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Characteristics and Influencing Factors of Intra-Dialysis Blood Pressure Variability in Hemodialysis Patients: A Retrospective Study

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Objective: To investigate the correlation between background factors and blood pressure variability (BPV), and the prognostic value of intra-dialytic BPV metrics for cardiovascular death and all-cause mortality in hemodialysis (HD) patients.

Methods: A retrospective study of 264 hD patients was followed up for 36 months. The intra-dialytic BP during the 3-month period for each patient was used to calculate BPV metrics, including standard deviation (SD), coefficient of variation (CV), average real variability (ARV), blood pressure change (ΔBP), and percent change in blood pressure (ΔBP/pre-BP). The primary outcomes were CVD death and all-cause mortality.

Results: Age, body mass index (BMI), predialysis blood pressure, inter-dialytic weight gain rate (IDWG%), α- blockers, and cholesterol levels were positively correlated with intra-dialytic BPV. Hemoglobin and albumin are negatively associated with intra-dialytic BPV. In Cox regression analysis, SBP-ARV, ΔSBP, and ΔSBP/pre-SBP were independent risk factors for CVD death (HR: 1.087, 95% CI: 1.001–1.181, p = 0.047; HR: 1.072, 95% CI: 1.016–1.131, p = 0.011; HR: 1.107, 95% CI: 1.011–1.211, p = 0.028). SBP-ARV showed the largest AUC of 0.593 (p = 0.022) in predicting all-cause death. SBP-ARV, ΔSBP, and ΔSBP/pre-SBP showed relatively large area (AUC = 0.631, 0.639, and 0.620; p = 0.007, 0.004, and 0.013 respectively) in predicting CVD death.

Conclusion: Age, BMI, IDWG%, predialysis blood pressure, albumin, hemoglobin, α- blockers, and total cholesterol were significantly correlated with intra-dialytic BPV. SBP-ARV, ΔSBP, and ΔSBP/pre-SBP were independent risk factors for CVD mortality, and there were no differences in prognostic value among various BPV metrics.

Keywords: hemodialysis, blood pressure variability, influencing factors, all-cause mortality, cardiovascular death

Introduction

Chronic kidney disease (CKD) has become a global public issue, with 697.5 million cases worldwide in 2017 and nearly one-third of CKD patients living in China and India.[1] Maintenance hemodialysis (MHD) is one of the alternative treatments for end-stage renal disease. It has been reported that the risk and mortality of cardiovascular events in dialysis patients are significantly higher than that in the general population.[2–4] Hypertension, as a common cause and complication in patients with CKD, leads to the occurrence and progression of kidney disease. Intensive blood pressure control can reduce the morbidity and mortality of cardiovascular diseases (CVD).[5–7] However, it was found that cardiovascular events would not be significantly reduced even if the blood pressure control of these HD patients is basically up to standard in clinical work. Patients' blood pressure often shows significant variability during HD, resulting in an increased incidence of cardiovascular events and even death. Therefore, blood pressure variability (BPV), defined as the fluctuation of blood pressure over a certain period, has been gradually paid attention to, and the correlation between BPV with target organ damage and cardiovascular events in hypertensive patients has been confirmed. Several studies have shown an

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association between BPV and poor outcomes in chronic hemodialysis patients, highlighting the importance of BPV as an independent risk factor for cardiovascular events and death and as a new target for hypertension treatment.[2,8] BPV is affected by arterial stiffness, enhanced renin-angiotensin-aldosterone system activity, volume overload, sympathetic nerve, endothelial dysfunction, and other factors.[9,10] BPV, with its complex relationship to CVD and mortality, is a particularly compelling and understudied cardiovascular risk factor in the MHD population. There are various research methods on BPV. BPV in HD patients included intra-dialytic and inter-dialytic BPV. Liu et al found that intra-dialytic BPV was superior to visit-to-visit BPV in predicting CVD events in HD patients.[11]

The BPV metrics included standard deviation (SD), variability independent of the mean (VIM), coefficient of variation (CV), and average real variability (ARV). In recent years, some studies have explored the relationship of BPV to cardiovascular outcomes and death in patients on HD.[12–14] Long-term BPV, short-term BPV, and different BPV indicators were observed in these studies. However, there is no consensus on the best BPV indicators to predict cardiovascular risk and blood pressure management in patients with HD. In this study, we calculated the intra-dialytic BPV using HD Center routine blood pressure records, analysed the correlation between intra-dialytic BPV and CVD and death, and the risk factors of intra-dialytic BPV, and evaluated the predictive power of intra-dialytic BPV measures for CVD events and all-cause mortality.

Patients and Methods

Patients

We conducted a retrospective study with patients undergoing MHD at the First Affiliated Hospital of Chongqing Medical University from April 1, 2019 to June 30, 2019. Inclusion criteria: (1) Aged than 18 years old, (2) Undergoing MHD for at least three months, (3) Receive HD 3 times a week for 4–4.5 hours each time, (4) vascular access was an arteriovenous fistula. The exclusion criteria: (1) patients with incomplete records, (2) patients lost to follow-up, switched to peritoneal dialysis, kidney transplantation, or transferred to another renal unit, (3) patients with severe infections, severe valvular heart disease, malignant arrhythmias, or other serious heart diseases (such as cardiomyopathy, myocardial infarction, congestive heart failure), malignancies, systemic vasculitis, and other autoimmune diseases, (4) patients who died or suffered cardiovascular events (stroke, transient ischaemic attack, myocardial infarction, angina, or heart failure) during the 3-month period. This study was approved by the local independent ethics committee of the First Affiliated Hospital of Chongqing Medical University (K2023-244). This retrospective study is based on case data analysis and does not involve drugs or other intervention measures. Therefore, the patients did not sign consent forms.

Data Collection

The demographic and clinical data were collected: age, body mass index (BMI), smoking and drinking history, gender, comorbidities, and use of antihypertensive medications. The laboratory parameters were also collected: serum creatinine, hemoglobin, albumin, serum electrolytes, parathyroid hormone (PTH), total cholesterol (TC), and triglyceride (TG).

The dialysis-related variables were recorded, including dialysis vintage, urea clearance index (Kt/V), dry weight, and inter-dialytic weight gain rate (IDWG%). The average values during the 3-month period served as the baseline data.

Outcomes

Our primary outcomes were cardiovascular disease (CVD) death and all-cause mortality. The follow-up period was from July 1, 2019, to June 30, 2022. Cardiovascular events occurring during follow-up were also recorded. Cardiovascular events included heart failure, ventricular arrhythmias, myocardial infarction, cerebral infarction, cerebral hemorrhage, and peripheral artery disease required surgical intervention.

BPV Parameters

Intra-dialytic blood pressure was measured automatically at 0 (predialysis), 60, 120, 180, and 240 (post-dialysis) minutes by the dialysis apparatus, therefore, five measurements per intra-dialysis session were recorded. The patient was resting in a lying position. The intra-dialytic blood pressure for each patient during the 3-month period was used to calculate

BPV metrics (4 weeks per month, three intra-dialysis sessions per week, a total of about 36 intra-dialysis sessions from April 1, 2019, to June 30, 2019). Five different metrics were analysed: (1) SD; (2) CV was the SD divided by the mean and multiplied by 100%; (3) ARV was the mean of absolute differences between consecutive blood pressure readings during each intra-dialysis;[15] (4) blood pressure change (ΔBP), which refers to the highest blood pressure minus the lowest blood pressure during each intra-dialysis period; (5) percent change in blood pressure (ΔBP/pre-BP), calculated as ΔBP divided by predialysis blood pressure (pre-BP) and multiplied by 100%. For each individual, we calculated the above parameters for each dialysis session, and then computed the average of the 36 parameter values to represent the patient's blood pressure variability. The above systolic and diastolic blood pressure parameters were calculated separately to represent their respective variability.

Statistical Analysis

Continuous variables with a normal distribution were reported as mean ± standard deviation and analysed using the *t*-test. Continuous variables, not following a normal distribution, were presented as median with interquartile range (IQR) and compared using the Mann–Whitney *U*-test. Categorical variables were expressed as counts and percentages (n, %) and assessed using the Chi-square test. Variable filtering involved Spearman correlation test, and multiple regression analysis assessed the relationship between BPV metrics and covariates. Adjusted Cox proportional hazards models were used to explore the association between BPV with CVD and all-cause mortality. Receiver Operating Characteristic (ROC) curves compared the prognostic performance of different BPV metrics. All analyses used IBM SPSS Windows v. 27; P-values less than 0.05 were considered statistically significant.

Result

Characteristics of the Study Subjects

A total of 264 patients were recruited in this study. During the three-month period, 9504 hD treatments and 47,520 BP measurements were recorded. The study subjects' demographic, clinical, and biochemical characteristics are in Table 1. Patients aged 62.2 ± 14.5 years and composed of 59.1% male, and the median duration of dialysis was 84 months. The prevalence of comorbidities included 39.8% diabetes, 90.2% hypertension, 43.9% cardiovascular disease. During the follow-up period, 107 patients (40.5%) encountered cardiovascular events and 69 patients (26.1%) died, of which 43 deaths (62.3%) were attributed to cardiovascular causes (Table 1).

Table 1 Baseline Characteristics of HD Patients and Comparisons of Patients with or without Cardiovascular Events

Variables	Total (N=264)	CVD event (N=107)	Non-CVD event (N=157)	P value
Male, n (%)	156 (59.1)	65 (60.7)	91 (58.0)	0.651
Age (years)	62.2±14.5	69.7±11.1	57.0±14.3	<0.001
BMI (kg/m^2)	22.6 (20.6, 25.0)	23.0 (20.8, 25.6)	22.3 (20.4, 24.7)	0.047
Diabetes	105 (39.8)	62 (57.9)	43 (27.4)	<0.001
Hypertension	238 (90.2)	95 (88.8)	143 (91.1)	0.538
CVD	116 (43.9)	76 (71.0)	40 (25.5)	<0.001
Smoking, n (%)	119 (45.1)	58 (54.2)	61 (38.9)	0.014
Drinking, n (%)	96 (36.4)	47 (43.9)	49 (31.2)	0.035
Medications (RAS-I/ β-blocker/ α-blocker/CCB)	142/152/82/223	53/53/33/87	89/99/49/136	
K (mmol/L)	4.7±0.7	4.6±0.6	4.7±0.7	0.220
Na (mmol/L)	140.0 (138.0, 142.0)	140.0 (137.0, 141.9)	140.1 (138.4, 142.0)	0.169
Ca (mmol/L)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	2.2 (2.1, 2.3)	0.478

(*Continued*)

Table 1 (Continued).

Variables	Total (N=264)	CVD event (N=107)	Non-CVD event (N=157)	P value
P (mmol/L)	1.6 (1.3, 2.0)	1.6 (1.2, 1.9)	1.6 (1.3, 2.0)	0.325
PTH (pg/mL)	301.5 (153.0, 530.0)	250.0 (129.0, 439.6)	336.2 (187.8, 551.6)	0.059
Cr (mg/mL)	8.6 (6.3, 10.1)	8.9 (6.6, 10.2)	8.4 (5.8, 10.1)	0.287
Hb (g/L)	108.3±16.4	107.1±15.3	109.2±17.1	0.313
Alb (g/L)	40.5±5.1	38.7±4.6	41.7±5.0	<0.001
PLT (x10^9/L)	163.7±55.6	160.3±61.1	166.0±51.7	0.423
TC (mmol/L)	3.5 (3.0, 4.2)	3.5 (2.9, 4.1)	3.5 (3.1, 4.2)	0.533
TG (mmol/L)	1.5 (1.0, 2.0)	1.4 (1.0, 2.0)	1.5 (1.1, 1.9)	0.426
Duration of HD (months)	84 (72, 120)	72 (60, 108)	96 (72, 120)	<0.001
Kt/V	1.3 (1.1, 1.4)	1.3 (1.1, 1.4)	1.3 (1.1, 1.4)	0.403
IDWG%	4.3±1.1	4.6±1.0	4.1±1.1	<0.001
All-cause Death, n (%)	69 (26.1)	38 (35.5)	31 (19.7)	0.004

Abbreviations: HD, hemodialysis; CVD, cardiovascular diseases; BMI, body mass index; RAS-I, renin-angiotensin system inhibitor; CCB, calcium channel blocker; K, kalium; Na, natrium; Ca, calcium; P, phosphorus; PTH, parathyroid hormone; Cr, creatinine; Hb, hemoglobin; Alb, albumin; PLT, platelet; TC, total cholesterol; TG, triglyceride; Kt/V, urea clearance index; IDWG%, inter-dialytic weight gain rate.

The mean age of the patients with cardiovascular events was older than those without (69.7 ± 11.1 vs 57.0 ± 14.3, $p < 0.001$). Compared with patients without cardiovascular events, the patients with cardiovascular events had higher BMI (23.0 vs 22.3, $p = 0.047$), smoking rate (54.2% vs 38.9%, $p = 0.014$) and drinking rate (43.9% vs 31.2%, $p = 0.035$). Patients with cardiovascular events had a higher proportion of diabetes and cardiovascular disease compared with patients without cardiovascular events ($p < 0.001$). Compared to the patients without cardiovascular events, the serum albumin level and HD duration were significantly low, and the IDWG% was high in patients with cardiovascular events (all $p < 0.001$) (Table 1).

The DBP-CV, ΔDBP/pre-DBP, and SBP-BPV metrics in patients with cardiovascular events were significantly higher than those without cardiovascular events (all $p < 0.05$). Compared to patients without cardiovascular events, patients with cardiovascular events had lower pre-DBP, not pre-SBP metric (Table 2).

Table 2 Comparison of Various BP Parameters Between Patients with or without Cardiovascular Events

BP parameters	Total (N=264)	CVD event (N=107)	Non-CVD event (N=157)	P value
SBP parameters				
Pre-SBP (mmHg)	147.4±17.3	149.3±19.4	146.0±15.6	0.128
SD (mmHg)	14.6 (12.7, 17.8)	16.2 (12.8, 18.3)	14.2 (12.4, 16.7)	0.006
CV (%)	10.3 (9.0, 12.0)	10.8 (9.6, 12.1)	10.0 (9.0, 11.9)	0.037
ARV (mmHg)	13.5 (11.7, 16.5)	14.7 (12.1, 17.5)	12.9 (11.3, 15.6)	0.003
ΔSBP(mmHg)	18.6 (15.6, 22.7)	19.8 (16.9, 25.0)	17.8 (15.4, 21.6)	0.003
ΔSBP/pre-SBP (%)	13.0 (11.0, 15.1)	13.6 (11.6, 15.8)	12.7 (10.8, 14.6)	0.013
DBP parameters				
Pre-DBP (mmHg)	75.3±12.2	70.7±11.1	78.6±11.8	<0.001
SD (mmHg)	8.1 (7.1, 9.5)	8.0 (6.9, 9.5)	8.2 (7.2, 9.6)	0.306
CV (%)	11.2 (9.5, 13.1)	11.9 (9.7, 14.2)	10.8 (9.4, 12.6)	0.012
ARV (mmHg)	7.4 (6.5, 8.9)	7.3 (6.3, 8.8)	7.5 (6.5, 9.1)	0.457
ΔDBP(mmHg)	10.2 (8.8, 12.6)	10.1 (8.5, 12.6)	10.3 (8.9, 12.7)	0.544
ΔDBP/pre-DBP (%)	13.7 (11.7, 16.7)	14.3 (12.3, 17.6)	13.3 (11.3, 16.3)	0.022

Abbreviations: BP, blood pressure; CVD, cardiovascular diseases; SBP, systolic blood pressure; pre-SBP, pre-dialysis systolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; ΔSBP, systolic blood pressure change; DBP, diastolic blood pressure; pre-DBP, pre-dialysis diastolic blood pressure; ΔDBP, diastolic blood pressure change.

Association Between Each Kind of BPV Metric and Covariates

We used a single correlation analysis to filter variables (Supplementary Table 1 and 2), multiple regression analysis was performed for variables with $p < 0.05$ (Tables 3 and 4). The multiple regression analysis revealed positive correlations between SBP-SD, CV, ARV, ΔSBP, and ΔSBP/pre-SBP of patients with age, BMI, and IDWG%. TC showed a positive correlation with SBP-SD, ΔSBP, and ΔSBP/pre-SBP. Medication (α- blocker) showed a positive correlation with SBP-ARV. Additionally, the pre-SBP exhibited positive associations with SBP-SD, ARV, and ΔSBP in patients. Conversely, hemoglobin demonstrated a negative correlation with SBP-SD in patients ($p < 0.05$) (Table 3). BMI was positively correlated with all kinds of DBP-BPV metrics (SD, CV, ARV, ΔDBP, and ΔDBP/pre-DBP), and pre-DBP was positively correlated with DBP-SD, ARV, ΔDBP, and ΔDBP/pre-DBP, IDWG% was only positively correlated with DBP-SD and CV, while serum albumin level was negatively correlated with DBP-SD ($p < 0.05$) (Table 4).

Association of Different BPV and Outcomes

We initially screened variables according to the univariate Cox regression model. In order to avoid eliminating important variables, we included any variables with $p < 0.2$ in the univariate Cox regression model of all-cause death or cardiovascular death as the outcome event into the multivariate Cox regression model (Supplementary Table 3).

Multivariate Cox regression analysis revealed that SBP-ARV, ΔSBP, and ΔSBP/pre-SBP were independent risk factors of CVD mortality in adjusted models (HR: 1.087, 95% CI: 1.001–1.181, $p = 0.047$; HR: 1.072, 95% CI: 1.016–1.131, $p = 0.011$; HR: 1.107, 95% CI: 1.011–1.211, $p = 0.028$). However, there was no significant association between the other BPV parameters and all-cause mortality ($p > 0.05$) (Table 5).

Table 3 Association Between SBP Metrics and Covariates by Multiple Regression Analyses

Variable	SD		CV		ARV		ΔSBP		ΔSBP/pre-SBP	
	B	P	B	P	B	P	B	P	B	P
Age	0.067	<0.001	0.044	0.001	0.069	<0.001	0.094	<0.001	0.058	0.003
BMI	0.171	0.007	0.107	0.012	0.213	0.001	0.233	0.012	0.152	0.014
α-blocker	-	-	-	-	0.947	0.040	-	-	-	-
Pre-SBP	0.065	<0.001	-	-	0.073	<0.001	0.117	<0.001	-	-
Hb	−0.028	0.035	-	-	-	-	-	-	-	-
TC	0.492	0.019	-	-	-	-	0.602	0.049	0.414	0.043
IDWG%	1.326	<0.001	0.821	<0.001	0.898	<0.001	1.209	<0.001	0.751	<0.001
	R^2=0.395	<0.001	R^2=0.260	<0.001	R^2=0.335	<0.001	R^2=0.308	<0.001	R^2=0.179	<0.001

Abbreviations: SBP, systolic blood pressure; BMI, body mass index; Hb, hemoglobin; TC, total cholesterol; IDWG%, inter-dialytic weight gain rate; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; ΔSBP, systolic blood pressure change; pre-SBP, pre-dialysis systolic blood pressure.

Table 4 Association Between DBP Metrics and Covariates by Multiple Regression Analyses

Variable	SD		CV		ARV		ΔDBP		ΔDBP/pre-DBP	
	B	P	B	P	B	P	B	P	B	P
BMI	0.118	0.001	0.130	0.020	0.098	0.016	0.169	0.002	0.225	0.011
Pre-DBP	0.046	<0.001	-	-	0.038	0.001	0.062	<0.001	0.092	0.001
Alb	−0.067	0.007	-	-	-	-	-	-	-	-
IDWG%	0.307	0.008	0.466	0.008	-	-	-	-	-	-
	R^2=0.125	<0.001	R^2=0.223	<0.001	R^2=0.103	<0.001	R^2=0.092	<0.001	R^2=0.167	<0.001

Abbreviations: DBP, diastolic blood pressure; BMI, body mass index; Alb, albumin; IDWG%, inter-dialytic weight gain rate; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; ΔDBP, diastolic blood pressure change; pre-DBP, pre-dialysis diastolic blood pressure.

Table 5 Association of Different BPV and Outcomes in Hemodialysis Patients Using Cox Regression Analysis

Variable	All-cause death		CVD death	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[a]	HR (95% CI)[b]
SBP parameters				
SD	1.074 (1.015–1.137)*	1.023 (0.953–1.099)	1.105 (1.031–1.185)*	1.070 (0.978–1.170)
CV	1.083 (0.985–1.190)	1.014 (0.908–1.133)	1.132 (1.008–1.270)*	1.078 (0.939–1.237)
ARV	1.071 (1.017–1.129)*	1.040 (0.972–1.113)	1.101 (1.035–1.172)*	1.087 (1.001–1.181)*1
ΔSBP	1.058 (1.019–1.098)*	1.040 (0.995–1.087)	1.084 (1.036–1.133)*	1.072 (1.016–1.131)*2
ΔSBP/pre-SBP	1.070 (1.003–1.140)*	1.043 (0.970–1.120)	1.121 (1.039–1.209)*	1.107 (1.011–1.211)*3
DBP parameters				
SD	1.056 (0.942–1.185)	1.021 (0.901–1.157)	1.125 (0.978–1.293)	1.054 (0.905–1.226)
CV	1.044 (0.974–1.118)	0.990 (0.915–1.072)	1.084 (0.999–1.176)	1.013 (0.922–1.113)
ARV	1.051 (0.935–1.181)	1.026 (0.904–1.164)	1.096 (0.949–1.266)	1.032 (0.884–1.204)
ΔDBP	1.049 (0.973–1.131)	1.042 (0.962–1.129)	1.080 (0.986–1.184)	1.051 (0.953–1.158)
ΔDBP/pre-DBP	1.029 (0.982–1.079)	1.008 (0.955–1.063)	1.052 (0.996–1.110)	1.017 (0.953–1.085)

Notes: *P<0.05, was considered statistically significant; *1 p=0.047; *2 p=0.011; *3 p=0.028. [a]Unadjusted model. [b]Adjusted for demographic characteristics (age, sex), clinical factors (history of diabetes, and BMI), smoking habits, drinking habits, dialysis-related factors (pre-SBP, Duration of HD, IDWG%, Kt/V), laboratory measurements (serum albumin, hemoglobin, and PTH).

Table 6 showed the area under the ROC curves (AUC) for different BPV indicators predicting CVD death or all-cause death and the images were shown in Figure 1. The AUC of SBP-ARV was 0.593 (95% CI: 0.510–0.676, p = 0.022) in the prediction of all-cause death, and the cutoff value was 15.45 with a sensitivity 72.31% and a specificity 49.28%. The AUC of SBP-ARV, ΔSBP, and ΔSBP/pre-SBP were 0.631, 0.639, and 0.620 (p = 0.007, 0.004, and 0.013, respectively) in the prediction of CVD death, and the cutoff points were 14.80 mmHg with sensitivity 66.52% and a specificity 60.47%, 23.35 mmHg with a sensitivity 81.45% and a specificity 46.51%, and 26.10% with sensitivity 90.05% and a specificity 34.88%, respectively. Pairwise comparison of ROC curves with $p < 0.05$ was performed using the Delong test. No significant differences in ROC curves in predicting CVD death or all-cause death between intra-dialytic BPV metrics were discovered (all $p > 0.05$).

Table 6 AUC for Different BPV Metrics in Predicting All-Cause Death and CVD Death

Variable	All-cause death		CVD death	
	AUC (95% CI)	P value	AUC (95% CI)	P value
SBP parameters				
SD	0.571 (0.486–0.656)	0.081	0.599 (0.493–0.706)	0.039
CV	0.539 (0.454–0.624)	0.336	0.561 (0.455–0.667)	0.204
ARV	0.593 (0.510–0.676)	0.022	0.631 (0.528–0.733)	0.007
ΔSBP	0.591 (0.510–0.673)	0.024	0.639 (0.541–0.737)	0.004
ΔSBP/pre-SBP	0.559 (0.479–0.639)	0.149	0.620 (0.526–0.715)	0.013
DBP parameters				
SD	0.516 (0.436–0.596)	0.697	0.551 (0.455–0.647)	0.291
CV	0.545 (0.465–0.625)	0.266	0.584 (0.487–0.681)	0.080
ARV	0.526 (0.447–0.604)	0.529	0.556 (0.464–0.648)	0.246
ΔDBP	0.557 (0.478–0.636)	0.163	0.595 (0.504–0.686)	0.048
ΔDBP/pre-DBP	0.559 (0.478–0.639)	0.148	0.601 (0.504–0.698)	0.037

Abbreviations: AUC, area under curve; BPV, blood pressure variability; CVD, cardiovascular diseases; SBP, systolic blood pressure; pre-SBP, pre-dialysis systolic blood pressure; SD, standard deviation; CV, coefficient of variation; ARV, average real variability; ΔSBP, systolic blood pressure change; DBP, diastolic blood pressure; pre-DBP, pre-dialysis diastolic blood pressure; ΔDBP, diastolic blood pressure change.

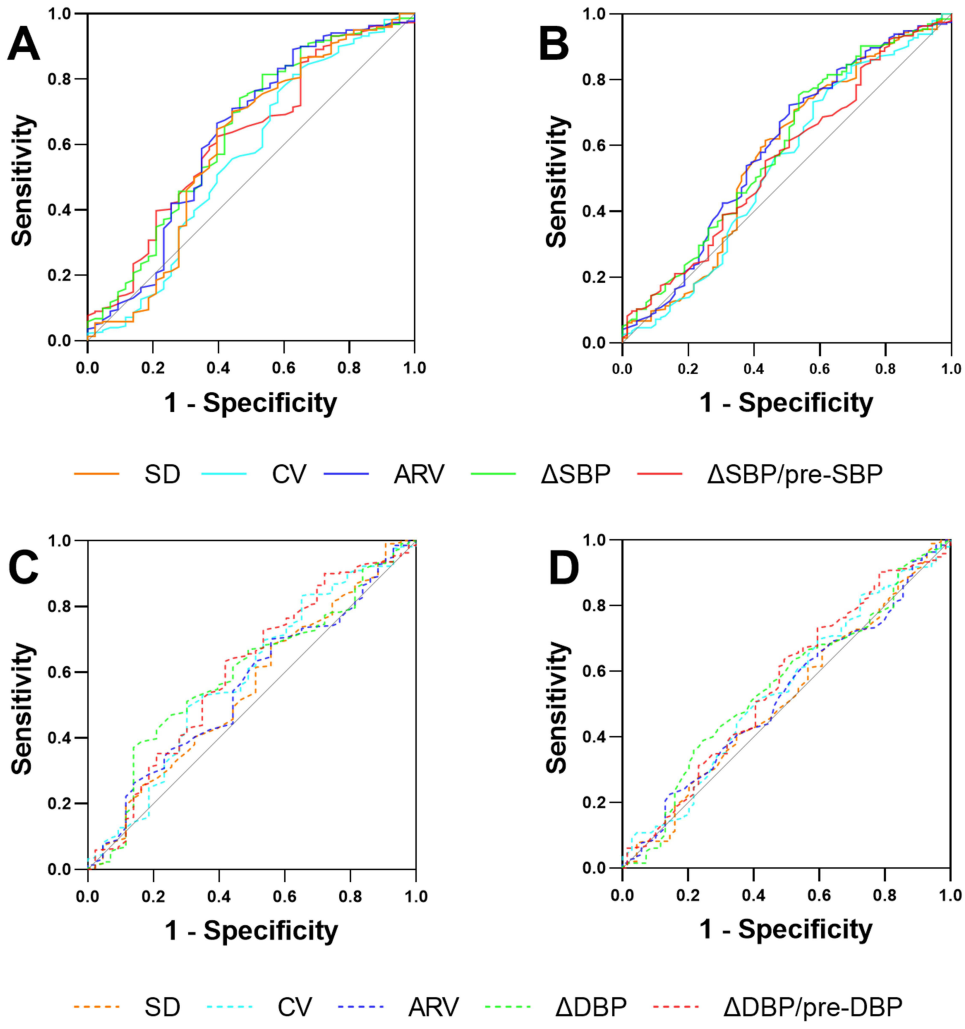

Figure 1 ROC curves for different SBP variability metrics to predict CCVD-death (**A**) and all-cause mortality (**B**). ROC curves for different DBP variability metrics to predict CCVD-death (**C**) and all-cause mortality (**D**).

Discussion

In this study, we recruited 264 patients on MHD and calculated the intra-dialytic BPV metrics using the intra-dialytic blood pressure measurements during the three-month period. We analysed the association between the intra-dialytic BPV metrics and cardiovascular events and mortality while examining the risk factors for intra-dialytic BPV metrics. We found that intra-dialytic SBP-ARV, ΔSBP, and ΔSBP/pre-SBP are independent risk factors for cardiovascular mortality but not all-cause mortality. Further analysis found that the age, BMI, and IDWG% were positively correlated with all kinds of SBP-BPV metrics by Multiple regression analysis.

Hemodialysis is one of the main treatments for end-stage renal disease. Patient's blood pressure tends to show significant variability during dialysis, resulting in an increased incidence of cardiovascular events and even death, and there are many factors affecting BPV. Approximately 40.5% (107/264) of patients had a cardiovascular event during follow-up. The intra-dialytic SBP-SD, CV, ARV, ΔSBP, ΔSBP/pre-SBP, DBP-CV, and ΔDBP/pre-DBP in patients with cardiovascular events were significantly higher than those without cardiovascular events, which suggested that the intra-dialytic BPV in HD patients may be one of the risk factors for cardiovascular events. CVD is the common cause of death in dialysis patients. In this study, 69 patients (26.1%) died during the follow-up period, of which CVD accounted for 62.3%. The mortality rate of patients with cardiovascular events was significantly higher than that of patients without

cardiovascular events. We also found that Cox regression analysis identified SBP-ARV, ΔSBP, and ΔSBP/pre-SBP as independent risk factors for CVD mortality.

Furthermore, a 1 mmHg increase in SBP-ARV was associated with an 8.7% higher risk of CVD death. Unlike SBP-ARV, ΔSBP and ΔSBP/pre-SBP reflect blood pressure fluctuation during intra-dialysis. Most previous studies have shown that the difference in blood pressure before and after HD is associated with poor prognosis of patients.[16,17] We analysed ΔBP intra-dialysis for the first time and found that each 1 mmHg increase in ΔSBP was associated with a 7.2% increased risk of cardiovascular death, and each 1% increase in ΔSBP/pre-SBP was associated with a 10.7% increased risk of cardiovascular death. The potential importance of the amplitude of blood pressure fluctuations (ΔBP) for cardiovascular events may have been overlooked. Previous studies have shown that the brain's regulation of blood pressure fluctuations is directional or lagging, and when ΔSBP is increased, the brain's cerebrovascular response to the decrease in arterial pressure is significantly reduced.[18]

Compared with the non-dialysis population, HD patients have impaired autonomic nervous function, lower baroreflex sensitivity values, endothelial dysfunction further impedes automatic regulation and poor ability to buffer hemodynamic changes caused by HD, massive systolic blood pressure changes (ΔSBP) during HD, and the brain is easily affected by circulatory fluctuations.[19] The hypo-perfusion of vital organs such as the brain, heart, kidney, and intestine in HD patients with more intra-dialytic BP drop leads to increased blood endotoxin levels, and endotoxemia is closely related to death.[20,21] Therefore, higher ΔSBP independently affected the end point of heart and brain death, suggesting that the control of blood pressure variation intra-dialysis helped improve the outcome.

BPV in HD patients is complex and varied, and each indicator assesses the complex BPV phenomenon in different aspects. Moreover, there is no uniform clinical and prognostic value at present. Multiple studies have consistently demonstrated a significant association between BPV during dialysis and CVD, as well as all-cause mortality.[11,22,23] However, limited research has been conducted to compare the prognostic capabilities of these measures. Our study found that intra-dialytic SBP-ARV, ΔSBP, and ΔSBP/pre-SBP were better predictors with higher AUC than other BPV metrics in predicting CVD death. However, we compared the ROC curves of these measures in pairs, found no significant difference in all-cause death or CVD and found no markers of BPV that predominate regarding prognostic value. Compared with SD and CV, ARV is the average of the absolute differences in continuous measurements, which is more stable as the sampling frequency of blood pressure measurements changes, and ARV metric considers the sequence of blood pressure changes between successive readings.[24] Therefore, ARV is sensitive to the sequence of a single blood pressure measurement and is an independent risk factor for CVD, which may be a relatively favorable target. There have been many studies on the blood pressure difference before and after HD, but few on ΔSBP. There may be large blood pressure fluctuations intra-dialysis, and the blood pressure value after HD may not accurately represent the minimum blood pressure intra-dialysis. The blood pressure change before and after HD has certain limitations as a prognostic indicator, because it cannot reflect the occurrence of hypotension or hypertension intra-dialysis. Studies have found that hypertension and hypotension intra-dialysis are significantly related to poor prognosis.[10,17,25,26] ΔSBP represents the range of blood pressure fluctuations in the short period of intra-dialysis, which can compensate for this shortcoming, which indicates its potential clinical application value. The study of BPV needs to establish a recognized, reasonable, reliable, and efficient measurement index, which can be practically applied to clinical blood pressure management. We can further explore by expanding the sample size and exploring new calculation methods.

This study showed that age, BMI, predialysis blood pressure, and IDWG% were significantly and positively correlated with BPV. Age was positively correlated with systolic BPV, independent of other factors. With aging, the arterial wall of elderly HD patients undergoes thickening, resulting in increased stiffness and decreased compliance; these lead to a disorder in pressure receptors and a reduced sensitivity of pressure reflex, ultimately causing an elevation in BPV.[27,28] BMI is significantly positively correlated with systolic and diastolic BPV. Adipose tissue can release many inflammatory factors, which cause long-term damage to endothelial cells, leading to increased vascular stiffness and BPV.[29,30] These suggest that patients' weight management can prevent or control arterial aging and reduce BPV.

The increase of IDWG% is significantly positively correlated with the BPV during the intra-dialysis period. Poor fluid control and excessive salt intake lead to an increase in body mass and blood flow in HD patients during the intra-dialytic period. The increase in ultrafiltration volume leads to an increase in BPV. The proper adjustment of ultrafiltration volume

is helpful to the dialysis adequacy of patients to achieve the purpose of reducing the volume load and making the blood pressure relatively stable during intra-dialysis. It has been reported that for elderly patients, the larger the IDWG%, the more serious the malnutrition.[31] Malnutrition accelerates the decline of endothelial function and increases arterial stiffness, possibly due to excessive intake of sodium and fluids and low intake of calories and protein. In addition, we also found that hemoglobin and albumin were significantly negatively correlated with BPV and cholesterol levels were positively correlated with BPV. Hemoglobin and serum cholesterol mainly affect SBP, and albumin affects DBP. High hemoglobin and albumin levels indicate that patients have good nutritional status and low micro-inflammation and oxidative stress levels in the body, so blood vessel damage is less severe.[32] Studies have found that ameliorating anemia can improve ventricular remodelling,[33] while high cholesterol can reduce vascular endothelial function and increase arteriosclerosis.[30] A reasonable diet could improve the nutritional status of patients, and correcting anemia and hypoproteinemia will help reduce blood pressure fluctuations during dialysis and improve patient prognosis.

We also found that predialysis of blood pressure as an indicator of hypertension management was independently correlated with SD, ARV, and ΔSBP -BPV metrics. These suggested the importance of inter-dialytic hypertension management in dialysis patients. In terms of blood pressure medication choice, we only found a significant positive association between the use of alpha receptor inhibitors and SBP-ARV, which probably because that our patients were all non-preferred α-receptor inhibitor antihypertensive treatment, and most of them use alpha-receptor blockers when the combination of other antihypertensive drugs still cannot control blood pressure, and such patients themselves were difficult to control blood pressure and had large BPV. Whether blood pressure medications are related to inter-dialytic BPV in dialysis patients is still controversial. It has been reported that the use of CCB drugs has advantages in the short-term control of BPV,[22] but there are also contrary reports.[34] This study did not show a significant association between antihypertensive therapy and other BPV metrics, possibly because the effect of dialysis on blood pressure exceeded the effect of antihypertensive drugs on blood pressure or because hemodialysis eliminated antihypertensive drugs in patients.

Our study also had some limitations. Firstly, it was a single-center retrospective study with a limited cohort size, which could lead to bias. Secondly, there may be confounding factors that we did not include, such as erythropoietin and lipid-regulating drugs, inflammation, and malnutrition.

Conclusion

Intra-dialytic BPV metrics SBP-ARV, ΔSBP, and ΔSBP/pre-SBP may be independent risk factors for cardiovascular death. Further studies are needed to confirm the potential predictive value of BPV for cardiovascular death. Age, BMI, IDWG%, predialysis BP, albumin, hemoglobin, α- blockers, and total cholesterol may influence BPV, and further studies of the pathophysiology of BPV are needed to develop potential therapeutic strategies to improve cardiovascular outcomes in HD.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (approval number: K2023-244). The data are anonymous, and the requirement for informed consent was therefore waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare.

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