Predicting the Likelihood for Severe CAD and CABG Indication on Elective Patients Comparison of Novel CHA2DS2-VASc-HSF with CHA2DS2 and CHA2DS2-VASc Score

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Predicting the Likelihood for Severe CAD and CABG Indication on Elective Patients: Comparison of Novel CHA2DS2-VASc-HSF with CHA2DS2 and CHA2DS2 -VASc Score

M J Al-Farabi ^{1,2}, I G P G Semita¹, K A Shonafi¹, R Ramadhiani⁴, B Jovie³ and A Andrianto ^{1,3*}

Abstract. Abundant scoring systems are available to assess the severity of coronary artery disease (CAD) and its intervention. However, the majority of them require advanced technologies. CHA2DS2-VASc-HSF is a novel and simple risk scoring, easily used for screening in primary care level. We hypothesize that CHA2DS2-VASc-HSF is predictive for severe CAD and indicative for coronary artery bypass grafting (CABG). Additionally, we compared its predictive value with CHA2DS2 and CHA2DS2-VASc score. A total of 210 consecutive patients who underwent elective coronary angiography were enrolled in our study. Anthropometric, laboratory, angiographic findings, and patient history were obtained from medical records and used to calculate CHA2DS2, CHA2DS2-VASc, and CHA2DS2-VASc-HSF score. Severe CAD is defined as Gensini Score >20. CABG indication was defined based on Class I recommendation from the American Heart Association (AHA). Statistical analyses were done using SPSS 25.0. Receiver operating characteristic (ROC) curve analysis showed the CHA_2DS_2 score (AUC [Area Under the Curve], 0.630; 95% CI, 0.555-0.706; p = 0.001), CHA2DS2-VASc score (AUC, 0.680; 95% CI, 0.608-0.752; p=0.000), and CHA2DS2-VASc-HSF score (AUC, 0.785; 95% CI, 0.723-0.846; p=0.000) were predictive of severe CAD. CHA₂DS₂-VASc-HSF score (AUC, 0.841; 95% CI, 0.711-0.971; p=0.00) were predictive of CABG indication. The CHA2DS2-VASc-HSF score provides the highest predictive value for severe CAD and CABG indication compared to the CHA2DS2 and CHA2DS2-VASc score, suggesting that CHA2DS2-VASc-HSF score may be used in primary care settings to suggest referral for coronary angiography and predict CABG possibilities.

1. Introduction

Coronary artery disease (CAD) remains the top cause of mortality and morbidity for a person aged 35 worldwide [1,2]. Failure to detect CAD and provide early treatment may cause CAD treatment to

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become more expensive and higher mortality rate [2]. It is estimated that around one-third of middle aged population in the USA will suffer from CAD manifestation [3]. In Indonesia, the Indonesian Ministry of Health also showed that CAD is the leading cause of morbidity, responsible for 12.9% of deaths [4].

Determining the best risk factor assessment for CAD is extremely important for early prevention and treatment. Screening for CAD using angiography is easily available in the developed countries with short waiting lists. However, in the developing countries, the awareness and accessibility of the cardiovascular disease screening is still low [5]. To obtain cost-effective prevention and treatment of CAD at the patient level, stratification of the cardiovascular risk using simple method is crucial. Cardiovascular risk screening will have a relevant implication for decision-making in early referral and healthcare resource allocation [6].

Currently, CHADS₂ and CHA₂DS₂-VASc score have been established as clinical predictors for cardiac thromboembolism and indication of antithrombotic therapy [7]. Both CHADS₂ and CHA₂DS₂-VASc component has similarities with the risk factors of CAD development [8]. The components within the CHADS₂ score also have proven in large cohort studies to be associated with CAD in with ischemic stroke patients [9]. CHA₂DS₂-VASc is the refinement of CHADS₂ score which has been proven to outperform its predecessor in the various patient groups, including AF patient who received elective electrical cardioversion [10]. This suggests CHA₂DS₂-VASc score may predict the risk for both cerebrovascular and cardiovascular diseases. However, these scores did not include the major risk factors of CAD, such as smoking, hyperlipidemia and family histories. Hence, this research aims to improve the validity of the CHA₂DS₂-VASc score by including new major risk factors of CAD which are Hyperlipidemia (H), Smoking (S) and Family history of CAD (F) and compare it with the previous CHADS₂ and CHA₂DS₂-VASc scores to predict severe CAD and indication of CABG in the patient.

2. Methods

2.1 Study Design

This cross-sectional study involves 210 consecutive patients who came to the outpatient department in Ramelan Navy Hospital, Surabaya, during January-December 2018. All participants were subjected to diagnostic coronary angiography for screening purposes. Coronary artery occlusion was assessed from angiograms using the Gensini score. Patients with infectious processes within two weeks before catheterization, hepatic dysfunction, thyroid dysfunction, cancer, and chronic kidney disease were excluded from the study. This study received ethical clearance (No.06/EC/KERS/2019) from the local ethics committee. Informed consents were obtained and details which disclosed patient's identity were omitted.

2.2 Risk Factor Data Collection

Clinical findings, 12-lead electrocardiogram, and echocardiographic examination were performed based on the American Society of Echocardiography guidelines [11]. The standard laboratory was performed to measure the fasting blood glucose, total cholesterol and renal function tests from the blood samples [12]. CHA₂DS₂-VASc-HSF scores, which consist of Congestive cardiac failure (C), Hypertension (H), Age >75 years(A), Diabetes Mellitus (D), Stroke (S), Vascular diseases (V), Age 65-74 years (A), Sex Category (Sc), Hyperlipidemia (H), Smoking (S) and Family history of cardiovascular disease (F), were obtained by thorough examination of medical records. Congestive cardiac failure (C) score was given if left ventricular ejection fraction was reduced (<45%) from echocardiography examination. Hypertension (H) was defined as systolic blood pressure >140mm Hg or diastolic <90mm Hg for repeated measurement, or when the patient was taking antihypertensive medications. Diabetes mellitus (D) type 2 was defined by fasting blood glucose >126mg/dl, previous diabetes diagnosis or when the patient was taking antidiabetic medications. Stroke (S) was defined as the history or current diagnosis of stroke or TIA which was given by the patients. Vascular disease (V)

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was defined from the existence of a pathologic condition which causes stenosis of at least 50% in the non-coronary artery. Hyperlipidemia (H) was defined as cholesterol level of more than 200mg/dL based on the National Cholesterol Education Program or when the patient was consuming of lipid-lowering medications. Cigarette smoking (S) was defined as the habit of smoking of more than five cigarettes per-day without a quit attempt for a minimum of one year. Family history of cardiovascular disease (F) was defined as the presence of cardiovascular disease or sudden cardiac-related death of a first degree-relative.

2.3 Coronary Angiography and Gensini Scoring

Judkins technique 4 with 5-F catheters was used to perform cannulation of coronary arteries. Kodak 35mm cinefilm was used to record the images at 30 frames/second. Computer-assisted coronary angiography analysis system was used to detect coronary stenosis (Mipron 1; Kontron, Tokyo, Japan). One minute after the injection of ISDN (2.5mg/5mL for 20 s) through the Judkins catheter, several projections were taken to observe the coronary angiography. Coronary atherosclerosis severity was measured using the Gensini scoring method as described previously [12].

Calculation of the Gensini score was done for each patient through severity score assignment based on coronary occlusion. Narrowing between 1-25% will be scored 1, 26-50% will be scored 2, 51-75% will be scored 3, 75-90% will be scored 8, 91-99% will be scored 16 and 100% will be scored 32. The score is then multiplied based on the location and importance of the artery. We multiply by factor 5 for left main coronary artery occlusion, 2.5 for both proximal circumflex artery and proximal left anterior descending artery, 1.5 for a mid-left anterior descending artery, and 1 mid or distal circumflex artery, for distal left anterior descending artery, and the right coronary artery. The multiplication factor for any other branch is 0.5 [3].

2.4 Statistical Analyses

Data analyses were performed using SPSS Statistics 25.0 and MedCalc 18.2.1. Continuous variables, presented as mean±SD, were compared using ANOVA test. Correlation between parametric variables was obtained using Spearman's rho followed by logistic regression. Specificity and sensitivity were obtained from the ROC curve and cutoff point analysis. AUC comparison was done using pairwise comparison as described previously [13].

3. Results

3.1. Clinical Characteristics of the Patients

A total of 210 patients were involved in this study. Table 1 shows the characteristics of the participants grouped based on the CAD severity. Of the 210 patients, 70 patients had normal angiogram (Gensini score=0, 33.3%), 48 patients had mild CAD (Gensini score=1-19, 22.9%) and 92 patients had obstructive/severe CAD (Gensini score >20, 43.8%) The comparison of the baseline demographics and characteristics of the three groups (normal coronary arteries, mild CAD, and severe CAD) are presented in Table 1.

Table 1: Characteristics of the patients based on CAD severity.

	Table 1. Characteristics of the patients based on Crib severity.					
Variables		CAD Severity				
	Normal	Mild CAD	Severe CAD			
	Angiogram	(n=48)	(n=92)			
	(n=70)	, ,	, ,			
Age (years)	50.97±8.95 ^{b,c}	53.87±10.90 ^a	54.65±9.13a	≤0.001		
SBP (mmHg)	131.81±26.17	123.00±16.67	130.90±23.05	0.691		
DBP (mmHg)	72.81±10.86	76.53 ± 9.12	77.58 ± 9.23	0.463		

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Weight (kg)	69.48±12.43	65.27±7.70	70.03 ± 9.88	0.369
Height (m)	164.06±8.59	164.33±3.90	165.45±5.79	0.208
BMI (kg/m ²)	25.67±3.26	24.22±3.28	25.55±3.15	0.341
Hb (g/dL)	14.01 ± 1.11	13.63±1.73	14.60±3.75	0.474
WBC (cells/μL)	7434.2±1725.5	6746.0±1624.1	7350.1±2108.5	0.292
HCT (%)	41.63±3.64	41.20±4.89	42.46±4.36	0.897
Platelet (x 10 ³ cells/μL)	273.00±78.55	271.66±47.73	258.12±52.97	0.268
PT (seconds)	13.31±1.28	13.56±2.67	13.56±3.46	0.301
APTT (seconds)	32.56±3.23	31.33 ± 6.19	33.39±5.27	0.097
FBG (mg/dL)	108.06±37.97°	114.13 ± 32.82	112.45±34.39a	0.032
Ureum (mg/dL)	12.45±3.15b,c	16.81 ± 5.20^a	16.45 ± 7.70^{a}	0.005
Creatinin (mg/dL)	$1.00\pm0.31^{b,c}$	1.27 ± 0.25^{a}	1.16 ± 0.26^{a}	0.005
Ejection Fraction (%)	57.65±18.31	64.73±5.96	52.15±16.85	0.474
CHADS ₂ Score	$0.68\pm0.65^{b,c}$	0.60 ± 0.99^{a}	1.08 ± 0.94^{a}	≤ 0.001
CHA ₂ DS ₂ -VASc Score	$1.32\pm0.83^{b,c}$	1.47 ± 1.06^{a}	1.95 ± 1.04^{a}	≤ 0.001
CHA2DS2-VASc-HSF	$2.06\pm0.77^{b,c}$	2.33±1.23a,c	$3.43\pm1.20^{a,b}$	≤ 0.001
Score				

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index, Hb, Hemoglobin; WBC, White Blood Cells; HCT, Hematocrit; PT, Prothrombin time; APTT, Activated partial thromboplastin time; FBG, Fasting Blood Glucose. Values are presented as a mean \pm standard deviation; different annotation showed a significant difference (p<0.05) for the post-hoc LSD test to: normal angiogram (a), mild CAD (b) and severe CAD (c).

From Table 1, significant differences between severe CAD and normal angiography group were observed on the age, Fasting Blood Glucose (FBG), ureum and creatinin, which are the CAD risk factors. CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-HSF scores were also significantly higher in patients with severe CAD compared to patients with normal angiography.

3.2. Correlations between Multiple Variables with CAD Severity

Table 2: Spearman's correlations between various independent variables with CAD Severity marked with Gensini score.

Variables*	Correlation		
	Coefficient (r)		
Age (years)	0.276**		
FBG (mg/dL)	0.180*		
Ureum (mg/dL)	0.232**		
Creatinin (mg/dL)	0.204**		
WBC	0.236**		
Ejection Fraction (%)	-0.215**		
CHA_2DS_2	0.315**		
CHA ₂ DS ₂ -VASc	0.395**		
CHA ₂ DS ₂ -VASc-HSF	0.612**		

FBG, Fasting Blood Glucose; WBC, White Blood Cells;

^{*:} significant correlation at p<0.05, **: significant correlation at p<0.01

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The correlation test was used to identify the factors associated with severity of CAD. Table 2 shows the results of Spearman's correlations between Gensini score and multiple independent variables in the subjects. Spearman's correlation analysis showed that the highest correlation was identified on the CHA₂DS₂-VASc-HSF score with Gensini score, which showed moderate to strong correlation (r = 0.612, $p = \le 0.001$).

3.3 Logistic Linear Regression Analysis of the Variables to Predict Severe CAD

Table 3: Univariate regression analysis for the predictors of severe CAD **Table 4:** Multivariate regression analysis for the predictors of severe CAD

Variables	Odds Rat	io 95% CI	P value
With CHADS ₂ Score			
Age (years)	1.017	0.985-1.049	0.298
FBG (mg/dL)	1.002	0.994-1.011	0.588
Ureum (mg/dL)	1.067	1.008-1.130	0.026
Creatinin (mg/dL)	2.828	0.893-8.960	0.077
CHADS ₂ Score	1.572	1.009-2.345	0.046
With CHA ₂ DS ₂ -VASc Score			
Age (years)	1.008	0.976-1.042	0.613
FBG (mg/dL)	1.002	0.994-1.010	0.601
Ureum (mg/dL)	1.065	1.006-1.129	0.032
Creatinin (mg/dL)	2.323	0.731-7.380	0.153
CHA ₂ DS ₂ -VASc Score	1.569	1.098-2.240	0.013
Variables	Odds Ratio	95% CI	P value
Age (years)	1.036	1.007-1.066	0.013
SBP (mmHg)	1.003	0.992-1.015	0.585
DBP (mmHg)	1.015	0.990-1.042	0.242
BMI (kg/m²)	1.016	0.933-1.106	0.721
Hb (g/dL)	1.072	0.861-1.335	0.551
WBC (cells/μL)	1.000	1.000-1.000	0.676
HCT (%)	0.995	0.899-1.102	0.929
Platelet (x 10 ³ cells/μL)	1.000	1.000-1.000	0.615
FBG (mg/dL)	1.009	1.001-1.017	0.024
Ureum (mg/dL)	1.103	1.045-1.164	≤0.001
Creatinin (mg/dL)	5.000	1.756-14.233	0.005
Ejection Fraction (%)	0.390	0.059-2.563	0.474
CHA ₂ DS ₂ Score	1.834	1.304-2.580	≤0.001
CHA ₂ DS ₂ -VASc Score	1.962	1.455-2.644	≤0.001
CHA2DS2-VASc-HSF Score	2.716	1.996-3.696	≤0.001

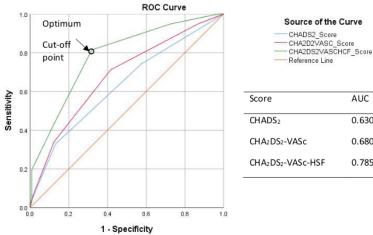
SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BMI, Body Mass Index, Hb, Hemoglobin; WBC, White Blood Cells; HCT, Hematocrit; PT, Prothrombin time; APTT, Activated partial thromboplastin time; FBG, Fasting Blood Glucose

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With CHA ₂ DS ₂ -VASc-HSF Score			
Age (years)	0.997	0.962-1.033	0.871
FBG (mg/dL)	0.997	0.989-1.006	0.516
Ureum (mg/dL)	1.065	0.998-1.137	0.056
Creatinin (mg/dL)	1.511	0.421-5.419	0.527
CHA ₂ DS ₂ -VASc-HSF Score	2.540	1.794-3.595	0.002

FBG, Fasting Blood Glucose; CI, Confidence Interval

Univariate and multivariate logistic linear regression analysis was done on various variables in predicting the outcome (severe CAD) as presented in Table 3 and Table 4. The analysis from Tables 3 and 4 showed that CHADS2, CHA2DS2-VASc, and CHA2DS2-VASc-HSF were significant predictors for severe CAD3.4 Specificity and Sensitivity Test Using ROC Curves



Diagonal segments are produced by ties.

AUC p-value CI 95% 0.630 0.001 0.555-0.706 0.680 ≤0.001 0.608-0.752 0.785 ≤0.001 0.723-0.846

Figure 1: ROC curve of CHADS2, CHA2DS2-VASc, and CHA2DS2-VASc-HSF score to predict severe CAD. AUC, Area Under the Curve; CI, Confidence Interval

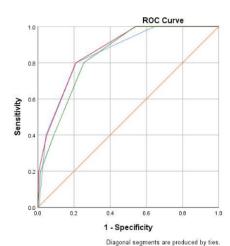
Table 5: Pairwise Comparison Between ROC Curves					
Variables	Differences	SE	95% CI	Z-	p-value

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	between areas			Statistic	
CHADS ₂ and CHA ₂ DS ₂ -VASc	0.0496	0.0227	0.0052-0.941	2.190	0.028
CHADS ₂ and CHA ₂ DS ₂ -VASc-HSF	0.154	0.0320	0.0914-0.217	4.819	≤0.001
CHA ₂ DS ₂ -VASc and CHA ₂ DS ₂ -VASc-HSF	0.105	0.0255	0.0546-0.154	4.105	≤0.001

SE, Standard Error; CI, Confidence Interval

From the ROC curves in Figure 1, it is suggested that CHA_2DS_2 -VASc-HSF score have higher AUC compared to CHA_2DS_2 -vASc and CHA_2DS_2 -vASc score. Optimum cutoff point analysis showed that the CHA_2DS_2 -vASc-HSF score ≥ 2.5 provided the highest predictive value for severe CAD (sensitivity = 81.4% and specificity = 68.1%). Pairwise comparison from Table 5 showed that the CHA_2DS_2 -vASc-HSF score was found to be the best scoring scheme to predict severe CAD compared to CHA_2DS_2 and CHA_2DS_2 -vASc score.



Source of the Curve

CHADS2_Score

CHA2DS2VASC_Score

CHA2DS2VASCHCF_Score

Reference Line

Score	AUC	p-value	CI 95%
CHADS ₂	0.854	0.007	0.709-0.999
CHA ₂ DS ₂ -VASc	0.867	0.005	0.739-0.996
CHA ₂ DS ₂ -VASc-HSF	0.841	0.009	0.711-0.971

Optimum cutoff point analysis showed that the CHA₂DS₂-VASc-HSF score \geq 3.5 provided the highest predictive value for CABG indication (sensitivity = 80.0% and specificity = 74.6%).

4. Discussion

The major findings of this research were (1) CHA₂DS₂-VASc-HSF score was significantly increased in both mild and severe CAD patients;(2) the CHADS₂, CHA₂DS₂-VASc and CHA₂DS₂-VASc-HSF scores had positive and significant correlation with CAD severity measured by Gensini score;(3) CHADS₂, CHA₂DS₂-VASc and CHA₂DS₂-VASc are significant predictors for severe CAD, with

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the highest odds ratio found on the CHA₂DS₂-VASc-HSF score; (4) CHA₂DS₂-VASc-HSF was the best score to predict severe CAD with the cutoff point of \geq 2.5; (5) CHA₂DS₂-VASc-HSF can predict severe CAD with the cutoff point of \geq 3.5.

The severe CAD may be fatal if remained undiagnosed and developed further into coronary total occlusion (CTO), which causes myocardial infarction. Hence, early detection of severe CAD is extremely important to prevent mortality and morbidity of the patients [3]. Coronary angiography is the gold standard to diagnose the severity of stable CAD; however, early coronary angiography screening is lacking in developing countries [14]. Hence, clinicians need reliable, simple, objective, and quantitative tools to identify these risk stratifications to refer the patient for early screening, modify the risk factor and provide early treatment [15]. Several scoring systems which involve major risk factors, such as European SCORE and Framingham risk score (FRS), have been developed to assess the risk of CAD [16]. FRS is the most widely used score and which estimates 10-year risk of developing CAD risk. However, this score cannot assess the severity of CAD. Furthermore, FRS also overestimates cardiovascular mortality rates in a low-risk population and underestimates it at the high-risk populations [17,18]. Because of its multiplicity and complexity, FRS, SCORE and other scoring system are considered to be impractical for daily use for primary care physicians [19, 20]. Hence, alternative scoring, such as that of CHADS2, CHA2DS2-VASc and CHA2DS2-VASc-HSF, may offer a better alternative which is easy to be applied by the physician without any additional cost.

This study showed that CHADS2, CHA2DS2-VASc, and CHA2DS2-VASc-HSF as having a positive and significant correlation with CAD severity measured by Gensini score. The highest correlation was found in the CHA2DS2-VASc-HSF score. This was in accordance with previous research that showed both CHADS2 and CHA2DS2-VASc score are significantly correlated with the Gensini score with almost similar r-value (r = 0.383, p <0.001; r = 0.300, p =0.001) [15]. When CHA2DS2-VASc score was modified by adding hyperlipidemia (H) and smoking (S), a stronger and significant correlation was found between CHA2DS2-VASc-HS score and Gensini score (r=0,813, p<0.001) [21]. Similar to this research, CHA2DS2-VASc-HSF also have a stronger and significant correlation with severity of CAD measured by syntax score in NSTEMI patients compared to CHADS2 and CHA2DS2-VASc [22]. This suggested that CHA2DS2-VASc-HSF score has a superior association with CAD severity compared to CHADS2 and CHA2DS2-VASc scores.

We investigated whether the CHADS2-VASc-HSF scores could help clinicians to predict the patient who has higher odds of severe CAD and which needs immediate diagnosis and treatments. This research showed that CHA2DS2-VASc-HSF has the highest odds ratio to predict severe CAD compared to CHADS2 and CHA2DS2-VASc. Previously, the CHADS2 score, as one of the rapid and very practical scores for risk stratification for thromboembolism, was also shown able to predict CAD in ischemic stroke patients [23]. Development of CHADS2 into CHA2DS2-VASc score also has been shown to have better predictive power for long-term mortality for patients with severe CAD [24]. This suggested that the improvement of CHA2DS2-VASc into CHA2DS2-VASc-HSF may provide a better prediction for the odds of having severe CAD.

The CHADS₂ score is considered as rapid, wide ranged and very practical for risk stratification for thromboembolism, which was also developed to predict CAD in ischemic stroke patients [23]. CHA₂DS₂-VASc is the development of CHADS₂ score, which showed better predictive power for long-term mortality for patients with CAD [24]. When compared with TIMI, GRACE score, CHA₂DS₂-VASc showed the capability to predict severe CAD measured by syntax score [25]. Modification of CHA₂DS₂-VASc into CHA₂DS₂-VASc-HS score has also been shown to improve its predictive value for severe CAD compared to both CHADS₂ into CHA₂DS₂-VASc with the sensitivity of 85.2% and specificity of 57.5% at the cutoff value of >2 [13]. In this research, modification of

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CHA₂DS₂-VASc into CHA₂DS₂-VASc-HSF score also showed higher AUC area compared to both CHADS₂ into CHA₂DS₂-VASc score with the sensitivity of 81.4% and specificity of 68.1% at the cutoff value of >2.5. CHA₂DS₂-VASc-HSF has also been shown to be the best scoring scheme for severe CAD prediction compared to CHADS₂ and CHA₂DS₂-VASc score. This suggests that CHA₂DS₂-VASc-HSF score is a better scoring method which can easily be used by a physician to screen patient with angina, which may require referral for coronary angiography and early treatment.

To predict the CABG indication, this research also showed that CHA₂DS₂-VASc-HSF is able to predict the likelihood of CABG indication at cutoff value of >3.5 with the sensitivity and specificity of more than 70%. Previous research showed that the prediction of CABG indication can be done using GRACE score. However, the sensitivity and specificity of GRACE score to predict CABG indication was only less than 70% [26]. Hence, it is suggested that CHA₂DS₂-VASc-HSF may be superior to previous scoring methods.

However, this study is not possible to be generalized since it only involved single-center as the source of data. This study also used consecutive samplings from all patients who were admitted for diagnostic coronary angiography. Hence, selection bias might occur. In the future, it is suggested to involve more cardiac centers and stratify the sample based on several factors, such as race and social status, to ensure the validity of the score among various demographic characteristics.

5. Conclusion

The CHA₂DS₂-VASc-HSF score provides the highest predictive value for severe CAD and CABG to suggest referral for coronary angiography and predict CABG possibilities.

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