Acta Cardiol Sin 2017;33:429–435
Original Article
doi: 10.6515/ACS20170221A

General Cardiology

The Association between CHA_2DS_2-VASc Score and Mortality in Patients with Heart Failure with Reduced Ejection Fraction

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Background: Heart failure (HF) is associated with significant mortality and morbidity. Therefore, identifying high-risk patients may optimize treatment for HF patients and reduce adverse events. The aim of this study was to assess the role of the CHA_2DS_2-VASc score to predict mortality in patients with reduced left ventricular ejection fraction (LVEF).

Methods: A total of 106 patients with reduced LVEF were enrolled in this study. All patients completed a one-year follow-up, and a CHA_2DS_2-VASc score was calculated for each patient.

Results: Twenty-one patients (19.8%) died during the 1-year follow-up. We found that baseline functional status, CHA_2DS_2-VASc score, brain natriuretic peptide, blood urea and hemoglobin levels were associated with mortality. In the multivariate analysis, CHA_2DS_2-VASc score and functional capacity were the only predictors of 1-year mortality.

Conclusions: Use of the CHA_2DS_2-VASc score appears to be feasible for risk stratification and mortality prediction in patients with reduced LVEF.

Key Words: CHA_2DS_2-VASc score • Heart failure • Mortality

INTRODUCTION

Heart failure (HF) has become a major global public health problem due to its increasing incidence and prevalence, with a reported general prevalence rate of 0.3 and 2% and up to 25% in those over 75 years of age.[1,2]

Despite advances in the technology and management, the prognosis for patients who suffer HF still remains poor.[3] Approximately half of the patients diagnosed with HF die within 5 years, and more than half of the individuals with advanced HF die within a year.[3,4] Therefore, there is a need to develop optimal treatment and follow-up measure for HF patients.

CHA_2DS_2-VASc is a risk score that was developed for prediction of stroke in patients with atrial fibrillation (AF),[5] wherein higher scores indicate a higher risk of cerebrovascular events.[5] Recent studies have reported that CHA_2DS_2-VASc score might be useful prognostic marker in those patients with ST-segment elevation myocardial infarction and acute pulmonary embolism.[6-8]

In this study, we aimed to evaluate the association between CHA_2DS_2-VASc score and mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Received: June 5, 2016 Accepted: February 21, 2017
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MATERIALS AND METHODS

Study population and study design

This prospective observational study was conducted between June and November 2013, and 106 consecu-

tive patients diagnosed HFrEF [left ventricular ejection fraction (LVEF) of ≤ 35%] were enrolled. Patients with active infection, malignancy, chronic liver disease, autoimmune disease and those under the treatment of steroid therapy were excluded.

The primary end point of the study was the incidence of all-cause mortality within one year. Survival status during follow-up period was assessed by reviewing medical files and by telephone contacts. One-year follow-up was completed in all patients. The study protocol was approved by the local ethics committee.

Clinical, echocardiographic, laboratory findings, medications and presence of implantable cardioverter defibrillator (ICD) were recorded for each subject. Functional status was evaluated according to the definition of the New York Heart Association Functional Classification. Hypertension was defined as blood pressure > 140/90 mm Hg on > 2 occasions during office measurements, or the use of antihypertensive treatment. Hyperlipidemia was defined according to current guidelines or use of antihyperlipidemic treatment.[9] Diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dl or use of antidiabetic treatment.

All patients underwent transthoracic echocardiography performed using a system Vivid 7 (General Electric, Horten, Norway) device. LVEF was measured using the modified Simpson's method.

Blood samples for troponin I and brain natriuretic peptide (BNP) were obtained upon admission, and measured with an autoanalyzer (Access 2) running commercial assays (Beckman-Coulter, Indianapolis, IN, USA). Hemoglobin and white blood cell count values were measured using an automated hematology analyzer Coulter LH 780 (Beckman-Coulter, USA). Accordingly, C reactive protein (CRP), glucose and creatinine levels were measured with Coulter AU 680 (Beckman-Coulter, USA). The CHA_2DS_2-VASc scores of the patients were measured upon admission and contains congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (2-points), diabetes, stroke (2-points), vascular disease (previous myocardial infarction, peripheral arterial disease or aortic plaque), age 65-74, and gender (female).

Statistical analyses

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range, and categorical variables were expressed as percentages and numbers. Categorical variables were compared with the Chi-square or Fisher test; continuous variables were compared with the two-sample t-test or the Mann-Whitney U test, as appropriate. Spearman's correlation analysis was performed to evaluate the relation of CHA_2DS_2-VASc score with other variables. Univariate Cox regression analysis was performed to assess the association of the variables with mortality and variables that had $p < 0.05$ in the univariate analysis were further analyzed with multivariate Cox regression model. Results of the Cox regression analysis were reported with hazard ratios (HR) and confidence intervals of 95%. Receiver operating characteristic (ROC) curve was used to detect the optimal cut-off point of CHA_2DS_2-VASc score to estimate 1-year survival. Kaplan-Meier survival curves and log-rank values were used to assess survival in patient subgroups. All statistical analysis were performed using the SPSS program (version 21.0, SPSS, Chicago, Illinois, USA). The threshold of statistical significance was established at $p < 0.05$.

RESULTS

A total of 106 patients (mean age 60, 81.1% male) were included in this study. Table 1 summarizes the demographic and clinical patient characteristics, use of medications, echocardiography findings, and laboratory results.

Of the 106 patients included, 50 (47.2%) had diabetes mellitus and 55 (51.9%) had hypertension. Twenty-seven patients (25.5%) were current smokers, and 38 (35.8%) had hyperlipidemia. In 70 patients (66%), cardiomyopathy was of ischemic origin, and a total of 60 patients (56.6%) had ICD/cardiac resynchronization therapy (CRT)/CRT-D. Atrial fibrillation was present in 28 subjects (26.4%) and bundle branch block was present in 22 patients (20.8%). The overall mean CHA_2DS_2-VASc score was 3.07 ± 1.49 and the average LVEF was 24.7 ± 6.4. Severe mitral regurgitation was present in 22 (20.8%) patients. Also, 25 (23.6%) patients were taking oral anticoagulants. The mean BNP was 714 (285.3-1695.5) and mean hemoglobin was 12.7 ± 1.9 mg/dl.

Patients were followed up for 1 year after discharge. During the follow-up period, 21 patients died (19.8%).

Table 1. Comparison of clinical characteristics of the study patients according to mortality

	All patients (106)	Mortality (-) (n = 85)	Mortality (+) (n = 21)	p
Demographics, comorbidities and predisposing conditions				
Male	81.1% (86)	83.5% (71)	71.4% (15)	0.22
Age (years)	60 ± 12.9	59.2 ± 12.1	61.3 ± 16.0	0.65
Diabetes mellitus	47.2% (50)	43.5% (37)	61.9% (13)	0.13
Stroke	4.71% (5)	4.70% (4)	4.76% (1)	0.94
Hypertension	51.9% (55)	48.2% (41)	66.7% (14)	0.15
Hyperlipidemia	35.8% (38)	36.5% (31)	33.3% (7)	0.79
Smoking	25.5% (27)	29.4% (25)	9.5% (2)	0.06
Ischemic cardiomyopathy	66% (70)	67.1% (57)	61.9% (13)	0.66
Cardiac device	56.6% (60)	57.6% (49)	52.4% (11)	0.66
Atrial fibrillation	26.4% (28)	29.4% (25)	14.3% (3)	0.16
Bundle branch block	20.8% (22)	20% (17)	23.8% (5)	0.77
Functional status > 2	57.5% (61)	51.8% (44)	81% (17)	**0.02**
CHA_2DS_2-VASc score	3.07 ± 1.49	3.04 ± 1.46	4.05 ± 1.8	**0.004**
Drugs				
Acetylsalicylic acid	59.4 (63)	57.6% (49)	66.7% (14)	0.45
Oral anticoagulant	23.6 (25)	25.9% (22)	14.3% (3)	0.39
ACEI/ARB	84 (89)	87.1% (74)	71.4% (15)	0.1
Beta blocker	92.5 (98)	92.9% (79)	90.5% (19)	0.66
Spironolactone	41.5 (44)	41.2% (35)	42.9% (9)	0.89
Antiarrhythmic	2.8 (3)	2.4% (2)	4.8% (1)	0.49
Diuretics	76.4 (81)	75.3% (64)	81% (17)	0.78
Echocardiography				
LVEF (%)	24.7 ± 6.4	25.0 ± 6.2	23.5 ± 7.1	0.34
Severe mitral regurgitation	20.8 (22)	17.6% (15)	33.3% (7)	0.14
Severe tricuspid regurgitation	27.4 (29)	25.9% (22)	33.3% (7)	0.49
Laboratory parameters on admission				
Glucose (mg/dL)	109.5 (98-152.3)	112 (98.5-153.5)	108 (89.5-149)	0.43
Urea (mg/dL)	58 (43.8-92)	54 (43-88.5)	77 (60-125)	**0.01**
Creatinine (mg/dL)	1.19 (0.96-1.57)	1.15 (0.9-1.49)	1.41 (1.09-2.07)	**0.009**
Sodium (mmol/L)	134 ± 6	134.5 ± 6.2	133.9 ± 5	0.68
Potassium (mmol/L)	4.3 ± 0.6	4.3 ± 0.6	4.5 ± 0.6	0.14
BNP (pg/ml)	714 (285.3-1695.5)	524 (220.6-1492.8)	1651.7 (715-2639.8)	**< 0.001**
Troponin (ng/ml)	0.06 (0.02-0.11)	0.06 (0.03-0.1)	0.03 (0.02-0.16)	0.95
Cholesterol (mg/dL)	138 (107.3-162)	138 (109-163)	118 (97-144)	0.26
HDL (mg/dL)	33 (24.8-40.3)	33 (26.5-40)	33 (20-46)	0.61
LDL (mg/dL)	81 (60.8-98)	81 (60.5-91.5)	68 (51-115.5)	0.73
Triglyceride (mg/dL)	95 (78-127.3)	102 (79-133)	87 (75.5-101.5)	0.12
Hemoglobin (g/dL)	12.7 ± 1.9	13 ± 1.9	11.5 ± 1.4	**< 0.001**
White blood cell ($\times 10^3$ μl)	7.6 ± 1.9	7.6 ± 1.8	7.2 ± 2.2	0.39

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction.

Mortality rates were higher in patients with poor functional status, and in those that had higher urea, creatinine, BNP, and CHA_2DS_2-VASc score, and lower hemoglobin levels.

The association between CHA_2DS_2-VASc score and other variables is summarized in Table 2. There was a negative correlation between hemoglobin and CHA_2DS_2-VASc score (r = -0.31, p = 0.001). BNP (r = 0.22, p = 0.03), creatinine (r = 0.32, p = 0.001), urea (r = 0.34, p < 0.001) glucose (r = 0.32, p = 0.001) were positively cor-

related with CHA_2DS_2-VASc score.

In the multi-variate regression analysis, CHA_2DS_2-VASc score [HR 2.15, confidence internal (CI) 95% 1.48-3.15, p < 0.001] and functional capacity (HR 2.23, CI 95% 1.33-3.74, p = 0.003) were found as independent predictors for mortality. The results of the regression analysis are shown in Table 3.

According to ROC analysis, a CHA_2DS_2-VASc score greater than 3 could predict mortality with 67% sensitivity and 77% specificity (area under the curve 0.75, p < 0.0001, 95% CI 0.6-0.83) (Figure 1).

Table 2. The correlation analysis of CHADS-VASc score and other variables

	Correlation coefficient	p
Age	0.58	**< 0.001**
Left ventricular ejection fraction	0.28	**0.004**
Troponin	-0.01	0.89
Brain natriuretic peptide	0.22	**0.03**
Hemoglobin	-0.31	**0.001**
Creatinine	0.32	**0.001**
Urea	0.34	**< 0.001**
Sodium	0.01	0.92
Glucose	0.32	**0.001**

During the 12 months of follow-up, the mortality rates according to different CHA_2DS_2-VASc scores were

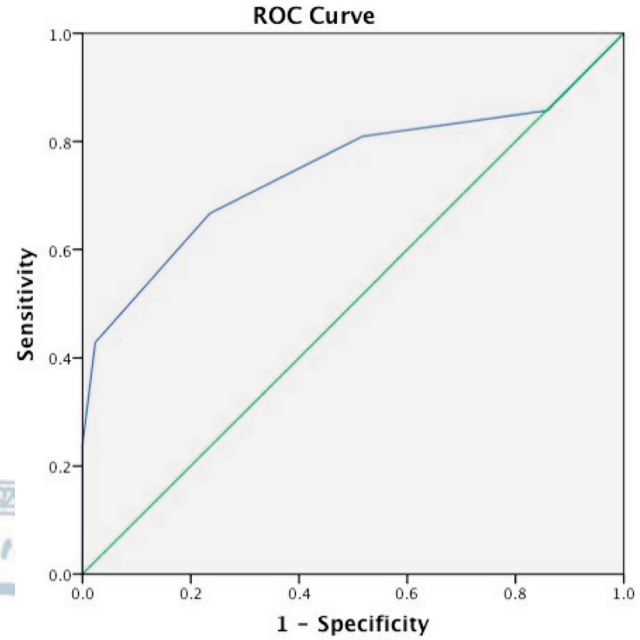

Figure 1. *CHA_2DS_2-VASc score greater than 3 could predict mortality with 67% sensitivity and 77% specificity in receiver operating characteristic (ROC)-curve (area under the curve 0.75, p < 0.001, 95% CI 0.6-0.83).*

Table 3. Results of the univariate and multivariate Cox regression analysis to predict 1-year mortality

	Univariate Analysis			Multivariate Analysis		
	HR	CI	p	HR	CI	p
Female	1.95	0.76-5.02	0.17			
Age	1.01	0.97-1.05	0.6			
Hypertension	1.11	0.44-2.79	0.83			
Ischemic cardiomyopathy	1.27	0.53-3.1	0.6			
Cardiac device	0.83	0.35-1.95	0.83			
Atrial fibrillation	0.43	0.13-1.46	0.18			
Bundle branch block	1.23	0.45-3.37	0.68			
Functional status	2.23	1.33-3.74	0.003*	2.19	1.27-3.77	0.005
ACEI/ARB	0.43	0.17-1.1	0.08*	0.788	0.203-3.061	0.731
Beta blocker	0.76	0.18-3.25	0.71			
Spironolactone	1.08	0.46-2.57	0.86			
Severe mitral regurgitation	2.18	0.88-5.41	0.09*	1.034	0.406-2.636	0.944
Urea	1.02	1-1.02	< 0.001*	1.007	0.992-1.022	0.356
Creatinine	1.37	1-1.89	0.05*	1.528	0.729-3.204	0.262
Sodium	0.98	0.92-1.05	0.57			
BNP	1.254	1.073-1.466	0.006*	1.15	0.955-1.385	0.139
Troponin	1.66	0.5-5.53	0.41			
Hemoglobin	0.67	0.53-0.85	0.001*	0.630	0.439-0.905	0.098
CHA_2DS_2-VASc score	2.15	1.48-3.15	< 0.001*	2.06	1.38-2.9	< 0.001

* Parameters included in multivariate analyses.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CI, confidence interval; HR, hazard ratio.

estimated using Kaplan-Meier analyses (Figure 2).

DISCUSSION

In this study, 21 patients (19.8%) died during the 1-year follow up period. Functional status and CHA_2DS_2-VASc score were identified as independent predictors of the mortality. While a one point increase in CHA_2DS_2-VASc score was associated with a 2-fold increased risk mortality, patients with higher scores had higher mortality rates as shown in the Kaplan Meier curves. CHA_2DS_2-VASc score may be used for risk stratification in patients with low LVEF HF.

Patients with HF and without AF are at increased risk of ischemic stroke and thromboembolism. In recent randomized trials, warfarin therapy reduced these end points.[10,11] CHA_2DS_2-VASc is a practical scoring system used to evaluate the risk of systemic thromboembolism in patients with AF. Compared with the previously utilized $CHADS_2$ scoring system, it is more sensitive and includes additional parameters such as female gender, vascular disease, and different thresholds of age. This score can be very accurately calculated using patients' medical history. Freeman et al. found that higher CHA_2DS_2-VASc score in patients with AF undergoing percutaneous coronary intervention, are associated with significantly worse outcomes.[12] Irrespective of the presence of AF, it is closely associated with the risk of mortality.[13]

Previous studies found that the CHA_2DS_2-VASc score was indicative of thromboembolic risk as well as the risk of major cardiovascular events. In patients with a CHA_2DS_2-VASc score ≥ 3, there was an increased frequency of cerebral infarction and coronary artery disease.[14-16] In a recently published study, CHA_2DS_2-VASc score was found to correlate with adverse events in patients with coronary syndrome.[17] Previous studies also evaluated CHADS score and its relation to adverse outcomes in different patient population. The $CHADS_2$ score predicted atrial and ventricular arrhythmias in patients with a history of prior myocardial infarction.[18] In this study, the incidence of AF increased with higher $CHADS_2$ scores. Crandall et al. evaluated the value of $CHADS_2$ score in predicting myocardial infarction and major cardiac events and found significant associations with CHADS score and increased risk of stroke.[19] In a study

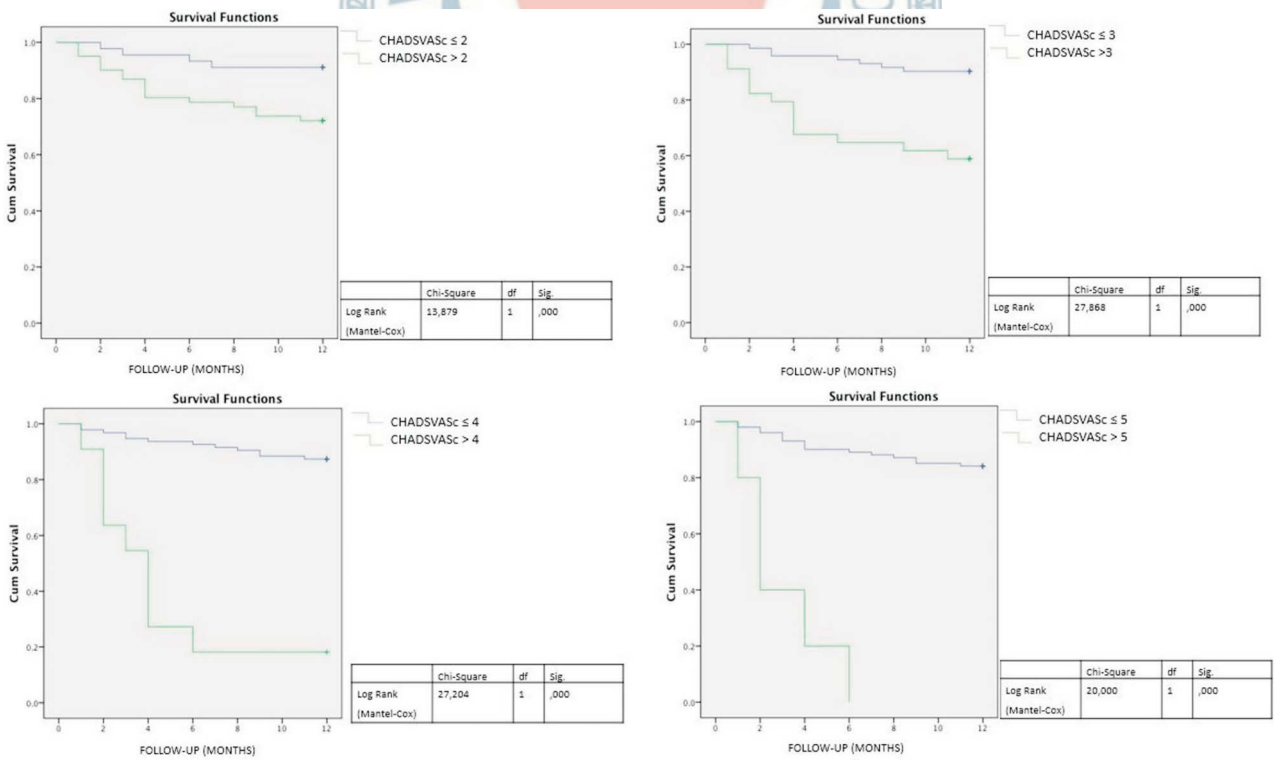

Figure 2. *The mortality rates according to different CHA_2DS_2-VASc scores.*

examining the association between $CHADS_2$ and mortality in patients with acute coronary syndrome, a parallel increase in the rates of hospitalization and mortality was observed with increasing $CHADS_2$ scores.[13]

There is a cause and effect relationship between ventricular dysfunction and AF. While ventricular dysfunction may lead to AF, AF may trigger tachycardiomyopathy.[20] The Framingham study showed an increased risk of mortality in HF patients with AF.[21] According to our results, even in the absence of AF, a high CHA_2DS_2-VASc score seems to be associated with an increased risk of mortality in patients with HF. The proportion of patients with AF was lower among those who died during the 1-year follow-up as compared to those who survived, which supports the proposition that this scoring system has a predictive value for mortality independent of the presence of AF.

In the current study, CHA_2DS_2-VASc score proved to have a significant predictive value for 1-year mortality. The components of this scoring system, such as presence of vascular disease or advanced age, may have identified patients with a poor functional status due to the presence of several comorbidities.

The main limitation of the study was the small sample size. This was a single-center study with a relatively small sample size. Consequently, the number of events was relatively lower than the number of variables, which may have decreased the strength of the regression analysis. Also, the causes of death were not sufficiently documented in detail.

CONCLUSIONS

CHA_2DS_2-VASc score appears to be a practical mortality assessment tool that can be readily implemented at the bed side. Patients with higher scores may require short follow-up periods.

ACKNOWLEDGEMENT

None.

DISCLOSURE

No conflicts of interest.

FUNDING/SUPPORTING INSTITUTIONS

None.

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