Long-Term Predialysis Systolic Blood Pressure Variability and Intradialytic Cardiac Hemodynamics in Hemodialysis Patients

Jingjuan Yang
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Jian Huang
Department of Nephrology, Central Hospital of Jinhua
Biying Yu
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Qian Zhang
Kidney Disease Center, the First Affiliated Hospital, Zhejiang University School of Medicine
Shanshan Zhang
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Longlong Wu
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Lin Luo
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Lizhu Li
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Li Li
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine
Fei Han
Kidney Disease Center, the First Affiliated Hospital, Zhejiang University School of Medicine
Christopher S. Wilcox:
Division of Nephrology and Hypertension, and Hypertension Center, Georgetown University
En Yin Lai
Department of Physiology, School of Basic Medical Sciences, Zhejiang University School of Medicine
Yi Yang (yangyixk@zju.edu.cn)
Department of Nephrology, the Fourth Affiliated Hospital, Zhejiang University School of Medicine

Research Article

Keywords: predialysis systolic blood pressure, cardiac hemodynamics, hemodialysis

Posted Date: December 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-112584/v1

Abstract

The association in hemodialysis patients between long-term predialysis blood pressure variability and intradialytic cardiac hemodynamics was assessed prospectively in 1070 patients receiving maintenance hemodialysis for more than 3 months. Predialysis blood pressure variability was assessed over 1-year intervals. Outcomes included factors were intradialytic hypotension and change in rate-pressure product. The final cohort's mean age was 59 years, and 57% were males. Greater predialysis systolic blood pressure variability was associated with an increased risk of intradialytic hypotension (adjusted hazard ratio, 1.097; 95% confidence intervals 1.055 to 1.140) and change in rate-pressure product (adjusted hazard ratio, 1.213; 95% confidence intervals 1.163 to 1.265). Results were similar when blood pressure variability was stratified by baseline systolic blood pressure. Factors associated with higher systolic blood pressure variability were older age, female sex, longer duration of dialysis, and diagnosis of diabetic nephropathy, and lower levels of serum albumin. In conclusion, greater predialysis systolic blood pressure variability among hemodialysis patients was associated with greater intradialytic cardiac hemodynamic instability. Strategies to reduce blood pressure variability might be beneficial for hemodialysis patients.

Introduction

Hypertension is reported in greater than 90% of patients receiving long-term hemodialysis and may contribute to morbidity and cardiovascular diseases (CVD) [1]. However, the relationship between blood pressure (BP) and CVD in hemodialysis patients is complex and confounded by many associations [2].

Fluctuations in BP or BP variability (BPV) is common in hemodialysis patients. Those fluctuations entail changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) that occurs before (predialysis), during (intradialytic), or after (post-dialytic) the treatments[3]. BPV can be short-term, midterm, or long-term. Short-term BPV includes beat-to-beat, minute-to-minute, hour-to-hour, and circadian variability over a period of 24 hours; midterm BPV includes variability over a periods of days; long-term BPV includes variability over weeks, months, seasons, and even years [4].

The goal of this study was to elucidate the role of some readily available clinical and demographic factors in BPV, including predialysis BP and BPV in cardiac hemodynamics [3]. The present study recruited incident hemodialysis patients from 9 centers studied over one year to assess the association of long-term predialysis BPV with intradialytic cardiac hemodynamic instability, including intradialytic hypotension (IDH), and myocardial ischemia.

Results

BPV parameters

The mean VIM_{SBP} that was used for the BPV metric was 15.44±3.85, and mean VIM_{DBP} was 8.69±2.13 (Table 1).

Baseline characteristics

The final study cohort comprised 1070 in-center maintenance hemodialysis patients at 9 hemodialysis centers that represented 75% of the initial cohort (Figure 1). Demographic, clinical, and biochemical characteristics are shown in Table 2. Mean age was 59±14 years, and 57% were male, and 14% had a history of smoke. Glomerulonephritis accounted for 56% of the causes of end-stage renal disease (ESRD), with 74% having hypertension and 24% having diabetes mellitus and 14% having a history of a cardiocerebrovascular event. The median dialysis vintage was 52 months, the mean dry weight was 57±12 kg and the ratio of excess predialysis weight at start of hemodialysis to dry weight was 4.37±2.39 %.

BPV and intradialytic cardiac hemodynamic instability

Intradialytic hypotension:

The incidence of IDH over the 1-year was 26%. The risk of IDH was associated with higher VIM_{SBP} in both the unadjusted and fully adjusted models (Table 3). In the fully adjusted model, each 1 SD increase in the VIM_{SBP} was associated with 9.7% higher risk of IDH (95% confidence interval [95% CI], 5.5% to 14.0%).

Myocardial ischemia:

The changes in rate-pressure product (RPP) during a dialysis session were used to estimate myocardial ischemia and were divided into binary variables based on their median. A higher VIM_{SBP} was associated with an increased risk of great change in RPP in both unadjusted and fully adjusted models (Table 3). In the fully adjusted model, each 1 SD increase in the VIM_{SBP} was associated with 21.3% higher risk of great change in RPP (95% CI, 16.3% to 26.5%).

Sensitivity analyses:

VIM_{SBP} analyzed as tertiles had a similar association with outcomes as the primary analysis (Table S1). After stratification by baseline SBP, the magnitude and direction of the association between VIM_{SBP} and outcomes remained similar to the primary analysis in each of the categories, suggesting that the association between VIM_{SBP} and outcomes was not dependent on baseline BP (Table S2).

Predictors of BPV:

The association between predialysis VIM_{SBP} and patient baseline characteristics was shown in Table 4. After multivariate adjustment, older age, longer dialysis vintage, and a lower serum albumin were associated with higher VIM_{SBP}.

Additional analyses:

Higher predialysis VIM_{DBP} was associated with an increased risk of IDH in both unadjusted and fully adjusted models. In the fully adjusted model, each 1 SD increase in the BPV was associated with 10.0% higher risk of IDH (95% CI, 2.9% to 17.6%) and with an increased risk of great change in RPP. In the fully adjusted model, each 1 SD increase in the BPV was associated with 15.4% higher risk of great change in RPP (95% CI, 8.1% to 23.2%) (Table S3).

Discussion

Predialysis SBP is most commonly selected to diagnose and manage BP in hemodialysis patients [3]. SBP is the major determinant of pulse pressure, since both dependent quite strongly on inelasticity of major conduit vessels and pulse wave velocity. Therefore, predialysis systolic BPV was selected to assess the association between predialysis BPV and intradialytic cardiac hemodynamic instability. The results from this prospective study of 1070 incident in-center hemodialysis patients demonstrated that higher predialysis systolic BPV was independently associated with an increased risk of IDH and myocardial ischemia during hemodialysis sessions. This association persisted across all baseline SBP categories and after adjustment for a number of potential confounding factors. Thus, the predialysis systolic BPV emerges as a potentially modifiable risk factor for cardiac hemodynamic instability in hemodialysis patients. Greater predialysis diastolic BPV was found to be independently associated with an increased risk of intradialytic cardiac hemodynamic instability, including IDH, and myocardial ischemia.

IDH and myocardial ischemia are frequent complications of hemodialysis [5]. IDH may result from a failure to tolerate ultrafiltration leading to an imbalance between central hypovolemia and reflex-mediated hemodynamic responses [6], and is clearly associated with adverse outcomes[7-9], and all-cause mortality [7]. Current guidelines recommended to address IDH include regular assessment of dry weight; control of inter-dialytic weight gain by dietary fluid and salt restriction; optimization of ultrafiltration and dialysate composition; use of a cool dialysate; careful assessment of dosing and timing of antihypertensive drugs; prolonged dialysis time and increased dialysis frequency[10]. However, even with aplenty management, some patients remain prone to IDH. The finding that a higher predialysis systolic BPV was associated with an increased risk of IDH suggests that maintaining a stable predialysis BP may reduce the incidence of IDH.

Previous studies have demonstrated that the RPP highly correlates with invasive measurement of myocardial oxygen consumption, and it is used as an index of myocardial workload and oxygen demand to predict cardiac function, morbidity and mortality [11,12]. Cardiovascular reactivity to acute stress is mediated via the activation of the sympathetic nervous system and hypothalamus-pituitary-adrenal axis, leading to increase in heart rate, blood pressure, vasoconstriction, and vagal withdrawal [13]. A greater hemodynamic response to acute stress including an exaggerated increase in blood pressure or heart rate was associated with incident hypertension and a higher mortality rate [14]. In the present study, the RPP change during hemodialysis was assessed to evaluate the hemodynamic response. A higher predialysis systolic BPV was significantly associated with the risk of a greater change in RPP. Thus, strategies to

reduce fluctuations in predialysis BP might be considered to decrease cardiac hemodynamic stability during hemodialysis.

The BPV is one compelling putative risk factor to explain the strikingly high rate of CVD in hemodialysis patients [15]. Indeed, BPV is significantly associated with CVD and mortality in these patients [1,16]. Their BPV may have unique determinant including volume and osmolar shifts, and impaired counter-regulatory responses [17]. Additionally, BPV in hemodialysis patients may entail vascular remodeling, overactivation of the sympathetic nervous system and loss of compliance of conduit vessels with increases in arterial pulse wave velocity [18]. Patients receiving hemodialysis can experience IDH, or myocardial ischemia, both of which increase risk of mortality [19]. Our data extend the retrospective report on 11291 incident hemodialysis patients treated at 210 dialysis clinics in the United States that a greater predialysis systolic BPV was a risk factor for all-cause mortality, cardiovascular mortality, and cardiovascular events [3]. A recent retrospective analysis also confirmed above findings[20]. The present study has found, for the first time, that higher predialysis systolic BPV was significantly associated with an increased risk of intradialytic cardiac hemodynamic instability, including IDH and a greater change in RPP. The BPV metric was an indicator of BPV independently of mean level of BP [21]. The association between predialysis systolic BPV and cardiac hemodynamic instability remained significant after stratification by baseline SBP category. Therefore, a goal of management of hemodialysis patients to contast their very high CVD mortality might be to maintain cardiac hemodynamic stability.

In the present study, we found that dry weight, or the ratio of excess weight at hemodialysis start to dry weight, was not significantly associated with predialysis BPV. Meanwhile, the adjustment for the dry weight and the ratio of excess weight at hemodialysis start to dry weight in the finally outcomes model did not change the association between BPV and outcomes. In a previous retrospective study on the association between predialysis BPV and outcomes, they observed that achievement of prescribed dry weight was associated with lower predialysis BPV, but the adjustment for achievement of prescribed dry weight in the finally outcomes model did not change the association between BPV and outcomes [3]. Meanwhile, a randomized clinical trial confirmed that dry weight reduction did not affect BPV levels [22]. It is hypothesized that volume losses that occur with dialysis induce baroreceptor-dependent changed in autonomic function that stabilizes venous return (capacitance vessel constriction) and peripheral constriction (arteriolar constriction) subjects with inelastic conduit vessels cannot adequately sense the fluctuations in BP and do not mount an effective -counter-regulatory response [18]. BPV reduction is not always accompanied by BP reduction; whether BPV changes depends largely on modification of the responsible pathogenesis, which may be influenced by specific but not all antihypertensive interventions.

The predialysis systolic BPV was predicted by older age, and longer duration of dialysis. All of these also predict increased pulse wave velocity and conduit vessel stiffness. Moreover, impaired baroreceptor activation (as in old age) drives the sympathetic nervous system that could contribute to the associated with RPP and cardiac disease [18]. Potentially modifiable factor included serum albumin that was associated with predialysis systolic BPV. Low serum albumin was associated with inflammation, arterial

stiffness and atherosclerosis [20]. Several studies have reported that malnutrition and inflammation could result in atherosclerosis and enhanced BPV [23,24]. Thus, nutritional intervention might help to reduce BPV. Dietary modification, such as folic acid supplementation, might contribute to the reduction of BPV. A clinical trial in primary prevention of stroke among adults with hypertension in China found that supplemental folic acid dramatically reduced stroke in the hypertensive Chinese population where (unlike United States and Europe) food is not fortified with folate and there may be widespread folate deficiency [25]. This could be exacerbated by loss of B vitamin and folate during dialysis. Moreover, the elevated levels of homocysteine could be reduced by the folic acid supplementation, which could modify stroke in Chinese hypertensive patients [26]. Therefore, dietary intervention might help to reduce the risk of CVD. Further study will be deserved to explore available pharmacological and non-pharmacological interventions.

This study aimed to minimize confoundering influence on the measured variables. It is well known that blood pressure fluctuates with season changes [27]. Therefore, in this study, we measured a consecutive 12 months of predialysis blood pressure to determine BPV. Predialysis BP was measured when patients took a rest after arriving in waiting room prior to dialysis, which was equivalent to visit-to-visit BP. Therefore, it could reflect the long-term degree of BP control and stability [28]. In this multi-center prospective observational study, we demonstrated that greater predialysis systolic BPV was associated with intradialytic cardiac hemodynamic instability. Thus, both reduction in average BP levels and reduction of fluctuations in BP should be emphasized in hemodialysis patients. Interventions aimed at reducing BPV might be beneficial in improving adverse outcomes for hemodialysis patients. There are several limitations to our study. First, we only explored the association between predialysis systolic and diastolic BPV, but not other components of BP, such as mean arterial pressure, intradialytic or postdialysis BP. Fluctuation in these BP components may be risk factors for poor outcomes and needs additional research. Second, the final cohort recruited most prevalent hemodialysis patients, not incident hemodialysis patients, whose dialysis history might influence the adverse outcome. However, after adjusted for dialysis vintage, the association still remains. Third, this is a prospective observational study. The results could only explain the association and provide clues for treatment to reduce blood pressure variability. Further study will be deserved to explore optimal blood pressure management strategy and relevant mechanisms in hemodialysis patients.

In conclusion, greater predialysis systolic BPV was associated with intradialytic cardiac hemodynamic instability in hemodialysis patients. Reducing BPV might be beneficial in improving adverse outcomes for hemodialysis patients.

Methods

Study Population of Patients

Adult patients (aged ≥18 years) receiving maintenance hemodialysis were recruited from the Fourth Affiliated Hospital, Zhejiang University School of Medicine and 8 public hospitals in Jinhua city, Zhejiang

Province of China (Central Hospital of Jinhua, People's Hospital of Jinhua, Central Hospital of Yiwu, People's Hospital of Yongkang, People's Hospital of Pujiang, Dongyang Hospital of Traditional Chinese Medicine, People's Hospital of Lanxi, and Lanxi Hospital of Traditional Chinese Medicine). Inclusion criteria included: (1) maintenance hemodialysis for more than 3 months prior to August 1, 2018; (2) receiving regular 3-times weekly hemodialysis for 4 hours. Exclusion criteria were: (1) patients who died or received a kidney transplant or were changed to peritoneal dialysis or transferred to a different renal unit during follow-up period; (2) those who could not write informed consent. This study was approved by the Research Ethics Committee of the Fourth Affiliated Hospital, Zhejiang University School of Medicine (K20190047) and was recorded in the Chinese Clinical Trial Register (ChiCTR2000028945). All methods were performed in accordance with the approved guidelines and relevant regulations. Written informed consent was obtained from all participants.

Study Protocol

The hemodynamic data was collected prospectively for all of the hemodialysis sessions of the participants. At each session, patients were assessed for pre- and post- hemodialysis weight, and predialysis and intradialytic SBP, DBP and heart rate (HR) from August 1, 2018 to July 31, 2019. The BP and HR were measured with patient seated in a chair with feet on the floor and back supported. Measurement were made by trained research assistants with a validated automated oscillometric brachial BP monitor (Omron 907XL; Omron Healthcare, Lake Forest, IL). Predialysis BP and HR were measured after a 10-minute rest period in a chair before dialysis. BP was measured three times consecutively before each dialysis, with a 1-minute interval and the results averaged. Intradialytic BP and HR were measured automatically at 30, 60, 120, 180, and 240 minutes by the dialysis apparatus.

Patients were dialyzed on either Monday-Wednesday-Friday or Tuesday-Thursday-Saturday schedules. Prescriptions for patient's dry weight and antihypertensive drug were made by the nephrologist during their weekly visits. Dry weight was assessed by cardiopulmonary radiology and clinical symptoms including peripheral edema, pulmonary congestion, intra- and extra-dialytic BP and muscle spasm. Excess predialysis weight was defined as the difference between predialysis and dry weight.

Cardiac hemodynamic instability during hemodialytic procedure were evaluated by IDH, and myocardial ischemia. A decrease in SBP $\geq$ 20 mmHg or mean arterial pressure (MAP) $\geq$ 10 mmHg was required to quantify hypotension and $\geq$3 episodes hypotension per 10 hemodialysis treatments were required to diagnose IDH [29]. The rate-pressure product (RPP) was calculated as SBP multiplied by HR and the change in RPP as the percentage difference between the maximum value and the minimum value during dialysis session [13]. The change in RPP during hemodialysis procedure was used to assess myocardial ischemia, which could represent the early change in cardiac hemodynamics [30].

BPV and other measurements

For each BP measurements, the SD was calculated (SD_{SBP} and SD_{DBP}) with the coefficient of variation (CV, CV_{SBP} and CV_{DBP}) and the variability independent of the mean (VIM, VIM_{SBP} and VIM_{DBP}). The CV was

SD factored by mean BP values (M_{SBP} and M_{DBP}), and the VIM by the SD factored by the mean to the power x, which was obtained by fitting a curve to the plot of SD against the mean blood pressure level [31].

The following demographic and clinical data were collected: age, gender, comorbidity (diabetes, hypertension, cardiocerebrovascular events), body mass index (BMI), use of antihypertensive medications, dialysis vintage, and occurrence of their cardiocerebrovascular events include myocardial infarction, angina, coronary heart disease, stroke, heart failure and post-cardiac arrest. The diagnosis of hypertensive nephropathy is based on characteristic clinical features, excluding other renal diseases and eventually on the features of kidney biopsy [32]. The following laboratory parameters were also collected: Kt/V, blood hemoglobin, serum albumin, calcium, phosphate, and parathyroid hormone (PTH). All laboratory values were measured using standardized automated methods. Laboratory values were measured monthly except PTH that was measured quarterly. The averaged or median values during the exposure period served as the baseline data.

Statistical Analysis

The baseline characteristics of all the patients were compared tertiles of BPV to assess factors that were associated independently with BPV at baseline using linear mixed effects models with a random intercept for the clinic to account for clustering of outcomes by providers. The follow factors were also incorporated as explanatory variables: demographic characteristics (age, sex), clinical factors (history of diabetes, hypertension, cardiocerebrovascular events, smoke, and BMI), dialysis-related factors (cause of ESRD, dialysis vintage, Kt/V, dry weight, and the ratio of excess weight at hemodialysis start to dry weight), laboratory measurements (serum albumin, calcium, phosphate, hemoglobin, and PTH), and use of antihypertensive medications. The association of BPV with intradialytic cardiac hemodynamic instability, including IDH and myocardial ischemia was assessed by discrete time proportional hazards models using binary regression. HRs were calculated for each outcome per 1 SD increase in BPV after adjustment for the same a pre–defined potential confounders. A sensitivity analyses for BPV was undertaken by tertiles to quantify the association of BPV with outcomes after stratification by categories of SBP at baseline (tertiles of SBP). Statistical significance was taken as $P<0.05$ using two-tailed tests. Statistical analyses were undertaken by using SPSS Statics 22.0 (IBM, New York).

Declarations

Author contributions statement

Research idea and study design: EYL, YY; data acquisition: JJY, JH; data analysis/interpretation: BYY, QZ, SSZ, LLW, LL, LZL, LL; statistical analysis: JJY; supervision or mentorship: FH, CSW. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding

This work was supported by the grant to Yi Yang from the National Nature Science Foundation of China (81670621) and the Nature Science Foundation of Zhejiang Province (LY16H050001), and grant to En Yin Lai from the National Nature Science Foundation of China (31671193).

Competing interests

The authors declare no competing interests.

Data availability

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

References

1. Rossignol, P., Cridlig, J., Lehert, P., Kessler, M. & Zannad, F. Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL. *Hypertension***60**, 339-346, doi:10.1161/hypertensionaha.111.190397 (2012).
2. Liao, R. *et al.* Association of Peridialysis Blood Pressure and Its Variability with Cardiovascular Events in Hemodialysis Patients. *Kidney Blood Press Res***43**, 1352-1362, doi:10.1159/000492595 (2018).
3. Shafi, T. *et al.* Predialysis systolic BP variability and outcomes in hemodialysis patients. *J Am Soc Nephrol***25**, 799-809, doi:10.1681/asn.2013060667 (2014).
4. Huang, J. T. *et al.* Increased Nighttime Pulse Pressure Variability but Not Ambulatory Blood Pressure Levels Predicts 14-Year All-Cause Mortality in Patients on Hemodialysis. *Hypertension***74**, 660-668, doi:10.1161/hypertensionaha.119.13204 (2019).
5. Gullapudi, V. R. L., Kazmi, I. & Selby, N. M. Techniques to improve intradialytic haemodynamic stability. *Curr Opin Nephrol Hypertens***27**, 413-419, doi:10.1097/mnh.0000000000000449 (2018).
6. Reilly, R. F. Attending rounds: A patient with intradialytic hypotension. *Clin J Am Soc Nephrol***9**, 798-803, doi:10.2215/cjn.09930913 (2014).
7. Yu, J. *et al.* Intradialytic Hypotension as an Independent Risk Factor for Long-Term Mortality in Maintaining Hemodialysis Patients: A 5-Year Follow-Up Cohort Study. *Blood Purif***45**, 320-326, doi:10.1159/000486231 (2018).
8. Chou, J. A. *et al.* Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant***33**, 149-159, doi:10.1093/ndt/gfx037 (2018).
9. Shoji, T., Tsubakihara, Y., Fujii, M. & Imai, E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. *Kidney Int***66**, 1212-1220, doi:10.1111/j.1523-1755.2004.00812.x (2004).
10. Kooman, J. *et al.* EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant***22 Suppl 2**, ii22-44, doi:10.1093/ndt/gfm019 (2007).

11. Krishnamoorthy, V. *et al.* Association of Early Myocardial Workload and Mortality Following Severe Traumatic Brain Injury. *Crit Care Med***46**, 965-971, doi:10.1097/ccm.0000000000003052 (2018).
12. Verma, A. K. *et al.* Rate pressure product and the components of heart rate and systolic blood pressure in hospitalized heart failure patients with preserved ejection fraction: Insights from ASCEND-HF. *Clin Cardiol***41**, 945-952, doi:10.1002/clc.22981 (2018).
13. Kim, J. H. *et al.* Peripheral Vasoconstriction During Mental Stress and Adverse Cardiovascular Outcomes in Patients With Coronary Artery Disease. *Circ Res***125**, 874-883, doi:10.1161/circresaha.119.315005 (2019).
14. Carroll, D. *et al.* Increased blood pressure reactions to acute mental stress are associated with 16-year cardiovascular disease mortality. *Psychophysiology***49**, 1444-1448, doi:10.1111/j.1469-8986.2012.01463.x (2012).
15. Kikuya, M. *et al.* Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension***52**, 1045-1050, doi:10.1161/hypertensionaha.107.104620 (2008).
16. Flythe, J. E. *et al.* Association of intradialytic blood pressure variability with increased all-cause and cardiovascular mortality in patients treated with long-term hemodialysis. *Am J Kidney Dis***61**, 966-974, doi:10.1053/j.ajkd.2012.12.023 (2013).
17. Flythe, J. E. *et al.* Factors associated with intradialytic systolic blood pressure variability. *Am J Kidney Dis***59**, 409-418, doi:10.1053/j.ajkd.2011.11.026 (2012).
18. Zhou, T. L. *et al.* Blood Pressure Variability, Arterial Stiffness, and Arterial Remodeling. *Hypertension***72**, 1002-1010, doi:10.1161/hypertensionaha.118.11325 (2018).
19. Palmer, B. F. & Henrich, W. L. Recent advances in the prevention and management of intradialytic hypotension. *J Am Soc Nephrol***19**, 8-11, doi:10.1681/asn.2007091006 (2008).
20. Wang, Y. *et al.* Variability in Predialysis Systolic Blood Pressure and Long-Term Outcomes in Hemodialysis Patients. *Kidney Blood Press Res***43**, 115-124, doi:10.1159/000487111 (2018).
21. Hoshide, S., Yano, Y., Mizuno, H., Kanegae, H. & Kario, K. Day-by-Day Variability of Home Blood Pressure and Incident Cardiovascular Disease in Clinical Practice: The J-HOP Study (Japan Morning Surge-Home Blood Pressure). *Hypertension***71**, 177-184, doi:10.1161/hypertensionaha.117.10385 (2018).
22. Loutradis, C. *et al.* Lung Ultrasound-Guided Dry-Weight Reduction in Hemodialysis Patients Does Not Affect Short-Term Blood Pressure Variability. *Am J Hypertens***32**, 786-795, doi:10.1093/ajh/hpz064 (2019).
23. Stenvinkel, P., Heimbürger, O., Lindholm, B., Kaysen, G. A. & Bergström, J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant***15**, 953-960, doi:10.1093/ndt/15.7.953 (2000).
24. Locatelli, F. *et al.* Nutritional status in dialysis patients: a European consensus. *Nephrol Dial Transplant***17**, 563-572, doi:10.1093/ndt/17.4.563 (2002).

25. Huo, Y. *et al.* Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *Jama***313**, 1325-1335, doi:10.1001/jama.2015.2274 (2015).
26. Zhou, Z. *et al.* Effect of Smoking and Folate Levels on the Efficacy of Folic Acid Therapy in Prevention of Stroke in Hypertensive Men. *Stroke***49**, 114-120, doi:10.1161/strokeaha.117.018273 (2018).
27. Hanazawa, T. *et al.* Seasonal variation in self-measured home blood pressure among patients on antihypertensive medications: HOMED-BP study. *Hypertens Res***40**, 284-290, doi:10.1038/hr.2016.133 (2017).
28. Kollias, A., Stergiou, G. S., Kyriakoulis, K. G., Bilo, G. & Parati, G. Treating Visit-to-Visit Blood Pressure Variability to Improve Prognosis: Is Amlodipine the Drug of Choice? *Hypertension***70**, 862-866, doi:10.1161/hypertensionaha.117.10087 (2017).
29. Tian, M., Zha, Y., Qie, S., Lin, X. & Yuan, J. Association of Body Composition and Intradialytic Hypotension in Hemodialysis Patients. *Blood Purif*, 1-7, doi:10.1159/000504245 (2020).
30. Atkinson, G., Leary, A. C., George, K. P., Murphy, M. B. & Jones, H. 24-hour variation in the reactivity of rate-pressure-product to everyday physical activity in patients attending a hypertension clinic. *Chronobiol Int***26**, 958-973, doi:10.1080/07420520903044455 (2009).
31. Da, J. *et al.* Blood pressure variability is independent of systolic pressure in adolescent and young adult patients undergoing hemodialysis. *Pediatr Res***83**, 615-621, doi:10.1038/pr.2017.293 (2018).
32. Tylicki, L. & Rutkowski, B. [Hypertensive nephropathy: pathogenesis, diagnosis and treatment]. *Pol Merkur Lekarski***14**, 168-173 (2003).

Tables

Table 1. Blood Pressure Variability Parameters

Parameters	Mean±SD
Systolic Blood Pressure	
1.Mean	138.84±17.21
2.SD	15.45±4.29
3.CV	0.11±0.03
4.VIM	15.44±3.85
Diastolic Blood Pressure	
1.Mean	77.76±10.01
2.SD	8.67±2.21
3.CV	0.11±0.03
4.VIM	8.69±2.13

SD: standard deviation; CV: coefficient of variation; VIM: variability independent of the mean.

Table 2. Baseline Characteristics of Study population by Tertiles of predialysis VIM_{SBP}

Characteristics	Overall	Tertiles of VIM_{SBP}			P value
		Lowest (<13.5421)	Middle (13.5421-16.6810)	Highest (>16.6810)	
N (%)	1070	356	358	356	
Age (y)	59.08±13.79	55.35±14.12	59.86±12.96	62.02±13.45	<0.001
Male (%)	615 (57.48)	221 (62.08)	205 (57.26)	189 (53.09)	0.052
Comorbidities					
Diabetes (%)	256 (23.93)	67 (18.82)	93 (25.98)	96 (26.97)	0.021
Hypertension (%)	792 (74.02)	260 (73.03)	276 (77.09)	256 (71.91)	0.251
Cardiocerebrovascular events (%)	155 (14.49)	46 (12.92)	51 (14.25)	58 (16.29)	0.437
BMI (kg/m^2)	21.65±4.02	21.76±3.45	21.87±4.58	21.33±3.94	0.165
Smoke (%)	111 (10.37)	43 (12.08)	34 (9.50)	34 (9.55)	0.434
Cause of ESRD (%)					0.002
Diabetic nephropathy	223 (20.84)	53 (14.89)	79 (22.07)	91 (25.56)	
Hypertensive nephropathy	82 (7.66)	20 (5.62)	30 (8.38)	32 (8.99)	
Glomerulonephritis	600 (56.07)	230 (64.61)	192 (53.63)	178 (50.00)	
Other diagnoses	165 (15.42)	53 (14.89)	57 (15.92)	55 (15.45)	
Dialysis vintage (mo)	52.38±45.11	48.01±42.58	50.20±44.93	58.94±47.09	0.003
Dry weight (kg)	56.86±11.55	57.33±12.02	57.22±11.08	56.04±11.50	0.257
Excess weight at HD start/ Dry weight (%)	4.37±2.39	4.39±2.38	4.24±2.54	4.48±2.24	0.393
Laboratory parameters					
Kt/V	1.51±0.61	1.49±0.42	1.49±0.45	1.54±0.86	0.518
HB (g/L)	103.95±12.81	105.20±13.88	103.09±11.30	103.57±13.05	0.070
Alb (g/L)	39.26±3.46	40.05±3.26	39.50±3.31	38.24±3.57	<0.001
Ca (mmol/L)	2.21±0.33	2.22±0.17	2.21±0.51	2.19±0.17	0.639
P(mmol/L)	1.68±0.44	1.70±0.38	1.69±0.46	1.65±0.48	0.285
PTH (ng/L)	297.64	303.13	292.07	287.35	0.627

	(158.61-507.68)	(156.61-484.40)	(164.50-509.10)	(151.23-553.09)	
Use of antihypertensive medications (%)					0.011
Any RAS regimen (without β-blocker)	226 (21.12)	63 (17.70)	80 (22.35)	83 (23.31)	
Any β-blocker regimen (without RAS)	124 (11.59)	45 (12.64)	39 (10.89)	40 (11.24)	
β-blocker + RAS combination	115 (10.75)	28 (7.87)	34 (9.50)	53 (14.89)	
Other medications and combinations	605 (56.54)	220 (61.80)	205 (57.26)	180 (50.56)	
Intradialytic hypotension (%)	283 (26.45)	58 (16.29)	98 (27.37)	127 (35.67)	<0.001
RPP (*10^3)	10.23±1.49	10.23±1.49	10.23±1.41	10.25±1.56	0.353
Change in RPP	0.23±0.08	0.20±0.07	0.22±0.08	0.26±0.09	<0.001

Data are presented as mean (SD) or column percent. BMI: body mass index; ESRD: end stage renal disease; HD: hemodialysis; HB: hemoglobin; Alb: albumin; PTH: parathyroid hormone; RAS: renin angiotensin system; RPP: rate-pressure product.

Table 3. Association of Predialysis VIM_{SBP} and Intradialytic Cardiac Hemodynamic Instability

Outcomes	Events	Crude[a]		Fully Adjusted[b]	
		HR (95% CI)	P Value	HR (95% CI)	P Value
IDH	283	1.110 (1.071-1.150)	<0.001	1.097 (1.055-1.140)	<0.001
Great Change in RPP	535	1.237 (1.190-1.285)	<0.001	1.213 (1.163-1.265)	<0.001

[a] Unadjusted model.

[b] Adjusted for demographic characteristics (age, sex), clinical factors (history of diabetes, hypertension, cardiocerebrovascular events, smoke, and BMI), dialysis-related factors (cause of ESRD, dialysis vintage, Kt/V, dry weight, and the ratio of excess weight at HD start to dry weight), laboratory measurements (serum albumin, calcium, phosphate, hemoglobin, and PTH), and use of antihypertensive medications.

IDH: intradialytic hypotension; RPP: rate-pressure product; CI: confidence interval.

Table 4. Factors associated with predialysis VIM_{SBP} in 1070 incident hemodialysis patients

Characteristics	Coefficient (95% CI)[a]	P value
Age (y)	0.038 (0.020 to 0.056)	<0.001
Male versus Female	-0.545 (-1.102 to -0.012)	0.055
Comorbidities		
Diabetes (%)	0.224 (-0.832 to 1.279)	0.678
Hypertension (%)	0.134 (-0.416 to 0.683)	0.633
Cardiocerebrovascular events (%)	0.003 (-0.664 to 0.657)	0.992
BMI (kg/m^2)	-0.052 (-0.141 to 0.037)	0.250
Smoke (%)	0.497 (-0.263 to 1.256)	0.200
Cause of ESRD (%)		
Diabetic nephropathy	Reference	
Hypertensive nephropathy	-0.975 (-2.279 to 0.328)	0.142
Glomerulonephritis	-1.464 (-2.573 to -0.356)	0.010
Other diagnoses	-1.259 (-2.497 to -0.021)	0.046
Dialysis vintage (mo)	0.015 (0.009 to 0.020)	<0.001
Dry weight (kg)	0.024 (-0.012 to 0.059)	0.188
Excess weight at HD start/ Dry weight (%)	1.372 (-8.185 to 10.928)	0.778
Laboratory parameters		
Kt/V	0.141 (-0.228 to 0.511)	0.453
HB (g/L)	-0.009 (-0.027 to 0.009)	0.326
Alb (g/L)	-0.205 (-0.274 to -0.136)	<0.001
Ca (mmol/L)	-0.462 (-1.143 to 0.219)	0.183
P(mmol/L)	-0.110 (-0.646 to 0.426)	0.688
PTH (ng/L)	0.00	0.627
Use of antihypertensive medications (%)		
Any β-blocker regimen (without RAS)	Reference	
Any RAS regimen (without β-blocker)	0.251 (-0.576 to 1.078)	0.551
β-blocker + RAS combination	0.303 (-0.648 to 1.254)	0.533
Other medications and combinations	-0.563 (-1.292 to 0.167)	0.130

[a] Coefficient for multivariable linear mixed effects models with a random intercept for the clinic to account for outcome clustering by providers. Value of coefficient represents change in VIM_{SBP} per 1 unit change in the factors. Positive numbers indicate higher VIM_{SBP} per 1 unit change in factors, and negative numbers indicate lower VIM_{SBP} per 1 unit change in factors.

BMI: body mass index; ESRD: end stage renal disease; HD: hemodialysis; HB: hemoglobin; Alb: albumin; PTH: parathyroid hormone; RAS: renin angiotensin system; RPP: rate-pressure product; CI: confidence interval.

Supplementary Materials

Table S1: Association of Predialysis VIMSBP Analyzed as Tertiles and Intradialytic Cardiac Hemodynamic Instability.

Table S2: Association of Predialysis VIMSBP with Intradialytic Cardiac Hemodynamic Instability after Stratification by predialysis SBP categories.

Table S3: Association of Predialysis VIMDBP and Intradialytic Cardiac Hemodynamic Instability.

Figures

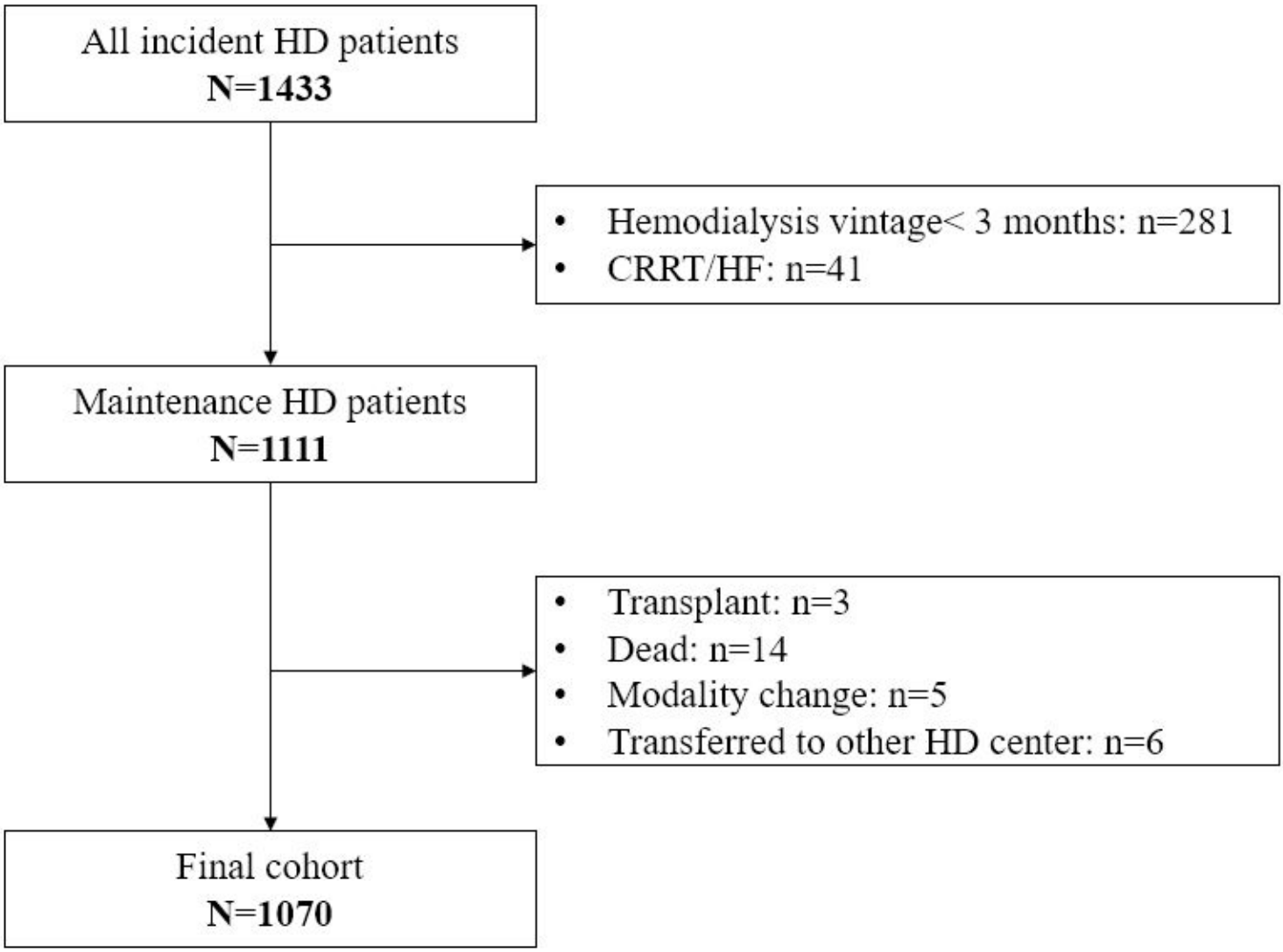

Figure 1

Overview of cohort formation. Selection of the final cohort of 1070 maintenance hemodialysis patients from 9 hemodialysis centers in Zhejiang Province of China.

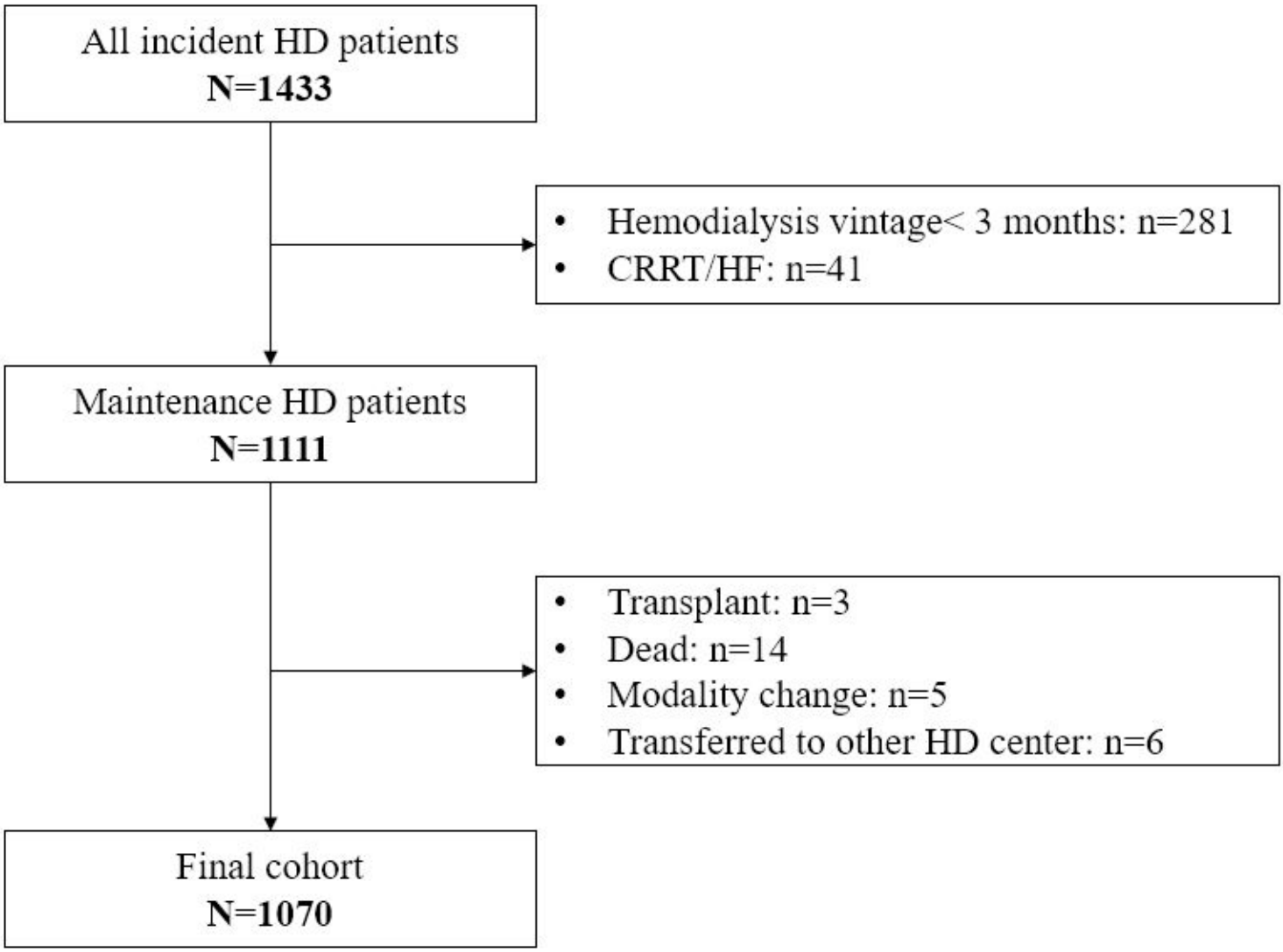

Figure 1

Overview of cohort formation. Selection of the final cohort of 1070 maintenance hemodialysis patients from 9 hemodialysis centers in Zhejiang Province of China.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplemantal.docx
- Supplemantal.docx