Cardiovascular Topics

The role of C-reactive protein:albumin ratio and neutrophil:lymphocyte ratio in predicting coronary artery disease

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Abstract

Introduction: Acute coronary syndrome (ACS), one of the most common causes of death worldwide, is a condition characterised by ischaemia and/or infarction due to reduced coronary blood flow. The most prevalent cause of ACS is coronary artery disease. In this study, we aimed to investigate the relationship between blood parameters that we commonly use in the laboratory [C-reactive protein (CRP), albumin, neutrophils and lymphocytes] and coronary artery disease (CAD).

Methods: This retrospective, single-centre study included 100 patients who underwent coronary angiography, with the diagnosis of acute coronary syndrome between January and June 2023, and 106 patients with high clinical suspicion and normal coronary arteries as a control group. The NLR was obtained from the ratio of neutrophils to lymphocytes and the CAR was obtained from the ratio of CRP to albumin. We analysed the relationship between CAD and NLR and CAR according to laboratory findings and demographic characteristics of the patients.

Results: The average age of the study group was 59 ± 10 years. NLR and CAR values were higher in the patient group than the control group (5.2 ± 3.3 vs 2.27 ± 1.2, $p = 0.004$ and 0.5 ± 0.1 vs 0.097 ± 0.095, respectively, $p < 0.001$). Albumin ratios were found to be statistically significantly lower in the patient group than the patient group (42.4 ± 4 vs 44 ± 3.3, respectively, $p = 0.01$). In addition, CAR and NLR showed a significant diagnostic value for CAD in receiver operating characteristic curve analysis (area under the curve: 0.68 ± 0.07, $p = 0.003$; 0.66 ± 0.09 $p \leq 0.001$).

Conclusion: NLR and CAR values, which are important indicators of inflammation, were found to be higher in the patient group. We believe it may be important to monitor these patients more frequently and follow them closely in terms of CAD, especially if the rate is higher in individuals without CAD who come for out-patient clinic check-ups.

Keywords: coronary artery disease, C-reactive protein:albumin ratio, neutrophil:lymphocyte ratio, coronary angiography

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Acute coronary syndrome (ACS), one of the most common causes of death worldwide, is a condition characterised by ischaemia and/or infarction due to reduced coronary blood flow.[1] The most prevalent cause of ACS is coronary artery disease (CAD).[2] ACS is categorised into ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina.[3]

The pathophysiology of ACS involves a complex series of reactions, including rupture of atheroma plaque, platelet activation, aggregation leading to thrombus formation, endothelial dysfunction, vasospasm and revascularisation.[4] Primarily, troponin is used as a cardiac marker in laboratory tests, especially in the absence of specific findings on the electrocardiogram (ECG). However, due to the long duration to obtain test results, its low diagnostic value within the first 12 hours, and the fact that it yields negative results in 14 to 20% of cases, there is a growing importance for additional laboratory tests that are easy, fast and cost-effective for patients.

Recently, the World Health Organisation has recognised that prevention is the most effective method in combating cardiovascular diseases (CVD).[5,6] Subsequently, there is a need for low-cost, rapid, specific, non-invasive and predictive tools to identify individuals at high risk of developing CVD events. In this context, molecular biomarkers such as asymmetric dimethylarginine, adipocyte-fatty acid binding protein, chemerin, adiponectin, troponin and C-reactive protein (CRP) have been successfully utilised in extensive prospective studies.[7,8] However, in developing countries, the use of these molecular biomarkers in the general population is not feasible due to the high cost of analysis. As a result, more affordable alternatives are needed to identify high-risk populations. Various cost-effective tools have been developed and proposed as significant and valuable biomarkers for predicting atherosclerosis and cardiovascular diseases.[9]

Numerous studies have investigated inflammatory mechanisms in both cardiac and non-cardiac diseases, revealing that these mechanisms are crucial in the formation and prognosis of ACS.[10] Inflammatory mediators have been shown to be associated with atherosclerosis, inducing thrombus formation and increasing the

risk of plaque rupture. For this reason, various inflammation mediators such as leukocytes, neutrophils, lymphocytes and CRP are used to predict ischaemic vascular events in asymptomatic patients.[10]

Other parameters, the ratio of neutrophils to lymphocytes (NLR) and the ratio of CRP to albumin (CAR), associated with mortality in ACS, have been identified as the most robust prognostic marker among haematological markers because they include two parameters evaluating the degree of inflammation.[11,12] NLR has also been studied in various clinical scenarios and has been used as a marker of chronic systemic inflammation. For example, in the literature, it has been reported to be used as an activity parameter in ulcerative colitis or as an indicator of the presence of Hashimoto's thyroiditis.[13,14] Therefore, this research aimed to evaluate clinical prognostic markers to identify cost-effective, specific and useful tools for identifying individuals at high risk of developing cardiovascular events.

Methods

This retrospective study was conducted at the Cardiology Clinic of Erzurum City Hospital between 1 January and 1 June 2023. It included 100 patients who underwent coronary angiography at the cardiology clinic, with a diagnosis of ACS. As a control group, 106 patients with normal coronary arteries from non-invasive test results and high clinical suspicion, who were matched based on age and gender, were also included.

Haemogram values in samples taken from patients were studied with the Sysmex XN-1000 clinical system. Biochemical biomarkers were analysed on the Beckman Coulter AV 5800 clinical system. Data were recorded by questioning clinical and demographic characteristics.

The study was approved by the institutional ethics committee (date: 13 December 2023; decision number: 2023/08-97) and was conducted in accordance with the Declaration of Helsinki.

Patients with a known history of chronic inflammatory disease, heart failure with reduced ejection fraction [left ventricular ejection fraction (LVEF) ≤ 40%], and heart failure with moderate ejection fraction (LVEF 41–49%), severe valve disease, a history of prosthetic valves, a history of malignancy, a history of autoimmune disease, kidney and/or liver failure and chronic obstructive pulmonary disease were excluded from our study.

Biochemical laboratory parameters of the patients were recorded. The CRP value was proportioned to albumin and recorded as the CAR. The neutrophil parameter was proportioned to the lymphocyte count and recorded as the NLR value.

Statistical analysis

Data were analysed using IBM SPSS V23. Normal distribution compliance was examined with the Kolmogorov–Smirnov and Shapiro–Wilk tests. The independent two-sample *t*-test was used for examining data that were normally distributed across binary groups. The Mann–Whitney *U*-test was utilised for data not normally distributed across binary groups. Yates correction was applied for comparing categorical data among groups. Analysis results are presented as mean ± standard deviation and median (minimum–maximum) for quantitative data, and as frequency (percentage) for categorical data. The significance level was set at $p < 0.050$. NLR and CAR were used as diagnostic tests in predicting CAD, and specificity and sensitivity values were calculated using the receiver operating characteristic (ROC) curve. For *p*-values < 0.05, it was considered statistically significant.

Results

In our study, the average patient age was 59 ± 10 years. There was no significant gender difference between the groups. In the control group, there were no instances of smoking, hypertension, or diabetes mellitus. NLR and CAR values were higher in the patient group than in the controls (5.2 ± 3.3 vs 2.27 ± 1.2, $p = 0.004$ and 0.5 ± 0.1 vs 0.097 ± 0.095, $p < 0.001$, respectively). Albumin levels were statistically significantly lower in the patient group than in the controls (42.4 ± 4 vs 44 ± 3.3, respectively, $p = 0.01$). A comparison of the demographic characteristics and laboratory parameters of the study groups is shown in Table 1.

Factors affecting coronary angiography results were examined using a binary logistic regression model (Table 2). In the univariate model, as the NLR value increased, the probability of lesions in the coronary arteries increased 1.42 times ($p = 0.032$). In the multivariate model, this ratio was found to be 1.37. In both univariate and multivariate models, the effect of CAR value on CAD was found to be statistically significant ($p = 0.004$ and $p = 0.037$, respectively).

Table 1. Demographic characteristics of the patient and control groups

Variables	*Patients* (n = *100*)	*Controls* (n = *106*)	p-*value*
STEMI/NSTEMI	77/23	–	< 0.001
Age	59 ± 10	44 ± 10	< 0.001
Female/male	18/82	52/54	0.001
HT	76	0	< 0.001
DM	32	0	< 0.001
Smoking	64	0	< 0.001
CAG result	100	0	< 0.001
Hg (g/dl)	14.1 ± 2.5	14.9 ± 1.9	0.25
Neutrophils (× 10^9 cells/l)	7.1 ± 3.7	5 ± 1.9	0.003
Lymphocytes (× 10^9 cells/l)	2.4 ± 2.1	2.5 ± 0.7	0.016
WBC (× 10^9 cells/l)	10.03 ± 3.4	8.4 ± 2.1	0.01
PLT (× 10^9 cells/l)	258 ± 76.7	292 ± 72.3	0.01
CRP (mg/l)	20.1 ± 4.2	4.2 ± 4	< 0.001
Glucose (mg/dl) (mmol/l)	138 ± 69	90 ± 16	< 0.001
Creatinine (mg/dl)	0.9 ± 0.8	0.7 ± 0.1	0.004
Albumin (g/l)	42.4 ± 4	44 ± 3.3	0.01
Sodium (mmol/l)	139 ± 3	140 ± 2.4	0.04
Uric acid (mg/dl)	5.4 ± 1.6	4.8 ± 1.2	0.09
Potassium (mmol/l)	4.1 ± 0.5	4 ± 0.2	0.85
Calcium (mg/dl)	9.1 ± 0.6	9.5 ± 0.4	0.001
Magnesium (mg/dl)	1.9 ± 0.3	1.8 ± 0.2	0.13
Triglyceride (mg/dl)	170 ± 103	172 ± 103	0.9
LDL-C (mg/dl) (mmol/l)	140 ± 53	120 ± 33	0.02
HDL-C (mg/dl) (mmol/l)	33.7 ± 10	42 ± 13	< 0.001
Cholesterol (mg/dl) (mmol/l)	194 ± 59	180 ± 40	0.2
NLR	5.2 ± 3.3	2.27 ± 1.2	0.004
CAR	0.5 ± 0.1	0.097 ± 0.095	< 0.001

STEMI/NSTEMI: ST-elevation myocardial infarction/non-ST-elevation myocardial infarction, HT: hypertension, DM: diabetes mellitus, CAG: coronary artery disease, Hg: haemoglobin, WBC: white blood cells, PLT: platelets, CRP: C-reactive protein, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, NLR: neutrophil:lymphocyte ratio, CAR: C-reactive protein:albumin ratio.

Table. 2. Examination of factors affecting the result of coronary angiography using a binary logistic regression model

Variables	*Univariate*	p-*value*	*Multivariate*	p-*value*
NLR	1.42 (1.10–1.83)	0.006	1.37 (1.03–1.82)	0.032
CAR	3.2 (1.8–4.98)	0.004	4.3 (1.33–11.29)	0.037
PLT	0.94 (0.88–0.98)	0.01	0.94 (0.98–1.02)	0.057

NLR: neutrophyl:lymphocyte ratio, CAR: C-reactive protein:albumin ratio; PLT: platelets.

Specificity for NLR and CAR was found to be significant in the ROC curve analysis [NLR area under the curve (AUC) = 0.68 ± 0.07, $p = 0.003$; CAR AUC = 0.66 ± 0.09, $p < 0.001$] (Fig. 1).

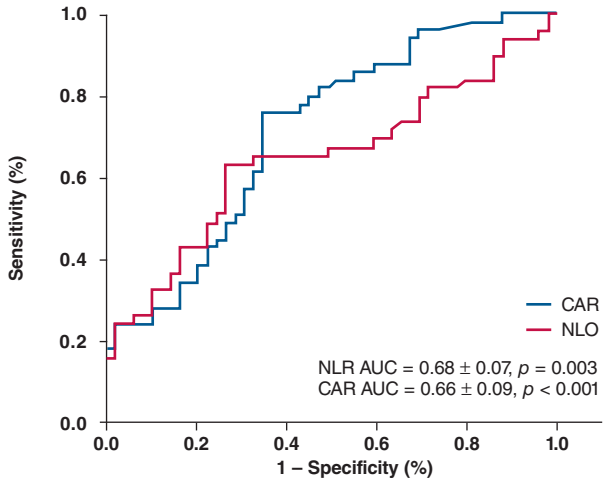

Fig. 1. ROC curve analysis. AUC, area under the curve.

Discussion

The main finding of this study was that the levels of NLR and CAR were statistically significantly higher in the group with CAD compared to the healthy control group. These results provide substantial evidence suggesting that increased levels of NLR and CAR may play a role in the pathophysiology of CAD. This is the first study in the literature to report that NLR and CAR levels were higher in predicting CAD compared to a healthy control group. Another notable finding of our study is that CRP, one of the parameters used in the calculation of CAR, was significantly high, while albumin levels were significantly low.

The use of inflammatory biomarkers in the diagnosis and screening of atherosclerotic heart disease is increasingly being recognised.[15] It is well known that CRP and albumin, among the most commonly used biomarkers for this purpose, have a strong relationship with their individual formation and presentation patterns.[16,17] The CAR reflects the stability of albumin and CRP levels in the body. It has been demonstrated to better reflect the inflammatory status and prognosis than high-sensitivity CRP (hs-CRP) or albumin alone in critically ill patients, those with acute medical conditions and cancer patients.[18]

In a study, the relationship between an hs-CRP test and thrombus burden was investigated and a statistically significant difference was found between thrombus burden and CAR.[19] In our study, both CAR and NLR were found to be statistically significant in predicting CAD. Inflammation is a crucial factor involved in all stages of the atherosclerotic process and plaque destabilisation. CRP and albumin are inflammatory biomarkers routinely used in clinics. It has been demonstrated that increased CRP levels are associated with stable angina pectoris, the development of myocardial infarction and stroke, and the severity of CAD.[20] All of these conditions are thought to result from endothelial dysfunction and lipid peroxidation.

In our study, the higher CRP values in CAD patients were consistent with studies in the literature investigating the relationship between CRP and CVD. In another study, the relationship between CAR and coronary slow-flow phenomenon was mentioned.[21] In our study, CAR predicted CAD, and serum albumin levels in CAD patients where the inflammatory process was active were found to be lower than in patients with normal coronary arteries.

Recent studies have reported that CAR is a more sensitive parameter for inflammation than CRP and albumin alone.[22] Previous studies have shown that CAR is associated with the severity of CAD and has an impact on stent restenosis in patients with stable angina.[23] In two other studies, CAR predicted CAD, and CAR together with systemic immune inflammation predicted acute stent thrombosis.[24,25] Our study supports these findings, indicating that CAR was statistically significant in predicting CAD compared to the control group. Additionally, NLR was also found to be statistically significant in predicting CAD compared to the control group.

The primary mechanism responsible for CAD and ACS is inflammation.[26] In the literature, the relationship between the degree of inflammation and the levels of haematological markers has been examined in various diseases.[27] During the inflammatory process, blood cells have been the subject of studies because they both encompass and are affected by the inflammatory process.

The relationship between the prognosis of ACS and haematological markers continues to be a topic of research. Their use in prognostic classification offers advantages due to their wide availability and cost effectiveness. NLR, which is associated with mortality in ACS, is the most potent prognostic marker among haematological markers because it includes two parameters used to evaluate the degree of inflammation.[28] Our study supports existing literature and found that NLR was statistically significant in the patient group compared to the control group.

NLR has also been studied in various clinical scenarios and has been used as a marker of chronic systemic inflammation. For instance, in the literature, it has been used as an activity parameter in ulcerative colitis or as an indicator of the presence of Hashimoto's thyroiditis.[29] Our study corroborates existing studies and found that NLR was statistically significant in predicting CAD.

The limitation of this study is the relatively small number of patients. Our study results should be supported by multicentre research involving larger populations and requiring long-term follow up.

Conclusion

We found that CAR and NLR values were statistically significant in predicting CAD compared to the control group. CAR and

NLR are essential biomarkers that are cheap, quick and easy to apply and can be used in the diagnosis and prognosis of ACS.

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