To cite this article: Doganay B. Relationship between the Castelli risk indeces and the presence and severity of ischemia in non-geriatric patients with suspected coronary artery disease. Turk J Clin Lab 2023; 1: 128-136

Original Article

Relationship between the Castelli risk indeces and the presence and severity of ischemia in non-geriatric patients with suspected coronary artery disease

Koroner arter hastalığı şüphesi olan non-geriatrik hastalarda Castelli risk indeksleri ile iskeminin varlığı ve şiddeti arasındaki ilişki

Birsen Doganay*

Department of Cardiology, Ankara City Hospital, Ankara, Turkey.

Abstract

Aim: This study aimed to investigate the relationship between ischemia severity and Castelli risk indices (CRI) levels in non-geriatric patients with suspected coronary artery disease (CAD) referred to myocardial perfusion scintigraphy (MPS) with gated single photon emission computed tomography (SPECT).

Material and Methods: This retrospective study included 417 non-geriatric patients referred to SPECT MPS for suspected CAD at the Cardiology Clinic between January 2019 and January 2021. Patients were divided into normal, mild, moderate, and severe ischemia groups according to MPS. CRIs were calculated as follows: CRI-I = total cholesterol / high-density lipoprotein cholesterol (HDL) ratio; CRI-II = low-density lipoprotein cholesterol / HDL ratio.

Results: The CRIs levels were higher in ischemia group than non-ischemia group. Increase in CRI-II level was associated with increased ischemia severity. Increased CRI-II level was found to be an independent predictor of mild, moderate and severe ischemia group, but CRI-I was similar in moderate and severe ischemia groups. The threshold value of CRI-II for predicting the presence of ischemia was >2.1 (Area under the curve [AUC] ± standard error = 0.787 ± 0.02, sensitivity = 79.5%, specificity = 71.4%). The threshold values of CRI-II showed a gradual increase in predicting the severity of ischemia.

Conclusion: CRI-II offers offers gradually increasing threshold values in distinguishing patients with suspected CAD but without perfusion defects or determining its severity in the case of ischemia. CRI-II can be a potential screening tool for patients with suspected CAD and it can be used for risk stratification.

Keywords: Castelli risk index, coronary artery disease, ischemia, lipids.

Corresponding Author*: Birsen Doganay, Department of Cardiology, Ankara City Hospital, Ankara, Türkiye.
E-mail: doganay.brsn@gmail.com
Orcid:0000-0003-4659-3596
Doi: 10.12663/tjcl.1252801
Recevied: 18.02.2023 accepted: 07.03.2023

TJCL Volume 14 Number 1 p: 128-136

Öz

Amaç: Bu çalışmada, kapılı tek foton emisyonlu bilgisayarlı tomografi (SPECT) ile miyokardiyal perfüzyon sintigrafisine (MPS) yönlendirilen koroner arter hastalığı (KAH) şüphesi olan non-geriatrik hastalarda iskemi şiddeti ile Castelli risk indeksleri (CRI) arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2019 ile Ocak 2021 arasında Kardiyoloji Kliniğinde KAH şüphesi nedeniyle SPECT MPS'ye yönlendirilen 417 non-geriatrik hastayı dahil edildi. Hastalar MPS'ye göre normal, hafif, orta ve ağır iskemi gruplarına ayrıldı. CRI düzeyleri CRI-I = toplam kolesterol / yüksek yoğunluklu lipoprotein kolesterol (HDL) oranı; CRI-II = düşük yoğunluklu lipoprotein kolesterol / HDL oranı olarak hesaplandı.

Bulgular: CRI seviyeleri iskemi grubunda iskemisi olmayan gruba göre daha yüksekti. CRI-II seviyesindeki artış, artan iskemi şiddeti ile ilişkili saptandı. Artmış CRI-II düzeyi, hafif, orta ve ağır iskemi grubu için bağımsız bir belirteç olarak bulundu, ancak CRI-I, orta ve ağır iskemi gruplarında benzerdi. CRI-II'nin iskemi varlığını öngörme eşik değeri >2,1'dir [Eğri altındaki alan (AUC) ± standart hata = 0,787 ± 0,02; duyarlılık = %79,5; özgüllük = %71,4]. İskeminin ciddiyetini öngörmede CRI-II'nin eşik değerleri kademeli bir artış gösterdi.

Sonuçlar: CRI-II, KAH şüphesi olan ancak perfüzyon kusurları veya normal koroner arterleri olmayan hastaları ayırt etmede ve iskemi ciddiyetini belirlemede kademeli artan eşik değerler sunar. Bu nedenle, CRI-II KAH şüphesi olan hastalar için potansiyel bir tarama aracı olabilir ve risk sınıflandırması için kullanılabilir.

Anahtar kelimeler: Castelli risk indeksi, iskemi, koroner arter hastalığı, lipid.

Introduction

Coronary artery disease (CAD), which develops as a result of narrowing or occlusion of the coronary arteries due to atherosclerosis, is an important cause of mortality as well as being an important cause of global health burden and expenditures [1]. Evaluation of CAD requires both anatomical and functional information. Radionuclide cardiac imaging methods, especially myocardial perfusion scintigraphy (MPS), provide high-level evidence for the diagnosis and prognosis of CAD [2]. MPS, which is frequently used in clinical routine for diagnosis and risk determination or treatment planning in CAD, offers superiority in reducing the number of unnecessary coronary angiography (CAG) despite its radiation risk and cost. However, it is not easy to access because it is not available in every hospital [3]. Therefore, the use of easy, cheap and accessible markers among screening methods has an increasing importance [4].

Early diagnosis of atherosclerosis and determination of risk lesions in the coronary arteries have an important place in reducing cardiovascular diseases [5]. It is known that lipid metabolism plays an important role in the initiation and acceleration of atherosclerosis [6]. Lipid profiles are among the traditional risk factors for CAD [7]. Castelli risk indices (CRI) derived from lipid parameters have been shown to exhibit superior diagnostic performance in predicting cardiovascular diseases and events. CRI-I index obtained by dividing total cholesterol by high-density lipoprotein (HDL) cholesterol reflects the coronary plaques formation [8], while CRI-II obtained by dividing low-density lipoprotein (LDL) cholesterol by HDL cholesterol has been shown to be an excellent marker for cardiovascular risk [9]. Despite these prognostic findings of CRIs, to the best of our knowledge, we could not find any study evaluating the relationship between CRIs and severity of ischemia.

We hypothesized that CRIs levels could be easy, cheap and accessible markers for the classification of severity of ischemia due to atherosclerosis, which is play a role in the pathogenesis of CAD. This study aimed to investigate the relationship between ischemia severity and CRIs levels in non-geriatric patients with suspected CAD referred to MPS with gated single photon emission computed tomography (SPECT).

Material and Methods

This retrospective study included patients with suspected CAD who were referred for SPECT MPS in XXXXXX Hospital Cardiology Clinic between January 2019 and January 2021. The study initiated with the approval of the XXXXXX Hospital Ethics Committee (Date: 02.2023, Decision No: E1-23-3325) and was carried out in accordance with relevant ethical guidelines and the Declaration of Helsinki (revised in 2013, Brazil). Because of retrospective design, the waiver of informed approval was deemed appropriate by the ethics committee that approved the study.

Study Population

A total of 1512 non-geriatric patients with suspected CAD were assessed retrospectively and 1095 patients who did not meet the inclusion criteria were excluded. Exclusion criteria were geriatric age (>65 years), a history of any systemic inflammatory or autoimmune disease, history of CAD, history of myocardial infarction or heart failure, thyroid dysfunction, liver or kidney diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid or nephrotoxic drugs, pregnancy or delivery within the last 90 days, and missing clinical data. After the exclusion process, 417 patients were included in this study.

The hospital's electronic information system and patient files were used to gather clinical data. In repeated measurements, blood pressure of > 140 / 90 mmHg or use of anti-hypertensive drugs was defined as hypertension, and a fasting plasma glucose level of ≥ 126 mg/dL or use of anti-diabetic drugs was defined as diabetes mellitus.

Laboratory Measurements

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Blood samples were taken at the time of admission and during follow-up and were measured using a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Levels of hemoglobin (photometrically), platelets (impedance method), C-reactive protein (CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides and total cholesterol (enzymatic colorimetric method), and HDL (homogeneous enzymatic colorimetric method) were determined. The Friedewald formula was used to determine LDL levels [10]. CRIs were calculated as follows: CRI-I = total cholesterol / HDL ratio; CRI-II = LDL / HDL ratio.

Myocardial Perfusion Imaging

Myocardial perfusion assessment had a 2-day stress and rest imaging protocol involving the use of technetium 99-m methoxy-isobutylisonitrile (Tc-99m MIBI). Radiopharmaceutical agents were administered on the peak hyperemia period or modified Bruce protocol during the peak exercise. An infusion of dipyridamole (0.142 mg/kg/min) or adenosine (0.28 mg/min) was administered for stress imaging. All imaging was initiated 30 to 45 minutes after injection of 15 to 20 mCi Tc-99m MIBI. If any perfusion defect was suspected in the stress images of the patients, a similar dose injection was applied to transmit the rest imaging.

SPECT Imaging Protocol

All images were acquired via low energy high resolution SPECT computed tomography (CT) scanner (GE Infinia Hawkeye 4, GE Healthcare, Buckinghamshire, UK) collimators, including 256×256 matrix utilizing 20% energy window focused on 140.5 keV photopeak of Tc-99m. Images were taken in a position where the patients were lying in the position of supine with their arms raised above their heads. Noise reduction and relative risk parameters were utilized for the images created via SPECT/CT analysis. The images were then reconstructed on workstation. After completion of each acquisition, a low dose CT scan of chest (120 kV, 20 mAs, pitch 0.938, collimation 16 ×1.25) was made to obtain a map of attenuation automatically applied through the processing software to allow for the correction of the emission data. The dataset of MPS was remapped via the attenuation map in CT to create the attenuation-corrected images.

The ischemia degree was classified by percentage of ischemia obtained in MPS images. According to this; zero was defined as "No ischemia", "Mild ischemia" if the percent ischemia is <5%, "moderate ischemia" if the percent ischemia is 5–9.9%, and "Severe ischemia" if the percent ischemia is ≥ 10%. Patients without ischemia were considered as the normal group.

Statistical Analysis

IBM SPSS Statistics for Windows 20.0 (IBM Corp., USA) was utilized in the analysis of all data obtained in this study. In light of the results of the Kolmogorov-Smirnov test, numerical data with normal distribution were identified and presented as mean ± standard deviation, while data found to have non-normal distribution were presented as median values with interquartile ranges (IQR). The Mann-Whitney U test and Student T-test were utilized when comparing two groups of data with normal distribution. For comparisons between more than two groups, the ANOVA (post-hoc: Benferroni test) and Kruskall-Wallis H test (post hoc: Dunn's test) were utilized according to the normality of the distribution. Categorical variables were assessed with numbers with percentages (%), and Fisher exact and Chi square tests were utilized in drawing comparisons between these groups of data. Stepwise multivariable multinomial logistic regression analysis was assessed to identify any possible independent predictors of severity of ischemia. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance and results are presented with area under the curve (AUC), standard error (SE), sensitivity, and specificity. Threshold values were calculated with the Youden index method. Values of $p < 0.05$ were considered statistically significant.

Results

A total of 417 patients, 235 males and 182 females, with a mean age of 57.8 ± 6.7 years were included in the analysis. The baseline characteristics of the patients are presented in Table 1. Ischemia was detected in 73.6% (n = 307) of the patients referred to MPS. Severe ischemia was detected in 10.6% (n = 44) of all patients, moderate ischemia in 26.9% (n = 112) and mild ischemia in 36.2% (n = 151). The rates of diabetes mellitus (46.6% vs. 32.7%, p = 0.013) and hypertension (68.1% vs. 52.7%, p = 0.004) were higher in ischemia group. The rate of angiotensin-converting enzyme inhibitor (ACEi) / angiotensin receptor blockers (ARBs) and β-blocker users were higher in ischemia group. Median CRI-I and median CRI-II (3.8 vs. 2.3, p < 0.001) levels were higher in ischemia group than non-ischemia group (For CRI-I =3.8 vs. 2.3, p < 0.001; For CRI-II =3.0 vs. 1.7, p < 0.001) (Table 1).

Table 1. Demographic and laboratory findings associated with the presence of ischemia.

Variables	Study population n=417	Ischemia		p
		No n=110	Yes n=307	
Demographic findings				
Age, years	57.8 ± 6.7	57.3 ± 7.9	58.1 ± 6.2	0.282
Gender, n (%)				
Male	235 (56.4)	54 (49.1)	181 (59.0)	0.073
Female	182 (43.6)	56 (50.9)	126 (41.0)	
Smoking (%)	226 (54.2)	57 (51.8)	169 (55.0)	0.560
Diabetes mellitus, n (%)	179 (42.9)	36 (32.7)	143 (46.6)	0.013*
Hypertension, n (%)	267 (64.0)	58 (52.7)	209 (68.1)	0.004*
Drugs, n (%)				
ACEi / ARBs	218 (52.3)	47 (42.7)	171 (55.7)	0.019*
β-blocker	195 (46.8)	37 (33.6)	158 (51.5)	0.002*
CCBs	138 (33.1)	32 (29.1)	106 (34.5)	0.302
Diuretics	102 (24.5)	26 (23.6)	76 (24.8)	0.815
Oral antidiabetic drug	153 (36.7)	36 (32.7)	117 (38.1)	0.315
Laboratory findings				
Hemoglobin, g/dL	13.2 ± 1.5	13.3 ± 1.3	13.2 ± 1.6	0.539
Neutrophil, x109/L	4.8 ± 1.4	4.2 ± 1.2	5.0 ± 1.4	<0.001*
Platelet count, x109/L	240.0 ± 64.4	233.7 ± 73.5	242.3 ± 60.5	0.228
Lymphocyte, x109/L	2.2 ± 0.7	2.2 ± 0.7	2.2 ± 0.7	0.985
Monocyte, x109/L	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	<0.001*
RDW, %	13.9 ± 1.5	13.7 ± 1.4	13.9 ± 1.5	0.542
HDL, mg/dL	44.1 ± 9.7	48.9 ± 11.7	42.4 ± 8.2	<0.001*
LDL, mg/dL	112.6 ± 38.4	90.4 ± 35.6	115.5 ± 40.8	<0.001*
Triglycerides, mg/dL	136 (105-198)	114 (91-130)	166 (118-218)	<0.001*
Creatinine, mg/dL	0.8 (0.7-0.9)	0.8 (0.6-0.9)	0.8 (0.6-1.0)	0.427
CRP, mg/dL	0.4 (0.2-0.7)	0.3 (0.2-0.5)	0.5 (0.2-0.8)	<0.001*
CRI-I	3.1 (2-5.5)	2.3 (1.8-3.1)	3.8 (2.6-5.7)	<0.001*
CRI-II	2.8 (2.2-3.5)	1.7 (1.2-2.4)	3.0 (2.2-3.6)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * P <0.05 shows statistical significance.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CRI, Castelli risk index; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; RDW, red cell distribution width.

Multivariable regression analysis results, which included findings related to the presence of ischemia, showed that hypertension (OR = 1.88; p = 0.015), monocytes (OR = 5.16; p = 0.041), and CRI-II (OR = 2.33; p < 0.001), were independent predictors for the presence of ischemia. The threshold value of CRI-II for predicting the presence of ischemia was >2.1 (AUC ± SE = 0.787 ± 0.02, sensitivity = 79.5%, specificity = 71.8%). CRI-II levels showed superior diagnostic performance in predicting the presence of ischemia (Figure 1).

Table 2. Independent predictors for presence of ischemia.

	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
Gender						
Male	ref			ref		
Female	0.67	0.43-1.04	0.074	-	-	-
Diabetes mellitus	1.79	1.14-2.83	0.012*	-	-	-
Hypertension	1.91	1.23-2.98	0.004*	1.88	1.13-3.15	0.015*
Neutrophil	1.56	1.30-1.85	<0.001*	-	-	-
Monocyte	2.82	1.40-4.05	<0.001*	2.56	1.07-4.26	0.041*
CRP	1.38	1.04-1.75	<0.001*	-	-	-
CRI-I	1.94	1.60-2.36	<0.001*	-	-	-
CRI-II	2.30	1.81-2.92	<0.001*	2.33	1.80-3.00	<0.001*
				Nagelkerke R2=0.386; p < 0.001*		

In the multivariate regression analysis, the effects of age and drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: CI, confidence interval; CRI, Castelli risk index; CRP, C-reactive protein; OR, odds ratio.

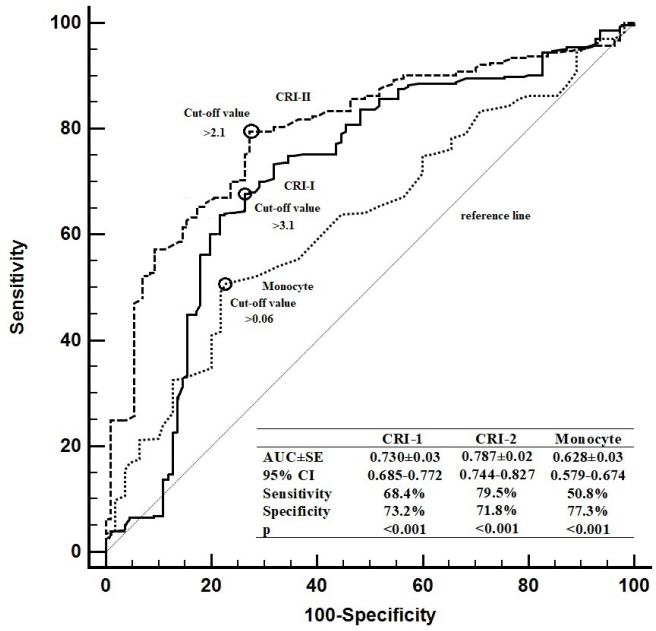

Figure 1. Diagnostic performance assessment of CRI in predicting presence of ischemia.

The rates of diabetes mellitus and hypertension were similar in moderate and severe ischemia groups, while their rates were higher than mild ischemia and non-ischemia group. The rates of diabetes mellitus and hypertension were similar in mild ischemia and non-ischemia group. Median CRI-I level was similar in moderate and severe ischemia groups, while it was higher compared to mild ischemia and non-ischemia group. Median CRI-II level was lower in the normal group than other ischemia groups, while it increased as the severity of ischemia increased (Table 3).

The results of the multivariable regression model analysis, which included the findings related to severity of ischemia, are presented in Table 4. An increased CRI-II levels was independent predictors of mild ischemia group (vs. normal groups) (OR = 2.29, p < 0.001) moderate ischemia group (vs. mild ischemia groups) (OR = 1.98, p = 0.002) and severe ischemia group (vs. moderate ischemia group) (OR = 1.77, p = 0.003). Diagnostic performance assessment of CRI in predicting severity of ischemia is shown in Table 5. Accordingly, it was determined that the threshold values of CRI showed a gradual increase in predicting the severity of ischemia.

There was a positive correlation between CRI-I levels and neutrophil level (r = 0.284, p = 0.023), platelet level (r = 0.271, p = 0.031), and CRP level (r = 0.288, p = 0.018). CRI-II levels were also positively correlated with neutrophil level (r = 0.308, p = 0.001), platelet level (r = 0.292, p = 0.018) and CRP level (r = 0.314, p < 0.001).

MPS results were normal in 79 patients with CRI-II levels of <2.1. These patients constituted 18.9% of all population.

Discussion

The main findings of this study, which evaluated for the first time the relationship between the CRI and presence and severity of ischemia in patients with suspected CAD referred to MPS, were as follows: 1) Higher CRI levels were detected in patients with ischemia, while CRI-II levels was correlated with ischemia severity, but not CRI-I. 2) CRI-II was a co-independent predictor of presence and severity of ischemia (3) CRI-II threshold levels showed a gradual increase in predicting ischemia severity.

MPS is a non-invasive imaging method that is frequently used in the diagnosis of CAD and in monitoring the effectiveness of interventional or medical treatment [11].. However, a significant

Table 3. Demographic and laboratory findings associated with the grade of ischemia.

Variables	Normal (No Ischemia) n=110	Severity of Ischemia			p
		Mild n=151	Moderate n=112	Severe n=44	
Demographic findings					
Age, years	57.3 ± 7.9	57.8 ± 6.6	58.1 ± 5.6	58.5 ± 5.5	0.257
Gender, n (%)					
Male	54 (49.1)	73 (48.3)	78 (69.6)	30 (68.2)	0.001*
Female	56 (50.9)	78 (51.7)	34 (30.4)	14 (31.8)	
Smoking (%)	57 (51.8)	78 (51.7)	63 (56.3)	28 (63.6)	0.491
Diabetes mellitus, n (%)	36 (32.7)	64 (42.4)	57 (50.9)	22 (50.0)	0.036*
Hypertension, n (%)	58 (52.7)	89 (58.9)	86 (76.8)	34 (77.3)	<0.001*
Drugs, n(%)					
ACEi / ARBs	47 (42.7)	64 (42.4)	79 (70.5)	28 (63.6)	<0.001*
β-blocker	37 (33.6)	62 (41.1)	68 (60.7)	28 (63.6)	<0.001*
CCB	32 (29.1)	49 (32.5)	41 (36.6)	16 (36.4)	0.564
Diuretics	26 (23.6)	35 (23.2)	28 (25.0)	13 (29.5)	0.834
Oral antidiabetic drug	36 (32.7)	55 (36.4)	44 (39.3)	18 (40.9)	0.698
Laboratory findings					
Hemoglobin, g/dL	13.3 ± 1.3	13.3 ± 1.6	13.2 ± 1.6	13.2 ± 1.8	0.168
Neutrophil, x109/L	4.2 ± 1.2	4.7 ± 1.4	5.3 ± 1.5	5.2 ± 1.4	<0.001*
Platelet, x109/L	233.7 ± 73.5	234.8 ± 59.2	246.3 ± 55.8	257.9 ± 74.8	0.109
Lymphocyte, x109/L	2.2 ± 0.7	2.2 ± 0.6	2.2 ± 0.7	2.1 ± 0.6	0.726
Monocyte, x109/L	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	<0.001*
RDW, %	13.7 ± 1.4	13.8 ± 1.6	13.9 ± 1.3	13.8 ± 1.6	0.278
HDL-C, mg/dL	48.9 ± 11.7	43.1 ± 8.0	42.4 ± 8.6	39.0 ± 7.5	<0.001*
LDL-C, mg/dL	90.4 ± 35.6	110.8 ± 42.0	125.3 ± 38.6	127.0 ± 34.0	<0.001*
Triglycerides, mg/dL	114 (91-130)	135 (102-175)	164 (118-240)	175 (123-230)	<0.001*
Creatinine, mg/dL	0.8 (0.6-0.9)	0.8 (0.7-0.9)	0.8 (0.6-1.0)	0.9 (0.8-1.0)	0.215
CRP, mg/dL	0.3 (0.2-0.5)	0.3 (0.2-0.6)	0.6 (0.3-1.0)	0.9 (0.5-1.3)	<0.001*
CRI-I	2.3 (1.8-3.1)	3.0 (2.4-4.6)	3.8 (2.7-5.5)	3.9 (2.7-6.0)	<0.001*
CRI-II	1.7 (1.2-2.4)	2.2 (1.6-3.0)	2.9 (2.3-3.6)	3.4 (2.6-4.2)	<0.001*

Numerical variables were shown as mean ± standard deviation or median (IQR). Categorical variables were shown as numbers (%). * P <0.05 shows statistical significance. Bold characters indicate the difference between groups.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; CRI, Castelli risk index; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; RDW, red cell distribution width.

proportion of patients with suspected CAD may have normal MPS findings, as demonstrated in current study. Considering both the radiation risk and high costs in these patients with normal MPS results [3, 12], there is a need for easy and accessible biomarkers without radiation risk for the classification of patients with suspected CAD in clinical practice.

CAD is primarily caused by atherosclerosis, while atherosclerosis-related diseases often have a poor prognosis [13]. It is known that mechanisms such as lipid accumulation in the arterial intima, activation of inflammatory cells such as monocytes and T lymphocytes, and production of matrix proteins play a role in the pathogenesis of atherosclerosis [14, 15]. This is consistent with the detection of impaired lipid metabolism, elevated monocytes and CRP levels in patients with presence or severity of ischemia. Previous studies have demonstrated the role of CRI created from lipid profiles in predicting cardiovascular disease. Zhang et al. [16] reported that CRI-I, which reflects coronary plaque formation, is associated with the risk of ischemic stroke in both men and women. Dai et al. [17] reported that aortic calcification exhibits a positive correlation with both CRI-I and CRI-II. Afsin et al. [18] showed that CRI-II is an independent predictor of slow coronary flow. Although these findings support that CRI can be an important screening tool in predicting CAD, there are studies reporting the opposite. In a study conducted with non-ST-segment elevation myocardial infarction patients, it was reported that there was a low correlation between CAD severity and CRI-I, but CRI-II did not show a significant relationship [19]. On the other hand, previous studies have reported a positive correlation between the myocardial damage and extent of CAD [20-22]. In the current study, CRI levels were higher in patients with ischemia. While CRI-II showed significant differences in ischemia severity, CRI-I did not provide a significant diagnostic distinction in patients with moderate and severe ischemia. However, this study,

Table 4. Independent predictors for presence and severity of ischemia.

	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
Mild (ref: Normal)						
Gender						
Male	ref					
Female	1.03	0.63-1.68	0.905	-	-	-
Diabetes mellitus	1.51	0.91-2.52	0.114	-	-	-
Hypertension	1.28	0.78-2.11	0.318	-	-	-
Neutrophil	1.34	1.10-1.63	0.003*	1.26	1.02-1.55	0.032*
Monocyte	2.09	0.46-9.44	0.338	-	-	-
CRP	1.05	0.96-1.12	0.718	-	-	-
CRI-I	2.05	1.64-2.56	<0.001*	-	-	-
CRI-II	2.34	1.80-3.05	<0.001*	2.29	1.76-2.98	<0.001*
				Nagelkerke R2 = 0.302; p < 0.001*		
Moderate (ref: Mild)						
Gender						
Male	ref					
Female	0.41	0.24-0.68	0.001*	-	-	-
Diabetes mellitus	1.35	1.02-2.15	0.049*	-	-	-
Hypertension	2.30	1.34-3.98	0.003*	2.07	1.16-3.70	0.014*
Neutrophil	1.35	1.13-1.61	0.001*	-	-	-
Monocyte	2.05	1.22-3.10	<0.001*	-	-	-
CRP	2.72	1.69-3.85	<0.001*	2.65	1.22-3.98	0.024*
CRI-I	1.64	1.09-2.20	0.012*	-	-	-
CRI-II	1.85	1.32-2.40	<0.001*	1.98	1.45-2.50	0.002*
				Nagelkerke R2 = 0.324; p < 0.001*		
Severe (ref: Moderate)						
Gender						
Male	ref					
Female	1.07	0.51-2.27	0.859	-	-	-
Diabetes mellitus	0.96	0.48-1.94	0.920	-	-	-
Hypertension	1.03	0.45-2.36	0.948	-	-	-
Neutrophil	0.98	0.77-1.26	0.913	-	-	-
Monocyte	0.56	0.09-3.25	0.520	-	-	-
CRP	2.25	1.16-4.37	0.016*	2.40	1.21-4.78	0.013*
CRI-I	0.99	0.88-1.12	0.975	-	-	-
CRI-II	1.72	1.20-2.46	0.003*	1.77	1.22-2.55	0.003*
				Nagelkerke R2=0.270; p < 0.001*		

In the multivariate regression analysis, the effects of age and drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: CI, confidence interval; CRI, Castelli risk index; CRP, C-reactive protein; OR, odds ratio.

which presented the relationship between CRI and ischemia severity, supported the prognostic role of CRI-II.

Inflammatory activation can accelerate atherosclerosis [23]. Following tissue damage, an inflammatory response causes macrophages to accumulate in the damaged tissue. It has also been suggested that HDL may inhibit leukocyte activation and migration [24]. Activated monocytes transform into macrophages by engulfing oxidized LDL cholesterol molecules. HDL cholesterol plays a role in reducing monocyte activation and reversing the effects of oxidized LDL [25, 26]. This results in the secretion of pro- and anti-inflammatory cytokines and increased CRP production. Thus, an inflammatory response accelerates atherosclerosis [27]. This mechanism was consistent with the positive correlation between CRIs and markers of inflammation. Previous studies reported a positive correlation between CRP levels and ischemia severity in CAD patients [28-30]. These mechanisms may explain the diagnostic performance power of CRI-II derived from LDL and HDL cholesterol levels. Moreover, CRI-II offered a gradual threshold values for distinguishing ischemia severity. Before the referral of patients with suspected CAD to MPS, CRI-II can be an inexpensive and easy screening tool to predict the severity of ischemia beyond presence of ischemia. In addition, the threshold value of the CRI-II level in predicting the presence of ischemia could have prevented 19% of all patients from being referred to MPS and the risk of radiation.

Table 5. Diagnostic performance assessment of CRI in predicting severity of ischemia		
ROC Curve findings	CRI-I	CRI-II
Mild (ref: Normal)		
AUC±SE	0.733±0.03	0.774±0.03
95% CI	0.686-0.784	0.719-0.824
Sensitivity	70.2%	80.8%
Specificity	75.1%	72.7%
Cut-off point	>2.9	>2.1
p	<0.001	<0.001
Moderate (ref: Mild)		
AUC±SE	0.704±0.04	0.700±0.04
95% CI	0.640-0.760	0.637-0.760
Sensitivity	70.6%	78.7%
Specificity	69.4%	65.3%
Cut-off point	>3.7	>2.8
p	<0.001	
Severe (ref: Moderate)		
AUC±SE	0.539±0.5	0.689±0.04
95% CI	0.457-0.619	0.609-0.763
Sensitivity	70.5%	%75.5
Specificity	40.3%	%68.7
Cut-off point	>3.9	>3.3
p	0.459	<0.001
Abbreviations: AUC, area under the curve; CI, confidence interval; CRI, Castelli risk index; SE, standard error.		

Although this study is the first study evaluating the relationship between CRI and MPS, it has some limitations. Initially, it had a single-center and retrospective design. Second, the coronary angiography results of the patients could not be evaluated. Finally, this study did not include patients with a history of CAD and acute coronary syndrome.

Conclusion

High CRI-II levels are an independent predictor of severity of ischemia beyond presence of ischemia. CRI-II offers an important threshold value in distinguishing patients with suspected CAD but without perfusion defects or normal coronary arteries. CRI-II can be a potential screening tool for patients with suspected CAD and can be used for risk stratification.

Conflicts of Interest

The author declare they have no conflicts of interest.

Funding

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

Ethics approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ankara City Hospital Clinical Research Ethics Committee (Decision Date/No: 02.2023/ E1-23-3325).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author, [B.D].

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