Meta-Analysis

Blood Pressure Variability and Outcomes in End-Stage Renal Disease Patients on Dialysis: A Systematic Review and Meta-Analysis

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Keywords

Blood pressure variability · End-stage renal disease · Hemodialysis · Systematic review · Meta-analysis

Abstract

Objective: Previous studies have suggested that blood pressure variability (BPV) is associated with an increased risk of mortality and cardiovascular events in patients on dialysis. However, the results are inconsistent. A comprehensive literature review was conducted to analyze the association between BPV and outcomes in patients on dialysis. **Methods:** Articles in Embase, Medline, and Web of Science from the date of inception through January 1, 2020, were identified. The outcomes were all-cause and cardiovascular mortality and cardiovascular events. The risk of bias was assessed using the Newcastle-Ottawa scale tool. Random effects models were used to pool the overall effect sizes. Two reviewers extracted the data independently. Meta-regression and subgroup analyses were performed to explore potential heterogeneity. **Results:** Fifteen eligible studies were included, and all enrolled hemodialysis recipients only. The overall risk of bias for the included studies was low. A 1-SD increase in systolic BPV was associated with higher risks of all-cause mortality (HR = 1.18; 95% CI 1.11–1.26, I^2 = 53.8%), cardiovascular mortality (HR = 1.23; 95% CI 1.10–1.37, I^2 = 57.2%), and cardiovascular events (HR = 1.27; 95% CI 1.07–1.51, I^2 = 69.3%). Likewise, a 1-SD increase in diastolic BPV was associated with higher HR for all-cause and cardiovascular mortality (HR = 1.14; 95% CI 1.05–1.23, I^2 = 0.0%, and HR = 1.14; 95% CI 0.94–1.38, I^2 = 0.0%, respectively). **Conclusions:** A greater

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BPV is associated with higher risks of cardiovascular and mortality outcomes in patients on hemodialysis. Further research is required to determine whether BPV may be useful either as a marker enabling individualized treatment of cardiovascular risk or as a treatment target in its own right.

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Introduction

Despite technical advances in hemodialysis (HD) and peritoneal dialysis (PD), patients on dialysis have substantially higher risks of cardiovascular events and mortality rates than the general population [1–4]. The prevalence of hypertension is high in those with end-stage renal disease (ESRD) receiving dialysis, and it is a prominent risk factor for cardiovascular disease morbidity and mortality and contributes to heart failure and arrhythmias [5]. Accurate, appropriate blood pressure (BP) measurement is vital. As in the general population, treatment of hypertension may have a significant impact on the survival of patients receiving dialysis [6, 7].

Mean BP might not fully describe the relationship between BP and cardiovascular disease or mortality. BP variability (BPV) describes the extent of BP fluctuations over time. Based on the time interval of BP measurements, BPV is classified into long- and short-term BPV. Long-term BPV usually refers to visit-to-visit BPV, whereas short-term BPV is usually measured by ambulatory BP monitoring during a 24- to 48-h period [8]. Various factors, such as age, increased vascular stiffness, sympathetic nervous system activity, seasonal changes, and treatment-related factors, may influence BP fluctuations [9]. Growing evidence suggests that BPV is linked to greater risks of heart disease and incident chronic kidney disease (CKD) and stroke, independently of the effects of the mean BP, in the general population, as well as in patients with hypertension or diabetes [10–13].

Patients with CKD have increased BPV [14]. Patients undergoing HD regularly have fluids removed for short periods of time and are prone to greater BPV, which may contribute to their burden of cardiovascular disease [14]. Studies have found an association between the mean BP and outcomes in patients on HD [15–17]. Over the last decade, more studies have explored the impact of BPV on the prognosis of HD patients, with inconsistent results [18–25]. Therefore, we conducted a systematic review and meta-analysis to assess the prognostic significance of BPV on cardiovascular and all-cause mortality and cardiovascular events in ESRD patients on dialysis.

Methods

Search Strategy

This study was conducted in accordance with Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [26]. The methodology complied with the Cochrane Handbook for Interventional Systematic Reviews [27]. This article was written in a manner that adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28]. Two reviewers (H.L. and J.X.) independently searched Medline (for studies published from January 1, 1946, to January 1, 2020), Embase (from January 1, 1960, to January 1, 2020), and Web of Science (from the date of inception to January 1, 2020) for eligible articles in English or Chinese. The search strategy was devised by an experienced librarian at Central South University and is available in the supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000508979). The following search

terms were used: “blood pressure variability,” “hemodialysis,” “peritoneal dialysis,” and other comparable search terms. We also searched the reference lists of relevant articles manually for potential additional studies.

Inclusion and Exclusion Criteria

The included studies were required to meet the following criteria: (1) cohort design studies, including prospective or retrospective cohorts; (2) population of ESRD patients on either HD or PD; (3) BPV was monitored; and (4) at least 1 of the following outcomes was reported: all-cause mortality, cardiovascular mortality, and cardiovascular events (including coronary heart disease, myocardial infarction, heart failure, and stroke).

Studies were excluded if they were a review, a supplement, a commentary article, an editorial, or a conference article. If more than 1 study reported on an overlapping population, the study with the shorter follow-up duration or the smaller population was excluded. Discrepancies were resolved by discussion.

Data Extraction

Two independent investigators extracted information, including the study characteristics (first author’s name, publication year, country, database, study design, follow-up duration, sample size, age, and sex), exposure assessment (BP measurement and BPV metrics), outcome assessment (all-cause mortality, cardiovascular mortality, and cardiovascular events), and association estimates (most fully adjusted HR and 95% CI for the corresponding category), using prespecified forms. A third investigator (W.C.) was consulted in the case of disagreement.

Assessment of Study Quality

The risk of bias in the study design was assessed using the Newcastle-Ottawa scale for cohort studies [29]. Specifically, studies were assessed using a quality score in the following 3 domains: selection of the study groups (maximum 4 points), group comparability (maximum 2 points), and ascertainment of outcome in the cohorts (maximum 3 points). A higher score indicated better quality.

Data Synthesis and Statistical Analysis

All statistical analyses were conducted using Stata version 12 (Stata, College Station, TX, USA). The included studies examined BPV in multiple metrics. The BPV metrics included in the meta-analyses were considered in the following order: coefficient of variation (CV), SD, variability independent of the mean (VIM), average real variability (ARV), and residual variability. To allow quantitative synthesis of estimates across studies, we pooled HR for a 1-SD change to measure the effect of the association between BPV and outcomes using random effects models. When HR indicated specific BPV increment intervals (e.g., 1 or 10 mm Hg), HR for the 1-SD increment were calculated with the corresponding root of the original value. For instance, if the reported HR for a 1-mm Hg increment were 1.20, and the SD of the BPV were 3.0 mm Hg, then the HR per SD increment change would be the third power of 1.20 (i.e., 1.73) [30, 31]. When HR were reported for quintiles, quantiles, or tertiles of the BPV, the HR for a 1-SD increment were estimated as $1/2.80$ times the log HR to compare the top and bottom quintiles, $1/2.54$ times the log HR to compare the top and bottom quartiles, and $1/2.18$ times the log HR to compare the top and bottom tertiles [32]. Between-study heterogeneity was assessed using Cochrane Q and I^2 statistics, and a p value <0.10 or $I^2 >50\%$ was considered heterogeneous [33]. Meta-regression and subgroup analyses were used to explore the sources of heterogeneity in our main finding. In addition, to determine the influence of individual studies on the overall effect, we performed a sensitivity analysis by repeating the meta-

Fig. 1. Flowchart of the literature search.

analysis and removing one study at a time. Publication bias was assessed using the Begg test and presented graphically with funnel plots of precision [34]. Two-sided $p < 0.05$ was considered statistically significant unless otherwise specified.

Results

Characteristics of the Included Studies

Figure 1 summarizes the results of the literature search, which yielded 1,394 citations after deduplication, 1,345 of which were excluded after title and abstract review. The full texts of the remaining 49 articles were reviewed, and 34 were excluded because the population, exposure, or outcomes were not of interest or the article was a review, editor's comment, or reference abstract. One study presented overlapping data using the same datasets and was excluded [19]. Ultimately, the review included 15 eligible studies [18, 20–25, 35–42]. Results from 2 studies did not provide sufficient data for the pooled analysis [22, 42]. Thus a total of 13 studies were included in the meta-analyses [18, 20, 21, 23–25, 35–41].

The characteristics of the included studies are summarized in Table 1. The review included 31,841 patients on HD; no PD patients were included. The follow-up ranged from 0.5 to 14 years. Of the included studies, 7 were conducted in Asia (4 in China, 2 in Japan, and

Table 1. Characteristics of the included cohorts

Study	Publication year	Location	Study design	Data sets	BP measures	BPV metrics	Patients, n	Mean age at baseline (±SD), years	Women, %	Median follow-up, years
Amari et al. [36]	2019	Japan	Retrospective	Data from 3 clinics in the Osaka Prefecture, Japan	Clinic visit-to-visit BP (average number of readings: 4.5)	VIM, BP change	324	70	43.5	5
Huang et al. [35]	2019	Taiwan, China	Retrospective	Data from Taipei Veterans General Hospital, a nearby community hospital, and 8 local dialysis centers	ABPM (48 h)	ARV	149	54.5±15.1	47	14
Sarafidis et al. [18]	2019	Greece	Prospective	Data from 5 affiliated hemodialysis centers in Northern Greece	ABPM (48 h)	CV, SD, ARV, wSD	227	62.8±14.2	38.8	2.51
Wang et al. [37]	2018	China	Retrospective	Data from the hemodialysis center of Peking Union Medical College Hospital	Clinic visit-to-visit predialysis BP (12 months)	CV, SD, VIM	99	61.1±12.4	65.7	5.67
Liao et al. [20]	2018	China	Retrospective	Data from the dialysis Center of West China Hospital	Clinic visit-to-visit predialysis BP (12 months)	CV, ARV, BP residual, BP change	526	56±16	42.6	>3.3
Feng et al. [21]	2018	China	Prospective	Data from the dialysis Center in Beijing, China	ABPM (44 h)	CV, SD, ARV	103	57.5±12.8	41.8	2
Shafi et al. [38]	2014	USA	Prospective	Data from Dialysis Clinic, Inc. (DCI)	Clinic visit-to-visit predialysis BP (3 months)	Residual SD	11,291	61.9±14.9	45.2	1.83
Selvarajah et al. [39]	2014	UK	Retrospective	Data from Addenbrookes Hospital and 4 satellite units in East Anglia, UK	Clinic visit-to-visit predialysis BP (3 months)	CV, SD, VIM	203	66±15	34	2
Chang et al. [40]	2014	USA	Retrospective	The HEMO study	Clinic visit-to-visit predialysis BP (at least 3 readings)	CV, ARV	1,844	57.6±14.1	56.2	2.5
Kim et al. [22]	2013	Korea	Retrospective	Data from Chonnam National University Hospital	Clinic visit-to-visit BP (1 month)	BP change	2,174	58.8	40.3	5
Flythe et al. [41]	2013	USA	Retrospective	Data from 1 large dialysis organization	Clinic visit-to-visit intradialytic BP (1 month)	BP residual, SD	6,320	59.7±14.5	46.5	0.87
Rossignol et al. [23]	2012	France	Retrospective	The Fosinopril in Dialysis (FOSIDIAL) Study	Clinic visit-to-visit predialysis BP (17 readings)	CV, SD, BP change	388	66.8	48.7	2
Di Iorio et al. [42]	2013	Italy	Retrospective	Data from 9 hospitals (8 in Campania and 1 in Basilicata, Italy)	Clinic visit-to-visit predialysis BP	CV	1,088	64.8±12.4	41.4	5
Brunelli et al. [24]	2008	USA	Retrospective	The Accelerated Mortality on Renal Replacement (A-MORR) cohort	Clinic visit-to-visit predialysis BP (3 months)	Average residual-intercept ratio	6,961	61.9±15.1	46	0.5
Tozawa et al. [25]	1999	Japan	Prospective	Data from a single dialysis unit in Okinawa, Japan	Clinic visit-to-visit predialysis BP (12 months)	CV, BP change	144	52	40.5	2.93

ABPM, ambulatory BP monitoring; BP change, absolute difference between BP readings.

Fig. 2. Forest plot of the relationship between a 1-SD increment in SBPV and all-cause mortality. Boxes represent HR and lines represent 95% CI for individual studies. The diamonds and their width represent pooled HR and 95% CI, respectively. SBP, systolic BP.

1 in Korea) and the remaining 8 were conducted in North America or Europe (4 in the USA, 1 in France, 1 in Greece, 1 in Italy, and 1 in the UK). All of the studies reported adjusted estimates. The overall quality of the included studies was high according to the Newcastle-Ottawa scale assessment tool (online suppl. Table S1).

Association between Systolic BPV and Outcomes

Ten studies were included in the analysis of the association between systolic BPV (SBPV) and all-cause mortality. A 1-SD increase in SBPV was associated with an 18% higher risk of all-cause mortality in HD patients (HR = 1.18; 95% CI 1.11–1.26, $I^2 = 53.8\%$; Fig. 2). The heterogeneity was moderate. Nine studies described the association between each SD increment in SBPV and cardiovascular mortality. The HR for cardiovascular mortality associated with each 1-SD increase in SBPV was 1.23 (95% CI 1.10–1.37, $I^2 = 57.2\%$; Fig. 3). For cardiovascular events, the meta-analysis included 4 studies. The HR associated with each 1-SD increase in SBPV was 1.27 (95% CI 1.07–1.51, $I^2 = 69.3\%$; Fig. 4).

Association between Diastolic BPV and Outcomes

Three studies reported an association between diastolic BPV (DBPV) and all-cause mortality. A 1-SD increase in DBPV was associated with a 14% higher risk of all-cause mortality in HD patients (HR = 1.14; 95% CI 1.05–1.23, $I^2 = 0.00\%$; Fig. 5). Two studies described an association between each SD increment in DBPV and cardiovascular mortality. The HR for cardiovascular mortality associated with a 1-SD increase in DBPV was 1.14 (95% CI 0.94–1.38, $I^2 = 0.00\%$; Fig. 6). One study reported a relationship between cardiovascular events and DBPV [18]. The HR was 1.35 (95% CI 1.02–1.79) with a 1-SD increase in DBPV for cardiovascular events.

Fig. 3. Forest plot of the relationship between a 1-SD increment in SBPV and cardiovascular mortality. Boxes represent HR and lines represent 95% CI for individual studies. The diamonds and their width represent pooled HR and 95% CI, respectively. SBP, systolic BP.

Association between Long-Term BPV and Outcomes

Eight studies examined long-term SBPV and all-cause mortality. A 1-SD increase in long-term SBPV was associated with a 19% higher risk of all-cause mortality (HR = 1.19; 95% CI 1.10–1.28, $I^2 = 64.0\%$; online suppl. Fig. S1). Six studies assessing long-term SBPV and cardiovascular mortality showed a significant relation (HR per 1-SD increase = 1.20; 95% CI 1.06–1.37, $I^2 = 67.6\%$; online suppl. Fig. S2). Three studies examining long-term SBPV and cardiovascular events were included in the meta-analysis (HR per 1-SD increase = 1.20; 95% CI 1.02–1.41, $I^2 = 61.1\%$; online suppl. Fig. S3). Only 1 study provided sufficient data assessing long-term DBPV and all-cause mortality (HR per 1-SD increase = 1.15; 95% CI 1.06–1.26) [24]. No study reported the relation between a 1-SD increase in long-term DBPV and cardiovascular mortality and cardiovascular events.

Association between Short-Term BPV and Outcomes

Two studies examined short-term SBPV and all-cause mortality. The HR for all-cause mortality associated with a 1-SD increase in SBPV was 1.19 (95% CI 0.98–1.44, $I^2 = 0.00\%$; online suppl. Fig. S4). Three studies examined short-term SBPV and cardiovascular mortality. The HR for a 1-SD increase in short-term SBPV and cardiovascular mortality was 1.32 (95% CI 1.06–1.65, $I^2 = 8.6\%$; online suppl. Fig. S5). One study provided sufficient data assessing short-term SBPV and cardiovascular events (HR per 1-SD increase = 1.52; 95% CI 1.14–2.04) [18].

Two studies examining long-term DBPV and all-cause mortality were included in the meta-analysis (HR per 1-SD increase = 1.09; 95% CI 0.91–1.30, $I^2 = 0.00\%$; online suppl. Fig. S6). Two studies examined short-term DBPV and cardiovascular mortality. The HR for cardiovascular mortality associated with a 1-SD increase in DBPV was 1.14 (95% CI 0.94–1.38, $I^2 =$

Fig. 4. Forest plot of the relationship between a 1-SD increment in SBPV and cardiovascular events. Boxes represent HR and lines represent 95% CI for individual studies. The diamonds and their width represent pooled HR and the 95% CI, respectively. SBP, systolic BP.

0.00%; online suppl. Fig. S7). One study provided sufficient data assessing short-term DBPV and cardiovascular events (HR per 1-SD increase = 1.35; 95% CI 1.02–1.79) [18].

Meta-Regression and Subgroup Analyses

Moderate heterogeneity was seen in the meta-analysis of the association between SBPV and outcomes. To investigate the impact of the study characteristics on the study estimates of HR in the analysis of SBPV on all-cause mortality, we performed a meta-regression analysis on the study region (Asia vs. the others, $p = 0.30$), study design (prospective and retrospective, $p = 0.27$), age (mean age >60 and ≤ 60 years, $p = 0.51$), sex (>50 and $\leq 50\%$ women, $p = 0.06$), follow-up duration ($p = 0.84$), and adjustment factors (adjusted or not adjusted for interdialytic weight gain, $p = 0.61$). The meta-regression did not reveal a significant source of heterogeneity. The results of different subgroup analyses are shown in Table 2. The HR values were not significant in the subgroup analyses of CV, ARV, and groups with $>50\%$ women. The other subgroups remained significant.

Bias and Sensitivity Analysis

Among the studies, there was no evidence of publication bias according to the Begg test (Begg test $z = 1.07$, $p > 0.228$; online suppl. Fig. S8). The results remained consistent during sensitivity analysis, indicating that the meta-analysis was stable (online suppl. Fig. S9).

Discussion and Conclusion

This study found that a greater BPV was associated with higher risks of all-cause mortality, cardiovascular-related mortality, and cardiovascular events in patients on regular HD. Both SBPV and DBPV were strong predictors of adverse outcomes. To our knowledge, this is the

Fig. 5. Forest plot of the relationship between a 1-SD increment in DBPV and all-cause mortality. Boxes represent HR and lines represent 95% CI for individual studies. The diamonds and their width represent pooled HR and the 95% CI, respectively. DBP, diastolic BP.

Fig. 6. Forest plot of the relationship between a 1-SD increment in DBPV and cardiovascular mortality. Boxes represent the HR and lines represent 95% CI for individual studies. The diamonds and their width represent pooled HR and the 95% CI, respectively. DBP, diastolic BP.

first systematic review and meta-analysis to explore the potential relationship between BPV and adverse outcomes in ESRD patients on HD.

A previous study by Tai et al. [31] reported associations between BPV and mortality and cardiovascular events in patients from multiple populations, including general populations, diabetic patients, and CKD patients who are or are not undergoing dialysis. In general, the results showed that SBPV was associated with higher risks of all-cause mortality (SBP SD for a 1-mm Hg increase: HR = 1.03; 95% CI 1.02–1.04; SBP CV for a 1% increase: HR = 1.04; 95%

Table 2. Association of all-cause mortality with a 1-SD increase in SBPV in subgroup analyses

Variable	Studies, <i>n</i>	HR (95% CI)	<i>I</i> ² , %
BPV			
SD	4	1.27 (1.06–1.51)	38.5
CV	5	1.30 (0.99–1.70)	56.4
ARV	4	1.22 (0.96–1.55)	66.6
Study region			
Asia	4	1.62 (1.02–2.57)	49
Other	6	1.17 (1.10–1.24)	58.9
Study design			
Prospective	3	1.24 (1.09–1.41)	21
Retrospective	7	1.16 (1.07–1.25)	44.7
Age			
>60 years	5	1.21 (1.10–1.33)	50.4
≤60 years	5	1.16 (1.05–1.28)	44.5
Women			
>50%	2	1.80 (0.53–6.13)	80.1
≤50%	8	1.21 (1.16–1.25)	0
Follow-up duration			
>5 years	2	1.89 (0.62–5.80)	75.2
≤5 years	8	1.18 (1.10–1.25)	53.6
Adjustment factors			
Adjusted for IDWG	4	1.21 (1.11–1.31)	0
Not adjusted for IDWG	6	1.17 (1.08–1.28)	69.4

IDWG, interdialytic weight gain.

CI 1.02–1.06). For cardiovascular mortality, the corresponding HR for SD and CV were 1.10 (95% CI 1.02–1.17) and 1.01 (95% CI 0.99–1.03), respectively. The subgroup analysis for all-cause mortality in CKD patients included only 2 studies [42, 43], and the combined HR was 1.03 (95% CI 1.01–1.05). Another systematic review conducted by Stevens et al. [44] included patients not on HD, and it was found that the long-term variability in BP was associated with cardiovascular and mortality outcomes, independently of the mean BP. Compared with previous systematic reviews [31, 44], the population in our study was comprised of patients undergoing dialysis, in whom changes in BP are more common than in the general population. Our results showed that a 1-SD increase in SBPV was significantly associated with an 18% higher risk of all-cause mortality, a 23% higher risk of cardiovascular mortality, and a 27% higher risk of cardiovascular events. The results of our study suggest that BPV is a strong predictor of mortality and cardiovascular events among individuals on renal dialysis in addition to the general population. The evidence may offer an important insight into the importance of monitoring the BP fluctuations in patients on dialysis. Clinicians usually emphasized SBPV instead of DBPV. Indeed, the associations with organ damage were usually reported for SBPV [45, 46]. To the best of our knowledge, no meta-analysis has been done to address the prognostic value of DBPV in CKD patients or dialysis patients. Thus we performed the analyses for DBPV in HD patients. Our study demonstrated that associations were still statistically significant for DBPV and all-cause mortality, cardiovascular mortality, and cardiovascular events (HR = 1.14; 95% CI 1.05–1.23; HR = 1.14; 95% CI 0.94–1.38; and HR = 1.35; 95% CI 1.02–1.79, respectively).

Some studies have reported that a higher BPV is related to greater risks of heart disease, stroke, and incidence of CKD [10–13]. Our results imply that BPV is a compelling risk factor for cardiovascular events and mortality among patients undergoing HD. The underlying

mechanisms that contribute to the relationship in patients with dialysis are complex and poorly understood. We discussed several possible explanations. Patients on maintenance HD are prone to wide BP fluctuations. Increased BPV might be a manifestation of extracellular fluid volume status. The volume status changes as body fluids are removed over several hours during HD, and fluids are progressively retained during the interdialytic interval. A greater interdialytic weight gain or ultrafiltration volume was associated with increased BPV [47, 48]. Dialysis patients have poor volume control with excessive interdialytic weight gain and higher ultrafiltration rates or volumes during an HD session, leading to increased risks of mortality and cardiovascular morbidity [49]. Our subgroup analysis showed that additional adjustments for interdialytic weight gain or ultrafiltration volume did not change the statistical difference of the results. The results indicated that the underlying mechanism might be independent of interdialytic weight gain or ultrafiltration volume.

Apart from volume-related influences, various factors, such as arterial rigidity, antihypertensive medications, and the sympathetic nervous system, might also facilitate amplification of the BPV [9]. Greater BPV is associated with arterial stiffness [50], which is a very common alteration in CKD patients. Increased arterial stiffness causes left ventricular hypertrophy and reduces myocardial perfusion, which is related to cardiovascular morbidity and mortality [51]. SBPV was reported to be associated with endothelial dysfunction [52]. Greater BPV may induce endothelial inflammation and produce vascular damage. Endothelial dysfunction was related to an increased risk of cardiovascular mortality [53]. The role of the sympathetic nervous system was examined in animal experiments. In rats, sinoaortic denervation increased BPV independently of the mean BP. These rats develop left ventricular hypertrophy and renal sclerosis [54]. Thus, increased BPV may be a marker of underlying autonomic dysfunction.

Various BPV metrics have been applied across studies to describe BP fluctuations. The SD is a classic metric that is used to evaluate variability. It is easy to calculate, and it is often strongly correlated with the mean BP. CV, VIM, and ARV are other commonly used BPV metrics. However, VIM and ARV, despite advantages for reflecting fluctuations in BP, require complex calculations and have limited clinical application [14, 55]. CV is a commonly reported BPV metric; we preferred this metric because it accounted for the mean BP [9]. BPV might be difficult to assess in clinical practice, as it requires multiple BP measurements and calculations. However, it may be important as a patient with a high BPV is at a greater risk even when the mean BP is within the normal range.

Our results may help clinicians gain a better understanding of the impact of BPV in HD patients. However, our study had several limitations. First, moderate heterogeneity was present in the analyses of the associations between SBPV and the outcomes. We performed meta-regression and subgroup analyses to identify potential sources of heterogeneity, but heterogeneity remained after these analyses. Because all included studies were observational, this would lead to bias and cofounders for which it is difficult to adjust. Second, most studies reported SBPV and adverse health outcomes. SBP was reported to cause greater risks than DBP [56]. Our study indicated that both SBPV and DBPV have similar predictive roles in mortality and cardiovascular outcomes. However, there was less data on DBPV, and the conclusion regarding the role of DBPV was weak because of the small sample size. Third, no studies reported associations between BPV and mortality or cardiovascular risk in patients on PD. It is still unclear whether BPV has the same predictive role as in HD patients. Future prospective studies need to address this question. Fourth, the therapeutic effect of reducing BPV is still uncertain. There is no randomized data proving that reducing BPV would improve clinical outcomes. However, our results strengthen the link between BPV and adverse outcomes among HD patients. It is reasonable to believe that strategies (such as adequate antihypertensives treatment, a slower ultrafiltration rate, and minimization of interdialytic

weight gain) to reduce BPV may be beneficial for this vulnerable group of patients. Still, future randomized clinical trials are needed to verify the hypotheses.

In conclusion, the findings of this systematic review and meta-analysis suggest that increased SBPV and DBPV are associated with the risks of all-cause mortality, cardiovascular mortality, and cardiovascular events. Given the presence of moderate heterogeneity, further interventional studies are needed to verify our conclusions in real time and in real patients. Our results indicate that identifying those with a high BPV is important, and preventing large fluctuations in BP may be an additional therapeutic target in BP management in HD patients.

Statement of Ethics

The authors have no ethical conflicts to declare.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

This study was financially supported by the National Youth Science Foundation of China (No. 81600536), the Natural Science Foundation of Hunan Province of China (No. 2018JJ3833), and China's Xiangya medical big data project (No. 33020125032).

Author Contributions

W.C.: conceptualization. H.L. and J.X.: data curation. J.X. and W.C.: formal analysis and methodology. Q.Z.: supervision. H.L., X.L., and P.Z.: writing of the original draft. W.C. and W.D.: writing – review and editing.

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