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Utility of Global longitudinal strain and strain rate imaging to identify potential coronary artery disease in patients with subclinical left ventricular systolic dysfunction.

Running title: GLS & SR imaging in CAD with LV systolic dysfunction.

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ABSTRACT:

Background: During recent years, velocity imaging, displacement imaging and deformation imaging (strain and strain-rate imaging) have emerged as valuable tools for more comprehensive and reliable echocardiographic assessment of myocardial function, which is vital in determining the extent of tissue damage and functional restriction in ischemic conditions.

Methodology:151 study subjects were evaluated with Duke's clinical score, TMT, 2D Speckle Tracking Echocardiography and subsequently coronary angiogram was performed.

Results:Majority of the cases in low Duke's score group had normal coronaries (63%, p<0.0001), whereas in medium and high Duke's score group majority had obstructive CAD (23%, p=0.1939 and 30%, p<0.0001). Mean GLSR values of -0.93, -0.87 and -0.78 were found in patients with normal coronaries, non-obstructive CAD and obstructive CAD respectively. Differences between the mean values of GLSR of these groups is statistically significant. Mean GLS values of -15.56, -17.13 and -20 were found in patients with obstructive CAD, non-obstructive CAD and normal coronaries patients. Receiver Operating Characteristic (ROC) curve analysis revealed that Duke's clinical score has highest specificity and positive predictive value (PPV) whereas GLS has highest sensitivity and negative predictive value (NPV). Multivariate analysis showed Duke's Clinical Score, GLS and TMT were found as an independent factor associated with obstructive CAD.

Conclusion: Measurement of GLS (at a value of -18) had an incremental effect in prediction of obstructive CAD over Duke's clinical scoring system and TMT. GLSR value of ≥-0.78 and GLS value of ≥-18 were more sensitive and more specific in prediction of Obstructive CAD.

Key words:Global longitudinal strain; left ventricular systolic dysfunction; strain rate imaging; Duke's score.

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INTRODUCTION:

Coronary Artery Disease (CAD) is a leading cause of morbidity and mortality in both developing and developed countries.[1] Various investigatory modalities were developed, and few are under development for early and effective detection of CAD. They include cardiac biomarkers, electrocardiography, exercise testing, echocardiography, nuclear cardiac imaging, Cardiac Magnetic Resonance Imaging, Computed Tomography, Cardiac Catheterization, Coronary arteriography and Intracoronary imaging.Coronary angiography/Cardiac catheterization is considered the gold standard investigatory modality for detection of CAD.

In recent years it has become increasingly apparent that a large number of patients classified as low risk for acute coronary syndrome (ACS).[2-4] Up to one-third of patients with chest pain who are subjected to coronary angiography have no significant coronary artery stenosis.[5] Though this investigation is generally safe, but it has well known risk of complications and is also costly. Exercise testing is widely used for selecting patients for coronary angiography but has its clear limitations.[6]In stable coronary artery disease, coronary computed tomography angiography (CTA) is a non-invasive alternative to assess coronary anatomy, but according to expert consensus only selected patients should be considered for CTA.[6] In guidelines concerning ACS,[7] CTA is said to be useful to exclude ACS or other causes of chest pain, but due to limited availability and also the concern of radiation it is not commonly used in this setting worldwide. Thus, we are in need of a simple, non-invasive method to improve the selection of patients who are referred to coronary angiography.

Although conventional echocardiography is considered to be reliable for ventricular wall motion analysis and assessment of regional myocardial function, the visual estimation of wall motion is very subjective and therefore highly operator dependent.[8] Assessment of myocardial function is vital in determining the extent of tissue damage and functional restriction in ischemic conditions. During recent years, velocity imaging, displacement imaging and deformation imaging (strain and strain-rate imaging) have emerged as valuable tools for more comprehensive and reliable echocardiographic assessment of myocardial function.[9]

METHODOLOGY:

This cross-sectional observational study was conducted in the department of Cardiology, Sri Venkateswara Institute of Medical Sciences from June-2019 to July-2020. This study was approved by the Institutional Ethics Committee and a written informed consent was obtained from all the study participants prior to their inclusion.

Outpatients referred to Coronary angiography for coronary evaluation, because of increased risk profile and/or stable chest pain, positive stress test were included in the study. Patients with overt Left Ventricular systolic dysfunction (LVEF <50%), LV wall motion abnormalities, Cardiomyopathy, Significant valvular heart disease, Congenital heart disease, Rhythm other than sinus, conduction abnormalities, technically inadequate echocardiographic studies and contraindications to CAG were excluded.

Data collection:

151 consecutive patients satisfying the inclusion criterion were considered as study subjects. Detailed history was obtained from the patients, or the patient attendants and thorough physical examination was done after getting an informed written consent. All the study subjects

were evaluated with Duke's clinical score, Tread mill test (TMT), 2D Speckle Tracking Echocardiography and subsequently coronary angiogram was performed.

Out of 34 patients who had low risk as per Duke's clinical score and whose TMT was negative, 23 patients were subjected to coronary angiogram (CAG) at the request of their attendants. Remaining 11 patients were subjected to CAG considering the age, risk factors and possible atypical presentations. (Eg: elderly female patients with Diabetes mellitus; hypertensive patients who were being treated with beta blockers etc.,).

Patients with Duke's clinical score showing low or medium risk were considered as a single group whereas patients with high risk of CAD as per Duke's clinical score were considered as another group for facilitating the calculation of results.

Following CAG, patients with obstructive CAD were considered to have the disease under study and those with normal coronaries and non-obstructive CAD were considered not to have the diseaseAll the necessary data and test results were noted and tabulated and at the end of the study, outcome of interest was measured using appropriate statistical methods.

Statistical analysis:

Continuous variables are expressed as mean and standard deviation. Categorical data are presented as absolute numbers and percentages. Differences in continuous and categorical variables between patients with normal coronary arteries, non-obstructive CAD, and obstructive CAD at coronary angiography were assessed using the one-way analysis of variance (ANOVA) test and the χ^2 test. Univariate and multivariate logistic regression analysis were performed to evaluate the association between the presence of obstructive CAD at coronary angiography, the traditional assessment of pretest likelihood of obstructive CAD (Duke Clinical Score), and the following echocardiographic variables: left ventricular ejection fraction (LVEF), LV mass index, E/E' ratio, global longitudinal strain (GLS), global longitudinal strain rate (GLSR) and TMT. Receiver operator characteristic (ROC) curve analysis was performed to determine the accuracy of GLS to detect obstructive CAD, with an area under the curve value of 0.50 indicating no accuracy and a value of 1.00 indicating maximal accuracy. Statistical analysis was performed using the SPSS v.20.0 (IBM Corp, Somers, NY, USA). A p-value ≤0.05 was considered statistically significant.

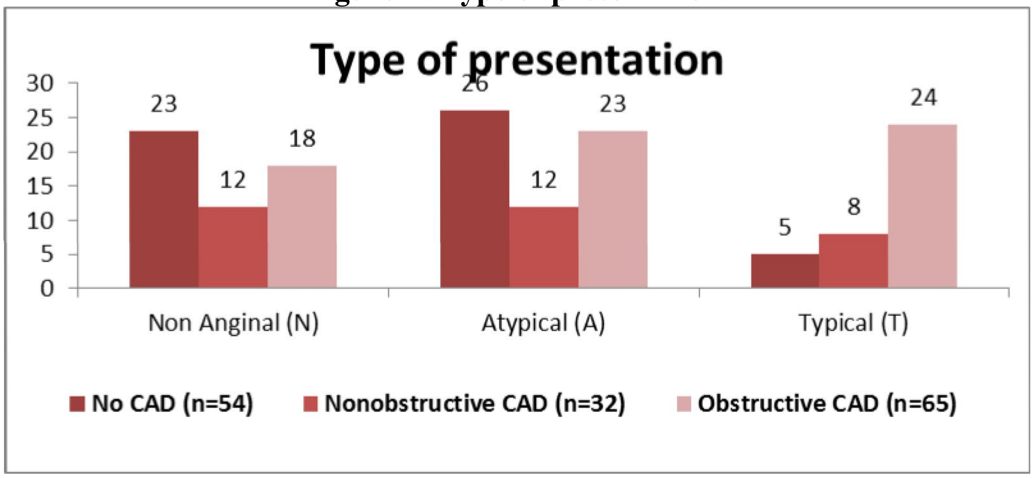
RESULTS:

The study participants were classified into three groups based on CAG report – patients with (1) normal coronaries (n=54; 35.7%), (2) non-obstructive CAD (n=32; 21.2%) and (3) obstructive CAD (n=65; 43.1%). Majority of the study population is contributed by patients aged >60 years, (n=50). Out of these patients, 7 had no CAD, 17 had non obstructive CAD and 26 had obstructive CAD. None of the patients aged <40 years had obstructive CAD. In the present study, males constituted 61.6% of total cases (n=93) whereas females were only 38.4% (n=58). Obstructive CAD was more common in men (83%).

Obstructive CAD was found in 54% of hypertensive subjects (p=0.00907), 56% of diabetics (p= 0.0003), 68.5% of patients with dyslipidemia (p= 0.0006), 71% of patients with a significant family history(p= 0.0368) and 44% of smokers(p= 0.8957).

Majority of the patients presented with atypical angina (40.3%) followed by non-anginal symptoms (35.2%) and typical angina (24.5%). Majority of the patients presenting with typical chest pain (64.8%) had obstructive CAD (p=0.0021). [figure-1]

Figure 1: Type of presentation.



CAD: coronary artery disease.

Table-1: Baseline characteristics.

Characteristic	**No CAD group (n=54)**	**Non-obstructive CAD (n=32)**	**Obstructive CAD (n=65)**	**p-value**
Age (in years)	52.2±3.2	58.6±2.8	61.8±2.5	<0.0001*
Age distribution:				
≤40 yrs	07	04	0	<0.0001*
41 – 50 yrs	29	05	16	
51 – 60 yrs	11	06	23	
>60 yrs	07	17	26	
Sex:				
Male	23	16	54	<0.0001*
Female	31	16	11	
Hypertension	18	16	40	0.00907*
Diabetes Mellitus	19	17	47	0.0003*
Dyslipidaemia	06	05	24	0.0006*
Family history	02	02	10	0.0368*
Smokers	05	05	08	0.8957

CAD: coronary artery disease; yrs: years. *indicates significant p-value.

Duke's clinical scoring system showed that 65 patients had low risk, 45 had medium risk and 41 had high risk. Majority of the cases in low Duke's score group had normal coronaries (63%, p<0.0001), whereas in medium and high Duke's score group majority had obstructive CAD (23%, p=0.1939 and 30%, p<0.0001 respectively).

Findings of echocardiographic examination are summarized in table-2. Mean GLSR values of -0.93, -0.87 and -0.78 were found in patients with normal coronaries, non-obstructive CAD and

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obstructive CAD respectively. Differences between the mean values of GLSR of these groups is statistically significant (figure-2). Mean GLS values of -15.56, -17.13 and -20 were found in patients with obstructive CAD, non-obstructive CAD and normal coronaries patients. Differences between the mean values of GLS of these groups is statistically significant (figure-3).

Table 2: Echocardiographic measurements.

Means of Echocardiographic parameters	No CAD (n=54)	Non-obstructive CAD (n=32)	Obstructive CAD (n=65)
LV EDV (ml)	97.3	101.1	105.3
LV ESV (ml)	40.1	38.2	41.2
LV mass index (ml)	91.8	98.9	108.9
LV EF (%)	63.6	62.3	62

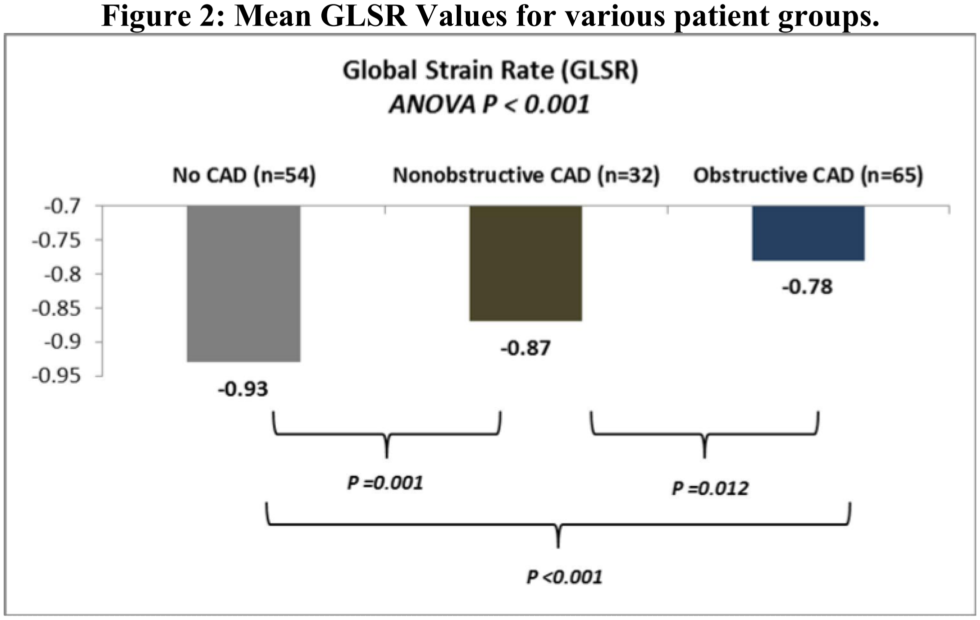
CAD: coronary artery disease; LV: left ventricle; EDV: end diastolic volume; ESV: end systolic volume; EF: ejection fraction.

Table 3: TMT results versus type of CAD.

TMT Result	No CAD (n=54)	Non-obstructive CAD (n=32)	Obstructive CAD (n=65)
Negative (n=72)	29	20	23
Positive (n=79)	25	12	42

TMT: tread mill test; CAD: coronary artery disease.

Figure 2: Mean GLSR Values for various patient groups.



GLSR: global longitudinal strain rate; CAD: coronary artery disease.

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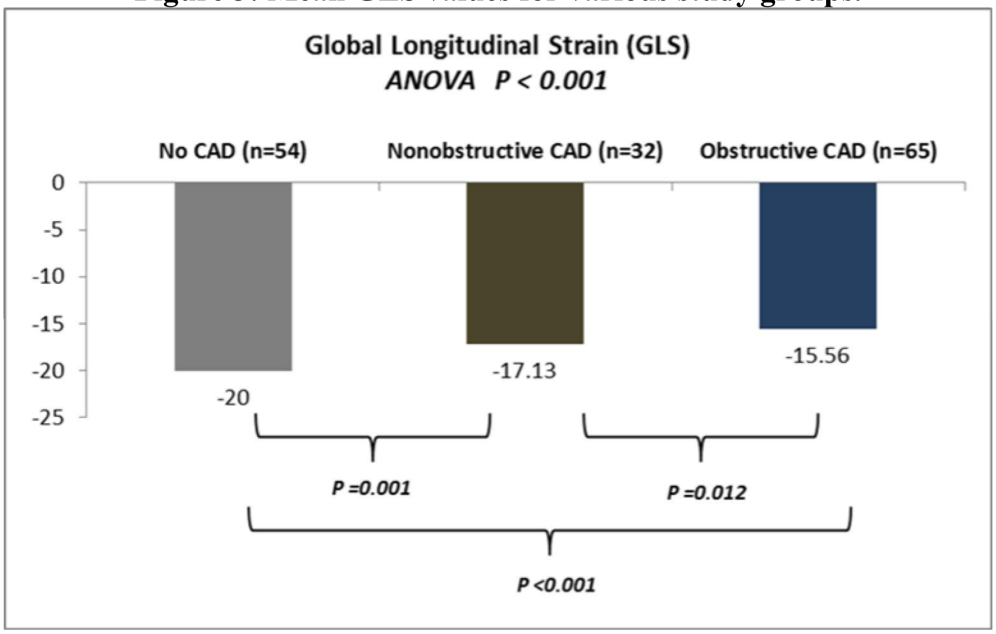
Figure 3: Mean GLS values for various study groups.



GLS: global longitudinal strain; CAD: coronary artery disease.

When the study subjects were evaluated with TMT, 72 were found normal (no ischemic changes in ECG after TMT). Out of these 72 patients, 29, 20 and 23 patients had normal coronaries, non-obstructive and obstructive CAD on further angiographic evaluation. 79 patients had ECG changes with exercise, among whom, 25, 12 and 42 patients were found to have no CAD, Non-obstructive CAD and obstructive CAD with further angiographic evaluation.Exercise electrocardiogram has the ability to predict obstructive CAD (p= 0.0087). [table-3]

Receiver Operating Characteristic (ROC) curve analysis revealed that Duke's clinical score has highest specificity and positive predictive value (PPV) whereas GLS has highest sensitivity and negative predictive value (NPV). Sensitivity, specificity, positive and negative predictive values of Duke's score, TMT and GLS are summarised in table-4.GLS ≥−18 % had the highest sensitivity and specificity for identification of patients with obstructive CAD (80% and 76%, respectively).

Table 4: Diagnostic validity of Duke's score, TMT and GLS.

	Sensitivity	**Specificity**	**PPV**	**NPV**	**AUC**
Duke's clinical Score	46%	87%	73%	68%	0.75
TMT	65%	57%	53%	68%	0.77

GLS	80%	76%	71%	83%	0.821
Duke's clinical score + TMT	69%	81%	75%	72%	0.78
Duke's clinical score + TMT + GLS	83%	86%	77%	88%	0.84

TMT: treadmill test; GLS: global longitudinal strain; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

Univariate analysis showed that Duke's Clinical Score, LVEF, LV mass index, GLS, GLSR, and TMT were significantly associated with obstructive CAD.However, at multivariate analysis, only Duke's Clinical Score, GLS (OR: 1.73, 95% CI: 1.39-2.15, p<0.001) and TMT (OR: 2.758, 95% CI: 1.15-6.64, p=0.0236) were found as independent factors associated with obstructive CAD. [Table-5]

Table-5: Univariate and multivariate analysis of various variables as correlates of CAD.

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Duke's Clinical Score:				
Intermediate vs Low	4.62 (1.96-10.88)	0.0005	4.91 (1.74-13.91)	0.0027*
High vs Low	12.04 (4.74-30.61)	<0.0001	8.58 (2.78-26.47)	0.0002*
LVEF	0.83 (0.73-0.95	0.0087	-	-
LV Mass Index	2.17 (1.48-3.16)	<0.0001	-	-
E/E' ratio	3.12 (2.09-4.65)	<0.0001	-	-
GLS	1.734 (1.44-2.09)	<0.0001	1.73 (1.39-2.15)	<0.0001*
GLSR	0.003 (0.001-0.024)	<0.0001	0.002 (0.001-0.005)	0.11
TMT	2.42 (1.24-4.69)	0.009	2.76 (1.15-6.64)	0.024*

LVEF: left ventricular ejection fraction; LV: left ventricle; GLS: global longitudinal strain; GLSR: global longitudinal strain rate; TMT: tread mill test; CI: confidence intervals. *indicates significant p-value.

DISCUSSION:

In this study,a total of 151 cases of stable ischemic heart disease were enrolled, and were evaluated with Duke's clinical score, Exercise stress testing, and 2D Speckle Tracking Echocardiography (2D STE). Subsequently, coronary angiogram was done. Later all the results were analyzed and calculation of pretest probability of coronary artery disease (CAD) using GLS measurement with 2D STE was found to be incremental to TMT and Duke's clinical score.

Major portion of the study population is contributed by patients aged >60 years, (n=50). Majority of patients with obstructive CAD was constituted by patients in the age group >60 years, (n=26), followed by 51-60 years age group (n=23). Obstructive CAD was more common in men (83%) whereas 57% of cases with normal coronaries were women. Non obstructive CAD was found to be of equal incidence in both genders. These findings are supported by data fromINTERHEART study, which shows a three-fold rise in CAD incidence in males compared

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to females and increased incidence with ageing, an approximate 50% incidence in the age group >60 years.[10]

It has been showed that the increasing incidence of non-obstructive CAD among women, who are less likely to have flow-limiting obstructive CAD compared with men presenting with similar symptoms.[11,12] This non obstructive CAD pattern and the tendency among women to have plaque erosion with subsequent thrombus formation has been studied and probably might be the reason for equal incidence of nonobstructive CAD among men and women in the present study.

The present study also signifies the association of unmodifiable and modifiable risk factors on both incidence and severity of CAD. Obstructive CAD was found in 54% of hypertensive subjects, 56% of diabetics, 68.5% of patients with dyslipidemia, 71% of patients with a significant family history and 44% of smokers. Third National Health Nutrition Examination Survey (TNHNES) stated that risk of CAD increases two-fold in patients with metabolic syndrome.[13] Other Indian studies signified that tobacco consumption was associated with 65% of cases, hypertension with 33% cases, diabetes with 32% cases, family history of CAD with 14% cases, Obesity with 13% cases and dyslipidemia with 12% of cases in a study conducted in a tertiary care institute in North India.[14] Bakhoum SWG showed a similar association of CAD with risk factors in which 59%, 72%, 64% and 41% association with Diabetes, Hypertension, dyslipidemia, and smoking respectively.[15]

The present study is comparable to Biering-Sørensen study, where 36% of the patients with non-significant CAD presented with typical angina, 41% with atypical angina and 23% with non-anginal pain. Out of 107 patients presenting with significant CAD, 79% presented with typical angina, 14% presented with atypical chest pain and 7% presented with non-angina symptoms.[16]

Out of 151 patients, 65 (43.1%) had low Duke's risk, 45 (29.8%) had medium risk and 41 (27.1%) had high risk scores. Among low Duke's risk score group, majority of the patients had normal coronaries (63%). Whereas in medium and high Duke's risk score groups, majority of the patients had Obstructive CAD (51.1% in medium and 73.1% in high Duke's risk groups respectively). These findings are correlated with the study findings of Nucifora et al.[17] in which 45% were found with intermediate Duke's risk score, 33% with high Duke's risk score and 22% with low Duke's score in Obstructive CAD. Study by Takamura K et al.[18] showed that 26% of the patients presented with low Duke's score, 37.2% with intermediate risk on Duke's score and 36.7% of patients with high Duke's score. In the present study, prediction of CAD risk using Duke's clinical score is found to have a sensitivity of 46%, specificity of 87%, PPV of 73% and NPV of 68%.

Echocardiographic results of our study are similar to that of study done by Bakhoum SWG et al. in which average LVEDV of 51.8 ml in patients with normal coronaries and 48.6 ml in patients with Significant CAD. LVESV was on an average, 31.4 ml in patients with normal coronaries and 30.4 ml in patients with significant CAD. Mean value EF was 67.7% and 67.2% in patients with normal coronaries and significant CAD respectively.[15] Another study showed the mean LVEDV for patients with normal coronaries, non-obstructive CAD and obstructive CAD were found to be 107 ml, 105 ml and 111 ml respectively. Mean LVESV was found to be 41 ml, 40 ml and 43 ml respectively for those with no CAD, nonobstructive CAD and Obstructive CAD. LV mass index on an average was 92 gm/m2 for patients with normal coronaries,

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99gm/m^2 for patients with non-obstructive CAD and 109 gm/m2 for patients with Obstructive CAD.[17]

In our study 72 patients were found negative on TMT, among which 29 had normal coronaries, 20 had non-obstructive CAD and 23 had obstructive CAD on angiographic evaluation. Furthermore, this study revealed sensitivity, specificity, PPV and NPV of 65%, 57%, 53% and 68% respectively for TMT. As per ACC/AHA 2002 guideline update for exercise testing, the sensitivity and specificity of TMT were found to be 68% and 77% respectively.[19]

The mean GLS of -15.56, -17.13 and -20 was obtained for patients with obstructive CAD, non-obstructive CAD and normal coronaries respectively. In our study, the mean GLSR values of -0.93, -0.87 and -0.78 were found in patients with normal coronaries, nonobstructive CAD and obstructive CAD respectively. GLS measurement at a value of -18 as a predictor of CAD has a sensitivity of 80%, specificity of 76%, PPV of 71% and NPV of 83% in our study. Our findings are similar to that of studies done by Bakhoum SWG et al. and Nucifora G et al.[15,17]

The present study shows that Duke's clinical score alone can predict the possibility of CAD by 75% accuracy and along with TMT, the predictability increased to 78%. GLS measurement (at a value of -18) alone can predict CAD possibility by 82.1% accuracy. However, GLS measurement along with Duke's score and TMT increases the accuracy of prediction of CAD possibility by 84%. Studies have shown a similar incremental effect of GLS in CAD prediction.In a study done by Biering-Sørensen T et al., the diagnostic performance of the exercise test was significantly improved by GLS in terms of a significant increased AUC for the exercise test in combination with GLS compared with the exercise test alone (84% versus 78%; p=0.007).[16]

Limitations: The current study doesn't consider Radial, circumferential strain and, Diastolic dysfunction in assessment of coronary artery disease.It is a single centre study.

CONCLUSIONS:

Duke's score is a good predictor of Obstructive CAD. Measurement of GLS (at a value of -18) had an incremental effect in prediction Obstructive CAD over Duke's clinical scoring system and TMT.GLSR value of ≥-0.78 and GLS value of ≥-18 were more sensitive and more specific in prediction of Obstructive CAD. Duke Clinical Score,TMT and GLS are independent factors associated with obstructive CAD.

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