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THE DIAGNOSTIC PERFORMANCE OF CORONARY COMPUTED TOMOGRAPHIC ANGIOGRAPHY COMPARED WITH INVASIVE CORONARY ANGIOGRAPHY IN SYMPTOMATIC PATIENTS: LONG–TERM PROGNOSTIC IMPLICATIONS

SEMPTOMATİK HASTALARDA İNVAZİV KORONER ANJİYOGRAFİ İLE KARŞILAŞTIRILDIĞINDA KORONER BİLGİSAYARLI TOMOGRAFİK ANJİYOGRAFİNİN TANISAL PERFORMANSI: UZUN DÖNEM PROGNOSTİK ETKİLER

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ABSTRACT

Objective: We aimed to investigate the diagnostic accuracy of 64-multidetector coronary computed tomographic angiography (CCTA) for stable symptomatic patients and evaluate the relationship between severity of coronary artery disease (CAD), cardiovascular risk scores, and coronary artery calcium (CAC) scores. We also assessed the possible predictors of all-cause mortality at a median of 10 years of follow-up.

Materials and Methods: This retrospective, observational study included 45 patients with suspected CAD who had undergone CCTA and invasive coronary angiography within the previous two weeks (67% male, mean age 62.1±10.72 years). Using CCTA, sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated on a segment and patient basis analysis. The total CAC (Agatston units [AU]) and systematic coronary risk evaluation (SCORE) scores were calculated for each patient.

Results: The CCTA NPV and PPV for the segment- and patient-based analyses were 97% and 100%, and 94% and 88%, respectively. CAC scores >100 AU reflected a higher incidence of significant CAD (OR=4.88, 95% CI 1.62–14.68 p<0.001), and CAC scores were significantly correlated with SCORE risk values (r=0.669, p<0.001). Ultimately, 6 patients (13.3%) died. Com-

ÖZET

Amaç: Bu araştırmada, stabil semptomatik hastalarda 64 çok-kesitli koroner bilgisayarlı tomografik anjiyografinin (ÇKBTA) tanısal doğruluğu ile koroner arter hastalığı (KAH) ciddiyeti, kardiyovasküler risk skorları ve koroner kalsiyum skoru (KKS) arasındaki ilişkiyi incelemek amaçlanmıştır. Ayrıca, ortalama 10 yıllık takipte, tüm nedenlere bağlı mortalitenin olası prediktörlerini değerlendirdik.

Gereç ve Yöntem: Bu retrospektif, gözlemsel çalışmaya, şüpheli KAH olan ve iki hafta içinde ÇKBTA ve invaziv koroner anjiyografi yapılmış 45 hasta dahil edildi (%67 erkek, ortalama yaş 62,1±10,72 yıl). Duyarlılık, özgüllük, pozitif ve negatif kestirim değerleri (PKD ve NKD), ÇKBTA için segment ve hasta bazlı analizde hesaplandı. Toplam KKS (Agatston units [AU]) ve sistematik koroner risk değerlendirme (SCORE) skorları her hasta için hesaplandı.

Bulgular: Segment ve hasta bazlı analizde, ÇKBTA'nın NKD ve PKD sırasıyla %97 ve %100, ve %94 ve %88 idi. KKS >100 AU olan grup daha yüksek ciddi KAH insidansı ile ilişkili bulundu (OR=4,88, 95% CI 1,62–14,68 p<0,001). KKS ile SCORE risk değerleri arasında önemli pozitif korelasyon mevcuttu (r=0,669, p<0,001). Takipte, 6 (%13,3) hasta öldü. KKS, SCORE risk değeri ve yaş birlikte, ortalama 10 yıllık takipte tüm nedenlere bağlı

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bined CAC and SCORE value and age significantly improved the prediction of all-cause mortality at a median of 10 years of follow-up (AUC=0.833, 95% CI 0.693–0.974, p=0.009).

Conclusion: 64-multidetector CCTA has high diagnostic accuracy for detecting or excluding significant CAD. Moreover, CAC and SCORE risk score may provide valuable prognostic information for predicting long-term mortality and improving preventive therapies.

Keywords: Multidetector computed tomography angiography, coronary artery disease, mortality, cardiovascular risk

ölüm tahminini önemli ölçüde iyileştirdi (AUC=0,833, 95% CI 0,693–0,974, p=0,009).

Sonuç: 64-ÇKBTA, ciddi KAH'ı dışlamak veya belirlemek için yüksek tanısal doğruluğa sahiptir. Ayrıca, KKS ve SCORE risk skoru uzun dönem mortaliteyi öngörmek ve koruyucu tedavileri iyileştirmek için değerli prognostik bilgiler sağlayabilir.

Anahtar Kelimeler: Çok kesitli bilgisayarlı tomografik anjiyografi, koroner arter hastalığı, mortalite, kardiyovasküler risk

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide (1). Although invasive coronary angiography (ICA) is the standard reference method for the assessment of obstructive CAD, it is invasive, expensive, and carries morbidity and mortality risks for patients (2).

Coronary computed tomographic angiography (CCTA) is a potential noninvasive procedure for detecting and excluding significant CAD (3). Previous studies have shown that the diagnostic performance of 64-multidetector computed tomography (MDCT) improves CCTA for accurate diagnosis of coronary artery stenosis (3). Multicenter trials have shown that new-generation MDCT is highly sensitive in diagnosing significant CAD compared to the reference method (ICA) (3-5).

CCTA allows for a comprehensive evaluation of the coronary arteries and visualization of both the lumen and atherosclerotic plaques and calcifications in the coronary arterial walls. MDCT-identified coronary calcium is an important indicator of CAD, and the quantity of calcification in coronary arteries is a strong predictor of coronary events (6). Also, coronary calcification can be used for cardiovascular risk stratification. Coronary calcification is an indicator of atherosclerotic plaques in the coronary arteries, and the amount of coronary calcification correlates strongly with the total coronary atherosclerotic plaque burden (1). Coronary artery calcium (CAC) scores are an important diagnostic tool for identifying or excluding significant CAD in symptomatic patients (1). Previous studies have reported that CAC scores have excellent negative predictive value for excluding significant CAD (7).

The use of global risk scores, such as Framingham or systematic coronary risk evaluation (SCORE) scores, is fundamental in the cardiovascular risk assessment of individuals. SCORE values are important for determining future fatal atherosclerotic events. These risk scores could also improve clinical management strategies. Although assessing risk scores is the first step in cardiovascular risk stratification, when used alone, its effectiveness is limited (1). Therefore, as supplementary clinical tools, CAC scores and CCTA may provide more valuable prognostic information for cardiovascular events (8).

We aimed to investigate the diagnostic accuracy of 64-multidetector CCTA for stable symptomatic patients, compared with ICA as the reference method, and to evaluate the relationship between the severity of coronary artery stenosis, calcific plaque burden, and cardiovascular risk (SCORE) scores. We also evaluated the possible predictors of all-cause mortality as a primary clinical outcome at a median of 10 years of follow-up.

MATERIALS AND METHODS

Study population

This retrospective, observational, and cross-sectional study included 45 stable symptomatic patients with suspected or known CAD who had undergone CCTA and ICA within the previous 2 weeks according to clinical indications in 2010–2013. The local ethics committee of Istanbul University approved the study (Date: 16.08.2013, No: 2013/1086).

Patients were included in this work if they were >18 years old and had sinus rhythm. Exclusion criteria were impaired renal function (eGFR<60 ml/min/1.73 m^2), irregular cardiac rhythm or atrial fibrillation, abnormal thyroid function, pregnancy, and severe congestive heart failure (NYHA functional class IV).

All CCTA scans were performed using an Aquilion 64-multidetector row scanner (Toshiba Systems, Tokyo, Japan). The CCTA images for each patient were interpreted independently by an experienced radiologist from the hospital's radiology department, blinded to all patient characteristics and ICA results. ICA methods were performed on every patient using the standard protocol from the Judkins femoral artery approach. Obstructive, significant CAD was defined as ≥50% luminal stenosis. All ICA images were interpreted by two independent experienced cardiologists blinded to all patient characteristics and CCTA results.

Coronary artery segments were scored using the American Heart Association (AHA) 15-segment model, as pre-

viously described (9). Due to anatomical variations and poor image quality, non-evaluable coronary segments with a typical luminal diameter <2 mm (segments 4, 10, and 14) were excluded.

Study design

The performance characteristics of CCTA were assessed using segment-based and patient-based analyses to determine significant CAD using ICA as the reference standard. For both the patient- and segment-based analyses, a true positive was considered as the presence of ≥1 coronary artery segment with significant stenosis on both CCTA and ICA.

Baseline clinical characteristics and laboratory findings were recorded for all patients by an investigator who was blinded to the study data. The study population was divided into two groups according to significant coronary stenosis on ICA.

The total CAC (AU) score was calculated for each patient. In previous studies, CAC scores were classified as follows: 0, no calcification; 1–100, mild calcification; 101–400, moderate calcification; and >400, severe calcification (8).

European SCORE scores, to estimate the risk of a first fatal cardiovascular event within 10 years, were calculated for all subjects with a ≥1 cardiovascular risk factor. Data on age, gender, smoking status, systolic blood pressure, diabetes mellitus, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels were recorded.

SCORE values have four risk levels (low, moderate, high, and very high) with different cut-off values, as previously described (10). A calculated SCORE value <1% indicates a low risk; 1-5%, a moderate risk; 5-10% , high risk; and ≥10%, very high risk based on European Society of Cardiology (ESC) guidelines (10).

The SCORE risk chart for high risk countries was used for risk estimation, since Turkiye is included in the high risk countries group (10).

Clinical outcomes of the study

The primary clinical outcome of the study was all-cause mortality at a median of 10 years of follow-up. The vital status of all patients were collected from the National Death Reporting System.

Statistical analysis

The normality of the data was analyzed using the Kolmogorov–Smirnov test. Continuous data are presented as means±standard deviations (SDs), and categorical data are presented as counts and percentages. A chi-squared or Fisher's exact test was used to determine the differences in categorical variables between the groups. Unpaired samples were compared using the Student's t-test or Mann–Whitney U test, as required. The correlations between the parameters were evaluated using Pearson's or Spearman's correlation analysis according to the normality of the data. Univariate and multivariate logistic regression analyses were performed to identify the independent predictors for significant stenosis on ICA. Variables with p-values <0.05 in the univariable analysis were selected for the multivariable model. A stepwise method was utilized to determine significant variables for the multivariate logistic regression analysis. The results of the univariate and multivariate regression analyses are expressed as odds ratios (OR) with 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves were obtained, and an optimal combination of variables for predicting mortality was established. Cumulative survival curves were derived according to the Kaplan–Meier method. The effect of the variables on survival was evaluated using Cox proportional hazard models. The CCTA sensitivity, specificity, and positive and negative predictive values (PPV and NPV), calculated from the chi-squared tests of contingency, were used to detect or exclude significant CAD. Significance was considered at a two-sided value of $p<0.05$. All statistical tests were conducted using SPSS® Statistics 26.0 for Windows (IBM, Armonk, NY, USA).

RESULTS

Clinical characteristics

After adjusting the exclusion criteria, 45 patients were enrolled in the study. Of these, 30 (67%) were male, and 15 (33%) were female. The mean age of the participants was 62.1±10.72 years. Table 1 shows the baseline clinical characteristics and laboratory findings of the study participants. Eight patients (17.8%) had a previous history of CAD and/or prior interventional treatment. As shown in Table 1, CAC and SCORE values were higher, and there were more patients with significant CAD on CCTA, in the group with significant ICA-identified CAD ($p<0.001$).

Comparison of coronary artery stenosis using a segment-based analysis

According to the AHA 15-segment model, 540 coronary segments were used for comparison with ICA. Of the 80 segments with significant CAD on ICA, CCTA correctly identified 65 (sensitivity 81%; Table 2A). Fifteen segments with significant CAD could not be detected by CCTA. Of the 460 segments without significant stenosis on ICA, 456 were correctly determined by CCTA (specificity 99%). ICA revealed significant CAD in 65 of the 69 stenotic segments observed with CCTA (PPV 94%). There were four false positive segments with CCTA. Consequently, for a total segment-based analysis, the overall sensitivity was 81%, specificity was 99%, PPV was 94%, and NPV was 97% (Table 2A).

Table 1: Baseline clinical characteristics, and laboratory findings of the patients with and without significant coronary artery disease according to invasive coronary angiography

	Total patients (n=45)	Patients with significant CAD (n=28)	Patients without significant CAD (n=17)	p-value
Clinical characteristics				
Age, (years)	62.16±10.7	63.39±10.9	60.12±10.4	0.326
Gender Male, n (%)	30 (66.7%)	22 (78.6%)	8 (47.1%)	0.030*
Female, n (%)	15 (33.3%)	6 (21.4%)	9 (52.9%)	0.030*
HT, n (%)	29 (64.4%)	19 (67.9%)	10 (58.8%)	0.539
DM, n (%)	6 (13.3%)	3 (10.7%)	3 (17.6%)	0.658
Hyperlipidemia, n (%)	17 (37.8%)	11 (39.3%)	6 (35.3%)	0.789
Smoking, n (%)	14 (31.1%)	10 (35.7%)	4 (23.5%)	0.392
Family history, n (%)	12 (26.7%)	9 (32.1%)	3 (17.6%)	0.286
Previous CVD	8 (17.8%)	8 (28.6%)	0 (0%)	0.017*
Laboratory findings				
Fasting plasma glucose (mg/dL)	97 (82-323)	94.5 (82-323)	98 (88-115)	0.964
Creatinine (mg/dL)	0.8 (0.56-1.2)	0.85 (0.56-1.2)	0.7 (0.6-1.2)	0.752
Urea (mg/dL)	31.87±12.4	30.48±10.5	33.86±15.3	0.596
Uric acid (mg/dL)	5.7±1.9	5.75±1.9	5.63±1.8	0.899
Sodium (mmol/L)	140 (138-146)	140 (139-143)	141 (138-146)	0.470
Potassium (mmol/L)	4.5 (3.8-5.1)	4.42 (3.8-5.1)	4.5 (4.2-4.9)	0.370
AST (U/L)	22 (13-94)	20.5 (13-44)	29 (16-94)	0.266
ALT (U/L)	22 (12-97)	22 (12-53)	27 (15-97)	0.722
CRP (mg/L)	7 (1.54-64.7)	8.8 (4.2-64.7)	4 (1.54-9)	0.004*
Total cholesterol (mg/dL)	205±66.7	220±85.2	187.86±35.4	0.371
HDL-C (mg/dL)	42.27±7.1	39.13±6.9	45.86±5.6	0.035*
LDL-C (mg/dL)	138.67±59.4	150.75±77.3	124.86±29.1	0.423
Triglyceride (mg/dL)	147.67±70.6	152.13±90.7	142.57±44.4	0.711
Hgb (gr/dL)	13.25±1.8	13.19±1.9	13.33±1.9	0.912
Hematocrit (%)	39.62±5.1	39.44±5.4	39.87±5	0.932
WBC (10^3/µL)	7.6 (5.7-11.3)	7.7 (5.7-11.3)	7.3 (5.7-11)	0.689
RBC (10/µL)	4.64±0.5	4.6±0.6	4.69±0.3	0.785
Platelet (10^3/µL)	225.65±49.9	208.02±48.2	250.83±43.6	0.045*
Coronary Calcium Score, (AU)	126 (0-3500)	372 (0-3500)	0 (0-276)	<0.001*
SCORE risk score, (%)	5 (0-29)	7 (0-29)	2 (0-20)	<0.001*
Patients with significant CAD in CCTA on patient-based, n (%)	32 (71.1%)	28 (100%)	4 (23.5%)	<0.001*
Mortality, n (%)	6 (13.3%)	5 (18.5%)	1 (5.9%)	0.380

CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes mellitus, CVD: Cardiovascular disease, AST: Aspartate transaminase, ALT: Alanine transaminase, CRP: C reactive protein, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, Hgb: hemoglobin, WBC: White blood cell, RBC: Red blood cell, AU: Agatston units, SCORE: Systematic Coronary Risk Evaluation, CCTA: Coronary computed tomographic angiography. *: p significance <0.05

Table 2A: Comparison of coronary artery stenosis on a segment-based analysis

	Segment-based analysis				Sensitivity	Specificity	PPV	NPV
		CCTA						
		<50%	≥50%					
ICA	<50%	456	4	460	81%	99%	94%	97%
	≥50%	15	65	80				
		471	69	540				

CCTA: Coronary computed tomographic angiography, ICA: Invasive coronary angiography, PPV: Positive predictive value, NPV: Negative predictive value

Table 2B: Comparison of coronary artery stenosis on a patient-based analysis

	Patient-based analysis				Sensitivity	Specificity	PPV	NPV
		CCTA						
		<50%	≥50%					
ICA	<50%	13	4	17	100%	77%	88%	100%
	≥50%	0	28	28				
		13	32	45				

CTA: Coronary computed tomographic angiography, ICA: Invasive coronary angiography, PPV: Positive predictive value, NPV: Negative predictive value

We evaluated significant coronary artery stenosis for each segment separately using CCTA (Table 3). In particular, CCTA had high sensitivity for segments 5, 6, 7, 11, and 15 (Table 3).

Table 3: Comparison of all segments according to significant coronary artery disease on invasive coronary angiography

Segment	Sensitivity	Specificity	PPV	NPV
Segment 1	83.3%	100%	100%	97.5%
Segment 2	83.3%	97.4%	83.3%	97.4%
Segment 3	62.5%	100%	100%	92.5%
Segment 5	100%	100%	100%	100%
Segment 6	92.3%	96.9%	92.31%	96.9%
Segment 7	100%	96.6%	94.1%	100%
Segment 8	60%	100%	100%	95.2%
Segment 9	44.4%	100%	100%	87.8%
Segment 11	100%	97.7%	50%	100%
Segment 12	80%	100%	100%	97.6%
Segment 13	80%	100%	100%	97.6%
Segment 15	100%	100%	100%	100%

PPV: Positive predictive value, NPV: Negative predictive value

Patient-based analysis

Patients with significant CAD were defined as those with coronary artery stenosis (≥50% luminal obstruction) in at least one evaluable coronary segment. ICA indicated that 28 of the 45 patients had significant CAD, and CCTA correctly identified all of them, with an overall sensitivity per patient of 100% (Table 2B). CCTA correctly ruled out significant stenosis in 13 of 45 patients (29%; per-patient specificity 77%). ICA revealed significant stenosis in 28 of 32 patients observed with CCTA. Patient-based analysis indicated that four patients were evaluated falsely positive by CCTA, leading to a positive predictive value of 88%. Consequently, for the patient-based analysis, the overall sensitivity was 100%, specificity was 77%, PPV was 88%, and NPV was 100% (Table 2B).

In our study, we considered CAC scores >100 AU as evidence of significant coronary artery calcification. We classified CAC scores as >0 and ≤100 AU versus >100 AU thresholds and examined significant CAD using ICA for each threshold value. The median CAC score was 126 AU (range 0–3500 AU). Twenty-two patients (49%) had a low calcium score (≤100 AU), 12 of whom (27%) had a 0 calcium score.

When we defined the threshold value as 0 for CAC, 26 of 28 patients with significant CAD on ICA had CAC scores >0 (sensitivity 92.8%). Twenty-six of 33 patients with CAC scores >0 using CCTA also had significant CAD on ICA (PPV 78.8%). Ten of 12 patients with 0 calcium scores had no significant stenosis on ICA (NPV 83.3%; Table 4). The overall sensitivity was 92.8%, specificity was 58.8%, PPV was 78.8%, and NPV was 83.3% (Table 4).

Table 4: Comparison of coronary calcium score according to coronary stenosis on invasive coronary angiography

Coronary Calcium Score		ICA		Sensitivity	Specificity	PPV	NPV
		<50%	≥50%				
For threshold value "0"	≤0	10	2	92.8%	58.8%	78.8%	83.3%
	>0	7	26				
For threshold value "100"	<100	14	8	71.4%	82.3%	86.9%	63.6%
	>100	3	20				

ICA: Invasive coronary angiography, PPV: Positive predictive value, NPV: Negative predictive value

Table 5: Comparison of SCORE risk score according to CCTA and ICA identified coronary artery stenosis

		SCORE Risk Score		OR	95% CI	p value
		<5% (Low Value)	≥5% (High Value)			
CCTA	<50%	11	2	2.71	1.54-4.76	0.001*
	≥50%	10	22			
ICA	<50%	14	3	3.29	1.67-6.49	<0.001*
	≥50%	7	21			

SCORE: Systematic Coronary Risk Evaluation, CCTA: Coronary computed tomographic angiography, ICA: Invasive coronary angiography, OR: Odds ratio, CI: Confidence intervals. *: p significance <0.05

When we defined the threshold value as 100 for CAC, 20 of the 28 patients with significant coronary stenosis on ICA had CAC scores >100 AU (sensitivity 71.4%). Moreover, 20 of the 23 patients with CAC scores >100 according to CCTA also had significant CAD on ICA (PPV 86.9%; Table 4). The overall sensitivity was 71.4%, specificity was 82.3%, PPV was 86.9%, and NPV was 63.6% (Table 4).

When comparing CAC scores with the severity of CAD on ICA, CAC scores >0 AU versus 0 AU were associated with a greater incidence of significant CAD on ICA (OR=3.93, 95% CI 1.94–7.95, p<0.001). Likewise, CAC scores >100 AU versus ≤100 AU were associated with a greater incidence of significant CAD on ICA (OR=4.88, 95% CI 1.62–14.68, p<0.001).

The SCORE risk scores indicated a risk of cardiovascular death within 10 years, as previously described. In our study, a 10-year risk of cardiovascular death of ≥5% was considered high risk (11). The study population was divided into two groups according to the SCORE risk values: a low SCORE value group (calculated score <5%, n=21) and a high SCORE value group (risk score ≥5%, n=24). We evaluated significant ICA- and CCTA-identified CAD for the groups. The median calculated SCORE value was 5% (range 0–29%).

Twenty-two patients in the high SCORE value group (≥5%) compared to the low SCORE value group (<5%) had a significantly greater incidence of significant CAD on CCTA (OR=2.71, 95% CI 1.54–4.76, p=0.001; Table 5 and Figure 1). When compared with ICA, 21 patients with

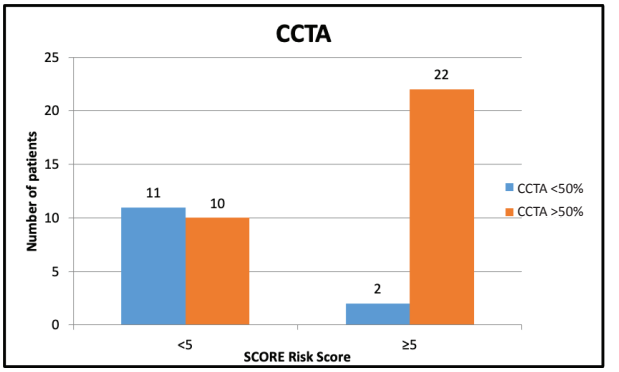

Figure 1: Comparison of SCORE risk score according to coronary artery stenosis on CCTA

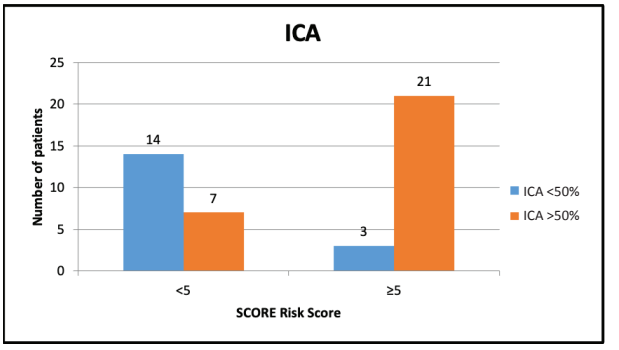

Figure 2: Comparison of SCORE risk score according to coronary artery stenosis on ICA

Table 6: Correlation of coronary calcium score with SCORE risk score and stenotic segment number on CCTA

	Variable	r	p
Coronary calcium score	Number of segments with significant stenosis on CCTA	0.783	<0.001*
	SCORE risk score	0.669	<0.001*
SCORE risk score	Number of segments with significant stenosis on CCTA	0.656	<0.001*

SCORE: Systematic Coronary Risk Evaluation, CCTA: Coronary computed tomographic angiography. *: p significance <0.05

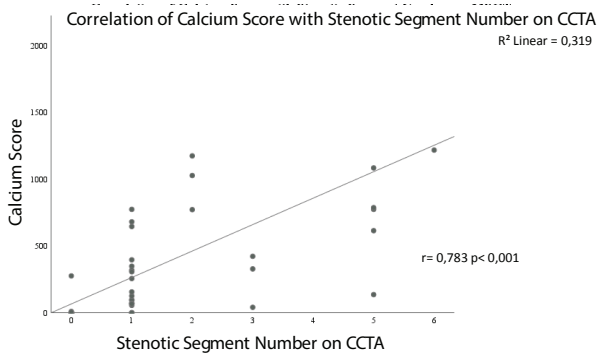

Figure 3a: Correlation of calcium score with stenotic segment number on CCTA

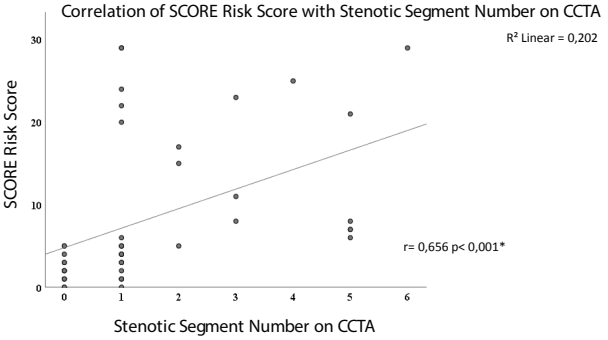

Figure 3b: Correlation of SCORE risk score with stenotic segment number on CCTA

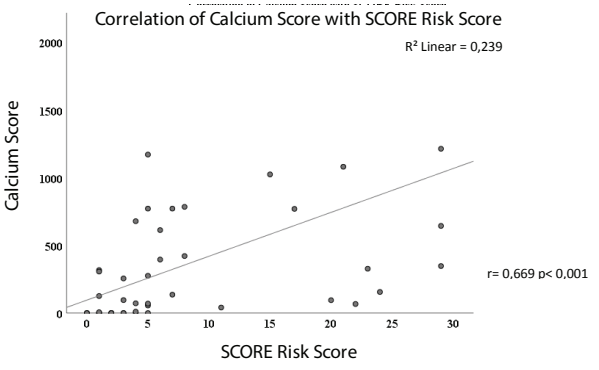

Figure 3c: Correlation of calcium score with SCORE risk score

a high score value (≥5%) compared to those with a low score value (<5%) had a significantly higher incidence of significant CAD on ICA (OR=3.29, 95% CI 1.67–6.49, p<0.001; Table 5 and Figure 2).

In the correlation analysis, CAC scores were significantly positively correlated with the number of segments with significant stenosis on CCTA and the SCORE risk score (r=0.783, p<0.001 and r=0.669, p<0.001, respectively; Table 6 and Figure 3). Also, there was a significant positive correlation between SCORE risk scores and the number of segments with significant CCTA-identified stenosis (r=0.656, p<0.001; Table 6, Figure 3).

In the multivariate regression analysis, CAC score was an independent predictor of significant coronary stenosis on ICA (OR=1.007, 95% CI 1.000–1.014, p=0.038; Table 7).

Table 7: Multivariate regression analysis for predicting significant coronary artery stenosis on invasive coronary angiography

Variables	OR	95% CI	p-value
Male gender	0.924	0.154-5.532	0.931
Calcium score	1.007	1.000-1.014	**0.038***
SCORE risk score	1.108	0.957-1.281	0.170

SCORE: Systematic Coronary Risk Evaluation, OR: Odds ratio, CI: Confidence intervals. *: p significance <0.05

Long-term outcomes of the study

The primary clinical outcome of the study in the long-term follow-up was all-cause mortality. The median follow-up duration was 119 months (range 29–144 months). Ultimately, 6 patients (13.3%) died. In the ROC analysis, the AUC predicting all-cause mortality at a median of 10 years was 0.559 for the CAC score, 0.704 for the SCORE risk score, 0.649 for the significant CCTA-identified coronary stenosis, 0.750 for the CAC score plus SCORE risk score plus significant coronary stenosis indicated by CCTA, and 0.833 for the CAC score plus SCORE risk score plus age (p=0.009, AUC 0.833, 95% CI 0.693–0.974; Figures 4 and 5).

In the Cox regression analysis, age was an independent predictor of mortality at a median of 10 years (HR=1.157, 95% CI 1.031–1.299, p=0.013; Table 8).

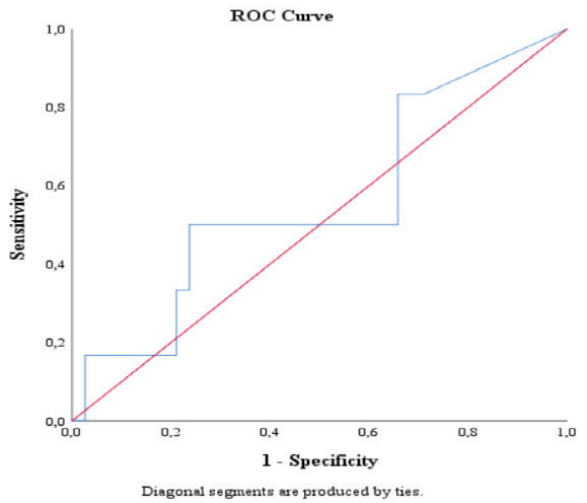

Figure 4a: The receiver operating characteristics (ROC) curve analysis of coronary calcium score in predicting mortality

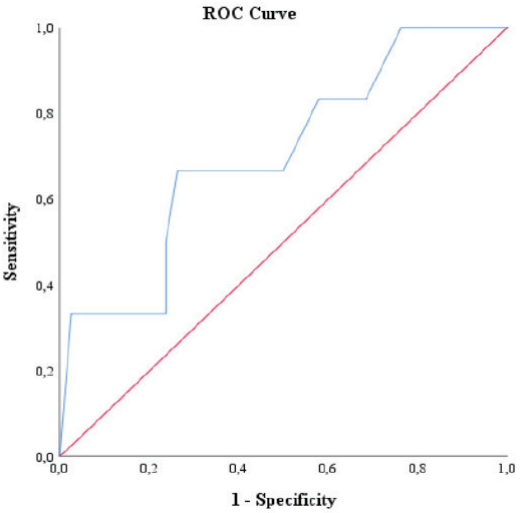

Figure 4b: ROC curve analysis of SCORE risk score in predicting mortality

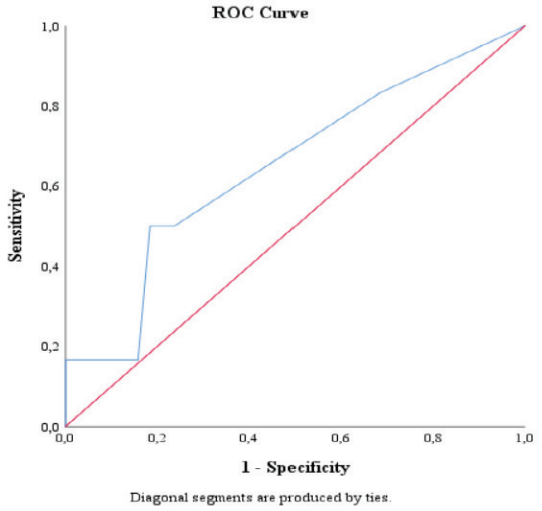

Figure 4c: ROC curve analysis of stenotic segment number on CCTA in predicting mortality

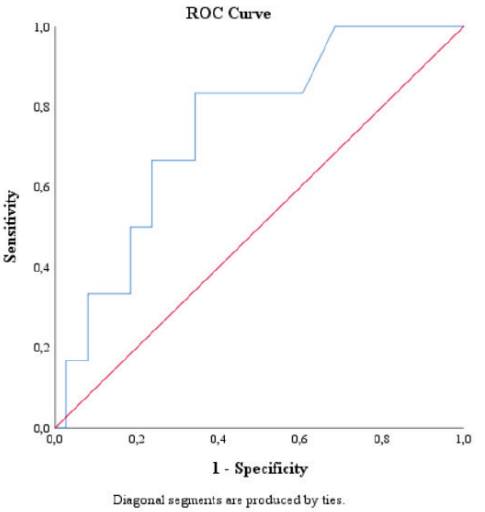

Figure 4d: ROC curve analysis of calcium score with SCORE risk score in predicting mortality

Table 8: Cox regression analysis to predict independent variables for mortality

Variable	HR	95% CI	p-value
Age	1.157	1.031-1.299	0.013*
Male Gender	4.067	0.264-62.608	0.315
SCORE risk score	1.087	0.973-1.215	0.140
Calcium score	1.000	0.998-1.002	0.703
SCORE risk score ≥5%	0.153	0.007-3.121	0.222
Calcium score >100	0.873	0.079-9.670	0.912

SCORE: Systematic Coronary Risk Evaluation, HR: Hazard ratio, CI: Confidence intervals, *: p significance <0.05

According to the Kaplan-Meier survival analysis, the survival rate for 10-year mortality was 0.87. Also, no significant difference was found between the patients with and without significant stenosis on ICA (p=0.279; Figure 6).

DISCUSSION

The present study investigated the diagnostic accuracy of 64-multidetector CCTA for stable symptomatic patients with suspected cardiovascular disease compared to ICA as the reference standard method. The following sections highlight the notable findings of our study.

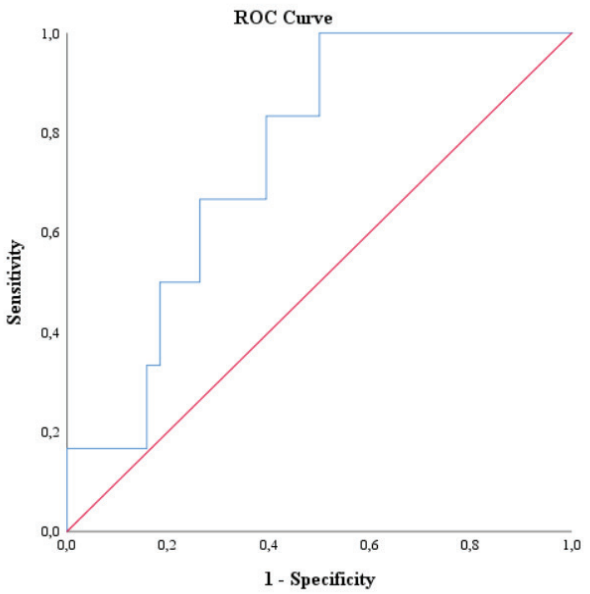

Figure 5a: ROC curve analysis of calcium score in combination with SCORE risk score and stenotic segment number on CCTA in predicting mortality

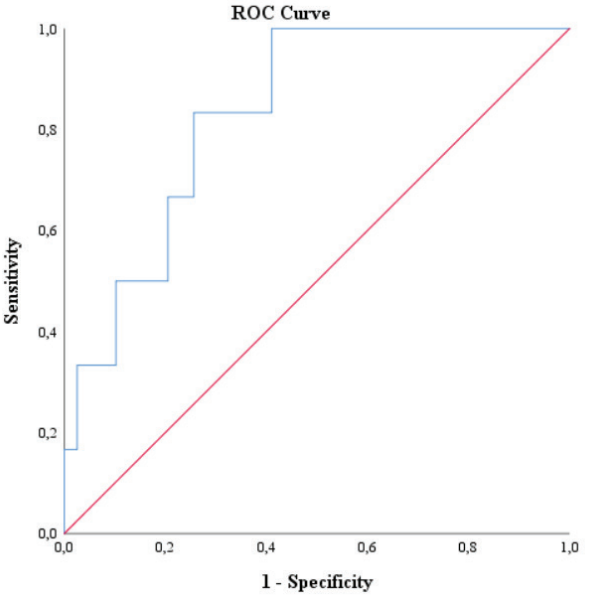

Figure 5b: ROC curve analysis of calcium score in combination with SCORE risk score and age in predicting mortality

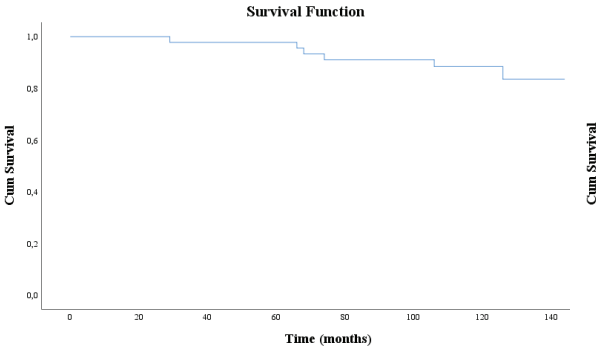

Figure 6a: Kaplan-Meier cumulative survival curves for mortality during follow-up

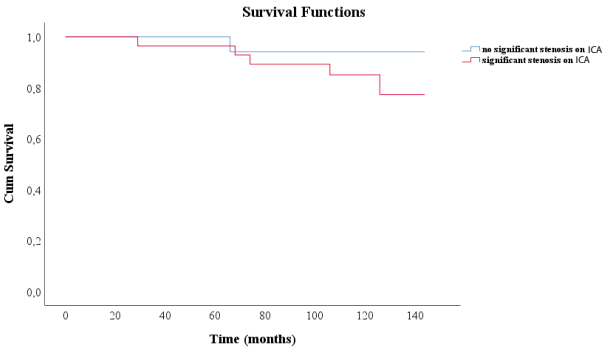

Figure 6b: Kaplan-Meier survival analysis according to significant coronary stenosis on ICA during follow-up

The NPV and PPV remained high in both the segment-based and patient-based analyses (97% and 100%, and 94% and 88%, respectively). We showed that higher CAC values were associated with a higher incidence of significant CAD and higher SCORE cardiovascular risk scores. Furthermore, we evaluated the role of CCTA and CAC scores in both diagnostic and prognostic evaluation and analyzed the role of the CAC, CCTA and SCORE risk scores in predicting all-cause mortality at a median of 10 years as a long-term prognostic implication. To the best of our knowledge, our 10-year follow-up was substantially longer than the trials in the literature.

Cardiovascular diseases and CAD are the most common causes of mortality worldwide; thus, CAD-related morbidity and mortality indicators are important for public health policies (1, 12). Previous reports have shown that CCTA can effectively diagnose CAD and may therefore improve treatments, investigations, and clinical outcomes for symptomatic patients with angina pectoris due to CAD (13). A previous study demonstrated that CCTA led to the appropriate selection of patients for ICA, resulting in lower normal ICA rates and higher obstructive CAD rates. They showed that coronary revascularization was high in patients for whom CCTA had changed the initial diagnosis and identified the presence of obstructive CAD (13).

Many studies have shown the significant ability of CCTA to exclude CAD (3, 5, 7, 14). A prospective multicenter

trial (PROMISE) demonstrated that the use of CCTA leads to reductions in normal ICA rates (15). A previous multicenter study evaluated the diagnostic accuracy of 64-multidetector CCTA, which is a highly effective noninvasive alternative method to ICA for excluding significant CAD (3). Diagnostic sensitivity and NPV were higher than for other noninvasive imaging modalities (3). In another multicenter study (the CORE 64 study), the sensitivity and specificity of CCTA were 85% and 90%, respectively, according to a per-patient analysis. The PPV and NPV was 91%, and 83%, respectively (5).

Previous studies have reported that CCTA has the greatest potential benefit for intermediate-risk patients with chest pain or acute coronary syndrome (16).

CCTA clearly provides high accuracy for detecting obstructive CAD, and the high NPV determines CCTA as an effective non-invasive imaging procedure to exclude significant CAD in all risk groups, including stable symptomatic patients and those with acute coronary syndrome (17-20). A previous study showed that up to 80% of ICAs can be avoided for patients with a low prevalence of CAD, since CCTA can effectively determine the need for ICA (21-23).

Consistent with previous results, our study found that CCTA provides a valuable NPV and a high PPV for determining or excluding significant CAD. The high NPV and PPV for coronary artery stenosis make CCTA crucial for evaluating patients with suspected obstructive CAD. However, Ramjattan et al have reported that CCTA was more sensitive for assessing the proximal and large coronary artery segments, consistent with our study results (24). We found that CCTA had high sensitivity for segments 5, 6, 7, 11, and 15 which are proximal coronary artery segments according to AHA 15-segment model (9). The motion artifacts, insufficient resolution, and a small vessel diameter ≤2 mm can be the major limitations of CCTA technique (25). Therefore, segments 4, 10, and 14 were excluded from this study due to the anatomical variations, poor image quality, and being non-evaluable with a luminal diameter <2 mm, as described previously.

CCTA reveals luminal stenosis, coronary arterial wall abnormalities, and atherosclerotic plaques. Such plaques may not be observed during ICA due to the compensatory expansion of the coronary arteries unless the intravascular ultrasound technique is used (26). However, the main cause of acute coronary syndromes is generally the rupture of plaque rather than luminal stenosis. Coronary artery calcification indicates atherosclerotic plaques in the coronary arteries and correlates strongly with the total coronary atherosclerotic plaque burden and coronary artery stenosis. Therefore, CAC measurement using CCTA is important for the early detection of CAD, which requires preventive strategies. Preventive therapies such as aspirin or statin and lifestyle modification can be prescribed for severe CCTA-identified CAD (27-29).

In this regard, we analyzed the relationship between CAC scores and significant CAD using ICA for two cut-off values. The patients with higher CAC scores had a higher incidence of significant CAD on ICA. Additionally, CAC scores were found to be an independent predictor of significant ICA-identified CAD in our multivariate regression model.

Furthermore, in our study, we found a significant correlation between CAC values and SCORE values. Risk scores are highly important for assessing cardiovascular morbidity or mortality risk in individuals. For this purpose, the risk factors for atherosclerotic cardiovascular diseases may be modified by lifestyle changes, and the assessment of risk scores can support appropriate medical treatment. Risk stratification using conventional risk calculators can improve prognosis evaluation. SCORE risk scores evaluate the risk of atherosclerotic cardiovascular mortality within 10 years and can be used to determine appropriate medical interventions and to improve prognosis. Sonya et al found that the severity of coronary stenosis is associated with SCORE risk scores (8). Similar to their results, we showed that higher SCORE risk scores were associated with a higher incidence of significant CAD. Therefore, the results of risk score calculators can be used to perform the more appropriate medical therapy for treating the patients.

However, clinical risk scores have a limited ability to stratify global cardiovascular risk when used alone (1). CAC measurements may help patients' clinical management for cardiovascular diseases. Also, some studies showed a correlation between CAC scores and cardiac death (7, 8). In our study, we found that CAC scores combined with SCORE risk scores and age significantly predicted mortality within 10 years of follow-up in the ROC analysis. We suggest that adding CAC scores to clinical risk scores can provide better prognostic information than cardiovascular risk scores alone.

In the present study, we determined all-cause mortality at a median of 10 years of follow-up as a long-term prognostic outcome. According to Kaplan–Meier survival analysis, the survival rate for 10-year mortality was 0.87. In our Cox regression model, age was the only independent predictor of all-cause mortality among variables such as male gender and CAC and SCORE risk scores. This result may be explained by the small number of patients who died in our cohort (n=6) during the median 10 years of follow-up.

CCTA, as a readily applicable noninvasive method, may change diagnostic measures for symptomatic patients with suspected CAD before ICA procedures. Thus, CCTA can direct physicians in the effective utilization of ICA for

stable symptomatic patients. Moreover, detection of calcific atherosclerotic plaques using CAC scores and adding risk score calculations, particularly for elderly patients, may provide important clues to long-term mortality and facilitate early-stage preventive strategies.

Study limitations

This study has some limitations. Firstly, it is a single-center study with a retrospective design, and it has a small sample size. Secondly, the study was conducted with a 64-multidetector CCTA. If it had been performed with new-generation multidetector row CCTA technology, we would have obtained more valid results. Finally, we did not use the "SCORE 2 risk prediction model" according to the new ESC Prevention Guidelines. Use of the earlier SCORE risk algorithm is another limitation of this study. The study findings should be supported by prospective investigations with larger sample sizes.

CONCLUSION

In conclusion, CCTA has high diagnostic accuracy for identifying or excluding significant CAD and facilitates the appropriate selection of patients for ICA. As determined by previous studies, CCTA may reduce coronary events and change the application of coronary revascularization. Moreover, CAC measurements and SCORE risk scores may provide valuable prognostic information for predicting long-term mortality and, therefore, may support patients' clinical management and improve the prescription of preventive therapies.

Ethics Committee Approval: This study was approved by the ethics committee of Istanbul University, Istanbul Faculty of Medicine ((Date: 16.08.2013, No: 2013/1086).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.B., M.D., F.E.; Data Acquisition- E.A.G, Z.G.D, E.B.K; Data Analysis/Interpretation- E.A.G., D.B., F.E.; Drafting Manuscript- E.A.G., D.B., E.B.K; Critical Revision of Manuscript- A.E., D.B., F.E; Approval and Accountability: A.E., M.D., A.E.; Material and Technical Support- E.A.G., Z.G.D.; Supervision- F.E., A.E., M.D.

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