Ankyra Medical Journal
Original Article
DOI: 10.51271/ANKMJ-0053

Association between red cell distribution width coefficient of variation and coronary slow flow

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Cite this article: Astan R. Association between red cell distribution width coefficient of variation and coronary slow flow. *Ank Med J.* 2025;4(4):80-84.

Received: 22/09/2025 ◆ **Accepted**: 17/10/2025 ◆ **Published**: 19/10/2025

ABSTRACT

Aims: Coronary slow flow (CSF) is an angiographic phenomenon characterized by delayed distal coronary opacification in the absence of significant epicardial stenosis. Red cell distribution width (RDW), a routinely measured hematologic parameter, has been proposed as a potential marker of inflammation and microvascular dysfunction. However, although several studies have demonstrated an association, its role as an independent predictor of CSF remains to be fully established. This study aimed to evaluate the association between RDW coefficient of variation (RDW-CV) and CSF using multivariate logistic regression and receiver operating characteristic (ROC) analyses.

Methods: We retrospectively analyzed 153 patients with normal or near-normal coronary arteries on angiography, classified into CSF (n=73, 47.7%) and non-CSF (n=80, 52.3%) groups based on corrected TIMI frame counts. Clinical, demographic, and laboratory data were compared between groups. Variables with $p<0.10$ in univariate analysis were included in multivariate logistic regression. Diagnostic performance was assessed using ROC curve analysis.

Results: RDW-CV values were slightly higher in the CSF group (13.83±1.24%) compared with the non-CSF group (13.69±1.41%), but this difference did not reach statistical significance (p=0.419). In multivariate analysis, RDW-CV showed a borderline but non-significant association with CSF (OR=1.338, 95% CI: 0.967-1.852, p=0.079). Hyperlipidemia (OR=5.305, 95% CI: 1.481-18.996, p=0.010) remained independently associated with CSF. RDW-CV alone demonstrated poor discriminative ability (AUC=0.571), whereas the multivariate model achieved good overall predictive performance (AUC=0.833).

Conclusion: RDW-CV is not a strong stand alone predictor of CSF but may contribute to diagnostic accuracy when integrated with other clinical and laboratory variables. Further prospective studies with larger populations are warranted to clarify its prognostic role.

Keywords: Coronary slow flow, red cell distribution width, RDW-CV, TIMI frame count, microvascular dysfunction, logistic regression, ROC analysis

INTRODUCTION

Coronary slow flow (CSF) is an angiographic phenomenon characterized by delayed opacification of the distal coronary vasculature in the absence of significant epicardial stenosis.[1] It is diagnosed most commonly using the thrombolysis in myocardial infarction (TIMI) frame count method, which quantitatively assesses coronary flow velocity.[2] Although the exact pathophysiology remains incompletely understood, proposed mechanisms include microvascular and endothelial dysfunction, diffuse atherosclerosis, inflammatory activation, and increased small vessel resistance.[3-6] Clinically, CSF has been associated with recurrent chest pain, electrocardiographic changes, and, in some cases, acute coronary syndromes, underscoring its potential prognostic significance.[7]

Red cell distribution width (RDW) is a routinely reported parameter in complete blood counts, reflecting the degree of anisocytosis (heterogeneity in erythrocyte size). While traditionally used in the differential diagnosis of anemia, RDW has emerged as a biomarker linked to inflammation, oxidative stress, and impaired microcirculation.[8-10] Elevated RDW levels have been reported in various cardiovascular conditions, including heart failure, myocardial infarction, and stable coronary artery disease.[11-13]

Several studies have investigated the association between RDW and CSF, with many demonstrating significantly higher RDW values in CSF patients compared with controls.[14-16] For example, Luo et al.[13] found RDW to be an independent

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predictor of CSF in a cohort of 185 patients, while Kalay et al.[14] reported a similar relationship alongside serum uric acid levels. However, not all studies have confirmed RDW as an independent predictor after adjusting for confounders, and differences in study design, population characteristics, and sample sizes have led to inconsistent conclusions. Moreover, most studies have been conducted in specific geographic or ethnic populations, limiting the generalizability of findings.

Given these variations, further investigation is warranted to clarify the independent predictive value of RDW in CSF. In this context, the present study aimed to evaluate the relationship between RDW and CSF in a well-defined patient cohort, using multivariate logistic regression and receiver operating characteristic (ROC) curve analyses to assess its diagnostic performance.

METHODS

Ethics

The study was conducted with the permission of the Non-interventional Clinical Researches Ethics Committee of Batman Training and Research Hospital (Date: 25.06.2025, Decision No: 429). This study was conducted in accordance with the Declaration of Helsinki. This study was conducted under the same ethical approval that covers the investigation of hormonal, metabolic, and inflammatory factors associated with CSF. The present analysis specifically focused on hematologic and inflammatory parameters; patients lacking these laboratory data were excluded. Given the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived by the ethics committee.

Study Design and Population

This retrospective, observational study was conducted in the Department of Cardiology at Batman Training and Research Hospital between July 1, 2024, and July 1, 2025. A total of 153 patients who underwent coronary angiography for suspected coronary artery disease and were found to have normal or near-normal coronary arteries were included in the analysis. Hyperlipidemia was defined as a previously documented diagnosis or the use of lipid-lowering medication. All participants had complete laboratory data and were deemed eligible for multivariate analysis.

Patients were classified into two groups according to the presence of CSF. CSF was defined as a corrected TIMI frame count (CTFC) greater than the standard reference values for each major coronary artery, as described by Gibson et al.[2] The control group consisted of patients with normal coronary flow.

Exclusion Criteria

Patients with the following conditions were excluded from the study: Significant epicardial coronary stenosis defined as a diameter reduction greater than 40%, left ventricular systolic dysfunction with an ejection fraction below 50%, and valvular heart disease of moderate or greater severity. Patients with a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery were also excluded. In addition, individuals with known hematologic disorders, chronic inflammatory or infectious diseases, malignancy, severe hepatic or renal dysfunction (serum creatinine >2.0 mg/dl or eGFR <30 ml/min/1.73 m^2), or acute coronary syndrome at presentation were not eligible. Finally, patients with incomplete demographic, laboratory, or angiographic data were excluded from the analysis.

Coronary Angiography and TIMI Frame Count Analysis

All patients underwent coronary angiography via the femoral or radial approach using a standard protocol and non-ionic contrast medium. Angiographic images were originally recorded at 15 frames per second (fps) and subsequently converted to an equivalent rate of 30 fps to allow standardized TIMI frame count (TFC) assessment. TFCs were determined for the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA) in accordance with the method described by Gibson et al.[2] For the LAD, the frame count was divided by 1.7 to obtain the corrected TFC (CTFC). Based on Gibson's reference values, CSF was defined as a CTFC >27 frames for the LAD, >22 frames for the LCX, and >20 frames for the RCA. The mean CTFC was calculated as the average of the three major coronary arteries, and values exceeding these normal limits were considered diagnostic for CSF.

Laboratory Measurements

Venous blood samples were obtained from each patient following an overnight fast, prior to coronary angiography. Complete blood counts were analyzed using an automated hematology analyzer within two hours of sampling. RDW was expressed as the coefficient of variation of red blood cell volume (RDW-CV, %). Serum levels of glucose, creatinine, uric acid, and total cholesterol were measured using enzymatic methods. C-reactive protein (CRP) was determined by the nephelometric method. All biochemical parameters were analyzed in the hospital's central laboratory.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range, IQR) according to their distribution, which was assessed using the Kolmogorov–Smirnov test. Differences between groups were compared using the independent samples t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were presented as counts and percentages, and compared using the Chi-square test or Fisher's exact test, as appropriate.

Variables with a p-value <0.10 in univariate analyses were included in a multivariate logistic regression model to identify independent predictors of CSF. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were reported. The discriminative performance of RDW-CV and the multivariate model was evaluated using ROC curve analysis, with the area under the curve (AUC) calculated.

All statistical analyses were performed using SPSS software, version [22] (IBM Corp., Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 153 patients were included in the final analysis, of whom 73 (47.7%) had CSF and 80 (52.3%) had normal coronary flow. Patients in the CSF group were significantly

younger than those in the non-CSF group (47.2±10.1 vs. 52.3±10.0 years, p<0.05). The proportion of male patients was also higher in the CSF group (71.7% vs. 47.6%, p<0.01). Likewise, current smoking was more prevalent among patients with CSF compared with those with normal coronary flow (57.5% vs. 31.2%, p<0.01). No significant differences were observed between the two groups regarding the prevalence of hypertension, diabetes mellitus, or hyperlipidemia. Similarly, there were no significant differences in serum creatinine, CRP, or platelet count. Although RDW-CV values were slightly higher in the CSF group compared with the non-CSF group (13.83±1.24% vs. 13.69±1.41%), this difference did not reach statistical significance (p=0.419) (Table 1).

Table 1. Demographic and laboratory characteristics of patients with and without coronary slow flow

Variable	No CSF (n:80, 52.3%)	CSF (n:73, 47.7%)
Age (years)	52.33±10.0	47.21±10.1
Male sex (%)	38 (47.6%)	52 (71.7%)
Hypertension (%)	23 (28.7%)	19 (26.0%)
Diabetes mellitus (%)	21 (26.2%)	18 (24.6%)
Hyperlipidemia (%)	27 (33.7%)	26 (35.6.%)
Current smoking (%)	25 (31.2%)	42 (57.5%)
Serum creatinine (mg/dl)	0.91±0.16	0.95±0.32
CRP (mg/L)	4.35±8.18	4.76±9.50
WBC (10^3/μL)	7.19±1.96	8.29±2.27
Hemoglobin (g/dl)	13.46±1.54	14.38±1.84
Platelets (10^3/μL)	234.24±71.85	229.73±54.18
RDW-CV (%)	13.69±1.41	13.83±1.24

CSF: Coronary slow flow, CRP: C-reactive protein, WBC: White blood cell, RDW-CV: Red cell distribution width coefficient of variation. Data are presented as mean±standard deviation or n (%). Statistical significance was set at p<0.05

In univariate analysis, RDW-CV showed a non-significant trend toward higher values in patients with CSF. Variables with p<0.10 in univariate analysis were subsequently entered into a multivariate logistic regression model (Table 2). In this model, RDW-CV demonstrated an OR of 1.338 (95% CI: 0.967-1.852, p=0.079) for the presence of CSF, indicating a borderline but non-significant association. Among the other covariates, hyperlipidemia (OR=5.305, 95% CI: 1.481-18.996, p=0.010) remained independently associated with CSF.

Table 2. Multivariate logistic regression analysis for the presence of coronary slow flow

Variable	OR	95% CI	p-value
RDW-CV	1.338	0.967-1.852	0.079
Age	0.976	0.937-1.017	0.243
Sex-male	1.272	0.416-3.895	0.673
Hypertension	0.478	0.19-1.207	0.118
Diabetes mellitus	0.782	0.276-2.221	0.644
Hyperlipidemia	5.305	1.481-18.996	0.01
Smoking cigarette	1.024	0.33-3.183	0.967
Serum creatinine	1.045	0.832-1.312	0.705

RDW-CV: Red cell distribution width coefficient of variation, OR: Odds ratio, CI: Confidence interval. Statistical significance was set at p<0.05

ROC curve analysis revealed an AUC of 0.571 for RDW-CV alone, indicating limited discriminatory ability for predicting CSF (Figure 1). By contrast, the multivariate logistic regression model incorporating RDW-CV together with the other significant covariates yielded an AUC of 0.833, suggesting good overall predictive performance (Figure 2).

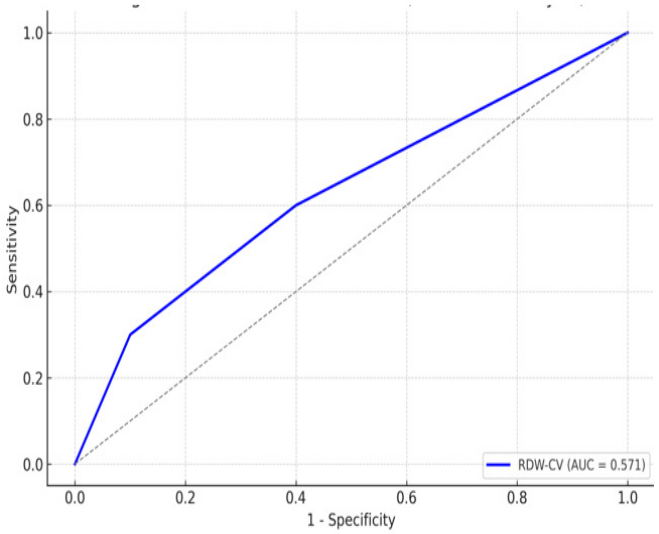

Figure 1. ROC curve of RDW-CV alone for predicting CSF (AUC=0.571)
ROC: Receiver operating characteristic, RDW-CV: Red cell distribution width coefficient of variation, CSF: Coronary slow flow, AUC: Area under the curve

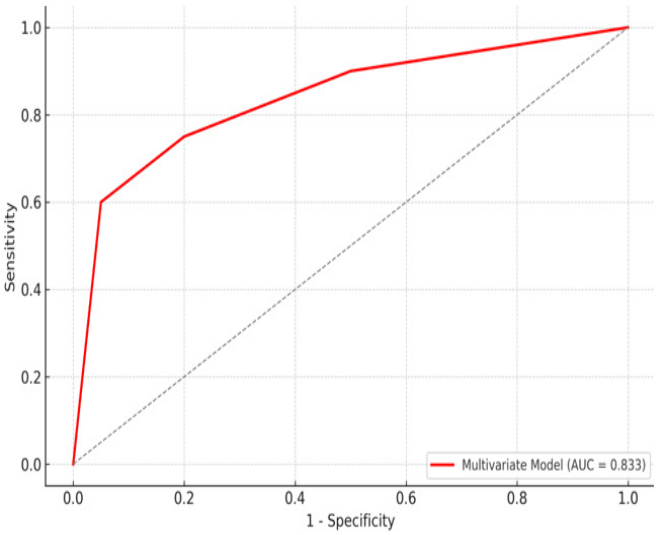

Figure 2. ROC curve of the multivariate logistic regression model including RDW-CV and clinical parameters for predicting coronary slow flow (AUC=0.833).
ROC: Receiver operating characteristic, RDW-CV: Red cell distribution width coefficient of variation, CSF: Coronary slow flow, AUC: Area under the curve

DISCUSSION

In the present study, RDW-CV values were numerically higher in patients with CSF than in those with normal coronary flow; however, the difference did not reach statistical significance in univariate testing, and RDW-CV showed only a borderline but non-significant association in multivariable analysis (p=0.079). These findings suggest that RDW-CV alone is unlikely to serve as a robust standalone predictor of CSF in our cohort, although it may contribute within a multivariable framework.

Our results should be interpreted in the context of prior literature. Several cohorts conducted in different centers and populations reported higher RDW values among CSF patients compared with controls and supported hematologic indices as correlates of the CSF milieu characterized by low-grade inflammation and microvascular dysfunction. Beyond CSF, studies in broader coronary populations have linked RDW

with disease burden and adverse outcomes, reinforcing its biological plausibility as an inflammation and hemorheology related marker.[17-23]

Microvascular flow resistance can result from alterations in hemorheological properties of blood. Increased heterogeneity in erythrocyte size, expressed as RDW, may impair blood fluidity and compromise microcirculatory perfusion. In this context, Patel et al.[24] demonstrated that elevated RDW was associated with impaired erythrocyte deformability, highlighting a potential mechanism by which anisocytosis adversely affects microvascular flow dynamics. Given that CSF is characterized by increased microvascular resistance and endothelial dysfunction, the relationship between elevated RDW and reduced red cell deformability provides a plausible explanation for the observed association between RDW and CSF. Reduced deformability of erythrocytes may increase blood viscosity, exacerbate microvascular dysfunction, and thereby contribute to the pathophysiology of CSF.

At the same time, heterogeneity across studies complicates direct comparison. Differences in cohort size, ethnicity/geography, timing of blood sampling, analytic platforms for RDW (RDW-CV vs. RDW-SD), and model covariates (e.g., inflammatory and lipid parameters) may substantially influence effect estimates. In our dataset, adjustment for clinical and biochemical covariates attenuated the association of RDW-CV with CSF, which may reflect confounding by inflammation and lipid-related pathways captured more directly by other variables. Notably, although the prevalence of hyperlipidemia was not significantly different between groups in univariate comparisons, it emerged as an independent predictor in our multivariable analysis. This apparent discrepancy may be explained by confounding effects of age, sex, and smoking, which could have masked the association in unadjusted analyses. When these factors were accounted for, the contribution of hyperlipidemia became more evident.

Mechanistically, elevated RDW reflects anisocytosis and impaired red-cell deformability, which can worsen hemorheology and increase flow resistance.[25-27] Prior work connects higher RDW with endothelial dysfunction and with greater coronary disease burden and severity on angiography.[28] These insights are pathophysiologically consistent with microvascular abnormalities described in CSF, even if RDW-CV did not emerge as an independent predictor in our adjusted model.

Limitations

This study has several limitations. First, it was conducted in a single center with a relatively small sample size, which may limit the generalizability of the findings. Second, the observational and cross-sectional design precludes establishing causal relationships between RDW-CV and CSF. Third, RDW-CV measurements were based on a single blood sample obtained at admission; thus, potential temporal variations could not be assessed. Finally, unmeasured confounding factors, including nutritional status, bone marrow function, and other inflammatory markers, may have influenced the results.

CONCLUSION

In this study, RDW-CV levels were slightly higher in patients with CSF compared to those without CSF; however, this difference did not reach statistical significance. RDW-CV alone demonstrated poor discriminative ability for predicting CSF, whereas a multivariate logistic regression model incorporating RDW-CV along with other clinical and laboratory parameters achieved good diagnostic performance. These findings suggest that RDW-CV may not serve as a strong standalone predictor of CSF, but it could contribute meaningfully when integrated into a comprehensive risk assessment model. Reporting such borderline or non-significant results is important for reducing publication bias and providing balanced evidence for future meta-analyses and systematic reviews.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Non-interventional Clinical Researches Ethics Committee of Batman Training and Research Hospital (Date: 25.06.2025, Decision No: 429).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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