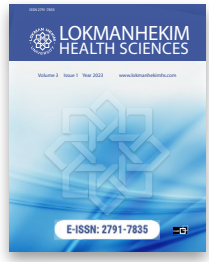
LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2022.80006
Lokman Hekim Health Sci 2023;3(1):32–37

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ORIGINAL ARTICLE

# C-Reactive Protein to Albumin Ratio May Be an Inflammatory Indicator for the Coronary Slow Flow Phenomenon

## *C-Reaktif Proteinin Albümine Oranı Koroner Yavaş Akış Fenomeni İçin İnflamatuvar Bir Gösterge Olabilir*

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**Abstract**

**Introduction:** Coronary slow flow phenomenon (CSFP) is defined by the low-speed filling of contrast material in the distal portion of one or more coronary arteries despite the absence of stenosis of the coronary arteries on coronary angiography (CAG). Although the pathophysiology of this phenomenon is not known, suggested mechanisms include increased oxidative stress and inflammation, disturbed endothelial function, and microvascular dysfunction. The C-reactive protein (CRP)/albumin ratio (CAR) is a sensitive indicator of the severity and progression of the inflammatory reaction. In our study, we planned to examine the relationship between CSFP and CAR.

**Methods:** In this prospective and single-center study, 45 patients with CSFP detected in CAG between June 2021 and June 2022 were included. In the control group, 49 people with normal coronary arteries matched for gender and age were included. We analyzed the relationship between CSFP and CAR according to laboratory findings and patient demographics.

**Results:** The mean age of the study group was 56.43±9.66 years. CRP (4.69±3.69 vs 2.93±1.93, p=0.006) and CAR (1.14±0.86 vs 0.66±0.41, p=0.002) were significantly higher in the CSFP group compared with controls. Albumin levels were significantly lower in CSFP (4.05±0.90 mg/dL vs 4.40±0.71 mg/dL, p=0.037). In addition, CAR showed a significant diagnostic value for CSFP in receiver operating characteristic curve analysis (area under the curve: 0.65±0.06, p=0.0130).

**Discussion and Conclusion:** CAR values, which are important indicators of inflammation, were higher in patients with CSFP. This finding may reveal that inflammation is also effective in the pathogenesis of CSFP, and we think CAR can be used for screening and predicting prognosis in this patient group.

**Keywords:** Coronary slow flow phenomenon; C-Reactive protein to albumin ratio; Inflammation; Coronary angiography

***Cite this article as:*** *Ardahanlı İ, Özmen M. C-Reactive Protein to Albumin Ratio May Be an Inflammatory Indicator for the Coronary Slow Flow Phenomenon. Lokman Hekim Health Sci 2023;3(1):32–37.*

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**E-mail:** isaardahanli@gmail.com **Submitted:** 29.08.2022 **Revised:** 03.10.2022 **Accepted:** 07.11.2022

Coronary slow flow phenomenon (CSFP) is a pathology characterized by delayed progression of the contrast material in coronary angiography (CAG) without an obstructive coronary artery disease (CAD).[1] Its incidence has been reported to be between 1% and 7% in previous studies.[2] The potential molecular mechanism of CSFP is not clearly known. However, endothelial dysfunction, inflammatory process, microvascular dysfunction, and neurohumoral imbalances are the underlying conditions associated with CSFP.[3–5] Diagnosis and treatment are very important due to recurrent angina attacks, fatal arrhythmias, unnecessary hospitalizations, and recurrent unnecessary interventions observed in this phenomenon.[6,7]

It is known that the inflammatory process accelerates the atherosclerotic process by destabilizing the coronary arteries.[8] Therefore, it has been reported in recent studies that biomarkers of inflammation can be used for screening and prognosis in many cardiovascular diseases.[9–11] Inflammation indicators commonly used in the clinic are CRP, which is a positive acute phase reactant, and albumin, which is a negative acute phase reactant. The presence of atherosclerosis in both parameters is associated with its severity and adverse cardiovascular events.[12] CAR, on the other hand, is a newly introduced parameter and shows the inflammatory state more sensitively than CRP and albumen alone.[13]

There are few studies on this issue, and the information reported by this study adds information to the literature. In our current study, we purposed to evaluate whether there is a relationship between CSFP and CAR.

## Materials and Methods

### Study Population

In this prospective study, 45 patients who underwent CAG and were diagnosed with CSFP within the indications between June 2021 and June 2022 and 49 patients with age-gender-matched normal coronary arteries (NCA) were included. Indications for CAG were based on results of noninvasive stress testing or high clinical doubt for CAD. The medical histories of the entire study group were questioned before the CAG procedure, and a complete physical examination was performed. The data were recorded by questioning the clinical and demographic characteristics. All participants were informed about the study, and their written consent was obtained. The study was approved by the Institutional Ethics Committee (Date: June 22, 2021; Decision number: 514-99) and was conducted following the Declaration of Helsinki.

The exclusion criteria in the study are shown below:

- Active infection
- Any known chronic inflammatory disease
- Use of antibiotic therapy
- Those with active COVID-19 infection
- Heart failure with reduced ejection fraction (left ventricular ejection fraction (LVEF) ≤40%) and heart failure with midrange ejection fraction (LVEF between 41% and 49%)
- History of acute coronary syndrome
- Severe heart valve disease
- Prosthetic valve history
- History of malignancy
- Autoimmune disease history
- Kidney and/or liver failure
- Chronic obstructive pulmonary disease

### Coronary Angiography

CAG was performed in the entire study group in the catheterization department of our hospital, using the Judkins technique with radial and femoral interventions, according to standard protocols. AXIOM Sensis (Siemens AG, Munich, Germany) branded angiography device was used for imaging the coronary arteries, and the images were recorded digitally. Iohexol (Omnipaque, Nycomed Ireland, Cork, Ireland) was used as the radiopaque agent in angiography. All CAG measurements were made independently by two experienced invasive cardiologists blinded to the clinical details of the study groups. For the quantitative measurement of coronary blood flow, the thrombolysis in myocardial infarction frame count method was used as described in the literature. As previously defined, the time taken for contrast to reach distal landmarks for each coronary artery was expressed as the number of frames. As the starting point, the moment when the contrast material touches both sides of the artery and starts to progress. As the endpoint, the distal bifurcation of the longest branch for the circumflex (CX) is visualized when the contrast medium reaches the distal branching point called the mustache for the left anterior descending (LAD) and gives the first lateral branch of the posterolateral artery for the right coronary artery (RCA). As LAD has a longer course than the others, the value found was standardized by dividing by 1.7. Frame numbers obtained by shooting at 12 fps were multiplied by 2.4, which is a fixed number since previous studies had shot at 30 fps. Patients with at least one coronary artery with a frame count above the given standard deviations of 20.4±3.0 for RCA 22.2±4.1 for CX, and 36.2±2.6 for LAD were included in the exclusion criteria, determined as CSFP.

### Laboratory Analyses

Complete blood count and biochemical analysis were performed in the whole study group by taking blood samples with the standard venipuncture technique after an 8-h night fasting before CAG. In the biochemical analysis, fasting blood glucose, sodium, potassium, blood urea nitrogen, uric acid, creatinine, aspartate transaminase, alanine transaminase, C-reactive protein (CRP), albumin, and lipid parameters were measured. CRP and albumin levels were measured with the help of Cobas 8000 c502 analyzer (Roche Diagnostics, Japan). The CRP value was proportioned to albumin and recorded as CAR.

### Statistical Analysis

IBM SPSS 22.0 (Armonk, NY, USA) was used for the statistical analysis of the data. The normality of the distribution of continuous variables was confirmed by the Kolmogorov–Smirnov test. Continuous variables with normal distribution were expressed as mean±standard deviation and compared using the analysis of variance test. Normally distributed (parametric) variables were expressed as mean and standard deviation. Non-normally distributed (non-parametric) data were expressed as median value (interquartile range), and categorical variables were expressed as percentages. Student's t test or the Mann–Whitney U test was used for numerical variables, and the Chi-squared test was used for the analysis of categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to select a cut-off value that distinguishes it from "normal" and "abnormal" CAR levels. To aid decision-making, a balance of sensitivity and specificity was plotted as a ROC curve. The mean area under the curve (AUC)±95% confidence standard error was evaluated. This quantifies the overall ability of the test to distinguish between patients and healthy individuals.

## Results

The mean age was similar in the CSFP group and control group (56.6±10.1 years and 57.1±8.8 years, respectively). There was no gender difference between the groups. There was no difference between accompanying comorbidities except smoking status. Smoking was significantly higher in the CSFP group (p=0.042). CRP and CAR values were significantly higher in the CSFP group (4.69±3.69 vs 2.93±1.93, p=0.006 and 1.14±0.86 vs 0.66±0.41, p=0.002, respectively). Albumin levels were statistically significantly lower in the CSFP group (4.05±0.9 mg/dL vs 4.40±0.71 mg/dL, p=0.037). A comparison of demographic characteristics and laboratory parameters of the study groups is shown in Table 1.

**Table 1.** Baseline characteristics and laboratory parameters of patients

| | Mean±SD | | p |
|---|---|---|---|
| | CSFP group (n=45) | Control group (n=49) | |
| Age (years) | 56.6±10.1 | 57.1±8.8 | 0.840 |
| Female, n (%) | 15 (33.3%) | 16 (32.7%) | 0.854 |
| Hypertension, n (%) | 22 (48.8) | 21 (42.9) | 0.700 |
| Diabetes mellitus, n (%) | 10 (22.2) | 9 (18.36) | 0.644 |
| Hyperlipidemia (%) | 21 (46.6) | 22 (44.9) | 0.864 |
| Smoking, n (%) | 26 (57.8) | 18 (36.7) | **0.042** |
| Systolic blood pressure (mmHg) | 129.7±10.2 | 127.9±8.9 | 0.395 |
| Diastolic blood pressure (mmHg) | 78.4±11.7 | 78.7±9.4 | 0.858 |
| Hemoglobin (g/dL) | 13.6±1.7 | 13.9±1.4 | 0.486 |
| WBC ($\times 10^3$ $\mu L^{-1}$) | 7.96±2.43 | 7.82±2.47 | 0.283 |
| Platelet ($\times 10^3$ $\mu L^{-1}$) | 254±72 | 256±73 | 0.875 |
| FBG (mg/dL) | 131.6±38.8 | 137.6±35.2 | 0.601 |
| Creatinine (mg/dL) | 0.81±0.23 | 0.82±0.15 | 0.141 |
| Na (mEq/L) | 138.3±5.9 | 137.6±4.3 | 0.537 |
| K (mEq/L) | 4.57±0.61 | 4.46±0.48 | 0.368 |
| Uric acid (mg/dL) | 5.75±2.39 | 4.45±1.41 | **0.003** |
| AST (IU/L) | 28.10±12.44 | 28.35±12.03 | 0.926 |
| ALT (IU/L) | 26.80±17.71 | 26.67±11.34 | 0.327 |
| Total cholesterol (mg/dL) | 214.6±43.7 | 205.1±33.3 | 0.253 |
| Triglyceride (mg/dL) | 174.7±57.7 | 171.9±52.1 | 0.815 |
| HDL cholesterol (mg/dL) | 43.5±5.7 | 45.6±5.9 | 0.102 |
| LDL cholesterol (mg/dL) | 136.2±46.7 | 125.1±37.5 | 0.226 |
| Albumin (mg/dL) | 4.05±0.90 | 4.40±0.71 | **0.037** |
| CRP (mg/dL) | 4.69±3.69 | 2.93±1.93 | **0.006** |
| CAR | 1.14±0.86 | 0.66±0.41 | **0.002** |

CSFP: Coronary slow flow phenomenon; SD: Standard deviation; WBC: White blood cell; FBG: Fasting blood glucose; Na: Sodium; K: Potassium; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; CAR: CRP/albumin ratio.

Specificity was found to be significant in the ROC curve analysis (p<0.01). The AUC was =0.65±0.06 (Fig. 1).

## Discussion

The main finding of this study is the statistically significantly higher CAR level in CSFP compared with healthy control subjects. These results provide important evidence that increased CAR levels may play a role in the pathophysiology of CSFP. This is the first study in the literature to report that CAR levels in CSFP are higher than in the healthy control group. Another striking finding of our study is that the CRP was significantly higher and albumin levels were significantly lower, which are the parameters used in the calculation of CAR.

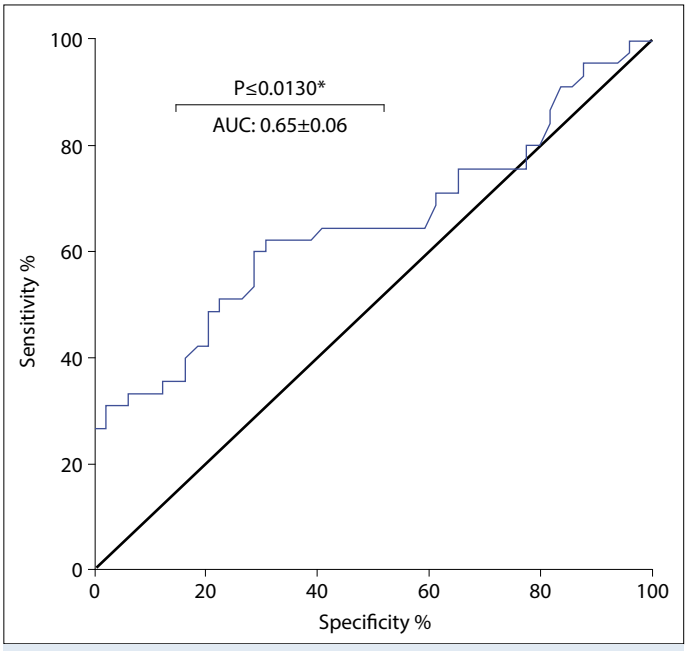


**Figure 1.** Graph of receiver operating characteristic curve analysis.
AUC: Area under the curve.

CSFP is an angiographic entity defined as slow progression and slow discharge of the contrast agent within the coronary arteries. Different pathophysiological mechanisms have been suggested previously for CSFP, including the propensity for thrombosis, microvascular disease, microvascular injury, endothelial dysfunction, and atherosclerosis.[14–16] CSFP has a diverse presentation ranging from mild chest pain to ST-segment elevation myocardial infarction.[17–19] Previous studies have shown the long-term prognostic importance of CSFP in the development of forthcoming major adverse cardiovascular events.[20,21] Therefore, CSFP should not be considered a purely benign condition and should be detected at the earliest stage. Although CAG is the gold standard for the diagnosis of CSFP, it is an invasive procedure and is not always easily accessible, especially in developing countries. Besides, since angiographic examinations are costly and invasive procedures, they do not allow long-term clinical follow-up and dynamic treatment evaluation. Therefore, well-performing and cost-effective biomarkers can be integrated into clinical decision-making protocols.

Inflammation is an important factor implicated in all developmental stages of the atherosclerotic process and plaque destabilization. Endothelial dysfunction caused by it plays a major role in the initiation and progression of CSFP. CRP and albumin are inflammation biomarkers routinely used in clinics. It has been shown that increased CRP level is associated with stable angina pectoris, development of myocardial infarction, stroke, and severity of CAD.[22,23] It is thought that all these are caused by endothelial dysfunction and lipid peroxidation. In our study, the CRP value was higher in CSFP patients, and it was similar to the studies in the literature that investigated the relationship between CRP and cardiovascular diseases. In addition, it has been reported that the decrease in serum level of albumin, which is a negative acute phase reactant, causes endothelial dysfunction and an increase in inflammatory cytokines, leading to cardiovascular diseases.[24] Similarly, in our study, the serum albumin levels in CSFP, which is a condition in which the inflammatory process is effective, were lower than those with NCA. In recent studies, it has been reported that CAR is a more sensitive parameter in inflammation than CRP and albumin alone.[25] Previous studies have shown that CAR is associated with the severity of CAD and has an effect on stent restenosis in patients with stable angina.[26] Yesin M. et al.[27] showed that a high CAR level is an independent predictor of CSFP. Conditions such as atherosclerosis, microcirculation disorder, endothelial dysfunction, and inflammatory reaction are all closely related to the development of CSFP.[14–16] The roles of the inflammatory response marker CRP, the oxidative stress marker homocysteine, and the endothelial function marker arginine in CSFP are frequently observed.[28] Li et al.[29] reported that CRP level and interleukin-6 were significantly increased in CSFP patients. Canpolat et al.[30] reported in their study that hsCRP level and monocyte-to-high-density lipoprotein cholesterol ratio, which is another systemic inflammation indicator, increased in CSFP. The common feature of all studies in this line is that inflammatory biomarkers are increased in CSFP. However, apart from all these inflammatory parameters, we used CAR, which is a more sensitive, inexpensive, and accessible indicator in our study.

## Conclusion

We found that CAR is a CSFP-related inflammatory parameter and an independent predictor. Our study is important in showing that CSFP, a condition that may predispose to coronary atherosclerosis and acute coronary syndrome, is closely related to CAR values, which are indirect indicators of the atherosclerotic process.

This study has several limitations. First, due to the cross-sectional nature of the study, it does not show results on prognostic value and molecular mechanisms between CSFP and CAR values. Another limitation is the relatively low number of patients. Our study results should be supported by multicenter and large populations that require long-term follow-ups. We hope to update the study with wider patient participation in the future. Finally, the diagnosis of CSFP in this study was made by visual evaluation

of CAG, which did not provide sufficient information about true coronary blood flow. Our study lacks an assessment of coronary endothelial function using intravascular ultrasound or combined pressure and flow examinations.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: İA, MÖ; Design: İA, MÖ; Supervision: İA, MÖ; Data Collection or Processing: İA, MÖ; Analysis or Interpretation: İA, MÖ; Literature Search: İA, MÖ; Writing: İA; Critical Review: İA.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study received no financial support.

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