Eosinophil-to-Leukocyte Ratio as an Inflammatory Marker in Patients With Coronary Artery Disease—A Retrospective Cohort Study

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Abstract

BACKGROUND: Cardiovascular disease remains one of the leading causes of death and major causes of disability and loss of productivity in adults worldwide. Inflammation is a key feature of atherosclerosis and its clinical manifestations. Because inflammation plays a key role in atherosclerosis and its end results, discovering new biomarkers of inflammation becomes important to help diagnostic accuracy and provide prognostic information about coronary artery disease (CAD). The eosinophil count and eosinophil-to-leukocyte ratio (ELR), in particular, have become novel biomarkers for risk assessment in patients with CAD. The current study aimed to evaluate the association of ELR with presence of CAD.

OBJECTIVES: The aim of this study was to investigate the prognostic value and predictive performance of ELR in patients with suspected CAD. Furthermore, if proven of value, this study aims to use ELR as a biomarker for screening patients at risk for CAD for early prevention and intervention.

METHODS: This is a retrospective cohort study involving a chart review of CAD suspects 40 years or older who underwent elective coronary angiogram from January 2019 to December 2019. Eosinophil-to-leukocyte ratio was calculated by dividing the number of eosinophils by the number of leukocytes.

RESULTS: A total of 436 patients were included in this study. With an optimal cutoff value of 0.5 (area under the curve, 0.9911; sensitivity, 96.63%; specificity, 95.27%), ELR demonstrated efficiency in detecting CAD.

CONCLUSION: Patients with CAD has a higher ELR than those without CAD in the control group. Furthermore, this study supports the positive association of ELR in predicting CAD.

KEYWORDS: eosinophil-to-leukocyte ratio, coronary artery disease

INTRODUCTION

Cardiovascular disease (CVD) remains one of the leading causes of death and major causes of disability and loss of productivity in adults worldwide. According to the World Health Organization, approximately 17.9 million people died because of CVD last 2016 representing 31% of all global deaths.[1] Of these deaths, approximately 7.3 million were due to coronary heart disease (CHD). By 2030, it is estimated that more than 23.3 million people will die of CVDs annually.

Coronary artery disease (CAD) is usually caused by atherosclerosis. In the past, atherosclerosis was thought to be due to passive lipid accumulation in the vessel wall. However, recent studies showed that it is now considered as a chronic inflammatory disease from plaque formation that can erode or rupture.[2] Furthermore, immune cells release substances that accelerate the progression of lesions and induce activation of inflammation that can elicit acute coronary syndromes. Leukocytes play a key role in inflammation and host defense to injury. Studies show that increased white blood cell (WBC) count (ie, leukocyte count) has been associated with a worse outcome in patients with stable coronary disease, in acute coronary syndromes, and even in the general population. Furthermore, the relationship between WBC count and CAD is strong, consistent, biologically plausible, and coherent with the current paradigm of the inflammatory origin of atherosclerosis and appears to be independent of other traditional coronary risk factors. Older studies available have shown that elevated levels of almost all subtypes of WBC counts, including eosinophils, were associated with an increased risk of CHD.[3] Eosinophils are multifunctional leukocytes implicated in the pathogenesis of numerous inflammatory processes including allergic diseases, tumor immunity tissue injury, bacterial and viral infections, and parasitic helminths.[4] Because inflammation plays a major role in atherosclerosis, discovering new biomarkers of inflammation becomes important in order to help diagnostic accuracy and to provide prognostic information about this disease. The relative impact of eosinophil-to-leukocyte ratio (ELR), which is inexpensive, commonly used, reproducible, and widely available in clinical practices, was not yet fully explored. Thus, this study aimed to evaluate whether ELR can be used as a biomarker to predict CAD.

METHODS

Study Design and Setting

This is a retrospective cohort study. A chart review of suspected CAD patients who underwent diagnostic coronary angiography between January 2019 and December 2019 was done. This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki. In order to ensure the safety of the subjects and to protect the institution and the researcher from any unethical issues, the protocol was approved by the Research Ethics Review Board of the institution before implementation.

Inclusion and Exclusion Criteria

Patients suspected to have CAD who presented with stable (nonemergent) typical or atypical symptoms suggestive of CAD (eg, chest pain, chest tightness, chest burning, shoulder pain, palpitations, jaw pain, or non–chest pain symptoms, such as dyspnea or worsening effort tolerance), 40 years or older, who underwent elective coronary angiogram were included in this study. Exclusion criteria included recent acute coronary syndrome (<2 weeks), history of previous coronary intervention or coronary artery bypass graft, congenital heart disease, severe valvular heart disease, decompensated heart failure, decompensated liver disease, end-stage renal disease, cerebrovascular disease, thyroid disease, autoimmune disease, hematologic disease, acute or chronic infections, allergic diseases, or malignancies.

Sampling Method and Sample Size

Using G*Power 3.1.9.2 (Heinrich Heine University, Dusseldorf, Germany), a minimum of 353 patients was required for this study. This is based on 0.716 odds ratio of ELR to predict CAD. This computation also accounts for 5% level of significance and 80% power.

Data Collection

Profiles of CAD suspects who underwent elective coronary angiogram on year 2019 were collected. Patient's baseline age, sex, height, weight, body mass index, comorbidities, WBC count, eosinophil count and angiogram result were obtained and were entered in an electronic database. This study relied only on the official coronary angiography report and therefore was not reevaluated. For all patients, the ELR was calculated by dividing the eosinophil count by the WBC count.

Statistical Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non–normally distributed continuous variables, and mean and SD for normally distributed continuous variables. Independent-samples t test, Mann-Whitney U test, and Fisher exact/χ^2 test were used to determine the difference of mean, rank, and frequency, respectively, between patients with and without CAD. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors for CAD. Sensitivity, specificity, negative predictive value, positive predictive value, and area under the receiver operating characteristic curve were used to determine the diagnostic accuracy of ELR to predict CAD. All statistical tests were two-tailed test. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α level of significance. STATA 13.1 (StataCorp, College Station, Texas) was used for data analysis.

RESULTS

The baseline demographic and clinical profiles of all 436 patients are summarized in Table 1. The study subjects consisted of 267 patients with CAD (CAD group, 76.4% male,

Table 1. Demographic and Clinical Profile of the Patients

	Total (n = 436)	With CAD (n = 267 [61.24%])	Without CAD (n = 169 [38.76%])	*P*
	Frequency (%), Mean ± SD, Median (IQR)			
Age, y	61.41 ± 12.17	63.7 ± 11.25	57.79 ± 12.72	<0.001
Sex				<0.001
Male	292 (66.97)	204 (76.4)	88 (52.07)	
Female	144 (33.03)	63 (23.6)	81 (47.93)	
BMI, kg/m^2	25.97 ± 4.57	25.74 ± 4.63	26.34 ± 4.47	0.181
Comorbidities				
Hypertension	355 (81.42)	239 (89.51)	116 (68.64)	<0.001
Type 2 DM	181 (41.51)	134 (50.19)	47 (27.81)	<0.001
Dyslipidemia	164 (37.61)	104 (38.95)	60 (35.5)	0.469
CKD	47 (10.78)	33 (12.36)	14 (8.28)	0.181
Angina	381 (87.39)	214 (80.15)	167 (98.82)	<0.001
Previous MI	84 (19.27)	76 (28.46)	8 (4.73)	<0.001
Smoker	124 (28.44)	84 (31.46)	40 (23.67)	0.079
Eosinophil	4 (2–7)	6 (5–8)	2 (1–2)	<0.001
Eosinophil-to-leukocytic ratio	0.7 (0.29–0.87)	0.83 (0.74–1.01)	0.23 (0.13–0.33)	<0.001

BMI=body mass index; CAD=coronary artery disease; CKD=chronic kidney disease; DM=diabetes mellitus; IQR=interquartile range; MI=myocardial infarction.

Table 2. Factors Associated With CAD

	Crude Odds Ratio	95% CI	*P*
Eosinophil-to-leukocytic ratio (multiplied by 100)	1.1971	1.1444–1.2521	<0.001
Age	1.0429	1.0253–1.0609	<0.001
Male	2.9805	1.9713–4.5063	<0.001
Hypertension	3.8999	2.3447–6.4867	<0.001
Type 2 DM	2.6153	1.7299–3.9535	<0.001
Angina	0.0484	0.0116–0.2013	<0.001
Previous MI	8.0079	3.7522–17.090	<0.001
Eosinophil	8.0686	5.1251–12.671	<0.001

CAD=coronary artery disease; CI=confidence interval; DM=diabetes mellitus; MI=myocardial infarction.

with a mean age of 63.7 ± 11.25 years) and 169 patients without CAD (control group, 52.07% male, with a mean age of 57.79 ± 12.72 years). The diagnosis of CAD was based on the current American Heart Association/American College of Cardiology guidelines. Patients with CAD were notably a bit older with more conventional CAD risk factors. The rates of male sex, hypertension, type 2 diabetes mellitus, angina, and previous myocardial infarction (MI) were also higher in the study group as compared with the control group (P < 0.001). Patients with CAD showed a higher eosinophil count. Furthermore, ELRs were notably higher in the CAD group.

Binary logistic analysis was used to assess 12 clinicopathological characteristics: age, sex, body mass index, hypertension, diabetes, dyslipidemia, chronic kidney disease, angina, previous MI, smoker, eosinophils, and ELR. Results shown in Table 2 demonstrate ELR (odds ratio, 1.1971; 95% confidence interval, 1.14–1.25) as an independent risk factor of

Table 3. Diagnostic Accuracy of ELR Compared With Coronary Angiography Result in Predicting CAD

		With CAD	Without CAD	Total
ELR	≥0.5063	258 (96.63)	8 (4.73)	266 (61.01)
	<0.5063	9 (3.37)	161 (95.27)	170 (38.99)
	Total	267 (100)	169 (100)	436 (100)
Sensitivity		96.63% (93.70–98.45)	Positive LR	20.41 (10.38–40.16)
Specificity		95.27% (90.89–97.93)	Negative LR	0.04 (0.02–0.07)
PPV		96.99% (94.25–98.45)	Prevalence	61.24% (56.49–65.84)
NPV		94.71% (90.39–97.15)	Accuracy	96.10% (93.83–97.71)

CAD=coronary artery disease; ELR=eosinophil-to-leukocytic ratio; LR=likelihood ratio; NPV=negative predictive value; PPV=positive predictive value.

CAD together with age, male sex, hypertension, type 2 diabetes mellitus, angina, previous MI, and eosinophils. For every year increase in age, the odds of having CAD also increase by 4.29%. Male patients had almost three times the odds of having CAD compared with female patients. Patients with hypertension had 3.90 odds of having CAD. Patients with type 2 diabetes mellitus had 2.62 odds of having CAD. Patients with previous MI had 8.01 odds of having CAD. For every unit increase in eosinophils, the odds of having CAD also increase by more than eightfold, and for every unit increase in ELR (multiplied by 100), the odds of having CAD also increase by 19.71%. As shown in Table 3, ELR of 0.5 or greater was shown to predict CAD with sensitivity of. 96.63%, specificity of 95.27%, and accuracy of 96.10% (93.83–97.71). Furthermore, this study showed that an ELR of 0.5 or greater has a positive predictive value of 96.99% (94.25–98.45), negative predictive value of 94.71% (90.39–97.15), positive likelihood ratio of 20.41 (10.38–40.16), and negative likelihood ratio of 0.04 (0.02–0.07). Multivariate analysis was used to test for confounding variables to CAD; results are shown in Table 4.

The receiver operating characteristic curve analysis shown in Figure 1 demonstrated that ELR is efficient in detecting CAD with an area under the curve of 0.9911 (95% confidence interval, 0.98364–0.99854) with an optimal cutoff value of 0.5.

DISCUSSION

Adequate risk assessment for patients with CAD is crucial to prevent recurrent events. If proven of value, ELR, which is inexpensive, commonly used, reproducible, and widely available in clinical practices, may be used as a biomarker for screening patients at risk for CAD for early prevention and intervention.

This study was able to include a total of 436 patients suspected of having CAD where association between ELR and CAD was analyzed retrospectively. The results of this study showed that the absolute eosinophils as well as ELR were significantly elevated in the CAD group compared with the control group.

Atherosclerosis is the culprit pathology driving CAD and is characterized by the presence of lipid and inflammatory cells during initiation, progression, and destabilization of an atherosclerotic plaque.[3] There are several risk factors for CAD, but almost 50% of patients with CAD cannot be identified with a major risk factor.[5] Inflammation is a key feature of atherosclerosis and plays an important role in all stages of atherogenesis—from recruitment of leukocytes at the endothelium to the atherosclerotic plaque rupture causing the clinical symptoms of the disease.[4] Several studies have been done to evaluate the association between leukocytes and its subtypes with the presence and prognosis of CAD.[6]

Eosinophil-to-leukocyte ratio, which is a combination of two independent markers of inflammation, is an inexpensive and widely available marker and can be easily calculated. In our study, it was found that the ELR values were significantly higher in patients with CAD. Furthermore, it is also noteworthy that for every unit increase in eosinophils, the odds of having CAD also increase by more than eightfold, and for every unit increase in ELR, the odds of having CAD also increase by 19.71%. In a receiver operating characteristic curve analysis, this study suggests that the optimal cutoff point of ELR for the presence or absence of CAD was 0.5 with a sensitivity of 96.63% and a specificity of 95.27% (area under the curve, 0.99). A study by Nadimi et al[6] supported the idea of eosinophils with a role in the pathogenesis of cardiovascular disease. The exact mechanisms remain to be determined but are thought to be involved in inflammatory reactions and cellular activation.[6] Eosinophils synthesize and release bioactive mediators that stimulate the release of platelet-activating factor and platelet-dependent smooth muscle hyperplasia, which may influence atherosclerosis pathogenesis.[5] Based on our data, this study demonstrated that elevated ELR may play a role in the pathogenesis of atherosclerosis and may be a marker of elevated inflammatory state.

The major limitation to this study is that coronary angiogram was not reevaluated; hence, surface and subsurface

Table 4. Testing for Confounding Variables to CAD

Predictor	Confounding Variable	Change in OR, %
ELR (multiplied by 100) Crude OR, 1.1971	Age	–0.11
	Male	0.71
	Height	0.35
	Weight	0.39
	BMI	0.15
	Comorbidities	
	Hypertension	0.76
	Type 2 DM	0.16
	Dyslipidemia	0.33
	CKD	0.12
	Angina	–0.01
	Previous MI	–0.26
	Smoker	0.68
	Eosinophil	–1.14
Age Crude OR, 1.0429	ELR (multiplied by 100)	–2.20
	Male	0.82
	Height	0.37
	Weight	0.01
	BMI	0.01
	Comorbidities	
	Hypertension	–0.46
	Type 2 DM	–0.70
	Dyslipidemia	–0.01
	CKD	–0.08
	Angina	0.02
	Previous MI	0.51
	Smoker	0.16
	Eosinophil	0.16
Male Crude OR, 2.9805	Age	23.91
	ELR (multiplied by 100)	21.25
	Height	23.57
	Weight	–66.54
	BMI	–67.40
	Comorbidities	
	Hypertension	30.85
	Type 2 DM	–12.25
	Dyslipidemia	–61.11
	CKD	–47.61
	Angina	–98.38
	Previous MI	168.68
	Smoker	–50.33
	Eosinophil	170.38

(continuation of Table 4)

Predictor	Confounding Variable	Change in OR, %
Hypertension Crude OR, 3.8999	Age	–11.73
	Male	14.75
	Height	–1.69
	Weight	1.74
	BMI	2.17
	Comorbidities	
	Type 2 DM	–13.89
	Dyslipidemia	–0.10
	CKD	–2.18
	Angina	3.57
	Previous MI	–1.65
	Smoker	11.18
	Eosinophil	331.37
	ELR (multiplied by 100)	419.40
Type 2 DM Crude OR, 2.6153	Age	–16.70
	Male	1.03
	Height	–0.61
	Weight	1.57
	BMI	3.37
	Comorbidities	
	Hypertension	–13.55
	Dyslipidemia	1.75
	CKD	–1.95
	Angina	–1.42
	Previous MI	10.82
	Smoker	11.18
	Eosinophil	55.16
	ELR (multiplied by 100)	79.38
Angina Crude OR, 0.0484	Age	2.27
	Male	4.34
	Height	2.89
	Weight	–0.62
	BMI	0.62
	Comorbidities	
	Hypertension	–3.93
	Type 2 DM	1.65
	Dyslipidemia	–8.06
	CKD	–1.65
	Previous MI	169.42

(continuation of Table 4)

Predictor	Confounding Variable	Change in OR, %
Angina Crude OR, 0.0484	Smoker	1.24
	Eosinophil	7.23
	ELR (multiplied by 100)	–71.07
Previous MI Crude OR, 8.0079	Age	14.15
	Male	–7.06
	Height	–1.94
	Weight	0.46
	BMI	–0.08
	Comorbidities	
	Hypertension	–1.45
	Type 2 DM	10.67
	Dyslipidemia	4.51
	CKD	3.27
	Angina	–54.57
	Smoker	1.16
	Eosinophil	–67.18
	ELR (multiplied by 100)	–24.13
Eosinophil Crude OR, 8.0686	Age	4.71
	Male	0.35
	Height	0.76
	Weight	–0.30
	BMI	0.16
	Comorbidities	
	Hypertension	27.04
	Type 2 DM	5.22
	Dyslipidemia	9.45
	CKD	–0.10
	Angina	–6.52
	Previous MI	–6.44
	Smoker	5.75
	ELR (multiplied by 100)	–85.20

BMI=body mass index; CAD=coronary artery disease; CKD=chronic kidney disease; DM=diabetes mellitus; ELR=eosinophil-to-leukocytic ratio; MI=myocardial infarction; OR=odds ratio.

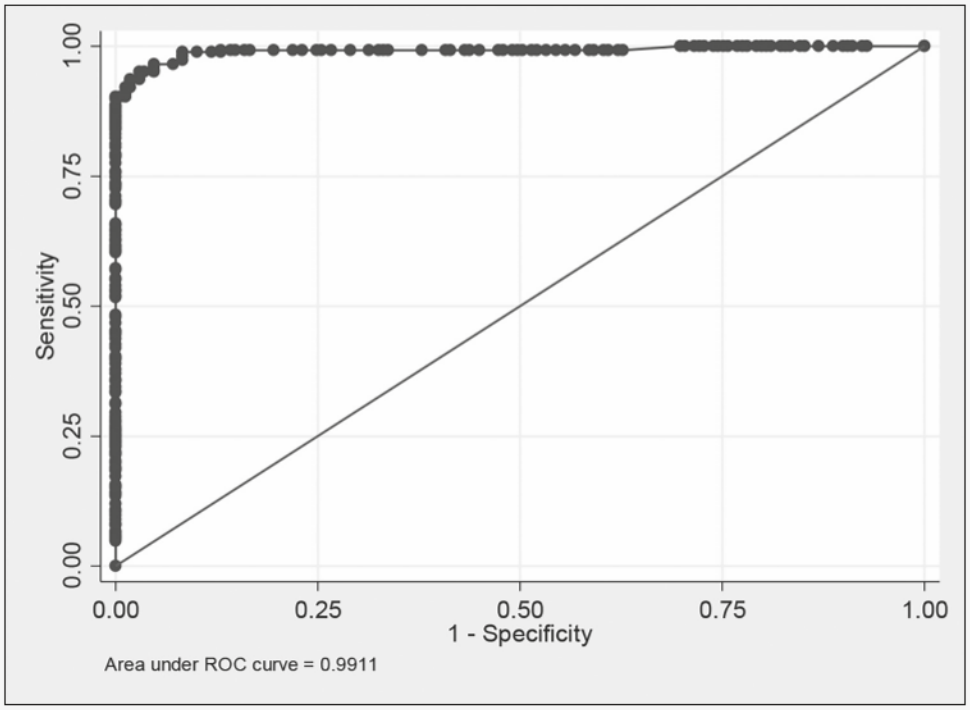

Figure 1. Area under the receiver operating characteristic curve of ELR to predict CAD.
CAD=coronary artery disease; ELR=eosinophil-to-leukocytic ratio.

morphology, as well as internal plaque composition, was not identified. Furthermore, baseline complete blood count was not done from the same institution. Other inflammatory markers, such as C-reactive protein, interleukin 6, and tumor necrosis factor α, were also not evaluated in this study. In addition, even though multivariate analysis was used to identify the independent predictors of CAD, there may still be some unmeasured confounders that could have an impact on the study's findings.

Further studies may include a scoring system (SYNTAX, Gensini) to further assess the correlation of ELR with the severity of CAD (mild, moderate, severe). Finally, more prospective studies with a larger sample size are needed to confirm the relationship between ELR and CAD.

CONCLUSION

Patients with suspected CAD may do preprocedural ELR, a widely available and inexpensive inflammatory biomarker, which may be helpful to predict CAD.

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