Correlation between Blood Urea Nitrogen-to-Serum Albumin Ratio and Carotid Artery Plaque in Patients with Coronary Heart Disease (Postprint)

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Abstract

Background: The blood urea nitrogen to serum albumin ratio (BAR) is an emerging biomarker that has recently been associated with adverse outcomes in various cardiopulmonary diseases, but the relationship between BAR and carotid plaque in patients with coronary heart disease (CHD) remains unclear.

Objective: To investigate the correlation between BAR and carotid plaque in CHD patients.

Methods: Data from CHD patients hospitalized in 6 hospitals in Tianjin from January 2014 to September 2019 were retrospectively selected. BAR was calculated as BUN/ALB. Logistic regression analysis was used to evaluate the association between BAR and the risk of carotid plaque, plaque number, and plaque characteristics in CHD patients, with further analysis after adjusting for confounding factors. Receiver operating characteristic (ROC) curve for BAR in diagnosing carotid plaque risk was plotted, and the area under the ROC curve (AUC) was calculated.

Results: A total of 10,808 CHD patients were included. Among them, 8,158 had carotid plaque, with a prevalence of 75.5%. The 10,808 CHD patients were divided into 4 groups according to BAR quartiles (Q1, Q2, Q3, Q4). The Q1 group had BAR $\leq$ -0.3954, and the Q2 group had -0.3954 $<$ BAR $\leq$ 0.1324. Compared with the Q1 group, after multivariate adjustment, the Q4 group showed the strongest association between BAR and carotid plaque formation (OR = 1.512, 95% CI = 1.273–1.795, P $<$ 0.001). The AUC of BAR for diagnosing carotid plaque risk in CHD patients was 0.612 (95% CI = 0.600–0.624). In the female population, there was a stronger association between BAR level and plaque (OR = 1.583, 95% CI = 1.260–1.989, P $<$ 0.001), and in the elderly

population, there was a stronger association between BAR and plaque (OR = 1.810, 95% CI = 1.459-2.246, P < 0.001). Moreover, the association between BAR and carotid plaque was not affected by diseases such as hypertension, hyperlipidemia, and diabetes.

Conclusion: Elevated BAR is associated with carotid plaque formation, and this association is more pronounced in female and middle-aged/elderly populations. Increased BAR may help in early identification of carotid plaque formation in CHD patients, thereby avoiding the occurrence of major adverse cardiovascular events.

Full Text

Association between Blood Urea Nitrogen to Serum Albumin Ratio and Carotid Plaque in Patients with Coronary Heart Disease

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Abstract

Background: The ratio of blood urea nitrogen (BUN) to serum albumin (ALB) (BAR) is an emerging biomarker that has recently been recognized to associate with adverse outcomes in a variety of cardiorespiratory disorders. However, the relationship between BAR and carotid plaque in patients with coronary heart disease (CHD) is currently unclear.

Objective: To investigate the correlation between BAR and carotid plaque in CHD patients.

Methods: Admission medical data of CHD patients hospitalized in six hospitals in Tianjin from January 2014 to September 2019 were retrospectively analyzed. BAR was calculated by dividing BUN by ALB. Logistic regression analysis was used to evaluate the correlation of BAR with the occurrence, number, and characteristics of carotid plaque in CHD patients before and after adjusting for confounding factors. A receiver operating characteristic (ROC) curve was drawn to assess the diagnostic value of BAR for carotid plaque risk, and the area under the ROC curve (AUC) was calculated.

Results: A total of 10,808 CHD patients were included, among whom 8,158 had carotid plaque, yielding a prevalence of 75.5%. Patients were divided into four groups according to BAR quartiles (Q1, Q2, Q3, Q4): Q1 ≤ -0.3954, -0.3954 < Q2 ≤ -0.1587, -0.1587 < Q3 ≤ 0.1324, and Q4 > 0.1324. Compared

with Q1, Q4 showed the strongest association with carotid plaque formation after multivariate adjustment (OR = 1.512, 95% CI = 1.273–1.795, P < 0.001). The AUC of BAR for diagnosing carotid plaque risk in CHD patients was 0.612 (95% CI = 0.600–0.624). The association between BAR and plaque was stronger in females (OR = 1.583, 95% CI = 1.260–1.989, P < 0.001) and in the elderly population (OR = 1.810, 95% CI = 1.459–2.246, P < 0.001). Moreover, the significant correlation between BAR and carotid plaque was not affected by hypertension, hyperlipidemia, or diabetes.

Conclusion: Elevated BAR is associated with carotid plaque formation, particularly in women and middle-aged/elderly populations. Increased BAR may help identify CHD patients at risk for carotid plaque formation early, thereby preventing major adverse cardiovascular events.

Keywords: Coronary heart disease; Blood urea nitrogen; Serum albumin; Carotid artery plaque; Root cause analysis; Tianjin

Introduction

Carotid plaque represents a manifestation of carotid atherosclerosis that is associated with atherosclerotic cardiovascular disease and increases the risk of major adverse cardiovascular events (MACEs). Recent studies indicate that nearly one-quarter of Chinese adults have carotid plaque, and carotid plaque hemorrhage is an independent risk factor for coronary heart disease (CHD). Early prevention, treatment, and intervention targeting risk factors have proven beneficial, underscoring the need for simple biomarkers to identify and prevent carotid plaque risk in CHD patients.

Blood urea nitrogen (BUN) is an important indicator of renal function. Research has shown that elevated BUN levels can cause endothelial dysfunction and correlate with the risk of carotid atherosclerosis, with some scholars recommending special consideration of BUN levels in CHD risk prediction and prevention among middle-aged and elderly Chinese populations. Serum albumin (ALB), a key indicator of liver function, has also been implicated in atherosclerotic thrombosis formation. The BUN-to-ALB ratio (BAR) is an emerging biomarker that combines these two important parameters to assess combined hepatic and renal dysfunction. Recent evidence links BAR to adverse outcomes in various conditions, including myocardial infarction, heart failure, pneumonia, and COVID-19, as well as poor prognosis in cardiac surgery patients, where elevated preoperative BAR predicts adverse outcomes.

This study aimed to examine the association between BAR and carotid plaque in CHD patients and to explore whether this relationship varies by age and sex, thereby enabling early assessment of CHD patients to prevent MACEs caused by atherosclerosis.

Methods

Study Population

We retrospectively analyzed admission data from 107,301 CHD patients hospitalized between January 2014 and September 2019 at six hospitals in Tianjin: the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin Chest Hospital, Tianjin Nankai Hospital, Tianjin Medical University General Hospital, and the Affiliated Hospital of Tianjin Academy of Traditional Chinese Medicine. CHD was defined according to International Classification of Diseases (ICD) codes: I25 (coronary heart disease), I20 (angina pectoris), I49 (arrhythmia), I50 (heart failure), and I24 (acute coronary syndrome).

The study was approved by the Tianjin University of Traditional Chinese Medicine Ethics Committee (approval number: TJUTCM-EC20190008), registered with the Chinese Clinical Trial Registry (ChiCTR-1900024535) on July 14, 2019, and with ClinicalTrials.gov (NCT04026724) on July 18, 2019. Patients aged <35 or >80 years, those lacking BUN, ALB, or carotid ultrasound data, and those with tumors, severe infectious diseases, or severe renal disease were excluded. A total of 96,463 cases were excluded, leaving 10,808 patients for final analysis.

Data Collection

Baseline data collected included age, sex, BUN, ALB, serum creatinine (Scr), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glycated hemoglobin A1c (HbA1c), smoking history, alcohol consumption history, and medication use.

Fasting venous blood samples were collected after 8–10 hours of fasting. BUN, ALB, Scr, FBG, TC, TG, LDL-C, and HDL-C were measured using an automatic biochemical analyzer; HbA1c was measured by high-pressure liquid chromatography. Smoking and alcohol consumption histories were obtained via standardized questionnaires administered by trained medical staff. "Never smoking" and "never drinking" or "occasional drinking without excessive consumption" were defined as "no," while "quit smoking," "current smoking," "regular drinking," or "excessive drinking" were defined as "yes."

All participating clinical laboratories underwent external quality control assessments to ensure measurement comparability. BAR (mg/g) was calculated as BUN (mg/dL) divided by ALB (g/dL). BAR data were standardized using the z-score function: z-score = (raw value -sample mean) / sample standard deviation. Severe renal disease was defined as estimated glomerular filtration rate (eGFR) $<30\ \mathrm{mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$, calculated using the formula: eGFR =

$186 \times \mathrm{Scr}^{-1}.^{154} \times \mathrm{age}^{-0}.^{203} \times (0.742 \text{ if female}) \times (1.233 \text{ if Chinese})$.

Carotid ultrasound examinations were performed by certified technicians using diagnostic ultrasound systems, with results evaluated by trained and certified professionals. Plaque number was categorized as single ($n = 1$) or multiple ($n \geq 2$). Based on morphological and acoustic characteristics, plaques were classified as hypoechoic, isoechoic, hyperechoic, or mixed-echo; isoechoic and hyperechoic plaques were considered stable, while hypoechoic and mixed-echo plaques were considered vulnerable.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 25.0. Continuous variables were non-normally distributed and expressed as median (P25, P75), with group comparisons performed using the Kruskal-Wallis test. Categorical variables were expressed as percentages and analyzed using the ^{2} test. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between BAR and carotid plaque, with $P < 0.05$ considered statistically significant. Model a was unadjusted; Model b adjusted for age and sex; Model c adjusted for age, sex, SBP, DBP, FBG, TC, TG, LDL-C, HDL-C, and HbA1c; Model d adjusted for all Model c variables plus smoking history, alcohol consumption, antihypertensive medication, lipid-lowering medication, anticoagulant medication, diabetes, and acute coronary syndrome.

ROC curve analysis was performed to evaluate the diagnostic value of BAR for carotid plaque risk, with AUC calculated. Patients were divided into four groups based on BAR quartiles: Q1 (BAR $\leq$ -0.3954), Q2 (-0.3954 $<$ BAR $\leq$ -0.1587), Q3 (-0.1587 $<$ BAR $\leq$ 0.1324), and Q4 (BAR $>$ 0.1324).

Results

Baseline Characteristics

Among the 10,808 CHD patients included, 5,431 (50.2%) were female and 5,377 (49.8%) were male. The prevalence of carotid plaque was 75.5% (8,158 cases), with mixed-echo plaque present in 23.7% (2,564 cases). Significant differences were observed among the four BAR quartile groups in sex, age, DBP, FBG, TC, TG, LDL-C, HDL-C, HbA1c, smoking history, alcohol consumption, and proportions using antihypertensive, lipid-lowering, and anticoagulant medications, as well as diabetes prevalence ($P < 0.05$). Other indicators showed no significant differences among groups ($P > 0.05$) .

Association between BAR and Carotid Plaque Risk in CHD Patients

When BAR was treated as a continuous variable, binary logistic regression showed BAR was a significant predictor of carotid plaque (OR = 1.981, 95% CI = 1.785–2.199, $P < 0.001$), though this association disappeared after multivariate adjustment (OR = 1.115, 95% CI = 0.997–1.248, $P = 0.057$).

When BAR was treated as a categorical variable with Q1 as reference, Q2, Q3, and Q4 were all associated with carotid plaque risk, with Q4 showing the strongest association (OR = 2.845, 95% CI = 2.491–3.249, P < 0.001). After adjusting for confounders, this relationship persisted (OR = 1.512, 95% CI = 1.273–1.795, P < 0.001) .

Diagnostic Value of BAR for Carotid Plaque

The AUC of BAR for diagnosing carotid plaque risk in CHD patients was 0.612 (95% CI = 0.600–0.624) [Figure 1: see original paper].

Association of BAR with Plaque Number and Echo Characteristics

When BAR was analyzed as a continuous variable, it was associated with plaque number, particularly multiple plaques (OR = 2.007, 95% CI = 1.807–2.229, P < 0.05), though this association was attenuated after multivariate adjustment (OR = 1.114, 95% CI = 0.995–1.246, P = 0.060). As a categorical variable, Q4 BAR was significantly associated with multiple plaques (OR = 2.899, 95% CI = 2.536–3.314, P < 0.001), remaining significant after adjustment (OR = 1.504, 95% CI = 1.265–1.788, P < 0.001) .

Multinomial logistic regression showed BAR as a continuous variable was most strongly associated with mixed-echo plaques (OR = 2.024, 95% CI = 1.815–2.258, P < 0.001). As a categorical variable, Q4 BAR showed the strongest association with mixed-echo plaques (OR = 3.358, 95% CI = 2.857–3.947, P < 0.001), persisting after full adjustment (OR = 1.703, 95% CI = 1.389–2.088, P < 0.001) .

Association of BAR with Carotid Plaque across Sex, Age, and Comorbidity Subgroups

Binary logistic regression across subgroups showed significant associations between BAR and carotid plaque in all sex, age, and disease subgroups. After multivariate adjustment, the association remained stronger in females (OR = 1.473, 95% CI = 1.228–1.766, P < 0.001) and elderly patients (OR = 1.667, 95% CI = 1.408–1.973, P < 0.001). When BAR was analyzed categorically with Q1 as reference, Q4 BAR was associated with carotid plaque across all subgroups, including those with hypertension, hyperlipidemia, and diabetes, with associations remaining significant after multivariate adjustment (P < 0.05) .

Discussion

Our findings indicate that the association between BAR and carotid plaque risk in CHD patients depends on variable type and adjustment status. As a continuous variable, BAR was significantly associated with carotid plaque risk before adjustment (P < 0.001) but not after multivariate correction. However, when BAR was treated categorically, Q4 showed the strongest association with

plaque formation, persisting after full adjustment ($P < 0.001$). This suggests a potential non-linear relationship or threshold effect: when BAR exceeds a certain cutoff (e.g., Q4 level), its association with plaque formation may be independent of traditional cardiovascular risk factors, whereas as a continuous variable, its effect may be confounded.

Across subgroup analyses, Q4 BAR consistently showed the strongest association with carotid plaque, indicating that higher BAR correlates with increased plaque risk. Similarly, Q4 BAR was most strongly associated with mixed-echo plaques, suggesting that higher BAR correlates with vulnerability plaque characteristics.

Elevated BAR reflects high BUN and low ALB levels. First, BUN, a marker of renal function, may promote atherosclerosis by inducing oxidative stress and endothelial dysfunction. Studies show BUN increases reactive oxygen species (ROS) in arterial endothelial cells, impairing endothelial function. Increased ROS inactivates prostacyclin I2 synthase, a key endothelial-specific anti-atherosclerotic enzyme, thereby promoting carotid plaque formation. Mixed-echo plaques are considered vulnerable, containing more lipids and prone to rupture. ROS plays a crucial role in vulnerable plaque formation by oxidizing and destabilizing membrane lipids and proteins. Oxidative stress-induced inflammation is a primary determinant of plaque destabilization, and antioxidant capacity is a favorable factor for assessing plaque inflammatory activity and vulnerability. Both ROS and endothelial dysfunction are key contributors to unstable plaque formation.

Second, low ALB may accelerate atherosclerosis through multiple pathways. Beyond maintaining colloid osmotic pressure, low ALB reflects systemic inflammation, a critical driver of atherosclerosis. Physiologically low ALB may increase blood viscosity, impair endothelial function, and reduce vascular antioxidant capacity, making vessels more susceptible to oxidative stress and promoting vulnerable carotid plaque formation.

Plaque hemorrhage is an independent risk factor for CHD that increases stroke risk and mortality. Thus, elevated BAR may serve as a cardiovascular risk indicator, particularly for assessing vulnerable carotid plaque formation in CHD patients.

This study benefits from a large sample size, enhancing result reliability. However, limitations exist. BMI is an important confounder for CHD and carotid plaque, but was not included due to missing data. Additionally, as a cross-sectional study, causality cannot be established without temporal considerations. Future prospective studies should further explore this relationship.

In conclusion, CHD patients with elevated BAR, particularly women and middle-aged/elderly individuals, require heightened attention to carotid plaque risk and enhanced screening to prevent MACEs.

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Author Contributions: SHENG Jingyu and LIU Fanfan designed the study, conducted research, and wrote the initial draft; MA Mei collected and analyzed/interpreted data; TIAN Lin, LIU Yutong, and LIU Fengmin collected data, performed investigations, and executed operations; GAO Shan and YU Chunquan critically reviewed intellectual content, obtained funding, and provided technical/material support.

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