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ORIGINAL ARTICLE

Incremental Value of CHA_2DS_2-Vasc Score in Boosting the Diagnostic Performance of Dobutamine Stress Echocardiography

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ABSTRACT

Background: Stress echocardiography today is a robust imaging modality used for diagnosing coronary artery disease (CAD). The CHA_2DS_2-VASc score is a validated risk score, its utility has been expanded beyond predicting the stroke risk in patients with atrial fibrillation to CAD prediction and risk assessment in many studies.
We hypothesized that calculation of CHA_2DS_2-VASc score in cases with positive DSE for coronary ischemia may provide an incremental value in improving the diagnostic accuracy of DSE and predicting truly positive cases.
Methods: Our cross-sectional study involved 60 patients who received positive DSE results for coronary ischemia and underwent subsequent coronary angiography, they were divided according to the presence of CAD as true positive and false positive groups. CHA_2DS_2–VASc score was calculated and correlated to the wall motion score index at peak stress and the presence of CAD.
Results: We observed a significant association between CHA_2DS_2–VASc score ≥2 and the presence of CAD, p=0.001. Also, combining the WMSI at cut of >1.17 and CHA2DS VAS2C score ≥ 2 revealed a sensitivity of 80.5%, a specificity of 79%.and 80% accuracy and PPV of 89.2% for prediction of truly positive CAD in patients with positive DSE,
Conclusions: We can conclude that the addition of the CHA_2DS_2–VAS_2C score to the DSE positive model can improve the diagnostic accuracy of the test and its predictive value for true positive cases.
Keywords: CHA_2DS_2–VAS_2C score; Dobutamine stress echocardiography; Coronary artery disease.

INTRODUCTION

Stress echocardiography is a reliable non-invasive tool for diagnosis of myocardial ischemia. It has been validated to diagnose and assess patients presenting with chest pain with an intermediate probability of obstructive coronary artery disease. DSE has the best specificity (88%) and high negative predictive value for CAD detection among the other tests [1]. Despite its high specificity, we continue to find a patient category having false-positive results with subsequent unnecessary interventions [2].
CHA_2DS_2–VASc score which is a validated score in thromboembolic risk assessment and the guidance of antithrombotic therapy in atrial fibrillation patients is among the clinical scores in common use for risk stratification of patients with coronary artery disease and has been introduced as a scoring system to predict the severity of CAD in recent research [3-4]. So we intended to apply the CHA_2DS_2–VAS_2C score in positive DSE models and investigate its possible role in boosting the test specificity and predictive value for true positive cases.

METHODS

This Observational cross-sectional study involved sixty patients who were diagnosed with DSE to be positive for ischemia and who underwent subsequent coronary angiography were recruited in our study. They were divided according to coronary angiography results as true positive and false positive cases according to evidence of CAD (diagnosed when ≥ 50% of the luminal diameter at a major epicardial vessel. It has been carried out at the Department of Cardiology, Zagazig University Hospitals, and was approved by the local research

ethics committee of the Faculty of Medicine, Zagazig University at number, ZU-IRB#9738-30-8-2022. The work was concordant with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consents were obtained from all participants and patients with negative DSE were excluded.

Dobutamine Stress Echocardiography:

As standard for DSE testing, gradual dobutamine infusion is started at a rate of 5 mcg/kg/min and increased at three-minute intervals to 10, 20, 30, and 40 mcg /kg/min. During the test protocol, images are acquired before starting the infusion, at the end of each stage, and during the recovery stage. Endpoints are reaching the target heart rate (85% of the age-predicted maximum heart rate), new or worsening segmental wall motion abnormalities, significant arrhythmias, and intolerable symptoms. If the target heart rate is not achieved, atropine is added in divided doses of 0.25 mg to 0.5 mg for a total of 2 mg [5]. Segmental wall motion was judged by experienced cardiologists as the following: Normal=1, Hypokinesia=2. Akinesia=3, dyskinesia=4. The wall motion score index (WMSI) represents the average value of analyzed segments. It is calculated by dividing the sum of the wall motion scores of all segments by 17 [6].

Calculation of CHA_2DS2−VASc score:

The CHA2DS2−VASc score was calculated, (one point each for the following parameters; congestive heart failure, hypertension, diabetes mellitus, age between 65 and 75 years, vascular disease and female sex), and two points for stroke/transient ischemic attack and age greater than 75 years. The maximum score was nine points [7]

Coronary angiography:

DSE-positive patients who underwent subsequent coronary angiography were included in our study. Standard coronary angiography was done via a transfemoral approach using Seldinger's technique. The angiograms were done in all the standard views using right and left coronary catheters. CAD was diagnosed when ≥ 50% of the luminal diameter at a major epicardial vessel was stenosed [8].

Statistical Analysis:

IBM Corp was used for Data tabulation and analysis. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. t-test was used to compare two groups of normally distributed variables. The chi-square test with Fisher exact was used for comparing categorical variables when appropriate. Logistic regression to predict the dependent variable from independent variables. All tests were two-sided. p-value < 0.05 was considered statistically significant, while p-value ≥ 0.05 was considered insignificant. Receiver Operating Characteristic (ROC) curve to draw the roc curve; the true positive rate (Sensitivity) is plotted on the (y) axis and the false positive rate (100- Specificity) on the (x) axis.

RESULTS

In our study nineteen patients (31.7 %) had false positive DSE, they showed a lower prevalence of diabetes p<0.001, lower values of HBA1C p<0.026, lower previous vascular events p< 0.04 and ICU admission (p < 0.04) were observed to be lower. Regarding other clinical variables; age, sex, smoking hypertension, BMI and dyslipidemia were similar to the true positive group (p >0.05) (table 1).

Our study showed higher WMSI in the positive group with a statistically significant difference (1.23±0.13 vs 1.14±0.05 at p <0.005). and the interpreted CHA_2DS_2-VASc score between groups showed higher values; 2, 3, and 4 among positive cases (p < 0.02, 0.004 & 0.02 respectively) while low values were recorded in the negative group (table2).

We found a direct correlation between CHA2DS VAS2C score and WMSI and (r= 0.349, p<0.006) (table 3)

When we combined CHA_2DS_2-VASc at cut off value of ≥ 2 and WMSI at cut off value of>1.17, we observed that 23 patients (88.5%) of patients could be correctly diagnosed true positive while only three patients (11.5%) showed false positive results, p=0.003 (table 4).

Multivariate logistic regression analysis revealed that CHA_2DS_2-VASc score ≥2 added to DSE could predict true positive CAD at 18 odds ratio with 95% CI (4.13 -78.7) P < 0.001. While WMSI at peak stress >1.17 at 4.55 odds ratio, 95% CI (1.025-20.206), p <0.046 can predict coronary artery disease (table 5).

WMSI alone at peak stress at a cutoff value of >1.17, revealed a sensitivity of 75.6%, a specificity of 52.6%, PPV 77.5 % and 68.3% accuracy. AUC (0.72(95%CI, 0.59 -0.85) So, WMSI alone is fair in the diagnosis of coronary disease in patients with DSE. (table 6 and Figure 1).

The addition of CHA_2DS_2-VASc score at a cut-off value ≥ 2 to WMSI at a cut-off value >1.17 robustly improved the dobutamine stress echocardiography sensitivity for the diagnosis of CAD; 80.5%, with a specificity of 79 %., PPV of 89.2% and 80% accuracy AUC, 0.84 (95%CI, 0.73-0.94) (table 7 and Figure 2).

Table 1: Demographic characteristics, risk factors, laboratory and clinical data in studied groups**.**

Patients characteristics	CAD groups		T	p-value
	True Positive n.41 Mean± SD Median (range)	False Positive n.19 Mean± SD Median (range)		
Age per years	60.8±59 60(45-69)	57.7±7.3 60(48-75)	1.76	0.089
Sex (n%) Females Males	17(41.5%) 24(58.5%)	3(15.8%) 16(84.2%)	χ^2 3.9	0.051
Weight(kg)	82.93±11.3 80(62-120)	84.53±11.4 85(65-100)	0.51	0.61
Height (m)	1.66±0.09 1.65(1.5-1.77)	1.7±0.05 1.7(1.6-1.8)	1.92	0.056
BMI	30.3±4.91 28.7(24.7-41.5)	28.6±3.87 28.4(21.6-34.6)	1.35	0.18
Body surface area (m^2)	1.97±0.15 1.98(1.6-2.4)	1.98±0.14 1.98(1.8-2.2)	0.22	0.83
Cholesterol mg/dL	200.22±17.34	193.07±11.5	1.63	0.11
LDL mg/dL	107.99±18.1	98.9±18.05	1.810	0.075
HDL mg/dL	39.39±4.62	37.5±2.87	1.62	0. 11
HBA1C%	6.7±1.03	6.11±0.66	2.292	0.026*
Creatinine mg/dL	0.84±0.18	0.89±0.21	1.06	0.29
Hypertension %	27 (65.9%)	9 (47.4%)	1.85	0.12
Chronic Heart disease %	3 (7.3%)	2 (10.5%)	1.06	0.68
Diabetes %	21 (51.2%)	2 (10.5%)	9.1	0.001*
Smoking %	17 (41.5%)	10 (52.6%)	0.65	0.42
previous ICU admission %	12 (29.3%)	1 (5.3%)	4.41	0.04*
Previous PCI %	10 (24.4 %)	1 (5.3%)	3.17	0.08
History of CABG %	2 (4.9%)	0	F	0.49
Stroke %	2 (4.9 %)	0	F	0.49
Vascular event %	12 (29.3 %)	1 (5.3 %)	4.41	0.04*

χ^2 Chi square test , f =Fisher exact test , *p<0.05 significant t Test , χ^2 Chi square test , no significant p>0.05, BMI; body mass index, LDL; low density lipoprotein, HDL; high density lipoproteinICU; intensive care unit, PCI;percutaneous coronary intervention, CABG;coronary artery bypass graft,

Table 2: Comparison of WMSI and CHA2DS2-VASc score between groups

Variables Mean± SD Median (range)	CAD Group				U	p-value
	True Positive n.=41		False Positive n.=19			
WMSI	1.23±0.13		1.14±0.05		2.8	0.005*
CHA_2DS_2-VASc SCORE	2.34±1.1 2(0-4)		0.89±0.87 1(0-3)		U	0.0001
Zero	3	5	7	36.8	Ref	
1.00	5	8.3	8	13.3	0.99	
2.00	14	23.3	3	15.8	0.02*	
3.00	13	21.7	1	1.7	0.004*	
4.00	6	10	0	.0	0.02*	

WMSI; wall motion score index, Ref: Reference group, U: Mann Whitney Test, f: Fisher exact test, *p<0.05 significant

Table 3: Correlation matrix between WMSI Score, CHA_2DS_2-VASc score and different studied parameters.

Variables	CHA2DS VAS2C SCORE		WMSI	
	r	P	r	P
WMSI	**0.349****	**0.006**	1	.
age per years	0.017	0.899	0.099	0.454
Weight kg	-0.166	0.205	0.056	0.672
Height m	-0.133	0.311	0.039	0.765
Body mass index	-0.043	0.743	0.092	0.486
Body surface area m^2	-0.156	0.233	0.041	0.75
Total Cholesterol mg/dl	**.335****	**0.009**	0.166	0.206
LDL mg/dl	0.081	0.539	0.036	0.782
HDL mg/dl	0.112	0.395	.211	0.097
HBA1C	**.594****	**0.0001**	0.161	0.22
Creatinine mg/dl	0.127	0.335	-0.225	0.083

WMSI; wall motion score index LDL; low density lipoprotein, HDL; high density lipoprotein **r** correlation coefficient ** Correlation is significant at the 0.01 level (2-tailed) * Correlation is significant at the 0.05 level (2-tailed)

Table (4): Combined CHA_2DS_2-VASc score and WMSI at the studied cut-off values and their association with CAD, coronary territory lesion in the studied patients:

Variables			Both CHA_2DS_2-VASc score + WMSI		χ^2	p-value
			Yes	No		
CAD disease	**True Positive**	N	23	18	8.6	0.003*
		%	88.5%	52.9%		
	False Positive	N	3	16		
		%	11.5%	47.1%		
Coronary artery territory	**LAD**	N %	14 (60.9%)	11(61.1%)	0.01	0.99
			9(39.1%)	7(38.9%)		
	Non LAD		10 (33.3%)	8(72.7%)		

χ^2 Chi-square test f: Fisher exact test p>0.05: Non-significant * p<0.05: Significant

WMSI; wall motion stress index, CAD; coronary artery disease, LAD ; left anterior descending

Table 5: Multivariate Logistic regression for prediction of true positive CAD cases in patients with positive DSE

	B	Sig.	Exp(B)	95% C.I. for EXP(B)	
				Lower	Upper
Multivariate Logistic					
CHA2DS VAS2C ≥2	2.89	0.0001*	18.1	4.13	78.7
WMSI >1.17	1.51	0.046*	4.550	1.025	20.206

WMSI; wall motion stress index, Exp (B) : odds ratio (OR), C.I: confidence level. *P<0.05: significant

Table 6: Predictive value of WMSI for CAD diagnosis in patients with positive DSE.

Cut off level	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (95%CI)	P
WMSI >1.17	75.6%	52.6%	77.5%	50.0%	68.3%	0.72(0.59 -0.85)	0.007

PPV; positive predictive value, NPV; negative predictive value, AUC: area under the curve, CI: confidence interval.

Table 7: Predictive value combined CHA_2DS_2-VASc and WMSI for CAD diagnosis in patients with positive DSE.

Cut off level	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (95%CI)	P
CHA_2DS_2-VASc score ≥2 and WMSI >1.17	80.5%	79%	89.2%	65.2%	80%	0.84(0.73-0.94)	0.0001*

PPV; positive predictive value, NPV; negative predictive value ,AUC: area under the curve, CI: confidence interval, *p=significant

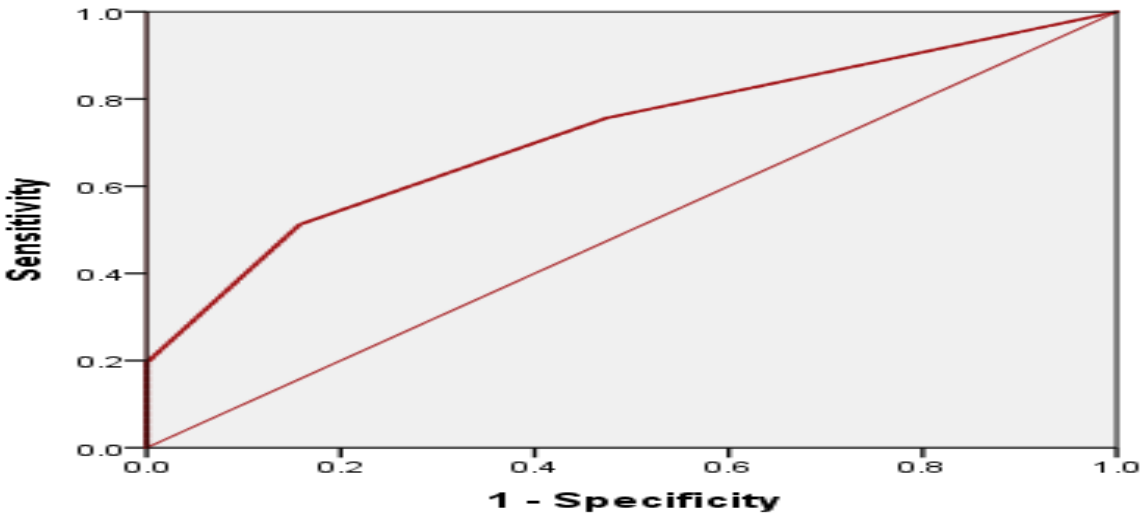

Figure 1: ROC curve of WMSI for prediction of CAD in patients with positive DSE.

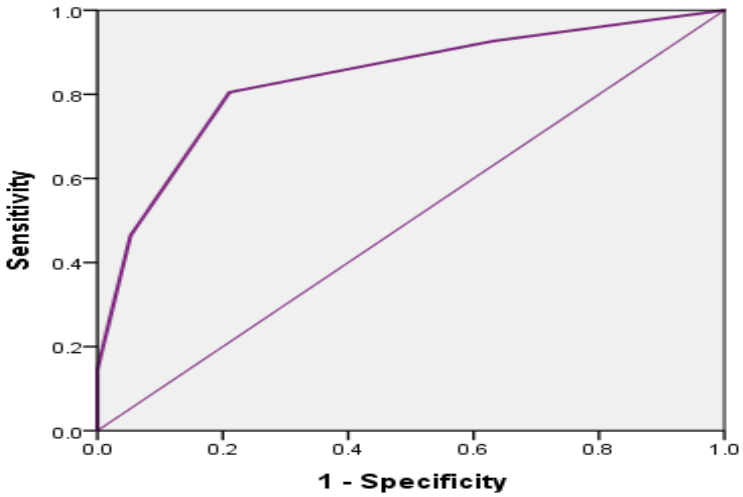

Figure 2: ROC curve of combined WMSI SCORE >1.17 and CHA_2DS_2-VASc score for prediction of coronary artery disease in patients with positive DSE.

DISCUSSION

Despite the high specificity and sensitivity of DSE for CAD diagnosis, false-positive tests (<50% luminal diameter stenosis on the subsequent coronary angiogram) are continuously found. Diverse clinical conditions may contribute to such results; hypertensive response to stress, microvascular abnormalities, endothelial dysfunction and epicardial coronary artery spasm which may precipitate ischemia in absence of fixed obstructive lesions [9, 10].

Clinical risk scores are key elements which facilitate proper diagnostic evaluation and guiding management. In our study, we combined the CHA_2DS_2-VASc score with DSE positive model, to study its added value in the prediction of true positive cases and improve the test specificity in our echo lab. We observed that there was a significant difference between the studied groups; with a high prevalence of DM and higher HBAIC level in the true positive group ($p<0.001$ & $p<0.026$ respectively). This is concordant with previous studies that reported non-significant differences between true positive and false positive DSE regarding clinical risk factors other than diabetes ($p<0.05$) [11].

Patients with true positive DSE showed higher WMSI at peak stress & higher CHA_2DS_2–VASc score, $p<0.005$ and $p<0.001$ respectively. This concord with Guerreiro et al., who reported a significantly higher WMSI in true positive than false positive cases. [11].

Barman et al. also reported that the CHA2DS2–VASc score was independently associated with the presence of coronary artery ectasia [12]

Our study showed a relatively lower specificity when WMSI alone was applied for the prediction of test specificity, this may be attributed to over-interpretation, especially for basal inferior & basal septal segments. Also, microvascular abnormalities may be a source of such false positive cases.

To the best of our knowledge, we are the first to introduce the CHA2DS VAS2C score in addition to DSE to assess the possible improvement in diagnostic accuracy. Its utility has been expanded beyond thromboembolic risk prediction in patients with atrial fibrillation, several recent studies have shown that CHA2DS2-VASc score can also be used to predict CAD and adverse events in patients with an acute coronary syndrome without AF, including no-reflow after PCI [13].

There was a significant association with true positive cases when CHA_2DS_2-VASc was combined with WMSI, $p=0.003$.

WMSI revealed a sensitivity of 75.6%, a specificity of 52.6% and 68.3% accuracy, so it was fair to predict true positive cases alone. the combination of the CHA_2DS_2-VASc score at a cut-off value of ≥ 2 and WMSI at peak stress >1.17 improved the diagnostic accuracy of the test in our study by 26% and its predictive value for true positive cases. This revealed a sensitivity of 80.5%, a specificity of 79%.and 80% accuracy (AUC; 0.84, CI (0.73-0.94), P value <0.001)

Previous research investigated the predictive value of CHA_2DS_2-VASc score for CAD, reported a cut-off

value of 1.5 as an effective cutoff point for coronary artery ectasia with 73% sensitivity and 51% specificity (AUC = 0.71, 95% CI [0.64-0.78], P = 0.001) (12). while higher specificity was reported by Barman et al.; with a cut-off value of 2.5, for the CHA2DS2-VASc score (without age), was found to be a good predictor of no-reflow with a 78% sensitivity and 81% specificity (AUC: 0.860, 95% CI: 0.815–0.904) [13].

Cetin et al. showed the CHA2DS2-VASc-HS score at a cut-off value of >2 could predict severe CAD, at a sensitivity of 85.2% and specificity of 57.5% (AUC 0.80, 95% CI, 0.76 to 0.83, p-value <0.001) [14].

CONCLUSIONS

We can conclude that reappraisal of DSE-positive cases after the addition of the $CHA2DS_2$–VAS2C score may improve the diagnostic accuracy of the test and its predictive value for true positive cases of coronary artery disease so unnecessary invasive intervention can be avoided.

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