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ORIGINAL ARTICLE

Comparison of intradialytic blood pressure metrics as predictors of all-cause mortality

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ABSTRACT

Background. Intradialytic hypotension (IDH) has been reported to be an important prognostic factor in hemodialysis patients. However, a standard definition of IDH has not yet been determined.

Methods. We retrospectively analyzed blood pressure (BP) metrics obtained during serial dialysis sessions over a 90-day period from a single dialysis center from 2016 to 2017. The mean values and the frequency of specific values of BP were analyzed as predictors of 3-year mortality.

Results. A total of 430 patients who underwent maintenance dialysis were included. The mean age was 63.3 ± 12.4 years and 58.6% were male. A low minimum systolic blood pressure (SBP) <110 mmHg during dialysis was significantly associated with increased all-cause mortality. The frequency of a minimum SBP <100 mmHg was the most significant predictor of 3-year mortality, with an area under the curve (AUC) of 0.722. Furthermore, the frequency of a minimum SBP <100 mmHg significantly increased the predictability of mortality when combined with the presence of other clinical factors including age, body mass index and vascular access type (AUC 0.786 vs. 0.835; p = 0.005).

Conclusion. Among the various intradialytic BP metrics, the frequency of a minimum SBP <100 mmHg is the most significant factor related to all-cause mortality. The guidelines for the management of blood pressure in dialysis patients should consider including a minimum SBP <100 mmHg as a definition for IDH.

Keywords: blood pressure, end-stage renal disease, hemodialysis, intradialytic hypotension, mortality, prediction, receiver operating characteristics

INTRODUCTION

Intradialytic hypotension (IDH) is a frequent and serious issue in hemodialysis patients. In dialysis clinics, fluid administration and early dialysis termination for recovery of IDH make it difficult to control the fluid volume of dialysis patients, resulting in an increased risk of cardiovascular morbidity [1, 2]. IDH occurs due to an interaction between the ultrafiltration rate, cardiac output and arterial tone, increasing the risk of myocardial infarction, hospitalization and cerebral ischemia [3]. Furthermore, myocardial stunning due to recurrent reversible ischemia caused by IDH leads to myocardial fibrosis and an increased risk of mortality [4–6]. Despite various previous studies regarding

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blood pressure (BP) control in dialysis patients, a clinical definition of IDH has yet to be determined [7–11]. Some studies have reported that the nadir systolic BP (SBP) is the main factor related to prognosis in dialysis patients [8, 9], while other studies have reported that the change or decrease in SBP during dialysis is important [9, 12, 13]. Yet another study defined IDH as a combination of metrics related to BP, including the nadir values and intradialytic changes in BP parameters [8, 10]. While the effects of intradialytic BP on mortality in dialysis patients have been reported, there are no studies regarding the ability of intradialytic BP to predict mortality. Therefore the aim of this study was to identify the most important factors associated with mortality among various BP metrics, including mean values and frequencies, and to clarify the definition of IDH by assessing the clinically important BP metrics that can predict mortality.

MATERIALS AND METHODS

Study design and patients

The study was approved by the institutional review board of the Korea University Guro Hospital (approval number 2021GR0078) and conducted in accordance with the Declaration of Helsinki. The requirement of informed consent was waived by the board due to the retrospective nature of this study. This retrospective observational study included adult patients who were undergoing hemodialysis between January 2016 and December 2017 at Korea University Guro Hospital. Maintenance hemodialysis was defined as ≥12 hemodialysis sessions in a 90-day period.

Data collection and definitions

All clinical data of patients were analyzed via a review of the electronic medical records. Demographic characteristics including age, sex and body mass index (BMI) were collected. For the BMI calculation, the dry body weight at the time of inclusion was used. Patients' medical histories, including a history of diabetes mellitus, hypertension or cardiovascular disease, were assessed. The type of vascular access at the time of inclusion was also collected.

We assessed all medical records of each dialysis session and collected all systolic BP (SBP), diastolic BP (DBP) and ultrafiltration rate data. Minimum BP was defined as the average of the lowest BP from each dialysis session. The ΔBP was defined as the average value of the difference between the predialysis BP and the minimum BP of each session. The start-to-end BP was defined as the average value of the difference between the predialysis and postdialysis BP of each session.

The frequency of specific BP metrics among the dialysis sessions was assessed using the number of dialysis sessions in which the condition occurred divided by the total number of sessions in a 90-day period.

Outcome measures

The primary outcome was all-cause mortality. All patients were followed until September 2020.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as numbers and percentages. A survival analysis for all-cause mortality was performed using univariable and multivariable Cox proportional hazards regressions. For the predictability and probability of 3-year mortality by each BP parameter, receiver operating characteristic (ROC) curve analyses were conducted and the area under the ROC curve (AUC) was calculated. The comparison between AUCs was performed using permutation tests. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, TX, USA) and Python 3.7 (Python Software Foundation, Fredericksburg, VA, USA).

RESULTS

Baseline characteristics

Among the 465 adult patients who underwent dialysis at our hospital, 430 underwent maintenance dialysis and were included in this study. The mean patient age was 63.3 ± 12.4 years and 58.6% of the patients were male. More than half of the patients had hypertension (56.7%) and 84.7% had diabetes. The median duration of dialysis before inclusion was 0 years (IQR 0–9.2 months) and the median number of dialysis sessions included in BP measurement was 53 (IQR 25-95). The median minimum SBP was 125.4 mmHg (IQR 115.0–133.2), median minimum DBP was 64.6 mmHg (IQR 58.7–71.7), median ΔSBP was 16.9 mmHg (IQR 13.8–22.1) and median ΔDBP was 8.5 mmHg (IQR 6.9–10.6). The median start-to-end SBP and DBP were 4.4 mmHg (IQR −3.0–15.2) and 0.4 mmHg (IQR −3.3–4.7), respectively. The patients' baseline characteristics are shown in Table 1.

All-cause mortality and intradialytic systolic, diastolic and Δ BPs

The median follow-up period was 2.7 years (IQR 1.3–3.7) and 60 patients (13.95%) died during this study. Age, sex and vascular access type were identified as risk factors associated with mortality (Supplementary Table 1). Minimum SBP and minimum DBP were significantly associated with mortality in the univariate analysis, while only minimum SBP was significant in the multivariable analysis, adjusting for age, sex and access type. A minimum SBP 90–110 mmHg {hazard ratio [HR] 2.25 [95% confidence interval (CI) 1.03–4.93]} and a minimum SBP <90 mmHg [HR 7.59 (95% CI 2.12–27.20)] were identified as significant risk factors for mortality compared with an SBP ≥130 mmHg (Figure 1 and Table 2).

Frequency and values of intradialytic minimum SBP for predicting 3-year all-cause mortality

The 3-year all-cause mortality rate was 13.26% (57 patients). The minimum SBP was significantly associated with the 3-year mortality risk as assessed by logistic regression analysis (AUC = 0.665; cutoff 118 mmHg; Supplementary Table 2).

To account for the interdialysis variability of BP we assessed the frequency of measurements within a specific range of minimum SBP over a 90-day dialysis period. The average frequencies of minimum SBP <90, <100 and <110 mmHg were 2.3, 7.2 and 17.2% in surviving patients and 8.0, 18.9 and 33.6% in the patients who died in 3 years, respectively. As the frequency measured below each minimum SBP threshold increased, the 3-year mortality rate increased. When the frequency of SBP <90 or <100 mmHg increased by 1%, the mortality rate increased by 8% and 3%, respectively (Supplementary Table 3). Comparing the predictive power for the 3-year survival of each specific range of minimum SBP and the mean value of minimum SBP, the frequency of minimum SBP <100 mmHg had a higher AUC than the mean value of

the minimum SBP (bootstrap p = 0.043; Figure 2). When a minimum SBP <100 mmHg was present in one-third or two-thirds of the dialysis sessions, the positive predictive value of 3-year mortality was 38.5% and 50.0%, respectively.

When the mean minimum SBP and frequency of minimum SBP < 100 mmHg were combined with clinical factors including age, BMI and access type, the predictive power for 3-year mortality had higher AUC values (AUC = 0.798 and 0.832, respectively) than the clinical factors alone (AUC = 0.778). The predictive power of the frequency of minimum SBP <100 mmHg was significantly higher than that of the mean minimum SBP combined with clinical factors (bootstrap p = 0.01) and that of the clinical factors alone (bootstrap p = 0.005). At the optimal cutoff, the sensitivity and specificity of the frequency of minimum SBP <100 mmHg and clinical factors were 75.4% and 76.1%, respectively (positive predictive value 76.0%; Figure 3).

Table 1. Baseline characteristics of the maintenance hemodialysis patients (N = 430)

Variable	Values
Age (years), mean ± SD	63.3 ± 12.4
Male, *n* (%)	252 (58.6)
Ethnicity(Asian), *n* (%)	430 (100.0)
BMI (kg/m^2), mean ± SD	23.3 ± 4.3
Diabetes mellitus, *n* (%)	244 (56.7)
Hypertension, *n* (%)	364 (84.7)
Cardiovascular disease, *n* (%)	85 (19.8)
Type of vascular access, *n* (%)	
Arteriovenous fistula	319 (74.2)
Arteriovenous graft	23 (5.4)
Internal jugular catheter	4 (0.9)
Permanent catheter	84 (19.5)
Dialysis duration (months), median (IQR)	0 (0–9.2)
Number of dialysis sessions during the study period, median (IQR)	53 (25–95)
Start SBP (mmHg), median (IQR)	142.1 (130.7–151.2)
Start DBP (mmHg), median (IQR)	71.6 (66.4–78.0)
Minimum SBP (mmHg), median (IQR)	125.4 (115.1–133.2)
Minimum DBP (mmHg), median (IQR)	64.6 (58.7–71.7)
ΔSBP (mmHg), median (IQR)	20.8 (16.7–25.6)
ΔDBP (mmHg), median (IQR)	11.0 (8.9–13.5)
Start-to-end SBP (mmHg), median (IQR)	4.4 (−3.0–15.2)
Start-to-end DBP (mmHg), median (IQR)	0.4 (−3.3–4.7)
End SBP (mmHg), median (IQR)	136.2 (126.2–144.7)
End DBP (mmHg), median (IQR)	71.5 (66.8–76.5)
Ultrafiltration rate (mL/kg/h), median (IQR)	7.6 (5.0–10.2)
Ultrafiltration volume (L), median (IQR)	1.7 (1.2–2.3)
Ultrafiltration volume/body weight (%), median (IQR)	3.0 (2.0–4.1)

Prediction of 3-year mortality according to the cause of death using minimum SBP

Among the 57 deaths that occurred during the study period, 16 were due to cardiovascular causes, 19 to infections, 11 to cancer and 11 to other or unknown causes. The AUCs of the frequency of minimum SBP <100 mmHg combined with clinical factors for cardiovascular death and of other deaths were 0.835 and 0.815, respectively. For both cardiovascular death and other deaths, the model including the frequency of minimum SBP <100 mmHg showed higher predictive power than the model including the mean minimum SBP (Supplementary Figure 1).

DISCUSSION

A lower minimum SBP during dialysis was significantly associated with mortality. The frequency of a minimum SBP <100 mmHg during 90 days of dialysis had greater predictive power for 3-year mortality than the mean minimum SBP during 90 days. Furthermore, combining the frequency of a minimum SBP <100 mmHg with other clinical characteristics further increased the predictive power. Our results suggest that monitoring hypotensive events of an SBP <100mmHg during serial dialysis sessions is important for identifying high-risk patients.

The association between intradialytic BP and poor prognosis remains an important issue in dialysis patient management, though the relationship between intradialytic and ambulatory BP is weak [14, 15]. During hemodialysis, the fluctuation of intravascular fluid volume and changes in cardiac output affect

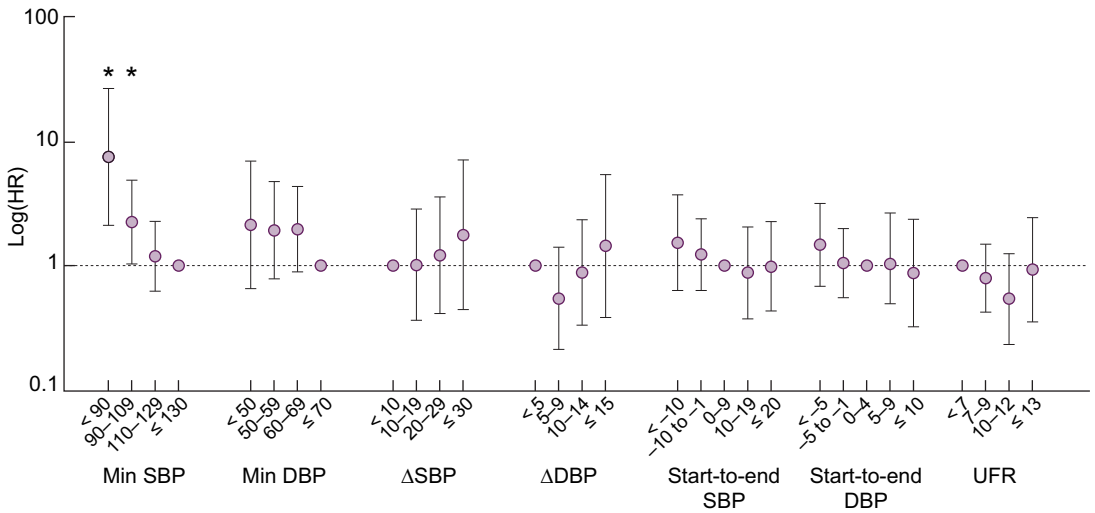

FIGURE 1: HR for all-cause mortality according to intradialytic BP metrics and ultrafiltration rate.
Asterisks represent a P-value <0.05. max, maximum; min, minimum; UFR, ultrafiltration rate.

Table 2. All-cause mortality risk according to the intradialytic BP metrics and ultrafiltration rate in hemodialysis patients

BP metrics	Number of patients	Univariable		Multivariable*	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Minimum SBP (mmHg)					
<90	6	9.85 (3.23–29.98)	<0.001	7.59 (2.12–27.20)	0.002
90–109	54	3.22 (1.51–6.86)	0.002	2.25 (1.03–4.93)	0.042
110–129	217	1.58 (0.83–2.99)	0.162	1.19 (0.62–2.28)	0.597
≥130	153	1 (ref)		1 (ref)	
Minimum DBP (mmHg)					
<50	23	3.72 (1.25–11.09)	0.019	2.14 (0.65–7.04)	0.212
50–59	99	3.69 (1.69–8.06)	0.001	1.93 (0.78–4.80)	0.155
60–69	175	2.39 (1.12–5.13)	0.025	1.97 (0.89–4.38)	0.096
≥70	133	1 (ref)		1 (ref)	
ΔSBP (mmHg)					
<10	32	1 (ref)		1 (ref)	
10–19	253	0.96 (0.34–2.72)	0.945	1.01 (0.36–2.88)	0.981
20–29	124	1.16 (0.39–3.41)	0.787	1.21 (0.41–3.60)	0.732
≥30	21	1.34 (0.34–5.49)	0.676	1.77 (0.44–7.19)	0.424
ΔDBP (mmHg)					
<5	31	1 (ref)		1 (ref)	
5–9	255	0.67 (0.26–1.72)	0.405	0.54 (0.21–1.41)	0.208
10–14	125	0.96 (0.36–2.55)	0.939	0.88 (0.33–2.35)	0.802
≥15	19	1.33 (0.36–4.97)	0.669	1.45 (0.38–5.46)	0.586
Start-to-end SBP (mmHg)					
<−10	38	1.46 (0.61–3.49)	0.398	1.53 (0.63–3.74)	0.346
−10–1	106	1.21 (0.63–2.33)	0.566	1.23 (0.63–2.40)	0.549
0–9	133	1 (ref)		1 (ref)	
10–19	73	0.72 (0.31–1.66)	0.443	0.88 (0.37–2.06)	0.765
≥20	76	0.85 (0.38–1.89)	0.690	0.98 (0.43–2.27)	0.968
Start-to-end DBP (mmHg)					
<−5	62	1.05 (0.50–2.24)	0.890	1.48 (0.68–3.19)	0.323
−5–1	131	0.87 (0.46–1.63)	0.664	1.05 (0.55–2.00)	0.883
0–4	129	1 (ref)		1 (ref)	
5–9	61	0.58 (0.24–1.44)	0.244	1.03 (0.49–2.67)	0.956
≥10	43	0.73 (0.27–1.92)	0.518	0.87 (0.32–2.37)	0.792
Ultrafiltration rate (mL/h/kg)					
<7	191	1 (ref)		1 (ref)	
7–9	125	0.67 (0.36–1.23)	0.195	0.79 (0.42–1.49)	0.465
10–12	86	0.46 (0.20–1.04)	0.061	0.54 (0.23–1.25)	0.148
≥13	28	0.99 (0.39–2.55)	0.991	0.93 (0.35–2.45)	0.884

All the BP metrics and ultrafiltration rate were calculated by the mean value of dialysis sessions during 90 days.
*Adjusted for age, BMI and vascular access type.

cardiovascular homeostasis, and these changes increase the cardiac burden in hemodialysis patients [16, 17]. The rate of cardiovascular adverse events is higher among patients undergoing hemodialysis than the general population, likely due to cardiac instability, vascular calcification, uremia and other cardiovascular risk factors [18–20]. Several studies have been conducted to determine the effects of intradialytic BP changes on the prognosis of patients. Intravascular hypotension has been studied frequently; however, the definition of IDH varies among studies [8–11]. Some researchers use ΔSBP to define IDH. Park et al. [21] showed that a decrease in SBP >30 mmHg over the course of a dialysis session increases the risk of mortality, while Shoji et al. [12] reported increased mortality with a decrease >40 mmHg and Stefansson et al. [13] reported increased mortality with a decrease >20 mmHg. In contrast, other researchers use the minimum SBP to define IDH. Flythe et al. [2] reported an increased mortality risk with a minimum SBP <90 mmHg during dialysis. Chou et al. [9] showed that mortality was associated with both a minimum SBP <90 mmHg and a change in SBP ≥50 mmHg. Several other studies have also used a combination of BP metrics to define IDH. Tisler et al. [10] reported that the combination of a minimum SBP <90 mmHg and a change in SBP ≥30 mmHg was not significantly associated with mortality, whereas Sands et al. [8] reported an increased risk of mortality using the same BP metrics.

As these studies use various definitions of IDH, the importance of specific BP metrics on the prognosis of dialysis patients is unclear. In addition, only a few studies consider the occurrence of repetitive events in serial dialysis sessions [2, 8–10] and no studies have determined the effects of DBP during dialysis. In our study, we measured the mortality risk of various intradialytic BP metrics, including the frequency and mean of SBP and DBP, and selected BP metrics that were significantly associated with mortality to identify intradialytic BP metrics that could be

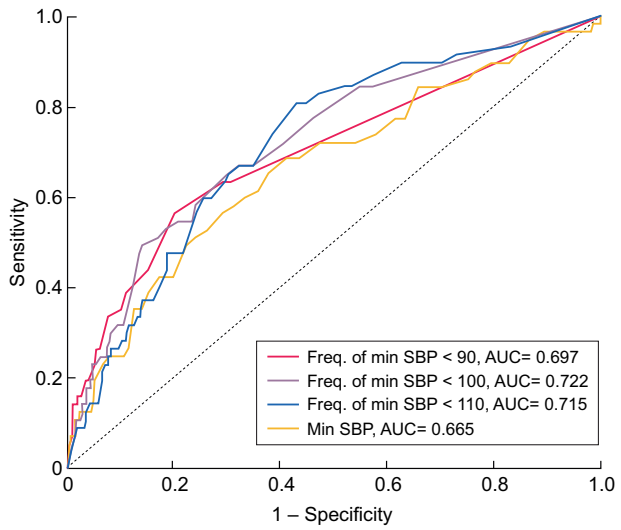

FIGURE 2: Comparison of AUCs between mean minimum SBP and the frequency of minimum SBP.
The yellow line represents the ROC curve for 3-year mortality of the mean minimum SBP over a 2-year period. The red, green and navy lines represent the ROC curves for 3-year mortality of the frequency of minimum SBP <90, 100 and 110 mmHg, respectively.

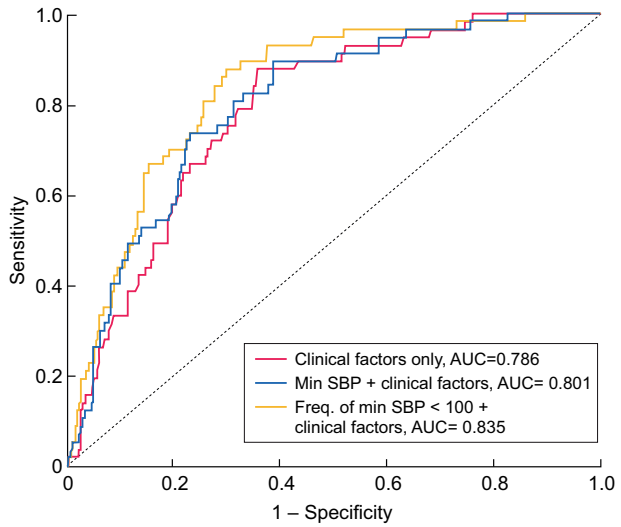

FIGURE 3: Comparison of AUCs between mean or frequency of minimum SBP combined with clinical factors.
The green line represents the ROC curve for 3-year mortality of the mean minimum SBP combined with clinical factors. The yellow line represents the ROC curve for 3-year mortality of the frequency of minimum SBP <100 mmHg combined with clinical factors including age, BMI and vascular access type, which are the factors identified as being associated with all-cause mortality in the Cox regression analysis (Supplementary Table 1).

used to predict mortality among patients undergoing maintenance hemodialysis.

We found that the most significant predictor of 3-year all-cause mortality in dialysis patients was the frequency of minimum SBP <100 mmHg in serial dialysis sessions. The use of a minimum SBP <100 mmHg, which was identified as a reference value for IDH in this study, is different from the suggested values in previous studies [9, 10]. Although previous studies reported a minimum SBP <90 mmHg as a risk factor of mortality [9, 10], this study found that a minimum SBP of 90–110 mmHg and a minimum SBP <90 mmHg both significantly increased the risk of mortality. Additionally, with the combined results of the survival analysis and ROC analysis for each BP category, a higher threshold for a minimum SBP <100 mmHg for IDH was identified. The results of this study suggest that the frequency of a specific range is more important than the average blood pressure; how to prevent recurrent hypotension is more important in patients with IDH than how much the blood pressure needs to be raised.

In contrast, whether intradialytic BP changes are associated with mortality is controversial. Similar to our study, Flythe et al. [2] showed no relationship between BP fluctuation and poor prognosis in dialysis patients. However, other studies have reported an association between mortality and decreased SBP during dialysis [9, 12, 13]. These differences between previous studies and our study may be due to differences in the study population and design, as only five patients (1.2%) in our study had a mean ΔSBP ≥50 mmHg and we used BP metrics from several dialysis sessions to quantitatively define IDH. Currently the Kidney Disease Outcomes Quality Initiative (KDOQI) and European Best Practice Guidelines define IDH as a ≥20 mmHg reduction of SBP or a mean arterial pressure ≥10 mmHg [22, 23]. However, considering these controversial results, more studies are needed to determine the best way to define IDH.

This study analyzed serial BP metrics over a long study period to determine the effects of repeated BP metrics during dialysis sessions and is the first study that assessed ROCs to predict mortality using intradialytic BP metrics. However, this study has some limitations. A relatively small number of patients were enrolled, as this study was performed at one institution. Also, there is a lack of data regarding patient symptoms during changes in BP, which can be an important factor in determining the appropriate intervention. For this longitudinal analysis we included selected patients who had serial BP data during dialysis sessions available, which may have led to a selection bias. In addition, the majority of included patients had started dialysis less than 6 months prior to the study. Lastly, this study evaluated only Asian dialysis patients, and the range and frequency of target SBP may vary in patients of other ethnicities.

We found that avoiding a low SBP during dialysis is important for long-term survival and active strategies to treat and prevent IDH are necessary, especially in patients with SBP <100 mmHg. Although various IDH prevention strategies including a low dialysate temperature, increased dialysis time or frequency and pharmacologic therapies are currently being studied, methods for preventing IDH that have a high patient compliance rate and a clear prognostic benefit have not been developed. We suggest monitoring the frequency of SBP <100 mmHg during dialysis sessions to identify patients with a higher risk of mortality.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly to protect the privacy of individuals that participated in the study.

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