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The Optimal Cut-off Value of Ankle Brachial Index for Screening Cardiovascular Disease Risk in Hemodialysis Patients

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Severe atherosclerosis and vascular calcification, causing coronary artery stenosis or peripheral artery diseases (PAD), are frequently detected in hemodialysis (HD) patients. Ankle brachial index (ABI) is a useful marker for detecting PAD, as well as being predictive of the development of cardiovascular diseases (CVD). However, obvious atherosclerotic vascular changes in HD patients might elevate the optimal cut-off value of ABI for screening CVD over the conventional ABI cut-off value, 0.9. Moreover, the ABI cut-off value may be altered by the presence of diabetes mellitus (DM) in HD patients. This retrospective cohort study involved 110 patients on maintenance HD. The ABI cut-off value predicting CVD in HD patients was determined by receiver operating curve (ROC) analysis. ABI cut-off values were also compared in groups of subjects with and without DM. The ABI cut-off value predictive of CVD in all 110 HD patients was 0.960 (area under the curve [AUC] 0.761, sensitivity 0.641, specificity 0.803). The cut-off value of ABI was 1.045 in the DM group (AUC 0.735, sensitivity 0.813, specificity 0.606) and 0.960 in the non-DM group (AUC 0.773, sensitivity 0.714, specificity 0.868). Kaplan-Meier analysis showed that patients with ABI below the cut-off values in each group were significantly more likely to develop CVD. The optimal ABI cut-off values for screening high-risk HD patients with CVD should be set at higher levels than the conventional cut-off value (0.9), and that the optimal cut-off values might differ in HD patients with and without DM, at 1.045 and 0.960, respectively. *Shinshu Med J 64 : 135—146, 2016*

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Key words : ankle brachial index (ABI), cardiovascular diseases, hemodialysis

Abbreviations : PAD, peripheral artery diseases ; HD, hemodialysis ; ABI, ankle brachial index ; CVD, cardiovascular diseases ; DM, diabetes mellitus ; ROC, receiver operating curve ; AUC, area under the curve

I Introduction

Severe atherosclerosis and vascular calcification, which can lead to coronary artery stenosis and/or peripheral artery diseases (PAD), are frequently detected in patients on hemodialysis (HD)[1)2)]. Although these cardiovascular diseases (CVD) are major causes of death in HD patients, their detection is difficult, because they progress asymptomatically. Fewer HD patients with acute myocardial infarction (AMI) had chest pain than non-HD patients[3)]. Therefore, evaluation of disease severity of atherosclerosis could have prognostic implications in HD patients and has predictive value for CVDs. In general, ankle brachial index (ABI) is a useful marker for detecting PAD, and for predicting future CVDs including myocardial infarction and stroke[4)–6)]. Recent reports showed that ABI cut-off values below 0.9 are useful for predicting future CV

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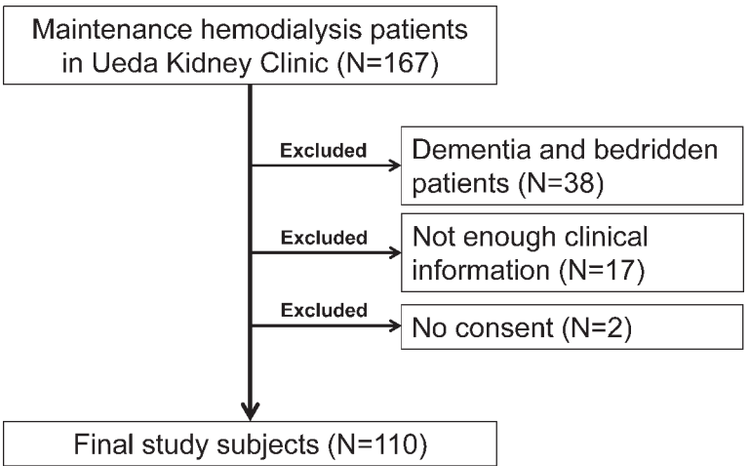

Fig. 1 Chart of the study flow

events[4)–8)]. In HD patients, however, the appropriate ABI cut-off value predicting CVD is unknown. We hypothesized that it would be higher than that of non-HD patients, since dialysis patients are more likely to develop severe arterial calcification[8)]. Furthermore, previous reports suggested that diabetes mellitus (DM) causes more severe arterial calcification as well as atherosclerotic lesions than other diseases[8)9)]. The difficulties encountered in compressing calcified arteries lead to increases in blood pressure, suggesting that DM alters the ABI cut-off value[8)].

In the HD patients including DM patients, sensitivity of the ABI cut-off value below 0.9 for diagnosing PAD was only 29.9 %[10)]. Thus, sensitivity of the ABI cut-off value below 0.9 for screening CVD is expected to be low in HD patients. This study was therefore designed to determine the optimal ABI cut-off value for screening high risk HD patients with CVD, as well as to assess the effects of DM on ABI cut-off values.

II Materials and Methods

A Study design and subjects

This retrospective cohort study was designed to determine the ABI cut-off value predictive of CVD in HD patients. Beginning in January 2010, 167 patients were undergoing conventional maintenance HD in Jishyukai Ueda Kidney Clinic, with almost all of them screened by ABI. Stable outpatients who agreed to participate in the study were enrolled. Patients were excluded if clinical data, including background clinical information, laboratory values, measurements of ABI, cardio-ankle vascular index (CAVI), and aortic arch calcification score (AoACS), were missing. Patients with severe active infectious diseases or malignancies at the time of study entry, and those who could not be followed up until CVD, death, or December 2013, were excluded. Of the 167 patients, 57 were excluded. These patients included 38 in the geriatric medical care facility for the elderly who had dementia, were bedridden, and were in poor physical condition; 17 who lacked sufficient clinical information, such as past complications or history of CVD; and two who refused informed consent. Thus, 110 outpatients were enrolled (**Fig. 1**). The study protocol was approved by the institutional review board of the ethics committee of Shinshu University (approval number: 1996) and conformed to the Declaration of Helsinki as revised in 2008. Written informed consent was obtained from each patient before study entry.

B Baseline examinations

ABI was evaluated in each patient with a Vasera VS-1500A (Fukuda Denshi, Tokyo, Japan) just before the start of an HD session at the beginning of a week. Briefly, patients were placed in a supine position and their systolic blood pressure was measured in the brachial artery of the arm without vascular access and in the posterior tibial arteries

of both legs. ABI was defined as the ratio of blood pressure in each leg to the blood pressure in the upper arm, with the lower of the two values used for analysis. CAVI was evaluated by the same automatic oscillometric cuff measurement device. The cuffs were applied to both upper arms and ankles. Electrodes were fixed to each wrist and a heart sound sensor was placed on the second intercostal sternum. The methods of measuring and calculating CAVI have been described[11]. AoACS was calculated as the number of sectors with aortic arch calcification in plain chest X-rays, divided into 16 circumferences[12]. Blood samples obtained before the start of an HD session at the beginning of a week were analyzed by BML, Inc, Japan.

C Endpoint and diagnosis of CVD

The study endpoint was the incidence of CVD, including ischemic heart diseases (IHDs), PAD, and cerebral infarction (CI). IHDs included angina pectoris (AP) and acute myocardial infarction (AMI). AP was defined based on coronary angiography, followed by percutaneous coronary intervention or coronary artery bypass graft surgery. AMI was defined as symptoms of myocardial ischemia ; new or presumed significant ST-segment to T-wave (ST-T) changes or new left bundle branch block on electrocardiograms ; or an increase in the cardiac enzyme marker creatinine kinase MB type. CI was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of the infarction, which was not reversible within 24 hours and was symptomatic. PAD was defined based on peripheral angiography, followed by percutaneous peripheral artery intervention, an open surgical procedure, or medication. The occurrence of a CVD for each patient was evaluated by more than two researchers.

Past history of CVD was defined as a previous occurrence of AP, AMI, CI, cerebral hemorrhage, PAD, aortic dissection, or aortic aneurysm. Cerebral hemorrhage was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of the hemorrhage, which was not reversible within 24 hours. Aortic dissection was defined as the acute onset of chest or back pain, and a diagnosis of dissected aorta on computed tomography (CT) following surgery or medication. An aortic aneurysm was defined by a dilated aorta diagnosed by CT following an operation. The definitions of AP, AMI, CI, and PAD were the same as above.

D Statistical analysis

Continuous variables were compared by Mann-Whitney U tests, and categorical variables by Fisher's exact tests. Factors associated with CVD were evaluated by Cox proportional hazard regression analysis. Receiver operating curve (ROC) analysis was used to evaluate the ABI cut-off value predictive of CVD in HD patients. To evaluate whether DM altered the ABI cut-off value, subjects were separated into those with and without DM and their cut-off values compared. Kaplan-Meier analysis was used to determine the cumulative incidence of CVD. All statistical analyses were performed using SPSS Statistics version 22.0J (IBM Corp., Armonk, NY, USA), with statistical significance defined as a $p<0.05$.

Ⅲ Results

A Baseline clinical characteristics

The baseline clinical characteristics of all 110 patients enrolled in this study are shown in **Table 1**. Of these patients, 39 experienced CVD during follow-up, and 71 did not. Fifteen patients had IHD, 7 patients CI, and 17 patients PAD. Median ABI, rate of chronic glomerulonephritis (CGN) and hemoglobin concentration were significantly lower, while the rates of DM, past history of CVD, and deaths from all causes were significantly higher, in the CVD (+) than in the CVD (−) group. The median follow-up period was 25 months. None of the other demographic and clinical characteristics differed significantly in the two groups.

B Factors associated with the incidence of CVD

Multivariate Cox proportional hazard regression analysis, performed to detect factors independently associated with the incidence of CVD, showed that

Table 1 Background data of all patients with or without CVD

	N=110		CVD (−) (N=71)		CVD (+) (N=39)		*P*-value
Age (years)	69	(30-92)	68	(30-92)	70	(45-90)	0.28
Male (n, %)	77	70.0 %	47	66.2 %	30	76.9 %	0.28
BMI >25 kg/m² (n, %)	19	17.2 %	10	14.1 %	9	23.1 %	0.29
Duration of HD (months)	44	(1-225)	39	(1-225)	46	(3-156)	0.47
SBP (mmHg)	146	(98-221)	146	(105-221)	146	(98-205)	0.48
DBP (mmHg)	75	(45-105)	76	(48-105)	72	(45-98)	0.63
HR	69	(32-107)	68	(47-107)	71	(32-101)	0.39
ABI	1.02	(0.30-1.29)	1.08	(0.40-1.29)	0.84	(0.30-1.21)	<0.001***
CAVI	9.1	(5.4-17.0)	9.2	(5.4-12.8)	9	(6.1-17.0)	0.56
AoACS	5	(0-16)	5	(0-16)	7	(0-15)	0.12
Past history (n, %)							
Smoking	53	48.2 %	34	47.9 %	19	48.7 %	1.00
Diabetes mellitus	65	59.1 %	33	46.5 %	32	82.1 %	<0.001***
Hypertension	108	98.2 %	71	100.0 %	37	94.9 %	0.12
Hyperlipidemia	27	24.5 %	18	25.4 %	9	23.1 %	1.00
Past history of CVD	29	26.3 %	12	16.9 %	17	43.6 %	0.003***
Cause of ESRD (n, %)							
Diabetes mellitus	65	59.1 %	33	46.5 %	32	82.1 %	<0.001***
Hypertension	20	18.2 %	14	19.8 %	6	15.4 %	0.62
CGN	16	14.5 %	16	22.5 %	0	0.0 %	0.001***
PKD	5	4.5 %	4	5.6 %	1	2.5 %	0.65
other	4	3.7 %	4	5.6 %	0	0.0 %	0.30
Laboratory data							
Hb (g/dl)	10.6	(5.5-13.4)	10.8	(5.5-13.3)	10.1	(6.9-13.4)	0.05
Alb (g/dl)	3.7	(2.3-4.3)	3.8	(2.3-4.3)	3.7	(2.5-4.2)	0.26
UN (mg/dl)	58	(27-106)	56	(27-106)	59	(28-93)	0.89
Cr (mg/dl)	10.1	(2.5-16.4)	9.4	(2.5-15.8)	10.4	(5.2-16.4)	0.39
UA (mg/dl)	6.9	(4.1-10.9)	7.1	(4.4-10.9)	6.8	(4.1-10.4)	0.43
TC (mg/dl)	146	(94-233)	151	(94-220)	133	(95-233)	0.14
HDL-C (mg/dl)	40	(17-86)	39	(17-86)	41	(17-84)	0.86
LDL-C (mg/dl)	85	(33-157)	84	(36-157)	85	(33-137)	0.84
TG (mg/dl)	95	(28-697)	93	(28-697)	102	(39-245)	0.25
Adjusted Ca (mg/dl)	9	(7.8-10.9)	8.9	(7.8-10.7)	9	(8.0-10.9)	0.56
iP (mg/dl)	5.2	(2.2-10.6)	5.1	(2.2-9.1)	5.2	(3.2-10.6)	0.86
Intact-PTH (pg/ml)	93	(8-497)	95	(19-396)	73	(8-497)	0.25
HbA1c (NGSP %)	5.7	(4.0-8.1)	5.8	(4.0-7.6)	5.7	(4.2-8.1)	0.95
Medications (n, %)							
ARB/ACEi	85	77.3 %	57	80.3 %	28	71.8 %	0.35
Ca blocker	77	70.0 %	51	71.8 %	26	66.7 %	0.67
beta blocker	31	28.2 %	18	25.4 %	13	33.3 %	0.39
Diuretics	62	56.4 %	38	53.5 %	24	61.5 %	0.43
CPBs	60	54.5 %	40	56.3 %	20	51.3 %	0.69
Sevelamer	27	24.5 %	13	18.3 %	14	35.9 %	0.06
Lanthan	18	16.4 %	10	14.1 %	8	20.5 %	0.43
Vitamin D	71	64.5 %	46	64.8 %	25	64.1 %	1.00
Cinacalcet	9	8.2 %	5	7.0 %	4	10.3 %	0.72
Statin	19	17.3 %	12	16.9 %	7	17.9 %	1.00
anti-platelet agents	43	39.1 %	23	32.4 %	20	51.3 %	0.07
Events (n, %)							
All causes of death	21	19.1 %	8	11.3 %	13	33.3 %	0.010*
All cases of CVD	39	35.5 %	0	0.0 %	39	100.0 %	-
IHD	15	13.6 %	-	-	15	38.5 %	-
CI	7	6.4 %	-	-	7	17.9 %	-
PAD	17	15.5 %	-	-	17	43.6 %	-
Asymptomatic CVD	16	14.5 %	0	0.0 %	16	41.0 %	-
Asymptomatic IHD	6	5.5 %	-	-	6	15.4 %	-
Asymptomatic PAD	10	9.1 %	-	-	10	25.6 %	-

Table 2 Cox proportional hazard regression analysis for the factors associated with CVD

	Univariate analysis			Multivariate analysis		
	HR	95 %CI	*P* value	HR	95 %CI	*P* value
Age	1.018	(0.991–1.046)	0.18	1.026	(0.992–1.061)	0.14
Sex (male)	1.508	(0.716–3.178)	0.28	1.432	(0.649–3.157)	0.37
Duration of HD	0.998	(0.992–1.004)	0.53	0.994	(0.985–1.002)	0.14
Past history of CVD	3.058	(1.621–5.771)	0.001**	2.018	(0.950–4.288)	0.07
ABI	0.068	(0.021–0.223)	<0.001***	0.131	(0.028–0.619)	0.010*
DM	3.702	(1.632–8.396)	0.002**	3.024	(1.190–7.688)	0.020*
Hb	0.855	(0.685–1.068)	0.17	0.972	(0.779–1.213)	0.80
Adjusted Ca	1.229	(0.777–1.946)	0.38	1.591	(0.926–2.735)	0.09
iP	1.068	(0.849–1.343)	0.58	0.997	(0.794–1.252)	0.98

Significant differences are indicated with asterisks (***$p<0.001$, **$p<0.01$, *$p<0.05$).
ABI, ankle brachial index ; Ca, calcium ; CI, confidence interval ; CVD, cardiovascular diseases ; DM, diabetes mellitus ; Hb, hemoglobin ; HD, hemodialysis ; HR, hazard ratio ; iP, inorganic phosphorus.

ABI and the presence of DM were significantly associated with the incidence of CVD (**Table 2**).

C ABI cut-off value predictive of CVD between patients with and without DM

The distribution of ABI is shown in **Fig. 2**. The median ABI was 1.02 (range 0.30–1.29), with no patient having an extremely high ABI (>1.3). ROC analysis with Youden's index in all patients showed an optimal ABI cut-off value predictive of CVD of 0.960, with a sensitivity of 0.641 and a specificity of 0.803 (**Fig. 3A**). We had hypothesized that the ABI cut-off value might differ in patients with and without DM. The baseline characteristics of the groups of patients with and without DM are shown in **Table 3**. Duration of HD treatment was significantly shorter and ABI significantly lower in the DM than in the non-DM group. The percentages of males ; obese individuals (body mass index >25 kg/m^2) ; patients with histories of smoking and CVD ; IHD ; and treatment with an angiotensin II receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi), were significantly higher in the DM than in the non-DM group. ROC analysis with Youden's index showed that the ABI cut-off values predictive of CVD were 0.960 in the non-DM group (sensitivity 0.714, specificity 0.868 ; **Fig. 3B**) and 1.045 in the DM group (sensitivity 0.813, specificity 0.606 ; **Fig. 3C**). **Table 4** shows the differences in sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) between the conventional ABI cut-off value (0.9) and the ABI cut-off values for our DM and non-DM groups in predicting CVD. Sensitivity and NPV in all patient groups were higher using our proposed

Table 1 Data are presented as follows : continuous variables were expressed as median and range, categorical variables were expressed as n number and percentages. Significant differences are indicated with asterisks (***$p<0.001$, **$p<0.01$, *$p<0.05$).
ABI, ankle brachial index ; Alb, albumin ; AoACS, aortic arch calcification score ; ARB/ACEi, angiotensin II type receptor blocker/angiotensin converting enzyme inhibitor ; BMI, body mass index ; Ca, calcium ; CAVI, cardio-ankle vascular index ; CGN, chronic glomerulonephritis ; CI, cerebral infarction ; CPBs, calcium-containing phosphate binders ; Cr, creatinine ; CVD, cardiovascular diseases ; DBP, diastolic blood pressure ; ESRD, end stage renal disease ; Hb, hemoglobin ; HbA1c, hemoglobin A1c ; HD, hemodialysis ; HDL-C, high-density lipoprotein cholesterol ; HR, heart rate ; IHD, ischemic heart disease ; Intact-PTH, intact-parathyroid hormone ; iP, inorganic phosphorus ; LDL cholesterol, low-density lipoprotein cholesterol ; PAD, peripheral artery disease ; PKD, polycystic kidney disease ; SBP, systolic blood pressure ; TC, total cholesterol ; TG, triglycerides ; UA, uric acid ; UN, urea nitrogen.

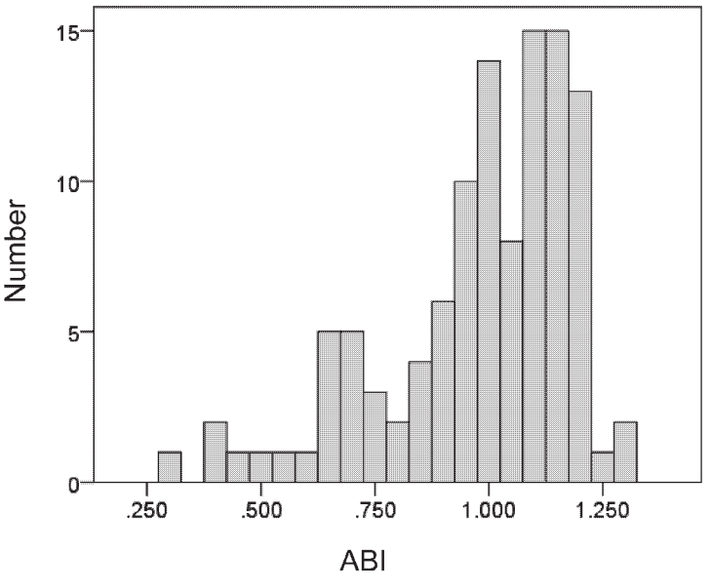

Fig. 2 Distribution of ABI among all patients

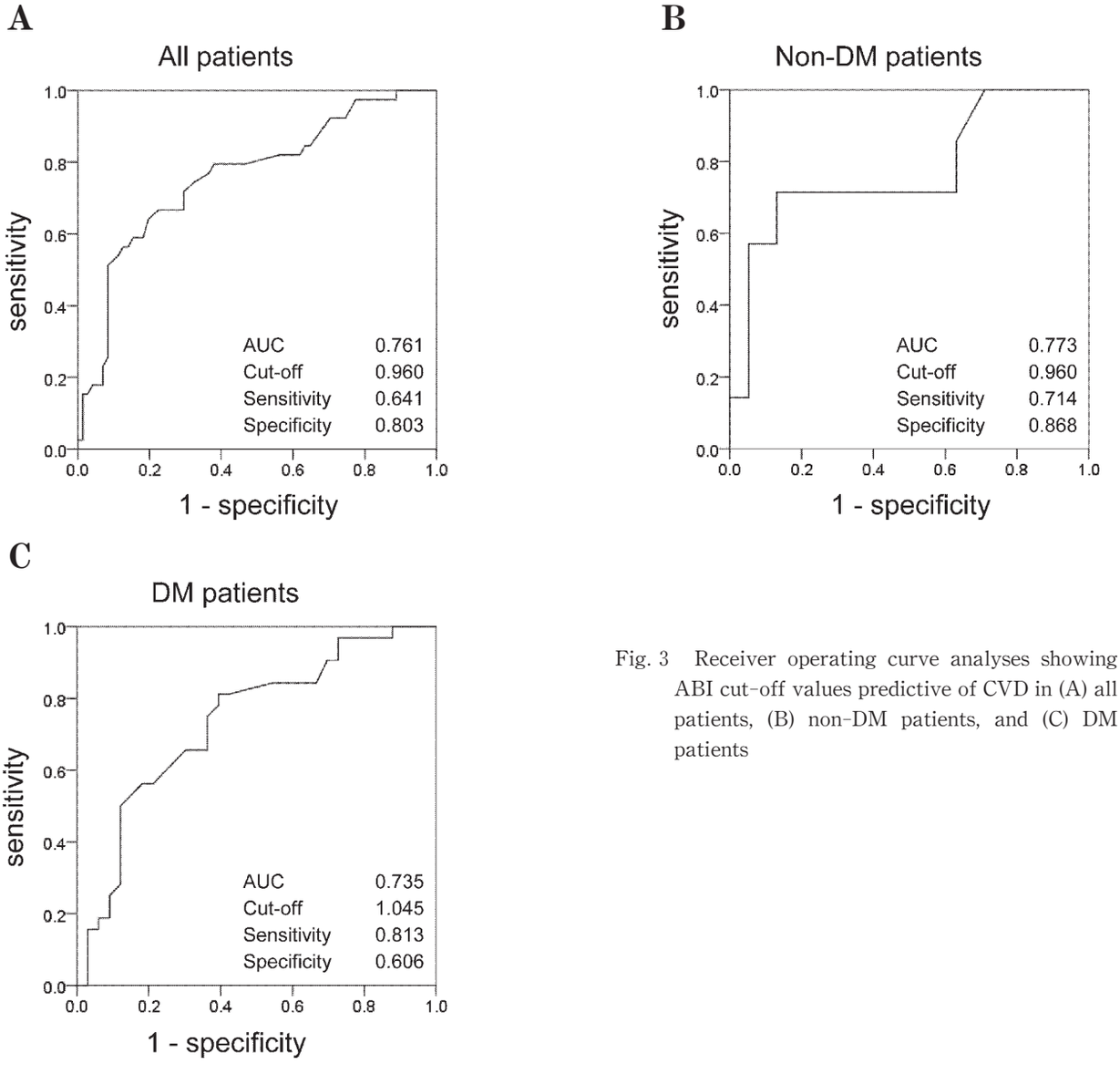

Fig. 3 Receiver operating curve analyses showing ABI cut-off values predictive of CVD in (A) all patients, (B) non-DM patients, and (C) DM patients

cut-off values. Furthermore, separate analysis according to the presence of DM improved the sensitivity over the whole patient analysis. Kaplan-Meier analysis showed that patients with ABIs lower than our cut-off values in each group were more likely to develop CVD (**Fig. 4A-C**).

Ⅳ Discussion

To our knowledge, this is the first report to show that ABI cut-off values predictive of CVD in HD patients are altered by DM. The ABI cut-off value predictive of PAD in HD patients has been reported to be 1.05[13], and ABI cut-off values should be set at higher levels in HD than in non-HD patients[8)10)14)]. Moreover, the presence of DM alters the ABI cut-off value diagnostic of PAD in non-HD patients, being 1.04 and 1.00 in patients with and without DM, respectively[15]. Setting the ABI cut-off value at 0.9 therefore reduced its sensitivity in diagnosing PAD in patients with DM[15]. Most reports indicating that ABI is predictive of CVD have set ABI cut-off values at <0.9[4)-8)]. However, the distribution of ABIs moved to higher levels in HD than in non-HD patients[10], suggesting that an ABI cut-off value $<$ 0.9 may be too low in HD patients. We found that setting the ABI cut-off value at <0.9 reduced its sensitivity and NPV for CVD in HD patients with and without DM. In evaluating the risk of CVD, it is important to use a highly sensitive marker with a high NPV. The ABI cut-off values proposed in HD patients with and without DM had a higher sensitivity and NPV than the conventional cut-off value of 0.9. Furthermore, using the separate ABI cut-off values according to the presence of DM improves the sensitivity of the predictive value for CVD. To screen the high-risk HD patients with CVD, these cut-off values are more useful than conventional ABI cut-off values below 0.9.

Dialysis patients often experience vascular calcification in arterial media due to chronic kidney disease-mineral and bone disorder[16]. The difficulties encountered in compressing calcified arteries lead to increases in blood pressure[8]. DM is also a major cause of vascular calcification, with advanced glycation end products triggering arterial calcification[17]. Therefore, the combination of DM and HD may result in severe vascular calcification, increasing ABI.

Low ABI has been shown to be a risk factor for IHD, PAD, and CI[4)-8)], making ABI a useful predictor of CVD. ABI is a ratio of blood pressure in the leg to that in the arm, with low ABI values indicating low leg blood pressure, in short, stenosis of a leg artery. The mechanism by which simple ABI can predict CVD is unclear. However, because the diameter of the leg artery is larger than that of a coronary or brain artery, stenosis of these arteries precedes stenosis of the leg artery, because atherosclerotic and vascular calcific lesions, which cause arterial stenosis, usually occur in systemic arteries. Low ABI has been reported to be closely related to calcification of main arteries, such as the aorta and iliac-femoral artery, suggesting that systemic arterial calcification occurs in patients with a low ABI value[18].

Among the many non-invasive methods reported to be useful in evaluating the risk of CVD are ABI, CAVI, pulse wave velocity, and AoACS[4)-8)11)12)]. However, we found that CAVI and AoACS were not predictive of CVD. Moreover, ABI has been reported to be a stronger predictor of systemic atherosclerotic morbidity and mortality than pulse wave velocity in HD patients[7]. Taken together, these findings suggest that ABI may be useful in evaluating the risk of CVD in HD patients.

The rate of CVD events in this study might be higher than in previous Japanese reports. Careful checking of all patients in this study to determine whether they had a CVD identified a high percentage (40 %) with an asymptomatic CVD. CVDs included IHD (AP and AMI), CI, and PAD. Of the 15 patients with an IHD, 14 had AP and one had an AMI. The rate of AP in previous reports cannot be clearly determined, both because of differences in the definition of AP or because the rate of asymptomatic AP was unclear. Several informative studies have suggested that 20 to 35.3 % of asymptomatic HD patients who underwent coro-

Table 3 Background data of patients with or without diabetes mellitus

	DM (−) (N=45)		DM (+) (N=65)		*P*-value
Age (years)	72	(30-90)	66	(39-92)	0.06
Sex (male)	25	55.6 %	52	80.0 %	0.010*
BMI >25 kg/m² (n, %)	3	6.7 %	16	24.6 %	0.020*
Duration of HD (months)	54	(1-225)	39	(1-198)	0.034*
SBP (mmHg)	140	(98-221)	149	(109-205)	0.10
DBP (mmHg)	74	(45-105)	75	(50-102)	0.89
HR	67	(47-107)	72	(32-101)	0.11
ABI	1.06	(0.30-1.29)	0.99	(0.40-1.28)	0.047
CAVI	9.1	(5.4-12.1)	9.1	(5.9-17.0)	0.71
AoACS	5	(0-16)	6	(0-15)	0.51
Past history (n, %)					
Smoking	9	20.0 %	44	67.8 %	<0.001***
Hypertension	44	97.8 %	64	98.5 %	1.00
Hyperlipidemia	8	17.8 %	19	29.2 %	0.19
Past history of CVD	6	13.3 %	23	35.3 %	0.015*
Laboratory data					
Hb (g/dl)	10.7	(6.9-13.3)	10.4	(5.5-13.4)	0.53
Alb (g/dl)	3.8	(2.5-4.3)	3.7	(2.3-4.3)	0.11
UN (mg/dl)	57.4	(32.4-97.1)	58.2	(26.9-105.8)	0.59
Cr (mg/dl)	10.4	(2.5-16.4)	10.1	(3.7-15.8)	0.69
UA (mg/dl)	7.1	(4.1-10.9)	6.9	(4.4-10.4)	0.85
TC (mg/dl)	147	(95-215)	145	(94-233)	0.96
HDL-C (mg/dl)	45	(17-86)	39	(23-70)	0.11
LDL-C (mg/dl)	88	(33-151)	79	(36-157)	0.17
TG (mg/dl)	91	(28-301)	102	(39-697)	0.07
Adjusted Ca (mg/dl)	9.1	(7.9-10.7)	8.9	(7.8-10.9)	0.46
iP (mg/dl)	5.2	(2.2-8.3)	5	(2.7-10.6)	0.92
Intact-PTH (pg/ml)	95	(12-396)	84	(8-497)	0.26
HbA1c (%)	-	-	5.7	(4-8.1)	-
Medications (n, %)					
ARB/ACEi	30	66.7 %	55	84.6 %	0.037*
Ca blocker	29	64.4 %	48	73.8 %	0.30
beta blocker	9	20.0 %	22	33.8 %	0.13
Diuretics	21	46.7 %	41	63.0 %	0.12
CPBs	24	53.3 %	36	55.4 %	0.85
Sevelamer	11	24.4 %	16	24.6 %	1.00
Lanthan	4	8.9 %	14	21.5 %	0.12
Vitamin D	29	64.4 %	42	64.6 %	1.00
Cinacalcet	5	11.1 %	4	6.2 %	0.48
Statin	4	8.9 %	15	23.1 %	0.07
anti-platelet agents	13	28.9 %	30	46.2 %	0.08
Events (n, %)					
All causes of death	6	13.3%	15	23.1%	0.23
All cases of CVD	7	15.6%	32	49.2%	<0.001
IHD	2	4.4%	13	20.0%	0.023
CI	2	4.4%	5	7.7%	0.70
PAD	3	6.7%	14	21.5%	0.06
Asymptomatic CVD	2	4.4 %	14	21.5 %	0.06
Asymptomatic IHD	0	0.0 %	6	9.2 %	0.08
Asymptomatic PAD	2	4.40 %	8	12.3 %	0.19

Table 4 The relationship between ABI cut-off value and sensitivity, specificity, positive predictive value, and negative predictive value

	Cut off value of ABI	sensitivity	specificity	PPV	NPV
All patients					
	0.9	0.538	0.887	0.724	0.778
	0.960	0.641	0.803	0.641	0.800
DM (−)					
	0.9	0.571	0.947	0.571	0.921
	0.960	0.714	0.868	0.500	0.943
DM (+)					
	0.9	0.531	0.848	0.773	0.651
	1.045	0.813	0.606	0.667	0.769

ABI, ankle brachial index ; DM, diabetes mellitus ; NPV, negative predictive value ; PPV, positive predictive value.

nary angiography had significant coronary arterial stenosis in more than one vessel, with high percentages of patients with stenosis in multiple coronary arteries undergoing percutaneous coronary intervention or coronary artery bypass graft surgery[19)20)]. Based on this description, the incidence of IHD in our patients would be not so high (13.6 %). The incidence of CI has been reported to be 2.53 per 100 person-years[21)]. Estimating the number of patients who experienced CI based on this incidence, the number of patients, 110, and the median follow-up period, 25 months, we estimated that 5.8 patients would experience a CI. In actuality, seven of our patients experienced a CI, a finding that did not differ significantly from the estimate. A previous study assessing PAD found that, of 72 legs with or without symptoms, 12 (16.7 %) had leg artery stenosis >75 % above the knee[10)]. In comparison, 15.5 % of our patients experienced PAD. However, the definitions of PAD have been found to differ widely. Thus, the higher CVD event rate in our study than in previous Japanese studies was likely due to our inclusion of patients with asymptomatic CVD, amounting to 40 % of all CVD patients, and the differences in definitions of CVD.

This study had several limitations, including its relatively small sample size, the absence of patients with extremely high ABI (>1.3), short follow-up period, and being a retrospective study. Patients with extremely high ABI have been reported to have a poorer prognosis and a higher incidence of CVD than patients with high ABI, suggesting the need to analyze patients with extremely high ABI undergoing HD[8)]. Second, fifty-seven (34 %) patients were excluded from this single center study, with most excluded patients being bedridden and frail.

Table 3 Data are presented as follows : continuous variables were expressed as median and range, categorical variables were expressed as n number and percentages. Significant differences are indicated with asterisks (***$p<0.001$, **$p<0.05$).
ABI, ankle brachial index ; Alb, albumin ; AoACS, aortic arch calcification score ; ARB/ACEi, angiotensin II type receptor blocker/angiotensin converting enzyme inhibitor ; BMI, body mass index ; Ca, calcium ; CAVI, cardio-ankle vascular index ; CI, cerebral infarction ; CPBs, calcium-containing phosphate binders ; Cr, creatinine ; CVD, cardiovascular diseases ; DBP, diastolic blood pressure ; Hb, hemoglobin ; HbA1c, hemoglobin A1c ; HD, hemodialysis ; HDL-C, high-density lipoprotein cholesterol ; HR, heart rate ; IHD, ischemic heart disease ; Intact-PTH, intact-parathyroid hormone ; iP, inorganic phosphorus ; LDL cholesterol, low-density lipoprotein cholesterol ; PAD, peripheral artery disease ; SBP, systolic blood pressure ; TC, total cholesterol ; TG, triglycerides ; UA, uric acid ; UN, urea nitrogen.

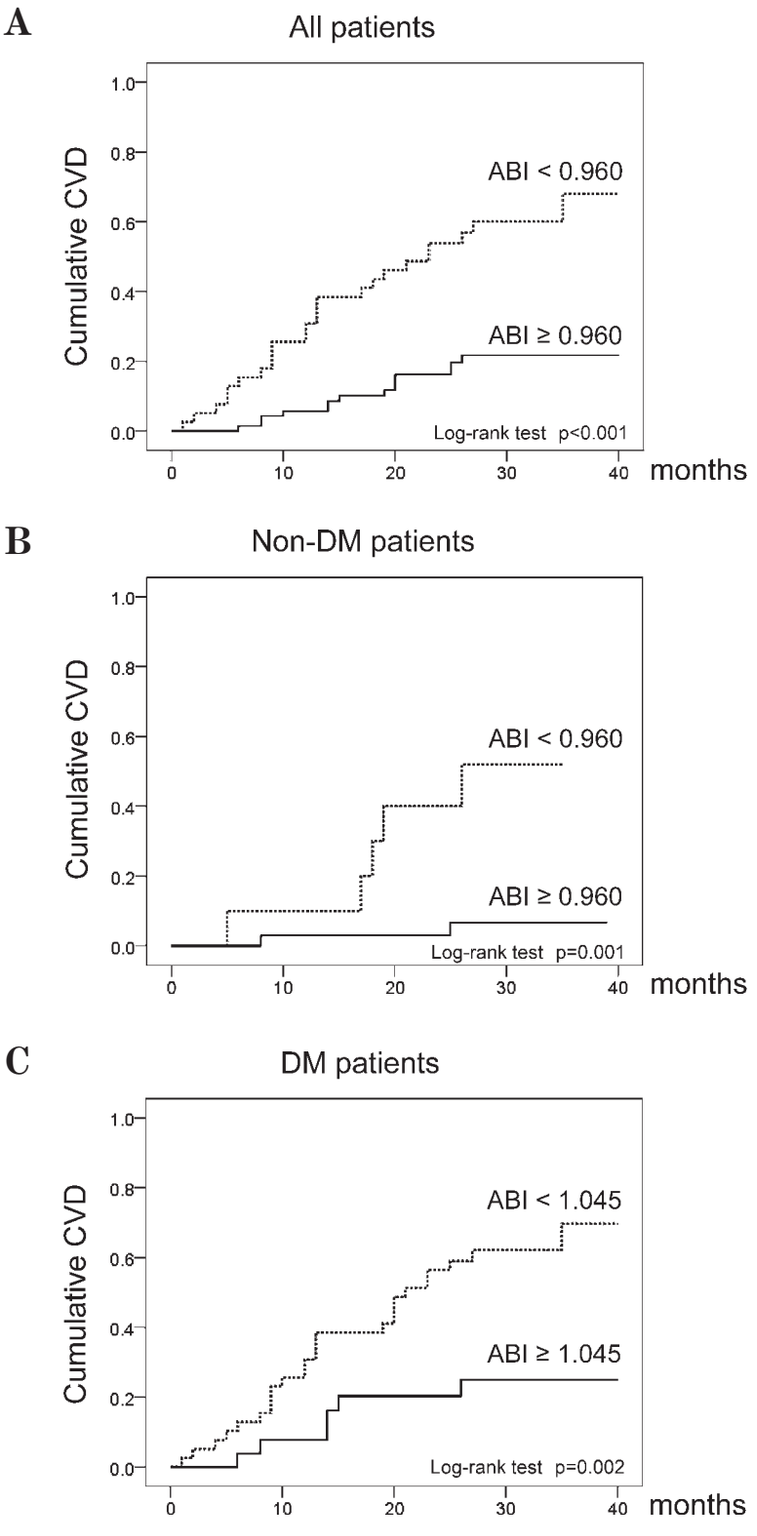

Fig. 4 Kaplan-Meier analysis of cumulative CVD

(A) Assessment of all patients, showing that those with ABI <0.960 had a higher incidence of CVD than those with ABI ≥0.960 (log-rank test, $p<0.001$).

(B) Analysis of non-DM patients, showing that those with ABI <0.960 had a higher incidence of CVD than those with ABI ≥0.960 (log-rank test, $p=0.001$).

(C) Analysis of DM patients showing that those with ABI <1.045 had a higher incidence of CVD than those with ABI ≥1.045 (log-rank test, $p=0.002$).

Third, the median follow-up period was short (25 months), so we need to analyze a longer duration. Fourth, the current study was a retrospective cohort design. Therefore, large multicenter prospective cohort studies are needed to properly clarify the association between ABI and CVD.

In conclusion, the current study suggests that the optimal ABI cut-off values for screening high-risk HD patients with CVD should be set at higher levels than the conventional cut-off value (0.9), and that the optimal cut-off values might differ in HD patients with and without DM, at 1.045 and 0.960, respectively.

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Disclosure

The authors have declared that no conflicts of interest exist.

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