ORIGINAL ARTICLE

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The prognostic value of the CHA_2DS_2-VASc score in coronary collateral circulation and long-term mortality in coronary artery disease

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SUMMARY

BACKGROUND: The CHA_2DS_2-VASc score is used to determine thromboembolic risk in cases of atrial fibrillation. The predictive value of this score in predicting coronary collateral circulation in chronic total occlusion is unknown.

OBJECTIVE: The aim of this study was to investigate the relationship between the CHA_2DS_2-VASc score and coronary collateral circulation in patients with chronic total occlusion.

METHODS: A total of 189 patients, who underwent coronary angiography and had a chronic total occlusion in at least one coronary artery, were enrolled in this study. The Rentrop scoring system was used for grouping the patients, and patients were classified as having poorly developed coronary collateral circulation (Rentrop grade 0 or 1) or well-developed coronary collateral circulation (Rentrop grade 2 or 3).

RESULTS: The CHA_2DS_2-VASc score of the good coronary collateral circulation group was significantly lower than the other group (3.1±1.7 vs. 3.7±1.7, p=0.021). During the follow-up period, 30 (32.2%) patients in the poorly developed coronary collateral circulation group and 16 (16.7%) patients in the well-developed coronary collateral circulation group died (p=0.028). According to the multivariable Cox regression model, the CHA_2DS_2-VASc score [hazard ratio (HR): 1.262, p=0.009], heart rate (HR: 1.049, p=0.003), LVEF (HR: 0.975, p=0.039), mean platelet volume (HR: 1.414, p=0.028), and not taking acetylsalicylic acid during admission (HR: 0.514, p=0.042) were independently associated with a higher risk of mortality.

CONCLUSIONS: The CHA_2DS_2-VASc score is closely related to coronary collateral development and predicts mortality in patients with chronic total occlusion.

KEYWORDS: Collateral circulation. CHA_2DS_2-VASc score. Rentrop grade. Coronary occlusion. Coronary artery disease. Mortality.

INTRODUCTION

Coronary collateral circulation (CCC) is a physiologic protective mechanism of a heart in case of critical coronary artery stenosis and ischemia. A well-developed CCC reduces myocardial ischemia and anginal symptoms, protects cardiac function, improves the prognosis of patients with stable coronary artery disease (SCAD), and reduces the incidence of cardiogenic shock and mortality after acute myocardial infarction (MI)[1]. However, the influencing factors and possible mechanisms of collateral circulation formation in patients with CAD have not been fully elucidated. In previous studies, inflammation and inflammatory markers such as C-reactive protein (CRP) and acute-phase reactants were found to be responsible for poor CCC development[2].

The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, previous stroke or transient ischemic attack (TIA) [doubled], vascular disease, age 65–74 years, female gender) score was first applied to patients with atrial fibrillation (AF) to determine their thromboembolic risks. Recently, some studies have found a positive correlation between CHA_2DS_2-VASc score and increased inflammatory status[3,4].

However, the association between CHA_2DS_2-VASc score and CCC has not been investigated. Our aim in this study was to determine the relationship between CHA_2DS_2-VASc score and CCC and mortality in patients with CAD.

METHODS

A total of 189 patients, who underwent coronary angiography (CAG) and had a chronic total occlusion (CTO) in at least one coronary artery between January 2019 and January 2021, were enrolled in this study. CTO was defined as a total occlusion of a coronary vessel with a distally TIMI 0 or TIMI 1 flow for at least 3 months. Patients were excluded from the study if they had acute coronary syndrome in the

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past 3 months, coronary artery bypass surgery of coronary stenting before, symptomatic heart failure (NHYA class III or IV), severe cardiac valvular disease (class III or IV), hepatic failure, active infectious disease, malignancy, and thyroid disease. The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki.

Basic demographic information regarding age and sex, and CAD risk factors (e.g., hypertension, diabetes, dyslipidemia, history of smoking, and family history) were obtained from the hospital database. Blood results taken before CAG were screened from hospital records, and fasting blood glucose and cholesterol parameters were determined. Left ventricular ejection fraction (LVEF) was also gathered from echocardiography records, which was done before or after CAG. Medications of the patients were recorded. Patients who were taking antihypertensive medications were categorized as hypertensives. Dyslipidemia was defined according to the European Society of Cardiology guidelines[5]. Diabetics were determined by patients who had already been diagnosed with diabetes and taking antidiabetic medications and other patients who did not know their diabetes status but had high blood glucose according to the American Diabetes Association's criteria[6].

Coronary angiography was performed by transfemoral or transradial access with the routine Judkins technique. CAG data were interpreted by two cardiologists, and CCC was classified by the Cohen-Rentrop standard[7]. According to Rentrop classification, grade 0 was defined as no visible collateral circulation, grade 1 was defined as filling of the side branches without distal main epicardial vessel filling, and grades 2 and 3 were defined as partial and complete filling of the distal main epicardial vessel, respectively. Patients who had grades 0 and 1 were accepted as having poor collaterals, whereas patients who had grades 2 and 3 were accepted as having good collaterals.

The CHA_2DS_2-VASc score was calculated according to the following criteria: 1 point for the presence of chronic heart failure (LVEF<40%), hypertension, diabetes, age between 65 and 74, vascular disease (previous MI or CAD and peripheral arterial disease), and female sex; and 2 points for the presence of stroke and/or TIA history and age 75 or above. Patients get a CHA_2DS_2-VASc score between 0 and 9.

Analysis of statistics was performed by using SPSS version 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, United States). The distribution pattern of parameters, whether normal or not, was determined by the Kolmogorov–Smirnov test. Continuous parameters with normal distribution were presented as mean±standard deviation, whereas parameters with non-normal distribution were presented as median (interquartile range); categorical variables were presented with number and percentage values. A Student's t-test was used to compare continuous variables between groups when the distribution was normal, and the rank-sum test (Mann–Whitney U-test) was used to compare continuous variables between groups when the distribution was non-normal. The chi-square test was used to compare categorical variables. The effects of different variables on mortality were assessed by the Cox regression analysis. Inclusion of covariates in the multivariable model was first determined by selecting those that exhibited two-sided $p<0.10$ in unadjusted analyses. Inclusion of additional covariates was determined by performing a stepwise backward selection process until all the other variables in the model exhibited $p<0.10$. The survival curves during hospitalization for the collateral groups were analyzed using the Kaplan–Meier method, and statistical assessment was performed using the log-rank test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 189 patients were divided into two groups according to the Rentrop grades. The poorly developed CCC group (Rentrop 0 or 1) comprised of 93 patients, and 96 patients had well-developed CCC (Rentrop 2 or 3). Both groups were similar in age, sex, presence of diabetes, hypertension, hyperlipidemia, and smoking status. There was no significant difference in terms of heart rate (HR), systolic blood pressure, diastolic pressure, and previous medications other than acetylsalicylic acid (ASA). However, the LVEF of the poor collateral group was significantly lower (p=0.033).

The CHA_2DS_2-VASc score of the well-developed collateral group was significantly lower than the other group (3.1±1.7 vs. 3.7±1.7, p=0.021). The mean duration of the follow-up was 31.5±13.9 months. During the follow-up period, 30 (32.2%) patients in the poorly developed CCC group and 16 (16.7%) patients in the well-developed CCC group died (p=0.028). When we grouped the patients according to the CHA_2DS_2-VASc score <2 and ³2, the mortality rate was also significantly higher in CHA_2DS_2-VASc score group (31% vs. 7%, p<0.001) (Table 1). Hemoglobin and platelet counts, glomerular filtration rate, and cholesterol levels have no significant difference in the two groups.

In the multivariable Cox regression model, the CHA_2DS_2-VASc score [hazard ratio (HR): 1.262, p=0.009], HR (1.049, p=0.003), LVEF (HR: 0.975, p=0.039), mean platelet

Table 1. Demographic and clinical characteristics of the study population according to CHA_2DS_2-VASc score.

Characteristics	All patients (n=189)	CHA_2DS_2-VASc≤2 (n=55)	CHA_2DS_2-VASc>2 (n=134)	p-value
Age (years), mean±SD	68.2±10.7	61±8.3	71.2±10.1	**<0.001**
Male, n (%)	154 (81.4)	53 (96.4)	101 (75.3)	**<0.001**
SBP, mm Hg	127.6±17.8	124.9±15	128.7±18.9	0.178
DBP, mm Hg	75.6±12.3	73.4±9.2	76.6±13.3	0.109
Current smoker, n (%)	40 (21.1)	20 (36.4)	20 (14.9)	**0.002**
CKD, n (%)	52 (27.5)	6 (10.9)	46 (34.3)	**0.001**
Hyperlipidemia, n (%)	17 (8.9)	4 (7.3)	13 (9.7)	0.596
Family history of CVD, n (%)	16 (8.5)	4 (7.3)	12 (8.9)	0.706
Prior MI, n (%)	87 (46)	10 (18.1)	77 (57.4)	**<0.001**
Multivessel disease, n (%)	134 (70.9)	39 (70.9)	95 (70.9)	1
EF, %, mean±SD	46.3±12.4	51.7±11.2	44.1±12.2	**<0.001**
ECG, n (%)				
Sinus rhythm	175 (92.6)	54 (98.2)	121 (90.3)	0.060
Atrial fibrillation	14 (7.4)	1 (1.8)	13 (9.7)	0.060
CTO location, n (%)				
LAD	50 (26.4)	15 (27.2)	35 (26.1)	0.858
Cx	28 (14.8)	11 (20)	17 (12.7)	0.259
RCA	104 (55)	26 (47.3)	78 (58.2)	0.199
Other	25 (13.2)	6 (10.9)	19 (14.2)	0.642
Gensini score, mean±SD	59.8±25.2	62.2±24.8	58.9±25.4	0.406
CCC, n (%)				
Poorly developed	93 (49.2)	19 (34.5)	77 (57.5)	**0.006**
Well developed	96 (50.8)	36 (65.4)	57 (42.5)	**0.006**
CHA_2DS_2-VASc score, mean±SD	3.4±1.7	1.3±0.7	4.2±1.2	**<0.001**
Mortality, n (%)	46 (24.3)	4 (7.3)	42 (31.3)	**<0.001**

CCC: coronary collateral circulation; CHF: chronic heart failure; CKD: chronic kidney disease; CTO: chronic total occlusion; CVD: cardiovascular disease; Cx: circumflex coronary artery; DBP: diastolic blood pressure; EF: ejection fraction; LAD: left anterior descending coronary artery; LDL-C: low-density lipoprotein cholesterol; RCA: right coronary artery; SBP: systolic blood pressure. Bold indicates statistically significant values.

volume (MPV) (HR: 1.414, p=0.028), and not taking ASA during admission (HR: 0.514, p=0.042) were independently associated with a higher risk of mortality (Table 2). Finally, Kaplan–Meier survival curves stratified by the CHA_2DS_2-VASc score (≤2 vs. >2) and CCC groups (well vs. poor) represented that higher CHA_2DS_2-VASc score and poor CCC were associated with higher mortality rates, as shown in Figure 1.

DISCUSSION

To the best of our knowledge, this is the first study that shows the CHA_2DS_2-VASc score is related to coronary collateral development and predicts long-term mortality in patients with CAD. Other than the CHA_2DS_2-VASc score, increased HR, low LVEF, increased platelet volume, and not taking ASA during admission were also found to be related to mortality.

Collaterals are the small vessel formations that supply blood to the ischemic area[8]. It works as a compensatory mechanism to protect myocardial muscles from ischemic damage in case of obstruction of the main epicardial vessels. Studies have shown that patients with good collaterals have a better myocardial contractile function, lower infarct size, and positive remodeling process after acute MI[1]. However, although the severity of the obstruction of the epicardial vessels is the same, some patients have well-developed collaterals but some patients do

not. Several studies have been conducted to clarify this issue until now, and it has been clearly demonstrated that higher inflammatory status in the myocardium and higher inflammatory markers are responsible for the prevention of the development of collaterals[9,10].

The CHA_2DS_2-VASc score is a well-validated clinical scoring system to predict thromboembolic risk in patients with non-valvular AF[11]. In previous studies, this score has been found to be related to increased inflammation and worse prognosis in patients with many diseases like CAD[12], heart failure[13], stroke[14], chronic kidney disease[15], and, recently, COVID-19[16]. We found that higher CHA_2DS_2-VASc score causes low-grade collateral formation in coronary vessels. This result can be interpreted with the negative effects of inflammation on collateral formation, because the components of the CHA_2DS_2-VASc score are the well-known risk factors for atherosclerosis, which is a chronic inflammatory process of the coronary vessel.

Another important result of our study is the increased mortality rates of the poorly developed collateral group during follow-up, and this can be the consequence of both the high CHA_2DS_2-VASc score and the presence of poor collaterals. Because both of these scenarios have been shown as the cause of increased mortality in CAD patients earlier[12,17]. In a meta-analysis that included about 6500 patients earlier, it was shown that patients with high collateralization had a 36% reduced mortality risk compared with patients with low collateralization[17]. However, in our study according to the Cox regression analysis, although the CHA_2DS_2-VASc score increases mortality risk with a HR of 1.262, coronary collateral grades were not found to be related to mortality. This may be the effect of the presence of robust predictors like HR, ejection fraction, MPV, red cell distribution width, and ASA usage in the regression model.

There are some limitations to this study. First, this is a cross-sectional, single-center, retrospective study, which has a relatively small sample size; our study cannot clarify the exact mechanisms linking with the CHA_2DS_2-VASc score and poor development of collaterals in patients with CAD, and thus, further studies are needed. Second, the CCC classification adopts the Rentrop classification standard, which means that the small, microscopic vessels may not be visualized angiographically.

Table 2. Multivariable Cox regression analysis of risk factors for mortality.

Variables*,**	Hazard ratio, 95%CI	p-value
Hemoglobin	0.862 (0.741–1.002)	0.053
Mean platelet volume	1.414 (1.039–1.925)	**0.028**
Heart rate	1.020 (1.001–1.039)	**0.038**
Acetylsalicylic-acid usage	0.514 (0.271–0.977)	**0.042**
Ejection fraction	0.975 (0.952–0.999)	**0.039**
Gensini score	1.010 (1.000–1.020)	0.059
CHA_2DS_2-VASc score	1.262 (1.060–1.502)	0.009

CI: confidence interval. Bold indicates statistically significant values. *Model included age, diabetes, stroke, heart rate, ejection fraction, hemoglobin, mean platelet volume, red cell distribution width, acetylsalicylic acid usage, presence of chronic total obstruction in the right coronary artery, the circumflex artery, and the left anterior descending artery, collateral grade, Gensini score, and CHA_2DS_2-VASc score. **Selection of covariates for multivariable models is explained in the "Methods" section. Unless otherwise indicated, hazard is interpreted as the presence (vs. absence) of each categorical variable or an increase of 1 unit of each continuous variable.

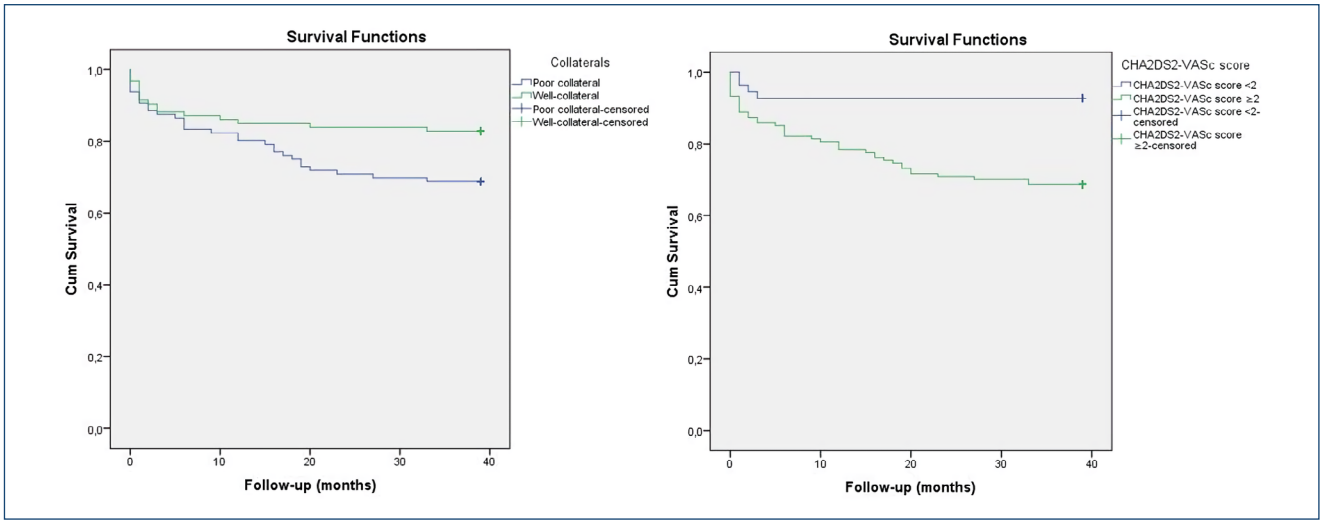

Figure 1. Kaplan–Meier survival curves stratified by the CHA_2DS_2-VASc score and coronary collateral circulation for mortality.

CONCLUSION

In this study, we have found a relationship between the CHA_2DS_2-VASc score, which has an expanding clinical use, and collateral development and mortality. This is an easy score to calculate and may be very useful to find high-risk patients with poor CCC for adverse cardiac events and mortality.

AUTHORS' CONTRIBUTIONS

MKA: Conception and Study Design, Acquisition, Analysis, Interpretation of Data, and Manuscript Revision. **AT:** Acquisition, Analysis, and Interpretation of Data. **SY:** Conception and Study Design, Acquisition, Analysis, Interpretation of Data, and Manuscript Revision.

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