Effect of Ultrafiltration Rate in Long Interdialytic Interval Hemodialysis Session versus Average Weekly Ultrafiltration Rate on Mortality Rate and Adverse Cardiovascular Outcomes in Maintenance Hemodialysis Patients

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ABSTRACT

Objective: Cardiovascular events are more commonly observed during hemodialysis sessions after a long interdialytic interval compared to average weekly hemodialysis sessions, and ultrafiltration rate (UFR) was reported to be associated with cardiovascular outcomes. Whether the UFR during hemodialysis sessions after a long interdialytic interval is a better predictor of cardiovascular outcome than the average weekly UFR is unknown.

Methods: The charts of patients aged >18 years with end-stage renal disease that received hemodialysis treatment Siriraj Hospital during January 2008 to December 2017 were retrospectively reviewed.

Results: Two hundred and forty-one patients (52.8% females) were included. During the median time follow-up of 54 months, the rate of adverse cardiovascular outcomes was 7.26 events/100-patient-years, and the mortality rate was 8.40 deaths/100-patient-years. Mean UFR was significantly higher in the long interdialytic interval hemodialysis sessions than in the average weekly UFR sessions (14.07±5.29 *vs.* 13.13±5.14 ml/h/kg, $p<0.001$). Compared with UFR of ≤10 ml/h/kg, the adjusted hazard ratio (HR) for mortality in the UFR >13 ml/h/kg subgroup was 1.29 (95% CI: 0.65-2.56) and 1.05 (95% CI: 0.55-2.03) in the long interdialytic interval hemodialysis sessions and the average weekly UFR, respectively. The adjusted HR for adverse cardiovascular outcome in the UFR >13 ml/h/kg subgroup was 1.32 (95% CI: 0.64-2.80) and 0.72 (95% CI: 0.36-1.35) in the long interdialytic interval hemodialysis sessions and the average weekly UFR, respectively.

Conclusion: This study revealed that the UFR in long interdialytic hemodialysis sessions has the trend to be associated with more adverse cardiovascular outcomes and all-cause mortality than the average weekly UFR. A larger population is needed to further elucidate the relationship between UFR and outcomes in Thai hemodialysis population.

Keywords: Ultrafiltration rate; cardiovascular outcomes; mortality, maintenance hemodialysis patients; long interdialytic interval hemodialysis; weekly hemodialysis (Siriraj Med J 2020; 72: 391-398)

INTRODUCTION

Volume management in maintenance hemodialysis (HD) patients is challenging. An increasing body of evidence points to association between fluid-related factors and treatment outcomes in these patients. Moreover, fluid retention or excessive interdialytic weight gain (IDWG) was found to be associated with adverse cardiovascular outcomes.[1-3] Experts suggest that

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Received 30 August 2019 Revised 17 February 2020 Accepted 19 February 2020
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http://dx.doi.org/10.33192/Smj.2020.53

normalization of extracellular fluid volume should be added to the traditional goals of dialysis that include molecule clearance and patient well-being.[4] Rapid fluid removal was also found to be associated with adverse cardiovascular outcomes and mortality in maintenance hemodialysis patients.[5-8] In addition, long interdialytic interval was found to be associated with cardiovascular morbidity, mortality, and higher risk of sudden death[9,10], which further suggests that volume abnormalities may be complicit. IDWG is commonly observed to be higher during dialysis after long interdialytic intervals compared to midweek dialysis, and this leads to a need for a higher ultrafiltration rate (UFR). Whether the UFR used during a long interdialytic interval hemodialysis session is a better predictor of patient outcomes compared to the UFR used during average weekly HD is still unclear. Accordingly, the aim of this study was to investigate the effect of ultrafiltration rate in long interdialytic interval hemodialysis session versus average weekly ultrafiltration rate on mortality rate and adverse cardiovascular outcomes in maintenance hemodialysis patients.

MATERIALS AND METHODS

Study design

The electronic medical charts of patients aged greater than 18 years with end-stage renal disease (ESRD) that received hemodialysis treatment at the Division of Nephrology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 1 January 2008 to 31 December 2017 were retrospectively reviewed. Patients were enrolled in the following phases: phase 1 – starting on 1 January 2008; phase 2 – starting on 1 January 2010; phase 3 – starting on 1 January 2012; and, phase 4 – starting on 1 January 2014. Each patient's baseline characteristics were considered at the time of enrollment. Baseline demographic characteristics and comorbidity data were collected. Baseline laboratory measurements were collected and calculated for difference in predialysis serum sodium (pre-HD SNa) and dialysate sodium (DNa), urea reduction ratio (URR), dialysis adequacy (single pool Kt/V), and normalized protein catabolic rate (nPCR). Hemodialysis data, including access type [arteriovenous fistula (AVF), arteriovenous graft (AVG), permanent catheter (PC), or double lumen catheter (DLC)], DNa, dry weight, IDWG, UFR, pre-hemodialysis (pre-HD) and post-hemodialysis (post-HD) blood pressures, were also collected at baseline. The estimation of baseline mean average weekly UFR was calculated from average UFR of the first 2 weeks of consecutive hemodialysis sessions at the time of enrollment for each phase. The UFR in the long interdialytic interval was calculated from the mean UFR in the beginning of week of hemodialysis sessions after the longest interdialytic period in the first 2 weeks at the time of enrollment. Pre-HD and post-HD blood pressure data were collected in the same way that average UFR data were collected. Patients were followed forward in the historical timeline until death or until the end of the study (31 December 2017). The protocol for this study was approved by the Siriraj Institutional Review Board (Si 043/2019). The requirement to obtain written informed consent was waived due to this study's retrospective design.

Data collection

All data were retrieved from an electronic medical records search of our hospital database. Demographic and comorbidity data were recorded at the time of admission to the dialysis unit, and that information was updated based on the patient's clinical status during the follow-up period. Laboratory data were measured monthly according to the standard protocol of the dialysis unit. Hemodialysis details were recorded during each dialysis session.

Exposures and outcomes

Prescribed UFR was calculated from net ultrafiltration estimated from IDWG (milliliters, ml) divided by duration of prescribed dialysis session in hours (h) of each hemodialysis session. UFR normalized for body weight is expressed as ml/h/kg. We assumed that the prescribed UFR was constant during the study period, and the HD sessions in the first 14 days of each phase was used for calculations.

The primary outcome was all-cause mortality. Patients were considered at risk for the study outcome during the exposure period until death or censoring for loss to follow-up or end of study (31 December 2017). The secondary outcomes were adverse cardiovascular outcomes (myocardial infarction, stroke or death from cardiovascular cause) and hospitalization rate. The effect of the average UFR and the UFR at the beginning of weekly hemodialysis sessions on mortality and adverse cardiovascular outcomes was also compared.

Statistical analysis

Cross-sectional data at baseline is presented as descriptive data using percentage for categorical variables, mean ± SD for continuous variables with normal distribution, and median and range (minimum, maximum) for continuous variables with non-normal distribution. Patients were categorized into 1 of the 3 following UFR subgroups: ≤10, 10-13, or >13 ml/h/kg.

The UFR of ≤10 ml/h/kg was used as a reference for comparison with the other 2 UFR subgroups relative to clinical outcomes. The UFR cutoff of 13 ml/h/kg, which was used in previous studies, is equivalent to 3 kg of IDWG in a post-HD body weight of 60 kg.[7,8,11] Association between UFR and outcomes was analyzed using log rank test and survival analysis, while overall survival was analyzed using Kaplan-Meier survival analysis. Cox proportional hazard analysis was used to identify association between different factors and survival. The results of that analysis are presented as hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using SPSS Statistics software version 18 (SPSS, Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

Baseline demographic, clinical, and laboratory data were stratified by UFR category, as shown in Tables 1 and 2. A total of 241 Thai patients (52.8% females) were included. The median time of follow-up was 54.05 months (min: 1.77, max: 118.77). The number of patients recruited in phase 1, 2, 3, and 4 was 121, 47, 37, and 43, respectively. The prescribed dialysis treatment was 2 sessions per week in 19%, and 3 sessions per week in 81% of all patients. Compared with the group of patients with UFR <10 ml/h/kg, patients in the higher UFR groups (10-13 and >13 ml/h/kg) were significantly younger and had a lower percentage of DM, hypertension, dyslipidemia, and cardiovascular disease; however, they had more IDWG, longer dialysis vintage, lower body weight, and a lower percentage of preserved residual renal function.

Association between average weekly UFR and outcomes

All-cause mortality and cardiovascular events in each UFR subgroup of average weekly UFR are presented in Table 3. Median time to all-cause mortality was 98.6 months, with a 5-year survival rate of 68.08%. Median time to adverse cardiovascular outcome was 108.33 months. Outcomes were adjusted for age, gender, history of cardiovascular disease (CVD), history of diabetes, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD blood pressure, post-HD blood pressure, Kt/V, and normalized protein catabolic rate (nPCR). Mean UFR in the long interdialytic interval hemodialysis group was significantly higher than in the average weekly UFR group (14.07±5.29

TABLE 1. Patient demographic and clinical characteristics.

Characteristics	UFR (ml/h/kg)			*P*-value
	≤10 (n=64)	10-13 (n=69)	>13 (n=108)	
Age (years)	68.3±12.7	60.2±14.1	50.9±14.5	***<0.001***
Female gender	54.7%	50.7%	50.9%	0.87
Duration of follow-up (months)	45.67 (1.77, 118.77)	59.97 (1.87, 118.73)	58.98 (3.73, 118.77)	***0.04***
Residual urine	36.0%	15.9%	12.0%	***<0.001***
No. of anti-HT drugs	1 (0, 5)	1 (0, 5)	1 (0, 6)	0.37
Underlying disease				
Coronary artery disease	25.0%	17.4%	11.1%	***0.06***
Stroke	7.8%	5.8%	3.7%	0.51
Peripheral artery disease	3.1%	1.4%	0.0%	0.21
Hypertension	54.7%	49.3%	35.2%	0.11
Diabetes mellitus	37.5%	20.3%	14.8%	***0.02***
Dyslipidemia	43.8%	39.1%	25.0%	***0.02***

Data presented as mean ± standard deviation, percentage, or median (minimum, maximum)

A *p*-value<0.05 indicates statistical significance

Abbreviations: UFR, ultrafiltration rate; HT, hypertension

TABLE 2. Hemodialysis factors at baseline.

Factors	UFR (ml/hr/kg)			*P*-value
	≤10 (n=64)	10-13 (n=69)	>13 (n=108)	
Dialysis vintage (months)	20.7 (0.2, 139.6)	39.7 (0.2, 255.5)	60.7 (0.2, 282.7)	***0.001***
HD sessions				0.14
2 per week	15.6%	27.5%	16.7%	
3 per week	84.4%	72.5%	83.3%	
Access				0.28
AVF	55.2%	63.0%	67.9%	
AVBG	5.2%	9.3%	9.0%	
Permanent catheter	32.8%	20.4%	15.4%	
Double lumen catheter	6.9%	7.4%	7.7%	
Dry weight (kg)	60.63±13.22	59.46±11.22	52.80±10.83	***<0.001***
Dry weight				***0.001***
≤50 kg	25.0%	18.8%	41.7%	
50-60 kg	26.6%	39.1%	33.3%	
>60 kg	48.4%	42.0%	25.0%	
UF (L)	1.78±0.66	2.71±0.54	3.67±0.76	***<0.001***
UFR (ml/h/kg)	7.33±2.09	11.4±0.77	17.67±3.67	***<0.001***
IDWG (%DW)	2.93±0.84	4.56±0.31	7.07±1.47	***<0.001***
Pre-HD SBP (mmHg)	148.0±20.0	149.0±18.0	152.0±16.0	0.34
Pre-HD DBP (mmHg)	76.0±11.0	78.0±9.0	80.0±11.0	0.07
Post-HD SBP (mmHg)	150.0±23.0	145.0±18.0	150.0±17.0	0.18
Post-HD DBP (mmHg)	77.0±9.0	78.0±9.0	80.0±9.0	0.20
Pre-HD SNa (mmol/L)	139.0±4.0	139.0±3.0	138.0±3.0	0.20
Delta SNa - DNa (mmol/L)	1 (-10, 8)	1 (-8, 5)	0 (-7, 5)	0.78
Serum albumin (g/dl)	3.84±0.36	3.98±0.36	4.00±0.30	0.06
Pre-HD BUN (mg/dl)	64.12±22.80	71.01±19.08	76.79±20.17	0.06
URR	70.4±29.8	74.9±22.7	79.7±15.5	0.11
Kt/V				
HD 2 times per week	2.12±0.45	2.05±0.48	2.08±0.28	0.89
HD 3 times per week	2.05±0.40	2.12±0.39	2.22±0.38	0.53
nPCR (g/kg/day)	1.0±0.25	1.05±0.27	1.11±0.32	0.06

Data presented as median (minimum, maximum), percentage, or mean ± standard deviation

A *p*-value <0.05 indicates statistical significance

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; AVF, arteriovenous fistula; AVBG, arterioveneous bridge graft; UF, ultrafiltration; UFR, ultrafiltration rate; IDWG, interdialytic weight gain; DW, dry weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; SNa, serum sodium; DNa, dialysate sodium; BUN, blood urea nitrogen; URR, urea reduction ratio; Kt/V, dialysis adequacy

TABLE 3. Association between UFR and all-cause mortality and cardiovascular events in each UFR subgroup of patients that received average weekly UFR.

Factors	Number of patients (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality			
UFR >13 ml/h/kg	41 (38.0%)	0.62 (0.39-1.01)	1.05 (0.55-2.03)
UFR 10-13 ml/h/kg	28 (40.6%)	0.77 (0.46-1.29)	0.97 (0.53-1.79)
UFR ≤10 ml/h/kg	29 (45.3%)	Reference	Reference
Cardiovascular events			
UFR >13 ml/h/kg	33 (30.6%)	0.67 (0.39-1.15)	0.72 (0.36-1.35)
UFR 10-13 ml/h/kg	24 (34.8%)	1.14 (0.64-2.02)	0.72 (0.38-1.35)
UFR ≤10 ml/h/kg	31 (48.4%)	Reference	Reference

[a]Adjusted for age, gender, history of CVD, DM, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD BP, post-HD BP, Kt/V, nPCR

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; HR, hazard ratio; CI, confidence interval

vs. 13.13±5.14 ml/h/kg, $p<0.001$). The median unadjusted HR for all-cause mortality and adverse cardiovascular outcome for patients in the average weekly UFR >13 ml/h/kg subgroup was 0.62 (0.39-1.01) and 0.67 (0.39-1.15), respectively. After adjusting for relevant factors, the higher average weekly UFR subgroups (UFR 10-13 and >13 ml/h/kg) were not found to be associated with increased all-cause mortality or adverse cardiovascular outcomes.

Association between UFR in long interdialytic hemodialysis session and outcomes

All-cause mortality and adverse cardiovascular events in each subgroup of UFR in the long interdialytic interval hemodialysis group are presented in Table 4. The mean IDWG of the hemodialysis sessions after the longest interval was 3.08±1.04 kg, and the mean UFR was 14.07±5.29 ml/h/kg. The two higher UFR (10-13 and >13 ml/h/kg) subgroups showed an increasing trend in all-cause mortality and adverse cardiovascular outcomes after adjustment for all relevant factors. A subgroup analysis in patients with 3 hemodialysis sessions per week was also performed, and a similar result was observed.

DISCUSSION

Previous studies have examined the association between mean UFR and mortality. Kim, *et al.* examined a US cohort of 110,800 patients who started hemodialysis and found a linear association between UFR and both all-cause and CV mortality, and UFR of more than 10 ml/h/kg was found to have the highest risk.[8] From the international Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort of 21,919 participants, Wong, *et al.* reported an elevated risk of mortality with relative IDWG of greater than 5.7%.[12] Using DOPPS cohort data, Saran, *et al.* found longer treatment time and slower UFR to be associated with lower mortality rate, and that UFR of >10 ml/h/kg was associated with more episodes of hypotension and higher mortality.[13] Assimon, *et al.* reported higher mortality in hemodialysis patients with higher UFR after being normalized for body weight, body mass index, and body surface area.[7]

In the present study, unadjusted HR for mortality and adverse cardiovascular outcomes tended to be higher in the UFR ≤10 ml/min group. This may be due to several confounding factors, including older age and more underlying diseases (diabetes, CAD, and

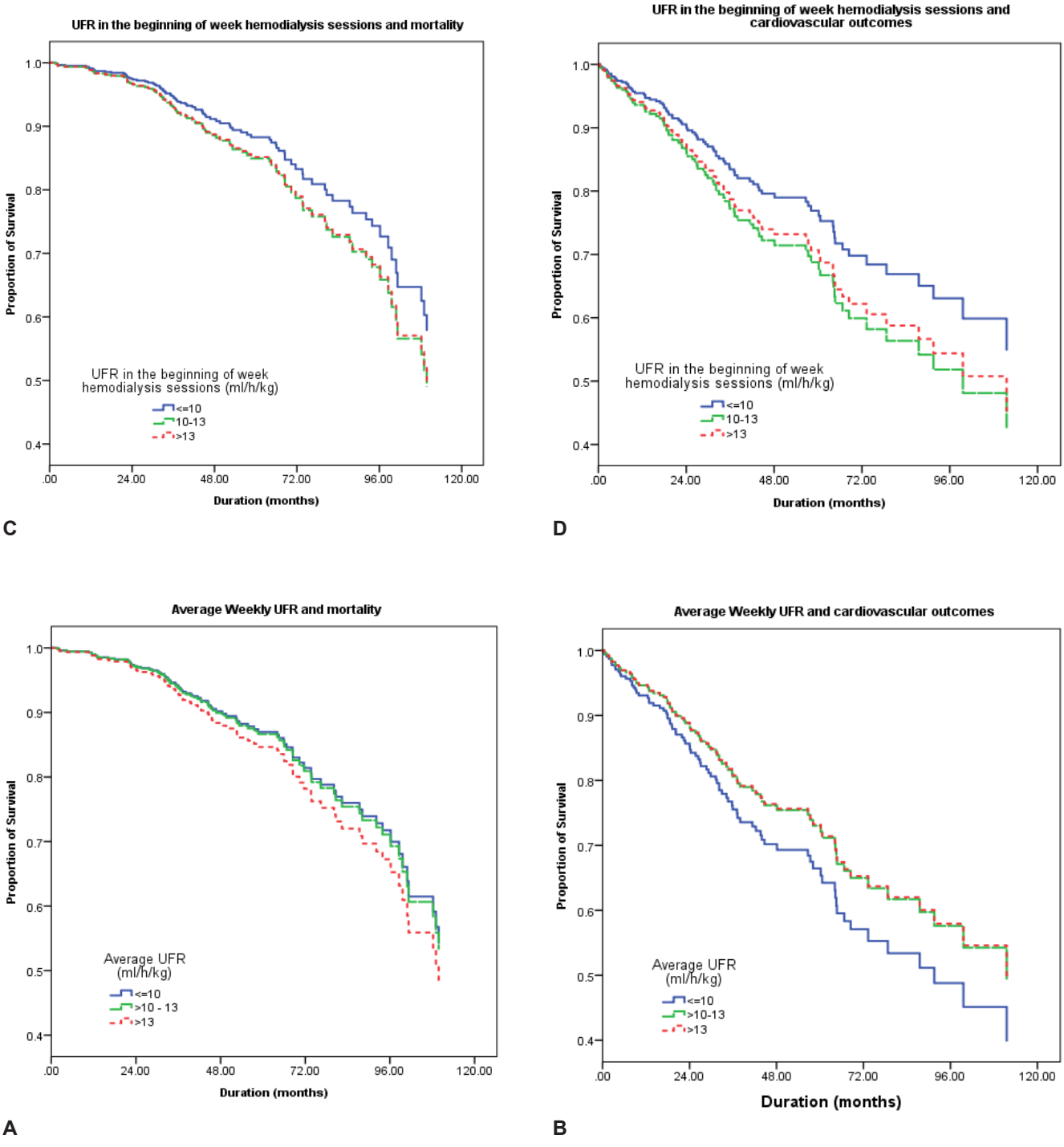

Fig 1. Kaplan-Meier survival analysis. UFR was categorized into 3 groups, as follows: ≤10 ml/h/kg shown in blue, 10-13 ml/h/kg shown in green, and >13 ml/h/kg shown in red. The associations between subgroup of UFR and outcomes are shown. Association between UFR after the longest interval and mortality **(A)**, and between UFR after the longest interval and adverse cardiovascular outcomes **(B)**. Association between average weekly UFR and mortality **(C)**, and adverse cardiovascular outcomes **(D)**.

TABLE 4. Association between UFR and all-cause mortality and cardiovascular events in each UFR subgroup of long interdialytic interval HD.

Factors	Number of patients (%)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
All-cause mortality			
UFR >13 ml/h/kg	47 (37.0%)	0.76 (0.45-1.27)	1.29 (0.65-2.56)
UFR 10-13 ml/h/kg	30 (48.4%)	1.05 (0.60-1.83)	1.31 (0.66-2.59)
UFR ≤10 ml/h/kg	21 (40.4%)	Reference	Reference
Cardiovascular events			
UFR >13 ml/h/kg	39 (30.7%)	0.47 (0.28-0.78)	1.32 (0.64-2.80)
UFR 10-13 ml/h/kg	29 (46.8%)	0.62 (0.37-1.03)	1.43 (0.70-2.89)
UFR ≤10 ml/h/kg	20 (38.5%)	Reference	Reference

[a]Adjusted for age, gender, history of CVD, DM, underlying diseases, dialysis vintage duration, number of dialysis sessions per week, phase, dry weight, pre-HD BP, post-HD BP, Kt/V, nPCR

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis; HR, hazard ratio; CI, confidence interval

dyslipidemia), whereas patients in the UFR >10 ml/hr/kg group were significantly younger. After adjusting for the relevant confounding factors, high average weekly UFR was not found to be associated with increased all-cause mortality (HR: 1.05) or adverse cardiovascular outcomes (HR: 0.97). In contrast, high UFR in the long interval hemodialysis sessions showed a trend of increasing risk for both all-cause mortality (HR: 1.29-1.31) and adverse cardiovascular outcomes (HR: 1.32-1.43). Our study found that higher UFR in long interdialytic hemodialysis session is a better predictor of all-cause mortality and adverse cardiovascular outcomes than average weekly UFR.

Limitations

The limitations of this study include its retrospective design and the small size of the study population. Moreover, we only observed the UFR over a short period, so it is possible that all UFRs that were prescribed in these patients were not included in our analysis, and this could mean that all statistical differences and associations between UFR and outcomes were not identified. To our knowledge, no previous study has compared the effects of UFR between long interdialytic hemodialysis sessions and average weekly UFR relative to all-cause mortality and cardiovascular outcome.

CONCLUSION

The results of this study showed that the UFR in long interdialytic hemodialysis sessions has the trend to be more strongly associated with adverse cardiovascular outcomes and all-cause mortality than the average weekly UFR. A larger study population is needed to confirm these findings, and to further elucidate the relationship between UFR and outcomes in Thai hemodialysis population.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Ms.Khemajira Karaketklang of the Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand for assistance with statistical analysis.

Conflict of interest declaration: All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

Funding disclosure: This was an unfunded study.

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