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Original Research

The evaluation of the newly defined CHA2DS2-VASc-HSF score in the severity of coronary artery disease and short-term prognosis

Sara Cetin Sanlialp[1], Gokay Nar[2]
[1]Department of Cardiology, Servergazi State Hospital
[2]Department of Cardiology, Faculty of Medicine, Pamukkale University, Denizli, Turkey

Abstract
Aim: In this study, we aimed to evaluate the ability of the CHA2DS2-VASc-HSF score to predict short-term prognosis in acute coronary syndrome (ACS) patients. Material and Methods: A total of 167 patients who underwent coronary angiography were included in this retrospective study. The patients were divided into two groups according to CHA2DS2-VASc-HSF: the low-score group (≤ 4 points) and the high score group (> 4 points). Primary and secondary endpoints were defined. CHA2DS2-VASc and GRACE scores were calculated, and the severity of coronary artery disease (CAD) was evaluated using SYNTAX I score (SSI). Results: Patients in the high score group had increased CHA2DS2-VASc, GRACE scores and SSI. Also, in-hospital death and MACE within 30 days were more common in this group. There was a strong correlation between the CHA2DS2-VASc-HSF score and SSI (r=0.825, p<0.001). In the ROC analysis, CHA2DS2-VASc-HSF predicted in-hospital death and MACE within 30 days with cut off value 5.5 and 4.5, respectively (AUC= 0.803, p<0.001; AUC= 0.877, p<0.001). In multivariate binary logistic regression analysis, CHA2DS2-VASc-HSF, CHA2DS2-VASc, GRACE and age were independent predictors of short-term prognosis. Discussion: We evaluated the role of the CHA2DS2-VASc-HSF score in CAD severity and short-prognosis, and we agree that this new score can be used to predict CAD severity and short-term prognosis in patients presenting with ACS.

Keywords
Cardiovascular disease; CHA2DS2-VASc-HSF Score; GRACE; Prognosis; SYNTAX I

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Corresponding Author: Sara Cetin Sanlialp, Servergazi State Hospital, Department of Cardiology, Bereketler No: 1, 20000, Merkezefendi, Denizli, Turkey.
E-mail: saracetin@hotmail.com.tr P: +90 5468574067
Corresponding Author ORCID ID: https://orcid.org/0000-0001-9328-9197

Introduction

Acute coronary syndrome (ACS) including unstable angina (UA), ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI), is closely associated with morbidity and mortality [1]. Early risk stratification in ACS may be useful in predicting prognosis or in determining appropriate therapy options. Various risk scores have been developed to identify patients who may need more aggressive treatment and who may be at high risk for major adverse cardiovascular events (MACE). For risk stratification, the Global Registry of Acute Coronary Events (GRACE) or thrombolysis in myocardial infarction (TIMI) are generally preferred in clinical practice [2,3].

CHADS2 and CHA2DS2-VASc are clinical scores used in evaluating the risk of cardiac thromboembolism and in the decision of antithrombotic therapy in patients with non-valvular atrial fibrillation (NVAF). Also, these scores include traditional cardiovascular risk factors predisposing to coronary artery disease (CAD) [4,5]. Several studies have shown that these scores may predict the severity of CAD, peripheral artery disease (PAD) and the adverse cardiovascular outcomes in CAD patients [6,7]. In addition, Cetin et al. reported that a newly defined CHA2DS2-VASc-HS score, such as CHADS2, CHA2DS2-VASc, may indicate the CAD severity [8]. Recently, a new scoring has been developed by adding hyperlipidemia, smoking, family history and, male gender instead of the female gender to the CHA2DS2-VASc score and has been shown its association with CAD severity and complexity [9,10]. In addition, Kalyoncuoglu et al. showed that the performance of this score was successful in showing the long-term prognosis, similar to GRACE score, in NSTEMI patients [11]. However, to our knowledge, no studies have been reported on the relationship between CHA2DS2-VASc-HSF score and short-term prognosis, including in-hospital death and MACE within 30 days. Thus, in this study, we aimed to evaluate the role of the CHA2DS2-VASc-HSF score in determining CAD severity and short-term prognosis in patients with ACS.

Material and Methods

Study Design

In this retrospective observational study, medical records of 167 ACS patients who underwent coronary angiography with or without percutaneous coronary intervention (PCI) from January 2020 to July 2020 were analyzed using the hospital database. Malignancy, active infection, autoimmune disease, connective tissue disease, end-stage renal disease, coronary ectasia, myocardial bridging or vasospastic angina, severe liver disease and missing data in the analysis were determined as exclusion criteria. This study was approved by the Pamukkale University Faculty of Medicine Hospital Ethics Review Board in accordance with the Declaration of Helsinki, and all patients gave informed consent before enrolling in the study. (12/2020-24, protocol no: 10.150.1.90 /020-11760)

Data Analysis and Definitions

Each patient's medical history, family pre-mature CAD history were reviewed. The physical examination, electrocardiographic findings, echocardiographic and laboratory data were analyzed. Medical history consisted of hypertension, diabetes, smoking history, chronic heart failure, stroke or transient ischemic attack (TIA), previous MI or CAD and PAD. The diagnosis of ACS was made in accordance with current clinical practice guidelines based on symptoms, electrocardiographic and imaging methods [12,13].

HT was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or under medical treatment. Diabetes was defined as fasting blood glucose ≥126 mg/dL or blood glucose at any time ≥200 mg/dL or antidiabetic drug use. Hyperlipidemia was defined as increased LDL-C level or lipid-lowering drug use according to the recommendations of the National Cholesterol Education Program-3. Family history was defined as the presence of a diagnosis of CAD in the first degree relative of a patient before age 65 years in women and 55 years in men. The ischemic cerebrovascular event was defined as TIA or ischemic stroke. Vascular disease was defined as a history of revascularization or MI, amputation or angiographic evidence of PAD. Chronic heart failure (HF) was defined as verification of identified signs and symptoms of HF using objective evidence of cardiac dysfunction. Current smoking was defined as >10 cigarettes per day for at least 1 year without any cessation attempt.

Risk Scoring and the evaluation of CAD severity

The patients were evaluated in terms of GRACE, CHA2DS2-VASc and CHA2DS2-VASc-HSF scores. The GRACE score, consisting of age, heart rate, systolic blood pressure, creatinine level, Killip class, ST deviation, cardiac biomarker, and cardiac arrest was measured for each patient. The CHA2DS2-Vasc score was the sum of 1 point each for chronic HF, hypertension, diabetes, and vascular disease, 1 point for 65-74 years old, 2 points for >75 years old and prior stroke or TIA, and 1 point for the female gender. Compared to the CHA2DS2-VASc score, hyperlipidemia, smoking, family history of CAD and, male gender instead of female in the gender category were added to the newly defined CHA2DS2-VASc-HSF score, and these risk factors were scored as 1 point. Then the patients were divided into two groups as CHA2DS2-VASc-HSF score >4 points and score ≤4 points. Diagnostic angiogram views, previously recorded on digital media, were analyzed by experienced clinicians who were blind to the patients' clinical and laboratory data. Significant CAD was defined as>50% narrowing of the lumen diameter in any of the main epicardial coronary arteries. CAD severity was evaluated using the SYNTAX I score (SSI). To calculate SSI, the online calculator (www.syntaxscore.com) was used for each lesion with ≥ 50% diameter stenosis in vessels ≥ 1.5 mm in diameter [14].

Study Endpoints

The primary endpoint of the study was in-hospital death and the secondary endpoint was MACE, including all-cause mortality, objective findings of coronary ischemia, recurrent MI, or unplanned revascularization in 30 days.

Statistical Analysis

SPSS v.17.0 for Windows (SPSS, Inc., Chicago, Ill., USA) was used for data analysis. Qualitative variables were shown as percentages (numbers), and quantitative variables were presented as mean ± SD. The Kolmogorov-Smirnov test was used to determine the normal distribution. Variables were evaluated based on normality distribution using Student's t-test

or Mann-Whitney U test. Categorical variables were compared using the x2 test. The relationship between the variables was analyzed using the Pearson or Spearman correlation. Receiver operating characteristic (ROC) curves were used to assess the sensitivity and specificity of the CHA2DS2-VASc-HSF score in predicting in-hospital mortality and MACE within 30 days. Multivariate binary logistic regression analysis was used to examine independent factors for clinical endpoints, and p<0.05 was considered statistically significant.

Results

The study population consisted of 118 patients with low scores (≤ 4) and 49 patients with high scores (>4) according to the CHA2DS2-VASc-HSF scoring model. Baseline characteristics and the clinical data, including laboratory, echocardiographic and angiographic parameters of the patients are listed in Table 1. Patients in the high score group were older and involved a higher percentage of the male gender, compared with the patients in the low-score group (for all p<0.05). Hypertension, diabetes, dyslipidemia, smoking, a history of any vascular disease, stroke or TIA, and heart failure were more common in the patients with high scores (for all p<0.05). However, the type of ACS did not differ between the groups.

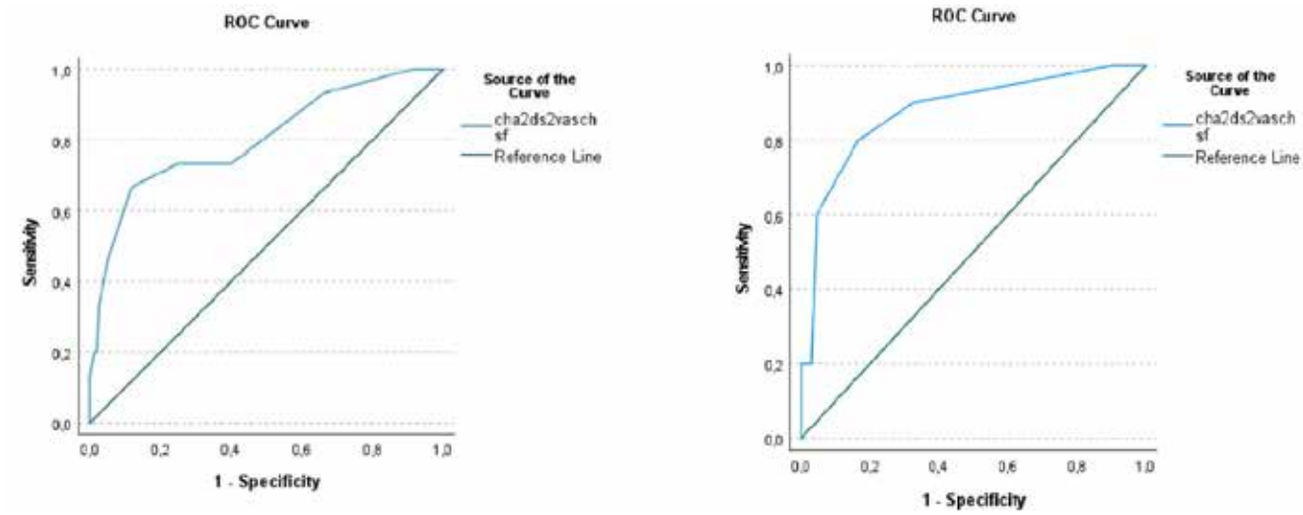
In laboratory parameters, patients with a high score showed significantly increased levels of fasting glucose, creatinine and hemoglobin, however there were no significant differences in lipid parameters and white blood cell counts between the groups. LVEF was significantly lower in patients with high scores (p=0.008).

The medians of CHA2DS2-VASc and CHA2DS2-VASc- HSF in the patients with low and high scores were 2 vs 4 and 3.5 vs 6, respectively (for all p<0.001). In addition, there was a significant difference in the GRACE scores in the groups (110 vs 151, p<0.001). Hospital deaths occurred in 2% of patients with low score and in 14% of patients with high score (p<0.001). MACE within 30 days occurred in 3% and 22% of the patients with low and high scores, respectively (p<0.001). In the ROC analysis, the

Table 1. Basic characteristics and clinical data of the study population divided into low-risk (≤ 4) and high-risk (> 4) groups based on the CHA2DS2 -VASc-HSF score

Variables	Low-score group (n=118)	High-score group (n=49)	p-value
Age (median)	63.50	78.00	<0.001
Male gender, n (%)	74 (63)	41 (84)	0.006
Hypertension, n (%)	53 (45)	37 (76)	<0.001
Diabetes, n (%)	36 (31)	28 (57)	<0.001
Dyslipidemia, n (%)	16 (14)	24 (49)	<0.001
Smoking, n (%)	33 (28)	22 (45)	0.034
Family history, n (%)	15 (13)	15 (30)	0.006
Vascular disease history, n (%)	7 (5)	16 (33)	<0.001
Stroke/TIA history, n (%)	1 (0.8)	5 (10)	<0.001
Heart failure history, n (%)	8 (7)	16 (33)	<0.001
UA, n (%)	26 (22)	8 (16)	0.397
NSTEMI, n (%)	46 (39)	21 (43)	0.642
STEMI, n (%)	46 (39)	20 (41)	0.825
GRACE (median)	110.00	151.00	<0.001
CHA2DS2 -VASc (median)	2.00	4.00	<0.001
CHA2DS2-VASc-HSF (median)	3.50	6.00	<0.001
In-hospital mortality, n (%)	2 (2)	7 (14)	<0.001
MACE within 30 days, n (%)	4 (3)	11 (22)	<0.001
Fasting glucose, mg/dL (median)	123.50	175.00	<0.001
Creatinine, mg/dL (median)	0.85	1.01	<0.001
TG, mg/dL (median)	113.00	124.00	0.457
Tchol, mg/dL (median)	162.00	172.00	0.255
LDL-C (mg/dL)	106.84±31.47	118.61±36.23	0.475
HDL-C, mg/dL (median)	41.00	39.00	0.217
Hemoglobin, g/ dL (median)	13.25	12.40	0.005
WBC, cells/μL (median)	9.43	10.08	0.111
LVEF %, (median)	50.00	40.00	0.008
SSI	20.24±12.38	28.46±9.67	<0.001

TIA, transient ischemic attack; UA, unstable angina; NSTEMI, non- ST- elevation myocardial infarction; STEMI, ST- elevation myocardial infarction; MACE, major adverse cardiovascular event; TChol; total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density, lipoprotein cholesterol; TG, triglycerides; WBC, white blood cells; LVEF, left ventricular ejection fraction; SSI, SYNTAX score I



CHA2DS2-VASc-HSF	Cut-off value	Sensitivity	Specifity	(AUC 95%CI)	p- value
In-hospital death	5.50	0.66	0.88	0.803 (0.670-0.935)	<0.001
MACE within 30 days	4.50	0.80	0.83	0.877 (0.790-0.964)	<0.001

Figure 1. Receiver operating characteristic (ROC) curves in predicting in-hospital mortality and MACE within 30 days

cut-off value for in-hospital death was 5.5 with 88 % specificity and 66% sensitivity, and the cut-off value for MACE within 30 days was 4.5 with 83% specificity and 80% sensitivity (AUC = 0.803, p<0.001; AUC= 0.877, p<0.001) (Figure 1).

The CAD severity was evaluated using SSI, and SSI more increased in the patients with CHA2DS2-VASc-HSF>4 (20.24±12.38 vs 28.46±9.67, p<0.001). When the patients were divided into three groups according to SSI; CHA2DS2-VASc-HSF, CHA2DS2-VASc and GRACE scores differed between low and intermediate tertile and low and high tertile. However, all scores were similar between intermediate and high tertile (Table 2, Figure 2). In addition, there was a strong correlation between CHA2DS2-VASc-HSF and SSI (r= 0.825, p<0.001) (Figure 2). In a binary multivariate logistic regression analysis, CHA2DS2-VASc-HSF, CHA2DS2-VASc, GRACE, age were found to be independent predictors for primary and secondary clinical endpoints (for all p<0.05). However, SSI score and LVEF were only independent predictors for in-hospital death (Table 3)

Table 2. Comparison of CHA2DS2-VASc, CHA2DS2-VASc-HSF, GRACE scores of the study population grouped based on SYNTAX I score

Variables	Low tertile SSI≤ 22	Intermediate tertile 22<SSI<32	High tertile SSI>32	p- value
CHA2DS2-VASc (IQR)	2.00 (1-3)	3.00 (2.5-4)	4.00 (3-5)	<0.001 I vs II<0.001 I vs III<0.001 II vs III=0.528
CHA2DS2-VASc-HSF (IQR)	3.00 (2-3)	5.00 (4-5)	5.00 (4-5)	<0.001 I vs II<0.001 I vs III<0.001 II vs III=0.189
GRACE, (IQR)	109.00 (96.25-122.75)	139.00 (130-143.5)	162.00 (150.75-183)	<0.001 I vs II<0.001 I vs III <0.001 II vs III=0.06

Table 3. Multivariate binary logistic analysis to predict in-hospital death and MACE within 30 days

Variables	In-hospital death				In-30 days MACE			
	OR	95% CI		p- value	OR	95% CI		p- value
		Lower bound	Upper bound			Lower bound	Upper bound	
GRACE	1.038	0.981	1.019	0.018	1.120	1.009	1.242	0.012
CHA2DS2-VASc	1.156	0.985	1.356	0.039	0.703	0.528	0.937	0.028
CHA2DS2-VASc-HSF	1.150	0.723	1.728	0.026	1.109	0.551	2.234	0.019
SYNTAX I	1.032	0.902	1.195	0.048	0.980	0.833	1.152	0.278
Age	0.998	0.919	1.062	0.035	0.946	0.856	1.046	0.037
Fasting blood glucose	1.003	0.998	1.009	0.266	1.005	0.997	1.014	0.634
Creatinine	0.203	0.44	0.941	0.223	7.038	0.889	55.725	0.536
Hemogram	0.855	0.591	1.235	0.641	1.527	1.045	2.232	0.793
LVEF	0.960	0.897	1027	0.046	0.971	0.911	1.036	0.195

LVEF, left ventricular ejection fraction

Discussion

The main findings of our study were as follows: (1) Patients with CHA2DS2-VASc-HSF score >4 had more common cardiovascular risk factors or a history of CVD. Also, LVEF was lower and CHA2DS2-VASc, GRACE scores were higher in this group; (2) CHA2DS2-VASc-HSF was strongly correlated with CAD severity identified by SSI; (3) Patients in the high CHA2DS2-VASc-HSF group showed a significant increase in in-hospital death and MACE within 30 days; (4) The cut-off values of CHA2DS2-VASc-HSF were 5.5 and 4.5 in hospital deaths and MACE within 30 days, respectively; (5) In a binary multivariate logistic regression analysis, CHA2DS2-VASc-HSF score was an independent predictor of in-hospital death and MACE within 30 days.

ACS may be fatal if undiagnosed early and is associated with a poor prognosis. Although coronary angiography is the gold standard to diagnose, unfortunately, the lack of angiography units in developing countries makes it difficult to access patients. Hence, easy-to-use and inexpensive assessment tools are needed in clinical practice to determine cardiovascular risk profiles in the patients and to modify risk factors [15,16]. The CHA2DS2-VASc score, which is used to stratify the risk for stroke in NVAF patients, includes risk factors that trigger atherosclerosis, such as hypertension, diabetes, and increasing age [8]. Studies have reported that increased CHA2DS2-VASc score may indicate the severity of CAD and may be associated with acute stent thrombosis [17,18]. Recently, CHA2D2DS2-VASc-HS and CHA2D2DS2-VASc-HSF scores, including hyperlipidemia, smoking, female gender instead of male gender and family story have been developed for more reliable determination of the severity of CAD [19]. In a study involving 2976 people in Northern India, CHADS2, CHA2DS2-VASc, CHA2DS2-VASc-HS and CHA2DS2-VASc-HSF scores were associated with increased GENSINI score and number of diseased vessels. In another study, there was a significant relationship between SSI with CHA2DS2-VASc and CHA2DS2-VASc-HSF in patients with STEMI [9,20]. In our study, patients with CHA2DS2VASc-HSF score>4 had a high SSI score and had a strong correlation with the severity of CAD as assessed by SSI similar to these studies. Especially, when patients were divided into three groups according to SSI, there was a remarkable difference in CHADS2-VASc and CHADS2-VASc-HSF among those with medium and high SSI and those with low SSI.

The prognostic value of CHA2DS2-VASc has been evaluated in several studies in patients with CAD. Rozenbaum et al. showed that the increase of CHA2DS2-VASc was associated with in -hospital death, MACE within 30 days and increased 1-year all-cause mortality [21]. In another study, Bozbay et al.

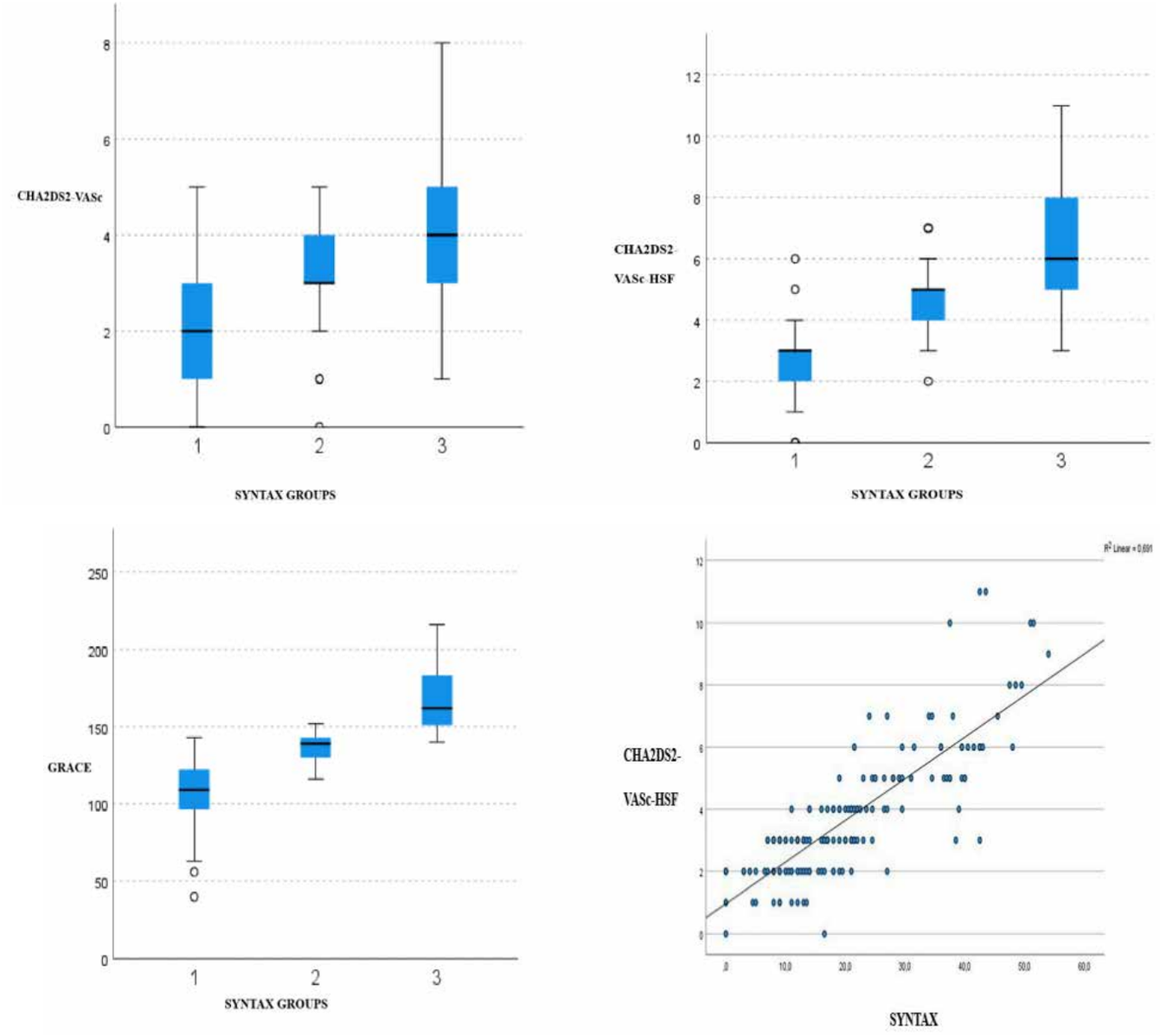


Figure 2. The relationship between SYNAX I and CHA2DS2-VASc, CHA2DS2-VASc-HSF, GRACE scores

showed more in-hospital death occurred in patients with high CHA2DS2-VASc score, and CHA2DS2-VASc was an independent predictor of long-term cardiovascular mortality [17]. To our knowledge, the relationship between the CHA2DS2-VASc-HSF score and the short-term prognosis has not been previously evaluated. Similar to these studies, increased CHA2DS2-VASc and CHA2DS2-VASc-HSF scores were associated with in-hospital mortality and MACE in the first 30 days in our study, and this relationship remained after multivariate regression analysis. Recently Kalyoncuoğlu et al. reported that in-hospital death, one-year mortality and one-year adverse cardiovascular outcomes were significantly higher in patients with a CHA2DS2-VASc-HSF score> 4 compared to low-risk patients in NSTEMI [11]. In addition, the high-risk patients in this study showed an increased GRACE score similar to our study. But they emphasized that in-hospital mortality results were not certain due to the small number of patient deaths, and did not provide information about the first 30-days prognosis in this study. Moreover, they showed that one-year mortality and adverse cardiovascular events were higher in patients with high SSI. Although we found that high SSI was an independent predictor for in-hospital death, a significant correlation was not observed between SSI and MACE within 30 days, unlike this study. The difference between the study results may be due to the type of ACS, the characteristics of the study population, the number of patients treated with PCI, the heterogeneity in aggressive treatment options, and duration of follow-up. However, in a study in which NSTEMI patients were evaluated with CHA2DS2-VASc-HS, demonstrating severe CAD and an increase of in-hospital mortality in patients with high scores supports our study [22].

Study Limitations

There were several limitations in this study, such as a retrospective single-center design and a relatively small sample. However, the real-world unselected population was evaluated. Visual X-ray coronary angiogram was performed for SSI calculation based on luminal stenosis, and advanced imaging methods enabling a more detailed evaluation of CAD were not used. In addition, we aimed to investigate the short-term prognostic significance of the CHA2DS2-VASc-HSF score, so

we could not determine its role on long-term clinical outcomes.

Conclusion

The CHA2DS2-VASc-HSF score was correlated with CAD severity and may be used to predict short-term prognosis. Using the CHAD2DS2VASc-HSF score, patients at high risk can be identified and more aggressive treatment strategies can be followed to reduce death and adverse cardiovascular events. In addition, multi-center prospective large-scale studies should be performed to clearly demonstrate the prognostic significance of the CHA2DS2-VASc-HSF score.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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