Original Paper

Hemoglobin A1c Risk Score for the Prediction of Coronary Artery Disease in Subjects with Angiographically Diagnosed Coronary Atherosclerosis

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Key Words

Hemoglobin A1c • Coronary heart disease • Receiver-operating characteristic curve analysis • Area under the curve

Abstract

Objective: To develop a risk score by incorporating Hemoglobin A1c (HbA1c) with traditional risk factors for the prediction of coronary artery disease (CAD) in Chinese subjects. **Methods:** A total of 196 consecutive subjects (131 males and 65 females) aged 38–89 years who underwent coronary angiography were enrolled in this study. HbA1c risk score sheets for the prediction of CAD were developed using age, gender and HbA1c. A receiver-operating characteristic curve analysis was used to determine the optimum cut-off levels of the HbA1c risk score for predicting CAD. **Results:** In the ROC curve analysis, the optimal cut-off value of the HbA1c score for predicting CAD was 5.1, with a sensitivity of 72.0% and a specificity of 75.5% (area under the curve 0.781, 95% confidence interval 0.709 to 0.854, $p=0.000$). **Conclusions:** The HbA1c score system is a simple and feasible method that can be used for the prediction of CAD. Large-scale studies are needed to further substantiate these results.

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Introduction

Glycated hemoglobin or glycosylated hemoglobin (HbA1c) is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement [1]. Recently, it has been reported that high HbA1c levels are associated with an increased risk of all-cause mortality and death from cardiovascular disease, coronary heart disease, and cerebral infarction in the general East Asian population, similar to Western populations [2]. Further, subjects with a HbA1c $\geq 6.5\%$ have a more unfavorable cardiovascular and metabolic risk profile than those with HbA1c $< 6.5\%$, especially in the oral glucose tolerance test (OGTT)-negative Chinese population [3]. A parallel nested case-control study suggested that HbA1c is associated with coronary heart disease risk among apparently healthy, non-diabetic women and men and may be an important early clinical marker of disease risk [4]. HbA1c is significantly associated with the complexity of coronary lesions, an association that is even observed in non-diabetic adults [5]. However, another study concluded that glycated albumin, not HbA1c, was independently associated with significant coronary heart disease in type 2 diabetic patients [6]. The predictive value of HbA1c for coronary artery disease (CAD) has not been elucidated. Therefore, we aimed to develop a risk score incorporating HbA1c with traditional risk factors for the prediction of CAD in Chinese subjects. We hypothesized that a high HbA1c score would be associated with CAD based on the angiography.

Materials and Methods

Study subjects

From 2010 to 2013, 196 consecutive subjects (131 males and 65 females) age 38-89 years who underwent coronary angiography for suspected or known coronary atherosclerosis at the First Affiliated Hospital of Nanjing Medical University and the Friendship Hospital of Ili Kazakh Autonomous Prefecture in China were enrolled in this study. The exclusion criteria included: subjects with spastic angina pectoris, infectious processes within 2 weeks, heart failure, adrenal dysfunction, and thyroid dysfunction. This study was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University and the Friendship Hospital of Ili Kazakh Autonomous Prefecture in China. All subjects gave written informed consent.

Coronary Angiography

Coronary arteries were cannulated by either the Judkins technique [7] or through a radial approach with 6F catheters and recorded at a rate of 30 frames/s. The presence of coronary artery stenosis was evaluated after the direct intracoronary injection of isosorbide dinitrate (ISDN; 2.5 mg/ 5 ml solution over 20 s). One minute after the injection of ISDN through the Judkins catheter, coronary angiography was performed from several projections after the injection of ISDN through the Judkins catheter for one minute. Significant CAD was diagnosed if there was a 50% stenosis in the diameter of at least one major epicardial coronary artery or main tributary [8, 9].

Cigarette smoking

Cigarette smoking was assessed by a standardized questionnaire. Subjects' smoking status was classified as either "never smoking" or "smoking" (the latter group included both former and current smokers).

Blood pressure measurement

Blood pressure was measured in the right arm with the participant seated and the arm exposed. Three readings were recorded for each individual, and the mean value of the systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) was recorded.

Table 1. Subject characteristics and angiographic CAD. HDL-c, fasting high-density lipoprotein cholesterol; LDL-c, fasting low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure

Characteristic	Non-CAD (n=53)	CAD (n=143)	F or chi-square test	P
Age (years)	57.74±10.95	62.97±10.39	-3.085	0.002
Sex (male/female)	26/27	105/38	10.361	0.001
Smoking status (yes/no)	16/37	63/80	3.091	0.079
Total cholesterol (mmol/L)	4.55±0.90	4.51±1.28	0.802	0.042
Triglycerides (mmol/L)	1.38(1.12~2.06)	1.59(1.17~2.20)	-0.996	0.319
Glucose (mmol/L)	5.09(4.80~5.70)	5.63(4.93~6.73)	-2.805	0.005
HDL-C (mmol/L)	1.25(1.07~1.54)	1.24(1.03~1.58)	-0.366	0.714
LDL-C (mmol/L)	2.73±0.63	2.74±1.05	-0.120	0.905
SBP(mmHg)	130(120~140)	130(120~140)	-1.421	0.155
DBP(mmHg)	80(72~90)	80(70~85)	-1.030	0.303
HbA1c	5.70(5.40~6.20)	6.20(5.70~7.25)	-3.707	0.000
HbA1c score	4.61(4.25~5.09)	5.48(4.89~6.30)	-6.043	0.000

Laboratory measurements

Total cholesterol (TCH, mmol/L), triglyceride (TG, mmol/L), fasting blood glucose (FBG, mmol/L), fasting high-density lipoprotein cholesterol (HDL-c, mmol/L) and fasting low-density lipoprotein cholesterol (LDL-c, mmol/L) were determined by enzymatic procedures on an automated autoanalyzer (AU 2700 Olympus, 1st Chemical Ltd, Japan). HbA1c was measured by a high-pressure lipid chromatographic assay (VARIANT, BIO-RAD Lab., Hercules, CA, USA)

Statistical analysis

Data were statistically analyzed using Statistics Package for Social Sciences (ver. 16.0; SPSS Incorporated, Chicago, IL, USA). Subjects were classified into 2 groups according to CAD status. Data for age, TCH, and LDL-c were normally distributed parameters and presented as the mean $\pm$ SD, and comparisons were analyzed by the independent-samples T test. Skewed data, including the TG, FBG, fasting HDL-C, SBP, DBP, HbA1c, and HbA1c score level, were expressed as median and quartile ranges, and comparisons were analyzed by the Mann-Whitney U test. Categorical variables of gender and smoking status were compared between the groups of patients by a chi-squared analysis. Odds ratios (OR) for the presence of obstructive CAD were determined by logistic regression and are presented with 95% CI. HbA1c risk score sheets for the prediction of CAD were developed using age, gender and HbA1c. The sheet adapted the results of logistic regressions by use of a system that assigned points for each risk factor based on the value for the corresponding β -coefficient of the regression analyses [10]. According to the univariate logistic regression results, the equation for the HbA1c risk score was as follows: HbA1c score = $0.047 \times \text{age} - 1.054 \times \text{sex} (\text{male}=1, \text{female}=2) + 0.604 \times \text{HbA1c}$. ROC curve analysis was used to determine the optimum cut-off levels of age, HbA1c, and the HbA1c risk score that predicted CAD. Differences were considered to be significant if the null hypothesis could be rejected with >95% confidence. All *p*-values are two-tailed.

Results

Baseline Characteristics of the subjects in the study

A total of 196 subjects (131 males and 65 females) with a mean age of 61.55 years were enrolled in the study, there were 30 subjects with acute myocardial infarction, 100 subjects with unstable angina pectoris, and 66 subjects with chest pain. The demographic and clinical characteristics of the subjects are presented in Table 1. There were significant differences between CAD and non-CAD subjects with respect to age ($p=0.002$), sex ($p=0.001$), total cholesterol ($p=0.042$), fasting glucose ($p=0.005$), HbA1c ($p=0.000$), and HbA1c score ($p=0.000$). However, there was no statistically difference in triglyceride ($p=0.319$), HDL-c ($p=0.714$) and LDL-c ($p=0.905$) levels, smoking status ($p=0.079$), SBP ($p=0.155$), and DBP ($p=0.303$) between CAD and non-CAD subjects.

Table 2. Logistic regression for the presence of obstructive CAD. HDL-c, fasting high-density lipoprotein cholesterol; LDL-c, fasting low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure

Characteristic	β -coefficient	OR	95%CI	P
Age (years)	0.047	1.048	1.016, 1.080	0.003
Sex (male=1, female=2)	-1.054	0.349	0.181, 0.670	0.002
Smoking status (yes=1, no=0)	0.599	1.821	0.929, 3.569	0.081
Total cholesterol (mmol/L)	-0.030	0.970	0.739, 1.274	0.829
Triglycerides (mmol/L)	0.228	1.256	0.869, 1.814	0.225
Glucose (mmol/L)	0.272	1.312	1.040, 1.656	0.022
HDL-C (mmol/L)	0.038	1.038	0.571, 1.890	0.902
LDL-C (mmol/L)	0.017	1.017	0.723, 1.431	0.923
SBP (mmHg)	0.013	1.013	0.994, 1.032	0.185
DBP (mmHg)	-0.019	0.981	0.949, 1.014	0.252
HbA1c	0.604	1.829	1.269, 2.635	0.001
HbA1c score	1.209	3.348	2.096, 5.348	0.000

Table 3. Receive operating characteristic analysis of age in predicting coronary heart disease. Area under the curve 0.636, 95% confidence interval 0.547 to 0.725, $p=0.045$

Cut-off	Sensitivity	Specificity	Youden index	Cut-off	Sensitivity	Specificity	Youden index
37.0	1.000	0.000	0.000	61.5	0.580	0.623	0.203
38.5	1.000	0.019	0.019	62.5	0.531	0.660	0.191
39.5	1.000	0.038	0.038	63.5	0.510	0.679	0.189
40.5	0.979	0.038	0.017	64.5	0.469	0.698	0.167
41.5	0.979	0.057	0.036	65.5	0.448	0.755	0.203
42.5	0.972	0.094	0.066	66.5	0.441	0.774	0.215
43.5	0.965	0.094	0.059	67.5	0.399	0.774	0.173
44.5	0.965	0.113	0.078	68.5	0.336	0.792	0.128
45.5	0.944	0.132	0.076	69.5	0.294	0.830	0.124
46.5	0.930	0.189	0.119	70.5	0.259	0.830	0.089
47.5	0.923	0.208	0.131	71.5	0.224	0.868	0.092
48.5	0.895	0.208	0.103	72.5	0.203	0.887	0.090
49.5	0.860	0.283	0.143	73.5	0.168	0.906	0.074
50.5	0.846	0.321	0.167	74.5	0.133	0.906	0.039
51.5	0.839	0.321	0.160	75.5	0.112	0.962	0.074
52.5	0.818	0.377	0.195	76.5	0.091	0.962	0.053
53.5	0.797	0.377	0.174	77.5	0.063	0.962	0.025
54.5	0.776	0.377	0.153	78.5	0.042	0.981	0.023
55.5	0.776	0.396	0.172	79.5	0.021	0.981	0.002
56.5	0.741	0.491	0.232	80.5	0.021	1.000	0.021
57.5	0.685	0.528	0.213	82.0	0.014	1.000	0.014
58.5	0.643	0.566	0.209	86.0	0.007	1.000	0.007
59.5	0.629	0.604	0.233	90.0	0.000	1.000	0.000
60.5	0.587	0.604	0.191				

The logistic regression analysis of characteristics between the CAD and non-CAD groups

The results of the logistic regression analysis of the characteristics between the CAD and non-CAD groups are shown in Table 2. A one year increase was associated with a 4.8% increased risk for CAD (odds ratio [OR], 1.048; 95% confidence interval [CI], 1.016-1.080, $p=0.003$). Compared to the male subjects, the risk for CAD in female subjects decreased 65% (odds ratio [OR], 0.349; 95% confidence interval [CI], 0.181-0.670, $p=0.002$). Subjects with a higher HbA1c were 82.9% more likely to suffer from CAD (OR, 1.829; 95% CI, 1.269-2.635, $p=0.001$). In this population, the HbA1c score was a better indicator of CAD risk than age, sex, and HbA1c alone. Subjects with a higher HbA1c score were 235% more likely to have CAD (OR, 3.348; 95% CI, 2.096-5.348, $p=0.000$).

ROC analysis of age for predicting coronary heart disease

The ROC analysis of age for predicting CAD is shown in Table 3 and Figure 1. The optimal cut-off value of age that predicted CAD was 59.5, with a sensitivity of 62.9% and a specificity

Table 4. Receive operating characteristic analysis of HbA1c in predicting coronary heart disease. Area under the curve 0.672, 95% confidence interval 0.592 to 0.752, $p=0.041$

Cut-off	Sensitivity	Specificity	Youden index	Cut-off	Sensitivity	Specificity	Youden index
3.40	1.000	0.000	0.000	7.15	0.287	0.925	0.212
4.45	0.993	0.019	0.012	7.25	0.259	0.925	0.184
4.60	0.986	0.019	0.005	7.30	0.259	0.943	0.202
4.75	0.986	0.057	0.043	7.40	0.231	0.943	0.174
4.85	0.986	0.075	0.061	7.55	0.210	0.943	0.153
4.95	0.979	0.075	0.054	7.65	0.210	0.962	0.172
5.05	0.972	0.094	0.066	7.75	0.196	0.962	0.158
5.15	0.958	0.113	0.071	7.85	0.175	0.962	0.137
5.25	0.944	0.151	0.095	7.95	0.168	0.962	0.130
5.35	0.888	0.170	0.058	8.10	0.161	0.962	0.123
5.45	0.860	0.264	0.124	8.25	0.147	0.962	0.109
5.55	0.811	0.321	0.132	8.35	0.126	0.962	0.088
5.65	0.769	0.434	0.203	8.50	0.112	0.962	0.074
5.75	0.692	0.509	0.201	8.70	0.105	0.962	0.067
5.85	0.650	0.528	0.178	8.85	0.091	0.962	0.053
5.95	0.615	0.604	0.219	8.95	0.070	0.962	0.032
6.05	0.559	0.660	0.219	9.05	0.063	0.962	0.025
6.15	0.510	0.736	0.246	9.15	0.056	0.962	0.018
6.25	0.483	0.849	0.332	9.40	0.056	0.981	0.037
6.35	0.455	0.868	0.323	9.90	0.049	0.981	0.030
6.45	0.434	0.887	0.321	10.25	0.042	0.981	0.023
6.55	0.420	0.887	0.307	10.50	0.042	1.000	0.042
6.65	0.399	0.925	0.324	10.85	0.028	1.000	0.028
6.75	0.371	0.925	0.296	11.60	0.021	1.000	0.021
6.85	0.350	0.925	0.275	12.50	0.014	1.000	0.014
6.95	0.343	0.925	0.268	19.40	0.007	1.000	0.007
7.05	0.329	0.925	0.254	27.0	0.000	1.000	0.000

Fig. 1. Receive operating characteristic analysis of age in predicting coronary heart disease. **Fig. 2.** Receive operating characteristic analysis of HbA1c in predicting coronary heart disease.

of 60.4% (area under the curve 0.672, 95% confidence interval 0.592 to 0.752, $p=0.041$).

ROC analysis of HbA1c for predicting coronary heart disease

The ROC analysis of HbA1c for predicting CAD is shown in Table 4 and Figure 2. The optimal cut-off value of HbA1c that predicted CAD was 6.25%, with a sensitivity of 48.3%

Table 5. Receive operating characteristic analysis of HbA1c score in predicting coronary heart disease. Area under the curve 0.781, 95% confidence interval 0.709 to 0.854, $p=0.000$

Cut-off	Sensitivity	Specificity	Youden index	Cut-off	Sensitivity	Specificity	Youden index
1.953	1.000	0.000	0.000	5.283	0.601	0.811	0.412
3.074	1.000	0.019	0.019	5.296	0.594	0.811	0.405
3.242	1.000	0.038	0.038	5.306	0.587	0.811	0.398
3.373	1.000	0.057	0.057	5.316	0.580	0.811	0.391
3.480	1.000	0.075	0.075	5.323	0.580	0.811	0.391
3.520	1.000	0.094	0.094	5.333	0.573	0.830	0.403
3.557	1.000	0.113	0.113	5.349	0.566	0.849	0.415
3.651	1.000	0.132	0.132	5.356	0.559	0.849	0.408
3.752	0.993	0.132	0.125	5.367	0.552	0.849	0.401
3.792	0.993	0.151	0.144	5.384	0.545	0.849	0.394
3.829	0.993	0.170	0.163	5.393	0.538	0.849	0.387
3.866	0.986	0.170	0.156	5.399	0.531	0.849	0.380
3.943	0.979	0.170	0.149	5.424	0.524	0.849	0.373
4.051	0.972	0.170	0.142	5.460	0.524	0.868	0.392
4.098	0.965	0.170	0.135	5.481	0.517	0.868	0.385
4.108	0.958	0.170	0.128	5.484	0.510	0.868	0.378
4.124	0.958	0.189	0.147	5.487	0.497	0.868	0.365
4.158	0.958	0.208	0.166	5.494	0.490	0.868	0.358
4.212	0.958	0.226	0.184	5.511	0.483	0.887	0.370
4.249	0.958	0.245	0.203	5.548	0.476	0.887	0.363
4.256	0.951	0.264	0.215	5.571	0.469	0.887	0.356
4.262	0.951	0.283	0.234	5.585	0.462	0.887	0.349
4.269	0.944	0.283	0.227	5.599	0.455	0.887	0.342
4.276	0.944	0.302	0.246	5.612	0.448	0.887	0.335
4.289	0.937	0.302	0.239	5.642	0.448	0.906	0.354
4.313	0.937	0.321	0.258	5.665	0.441	0.906	0.347
4.336	0.937	0.340	0.277	5.678	0.434	0.906	0.340
4.353	0.930	0.340	0.270	5.688	0.434	0.925	0.359
4.376	0.923	0.340	0.263	5.722	0.427	0.925	0.352
4.393	0.916	0.340	0.256	5.759	0.420	0.925	0.345
4.400	0.916	0.358	0.274	5.769	0.413	0.925	0.338
4.407	0.909	0.358	0.267	5.799	0.406	0.925	0.331
4.423	0.909	0.377	0.286	5.836	0.399	0.925	0.324
4.450	0.902	0.377	0.279	5.857	0.399	0.943	0.342
4.474	0.902	0.396	0.298	5.870	0.392	0.943	0.335
4.487	0.902	0.415	0.317	5.880	0.385	0.943	0.328
4.494	0.895	0.415	0.310	5.890	0.378	0.943	0.321
4.507	0.895	0.434	0.329	5.900	0.371	0.943	0.314
4.534	0.895	0.453	0.348	5.917	0.364	0.943	0.307
4.564	0.888	0.453	0.341	5.931	0.350	0.943	0.293
4.581	0.888	0.472	0.360	5.940	0.343	0.943	0.286
4.588	0.881	0.472	0.353	5.964	0.336	0.943	0.279
4.595	0.874	0.472	0.346	5.984	0.329	0.943	0.272
4.605	0.874	0.491	0.365	5.988	0.322	0.943	0.265
4.621	0.874	0.509	0.383	5.998	0.315	0.943	0.258
4.638	0.867	0.509	0.376	6.014	0.308	0.943	0.251
4.645	0.860	0.509	0.369	6.021	0.301	0.943	0.244
4.655	0.853	0.509	0.362	6.031	0.294	0.943	0.237
4.672	0.846	0.509	0.355	6.048	0.287	0.943	0.230
4.682	0.839	0.528	0.367	6.054	0.280	0.943	0.223
4.685	0.832	0.528	0.360	6.115	0.273	0.943	0.216
4.702	0.825	0.528	0.353	6.216	0.273	0.962	0.235
4.729	0.818	0.528	0.346	6.256	0.266	0.962	0.228
4.739	0.818	0.528	0.346	6.259	0.259	0.962	0.221
4.742	0.811	0.566	0.377	6.279	0.252	0.962	0.214
4.749	0.804	0.566	0.370	6.299	0.238	0.962	0.200
4.762	0.797	0.585	0.382	6.357	0.231	0.962	0.193
4.782	0.790	0.585	0.375	6.414	0.224	0.962	0.186
4.799	0.790	0.604	0.394	6.441	0.217	0.962	0.179
4.806	0.790	0.623	0.413	6.488	0.210	0.962	0.172
4.813	0.783	0.623	0.406	6.518	0.203	0.962	0.165
4.826	0.776	0.623	0.399	6.538	0.196	0.962	0.158
4.833	0.776	0.642	0.418	6.554	0.189	0.962	0.151
4.836	0.769	0.642	0.411	6.564	0.182	0.962	0.144
4.846	0.762	0.642	0.404	6.578	0.175	0.962	0.137
4.873	0.755	0.642	0.397	6.612	0.168	0.962	0.130
4.897	0.748	0.642	0.390	6.652	0.154	0.962	0.116
4.907	0.741	0.642	0.383	6.679	0.147	0.962	0.109
4.930	0.741	0.660	0.401	6.726	0.140	0.962	0.102
4.954	0.734	0.660	0.394	6.823	0.133	0.962	0.095
4.967	0.734	0.679	0.413	6.900	0.126	0.962	0.088
4.997	0.734	0.717	0.451	6.977	0.119	0.962	0.081
5.028	0.727	0.717	0.444	7.044	0.112	0.962	0.074
5.034	0.720	0.717	0.437	7.071	0.105	0.962	0.067
5.051	0.720	0.736	0.456	7.108	0.098	0.962	0.060
5.068	0.720	0.755	0.475	7.149	0.091	0.962	0.053
5.071	0.713	0.755	0.468	7.202	0.084	0.962	0.046
5.091	0.706	0.755	0.461	7.303	0.084	0.981	0.065
5.111	0.699	0.755	0.454	7.403	0.077	0.981	0.058
5.115	0.699	0.774	0.473	7.464	0.070	0.981	0.051
5.125	0.685	0.774	0.459	7.531	0.063	0.981	0.044
5.142	0.678	0.774	0.452	7.591	0.056	0.981	0.037
5.169	0.671	0.774	0.445	7.709	0.049	0.981	0.030
5.195	0.657	0.774	0.431	7.816	0.042	0.981	0.023
5.205	0.650	0.792	0.442	7.863	0.035	0.981	0.016
5.219	0.643	0.792	0.435	8.034	0.028	0.981	0.009
5.232	0.636	0.792	0.428	8.309	0.028	1.000	0.028
5.242	0.629	0.792	0.421	8.501	0.021	1.000	0.021
5.256	0.622	0.792	0.414	8.611	0.014	1.000	0.014
5.263	0.615	0.811	0.426	13.161	0.007	1.000	0.007
5.269	0.608	0.811	0.419	18.658	0.000	1.000	0.000

Fig. 3. Receive operating characteristic analysis of HbA1c score in predicting coronary heart disease.

sensitivity and a specificity of 84.9% (area under the curve 0.672, 95% confidence interval 0.592 to 0.752, $p=0.041$).

ROC analysis of HbA1c score for predicting coronary heart disease

The ROC analysis of the HbA1c score for predicting CAD is shown in Table 5 and Figure 3. The optimal cut-off value of HbA1c that predicted CAD was 5.1 with a sensitivity of 72.0% and specificity 75.5% (area under the curve 0.781, 95% confidence interval 0.709 to 0.854, $p=0.000$).

Discussion

In the hospital-based diagnostic test of adult Chinese subjects with angiographic evidence of coronary atherosclerosis, the main findings from our study are that the HbA1c score may predict the presence of CAD and that the optimal cut-off value to predict CAD was 5.1 with a sensitivity of 72.0% and a specificity of 75.5% (area under the curve 0.781, 95% confidence interval 0.709 to 0.854, $p=0.0000$).

CAD continues to be a leading cause of morbidity and mortality among adults around the world [11]. Coronary angiography remains the gold standard for defining the presence and severity of CAD in symptomatic patients. However, because slightly more than one third of patients without known disease who undergo elective cardiac catheterization have obstructive CAD, risk stratification in routine clinical practice is needed to increase the diagnostic yield of cardiac catheterization [12]. Though risk algorithms such as Framingham and SCORE are linearly associated with the extent of angiographic disease, a number of common variables such as cholesterol and blood pressure have been shown to be poor indicators of CAD, possibly due to high rates of risk factor modification with statins and antihypertensive therapy. Therefore, a score is necessary to improve diagnostic precision, particularly because the prevalence of non-obstructive CAD on angiography may be greater than 50% in some populations [9]. The results from a community-dwelling Japanese population suggest that HbA1c levels are an independent risk factor for CAD [13]. Another study indicated that HbA1c was an independent risk factor for the presence of severe CAD (Beta = 0.374, $p < 0.001$). In a ROC curve analysis, the optimal cut-off value of HbA1c that predicted severe CAD was 6.52% with a sensitivity of 74.4% and a specificity of 75.1% (area under the curve 0.781, 95% confidence interval 0.661 to 0.901, $p < 0.001$) [14]. However, the results of this study were limited to subjects who were less than 40 years old. The ideal cut-off value of HbA1c for predicting the occurrence of CAD in non-diabetic subjects was 5.6% (sensitivity: 60.5%, specificity: 52%) [15]. In the present study, the optimal cut-off

value of HbA1c that predicted CAD was 6.25%, with a sensitivity of 48.3% and a specificity of 84.9% (area under the curve 0.672, 95% confidence interval 0.592 to 0.752, $p=0.041$). These results agree with those from the study that focused on the relationship between HbA1c levels and the severity of CAD in patients less than 40 years old.

Easy-to-perform and reliable parameters are needed to predict the presence of CAD and to implement efficient diagnostic and therapeutic modalities. The Framingham risk scoring system has been studied to determine its diagnostic value in detecting CAD. A cut-off level of 7.5 for the Framingham risk scoring system predicted severe CAD with a sensitivity of 68% and a specificity of 73.6% (ROC area under curve: 0.776, 95%CI: 0.706-0.845, PPV: 78.1%, NPV: 62.3%, $p<0.0001$) [16]. However, the Framingham risk scoring system predicts the presence of CAD by taking into account sex, age, blood lipid, blood pressure, and a history of diabetes and smoking. Due to the high rates of risk factor modification with statins and antihypertensive therapy, the Framingham risk scoring system was not a simple and feasible method for the prediction of CAD. In the present study, the optimal cut-off value of the HbA1c score that consisted of age, sex, and HbA1c predicted CAD with a sensitivity of 72.0% and a specificity of 75.5% (area under the curve 0.781, 95% confidence interval 0.709 to 0.854, $p=0.000$).

This study has a number of limitations. For one, the sample size was small and large-scale studies are necessary to substantiate our findings. Further, there is a fundamental difference between the Framingham and the present study. The Framingham study was a prospective study that helped to establish the causal relationship between hypertension, high cholesterol, diabetes and CAD. Additionally, the study created risk scores to predict death and coronary heart disease. The association between age, gender, HbA1c and CAD is not original. Though interesting, the practical application of the risk score developed in the present study may be limited and may not substantially change the clinical indication for performing a coronary angiogram.

The present study suggests that the HbA1c score system is a simple and feasible method that can be used to predict CAD. The exact mechanism underlying the association needs further study.

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