

Coronary Artery Calcium Score (CCS) and Framingham Risk Score (FRS) in Symptomatic Indian Population-Any Correlation with Coronary Artery Disease (CAD) Severity?

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ABSTRACT

Introduction: Coronary Artery Disease (CAD) is the most important reason of morbidity and mortality worldwide. Measurement of coronary calcification with the help of CT-based Coronary Calcium Score (CCS) is a considerable indicator of coronary atherosclerosis and correlates well with the risk for future cardiovascular events.

Aim: To evaluate the relationship between CCS and the presence of significant CAD in low to intermediate risk in Indian subjects with cardiac chest pain undergoing CT Coronary Angiography (CTCA). In addition, we sought to identify the additive value of the CCS to the traditional Framingham Risk Score (FRS) in an Indian population.

Materials and Methods: Multi-centric prospective study was conducted in subjects referred for CTCA due to cardiac chest pain. Patients were excluded if they had Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angiography (PTCA), previous myocardial infarction and other

CTCA contraindications. Scans were performed on a 128-slice MDCT with contemporary protocols. CCS and CAD severity were classified as per Society of Cardiovascular Computed Tomography (SCCT) guidelines. Significant CAD (>70% stenosis of epi-cardial coronary artery or >50% of left main coronary artery). FRS was calculated to predict long term risk of CAD.

Results: We enrolled a total of 306 subjects (52±9 years; 59% males). The mean CCS was 79±10 AU. Significant CAD was present in 44 of the 99 subjects (44%) with a CCS=0 who were classified as low risk by FRS and 16 of 20 subjects (80%) who had an intermediate risk FRS and a CCS=0 AU had significant CAD on CTCA. There was no correlation between FRS and presence of significant CAD.

Conclusion: Unlike Western countries, low CCS have poor correlation with absence of CAD in this population, whereas in the present study there was no relation between FRS and presence of CAD.

Keywords: Atherosclerosis, Coronary calcification, Stenosis

INTRODUCTION

CAD is the leading cause of morbidity and mortality worldwide. Indian population has the highest number of people with CAD [1], with onset of CAD at least one decade earlier and a severity that is twice that of Western populations [2]. Largely attributed to increased genetic predisposition, mutations in apolipoprotein, hyperhomocysteinemia, sedentary lifestyle, and a higher prevalence of diabetes, hypertension, dyslipidaemia, and abdominal obesity [3].

Measurement of coronary calcification using the CT-based CCS is an important marker of coronary atherosclerosis and correlates well with the risk for future cardiovascular events. In asymptomatic patients, a score of 0 AU represents a low future risk of coronary events, whereas a score >400 AU indicates a high risk [4]. In a retrospective study, asymptomatic and symptomatic patients undergoing CT Coronary Angiography (CTCA) for evaluation of suspected CAD and a CCS=0 AU, the prevalence of significant CAD is only 5% (good negative predictive value) [5].

However, these data have been derived from Western populations and asymptomatic Indian populations, and our clinical experience suggests that the negative predictive value of a zero calcium score may be of less value in a symptomatic Indian population undergoing CTCA to "rule out" significant CAD (>70% stenosis of epicardial coronary artery or >50% stenosis of left main coronary artery).

The purpose of this study was to evaluate the relationship between CCS and the presence of significant CAD in low to intermediate risk in Indian subjects with cardiac chest pain undergoing CTCA. In addition, we sought to identify the additive value of the CCS to the traditional FRS in an Indian population.

MATERIALS AND METHODS

A prospective study was conducted at two large tertiary hospitals in India from March 2015 to June 2017, with referral populations covering a wide geographic diversity. A total of 306 subjects were enrolled, aged between 18-75 years and were referred for CTCA due to cardiac chest pain. Subjects were excluded if they had known CAD (including CABG, PTCA, or previous myocardial infarction), were referred for pre-operative evaluation, or contraindications to CTCA. The study was approved by the Ethics Committee-Reference number: SSSIHMS (WF) HR/15/1547. All subjects gave written informed consent.

CTCA Acquisition: CTCA studies were performed on a 128-slice MDCT scanner (GE Healthcare, Milwaukee, Wisconsin USA) with motion correction software to reduce motion artefact, i.e., Snap Shot Freeze. Effective temporal resolution of 29msec; Equivalent gantry rotation of 0.05 sec with highest spatial resolution of 18.2lp/cm²; Slice thickness was 0.6 mm.

Oral and intravenous metoprolol, oral ivabradine, and sublingual nitro-glycerine were given prior to the scan to reduce heart rate and optimize image quality.

For the CCS, non-enhanced ECG gated CT images were acquired from the carina to the diaphragm and the images were post processed offline in AW workstation and CCS for each coronary artery and combined calcium scoring was done based on the area-density method using the Smart Score software.

For the contrast enhanced scan, Low osmolar contrast medium (Contrapaque, JB Chemicals and Pharmaceuticals Ltd., Mumbai) at a dose of 1 ml/kg was injected at a rate of 5-5.5 ml/sec, followed

by a normal saline wash out of 30 ml at the same rate. Either prospectively triggered axial (sequential) scanning or retrospectively gated helical scanning was used, based on patient heart rate.

In subjects in whom the calcium score detected significant calcium (generally >400 AU), Gemstone Spectral Imaging (GSI) mode was used to minimize the effects of calcium blooming and/or streak artefacts. Gemstone Spectral Imaging (GSI) uses rapid kV switching and GSI. A 0.25msec ultrafast kV switching was used with iterative reconstruction which has proved to reduce 82% of radiation dose. GSI uses prospective gating and is found to deliver less than 1 mSV dose.

To reduce radiation dose, scan range were minimized, prospective gating and tube modulation were used whenever possible, auto mA option was used to minimize tube current, and optimal tube voltage were selected based on subject size. Average radiation dose for prospective study was 1-3 mSV and for retrospective study was 8-10 mSV.

Image Analysis: Images were reviewed by blinded observers on a dedicated CT workstation with advanced cardiac analysis software (GE AW version 4.6, GE Healthcare, Milwaukee, USA) by 2 observers of 14 years and 5 years experience respectively and who were blinded to the subjects' clinical status. Cardiac motion correction software (Snap Shot Freeze, GE Healthcare, and Milwaukee, USA) was applied to reduce cardiac motion artefact. CCS quantified based on the area-density method. For CTCA data, a combination of axial source images, maximum intensity projections, curved and straight multi-planar reformation, and volume rendered images were used for analysis as appropriate. Stenosis severity were graded semi-quantitatively as minimal (<25% diameter stenosis), mild (26-50%), moderate (51-69%), and severe (\geq 70%). Significant CAD by CTCA was defined as severe (>70% diameter) stenosis of an epicardial coronary artery or more than 50% stenosis of the LMCA (left main coronary artery). Scans were acquired, post-processed, and reported in accordance with guidelines of the Society for Cardiovascular Computed Tomography (SCCT) [6-10].

Framingham Risk Score: FRS is a sex-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. For every patient enrolled in the study fasting glucose and lipid profile was obtained. History of ex-smoking and present smoking, whether a known hypertensive with or without medication was obtained. FRS was calculated separately for males and females respectively and an assessment of 10 year cardiovascular risk of every patient was obtained. Subjects were classified as low risk (<10% risk of an event within 10 years), intermediate risk (\geq 10 and \leq 20% risk of an event within 10 years), or high risk (>20% risk of an event within 10 years) [11-13].

STATISTICAL ANALYSIS

Data was analysed using IBM SPSS Statistics, Version 22 (IBM Corporation, Armonk, New York USA). Descriptive data were presented in the form of frequency, percentage, mean, median, standard deviation and quantiles. Presence or absence of coronary artery stenosis was assessed and categorised as >50% and >70% stenosis. Comparisons of the categorical variables between the two groups were performed using the chi-square test. Receiver Operating Characteristic (ROC) curve analysis was done to evaluate the correlation of CCS and severity of CAD. The area under the ROC curve was calculated to summarize the CCS with >50% stenosis and CCS with >70% stenosis. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy with CCS with >50% stenosis and CCS with >70% stenosis was assessed using the cut-off value obtained with minimum C1 error from the ROC analysis. The p-value < 0.05 was considered as statistically significant. Framingham score were categorised as low, intermediate and high risk categories and each one was calculated separately in male and female study population and assessment of presence or absence of severity of stenosis was done in each category.

RESULTS

We enrolled 306 subjects (mean age 52 \pm 9 years, 59% males). Of these, 35% had diabetes, 47% had hypertension, 18% had dyslipidaemia, and 15% were obese. A total of 5508 coronary artery segments were evaluated by CTCA. Of these, 6% (n=330) were not evaluable due to either respiratory and/or cardiac motion, 3% (n=165) were not well seen due to small size; and 6% (n=330) not evaluated due to dense calcified plaques (>400 AU). A total of 4683 (85%) of coronary artery segments were available for evaluation and included in the study. Complete demographic details of the study population are available in [Table/Fig-1].

Demographic data	Overall population	CAD absent	CAD present	p-value
Age <50	130 (42%)	60 (46%)	70 (54%)	0.57
Age \geq 50	176 (58%)	87 (49%)	89 (51%)	0.57
Male	180 (59%)	70 (39%)	110 (61%)	<0.001*
Female	126 (41%)	77 (61%)	49 (39%)	<0.001*
Diabetes	106 (35%)	37 (35%)	69 (65%)	0.001*
Hypertension	143 (47%)	58 (41%)	85 (59%)	0.01*
Dyslipidaemia	55 (18%)	14 (26%)	41 (74%)	<0.001*
Obesity	47 (15%)	14 (30%)	33 (70%)	0.006*
Smoking	37 (12%)	15 (41%)	22 (59%)	0.33(NS)*
Family history of CAD	16 (5%)	6 (38%)	10 (62%)	0.39(NS)*
Known previous vascular disease	8 (3%)	1 (13%)	7 (87%)	0.07(NS)*

[Table/Fig-1]: Significant CAD present on CCTA in males and females and with various risk factors.

*Fishers-exact test; *p<0.05 statistically significant; p>0.05 NS: Non-Significant

CCS and Significant CAD: In the overall study population, 40% subjects had CCS=0, 38% subjects had CCS=1-100 and 22% subjects had CCS >100. Overall, 48% (n=147) of subjects had no CAD and 52% subjects had significant CAD. Among the subjects who had CCS = 0 AU (n=121), 25% (n=30) had significant CAD on CTCA, who had a CCS 1-100 AU (n=117), 65% (n=76) had significant CAD on CTCA [Table/Fig-2]. The odds ratio of significant CAD for CCS \geq 1 AU was 8.23 (95% confidence interval (4.93, 13.74), p <0.001) [Table/Fig-3].

	CCS	CAD absent	CAD present	Overall population	p-value
Calcium	0	91	30	121	<0.001*
		75%	25%	100%	
	1-100	41	76	117	
		35%	65%	100%	
	>100-<400	14	43	57	
		25%	75%	100%	
	>400	1	10	11	
		9%	91%	100%	

[Table/Fig-2]: Incidence of significant CAD with CCS.

CALCIUM	CAD		Total	Chi-square test	
	Absent	Present		Chi-square value	p-value
<8.5	107 (73%)	39 (27%)	146	71.31	<0.001*
>8.5	40 (25%)	120 (75%)	160		
Total	147 (48%)	159 (52%)	306		
Odds ratio (95% CI)	8.23 (4.93,13.74)				

[Table/Fig-3]: Distribution of subjects with and without significant CAD according to calcium score.

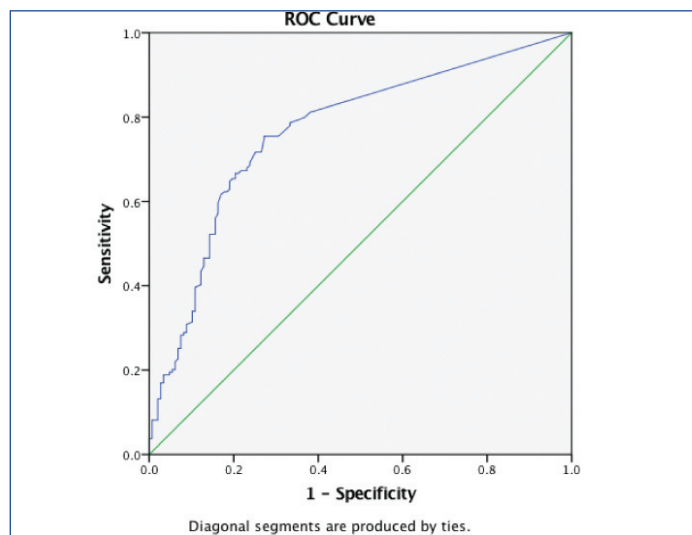
*p<0.05 statistically significant; p>0.05 Non-Significant; NS

CCS alone had moderate diagnostic accuracy for the detection of significant CAD, with a sensitivity of 76% and specificity of 73%, negative predictive value was 56% [Table/Fig-4]. On ROC analysis, the relationship between CCS and significant CAD was moderate ($R=0.77$, [Table/Fig-5]). Increasing CCS was associated with increasing extent and severity of significant CAD. The plaques were localized most frequently in the proximal Left Anterior Descending (LAD) artery (30%).

	CAD on CCTA
Sensitivity	76%
Specificity	73%
Positive predictive value	90%
Negative predictive value	56%
Diagnostic accuracy	66%
Likelihood ratio of a positive test	1.07
Likelihood ratio of a Negative test	1.02
Area under curve	0.77

[Table/Fig-4]: Diagnostic accuracy of CCS alone for Significant CAD.

*Cut-off value for calcium: 8.5



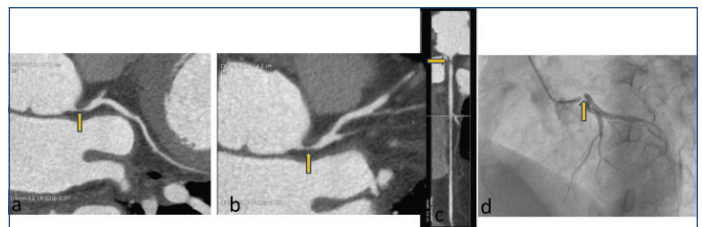
[Table/Fig-5]: ROC curve-calcium score – CAD on CCTA.

Gender	Risk	CAD on CCTA		Total
		Absent	Present	
Male	Low	35 (34%)	69 (66%)	104 (58%)
	Intermediate	30 (50%)	30 (50%)	60 (33%)
	High	5 (31%)	11 (69%)	16 (9%)
	Total	70 (39%)	110 (61%)	180 (59%)
Female	Low	77 (61%)	49 (39%)	126 (100%)
	Total	77 (61%)	49 (39%)	126 (100%)

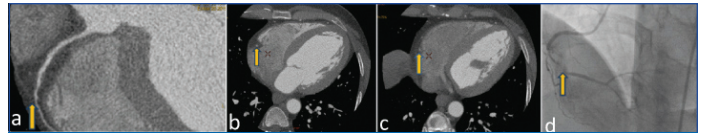
[Table/Fig-6]: FRS risk categories significant CAD on CCTA.

Framingham Score: Overall 75% ($n=230$) of the study population was categorised as low risk, 20% ($n=60$) as intermediate risk and 5% ($n=20$) as high risk. In male subjects 66% ($n=69$) and 50% ($n=30$) who were categorised as low and intermediate risk, respectively had significant CAD on CTCA. In comparison, 39% ($n=49$) of female subjects who were categorised as low risk by FRS had significant CAD on CTCA [Table/Fig-6].

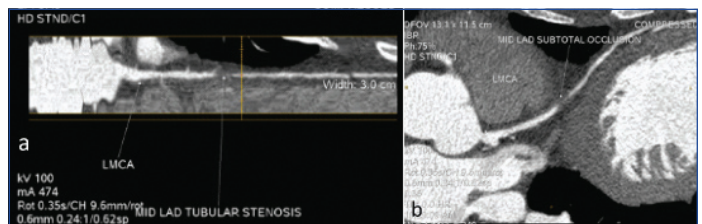
In subjects with $CCS=0$ ($n=121$), 82% ($n=99$) were categorised as low risk and 16% ($n=20$) were categorised as intermediate risk population. Of these, significant CAD was present in 44 of the 99 subjects (44%) who were classified as low risk by FRS and had a $CCS = 0$ AU. In comparison, 16 of 20 subjects (80%) who had an intermediate risk FRS and a $CCS=0$ AU had significant CAD on CTCA. Representative images are described in [Table/Fig-7-9].



[Table/Fig-7 (a-d)]: A 42-year-old male presented with chest pain on exertion and known diabetic on treatment; Curved and straight multi-planar reformatted CTCA images demonstrate severe stenosis of LMCA; which was confirmed on conventional angiogram (arrows); CCS was zero and the patient underwent CABG.



[Table/Fig-8 (a-d)]: A 51-year-old male presented with chest pain on rest and known diabetic and hypertensive on treatment; Curved CTCA images demonstrate severe stenosis of RCA; which was confirmed on conventional angiogram (arrows); CCS was zero and the patient underwent PTCA with stenting to mid RCA.



[Table/Fig-9 (a,b)]: A 49-year-old male presented with chest pain on exertion and not known diabetic or hypertensive; Curved and straight multi-planar reformatted CTCA images demonstrate severe stenosis of LAD (arrows); CCS was zero and the patient underwent Percutaneous Coronary Intervention (PCI).

DISCUSSION

We evaluated the utility of a zero CCS in excluding significant CAD in symptomatic Indian subjects who presented with cardiac chest pain. We also evaluated the additive value of the CCS to the traditional FRS. The main findings of our study are: 1) In a population of predominantly low to intermediate risk subjects from India with cardiac chest pain undergoing CTCA, a $CCS=0$ AU does not “rule out” significant CAD; 2) In symptomatic Indian subjects, the FRS has poor correlation with the absence of CAD.

Zero CCS: CCS, is a specific marker for coronary atherosclerosis. In general, an increasing CCS is associated with a higher burden of CAD. In our study, however, in symptomatic Indian subjects with a $CCS=0$ AU, the incidence of significant CAD was also high (25%; 30 out of 121 subjects). This is likely reflective of the overall high prevalence as well as the lower age of onset of significant CAD in the symptomatic Indian population. Since CCS is also associated with increasing age, the relatively lower age of our study population (52 ± 9 years) likely also contributes to the low or zero CCS in patients with significant CAD.

The prevalence of significant CAD in subjects with a $CCS=0$ AU varies according to the population being studied. Kelly JL et al., reported rates of 51% in a South American population, similar to our study [14]. Prevalence rates were reported to be 6.5% by Cheng YV et al., in a Chinese population, Choi EK et al., reported 10% in a South Korean population, Sosnowski M et al., reported 12% in an Iranian population, It was 20% by Ergün E et al., in a Central American population, and 17.4% Büyükterzi M et al., in a Turkish population, It was 8.2% by Akram K et al., in a Saudi Arabian population [15-20]. However, the definition of significant CAD varied across these studies, with most using a more lenient definition of $\geq 50\%$ diameter stenosis as significant CAD, whereas our study used a stricter cut threshold of $\geq 70\%$ diameter stenosis in an epicardial coronary artery or $\geq 50\%$ diameter stenosis in the left main coronary artery. The more lenient definition would result in a higher reported prevalence of significant CAD.

Unlike, North American, European, or East Asian populations, the correlation between a CCS=0 AU and the absence of significant CAD was weak in our study population. The relationship between the presence of coronary calcification and the severity of coronary artery stenosis was moderate ($R = 0.77$). In our study population, a number of subjects with no CCS or with a low CCS have significant CAD.

We observed that, regardless of CCS, atherosclerotic plaques were most frequently localized in the proximal segment of the LAD artery (30%), followed by the proximal LCX artery (16%). Eight cases (2.6%) had a plaque in the LMCA. When all plaques were considered, the plaques most commonly (49%) found were in the proximal segments and least common in the distal segments (3%) of the coronary arteries. This finding is consistent with other studies which also observed that atherosclerotic plaques (both calcified and non-calcified) are more common proximally, regardless of the CCS [14].

Intermediate or High CCS Strongly Associated with Significant CAD: The incidence of significant CAD higher in subjects with a CCS 1-100 AU (65%, $n = 117$), CCS >100-≤400 AU (75%, $n=57$), and CCS >400 AU (91% of subjects, $n=11$). This is consistent with the general observation across multiple populations that an increasing CCS is associated with a higher CAD burden. However, our study population is different in that the severity of CAD was high even in subjects in whom the CCS was considered intermediate (11-100 AU). Although the mean CCS was only 79 ± 10 AU, 48% of the study population had ≥ 1 vessel with significant CAD.

Coronary calcium leads to calcium blooming artefact which can cause overestimate of coronary artery stenosis severity. This may have contributed slightly to the higher incidence of CAD in subjects with very high CCS (>400 AU), although the high incidence even at low CCS scores would argue against this. At many centres, CTCA is not done if the CCS is more than a certain cut-off value (400-600 AU at our centre). Often, subjects who are not able to tolerate a CTCA due to breath hold, arrhythmia, or other problems will have high CCS due to underlying CAD.

FRS and Significant CAD: The FRS is a sex-specific algorithm used to estimate the 10-year cardiovascular risk of an individual, most commonly in asymptomatic subjects. FRS risk factors included age, sex, total cholesterol, high-density lipoprotein cholesterol, blood pressure, diabetes, and any smoking in the past year. Our study suggests that the FRS, if applied in symptomatic Indian population, could lead to an underestimation of the risk which in turn increases the cardio-vascular burden. In a study by Khanna R et al., in 200 symptomatic Indian population (mean age 57 ± 9 years), the prevalence of CAD was 61%, 87% and 92%, respectively in low, intermediate and high risk population [21]. In our study, CAD was present in 69%, 30% and 100% respectively in low, intermediate and high risk population. In subjects with CCS=0 AU, 44% ($n=99$) in low risk and 80% ($n=20$) in intermediate risk groups had CAD on CTCA. Male subjects 66% ($n=104$) categorised as low and 50% ($n=60$) categorised as intermediate had significant CAD as compared to 39% of female subjects ($n=126$), consistent with the general observation that the prevalence of significant CAD is higher in males than in females.

LIMITATION

Our study has several limitations which must be noted. First, stenosis severity was based on CTCA, rather than an independent reference standard such as Catheter Angiogram (CAG). In areas of dense calcification, there may have been an overestimation of stenosis severity due to calcium blooming artefact. Second, the study population was based on a convenience sample drawn from consecutive subjects who presented with cardiac chest pain and

who were referred for CTCA for evaluation of CAD. However, as our study population was enrolled from two different centres, we were able to include subjects from wide geographic areas and varied ethnicities/social classes. Two thirds of our study population were men, which is consistent with the overall clinical referral pattern for CTCA. The study findings may have varied slightly if a sample with older subjects was included.

CONCLUSION

CCS is a specific maker of coronary atherosclerosis. We found that in low to intermediate risk Indian subjects with cardiac chest pain undergoing CTCA, a CCS=0 AU does not "rule out" significant CAD. CCS is a better predictor for significant CAD than the conventional FRS. More studies are needed to evaluate the prognostic role of CCS and CTCA in low to intermediate risk symptomatic Indian subjects with cardiac chest pain.

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