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Relation	

Utility of CHA_2DS_2-VASc Score to Predict Mid-Term Clinical Outcomes in Hemodialysis Patients

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Short Title: CHA_2DS_2-VASc score predicts adverse events in Hemodialysis Patients

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Abstract

Background. The CHA_2DS_2-VASc score has been widely used to predict stroke in patients with atrial fibrillation (AF). Recently, it was reported that the CHA_2DS_2-VASc score helps predict cardiovascular disease (CVD) or all-cause mortality in patients with or without AF. However, few reports have examined the association between this score and mortality in hemodialysis patients.

Methods. We analyzed 557 consecutive patients who initiated hemodialysis at our facilities between February 2005 and October 2017. The CHA_2DS_2-VASc score was calculated at the time of initiation of hemodialysis. Patients were then categorized into three groups according to their CHA_2DS_2-VASc scores: 0–1 (low), 2–3 (intermediate), and 4–9 (high). Multivariate Cox proportional hazards analysis was used to assess independent risk factors for 3-year all-cause mortality.

Results. During the 3-year follow-up period, 153 (27.5%) patients died (cardiovascular death: n=88). According to multivariate analysis, serum albumin (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.43–0.85, P=0.003), creatinine (HR 0.91, 95% CI 0.84–0.99, P=0.049), and CHA_2DS_2-VASc score (HR 1.33, 95% CI 1.20–1.46, P<0.001) were associated with 3-year all-cause mortality. Compared with patients in the low CHA_2DS_2-VASc score group, those in the intermediate and high score groups had a

higher risk for all-cause and CVD mortality (all-cause mortality: HR 1.77, 95% CI 1.23–2.55, *P*=0.002 and HR 2.94, 95% CI 1.90–4.53, *P*<0.001, respectively; CVD mortality: HR 1.82, 95% CI 1.27–2.59, *P*=0.001 and HR 2.85, 95% CI 1.88–4.31, *P*<0.001, respectively).

Conclusion. The CHA_2DS_2-VASc score is a valuable predictor of 3-year all-cause and CVD mortality in incident hemodialysis patients.

Introduction

Cardiovascular disease (CVD) is the leading cause of death after initiating hemodialysis (HD). In this population, more than 50% of patients have comorbid CVD [1], and mortality resulting from CVD is 20 times higher than in the general population [2]. In this context, investigations of how to appropriately evaluate the risk of CVD in HD patients have been conducted. The CHA_2DS_2-VASc (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, **S**troke or transient ischemic attack, **V**ascular disease, **A**ge 65–74 years, **S**ex [female] **c**ategory) score has been conventionally used as a predictive score for stroke and thromboembolism in patients with atrial fibrillation (AF) [3]. However, in recent years some researchers have reported the use of this score as a predictor of future CVD morbidity or all-cause mortality with or without chronic AF [4-6]. Patients on HD are more likely to have chronic AF in comparison with the general population: 11.6% have AF, and a further 50% have any form of arrhythmia, including paroxysmal AF [7]. Dialysis patients have a higher incidence of CVD and a higher rate of arrhythmia as a comorbidity. However, there are limited studies examining the utility of the CHA_2DS_2-VASc score for mortality after the initiation of HD. The CHA_2DS_2-VASc score was reported to be associated with 1-year mortality in HD patients [8]. Nevertheless, the association between the

75 CHA_2DS_2-VASc score and mid-term prognosis (3 years) after the start of dialysis
76 remains unclear. In this study, we aimed to clarify the association between the
77 CHA_2DS_2-VASc score and all-cause or CVD mortality in HD patients over a follow-up
78 of 3 years after initiating HD. Moreover, we examined the factors that may have the
79 most impact on the mid-term prognosis of patients at the initiation of HD.
80
81 **Materials and Methods**
82 **Study population and design**
83 This study was a retrospective observational study conducted in Ichiyokai Harada
84 Hospital, and included three dialysis clinics. The subjects were 557 patients undergoing
85 chronic HD or on-line hemodiafiltration (HDF) from February 2005 to October 2017.
86 All patients had vascular access providing a blood flow rate ≥200 mL/min and received
87 4-h HD or 4-h predilution on-line HDF using high-flux membranes, with a total
88 convective volume of 40 L per session (thrice per week). A standard bicarbonate
89 dialysis fluid (140 mEq/L sodium, 2.0 mEq/L potassium, 3.0 mEq/L calcium, 1.0 mEq/L
90 magnesium, and 100 mg/dL glucose) delivered using a central dialysis fluid delivery
91 system was used for HD and on-line HDF. The observation period started at the
92 initiation of dialysis and ended at one of the following events, whichever occurred first:

death, transfer to another facility, or the end of the study (3 years after study enrollment). The exclusion criteria were <20 years of age, and history of advanced cancer in the month leading up to the study. Demographic, clinical, and laboratory data at the initiation of HD or HDF were collected from the electronic medical records of each patient, and the CHA_2DS_2-VASc score [3] at the initiation of HD was calculated for each patient accordingly. Patients were given 1 point for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus (DM), vascular disease, and female sex, and 2 points for age ≥75 years and previous stroke or transient ischemic attack (Supplemental Table 1) [9]. Patients were classified into three groups according to their CHA_2DS_2-VASc scores: 0–1 (low), 2–3 (intermediate), and 4–9 (high). Hypertension was defined as systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥80 mmHg, a history of hypertension treatment from medical records, or use of antihypertensive drugs [10]. DM was defined by a hemoglobin A1c level ≥6.5%, 2-h plasma glucose ≥200 mg/dL with a 75-g oral glucose tolerance test, fasting plasma glucose ≥126 mg/dL, or medical history of DM [11]. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or use of lipid-lowering drugs. Body mass index (BMI) was calculated as dry weight in kilograms divided by the square of height in meters.

The primary endpoint was the composite of all-cause and CVD mortality during the 3 years of HD or HDF. We defined 3-year mortality as the mid-term prognosis [12, 13]. Mortality data and data regarding CVD events within the 3 years were obtained from the medical records. CVD events were defined as coronary artery disease (coronary artery bypass surgery, percutaneous intervention, or myocardial infarction), heart failure, ventricular arrhythmia, cerebrovascular accident (cerebral infarction, transient ischemic attack, or cerebral hemorrhage), or peripheral arterial disease (peripheral vascular revascularization or amputation). This study was performed following the Declaration of Helsinki, and the protocol was licensed by the hospital ethics committees of the hospital ethics committee of Ichiyokai Harada Hospital.

Statistical analysis

Data are presented as mean values ± standard deviation (SD) or median and interquartile range (25th–75th percentiles) for skewed distributions. Differences between the groups were analyzed using the chi-squared test or Mann–Whitney U test, and Fisher's exact test. We constructed receiver-operating characteristic (ROC) curves for the baseline CHA_2DS_2-VASc score within 3-year all-cause mortality and determined the area under the curve (AUC). The optimal cut-off value for balancing the sensitivity

and specificity of each factor was identified as the point on the ROC curve closest to the upper left-hand corner. Cox proportional hazards models were used to assess independent predictors of 3-year all-cause mortality, presented as hazard ratio (HR) and 95% confidence interval (CI). These parameters were included as explanatory variables in the models based on a recent meta-analysis [14-16]. All statistical analyses were performed using R3.6.2 and the JMP statistical package (version 16; SAS Institute, Cary, NC, USA). A *P* value of <0.05 was considered statistically significant.

Results

A total of 557 patients were enrolled in the present study, with 32 patients (30 because of hospital transfer or relocation and two because of kidney transplantation) lost to follow-up within 3 years. The primary renal diseases were chronic glomerulonephritis (n=123, 22.1%), diabetic nephropathy (n=270, 48.5%), nephrosclerosis (n=104, 18.7%), polycystic kidney disease (n=16, 2.9%), other diseases (n=19, 3.4%), and unknown conditions (n=25, 4.5%). In the present study, hemodialysis was initiated with an arteriovenous fistula (n=519, 93.2%), arteriovenous graft (n=34; 6.1%), or a central venous catheter (n=2, 0.4%). The mean age was 69.50 ± 13.58 years, and 62% (n=346) of the patients were men. There were 25 cases of chronic AF, and 89 patients had a

147 history of cerebral infarction at the initiation of HD. During the 3-year follow-up period,
148 153 patients died (88 following CVD events). We divided the participants into three
149 groups according to their CHA_2DS_2-VASc score: 0–1 (low), 2–3 (intermediate), and 4–9
150 (high). The baseline clinical characteristics of each group are shown in Table 1.
151 Patients with a higher CHA_2DS_2-VASc score groups were older, more frequently
152 women, and had more of the following items: a corrected calcium value, C-reactive
153 protein, comorbidities (dyslipidemia and DM), medical history (heart failure, stroke, or
154 vascular disease), and the proportion of patients taking antiplatelet drugs. Additionally,
155 the serum albumin, blood urea nitrogen, creatinine, uric acid, potassium, sodium, and
156 phosphorus values were significantly lower in patients with higher CHA_2DS_2-VASc
157 scores. Table 2 shows the results of multivariate analyses for 3-year all-cause mortality.
158 In a multivariate analysis, serum albumin, creatinine, and CHA_2DS_2-VASc score were
159 associated with 3-year all-cause mortality (serum albumin: HR 0.60, 95% CI 0.43–0.85,
160 P=0.003; creatinine: HR 0.91, 95% CI 0.84–0.99, P=0.049; CHA_2DS_2-VASc score: HR
161 1.33, 95% CI 1.20–1.46, P<0.001). Kaplan–Meier survival curves for the three groups
162 divided according to the CHA_2DS_2-VASc score showed that patients with a high score
163 had a higher risk of 3-year all-cause and CVD mortality (Figure 1). Multivariate
164 analysis using the CHA_2DS_2-VASc score group of 0–1 as the reference group showed

that the intermediate and high groups had a higher risk for all-cause and CVD mortality (all-cause mortality: HR 1.77, 95% CI 1.23–2.55, P=0.002 and HR 2.94, 95% CI 1.90–4.53, P<0.001, respectively; CVD mortality: HR 1.82, 95% CI 1.27–2.59, P=0.001 and HR 2.85, 95% CI 1.88–4.31, P<0.001, respectively) (Table 3). The results of multivariate analysis on 3-year all-cause and CVD mortality with each item of the CHA_2DS_2-VASc score included as a factor are shown in Supplemental Table 2. Age ≥75 years (P<0.001), prior stroke or transient ischemic attack (P<0.001), albumin (P=0.01), and creatinine (P=0.02) were associated with all-cause mortality. For CVD mortality, age ≥75 years (P<0.001), prior stroke or transient ischemic attack (P<0.001), albumin (P=0.001), creatinine (P=0.006), and uric acid (P=0.01) were significant risk factors. Multivariate analysis of the CHA_2DS_2-VASc score alone showed that age, DM, and prior stroke were significantly associated with both all-cause and CVD mortality (Supplemental Table 3). In addition, Supplemental Figure 1 shows the ROC curve of baseline age for all-cause mortality, where the optimal cut-off value for age was 74 years (sensitivity, 0.71; specificity, 0.68). The type of vascular access at the initiation of HD was not associated with 3-year mortality in this study (Supplemental Table 4).

Discussion

We showed an association between the CHA_2DS_2-VASc score and mid-term mortality of HD patients. The 3-year all-cause and CVD mortality were significantly higher in patients with a higher CHA_2DS_2-VASc score. Compared with patents in the low CHA_2DS_2-VASc score group, those in the high score group had an approximately 3-fold increased risk for all-cause mortality. To our knowledge, this study is the first report that shows an association between the CHA_2DS_2-VASc score and med-term prognosis among incident HD patients.

Patients with end-stage kidney disease often have some risk factors for atherosclerosis, such as diabetes, hypertension, and abnormal lipid metabolism. Furthermore, it has become well recognized in recent decades that advanced chronic kidney disease itself is a risk factor for atherosclerosis. The high rate of cardiovascular morbidity and resulting mortality in end-stage kidney disease, in particular after the introduction of maintenance dialysis, have been noted in previous studies [1, 2]. Thus, it is essential in clinical practice to identify patients at high risk of death at the induction of HD therapy, and many tools for predicting the life expectancy of patients starting dialysis have been reported [17, 18]. Although several studies reported precise predictive models or indexes, many of them required cumbersome calculations including several variables, such as anthropometric data, laboratory data, presence of

systemic complications, and information about activities of daily living [19]. If there are any missing data, the utility of these models and indexes massively decrease. For this reason, these newly proposal indexes are rarely used in current practice.

In contrast, the CHA_2DS_2-VASc score, a modified version of the $CHADS_2$ score, is widely used in clinical practice to assess the risk of stroke in patients with AF and is easy to calculate. Although this score has been used to determine whether patients with AF require treatment with anticoagulation or antiplatelet therapy, it has been associated with the risk of death in patients with several diseases with or without AF, including heart failure [20], stroke [21], acute pulmonary embolism [22], and in patients with implantable cardiac defibrillators [23]. Recently, the CHA_2DS_2-VASc score was reported to be useful in predicting all-cause and cardiovascular mortality in non-dialysis [24, 25] and even in dialysis CKD patients [8]. Schamroth Pravda M et al. reported that the CHA_2DS_2-VASc score was strongly associated with all-cause mortality and increased risk of myocardial infarction and stroke within the first year of HD initiation. However, their investigation did not mention the causes of death nor the number lost to follow-up during the 1-year follow-up. In addition, their cohort had a high 1-year mortality rate of 23.8%, which is higher than that reported in any other cohort in the world. First-year mortality of incident dialysis patients has been reported as follows:

20.5% in the United States [26], 12.5% in Europe [27], and 12.4% in Japan [28]. These differences may be caused by racial differences, quantities of pre-dialysis care, nutritional condition, medical environment or system, or timing of the start of HD. In a short period of 1 year, the prediction of prognosis after the introduction of dialysis may be more influenced by the pre-dialysis condition than the dialysis treatment, and the results may vary widely among countries and regions. In the present study, the 1-year mortality rate was 10% (data not shown), which was similar to that reported in Japan. Thus, we consider this an accurate study of general maintenance HD patients.

Additionally, we investigated the association with all-cause mortality and cardiovascular mortality, and showed that a higher CHA_2DS_2-VASc score was strongly associated with both factors. We showed that among items in the CHA_2DS_2-VASc score, age (≥75 years) and history of previous stroke were significantly associated with both 3-year all-cause and CVD mortality. Furthermore, the age cut-off value obtained using the ROC curve was 74 years, approximating the item (age ≥75 years) in the CHA_2DS_2-VASc score. Age (≥75 years) and history of previous stroke both add 2 points to the CHA_2DS_2-VASc score, suggesting that it could better reflect prognosis in HD patients. Moreover, various studies on the medium- to long-term prognoses of HD patients have been conducted. In the present study we also examined other risk factors, including

237 previously known poor prognostic factors such as serum albumin level [29], presence of
238 anemia [30, 31], and history of CVD [32] or stroke [33, 34]; the CHA_2DS_2-VASc score
239 was still a significant risk factor for 3-year mortality.

240 However, this study has several limitations. First, this was a retrospective
241 observational study. Thus, the casual effects between the CHA_2DS_2-VASc score and
242 prognosis were not examined. In addition, we were not able to evaluate whether the
243 CHA_2DS_2-VASc score could be an individual risk prediction in this study. For these
244 reasons, further prospective studies are needed. Second, we did not assess critical risk
245 factors, such as vascular calcification, left ventricular hypertrophy, and dialysis
246 adequacy. Third, our cohort included only Japanese people, whose survival is reportedly
247 one of the best globally, so the resulting data cannot be generalized to other populations.
248 Finally, we could not investigate changes in medication use or mode of dialysis
249 treatment (including change from HD to HDF) during the first 3 years after dialysis
250 induction. Despite these limitations, it is worthwhile to employ the CHA_2DS_2-VASc
251 score because it is easy to measure at the bedside and can significantly predict mortality
252 3 years after dialysis initiation.

In conclusion, patients with end-stage renal disease are at high risk of mortality and CVD even within 3 years after the introduction of HD. The CHA_2DS_2-VASc score was strongly associated with 3-year all-cause and CVD mortality in HD patients.

Statement of Ethics

The study is in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was licensed by the hospital ethics committee of Ichiyokai Harada Hospital (approval number 202004, registered March 24, 2020). Written informed consent was not required because of the non-intervention and retrospective design.

Conflict of Interest Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Author Contributions

Okubo A and Doi T designed the study, wrote, and edited the manuscript, Okubo A researched and analyzed data. Okubo A and Doi T wrote and reviewed the manuscript.

All the authors approved the final version of the manuscript to be published. Doi T is the guarantor of this work.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author [Toshiki Doi, E-mail: doitoshi@hiroshima-u.ac.jp] or data sharing committee [Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan. Tel.: +81-82-257-1506/Fax: +81-82-257-1508] upon reasonable request.

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Figure legends

Figure 1. Kaplan–Meier survival curves based on the CHA_2DS_2-VASc score. * $P<0.05$. (A) Three-year all-cause mortality. (B) Cardiovascular mortality.

Table 1. Comparison of clinical characteristics according to the CHA_2DS_2-VASc score

	All Patients	CHA_2DS_2-VASc Score			*P* Value
		0–1	2–3	4–9	
	n = 557	n = 81	n = 267	n = 209	
Age, years	69.50±13.58	53.69±12.11	68.45±12.01*	76.97±9.85*†	<0.001
Male, n (%)	346 (62.1)	67 (82.7)	179 (67.0)	100 (47.6)*†	<0.001
BMI, kg/m^2	22.11±4.15	24.37±15.32	22.16±4.31	21.88±4.25*	0.07
AVF, n (%)	521 (93.5)	79 (97.5)	248 (92.9)*	195 (93.3)*	0.90
3-year death, n (%)	153 (29.0)	6 (7.4)	60 (22.5)*	87 (41.6)*†	<0.001
Laboratory data					
Hemoglobin, g/dL	10.68±1.46	10.84±1.38	10.73±1.41	10.57±1.54	0.29
Albumin, g/dL	3.40 ± 0.54	3.67±0.46	3.45±0.45*	3.20±0.59*†	<0.001
BUN, mg/dL	56.94±17.66	61.84±18.76	59.07±17.53	52.32±16.40*†	<0.001
Creatinine, mg/dL	7.15 ± 2.83	9.24±3.31	7.40±2.66*	6.03±2.24*†	<0.001
Urinary acid, mg/dL	7.18±1.72	7.91±1.56	7.22±1.67*	6.85±1.63*†	<0.001
Sodium, mEq/L	138.00 ± 3.83	139.14±2.95	138.50±3.75	136.94±4.09*†	<0.001
Potassium, mEq/L	4.48 ± 0.77	4.64±0.78	4.56±0.73	4.32±0.78*†	<0.001
Calcium, mg/dL	8.93 ± 0.96	8.80±0.91	8.87±0.92	9.05±1.02*†	0.006
Phosphorus, mg/dL	4.96 ± 1.47	5.23±1.31	5.11±1.49	4.66±1.46*†	0.001
CRP, mg/dL	0.98 ± 2.90	0.53±1.50	0.89±2.99	1.27±3.18*†	<0.001
β2MG, mg/dL	22.94 ± 7.56	22.19±7.45	22.78±8.09	23.50±6.80	0.39
Comorbidities					
Hypertension, n (%)	536 (96.9)	76 (93.8)	258 (96.6)	202 (96.7)	0.84
Diabetes mellitus, n (%)	276 (49.9)	18 (22.2)	120 (44.9)*	138 (66.0)*†	<0.001
Dyslipidemia, n (%)	319 (57.8)	30 (37.0)	148 (55.4)*	141 (68.4)*	<0.001
Atrial fibrillation, n (%)	25 (4.5)	1 (1.2)	8 (3.0)	16 (7.7)	0.23
Medical history					
Heart failure, n (%)	95 (17.1)	2 (2.5)	22 (8.2)*	67 (32.6)*†	<0.001
Stroke, n (%)	89 (16.0)	4 (4.9)	34 (12.7)*	57 (27.3)*†	<0.001
Vascular disease, n (%)	36 (6.5)	2 (2.5)	11 (4.1)	23 (11.0)*†	<0.001
Medications					
Antiplatelet drugs, n (%)	166 (29.8)	5 (6.2)	56 (21.0)	105 (51.0)*†	<0.001
Anticoagulant drugs, n (%)	27 (4.5)	2 (2.5)	15 (5.6)	10 (4.8)	0.21

BMI, body mass index; AVF, arteriovenous fistula; BUN, blood urea nitrogen; CRP, C-reactive protein; β2MG, β2-microglobulin.

Data are mean ± SD for continuous variables. Differences between the groups were analyzed using the Mann–Whitney U test or chi-squared test. *P<0.05 versus low score group, † P<0.05 versus intermediate score group.

Table 2. Multivariate analysis (Cox proportional hazard model) of parameters related to 3-year all-cause mortality

	Multivariate Analysis		
	HR	95% CI	*P* Value
CHA_2DS_2-VASc score	1.33	1.20–1.46	<0.001
BMI, 1 kg/m^2	1.01	0.98–1.03	0.70
Smoking status	0.99	0.82–1.23	0.99
Hemoglobin, 1 g/dL	0.98	0.80–1.13	0.54
Albumin, 1 g/dL	0.60	0.43–0.85	0.003
BUN, 1 mg/dL	1.01	0.99–1.02	0.06
Creatinine, 1 mg/dL	0.91	0.84–0.99	0.049
Uric acid, 1 mg/dL	0.94	0.89–1.00	0.07
Sodium, 1 mEq/L	0.99	0.96–1.02	0.59
Potassium, 1 mEq/L	0.82	0.66–1.01	0.61
Calcium, 1 mg/dL	0.96	0.80–1.13	0.56
Phosphorus, 1 mg/dL	0.96	0.87–1.09	0.67
CRP, 1 mg/dL	1.05	0.96–1.13	0.29
Dyslipidemia	0.88	0.67–1.14	0.32

HR, hazard ratio; CI, confidence interval; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein.

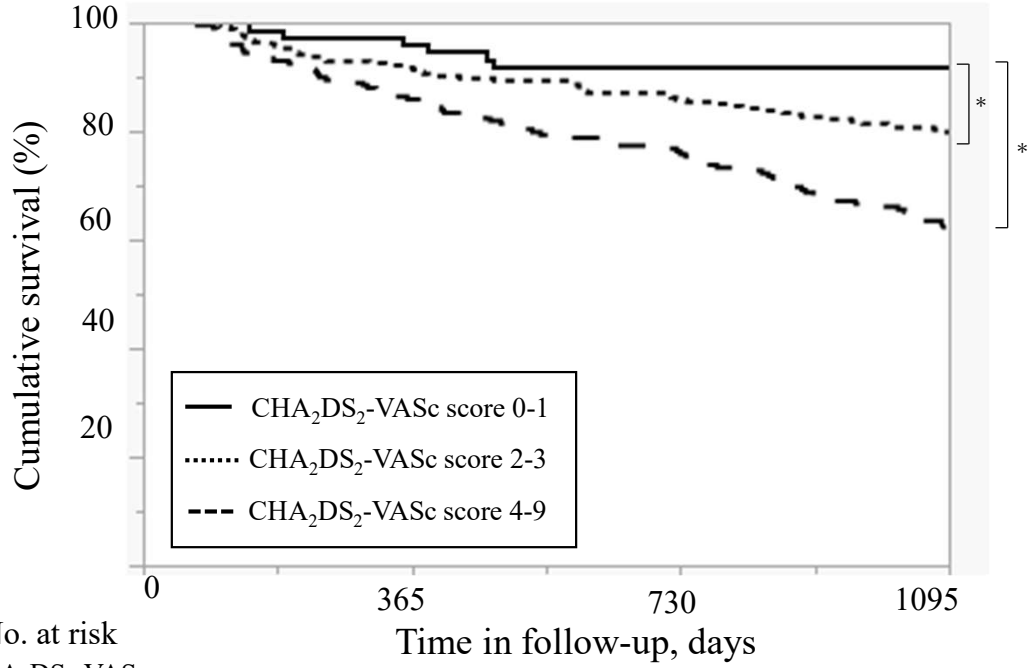
Table 3. Risk of all-cause mortality and cardiovascular mortality associated with the CHA_2DS_2-VASc score

	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1				
CHA_2DS_2-VASc score 0-1	1.00 (ref.)		1.00 (ref.)	
CHA_2DS_2-VASc score 2-3	1.80 (1.37–2.36)	<0.001	1.87 (1.43–2.44)	<0.001
CHA_2DS_2-VASc score 4-9	3.06 (2.25–4.18)	<0.001	3.28 (2.45–4.41)	<0.001
Model 2				
CHA_2DS_2-VASc score 0-1	1.00 (ref.)		1.00 (ref.)	
CHA_2DS_2-VASc score 2-3	1.77 (1.23–2.55)	0.002	1.82 (1.27–2.59)	0.001
CHA_2DS_2-VASc score 4-9	2.94 (1.90–4.53)	<0.001	2.85 (1.88–4.31)	<0.001

HR, hazard ratio; CI, confidence interval.

Multivariate Cox proportional hazards regression with crude (Model 1) and adjusted (Model 2) associations for the CHA_2DS_2-VASc score and mortality. The adjusted analysis included the following covariates: body mass index, smoking status, hemoglobin, serum albumin, blood urea nitrogen, creatinine, uric acid, potassium, sodium, corrected calcium, phosphorus, C-reactive protein, and history of dyslipidemia.

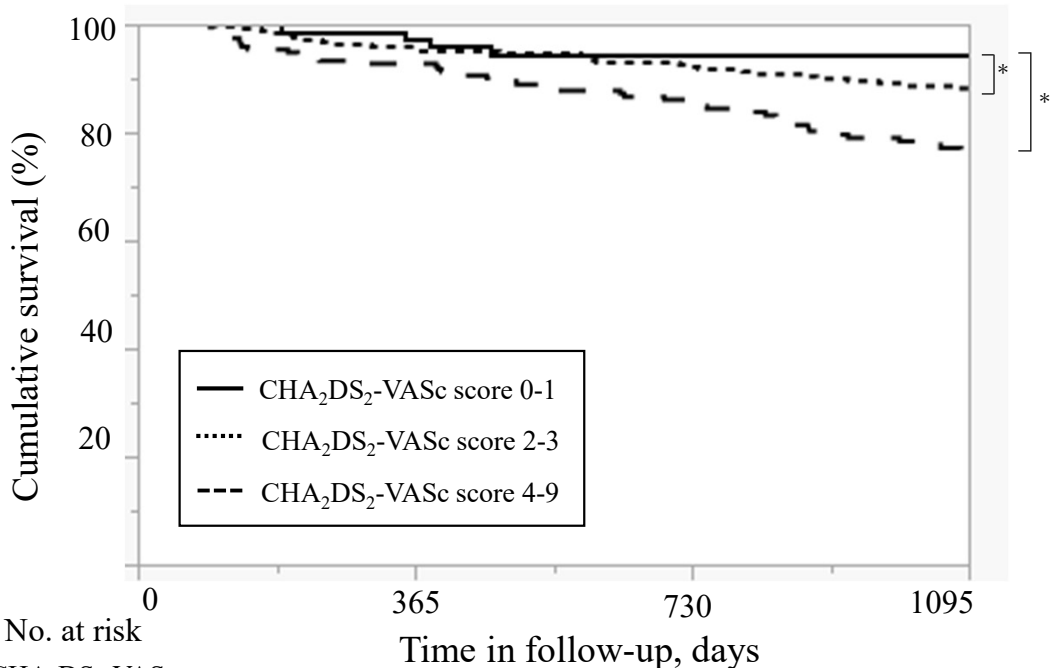
(A) All-cause mortality



No. at risk

CHA_2DS_2-VASc score				
0-1	74	72	66	63
2-3	253	233	217	199
4-9	199	171	151	117

(B) Cardiovascular mortality



No. at risk

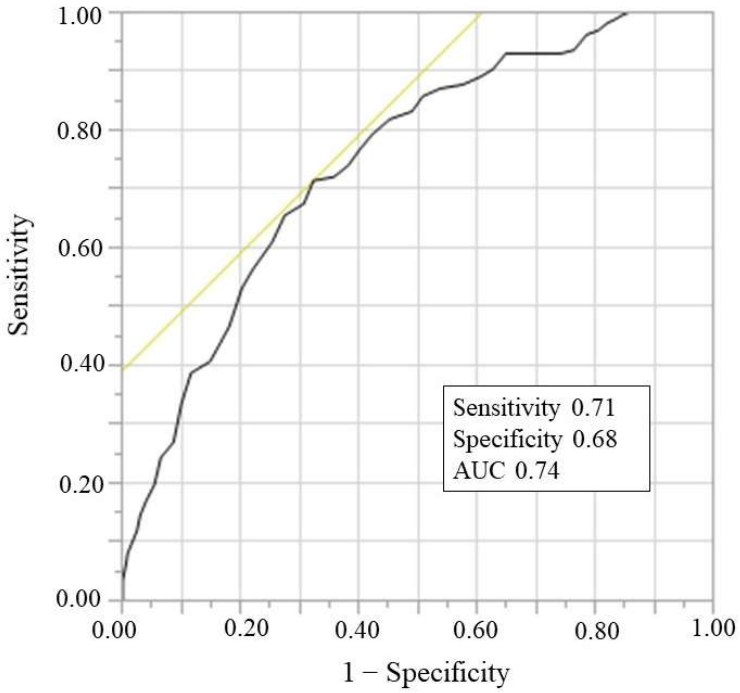
CHA_2DS_2-VASc score				
0-1	74	71	66	63
2-3	252	231	215	197
4-9	198	170	150	116

Supplementary Materials

Supplemental Figure legends

Supplemental Figure 1. Receiver-operating characteristic curve of baseline age and 3-year all-cause mortality. The area under the curve (AUC) (95% confidence interval) was 0.74, and optimal cut-off point (sensitivity, specificity) of 3-year all-cause mortality was 74 (0.71, 0.68).

Supplemental Figure 1. Receiver-operating characteristic curve of baseline age and 3-year all-cause mortality



Supplemental Table 1. Evaluation items for the CHA_2DS_2-VASc score

Risk Factor	Score
Chronic heart failure	1
Hypertension	1
Diabetes mellitus	1
Vascular disease	1
Age 65–74 years	1
Female	1
Age ≥75 years	2
Prior stroke or transient ischemic attack	2

Supplemental Table 2. Multivariate analysis of 3-year mortality with each item of CHA_2DS_2-VASc score included as a variable

	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age ≥75 years	2.04 (1.48–2.81)	<0.001	2.74 (1.75–3.21)	<0.001
Gender, 1 female	0.99 (0.60–1.70)	0.28	0.89 (0.60–1.01)	0.16
BMI, 1 kg/m^2	1.01 (0.98–1.04)	0.63	1.00 (0.97–1.03)	0.85
Smoking status	1.02 (0.72–2.22)	0.47	0.99 (0.71–1.14)	0.39
Hemoglobin, 1 g/dL	1.08 (0.99–1.18)	0.07	1.07 (0.99–1.15)	0.09
Albumin, 1 g/dL	0.63 (0.44–0.89)	0.01	0.60 (0.44–0.81)	0.001
BUN, 1 mg/dL	1.01 (0.99–1.02)	0.06	1.01 (0.99–1.02)	0.06
Creatinine, 1 mg/dL	0.90 (0.82–0.99)	0.02	0.89 (0.82–0.97)	0.006
Uric acid, 1 mg/dL	0.94 (0.88–1.00)	0.06	0.92 (0.87–0.98)	0.01
Sodium, 1 mEq/L	0.97 (0.94–1.00)	0.09	0.99 (0.96–1.02)	0.62
Potassium, 1 mEq/L	0.83 (0.67–1.02)	0.09	0.84 (0.69–1.01)	0.07
Calcium, 1 mg/dL	0.98 (0.82–1.17)	0.80	0.91 (0.86–1.18)	0.87
Phosphorus, 1 mg/dL	0.99 (0.88–1.19)	0.88	0.96 (0.85–1.07)	0.44
CRP, 1 mg/dL	1.04 (0.95–1.12)	0.35	1.08 (0.99–1.14)	0.05
Comorbidities				
Hypertension	0.51 (0.22–1.22)	0.13	0.77 (0.37–1.66)	0.52
Diabetes mellitus	1.09 (0.79–1.51)	0.58	1.01 (0.76–1.36)	0.93
Dyslipidemia	0.96 (0.69–1.33)	0.80	1.00 (0.75–1.34)	0.68
Medical history				
Heart failure	1.09 (0.71–1.51)	0.86	1.05 (0.75–1.46)	0.78
Stroke	2.04 (1.44–2.87)	<0.001	1.75 (1.27–2.40)	<0.001
Vascular disease	1.22 (0.66–1.92)	0.67	0.99 (0.60–1.60)	0.93

HR, hazard ratio; CI, confidence interval; BMI, body mass index, BUN, blood urea nitrogen; CRP, C-reactive protein.

Supplemental Table 3. Multivariate analysis of 3-year mortality with each item of CHA_2DS_2-VASc score

	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.05)	<0.001
Gender, 1 female	0.99 (0.48–1.18)	0.26	1.00 (0.81–1.22)	0.16
Hypertension	0.39 (0.18–1.00)	0.05	0.46 (0.45–1.00)	0.06
Diabetes mellitus	1.34 (1.09–1.66)	0.006	1.25 (1.03–1.52)	0.03
Heart failure	1.09 (0.77–1.50)	0.61	1.22 (0.91–1.61)	0.18
Vascular disease	1.07 (0.69–1.64)	0.77	1.00 (0.65–1.45)	0.93
Stroke	1.44 (1.08–1.89)	0.001	1.25 (1.01–1.64)	0.04

HR, hazard ratio; CI, confidence interval.

Supplemental Table 4. Multivariate analysis (Cox proportional hazard model) of parameters related to 3-year all-cause mortality

	Multivariate Analysis		
	HR	95% CI	*P* Value
CHA_2DS_2-VASc score	1.28	1.16–1.40	<0.001
BMI, 1 kg/m^2	1.01	0.98–1.03	0.70
Smoking status	0.99	0.81–1.23	0.99
Hemoglobin, 1 g/dL	1.12	1.02–1.22	0.01
Albumin, 1 g/dL	0.60	0.43–0.85	0.004
BUN, 1 mg/dL	1.01	0.99–1.02	0.06
Creatinine, 1 mg/dL	0.91	0.84–0.99	0.049
Uric acid, 1 mg/dL	0.94	0.89–1.00	0.07
Sodium, 1 mEq/L	0.99	0.96–1.14	0.58
Potassium, 1 mEq/L	0.82	0.66–1.01	0.67
Calcium, 1 mg/dL	0.95	0.80–1.14	0.60
Phosphorus, 1 mg/dL	0.96	0.87–1.10	0.67
CRP, 1 mg/dL	1.05	0.96–1.14	0.27
Dyslipidemia	0.88	0.67–1.14	0.33
Arteriovenous fistula	0.93	0.29–2.93	0.89

HR, hazard ratio; CI, confidence interval; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein.