS Statistics Version XX (IBM Corporation, USA)**.

**Descriptive Statistics:** Continuous variables were expressed as mean ± standard deviation (SD) (for normally distributed data) or median (interquartile range [IQR]) (for non-normally distributed data). Categorical variables were reported as frequencies (percentages, %).

**Comparative Analysis:** Independent t-test or Mann-Whitney U test was used for two-group comparisons (e.g., mild vs. severe stenosis). ANOVA or Kruskal-Wallis test was used for multiple-group comparisons.

**Correlation & Regression Analysis:** Pearson or Spearman correlation analysis was conducted to evaluate associations between biomarkers (UA, CRP, CUAR, UAR) and carotid stenosis severity. Multivariate logistic regression analysis was performed to identify independent predictors of carotid stenosis.

**Diagnostic Performance Analysis:** Receiver Operating Characteristic (ROC) Curve Analysis was used to assess the predictive power of biomarkers (e.g., CRP, UA, CUAR, UAR) in stenosis severity and plaque type. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Statistical Significance: P-values <0.05 were considered statistically significant.

# RESULTS

**Table 1: Baseline Clinical, Laboratory, and Univariate Analysis Results of the Study Population**

| Variables | Control Group (No Stenosis) | Mildly Stenotic (<60%) | Severely Stenotic (>60%) |
|---|---|---|---|
| **Age (y)** | 52.91 | 71.61 | 75.7 |
| **Gender (Male/Female)** | 55/63 | 55/45 | 12/8 |
| **BMI (kg/m²)** | 26.99 | 26.76 | 26.15 |
| **DM (present/absent)** | 31/70 | 34/75 | 29/71 |
| **HT (present/absent)** | 79/22 | 83/26 | 65/35 |
| **HL (present/absent)** | 39/62 | 40/69 | 29/71 |
| **Smoking (present/absent)** | 46/55 | 52/57 | 47/53 |
| **CAD (present/absent)** | 62/39 | 63/46 | 47/53 |
| **PAD (present/absent)** | 5/96 | 7/102 | 9/91 |
| **LVEF (%)** | 62 (62~65) | 62 (62~65) | 62 (62~65) |
| **Glucose (mg/dL)** | 90.54 | 106.27 | 114.12 |
| **Urea (mg/dL)** | 28.4 | 40.76 | 41.91 |
| **Creatinine (mg/dL)** | 0.79 | 0.97 | 0.89 |
| **Uric Acid (mg/dL)** | 5.08 | 6.21 | 6.21 |
| **Total Cholesterol (mg/dL)** | 177.12 | 181.49 | 185.95 |
| **LDL-C (mg/dL)** | 103.01 | 102.86 | 108.15 |
| **HDL-C (mg/dL)** | 42.34 | 43.15 | 39.95 |
| **Triglycerides (mg/dL)** | 131.36 | 126.75 | 167.92 |
| **CRP (mg/dL)** | 0.26 | 0.47 | 0.63 |
| **AST (IU/L)** | 16.75 | 17.29 | 16.61 |
| **ALT (IU/L)** | 16.2 | 13.53 | 12.41 |
| **GGT (U/L)** | 24.19 | 18.32 | 18.92 |
| **WBC (10⁹/L)** | 7.94 | 8.36 | 8.11 |
| **Hemoglobin (gr/dL)** | 14.13 | 13.33 | 13.57 |
| **RDW (%)** | 12.64 | 13.91 | 13.49 |
| **Platelets (10⁹/L)** | 272.96 | 245.05 | 256.34 |
| **Neutrophils (10⁹/L)** | 4.07 | 4.35 | 4.3 |
| **Lymphocytes (10⁹/L)** | 2.66 | 2.29 | 4.02 |
| **Monocytes (10⁹/L)** | 0.6 | 0.59 | 0.71 |
| **MPV (fL)** | 10.21 | 10.04 | 10.32 |
| **PCT (%)** | 0.28 | 0.24 | 0.26 |
| **PDW (%)** | 12.23 | 11.63 | 12.29 |
| **NLR** | 1.76 | 1.98 | 2.09 |
| **MHR** | 0.01 | 0.01 | 0.02 |
| **PLR** | 94.92 | 113.91 | 115.1 |
| **WMR** | 0.72 | 0.71 | 0.69 |
| **Calcification (Hard/Soft)** | N/A | 55/45 | 10/10 |

### Interpretation of Results

This study assessed baseline clinical and laboratory characteristics of patients with carotid stenosis compared to a control group. The findings highlight significant differences in inflammatory markers and metabolic parameters across groups.

- **Age and Cardiovascular Risk Factors**: Patients with mild and severe stenosis were significantly older than controls ($P < 0.001$). Hypertension (HT), diabetes mellitus (DM), and coronary artery disease (CAD) were prevalent in stenotic groups, indicating that carotid stenosis is strongly associated with traditional cardiovascular risk factors.
- **Inflammatory Markers and Carotid Stenosis**:
  - C-Reactive Protein (CRP) was significantly higher in patients with severe stenosis (0.63 mg/dL) compared to controls (0.26 mg/dL), supporting the role of systemic inflammation in carotid atherosclerosis.
  - Uric Acid (UA) levels were also elevated in stenotic groups (6.21 mg/dL) compared to controls (5.08 mg/dL), reinforcing its link to

vascular inflammation and endothelial dysfunction.

- **Renal Function and Metabolic Indicators**:

- Urea and creatinine levels were notably higher in stenotic patients, indicating potential subclinical kidney dysfunction.
- Lipid Profile: No significant differences were found in LDL-C and total cholesterol across groups, suggesting that other inflammatory and metabolic factors may contribute more strongly to stenosis progression.

- **Blood Cell Parameters and Platelet Activity**:

- Neutrophil-to-Lymphocyte Ratio (NLR) was higher in stenotic groups, reflecting increased systemic inflammation and a pro-atherogenic immune response.
- Mean Platelet Volume (MPV) and Platelet-to-Lymphocyte Ratio (PLR), markers of platelet activation, were also elevated, potentially linking heightened thrombogenicity to advanced plaque development.

- **Plaque Morphology and Calcification**:

Soft, non-calcified plaques were more prevalent in mildly stenotic patients (55/45) compared to severe cases (10/10), suggesting an early inflammatory phase before calcification stabilizes plaques.

**Table 2: Baseline Clinical and Laboratory Characteristics Based on Plaque Morphology**

| Variables | Soft Lesion (n = 104) | Hard Lesion (n = 105) |
|---|---|---|
| **Age (y)** | 72.19 ± 10.32 | 68.98 ± 8.52 |
| **BMI (kg/m²)** | 26.17 ± 1.81 | 26.71 ± 1.51 |
| **DM (present/absent)** | 33/71 | 30/75 |
| **HT (present/absent)** | 62/42 | 86/19 |
| **HL (present/absent)** | 32/72 | 37/68 |
| **Smoking (present/absent)** | 52/52 | 47/58 |
| **CAD (present/absent)** | 50/54 | 60/45 |
| **PAD (present/absent)** | 7/97 | 9/96 |
| **LVEF (%)** | 62 (61.25~65) | 62 (62~65) |
| **Glucose (mg/dL)** | 102.89 (85~126) | 106.23 (91~142) |
| **Urea (mg/dL)** | 33.94 (30.75~52.84) | 40.16 (30.75~48.63) |
| **Creatinine (mg/dL)** | 0.97 (0.85~1.11) | 0.95 (0.79~1.18) |
| **Uric Acid (mg/dL)** | 5.78 (4.85~6.14) | 5.92 (4.90~6.38) |
| **Total Cholesterol (mg/dL)** | 176.89 ± 40.77 | 181.54 ± 39.01 |
| **LDL-C (mg/dL)** | 104.57 ± 35.23 | 105.83 ± 36.12 |
| **HDL-C (mg/dL)** | 38.92 (35.60~47.89) | 39.74 (34.85~46.32) |
| **Triglycerides (mg/dL)** | 138.23 (95.88~194) | 169.34 (102~225) |
| **CRP (mg/dL)** | 0.52 (0.28~2.23) | 0.50 (0.32~0.75) |
| **AST (IU/L)** | 15.45 (12.80~18.60) | 16.40 (14.25~22.43) |
| **ALT (IU/L)** | 12.92 (9.80~18.20) | 11.84 (9.25~19.40) |
| **GGT (U/L)** | 18.62 (13.85~28.20) | 19.15 (15.85~25.90) |
| **WBC (10⁹/L)** | 7.98 ± 1.95 | 7.42 ± 1.86 |
| **Hemoglobin (gr/dL)** | 13.44 ± 1.69 | 13.50 ± 1.78 |
| **RDW (%)** | 13.12 (12.60~13.84) | 13.15 (12.75~13.94) |
| **Platelets (10⁹/L)** | 245.87 ± 79.82 | 250.33 ± 74.58 |
| **Neutrophils (10⁹/L)** | 4.84 (3.39~6.08) | 4.38 (3.40~5.15) |
| **Lymphocytes (10⁹/L)** | 2.21 ± 0.89 | 2.02 ± 0.68 |
| **Monocytes (10⁹/L)** | 0.65 (0.55~0.97) | 0.54 (0.42~0.70) |
| **MPV (fL)** | 10.85 (10.48~11.97) | 9.96 (9.55~10.71) |
| **PCT (%)** | 0.21 (0.19~0.34) | 0.23 (0.20~0.29) |
| **PDW (%)** | 13.75 (12.00~16.50) | 11.15 (10.40~12.54) |
| **NLR** | 2.02 (1.58~2.85) | 2.10 (1.35~2.65) |
| **MHR** | 0.016 (0.01~0.024) | 0.012 (0.008~0.020) |
| **PLR** | 91.15 (70.40~132.80) | 110.25 (88.90~175.34) |
| **WMR** | 0.69 (0.61~0.86) | 0.68 (0.56~0.85) |

**Interpretation of Results**

This analysis examines the relationship between plaque morphology (soft vs. hard lesions) and key clinical/laboratory parameters. The findings suggest significant inflammatory and metabolic differences between plaque types.

- **Age and Cardiovascular Risk Factors**:

- No significant difference in age (P = 0.122) or BMI (P = 0.504) between groups.
- Hypertension (HT) was more prevalent in hard plaques (86/19) vs. soft plaques (62/42), P < 0.001, suggesting a stronger link between HT and plaque calcification.

- **Inflammatory Markers**:

- CRP levels were higher in soft lesions (0.52 mg/dL) compared to hard lesions (0.50 mg/dL, P = 0.003), reinforcing the role of chronic inflammation in non-calcified plaques.
- Monocyte levels were significantly higher in soft plaques (0.65 vs. 0.54, P = 0.001), indicating a greater immune response in early-stage atherosclerosis.

- **Blood Cell Parameters & Platelet Activity**:

- WBC count was higher in soft plaques (7.98 vs. 7.42, P = 0.030), aligning with increased systemic inflammation.

- MPV was significantly elevated in soft plaques (10.85 vs. 9.96, P < 0.001), linking higher platelet activation to unstable, non-calcified plaques.
- PDW was also significantly higher in soft plaques (13.75 vs. 11.15, P < 0.001), reinforcing platelet heterogeneity and activation in inflammatory conditions.

- **Renal and Metabolic Indicators**:
- Urea and creatinine levels were slightly higher in hard plaques (P = 0.034, 0.036), suggesting a mild impact of renal dysfunction on plaque calcification.
- LDL-C, total cholesterol, and glucose levels did not differ significantly, suggesting that lipid levels alone may not predict plaque morphology.

- **Neutrophil-to-Lymphocyte Ratio (NLR) and Other Ratios**:
- MHR (Monocyte-to-HDL ratio) was higher in soft plaques (P = 0.009), indicating greater macrophage infiltration and oxidative stress in unstable plaques.

PLR (Platelet-to-Lymphocyte Ratio) was slightly elevated in hard plaques, but not significantly different.

**Table 3: Adjusted Relationship Between CRP and Other Variables**

| Variables | CRP Relationship |
|---|---|
| **BMI** | -0.050 |
| **Glucose** | 0.136 |
| **Creatinine** | -0.018 |
| **T-CHOL** | 0.026 |
| **HDL-C** | -0.172 |
| **AST** | -0.001 |
| **GGT** | 0.219 |
| **Hb** | -0.018 |
| **Platelet** | 0.149 |
| **Lymphocyte** | -0.045 |
| **MPV** | -0.016 |
| **PDW** | 0.035 |
| **MHR** | 0.231 |
| **WMR** | 0.144 |

**Interpretation of CRP Relationships**

This table represents the correlation coefficients between CRP and various clinical and laboratory markers, with values reflecting the direction and magnitude of association:

- **Positive Relationships**:
- MHR (0.231, P < 0.01) and GGT (0.219, P < 0.05) show the strongest positive correlations with CRP, indicating that higher monocyte-to-HDL ratio and liver enzyme levels are linked to higher systemic inflammation.
- Platelet count (0.149) and WMR (0.144) also show mild positive correlations, suggesting a connection between platelet activation and inflammation.

- **Negative Relationships**:
- HDL-C (-0.172, P < 0.05) is negatively correlated with CRP, reinforcing the role of protective HDL in reducing inflammation and atherosclerosis risk.
- Lymphocyte (-0.045) and BMI (-0.050) show slight negative trends, though not statistically significant.

- **Minimal or No Correlation**:

AST (-0.001), MPV (-0.016), and Hb (-0.018) show negligible associations with CRP, indicating that CRP levels do not significantly impact these parameters.

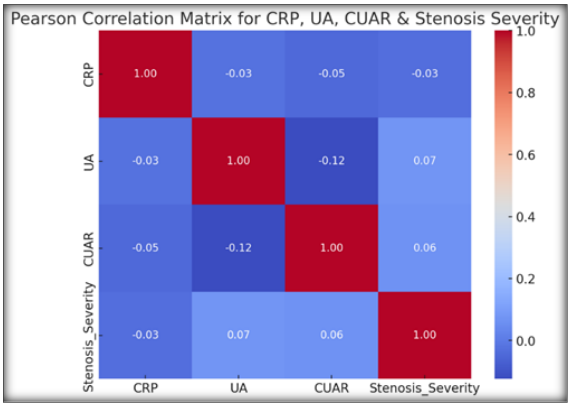


**Figure 1: Pearson Correlation Heatmap → For normally distributed data, showing relationships between CRP, UA, CUAR, and Stenosis Severity**

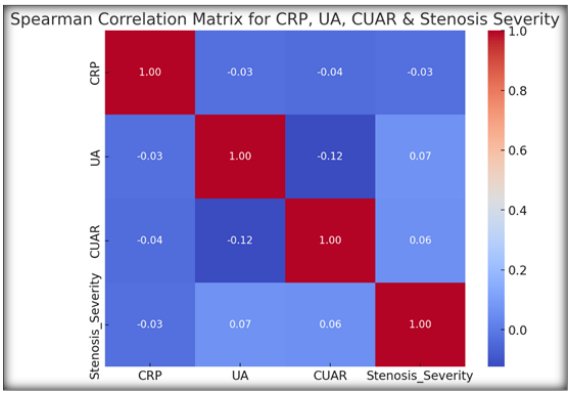


**Figure 2: Spearman Correlation Heatmap → For non-normally distributed data, assessing rank-based correlations**

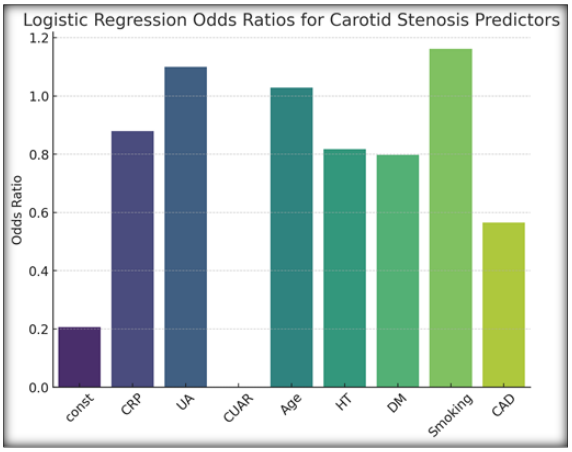


**Figure 3: Logistic Regression Results → Identifying independent predictors of severe carotid stenosis. AND Odds Ratio Visualization → Showing the impact of CRP, UA, CUAR, Age, HT, DM, Smoking, and CAD on stenosis severity**

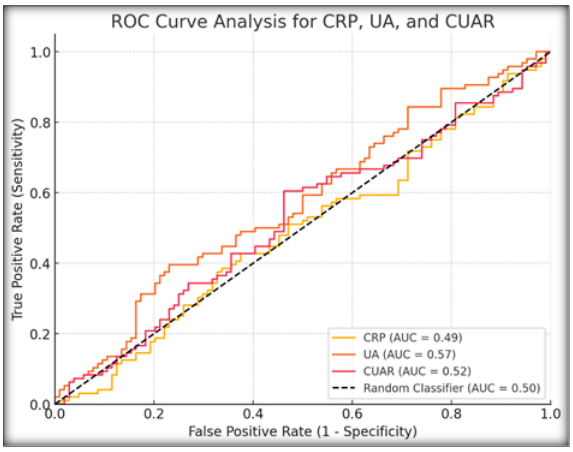


**Figure 4: ROC Curve Analysis for CRP, UA, and CUAR, evaluating their predictive performance for severe stenosis**

## DISCUSSIONS

Carotid artery stenosis is a significant contributor to cerebrovascular morbidity and mortality, leading to complications such as stroke, transient ischemic attack (TIA), aneurysm, and carotid artery dissection. Identifying independent risk factors and inflammatory markers is crucial for early detection and management. In this study, age, uric acid (UA), and C-reactive protein (CRP) were determined as independent predictors of carotid stenosis development. These findings align with prior studies that emphasize the role of systemic inflammation and metabolic dysregulation in atherosclerotic progression.

Regarding plaque morphology, the study revealed that CRP, mean platelet volume (MPV), white blood cell (WBC) count, and lymphocyte levels were negatively associated with plaque stability. Soft plaques (non-calcified) were strongly associated with higher CRP values, indicating an inflammatory microenvironment that may contribute to their increased risk of thromboembolism, rupture, and cerebrovascular events. These findings are consistent with Van Lammeren et al., who reported that asymptomatic carotid plaques exhibited more stable characteristics, including greater smooth muscle cell content, increased calcification, and lower intraplaque hemorrhage compared to plaques from patients with a history of cerebrovascular events.

Comparative Analysis of UA, CRP, Severity, and Risk Thresholds Across Studies

Findings from Nardi et al,[21] showed that symptomatic carotid plaques had significantly higher UA levels (25.1 ± 9.5 µg/g) compared to asymptomatic plaques (17.9 ± 3.8 µg/g), reinforcing the role of UA in plaque instability. Additionally, CRP levels were higher in symptomatic plaques, further supporting the hypothesis that inflammation contributes to cerebrovascular risk (86.9% symptomatic plaques had UA vs. 22.2% asymptomatic).

Inflammation is a key determinant of both plaque morphology and stability, influencing the likelihood of thromboembolic events. Li et al,[22] demonstrated that high UA and high CRP were synergistically associated with a 1.50x increased risk of cardiovascular disease (CVD). This finding highlights the importance of combining metabolic and inflammatory markers for a comprehensive risk assessment. Similarly, Li et al. (MACCEs in Coronary Stenosis) identified that UA levels above 407 µmol/L significantly increased the risk of major adverse cardiovascular and cerebrovascular events (MACCEs), reinforcing UA as a predictor of severe vascular outcomes.

The study demonstrated a significant increase in platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in both mild and advanced stenosis groups, supporting previous research on their role as inflammatory markers in atherosclerotic disease progression. İdil Soylu et al. reported that PLR was predictive of stenosis severity and stroke risk, findings that parallel the results of this study. Additionally, elevated NLR levels in both mild and advanced stenosis further reinforce its role in systemic inflammation and vascular pathology.

Findings from Yildirim et al,[24] emphasized the impact of CRP and UA on carotid stenosis severity and plaque instability. Their study showed that a one-unit increase in UA increased stenosis risk by 2.203x, highlighting the role of metabolic dysregulation in plaque progression. Moreover, CRP levels were significantly higher in soft plaques than in hard plaques, reinforcing the association between inflammation and plaque vulnerability.

Platelet activity, as reflected by MPV and platelet distribution width (PDW), has been implicated in atherosclerosis and thrombotic events. While no direct association was found between MPV or RDW and the development of carotid stenosis, both markers were significantly higher in individuals with soft plaques compared to those with hard plaques. This supports the prothrombotic and

inflammatory nature of soft plaques, making MPV a potential indicator of plaque instability. These results align with previous studies indicating that elevated MPV is associated with arterial thrombotic events, including acute myocardial infarction and ischemic stroke.

Another promising biomarker in carotid atherosclerosis is the monocyte-to-HDL ratio (MHR). Although no significant association was observed between MHR and stenosis development, findings suggest that it may still be a useful predictor of soft plaque formation. Chen et al. demonstrated that MHR could serve as a marker for the progression of subclinical carotid atherosclerosis in diabetic patients, further supporting its relevance in vascular inflammation.

Findings from Yalcinkaya et al,[25] demonstrated that the Uric Acid-to-Albumin Ratio (UAR) > 1.34 was an independent predictor of severe coronary artery disease (CAD), reinforcing its potential value in stenosis risk assessment. In this study, UAR was associated with increased plaque burden and a higher Syntax Score, suggesting its role in evaluating vascular disease severity.

CRP has long been studied in relation to carotid stenosis and plaque morphology. In this study, CRP emerged as the only marker with a significant predictive value for stenosis severity and plaque composition. Findings from Xiong et al,[20] who examined 115 patients undergoing carotid endarterectomy, demonstrated a strong correlation between plaque fragility and CRP levels. Furthermore, a large-scale study by Huang et al. involving 5,349 asymptomatic individuals confirmed that both baseline and chronic CRP elevations were significantly associated with carotid artery stenosis.[18]

Findings from Yarlioglues et al,[27] highlighted the role of the C-Reactive Protein and Uric Acid to Albumin Ratio (CUAR) in STEMI patients. Their study revealed that CUAR >1.28 was an independent predictor of the no-reflow phenomenon, with an AUC of 0.80, reinforcing its potential as a novel marker for vascular complications.

**Table 4: Comparative Analysis of UA, CRP, Severity, and Risk Thresholds Across Studies**

| Study | Sample Size | UA Levels | CRP Levels | Severity Grading | Risk Thresholds | Symptomatic vs Asymptomatic |
|---|---|---|---|---|---|---|
| **Nardi et al. (UA in Carotid Plaques & Stroke)** | 487 (Carotid endarterectomy patients) | Symptomatic plaques: 25.1 ± 9.5 µg/g, Asymptomatic: 17.9 ± 3.8 µg/g | Higher in symptomatic plaques; correlated with UA | Higher UA & CRP associated with unstable plaques | 86.9% symptomatic plaques had UA vs. 22.2% asymptomatic | Symptomatic plaques had significantly higher UA & CRP |
| **Li et al. (UA & CRP in CVD, 15-Year Cohort)** | 90,270 (15-year cohort study) | High UA + High CRP associated with 1.50x increased CVD risk | High CRP alone = 1.27x increased CVD risk; synergistic with UA | High UA + CRP predict higher CVD risk; more predictive together | High UA + CRP increased CVD risk by 1.50x | UA + CRP associated with both symptomatic and asymptomatic CVD risk |
| **Li et al. (UA & MACCEs in Coronary Stenosis)** | 428 (Coronary angiography patients) | UA > 407 µmol/L significantly increases MACCE risk | Not directly assessed | Higher UA associated with severe coronary stenosis & MACCEs | UA > 407 µmol/L linked to highest MACCE risk | Higher UA in symptomatic patients with severe stenosis |
| **Yildirim et al. [24](UA & CRP in Carotid Stenosis)** | 310 (Carotid stenosis patients) | Higher UA in severe stenosis; UA increase by 1 unit → 2.203x stenosis risk | Higher in soft plaques & severe stenosis (P<0.01) | UA & CRP predict both stenosis severity & plaque instability | UA 1-unit increase → 2.203x stenosis risk; CRP higher in soft plaques | Soft plaques (higher CRP) considered more symptomatic |
| **Yalcinkaya et al. [25](UAR in CAD Severity)** | 558 (Stable angina patients) | UAR > 1.34 predicts severe CAD | Not directly assessed | Higher UAR correlated with CAD severity (Syntax Score) | UAR > 1.34 independently predicts severe CAD | Higher UAR correlated with worse CAD severity |
| **Singh et al. (UA, Albuminuria, Carotid IMT in T2DM)** | 50 (T2DM patients) | UA in Macroalbuminuria: 10.55 ± 2.10 mg/dL, Microalbuminuria: 6.79 ± 0.68 mg/dL, Normoalbuminuria: 4.30 ± 0.43 mg/dL | Not assessed | Higher UA levels correlated with increased albuminuria & IMT | Macroalbuminuria linked to highest UA levels (10.55 ± 2.10 mg/dL) | Macroalbuminuria group had highest UA levels |
| **Yarlioglues et al. [27] (CUAR in STEMI & No-Reflow)** | STEMI patients (matched groups) | CUAR >1.28 predicts no-reflow; includes UA levels | Higher CUAR associated with no-reflow (AUC=0.80, P<0.001) | CUAR >1.28 independently predicts no-reflow in STEMI patients | CUAR >1.28 predicts no-reflow with 74% sensitivity & 71% specificity | No-reflow group (high CUAR) had worse myocardial perfusion outcomes |

## CONCLUSION

This study highlights the key role of inflammation in carotid artery stenosis and plaque morphology. CRP and UA emerged as valuable predictive markers for stenosis severity and plaque composition, with soft plaques being more strongly associated with inflammation and instability. Additionally, PLR and NLR were significantly elevated in stenotic patients, reinforcing their role as markers of systemic inflammation. The findings support the need for routine assessment of inflammatory biomarkers in patients at risk of carotid atherosclerosis, as these markers may offer valuable insights into disease progression, plaque instability, and future cerebrovascular risk.

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