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Assessing the Severity of Coronary Artery Disease Among Diabetic Patients and Generation of a Novel Coronary Artery Disease Risk in Diabetes Score (CADRIDS)

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Abstract
Background: *Diabetes increases the risk of microalbuminuria, increased carotid intima media thickness, and an abnormal ankle brachial pressure index. This study aims to evaluate the severity of CAD in relation to these three tests and generate a simple score to predict the risk of CAD in diabetic patients.*
Materials and Methods: *270 diabetic patients participated in this cross-sectional study. We performed these tests on diabetic patients undergoing coronary angiograms and compared the results with the obtained angiographic syntax scores. We generated and validated a new Coronary Artery Disease Risk in Diabetes Score.*
Results: *For severe CAD, microalbuminuria had good (84.5%) sensitivity and CIMT was highly specific (92.5%). For moderate-to-severe CAD (syntax >22), microalbuminuria was 80.9% sensitive and 87.6% specific. All three tests had a combined sensitivity of 96.9% and 90% for severe and moderate-severe CAD, respectively. There was a statistically significant relationship ($p < 0.001$) between each test and the severity of CAD. Also, CADRIDS is statistically significant ($p < 0.01$) in predicting the severity of CAD among diabetics.*
Conclusion:*To conclude, CADRIDS is an effective screening tool for predicting the severity of CAD in diabetics. The CADRIDS cut-off scores of 4, 3, and 2 are highly specific, with good sensitivity for severe, moderate-severe, and CAD, respectively. Clinicians can use CADRIDS as an effective screening tool to assess the community's atherosclerosis burden.*
Keywords*: coronary artery disease;diabetes;cardiovascular risk score;microalbuminuria;carotid intima media thickness; ankle brachial pressure index; syntax score.*

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I. INTRODUCTION

People with diabetes are more likely to get atherosclerosis for a number of reasons, such as (a) metabolic factors like high blood sugar, high cholesterol, and insulin resistance that affect endothelial cells[1,2], (b) platelet dysfunction, and (c) abnormal blood clotting[3]. Increased carotid intima media thickness (CIMT) confers a risk of vascular events like coronary artery disease (CAD) and stroke[4]. Diabetes greatly increases the risk of peripheral artery disease (PAD). Previous studies have reported a close correlation between low ankle brachial pressure index(ABPI) and various cardiovascular risk factors[5]. Microalbuminuria, in addition to serving as a marker of early kidney disease in diabetic patients, is also a predictor of CAD[6]. The albumin-creatinine ratio, also known as microalbuminuria, is a marker of atherogenesis[7]. Although established risk scores like the Framingham risk factors score have been present in screening people who are at increased risk of cardiac events, many patients seek medical advice after becoming symptomatic or with established coronary atherosclerosis. This affects the prevention of acute coronary events through early diagnosis[8]. In addition to more traditional

methods for early detection, less cutting-edge methods like CIMT[7,9], ABPI, and simple risk scores are becoming more and more important for diabetics. These can help with early detection before acute symptoms appear.

Despite the well-established potential hazards of consequent CAD in diabetic patients, there is a lack of studies that compare and study ABPI, CIMT, and microalbuminuria in the same patient, particularly in patients with diabetes mellitus and their relationship with CAD severity. Therefore, we generated the Coronary Artery Disease Risk in Diabetes Score (CADRIDS) using these three simple noninvasive screening tests in diabetic patients and correlated it with their corresponding coronary angiographic SYNTAX scores. This study aims to assess the severity of CAD among diabetic patients with CIMT, ABPI, and microalbuminuria, and to generate a simple score to predict the risk of CAD among diabetic patients.

II. MATERIAL AND METHODS

This is a cross-sectional study conducted on 270 patients with diabetes mellitus at the cardiology department of Government Chengalpattu Medical College Hospital between February 2023 and July 2023. We obtained Institutional Ethical Committee (IEC) approvaland informed consent. We included diabetic patients who underwent coronary angiograms (CAG) in the hospital. We excluded patients with macroalbuminuria, chronic kidney disease, vasculitis malignancy, vascular malformations, and those who were not willing to undergo CAG. Before cardiac catheterization, we subjected all included patients to three tests (Test A-urinary microalbumin (albumin creatinine ratio), Test B-CIMT, and Test C-ABPI) and correlated the results with the corresponding coronary angiographic SYNTAX scores. While a 24-hour urine collection remains the most effective method for detecting microalbuminuria, studies have shown that the urinary albumin-to-creatinine ratio (ACR) test is equally sensitive and specific, making it a convenient daily test[10]. The National Kidney Foundation (NKF) says that microalbuminuria (ACR 30-300 mg/g) is a moderately increased level of albuminuria. This means that the body is removing albumin at a rate that is above the normal range but below the total protein limit found by tests.

In each common carotid artery, the distal 1 cm of the far wall was measured as per the American Society of Echocardiography (ASE) Task Force statement[11]. Compared to the normative data[4], we considered CIMT at or above the 75th percentile for age, gender, and race to be increased[11]. We measured the systolic blood pressures of the dorsalis pedis and tibial artery, and the higher value was taken as the numerator. We chose the higher of the two systolic blood pressures of the right and left upper limbs as the denominator. The ratio between them defines the ankle brachial pressure index in accordance with theAmerican Heart Association and the Inter-Society Consensus guidelines for the treatment of peripheral artery disease. We classified an ABI value between 0.9 and 0.8 as mild arterial disease, a value between 0.4 and 0.8 as moderate PAD, and an ABI of less than 0.4 as severe PAD[12]**.** For PAD, an ankle brachial pressure index value of 0.9 or less has 100% sensitivity and 95% specificity, according to the literature[13]. Hence, a value of 0.9 or less was considered abnormal ABPI in this study.

The goal was to create a combination test with high sensitivity for effective community screening. Therefore, we performed these three tests (microalbuminuria, CIMT, and ABPI) in parallel, applying the OR rule, which considers a positive diagnosis if either test is positive. We assigned a syntax score to all of the patients' coronary angiograms. We categorized mild CAD (low risk), moderate (intermediate risk), and severe CAD (high risk) for syntax scores 1–22, 23–32, and more than 32, respectively, based on the risk.

The creation of anew Coronary Artery Disease Risk in Diabetes Score (CADRIDS)

We assigned scores of 0 and 1 to patients with normal ACR and microalbuminuria, respectively. In this study, almost all of the abnormal CIMT values were greater than 0.7 mm. Carotid intima media thickness values between 0.6 and 0.7 mm were considered normal in healthy middle-aged adults. A significantly high risk of CHD has been associated with CIMT 1 mm or above[14]. The mean and peak CIMT values reported in the literature for normal Indian adults were 0.67 and 0.70 mm, respectively[15]. A systematic review and meta-analysis by Lorenz et al. demonstrated that CIMT above 0.85 mm has a high positive predictive value and specificity for the presence of CAD[16]. Therefore, we assigned a score of 3 to CIMT exceeding 1 mm, a score of 2 to CIMT falling between 0.85 and 1 mm, a score of 1 to abnormal CIMT values based on reference values[4], all exceeding 0.7 mm in this study, and a score of 0 to normal CIMT. Patients with normal ABPI scored 0. Abnormal ABPI values <0.9 but > 0.8, which indicate some arterial disease[12], were given a score of 1; values between 0.4 and 0.8, which indicate moderate arterial disease, were given a score of 2. ABPI values less than 0.4 received a score of 3. In patients with diabetes, the duration carries a significant impact on cardiovascular risk. Diabetic individuals with a history of diabetes lasting more than 10 years can be at increased risk[17]. Patients with a 5- to 10-year duration of diabetes showed a statistically significant increase in the average syntax score, vessel score, and coronary collateral grade compared to those with a less than 5-year history[18]. Therefore, we assigned a score of 3 to patients with more than 10 years of diabetes history, 2 to those with 5–10 years of

duration, and 1 to those with less than 5 years of diabetes history. CADRIDS had a maximum and minimum score of 10 and 1, respectively (Table 1).

Table 1: Coronary Artery Disease Risk in Diabetes Score (CADRIDS)

Domain	0	1	2	3
Microalbuminuria	Absent	Present	-	-
CIMT (mm)	Normal range	Abnormal to <0.85	0.85-1	> 1
ABPI	Normal range	0.8- 0.9	0.4-0.8	< 0.4
Duration of diabetes	-	< 5 years	5- 10 years	>10 years

CIMT:carotid intima media thickness; ABPI:ankle brachial pressure index.

Statistical analysis

We entered CADRIDS, microalbuminuria, CIMT, ABPI measurements, angiographic SYNTAX scores, and other parameters into Microsoft Excel. SPSS software was used for statistical analysis. We calculated chi-square tests and p value less than 0.05 was considered statistically significant. We also calculated sensitivity, specificity, and positive and negative predictive tests for validating individual tests and CADRIDS.

III.RESULT

The Department of Cardiology at Govt. Chengalpattu Medical College conducted this study. The study included 270 diabetic patients, with a mean age of 54 years. 161 (59.6%) patients were males, and 109 (40.4%) were females. 257 (95.2%) patients had diabetes and were on oral hypoglycemic drugs, while 13 (4.8%) were on insulin. 197 (73%) patients had uncontrolled diabetes, and for 73 (27%) patients, the condition was under control. 118 (43.7%) were smokers, and 96 (35.5%) were alcoholics. 58 (21.5%) patients had severe CAD (syntax >32), 115 (42.6%) had moderate CAD (syntax 22–32), 69 (25.5%) individuals had low risk (syntax <22), and 28 (10.4%) people had normal epicardial coronaries. 152 (56.3%) patients had microalbuminuria, 57 (21.1%) had increased CIMT, and 39 (14.4%) had abnormal ABPI (Table 2).

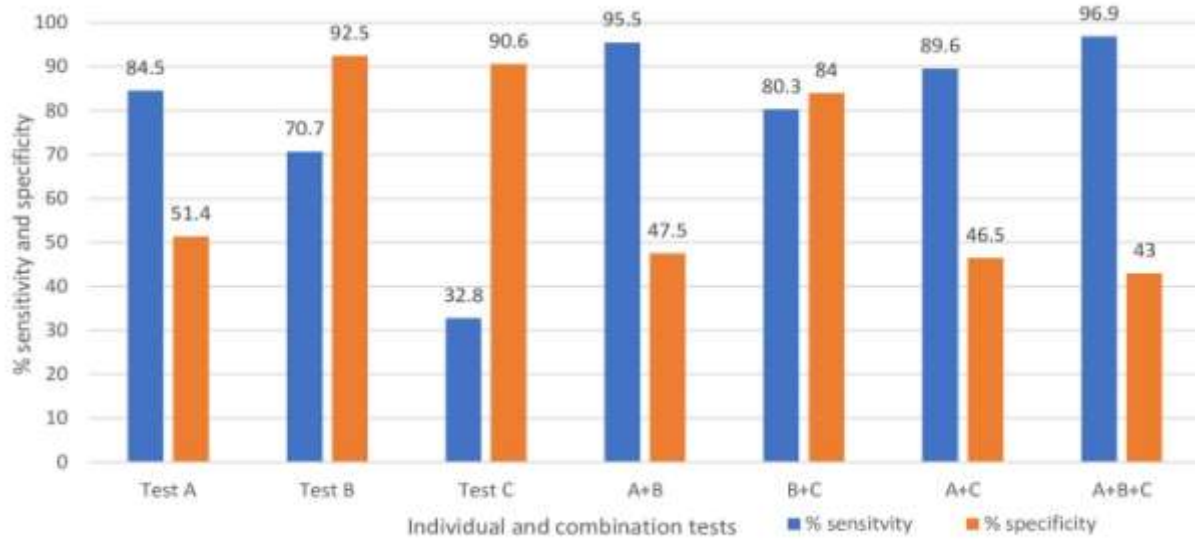
Table 2. Individual Tests and their corresponding syntax scores (severity of CAD)

SYNTAX SCORE	Test A: Microalbuminuria			Test B: CIMT			Test C: ABPI		
	present	absent	total	increased	normal	total	abnormal	normal	total
<22	12	85	**97**	3	94	**97**	2	95	**97**
22-32	91	24	**115**	13	102	**115**	18	97	**115**
>32	49	9	**58**	41	17	**58**	19	39	**58**
Total	**152**	**118**	**270**	**57**	**213**	**270**	**39**	**231**	**270**

CIMT: carotid intima media thickness; ABPI: ankle brachial pressure index.

The sensitivity and specificity of Test A (microalbuminuria) for predicting severe CAD (Syntax > 32) are 84.5% and 51.4%, respectively, with a high negative predictive value (NPV) of 92%. Microalbuminuria is 80.9% sensitive and 87.6% specific for moderate-severe CAD (Syntax > 22), with 72% NPV and 92% PPV. The sensitivity of Test B (CIMT) for predicting severe CAD (syntax > 32) was 70.7%, with 92.5% specificity. For moderate-severe CAD (Syntax > 22), CIMT is 31.2% sensitive and 96.9% specific, with a high PPV of 94.7%. Test C, an abnormal ABPI, is 32.8% sensitive and 90.6% specific for severe CAD, with a good NPV of 83%. It is 21.4% sensitive and 97.9% specific for moderate-to-severe CAD, with a 94.8% PPV. All of the chi-square values obtained separately for tests A, B, and C were statistically significant ($p < 0.001$) in predicting CAD severity. When testing A and B in parallel for severe CAD (syntax > 32), their sensitivity is 95.5% and their specificity is 47.5%. For A and C, it was 89.6% sensitive and 46.5% specific. It was 80.3% sensitive and 84% specific for predicting severe CAD in B and C, respectively. Combining two tests with a third (A+B+C) resulted in the highest sensitivity of approximately 96.9% and a specificity of 43% (Figure 1).

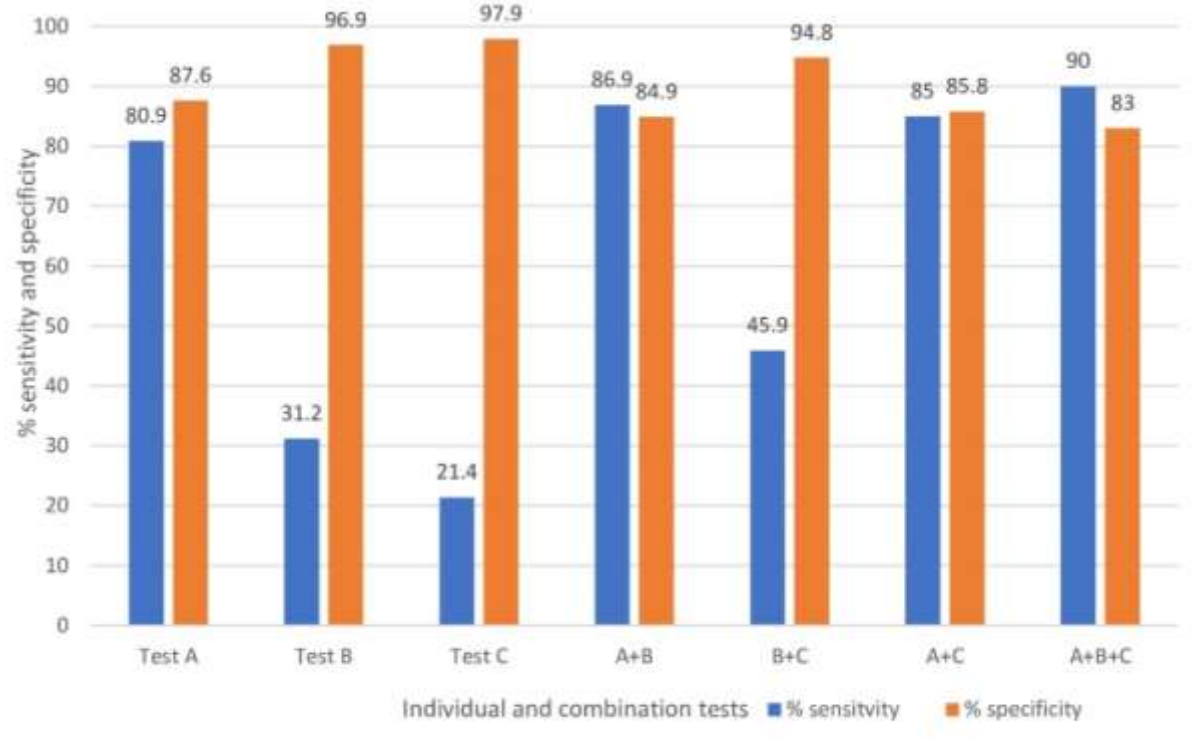
Figure 1: Validation of tests for severe CAD both individually and in combination



Test A: microalbuminuria; Test B: CIMT (carotid intima media thickness); Test C: ABPI (ankle brachial pressure index). A+B, B+C, A+C, A+B+C: Tests combined and done in parallel.

For predicting moderate-severe CAD (syntax > 22) combinations, tests with sensitivity and specificity were 86.9% and 84.9% (A+B); 85% and 85.8% (A+C); 45.9% and 94.8% (B+C), respectively. Combining the two combination tests with the third test (A+B+C) resulted in the highest sensitivity of about 90% and a specificity of 83% for predicting moderate-severe CAD (Figure 2).

Figure 2: Validation of tests for moderate-severe CAD both individually and in combination.



Test A: microalbuminuria; Test B: CIMT (carotid intima media thickness); Test C: ABPI (ankle brachial pressure index). A+B, B+C, A+C, A+B+C: Tests combined and done in parallel.

CADRIDS

As stated above, we obtained the Coronary Artery Disease Risk in Diabetes Score (CADRIDS). Seven patients, six with severe CAD and one with moderate and severe CAD (syntax > 22), achieved the highest score of 9. No patient achieved a score higher than 10, and the most common score was 1. (Table 3).

Table 3: Frequency of individual CADRIDS and severity of CAD.

CADRIDS	Syntax 0	Syntax 1-22	Syntax 22-32	Syntax >32	Total
1	26	40	7	2	75
2	2	17	26	2	47
3	0	9	56	9	74
4	0	1	8	4	13
5	0	2	7	4	13
6	0	0	2	14	16
7	0	0	7	9	16
8	0	0	1	8	9
9	0	0	1	6	7
10	0	0	0	0	0
Total	28	69	115	58	270

Syntax score 0: no CAD; Syntax score 1–22: low risk/mild CAD; Syntax score 22–32: moderate–severe CAD; Syntax score >32: severe CAD; CADRIDS: coronary artery disease risk in diabetes score.

The calculated chi-square value is greater than the table values, and hence there is a statistically significant relationship between CADRIDS ($p < 0.01$) and the severity of CAD as denoted by the syntax scores. We obtained the Receiver Operator Characteristic (ROC) curve separately for syntax >32 (Figure 3), syntax 22–32 (Figure 4), and syntax >0 (Figure 5). The ROC curve for severe CAD had an area under ROC (AUC) of 0.88 with Youden's J cut-off point of 4, which had 74% sensitivity and 89% specificity for severe CAD. The ROC curve for moderate-severe CAD had an area of 0.91 with Youden's J cut-off point of 3, which was 78% sensitive and 91% specific. The ROC curve for CAD (Syntax > 0) had an AUC of 0.9 with a cut-off of 2, which was associated with 84% sensitivity and 89% specificity.

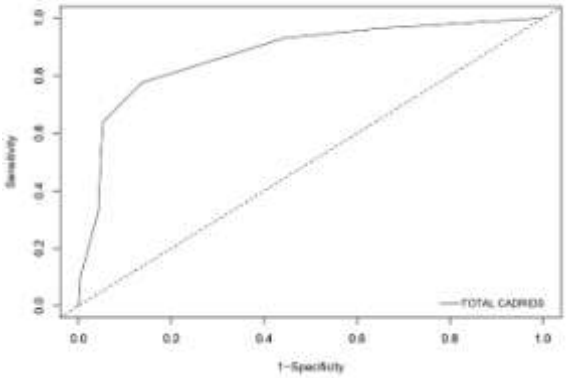


Figure 3: Receiver operator characteristic curve (ROC)of total CADRIDS for severe CAD (AUC= 0.88).

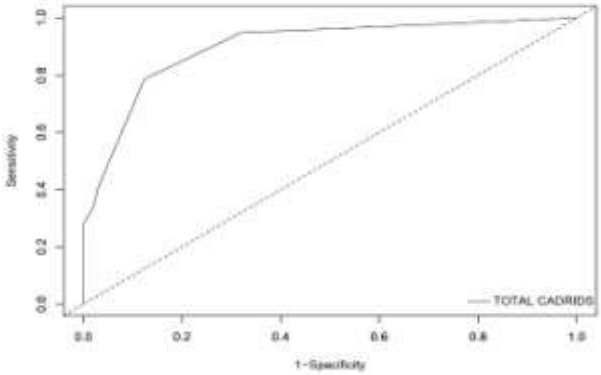


Figure 4: ROC of total CADRIDS for moderate-severe CAD(AUC= 0.91).

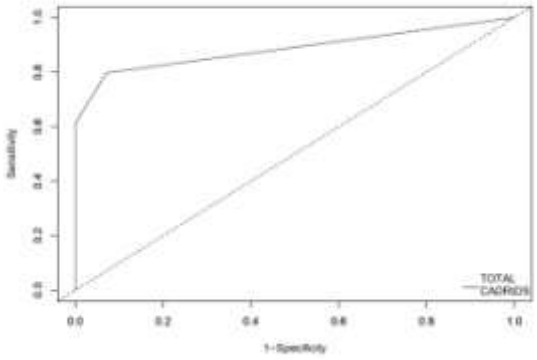


Figure 5: ROC of total CADRIDS for CAD, (AUC= 0.9).

IV. DISCUSSION

We conducted this study to determine the effectiveness of microalbuminuria, CIMT, and ABPI in predicting the severity of CAD among diabetic patients and to develop a novel risk score. We assessed 270 diabetic patients who underwent coronary angiograms. Males were more predominant than females, with a ratio of 1.5, as seen in the Dioum et al. study[19]. 152 (56.3%) had microalbuminuria as compared with 32.6% in the HOPE study[20]. Microalbuminuria had a good sensitivity (84.5%) for severe CAD. It had good sensitivity (80.9%) and specificity (87.6) for moderate-to-severe CAD (Syntax > 22). There was a strong relationship between the presence of microalbuminuria and the extent and severity of CAD ($p < 0.001$), as seen in the study by Sadaka et al.[21]. CIMT was 68% sensitive and 70% specific for the diagnosis of CAD, as mentioned in a meta-analysis[22]. In a study by Bytyci I et al.[23], CIMT ≥1.0 mm was 77% sensitive and 72% specific for CAD. This study separately derived the sensitivity for syntax >32 (severe) and syntax >22 (moderate-severe), rather than considering CAD as a whole. CIMT is 70.7% sensitive for severe CAD (syntax > 32), but has low sensitivity for syntax > 22. However, CIMT is highly specific for severe (92.5%) and moderate-severe CAD (96.9%). Increased CIMT significantly predicts the severity of CAD ($p< 0.001$). Abnormal ABPI has low sensitivity for severe CAD but has a good NPV (83%). Its sensitivity was also low for moderate-to-severe CAD. However, it was highly specific for severe (90.6%) and moderate-severe CAD (97.9%). There exists a statistically significant relationship ($p< 0.001$) between abnormal ABPI and the severity of CAD. In a study by Sharma M et al.[24] on diabetic patients, ABPI had a sensitivity of 84.5% and a specificity of 90.5% in predicting CAD.

We combined and performed the tests in parallel to improve sensitivity, as they could serve as an effective screening test. Combining CIMT and ABPI resulted in good sensitivity and specificity for severe CAD. Combining these tests with albuminuria and done in parallel resulted in an increase in sensitivity to 96.9% for severe CAD. When we did microalbuminuria and CIMT together, the test had good sensitivity (86.9%) and specificity (84.9) for finding moderate to severe CAD (Syntax > 22). Combining it with ABPI resulted in an increase in sensitivity to 90% and a good specificity of 83%. Therefore combining and testing all three tests in parallel resulted in 97% and 90% sensitivity for predicting severe and moderate-severe CAD, respectively.

We generated a simple and novel score, CADRIDS, and found a statistically significant relationship with the severity of CAD. We separately obtained the Receiver Operator Characteristic (ROC) curve for Syntax >32 (severe CAD), Syntax 22-32 (moderate-severe CAD), and Syntax >0 (CAD). ROC for severe CAD had a good area under curve (AUC) of 0.88, and CADRID score 4 was 74% sensitive and 89% specific for severe CAD. CADRIDS 3 was 78% sensitive and 91% specific, with a good AUC of 0.91 for moderate-severe CAD. The ROC curve for CAD (Syntax > 0) also had a good AUC of 0.90 with a cut-off of 2, which was 84% sensitive and 89% specific.

This study's limitations include its single-center design and exclusive focus on the diabetic population. We could have incorporated risk factors like smoking and alcoholism into the score during analysis and validation. We could have studied and compared other microvascular complications, like diabetic retinopathy.

V. CONCLUSION

The CADRIDS is a simple and effective screening tool for predicting the severity of CAD in diabetics. The CADRIDS cut-off scores of 4, 3, and 2 are highly specific, with good sensitivity for severe, moderate-severe, and CAD (including mild,moderate and severe CAD), respectively. Microalbuminuria and CIMT, respectively, exhibited the highest sensitivity and specificity for severe CAD. Microalbuminuria and ABPI,

respectively, demonstrated the highest sensitivity and specificity for moderate-to-severe CAD. Combining the third test with the other two in parallel results in high sensitivity for both severe and moderate-severe CAD.

The easy applicability and non-invasive nature of these tests make CADRIDS suitable for determining the atherosclerotic burden among diabetic patients in the community. By screening diabetic patients with this score, we can non-invasively identify patients with moderate and severe CAD and aggressively manage them with early intervention. In situations where CAG is not feasible or contraindicated due to patient factors, we can also use this score.

.Conflicts of interest: – none declared

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