



## Original Article

Correlation between echocardiographic calcium score and coronary artery lesion severity on invasive coronary angiography<sup>☆</sup>Suhas Hardas<sup>a</sup>, Pritam Titar<sup>a,\*</sup>, Ishwar Zanwar<sup>a</sup>, Deepak S. Phalgune<sup>b</sup><sup>a</sup> Dept. of Cardiology, Poona Hospital & Research Centre, Pune, India<sup>b</sup> Dept. of Research, Poona Hospital & Research Centre, Pune, India

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## ABSTRACT

**Objectives:** The direct correlation between Echocardiographic non-coronary calcium score (ECS) and lesion severity on invasive coronary angiography (ICA) is not reported. The aim of the present study was to find the correlation between ECS and Gensini score.

**Methods:** One hundred seventy patients aged  $\geq 18$  years posted for clinically indicated ICA were included. All the patients underwent standard transthoracic echocardiography. ECS and Gensini scores were calculated. The primary outcome measure was to find a correlation of ECS with Gensini score, whereas the secondary outcome measure was to correlate ECS with traditional risk factors for coronary artery disease. The Chi-square/Fisher exact test was used to compare qualitative variables. Spearman's correlation analysis was used for assessing the correlation between ECS score and the Gensini score. Receiver-operating characteristic curve analysis was performed to detect the cut-off value of the ECS score.

**Results:** The correlation of total ECS with Gensini score was positive and statistically significant ( $r = 0.550$ ,  $p$ -value  $< 0.0001$ ). As ECS increased, the Gensini score increased. ECS value of  $> 1$  detected CAD with 56.5% sensitivity, 79.5% specificity. Eight-nine percent of patients who had ECS  $> 1$ , had Gensini score  $\geq 18$ , whereas 44.3% of patients who had ECS  $\leq 1$ , had Gensini score  $\geq 18$ . The patients with ECS  $> 1$  had significantly higher Gensini scores than the patients with ECS  $\leq 1$ .

**Conclusions:** The correlation of total ECS with Gensini score was positive and statistically significant.

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## 1. Introduction

Coronary artery disease (CAD) is the leading cause of death globally.<sup>1</sup> An estimated 7.4 million people died from coronary heart disease in 2015, representing 12% of all global deaths.<sup>2</sup> The most common underlying cause of CAD is atherosclerosis, a disease process in which plaque (a complex and varied composition that includes lipids, inflammatory cells, smooth muscle cells and connective tissue) builds up on artery walls. The plaque formation can lead to the partial or complete blockage of coronary arteries. Recent data have shown that both aortic valve calcification (AVC) and mitral annular calcification (MAC) are active and highly regulated

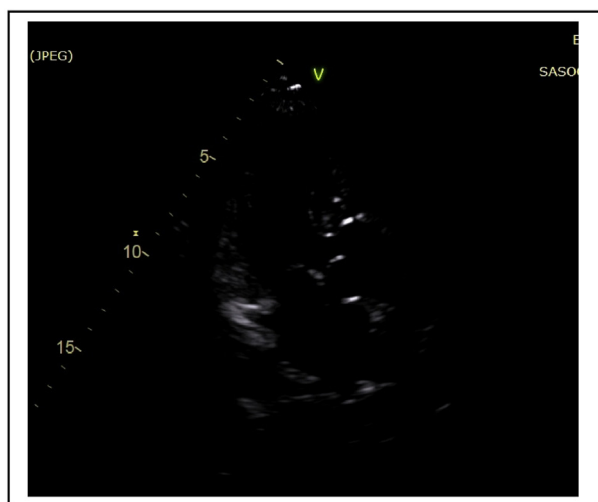
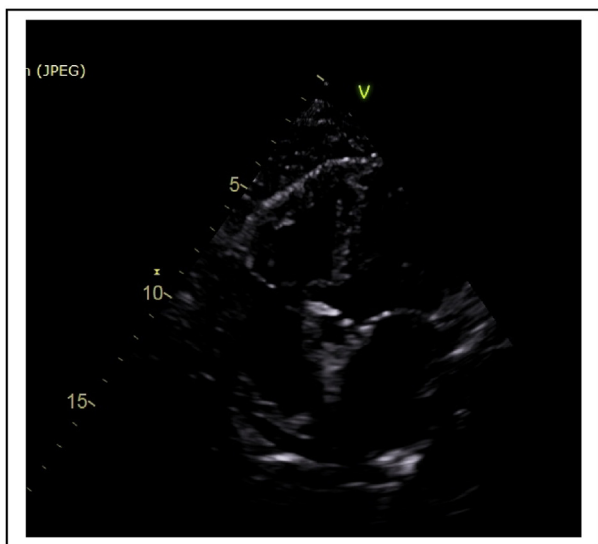
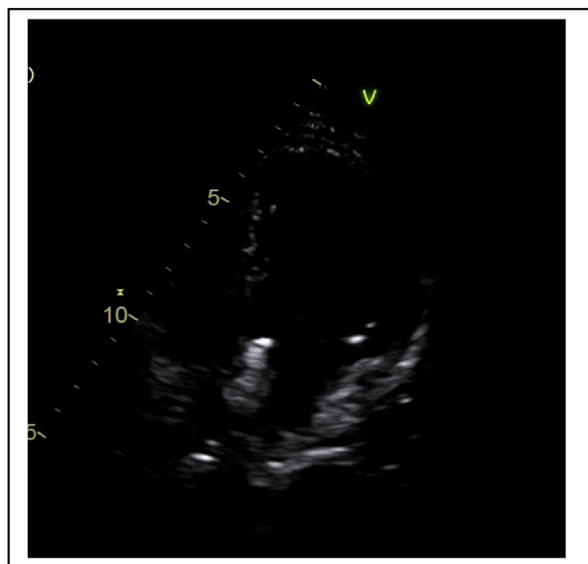
processes with histological similarities to atherosclerosis. These studies showed collections of foam cells, which represent early atherosclerotic lesions, on the ventricular surface of the posterior mitral leaflet and on the aortic aspects of each of the aortic valve cusps in patients who developed coronary atherosclerosis.<sup>3</sup> Furthermore, Drolet MC et al demonstrated similarities in the risk factors for AVC, MAC, and atherosclerosis, including age, hypertension, hyperlipidemia and diabetes mellitus (DM).<sup>4</sup> The data suggest that calcification of the aortic valve or mitral annulus may represent a form of atherosclerosis. These valvular calcifications are strongly associated with an increased risk of cardiovascular diseases (CVD) and death in the general population.<sup>5,6</sup> Similarly, as a part of the thoracic aortic calcification, the presence of aortic root calcification (ARC) has been independently associated with an increased risk of CVD mortality.<sup>7</sup>

The use of echocardiographic non-coronary calcium score (ECS) which comprehensively assess aortic and mitral valves, papillary muscle and the ascending aorta and range from no visible calcium to severe and diffused calcium deposits have also been associated with: 1) coronary and total cardiac calcium by computed

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**Fig. 1.** A: Two-dimensional echocardiogram, 4 chamber view: showing mitral annular calcification < 5 mm (ECS - 1), papillary muscle calcification (ECS - 1). B: 5 Chamber

tomography (CT); 2) CT coronary angiographically obstructive CAD; 3) worse prognosis in several patient subgroups; and 4) very recently, to ischemic stress echocardiography results.<sup>8–16</sup> No study has reported the direct correlation between ECS and lesion severity on invasive coronary angiography (ICA). Moreover, echocardiographic imaging is a radiation-free investigation that is potentially valuable for assessing atherosclerotic disease, as it may provide non-invasive information at low cost during a routine examination. The aim of the present study was to find the correlation between ECS and Gensini score (which measures coronary artery lesion severity on ICA).

## 2. Methods

This cross-sectional observation study was conducted between March 2018 and April 2019. After approval from the scientific advisory committee and the institutional ethics committee, written informed consent was obtained from all the patients prior to enrolment explaining the risks and benefits of the procedure.

Patients aged  $\geq 18$  years posted for clinically indicated ICA were included. Patients who had a history of previous heart surgery or percutaneous transluminal coronary angioplasty, suspected cardiac neoplastic mass, valvular heart disease and congenital heart disease were excluded. After signing a written informed consent form, all the patients underwent standard clinical evaluation and relevant investigations. All the patients underwent a standard transthoracic echocardiography (TTE) using Philips iE33 xMATRIX system (Manufactured by Philips Ultrasound Bothell, WA USA) equipped adult transthoracic probe. Standard echocardiography imaging views were used to grade aortic valve sclerosis (AVS)/calcifications, MAC, ARC and papillary muscle calcification (Fig. 1A and B, C). Minimal gain was used to provide an optimal image with good quality without dropout or blooming of signals. ECS was calculated as described in Table 1.<sup>17</sup>

Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance.<sup>18</sup> All coronary angiographies were assessed by two experienced independent observers who were blinded to the patient's echocardiographic measurements and clinical data. The Gensini score for each angiogram was obtained by averaging the scores assigned by these two observers.

The presence or absence cardiovascular risk factors such as patient's age, gender, and presence of other CAD risk factors (hypertension, DM, a family history of premature CAD, body mass index, hypercholesterolemia and cigarette smoking) were recorded. Hypertension, DM, a family history of CAD, hypercholesterolemia, body mass index and a positive history of cigarette smoking were defined as per the recommendations.<sup>19–24</sup>

The primary outcome measure was to find the correlation of ECS with Gensini score, whereas the secondary outcome measure was to correlate ECS with traditional risk factors for CAD, namely age, gender, DM, hypertension, hypercholesterolemia, BMI, smoking and a family history of CAD. We conducted a pilot study with the first 30 consecutive eligible patients.<sup>25</sup> These 30 patients were not included in the main study. This pilot study showed a coefficient of correlation  $r = 0.25$ . A sample size of 164 patients was calculated by formula<sup>26</sup> with 80% power and 5% probability of Type I error to reject the null hypothesis. We included 170 patients to validate the results.

view showing diffuse cusp increased reflectivity and cusp thickness >5 mm (ECS - 2).C: Two-dimensional echocardiogram, 3 chamber view: Aortic valve showing increased reflectivity (ECS - 1).

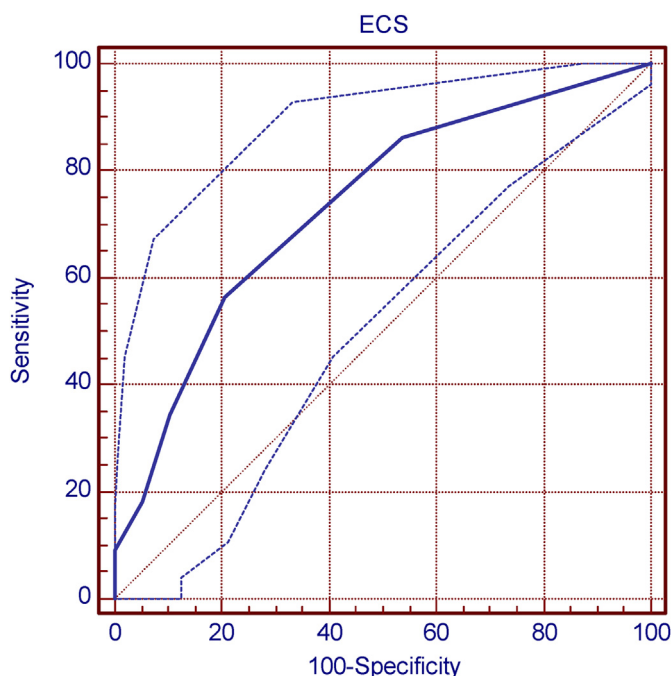


Fig. 2. Receiving operative curve for ECS. ECS- Echocardiographic noncoronary calcium score.

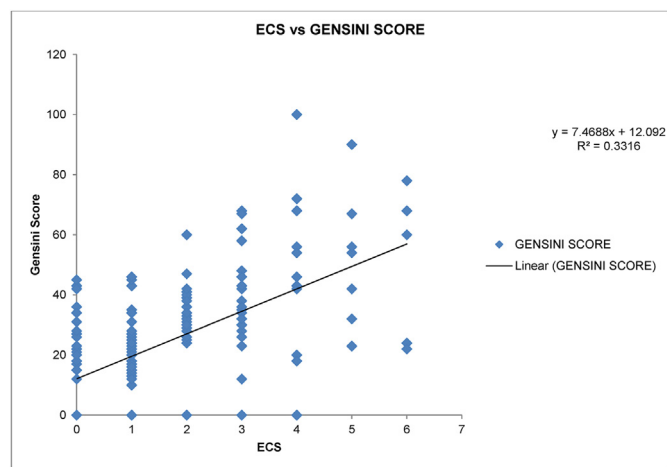


Fig. 3. Correlation between ECS and Gensini score. ECS- Echocardiographic non-coronary calcium score.

Table 1 Grading system echocardiographic noncoronary calcium score.

Grade	Papillary muscle calcium	Mitral annular calcium	Aortic valve sclerosis	Aorta root calcium
0	Absent	Absent	Absent	Absent
1	Present	Mild <5 mm	Mild	Present
2		Moderate 5–10 mm	Moderate	
3		Severe >10 mm	Severe	

Aortic valve sclerosis graded as follows.  
 Absent - Normal cusp thickness (<2 mm), and normal reflectivity.  
 Mild - Cusp thickness >2 mm and/or increased reflectivity.  
 Moderate - Thickness >4 mm and/or diffuse or focal cusp hyperreflectivity.  
 Severe - Thickness >6 mm and/or marked echorefectivity.  
 Final score is graded from 0 to 8.

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences for Windows, Version 20.0 from IBM Corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented as mean and standard deviation (SD). Comparison of the distribution of categorical variables was done using the Chi-Square or Fisher’s exact test. Spearman’s correlation analysis was used for assessing the correlation between ECS score and Gensini score. Receiver-operating characteristic (ROC) curve analysis was performed to detect the cut-off value of ECS score in predicting the occurrence of CAD (Gensini Score 0). The confidence limit for significance was fixed at 95% level with a p-value < 0.05.

3. Results

The baseline characteristics of the patients are evident from Table 2. Of 170 patients, 110 (64.7%) were males. Of 170 patients, 39 (22.9%) had Gensini score 0, whereas 131 had Gensini score > 0. Cut off value for ECS to detect the occurrence of CAD (Gensini > 0) was calculated using the ROC curve (Fig. 2). It was found that ECS value of >1 detected CAD with 56.5% sensitivity, and 79.5% specificity.

Gensini score was divided into subgroups with the help of a percentile method. Gensini score was 17 and 34 at 33.3 percentiles and 66.7 percentiles respectively. Therefore 0, 1 to 17, 18 to 34 and > 34 values were considered as Gensini score subgroups. Of 82

Table 2 Baseline characteristics.

Age in years	N	%
≤40	6	3.5
41–50	24	14.1
51–60	62	36.5
61–70	57	33.5
>70	21	12.4
Gender		
Male	110	64.7
Female	60	35.3
Diabetes mellitus Present	42	24.7
Hypertension Present	68	40
Body mass index		
≤18.5	0	0
18.5–24.9	85	50
25–29.9	76	44.7
≥30	9	5.3
Hypercholesterolemia Present	99	58.2
Smoking history Present	48	28.2
Family history of CAD Present	72	42.4

CAD- Coronary artery disease.

**Table 3**  
ECS as per the presence of CAD (Gensini Score).

CAD (Gensini Score)	ECS ≤ 1	ECS > 1	Total	p-value
	n (%)	n (%)		
0	31 (35.2)	8 (9.8)	39 (22.9)	<0.0001
1–17	18 (20.5)	1 (1.2)	19 (11.2)	
18–34	31 (35.2)	33 (40.2)	64 (37.6)	
>34	8 (9.1)	40 (48.8)	48 (28.3)	
Total	88 (100.0)	82 (100.0)	170 (100.0)	

Fisher's exact test was used.

ECS- Echocardiographic noncoronary calcium score.

CAD- Coronary artery disease.

patients who had ECS >1, 73 (89.0%) had Gensini score ≥ 18, whereas of 88 patients who had ECS ≤ 1, 39 (44.3%), had Gensini score ≥ 18 (Table 3). The patients with ECS >1 had significantly higher Gensini scores than the patients with ECS ≤ 1. The correlation of total ECS with Gensini score was positive and statistically significant ( $r = 0.550$ ,  $p < 0.0001$ ). As the ECS increased, Gensini score increased (Fig. 3). There was no statistically significant difference between ECS score ≤ 1 and ECS score >1 in relation to gender, BMI, DM, hypercholesterolaemia and a history of CAD, whereas there was a statistically significant difference in relation to age, hypertension and a history of smoking (Table 4).

#### 4. Discussion

In the present study, the patients with ECS >1 had significantly higher Gensini scores than the patients with ECS ≤ 1. The correlation of total ECS with the Gensini score was positive and statistically significant. There was a statistically significant difference between ECS score ≤ 1 and ECS score >1 in relation to age, hypertension and a history of smoking.

In the present study, out of 170 participants, 22.9% have no CAD (Gensini score 0). Kashani H et al reported that 320/1594 (20.1%) participants admitted with CAD symptoms and underwent ICA had a Gensini score of zero.<sup>27</sup> As ECS is a novel score, its normal values and ranges to predict the presence of CAD are not yet established. Therefore, we used the ROC curve for estimation of the cut off values of ECS to predict the occurrence of CAD. Cut off to predict

occurrence of CAD was ECS >1 with 56.5% sensitivity and 79.5% specificity. Gaibazzi N et al studied the correlation between ECS and coronary calcium on multidetector computed tomography. They reported that ECS cut off value to predict obstructive CAD was ECS > 1.<sup>17</sup> In the present study, we have used the same grading system to determine ECS score used by Gaibazzi N et al.

Gaibazzi N et al evaluated the value of the ECS using the same grading system to predict cardiac events in subjects without known CAD, who underwent stress echocardiography for suspected CAD. They reported that the best cut off for ECS to predict hard events (myocardial infarction and all-cause death) was ECS > 0.<sup>28</sup> Adler Y et al<sup>29</sup> evaluated MAC detected by TTE as a marker for high prevalence and severity of CAD in patients undergoing ICA. They observed that compared with controls; the MAC group had a significantly higher prevalence of CAD (89% vs 75%,  $p$ -value = 0.001) and higher rates of three-vessel disease (45% vs 24%,  $p$ -value = 0.001) and left main CAD (13% vs 5%,  $p$ -value = 0.009). Atar S et al reported that a higher prevalence of severe CAD in patients with MAC than in those without (88% v 68%,  $p = 0.0004$ ), and a higher prevalence of left main coronary artery disease (14% v 4%,  $p = 0.009$ ) and triple vessel disease (54% v 33%,  $p = 0.002$ ).<sup>30</sup> Harnirani YS et al also showed a strong association between MAC and CAD.<sup>31</sup> Conte L et al reported that the presence of AVS, in patients admitted for chest pain (with normal cardiac enzymes), was a strong predictor of obstructive CAD, independent of other CAD risk factors.<sup>32</sup>

Gaibazzi N et al<sup>33</sup> studied ECS along with ultrasound carotid parameters to predict angiographic CAD. The grading system to calculate ECS was the same as that of our study. The study population was divided into subjects at low (10%), intermediate (10–20%) and high (20%). Echocardiographic parameters were tested for their incremental value to predict CAD over Framingham risk score (FRS), in each pre-test risk category. ECS demonstrated significant incremental prediction over FRS, consistently in the three FRS categories ( $p$ -value < 0.01). In their study, only patients with stenosis >50% in any major epicardial coronary artery were considered to classify into the CAD group. No angiographic scoring system was used. In our study, we used Gensini score which is semi-continuous, one of the most widely used scoring system and it emphasizes more on the severity of CAD.<sup>34,35</sup>

**Table 4**  
ECS and risk factors.

Risk factors	ECS ≤ 1 n (%)	ECS > 1 n (%)	Total n (%)	P- value
Age in years				<0.001 <sup>a</sup>
≤40	5 (83.3%)	1 (16.7%)	6 (100%)	
41 to 50	21 (87.5%)	3 (12.5%)	24 (100%)	
51 to 60	44 (71%)	18 (29%)	62 (100%)	
61 to 70	18 (31.5%)	39 (68.5%)	57 (100%)	
>70	0 (0%)	21 (100%)	21 (100%)	
Gender				0.999 <sup>b</sup>
Male	57 (64.8)	53 (64.6)	110 (64.7)	
Female	31 (35.2)	29 (35.4)	60 (35.3)	
Body mass index kg/m <sup>2</sup>				0.063 <sup>a</sup>
18.5 to 24.9	44 (51.7%)	41 (49.3%)	85 (100%)	
25 to 29.9	36 (47.3%)	40 (53.7%)	76 (100%)	
>30	8 (88.9%)	1 (11.1%)	9 (100%)	
Diabetes mellitus Present	24 (27.3)	18 (21.9)	42 (24.7)	0.479 <sup>b</sup>
Hypertension Present	26 (29.5)	42 (51.2)	68 (40.0)	0.005 <sup>b</sup>
Hypercholesterolemia Present	49 (55.7)	50 (61.0)	99 (58.2)	0.535 <sup>b</sup>
History of smoking Present	33 (37.5)	15 (18.3)	48 (28.2)	0.006 <sup>b</sup>
Family history of CAD Present	38 (43.2)	34 (41.5)	72 (42.4)	0.877 <sup>b</sup>

ECS- Echocardiographic non-coronary calcium score.

CAD- Coronary artery disease.

<sup>a</sup> Fishers exact test was used.<sup>b</sup> Chi-square test was used.

In spite of extensive studies and development of various risk prediction models, traditional risk factors fail to predict the development of cardiovascular events in many patients. The extensive use of the most famous risk prediction model was proposed by the National Cholesterol Education Program III guidelines, in which the approach given by the FRS to estimate 10-year risk of cardiovascular events was embraced.<sup>22</sup> Today, it is clear that the FRS as well as various other risk factor assessment models can predict the long-term outcome in a large population, but may not be able to predict short-term risk for individual persons and cannot provide clear indications for cardiologists to identify, treat and prevent near future acute cardiovascular events.<sup>36,37</sup>

In the present study, it was found that ECS values were significantly higher ( $ECS > 1$ ) in elder patients, hypertensive and patients with a history of smoking. ECS values were not related to other risk factor e.g. DM, hypercholesterolemia, family history of CAD, gender and BMI. A study conducted by Allison MA et al<sup>38</sup> also reported significantly higher AVC and MAC in elderly patients ( $p$ -value  $< 0.01$ ), smokers and hypertensive ( $p$ -value  $< 0.01$ ). These findings are consistent with our results. Rossi A et al<sup>10</sup> evaluated AVS and its correlation with coronary angiographic findings. They reported AVS was associated with a 22.7 fold increased risk of any degree of CAD.

Noninvasive modalities for the diagnosis of CAD are the key for the stratification of symptomatic patients and to identify higher-risk subjects who could benefit more from ICA and possible subsequent revascularization (or in alternative maximal medical therapy). TTE has the advantage of being a simple, low-cost, radiation-free technique, which is widely available in clinical practice.

Our study has strengths and weaknesses. The use of a semi-quantitative total cardiac calcium score to assess aortic and mitral valves, papillary muscles and the ascending aorta has never been tested in the Indian population. Potential limitations of the study merit consideration. The study was cross-sectional and conducted in a single-center, potentially subjected to patient selection bias. The patients who underwent ICA were selected for this study; this inclusion criterion might have skewed the spectrum of the population toward advanced forms of CAD. The gain settings for Calcium score on Echocardiography are essentially subjective, based on operator's experience. ECS requires some operator experience to control gain settings in order to obtain reproducible results; we did not use a digitized method to identify AVS, AVC and MAC. This could have caused a verification bias and may affect the reproducibility in identifying cardiac calcifications. It is not always possible to distinguish sclerosis from calcification, which probably represents two phases of the same pathophysiologic process; accordingly, in our study sclerotic lesions were included along with calcified lesions in the ECS. We have not compared Gensini score and ECS in single vs multi-vessel disease. The sample size of the present study was small. The results of the present study may not extrapolate to the general population. A large observational registry-based well planned study should be conducted on a large population to assess the role of ECS as a predictor, prognostic marker and therapeutic target in CAD.

## 5. Conclusions

The correlation of total ECS with Gensini score was positive and statistically significant. As ECS increased, the Gensini score increased. ECS value of  $>1$  detected CAD with 56.5% sensitivity, 79.5% specificity. Eight-nine percent of patients who had  $ECS >1$ , had Gensini score  $\geq 18$ , whereas 44.3% of patients who had  $ECS \leq 1$ , had Gensini score  $\geq 18$ . The patients with  $ECS >1$  had significantly higher Gensini scores than the patients with  $ECS \leq 1$ . There was a

statistically significant difference between ECS score  $\leq 1$  and ECS score  $>1$  in relation to age, hypertension and history of smoking.

### 5.1. What is already known?

The use of echocardiographic noncoronary calcium score (ECS) which comprehensively assess aortic and mitral valves, papillary muscle and the ascending aorta and range from no visible calcium to severe and diffused calcium deposits have also been associated with coronary and total cardiac calcium by computed tomography, CT coronary angiographically obstructive CAD, worse prognosis in several patient subgroups and ischemic stress echocardiography results.

### 5.2. What does this study add?

There are not any studies that have reported a direct correlation between ECS and the Gensini score. In the present study the cut off value for ECS to detect the occurrence of CAD (Gensini  $> 0$ ), and correlation of ECS with Gensini score was calculated.

## Author contribution

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

## Declaration of competing interest

Dr. Suhas Hardas, Dr. Pritam Titar, Dr. Ishwar Zanwar and Dr. Deepak Phalguni declare that they have no conflict of interest.

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