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ARTICLE

Characteristics of visit-to-visit blood pressure variability in hemodialysis patients

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Abstract

Visit-to-visit blood pressure variability (VVBPV) is an independent risk factor for cardiovascular morbidity and mortality in the general population. Hemodialysis (HD) patients have a poor prognosis due to an increased prevalence of cardiovascular disease. Intradialytic hypotension is associated with excess mortality, but whether VVBPV influences mortality is still unclear in HD patients. The present study aimed to investigate the characteristics of VVBPV in these patients. A total of 324 maintenance HD patients, who could be followed for 60 months, were recruited. We used variation independent of the mean (VIM) in pre-dialysis systolic blood pressure (pre-VIM-SBP) as an index of VVBPV. We investigated (1) the reproducibility of pre-VIM-SBP, (2) the relationship between pre-VIM-SBP and background factors, and (3) the association between pre-VIM-SBP and mortality. Pre-VIM-SBP showed significant reproducibility [intraclass correlation, 0.45 ($P < 0.001$)]. Higher pre-VIM-SBP was associated with less physical activity and worse left ventricular diastolic function. Higher pre-VIM-SBP was associated with a higher rate of cardiovascular deaths independent of other factors. These data suggest that VVBPV in HD patients is reproducible and associated with various background factors. VVBPV is independently correlated with cardiovascular mortality (hazard ratio: 1.166, 95% confidence interval: 1.030-1.320, $P = 0.015$). Further studies are necessary to confirm the mechanism of increased VVBPV and to clarify whether reducing VVBPV will improve the prognosis for HD patients.

Keywords Variation independent of the mean · Reproducibility · Prognosis · Cardiovascular death · Arteriosclerosis

Introduction

Visit-to-visit blood pressure (BP) variability (VVBPV) is an independent risk factor for mortality in the general population [1, 2]. VVBPV is a robust predictor of stroke and coronary events in patients treated for hypertension and those with a history of transient ischemic attack. These predictions are independent of mean systolic BP (SBP) [3]. Excessive VVBPV is also a significant indicator for deterioration of renal function and proteinuria [4, 5] and carotid artery atherosclerosis [6].

Hemodialysis (HD) patients have a poor prognosis due to an increased prevalence of cardiovascular disease [7, 8]. It has been reported that masked hypertension is associated with increased arterial stiffness [9] and intradialytic hypotension is an independent risk factor for mortality in HD patients [10, 11]. Recent studies show VVBPV to be an independent risk factor for total deaths and cardiovascular deaths in HD patients [12-14]. However, most studies were limited by small sample sizes or short duration of follow-up

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[13, 14], and by use of VVBPV data from measurements such as standard deviation (SD) [14] and coefficient of variation (CV) [12, 13], which can be affected by the absolute value of SBP. Moreover, the reproducibility of VVBPV in HD patients is not well studied. Variation independent of the mean (VIM) is a transformation of SD that is not correlated with mean levels [3]. Therefore, as an index of VVBPV, we selected VIM in SBP, which is less affected by the absolute value of SBP [3], and used this statistic to evaluate reproducibility of VIM in SBP. Further, we investigated relationships between VIM in SBP and background factors and those between VIM in SBP and mortality in patients undergoing maintenance HD.

Methods

Study subjects

Subjects were outpatients on maintenance HD at Kadoma Keijinnkai Clinic, Neyagawa Keijinnkai Clinic, or Moriguchi Keijinnkai Clinic in Osaka Prefecture, Japan. Both clinics are affiliated with Moriguchi Keijinkai Hospital, Osaka, Japan. A total of 324 maintenance HD patients who could be followed for 60 months were recruited consecutively from January 2011 to March 2012. The study excluded subjects who received renal transplants. Each patient underwent HD therapy three times a week for 3-4 h at the same time of the day. All participants were enrolled after obtaining written informed consent as required by the ethical committee of Moriguchi Keijinnkai Hospital.

Background factors

At the start of this study, we collected information for the target study population including age, gender, body mass index (BMI), performance status (PS), duration of HD, smoking history, primary disease (diabetic or not), history of cardiovascular diseases, such as stroke, transient ischemic attack (TIA), myocardial infarction, angina, heart failure, peripheral vascular disease, and selected medications. BMI was calculated using BMI = {[post-dialysis value of body weight (kg)]/[height (m)]^2} × 100. PS reflects patients' daily living capabilities using a scale developed by the Eastern Cooperative Oncology Group (ECOG). ECOG scores are defined as follows: 0—patient is fully active, able to carry on all pre-disease activities without restriction; 1—patient is restricted from physically strenuous activity, but is ambulatory and able to carry out light or sedentary work; 2—patient is ambulatory and capable of all self-care, but is unable to carry out any work activities that take more than 50% of waking hours; 3—patient is capable of only limited self-care, is confined to bed or chair for more than 50% of waking hours; 4—patient is completely disabled, cannot carry out any self-care, and is totally confined to bed or chair; and 5—patient is deceased) [15].

Information also included dialysis-related data, such as the percentage of body weight gain (%BW) and KT/V. The %BW was calculated using; %BW = (interdialytic weight gain/dry weight) × 100. Kt/V was calculated on the first dialysis day of the week using the formula of Daugirdas [16]: Kt/V = −Ln [post-dialysis value of blood urea nitrogen (BUN)/pre-dialysis value of BUN − 0.008 × dialysis time + (4 − 3.5 × post-dialysis value of BUN/pre-dialysis value of BUN) × (amount of drainage/post-dialysis body weight)]. Post-dialysis values for cardiothoracic ratio (CTR) were obtained on the first dialysis day of the week.

BP measurements and definitions of BP variability

Evaluation of risk should consider SBP rather than diastolic BP (DBP) [17]. Benefits of treating high SBP are established, especially in older subjects [18, 19]. VVBPV for SBP but not for DBP is associated with mortality [1, 2]. Therefore, we selected SBP instead of DBP for evaluation of VVBPV. SBP at the start (pre-dialysis) and end (post-dialysis) as well as during each HD session were measured in a supine position by trained HD nurses using validated oscillometric BP monitor equipped HD machines. The minimum and average number of BP readings were 2 and 4.5, respectively. During a series of 12 consecutive visits from the beginning of the observation period, seven kinds of SBP values were estimated. The first was VIM for pre-dialysis SBP (pre-VIM-SBP) and the second was VIM for post-dialysis SBP (post-VIM-SBP).

VIM-SBP is a transformation of the standard derivation (SD) that is uncorrelated with mean BP and is calculated as (2): VIM-SBP = (k × SD-SBP)/(Mean-SBP)$^{\text{power X}}$, where power X is approximated using the curve of mean values on the horizontal axis plotted against SD on the vertical axis, and k = Mean (Mean-SBP)$^{\text{power X}}$.

The third estimate was the maximum of 12 values of differences between the highest and lowest SBP values during dialysis (i.e., the maximum Δ SBP). The fourth estimate was the average of 12 values of Δ SBP (average Δ SBP). The fifth was the average of 12 values of the percentage of Δ SBP (percentage of Δ SBP = Δ SBP × 100/the highest SBP). The sixth was the minimum of 12 values of the lowest SBP during dialysis (minimum of the lowest SBP). The seventh was the average of 12 values of the lowest SBP during dialysis (average of the lowest SBP).

Subjects were divided into two groups (higher and lower groups) according to the median of SBP values. Subjects groups with lowest BP values were divided into two subgroups depending on whether median SBP was lower than

110 mmHg. This cutoff reflects a previous report that intradialytic hypotension was an independent risk factor for mortality in HD patients with values 110 mmHg [10].

Blood examinations

Blood samples were taken with patients in a supine position on a bed after at least 15 min of rest on the first dialysis day of the week. Pre-dialysis values of hemoglobin (Hb), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), albumin-corrected calcium (Ca), inorganic phosphorus (IP), intact-parathyroid hormone (intact-PTH), creatinine (Cre), uric acid (UA), C-reactive protein (CRP), albumin (Alb), and glycoalbumin (GA), and post-dialysis values of human atrial natriuretic peptide (hANP) and brain natriuretic peptide (BNP) were measured by conventional methods at an external testing laboratory (Kishimoto, Inc., Tomakomai City, Japan).

Physiological function tests

Echocardiography

Echocardiography was performed on a non-dialysis day using a Vivid S6 System (GE Healthcare, Milwaukee, WI, USA), and cardiac functions, including left ventricular mass index (LVMI), a marker of cardiac hypertrophy [20]; left ventricular ejection fraction (LVEF), a marker of left ventricular contractile activity; and E over A (E/A) and deceleration time (Dec-T), markers of left ventricular diastolic function [21], were recorded.

Brachial-ankle pulse wave velocity (baPWV)

The ankle-brachial index (ABI) and baPWV values (higher values and average values) were measured on a non-dialysis day using a volume-plethysmographic apparatus PWV/ABI (Omron Healthcare Co., Ltd, Kyoto, Japan) following previously described methods [22]. BaPWV cannot be estimated properly when ABI is less than 0.9 because arterial occlusion retards baPWV [23, 24]. Therefore, patients with ABI < 0.9 were excluded from this analysis.

Study protocols

We determined each SBP parameter (pre-VIM-SBP, post-VIM-SBP, maximum Δ SBP, average Δ SBP, percentage of Δ SBP, minimum of the lowest SBP, and average of the lowest SBP) at the start of the study and 6 months after start of the study and assessed reproducibility of these measures by calculating intraclass correlations (ICC) for each patient.

Relationships between each SBP parameter including VIM in SBP (the pre-VIM-SBP and the post-VIM-SBP) and background factors were examined. Subjects were followed until death from any cause or for 60 months. We also examined cardiovascular deaths and non-cardiovascular deaths. As a detailed analysis of prognosis, the subjects were divided into two groups (higher and lower groups) according to the values of each SBP parameter, and we compared total mortality, cardiovascular mortality, and non-cardiovascular mortality between the two groups of each kind of SBP parameter. Finally, we examined the association between VIM in SBP (the pre-VIM-SBP and the post-VIM-SBP) and all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality.

Statistical analysis

Parametric variables and nonparametric continuous variables were expressed as mean ± SD or median with interquartile ranges (twenty fifth and seventy fifth percentiles), respectively. Categorical variables are presented as the number of patients. Power X was modeled as $SD = a \times mean^{x}$ and was derived by nonlinear regression analysis as implemented in the PROC NLIN procedure of the SAS package (SAS Inc Cary, NC, USA). Reproducibility analyses were performed to determine ICC. An ICC reflects the proportion of variance in a measurement that is due to differences among subjects. An ICC ≥ 0.75 was considered indicative of excellent reproducibility, an ICC of $0.4 \le ICC < 0.75$ was considered indicative of fair reproducibility, and an ICC of $ICC < 0.4$ was considered indicative of poor reproducibility [25, 26].

We calculated the Spearman's rank correlation coefficient between each kind of SBP parameter and background factors, blood data and physiological function data. Multiple regression analyses were done by using factors that showed significant correlation with each SBP parameter as independent variables. Kaplan–Meier plots and log-rank tests were also used to compare all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality between the two groups (higher versus lower median SBP) for pre-VIM-SBP and post-VIM-SBP. Background factors contributing to all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality were analyzed using univariate Cox proportional hazard regression. In addition, we constructed multivariate Cox proportional hazard regression models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for all-cause mortality, cardiovascular mortality, and non-cardiovascular mortality using factors that showed a significant correlation as covariates with mortality. The level of significance was defined as $P < 0.05$. All analyses, except the determination of Power X, were performed using Bell Curve for

Excel (Social Survey Research Information Co., Ltd, Tokyo, Japan).

Results

Characteristics of the study subjects

Table 1 details baseline characteristics of study subjects and includes each SBP parameter, blood data, and physiological function data. The number of patients with measurements of ABI and baPWV was limited to 158. In addition, 28 patients showed ABI of <0.9. As a result, a total of 130 patients are reflected in the analysis of baPWV.

Reproducibility of VIM in SBP and other SBP parameters

Table 2 provides reproducibility estimates for SBP parameters. All parameters were statistically significant ($P < 0.05$). Maximum Δ SBP showed significant but poor reproducibility and other SBP parameters showed significant and fair reproducibility.

Relationships between each kind of SBP parameter and background factors

The pre-VIM-SBP estimates showed significant positive relationships with PS, primary disease [diabetes mellitus (DM)], and Dec-T values, and significant negative relationships with Ca, Cre, and Alb levels (Table 3). Multiple regression analyses identified PS and Dec-T as significant predictors of higher pre-VIM-SBP (Table 4). Post-VIM-SBP showed significant positive relationships with age, PS, primary disease (DM), duration of HD therapy, average %BW, hANP, and baPWV levels, and significant negative relationships with Alb levels (Table 3). Multiple regression analyses identified PS and primary disease (DM) as significant predictors of higher post-VIM-SBP (Table 4). Maximum Δ SBP showed significant positive relationships with PS, duration of HD therapy, average %BW, Kt/V, CTR, LDL-C, and baPWV levels, and significant negative relationships with medication [calcium channel blocker (CCB)] (Table 3). Multiple regression analyses identified PS, average %BW, and LDL-C as significant predictors of higher maximum Δ SBP, and medication (CCB) as a significant predictor of lower maximum Δ SBP (Table 4). Average Δ SBP showed significant positive relationships with PS, primary disease (DM), duration of HD therapy, average %BW, Kt/V, and LVEF levels, and significant negative relationships with gender (male) and medication (CCB) (Table 3). Multiple regression analyses identified PS, primary disease (DM), and average %BW as significant predictors of higher average Δ SBP, and gender (male) as a significant predictor of lower average Δ SBP (Table 4). The percentage of Δ SBP showed significant positive relationships with age, PS, primary disease (DM), duration of HD therapy, average %BW, Kt/V, CTR, Hb, and LVEF levels and significant negative relationships with gender (male), medications (CCB), BNP, and LVMI levels (Table 3). Multiple regression analyses identified PS, primary disease (DM), average %BW, and Hb as significant predictors of higher percentage of Δ SBP and gender (male), medications (CCB), and BNP as significant predictors of lower percentage of Δ SBP (Table 4). The minimum of the lowest SBP showed significant positive relationships with gender (male), smoking history, medications [renin-angiotensin system inhibitor (RAS-I)], medications (CCB), BNP, and LVMI levels and significant negative relationships with age, PS, duration of HD therapy, average %BW, Kt/V, CTR, Hb, TG, and CRP levels (Table 3). Multiple regression analyses identified gender (male), medications (CCB), and BNP as significant predictors of higher minimum of the lowest SBP, and age, PS, average %BW, Hb, TG, and CRP as significant predictors of lower minimum of the lowest SBP (Table 4). The average of the lowest SBP showed significant positive relationships with gender (male), smoking history, medications (RAS-I and CCB), HDL-C, BNP, and LVMI levels, and significant negative relationships with age, PS, duration of HD therapy, average %BW, Kt/V, CTR, Hb, and TG levels (Table 3). Multiple regression analyses identified gender (male), medications (CCB), HDL-C, BNP, and LVMI as significant predictors of higher average of the lowest SBP, and average %BW and Hb as significant predictors of lower average of the lowest SBP (Table 4).

Association between VIM in SBP and prognosis

During the 60-month follow-up period, 130 deaths (40.2%) were recorded, including 88 cardiovascular deaths (27.0%), two due to acute myocardial infarction, 27 due to congestive heart failure, six due to lethal arrhythmia, seven due to cerebral hemorrhage, three to stroke, and 43 sudden unexpected deaths. Forty-two non-cardiovascular deaths (13.0%) were recorded, 17 due to infectious diseases, six to cachexia, 12 to cancer, five to suffocation, and two to liver failure. One-year survival rate was 98.1%, 2-year survival rate 86.7%, 3-year survival rate 77.4%, 4-year survival rate 70.0%, and 5-year survival rate 60.0%.

The group with higher pre-VIM-SBP (≥12.5, $n = 160$) had higher total and cardiovascular death rates than the lower group (<12.5, $n = 164$), and the group with higher post-VIM-SBP (≥12.3, $n = 164$) had higher total and non-cardiovascular death rates than the lower group (<12.3, $n = 160$) (Table 5, Fig. 1). In contrast, total, cardiovascular and

Table 1 Characteristics of Study Subjects

Variable	Total sample ($n = 324$)
Age (years old)	70 (26–97)
Gender (male/female)	183/141
Body mass index (kg/m^2)	21.5 (19.2–23.9)
Performance status (0/1/2/3/4)	0/143/96/68/17
Primary disease (DM/non DM)	157/167
Duration of hemodialysis therapy (months)	2.0 (0.5–5.0)
Smoking history (yes/no)	84/240
Past history of cardiovascular diseases (yes/no)	128/196
Antihypertensive treatment (RAS-I/β-blocker/CCB)	249/96/211
Kt/V	1.36 (1.2–1.56)
CTR (%)	51.2 (48.0–56.0)
Average of %BW (%)	4.1 (3.0–5.3)
Blood tests	
Hemoglobin (g/dl)	10.8 ± 1.2
HDL-cholesterol (mg/dl)	46.0 (37.0–57.0)
LDL-cholesterol (mg/dl)	83.5 ± 28.4
Triglyceride (mg/dl)	97.0 (67.0–134.0)
Calcium (mg/dl)	8.8 (8.4–9.2)
Inorganic phosphorus (mg/dl)	4.9 (4.1–5.9)
Intact-Parathyroid hormone (pg/ml)	114.0 (70.9–168.0)
Creatinine (mg/dl)	8.8 ± 2.6
Uric acid (mg/dl)	6.6 (5.9–7.6)
CRP (mg/dl)	0.1 (0.1–0.3)
hANP (pg/ml)	66.0 (46.8–94.3)
BNP (pg/ml)	148.9 (75.1–313.9)
Albumin (g/dl)	3.9 (3.6–4.0)
Glycoalbumin (%)	19.1 (16.2–22.7)
Physical function tests	
Echocardiography	
LVEF (%)	67.1 (61.0–75.2)
LVMI (g/m^2)	169.9 (138.8–206.7)
E/A	0.74 (0.61–0.91)
Dec-T (ms)	232.3 (189.4–282.0)
baPWV (cm/s)	
Higher values	1970.0 (1677.0–2335.0)
Average values	1927.5 (1638.5–2289.5)
SBP parameters (at beginning/after 6 months)	
Pre-VIM	12.5 (9.9–15.3)/11.3 (9.3–14.5)
Post-VIM	12.3 (9.4–15.6)/11.3 (8.8–14.1)
Maximum of Δ (mmHg)	60 (46–78)/54 (42–70)
Average of Δ (mmHg)	33.3 (27.2–44.2)/31.2 (25.7–39.9)
Percentage of Δ (%)	20.6 (16.9–26.8)/19.7 (16.6–24.9)
Minimum of the lowest SBP (mmHg)	103 ± 12/106 (90-106)
Average of the lowest SBP (mmHg)	125 ± 11/123 ± 6

DM diabetes mellitus, *RAS-I* renin-angiotensin system inhibitor, *CCB* calcium channel blocker, *CTR* cardiothoracic ratio, *%BW* percentage of body weight gain, *SBP* systolic blood pressure, *VIM* variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP, *Δ SBP* difference between the highest and lowest values of SBP, *percentage of Δ SBP* Δ SBP × 100/ the highest SBP, *CRP* C-reactive protein, *hANP* human atrial natriuretic peptide, *BNP* brain natriuretic peptide, *LVMI* left ventricular mass index, *LVEF* left ventricular ejection fraction, *E/A* early filling over atrial filling, *Dec-T* deceleration time, *baPWV* brachial-ankle pulse wave velocity

Table 2 Reproducibility of SBP parameters

Variable	ICC (95% CI)	*P*
Pre-VIM-SBP	0.450 (0.318 to 0.559)	<0.001
Post-VIM-SBP	0.464 (0.333 to 0.569)	<0.001
Maximum Δ SBP	0.191 (−0.006 to 0.350)	0.029
Average Δ SBP	0.671 (0.591 to 0.736)	<0.001
Percentage of Δ SBP	0.691 (0.614 to 0.752)	<0.001
Minimum of the lowest SBP	0.605 (0.508 to 0.682)	<0.001
Average of the lowest SBP	0.690 (0.614 to 0.751)	<0.001

SBP systolic blood pressure, *VIM* variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP, *Δ SBP* difference between the highest and lowest values of SBP, *percentage of Δ SBP* Δ SBP × 100/the highest SBP

non-cardiovascular death were not significantly different between the higher and lower groups based on maximum Δ SBP (≥60 mmHg, $n = 164$ vs <60 mmHg, $n = 160$), average Δ SBP (≥33.3 mmHg, $n = 160$ vs <33.3 mmHg, $n = 164$), percentage of Δ SBP (≥20.6%, $n = 160$ vs <20.6, $n = 164$), minimum of the lowest SBP (≥106 mmHg, $n = 175$ vs <106 mmHg, $n = 149$ and ≥110 mmHg, $n = 117$ vs <110 mmHg, $n = 207$), and average of the lowest SBP (≥125 mmHg, $n = 162$ vs <125 mmHg, $n = 162$ and ≥110 mmHg, $n = 262$ vs <110 mmHg, $n = 62$) (Table 5).

Univariate Cox regression analyses demonstrated that age, PS, primary disease (DM), history of cardiovascular diseases, CTR, hANP, BNP, LVMI, and baPWV (average values) levels were significantly and positively correlated, and BMI, medications (RAS-I), medications (CCB), IP, Cre, Alb, and LVEF were significantly and negatively correlated with total death (Table 6). Age, gender (male), PS, primary disease (DM), history of cardiovascular diseases, CTR, hANP, BNP, LVMI, and baPWV (average values) levels were significantly and positively correlated,

Table 3 Single correlation analyses with SBP parameters

Variable	Pre-VIM-SBP		Post-VIM-SBP		Maximum Δ SBP		Average Δ SBP		Percentage of Δ SBP		Minimum of the lowest SBP		Average of the lowest SBP	
	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*
Age	0.101	0.068	0.181	0.001	0.083	0.134	0.071	0.204	0.111	0.046	−0.156	0.005	−0.158	0.004
Gender	−0.076	0.171	0.028	0.610	−0.099	0.076	−0.115	0.039	−0.151	0.006	0.155	0.005	0.177	0.001
Body mass index	−0.049	0.380	−0.064	0.248	−0.021	0.700	−0.025	0.649	−0.018	0.747	0.000	0.996	−0.032	0.566
Performance status	0.231	<0.001	0.218	<0.001	0.216	<0.001	0.230	<0.001	0.235	<0.001	−0.187	<0.001	−0.123	0.027
Primary disease	0.112	0.044	0.212	<0.001	0.109	0.050	0.161	0.004	0.131	0.018	−0.062	0.263	0.026	0.638
Duration of hemodialysis therapy	0.028	0.615	0.125	0.024	0.189	<0.001	0.207	<0.001	0.242	<0.001	−0.172	0.002	−0.185	<0.001
Smoking history	0.009	0.865	−0.008	0.886	−0.023	0.680	−0.017	0.755	−0.061	0.272	0.116	0.037	0.143	0.010
Past history of cardiovascular diseases	0.028	0.619	0.062	0.261	0.033	0.554	−0.016	0.775	−0.013	0.819	−0.066	0.234	−0.025	0.656
Medications (RAS-I)	−0.070	0.207	0.020	0.717	0.039	0.479	−0.015	0.794	−0.081	0.144	0.140	0.012	0.238	<0.001
Medications (β-blocker)	0.069	0.214	0.068	0.225	0.092	0.098	0.083	0.136	0.073	0.187	−0.080	0.152	0.001	0.990
Medications (CCB)	−0.089	0.108	0.008	0.893	−0.112	0.043	−0.125	0.024	−0.222	<0.001	0.306	<0.001	0.377	<0.001
Average %BW	0.044	0.429	0.164	0.003	0.302	<0.001	0.309	<0.001	0.320	<0.001	-0.306	<0.001	−0.193	<0.001
Kt/V	−0.058	0.298	−0.037	0.505	0.126	0.023	0.168	0.002	0.207	<0.001	−0.172	0.002	−0.202	<0.001
CTR	0.085	0.128	0.049	0.374	0.117	0.035	0.091	0.101	0.110	0.048	−0.145	0.009	−0.134	0.016
Hemoglobin	0.031	0.579	0.055	0.323	0.070	0.209	0.092	0.097	0.131	0.018	−0.158	0.004	−0.172	0.002
HDL-cholesterol	−0.002	0.972	−0.017	0.770	−0.002	0.977	−0.016	0.771	−0.058	0.306	0.097	0.084	0.155	0.006
LDL-cholesterol	0.080	0.153	0.003	0.964	0.121	0.030	0.081	0.145	0.073	0.192	−0.047	0.399	−0.014	0.796
Triglyceride	0.000	0.994	−0.075	0.183	0.036	0.527	0.042	0.453	0.102	0.070	−0.162	0.004	−0.172	0.002
Calcium	−0.170	0.002	−0.106	0.057	−0.068	0.218	−0.033	0.557	−0.033	0.552	−0.008	0.882	−0.018	0.740
Inorganic phosphorus	−0.010	0.859	0.042	0.451	0.084	0.131	0.054	0.328	0.041	0.459	−0.016	0.777	−0.001	0.986
Intact-parathyroid hormone	0.056	0.314	−0.105	0.058	−0.007	0.903	−0.024	0.669	−0.051	0.361	0.050	0.373	0.056	0.317
Creatinine	−0.130	0.019	−0.026	0.637	0.029	0.605	0.020	0.722	0.026	0.646	0.014	0.800	−0.003	0.950
Uric acid	−0.074	0.184	−0.011	0.837	0.056	0.316	0.052	0.351	0.060	0.283	−0.032	0.564	−0.033	0.554
CRP	0.063	0.255	0.097	0.081	0.048	0.384	0.037	0.503	0.060	0.277	−0.147	0.008	−0.108	0.051
Albumin	−0.148	0.007	−0.131	0.018	0.015	0.784	0.044	0.434	0.057	0.302	−0.055	0.323	−0.068	0.218
Glycoalbumin	0.091	0.234	0.048	0.535	−0.024	0.758	0.033	0.669	0.049	0.520	0.001	0.988	−0.015	0.844
hANP	0.107	0.054	0.159	0.004	0.102	0.066	0.101	0.070	0.067	0.232	−0.034	0.543	0.036	0.519
BNP	0.022	0.703	0.069	0.228	0.012	0.836	−0.036	0.525	−0.116	0.042	0.155	0.006	0.230	<0.001
LVMI	−0.045	0.433	−0.043	0.453	−0.022	0.702	−0.068	0.232	−0.127	0.026	0.164	0.004	0.229	<0.001
LVEF	−0.037	0.518	0.106	0.064	0.105	0.065	0.141	0.014	0.145	0.011	−0.082	0.150	−0.076	0.185
E/A	−0.075	0.205	−0.007	0.901	−0.074	0.208	−0.109	0.064	−0.111	0.059	0.027	0.646	0.084	0.152
Dec-T	0.130	0.023	0.078	0.173	0.109	0.057	0.084	0.144	0.091	0.113	−0.035	0.545	−0.053	0.353
baPWV (higher)	0.003	0.971	0.178	0.040	0.178	0.041	0.161	0.064	0.129	0.139	−0.097	0.266	−0.031	0.727
baPWV (average)	0.009	0.918	0.184	0.034	0.179	0.039	0.166	0.056	0.137	0.115	−0.099	0.255	−0.041	0.641

SBP systolic blood pressure, *VIM* variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP, *Δ SBP* difference between the highest and lowest values of SBP, *percentage of Δ SBP* Δ SBP × 100/the highest SBP, *RAS-I* renin-angiotensin system inhibitor, *CCB* calcium channel blocker, *CTR* cardiothoracic ratio, *%BW* percentage of body weight gain, *CRP* C-reactive protein, *hANP* human atrial natriuretic peptide, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *E/A* early filling over atrial filling, *Dec-T* deceleration time, *baPWV* brachial-ankle pulse wave velocity

and BMI, medications (RAS-I), medications (CCB), Kt/V, IP, Cre, Alb, and LVEF were significantly and negatively correlated with cardiovascular death (Table 6). In addition, age, PS, primary disease (DM), duration of HD therapy, CTR, hANP, and baPWV (average values) levels were significantly and positively correlated, and BMI, smoking history, medications (RAS-I and CCB), Cre, and Alb were significantly and negatively correlated with non-cardiovascular death (Table 6). Results of multivariate Cox regression analyses for total, cardiovascular, or non-cardiovascular mortality are shown in Table 7. Factors with significant correlation to total death by univariate analyses (Table 6), in addition to pre-VIM-SBP, were used as covariates in model 1. Similarly, factors correlated with cardiovascular death and pre-VIM-SBP, factors correlated with total death and post VIM-SBP, and factors correlated with non-cardiovascular death and post-VIM-SBP were used as covariates in models 2, 3, and 4, respectively. Pre-VIM-SBP was not significantly correlated with total death (model 1), but did show a significant positive relationship with cardiovascular death (HR: 1.166, 95% CI: 1.030–1.320, $P = 0.015$) (model 2). Post-VIM-SBP did not show

Table 4 Multiple regression analyses with SBP parameters

Variable	Pre-VIM-SBP		Post-VIM-SBP		Maximum Δ SBP		Average Δ SBP		Percentage of Δ SBP		Minimum of the lowest SBP		Average of the lowest SBP	
	β	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Age	–	–	–	–	–	–	–	–	–	–	−0.219	0.026	−0.109	0.183
Gender (male)	–	–	–	–	–	–	−3.306	0.026	−2.083	0.009	5.006	0.029	5.413	0.006
Performance status	0.930	<0.001	1.026	0.025	4.903	0.030	3.214	<0.001	2.076	<0.001	−3.507	0.008	−1.586	0.161
Primary disease (DM)	0.845	0.081	2.385	0.001	–	–	4.531	0.002	1.896	0.016	–	–	–	–
Duration of hemodialysis therapy	–	–	0.155	0.110	–	–	0.272	0.103	–	–	–	–	–	–
Smoking history	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Antihypertensive treatment (CCB)	–	–	–	–	−8.207	0.037	−2.811	0.066	−3.276	<0.001	11.237	<0.001	12.090	<0.001
Kt/V	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CTR	–	–	–	–	–	–	–	–	–	–	–	–	−0.239	0.177
Average %BW	–	–	–	–	3.989	<0.001	2.212	<0.001	1.362	< 0.001	−3.517	<0.001	−2.012	<0.001
Hemoglobin	–	–	–	–	–	–	–	–	0.834	0.009	−2.163	0.019	−1.819	0.018
HDL-cholesterol	–	–	–	–	–	–	–	–	–	–	–	–	0.133	0.039
LDL-cholesterol	–	–	–	–	0.150	0.026	–	–	–	–	–	–	–	–
Triglyceride	–	–	–	–	–	–	–	–	–	–	−0.045	0.002	−0.022	0.137
Calcium	−0.771	0.054	–	–	–	–	–	–	–	–	–	–	–	–
CRP	–	–	–	–	–	–	–	–	–	–	−2.639	0.005	–	–
hANP	–	–	0.009	0.111	–	–	–	–	–	–	–	–	–	–
BNP	–	–	–	–	–	–	–	–	−0.004	0.001	0.009	0.005	0.009	<0.001
Albumin	−1.246	0.055	–	–	–	–	–	–	–	–	–	–	–	–
LVEF	–	–	–	–	–	–	0.118	0.058	–	–	–	–	–	–
LVMI	–	–	–	–	–	–	–	–	–	–	0.028	0.168	0.037	0.032
Dec-T	0.012	<0.001	–	–	–	–	–	–	–	–	–	–	–	–
	$R^2 = 0.126$	$R^2 = 0.157$	$R^2 = 0.251$	$R^2 = 0.248$	$R^2 = 0.314$	$R^2 = 0.328$	$R^2 = 0.331$							
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$							

SBP systolic blood pressure, *VIM* variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP, *Δ SBP* difference between the highest and lowest values of SBP, *percentage of Δ SBP* Δ SBP × 100/the highest SBP, *DM* Diabetes mellitus, *CCB* calcium channel blocker, *CTR* cardiothoracic ratio, *%BW* percentage of body weight gain, *CRP* C-reactive protein, *hANP* human atrial natriuretic peptide, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *Dec-T* deceleration time

Table 5 Kaplan–Meier survival plots comparing higher and lower groups for BP result

Variable	Total death (*P*-value)	Cardiovascular death (*P*-value)	Non-cardiovascular death (*P*-value)
Pre-VIM-SBP (higher group ≥12.5)	0.020	0.047	0.227
Post-VIM-SBP (higher group ≥12.3)	0.013	0.236	0.008
Maximum Δ SBP (higher group ≥60 mmHg)	0.225	0.324	0.479
Average Δ SBP (higher group ≥33.3 mmHg)	0.071	0.121	0.350
Percentage of Δ SBP (higher group ≥20.6 %)	0.364	0.954	0.151
Minimum of the lowest SBP (higher group ≥106 mmHg)	0.140	0.316	0.184
Average of the lowest SBP (higher group ≥125 mmHg)	0.429	0.916	0.322
Minimum of the lowest SBP (higher group ≥110 mmHg)	0.107	0.168	0.324
Average of the lowest SBP (higher group ≥110 mmHg)	0.181	0.462	0.205

VIM variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP, *SBP* systolic blood pressure, *Δ SBP* difference between the highest and lowest values of SBP, *percentage of Δ SBP* Δ SBP × 100/the highest SBP

significant relationships with total (model 3) or non-cardiovascular death (model 4).

Discussion

The present study demonstrates three major findings regarding VIM in SBP as defined by VVBPV estimates from maintenance of HD patients. First, each SBP parameter including VIM in SBP is reproducible. Second, VIM in SBP is correlated with several background factors. Finally, pre-VIM-SBP is independently associated with cardiovascular mortality. These data suggest that pre-VIM-SBP could be used as a predictive marker for cardiovascular events for HD patients.

Reproducibility of VIM in SBP and other SBP parameters

Howard et al. demonstrated the reproducibility of VVBPV in patients who had suffered a TIA or minor ischemic stroke [27]. In contrast, VVBPV in HD patients may be influenced by many factors, such as interdialytic weight gain, anemia, nutritional condition, medications, and modulation of autonomic function. VVBPV in HD patients might thus be expected to show low reproducibility. The present study is the first attempt to estimate the reproducibility of several SBP parameters, including VIM in HD patients. Interestingly, all SBP parameters examined revealed significant reproducibility. Both pre-VIM-SBP and post-VIM-SBP reproducibility tended to be less than average ΔSBP, percentage of ΔSBP, minimum of the lowest SBP, and average of the lowest SBP, but greater than maximum ΔSBP (Table 2). The mechanism behind differences in reproducibility among SBP parameters remains unknown; however, our study shows, for the first time, significant reproducibility of VVBPV in HD patients.

Relationships between SBP parameters and background factors

Previous studies report a correlation between Δ SBP or the lowest SBP and background factors [10, 11]. Similarly, in our study, SBP parameters were correlated with different background factors (Tables 3 and 4). However, to our knowledge, this report is the first to show that VIM in SBP correlates with background factors in HD patients. PS, a marker of physical activity, and Dec-T, a marker of left ventricular diastolic function, showed significant positive relationships with pre-VIM-SBP, independent of other factors. Less physical activity and worse left ventricular diastolic function are independently associated with increased pre-VIM-SBP. In contrast, PS and primary disease (DM) showed significant positive relationships with post-VIM-SBP, independent of other factors. Accordingly, less physical activity and presence of DM may be independently associated with elevated post-VIM-SBP.

The reason for differences in background factor relationships between pre-VIM-SBP and post-VIM-SBP is unclear, but a possibility is that pre-VIM-SBP is influenced by cardiac function, while post-VIM-SBP is influenced by changes due to DM. However, this possibility should be investigated in detail. Past reports showed that older age is associated with higher VVBPV in patients with chronic kidney disease (CKD) [1, 28]. Di Iorio et al. reported that, in HD patients, this association was not seen consistently [29]. In this study, pre-VIM-SBP did not correlate with age. This discrepancy could be explained by the inclination that older patients with CKD are more likely to die than to initiate dialysis [30]. Webb et al. reported that VVBPV was higher in patients administered RAS-Is and β-blockers and lower when administered CCBs in a random-effects meta-analysis [31]. Di Iorio et al. reported that VVBPV was higher in patients with CKD using RAS-Is and CCBs [28]. In our study, VIM in SBP did not correlate with treatment

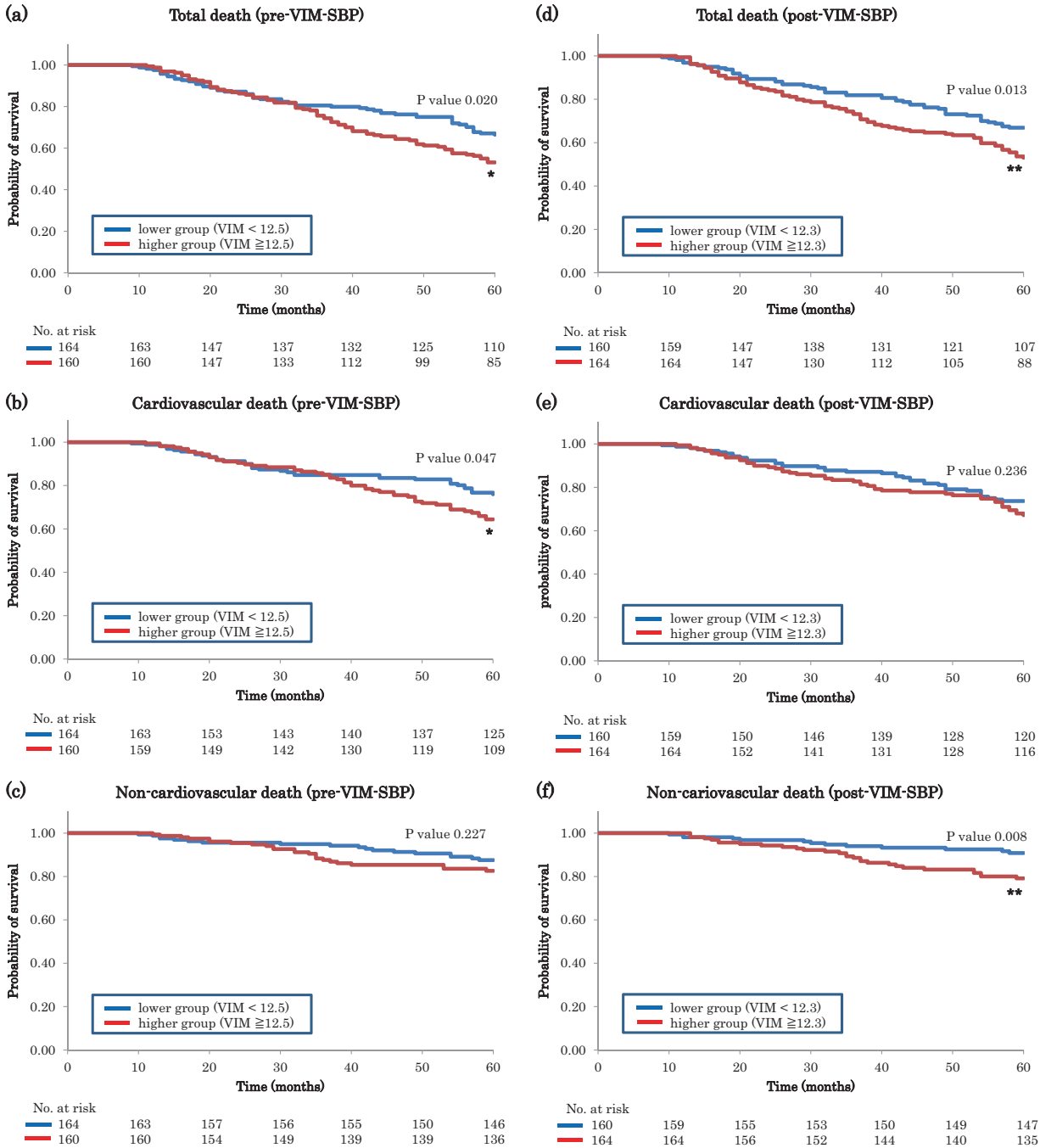

Fig. 1 Kaplan–Meier survival plots. Kaplan–Meier survival plots comparing patients in groups with higher and lower pre-VIM-SBP (left) and post-VIM-SBP (right). *VIM* variation independent of mean, *SBP* systolic blood pressure

with antihypertensive drugs, consistent with prior studies of HD patients [12]. This lack of association between classes of antihypertensive medications and VVBPV might be due to the numbers of patients receiving antihypertensive drugs (76.9% were taking RAS-Is and 65.1% were taking CCBs). Statistical group comparisons between patients with and without antihypertensive drug therapy are less robust because of the large difference in population sizes. This issue should also be addressed by further investigations.

Association between each kind of SBP parameter and prognosis

Several studies indicate that VVBPV is associated with total deaths in HD patients [12, 13, 14]. In these studies, VVBPV was assessed using SD [14] or CV [12, 13] of pre-dialysis SBP. CV is influenced by the absolute value of SBP [3]. To determine the prognostic value of variability, independently from the absolute value of SBP, a measure of variability that

Table 6 Univariate cox regression analyses for total, cardiovascular, and non-cardiovascular deaths

Variable	Total death			Cardiovascular death			Non-cardiovascular death		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.070	1.050–1.090	<0.001	1.038	1.013–1.064	0.003	1.105	1.074–1.137	<0.001
Gender (male)	1.363	0.960–1.937	0.083	1.847	1.076–3.169	0.026	N.S.	N.S.	N.S.
Body mass index	0.891	0.845–0.941	<0.001	0.902	0.835–0.975	0.009	0.876	0.812–0.945	<0.001
Performance status	2.203	1.834–2.645	<0.001	1.917	1.466–2.508	<0.001	2.495	1.934–3.217	<0.001
Primary disease (DM)	1.818	1.284–2.574	<0.001	1.916	1.148–3.197	0.013	1.857	1.144–3.013	0.012
Duration of hemodialysis therapy	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	1.048	1.004–1.093	0.031
Smoking history	0.747	0.495–1.127	0.164	N.S.	N.S.	N.S.	0.402	0.200–0.811	0.011
Past history of cardiovascular diseases	1.693	1.204–2.379	0.002	2.296	1.389–3.796	0.001	N.S.	N.S.	N.S.
Medications (RAS-I)	0.556	0.383–0.805	0.002	0.545	0.317–0.936	0.028	0.544	0.326–0.910	0.020
Medications (β-blocker)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Medications (CCB)	0.529	0.375–0.744	<0.001	0.499	0.303–0.822	0.006	0.562	0.349–0.906	0.018
Kt/V	0.686	0.387–1.216	0.197	0.345	0.146–0.814	0.015	N.S.	N.S.	N.S.
CTR	1.078	1.051–1.105	<0.001	1.066	1.027–1.108	<0.001	1.087	1.050–1.124	<0.001
Average of %BW	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	1.090	0.971–1.223	0.144
Hemoglobin	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
HDL-cholesterol	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
LDL-cholesterol	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Triglyceride	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Calcium	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Inorganic phosphorus	0.787	0.682–0.909	0.001	0.711	0.572–0.884	0.002	0.851	0.701–1.033	0.103
Intact-parathyroid hormone	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Creatinine	0.838	0.779–0.902	<0.001	0.777	0.695–0.868	<0.001	0.892	0.808–0.985	0.024
Uric acid	0.919	0.823–1.027	0.135	N.S.	N.S.	N.S.	0.891	0.766–1.038	0.139
CRP	1.083	0.994–1.181	0.068	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
hANP	1.006	1.004–1.008	<0.001	1.006	1.003–1.009	<0.001	1.006	1.003–1.009	<0.001
BNP	1.001	1.000–1.001	<0.001	1.001	1.000–1.001	<0.001	1.000	1.000–-1.001	0.063
Albumin	0.427	0.297–0.613	<0.001	0.363	0.218–0.604	<0.001	0.559	0.326–0.959	0.035
Glycoalbumin	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
LVEF	0.973	0.959–0.988	<0.001	0.963	0.943–0.984	<0.001	0.984	0.963–1.006	0.149
LVMI	1.003	1.000–1.006	0.030	1.005	1.001–1.009	0.022	N.S.	N.S.	N.S.
E/A	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Dec-T	N.S.	N.S.	N.S.	0.997	0.994–1.001	0.179	N.S.	N.S.	N.S.
baPWV (average values)	1.001	1.000–1.001	<0.001	1.001	1.000–1.000	0.004	1.001	1.000–1.001	0.002

N.S. not selected as a potential covariate, *DM* Diabetes mellitus, *RAS-I* renin-angiotensin system inhibitor, *CCB* calcium channel blocker, *CTR* cardiothoracic ratio, *%BW* percentage of body weight gain, *CRP* C-reactive protein, *hANP* human atrial natriuretic peptide, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *E/A* early filling over atrial filling, *Dec-T* deceleration time, *baPWV* brachial-ankle pulse wave velocity

is uncorrelated with this statistic is needed. VIM is a transformation of SD that is defined to be uncorrelated with the mean [3]. As an index of VVBPV, we selected VIM in SBP, which is less influenced by the absolute value of SBP.

In our study, VIM in SBP (both pre-VIM-SBP and post-VIM-SBP) was associated with total deaths in HD patients (Table 5 and Fig. 1). Further, pre-VIM-SBP was independently associated with cardiovascular deaths (Table 7). Some reports demonstrate that other indices of VVBPV such as CV are associated with cardiovascular events [12, 29, 32]. Selvarajah et al. reported that pre-VIM-SBP is independently associated with all-cause mortality in HD patients [33]. No previous reports demonstrate an association with cardiovascular deaths. To the best of our knowledge, this study is the first to demonstrate that pre-VIM-SBP is associated with such deaths.

Mechanisms which cause VVBPV to increase in HD patients are not known. Mena et al. demonstrated that disruption of BP homeostasis and large and small artery damage amplify BP fluctuations in response to

Table 7 Multivariate Cox regression analyses for total, cardiovascular, and non-cardiovascular death

Variable	Model 1			Model 2			Model 3			Model 4		
	Total death			Cardiovascular death			Total death			Non-cardiovascular death		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.086	1.047–1.127	<0.001	1.060	1.007–1.116	0.026	1.086	1.047–1.127	<0.001	1.081	1.028–1.137	0.002
Gender (male)	–	–	–	20.257	3.265–125.691	0.001	–	–	–	–	–	–
Body mass index	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0.871	0.743–1.021	0.088
Performance status	N.S.	N.S.	N.S.	1.839	1.038–3.258	0.037	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Primary disease (DM)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	3.758	1.375–10.271	0.010
Duration of hemodialysis therapy	–	–	–	–	–	–	–	–	–	1.115	1.005–1.236	0.040
Smoking history	–	–	–	–	–	–	–	–	–	N.S.	N.S.	N.S.
Past history of cardiovascular diseases	7.193	3.365–15.376	<0.001	10.868	3.124–37.801	<0.001	7.193	3.365–15.376	<0.001	–	–	–
Medication (RAS-I)	N.S.	N.S.	N.S.	0.217	0.052–0.912	0.037	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Medication (CCB)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Kt/V	–	–	–	N.S.	N.S.	N.S.	–	–	–	–	–	–
CTR	N.S.	N.S.	N.S.	1.066	0.974–1.167	0.163	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Inorganic phosphorus	0.547	0.385–0.777	<0.001	0.419	0.262–0.671	<0.001	0.547	0.385–0.777	<0.001	–	–	–
Creatinine	1.204	1.016–1.426	0.032	N.S.	N.S.	N.S.	1.204	1.016–1.426	0.032	N.S.	N.S.	N.S.
hANP	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
BNP	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	–	–	–
Albumin	0.160	0.060–0.426	<0.001	N.S.	N.S.	N.S.	0.160	0.060–0.426	<0.001	0.383	0.116–1.264	0.115
LVEF	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	–	–	–
LVMI	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	–	–	–
baPWV (average values)	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
pre-VIM-SBP	N.S.	N.S.	N.S.	1.166	1.030–1.320	0.015	–	–	–	–	–	–
post-VIM-SBP	–	–	–	–	–	–	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. not selected as a potential covariate, *DM* Diabetes mellitus, *RAS-I* renin-angiotensin system inhibitor, *CCB* calcium channel blocker, *CTR* cardiothoracic ratio, *hANP* human atrial natriuretic peptide, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *baPWV* brachial-ankle pulse wave velocity, *SBP* systolic blood pressure, *VIM* variation independent of mean, *pre-VIM-SBP* VIM of pre-dialysis SBP, *post-VIM-SBP* VIM of post-dialysis SBP

environmental or central stimuli [34, 35]. Other studies showed that endothelial cell injury was a sign of vascular injury, and it could increase the risk of death due to cardiovascular disease [36-38]. A recent study showed that VVBPV was associated with endothelial cell injury in patients with CKD [39]. Higher pre-VIM-SBP may then exacerbate endothelial injury and may be a factor in end-organ damage, cardiovascular events, and cardiovascular deaths.

Intriguingly, in the present study, higher post-VIM-SBP is associated with increased non-cardiovascular deaths (Table 5 and Fig. 1), although the association was not independent of other factors. No clear explanation for this finding is available. However, higher post-VIM-SBP was associated with less physical activity and primary disease (DM). Patients with DM have a poor prognosis due to an increased prevalence of not only cardiovascular disease [7, 8] but also non-cardiovascular diseases such as infection [40] and cancer [41]. Both of these latter conditions were important causes of deaths in this study (17 deaths due to infectious diseases and 12 deaths due to cancer). Thus, higher post-VIM-SBP may be associated with increased non-cardiovascular deaths due to the presence of DM.

Prior reports show that Δ SBP [11] and intradialytic hypotension [10] are risk factors for mortality in HD patients. Zager et al. advocated a U-shaped association between post-dialysis SBP and cardiovascular mortality, with increased mortality when SBP was ≥180 mmHg and <110 mmHg [42]. However, in contrast, no SBP parameters other than VIM in SBP showed associations with increased mortality in the present study. VIM in SBP appears to be a better predictor for prognosis in HD patients than other SBP parameters, and thus may be clinically more useful for such patients.

Limitations

Several limitations of the present study warrant mention. First, our sample size was relatively small. Second, we had no information for dosages of antihypertensive drugs, times when medications were taken, and compliance with medication management, all of which may be associated with VVBPV in HD patients [43]. Third, a causal relationship between VIM in SBP and prognosis remains undetermined. Further studies will be required to clarify whether reducing VVBPV will improve prognoses for HD patients.

Conclusion

The present study presents data that VIM in SBP and other SBP parameters during HD therapy are reproducible and associated with various background factors. Also, pre-VIM-SBP is independently correlated with cardiovascular mortality. Pre-VIM-SBP could be used as a predictive marker for cardiovascular events in HD patients. Further studies are necessary to confirm the mechanism for underlying increases in VVBPV and to clarify whether reducing VVBPV improves prognoses for HD patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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