ABENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Original article

Hemoglobin A1c in Non-Diabetic NSTEMI Patients as a Predictor of Severity of Coronary Artery Disease

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Received:
Accepted:

Abstract:

Background: Atherosclerotic cardiovascular disease [ASCVD] is a leading cause of morbidity and mortality in diabetic and non-diabetic patients. The association between hemoglobin A1c[HbA1c] levels and coronary artery disease [CAD] severity in non-diabetic patients remains contentious. This study aimed to evaluate the association between HbA1c level and the severity of coronary artery disease in non-diabetic patients presenting with NSTEMI using SYNTAX score. **Methods:** This observational, dual-center, cross-sectional study included 74 non-diabetic patients with NSTEMI who underwent emergency coronary angiography. Patients were divided into two groups: those with HbA1c > 5% [Group 1] and those with HbA1c ≤ 5%[Group 2]. The severity of CAD was assessed using the SYNTAX score, and logistic regression was performed to identify predictors of CAD severity. **Results:** Group 1 had significantly higher HbA1c levels [5.8% vs. 4.6%, P < 0.001] and a higher incidence of multi-vessel disease compared to Group 2[P = 0.045]. Chronic total occlusion was also more prevalent in Group 1[32.43% vs. 8.11%, P = 0.019]. HbA1c levels were significantly correlated with higher SYNTAX scores [r = 0.353, P = 0.002], and logistic regression analysis identified HbA1c as an independent predictor of CAD severity. HbA1c had an area under the curve [AUC] of 0.742, with 82.35% sensitivity and 62.35% specificity at a cutoff of >4.8%. **Conclusion:** HbA1c levels > 4.8% are associated with increased CAD severity in non-diabetic NSTEMI patients, making HbA1c a potential independent predictor of coronary artery disease complexity.

Keywords: Hba1c; Coronary Artery Disease; NSTEMI; SYNTAX Score; Non-Diabetic; Cardiovascular Risk.

Introduction

Atherosclerotic cardiovascular disease [ASCVD] is a leading cause of morbidity and mortality in diabetic patients. These patients usually need strict glycemic control and continuous monitoring. Hemoglobin A1c[HbA1c] has been considered a standard criterion to monitor and diagnose diabetes mellitus [1] for years. It has several advantages over fasting plasma glucose and oral glucose tolerance tests, including greater convenience, greater pre analytical stability, and lesser day-to-day perturbations during stress and illness [2].

The American Diabetes Association has recommended HbA1c as an effective diagnostic and prognostic tool for DM and its complications [3]. The complications of diabetes mellitus [DM0, including ASCVD, depend on many risk factors such as obesity, hyperglycemia, and dyslipidemia. The authors of Diabetes Control and Complication Trial showed the possible association between HbA1c levels and chronic diabetic complications, including cardiovascular events in type 1 DM [4].

The Atherosclerosis Risk in Communities trial showed that, among the non-diabetic adults, higher HbA1c levels lead to higher ASCVD and death [5]. A huge amount of researches has been done to display the linear relationship between HbA1c and ASCVD in non-diabetics in past years. Yet, few studies have shown that HbA1c is not related to the severity of coronary artery disease[CAD] in non-diabetic patients [6]. The association between HbA1c and the severity of CAD is still a contentious issue.

The purpose of this study was to evaluate the association between HbA1c level and the severity of coronary artery disease in non-diabetic patients presenting with NSTEMI using SYNTAX score 1.

Patients and methods:

This observational, dual-center and cross-sectional study included 74 non-diabetic patients presented by chest pain and diagnosed as NSTEMI and scheduled for emergency coronary angiography. Study was conducted at Nasser Institute and Benha University Hospital, during the period from January 2023 to January 2024

The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University and an informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number.

Inclusion criteria were patients of both sex who are older than 18 years old, non-diabetic with NSTEMI [Myocardial infarction detected by a rise in cardiac biomarkers, without ECG changes indicative of a STEMI].[7]

Exclusion criteria were all known diabetic patients, patients who had increased fasting plasma glucose of ≥126 mg/dl or HbA1c of ≥6.5 [3], patients with hemoglobin[Hb] levels of <10 g/dl, patients with STEMI or NSTEMI with normal coronary angiography because our study assesed severity of CAD using syntax score so required obstructive CAD not MINOCA[myocardial infarction with non-obstructive coronary arteries] which may be due to coronary causes as[plaque rupture or erosion, coronary spasm, spontaneous coronary artery dissection, coronary embolization, and coronary microvascular disorders] , cardiac cause as[Myocarditis, Takotsubo syndrome and cardiomyopathies] and extra-cardiac causes[stroke, pulmonary embolism, sepsis, renal failure, and hypoxemia]. [8]

Grouping: Patients were selected and divided into two matched groups: **Group 1:** Non-diabetic NSTEMI patients with HbA1c > 5. **Group 2:** Non-diabetic NSTEMI patients with HbA1c ≤ 5.

All studied cases were subjected to the following: Detailed history taking, including **[**Personal history; name, age, gender and body mass index [BMI], Present history: course of the disease and duration, Past history of any medical condition or previous hospital admission and Family history of similar condition]. Full clinical examination: General examination including [particular emphasis on vital signs as [pulse, systolic and diastolic blood pressure]. Local examination including [auscultation of the heart and auscultation of the back to elicit the presence of any clinically detectable pulmonary venous congestion] Routine laboratory investigations **[**complete blood count[Hb, WBCs, Platelets], Troponin & CK MB, kidney function tests and liver function tests, HBA1C, Lipid profile].

ECG was performed on each patient to detect ischemic changes, also participants were subjected to echocardiographic evaluation, and measurements were taken according to the recommendations of the American Society of Echocardiography[ASE] [7], Ejection fraction was calculated using the Simpson method, EF > 50% was considered as being normal [10].

Wall motion was assessed using a segmental scoring system via transthoracic echocardiography. The left ventricular [LV] segments included 17 regions, ranging from the basal to the apical areas. Each segment was scored based on motion as follows: Normokinesia: 1 point, Hypokinesia: 2 points, Akinesia: 3 points, Dyskinesia: 4 points. The wall motion score index [WMSI] was calculated by dividing the total segmental score by the number of segments [18]. A WMSI of 1.0 indicates normal wall motion [10].

Coronary angiography was performed using a percutaneous femoral or radial approach, with sufficient right and left anterior oblique views to assess coronary artery lesions, CHD was defined as ≥50% lumen stenosis in at least one major coronary artery [LM, LAD, LCX, or RCA]. The number of vessels with ≥50% stenosis indicated the severity of coronary artery disease [CAD], The SYNTAX score was used to evaluate the distribution and anatomical complexity of coronary lesions in patients with multivessel CAD.

The coronary tree is divided into 16 segments based on the American Heart Association classification, later modified for the ARTS trials. These segments include key branches of the coronary arteries such as the right coronary artery [RCA], left main[LM], left anterior descending[LAD], circumflex[LCX], and their respective branches. Each segment plays a role in the SYNTAX score, which assesses coronary artery disease severity based on lesion location and involvement of these segments.

SYNTAX score1 is a lesion-based system that evaluates the severity and complexity of coronary artery disease using a computer program with twelve questions. The initial questions establish coronary dominance, lesion count, and involved segments. Each lesion receives a score based on its location and characteristics; occlusive lesions require additional inquiries regarding side branches and their sizes. Factors such as bifurcations, trifurcations, calcification, and lesion length are also assessed. The total score reflects the sum of points for each lesion, with higher scores indicating greater complexity, while lesions in vessels smaller than 1.5 mm are excluded. This score is instrumental in guiding treatment decisions for patients with coronary artery disease [1,11].

The SYNTAX score1 is calculated then patients are classified into two groups based on the SYNTAX score: high [>22] and low[≤22], allowing for the analysis of the correlation between HbA1c and the severity of coronary artery disease in non-diabetic NSTEMI patients

Approval code: MS 32-11-2022

Statistical analysis:

Statistical analysis was performed using SPSS v28[IBM©, Chicago, IL, USA]. Normality of data distribution was assessed using the Shapiro-Wilks test and histograms. Quantitative parametric data were reported as mean and standard deviation [SD] and analyzed using ANOVA with post hoc Tukey tests.

DOI: 10.21608/bmfj.2024.327152.2225

Qualitative variables were presented as frequencies and percentages and analyzed with the Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant. Pearson correlation was used to determine the correlation between two quantitative variables.

Receiver Operating Characteristic[ROC] curve analysis was employed to assess the diagnostic performance of tests, with the area under the curve[AUC] indicating overall performance; values >50% indicate acceptable performance, and values near 100% indicate the best performance [12]. Diagnostic sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV] were also evaluated. Additionally, logistic regression analysis was conducted to estimate the probability of various parameters predicting the severity of coronary artery disease [13].

Results:

The two groups were similar in age, sex, and risk factors such as family history, smoking, hypertension, and dyslipidemia. No significant differences were observed in heart rate, blood pressure, weight, BMI, hemoglobin level, triglycerides, total cholesterol, LDL, HDL, serum creatinine, or fasting blood glucose between the groups. However, HbA1c levels were significantly higher in group 1 compared to group 2 [5.8% vs. 4.6%, P<0.001], indicating a difference in long-term blood sugar control. Table 1

Table 1: Demographics and risk factors, Clinical examination and Laboratory investigations of the studied groups.

		Group 1[n=37]	Group 2[n=37]	P value
Age[years]	Mean ± SD	58.5 ± 8.55	55.5 ± 11.39	0.208
	Range	44 – 73	31 - 73	
Sex	Male	30[81.08%]	32[86.49%]	0.528
	Female	7[18.92%]	5[13.51%]	
Family history		4[10.81%]	6[16.22%]	0.495
Smoking		25[67.57%]	23[62.16%]	0.626
Hypertension		14[37.84%]	16[43.24%]	0.635
Dyslipidaemia		18[48.65%]	20[54.05%]	0.641
Heart rate[beats/min]	Mean ± SD	84 ± 8.03	81.4 ± 8.28	0.171
	Range	66 – 100	63 - 100	
SBP[mmHg]	Mean ± SD	127.2 ± 17.02	128 ± 17.97	0.843
	Range	90 – 160	90 - 170	
DBP[mmHg]	Mean ± SD	74.6 ± 9.67	76.2 ± 13.04	0.545
	Range	60 – 90	50 - 110	
Weight[kg]	Mean ± SD	87.6 ± 7.89	84.3 ± 9.85	0.119
	Range	70 – 105	68 - 102	
BMI[kg/m^2]	Mean ± SD	24.9 ± 3.33	24.4 ± 4.04	0.512
	Range	18 – 32	18 - 32	
Hemoglobin[g/dL]	Mean ± SD	14.1 ± 1.5	13.7 ± 1.5	0.261
	Range	11.5 - 17.1	11.1 - 17.1	
Triglycerides[mg/dL]	Mean ± SD	124 ± 38.62	138.1 ± 77.43	0.325
	Range	51 - 222	44 - 476	
Total cholesterol[mg/dL]	Mean ± SD	190.5 ± 35.94	189.8 ± 39.85	0.929
	Range	112 – 257	110 - 279	
LDL cholesterol[mg/dL]	Mean ± SD	103.8 ± 26.71	115.4 ± 33.44	0.104
	Range	53 - 167	66 - 219	
HDL cholesterol[mg/dL]	Mean ± SD	46.3 ± 9.81	44.2 ± 10.05	0.370
	Range	29 - 72	28 - 70	
Creatinine[mg/dL]	Mean ± SD	0.9 ± 0.25	0.9 ± 0.25	0.853
	Range	0.5 - 1.4	0.5 - 1.4	
FBG [mg/dL]	Mean ± SD	92 ± 7.46	93.6 ± 8.52	0.379
	Range	78 - 108	76 - 112	
HbA1c [%]	Mean ± SD	5.8 ± 0.35	4.6 ± 0.26	**<0.001***
	Range	5.1 - 6.3	4.1 - 5	

SBC: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FBG: fasting blood glucose, SD: standard deviation.

ECG findings were not significantly different between the two groups, with similar rates of normal findings, ST depression, T wave inversion, and both abnormalities combined. No significant differences were observed in LVESD, LVEDD, EF, or RWMSI. However, group 1 had a significantly higher Syntax score [18.4 vs. 13, P=0.033] and a higher incidence of multi-vessel coronary artery disease[CAD] compared to group 2[P=0.045]. There was no significant difference between the groups in single or two-vessel CAD. Although there was a trend toward left main [LM] vessel disease in group 1, no significant differences were found in the involvement of LAD, RCA, LCX, or LM between the two groups. Table 2

Chronic total occlusion was significantly higher in group 1 compared to group 2[32.43% vs. 8.11%, P=0.019]. However, there were no significant differences between the two groups regarding other coronary artery lesions, such as bifurcation, trifurcation, tortuosity, lesion length greater than 20 mm, calcifications, thrombus, and diffuse disease. Table 3

Patients were divided into two groups based on their Syntax score: those with a score >22 and those with a score ≤22. A significant relationship was found between higher Syntax scores and family history, lower HDL levels, higher HbA1c, and reduced left ventricular ejection fraction [LVEF]. Specifically, family history was more common [14% vs. 0%, P<0.001], HDL was lower [41.35 vs. 46.42, P=0.042], HbA1c was higher[5.65 vs. 5.11, P=0.004], and LVEF was lower[41.71 vs. 46.02, P=0.002] in patients with Syntax scores >22. No significant relation was found between Syntax score and age, sex, smoking, hypertension, dyslipidemia, BMI, heart rate, blood pressure, total cholesterol, triglycerides, LDL, or fasting blood glucose. Table 4

HbA1c can significantly predict severity of coronary artery disease with syntax score > 22 with AUC of 0.742, P value of <0.001, and at cutoff value >4.8 % with 82.35% sensitivity, 62.35% specificity, 30.4% PPV and 85.7% NPV. Figure 1

Table 2: ECG findings, echocardiographic data and angiographic findings between the studied groups.

		Group 1 [n=47]	Group 2 [n=45]	P value
ECG findings	Normal ECG	13[27.65%]	10[22.22%]	0.162
	ST depression	16[34.04%]	24[53.33%]	
	T wave inversion	18[38.29%]	11[24.44%]	
LVEDD[cm]	Mean ± SD	5.9 ± 0.33	5.9 ± 0.38	0.745
	Range	5 - 6.4	5.1 - 6.7	
LVESD[cm]	Mean ± SD	4.4 ± 0.47	4.4 ± 0.51	0.813
	Range	3.2 - 5.3	3.4 - 5.3	
EF[%]	Mean ± SD	44.8 ± 5.1	45.2 ± 4.87	0.710
	Range	35 – 60	32 - 56	
RWMSI	Mean ± SD	1.4 ± 0.26	1.4 ± 0.27	0.689
	Range	1 – 2	1.1 - 2.3	
Number of vessels	Single vessel	17[45.95%]	21[56.76%]	0.352
	2-vessels	8[21.62%]	11[29.73%]	0.425
	Multi-vessel	12[32.43%]	5[13.51%]	**0.045***
Vessel affected	LAD	29[78.37%]	25[67.57%]	0.295
	RCA	21[56.75%]	16[43.24%]	0.245
	LCX	15[40.54%]	14[37.42%]	0.812
	LM	4[10.81%]	1[2.70%]	0.357
Syntax score	Mean ± SD	18.4 ± 11.63	13 ± 9.73	**0.033***
	Range	2 - 40	1 - 34	

ECG: electrocardiogram, LVEDD: Left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EF: ejection fraction, RWMSI: regional wall motion score index, LAD: left anterior descending artery, RCA: right coronary artery, LCX: left circumflex artery, LM: left main.

DOI: 10.21608/bmfj.2024.327152.2225

Table 3: Coronary artery lesions of the studied groups.

	Group 1[n=37]	Group 2[n=37]	P value
Bifurcation	8[21.62%]	5[13.51%]	0.359
Chronic total occlusion	12[32.43%]	3[8.11%]	**0.019***
Trifurcation	1[2.7%]	1[2.7%]	1.00
Tortous	9[24.32%]	7[18.92%]	0.572
Length >20mm	13[35.14%]	11[29.73%]	0.619
Calcifications	9[24.32%]	5[13.51%]	0.235
Thrombus	13[35.14%]	11[29.73%]	0.619
Diffuse disease	10[27.03%]	6[16.22%]	0.259

*: statistically significant as p value <0.05.

Table 4: Relation between Syntax score and different parameters.

		Syntax score >22[N=17]	Syntax score ≤22 [N=57]	P value
Age[years]		57.24 ± 10.03	56.93 ± 10.22	0.913
Sex	**Male**	13[76.5%]	49[86.0%]	0.351
	Female	4[23.5%]	8[14.0%]	
Family history		8[14.0%]	0[0.0%]	**<0.001***
Smoking		13[76.5%]	33[57.9%]	0.166
HTN		9[52.9%]	19[33.3%]	0.143
Dyslipidemia		10[58.8%]	26[45.6%]	0.339
BMI[Kg/m^2]		24.68 ± 3.78	24.47 ± 3.45	0.828
HR[beats/min]		83.88 ± 7.94	82.37 ± 8.32	0.501
SBP[mmHg]		128.82 ± 17.46	127.19 ± 17.5	0.738
DBP[mmHg]		77.65 ± 11.61	74.74 ±11.39	0.371
Total cholesterol[mg/dL]		192.02 ± 36.3	183.88± 42.64	0.478
Triglycerides[mg/dL]		145.06 ± 89.94	126.91± 49.91	0.436
HDL[mg/dL]		41.35 ± 8.14	46.42 ± 10.16	**0.042***
LDL[mg/dL]		110.6 ± 32.51	106.0 ± 23.65	0.542
FBG[mg/dL]		92.88 ± 8.29	92.53 ±7.12	0.866
HbA1c[%]		5.65 ± 0.60	5.11 ± 0.64	**0.004***
LVEF[%]		41.71 ± 4.50	46.02 ± 4.68	**0.002***

HTN: hypertension, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: High density lipoprotein cholesterol, FBG: Fasting blood glucose, HbA1c: Glycated hemoglobin, LVEF: left ventricular ejection fraction, RWMSI: Regional wall motion score index, *: statistically significant as p value <0.05.

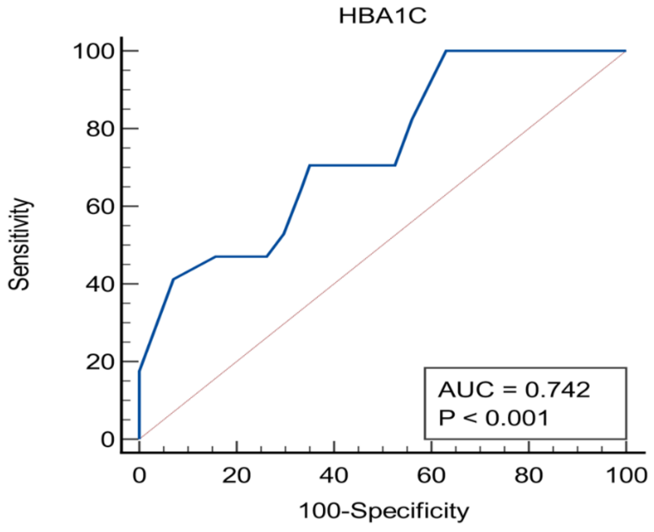

Figure 1: ROC curve analysis of HbA1c for prediction of severity of coronary artery disease.

Discussion:

According to our study, ECG findings were insignificantly different between both groups[P=0.162], In agreement with our findings, some authors who evaluated the impact of glycated Hb on CAD severity in non-diabetic patients reported that ECG findings were insignificantly different between groups with high and low HbA1c levels. The ECG findings revealed that 58 patients had normal findings[P=0.483], 32 patients had invented T-wave[P=0.342] and 3 patients had ST depression[P=0.651] [14].

In the current study, there was an insignificant difference between both groups regarding left ventricle end-systolic diameter [LVESD], left ventricle end-diastolic diameter [LVEDD], ejection fraction [EF] and regional wall motion score index [RWMSI]. In disagreement with us, some authors revealed that on-admission HbA1c% level was significantly higher in patients with EF ≤ 50% in comparison with EF >50% group[p-value=0.01]. This disagreement may be because that study was done on patients with unstable angina and did not include NSTEMI patients and also the groups in this study was divided according to EF% not HBA1c [15].

In the current study, there was an significant difference between both groups regarding the number of vessels affected with higher incidence of Multi-vessel CAD in group with high HA1C level[p=0.45], In agreement with us, a study conducted a study to determine the association between HbA1c and angiographically proven CAD and its severity in 299 nondiabetic individuals. They found that with increasing HbA1c levels, there was a significant increase in the number of vessels involved [16].

In the current study, there was an insignificant difference between both groups regarding the coroary vessels affected .There was atrend to have more LM coronary artery disease in patients with high HbA1c level, In disagreement with us, a research conducted that RCA, LCX, LM were significantly affected in high HbA1c level group compared to low HbA1c level group[p<0.001, p<0.001, and p<0.028 respectively]. This disagreement with our results may be due to the significant difference between the two groups regarding smoking[p=0.035] and Creatinine clerance[p=0.001] and coronary angiography in that study was elective [14].

In the present study, there were significant positive relations between HbA1c and chronic total occlusion and there was atrend to have more LM coronary artery disease in patients with high HbA1c level, In line with us, some authors found that higher HbA1c levels were associated in a graded fashion with the presence of CAD, chronic total occlusion , disease severity[higher number of diseased vessels and presence of left main and/or triple vessel disease], and disease complexity[higher SYNTAX score, higher number of patients in intermediate or high SYNTAX tertiles and coronary calcium] [17].

In the present study, there were significant positive correlations between HbA1c and Syntax score[r=0.353, P=0.002], In agreement with us, a study conducted on a cohort proved that with increasing HbA1c levels, there was a significant increase in the prevalence of CAD and its severity .[p= 0.009] [16]. Similarly, an author who performed an observational study to determine the correlation between the level of HbA1c and the severity of coronary artery disease in 64 non-diabetic non-ST elevation myocardial infarction [NSTEMI] patients, concluded that over half of the non-diabetic, NSTEMI patients with high-risk range HbA1c are likely to have severe CAD than those with HBA1c within normal range [18].

On logistic regression analysis, HbA1c was significant independent predictor of the severity of coronary artery disease.Many other studies shows that there is a positive correlation between HbA1c in Non-diabetics and severity of

DOI: 10.21608/bmfj.2024.327152.2225

CAD and reported that The HbA1c can be used as an independent predictor of severity of CAD in Non-diabetic patients [19, 20]. In contrast to our findings, an author conducted an observational, single-center, cross-sectional study on 119 non-diabetic adults presenting with acute coronary syndrome [ACS] and found no significant correlation between HbA1c and the SYNTAX score [correlation coefficient = 0.142; p = 0.124]. This discrepancy may be due to differences in population characteristics, as their study was conducted on a Pakistani population, which tends to have a lower normal average hemoglobin, and only half of the patients had non-ST-elevation myocardial infarction[NSTEMI][21].

In our findings, HbA1c was a significant predictor of coronary artery disease [CAD] severity, with an AUC of 0.742 and a P value <0.001. At a cut-off value >4.8%, HbA1c demonstrated 82.35% sensitivity, 62.35% specificity, 30.4% positive predictive value [PPV], and 85.7% negative predictive value[NPV]. HbA1c levels showed a linear incremental association with CAD in non-diabetic individuals and were independently correlated with disease severity and higher SYNTAX scores. Therefore, measuring HbA1c could enhance cardiovascular risk assessment in non-diabetic individuals.

Yet, the current study has some limitations such as relatively small sample size and the absence of a follow-up period. Additionally, the single measurement of HbA1c may not fully capture its association with the severity of CAD. The cross-sectional design and lack of randomization could introduce bias, and the study does not provide clinical outcome results, limiting the ability to assess long-term impacts of HbA1c on cardiovascular health.

Conclusion:

HbA1c levels > 4.8% are associated with increased CAD severity in non-diabetic NSTEMI patients, making HbA1c a potential independent predictor of coronary artery disease complexity.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Author contribution

The authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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To cite this article: Ahmed A. Mohamed, Yaser H. Abd El-Rahman, AL-Shimaa M. Sabry, Abdel Salam A. Abdel Kader. Hemoglobin A1c in Non-Diabetic NSTEMI Patients as a Predictor of Severity of Coronary Artery Disease. BMFJ XXX, DOI: 10.21608/bmfj.2024.327152.2225.