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Original Article

The association between ultrafiltration rate and mortality in a cohort of chronic hemodialysis patients with and without diabetes mellitus: a 7-year retrospective observational study.

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Abstract

Background: The ultrafiltration rate (UFR) is one of the important factors involved in long-term mortality in hemodialysis (HD) patients. Presence of diabetes mellitus often affects UFR due to abrupt hypotension during dialysis. In this study, we aimed to find the optimal UFR to improve the mortality in this population with and without diabetes mellitus (DM).
Methods: The effect of the UFR on mortality was retrospectively evaluated in 707 patients undergoing regular HD from 1 June 2010 to 30 June 2017. The relationship between the UFR and mortality in patients in the non-DM group and those in the DM group was evaluated. Logistic regression analyses were used to select the determinants of mortality. Receiver operating characteristic (ROC) curve analyses and survival analysis were used to determine the optimal cutoff points of UFR for mortality.
Results: The cutoff UFR values of the non-DM and DM groups were 12.07 ml/hr/kg and 9.66 ml/hr/kg, respectively. A survival curve showed that in the non-DM group, the 7-year survival rate of patients with a UFR <12.07 ml/hr/kg was 72.6% and that in those with a UFR ≥12.07 ml/hr/kg was 19.6% ($p<0.0001$). In the DM group, the 7-year survival rate of those with a UFR <9.66 ml/hr/kg was 66.7%, and it was 33.4% in those with a UFR ≥9.66 ml/hr/kg ($p<0.0001$).
Conclusion: Lower UFR is essential for the long-term mortality of HD patients, and optimal UFR would be different between patients with and without DM.

Key words: Hemodialysis, ultrafiltration rate, diabetes mellitus, mortality, nutrition

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Introduction

Excessive interdialytic weight gain (IDWG) is associated with poor outcomes [1-3]; however, hemodialysis (HD) patients with excessive IDWG might be often forced to receive a higher ultrafiltration rate (UFR) to reach the dry weight (DW). Previous studies have shown that an excessive UFR (12.37 ml/hr/kg of body weight) in patients on HD treatment is independently associated with an increased long-term risk of death [4]. Moreover, a rapid increase in the UFR can induce intradialytic hypotension (IDH), which is associated with cardiovascular complications such as myocardial ischaemia during HD [5]. IDH appears to occur more frequently in patients with diabetes mellitus (DM) than in those without [6]. Considering the specific dialytic complications in DM patients, strictly managing UFR is required to prevent poorer clinical outcomes. The evidence to determine the appropriate UFR based on the presence or absence of DM does not exist, and there are few reports about the most suitable UFR cutoff value for DM patients. In this study, we retrospectively assessed the impact of the UFR on long-term mortality in HD patients with and without DM.

Methods

Ethical considerations

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted (IRB approval number NCT03471299) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patients and study measurements

We enrolled 759 patients who had undergone maintenance HD for > 1 year at the hemodialysis hospital, Japan. We examined data from all individuals who underwent maintenance HD treatment three times weekly from 1 June 2010 to 30 June 2017. Four hundred thirty patients (57%) were men, 255 (34%) had DM, and 222 (29%) had cardiovascular disease (CVD). Patients were excluded if they had peritoneal dialysis combined with HD, did not have records of laboratory investigations during this period, or were transferred to another hospital or lost to follow-up.

We collected data regarding the demographic characteristics, DM history, CVD history, laboratory results, and the number and causes of death during the entire study period. The demographic characteristics included age (years), sex, dialysis history (years), primary kidney disease, height (cm), DW (kg), body mass index ([BMI], kg/m2), HD dose (Kt/Vure), IDWG (%), removal of body water ([RBW], %), % creatinine generation rate (%CGR), geriatric nutritional risk index (GNRI), and UFR (ml/hr/kg) at baseline (1 June 2010). CVD included the presence of ischaemic heart disease, peripheral vascular disease, and cerebral vascular disease. The DW was determined clinically and reflected the lowest weight the patient could tolerate without intradialytic symptoms and hypotension and without overt fluid overload. The DW was continuously updated according to the medical doctors' changes in orders throughout the observation period.

The BMI was calculated as the patient's DW divided by the square of the patient's height. The IDWG was calculated as the patients' weight before the HD session (beginning of the week) minus the weight after the previous HD session (end of the week), divided by the DW. The RBW was calculated as the patient's weight before the HD session minus that afterwards, divided by the DW. The UFR was obtained by subtracting the patient's weight after the HD session from that before, divided by the DW and then by the HD time. The UFR was adapted to reach the DW during the preset dialysis time in a basic direction. The IDWG, RBW, and UFR were determined us-

ing the median values of four different measurements at the beginning of one week in a month-long period and were calculated as the median values of all measurements during this period. The HD dose was calculated at the beginning of the week at the start of the study and every 6 months until its end. The Kt/Vure, %CGR, and GNRI were determined according to single-pool urea kinetics models [7]. The GNRI was calculated at baseline as: GNRI = (14.89 × serum albumin concentration [g/dL] + (41.7 × [body weight/ideal body weight]) [8]. The ideal body weight was calculated from the height and a BMI of 22 [9].

Blood samples (5 ml) were obtained immediately before the HD session began for pre-HD measurements and at the end of the HD session for post-HD measurements on the first day of the week. Pre-HD serum concentrations of blood urea nitrogen, albumin, calcium, and phosphorus were measured monthly, at the beginning of every week. Post-HD concentrations of blood urea nitrogen were measured once every 6 months (June and December). The blood flow rates ranged from 200-350 ml/min, the dialysate flow rate ranged from 500-700 ml/min, and the dialysate temperature ranged from 35-37°C.

The patient's blood pressure was measured before (pre-systolic and diastolic blood pressure) and after (post-systolic and diastolic blood pressure) each HD session with an automatic sphygmomanometer. A cuff band was wrapped around the upper arm, contralateral to the location of vascular access. All study data were obtained via a medical chart review. Since 52 patients were lost to follow-up because they were transferred from our hospital, the final sample size was 707 patients. The median (interquartile range [IQR]) of the patients' ages and dialysis durations were 67.8 (75.4-59.9) and 8.9 (14.9-4.5) years, respectively.

Statistical analysis

All data are expressed as a median with IQR. Patients were classified according to whether DM was present or absent. The presence or absence of DM was determined by patients whose primary disease for introducing HD was diabetic nephropathy and who are currently receiving treatment for DM. Differences between groups were assessed with Fisher's exact probability test and Mann-Whitney's U test. We performed a univariate logistic regression analysis to select the determinants of mortality. In the univariate logistic regression analysis, the presence or absence of death was the dependent variable. All-cause death was the endpoint. Age, sex, dialysis history, presence of DM, presence of CVD, IDWG, RBW, %CGR, UFR, GNRI, serum albumin concentration, and Kt/Vure were included in the models as univariate variables. In addition, we performed a multiple logistic regression analysis to estimate the adjusted association between these variables and mortality and establish the odds that variables would be associated with death. Risk factors with a significant association with death in the univariate logistic regression analysis were included in the model. However, if these factors did not have statistical significance in the univariate logistic regression analysis, the influential risk factors were retained in the models based on clinical precedent and evidence of plausibility, as the risk factors for mortality in patients undergoing HD [10]. We selected age and the GNRI as covariates to adjust the UFR to avoid multicollinearity in the statistical analysis. IDWG and RBW were discarded to avoid biased estimations, since collinear parameters contain highly redundant information. Survival curves were obtained using the Kaplan-Meier estimation method and compared using a log-rank test to determine the difference in survival rates between DM patients who died and those who survived. The survival time for each patient was determined by the number of days from the start of this study to the end of the observation period or the date of the patient's death. The sensitivity and specificity of the groups of non-DM and DM patients were calculated for each UFR cutoff value to generate receiver operating characteristic (ROC) curves, including the areas under the curve (AUC) and

their 95% confidence intervals (CI). P-values <0.05 indicated statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [11].

Results

Population

Table 1 shows the demographic characteristics of 707 patients. The patients' ages and dialysis durations at baseline are expressed as median values (IQR). DW, BMI, HD time, serum albumin concentration, pre-systolic and diastolic blood pressure, post-systolic and diastolic blood pressure, UFR, IDWG, BRW, GNRI, %CGR, and Kt/Vure during the study period are expressed as the median values (IQR) of all measurements. Among these patients, 399 (56%) were men, 236 (33%) had DM, and 215 (30%) had CVD. During the 7-year follow-up period, 196 patients (42%) in the non-DM group and 118 (50%) in the DM group died. In the non-DM group, the HD time, serum albumin concentration, pre-diastolic blood pressure, GNRI, %CGR, and Kt/Vure were significantly higher in patients who survived than in patients who died (all, $p<0.05$). However, in patients in the non-DM group who died, age, UFR, IDWG, and RBW were significantly higher than in patients who survived (all, $p<0.001$). In the DM group, DW, HD time, serum albumin concentration, GNRI, and %CGR were significantly higher in patients who survived than in those who died (all, $p<0.001$). However, in patients in the DM group who died, age, pre-systolic and pre-diastolic pressure, UFR, IDWG, and RBW were significantly higher than in patients who survived (all, $p<0.001$). In the non-DM and DM groups, no differences were observed between patients who survived and those who died regarding sex, BMI, post-systolic and post-diastolic pressure, and Kt/Vure (all, $p>0.05$).

Table1. Characteristics of patients with DM and those without DM in terms of 7-years mortality

	Overall	Non−DM group		*p*−values [a]	DM group		*p*−values [b]
		survived	died		survived	died	
Number of patients	707	275	196	–	118	118	–
Age, yr	67.8 (75.4–59.9)	62.2 (69.3–55.1)	74.1 (83.5–66.1)	<0.0001 **	63.5 (69.5–56.5)	74.2 (79.1–68.8)	<0.0001 **
Sex (men/women)	399 / 308	146 / 129	112 / 84	0.399	76 / 42	65 / 53	0.184
Dialysis vintage, yr	8.9 (14.9–4.5)	10.3 (17.7–5.9)	11.2 (20.2−4.7)	0.547	5.8 (9.6–2.8)	6.6 (10.3–3.6)	0.088
Duration of survival period, day	–	–	1305.6 (1871.52−567.5)	–	–	1244.5 (1757.3−591.5)	–
Dry weight, kg	53.0 (61.0–45.5)	54.0 (61.3–47.0)	50.0 (56.5–42.9)	<0.0001 **	59.8 (69.4–52.0)	49.3 (59.4–43.0)	<0.0001 **
Body mass index, kg/m^2	21.0 (23.4–18.9)	21.2 (23.5–19.3)	20.3 (22.1–18.5)	0.050	22.8 (25.9–20.8)	20.6 (22.9–17.9)	0.757
Heamodialysis time, hr	4.0 (5.0−4.0)	4.0 (5.0−4.0)	4.0 (4.0−4.0)	<0.0001 **	4.0 (5.0−4.0)	4.0 (4.0−4.0)	<0.001 **
Serum albumin concentration, g/dL	3.7 (4.0–3.5)	3.9 (4.1–3.7)	3.6 (3.8–33)	<0.0001 **	3.8 (4.0–3.6)	3.6 (3.8–3.2)	<0.0001
pre systolic blood pressure, mmHg	142 (155−129)	141 (153−128)	144 (156−131)	0.153	136 (148−121)	149 (161−134)	<0.0001 **
pre diastolic blood pressure, mmHg	76 (84−66)	80 (88−70)	75 (82−67)	<0.001 **	70 (79−59)	74 (82−63)	<0.0001 **
post systolic blood pressure, mmHg	128 (1410−1142)	128 (140−114)	129 (142−116)	0.305	120 (136−103)	130 (152−116)	0.065
post diastolic blood pressure, mmHg	67 (76−60)	70 (78−60)	68 (76−60)	0.164	64 (71−52)	64 (74−56)	0.233
History of cardiovascular disease	215	88	67	0.619	31	29	0.881
Ultrafiltration rate, ml/hr/kg	9.7 (12.4−7.4)	8.5 (10.7−6.6)	12.2 (15.3−9.4)	<0.0001 **	8.7 (10.7−7.9)	11.5 (13.5−8.5)	<0.0001 **
Interdialytic weight gain, %	4.2 (5.3−3.2)	3.9 (5.1−2.9)	4.4 (5.24−3.5)	<0.001 **	4.0 (5.0−3.2)	4.6 (5.9−3.7)	0.002 **
Removal of body water, %	3.8 (4.5−3.1)	3.6 (4.4−2.9)	4.0 (4.36−3.3)	0.006 *	3.6 (4.3−3.1)	4.0 (4.7−3.3)	0.009 **
Geriatric nutritional risk index	95.3 (99.1–90.3)	96.8 (99.8–93.7)	92.3 (96.8–86.2)	<0.0001 **	98.3 (100.8–93.8)	93.3 (96.8–84.7)	<0.0001 **
%Creatinine generation rate	112.4 (128.4–93.6)	122.3 (136.9–111.4)	104.3 (120.9–82.1)	<0.0001 **	110.2 (122.8–94.3)	101.1 (118.3–75.7)	0.006 **
Kt/V_{urea}	1.83 (2.04–1.62)	1.91 (2.12–1.64)	1.83 (2.04–1.62)	0.033 *	1.81 (2.00–1.60)	1.74 (1.93–1.62)	0.135

All values are expressed as the median (interquartile range).
DM: diabetes mellitus
Fisher's exact probability tests and Mann-Whitney's *U* tests were used in the analysis.
a indicates patients who survived vs. those who died in the non-DM group.
b indicates patients who survived vs. those who died in the DM group.
* there was a significant difference between patients who survived and those who died. ** $p<0.01$, * $p<0.05$.

Univariate and multiple logistic regression analyses

Table 2 shows the results of the univariate logistic regression analysis. In all patients, age, the presence of DM, RBW, IDWG, and UFR were associated with a significant increase in mortality (all, p<0.0001). The serum albumin concentration, BMI, %CGR, GNRI, and HD time were associated with a significant reduction in mortality (all, p<0.0001). In the non-DM group, age, RBW, IDWG, and UFR were associated with a significant increase in mortality (p<0.0001). The serum albumin concentration, BMI, Kt/Vure, %CGR, GNRI, and HD time were associated with a significant reduction in mortality (all, p<0.05). In the DM group, age, RBW, IDWG, and UFR were associated with a significant increase in mortality (all, p<0.0001). The serum albumin concentration, BMI, Kt/Vure, %CGR, GNRI, and HD time were associated with a significant reduction in mortality (all, p<0.001).

Table2. The univariate association between individual covariates and 7-years mortality in the non-DM and DM groupes in th logistic regression model

	Overall		Non–DM group		DM group	
	OR (95% CI)	*p*–values	OR (95% CI)	*p*–values	OR (95% CI)	*p*–values
Age, yr	1.10 (1.08–1.12)	<0.0001 **	1.10 (1.07–1.12)	<0.0001 **	1.11 (1.08–1.15)	<0.0001 **
Sex	1.00 (0.75–1.36)	0.975	0.85 (0.59–1.23)	0.384	1.48 (0.88–2.49)	0.145
Dialysis vintage, yr	1.01 (0.10–1.03)	0.166	1.02 (0.99–1.04)	0.071	1.05 (0.99–1.12)	0.098
History of diabetes mellitus	1.40 (1.02–1.92)	0.035	–	–	–	–
History of cardiovascular disease	1.04 (0.76–1.44)	0.804	1.22 (0.81–1.83)	0.334	0.74 (0.43–1.27)	0.275
Body mass index, kg/m^2	0.89 (0.85–0.93)	<0.0001 **	0.91 (0.86–0.96)	<0.01 **	0.84 (0.78–0.91)	<0.0001 **
Heamodialysis time, hr	0.37 (0.27–0.52)	<0.0001 **	0.44 (0.30–0.64)	<0.001 **	0.27 (0.14–0.52)	<0.001 **
Kt/V_{urea}	0.66 (0.41–1.06)	0.084	0.49 (0.28–0.86)	<0.05 *	2.06 (0.79–5.38)	0.141
Removal of body water, %	1.83 (1.61–2.09)	<0.0001 **	2.19 (1.83–2.60)	<0.0001 **	1.42 (1.17–1.72)	<0.001 **
Serum albumin concentration, g/dL	0.12 (0.08-0.19)	<0.0001 **	0.01 (0.05–0.17)	<0.0001 **	0.20 (0.10–0.40)	<0.0001 **
Interdialytic weight gain, %	1.34 (1.23–1.46)	<0.0001 **	1.55 (1.38–1.75)	<0.0001 **	1.06 (0.93–1.21)	0.368
Geriatric nutritional risk index	0.91 (0.88–0.93)	<0.0001 **	0.90 (0.87–0.92)	<0.0001 **	0.92 (0.89–0.95)	<0.0001 **
%Creatinine generation rate	0.97 (0.97–0.98)	<0.0001 **	0.97 (0.96–0.97)	<0.0001 **	0.99 (0.98–0.10)	<0.01 **
Ultrafiltration rate, ml/hr/kg	1.37 (1.29–1.45)	<0.0001 **	1.45 (1.35–1.57)	<0.0001 **	1.25 (1.14–1.36)	<0.0001 **

CI: confidence interval; DM: diabetes mellitus
Odds ratios and CIs were calculated using a univariate logistic regression analysis. ** p<0.01.
* there was a significant difference. ** p<0.01, * p<0.05.

Table 3 shows the results of the multiple logistic regression analysis. In the model, we included age, sex, dialysis duration, presence of CVD, IDWG, RBW, UFR, %CGR, GNRI, and serum albumin concentration. There was no statistically significant difference in patients with and those without CVD, but this factor was included and retained in the model based on clinical precedent and evidence from previous studies. After selection with the multiple logistic regression analysis, the factors with statistical significance for death were age, GNRI, IDWG, RBW, and UFR.

Table3. Odds ratios in the multiple logistic regression analysis for predicting 7-years mortality

	Odds ratio	95% CI	*p*–values
Age, yr	1.08	1.06–1.10	<0.0001 **
Geriatric nutritional risk index	0.94	0.92–0.96	<0.0001 **
Interdialytic weight gain, %	1.23	1.06–1.43	<0.01 **
Removal body water, %	0.51	0.34-0.77	<0.01 **
Ultrafiltration rate, ml/hr/kg	1.22	1.06–1.41	<0.01 **

CI: confidence interval
Odds ratios and CIs were calculated using a multiple logistic regression analysis. The model was adjusted for age, sex, dialysis history, presence of cardiovascular disease,

UFR cutoff values for mortality

Figure 1 shows the relative ROC curves for UFR in the non-DM and DM groups, as well as the AUC and its CIs. The discrimination potential of UFR was estimated to be evaluated at baseline, in predicting death at 7 years. The ROC curve and cutoff that minimized the absolute difference between the sensitivity and specificity were calculated for the UFR. In the non-DM group, the UFR cutoff for mortality was 12.07 ml/hr/kg, with 52% sensitivity and 91% specificity. In the DM group, the UFR cutoff for mortality was 9.66 ml/hr/kg, with 67% sensitivity and 66% specificity. The AUCs to predict the appropriate UFR in the non-DM and DM groups were 0.78 (95% CI: 0.74-0.83) and 0.70 (95% CI: 0.63-0.76), respectively.

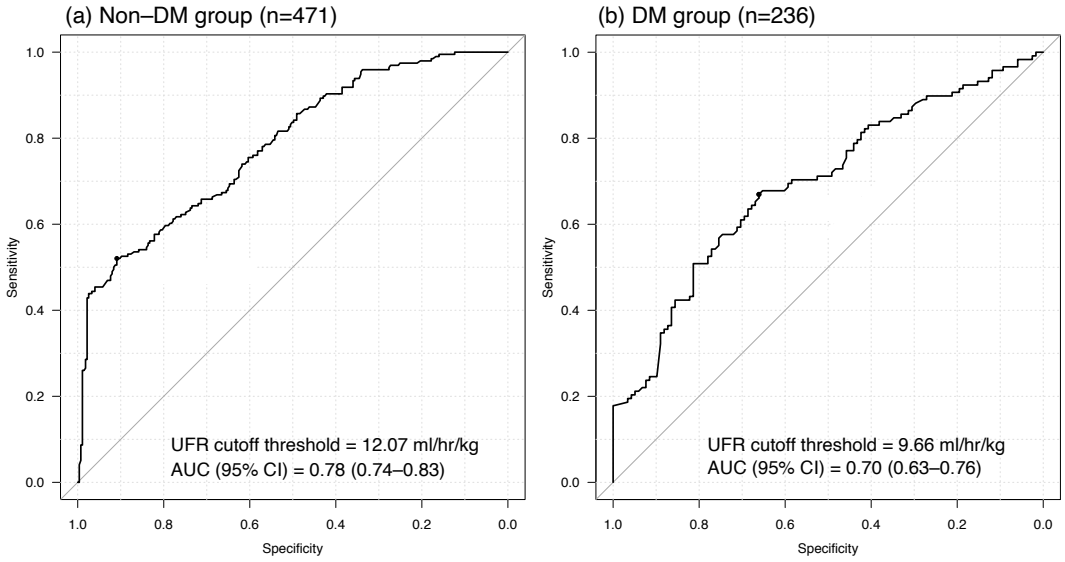

Fig. 1. ROC curve for UFRs and mortality

UFRs were adjusted for age and the geriatric nutritional risk index.
ROC: receiver operating characteristic; DM: diabetes mellitus; UFR: ultrafiltration rate; AUC: area under the curve

Survival analysis

Figure 2 shows the survival curves in the multiple logistic analysis for significant predictors in the non-DM and DM groups. Data were adjusted for age and GNRI. Age and GNRI were selected as covariates to adjust the UFR, in order to avoid multicollinearity in the statistical analyses. With a follow-up of 7 years, the volume of the UFR in each group were defined according to the ROC-derived UFR threshold of 12.07 ml/hr/kg (median 7.1 years versus 4.8 years, $p<0.0001$) and 9.66 ml/hr/kg (median 7.1 years versus 4.5 years, $p<0.0001$), respectively. The 470 patients (67%) in the non-DM group were divided into two sub-groups: UFR >12.07 ml/hr/kg (127 patients [27%]) and UFR ≤12.07 ml/hr/kg (344 patents [73%]). Similarly, the 236 patients (33%) in the DM group were divided into two sub-groups: UFR >9.66 ml/hr/kg (68 patients [29%]) and UFR ≤9.66 ml/hr/kg (168 patients [71%]). During the follow-up period, in the non-DM group, 102 patients (80%) with a UFR >12.07 and 94 (27%) with a UFR ≤12.07 ml/hr/kg died, and the median survival periods were 4.9 (6.4-2.4) and 7.1 (7.1-6.0) years, respectively. In the DM group, 50 patients (74%) with a UFR >9.66 and 68 (40%) with a UFR ≤9.66 ml/hr/kg died, and the median survival periods were 4.9 (6.4-2.4) and 7.1 (7.1-6.0) years, respectively.

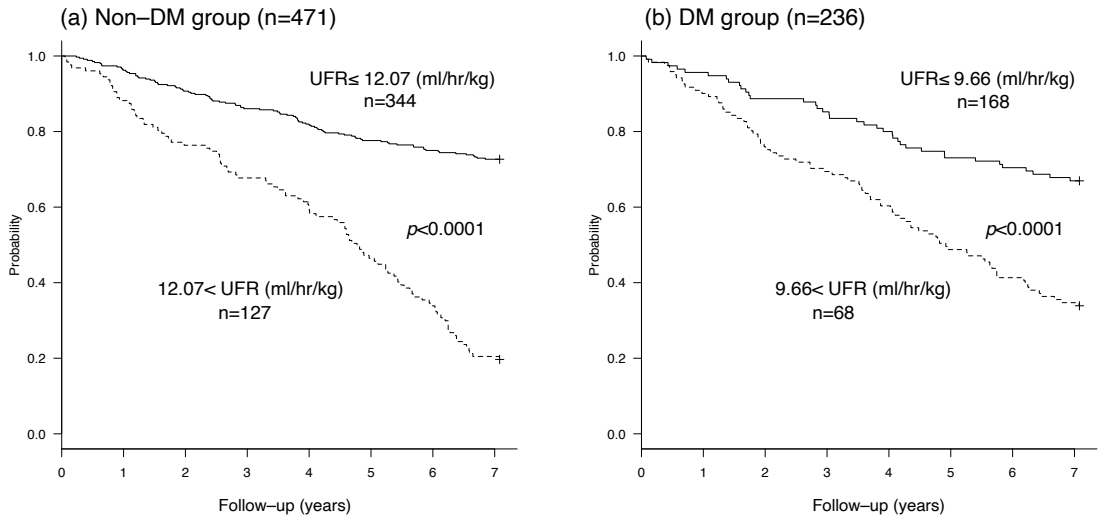

Fig. 2. Kaplan-Meier curves for the log-rank analysis, using the UFR as a categorical variable that was defined according to the ROC curve-derived ultrafiltration rate threshold of 12.07 ml/hr/kg in non-DM patients (a) and 9.66 ml/hr/kg in DM patients (b).

UFR: ultrafiltration rate; ROC: receiver operating characteristic; DM: diabetes mellitus

Discussion

We assessed the association between the UFR and long-term mortality in HD patients. UFRs over 12.07 and 9.66 ml/hr/kg were independently associated with increased odds of death in non-DM and DM patients, respectively. This is the first study to report the cutoff UFR values that are associated with mortality in a 7-year period, comparing non-DM and DM patients in the same HD environment.

Many investigations have reported that higher weight gain and overload were associated with increased mortality, and an excessively high UFR was strongly associated with mortality in HD patients. A previous 5-year prospective observational multicenter study observed better survival in patients with a UFR <12.37 ml/hr/kg body weight and recommended longer or more frequent dialysis sessions for these patients [4]. Another study in the US on 110,880 HD patients reported that a UFR ≥10 mL/hr/kg of body weight conferred the highest risk and was independently associated with higher all-cause and cardiovascular mortality in patients with incident HD [12]. Because a UFR of 15 ml/hr/kg is equal to the removal of 6% of body weight in water in 4 hours, the average UFR would be ≤15 ml/hr/kg, and >6% weight loss between two consecutive HD sessions was associated with a significant increase in the risk of death [13]. Recently, we reported that in patients with a UFR >15 ml/hr/kg, imbalance of the autonomic nervous activity occurred even without blood pressure variations during an HD session [14]. UFR has serious implications for morbidity and mortality, but the adequate management of UFR is a critical issue. There is no doubt that excessive UFRs are strongly related to adverse outcomes and mortality, and in many cases, a suitable UFR is a critical and challenging aspect of HD.

The major cause of HD-associated hypotension is a reduced circulating plasma volume due to a delay in the plasma refilling rate that is caused by excess water removal [15]. As the plasma volume decreases, the baroreceptor reflex acts as a compensatory mechanism, stimulating the sympathetic nervous system, enhancing cardiac contraction, and increasing heart rate and blood pressure. A decreased circulating plasma volume could result in myocardial ischaemia that is associated with cardiovascular risk and mortality [16]. Additionally, changes in autonomic nervous

activity and heart rate precede the appearance of transient myocardial ischaemia [17]. Moreover, autonomic nervous dysfunction, arteriosclerosis, and cardiac dysfunction are also cause of IDH. In this study, the cutoff UFR value in the DM group was less than that in the non-DM group. Thus, removing water rapidly from DM patients undergoing HD could be particularly hazardous clinically, as the removal of water would be linked to hemodynamic failure that is peculiar to patients with DM undergoing HD. This could result in a vicious cycle of decreased blood pressure.

Another finding was that the HD time and nutrition status possibly had a direct impact upon the survival of HD patients. Patients who died were significantly older, had a shorter HD time, and had lower Kt/Vure, GNRI, and %CGR values than did patients who survived (Table 1). Kt/Vure did not have an independent influence on patient survival in the multiple logistic regression analysis of the non-DM group, but it did have an impact in the DM group. Although these results do not negate the fact that a higher Kt/Vure reduces mortality, it indicates that higher Kt/Vure is due to a longer HD time. Increasing the HD time could enhance the beneficial effect of decreasing the UFR values and mortality.

Furthermore, the serum albumin concentration, GNRI, and %CGR were significantly lower in patients who died than in patients who survived, and these had an independent influence on patient survival in the multiple logistic regression analysis. Lower GNRI values suggested that patients who died had poorer nutritional status than did those who survived and that the GNRI value directly influenced survival, but BMI did not (Table 3). The GNRI is a synthetic variable of the serum albumin concentration and weight, and is strongly influenced by the serum albumin concentration. Furthermore, the GNRI reflects the influence of emaciation more strongly than that of obesity, because weight is set as equal to 1 of the upper limit of the weight if 1≤ the actual measured body weight/ideal weight. These results lead to a dignified for serum albumin concentration than for patients' weight, and agreed with that GNRI may have a better prognostic factor than serum albumin concentration or BMI alone [18].

Limitations

First, although we considered confounding variables that were possibly associated with both the UFR and mortality, other residual factors, especially CVD, are associated with UFR and dialytic hemodynamics such as IDH. In the present study, it was possible that dialytic hemodynamics such as IDH could have been responsible for variations in the UFR. Additionally, we did not consider lifestyle habits that might have been associated with weight gain such as the patients' physical activities, diet, smoking status, or alcohol intake. We also could not exclude variables such as antihypertensive or antihypotensive drug use and complications to minimize the risk of residual confounders. Second, this study was a retrospective, single-center nature. A well-designed, prospective study with a propensity score analysis will be needed to confirm our findings. Third, in the DM group, the AUC, sensitivity, specificity, and cutoff values were low. A higher sensitivity may be required in primary diagnostic settings. It may be more difficult to predict the prognosis of patients with DM when determining the survival risk using the UFR because of the complexity of the pathology of diabetes. Finally, observational UFR may have been introduced as misclassification bias. That is, diet and drinking volume during HD may be added to the amount of water removal in an HD session and may be different from the amount of water removal against real weight gain. With misclassification, the UFR might have been overestimated.

Conclusion

We show that high UFRs are associated with an increased mortality risk in patients undergoing HD. Better survival was observed with UFR ≤12.07 ml/h/kg and UFR ≤9.66 ml/h/kg in HD

patients with non-DM and DM, respectively. Lower UFR might be essential for improving the long-term mortality of HD patients.

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Compliance with ethical standards

Conflict of interest All authors declare no competing financial interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional, and national research committee at which the studies were conducted (IRB approval number NCT03471299) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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