

1 **Utility of CHA₂DS₂-VASc Score to Predict Mid-Term Clinical**

2 **Outcomes in Hemodialysis Patients**

3
4
5 Aiko Okubo, MD, PhD,¹ Toshiki Doi, MD, PhD,^{1,2} Kenichi Morii, MD, PhD,^{1,2} Yoshiko
6 Nishizawa, MD, PhD,¹ Kazuomi Yamashita, MD, PhD,¹ Kenichiro Shigemoto, MD,
7 PhD,¹ Sonoo Mizuiri, MD, PhD,¹ Koji Usui, MD, PhD,³ Michiko Arita, MD,⁴ Takayuki
8 Naito, MD, PhD,⁵ Takao Masaki, MD, PhD⁶

9
10 ¹Department of Nephrology, Ichiyokai Harada Hospital, Hiroshima, Japan

11 ²Department of Kidney Disease and Community Medicine, Hiroshima University
12 Hospital, Hiroshima, Japan

13 ³Ichiyokai Ichiyokai Clinic, Hiroshima, Japan

14 ⁴Iciyokai East Clinic, Hiroshima, Japan

15 ⁵Ichiyokai Yokogawa Clinic, Hiroshima, Japan

16 ⁶Department of Nephrology, Hiroshima University Hospital, Hiroshima, Japan

17
18 **Short Title:** CHA₂DS₂-VASc score predicts adverse events in Hemodialysis Patients

19

20 **Correspondence:**

21 Toshiki Doi, MD, PhD, Department of Kidney Disease and Community Medicine,

22 Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

23 Tel.: +81-82-257-1506/Fax: +81-82-257-1508

24 E-mail: doitoshi@hiroshima-u.ac.jp

25

26 **Number of Tables:** 3 tables

27 **Number of Figures:** 1 figure

28 **Word count:** 2886

29 **Keywords:** CHA₂DS₂-VASc score, Mortality, Hemodialysis

30

31

32 Abstract

33 **Background.** The CHA₂DS₂-VASc score has been widely used to predict stroke in
34 patients with atrial fibrillation (AF). Recently, it was reported that the CHA₂DS₂-VASc
35 score helps predict cardiovascular disease (CVD) or all-cause mortality in patients with
36 or without AF. However, few reports have examined the association between this score
37 and mortality in hemodialysis patients.

38 **Methods.** We analyzed 557 consecutive patients who initiated hemodialysis at our
39 facilities between February 2005 and October 2017. The CHA₂DS₂-VASc score was
40 calculated at the time of initiation of hemodialysis. Patients were then categorized into
41 three groups according to their CHA₂DS₂-VASc scores: 0–1 (low), 2–3 (intermediate),
42 and 4–9 (high). Multivariate Cox proportional hazards analysis was used to assess
43 independent risk factors for 3-year all-cause mortality.

44 **Results.** During the 3-year follow-up period, 153 (27.5%) patients died (cardiovascular
45 death: n=88). According to multivariate analysis, serum albumin (hazard ratio [HR]
46 0.60, 95% confidence interval [CI] 0.43–0.85, $P=0.003$), creatinine (HR 0.91, 95% CI
47 0.84–0.99, $P=0.049$), and CHA₂DS₂-VASc score (HR 1.33, 95% CI 1.20–1.46,
48 $P<0.001$) were associated with 3-year all-cause mortality. Compared with patients in the
49 low CHA₂DS₂-VASc score group, those in the intermediate and high score groups had a

50 higher risk for all-cause and CVD mortality (all-cause mortality: HR 1.77, 95% CI
51 1.23–2.55, $P=0.002$ and HR 2.94, 95% CI 1.90–4.53, $P<0.001$, respectively; CVD
52 mortality: HR 1.82, 95% CI 1.27–2.59, $P=0.001$ and HR 2.85, 95% CI 1.88–4.31,
53 $P<0.001$, respectively).

54 **Conclusion.** The CHA₂DS₂-VASc score is a valuable predictor of 3-year all-cause
55 and CVD mortality in incident hemodialysis patients.

56

57 **Introduction**

58 Cardiovascular disease (CVD) is the leading cause of death after initiating
59 hemodialysis (HD). In this population, more than 50% of patients have comorbid CVD
60 [1], and mortality resulting from CVD is 20 times higher than in the general population
61 [2]. In this context, investigations of how to appropriately evaluate the risk of CVD in
62 HD patients have been conducted. The CHA₂DS₂-VASc (Congestive heart failure,
63 **H**ypertension, **A**ge ≥ 75 years, **D**iabetes mellitus, **S**roke or transient ischemic attack,
64 **V**ascular disease, **A**ge 65–74 years, **S**ex [female] category) score has been
65 conventionally used as a predictive score for stroke and thromboembolism in patients
66 with atrial fibrillation (AF) [3]. However, in recent years some researchers have
67 reported the use of this score as a predictor of future CVD morbidity or all-cause
68 mortality with or without chronic AF [4-6]. Patients on HD are more likely to have
69 chronic AF in comparison with the general population: 11.6% have AF, and a further
70 50% have any form of arrhythmia, including paroxysmal AF [7]. Dialysis patients have
71 a higher incidence of CVD and a higher rate of arrhythmia as a comorbidity. However,
72 there are limited studies examining the utility of the CHA₂DS₂-VASc score for mortality
73 after the initiation of HD. The CHA₂DS₂-VASc score was reported to be associated with
74 1-year mortality in HD patients [8]. Nevertheless, the association between the

CHA₂DS₂-VASc score and mid-term prognosis (3 years) after the start of dialysis remains unclear. In this study, we aimed to clarify the association between the CHA₂DS₂-VASc score and all-cause or CVD mortality in HD patients over a follow-up of 3 years after initiating HD. Moreover, we examined the factors that may have the most impact on the mid-term prognosis of patients at the initiation of HD.

Materials and Methods

Study population and design

This study was a retrospective observational study conducted in Ichiyokai Harada Hospital, and included three dialysis clinics. The subjects were 557 patients undergoing chronic HD or on-line hemodiafiltration (HDF) from February 2005 to October 2017. All patients had vascular access providing a blood flow rate ≥ 200 mL/min and received 4-h HD or 4-h predilution on-line HDF using high-flux membranes, with a total convective volume of 40 L per session (thrice per week). A standard bicarbonate dialysis fluid (140 mEq/L sodium, 2.0 mEq/L potassium, 3.0 mEq/L calcium, 1.0 mEq/L magnesium, and 100 mg/dL glucose) delivered using a central dialysis fluid delivery system was used for HD and on-line HDF. The observation period started at the initiation of dialysis and ended at one of the following events, whichever occurred first:

93 death, transfer to another facility, or the end of the study (3 years after study
94 enrollment). The exclusion criteria were <20 years of age, and history of advanced
95 cancer in the month leading up to the study. Demographic, clinical, and laboratory data
96 at the initiation of HD or HDF were collected from the electronic medical records of
97 each patient, and the CHA₂DS₂-VASc score [3] at the initiation of HD was calculated
98 for each patient accordingly. Patients were given 1 point for congestive heart failure,
99 hypertension, age 65–74 years, diabetes mellitus (DM), vascular disease, and female
100 sex, and 2 points for age ≥75 years and previous stroke or transient ischemic attack
101 (Supplemental Table 1) [9]. Patients were classified into three groups according to their
102 CHA₂DS₂-VASc scores: 0–1 (low), 2–3 (intermediate), and 4–9 (high). Hypertension
103 was defined as systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥80 mmHg, a
104 history of hypertension treatment from medical records, or use of antihypertensive
105 drugs [10]. DM was defined by a hemoglobin A1c level ≥6.5%, 2-h plasma glucose
106 ≥200 mg/dL with a 75-g oral glucose tolerance test, fasting plasma glucose ≥126
107 mg/dL, or medical history of DM [11]. Dyslipidemia was defined as low-density
108 lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL,
109 triglycerides ≥150 mg/dL, or use of lipid-lowering drugs. Body mass index (BMI) was
110 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 \pm 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 CHA₂DS₂-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

history of cerebral infarction at the initiation of HD. During the 3-year follow-up period, 153 patients died (88 following CVD events). We divided the participants into three groups according to their CHA₂DS₂-VASc score: 0–1 (low), 2–3 (intermediate), and 4–9 (high). The baseline clinical characteristics of each group are shown in Table 1.

Patients with a higher CHA₂DS₂-VASc score groups were older, more frequently women, and had more of the following items: a corrected calcium value, C-reactive protein, comorbidities (dyslipidemia and DM), medical history (heart failure, stroke, or vascular disease), and the proportion of patients taking antiplatelet drugs. Additionally, the serum albumin, blood urea nitrogen, creatinine, uric acid, potassium, sodium, and phosphorus values were significantly lower in patients with higher CHA₂DS₂-VASc scores. Table 2 shows the results of multivariate analyses for 3-year all-cause mortality. In a multivariate analysis, serum albumin, creatinine, and CHA₂DS₂-VASc score were associated with 3-year all-cause mortality (serum albumin: HR 0.60, 95% CI 0.43–0.85, *P*=0.003; creatinine: HR 0.91, 95% CI 0.84–0.99, *P*=0.049; CHA₂DS₂-VASc score: HR 1.33, 95% CI 1.20–1.46, *P*<0.001). Kaplan–Meier survival curves for the three groups divided according to the CHA₂DS₂-VASc score showed that patients with a high score had a higher risk of 3-year all-cause and CVD mortality (Figure 1). Multivariate analysis using the CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-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

183 We showed an association between the CHA₂DS₂-VASc score and mid-term
184 mortality of HD patients. The 3-year all-cause and CVD mortality were significantly
185 higher in patients with a higher CHA₂DS₂-VASc score. Compared with patients in the
186 low CHA₂DS₂-VASc score group, those in the high score group had an approximately
187 3-fold increased risk for all-cause mortality. To our knowledge, this study is the first
188 report that shows an association between the CHA₂DS₂-VASc score and mid-term
189 prognosis among incident HD patients.

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

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

204 In contrast, the CHA₂DS₂-VASc score, a modified version of the CHADS₂ score, is
205 widely used in clinical practice to assess the risk of stroke in patients with AF and is
206 easy to calculate. Although this score has been used to determine whether patients with
207 AF require treatment with anticoagulation or antiplatelet therapy, it has been associated
208 with the risk of death in patients with several diseases with or without AF, including
209 heart failure [20], stroke [21], acute pulmonary embolism [22], and in patients with
210 implantable cardiac defibrillators [23]. Recently, the CHA₂DS₂-VASc score was
211 reported to be useful in predicting all-cause and cardiovascular mortality in non-dialysis
212 [24, 25] and even in dialysis CKD patients [8]. Schamroth Pravda M et al. reported that
213 the CHA₂DS₂-VASc score was strongly associated with all-cause mortality and
214 increased risk of myocardial infarction and stroke within the first year of HD initiation.
215 However, their investigation did not mention the causes of death nor the number lost to
216 follow-up during the 1-year follow-up. In addition, their cohort had a high 1-year
217 mortality rate of 23.8%, which is higher than that reported in any other cohort in the
218 world. First-year mortality of incident dialysis patients has been reported as follows:

219 20.5% in the United States [26], 12.5% in Europe [27], and 12.4% in Japan [28]. These
220 differences may be caused by racial differences, quantities of pre-dialysis care,
221 nutritional condition, medical environment or system, or timing of the start of HD. In a
222 short period of 1 year, the prediction of prognosis after the introduction of dialysis may
223 be more influenced by the pre-dialysis condition than the dialysis treatment, and the
224 results may vary widely among countries and regions. In the present study, the 1-year
225 mortality rate was 10% (data not shown), which was similar to that reported in Japan.
226 Thus, we consider this an accurate study of general maintenance HD patients.
227 Additionally, we investigated the association with all-cause mortality and cardiovascular
228 mortality, and showed that a higher CHA₂DS₂-VASc score was strongly associated with
229 both factors. We showed that among items in the CHA₂DS₂-VASc score, age (≥ 75
230 years) and history of previous stroke were significantly associated with both 3-year all-
231 cause and CVD mortality. Furthermore, the age cut-off value obtained using the ROC
232 curve was 74 years, approximating the item (age ≥ 75 years) in the CHA₂DS₂-VASc
233 score. Age (≥ 75 years) and history of previous stroke both add 2 points to the
234 CHA₂DS₂-VASc score, suggesting that it could better reflect prognosis in HD patients.
235 Moreover, various studies on the medium- to long-term prognoses of HD patients have
236 been conducted. In the present study we also examined other risk factors, including

previously known poor prognostic factors such as serum albumin level [29], presence of anemia [30, 31], and history of CVD [32] or stroke [33, 34]; the CHA₂DS₂-VASc score was still a significant risk factor for 3-year mortality.

However, this study has several limitations. First, this was a retrospective observational study. Thus, the casual effects between the CHA₂DS₂-VASc score and prognosis were not examined. In addition, we were not able to evaluate whether the CHA₂DS₂-VASc score could be an individual risk prediction in this study. For these reasons, further prospective studies are needed. Second, we did not assess critical risk factors, such as vascular calcification, left ventricular hypertrophy, and dialysis adequacy. Third, our cohort included only Japanese people, whose survival is reportedly one of the best globally, so the resulting data cannot be generalized to other populations. Finally, we could not investigate changes in medication use or mode of dialysis treatment (including change from HD to HDF) during the first 3 years after dialysis induction. Despite these limitations, it is worthwhile to employ the CHA₂DS₂-VASc score because it is easy to measure at the bedside and can significantly predict mortality 3 years after dialysis initiation.

253 In conclusion, patients with end-stage renal disease are at high risk of mortality and
254 CVD even within 3 years after the introduction of HD. The CHA₂DS₂-VASc score was
255 strongly associated with 3-year all-cause and CVD mortality in HD patients.
256

257 **Statement of Ethics**

258 The study is in accordance with the ethical standards of the National Research
259 Committee and with the 1964 Helsinki Declaration and its later amendments or
260 comparable ethical standards. The protocol was licensed by the hospital ethics
261 committee of Ichiyokai Harada Hospital (approval number 202004, registered March
262 24, 2020). Written informed consent was not required because of the non-intervention
263 and retrospective design.

264

265 **Conflict of Interest Statement**

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

267

268 **Funding Sources**

269 The authors received no specific funding for the present study.

270

271 **Author Contributions**

272 Okubo A and Doi T designed the study, wrote, and edited the manuscript, Okubo A
273 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.

References

1. Cozzolino M, Galassi A, Pivari F, Ciceri P, Conte. The cardiovascular burden in end-stage renal disease. *Contrib Nephrol*. 2017 191:44-57.
2. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant*. 2018 Oct 1;33(suppl_3):iii28-iii34.
3. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010 Feb;137(2):263-72.
4. Glotzer TV, Hellkamp AS, Lee KL, Lamas GA. CHA₂DS₂-VAS(C) and CHADS₂ Scores Predict Adverse Clinical Events in Patients With Pacemakers and Sinus Node Dysfunction Independent of Atrial Fibrillation. *Can J Cardiol*. 2015 Aug;31(8):1004-11.
5. Liu FD, Shen XL, Zhao R, Li GF, Wu YL, Tao XX, et al. Predictive role of CHADS₂ and CHA₂DS₂-VASc scores on stroke and thromboembolism in patients without atrial fibrillation: a meta-analysis. *Ann Med*. 2016 Aug;48(5):367-75.

- 302 6. Tu HT, Campbell BC, Meretoja A, Churilov L, Lees KR, Donnan GA, et al. Pre-
303 Stroke CHADS₂ and CHA₂DS₂-VASc Scores Are Useful in Stratifying Three-
304 Month Outcomes in Patients with and without Atrial Fibrillation. *Cerebrovasc Dis.*
305 2013;36(4):273-80.
- 306 7. Zimmerman D, Sood MM, Rigatto C, Holden RM, Hiremath S, Clase CM.
307 Systematic review and meta-analysis of incidence, prevalence and outcomes of
308 atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant.* 2012
309 Oct;27(10):3816-22.
- 310 8. Schamroth Pravda M, Cohen Hagai K, Topaz G, Schamroth Pravda N, Makhoul N,
311 Shuvy M, et al. Assessment of the CHA₂DS₂-VASc Score in Predicting Mortality
312 and Adverse Cardiovascular Outcomes of Patients on Hemodialysis. *Am J Nephrol.*
313 2020 51(8):635-40.
- 314 9. European Heart Rhythm Association; European Association for Cardio-Thoracic
315 Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al.
316 Guidelines for the management of atrial fibrillation: the Task Force for the
317 Management of Atrial Fibrillation of the European Society of Cardiology (ESC).
318 *Eur Heart J.* 2010 Oct;31(19):2369-429.
- 319 10. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison

320 Himmelfarb C, et al. 2017

321 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline

322 for the prevention, detection, evaluation, and management of high blood pressure in

323 adults: a report of the American College of Cardiology/American Heart Association

324 Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):1269-

325 324.

326 11. American Diabetes Association: 2. Classification and diagnosis of diabetes:

327 Standards of Medical Care in Diabetes-2020. Diabetes Care 2020. 43(Suppl 1):

328 S14-31.

329 12. Lu YA, Chen SW, Lee CC, Wu VC, Fan PC, Kuo G, et al. Mid-term survival of

330 patients with chronic kidney disease after extracorporeal membrane oxygenation.

331 Interact Cardiovasc Thorac Surg. 2020 Nov 1;31(5):595-602.

332 13. Grundmann D, Linder M, Goßling A, Voigtländer L, Ludwig S, Waldschmidt L, et

333 al. End-stage renal disease, calcification patterns and clinical outcomes after TAVI.

334 Clin Res Cardiol. 2021 Nov 13. doi: 10.1007/s00392-021-01968-y.

335 14. März W, Genser B, Drechsler C, Krane V, Grammer TB, Ritz E, et al. German

336 Diabetes and Dialysis Study Investigators: Atorvastatin and low-density lipoprotein

337 cholesterol in type 2 diabetes mellitus patients on hemodialysis. Clin J Am Soc

338 Nephrol. 2011 Jun;6(6):1316-25.

339 15. Bae E, Cho HJ, Shin N, Kim SM, Yang SH, Kim DK, et al. Lower serum uric acid
340 level predicts mortality in dialysis patients. Medicine (Baltimore). 2016
341 Jun;95(24):e3701.

342 16. C Choi SR, Lee YK, Cho AJ, Park HC, Han CH, Choi MJ, et al. Malnutrition,
343 inflammation, progression of vascular calcification and survival: Inter-relationships
344 in hemodialysis patients. PLoS One. 2019 May 2;14(5):e0216415.

345 17. Anderson RT, Cleek H, Pajouhi AS, Bellolio MF, Mayukha A, Hart A, et al.
346 Prediction of Risk of Death for Patients Starting Dialysis. Clin J Am Soc Nephrol.
347 2019 Aug 7;14(8):1213-1227.

348 18. Kanda E, Kato A, Masakane I, Kanno Y. A new nutritional risk index for predicting
349 mortality in hemodialysis patients: Nationwide cohort study. PLoS One. 2019 Mar
350 28;14(3):e0214524.

351 19. Robinson BM, Zhang J, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP, et
352 al. Worldwide, mortality risk is high soon after initiation of hemodialysis. Kidney
353 Int. 2014 Jan;85(1):158-65.

354 20. Chen YL, Cheng CL, Huang JL, Yang NI, Chang HC, Chang KC, et al. Mortality
355 prediction using CHADS₂/CHA₂S₂DS₂-VASc/R₂CHADS₂ scores in systolic heart

- 356 failure patients with or without atrial fibrillation. *Medicine (Baltimore)*. 2017
357 Oct;96(43):e8338.
- 358 21. Ntaios G, Lip GY, Makaritsis K, Papavasileiou V, Vemmou A, Koroboki E, et al.
359 CHADS₂, CHA₂DS₂-VASc, and long-term stroke outcome in patients without
360 atrial fibrillation. *Neurology*. 2013 Mar 12;80(11):1009-17.
- 361 22. Onuk T, Karataş MB, İpek G, Güngör B, Akyüz Ş, Çanga Y, et al. Higher
362 CHA₂DS₂-VASc Score Is Associated With Increased Mortality in Acute Pulmonary
363 Embolism. *Clin Appl Thromb Hemost*. 2017 Sep;23(6):631-637.
- 364 23. Hong C, Alluri K, Shariff N, Khattak F, Adelstein E, Jain S, et al. Usefulness of the
365 CHA₂DS₂-VASc Score to Predict Mortality in Defibrillator Recipients. *Am J*
366 *Cardiol*. 2017 Jul 1;120(1):83-86.
- 367 24. Hsu PC, Lee WH, Chen SC, Tsai YC, Chen YC, Chu CY, et al. Using CHADS₂
368 and CHA₂DS₂-VASc scores for mortality prediction in patients with chronic kidney
369 disease. *Sci Rep*. 2020 Nov 3;10(1):18942.
- 370 25. Vodošek Hojs N, Ekart R, Bevc S, Piko N, Hojs R. CHA₂DS₂-VASc Score as a
371 Predictor of Cardiovascular and All-Cause Mortality in Chronic Kidney Disease
372 Patients. *Am J Nephrol*. 2021;52(5):404-411.
- 373 26. The United States Renal Data System (USRDS). Available from:

374 <https://adr.usrds.org/2020/end-stage-renal-disease/5-mortality>.

375 27. Kramer A, Boenink R, Stel VS, Santiuste de Pablos C, Tomović F, Golan E, et al.

376 The ERA-EDTA Registry Annual Report 2018: a summary. Clin Kidney J. 2020

377 Dec 24;14(1):107-123.

378 28. Nitta K, Goto S, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, et al. Annual

379 dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility

380 data, incidence, prevalence, and mortality. Ren Replace Ther 2020;6:41.

381 29. Shimoda T, Matsuzawa R, Yoneki K, Harada M, Watanabe T, Yoshida A, et al.

382 Combined Contribution of Reduced Functional Mobility, Muscle Weakness, and

383 Low Serum Albumin in Prediction of All-Cause Mortality in Hemodialysis

384 Patients: A Retrospective Cohort Study. J Ren Nutr. 2018 Sep;28(5):302-308.

385 30. Locham S, Mathlouthi A, Dakour-Aridi H, Nejim B, Malas MB. Association

386 between Severe Anemia and Outcomes of Hemodialysis Vascular Access. Ann

387 Vasc Surg. 2020 Jan;62:295-303.

388 31. Kido R, Akizawa T, Fukuhara S: Haemoglobin concentration and survival of

389 haemodialysis patients before and after experiencing cardiovascular disease: a

390 cohort study from Japanese dialysis outcomes and practice pattern study (J-

391 DOPPS). BMJ Open. 2019 Sep 5;9(9):e031476.

- 392 32. Stirnadel-Farrant HA, Karaboyas A, Cizman B, Bieber BA, Kler L, Jones D, et al.
393 Cardiovascular Event Rates Among Hemodialysis Patients Across Geographical
394 Regions-A Snapshot From The Dialysis Outcomes and Practice Patterns Study
395 (DOPPS). *Kidney Int Rep.* 2019 Mar 28;4(6):864-72.
- 396 33. Kojima M, Inaguma D, Koide S, Koshi-Ito E, Takahashi K, Hayashi H, et al.
397 Relationship between History of Ischemic Stroke and All-Cause Mortality in
398 Incident Dialysis Patients. *Nephron.* 2019;143(1):43-53.
- 399 34. Findlay M, MacIsaac R, MacLeod MJ, Metcalfe W, Sood MM, Traynor JP, et al.
400 The Association of Atrial Fibrillation and Ischemic Stroke in Patients on
401 Hemodialysis: A Competing Risk Analysis. *Can J Kidney Health Dis.* 2019 Sep
402 27;6:2054358119878719. DOI: 10.1177/2054358119878719.

403 **Figure legends**

404

405 **Figure 1.** Kaplan–Meier survival curves based on the CHA₂DS₂-VASc score. * $P<0.05$.

406 (A) Three-year all-cause mortality. (B) Cardiovascular mortality.

407

408

Table 1. Comparison of clinical characteristics according to the CHA₂DS₂-VASc score

	All Patients n = 557	CHA ₂ DS ₂ -VASc Score			<i>P</i> Value
		0–1 n = 81	2–3 n = 267	4–9 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; β 2MG, β 2-microglobulin.

Data are mean \pm 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	<i>P</i> Value
CHA ₂ DS 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.

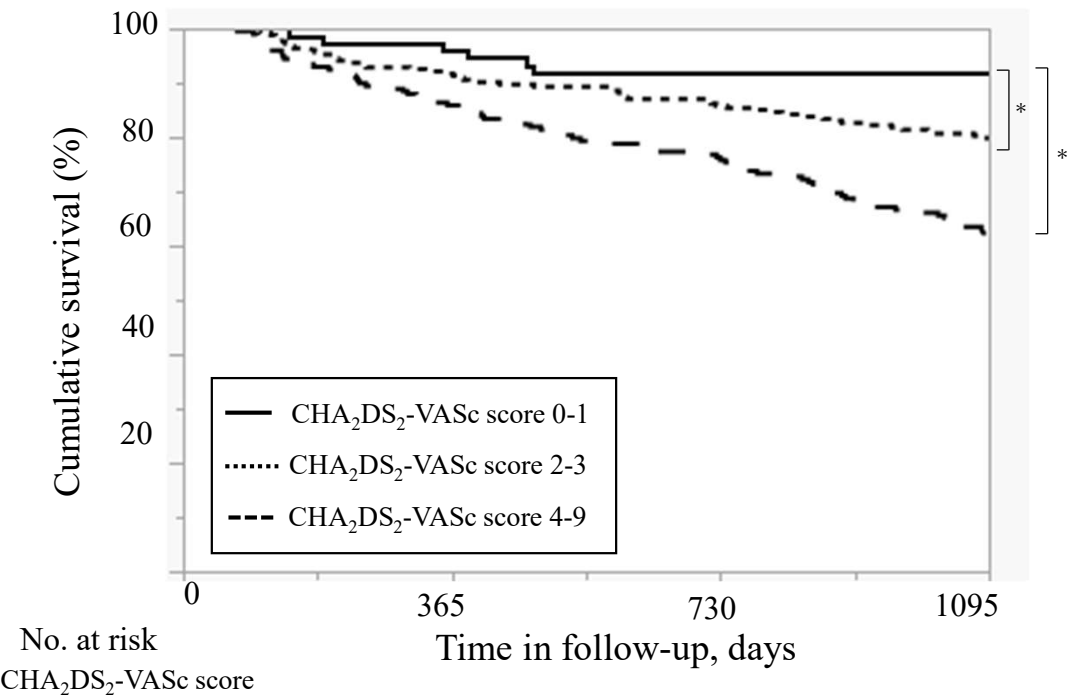
Table 3. Risk of all-cause mortality and cardiovascular mortality associated with the CHA₂DS₂-VASc score

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

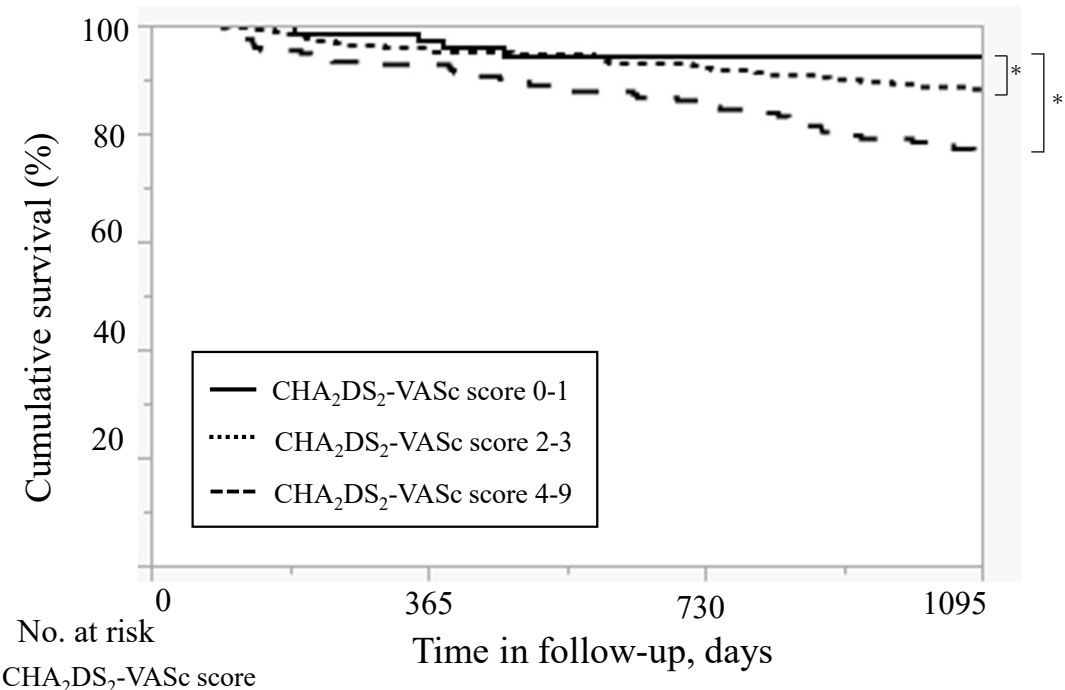
HR, hazard ratio; CI, confidence interval.

Multivariate Cox proportional hazards regression with crude (Model 1) and adjusted (Model 2) associations for the CHA₂DS₂-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



(B) Cardiovascular mortality

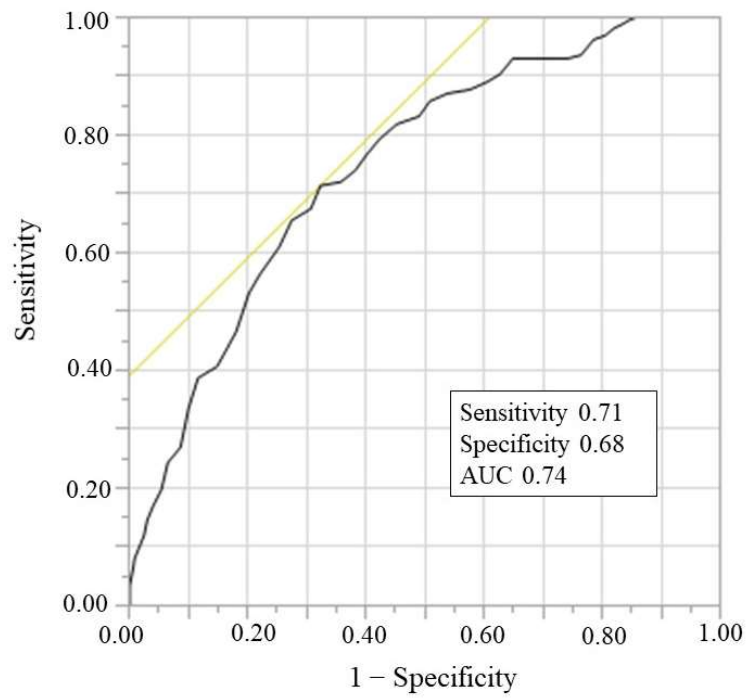


Supplementary Materials

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 CHA₂DS₂-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 CHA₂DS₂-VASc score included as a variable

	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> 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 CHA₂DS₂-VASc score

	All-Cause Mortality		Cardiovascular Mortality	
	HR (95% CI)	<i>P</i> Value	HR (95% CI)	<i>P</i> 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	<i>P</i> Value
CHA ₂ DS 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.