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ORIGINAL ARTICLE

Ankle-brachial blood pressure index predicts cardiovascular events and mortality in Japanese patients with chronic kidney disease not on dialysis

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The ankle-brachial blood pressure index (ABPI) has been recognized to have a predictive value for cardiovascular (CV) events and mortality in general or dialysis populations. However, the associations between ABPI and those outcomes have not been fully investigated in predialysis patients. The present study aimed to clarify the relationships between ABPI and both CV events and mortality in Japanese chronic kidney disease (CKD) patients not on dialysis. In this prospective observational study, we enrolled 320 patients with CKD stages 3–5 who were not on dialysis. At baseline, ABPI was examined and a low ABPI was defined as <0.9. CV events and all-cause deaths were examined in each patient. A Cox proportional hazards model was applied to determine the risk factors for CV events, as well as for mortality from CV and all causes. The median follow-up period was 30 months. CV events occurred in 56 patients and all-cause deaths occurred in 48, including 20 CV deaths. Multivariate analysis showed that age and low ABPI were risk factors for CV events. It was demonstrated that age, a history of cerebrovascular disease and low ABPI were determined as independent risk factors for CV mortality. In addition, age, body mass index and low ABPI were independently associated with all-cause mortality. In patients with CKD, low ABPI during the predialysis period is independently associated with poor survival and CV events, suggesting the usefulness of measuring ABPI for predicting CV events and patient survival in CKD.
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INTRODUCTION

Patients with chronic kidney disease (CKD) have high cardiovascular (CV) morbidity and mortality.[1] Manifestations of CKD, such as hyperphosphatemia, hyperparathyroidism and chronic inflammation, are implicated in atherosclerosis in addition to traditional risk factors, such as smoking, diabetes, dyslipidemia and hypertension.[2] CKD patients had more advanced arterial wall stiffness compared with healthy subjects,[3] which is strongly associated with atherosclerosis.[4] Therefore, the presence of CKD worsens CV disease outcomes because of advanced atherosclerosis in CKD patients.

The ankle-brachial blood pressure index (ABPI) is a simple, noninvasive and reliable method of evaluating systemic atherosclerosis and peripheral artery disease.[5,6] It was demonstrated that low ABPI levels, particularly those <0.90, are indicative of generalized atherosclerosis.[7] An ABPI <0.9 is also associated with increased CV and all-cause mortality in non-CKD populations.[8–13] Several studies have also shown that a low ABPI monitored during a maintenance dialysis period is associated with the outcome of CV morbidity and mortality.[14–19] However, very few studies have documented the relationship between ABPI during the predialysis period and either CV events or mortality in predialysis patients.[20,21] Moreover, there have been very few studies investigating the relationship between low ABPI and CV events or mortality in Japanese CKD patients not on dialysis.[20] The present study aimed to determine whether ABPI during the predialysis period is associated with CV events and with both CV and all-cause mortality in Japanese CKD patients.

MATERIALS AND METHODS

In this prospective observational study, we enrolled 320 consecutive Japanese patients with CKD stages 3–5 not on dialysis, who were admitted to our hospital for evaluation of and education about CKD between January 2005 and September 2012. Patients with any malignancy or history of treatment for peripheral artery disease were excluded from this study. All patients provided written informed consent to the protocol, which was approved by the Ethics Committee of the National Kyushu Medical Center Hospital.

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Blood samples (serum creatinine (SCr), C-reactive protein, hemoglobin, serum albumin and serum phosphorus levels) were obtained in the early morning after an overnight fast. Daily proteinuria was also measured. The estimated glomerular filtration rate (eGFR; ml min^{-1} per 1.73 m^2) was calculated using the following new Japanese equation: $194 \times \mathrm{SCr}^{-1.094} \times \mathrm{age}^{-0.287} \times 0.739$ (if female).[22]

All enrolled patients were interviewed and clinically examined at presentation. Their medical histories and outpatient records were also evaluated in detail. Demographic information (age and sex), medication history and atherosclerotic risk factors (hypertension, history of smoking, dyslipidemia and diabetes mellitus) at presentation were recorded for each patient. Hypertension was defined as systolic blood pressure $\geqslant$140 mm Hg or diastolic blood pressure $\geqslant$90 mm Hg, or the current use of antihypertensive drugs. Dyslipidemia was defined as plasma triglycerides $\geqslant$150 mg dl^{-1}, plasma low-density lipoprotein cholesterol $\geqslant$140 mg dl^{-1}, plasma high-density lipoprotein cholesterol $<$40 mg dl^{-1} or the use of lipid-lowering drugs based on a history of dyslipidemia. Diabetes mellitus was defined as previous or current plasma fasting glucose $\geqslant$126 mg dl^{-1} or the use of hypoglycemic agents. Present or past cigarette smoking was distinguished. Body mass index was calculated as weight in kg divided by height in m^2. Blood pressure was measured at three separate times in a sitting position on the second day of hospitalization; the average of the three readings was recorded. Pulse pressures were calculated as the difference between systolic and diastolic blood pressures.

Table 1 Baseline characteristics of study participants grouped by ABPI

	All (n = 320)	*ABPI $<$0.9 (n = 42)*	*ABPI $\geqslant$0.9 (n = 278)*	P-*value*
Age (years)	72 (62–78)	77 (70–82)	71 (61–77)	$<$0.01
Male	218 (68)	32 (76)	186 (67)	0.22
Smoking	174 (54)	29 (69)	145 (52)	0.04
Hypertension	300 (94)	40 (95)	260 (94)	0.66
SBP (mm Hg)	137 ± 18	146 ± 20	136 ± 18	$<$0.01
DBP (mm Hg)	72 ± 11	68 ± 10	73 ± 11	0.01
Pulse pressure (mm Hg)	65 ± 15	78 ± 16	63 ± 14	$<$0.01
Diabetes mellitus	162 (51)	30 (71)	132 (47)	$<$0.01
Dyslipidemia	232 (73)	33 (79)	199 (72)	0.33
History of IHD	60 (19)	15 (36)	45 (16)	$<$0.01
History of CVD	60 (19)	15 (36)	45 (16)	$<$0.01
Body mass index (kg m^{-2})	22 (20.2–24.9)	21.3 (19.4–22.7)	22.1 (20.4–25.3)	$<$0.01
Serum albumin (g dl^{-1})	3.5 (3.0–3.8)	3.3 (3.0–3.8)	3.5 (3.0–3.8)	0.49
C-reactive protein (mg dl^{-1})	0.09 (0.04–0.21)	0.11 (0.04–0.23)	0.09 (0.04–0.21)	0.75
Hemoglobin (g dl^{-1})	10.3 (8.7–11.7)	9.8 (8.6–11.3)	10.4 (8.8–11.7)	0.51
Serum phosphorus (mg dl^{-1})	3.8 (3.3–4.3)	3.7 (3.2–4.3)	3.8 (3.3–4.3)	0.73
Proteinuria (g per day)	1.5 (0.4–3.5)	1.4 (0.4–3.2)	1.5 (0.4–3.6)	0.95
eGFR (ml min^{-1} per 1.73 m^2)	18.4 (12.6–32.2)	21.3 (12.0–28.9)	18.1 (12.7–32.4)	0.85
ABPI	1.09 (0.98–1.16)	0.75 (0.66–0.82)	1.11 (1.04–1.17)	$<$0.01
Follow-up period (months)	30 (19–46)	27 (13–38)	30 (19–46)	0.12

Abbreviations: ABPI, ankle-brachial blood pressure index; CVD, cerebrovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; SBP, systolic blood pressure.
Values are expressed as the mean plus/minus s.d., number (percent) or median (interquartile range).

Table 2 Logistic regression analysis of determinant factors for low ABPI

	Univariate		*Multivariate*	
Variables	*OR (95% CI)*	P-*value*	*OR (95% CI)*	P-*value*
Age (years)	1.07 (1.03–1.11)	$<$0.01	1.06 (1.02–1.12)	$<$0.01
Male *vs.* female	1.58 (0.77–3.52)	0.22		
Smoking	2.05 (1.04–4.22)	0.04	2.09 (0.95–4.83)	0.07
Pulse pressure (mm Hg)	1.06 (1.04–1.08)	$<$0.01	1.05 (1.03–1.08)	$<$0.01
Diabetes mellitus	2.77 (1.39–5.82)	$<$0.01	1.65 (0.70–3.99)	0.25
Dyslipidemia	1.46 (0.69–3.36)	0.33		
History of IHD	2.88 (1.39–5.78)	$<$0.01	2.10 (0.92–4.74)	0.08
History of CVD	2.88 (1.39–5.78)	$<$0.01	2.54 (1.11–5.74)	0.03
Body mass index (kg m^{-2})	0.87 (0.79–0.96)	$<$0.01	0.17 (0.01–3.21)	0.24
Serum albumin (g dl^{-1})	0.84 (0.52–1.39)	0.49		
C-reactive protein (mg dl^{-1})	1.09 (0.57–1.75)	0.76		
Hemoglobin (g dl^{-1})	0.95 (0.80–1.11)	0.50		
Serum phosphorus (mg dl^{-1})	0.93 (0.61–1.37)	0.73		
Proteinuria (g per day)	1.00 (0.87–1.15)	0.95		
eGFR (ml min^{-1} per 1.73 m^2)	1.00 (0.98–1.03)	0.85		

Abbreviations: CI, confidence interval; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; OR, odds ratio.

Table 3 Cox hazards analysis for CV events and mortality from both CV and all causes

	CV events				*CV mortality*				*All-cause mortality*			
	Univariate		*Multivariate*		*Univariate*		*Multivariate*		*Univariate*		*Multivariate*	
Variable	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Age (years)	1.05 (1.02–1.08)	<0.01	1.03 (1.00–1.07)	0.02	1.08 (1.03–1.15)	<0.01	1.07 (1.01–1.13)	0.01	1.12 (1.08–1.16)	<0.01	1.10 (1.05–1.14)	<0.01
Male	1.64 (0.91–3.17)	0.10			2.82 (0.95–12.09)	0.06			1.48 (0.79–2.98)	0.22		
Smoking	1.26 (0.74–2.19)	0.40			1.02 (0.42–2.54)	0.96			0.81 (0.46–1.43)	0.47		
Pulse pressure (mm Hg)	1.02 (1.01–1.04)	<0.01	1.01 (0.99–1.03)	0.52	1.01 (0.99–1.04)	0.33			1.03 (1.01–1.04)	<0.01	1.00 (0.98–1.02)	0.84
Diabetes mellitus	1.68 (0.99–2.94)	0.06			1.80 (0.74–4.80)	0.20			1.22 (0.69–2.18)	0.50		
Dyslipidemia	1.28 (0.71–2.48)	0.42			0.69 (0.28–1.85)	0.45			0.87 (0.48–1.69)	0.68		
History of IHD	2.76 (1.50–4.88)	<0.01	1.82 (0.95–3.34)	0.07	2.44 (0.86–6.14)	0.09			2.60 (1.37–4.72)	<0.01	1.43 (0.73–2.72)	0.29
History of CVD	2.04 (1.09–3.63)	0.03	1.23 (0.63–2.33)	0.53	5.92 (2.45–14.70)	<0.01	4.32 (1.77–10.87)	<0.01	2.01 (1.05–3.69)	0.04	1.32 (0.66–2.55)	0.42
Body mass index (kg m^{-2})	0.93 (0.86–0.99)	0.03	0.98 (0.90–1.06)	0.64	0.90 (0.79–1.01)	0.08			0.85 (0.77–0.92)	<0.01	0.89 (0.79–0.99)	0.03
Serum albumin (g dl^{-1})	0.75 (0.52–1.10)	0.14			0.76 (0.41–1.44)	0.39			0.63 (0.43–0.94)	0.03	0.69 (0.40–1.20)	0.18
C-reactive protein (mg dl^{-1})	1.15 (0.79–1.49)	0.41			1.18 (0.57–1.76)	0.58			1.23 (0.85–1.58)	0.23		
Hemoglobin (g dl^{-1})	0.86 (0.75–0.98)	0.02	0.96 (0.81–1.13)	0.60	0.82 (0.65–1.02)	0.07			0.79 (0.68–0.91)	<0.01	0.92 (0.77–1.10)	0.39
Serum phosphorus (mg dl^{-1})	1.19 (0.88–1.59)	0.24			1.15 (0.70–1.82)	0.56			1.00 (0.71–1.37)	1.00		
Proteinuria (g per day)	1.06 (0.95–1.17)	0.29			0.89 (0.70–1.08)	0.25			0.91 (0.79–1.03)	0.15		
eGFR (ml min^{-1} per 1.73 m^2)	0.98 (0.96–1.00)	0.03	0.98 (0.96–1.01)	0.16	0.98 (0.94–1.01)	0.26			0.98 (0.96–1.00)	0.12		
ABPI <0.9	3.71 (2.04–6.46)	<0.01	2.47 (1.24–4.81)	0.01	5.40 (2.11–13.11)	<0.01	3.15 (1.21–7.84)	0.02	4.34 (2.34–7.77)	<0.01	2.16 (1.06–4.30)	0.03

Abbreviations: ABPI, ankle-brachial blood pressure index; CI, confidence interval; CV, cardiovascular; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IHD, ischemic heart disease.

For the measurement of ABPI, bilateral arm systolic blood pressure and bilateral ankle systolic blood pressure (posterior tibial artery) were taken with the subject in a supine position, and the measurement for each leg and ipsilateral arm was used to calculate ABPI. Patients who had ABPI <0.9 in either leg were categorized as having low ABPI.[23]

CV events were defined as follows: procedures of percutaneous coronary intervention or coronary artery bypass grafting for ischemic heart disease, congestive heart failure or cerebrovascular disease (such as brain infarction and hemorrhage); procedures of carotid endarterectomy for internal carotid artery stenosis; and procedures of percutaneous transcatheter angioplasty, lower-limb amputation or bypass surgery for peripheral artery disease; dissecting aneurysm of the thoracic and/or abdominal aorta, rupture of thoracic and/or abdominal aortic aneurysm, pulmonary embolism or sudden death.

Statistical analysis

Continuous data are expressed as either the mean ± s.d. or the median (interquartile range), depending on their distribution. Categorical data are expressed as numbers (with %). The significance of differences between ABPI <0.9 and ⩾0.9 was examined using the χ^2 test for categorical data, the Wilcoxon's rank-sum test for nonparametric data and the unpaired Student's *t*-test for parametric data. A logistic regression analysis was performed to elucidate the associations between low ABPI and traditional and nontraditional CV risk factors. Covariates associated with low ABPI in univariate analysis were analyzed by multivariate analysis to determine the independent risk factors for low ABPI. A Cox proportional hazards model was also applied to elucidate the traditional and nontraditional CV risk factors associated with CV events and both mortality and all-cause mortality. Covariates associated with these outcomes that were significant in univariate analysis were selected as risk factors in multivariate analysis. The odds and hazard ratios and the 95% confidence interval were calculated for each variable. Survival curves were estimated by the Kaplan–Meier method and evaluated by the log-rank test. Data were analyzed using the JMP10 statistics package (SAS Institute, Cary, NC, USA). A *P*-value below 0.05 indicated a significant difference.

RESULTS

The median age of the 320 patients (218 men and 102 women) in this study was 72 years (range, 30–92 years). The primary causes of renal disease were diabetic nephropathy (35%, 113 patients), hypertensive nephrosclerosis (33%, 104 patients), chronic glomerulonephritis (21%, 67 patients), other defined causes (8%, 27 patients) and unknown (3%, 9 patients). The median follow-up period was 30 months (range, 2–104 months). At the end of follow-up, 48 all-cause deaths were recorded. The causes of death were as follows: CV deaths in 20 patients, infection in 13, malignancy in 5, other defined causes in 8 and unknown in 2. In addition, CV events occurred in 56 patients.

The clinical characteristics of the patients with and without low ABPI are summarized in Table 1. Low ABPI was found in 42 patients (13%). The median age of patients with low ABPI was significantly higher than that of patients without low ABPI. The prevalences of smoking, diabetes mellitus and a history of ischemic heart disease or cerebrovascular disease were significantly higher in patients with low ABPI. Systolic, diastolic and pulse pressures were also significantly higher in patients with low ABPI, whereas body mass index was significantly lower. There were no significant differences in the values of serum albumin, C-reactive protein, hemoglobin, serum phosphorus, proteinuria and eGFR between the two groups.

Table 2 shows the results of logistic regression analysis of determinant factors for low ABPI. Univariate analysis demonstrated that age, smoking, pulse pressure, diabetes mellitus, history of ischemic heart disease and of cerebrovascular disease, and body mass index were significantly associated with low ABPI. Multivariate

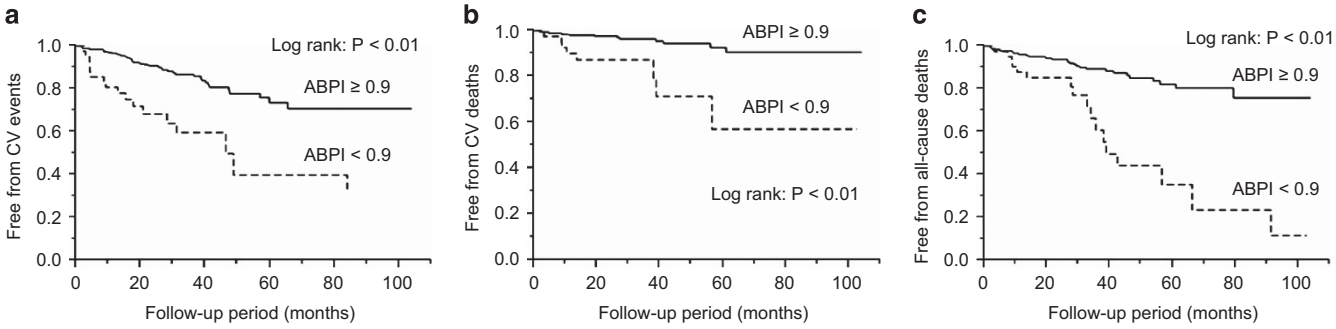

Figure 1 The associations between ankle-brachial blood pressure index (ABPI) and cardiovascular (CV) events, as well as with mortality from CV and all causes. Kaplan–Meier curves with log-rank tests of freedom from CV events (**a**) and deaths (**b**), and all-cause deaths (**c**) according to groups with ABPI <0.9 and $\geqslant 0.9$.

analysis showed that age, pulse pressure and history of cerebrovascular disease remained as independent determinant factors for low ABPI.

We analyzed the risk factors for CV events and both mortality and all-cause mortality using a Cox hazards analysis, as shown in Table 3. In multivariate analysis, age and low ABPI were independently associated with CV events. Age, a history of cerebrovascular disease and low ABPI were identified as independent risk factors for CV mortality. In addition, age, body mass index and low ABPI were independently associated with all-cause mortality. Figure 1 shows Kaplan–Meier curves of freedom from CV events (Figure 1a) and mortality (Figure 1b), as well as all-cause mortality (Figure 1c) in subjects with ABPI <0.9 and $\geqslant 0.9$. Patients with low ABPI experienced more CV events as well as both CV deaths and all-cause deaths.

DISCUSSION

Previous studies demonstrated the relationships between low ABPI and both CV events and mortality in predialysis patients. One report addressed the association of low ABPI with CV and all-cause mortality, but not with CV events.[21] In another report, clinical end points were defined as composite events of all-cause deaths or CV events.[20] On the other hand, the present study investigated separately the effects of low ABPI on CV events as well as on CV and all-cause mortality; it was demonstrated that low ABPI is independently associated with all these clinical end points. Additionally, although there have been limited data regarding the risk factors for having low ABPI in CKD patients,[24] our study simultaneously investigated those factors using a multivariate analysis to further explore the relationship between low ABPI and outcomes. In addition, given that very few studies regarding the association of low ABPI with outcomes have been conducted in Japanese predialysis patients,[20] the results of the present study may contribute to the clarification of the relationship between low ABPI and outcomes in this population.

In previous studies, old age, diabetes mellitus, a history of ischemic heart disease or cerebrovascular disease, increased pulse pressure, low serum albumin and low eGFR levels were identified as risk factors for atherosclerosis in patients with CKD.[25–27] In the present study, multivariate logistic regression analysis showed that pulse pressure, old age and a history of cerebrovascular disease were independent determinant factors for low ABPI. A previous study demonstrated that pulse pressure was a determinant factor for low ABPI in non-CKD patients.[28,29] On the other hand, patients with CKD exhibit vascular abnormalities, including arterial stiffness and early wave reflection, that contribute to elevated pulse pressure.[30,31] Pulse pressure was also positively and significantly associated with low ABPI in CKD patients.[32] In addition, higher levels of pulse pressure have been associated with carotid stenosis,[33] left ventricular hypertrophy,[34] myocardial infarction,[35] CV death[36] and congestive heart failure[37] in both normotensive and hypertensive populations. However, in the present study multivariate analysis showed that low ABPI, but not pulse pressure, was an independent risk factor for CV events and mortality. Taken together, these previous and present findings suggested that ABPI, rather than pulse pressure, was a useful method to predict CV events and mortality in CKD patients.

The present study also showed that low ABPI was an independent risk factor for all-cause mortality. No report thus far has explained clearly the association between low ABPI and all-cause mortality. Results of the National Health and Nutrition Examination Survey demonstrated that there are high prevalences of both traditional and nontraditional CV risk factors among persons with peripheral artery disease.[38] In addition, the Atherosclerosis Risk In Communities (ARIC) study reported that more patients with peripheral artery disease had hypertension, diabetes and a smoking habit.[39] In the present study, patients with low ABPI also had significantly higher prevalences of hypertension, diabetes, smoking, high pulse pressure and a history of ischemic heart and cerebrovascular disease compared with patients having normal ABPI. Previous studies demonstrated that hypertension,[40] diabetes[41] and smoking[42] are independent risk factors for all-cause mortality in general populations. Other studies also showed that pulse pressure was an independent risk factor for all-cause mortality in patients with CKD stages 4 and 5,[43] peritoneal dialysis[44] and hemodialysis.[45] All these clinical features might explain why patients with low ABPI had a higher mortality rate from CKD. However, risk factors such as pulse pressure and a history of cerebrovascular disease independently related to low ABPI were not associated with all-cause mortality in multivariate analysis. Therefore, the precise reason for the association between low ABPI and all-cause mortality has remained uncertain.

The present study has some limitations. First, the study subjects were in only one regional hospital; thus, the selection of patients was limited and the sample size was relatively small. Second, our study had an imbalanced gender ratio. Our study recruited the consecutive patients who were admitted to our hospital, and the number of male patients was two times the number of female patients. In general, male-predominant study groups tend to have a high risk of CV outcomes[46,47] and all-cause mortality. In patients on dialysis, previous studies with male predominance ($>60\%$) have addressed the association between male gender and mortality; one report showed a significant association between male gender and all-cause mortality

in a multivariate analysis,[15] but another study did not observe such a relationship.[16] In our present study, the univariate analysis showed that male gender was not associated with CV outcomes or all-cause mortality. Third, it has been reported that abnormally high ABPI ($\geqslant 1.3$) predicts both CV mortality and all-cause mortality in CKD and hemodialysis patients.[18,19] However, we could not find an association between an abnormally high ABPI and CV events or death from CV or all causes, because only 18 patients had ABPI $\geqslant 1.3$ in the present study. A larger cohort study will be needed to avoid study bias and to document more precisely the association between low ABPI and CV events, as well as mortality from CV and all causes.

In conclusion, the present study demonstrated that low ABPI was independently associated with CV events as well as with mortality from CV and all causes. This finding suggests that ABPI measurement could have a predictive value for CV disease outcome and patient survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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