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RESEARCH ARTICLE

Prognostic value of ultrafiltration rate variability in maintenance hemodialysis patients: a prospective cohort study

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Abstract **This single-center prospective cohort study establishes ultrafiltration rate variability (quantified by coefficient of variation, UFRCV) as an independent predictor of all-cause and cardiovascular mortality in maintenance hemodialysis patients. While absolute ultrafiltration rate thresholds represent established risk factors, dynamic fluid removal fluctuations remain prognostically uncharacterized. We longitudinally monitored ultrafiltration rate patterns during a 90-day observation period in 202 hemodialysis patients (median follow-up: 38.7 months). Stratification by median UFRCV (0.187) revealed significantly reduced survival among patients with elevated variability. This association demonstrated particular clinical significance in elderly individuals (> 60 years), those with recurrent intradialytic hypotension, and subjects exhibiting elevated predialysis systolic blood pressure variability. Notably, UFRCV exhibited stronger mortality prediction in patients with lower mean ultrafiltration volumes (< 2469 mL), indicating that current static ultrafiltration rate targets inadequately reflect dynamic hemodynamic vulnerability. These findings underscore the imperative to integrate ultrafiltration rate variability metrics into personalized volume management frameworks —a parameter currently absent from dialysis adequacy guidelines. Collectively, UFRCV assessment emerges as a critical indicator of subclinical hemodynamic compromise, providing pivotal insights for refining hemodynamic risk stratification in maintenance hemodialysis populations.**

Keywords maintenance hemodialysis; mortality; predialysis blood pressure variability; ultrafiltration rate variability; ultrafiltration volume

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are global health challenges with increasing prevalence, making hemodialysis (HD) a critical life-sustaining therapy for millions of patients worldwide [1–3]. Despite significant advancements in dialysis technologies and equipment, the long-term prognosis of HD patients remains suboptimal, with high rates of morbidity and mortality [4,5]. One of the central challenges in HD therapy is effective volume control [6], which is essential for achieving dialysis adequacy and improving patients' outcomes. The primary goals of HD are to remove uremic toxins and regulate fluid balance; however, volume imbalance remains a common and persistent issue among maintenance hemodialysis (MHD) patients [7]. This imbalance can lead to a cascade of complications, including hemodynamic instability, hypertension, cardiovascular and cerebrovascular events, infections, and malnutrition, mediated through mechanisms such as immune dysregulation, chronic inflammation, and nutritional deficiencies [8]. Therefore, optimal fluid management is the foundation of dialysis care, but achieving stable volume control remains a major clinical challenge due to the dynamic nature of fluid fluctuations in this population [8].

Among the key factors influencing volume management, the ultrafiltration rate (UFR), defined as the

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rate of fluid removal during dialysis, plays a pivotal role in maintaining hemodynamic stability and preventing complications. Excessive or rapid fluid removal can lead to intradialytic hypotension (IDH), cardiovascular stress, and increased mortality, while inadequate fluid removal may result in chronic volume overload, contributing to hypertension and cardiac remodeling [9–11]. Although extensive researches have been conducted to define the optimal UFR range [10–16], the variability of UFR over time, quantified by the coefficient of variation (UFRCV, coefficient of variation of ultrafiltration rate), has received limited attention despite its potential clinical significance [17–19].

UFR variability may influence patients' outcomes through multiple pathways. Fluctuations in UFR can induce hemodynamic instability, exacerbate cardiovascular stress [8], and disrupt fluid balance, all of which are closely associated with the high morbidity and mortality observed in ESRD patients. In addition, heterogeneity in dialysis demands and physiologic responses among patients may lead to different effects of UFRCV on prognosis. This variability might be important in patients with different average ultrafiltration volumes, and the impact of UFRCV on the results may vary significantly, due to patients' tolerance to fluid shifts or the activation of compensatory mechanisms, such as vascular reactivity or preserved cardiac function [10]. Understanding these dynamics is crucial for developing personalized dialysis strategies that can minimize risks and optimize outcomes.

This study aims to investigate the impact of UFRCV on the prognosis of HD patients, with a focus on its predictive value in specific subgroups. Furthermore, we explore the differential effects of UFRCV in patients with varying levels of median ultrafiltration volume, aiming to identify high-risk populations that may benefit from targeted interventions.

Materials and methods

Study design and patient population

This single-center prospective cohort study enrolled patients undergoing MHD at the Blood Purification Center of Zhongshan Hospital, Fudan University, Shanghai, China. Eligible participants were adults (⩾ 18 years) diagnosed with ESRD according to Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [20], who had remained on chronic HD for at least three months before January 2016. Exclusion criteria included patients with myocardial infarction, acute heart failure, malignant tumor, stroke, transient ischemic attack, thromboembolic events (deep vein thrombosis and pulmonary embolism) and severe infection in the past 6 months (Fig. 1). All participants provided written informed consent, and the study protocol was approved by the Ethics Committee of Zhongshan Hospital, Fudan University, in compliance with the *Declaration of Helsinki* (Approval Number: B2014-083). The primary endpoint was all-cause mortality, with follow-up extending until December 31, 2019.

Dialysis protocol and clinical data collection

Patients received thrice-weekly low-flux HD using 1.4 m^2 synthetic membrane dialyzers (BLS514SD, Sorin Group Italia; Polyflux14L, Gambro Dialysatoren GmbH). Standard bicarbonate dialysate (Na^+ 138.0 mmol/L,

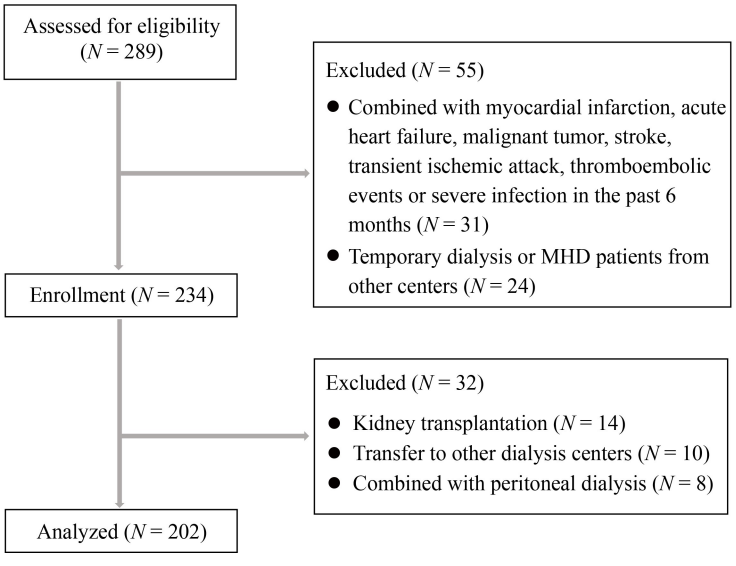

Fig. 1 Flowchart showing the procedure for the selection of study participants.

HCO_3^- 32.0 mmol/L, K^+ 2.0 mmol/L, Ca^{2+} 1.25 mmol/L, Mg^{2+} 0.5 mmol/L) was administered with a blood flow rate of 200–280 mL/min and a dialysate flow rate of 500 mL/min. Dry weight was targeted to achieve an edema-free state, as determined by clinical assessment. Patient demographics, comorbidities, biochemical parameters, and medication use were extracted from medical records at baseline.

Biochemical and echocardiographic assessments

Blood samples were collected on a midweek non-dialysis day between 8:00 and 10:00 AM after 30 min of quiet rest to minimize confounding from interdialytic rebound effects, circadian variations, and dialysis-induced volume shifts. Biochemical parameters were measured using standardized laboratory methods. Transthoracic echocardiography was performed using a Philips IE33 machine with a 3.5-MHz multiphase array probe by a single experienced cardiologist within 2 hours of blood sampling. Left ventricular internal dimensions, interventricular septal thickness, and posterior wall thickness were measured at end-diastole according to the Penn Convention, and left ventricular ejection fraction (LVEF) was calculated using two-dimensional echocardiography. The left ventricular mass index (LVMI) is obtained by dividing the left ventricular mass by height (measured in meters, raised to the power of 2.7).

Blood pressure monitoring and IDH definition

Intradialytic blood pressure (BP) was averaged from hourly measurements during a 3-month run-in phase. IDH was defined as intradialytic systolic BP (SBP) decline ⩾ 20 mmHg or mean arterial pressure (MAP) reduction ⩾ 10 mmHg requiring therapeutic intervention [21,22] within a 3-month interval. IDH-prone patients were defined as those who experienced more than 4 hypotensive events during 3 months period (10% of dialysis treatments) [23,24]. Predialysis BP variability was calculated as coefficient of variation (CV = standard deviation (SD)/mean) [25].

UFR variability assessment

The ultrafiltration volume was measured according to the weight change in during dialysis (i.e., pre-dialysis weight minus post-dialysis weight). UFR, expressed in mL/h/kg, was the ultrafiltration volume divided by dialysis time and target bodyweight [26,27]. Following 1 month adaptation period, UFR variability was evaluated over 3 consecutive months to ensure robust classification while reflecting standard clinical assessment cycles (Fig. S1). Each dialysis session was recorded as a visit, with UFR data used to calculate SD and CV. UFR variability was defined as the CV of UFR values (UFRCV) during the observation period [18,19].

Subgroup analysis

Patients were stratified into subgroups based on age (⩽ 60 years vs. > 60 years), gender, median value of albumin and predialysis SBPCV, and IDH-prone or not. The impact of UFRCV on all-cause mortality was analyzed within each subgroup using the same statistical methods as for the overall cohort.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range), while categorical variables were presented as frequencies and percentages. Group comparisons were performed using independent samples *t*-tests for normally distributed data, Mann–Whitney *U* tests for skewed data, and chi-square tests for categorical variables. Univariate and multivariate Cox proportional hazards models were used to assess the association between UFRCV and mortality. Covariates with $P < 0.1$ in univariate analysis were included in multivariate models. The consistency of the association between UFRCV and all-cause mortality across various subgroups was examined. Kaplan–Meier curves and Log-rank tests were employed to evaluate survival differences across UFRCV groups and ultrafiltration volume subgroups. All analyses were conducted using R version 4.4.0 and Zstats 1.0, with statistical significance set at $P < 0.05$ (two-sided).

Results

Demographic and clinical characteristics

The cohort comprised 202 patients (mean age 55.85 ± 14.48 years; 57.92% male). Median UFRCV was 0.187, dividing participants into high- and low-variability groups. High UFRCV patients exhibited advanced age, preserved residual renal function, lower dry weight, lower serum albumin/creatinine, elevated predialysis SBPCV, more use of calcium channel blockers (CCBs) and less comorbid with cardiovascular diseases ($P < 0.05$) (Table 1).

UFRCV and mortality

Over a mean follow-up period of 38.72 months, 30 deaths occurred (mortality rate: 4.95/100 person-years). Causes of death included 13 cardiovascular events, 8 cerebrovascular events, 5 severe infections, and 4 malignancies (Table S1). Survival analyses using the

Table 1 Demographic and clinical characteristics of the study cohort

Characteristics	Total (n = 202)	UFRCV		P value
		Low < 0.187 (n = 101)	High ⩾ 0.187 (n = 101)	
Age, year	55.85 ± 14.48	51.93 ± 12.52	59.94 ± 15.30	< 0.001
Male, n (%)	117 (57.92)	61 (60.40)	56 (55.45)	0.476
BMI, kg/m^2	23.09 ± 9.08	24.20 ± 10.55	22.00 ± 7.27	0.096
Preserved residual kidney function[a], n (%)	41 (20.30)	14 (13.86)	27 (26.73)	0.023
Dialysis vintage, months	69.36 ± 38.97	71.8 ± 38.09	66.64 ± 40.05	0.436
spKt/vurea	1.43 (1.26, 1.74)	1.42 (1.21, 1.70)	1.44 (1.28, 1.74)	0.558
Dry weight, kg	57.48 (50.83, 64.00)	58.39 (51.89, 68.18)	55.30 (49.95, 62.32)	0.014
UFRCV	0.191 ± 0.062	0.144 ± 0.042	0.238 ± 0.038	< 0.001
UFRSD, mL/h/kg	2.15 (1.74, 2.53)	1.89 (1.51, 2.28)	2.33 (1.97, 2.72)	< 0.001
EF, %	66.65 ± 6.60	66.49 ± 7.11	66.81 ± 6.08	0.770
LVMI, g/m$^{2.7}$	49.51 ± 18.92	46.57 ± 15.67	52.40 ± 21.38	0.063
NT-proBNP, pg/mL	3710.00 (1460.00, 8203.00)	3578.50 (1444.50, 6835.00)	3874.00 (1569.00, 12 214.00)	0.219
Hemoglobin, g/L	105.13 ± 15.20	106.14 ± 15.45	104.11 ± 14.96	0.346
Serum albumin, g/L	39.27 ± 3.69	40.06 ± 3.18	38.47 ± 3.99	0.002
Serum creatinine, μmol/L	1030.63 ± 279.21	1076.27 ± 296.00	984.98 ± 254.73	0.021
iPTH, pg/mL	429.59 ± 444.15	474.15 ± 445.22	385.47 ± 440.91	0.164
hs-CRP, mg/L	2.30 (0.70, 6.40)	2.50 (0.80, 5.60)	2.30 (0.70, 7.18)	0.754
IDH-prone patients, n (%)	88 (43.56)	42 (41.58)	46 (45.54)	0.570
Predialysis-SBPCV	0.110 ± 0.026	0.106 ± 0.026	0.114 ± 0.026	0.032
Predialysis-DBPCV	0.111 ± 0.024	0.105 ± 0.022	0.116 ± 0.025	0.001
Antihypertensive agents, tablets	2.64 ± 1.91	2.64 ± 1.81	2.65 ± 2.03	0.995
CCBs, tablets	0.98 ± 0.80	0.83 ± 0.65	1.13 ± 0.93	0.036
ARBs, tablets	0.57 ± 0.57	0.62 ± 0.56	0.50 ± 0.59	0.305
ACEIs, tablets	0.36 ± 0.55	0.33 ± 0.51	0.41 ± 0.59	0.471
α-blockers, tablets	0.20 ± 0.59	0.12 ± 0.43	0.32 ± 0.76	0.109
β-blockers, tablets	0.67 ± 0.55	0.65 ± 0.58	0.70 ± 0.51	0.632
Diuretics, tablets	0.07 ± 0.29	0.04 ± 0.19	0.11 ± 0.40	0.250
Current smoking[b], n (%)	17 (8.42)	9 (8.91)	8 (7.92)	0.800
Current alcohol drinking[c], n (%)	4 (1.98)	2 (1.98)	2 (1.98)	1.000
Comorbid conditions				
Cardiovascular disease[d], n (%)	18 (8.91)	13 (12.87)	5 (4.95)	0.048
Myocardial infarction, n (%)	4 (1.98)	3 (2.97)	1 (0.99)	0.614
Revascularization[e], n (%)	3 (1.49)	2 (1.98)	1 (0.99)	1.000
Hypertension[f], n (%)	129 (63.86)	66 (65.35)	63 (62.38)	0.660
Diabetes, n (%)	31 (15.35)	16 (15.84)	15 (14.85)	0.845
Stroke, n (%)	3 (1.49)	0 (0.00)	3 (2.97)	0.245
Peripheral artery disease, n (%)	4 (2.09)	3 (3.16)	1 (1.04)	0.606

Values are mean (SD) for continuous variables or median (interquartile range) and n (%) for categorical variables. P value, lower vs. higher UFRCV.
UFRCV, coefficient of variation of ultrafiltration rate; BMI, body mass index; UFRSD, standard deviation of ultrafiltration rate; EF, ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; iPTH, intact parathyroid hormone; hs-CRP, hypersensitive-C-reactive-protein; IDH, intradialytic hypotension; SBPCV, coefficient of variation of systolic blood pressure; DBPCV, coefficient of variation of diastolic blood pressure; CCBs, calcium channel blockers; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.
[a]24 h urine output over 100 mL; [b]defined as having smoked ⩾ 1 cigarette per day or ⩾ 18 packs in the past year; [c]defined as drinking alcohol at least 2 times per week in the past year; [d]coronary heart disease, cardiac valve disease and arrhythmia; [e]vascular recanalization refers to patients undergoing percutaneous coronary intervention and coronary artery bypass graft; [f]primary hypertension or hypertension of unknown origin, excluding renal hypertension.

Kaplan–Meier method revealed markedly increased mortality risks in patients exhibiting elevated UFRCV levels. The high UFRCV cohort demonstrated substantially greater all-cause mortality (HR 4.45, 95% CI 1.82–10.88, Log-rank $P < 0.001$) and cardiovascular mortality (HR 13.52, 95% CI 1.76–103.98, Log-rank $P = 0.001$) compared to low UFRCV group (Fig. 2 and S2, respectively). Initial Cox regression modeling identified UFRCV as a significant predictor of all-cause mortality (unadjusted HR 4.45, 95% CI 1.82–10.88, $P = 0.001$). This association persisted after comprehensive adjustment for potential confounders including demographic characteristics, comorbid conditions, laboratory values, cardiovascular status, and predialysis BPCV (adjusted HR 4.17, 95% CI 1.47–11.82, $P = 0.007$) (Table 2). The relationship between UFRCV and cardiovascular mortality remained robust across analytical approaches. Both univariate (HR 13.52, 95% CI 1.76–103.98, $P = 0.012$) and multivariate-adjusted (HR 12.52, 95% CI 1.42–110.46, $P = 0.023$) Cox models demonstrated significant associations (Table S2). However, the relatively small number of cardiovascular deaths ($n = 1$) in low UFRCV group suggests this point estimates should be interpreted with caution. Future multicenter

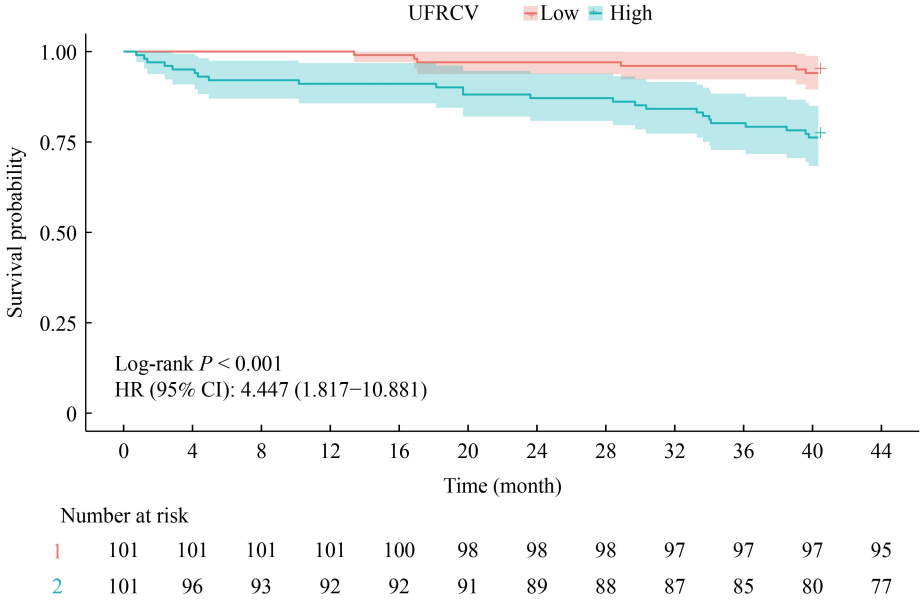

Fig. 2 Different levels of UFRCV on all-cause mortality.

Table 2 Cox regression models of UFRCV on all-cause mortality

Model	*P*	HR (95% CI)
Unadjusted (high UFRCV vs. low UFRCV)	0.001	4.45 (1.82–10.88)
Model 1	0.003	4.11 (1.64–10.26)
Model 2	0.005	3.85 (1.51–9.82)
Model 3	0.004	4.01 (1.55–10.38)
Model 4	0.006	3.85 (1.48–10.04)
Model 5	0.007	4.17 (1.47–11.82)

Model 1: adjusted for demographic data (age, sex, body mass index) + current smoking + current alcohol drinking + dialysis information (residual renal function, dialysis vintage and single-pool Kt/V).

Model 2: adjusted for Model 1 + comorbid conditions (history of cardiovascular disease, hypertension, diabetes, stroke and peripheral artery disease).

Model 3: adjusted for Model 2 + biochemical data (hemoglobin, serum albumin, pre-albumin, creatinine and hsCRP).

Model 4: adjusted for Model 3 + cardiac conditions (left ventricular ejection fraction, NT-proBNP, the onset of IDH).

Model 5: adjusted for Model 4 + predialysis blood pressure variability (variabilities of predialysis systolic blood pressure and diastolic blood pressure).

HR, hazard ratio; CI, confidence interval; UFRCV, coefficient of variation of ultrafiltration rate; hs-CRP, hypersensitive-C-reactive-protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; IDH, intradialytic hypotension.

Current smoking, defined as having smoked ⩾ 1 cigarette per day or ⩾ 18 packs in the past year; current alcohol drinking, defined as drinking alcohol at least 2 times per week in the past year; residual kidney function, 24 h urine output over 100 mL; hypertension, primary hypertension or hypertension of unknown origin, excluding renal hypertension; cardiovascular disease, coronary heart disease, cardiac valve disease and arrhythmia.

prospective studies with larger sample sizes are needed to validate these preliminary findings and evaluate their clinical applicability.

Notably, while mortality outcomes differed significantly between groups, the incidence rates of non-fatal cardiovascular events showed no statistically significant variation (18.81% vs. 26.73% for low vs. high UFRCV, respectively; $P = 0.180$).

Subgroup analysis

Subgroup analysis revealed that the predictive value of UFRCV for all-cause mortality varied across specific populations. Among patients aged ⩾ 60 years, UFRCV demonstrated a stronger predictive value (HR 6.56, 95% CI 1.24–34.52, $P = 0.027$). Similarly, patients prone to IDH (HR 4.66, 95% CI 1.12–19.45, $P = 0.035$) and those with higher predialysis SBPCV (stratified by the median value of 0.105) (HR 4.65, 95% CI 1.15–18.75, $P = 0.031$) exhibited an increased all-cause mortality risk associated with UFRCV (Fig. 3). However, no significant interactions were observed among the subgroups (P for interaction > 0.05), indicating the robustness of the observed association.

Ultrafiltration volume, UFRCV and mortality

Moreover, we evaluated the predictive value of UFRCV for mortality by stratifying patients into high and low ultrafiltration volume groups based on the median ultrafiltration volume (2469 mL). In the low ultrafiltration volume group, patients with high UFRCV had significantly higher all-cause mortality (HR 3.36, 95% CI 1.22–9.24, Log-rank $P = 0.013$) (Fig. 4A). In contrast, in the high ultrafiltration volume group, mortality did not differ significantly between patients with high and low UFRCV (HR 1.50, 95% CI 0.42–5.31, Log-rank $P = 0.529$) (Fig. 4B).

The low ultrafiltration volume subgroup was further divided into two groups based on the median UFRCV (0.219). Apart from variates of UFRCV/UFRSD, the baseline data between the two groups were comparable, as shown in Supplement Table S3. And UFRCV was an independent predictor of all-cause mortality in both univariate (HR 3.36, 95% CI 1.22–9.24, $P = 0.019$) and multivariate Cox regression analysis (adjusted for demographic factors, comorbidities, biochemical parameters, cardiac conditions) (HR 4.71, 95% CI 1.33–16.69, $P = 0.016$) (Table 3).

Discussion

This study demonstrates that UFRCV independently predicts all-cause mortality in MHD patients, with heightened risks observed in older adults, individuals prone to IDH, and those with elevated predialysis SBPCV. Notably, UFRCV exerts a more pronounced adverse effect in patients with lower ultrafiltration

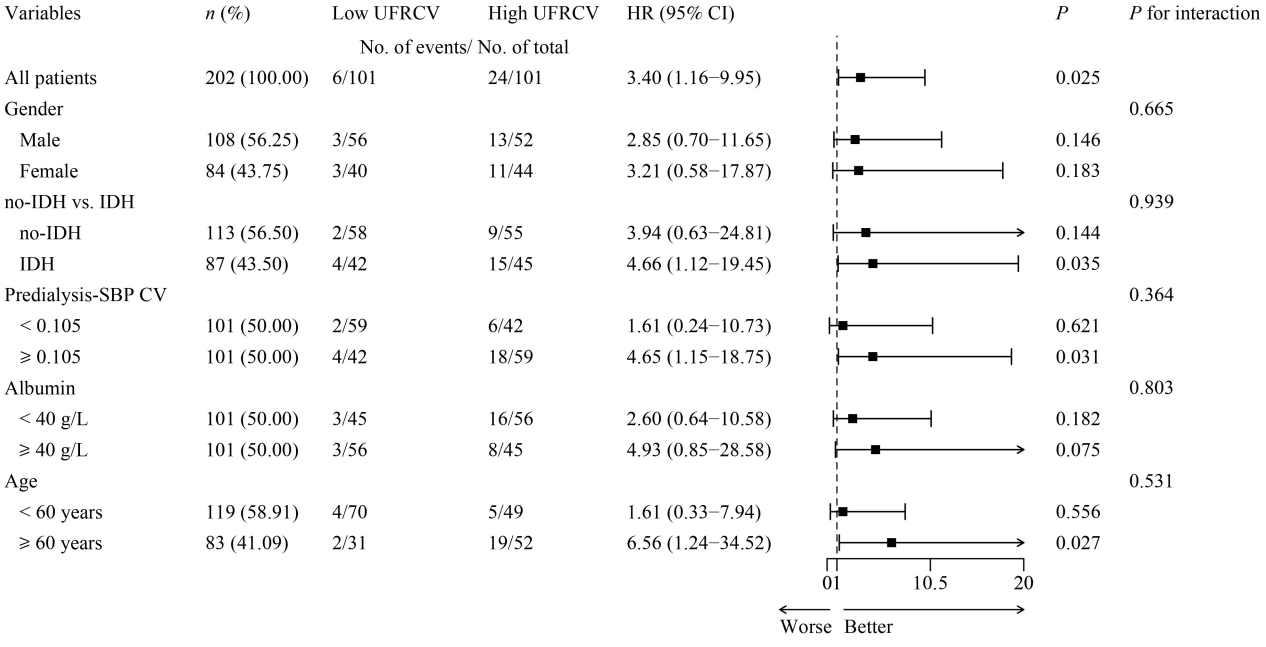

Fig. 3 Subgroup analysis according to age, gender, albumin, IDH-prone and predialysis SBPCV. Cox proportional hazard regression analyses of UFRCV on all-cause mortality; adjusted for demographic factors, comorbidities, biochemical parameters, cardiac conditions and predialysis BPCV. IDH, intradialytic hypotension; SBPCV, coefficient of variation of systolic blood pressure; UFRCV, coefficient of variation of ultrafiltration rate.

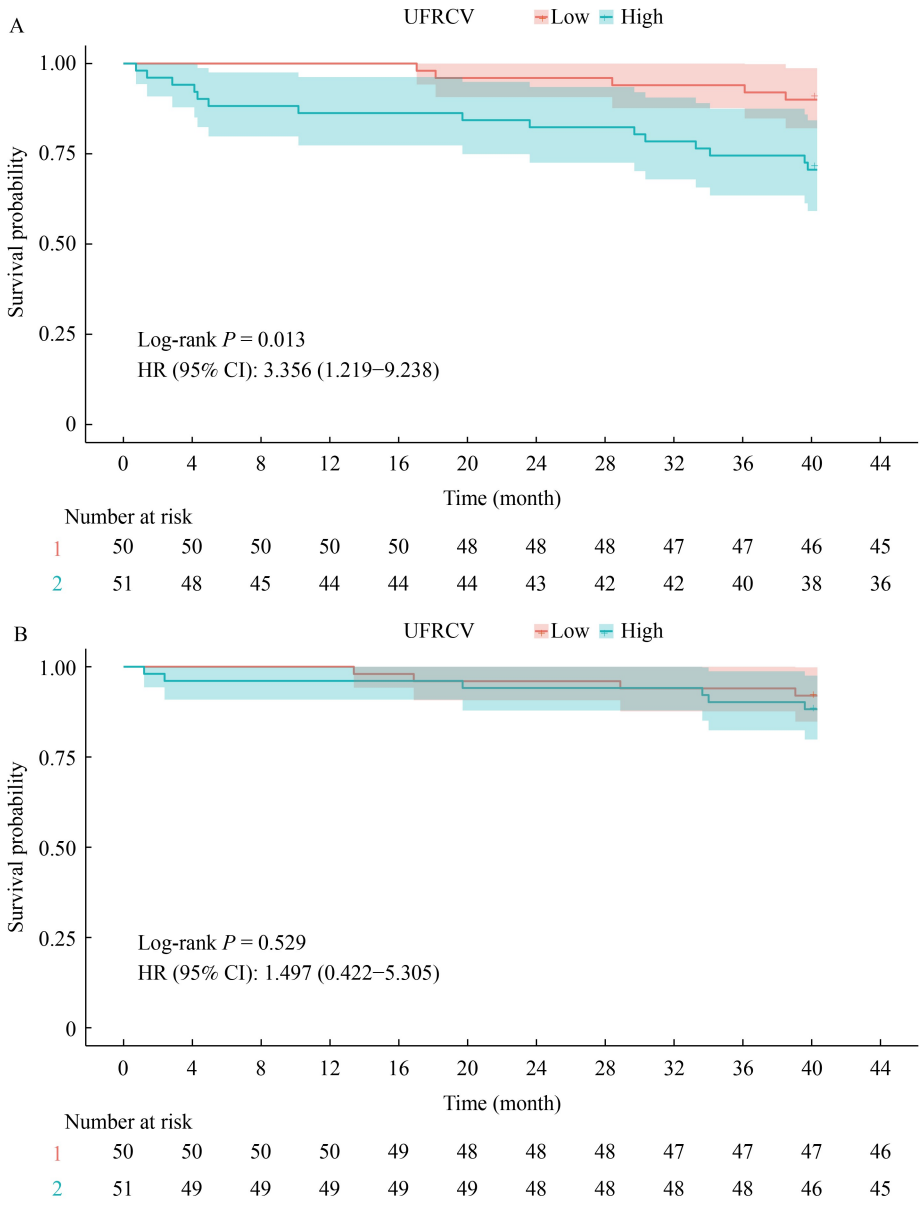

Fig. 4 Different levels of UFRCV and all-cause mortality in (A) low ultrafiltration volume group and (B) high ultrafiltration volume group.

volumes. These results emphasize the importance of monitoring and managing UFRCV as a critical component of dialysis care.

HD patients experience unique cyclical volume and BP shifts, characterized by interdialytic fluid accumulation and intradialytic ultrafiltration. This "hemodynamic rollercoaster" generates repetitive cardiovascular stress, contributing to endothelial dysfunction, myocardial ischemia, and vascular remodeling [7,8,28], contributing significantly to the high cardiovascular morbidity and mortality observed in HD patients [29–31].

Chronic volume overload exacerbates hypertension [32]. Targeted ultrafiltration to correct volume overload effectively reduces BP and ameliorates hypertension [33,34]. Persistent volume overload precipitates structural and functional cardiovascular damage, including accelerated vascular sclerosis [35], cardiac remodeling [13], and elevated risks of cardiovascular and all-cause mortality [36,37]. Conversely, aggressive UFR carry significant risks, most notably IDH. Excessive UFR is independently associated with left ventricular remodeling [23], silent myocardial ischemia [38], cerebrovascular events [39], and a decline in residual kidney function[12,40]. These pathological and physiologic cascade reactions ultimately lead to multi organ damage, emphasizing the delicate balance required for volume management [41].

While extending dialysis duration or frequency reduces hemodynamic stress [26,42–45], logistical and socioeconomic barriers often limit its implementation.

Table 3 Cox regression models of UFRCV on all-cause mortality in low ultrafiltration volume subgroup

Variables	Univariate					Multivariate				
	β	SE	*Z*	*P*	HR (95% CI)	*β*	SE	*Z*	*P*	HR (95% CI)
High vs. low UFRCV	1.21	0.52	2.34	0.019	3.36 (1.22–9.24)	1.55	0.65	2.40	0.016	4.71 (1.33–16.69)

Multivariate Cox regression analysis: adjusted for demographic factors, comorbidities, biochemical parameters, cardiac conditions and predialysis BPCV.

HR, hazard ratio; CI, confidence interval; UFRCV, coefficient of variation of ultrafiltration rate.

Consequently, proper UFR settings can help balance the risks of volume overload and hypotension, ultimately improving patient outcomes. Although prior studies have predominantly focused on absolute UFR thresholds as predictors of adverse events such as IDH, cardiovascular morbidity, and mortality [10–11,46], the dynamic nature of UFR variability over time (quantified as UFRCV) has been largely overlooked. Recent studies reported high ultrafiltration volume variability associated with elevated left ventricular hypertrophy and decreased LVEF [18], as well as all-cause mortality [17,19].

We found that elevated UFRCV (an indicator that better reflects the instability of individual fluid management in HD patients) independently portends increased all-cause and cardiovascular mortality in HD populations, persisting despite reduced baseline cardiovascular comorbidity burden in high UFRCV patients in our study —a paradoxical association confirming UFRCV's status as a hemodynamic risk factor. Although heart failure with preserved ejection fraction (HFpEF) constitutes the dominant phenotype in dialysis population, it remains a potent determinant of adverse outcomes [47–49]. Mechanistically, repetitive cycles of rapid fluid shifts impose recurrent hemodynamic stress, thereby activating maladaptive pathways: recurrent myocardial stretch driving TGF-β-mediated fibrosis; shear stress-induced microvascular rarefaction; and titin phosphorylation increasing ventricular stiffness—mechanisms collectively explaining the absence of baseline LVMI differences [49–52]. These insults manifest functionally as progressive diastolic dysfunction (elevated E/E' ratios, left atrial enlargement) preceding structural remodeling [52–54]. In our study, cardiovascular event rates showed non-significant differential incidence between low and high UFRCV groups. This statistical null significance likely reflects heterogeneity in clinical event documentation rather than biological equivalence. Given the clinically relevant trend, we hypothesis that UFVCV might ultimately drive the disproportionate HFpEF burden and mortality in HD populations through time-dependent, irreversible myocardial damage [55].

In this study, we found patients with high UFRCV exhibited advanced age, preserved residual renal function, poor nutritional status (lower dry weight and serum albumin/creatinine), heightened predialysis BP variability (SBPCV), increased use of CCBs, and fewer comorbid cardiovascular diseases. Elderly patients often exhibit vascular stiffness, impaired autonomic nervous system function, and diastolic cardiac dysfunction, which collectively diminish compensatory responses to volume fluctuations and require frequent UFR adjustments and amplifying UFRCV. Patients with preserved residual renal function experience unpredictable urine output fluctuations, leading to variable interdialytic weight gain (IDWG). Dynamic adjustments to ultrafiltration targets based on real-time urine volume often inaccurately measured may amplify UFRCV [12,40]. Reduced dry weight consistently correlated with inadequate nutritional intake (mean protein intake < 0.8 g/kg/day), poor interdialytic weight gain management and non-adherence to sodium restriction protocols, thus leading to increased UFRCV. Hypoalbuminemia reduces plasma oncotic pressure, promoting extravascular fluid sequestration and occult interdialytic accumulation. This necessitates aggressive ultrafiltration, increasing UFRCV. Concurrently, low serum creatinine, as a marker of muscle wasting, compromises the body's capacity to buffer fluid shifts. CCBs attenuate baroreflex sensitivity and myocardial contractility, exacerbating hypotension during ultrafiltration. Clinicians often respond by reducing single-session fluid removal, indirectly increasing UFRCV [10–11,56]. Elevated predialysis SBPCV reflects autonomic dysfunction and diminished vascular compliance, predisposing patients to extreme hemodynamic swings during HD, necessitating frequent UFR modifications and resulting high UFRCV [9,28]. Patients with less baseline cardiovascular comorbidities exhibited greater hemodynamic tolerance to elevated UFRCV, whereas those with preexisting cardiovascular disease required prudent fluid management limiting excessive UFR fluctuations in clinical practice. These findings suggest that specific patient subgroups exhibit reduced adaptability to hemodynamic shifts during HD.

Subgroup analyses in our study highlight the heterogeneous impact of UFRCV across different patient populations. For older patients, who frequently exhibit reduced cardiovascular reserves and heightened susceptibility to volume fluctuations, elevated UFRCV likely amplifies the risk of adverse outcomes [19]. IDH-prone patients face a higher risk of mortality when exposed to high levels of UFRCV. This may be due to the synergistic pathophysiological mechanisms amplifying hemodynamic instability and systemic organ damage

[24]. These patients typically exhibit pre-existing cardiovascular complications. High UFRCV can cause repeated hemodynamic fluctuations, leading to myocardial ischemia-reperfusion injury and accelerating cardiac remodeling. This double-blow effect significantly increases cardiovascular mortality [10]. Meanwhile, susceptibility to IDH is often associated with impaired sensitivity of pressure receptors and dysfunction of the autonomic nervous system. High UFRCV exacerbates these defects by triggering sudden changes in intravascular volume and overwhelming compensation mechanisms. Failure to maintain cerebral and coronary artery perfusion during dialysis may lead to fatal arrhythmias or cerebrovascular events [9,41]. Furthermore, clinicians often employ reactive strategies—such as reducing UFR or shortening treatment duration —to avoid IDH. Paradoxically, these interventions make chronic capacity overload permanent, thus requiring active ultrafiltration in subsequent treatments. This vicious cycle amplifies UFRCV, but fails to address potential hemodynamic fragility [11]. Similarly, in patients with high predialysis SBPCV, increased UFRCV may exacerbate intradialytic blood pressure instability, further elevating their overall risk profile [56–57].

In daily practice, clinicians set UFR based on the patients' previous tolerance for ultrafiltration volume. Therefore, we tested the differential effects of UFRCV observed in patients with varying ultrafiltration volumes. In the low ultrafiltration volume group, higher UFRCV was strongly associated with increased mortality, whereas no significant association was observed in the high ultrafiltration volume group. This may reflect the greater hemodynamic instability and cardiovascular stress experienced by patients with lower ultrafiltration volumes, who are often more vulnerable to rapid fluid shifts [9]. These findings suggest that UFRCV holds greater prognostic significance in patients with stricter fluid removal targets, where even small deviations from optimal fluid management can have profound clinical consequences.

These observations suggest that the effects of UFRCV are not uniform but rather modulated by individual clinical characteristics, such as age, cardiovascular comorbidities, and predialysis hemodynamic stability. This understanding emphasizes the importance of tailoring ultrafiltration management to specific patient subgroups, especially those at higher risk of hemodynamic impairment and with limited hemodynamic adaptability. By identifying these high-risk populations, our research findings lay the foundation for developing targeted interventions to mitigate the adverse effects of UFRCV.

While prior research established ultrafiltration volume variability as a mortality predictor [17,19], our study extends this paradigm by demonstrating that UFRCV, a hemodynamically individualized parameter, independently predicts all-cause mortality in MHD patients, with particularly amplified risk among elderly patients (> 60 years), those with recurrent IDH, and elevated predialysis SBPCV. Crucially, UFRCV demonstrated stronger prognostic effects in patients with lower ultrafiltration volumes (< 2469 mL), revealing a novel differential impact that challenges conventional static ultrafiltration thresholds. These findings underscore the imperative for individualized fluid management protocols accounting for hemodynamic reserve and ultrafiltration volume stratification.

This study acknowledges several methodological constraints. Its single-center design inherently limits external validity, necessitating multi-center validation to confirm broader clinical relevance. While cohort size provided adequate power for primary endpoint assessment, constrained sample size, low event incidence, and finite follow-up duration precluded more detailed subgroup analyses. Furthermore, UFRCV quantification did not integrate physiologic determinants such as vascular compliance or sodium intake variability, potentially introducing unmeasured confounding. Whether these observations extend to high-flux HD populations —despite the modality's increasing global adoption —requires confirmation. Subsequent researches should incorporate non-invasive hemodynamic monitoring technologies, employ standardized data collection frameworks, and validate findings in expanded cohorts with extended surveillance periods.

The clinical implementation framework necessitates automated UFRCV quantification via integrated electronic health records (EHR)-dialysis systems, utilizing validated risk thresholds to prioritize monthly monitoring for high-risk subgroups. Our study contributes to the growing evidence supporting UFRCV as a valuable prognostic marker and highlights the need for further researches to optimize UFR management in HD patients.

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Compliance with ethics guidelines

Conflicts of interest Jinbo Yu, Xiaohong Chen, Wuhua Jiang, Yang Li, Yuxin Nie, Bo Shen, Jianzhou Zou, Yaqiong Wang, and Xiaoqiang Ding declare that they have no conflict of interest.

The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Approval Number: B2014-083) and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients for being included in the study.

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