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Prognostic value of pre-dialysis blood pressure and risk threshold on clinical outcomes in hemodialysis patients

The Q-Cohort Study

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Abstract

The influence of pre-dialysis blood pressure (BP) on the prognosis of hemodialysis (HD) patients is still inconclusive.

A total of 3436 HD patients were prospectively followed up for 4 years. The patients were divided into quintiles of pre-dialysis systolic BP (SBP) and diastolic BP (DBP) levels [mm Hg]: Quintile 1 (Q1), SBP <134, DBP <66; Q2, SBP 134 to 147, DBP 66 to 72; Q3, SBP 148 to 158, DBP 73 to 79; Q4, SBP 159 to 171, DBP 80 to 85; Q5, SBP ≥172, DBP ≥86. The association between the pre-dialysis BP and outcomes were examined using a Cox proportional hazards model.

During a 4-year follow-up period, 564 (16.4%) patients died of any cause and 590 (17.2%) developed cardiovascular (CV) events. The lowest level of pre-dialysis SBP group (Q1) showed a significantly increased risk of all-cause mortality (hazard ratio [HR] 1.83, 95% confidence interval [CI] 1.40–2.39) and the highest group (Q5) significantly increased risk of CV events (HR 1.31, 95% CI 1.02–1.68) compared with the reference group (Q3), respectively. The highest level of pre-dialysis DBP group was significantly associated with increased risk for both all-cause mortality and CV events. Restricted cubic spline analysis for BP and outcomes suggested the optimal pre-dialysis BP value associated with the lowest risk of outcomes was SBP 152 mm Hg for all-cause mortality, SBP 143 mm Hg for CV events, and DBP 68 mm Hg for all-cause mortality.

Our results suggested that pre-dialysis BP was independently associated with all-cause mortality and CV events among Japanese HD patients.

Abbreviations: BP = blood pressure, CI = confidence interval, CKD = chronic kidney disease, CTR = cardiothoracic ratio, CV = cardiovascular, DBP = diastolic blood pressure, HD = hemodialysis, HR = hazard ratio, Q = quintile, SBP = systolic blood pressure.

Keywords: all-cause mortality, cardiovascular events, chronic hemodialysis, optimal blood pressure, prospective cohort

1. Introduction

Hypertension is a well-established modifiable risk factor for cardiovascular (CV) events and mortality in the general population and patients with chronic kidney disease (CKD).[1,2] Similarly, several observational studies for hemodialysis (HD) patients have suggested the significant relationships between blood pressure (BP) parameters (systolic blood pressure [SBP], and diastolic blood pressure [DBP]) and hard endpoints (e.g., CV events, and death).[3–7] Some studies have reported a U-shaped or J-shaped association between BP and all-cause mortality.[5,8,9] These findings suggest that higher BP as well as lower BP correlates with poor prognosis in HD patients, hence making it difficult to treat hypertension in HD patients.

The CV events are the leading cause of death in HD patients, accounting for 40% to 50% of all-cause death. The results of clinical trials have provided some evidence that lowering BP would reduce CV events in the general population and in mild CKD patients,[2] but it remains unclear whether or not such CV risk reduction due to lowering BP can be seen in HD patients.

The Kidney Disease Outcomes Quality Initiative (K-DOQI) clinical practice guideline recommended a pre-dialysis BP goal of below 140/90 mm Hg, the rationale for this recommendation is largely based in part on data in the non-dialysis population.[10] Therefore, the ideal BP target to improve prognosis for HD patients has been a matter of debate.

In the present study, we performed an examination to clarify the association between pre-dialysis BP and mortality and morbidity in HD patients. In addition, we explored the optimal BP at which the outcomes risk was at its lowest.

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2. Methods

2.1. Study design and population

The Q-Cohort Study is a multicenter, prospective, longitudinal observational cohort with 3598 outpatients ages 18 years or older who were undergoing hemodialysis in 39 dialysis facilities in Saga and Fukuoka Prefectures in Kyushu Island, Japan. The details of the study have been described previously.[11–14] Patients were enrolled from December 2006 to December 2007. Patients without demographic data (n = 65) and patients for whom clinical outcome was not available (n = 97) were excluded. The remaining 3436 patients were enrolled in this study. The study was conducted with approval from the Kyushu University Institutional Review Board for Clinical Research (Approval number 20–31). We obtained written informed consent from all patients. The study was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN000000556) and was performed according to the Ethics of Clinical Research (Declaration of Helsinki) requirements.

2.2. Follow-up survey

The patients were prospectively followed up from the study registration date to 31 December 2010. Their health condition was checked annually by local physicians at each dialysis facility and follow up of patients who moved to a facility without cooperative researchers were continued by mail or telephone.

2.3. Exposures

The main exposure was pre-dialysis BP levels at baseline. The BP was measured under supine position after a period of rest of at least 5-min duration before the start of dialysis at each facility according to the Japanese guideline.[15]

2.4. Potential confounders

The demographic data (e.g., age, sex, time on dialysis therapy) and clinical data (e.g., hemoglobin, serum albumin, serum calcium, serum phosphate, serum total cholesterol, serum C-reactive protein [CRP], serum ferritin, cardiothoracic ration [CTR], body mass index [BMI], normalized protein catabolic rate [nPCR], and Kt/V) were gathered from the patients' medical records at baseline. Blood samples were collected from a vascular access before dialysis at the beginning of the week. The corrected serum Ca value was obtained from serum Ca value and serum Alb value using Pyne's formula; corrected Ca (mg/dL) = observed total Ca (mg/dL) + (4.0 − serum albumin concentration [g/dL]). The BMI (kg/m^2) was calculated from body height and weight measured in light clothing without shoes. The CTR was calculated as reported previously.[14] Briefly, CTR is measured on a posterior-anterior view chest X-ray before dialysis at each dialysis facility, and the calculated ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter is then expressed as a percentage. Dialysis dose and nutritional status were assessed by single-pool Kt/V and nPCR, respectively, using the Daugirdas method.[16] The physicians at each dialysis facility checked the current use of antihypertensive drugs and history of diabetes or CV events. Patients were categorized as having a history of CV events if they had a history of cerebrovascular disease, coronary artery disease, congestive heart failure, and peripheral vascular disease.

2.5. Outcome assessment

The primary outcome was all-cause death and the secondary outcome was major CV events, which was defined as a 1st-ever development of cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina, coronary intervention (coronary artery bypass surgery or angioplasty), hospitalization for heart failure, and/or peripheral vascular disease. Each disease was defined as previously published.[11–14] Concisely, stroke was defined as a sudden-onset neurological impairment lasting for ≥24 hours. Stroke types were confirmed by brain imaging, including computed tomography (CT) and magnetic resonance imaging (CT), and were classified as either brain hemorrhage or infarction by the attending physician. Myocardial infarction was defined as a diagnosis based on prolonged severe chest pain, elevated levels of abnormal cardiac biomarker levels, electrocardiographic changes, and morphologic changes (including local asynergy of cardiac wall motion on electrocardiography or a persistent perfusion defect on cardiac scintigraphy). Unstable angina was defined as a medical condition involving chest pain, abnormally elevated levels of cardiac biomarkers, and diagnostic electrocardiographic changes that did not meet criteria for myocardial infarction. Heart failure was defined as an unplanned presentation to an acute-care setting with signs and symptoms that required active treatment for fluid removal. Peripheral artery disease was defined as tissue necrosis, lower-limb amputation, and revascularization procedure for the peripheral artery. All outcomes were collected from the patients' medical records.

2.6. Statistical analysis

Because the optimal blood pressure for patients undergoing dialysis has not yet been determined, participants were allocated to 5 groups according to quintiles of pre-dialysis BP with the aim of determining optimal blood pressure: Quintile 1 (Q1), SBP <134 mm Hg; Q2, SBP 134 to 147 mm Hg; Q3, SBP 148 to 158 mm Hg; Q4, SBP 159 to 171 mm Hg; Q5, SBP≥172 mm Hg, and Q1, DBP <66 mm Hg; Q2, DBP 66 to 72 mm Hg; Q3, DBP 73 to 79 mm Hg; Q4, DBP 80 to 85 mm Hg; Q5, DBP ≥86 mm Hg. Data are presented as mean ± standard deviation, median and interquartile range, or percentage for categorical variables, as appropriate. To evaluate trends in continuous and categorical values across the quintiles of pre-dialysis BP, we used the Jonckheere–Terpstra and Cochran–Armitage tests, respectively. Unadjusted, age- and sex-adjusted, and multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of all-cause mortality and CV events according to pre-dialysis BP were estimated using a Cox proportional hazards model. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of CV events, CTR, BMI, single pool Kt/V, hemoglobin level, serum levels of albumin, phosphate, total cholesterol, CRP, and taking antihypertensive drugs. These variables were based on a priori clinical judgment and the existing investigations. The heterogeneity in the association between subgroups was tested by adding a multiplicative interaction term in the relevant Cox model.

We analyzed the relationship between BP and nonlinearity by modeling BP as a continuous variable (rather than BP categorical values) using a restricted cubic spline with 3 knots. This method allows estimation of HRs compared with any single reference value.[17] This model uses a penalty smoothing spline in the Cox proportional hazards model to find a significant nonlinear effect of this prognostic factor. The hazard ratio curve plot is based on reference value. The reference value can be automatically defined

Table 1

Baseline characteristics of the study subjects.

Variable	Entire cohort (n = 3436)
Age, (years)	63.7 (12.8)
Male (%)	59.2
Diabetes (%)	28.9
Dialysis vintage (years)	5.5 (2.1–11.5)
Dialysis time (hours)	5.0 (4.0–5.0)
Pre-dialysis systolic blood pressure (mm Hg)	153.0 (23.4)
Pre-dialysis diastolic blood pressure (mm Hg)	76.4 (12.6)
History of cardiovascular events (%)	33.7
Body mass index (kg/m^2)	21.1 (3.1)
Cardiothoracic ratio (%)	50.5 (5.5)
Hemoglobin (g/dL)	10.5 (1.2)
Serum albumin (g/dL)	3.8 (0.4)
Serum corrected calcium (mg/dL)	9.4 (0.8)
Serum phosphate (mg/dL)	4.9 (1.2)
Serum C-reactive protein (mg/dL)	0.13 (0.06–0.30)
Serum total cholesterol (mg/dL)	155.8 (36.6)
Kt/V (single pool)	1.58 (0.28)
nPCR (g/kg/day)	0.96 (0.19)
Use of antihypertensive drugs (%)	62.6
Use of renin-angiotensin system inhibitors (%)	43.3
Use of erythropoiesis-stimulating agents (%)	84.0

Values are given as the mean (standard deviation) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables. nPCR = normalized protein catabolic ratio.

as the minimum (prob = 0) value of the HR curve. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of CV events, CTR, BMI, single pool Kt/V, hemoglobin level, serum levels of albumin, phosphate, total cholesterol, CRP, and taking antihypertensive drugs.

All analyses were conducted using JMP, version 11 for Windows (SAS Institute Inc., Cary, NC), and R statistical software, version 3.3.0 (R Foundation for Statistical Computing). A 2-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Our study population comprised 3436 patients. Their baseline clinical characteristics are shown in Table 1. The mean age was 63.7 years, the median dialysis vintage was 5.5 years, 59.2% were male, and 28.9% had diabetes. Mean pre-dialysis SBP was 153.0 mm Hg, and mean pre-dialysis DBP was 76.4 mm Hg, mean BMI was 21.1 kg/m^2, and up to 62.6% of patients were treated with antihypertensive drugs. Table 2 shows the clinical characteristics according to pre-dialysis SBP categories. In the highest pre-dialysis SBP category (Q5), there was a significantly higher mean age, higher proportion with diabetes mellitus, male sex, and history of cardiovascular events, shorter median dialysis vintage, higher BMI, larger CTR, and lower Kt/V than in the lowest category (Q1). Mean serum concentrations of Alb was higher and of CRP lower. Table 3 shows the clinical characteristics according to pre-dialysis DBP categories. In the highest pre-dialysis DBP category (Q5), there was a significantly lower mean age, higher proportion of male sex, lower proportion with history of cardiovascular events, shorter median dialysis vintage, higher BMI, and lower Kt/V than those in the lowest category (Q1). Mean hemoglobin concentration and mean serum concentrations of Alb and phosphorus were higher and mean serum concentration of CRP lower. In the highest pre-dialysis SBP and DBP categories (Q5), the proportion of patients using antihypertensive drugs (renin–angiotensin system blockade) was significantly higher than in the lowest category (Q1).

Table 2

Baseline characteristics according to pre-dialysis systolic blood pressure.

	Pre-dialysis systolic blood pressure					
Variables	Quintile 1 (SBP < 134) n = 658	Quintile 2 (134≤ SBP < 148) n = 702	Quintile 3 (148≤ SBP < 159) n = 678	Quintile 4 (159≤ SBP < 172) n = 688	Quintile 5 (172≤ SBP) n = 710	*P* for trend
Age (years)	62.5 (14.0)	63.1 (12.9)	64.1 (12.7)	64.0 (12.1)	64.7 (12.1)	.005
Male (%)	49.2	56.4	63.6	66.9	59.2	<.001
Diabetes (%)	16.3	23.1	26.3	31.7	46.3	<.001
Dialysis vintage (years)	7.1 (2.7–15.3)	5.1 (1.9–12.0)	5.6 (2.1–11.6)	5.5 (2.2–11.7)	4.7 (2.0–8.8)	<.001
Dialysis time (hours)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.5–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	.41
History of cardiovascular events (%)	31.3	30.8	32.0	35.0	39.0	<.001
Body mass index (kg/m^2)	20.9 (3.2)	21.1 (3.0)	21.0 (2.9)	21.2 (3.0)	21.4 (3.4)	.02
Cardiothoracic ratio (%)	50.3 (5.9)	49.9 (5.4)	50.2 (5.5)	50.5 (5.2)	51.6 (5.4)	<.001
Hemoglobin (g/dL)	10.5 (1.3)	10.6 (1.1)	10.6 (1.1)	10.6 (1.1)	10.5 (1.2)	.27
Serum albumin (g/dL)	3.7 (0.5)	3.8 (0.4)	3.8 (0.4)	3.8 (0.4)	3.9 (0.4)	<.001
Serum corrected calcium (mg/dL)	9.5 (0.8)	9.4 (0.8)	9.3 (0.8)	9.4 (0.7)	9.4 (0.8)	.02
Serum phosphate (mg/dL)	4.8 (1.2)	5.0 (1.2)	4.9 (1.2)	5.0 (1.2)	4.9 (1.2)	.82
Serum C-reactive protein (mg/dL)	0.13 (0.08–0.39)	0.13 (0.06–0.30)	0.13 (0.06–0.30)	0.13 (0.06–0.30)	0.13 (0.05–0.30)	.01
Serum total cholesterol (mg/dL)	156.5 (39.6)	155.1 (36.2)	154.7 (35.4)	155.7 (37.4)	156.9 (34.7)	.34
Kt/V (single pool)	1.61 (0.29)	1.61 (0.27)	1.59 (0.27)	1.55 (0.26)	1.53 (0.28)	<.001
nPCR (g/kg/day)	0.95 (0.20)	0.97 (0.19)	0.96 (0.19)	0.95 (0.18)	0.96 (0.21)	.13
Use of antihypertensive drugs (%)	39.1	60	63.9	70.5	78.3	<.001
Use of renin-angiotensin system inhibitors (%)	25.5	38.3	41.7	49.7	60.1	<.001
Use of erythropoiesis-stimulating agents (%)	81.8	82.6	85.5	82.4	87.5	.01

Values are given as the mean (standard deviation) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables. nPCR = normalized protein catabolic ratio, SBP = systolic blood pressure.

Table 3

Baseline characteristics according to pre-dialysis diastolic blood pressure.

Variables	Pre-dialysis diastolic blood pressure					
	Quintile 1 (DBP <66) n=610	Quintile 2 (66≤ DBP <73) n=755	Quintile 3 (73≤ DBP <80) n=645	Quintile 4 (80≤ DBP <86) n=692	Quintile 5 (86≤ DBP) n=734	*P* for trend
Age (years)	68.3 (12.5)	65.7 (12.2)	64.0 (12.2)	62.3 (12.4)	58.7 (12.6)	<.001
Male (%)	50.5	54.2	63.3	63.7	63.4	<.001
Diabetes (%)	29.3	32.7	27	24.1	30.9	.32
Dialysis vintage (years)	6.1 (2.1–13.6)	5.8 (2.2–11.7)	5.4 (2.1–12.3)	6.1 (2.4–11.4)	4.8 (1.9–9.8)	.001
Dialysis time (hours)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	.58
History of cardiovascular events (%)	40.0	36.2	33.2	28.2	31.5	<.001
Body mass index (kg/m^2)	20.9 (3.2)	21.0 (2.9)	21.1 (3.0)	21.2 (3.1)	21.4 (3.4)	.009
Cardiothoracic ratio (%)	51.0 (5.9)	50.6 (5.7)	50.2 (5.0)	50.4 (5.4)	50.5 (5.5)	.13
Hemoglobin (g/dL)	10.3 (1.2)	10.5 (1.1)	10.6 (1.2)	10.6 (1.1)	10.6 (1.2)	<.001
Serum albumin (g/dL)	3.7 (0.5)	3.8 (0.4)	3.8 (0.4)	3.9 (0.4)	3.9 (0.4)	<.001
Serum corrected calcium (mg/dL)	9.4 (0.8)	9.4 (0.7)	9.4 (0.8)	9.4 (0.8)	9.4 (0.8)	.15
Serum phosphate (mg/dL)	4.8 (1.2)	4.9 (1.1)	4.9 (1.2)	5.0 (1.2)	5.1 (1.3)	<.001
Serum C-reactive protein (mg/dL)	0.16 (0.10–0.40)	0.13 (0.05–0.30)	0.13 (0.07–0.30)	0.13 (0.05–0.30)	0.13 (0.05–0.30)	<.001
Serum total cholesterol (mg/dL)	154.1 (35.8)	157.5 (35.6)	152.9 (34.7)	155.6 (36.8)	158.0 (39.6)	.29
Kt/V (single pool)	1.63 (0.28)	1.59 (0.28)	1.57 (0.26)	1.56 (0.29)	1.54 (0.27)	<.001
nPCR (g/kg/day)	0.96 (0.20)	0.96 (0.19)	0.95 (0.18)	0.95 (0.17)	0.97 (0.22)	.83
Use of antihypertensive drugs (%)	53.8	59.7	63.1	64	71.3	<.001
Use of renin-angiotensin system inhibitors (%)	33.3	41.1	43.3	44.2	53.3	<.001
Use of erythropoiesis-stimulating agents (%)	85.4	84.1	85.1	84	81.7	.37

Values are given as the mean (standard deviation) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables. DBP = diastolic blood pressure, nPCR = normalized protein catabolic ratio.

3.2. Association of BP with risk for all-cause mortality and CV events

During the 4-year follow-up, 564 (16.4%) patients died from any cause with a crude incidence rate of 52.2 per 1000 patient-years, and 590 (17.2%) patients developed CV events with a crude incidence rate of 58.0 per 1000 patient-years.

3.3. Pre-dialysis SBP and all-cause mortality, and CV events

3.3.1. Categorical analysis. Table 4 shows unadjusted, age- and sex-adjusted, and multivariable-adjusted HRs associated with pre-dialysis SBP categories. In the unadjusted model, SBP categories were associated with significantly higher all-cause mortality risk in the lowest SBP (Q1) and the highest SBP (Q5) categories. After adjustment for potential confounders, patients with the lowest SBP levels (Q1) showed a 1.83-fold (95% CI, 1.40–2.39; $P < .0001$) higher risk for all-cause mortality than those with the reference group (Q3). With regard to CV events, in a multivariable-adjusted Cox proportional hazard model, patients with the highest SBP levels (Q5) showed a 1.31-fold (95% CI, 1.02–1.68; $P = .03$) higher risk compared with the reference group (Q3).

3.3.2. Continuous analysis. Multivariable-adjusted restricted cubic spline revealed HRs for all-cause mortality (Fig. 1A) and CV events (Fig. 1B). There was a U-shaped association of SBP with all-cause mortality (Fig. 1A) and of SBP with CV events

Table 4

Association of pre-dialysis systolic blood pressure and all-cause mortality, and cardiovascular events.

	Number of events/ number of patients	Unadjusted model (n=3436)		Age- and sex-adjusted model (n=3436)		Multivariable-adjusted model* (n=3436)	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality							
Q1 (pre-dialysis SBP <134)	143/658	1.80 (1.39–2.35)	<.001	2.08 (1.59–2.71)	<.001	1.83 (1.40–2.39)	<.001
Q2 (134≤ pre-dialysis SBP <148)	97/702	1.04 (0.78–1.38)	.81	1.15 (0.87–1.54)	.33	1.16 (0.87–1.55)	.32
Q3 (148≤ pre-dialysis SBP <159)	90/678	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Q4 (159≤ pre-dialysis SBP <172)	110/688	1.22 (0.93–1.62)	.16	1.27 (0.96–1.68)	.09	1.26 (0.95–1.67)	.10
Q5 (172≤ pre-dialysis SBP)	124/710	1.36 (1.04–1.79)	.03	1.40 (1.06–1.83)	.02	1.31 (1.00–1.73)	.05
Cardiovascular events							
Q1 (pre-dialysis SBP <134)	83/658	0.85 (0.64–1.13)	.26	0.96 (0.72–1.27)	.76	1.02 (0.77–1.36)	.89
Q2 (134≤ pre-dialysis SBP <148)	109/702	0.97 (0.74–1.26)	.81	1.05 (0.80–1.36)	.74	1.08 (0.83–1.41)	.57
Q3 (148≤ pre-dialysis SBP <159)	109/678	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Q4 (159≤ pre-dialysis SBP <172)	126/688	1.19 (0.92–1.54)	.19	1.18 (0.92–1.53)	.19	1.11 (0.85–1.43)	.45
Q5 (172≤ pre-dialysis SBP)	163/710	1.55 (1.21–1.97)	<.001	1.56 (1.23–2.00)	<.001	1.31 (1.02–1.68)	.03

* Adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, serum C-reactive protein concentration, and antihypertensive drugs. A 2-tailed *P* value <.05 was considered statistically significant. BMI = body mass index, CI = confidence interval, CTR = cardiothoracic ratio, HR = hazard ratio, Q = quintile, SBP = systolic blood pressure.

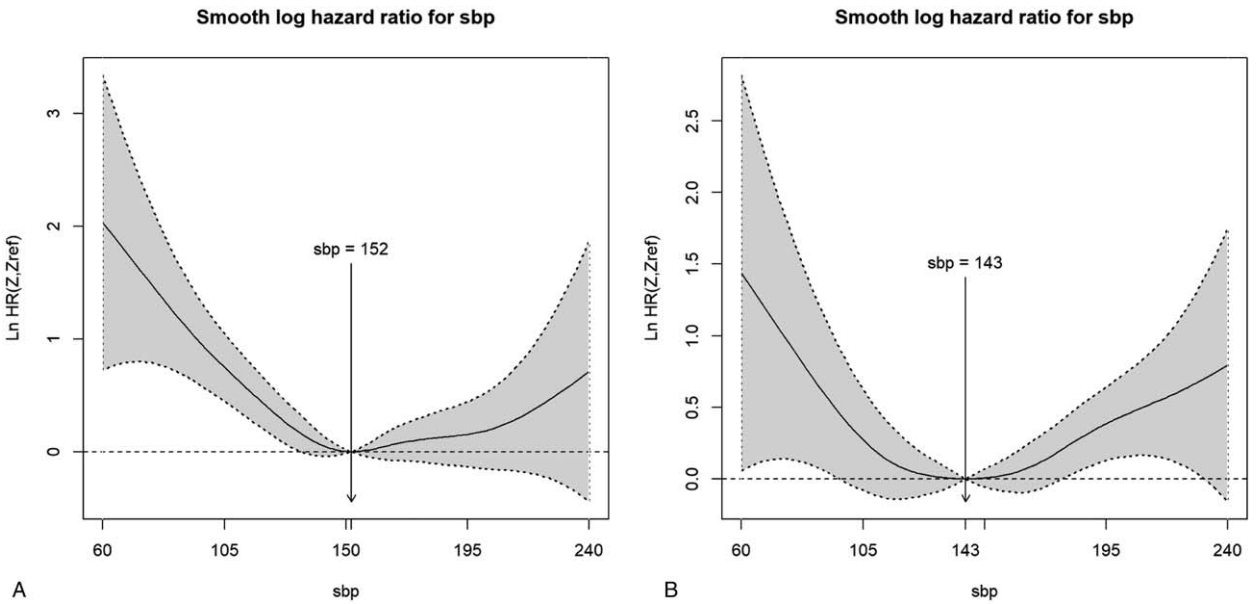

Figure 1. Multivariable-adjusted restricted cubic spline plots of hazard ratio for all-cause mortality (A) or CV events (B) according to pre-dialysis SBP levels. Solid line represents HR and gray part surrounded by dot lines represents 95% confidence interval. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, and serum C-reactive protein concentration, and taking antihypertensive drugs. BMI = body mass index, CTR = cardiothoracic ratio, CV = cardiovascular, SBP = systolic blood pressure.

(Fig. 1B). The nadir of SBP, at which the all-cause mortality risk and CV events risk was at its lowest, was 152 mm Hg and 143 mm Hg, respectively.

3.4. Pre-dialysis DBP and all-cause mortality, and CV events

3.4.1. Categorical analysis. Table 5 shows unadjusted, age- and sex-adjusted, and multivariable-adjusted HRs associated with pre-dialysis DBP categories. In the unadjusted model, DBP categories were associated with significantly higher all-cause mortality risk in the lowest DBP (Q1) categories.

In multivariable-adjusted Cox proportional hazard model, patients with the highest DBP levels (Q5) showed a 1.34-fold (95% CI, 1.02–1.76; $P = .04$) higher risk for all-cause mortality than those with the reference group (Q2). With regard to CV events, in a multivariable-adjusted Cox proportional hazard model, patients with the highest DBP levels (Q5) showed a 1.40-fold (95% CI, 1.09–1.79; $P = .009$) higher risk compared with the reference group (Q2).

3.4.2. Continuous analysis. Multivariable-adjusted restricted cubic spline revealed HRs for all-cause mortality and CV events. There was a U-shaped association of DBP with all-cause mortality (Fig. 2A), whereas the association of DBP with CV events appeared to be linear (Fig. 2B). The nadir of DBP, at which the all-cause mortality risk was at its lowest, was 68 mm Hg.

Table 5

Association of pre-dialysis diastolic blood pressure and all-cause mortality and cardiovascular events.

		Unadjusted model (n = 3436)		Age- and sex-adjusted model (n = 3436)		Multivariable-adjusted model * (n = 3436)	
	Number of events/ number of patients	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
All-cause mortality							
Q1 (pre-dialysis DBP <66)	145/610	1.65 (1.29–2.10)	<.001	1.35 (1.06–1.73)	.02	1.26 (0.99–1.62)	.06
Q2 (66≤ pre-dialysis DBP <73)	115/755	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Q3 (73≤ pre-dialysis DBP <80)	101/645	1.04 (0.79–1.35)	.80	1.11 (0.85–1.45)	.46	1.15 (0.88–1.51)	.32
Q4 (80≤ pre-dialysis DBP <86)	99/692	0.91 (0.70–1.20)	.52	1.10 (0.84–1.44)	.48	1.25 (0.95–1.64)	.11
Q5 (86≤ pre-dialysis DBP)	104/734	0.91 (0.70–1.19)	.51	1.38 (1.06–1.81)	.02	1.34 (1.02–1.76)	.04
Cardiovascular events							
Q1 (pre-dialysis DBP <66)	109/610	1.11 (0.86–1.43)	.44	0.97 (0.75–1.26)	.84	0.98 (0.75–1.26)	.86
Q2 (66≤ pre-dialysis DBP <73)	128/755	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Q3 (73≤ pre-dialysis DBP <80)	111/645	1.03 (0.80–1.33)	.80	1.06 (0.82–1.36)	.67	1.14 (0.88–1.47)	.33
Q4 (80≤ pre-dialysis DBP <86)	108/692	0.90 (0.70–1.16)	.41	0.99 (0.76–1.28)	.92	1.12 (0.87–1.46)	.38
Q5 (86≤ pre-dialysis DBP)	134/734	1.09 (0.85–1.38)	.50	1.40 (1.09–1.79)	.008	1.40 (1.09–1.79)	.009

* Adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, serum C-reactive protein concentration, and antihypertensive drugs. A 2-tailed *P* value <.05 was considered statistically significant. BMI = body mass index, CI = confidence interval, CTR = cardiothoracic ratio, DBP = diastolic blood pressure, HR = hazard ratio, Q = quintile.

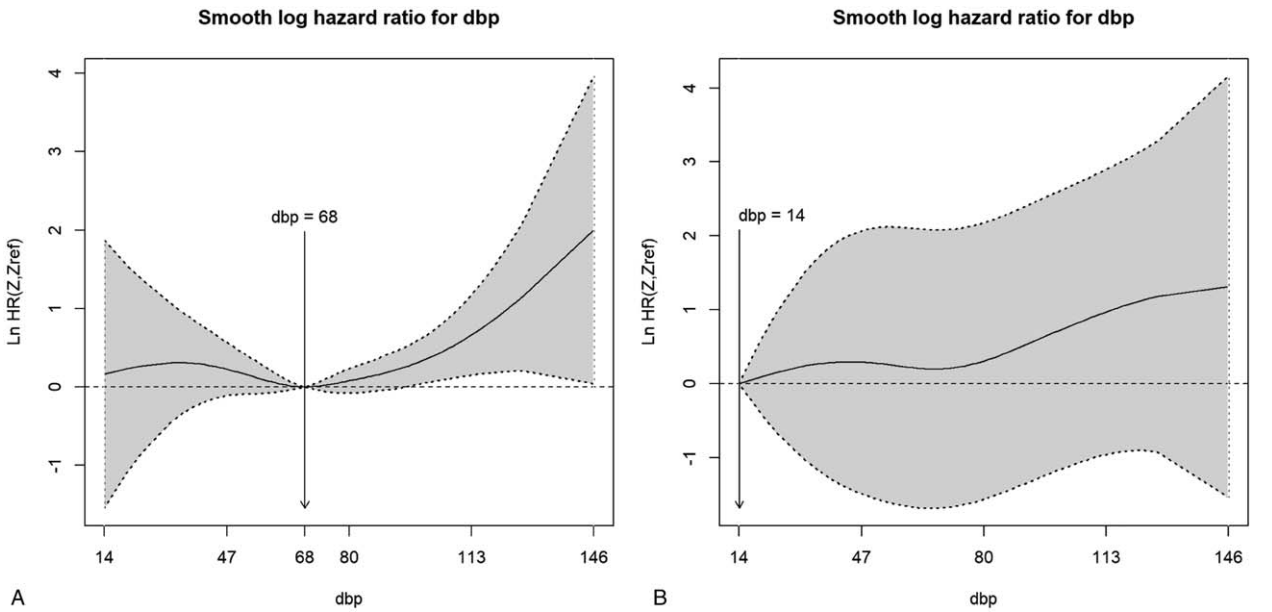

Figure 2. Multivariable-adjusted restricted cubic spline plots of hazard ratio for all-cause mortality (A) or CV events (B) according to pre-dialysis DBP levels. Solid line represents HR and gray part surrounded by dot lines represents 95% confidence interval. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, and serum C-reactive protein concentration, and taking antihypertensive drugs. BMI = body mass index, CTR = cardiothoracic ratio, CV = cardiovascular, DBP = diastolic blood pressure.

Meanwhile, the lower the DBP was, the lower the risk of CV events.

3.5. Subgroup analysis stratified by baseline characteristics

3.5.1. Interactions with pre-dialysis SBP. To assess the relationship between pre-dialysis SBP and patients' characteristics, the effect of modification of subgroups stratified by potential confounders was examined. There is no significant interaction between pre-dialysis SBP and all-cause mortality (Fig. 3A). Regarding CV events, there were significant interactions between pre-dialysis SBP and the following factors; age, dialysis vintage, history of CV events, CTR, and use of antihypertensive drugs (for all interactions, $P < .05$; Fig. 3B). This suggested that higher pre-dialysis SBP was more strongly associated with the risk of CV events in younger (<65 years) than older patients (≥65 years), those with shorter (<5 years) than longer dialysis vintage (≥5 years), those without than with a history of CV events, those with smaller (<50%) than larger CTR (≥50%), and those taking than not taking antihypertensive drugs.

3.5.2. Interactions with pre-dialysis DBP. To assess the relationship between pre-dialysis DBP and patients' characteristics, the effect of modification of subgroups stratified by potential confounders was examined. There was no significant interaction between pre-dialysis DBP and all-cause mortality (Fig. 4A). Regarding CV events, there were significant interactions between pre-dialysis DBP and the following factors; diabetes mellitus, CTR, and use of antihypertensive drugs (for all interactions, $P < .05$; Fig. 4B). This suggested that higher pre-dialysis DBP was more strongly associated with the risk of CV events in patients with than without diabetes mellitus, those with smaller (<50%) than larger CTR (≥50%), and those taking than not taking antihypertensive drugs.

4. Discussion

The results of the current prospective cohort study of 3436 HD patients indicated that pre-dialysis SBP and DBP were independently associated with all-cause mortality and CV events, even after adjustment for potential confounders. These relationships showed U-shaped associations. The lowest SBP group was associated with significantly increased risk of all-cause mortality, and the highest SBP group was associated with an increased risk of CV events. The highest DBP group was associated with significantly increased risk of both of all-cause mortality and CV events. The risk thresholds for mortality were SBP 152 mm Hg or DBP 68 mm Hg, and for CV events occurrence, SBP was 143 mm Hg. The present study revealed a significant association between pre-dialysis BP and mortality and morbidities in Japanese HD patients. Additionally, our findings suggest that there might exist an optimal management range of pre-dialysis BP to minimize the risk of mortality and CV events in HD patients.

Consistent with the past literature,[3–5,7,18,19] a U-shaped association was observed between BP and clinical outcomes in our cohort. These findings have highlighted that not only high BP but also an excessive lowering of BP may increase risk of death or CV events. There have been many strong points of evidences suggesting a link between high BP and unfavorable outcomes in dialysis patients.[9,20] High BP is strongly associated with progression of left ventricular hypertrophy (LVH),[21,22] which was reported to be an independent risk factor of all-cause mortality and CV events on patients undergoing HD.[23–26] In addition, elevated BP promotes the development of arterial stiffness, resulting in the increased risk of death and CV events in dialysis patients.[27–30] Furthermore, it is widely known that both atherosclerosis and vascular calcification are involved in the pathophysiology of arteriosclerosis in dialysis patients.[31,32] Therefore, elevated BP of dialysis patients might be a direct

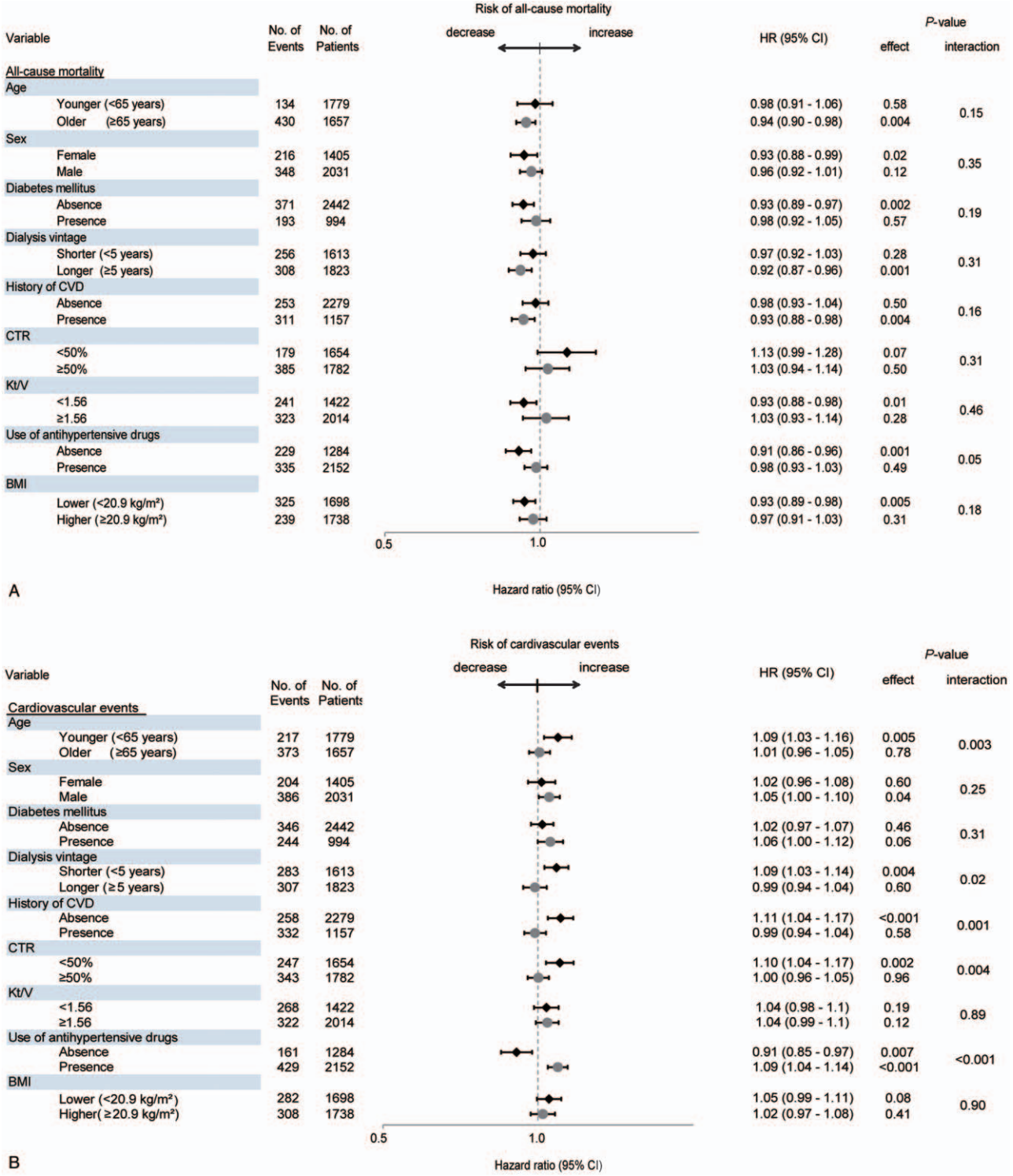

Figure 3. Multivariable-adjusted hazard ratio and 95% confidence interval for all-cause mortality (A) or CV events (B) for every 10 mm Hg increase in pre-dialysis SBP levels in subgroups stratified according to baseline characteristics and treatment. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, and serum C-reactive protein concentration, and taking antihypertensive drugs. Variables relevant to the subgroups were excluded from each model. BMI = body mass index, CTR = cardiothoracic ratio, CV = cardiovascular, SBP = systolic blood pressure.

indicator of reduced vascular compliance caused by the coexistence of arteriosclerosis and vascular calcification.[33–35] High BP may also indicate the potential risk of excessive fluid accumulation, which is involved in subsequent mortality and CV events.[36–38] Meanwhile, the influence of hypotension on the prognosis of dialysis patients has also been reported in several observational studies. We speculate that lower pre-dialysis BP is associated with comorbidity, including chronic heart failure,

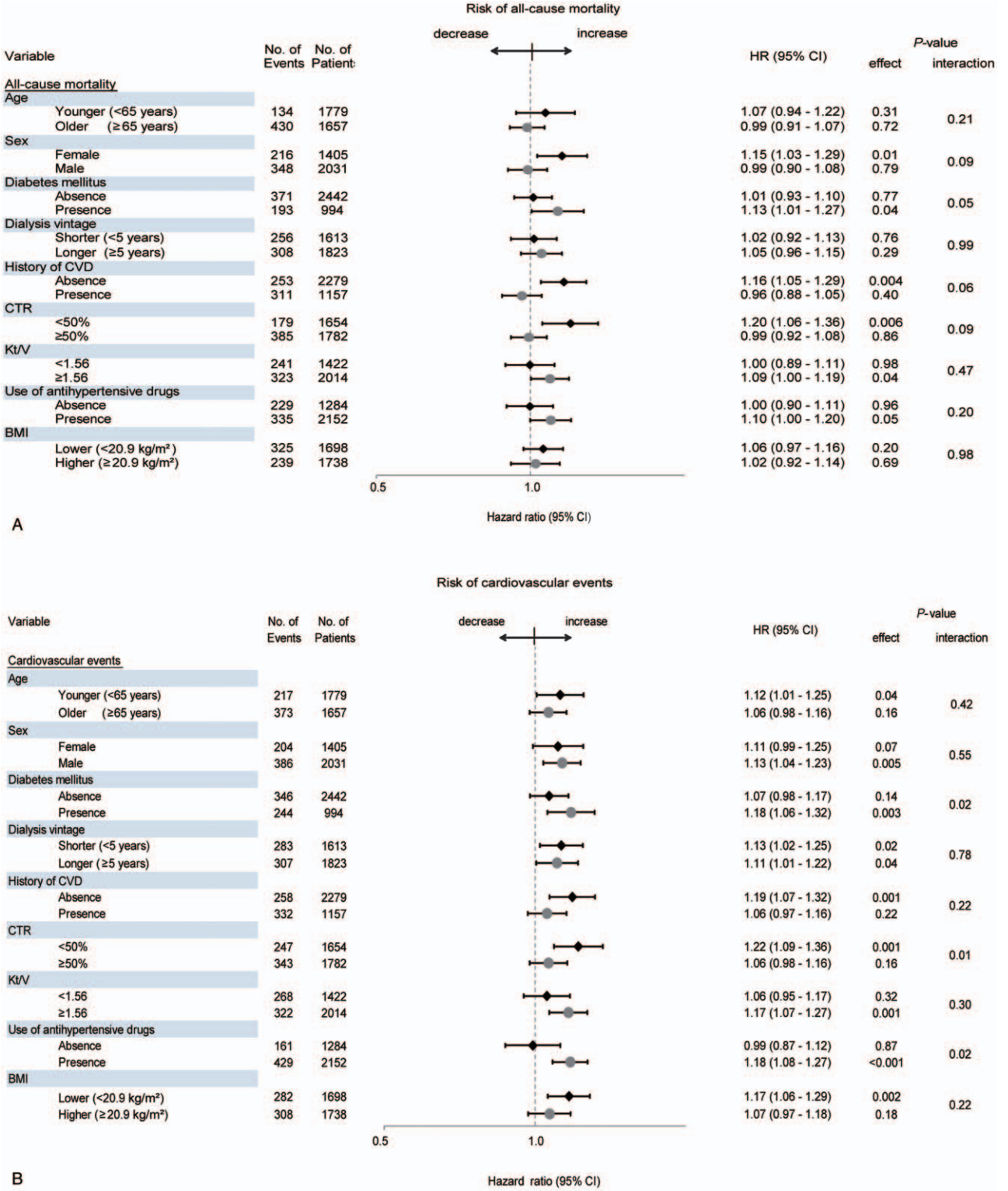

Figure 4. Multivariable-adjusted hazard ratio and 95% confidence interval for all-cause mortality (A) or CV events (B) for every 10 mm Hg increase in pre-dialysis DBP levels in subgroups stratified according to baseline characteristics and treatment. The multivariable-adjusted model was adjusted for age, sex, diabetes mellitus, dialysis vintage, history of cardiovascular events, CTR, BMI, single pool Kt/V, hemoglobin level, serum albumin concentration, serum phosphate concentration, serum total cholesterol concentration, and serum C-reactive protein concentration, and taking antihypertensive drugs. Variables relevant to the subgroups were excluded from each model. BMI = body mass index, CTR = cardiothoracic ratio, CV = cardiovascular, DBP = diastolic blood pressure.

ischemic cardiomyopathy, and liver cirrhosis, and that development of hypotension can lead to death, as reports previously.[23,39] Additionally, patients with lower pre-dialysis BP are at increased risk of intradialytic hypotension during ultrafiltration.[40] Repeated intradialytic ischemia leads to myocardial stunning and hibernation, ischemic brain damage, and gut endotoxin translocation, all of which can result from intradialytic hypotension, which is also associated with increased risk of

mortality and CV events.[41–46] Taken together, these mechanisms may explain the U-shaped associations seen in the present study.

In the present study, our results suggested that the optimal pre-dialysis SBP to lower mortality rate was 152 mm Hg, while it was 143 mm Hg for CV events. Additionally, the optimal pre-dialysis DBP to lower mortality rate was 68 mm Hg. In our results, SBP was higher and DBP was lower than the K-DOQI clinical practice guideline, but was consistent with the results of other observational studies.[3,7,18] The reason for the higher optimal pre-dialysis SBP in HD patients may be explained by the fact that the pre-dialysis SBP is represented by the BP, which is the most hypervolemic state at the beginning of the week.[15] The reason for lower target pre-dialysis DBP in HD patients may be that they have increased arterial stiffness and reduced vascular recoil due to accelerated medial calcification or atherosclerosis compared with the general population,[47] and such vascular abnormalities could result in lower DBP.[34]

Subgroup analysis stratified by baseline characteristics showed no significant evidence for interaction between pre-dialysis BP and all-cause mortality. However, regarding CV events, there were more significant associations between pre-dialysis SBP and CV events in patients who were younger (<65 years), patients with a shorter dialysis vintage (<5 years), those without a history of CV events, those with a smaller CTR (<50%), and patients who used antihypertensive drugs (for all interactions, $P < .05$). These results might reflect the possibility that patients with the above-mentioned background may often be related with a better nutritional state, excessive body fluids, and elevated BP, hence resulting in taking antihypertensive medication. Thus, we speculate that physicians should be cautioned to the increased risk for CV events caused by elevated pre-dialysis BP in the subgroup who are younger, have shorter dialysis vintage, have no history of CV events, and who do not use antihypertensive drugs.

There are several limitations to our report. First, BP data were collected at only the baseline examination. This may not account for intra-individual variability in levels over time and may, thus, lead to misclassification of study subjects into inappropriate BP-level categories. Second, we did not have data of body fluid volume and the parameter of arterial stiffness, such as pulse wave velocity, and vascular calcification at baseline. These may be important confounding factors regarding the increased outcome in patients in the higher pre-dialysis BP categories. Third, intra-dialysis BP values were not collected in our study. Intra-dialytic hypotension is associated with numerous adverse outcomes, including death.[41] However, we could not adjust for intra-dialytic hypotension. Fourth, we did not have data about the presence of comorbidity such as heart failure or liver cirrhosis, echocardiographic findings, abdominal echo findings, or markers of heart failure such as brain natriuretic peptide. These may be important confounding factors that account for the association of lower pre-dialysis BP patients with increased mortality. Fifth, we did not have data about cardiovascular death, which is the main cause of death in patients undergoing dialysis, and therefore could not assess associations between pre-dialysis BP and cause-specific death, particularly cardiovascular death. Finally, as with all observational studies, causality cannot be determined, and adjustment for confounders is limited to those who are recognized and measured.

In conclusion, pre-dialysis BP was associated with all-cause mortality and CV events. Our results indicated the U-shaped association between pre-dialysis SBP and mortality and CV events, and pre-dialysis DBP and mortality. These findings would suggest that a target of pre-dialysis BP value might affect clinical outcomes in Japanese HD patients. Importantly, our study revealed that the optimal cutoff values of SBP/DBP most relevant to clinical prognosis were 152/68 mm Hg, respectively. A well-designed randomized controlled trial that compares the effects of lower versus higher BP goals on mortality and CV events will be required.

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