Predictive Accuracy of the CHA_2DS_2-VASc-HSF Score in Determining One-Year Cardiovascular Outcomes in Patients with Non-ST-Elevation Acute Coronary Syndrome: A Retrospective Study

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ABSTRACT

Introduction: To investigate the predictive accuracy of the CHA_2DS_2-VASc-HSF score in predicting the one-year mortality and major adverse cardiac and cerebrovascular events (MACCEs) in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Patients and Methods: In this retrospective study, the study cohort was divided in to two groups based on the median CHA_2DS_2-VASc-HSF score: low-risk group (≤ 4 points) and high-risk group (> 4 points).

Results: We enrolled 394 patients with NSTE-ACS (mean age: 58.7 ± 11.8 years). The CHA_2DS_2-VASc-HSF score independently predicted the coronary artery disease (CAD) severity (p< 0.01), one-year mortality (p< 0.01), and MACCEs (p< 0.01). The Global Registry for Acute Coronary Events (GRACE) risk score (GRS 1.0) independently predicted the CAD severity (p< 0.01), whereas the revised GRACE 2.0 risk score (GRS 2.0) independently predicted the one-year mortality (p< 0.01) and MACCEs (p< 0.01). The diagnostic performance of CHA_2DS_2-VASc-HSF was similar to GRS 2.0 in predicting the one-year mortality and MACCEs [area under the curve (AUC), 0.75 and 0.69 vs. 0.78 and 0.67; p= 0.41, p= 0.38, respectively) and better than GRS 1.0 for the CAD severity (AUC, 0.85 vs. 0.79; p= 0.03). The Kaplan-Meier curves displayed significantly higher one-year mortality and MACCEs in the high-risk group (p< 0.01) compared with the low-risk group (p< 0.01).

Conclusion: The predictive accuracy of CHA_2DS_2-VASc-HSF is comparable to that of GRS 2.0 in determining the long-term cardiovascular outcomes; thus, it could be considered as a predictive model for patients with NSTE-ACS.

Key Words: Non-ST-elevation acute coronary syndrome; CHA_2DS_2-VASc-HSF; GRACE risk score; mortality

ST-Yükselmesiz Akut Koroner Sendromlu Hastalarda Bir Yıllık Kardiyovasküler Sonuçların Belirlenmesinde CHA_2DS_2-VASc-HSF Skorunun Prediktif Değeri: Retrospektif Bir Çalışma

ÖZET

Giriş: Bu çalışmada esas olarak modifiye CHA_2DS_2-VASc-HSF skorunun ST-yükselmesiz akut koroner sendromlu (STYz-AKS) hastalarda bir yıllık mortalite ve majör advers kardiyak ve serebrovasküler olayları (MACCEs) öngörüp öngörmediğini araştırmayı amaçladık.

Hastalar ve Yöntem: Hastane kayıtları kullanılarak tasarlanmış bu retrospektif çalışmada, çalışma popülasyonu ortanca CHA_2DS_2-VASc-HSF skoruna göre düşük (≤ 4 puan) ve yüksek riskli (> 4 puan) olarak iki gruba ayrılmıştır.

Bulgular: Çalışmaya ortalama 58.7 ± 11.8 yaşında olan 394 STYz-AKS hastası dahil edilmiştir. CHA_2DS_2-VASc-HSF skoru, koroner arter hastalığı (KAH) yaygınlığının, bir yıllık mortalitenin ve MACCEs'in bağımsız öngördürücüsü olarak bulunmuştur (sırasıyla, p< 0.01, p< 0.01, p< 0.01). Ayrıca "The Global Registry for Acute Coronary Events (GRACE)" 1.0 risk skorunun KAH yaygınlığı için (p< 0.01), güncellenmiş GRACE 2.0 risk skorunun ise bir yıllık mortalite ve MACCEs için bağımsız öngördürücü olduğunu saptadık (sırasıyla, p< 0.01, p< 0.01). CHA_2DS_2-VASc-HSF ve GRACE 2.0 risk skorlarının bir yıllık mortalite ve MACCEs'i öngörmede tanısal performanları istatistiksel olarak birbirine benzer iken [eğri altında kalan alan (AUC)= 0.75 ve 0.69 vs. 0.78 ve 0.67; sırasıyla, p= 0.41, p= 0.38), CHA_2DS_2-VASc-HSF KAH şiddetini öngörmede GRACE 1.0 risk skorundan daha iyi performans sergiledi (AUCs= 0.85 vs. 0.79; p= 0.03). Kaplan-Meier eğrisi CHA_2DS_2-VASc-HSF skoru > 4 puan olan hastalarda düşük riskli hastalara göre bir yıllık mortalite ve MACCEs'in istatistiksel olarak anlamlı derecede daha yüksek olduğunu gösterdi (sırasıyla, p< 0.01, p< 0.01).

Sonuç: CHA_2DS_2-VASc-HSF'nin uzun dönem kardiyovasküler sonuçları öngörmedeki doğruluğu GRACE 2.0 ile kıyaslanabilir düzeyde olup klinik uygulamada STYz-AKS hastaları için bir tahmin modeli olarak düşünülebilir.

Anahtar Kelimeler: ST-yükselmesiz akut koroner sendrom; CHA_2DS_2-VASc-HSF; GRACE risk skoru; mortalite

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INTRODUCTION

In patients with non-ST-elevation acute coronary syndrome (NSTE-ACS), the Global Registry for Acute Coronary Events (GRACE) risk score (GRS 1.0) is the most commonly applied risk score to predict the in-hospital and six-month mortality rates[1,2]. Lately, some studies have also demonstrated the correlation between GRS 1.0 and coronary artery disease (CAD) severity[3,4]. Recently, an updated GRACE risk score (GRS 2.0) was reported to be a more accurate tool than GRS 1.0 to predict the long-term mortality up to three-years after discharge[5].

CHA_2DS_2-VASc is a well-validated scoring system to predict the risk of cerebrovascular accident (CVA) in patients with nonvalvular atrial fibrillation[6,7]. In addition, the CHA_2DS_2-VASc score reportedly correlates with the CAD severity in patients with stable CAD[8] and adverse cardiovascular outcomes in patients with ACS[9-11]. Recently, a newly defined score, CHA_2DS_2-VASc-HSF, which includes hyperlipidemia, smoking, family history of CAD, and male sex rather than female sex, besides the CHA_2DS_2-VASc score elements, has been proposed to predict the CAD severity in patients with stable CAD[12] and ACS[13,14]. To the best of our knowledge, however, no previous study has evaluated the predictive value of the CHA_2DS_2-VASc-HSF score in long-term cardiovascular outcomes in patients with NSTE-ACS. Hence, this study aims to elucidate the predictive accuracy of the CHA_2DS_2-VASc-HSF score in determining the CAD severity and one-year cardiovascular outcomes in patients with NSTE-ACS in comparison with GRS 1.0 and GRS 2.0 scores, respectively.

PATIENTS and METHODS

Ethics committee approval was received for this study from the Ethics Committee of the Health Sciences University Haseki Training and Research Hospital (Decision Number: 87; Decision Date: April 15, 2019).

Study Population

In this retrospective study, we reviewed the medical records of consecutive patients admitted to the cardiology department of our hospital between January 2015 and January 2018. Patients diagnosed with NSTE-ACS and those who underwent coronary angiography with or without percutaneous coronary intervention (PCI) during the period of index hospitalization were enrolled. We obtained data about patients' baseline clinical and demographic characteristics, including body mass index, hypertension (HT), diabetes mellitus (DM), family history, hyperlipidemia, smoking, and vascular disease defined as a history of prior myocardial infarction (MI), peripheral arterial disease (PAD), ischemic stroke (IS), or transient ischemic attack (TIA) due to thromboembolism in the carotid or vertebral arteries.

We defined PAD as an atherosclerotic disease in the arteries other than the coronaries accompanied by exercise-related claudication, revascularization therapies, decreased or absent pulsation, amputation, or angiographic stenosis of > 50%. DM was diagnosed as a fasting blood glucose > 125 mg/dL or the current use of antidiabetic medications. HT was defined as a resting blood pressure of > 140/90 mmHg on, at least, two occasions or current antihypertensive pharmacological treatment. Hyperlipidemia was considered to be a low-density lipoprotein cholesterol level above the target level based on the National Cholesterol Education Program-3 recommendations or the use of lipid-lowering medications. Active cigarette-smoking status was defined as smoking > 10 cigarettes per day for, at least, one-year without any attempt to quit. Family history was defined as the presence of heart disease or sudden cardiac death in a male first-degree relative aged < 55 years or a female first-degree relative aged < 65 years. We defined chronic heart failure as a history of HF signs and symptoms confirmed using objective evidence supporting cardiac dysfunction or a left ventricular ejection fraction (LVEF) of < 40%. Furthermore, we obtained physical examination findings in this study.

The medical records of 727 patients were retrospectively reviewed and analyzed using our database. Finally, we enrolled 394 patients in this study. Of note, we excluded patients with a history of CAD treated with coronary artery bypass grafting (CABG; n= 96), malignancy (n= 21), active infection (n= 39), connective tissue disorder (n= 17), end-stage renal disease or who were receiving hemodialysis (n= 30), severe liver disease (n= 4), hematological disorder (n= 5), no significant CAD or other evident causes of coronary pain such as significant myocardial bridging or diffuse coronary spasm during angiography (n= 65), and any missing information (n= 56) from the analysis.

ACS was diagnosed according to symptoms, electrocardiographic findings, and other accessory examinations, based on the diagnostic criteria of ACS outlined in the current clinical practice guidelines[1,2]. Notably, a presentation with acute chest pain or overwhelming shortness of breath with the absence of persistent ST-elevation is considered to be an indicator of NSTE-ACS, except in patients with true posterior MI. Based on cardiac biomarkers of necrosis, such as cardiac troponin, NSTE-ACS can be further subdivided. With elevated cardiac biomarkers and appropriate clinical findings, the patient is considered to have non-ST-elevation MI (NSTEMI); else, the patient is considered to have unstable angina pectoris (UAP). Of note, all patients were treated in compliance with the current guidelines[1,2].

Laboratory Measurements

We obtained records of fasting venous blood samples on a follow-up to assess patients' plasma levels of fasting blood

glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and creatinine, as well as blood cell count. Using the Modification of Diet in Renal Disease formula, the estimated glomerular filtration rate was calculated. Next, LVEF was measured using the modified Simpson method in the apical four- and two-chamber views in both end-diastole and end-systole.

Clinical Risk Score Calculation

Both GRS 1.0 and GRS 2.0 scores involve the following eight variables evaluated at admission: age; heart rate; systolic blood pressure; plasma creatinine; Killip class; ST-segment deviation; elevated cardiac biomarkers; and cardiac arrest at admission. The final score ranges between 0 and 372 points. We evaluated the GRS 2.0 score using the model coefficients published on the GRACE project website (https://www.outcomesumassmed.org/grace/).

The CHA_2DS_2-VASc-HSF scoring system incorporates congestive HF (C), HT (H), age ≥ 75 years (A_2), DM (D), history of IS or TIA (S2), vascular disease (V), age 65-74 years (A), male sex (instead of the female sex), hyperlipidemia (H), smoking (S), and family history (F). We evaluated CHA_2DS_2-VASc-HSF scores for all patients by assigning 1 point each for the criteria of age 65-75 years, HT, DM, HF, male sex, vascular disease, hyperlipidemia, smoking, and family history, whereas 2 points were assigned for a history of IS or TIA and age ³ 75 years[12-14]. Of note, CAD at index hospitalization was not considered in this study. The maximum CHA_2DS_2-VASc-HSF score attainable was 12 points.

As the standard cutoff value has not been established yet, we stratified the study cohort into low-risk (≤ 4 points) and high-risk (> 4 points) groups based on the median CHA_2DS_2-VASc-HSF score [4 points with an interquartile range (IQR) of 3.0-5.0 points] as a cutoff value; this point was found to be the optimal cut-off value that was calculated from the point of the maximal sensitivity and specificity (Youden's index).

Angiographic Analysis

For quantitative analysis, coronary angiograms were recorded to digital media (DICOM viewer; MedCom GmbH, Darmstadt, Germany) and analyzed by 2 experienced interventional cardiologists blinded to the study participants' clinical and laboratory data. We defined CAD as a finding of stenosis of > 50% of the lumen diameter in any of the main coronary arteries. From the baseline diagnostic angiogram, we quantitatively evaluated the anatomic and clinical severity of coronary stenosis using the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score I (SS I) and II for PCI (SSII-PCI) from the downloadable version hosted at www.syntaxscore.com.

Study Endpoints

In this study, the primary endpoint was all-cause mortality during the follow-up, whereas the secondary endpoint was major adverse cardiac and cerebrovascular events (MACCEs), defined as a composite of all-cause death, any MI, any revascularization, and any stroke during the follow-up based on the Academic Research Consortium-2 consensus[15]. In addition, the national death notification system and hospital records were used to obtain mortality-related information.

Statistical Analysis

While continuous variables are expressed as means ± standard deviations if normally distributed and medians IQRs if not normally distributed, categorical variables are presented as percentages. We used the chi-square (x^2) test to compare categorical variables between the groups. Using the Kolmogorov-Smirnov test, we assessed the normality distribution of the variables. Based on the normality distribution, a Student's t-test or Mann-Whitney U-test was used to compare the continuous variables between the groups. In addition, we evaluated Pearson's coefficient to describe the degree of correlation. To determine the independent predictors of an intermediate-high SSI score, variables related to $p< 0.1$ level in the univariate analysis were included in the multivariate logistic regression analysis, with the results reported as the odds ratios (OR) and 95% confidence intervals (CI). Besides, we performed the univariate Cox regression analysis to assess the relationship of variables with mortality and MACCEs. Notably, variables expressing $p< 0.1$ in the univariate analysis were further analyzed with the multivariate Cox regression model. All results of the Cox regression analysis were reported with hazard ratios (HR) and 95% CI. To avoid model overfitting, we did not include the CHA_2DS_2-VASc-HSF score in the same multivariable logistic and Cox regression analysis models with both GRS (i.e., GRS 1.0 and GRS 2.0) modalities.

Furthermore, variables already included in the CHA_2DS_2-VASc-HSF and both GRS scores were not considered separately in the multivariable analysis independently of their significance the in univariable analysis. Using the receiver-operating characteristics (ROC) curve analysis, we evaluated the sensitivity and specificity of the risk scores and their cut-off values to predict the CAD severity and 1-year cardiovascular outcomes. Meanwhile, the area under the curve (AUC) was used as a measure of the predictive accuracy of the risk scores. Moreover, DeLong test was used[16] to compare the predictive performance of the CHA_2DS_2-VASc-HSF, CHA_2DS_2-VASc, and both GRS methods. Then, survival evaluations for the CHA_2DS_2-VASc-HSF groups were determined using the Kaplan-Meier and log-rank test. We established the threshold

of statistical significance at p< 0.05. In this study, all statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY). The ROC curves of the models were compared using Software bvba 13 (MedCalc Software, Ostend, Belgium).

RESULTS

The study cohort comprised 394 patients with NSTE-ACS (mean age: 58.7 ± 11.8 years). Of these, 42 patients were diagnosed with UAP and 352 with NSTEMI. While 29 (69%) of the patients diagnosed with UAP underwent PCI, 6 (14.3%) of them underwent CABG, and 7 (16.7%) were followed with medical treatment. In addition, 264 (75%) of patients with NSTEMI underwent PCI, 61 (17.3%) underwent CABG, and 27 (7.7%) were medically followed up. The median CHA_2DS_2-VASc, CHA_2DS_2-VASc-HSF, and GRS 2.0 (for one-year mortality) were 3.0 (2.0-3.0), 4.0 (3.0-5.0), and 4.1% (2.6%-7.6%), respectively. The mean GRS 1.0 score was 101.6 ± 24.8. Tables 1 and 2 present the detailed demographic, clinical parameters, and laboratory and angiographic parameters of all study participants and as compared between the two groups.

Factors Related to The CAD Extent and Severity

A total of 95 (24.1%) patients with intermediate-high SSI (≥ 23) were older (63.8 ± 12.7 vs. 56 ± 11 years; p< 0.01) and had higher frequencies of HT (p< 0.01), DM (p< 0.01), hyperlipidemia (p< 0.01), vascular disease (p= 0.02), HF (p< 0.01), and chronic kidney disease (CKD; p< 0.01). Moreover, these patients had lower LVEF (43.3 ± 6.9 vs. 51.3 ± 7.8; p< 0.01)

Table 1. Demographic and clinical characteristics of the study cohort grouped as low-risk (≤ 4) and high-risk (> 4) patients based on the CHA_2DS_2-VASc-HSF score

Variables	All population (n= 394)	Low-risk group (n= 256)	High-risk group (n= 138)	p
Male gender, n (%)	309 (78.4)	195 (76.2)	114 (82.6)	0.14
Age	58.7 ± 11.8	55.4 ± 10.7	64.5 ± 11.5	< 0.01
Body mass index (kg/m^2)	24.5 ± 2.1	25.4 ± 2.1	25.7 ± 2.0	0.13
Hypertension, n (%)	209 (53)	100 (39.1)	109 (79)	< 0.01
Diabetes mellitus, n (%)	127 (32.2)	54 (21.1)	73 (52.9)	< 0.01
Hyperlipidemia, n (%)	157 (39.8)	80 (31)	77 (56.8)	< 0.01
Smoking, n (%)	190 (48.2)	139 (54.3)	51 (37)	< 0.01
Family history, n (%)	192 (48.7)	115 (44.9)	77 (55.8)	0.04
Heart failure, n (%)	74 (18.8)	22 (8.6)	52 (37.7)	< 0.01
Vascular disease history, n (%)	116 (29.4)	45 (17.6)	71 (51.4)	< 0.01
Chronic kidney disease, n (%)	48 (12.2)	12 (4.7)	36 (26.1)	< 0.01
Cerebrovascular accident history, n (%)	13 (3.3)	1 (0.4)	12 (8.7)	< 0.01
Admission diagnosis, n (%)				
UAP	42 (10.7)	33(12.9)	9 (6.5)	0.05
NSTEMI	352 (89.3)	223 (87.1)	129 (93.5)	
High Killip classification, n (%)	57 (14.5)	14 (5.5)	43 (31.2)	< 0.01
CHA_2DS_2-VASc (IQR)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	4.0 (3.0-4.0)	< 0.01
CHA_2DS_2-VASc-HSF (IQR)	4.0 (3.0-5.0)	3.0 (2.0-4.0)	6.0 (5.0-6.0)	< 0.01
GRS 1.0	101.6 ± 24.8	93.1 ± 21	117.5 ± 23.5	< 0.01
GRS 2.0 in-hospital mortality (%) (IQR)	1.7 (1.1-3.1)	1.4 (1.0-2.0)	3.1 (1.9-4.7)	< 0.01
GRS 2.0 one-year mortality (%) (IQR)	4.1 (2.6-7.6)	3.3 (2.4-5.1)	7.8 (4.6-12.5)	< 0.01
In-hospital mortality, n (%)	13 (3.3)	2 (0.8)	11 (8)	< 0.01
One-year mortality, n (%)	47 (11.9)	14 (5.5)	33 (24.9)	< 0.01
One-year MACCEs, n (%)	88 (22.3)	36 (14.1)	52 (37.7)	< 0.01

UAP: Unstable angina pectoris, NSTEMI: Non-ST-elevated myocardial infarction, GRS 1.0: GRACE risk score, GRS 2.0: Updated GRACE risk score, MACCEs: Major adverse cardiac and cerebrovascular events, IQR: Interquartile range.

Table 2. Demographic and clinical characteristics of the study cohort grouped as low-risk (≤ 4) and high-risk (> 4) patients based on the CHA_2DS_2-VASc-HSF score

Variables	All population (n= 394)	Low-risk group (n= 256)	High-risk group (n= 138)	p
Laboratory parameters				
FBG, mg/dL (IQR)	122 (102-162)	114 (99-152)	131 (114.8-187.5)	< 0.01
eGFR, mL/min/1.73 m^2 (IQR)	93 (73-104)	97 (82-106)	80 (54.5-97)	< 0.01
TC, mg/dL	205 ± 44.6	207.4 ± 41.2	200.6 ± 50.3	0.15
LDL-C, mg/dL	130.5 ± 37.5	132.5 ± 36.6	126.6 ± 39	0.14
HDL-C, mg/dL (IQR)	39 (33-43)	38 (33-44)	39 (33-43)	0.45
Triglyceride, mg/dL (IQR)	170 (124-222.3)	170 (132.5-221.8)	169 (115-222.8)	0.89
LVEF (%)	49.8 ± 7.9	52.2 ± 7.3	44.3 ± 7.7	< 0.01
Angiographic parameters				
Unprotected LMCA, n (%)	21 (5.3)	4 (1.6)	17 (12.5)	< 0.01
Three-vessel disease, n (%)	88 (21.9)	24 (9.4)	64 (46.4)	< 0.01
Bifurcation, n (%)	81 (20.6)	38 (14.7)	43 (31.6)	< 0.01
CTO, n (%)	80 (20.3)	41 (16)	39 (28.3)	< 0.01
RCA dominance, n (%)	311 (78.9)	199 (77.7)	112 (81.2)	0.52
SSI (IQR)	13 (8-22)	10 (6-16)	23 (15-29)	< 0.01
SSII-PCI (IQR)	22 (18.6-33.8)	20.6 (16.8-26.8)	33.9 (27.4-42.3)	< 0.01

FBG: Fasting blood glucose, eGFR: Estimated glomerular filtration rate, TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, LMCA: Left main coronary artery, CTO: Chronic total occlusion, RCA: Right coronary artery, SSI: SYNTAX score I, SSII-PCI: SYNTAX score II for percutaneous coronary intervention, IQR: Interquartile range.

and higher GRS 1.0 (120.7 ± 24 vs. 95.6 ± 21.8; p< 0.01) and CHA_2DS_2-VASc-HSF [6.0 (5.0-6.0) vs. 4.0 (3.0-4.0); p< 0.01] scores than those with SSI < 23. In addition, patients with severe CAD had higher rates of one-year mortality (24/95 patients, 25.3%; p< 0.01) and MACCEs (35/95 patients, 36.8%; p< 0.001). The correlation analysis revealed that CHA_2DS_2-VASc-HSF correlated well with SSI and SSI-PCI (r= 0.569, p< 0.01 and r= 0.579, p< 0.01, respectively). On the other hand, while GRS 1.0 moderately correlated with SSI (r= 0.405, p< 0.01), it exhibited excellent correlation with the clinical SSII-PCI (r= 0.733, p< 0.01).

To determine the independent predictors of intermediate-high SSI, we performed the multivariable logistic regression analysis by including variables that displayed statistically significant correlations in the univariate analysis, except for the angiographic parameters. As both CHA_2DS_2-VASc-HSF and GRS 1.0 exhibited a relatively good correlation (r= 0.503, p< 0.01) and exerted a negative impact on each other's statistical significance, we performed two different multivariable regression models, defined as model 1 involving GRS 1.0 and model 2 involving CHA_2DS_2-VASc-HSF. Of note, the parameters in the CHA_2DS_2-VASc-HSF and GRS 1.0 scoring systems were not assessed separately in the multivariate analysis. In both multivariable logistic regression analysis models, CHA_2DS_2-VASc-HSF score (OR 2.626; p< 0.01), GRS 1.0 (OR 1.045; p< 0.01), hyperlipidemia (OR 3.734; p< 0.01), DM (OR 2.712; p< 0.03), and HF (OR 2.203; p= 0.02) were found to be statistically independent predictors of intermediate-high SSI (Table 3).

The ROC analysis revealed that the CHA_2DS_2-VASc-HSF score > 4 points displayed 77% sensitivity and 79% specificity in predicting intermediate-high SSI. DeLong test demonstrated that the AUC of CHA_2DS_2-VASc-HSF (AUC, 0.85; 95% CI: 0.81-0.88) was significantly superior to that of CHA_2DS_2-VASc (AUC, 0.72; 95% CI: 0.68-0.77; p< 0.01) and GRS 1.0 (AUC, 0.79; 95% CI: 0.74-0.83; p= 0.03; Figure 1).

Factors Associated with One-year Mortality and MACCEs

During the median 24 (19-34) month follow-up period, in-hospital mortality, one-year mortality, and -year MACCEs were noted in 13 (3.3%), 47 (11.9%), and 88 (22.3%) patients, respectively. The one-year mortality and MACCEs rates of the high-risk group were higher than those in the low-risk group (p< 0.01, p< 0.01, respectively), as observed in the in-hospital mortality rates (p< 0.01). Furthermore, patients with 1-year

Table 3. Factors that independently correlated with the CAD extent and severity in the univariate and multivariate logistic regression analyses

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Model 1 Multivariate Analysis				
Older age	1.053 (1.031-1.075)	< 0.01	-	-
Hypertension	2.332 (1.431-3.801)	< 0.01	1.040 (0.568-1.908)	0.9
Diabetes mellitus	3.837 (2.368-6.217)	< 0.01	2.712 (1.524-4.829)	< 0.01
Hyperlipidemia	3.570 (2.204-5.781)	< 0.01	3.734 (2.109-6.613)	< 0.01
Vascular disease	1.777 (1.093-2.888)	0.02	0.930 (0.506-1.710)	0.82
Heart failure	3.108 (1.818-5.313)	< 0.01	2.203 (1.136-4.273)	0.02
GRS 1.0	1.050 (1.037-1.063)	< 0.01	1.045 (1.031-1.060)	< 0.01
Model 2 Multivariate Analysis				
Chronic kidney disease	5.256 (2.803-9.858)	< 0.01	1.508 (0.702-3.241)	0.29
CHA_2DS_2-VASc-HSF	2.734 (2.179-3.429)	< 0.01	2.626 (2.073-3.326)	< 0.01

GRS 1.0: GRACE risk score, OR: Odds ratio, CI: Confidence interval, CAD: Coronary artery disease.

Table 4. Parameters that correlated with the one-year mortality and MACCEs in the univariable Cox regression analysis

Variables	One-year mortality		One-year MACCEs	
	HR (95% CI)	p	HR (95% CI)	p
Older age	1.066 (1.040-1.092)	< 0.01	1.036 (1.019-1.054)	< 0.01
Hypertension	2.719 (1.411-5.239)	< 0.01	2.106 (1.338-3.315)	< 0.01
Diabetes mellitus	2.833 (1.593-5.036)	< 0.01	2.081 (1.369-3.164)	< 0.01
Cerebrovascular accident	3.152 (1.131-8.788)	0.03	1.807 (0.662-4.930)	0.26
Heart failure	3.517 (1.972-6.272)	< 0.01	2.989 (1.924-4.643)	< 0.01
GRACE 2.0	1.069 (1.050-1.087)	< 0.01	1.063 (1.045-1.080)	< 0.01
CHA_2DS_2-VASc-HSF	1.534 (1.314-1.790)	< 0.01	1.358 (1.216-1.518)	< 0.01
Chronic kidney disease	7.909 (4.450-14.050)	< 0.01	4.395 (2.748-7.028)	< 0.01

MACCEs: Major adverse cardiac and cerebrovascular events, GRS 2.0: Updated GRACE risk score, HR: Hazard ratio, CI: Confidence interval.

mortality and MACCEs were older than those without mortality and MACCEs (67.2 ± 11.7 vs. 57.4 ± 11.3, p< 0.01; 63.4 ± 12.5 vs. 57.2 ± 11.2, p< 0.01, respectively).

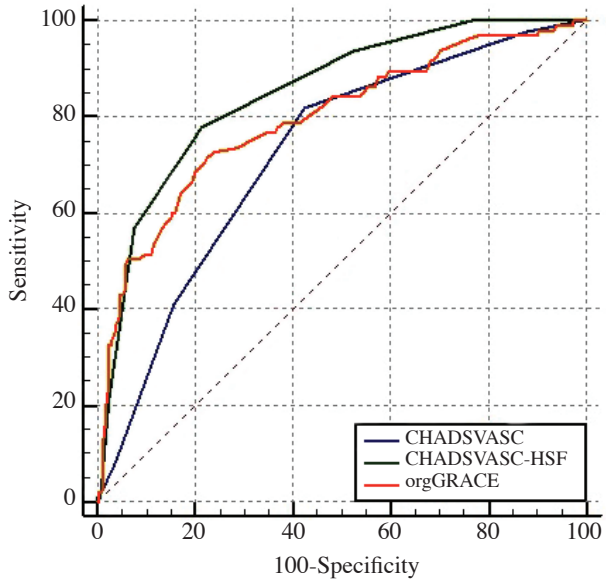
In the univariate Cox regression analysis, older age, HT, DM, HF, CKD, GRS 2.0, and CHA_2DS_2-VASc-HSF score correlated with one-year mortality and MACCEs (p< 0.05). In addition, CVA history (p= 0.03) correlated with mortality, but not with MACCEs (Table 4). Of note, newly added parameters of the modified CHA_2DS_2-VASc-HSF, such as hyperlipidemia (p= 0.58), smoking (p= 0.33), and family history (p= 0.47), did not differ between patients with or without one-year mortality. On the other hand, although not statistically significant, family history (p= 0.09) and smoking (p= 0.07) were higher among patients with one-year MACCEs than the others; however, hyperlipidemia was not different (p= 0.63). As in-hospital mortality was observed in only a small number of patients, we did not statistically analyze in-hospital mortality.

To determine the independent predictors of mortality and MACCEs, we performed the multivariate Cox regression analysis by using variables that exhibited statistically significant associations in the univariate analysis. As GRS 1.0 had not been tested for predictive accuracy beyond six-month mortality, and updated GRS 2.0 has been validated for long-term mortality up to 3 years(5), we used the GRS 2.0 score, rather than the GRS 1.0 score, in the regression analysis. For the same reasons mentioned above, we performed two separate multivariate analyses. Finally, independent predictors of one-year mortality and MACCEs were observed to be CHA_2DS_2-VASc-HSF (HR 1.304, p<

Table 5. Factors that independently correlated with the one-year mortality and MACCEs in multivariable Cox regression analysis models

Variables	One-year mortality		One-year MACCEs	
	HR (95% CI)	p	HR (95% CI)	p
Model 1 Multivariate Analysis				
Heart failure	1.986 (1.053-3.745)	0.03	2.038 (1.277-3.254)	< 0.01
Hypertension	1.823 (0.928-3.579)	0.08	1.556 (0.977-2.477)	0.06
Diabetes mellitus	2.412 (1.313-4.432)	< 0.01	1.816 (1.181-2.792)	< 0.01
Cerebrovascular accident	1.734 (0.604-4.980)	0.31	-	-
GRACE 2.0	1.063 (1.040-1.087)	< 0.01	1.053 (1.032-1.074)	< 0.01
Model 2 Multivariate Analysis				
Chronic kidney disease	4.935 (2.567-9.488)	< 0.01	2.908 (1.733-4.879)	< 0.01
CHA_2DS_2-VASc-HSF	1.304 (1.083-1.570)	< 0.01	1.181 (1.034-1.348)	< 0.01

MACCEs: Major adverse cardiac and cerebrovascular events, GRS 2.0: Updated GRACE risk score, HR: Hazard ratio, CI: Confidence interval.

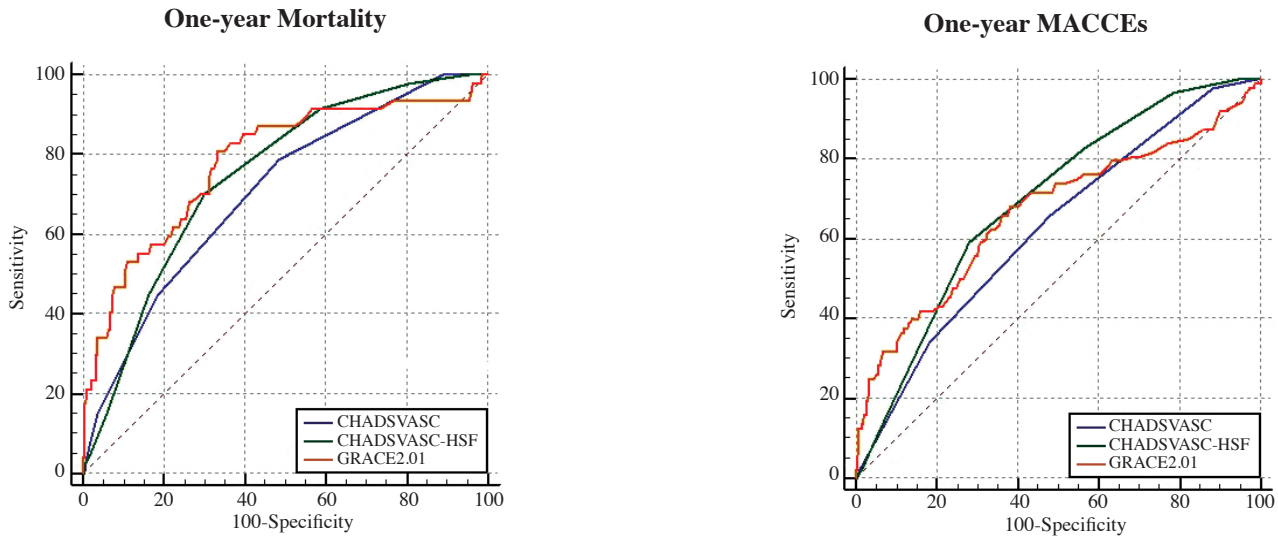


	Difference between areas	95% CI	Z-statistic	p
CHA_2DS_2-VASc-HSF vs. GRACE 1.0	0.063	0.007-0.120	2.170	**0.03**
CHA_2DS_2-VASc-HSF vs. CHA_2DS_2-VASc	0.125	0.084-0.167	5.915	**< 0.01**

Figure 1. The receiver-operating characteristics (ROC) curves of the CHA2DS2-VASc-HSF (green line), CHA_2DS_2-VASc (blue line), and GRACE 1.0 (orange line) for detecting intermediate-high SSI [area under the curve (AUC), 0.85; 95% confidence interval (CI): 0.81-0.88, p< 0.01; AUC, 0.72, 95% CI: 0.68-0.77, p< 0.01; AUC, 0.79, 95% CI: 0.74-0.83, p< 0.01, respectively).

0.01 and HR 1.181, p< 0.01, respectively), GRS 2.0 (HR 1.063, p< 0.01 and HR 1.053, p< 0.01, respectively), DM (HR 2.412, p< 0.01 and HR 1.816, p< 0.01, respectively), HF (HR 1.986, p= 0.03 and HR 2.038, p< 0.01, respectively), and CKD (HR 4.935, p< 0.01 and HR 2.908, p< 0.01, respectively (Table 5).

Furthermore, we performed the ROC curve analysis to test the diagnostic performance of CHA_2DS_2-VASc-HSF, CHA_2DS_2-VASc, and GRS 2.0 in predicting the one-year cardiovascular outcomes. For mortality and MACCEs, the AUCs of the CHA_2DS_2-VASc-HSF score were 0.75 (95% CI: 0.70-0.79; p< 0.01) and 0.69 (95% CI: 0.65-0.74; p< 0.01); the AUCs of the



	Difference between areas	95% CI	Z-statistic	p
1-year Mortality				
CHA_2DS_2-VASc-HSF vs. GRACE	0.035	-0.049-0.119	0.820	0.41
CHA_2DS_2-VASc-HSF vs. CHA_2DS_2-VASc	0.043	-0.018-0.105	1.377	0.17
1-year MACCEs				
CHA_2DS_2-VASc-HSF vs. GRACE	0.028	-0.035-0.092	0.871	0.38
CHA_2DS_2-VASc-HSF vs. CHA_2DS_2-VASc	0.069	0.021-0.116	2.850	< 0.01

Figure 2. Comparison of the receiver-operating characteristics (ROC) curves of the CHA_2DS_2-VASc-HSF (green line), CHA_2DS_2-VASc (blue line), and GRACE 2.0 (orange line) risk modalities for detecting the one-year mortality [area under the curve (AUC), 0.75, 95% confidence interval (CI): 0.70-0.79, p< 0.01; AUC, 0.70, 95% CI: 0.66-0.75, p< 0.01; AUC, 0.78, 95% CI: 0.74-0.82, p< 0.01, respectively) and MACCEs (AUC, 0.69, 95% CI: 0.65-0.74, p< 0.01; AUC, 0.63, 95% CI: 0.58-0.67, p< 0.01; AUC, 0.67, 95% CI: 0.62-0.71, p< 0.01, respectively).

CHA_2DS_2-VASc score were 0.70 (95% CI: 0.66-0.75; p< 0.01) and 0.63 (95% CI: 0.58-0.67; p< 0.01); and the AUCs of the GRS 2.0 score were 0.78 (95% CI: 0.74-0.82; p< 0.01) and 0.67 (95% CI: 0.62-0.71; p< 0.01). A statistical comparison performed using DeLong test revealed no significant difference between the AUCs of CHA_2DS_2-VASc-HSF and GRS 2.0 for mortality and MACCEs (p= 0.41 and 0.38, respectively). On the other hand, while predictive power of CHA_2DS_2-VASc-HSF in determining the one-year mortality was similar to that of CHA_2DS_2-VASc (p= 0.17), its predictive power in determining one-year MACCEs was better than that of CHA_2DS_2-VASc (p< 0.01; Figure 2). Besides, we observed that CHA_2DS_2-VASc-HSF > 4 points had a 68% sensitivity and a 70% specificity for mortality and had a 57% sensitivity and a 72% specificity for the prediction of MACCEs. The Kaplan-Meier curves revealed that the high-risk group had significantly higher mortality and MACCEs than the low-risk group during the follow-up period after index hospitalization (p< 0.01, p< 0.01, respectively; Figure 3).

DISCUSSION

The principal findings of this study are as follows: (i) both the CHA_2DS_2-VASc-HSF and GRS 1.0 scores significantly correlate with the CAD extent and severity, but CHA_2DS_2-VASc-HSF has better diagnostic accuracy; (ii) both the CHA_2DS_2-VASc-HSF and GRS 2.0 scores are independent predictors of one-year mortality and MACCEs, and have similar predictive accuracy; (iii) although CHA_2DS_2-VASc-HSF and CHA_2DS_2-VASc had similar predictive accuracy for one-year mortality, the predictive performance of CHA_2DS_2-VASc-HSF for one-year MACCEs was superior to that of CHA_2DS_2-VASc; and (iv) patients with CHA_2DS_2-VASc-HSF score > 4 points are at high risk for adverse long-term cardiovascular outcomes.

The CHA_2DS_2-VASc score considers similar traditional risk factors (e.g., increasing age, HT, and DM) for the development or presence of CAD[8]. All components of the CHA_2DS_2-VASc score have been reported to be predictors of poor outcomes following acute MI[17]. Several recent studies have examined

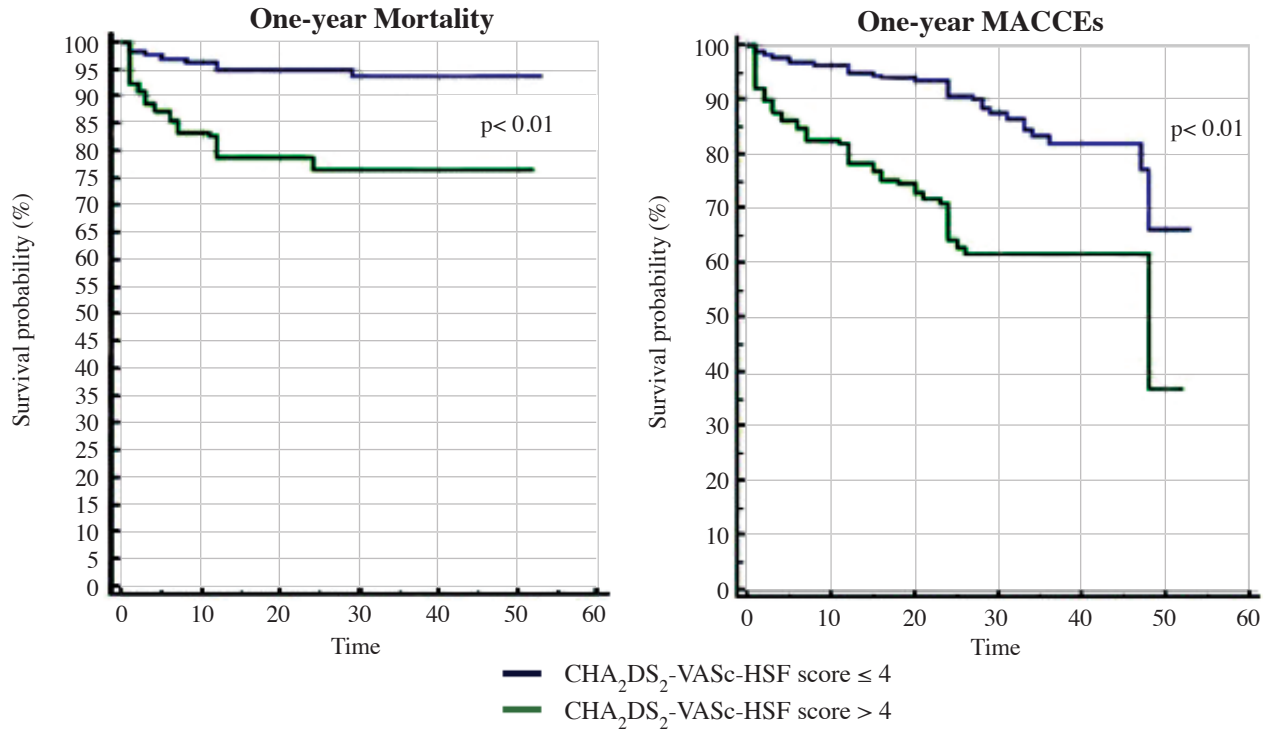


Figure 3. The Kaplan-Meier plots of survival curves of low-risk (blue line) and high-risk (green line) patients.

the prognostic value of the CHA_2DS_2-VASc score in patients ACS[9-11]. Reportedly, as hyperlipidemia, male sex, and smoking exacerbate the cardiovascular risk, they play a fixed role in the risk classification assessment[18]. Tasolar et al. proposed that modified CHA_2DS_2-VASc-HS, including male sex (as sex category), hyperlipidemia, and smoking as other major risk factors for CAD besides known CHA_2DS_2-VASc components, positively correlated with the CAD severity and in-hospital major adverse cardiac events in patients with NSTE-ACS[18]. Moreover, some previous prospective studies have demonstrated that cardiovascular risk prediction can be improved in prognostic models by adding a family history of CVD to conventional risk factors[19,20]. In addition, family history has been proposed to be a potential screening tool to identify patients at increased risk and candidates for advanced prevention strategies[21]. Thus, this study explored the newly defined CHA_2DS_2-VASc-HSF score, which includes family history of CAD, besides CHA_2DS_2-VASc-HS score elements. To the best of our knowledge, this is the first study to assess the predictive accuracy of the CHA_2DS_2-VASc-HSF score in determining the one-year mortality and MACCEs in comparison with the revised GRS 2.0 score among patients with NSTE-ACS. In this study, the CHA_2DS_2-VASc-HSF and GRS 2.0 scores-the latter has been validated to be useful for risk assessment and predicting long-term mortality at 1 and 3 years[5]-independently predicted the one-year mortality and MACCEs, and both exhibited similar predictive performance. As in-hospital mortality was observed in a small number of patients, the results for in-hospital mortality were inconclusive.

Each component of the CHA_2DS_2-VASc-HSF score has been reported to be associated with an increased risk of cardiovascular morbidity or mortality[11,18,22-24]. Corroborating the literature, among the CHA_2DS_2-VASc-HSF score components, HF and diabetes were found to be predictors of the primary and secondary endpoints in this study[25,26]. However, some conflicting data also exist about the correlation between traditional cardiovascular risk factors (e.g., hyperlipidemia, smoking, and family history) and cardiovascular outcomes[27]. In this study, CHA_2DS_2-VASc-HSF and CHA_2DS_2-VASc did not differ in terms of the predictive performance in determining the 1-year mortality; however, CHA_2DS_2-VASc-HSF was found to be better in terms of MACCEs. Perhaps, although not statistically significant, the finding mentioned above could be related to more family history and smoking in the MACCEs group. Indeed, Tamosiunas et al. reported that family history correlated with cardiovascular disease and CAD mortality, independent of other known lifestyle and biological risk factors; the authors proposed that the addition of family history to traditional risk factors enhances the prediction of CVD mortality and could be used to identify high-risk individuals[28]. Of note, smoking is

one of the leading causes of cardiovascular disease morbidity and mortality. Recently, Banks et al. reported that, compared with people who have never smoked, current tobacco smokers are, at least, twice the risk of developing the leading cardiovascular disease, including cerebrovascular disease and HF, and more than five times the risk of developing peripheral artery disease[29]. Thus, we believe that CHA_2DS_2-VASc-HSF could be a useful tool for additional risk stratification in patients with NSTE-ACS beyond the results provided by conventional risk factors for predicting 1-year mortality and MACCEs.

The complexity of CAD and lesion characteristics correlate with long-term mortality. Consistent with the literature, we found that 1-year mortality and MACCEs rates were higher in patients with severe CAD[30]. In addition, we observed that the CHA_2DS_2-VASc-HSF score exhibited markedly higher predictive performance than the CHA_2DS_2-VASc and GRS 1.0 scores. The correlation between CAD severity and CHA_2DS_2-VASc-HSF score could be another factor contributing to the function of CHA_2DS_2-VASc-HSF in predicting cardiovascular outcomes. Corroborating the literature, this study demonstrated a correlation between CHA_2DS_2-VASc-HSF score and CAD severity[12-14]. Al-Shorbagy et al. demonstrated a correlation between CHA_2DS_2-VASc-HSF score and the severity of atherosclerosis, defined as intermediate-high SSI in 50 patients with NSTEMI but not in patients with UAP; besides, they only evaluated the predictive value of the CHA_2DS_2-VASc-HSF score in predicting the CAD severity defined by anatomical SSI and did not compare the CHA_2DS_2-VASc-HSF score with GRS 1.0 in the prediction of the CAD severity[14]. Furthermore, Uysal et al. reported that the CHA_2DS_2-VASc-HSF score independently correlated with the severity of atherosclerosis, as assessed by SSI in patients with STEMI[13].

To date, several previous studies have proposed a correlation between GRS 1.0 score and CAD severity, as was also found in this study[5,6]. To the best of our knowledge, this is the first study to demonstrate that CHA_2DS_2-VASc-HSF offers better predictive accuracy than GRS 1.0 in determining the CAD severity. We believe that this finding could be attributable to the fact that the CHA_2DS_2-VASc-HSF score is a model that includes a combination of several factors related to the CAD severity, such as HT, DM, hyperlipidemia, positive family history, HF, stroke, and history of CAD and CAD-equivalent vascular diseases, compared with GRS 1.0[31-35]. Indeed, DM, hyperlipidemia, HF, HT, and vascular disease were found to be significantly related to intermediate-high SSI. Moreover, HT, DM, and HF were found to be independent predictors of the CAD severity. We know that GRS 1.0 is a risk prediction scoring system for in-hospital and six-month mortality in patients with ACS, rather than predicting the CAD severity; perhaps, this could be another reason why our study supports using CHA_2DS_2-VASc-HSF over GRS 1.0 to determine the extent and severity of CAD.

LIMITATIONS

This study has some limitations. First, this was a single-center-based retrospective study with small sample size. Second, the SSI calculation based on luminal stenosis was only assessed by visual X-ray coronary angiogram, which does not consider the functional impact and quantitative assessment of CAD. Finally, patients with a history of CABG were excluded because the SS algorithm was designed for patients with native CAD. Hence, more extensive prospective studies are warranted, and our findings need to be supported by population-based studies.

CONCLUSION

The CHA_2DS_2-VASc-HSF score could be considered as a simple, cost-effective, and time-saving handy risk stratification method that can be applied without any software and could be helpful for physicians to enhance prognoses and clinical outcomes by identifying high-risk patients. During the follow-up period, patients with a CHA_2DS_2-VASc-HSF score of > 4 points should be closely monitored and informed that they are at high risk.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Health Sciences University Haseki Training and Research Hospital (Decision Number: 87; Decision Date: April 15, 2019).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design – MK, GD; Analysis/Interpretation – MK, EB; Data Collection – MK, GD; Writing – MK, EB; Critical Revision – MK, GD; Final Approval – EB, MMC; Statistical Analysis – MK, EB; Overall Responsibility - MK

Conflict of Interest: The authors have no conflict of interest to declare.

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