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Role of Renal Resistive Index in Predicting the Severity of Coronary Artery Disease in Patients with Mild to Moderate Renal Insufficiency

Renal Resistive İndeks'in Hafif Orta Böbrek Yetersizliği Olan Koroner Arter Hastalarında Hastalık Şiddetini Belirlemedeki Yeri

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Abstract

Objectives: The aim of this study was to determine the renal resistive index (RRI) in patients with mild to moderate renal insufficiency, and to investigate the relationship between RRI and the severity of coronary artery disease (CAD) and renal function.

Materials and Methods: The study included 76 patients diagnosed with CAD on coronary angiography. The patients comprised 41 males and 35 females. Renal resistive index was determined using renal Doppler ultrasonography (RDU). Renal length, width, and parenchymal thickness was measured. The severity of CAD was graded according to Gensini score, and the patients were divided into two groups: mild atherosclerosis (Gensini score <20 points) and severe atherosclerosis (Gensini score ≥20 points). The estimated glomerular filtration rate (eGFR) was calculated for each patient. Based on GFR stage, the patients were divided into three groups, and the relationship between RRI and GFR stage was investigated.

Results: Gensini scores indicated that the RRI was significantly higher in the patients with severe CAD compared to those with mild CAD [0.62 (0.58-0.71)] *vs.* [0.71 (0.63-0.78)], *p*<0.001). No significant differences were observed in renal length, width, and parenchymal thickness. The eGFR was significantly lower in the patients with severe CAD compared to those with mild CAD (*p*=0.02). Grading of the patients based on GFR values indicated a significant correlation between GFR and RRI. RRI was [0.63(0.59-0.68)] in patients with stage 1 (GFR ≥ 90), was [0.77(0.71-0.84)] in patients with stage 2 (GFR 60–89) and was [0.81(0.73-0.85)] in patients with stage 3 (GFR 30–59) (*p*<0.001). The sensitivity and specificity of RRI in the diagnosis of CAD severity were 80.60% and 66.70%, respectively.

Conclusion: RRI shows a parallel increase with the severity of CAD and with the severity of renal insufficiency. RRI, as determined with non-invasive RDU, may provide additional information on the severity of CAD, kidney function and microcirculation.

Key words: Renal resistive index, renal parenchymal thickness, coronary artery disease, Gensini score, eGFR, chronic kidney disease

Öz

Amaç: Çalışmamızda hafif orta renal yetersizliği olan hastalarda renal resistive indeksini (RRİ)saptayarak bunun renal fonksiyonlar ve koroner arter hastalığının (KAH) şiddetiyle ilişkisini araştırdık.

Materyal ve Metot: Çalışmaya koroner angiografisi yapılarak KAH tanısı konmuş 41 erkek,35 kadın toplam 76 hasta alındı. Tüm hastalarda renal doppler ultrasonografi (US) ile RRİ' leri ölçüldü. Renal parankim kalınlığı, böbrek uzunluk ve genişlikleri ölçüldü. Gensini risk skorlama sistemiyle KAH şiddeti skorlanarak hastalar hafif-KAH (Gensini skoru ≤ 20) ve şiddetli-KAH (Gensini skoru > 20) olmak üzere iki guruba ayrılarak karşılaştırıldı. Ayrıca tüm hastalarda glomerular filtrasyon hızı (eGFR) hesaplanarak 3 ayrı sub gruba ayrıldı ve RRI ile ilişkisi araştırıldı.

Bulgular: Gensini skoruna göre şiddetli KAH olanlarda hafif KAH olanlara göre anlamlı derecede yüksek RRİ değerleri saptandı [0,62 (0,58-0,71)] karşı [0,71 (0,63-0,78)], p < 0,01]. Böbrek uzunluğu, böbrek genişliği, böbrek parankim kalınlıkları arasında anlamlı fark saptanmadı. eGFR, şiddetli KAH'lı hastalarda hafif KAH grubuna göre anlamlı derecede düşüktü(p= 0,02).

eGFR değerlerine göre evrelendirilen KAH'lı hastalarda ,renal yetersizlik evresi ile RRİ arasında anlamlı ilişki saptanmıştır. Evre 1 (GFR≥90) olanlarda RI [0,63(0,59-0,68)], evre 2(GFR 60-59) olanlarda RI [0,77(0,71-0,84)], evre 3(GFR 30-59) olanlarda ise RI [0,81(0,73-0,85)] idi, (p<0,01).

RRİ değerinin hafif ciddi koroner arter hastalığı tanısında, sensivite % 77, spesifite % 66 bulundu.

Sonuç: RRI değerleri KAH' lı hastalarda hastalık şiddetine paralel şekilde artış göstermektedir. İlaveten renal yetersizlik derecesi artıkça RRİ değerleri artmaktadır. Doppler US ile RRİ ölçümü KAH şiddetini

saptamada aynı zamanda böbrek fonksiyon ve mikrosirkülasyonu hakkında noninvaziv bir yöntem olarak ilave bilgiler sağlayabilir.
Anahtar kelimeler: Renal resistive indeks, renal parankim kalınlığı, koroner arter hastalığı, Gensini skoru, eGFR, kronik böbrek hastalığı

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Introduction

Cardiovascular disease (CVD) is a major cause of mortality in Turkey and around the world. Chronic kidney disease (CKD), which leads to increased risk of CVD, is increasingly becoming an important public health problem. The convalescence of patients with CVD is greatly influenced by renal function,[1] and CKD is a key predictor of CVD and cardiac mortality.[2,3]

Renal Doppler ultrasonography (RDU) is a non-invasive tool used for the diagnosis of renovascular disease and/or renal failure.[4,5] Microvascular destruction in the renal bed can be specifically evaluated through the indirect analysis of intrarenal circulation based on an examination of arterial flow. Assessment of the renal resistive index (RRI) on RDU allows for the evaluation of renal resistance and renal arteriolar damage.[6]

Analysis of macro- and microvascular circulation can be useful for early and effective detection of CVD and relevant vascular damage, and may also support primary and secondary prevention of CVD and identification of the most ideal treatments. Several studies have shown that RRI determined by RDU correlates with the events and outcomes related to CVD.[7,8] However, to our knowledge, no study in the English-language literature has documented the association between RRI and the severity of CVD and microvascular changes in the renal bed.

In this study, we aimed to investigate the relationship between the severity of coronary artery disease (CAD), as determined by Gensini score, and RRI.

Materials and Methods

Patients

This retrospective study evaluated 126 patients who were presented to the Dicle University Medical School Cardiology Clinic with chest pain, and who were diagnosed with CAD on coronary angiography, between August 2014 and May 2015. Of these, 50 patients with renal artery stenosis, obstructive uropathy, acute renal failure, end-stage CKD, uncontrolled hypertension, and uncontrolled diabetes mellitus were excluded from the study. Approval was obtained from the Dicle University Clinical Research Ethics Committee, and written consent was obtained from each patient.

The 76 patients included in the study were 41 (53.90%) males and 35 (46.10%) females. Body weight and heights were recorded, and body mass index (BMI) was calculated (body weight [kg] / height [m]^2) for each patient. Demographic characteristics, including age and gender, and clinical risk factors, including smoking status, hypertension, diabetes, and hyperlipidemia, were recorded.

The glomerular filtration rate (GFR) was calculated with the abbreviated Modification of Diet in Renal Disease (aMDRD): aMDRD = 186 × (serum creatinine, mg/dL) $^{-1.154}$ × (age) $^{-0.203}$ × 0.742 (if female) × 1.210 (if African).[9]

Coronary angiograms and Gensini scoring

Selective coronary angiography was performed using the Judkins technique.[10] The angiograms were recorded in multiple projections using a biplanar digital cardiac imaging system (Philips Integris DCI, Eindhoven, NL). Cineangiograms were evaluated by two experienced cardiologists. Each coronary angiogram was examined to determine the localization of coronary artery lesions and the percentage of luminal stenosis. According to the American College of Cardiology/American Heart Association (ACC/AHA) lesion classification system, CAD is defined as a diameter stenosis of ≥50%.[11] The severity of CAD was graded according to the Gensini score,[12] which is used to score and classify the extent and degree of coronary artery stenosis. With this method, narrowing of the lumen was grade 1 for 1%–25% stenosis, grade 2 for 26%–50%, grade 4 for 51%–75%, grade 8 for 76%–90%, grade 16 for 91%–99% and grade 32 for total occlusion. This score was multiplied by a factor that accounted for the importance of the lesion's position in the coronary arterial tree: 5 for the left main coronary artery; 2.5 for the proximal left anterior descending (LAD) coronary artery and left circumflex artery (LCX); 1.5 for the mid-segment LAD and LCX; 1 for the distal-segment LAD and LCX, first diagonal artery, first obtuse marginal artery, right coronary artery, posterior descending artery, and intermediate artery; and 0.5 for the second diagonal and second obtuse marginal arteries. The patients were divided into two groups: mild atherosclerosis (Gensini score ≤ 20 points) and severe atherosclerosis (Gensini score > 20 points), a classification consistent with the literature.[13,14]

Imaging techniques

Conventional ultrasonography (US) and Doppler US were performed using the Acuson S2000 ultrasound system (Siemens, Mountain View, CA, USA) with a 4-MHz curved array transducer. All images were obtained by a radiologist with 15 years of experience in sonographic examination, who was blinded to the clinical data. Images were obtained with the patient placed in the lateral decubitus position. Renal length and width were measured in both kidneys, while parenchymal thickness was measured between the thickest and thinnest sections, then averaged for each kidney. In the supine position, intrarenal RI was measured three times at the interlobular arteries in the upper, mid and lower poles of the kidneys using pulse-wave Doppler. The measurements were averaged for each kidney, and the average RI values of both kidneys were used for analysis. Intrarenal Doppler spectra were obtained and the RRI was calculated according to the following formula: RRI = (peak systolic velocity – end diastolic velocity) / peak systolic velocity.

Statistical analysis

SPSS (Statistical Package for the Social Sciences version 16.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov–Smirnov test was used to check the normality of the data. Parametric data were expressed as mean±standard deviation, and non-parametric data were expressed as median. For evaluation of the continuous variables, we used Student's t-test for the parametric data and the Mann–Whitney U test for the nonparametric data; the categorical valuables were analyzed with the Chi-Square test. The relationship between the parameters was analyzed with the Spearman and Pearson correlation tests. In order to predict the severity of CAD, we calculated the areas under the ROC curves for the kidney shear wave speed. A value of $p<0.05$ was accepted as significant.

Table 1. Comparison of Mann Whitney U Test Results for the patients with mild CAD (Gensini score ≤ 20) and Severe CAD (Gensini score >20)

Parameters	**Mild CAD***	**Severe CAD***	***Z***	***P****
Age, year	57 (49-65)	63(53-71)	-1.335	0.232
BMI, kg/m^2	26.3 (24.8-27.5)	26.6 (24.6-28.6)	-0.531	0.630
RRI	0.62 (0.58-0.71)	0.71 (0.63-0.78)	-2.298	< 0.001
Renal width,mm	44.5 (41.2-46-2)	42.5 (40-50)	-0.262	0.468
Renal length,mm	103 (96.5-109.2)	106 (97.7-114.2)	-0.727	0.499
Renal parenchymal thickness, mm	14.5 (13-16)	14 (13-17)	-0.150	0.903
Estimated GFR, ml/min/1.73 m^2	103.2 (79.8-121.8)	89.3 (70.9-102.8)	-2.233	0.023
Serum creatinine, mg/dl	112.8 (96-125)	87.4 (72.6-111.5)	-2.212	0.027
Urea, mg/dl	30 (25-40)	31.5 (28-43.7)	-1.004	0.338
Albumine, gr/dl	3.7 (3.5-3.9)	3.7 (3.4-4)	-0.291	0.840
Total protein , gr/dl	6.9 (6.8-7.4)	7 (6.6-7.4)	-0.085	0.974
Uric acid, mg/dl	5.8 (3.8-6.5)	5.7 (4.3-7)	-0.270	0.612
Triglyceride, mg/dl	196 (100-262)	148 (108.7-211.7)	-0.744	0.407
T,Cholesterol, mg/dl	197 (160-225)	177.5(149.5-206.7)	-1.251	0.125
LDL, Cholesterol, mg/dl	123 (89-155.5)	112 (83-130)	-1.485	0.150
HDL- Cholesterol, mg/dl	32 (30-39)	32.5 (30-36.7)	-0.104	0.908
SBP, mmHg	120 (110-125)	122.5(110-130)	-1.112	0.315
DBP,mmHg	75(70-85)	80 (75-85)	-1.252	0.07

Values are Median*; Mann-Whitney U test**; NS: Not Significant, BMI: Body mass index, RRI: Renal resistive index, GFR: Glomerular filtration rate, HDL: high-density lipoprotein; LDL: low-density lipoprotein

Results

The 76 patients included 41 (53.90%) males and 35 (46.10%) females, The mean age of patient with mild CAD was 57 (49-65) years, mean age of patient with severe CAD was 63(53-71). Between the patients with mild CAD and severe CAD, no significant difference was observed with regard to age, BMI, urea, albumin, total protein, uric acid, triglycerides, cholesterol, renal length and width, and renal parenchymal thickness. However, the eGFR and serum creatinine levels were significantly lower in the patients with severe CAD ($p<0.05$). Moreover, RRI was significantly higher in the patients with severe CAD compared to the patients with mild CAD ($p<0.001$) (Table 1, Figure 1).

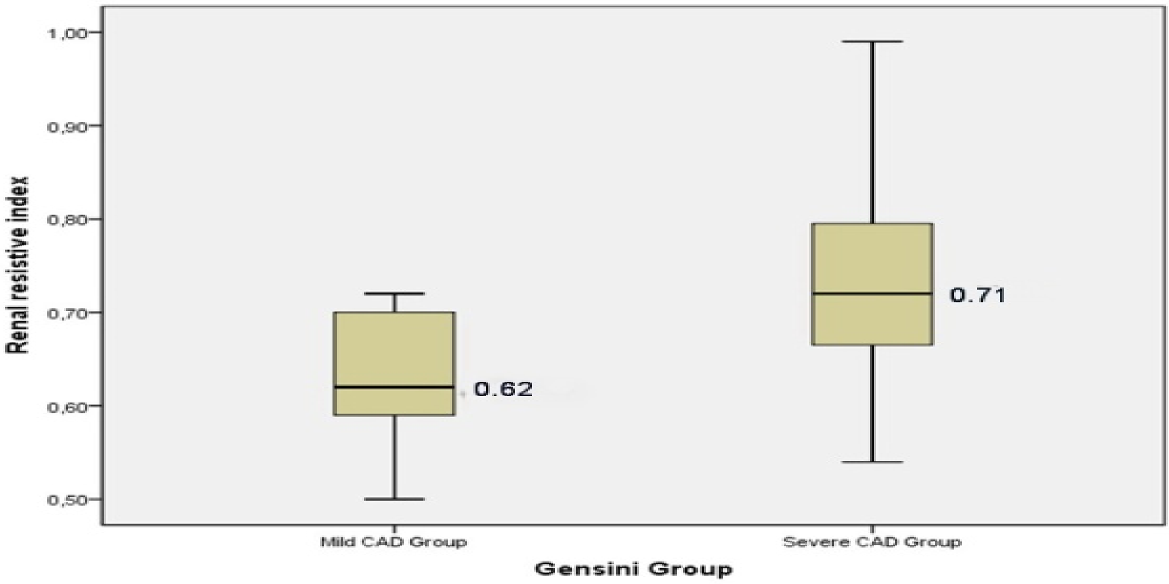

Figure 1. Comparison of Renal resistive index between patients with mild coronary artery disease (Gensini score ≤ 20) and severe coronary artery disease (Gensini score >20)

Grading of the patients based on the eGFR values indicated that RRI increased as eGFR decreased, and a significant correlation was found between the two parameters. RRI was [0.63(0.59-0.68)] in patients with stage 1 (GFR ≥90), [0.77(0.71-0.84)] in patients with stage 2 (GFR 60–89), and [0.81(0.73-0.85)] in patients with stage 3 (GFR 30–59), ($p<0.001$). (Table 2, Figure 2).

Table 2. Relationship between GFR and RI in patients with CAD

Stage	Descriptive	GFR	n	RI*	P**
1	Normal	≥90	37	0.63(0.59-0.68)	< 0.001
2	Mild	60-89	26	0.77(0.71-0.84)	
3	Moderately	30-59	13	0.81(0.73-0.85)	

*Values are Median (25%-75%); **Kruskal Wallis test

In all patients, the Gensini score established no significant correlation with age, BMI, renal length and width, and renal parenchymal thickness ($p>0.05$), but there was a significant correlation with the RRI ($p=0.03$) (Table 3). Similarly, a multivariate analysis indicated no significant relationship the effect of gender, BMI, lipid parameters, blood glucose level, blood pressure, diabetes mellitus and hypertension, except age and smoking (Tables 4). Diagnostic performance of the RRI values in ROC analyses based on gensini score; The Cut of value was 0.605, area under the ROC curve (AUC) was 0.706 (0.553–0.858) (CI: 95%) sensitivity was 80.60% and specificity was 66.70% (Figure 3).

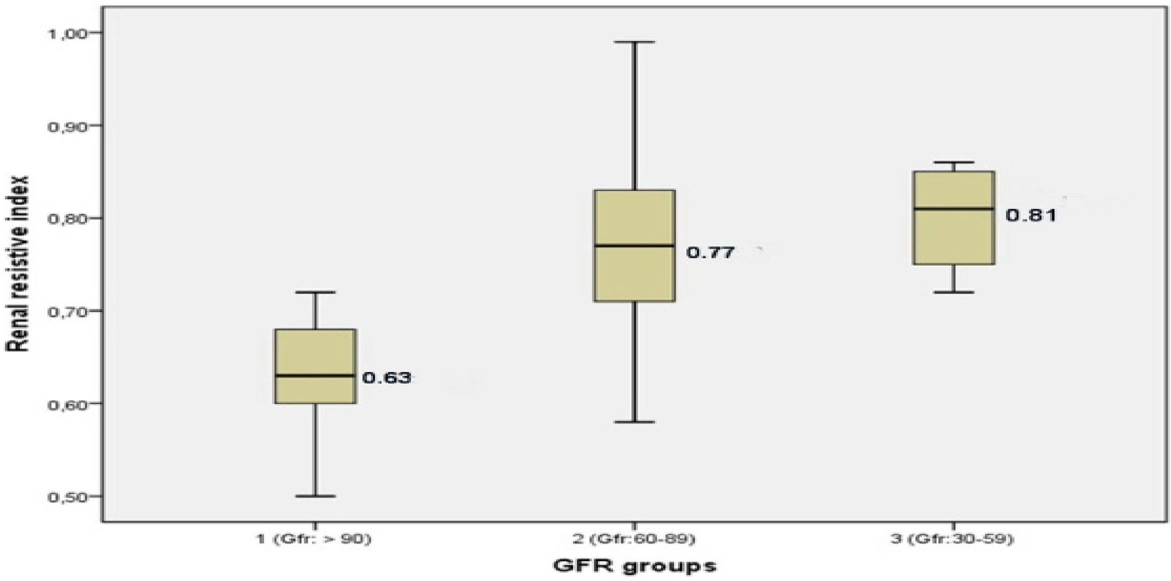

Figure 2. Comparison of Renal resistive index based on GFR groups in coronary artery disease

Table 3. Correlation between Gensini Score and RRI, age, BMI, Renal width, Renal length, Renal parenchymal thickness

Parameters	r	P*
Age , year	0.068	0.633
BMI, kg/m^2	0.171	0.280
RRI	0.357	0.016
Renal width,mm	0.160	0.276
Renal length,mm	0.120	0.417
Renal parenchymal thickness, mm	0.042	0.693

Pearson correlation tests*,BMI: Body mass index, RRI: Renal resistive index, GFR: Glomerular filtration rate, HDL - high-density lipoprotein; LDL - low-density lipoprotein

Table 4. The effect of parameters on RRI detected with multivariate analysis

Coefficients[a]							
Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	F	Sig.
	B	Std. Error	Beta				
Regresion						6.100	0.004[a]
(Constant)	0.455	0.080					
Age	0.004	0.001	0.354	20.748	0.008		
Smoking	0.064	0.029	0.285	2.214	0.032		

a: Dependent Variable: RRI

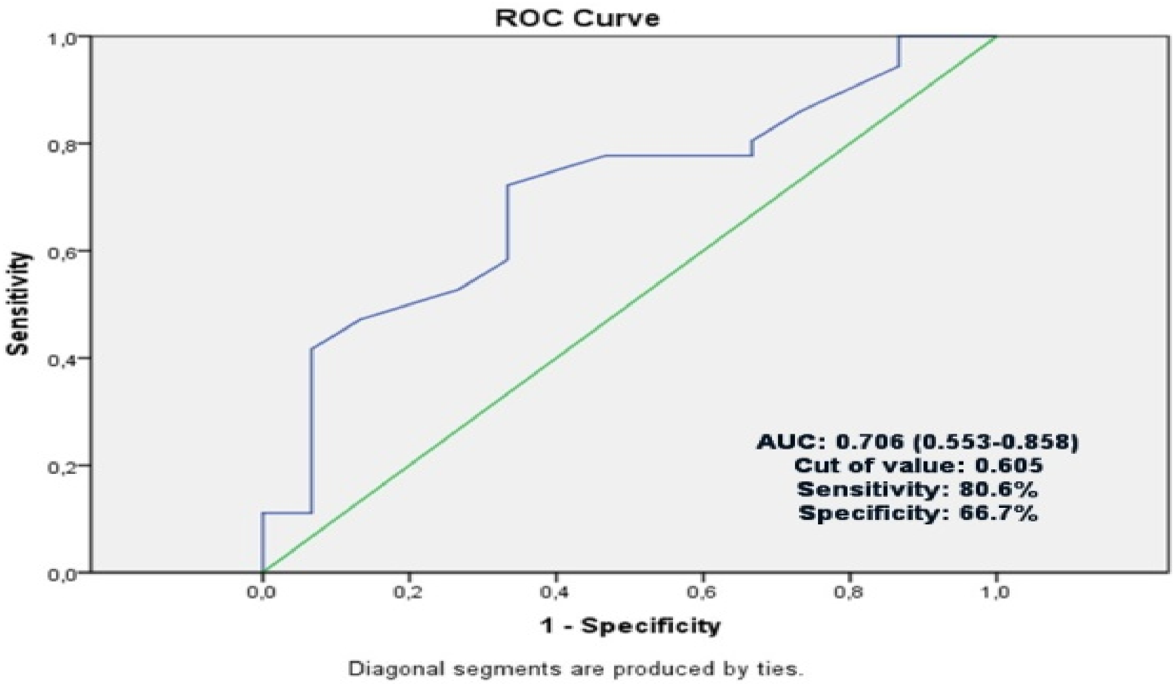

Figure 3. Performance of Renal resistive index for predicting coronary artery severity

Discussion

The RRI, determined by the non-invasive technique of RDU, has been shown to be a useful predictor for the progression of renal dysfunction, providing information for the diagnosis of various renal diseases.[15,16] The presence of CKD leads to increased risk of adverse outcomes and mortality in patients with CVD.[2,17,18] Mild renal insufficiency has been reported to be a strong and independent risk factor for cardiac mortality, even after controlling for all atherosclerotic risk factors.[19] These findings suggest that the RRI values determined by RDU can be used to obtain useful information about renal microvascularisation and function, which can be compared with the severity of CAD to determine the effectiveness of RRI in predicting its progression. In our study, RRI was significantly higher in the patients with severe CAD than in those with mild CAD. In a cohort study, Pearce et al. found significant associations between renal Doppler sonography parameters, including RRI, and CVD events after controlling for other significant risk factors.[8] Calabia et al. also found a significant association between RRI and arterial stiffness and carotid artery atherosclerotic burden, and suggested that this association might provide useful information about micro- and macrovascular impairment.[20] Similarly, Akgül et al. found a relationship between RRI and cardiovascular risk factors and carotid intima-media thickness.[21] Based on these findings and those obtained in our study, we suggest that RRI values determined by RDU may provide useful information about the progression of CAD before the vascular lesions become irreversible, and may also allow early treatment of CAD.

In our study, eGFR was lower in the patients with severe CAD compared to the patients with mild CAD. Grading of the patients based on eGFR values revealed that RRI increased as eGFR decreased. It was also revealed that kidney function decreased as the severity of CAD increased and, in a similar manner, RRI increased as the severity of CAD increased, suggesting that RRI can be used to predict the severity of CAD. Moreover, in light of the findings of this study, we believe that RRI may provide useful information about GFR, as well. This suggestion is consistent with the findings of Kawai et al. who reported that RRI is a more useful tool than GFR in the evaluation of acute renal injury.[22]

Calabia et al. found high rates of sensitivity and specificity for RRI in the determination of arterial stiffness.[20] Similarly, we also found high rates of sensitivity and specificity for RRI in the prediction of the severity of CAD (77% and 66%, respectively).

The present study was limited by two factors. First, it had a cross-sectional prospective design. Therefore, longitudinal prospective studies are necessary to further investigate the effects of RRI. Second, we had a small sample size, and thus further large-scale studies are needed to substantiate these findings.

In conclusion, RRI shows a parallel increase with the severity of CAD and the severity of renal insufficiency. Determination of RRI with non-invasive RDU may provide additional information about the severity of CAD, kidney function and microcirculation.

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