All-cause mortality in relation to changes in relative blood volume during hemodialysis

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ABSTRACT

Background. Relative blood volume (RBV) monitoring is widely used in hemodialysis (HD) patients, yet the association between intradialytic RBV and mortality is unknown.

Methods. Intradialytic RBV was recorded once/min during a 6-month baseline period; all-cause mortality was noted during follow-up. RBV at 1, 2 and 3 h into HD served as a predictor of all-cause mortality during follow-up. We employed Kaplan–Meier analysis, univariate and adjusted Cox proportional hazards models for survival analysis.

Results. We studied 842 patients. During follow-up (median 30.8 months), 249 patients (29.6%) died. The following hourly RBV ranges were associated with improved survival: first hour, 93–96% [hazard ratio (HR) 0.58 (95% confidence interval (CI) 0.42–0.79)]; second hour, 89–94% [HR 0.54 (95% CI 0.39–0.75)]; third hour, 86–92% [HR 0.46 (95% CI 0.33–0.65)]. In about one-third of patients the RBV was within these ranges and in two-thirds it was above. Subgroup analysis by median age ($\leq$/> 61 years), sex, race (white/nonwhite), predialysis systolic blood pressure (SBP; $\leq$/> 130 mmHg) and median interdialytic weight gain ($\leq$/> 2.3 kg) showed comparable favorable RBV ranges. Patients with a 3-h RBV between 86 and 92% were younger, had higher ultrafiltration volumes and rates, similar intradialytic average and nadir SBPs and hypotension rates, lower postdialysis SBP and a lower prevalence of congestive heart failure when compared with patients with an RBV >92%. In the multivariate Cox analysis, RBV ranges remained independent and significant outcome predictors.

Conclusion. Specific hourly intradialytic RBV ranges are associated with lower all-cause mortality in chronic HD patients.

Keywords: hemodialysis, mortality, relative blood volume, ultrafiltration

INTRODUCTION

In hemodialysis (HD) patients, adequate volume control is one of the major challenges. Between consecutive treatments, interdialytic weight gain (IDWG) results primarily in expansion of the extracellular volume (ECV) [1]. Excessive and chronic ECV expansion is associated with cardiovascular morbidity, such as hypertension, left ventricular hypertrophy, pulmonary congestion, inflammation and increased mortality [2–5]. In most HD sessions, the ultrafiltration rate (UFR) exceeds the refill rate of fluid from the interstitium into the vascular space, resulting in a decline in blood volume, potentially precipitating intradialytic hypotension (IDH) and decreased perfusion of vital organs [6–9].

Intradialytic monitoring of relative blood volume (RBV) has been introduced with the expectation that it may prevent IDH by allowing the staff or the dialysis machine to maintain the RBV above a patient-specific critical level [10–13]. Since some of the technologies derive RBV changes from measured hematocrit changes, the term 'crash-crit' has been coined. It was hoped that there would be a patient-specific critical RBV that could be identified, below which IDH would be more likely to occur. Unfortunately, no firm evidence for the existence of a reproducible patient-specific crash-crit (or, conversely, an RBV threshold) has been established. Andrulli *et al.* [14] were not able to identify critical RBV levels for the development of symptomatic hypotension, neither in hypotensive, normotensive nor hypertensive patients, showing the variability of RBV across patients and also across treatments. The randomized controlled Crit-Line Intradialytic Monitoring Benefit (CLIMB) Study [15] tested the hypothesis that the availability of hematocrit-based intradialytic RBV monitoring with the Crit-Line monitor (CLM) as a voluntary adjunct to clinical care would decrease morbidity associated with ultrafiltration in comparison with

patients managed using conventional clinical care. The primary outcome was hospitalization and the study team developed an intricate monitoring and intervention protocol that called for specific steps when certain predefined clinical and RBV threshold criteria were met. The study failed to yield positive results; in fact, the use of RBV monitoring was associated with increased morbidity and mortality.

Several manufacturers offer devices that allow for continuous measurement of RBV during HD and therefore RBV monitoring is frequently used to assist volume management during dialysis. However, there is a paucity of data that associate attained intradialytic RBV levels with outcomes, resulting in primarily empirical use of RBV monitoring. The goal of our research was to fill this knowledge gap by exploring the association between attained intradialytic RBV levels and all-cause mortality in a large and diverse HD population.

MATERIALS AND METHODS

Population and study design

This multicenter observational retrospective study was conducted in maintenance HD patients from 17 facilities of the Renal Research Institute (RRI) across the USA between January 2012 and December 2016. The CLM was deployed to the RRI dialysis clinics on a rolling basis and is the standard of care. A 6-month baseline period and an up to 54-month follow-up period were defined on a patient level (Supplementary data, Figure S1). We used the first treatment with eligible CLM data as the start date of the baseline period. All patients who had at least 10 eligible CLM recordings during the baseline period were included in the study. A treatment time of <200 min was the only exclusion criterion. Patient characteristics were assessed during baseline. All-cause mortality was recorded during follow-up. The New England Institutional Review Board (#14-446) waived the need for informed consent.

RBV calculation

The RBV (expressed in percent of the blood volume at the start of dialysis) at time t is calculated as follows:

RBV (%) at time $t = 100 \times HCT_0/HCT_t$.

HCT_0 and HCT_t are the hematocrits at the start and at a given time t during HD, respectively. Hematocrit was measured quasicontinuously using the CLM (Fresenius Medical Care North America, Waltham, MA, USA). The CLM reports the RBV once/min. The RBV data were electronically transferred to an RRI data repository and the study database. Patients' RBVs were calculated per treatment and then averaged across all treatments per patient and subsequently across patients. We used RBVs at 1, 2 and 3 h into the HD session as outcome predictors. To that end, we averaged the RBV data between minutes 50 and 70, 110 and 130 and 170 and 190, respectively.

Blood pressure measurement

In RRI clinics, blood pressure is automatically measured every 30 min oscillometrically. We calculated average predialysis, postdialysis and intradialytic systolic blood pressure

(SBP) and report nadir SBP and IDH rate; IDH was defined as intradialytic SBP <90 mmHg [16]. Intradialytic SBP during baseline was available for 10 181 treatments in 219 patients.

Laboratory data

Laboratory measurements (Spectra Laboratories, Rockleigh, NJ, USA) were downloaded to the RRI data warehouse and extracted to the study database.

Comorbidities

Congestive heart failure (CHF), diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) were documented using *International Classification of Diseases, Ninth Revision*, codes in the patients' electronic health records.

Statistical analysis

Descriptive statistics comprised means (±standard deviation) for continuous variables and percentages for categorical variables.

To explore the association between all-cause mortality and RBV at 1, 2 and 3 h, we built Cox proportional hazards models with spline terms, allowing us to model nonlinear effects of RBV as a continuous variable and its relationship with all-cause mortality at these three hourly time points. This spline analysis allowed us to identify hourly RBV ranges associated with hazard ratios (HRs) significantly <1 ('favorable') or >1 ('unfavorable'), respectively.

For additional analysis, we stratified patients into two groups as those being within the 'favorable' 3-h RBV range or not. Survival characteristics were compared using Kaplan–Meier plots, log-rank tests and Cox proportional hazards models. Minimally and fully adjusted Cox models complemented the crude survival analysis. The minimally adjusted model included age, sex, CHF and COPD. In addition, the fully adjusted model included serum albumin and hemoglobin, the neutrophil:lymphocyte ratio (NLR; an inflammatory marker [17]), UFR, predialysis SBP, diabetes and race. Patients were censored in the event of kidney transplantation, transfer to a non-RRI facility, dialysis treatment modality change or end of follow-up.

We also report baseline descriptive statistics, group differences and 95% confidence intervals in patients within or outside the 'favorable' 3-h RBV range, respectively.

To further explore these findings and to account for possible bias considering only 3 h and not the full treatment time, we examined the association between all-cause mortality and RBV by relative elapsed treatment time, with total treatment time defined as 100%. We used 25, 50, 75 and 100% of treatment time elapsed by averaging the RBV between 21–30, 46–55, 71–80 and 91–100% of the total treatment time, respectively.

Additionally, we also examined the association between RBV slope and all-cause mortality. The RBV slope was computed using simple linear regression with an intercept at 100% RBV (per definition the initial RBV).

We also conducted a sensitivity analysis excluding patients with RBVs below the favorable hourly RBV ranges.

Table 1. Baseline characteristics of all patients and after stratification into two groups based on the attained RBV 3 h into the HD treatment

Variable	All patients	RBV outside 86–92% at 3 h into dialysis	RBV inside 86–92% at 3 h into dialysis	Group difference, mean (95% CI)
Number of patients	842	569	273	n.a.
Number of eligible HD treatments during baseline (per patient)	33.4 ± 13.8	33.7 ± 13.4	32.7 ± 14.5	−1.0 (−3.0 to 1.0)
Age (years)	61.0 ± 14.8	63.6 ± 14.1	55.7 ± 14.9	−7.9 (−9.9 to −5.8)
White race, %	50.6	51.5	48.8	−2.8 (−4.5 to 10.0)
Males, %	62.1	63.8	58.6	−5.2 (−2.0 to 12.4)
HD vintage (years)	3.9 ± 4.1	3.9 ± 4.1	3.7 ± 4.2	−0.2 (−0.8 to 0.4)
BMI (kg/m^2)	29.8 ± 8.2	29.8 ± 8.6	29.9 ± 7.6	0.12 (−1.0 to 1.3)
Diabetes mellitus, %	55.8	57.1	53.1	−4.0 (−3.1 to 11.3)
CHF, %	24.0	26.2	19.4	−6.8 (0.7 to 12.5)
COPD, %	9.4	8.3	11.7	3.4 (−7.9 to 0.7)
Predialysis SBP (mmHg)	146.3 ± 20.1	146.5 ± 20.4	145.7 ± 19.6	−0.7 (−3.7 to 2.1)
Postdialysis SBP (mmHg)	136.6 ± 18.5	137.8 ± 19.1	134.2 ± 16.8	−3.6 (−6.1 to −1.0)
Intradialytic SBP (mmHg)[a]	135.3 ± 19.0	135.9 ± 20.4	134.2 ± 16.2	−1.7 (−6.7 to +3.3)
Nadir intradialytic SBP (mmHg)[a]	116.2 ± 19.0	117.1 ± 20.3	114.5 ± 16.1	−2.5 (−7.5 to +2.4)
IDH rate, %[a]	13.1	13.0	13.1	0.1
IDWG (kg)	2.4 ± 0.8	2.2 ± 0.8	2.7 ± 0.8	0.5 (0.4 to 0.6)
IDWG relative to postdialysis weight (%)	2.9 ± 1.0	2.7 ± 0.9	3.3 ± 0.9	0.6 (0.5 to 0.7)
UFV (L)	2.4 ± 0.8	2.2 ± 0.8	2.7 ± 0.8	0.5 (0.4 to 0.6)
UFR (mL/kg/h)	7.7 ± 2.7	7.1 ± 2.5	8.8 ± 2.7	1.7 (1.4 to 2.1)
Postdialysis weight (kg)	85.7 ± 23.5	85.7 ± 23.7	85.7 ± 23.1	0.0 (−3.4 to 3.4)
Treatment time (min)	227.5 ± 18.0	228.6 ± 18.1	225.1 ± 17.4	−3.4 (−6.0 to −0.8)
Equilibrated Kt/V_{urea}	1.5 ± 0.2	1.5 ± 0.3	1.5 ± 0.2	0.03 (−0.00 to 0.07)
Hgb (g/dL)	10.9 ± 0.9	10.9 ± 1.0	11.0 ± 0.9	0.1 (0.00 to 0.28)
Serum albumin (g/dL)	3.9 ± 0.4	3.9 ± 0.4	4.0 ± 0.3	0.07 (0.02 to 0.13)
enPCR (g/kg/day)	0.9 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	0.08 (0.05 to 0.11)
Serum sodium (mmol/L)	138.8 ± 2.6	139.0 ± 2.5	138.3 ± 2.8	−0.6 (−1.0 to −0.3)
Serum potassium (mmol/L)	4.8 ± 0.5	4.7 ± 0.5	4.8 ± 0.6	0.09 (0.02 to 0.17)
Intact PTH (pg/mL)	552.8 ± 498.8	546.9 ± 516.3	565.3 ± 460.3	18.4 (−51.2 to 88.0)
Serum bicarbonate (mmol/L)	23.2 ± 1.9	23.4 ± 1.9	22.8 ± 1.8	−0.6 (−0.8 to −0.3)
Leukocytes (1000/µL)	6.7 ± 2.0	6.6 ± 2.0	6.7 ± 1.9	0.1 (−0.2 to 0.4)
Platelets (1000/µL)	206.8 ± 65.0	203.4 ± 67.7	214.1 ± 58.3	10.7 (1.3 to 20.0)
NLR	3.8 ± 2.1	4.0 ± 2.3	3.3 ± 1.7	−0.7 (−0.9 to −0.4)
Transferrin saturation (%)	33.0 ± 5.1	32.4 ± 9.0	34.1 ± 8.5	1.7 (0.5 to 3.0)

Data are expressed as mean ± standard deviation unless stated otherwise.
BMI, body mass index; UFV, ultrafiltration volume; Hgb, hemoglobin; PTH, parathyroid hormone; n.a., not applicable.
[a]Intradialytic SBP and IDH events were available in 219 patients.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R i386 3.0.2 (library: ggplot2, splines, survival; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient baseline characteristics

We studied 842 patients with a total of 28 119 dialysis sessions with eligible RBV recordings during a 6-month baseline, resulting in 33.4 ± 13.8 eligible sessions per patient (Table 1). Age was 61.0 ± 14.8 years, dialysis vintage was 3.9 ± 4.1 years, 50.6% were white, 62.1% were male, 55.8% had diabetes, 24% had CHF and 9.4% had COPD. Intradialytic RBVs were 97.9 ± 1.9, 94.8 ± 2.6 and 93.1 ± 3.3% after 1, 2 and 3 h, respectively.

Intradialytic RBV and all-cause mortality

During the median follow-up of 30.8 months, 249 patients (29.6%) died. HRs for all-cause mortality were significantly <1.0 in patients with 1-h RBV 93–96%, 2-h RBV 89–94% and 3-h RBV 86–92%. Approximately 65% of the patients attained RBVs above, 32% within and ~2.5% below these RBV ranges (Table 2). RBV ranges associated with HRs significantly >1.0 were 97–100% (1 h), 95–99% (2 h) and 93–99% (3 h) (Figures 1 and 2). Half-hourly favorable RBV ranges are shown as supplementary data (Supplementary data, Figure S2). Multivariate Cox analysis corroborated the lower HRs for all-cause mortality in those patients whose RBV fell inside these RBV ranges (Table 3). Analysis by percent of elapsed treatment time instead of by hours showed materially identical results (Supplementary data, Figure S3). Subgroup analyses by median age (≤/>61 years), race (white, nonwhite), sex, pre-dialytic SBP (≤/>130 mmHg) and IDWG (≤/>2.3 kg) showed comparable favorable RBV ranges (Table 4).

Kaplan–Meier analysis and Cox proportional hazards models indicated a significantly better survival in patients with 3-h RBVs inside 86–92% compared with those patients outside this range (Figures 3 and 4).

Analysis on the RBV slope and all-cause mortality showed significantly increased HR, with a slope between −2.47 and −0.34%/h, and significantly reduced HR with a slope from −5.18 to −3.04%/h (Figure 5).

Patient characteristics relative to RBV level 3 h into the treatment

We compared clinical, laboratory and treatment variables between patients who did and did not attain the 3-h RBV of 86–92% (Table 1). RBVs of 273 patients (32.5%) were within this 3-h RBV range, while 554 patients (65.8%) had RBVs >92% and 15 patients (1.8%) <86%. Patients outside the 86–92% 3-h RBV range were older (63.6 ± 14.1 versus 55.7 ± 14.9 years; P < 0.001), more frequently had CHF (26.2% versus 19.4%; P = 0.03), lower IDWG (2.2 ± 0.8 versus 2.7 ± 0.8 kg; P < 0.001), lower normalized UFR (7.1 ± 2.5 versus 8.8 ± 2.7 mL/kg/h; P < 0.001), lower equilibrated normalized protein catabolic rate (enPCR; 0.9 ± 0.2 versus

1.0 ± 0.2 g/day/kg; P < 0.001), lower albumin levels (3.9 ± 0.4 versus 4.0 ± 0.3 g/dL; P = 0.003), lower transferrin saturation (32.4 ± 9.0 versus 34.1 ± 8.5%; P = 0.007) and higher NLR (4.0 ± 2.3 versus 3.3 ± 1.7; P < 0.001).

FIGURE 2: Intradialytic hourly RBV ranges that are associated with HRs significantly <1.0 for all cause mortality.

Table 2. Distribution of patients relative to the RBV ranges by hours into the HD session

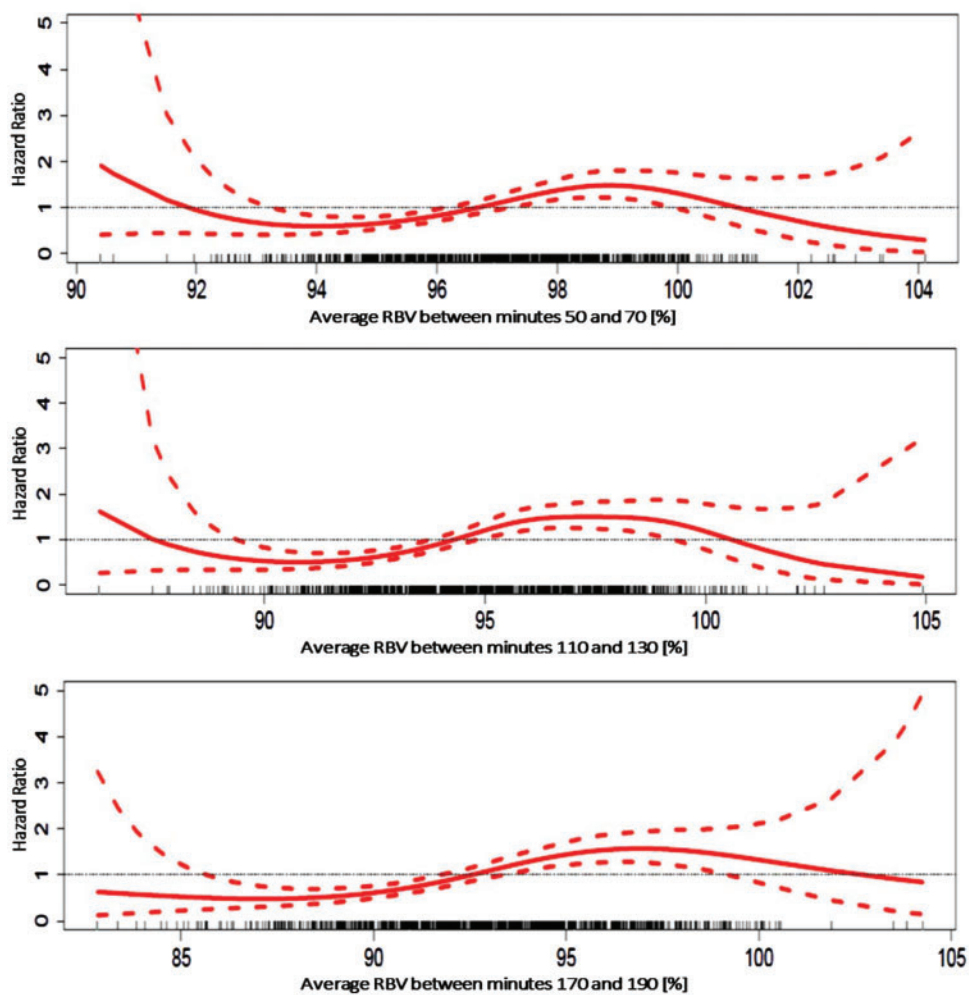| Favorable RBV range	1 h, 93–96%	2 h, 89–94%	3 h, 86–92%
Above, n (%)	550 (65.3)	551 (65.4)	554 (65.8)
Within, n (%)	270 (32.1)	273 (32.5)	273 (32.5)
Below, n (%)	22 (2.6)	18 (2.1)	15 (1.8)

FIGURE 1: Association between intradialytic RBV and all-cause mortality. HRs (solid line) and 95% CIs (dashed lines) of achieved RBV levels after 1 (top), 2 (middle) and 3 (bottom) h, respectively. The tick marks on the x-axis represent individual patients.

Table 3. Crude and adjusted HRs for all-cause mortality associated with attainment of favorable RBV ranges after 1, 2 and 3 h

Time (favorable RBV ranges)	Crude model[a]		Minimally adjusted model[b]		Fully adjusted model[c]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
First hour (93–96%)	0.57 (0.43–0.77)	0.0002	0.64 (0.48–0.87)	0.003	0.58 (0.42–0.79)	0.0005
Second hour (89–94%)	0.52 (0.38–0.69)	<0.001	0.63 (0.46–0.85)	0.002	0.54 (0.39–0.75)	<0.001
Third hour (86–92%)	0.43 (0.31–0.58)	<0.001	0.57 (0.42–0.79)	<0.001	0.46 (0.33–0.65)	<0.001

[a]Unadjusted model.
[b]Adjusted for age, sex, COPD and CHF.
[c]Adjusted for age sex, race, COPD, CHF, diabetes, albumin, hemoglobin, NLR, predialysis SBP and UFR.

Table 4. RBV ranges are associated with HRs significantly <1.0 for all-cause mortality in clinical subgroups

Subgroup (n)	RBV (%) 1 h	RBV (%) 2 h	RBV (%) 3 h
All patients (842)	93–96	89–94	86–92
Age (years)			
≤61 (421)	95–96	90–93	86–90
>61 (421)	93–96	90–94	88–92
Race			
White (426)	94–96	91–94	87–92
Nonwhite (416)	94–96	90–93	86–91
Sex			
Male (523)	94–96	90–94	87–92
Female (319)	93–96	90–93	86–91
Predialysis SBP (mmHg)			
≤ 130 (180)	94.8–95.2	90–94	87–92
>130 (662)	94–96	90–93	86–91
Interdialytic weight gain (kg)			
≤ 2.3 (421)	n.s.	n.s.	90–92
> 2.3 (421)	93–96	89–93	85–91

n.s., not significant.

FIGURE 4: Forest plot showing HRs of baseline clinical characteristics and attainment of favorable RBV ranges after 3 h.
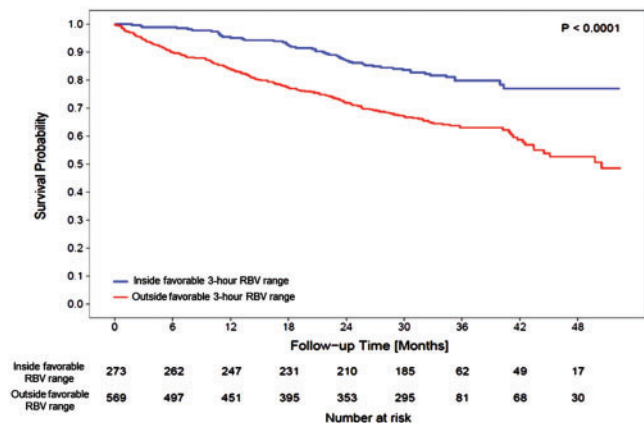

FIGURE 3: Kaplan–Meier analysis of survival probabilities for RBV achieved after 3 h (86–92%).

FIGURE 5: Association between intradialytic RBV slope and HRs for all-cause mortality. The RBV slope is expressed in percent RBV per hour. HRs (solid line) and 95% CIs (dashed lines) are shown. The tick marks on the x-axis represent individual patients.

Association between RBV, SBP and intradialytic hypotension

Mean predialysis, postdialysis, intradialytic and nadir SBPs were 146.3 ± 20.1, 136.6 ± 18.5, 135.3 ± 19.0 and 116.2 ± 19.0 mmHg, respectively. Neither predialysis nor SBP during dialysis differed between patients who did or did not attain 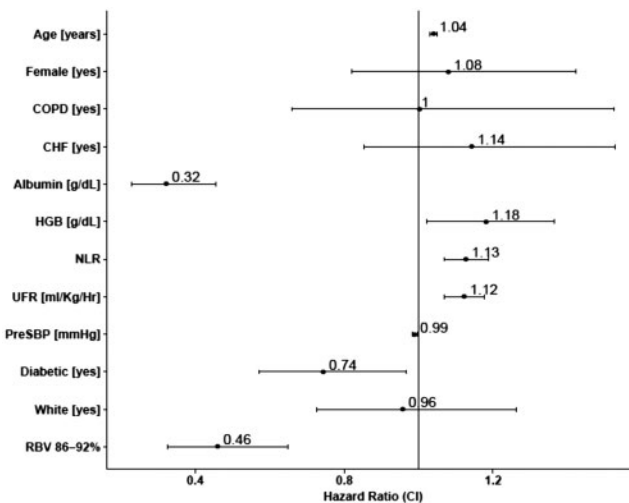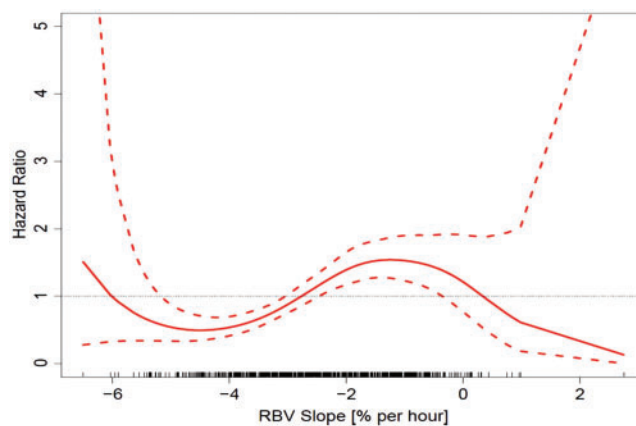a 3-h RBV of 86–92%. Postdialysis SBP was significantly higher in patients with RBV outside that range (Table 1, Figure 6).

To explore if the peridialytic SBP behavior was associated with specific RBV levels, we stratified patients based on
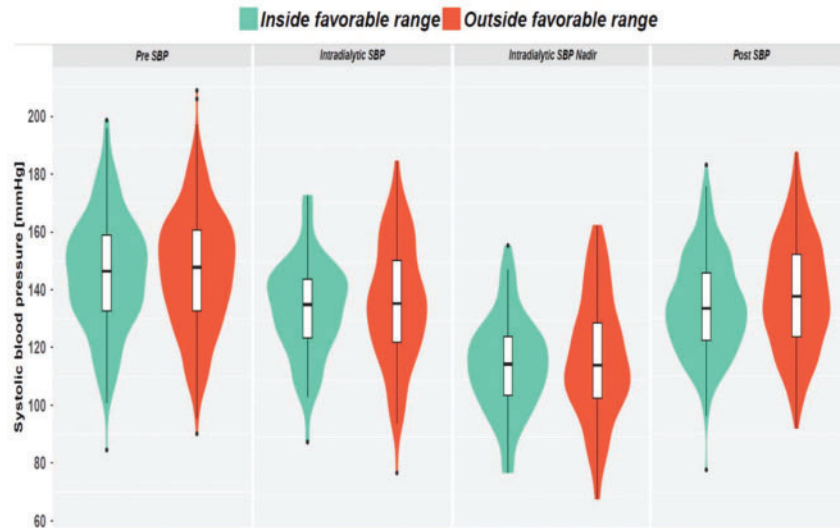
FIGURE 6: Violin plots and box and whisker plots showing the distribution and comparison of SBP at baseline between patients who attained RBVs within the favorable 3-h RBV range (86–92%) and those who did not. The width of the violin plot represents the frequency of measurements.

their peridialytic SBP change (posthemodialysis SBP − prehemodialysis SBP). We found that hourly RBV levels were comparable across all groups of peridialytic SBP change (Supplementary data, Table S1).

To explore the association between RBV and intradialytic SBP patterns we analyzed those 219 patients with available intradialytic RBV and SPB data. Seventy-six patients (34.7%) were inside the favorable 3-h RBV range and 143 (65.3%) were outside. Neither intradialytic average SBP nor nadir SBP and IDH rate differed between these two groups (Supplementary data, Tables S2 and S3). Treatment-level hourly RBVs were comparable between sessions with and without IDH, respectively (Supplementary data, Table S4).

Intradialytic fluid administration

Acknowledging the possible influence of fluid administration on RBV, we examined hourly RBV levels in treatments with documented fluid administration; hourly RBV levels were materially identical (Supplementary data, Table S5). Furthermore, neither fluid administration rate nor fluid administration rate in the presence of IDH differed between patients inside or outside the 86–92% 3-h RBV range, respectively (Supplementary data, Table S3).

Sensitivity analyses

To explore the influence of RBV levels below the favorable RBV ranges on outcomes, we computed HRs for all-cause mortality after excluding patients with RBVs below the lower limits of the hourly favorable RBV ranges. This sensitivity analysis showed materially identical results (Supplementary data, Table S6 and Figure S4).

To further explore the effect of intradialytic fluid administration on the association between RBV and all-cause mortality, we performed sensitivity analyses in patients with available intradialytic data. Cox proportional hazards models (crude,

minimally and fully adjusted models) excluding treatments with fluid administration showed essentially identical results (data not shown).

DISCUSSION

In this study we explored the association between hourly intradialytic RBV levels and all-cause mortality in a large and diverse cohort of chronic HD patients. The main finding is that specific intradialytic RBV ranges are associated with significantly lower all-cause mortality.

Since the inception of dialysis, fluid management has been of central concern. Fluid overload as well as fluid depletion have been related to cardiovascular events and increased mortality [3–5, 8, 18, 19]. Fluid management in standard in-center HD has been likened to sailing between Scylla and Charybdis: on the one hand, in patients without residual kidney function, ultrafiltration is the only means to remove fluid accumulated between HD treatments and to avoid fluid overload; on the other hand, excessive fluid removal may impact intradialytic hemodynamic stability. Indeed, ultrafiltration-induced blood volume reduction is considered a causal factor of intradialytic cardiovascular instability, depending on the rates of ultrafiltration and vascular refilling [6, 20]. Given these competing factors, it is conceivable that on a population level certain RBV ranges are associated with lower (or higher) mortality. While the genesis of the RBV curve is easy to understand qualitatively as the relative difference between UFR and vascular refilling rate, attempts to quantitatively model and predict RBV dynamics are notoriously complicated and currently not applicable to routine care [21, 22]. The matter is further complicated by the absence of randomized controlled trials (RCTs) looking at the relationship between RBV and patient outcomes. In this situation, clinical practitioners who use RBV monitoring resort to an empirical assessment of RBV curves, where flat curves are

considered to indicate fluid overload and steep curves indicate intravascular volume depletion that may precipitate IDH [23, 24].

This study is the first one to investigate the association between RBV levels attained in routine care and patient survival. We are cognizant of the fact that causality cannot be derived from observational studies and that this study cannot provide a recommendation for certain RBV ranges. Only one RCT explored the clinical use of RBV monitoring. In the CLIMB Study [15], 443 participants were randomized to either using RBV monitoring as a voluntary adjunct to clinical care or conventional care. Patients assigned to the intervention arm may have had their UFRs adjusted at the discretion of the staff using a suggested ultrafiltration algorithm when a pre-defined RBV target was reached. While RBV monitoring did not result in a marked change in UFR, increased hospitalization and mortality rates were noted in the intervention arm, calling into question the utility of blood volume monitoring. Of note, the RBV targets used in CLIMB were, to the best of our knowledge, not based on prior validated evidence [25].

In an observational study of 308 patients, Agarwal [26] used relative plasma volume (RPV) recordings from a single HD treatment to calculate RPV slopes. The author found that flatter RPV slopes (<1.39%/h) were associated with higher mortality (HR 1.72). After adjustment for several covariates, including interdialytic blood pressure, flat RPV slopes remained a significant predictor (HR 2.46). While it is difficult to compare these RPV and our RBV results, their directional agreement is notable. In another observational study, Ficociello et al. reported a 64.5% lower all-cause hospitalization rate in patients with an end-dialytic RBV <85% compared with patients with flat RBV (abstract, National Kidney Foundation meeting, 2015).

RBV monitoring was introduced with the hope of preventing IDH [13, 14, 27, 28]. However, several studies failed to demonstrate any relationship between changes in RBV and intradialytic blood pressure [14, 29, 30]. Most studies intended to find patient-specific RBVs associated with IDH, yet no critical RBV levels have been identified [11, 29]. These findings were corroborated in our study where, in patients who attained the favorable 3-h RBV range, IDH rates were not increased despite higher UFRs.

In our study, about two-thirds of patients attained RBVs above the favorable ranges and <3% of patients were below. These results support reports where a substantial fraction of patients had minor or no change in RBV during dialysis [23, 31]. Lopot et al. [23] reported that in 30% of their patients RBV did not decline, and Steuer et al. [31] reported an RBV reduction by <5 percentage points in 18% of their patients.

In our study, patients with a 3-h RBV above the upper limit of the favorable range had clinical signs of fluid overload, such as higher postdialysis SBP and a higher prevalence of CHF (Table 1). While plausible, this observation needs corroboration using objective measurements of fluid status, such as bioimpedance (currently not available in the USA for use in patients). Noteworthy, Agarwal [26] also concluded that flatter RBV slopes were a sign of fluid overload, consistent with our hypothesis.

Patients outside the favorable RBV range were older, had a higher prevalence of CHF, lower enPCR and lower UFRs compared with those patients within the favorable range. These findings are consistent with studies showing lower ultrafiltration volumes and rates in elderly patients [32], possibly because this group is particularly vulnerable to intradialytic morbid events [14]. Older age predisposes to comorbidities, including diabetes and CHF, which may prompt a more cautious approach to fluid removal. Therefore it cannot be excluded that higher RBVs indicate intolerance to fluid removal, which may explain in part the observed association with poor outcomes despite extensive adjustment for confounders.

Our study has several strengths: its large and diverse dialysis population, the substantial number of dialysis treatments, standardized care protocols, automated RBV and blood pressure recordings and the long follow-up period. While observational studies are ill-suited to guide general protocols for clinical practice, our results are valuable for the planning of future trials designed to attain (or avoid) specific RBV levels, for example, by using automatic UFR feedback control.

Study limitations are mainly due to its observational nature. Objective indicators of fluid status (e.g. bioimpedance) are missing; these would allow a more extensive probing into the relationship between RBV and fluid status. Second, data were incomplete for intradialytic blood pressure and for fluid administration and the dialysis staff was not blinded to RBV data. Despite statistical adjustments for baseline characteristics, residual confounding cannot be ruled out. Lastly, we acknowledge the lack of quantitative data on residual kidney function (RKF), which could have an impact on RBV behavior. However, the long HD vintage of our population makes substantial RKF unlikely [33, 34]. Also, substantial RKF would result in less IDWG, lower UFR and consequently flatter RBV curves. Since RKF is associated with better survival, the presence of RKF would have increased the odds for better outcomes with flatter RBV, contrary to what we observed.

In conclusion, our study indicates that specific intradialytic RBV ranges are associated with all-cause mortality in HD patients. These findings may serve as a valuable basis for future clinical trials into the relationship between RBV profiles, fluid status as determined by objective methods and patient outcomes.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

P.K., S.T. H.Z., P.P., J.K. and F.M.v.d.S. contributed to the design, implementation and discussion of the research. H.Z. analyzed the data and created the figures. P.P. wrote the manuscript with input from all coauthors. P.K. directed the project. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

P.K. holds stock and S.T. holds performance shares in Fresenius Medical Care. The remaining authors declare no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract form.

(See related article by Van Buren. Relative blood volume monitoring in hemodialysis patients: identifying its appropriate role. *Nephrol Dial Transplant* 2019; 34: 1251–1253)

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