JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2024; 8: 626-633
https://doi.org/10.30621/jbachs.1463098
RESEARCH ARTICLE

CAROTIS INTIMA-MEDIA THICKNESS, CORONARY CALCIUM SCORE AT DIFFERENT STAGES OF CORONARY ARTERY DISEASE

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Received: 04.05.2024; **Accepted:** 17.09.2024; **Available Online Date:** 30.09.2024

Cite this article as: Okan T, Doruk M, Ozturk A, Topaloglu C, Yilmaz BY. Evaluation of the Predictive Values of Carotid Intima-Media Thickness and Coronary Calcium Score for Different Stages of Coronary Artery Disease. J Basic Clin Health Sci 2024; 8: 626-633.

ABSTRACT

Purpose: Coronary Artery Calcium Score (CACS) and Carotid Artery Intima-Media Thickness (CIMT) are surrogate markers for atherosclerosis. CACS is a recognized indicator of coronary artery disease (CAD), but CIMT's role in CAD diagnosis is debated. This study aimed to assess how well CIMT and CACS predict CAD presence and severity as detected by coronary computed tomography angiography (CCTA).

Materials and Methods: In the study, 88 participants (57 CAD and 31 controls) underwent coronary angiography and CACS calculation using computerized tomography and CIMT measured according to the guidelines. Patients with CAD were classified by CACT results and further subdivided by CACS into three groups: Group I (<100), Group II (100-300), and Group III (≥300). The relationship between CIMT and CAD groups with zero Agatston scores, as well as the control group, was also examined.

Results: The CACS had 82% sensitivity and 100% specificity for predicting CAD, excluding CAD with 75.6% specificity. A CIMT max cut-off of ≥0.78 mm showed 76% sensitivity and 54% specificity for CAD. A CIMT max cut-off of ≥1.03 mm had 93% specificity but only 35% sensitivity, while ≤0.59 mm excluded CAD with 96% specificity but just 10% sensitivity. Patients with CIMT levels between 0.59 mm and 1.03 mm may need further testing to assess CAD risk accurately.

Conclusion: The CACS is more sensitive than CIMT in predicting CAD, and CIMT is not helpful when the CACS is zero. Determining an optimal CIMT cutoff for CAD prediction is challenging, and patients with CIMT between 0.59 mm and 1.03 mm may require additional testing.

Keywords: Carotis intima media thickness, coronary artery disease, coronary artery calcium score, agatston score

INTRODUCTION

Cardiovascular disease (CVD) represents the most prevalent cause of mortality and morbidity, with low- and middle-income countries bearing the majority of the associated burden. Amongst the various forms of CVD, ischaemic heart disease represents the primary cause of mortality, accounting for 38% of CVD-related deaths in women and 44% in men (1).

It is estimated that approximately half of all deaths related to CVD occur in individuals without a prior history of heart disease. This highlights the necessity of accurately assessing an individual's risk in the absence of symptoms to prevent these fatalities (2). The combined thickness of the intimal and medial layers of the carotid artery is determined through a test known as carotid intima-media thickness (CIMT), which serves to indicate the presence of widespread atherosclerosis (3). CIMT is typically quantified by measuring the distance between the echogenic media-adventitia layer and the echogenic lumen-intima layer using B-mode ultrasound images (4). It is regarded as a marker for forecasting the initial stages of atherosclerosis prior to a history of CVD. CIMT is linked to cardiovascular events and outcomes (5). CIMT serves as an indirect marker of coronary atherosclerotic burden. A number of clinical studies have demonstrated the relationship between CIMT and the occurrence, degree and extent of coronary artery disease (CAD) (6, 7).

Coronary computed tomography angiography (CCTA) is a non-invasive imaging technique that has been demonstrated to have high sensitivity for the identification of coronary artery disease (CAD). The indications for the use of CCTA as a Class I upgrade (8) in the diagnostic work-up of patients with stable symptoms and a low to intermediate risk for obstructive CAD have recently seen a significant increase in utilisation. The primary methodology employed in numerous investigations examining the correlation between carotid CIMT and CAD is invasive coronary angiography (ICA). These studies typically utilise lumenographic criteria and involve individuals with high-risk CAD. However, recent research suggests that, with regard to measuring atherosclerotic burden, CCTA is more accurate than ICA (9, 10).

In most of the studies investigating the relationship between CIMT and CAD, the extent of CAD was determined by ICA. In these studies, the CAD group typically consisted of individuals diagnosed with more than 50% coronary artery stenosis, whereas the control group consisted of individuals with less than 50% stenosis. However, it is important to note that patients with less than 50% stenosis and no luminal narrowing due to eccentric plaques with atherosclerosis may not fully represent a normal group without coronary atherosclerosis, especially in studies using ICA lumenographic criteria (6, 11, 12). The inclusion of patients with atherosclerosis in the control groups of these previous studies makes the interpretation of CAD prediction data unreliable. Furthermore, the determination of CAD severity by ICA is a methodology that needs to be questioned, as it does not take into account the presence of eccentric plaques that do not result in significant intraluminal plaque burden (9, 10, 13, 14).

In the present study, we used CCTA to investigate the association between CIMT, CACS, and CAD. This method provided more accurate data than ICA, allowing us to differentiate between patients with CAD and those with normal coronary arteries. The aim of the study was to assess the relationship between CIMT, CACS, and atherosclerosis in two groups: individuals with normal coronary arteries, as confirmed by CCTA, and patients with CAD identified by CCTA, who presented with soft, calcific, or mixed plaques at various stages of atherosclerosis, with differing Agatston scores and severity.

MATERIALS AND METHODS

A cohort of 128 consecutive patients with symptomatic chest pain was prospectively evaluated using carotid ultrasonography to assess CIMT and CCTA between September 2023 and January 2024. From this cohort, we excluded individuals with a history of known CAD (n=18), established non-ischemic cardiac conditions (n=16), contraindications to contrast media (n=1), impaired renal function defined as a creatinine clearance rate < 60 ml/min (n=2), and cardiac arrhythmias (n=3).

All participants underwent carotid ultrasonography and CCTA on the same day. The study excluded pregnant women, individuals with atrial fibrillation or age below 35, those using statins, individuals with renal dysfunction, and those with known coronary or peripheral artery disease

Of the 128 participants, 88 were included in this study. Among them, 31 participants with normal coronary arteries and an Agatston score of "0" constituted the control group, while 57 participants with coronary atherosclerosis of varying severity and calcification levels constituted the CAD group.

Demographic data such as sex, age, height, weight, and blood pressure were collected for all patients. In addition, clinical and laboratory data were also collected with patient consent, which includes information on diabetes mellitus (DM) medication,

smoking history, hyperlipidemia, family history of CAD, and levels of glycated hemoglobin (HbA1c), lipid profile, and creatinine. The study protocol was approved by the Ethical Committee of Bakırcay University, written informed consent was obtained from all patients.

CIMT Measurements

CIMT images were obtained by an experienced radiologist using high-resolution carotid ultrasound with a linear transducer (>7.5 MHz) at the same radiology centre where CCTA was performed. Following standard protocols, longitudinal B-mode images of the left and right carotid arteries were acquired to assess each common carotid artery (CCA). The mean and maximum CCA intima-media thickness (IMT) was measured within a 10 mm segment proximal to the carotid bulb. These measurements were performed using automated IMT measurement software on a Hitachi Arietta 850 ultrasound machine, and the assessments were independently verified by both an experienced radiologist and a cardiologist.

Computed Coronary Angiography

A 128-slice single-source computed tomography (CT) scanner (Somatom Go Top; Siemens Healthcare, Forchheim, Germany) was used to perform CCTA in all patients. The Agatston score was used to measure the CACS on the same CT scanner. CCTA was independently interpreted by an experienced radiologist and cardiologist. The patients were then divided into three groups based on their Agatston scores. Group I patients had a slightly increased risk, group II patients had a moderately increased risk, and group III patients had a moderate-to-severe increased risk. The Agatston scores of the patients fell between 0 and 99, between 100 and 299, and above 299, respectively. This classification system has been previously reported in the literature (2,15).

Statistical Analysis

A power analysis was conducted using G*Power 3.0.10 for Windows, with an α value of 0.05 and a study power of 0.90.

The statistical analysis was conducted using IBM SPSS Statistics, version 29 (IBM Corp., NY, USA). A Student's t-test was employed to ascertain whether there were any significant differences in the means of continuous numeric variables between the groups in question. A chi-square test was employed for the comparison of categorical variables. The Mann-Whitney U test was employed to assess the existence of statistically significant differences in CACS and CIMT levels between the two groups. In instances where there were more than two groups, the Kruskal-Wallis test was employed, followed by a post-hoc analysis with Bonferroni adjustment for multiple comparisons. A receiver operating characteristic (ROC) analysis was employed to calculate the area under the curve (AUC) and 95% confidence intervals for the purpose of evaluating the predictive value of CIMT for the presence and severity of CAD. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

There were no discernible variations in age, sex, body mass index (BMI), or smoking status between the CAD and control groups. Lipid profiles, blood pressure during both systolic and diastolic phases, and blood glucose and creatinine levels were also comparable (Table I). The study demonstrated a statistically significant relationship between the CACS of the patient group and the mean and maximum CIMT values of the right and left CCA. In particular, compared with low- and intermediate-risk patients (Group I and Group II), patients classified as high-risk with a CACS (Agatston score) higher than 300 (Group III) showed significantly higher CIMT values. Table II presents an overview of this relationship. According to the CACS, this study points to a possible link between elevated CIMT levels and an increased risk of coronary artery disease. In patients with a substantial CACS, high CIMT readings may be indicative of a higher cardiovascular risk.

Notably, Table III shows that there was no statistically significant difference in the CIMT values of patients with CAD who did not have CAC (Agatston=0) compared to the control group who had normal coronary arteries. Of the left and right CCA IMT readings.

In the study, CACS had 82% sensitivity and 100% specificity in predicting CAD, while also excluding CAD with 75.6% specificity.

The highest value (CIMT max) of the CIMT measurements showed the strongest statistically significant correlation for predicting the presence of CAD. Regarding CIMT Max Max value, a cut-off of 0.78 mm was identified as the most suitable for CAD

prediction, offering 76% sensitivity and 54% specificity. Alternatively, accepting a CIMT Max Max cut-off of ≥ 1.03 mm yielded 93% specificity but reduced the sensitivity to 35%. Conversely, a CIMT Max Max ≤ 0.59 cut-off enabled CAD exclusion with 96% specificity but decreased sensitivity to 10%. The study suggests that patients with CIMT Max Max levels between 0.59 mm and 1.03 mm may require additional diagnostic testing to accurately assess CAD risk. ROC curve analysis was used to determine the cutoff value of CIMT for CAD prediction (Figure 1).

DISCUSSION

In this study, we examined how well carotid CIMT and CACS predict the existence and severity of CAD detected by CCTA. Our research verified a correlation between CIMT, CACS, and the degree of CAD, as determined by CCTA. Similar to our findings, Pathokata et al. discovered a high association between CACS and CIMT and the severity of CAD, as determined by Gensini and SYNTAX Scores (16).

The CACS, which measures calcium deposits on arterial walls, is a crucial imaging biomarker for

Table 1. Baseline characteristics of study groups

	Coronary Artery Disease (n: 57)	Control (n: 31)	p
Female %	%31.5 (n: 18)	%35.4 (n: 11)	0.330
Age (years)	57.01±7.49	58.03±6.92	0.535
BMI (kg/m²)	27.43±3.23	27.07±3.88	0.640
Glucose (mg/dL)	110.75±38.62	99.76±37.80	0.209
Cholesterol (mg/dL)	224.21±49.69	235.48±41.77	0.286
LDL (mg/dL)	140.64±44.84	151.38±40.09	0.269
HDL (mg/dL)	53.36±10.55	54.45±17.18	0.891
Triglyserides (mg/dL)	196.33±118.53	149.09±86.36	0.054
Creatinin (mg/dL)	0.86±0.19	0.78±0.16	0.051
Smoking %	35.08%	29.03%	0.354
Diabetes Mellitus %	26.32%	22.58%	0.469
Systolic BP (mmHg)	134.50±17.81	131.32±12.80	0.514
Diastolic BP (mmHg)	78.96±11.67	77.38±8.96	0.514

Table 2. Statistical relationship between CAD groups based on CACS (Agatston score) and CIMT

	Group I Agatston<100 (n: 29)	Group II 100<Agatston<300 (n:12)	Group III Agatston≥300 (n: 16)	p#	p##	p###	p
CIMT (Mean Right) mm	0.65±0.23	0.64±0.15	0.84±0.30	0.986	0.001	0.001	0.005
CIMT (Max Right) mm	0.80±0.27	0.84±0.19	1.08±0.37	0.829	0.001	0.032	0.007
CIMT (Mean Left) mm	0.65±0.14	0.68±0.14	0.84±0.29	0.843	0.001	0.072	0.043
CIMT (Max Left) mm	0.85±0.18	0.87±0.18	1.13±0.39	0.780	0.001	0.018	0.026
CIMT (Max Mean) mm	0.70±0.21	0.72±0.11	0.94±0.36	0.811	0.001	0.048	0.020
CIMT (Max Max) mm	0.89±0.18	0.95±0.17	1.24±0.43	0.837	0.001	0.029	0.012

CIMT Max Max: The highest CIMT value of both carotid arteries, CIMT Max Mean: The highest mean CIMT values of both carotid arteries, p#: p value for Group I and Group II, p##: p value for Group I and Group III, p###: p value for Group II and Group III, p: comparison p value for three groups

Table 3: Comparison of CIMT between CAD group with zero Agatston value and normal coronary artery group

	Coronary Artery Disease with Agatston: 0 (n: 10)	Control group (n: 31)	p
IMT (Mean Right) mm	0.64 ± 0.25	0.60±0.10	0.747
IMT (Max Right) mm	0.78±0.26	0.73±0.13	0.925
IMT (Mean Left) mm	0.67±0.19	0.62±0.10	0.787
IMT (Max Left) mm	0.84±0.19	0.79±0.13	0.735
IMT Max Mean mm	0.70±0.22	0.64±0.11	0.791
IMT Max Max mm	0.90±0.20	0.80±0.15	0.276

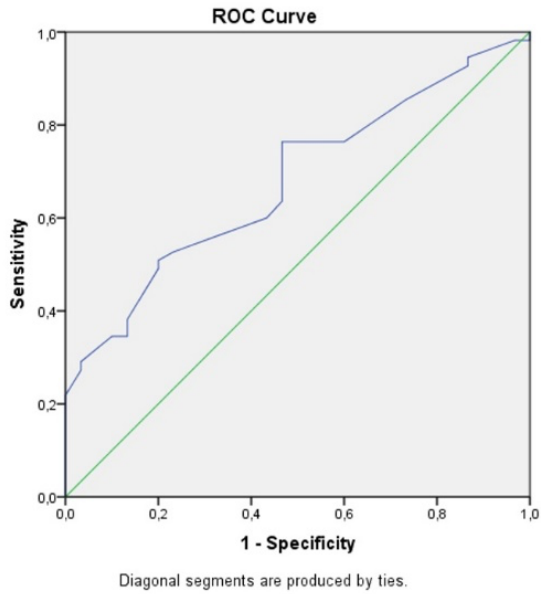

Figure 1. The cutoff value of CIMT for CAD prediction

heart health. Low-dose radiation (<1 mSv) scans without contrast enhancement are frequently used for evaluate it (9). Microcalcifications, a characteristic of susceptible (high-risk) plaques and indicator of active inflammation, are the form in which CACS is found in the early stages of atherosclerosis (17). On the other hand, the Agatston score, also known as the CACS, quantifies the extent of coronary calcium deposition typically observed in the later stages of atherosclerosis and associated with a stable plaque phenotype. Although CACS is an effective marker of total atherosclerotic plaque burden, it has a weak correlation with the degree of luminal stenosis. While there has been debate as to whether coronary artery calcium reflects plaque stability, the current consensus is that a high CACS identifies a vulnerable patient rather than indicating unstable plaques or vessels. An elevated calcium score is associated with an increased risk of major adverse cardiac events (MACE). One study demonstrated that a two-fold increase in the calcium score was associated with a 15 to 35% increased risk of major coronary events and a 18 to 39% increased risk of any coronary event (5,18,19). CACS is currently recommended for low- and intermediate-risk asymptomatic patients as IIb in the ESC guidelines and IIa in the ACC/AHA guidelines. (9).

In line with earlier research, we did not find a significant correlation between the CACS and the degree of coronary artery stenosis in our investigation. This phenomenon may be attributed to the existence of calcified deposits exhibiting minimal calcification but significant luminal narrowing, or alternatively, to the presence of dense calcifications with eccentric localization that do not result in notable luminal narrowing (2,18,19). A false-negative rate of 18% for CAD was observed in 10 patients with non-calcific soft plaques not detected by CACS among the 57 CAD patients in our study. The presence of calcium deposition in the coronary artery wall signifies permanent structural alterations that culminate in plaque stability of plaque (18,19). In contrast, theoretically soft, non-calcified plaques are more likely to rupture (vulnerable plaques). It is unfortunate that CACS is unable to identify non-calcified plaques and cannot always reliably rule out the possibility of a coronary event (20,22).

As CACS is unable to predict the disease in the CAD group with a CACS of zero, CIMT determination may prove to be a valuable diagnostic method for predicting the development of CAD. However, when our study analysed patients with a CACS value of zero, no statistically significant difference was found between the mean and maximum CIMT values of both carotid arteries in the CAD group and the non-CAD control groups.

In their study, Lester and colleagues examined 89 patients, aged between 36 and 59 years, with a CACS of zero. In their study, 47% of patients exhibited a calcium score of zero, indicative of coronary atherosclerosis based on CIMT. The authors proposed that while CIMT and CACS are both markers of subclinical atherosclerosis, CAC typically manifests later in the course of CAD. Consequently, the reliability of this method may be questionable, particularly in younger individuals with a CACS of zero. In this demographic, CIMT may offer a more valuable insight into the presence of CAD (23). It is possible that other factors may contribute to the inconsistencies observed in the predictive efficacy of CIMT in patients with non-calcified soft plaques. One potential explanation for this discrepancy is that the CAD group with a CACS of zero in our patient cohort was older than the patient group in the Lester et al. trial. Additionally, it is conceivable that the sample size was inadequate to yield definitive conclusions. Our findings suggest that CIMT measurement is an ineffective diagnostic technique, similar to CACS, in the early stages of

atherosclerosis. However, some studies have reported that it is an effective method for predicting CAD with soft, non-calcific plaques, the initial phase of coronary atherosclerosis, and that it allows the prediction of early CAD characterised by the presence of soft, non-calcific vulnerable plaques, especially in young patients (23–25). Similarly, Dokumaci et al. reached the same conclusion (26). The mean and maximum values of CIMT for both carotid arteries were significantly higher in the group with an Agatston score of 300 and above, as well as in the group exhibiting the most severe and extensive atherosclerosis, compared to patients with atherosclerosis scoring below 300, according to our study, which showed that CAD patients were divided into three groups based on the Agatston score. This outcome is in line with the higher CIMT associated with CACS on CCTA (12, 27,28).

In our study, the inability of CIMT to predict patients with zero CAD or a lower CACS level in the early atherosclerosis stage may be compensated for by its capacity to predict patients with an Agatston score above 300 who are at high risk of MACE. This may render CIMT a valuable tool in the identification of high-risk CAD patients for risk stratification, although not as a diagnostic method (19,29,30).

The diagnostic utility of CIMT for CAD has been a topic of considerable debate. The increased CIMT observed in the carotid artery has been linked to coronary artery disease (CAD) in several studies conducted over the past few decades. However, this relationship has not been confirmed by other investigations (31-34). In their evaluation of the correlation between CIMT and the severity of CAD, Lisowska et al. reported a diagnostic sensitivity of 91% and a specificity of 65% (36). In accordance with the findings of another study, CIMT is an effective method for excluding severe CAD in patients undergoing cardiac valve surgery. A study found that CIMT had 100% sensitivity and 50% specificity for diagnosing CAD (37). As demonstrated by Kanadasi et al., the specificity and diagnostic sensitivity were 86.4% and 14.3%, respectively (33). The CIMT cutoff value was 1 mm, with an associated sensitivity and specificity of 31.91% and 90.52%, respectively, according to the findings of Zhang et al. (38). The ESC guidelines do not recommend carotid ultrasound IMT for cardiovascular risk assessment (Class III). The results of our study support this recommendation. Specifically, the inability to determine an effective and reliable cut-off value for CIMT in CAD prediction, and the observation that CIMT values with high specificity for CAD exhibit very low sensitivity for the disease, corroborate the guidelines (8).

Limitations

The present study is limited by the relatively small size of the cohort and the fact that the findings represent a single-centre experience. Consequently, external validation is required. However, this pilot study has the potential to initiate a new line of research that could lead to more comprehensive studies in the future.

CONCLUSION

The degree and severity of CAD on CCTA can be predicted using both the CACS and CIMT measures; however, the CACS has a higher sensitivity. In patients with a calcium score of zero, CIMT is not as useful in predicting CAD as CACS. Predicting CAD is difficult when CIMT measurements need to be set at the ideal cut-off value. More diagnostic testing is required to accurately predict CAD in patients with CIMT levels between 0.59 mm and 1.03 mm, more diagnostic testing is required.

Acknowledgments: None.
Author contribution: In this article, both authors worked together to analyze the literature and write the article.
Conflict of interests: There is no conflict of interest between the authors.
Ethical approval: The study was approved by Izmir Bakircay University Non-Interventional Clinical Research Ethics Committee (Date: 24.08.2023, Decision No: 1154).
Funding: None.
Peer-review: Externally peer-reviewed.

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