


BMJ Open Evaluating the use of coronary artery calcium scoring as a tool for coronary artery disease (CAD) risk stratification and its association with coronary stenosis and CAD risk factors: a single-centre, retrospective, cross-sectional study at a tertiary centre in Pakistan

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ABSTRACT

Objective Coronary artery disease (CAD) risk stratification plays a fundamental role in the early detection and optimal management of CAD. The aim of our study is to investigate the use of coronary artery calcium scoring (CACS) as a tool for CAD risk stratification through evaluation of its correlation with the degree of coronary stenosis and its association with conventional cardiovascular risk factors in asymptomatic patients.

Design Single-centre, retrospective, cross-sectional study.

Setting The study was conducted at a tertiary centre (Shifa International Hospital) in Islamabad, Pakistan, through review of medical records of patients who underwent coronary CT between the years 2016 and 2020.

Participants A total of 1014 patients were included in the study. The study population was analysed for presence of conventional risk factors (gender, age, diabetes, hypertension, body mass index, dyslipidaemia) and association with CACS (zero: n=534; minimal: 0 to ≤10, n=70; mild: >10 to ≤100, n=130; moderate: >100 to ≤400, n=118; and severe: >400, n=49). The association of CACS with the degree of coronary artery stenosis seen on CT scan (significant: ≥50% stenosis, n=216; non-significant: <50% stenosis, n=685) was also analysed.

Outcome measures The main outcome was the association of coronary artery stenosis with CACS. The secondary outcome was the association of CACS with conventional CAD risk factors.

Results A significant positive association was shown between CACS and coronary artery stenosis (zero vs minimal: OR 0.39, 95% CI 0.20 to 0.79, p=0.01; zero vs mild: OR 0.16, 95% CI 0.10 to 0.27, p<0.0001; zero vs moderate: OR 0.05, 95% CI 0.03 to 0.08, p<0.0001; zero vs severe: OR 0.02, 95% CI 0.01 to 0.050, p<0.0001). Age >45 (OR 1.03, 95% CI 1.01 to 1.05, p<0.0001), hypertension (OR 1.16, 95% CI 0.79 to 1.71, p=0.001) and diabetes (OR 1.33, 95% CI 0.88 to 1.99, p<0.0001) were associated with an increased risk of coronary

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A strength of this study is the reporting of findings from a large, standardised data set from over a 4-year period in a South Asian population.
- ⇒ This was a retrospective study based on case note reviews and so risk of bias cannot be excluded.
- ⇒ Despite a large sample size, as a single-centre study, the study sample is not representative of the varied ethnic and regional subpopulations of Pakistan or South Asia.

artery stenosis. Moreover, plaques with higher calcium burden were found in the left anterior descending artery (mean CACS: 386.15±203.89), followed by right coronary (239.77±219.83) and left circumflex (175.56±153.54) arteries.

Conclusion The results indicate a strong positive association of CACS with coronary artery stenosis. CACS was also significantly associated with conventional CAD risk factors in this population.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality worldwide. In 2015 CAD affected 110 million people and resulted in 8.9 million deaths (15.9% of all deaths), making it the most common cause of death globally.^{1,2} South Asian populations are regarded as being at particularly high risk of development of CAD.³ According to a study conducted in Karachi, Pakistan, approximately 27% of the population were reported to have evidence of CAD.⁴ Risk stratification plays a fundamental role in the early detection and optimal management of CAD.⁵

This necessitates continuous development of newer techniques for disease evaluation that are rapid, non-invasive, economically feasible and provide improved risk assessment when used in adjunct to models that use conventional cardiovascular risk factors for risk prediction.

Measurement of radiographically detectable coronary artery calcium (CAC) is one such minimally invasive modality introduced in recent times. It has been found to be a strong indicator of the underlying atherosclerotic burden and can be measured either by fast electron beam CT or multidetector CT.⁶ It provides an indication of coronary plaque load and hence allows risk stratification of patients.⁷ Additionally, several studies have established its usefulness in providing incremental CAD risk prediction beyond the traditional risk factors.^{8–10} The coronary artery calcium score (CACS) has been found to be an independent predictor of CAD, with a higher score representing an increased likelihood of coronary artery stenosis.¹¹ An independent positive correlation has also been observed between CACS and other cardiovascular risk factors such as age, gender, diabetes mellitus (DM), hypertension and dyslipidaemia.^{12–13} Substantial differences have been observed in the prevalence and predictive value of coronary calcium among varying ethnicities,^{14–17} and to date very few studies evaluating the diagnostic prowess of CACS have focused on the South Asian population. Therefore, the aim of our study is to investigate the use of CACS as a tool for CAD risk stratification through evaluation of its correlation with the degree of coronary stenosis and also its association with the conventional cardiovascular risk factors.

METHODS

Data collection

This was a retrospective, cross-sectional study carried out at a tertiary centre (Shifa International Hospital (SIH)) in Islamabad, Pakistan, from December 2016 to December 2020. Data were collected from patients' medical records and laboratory results and included the following variables: age, gender, family history, hypertension, diabetes and smoking. The medical records of 1500 consecutive patients who underwent coronary CT angiography (CCTA) from 2016 to 2020 at SIH were reviewed. The included study population had at least one modifiable cardiovascular risk factor (hypertension, diabetes, dyslipidaemia and smoking) besides non-modifiable variables such as family history of cardiovascular disease (CVD), age and gender. Patients with incomplete information on symptomatic CAD, acute coronary syndromes and revascularisation were excluded from the study.

CCTA and CACS estimation

For CCTA, a multidetector tomography scanner (Toshiba Aquilion 640-slice scanner) was used. For every patient a prior scan without contrast to measure the coronary calcium burden was performed. Coronary calcium on CT was quantified using the Agatston score. This score

is calculated based on the area of calcification per coronary cross section, multiplied by a factor that depends on the maximum amount of calcium in a cross section (a weighted value system based on Hounsfield units of dense calcification in each major coronary artery). The sum of calcium in the right coronary, left anterior descending and left circumflex arteries gives the total Agatston calcium score. CACS was classified into zero ($n=534$), minimal ($0 \text{ to } \leq 10$, $n=70$), mild ($>10 \text{ to } \leq 100$, $n=130$), moderate ($>100 \text{ to } \leq 400$, $n=118$) and severe (>400 , $n=49$). Those with CACS less than 600 ($n=901$) underwent CT coronary angiography using 70–100 mL iso-osmolar contrast. The diagnosis and quantification of intraluminal coronary artery stenosis were established by a consultant radiologist using the eyeball technique. It was classified on the basis of severity of the intraluminal disease into significant ($\geq 50\%$, $n=216$) and non-significant ($<50\%$ stenosis, $n=685$) coronary artery stenosis.

Cardiovascular risk factors

Data on patients' cardiovascular risk factors were retrieved from their clinical notes. Patients were considered hypertensive if they had been clinically diagnosed with hypertension or were taking antihypertensive medication. Patients who met one of the following requirements were identified as having DM: (1) taking an oral hypoglycaemic agent, (2) using insulin, (3) known clinical diagnosis of DM or (4) haemoglobin A1c level $\geq 6.5\%$. Patients were identified to have dyslipidaemia if they met one of the following requirements: (1) diagnosis of hypercholesterolaemia, (2) medication history of lipid-lowering drugs, or (3) total cholesterol $>200 \text{ mg/dL}$ and low-density lipoprotein (LDL) $>100 \text{ mg/dL}$. Body mass index (BMI) was calculated from patients' height and body weight. Any family history of coronary heart disease was obtained by collecting information from patients' records, whether any member of their immediate family (parents, siblings or children) had a diagnosis of CAD, angina, fatal or non-fatal myocardial infarction, or coronary revascularisation. Patients with incomplete information on risk factors were documented as having missing values in the overall analyses.

Statistical analysis

SPSS V.23 was used for statistical analyses. Mean and SD were used to depict continuous variable distributions, while frequencies were used to summarise categorical variables. Continuous variables were compared by independent t-test between two groups and by one-way analysis of variance among more than two groups. For categorical variables, comparison between two and more groups was done using the χ^2 test. Binary logistic regression was used to assess the associations between different cardiovascular risk factors, coronary artery stenosis status and CACS. A p value of <0.05 was considered statistically significant.

Patient and public involvement

There was no patient and public involvement.

Table 1 Difference in the prevalence of significant coronary stenosis detected by coronary CT angiography with risk factors of coronary artery stenosis compared with those without in the study population

Risk factor	Patients with $\geq 50\%$ coronary stenosis (n)	Patients with $< 50\%$ coronary stenosis (n)	OR (95% CI)	P value
Age				
≥ 45	218	457	5.97 (3.64 to 9.80)	<0.0001*
< 45	19	238		
Gender				
Male	556	231	0.73 (0.52 to 1.02)	0.07
Female	174	53		
Diabetes				
Yes	89	156	2.06 (1.50 to 2.82)	<0.0001*
No	151	544		
Hypertension				
Yes	146	340	1.65 (1.22 to 2.22)	0.001*
No	94	360		
Dyslipidaemia				
Yes	138	87	1.28 (0.79 to 2.06)	0.35
No	347	27		
Smoking				
Yes	64	172	1.12 (0.80 to 1.56)	0.52
No	176	528		
Family history				
Yes	142	364	1.34 (0.99 to 1.80)	0.05
No	98	336		

χ^2 was applied.
*P<0.05 was considered significant.

RESULTS

A total of 1014 asymptomatic patients (787 men and 227 women) were included in the study. The mean \pm SD age of the participants was 53.18 \pm 11.98 years, with a significant difference between men (52.59 \pm 12.11) and women (55.22 \pm 11.31) ($p=0.004$, 95% CI 4.39 to 8.6). Of the patients, 52.2% had a diagnosis of systemic hypertension, 27.6% had type 2 diabetes, 25.6% were smokers and 53.5% had a positive family history. The mean \pm SD values of BMI, serum LDL, serum high-density lipoprotein (HDL) and serum triglycerides were all above the normal limits. The mean \pm SD BMI was 28.39 \pm 5.29 kg/m², LDL level was 118 \pm 37.17 mg/dL, HDL level was 38.4 \pm 9.6 mg/dL and triglyceride level was 190 \pm 186 mg/dL.

Patients were classified on the basis of severity of coronary artery stenosis into having significant ($\geq 50\%$, $n=216$) and non-significant ($< 50\%$ stenosis, $n=685$) intraluminal CAD. Of the patients, 24% had significant coronary stenosis, whereas 76% had $< 50\%$ stenosis.

Risk factors and coronary stenosis severity

The clinical and biochemical characteristics of the patients in relation to the degree of coronary stenosis are demonstrated in [table 1](#). Patients with significant stenosis ($\geq 50\%$

coronary artery stenosis) were found to be relatively older (age ≥ 45 , OR=5.97, 95% CI 3.64 to 9.80, $p<0.0001$) and had a higher prevalence of diabetes (OR=2.06, 95% CI 1.50 to 2.82, $p<0.0001$) and systemic hypertension (OR=1.65, 95% CI 1.22 to 2.22, $p=0.001$). Gender, BMI, smoking, dyslipidaemia and positive family history were not found to be associated with increased intraluminal coronary stenosis.

Multivariate risk factor predictors of significant coronary stenosis

[Table 2](#) shows the multiple binary regression analysis of the risk factors for coronary artery stenosis of the 1014 patients included in the study. Multivariate analyses showed that age, diabetes, hypertension and calcium score remained independent determinants of significant coronary stenosis ($p<0.0001$). CAC was found to be the most important predictor (OR=2.285, 95% CI 1.973 to 2.645, $p<0.0001$), followed by diabetes (OR=1.33, 95% CI 0.889 to 1.996, $p<0.0001$), hypertension (OR=1.16, 95% CI 0.791 to 1.718, $p=0.001$) and age (OR=1.03, 95% CI 1.017 to 1.056, $p<0.0001$).

CACS in patients with and without significant stenosis

[Table 3](#) shows a comparison of the number of patients with and without significant stenosis according to CACS.

Table 2 Binary logistic regression analysis of coronary stenosis with risk factors

Constant	OR	95% CI	P value
Age	1.036	1.017 to 1.056	<0.0001*
Gender	0.859	0.536 to 1.379	0.311
Diabetes	1.332	0.889 to 1.996	<0.0001*
Hypertension	1.165	0.791 to 1.718	0.001
Smoking	1.088	0.698 to 1.696	0.580
Family history	1.399	0.957 to 2.045	0.166
Calcium score	2.285	1.973 to 2.645	<0.0001*

Coronary stenosis was taken as the independent variable, whereas all the other risk factors were independent covariates.
*P<0.05 was considered significant.

CACS was classed as zero (n=534), minimal (0 to ≤10, n=70), mild (>10 to ≤100, n=130), moderate (>100 to ≤400, n=118) and severe (>400, n=49). The results showed a clear association between increasing CAC and severity of coronary stenosis (zero vs minimal: OR=0.39, 95% CI 0.206 to 0.797, p=0.01); zero vs mild: OR=0.16, 95% CI 0.105 to 0.272, p<0.0001; zero vs moderate: OR=0.05, 95% CI 0.0318 to 0.084, p<0.0001; zero vs severe: OR=0.02, 95% CI 0.011 to 0.050, p<0.0001).

In patients with no or low CACS (≤100), the proportion of significant coronary artery stenosis was low. Only 8.2% of patients with zero CACS had significant coronary stenosis, whereas in patients with higher CACS (>100) the severity of coronary artery stenosis proportionately increased.

Comparison of risk factors and CACS status

Table 4 shows a comparison of risk factors and CACS in our studied population. The results revealed that older age was associated with higher CACS (p<0.0001). Men had a significantly higher CACS (p=0.02) compared with women. Evaluation of the relationship of other cardiovascular risk factors and CACS showed significantly higher CACS in patients with diabetes (p<0.0001) and hypertension (p=0.012) compared with those without these risk factors. No difference in CACS was observed in patients

with dyslipidaemia, those who smoked or patients with positive CVD family history.

Pattern of CAD and degree of calcification

The association between the severity of CAD and CAC is demonstrated in figure 1, showing a linear increase in the number of coronary vessels with stenosis involved as the CACS increased (p<0.0001). The mean number of the main coronary arteries and their major branches involved in patients with mild CACS (score ≤100) was 1.17, in those with moderate CACS was 2.23, while the average number of coronary arteries involved in patients with scores >400 was 3.14. Moreover, in patients with significant coronary stenosis, left anterior descending arteries (p<0.0001, t=4.38, 95% CI 34.74 to 91.28) and left circumflex arteries (p=0.004, t=2.67, 95% CI 8.78 to 57.97) were more commonly involved (table 5). In addition, in our study population, plaques with higher calcium burden were found in the left anterior descending artery (mean CACS: 386.15±203.89), followed by right coronary arteries (mean CACS: 239.77±219.83) and left circumflex arteries (mean CACS: 175.56±153.54), respectively (tables 5 and 6).

DISCUSSION

Early diagnosis and management of CVD is cost-effective and is associated with improved morbidity and mortality.⁵ Identification of asymptomatic individuals at greater risk of experiencing future cardiovascular events is therefore fundamental to the implementation of cost-effective preventive strategies.¹⁸ Risk predictors and risk stratification models are useful in identifying early disease without the need for more invasive and expensive diagnostic tests in most cases.¹⁹ Pakistan is part of the ethnic group in South Asia which suffers from the highest prevalence of CAD.³ In low-income to middle-income countries like Pakistan, the use of such modalities for early detection of disease is relatively cost-effective and economically feasible.

CACS is an authentic and reproducible modality for cardiovascular risk stratification. It correlates well with underlying CAD severity and future major cardiac

Table 3 Distribution of different coronary artery calcium score groups in relation to the presence of coronary artery stenosis

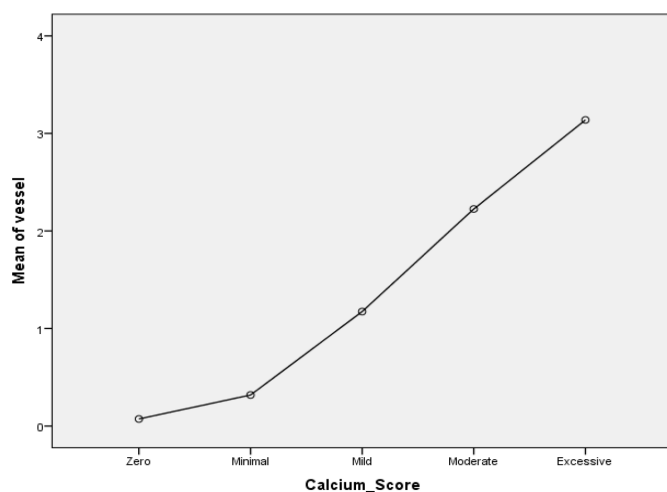
Calcium score	Patients with ≥50% coronary stenosis (n)	Patients with <50% coronary stenosis (n)	OR (95% CI)	P value
Zero (score=0)	44	490	Reference	
Minimal (0<score≤10)	13	57	0.39 (0.206 to 0.797)	0.01
Mild (10<score≤100)	45	85	0.16 (0.105 to 0.272)	<0.0001
Moderate (100<score≤400)	75	43	0.05 (0.0318 to 0.084)	<0.0001
Excessive (score >400)	39	10	0.02 (0.011 to 0.050)	<0.0001

A 2×2 χ^2 was applied with zero taken as reference.
P<0.05 was considered significant.
Values in bold show significant association

Table 4 Comparison of risk factors and CACS status of the study population

Risk factor	CACS					Pearson's χ^2 significance (two-sided)
	Zero (score=0) n (%)	Minimal (0<score≤10) n (%)	Mild (10<score≤100) n (%)	Moderate (100<score≤400) n (%)	Excessive (score >400) n (%)	
Age						
<45	226 (88)	6 (2)	12 (5)	11 (4)	2 (1)	<0.0001
≥45	308 (47)	64 (10)	115 (18)	107 (16)	57 (9)	
Gender						
Male	391 (56)	58 (8)	95 (14)	97 (14)	52 (8)	0.02
Female	145 (66)	12 (5)	33 (15)	21(10)	8 (4)	
Diabetes						
Yes	101 (43)	22 (10)	44 (19)	42 (18)	23 (10)	<0.0001
No	429 (63)	47 (7)	86 (13)	75 (11)	38 (6)	
Hypertension						
Yes	245 (52)	39 (8)	75 (16)	74 (16)	37 (8)	0.012
No	286 (65)	30 (7)	55 (13)	43 (10)	24 (5)	
Dyslipidaemia						
Yes	237 (56)	33 (8)	73 (17)	50 (12)	31 (7)	0.465
No	16 (44)	2 (6)	7 (19)	6 (17)	5 (14)	
Smoking						
Yes	126 (55)	16 (7)	30 (13)	36 (16)	20 (9)	0.486
No	404 (59)	53 (8)	100 (15)	81 (12)	41 (6)	
Family history						
Yes	277 (57)	35 (7)	73 (15)	67 (14)	34 (7)	0.526
No	247 (60)	34 (8)	57 (14)	50 (12)	27 (6)	

χ^2 was applied.
 P<0.05 was considered significant.
 Values in bold show significant association
 CACS, coronary artery calcium score.


Figure 1 Distribution of different coronary artery calcium score groups in relation to the number of coronary vessels involved.

coronary events (all-cause mortality, cardiac mortality and non-fatal myocardial infarction) in medium-term and long-term follow-up.¹⁸ Low or zero coronary calcium score is associated with low risk whereas higher score with higher incidence of intraluminal CAD.²⁰ CACS is used as a screening and risk stratification modality for CAD in some centres in developed countries.^{21–23} Very few studies, however, evaluating the diagnostic and risk stratification use of CACS have been carried out in the South Asian population. Our work, which is one of the largest studies of patients of South Asian origin, aimed at assessing and comparing our findings with the work carried out in the West.

Coronary artery calcification increases with age and is more common in men than in women.^{13 17 24} Furthermore, people with metabolic syndrome and diabetes, dyslipidaemia, tobacco use, hypertension, chronic kidney disease and high baseline C reactive protein level have been shown to be at increased risk of development

Table 5 Distribution of calcium scores in different coronary artery groups in relation to the presence of coronary artery stenosis

Coronary arteries	Calcium score		P value
	n	Mean±SD	
LAD			
Significant stenosis	163	135.30±145.34	<0.0001
No significant stenosis	160	72.29±110.14	
LCX			
Significant stenosis	111	72.94±93.06	0.004
No significant stenosis	70	39.56±59.17	
RCA			
Significant stenosis	116	89.40±121.01	0.156
No significant stenosis	79	65.23±108.89	
Others			
Significant stenosis	23	46.26±66.82	0.057
No significant stenosis	13	16.31±20.82	

P value calculated by Student's independent samples t-test.

P<0.05 indicates statistical significance.

Values in bold show significant association

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

of coronary artery calcification.^{25 26} Matthews and coworkers²¹ provided evidence on a link between increased blood pressure reactivity, psychological stress and the development of CAC during a 13-year follow-up of coronary artery risk development in a study of young adults. Other studies have shown that among all traditional cardiovascular risk factors, systolic hypertension had the strongest association with degree of CACS.^{27 28} In our study, advanced age, male gender, hypertension and diabetes were strongly linked while smoking, dyslipidaemia and BMI were not significantly linked with the presence of coronary calcium (table 4). Our finding of weak association between the extent of coronary artery calcification and some of the conventional risk factors (table 4), such as smoking, hypercholesterolaemia and positive family history, was consistent with other studies showing that such risk factors are attenuated in their associations with disease in old age.^{20 25 29}

In line with similar work, our study showed a clear association between CAC and the presence of intraluminal coronary artery stenosis (table 3). There was a proportional and linear correlation between CACS and severity of coronary stenosis. Low or zero calcium was associated with significantly lower incidence of coronary stenosis. In our study only 8.2% of patients with zero CACS have significant coronary stenosis, which is in line with other studies.³⁰⁻³²

Our work also looked into the relative differences in the distribution of CAC among coronary arteries and severity of CAD (figure 1). Our findings highlight the distribution of CAC in different coronary arteries in relation to the presence of coronary artery stenosis (table 5). Left anterior descending arteries had relatively high coronary calcium and corresponding coronary stenosis compared with other arteries, especially non-dominant left circumflex artery. This finding is important as a long-term

Table 6 Distribution of calcium score in different coronary artery groups in the study population

Coronary artery	Coronary artery calcium score (mean±SD)				P value
	Minimal (0<score≤10)	Mild (10<score≤100)	Moderate (100<score≤400)	Excessive (score >400)	
LAD	3.98±2.75	32.78±24.34	120.48±86.49	386.15±203.89	<0.0001
LCX	3.57±2.34	14.10±15.61	47.83±44.95	175.56±153.54	<0.0001
RCA	2.67±2.23	23.48±24.23	60.33±60.17	239.77±219.83	<0.0001
Others	4.40±3.58	9.56±11.60	33.17±32.48	80.14±85.93	0.012

P value calculated by one-way analysis of variance.

P<0.05 indicates statistical significance.

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

predictor since Framingham and other studies showed that CACS severity in a dominant coronary artery is a major risk for future coronary heart disease events.^{33–35}

The CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter), however, did not document any difference between left and right dominance with respect to coronary calcium, coronary stenosis and all-cause mortality.³⁶

Overall, our work is in line with similar studies in which CACS is found to be an independent predictor of CAD, with a higher score representing a higher likelihood of coronary artery stenosis and hence a higher risk of future cardiovascular event. A CACS of 0 can be helpful in reclassifying risk to a lower risk group; however, a score of 0 does not imply zero risk and the results of the test should always be incorporated with other known risk factors. We therefore recommend that CACS should be used to identify patients with high underlying risk.

In this study we have reported findings from a large, standardised data set from a single centre in Pakistan over a 4-year period, with no comparable study in South Asian population to date. Moreover, the association of CAD risk factors with respect to coronary stenosis and increasing CACS has not been reported previously in this population. However, the study has its limitations as this was a retrospective study from case note reviews and therefore risk of bias cannot be absolutely excluded. Despite a significant sample size, being a single-centred study, it does not fully represent the varied ethnic and regional subpopulations of this region (Pakistan/South Asia).

CONCLUSION

This study has shown CACS as a good predictor and risk stratification modality for coronary artery disease in patients of South Asian ethnicity. Our results indicate a linear association of CACS with degree of coronary artery stenosis. CACS is strongly associated with some of the conventional CAD risk factors (diabetes, hypertension and increasing age). These findings lay a foundation for further prospective studies to evaluate the use of this relatively low-cost, easily accessible diagnostic modality for early identification, risk stratification and optimal management through robust preventive strategies.

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Patient consent for publication Not required.

Ethics approval The study was approved by the Institutional Review Board (IRB no: 941-261-2018). It has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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