

Original Article

Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study

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Abstract

Background. High ultrafiltration rate on haemodialysis (HD) stresses the cardiovascular system and could have a negative effect on survival.

Methods. The effect of ultrafiltration rate (UFR; ml/h/kg BW) on mortality was prospectively evaluated in a cohort of 287 prevalent uraemic patients in regular HD from 1 January 2000 to 31 December 2005. Patients: 165 men and 122 women, age 66 ± 13 years, on regular HD for at least 6 months, median: 48 months (range 6–372 months). Mean UFR was 12.7 ± 3.5 ml/h/kg BW, Kt/V: 1.27 ± 0.13 , body weight (BW): 62 ± 13 kg, PCRn: 1.11 ± 0.20 g/kg/day, duration of dialysis: median 240 min (range 180–300 min), mean arterial blood pressure (MAP) 99 ± 9 mm/Hg. One hundred and forty nine patients (52%) died, mainly for cardiovascular reasons (69%). Multivariate Cox regression analysis was utilized to evaluate the effect on mortality of UFR, age, sex, dialytic vintage, cardiovascular disease (CVD), diabetes, dialysis modality, duration of HD, BW, interdialytic weight gain (IWG), body mass index (BMI), MAP, pulse pressure (PP), Kt/V, PCRn.

Results. Age (HR 1.06; CI 1.04–1.08; $P < 0.0001$), PCRn (HR 0.17, CI 0.07–0.43; $P < 0.0001$), diabetes (HR 1.81, CI 1.24–2.47; $P = 0.007$), CVD (HR 1.86; CI 1.32–2.62; $P = 0.007$) and UFR (HR 1.22; CI 1.16–1.28; $P < 0.0001$) were identified as factors independently correlated to survival. We estimated the discrimination potential of UFR, evaluated at baseline, in predicting death at 5 years, calculating the relative receiver operating characteristic (ROC) curves and the cut-off that minimizes the absolute difference between sensitivity and specificity.

Conclusions. High UFRs are independently associated with increased mortality risk in HD patients. Better survival was observed with $\text{UFR} < 12.37$ ml/h/kg BW. For patients with higher UFRs, longer or more frequent dialysis sessions should be considered in order to prevent the deleterious consequences of excessive UFR.

Keywords: haemodialysis; nutrition; survival; ultrafiltration rate

Introduction

Haemodialysis (HD) patients still have high mortality rates [1]. Association between mortality and cardiovascular disease, dose of dialysis and diabetes are well studied and confirmed [2]. Poor volume control can exacerbate hypertension and its many detrimental effects on the cardiovascular system [3]. Although higher interdialytic weight gain has been associated with better nutritional status [4], it can predispose to volume overload, abnormal ventricular remodelling, and finally heart failure [5]. Moreover, those patients with excessive interdialytic weight gain tend to receive a higher ultrafiltration rate (UFR), which means a greater rate of volume removal during HD, potentially resulting in a higher frequency of intradialytic hypotension episodes. Although intradialytic hypotension may result in dialysis intolerance, myocardial ischaemia, infarction, and even stroke, its association with higher mortality is far from clear [6]. While some studies have suggested that longer duration of HD sessions could be associated with better survival [7,8], other have failed to confirm this relationship [9,10], so no clear evidence for a direct association of UFR and patients outcome has emerged. The aim of this study was to evaluate if UFR could influence long-term

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survival in a large cohort of prevalent HD patients, controlled for multiple dialysis and clinical risk factors and followed for 5 years.

Patients and methods

We performed a prospective multicentre observational study to evaluate the impact of UFR on mortality in a cohort of prevalent HD patients followed at the Division of Nephrology, Spedali Civili and Section of Nephrology, University of Brescia, Dialysis Centre of Gardone VT and Nephrology and Dialysis Unit, ASL 6 Cirié (Turin) from 1 January 2000 to 31 December 2005. The study has been conducted according to the principles of the Declaration of Helsinki.

Source of data

Data information comes from a computerized data file that included demographic and clinical data of the patients. From a total HD population of 380 patients, we included only prevalent patients from each facility.

Inclusion criteria

Patients on regular thrice weekly HD treatment for at least 6 months. Urinary output ≤ 150 ml/24 h. Two hundred eighty seven patients met the inclusion criteria; 85% of patients were on low flux synthetic membranes, 15% on high flux synthetic membranes. Blood flow rate ranged from 250 to 350 ml/min (median 300), dialysate flow rate was 500 ml/min. Dialysate fluid composition was: sodium 140 mmol/l, potassium 2–4 mmol/l, calcium 1.25–1.75 mmol/l, bicarbonate 35 mmol/l, acetate 4 mmol/l, glucose 1 g/l. Duration of dialysis ranged from 180 to 300 min (median 240 min).

Variables examined

At the start of the study (1 January 2000), the following variables were collected: age (years), sex, dialytic vintage (months), cardiovascular diseases (CVD), diabetes, dialysis modality (bicarbonate/haemodiafiltration), duration of HD (min), body weight (BW; kg), body mass index (BMI; kg/m²), interdialytic weight gain (IWG, kg), ultrafiltration rate (UFR: ml/h/kg BW), pre-HD systolic and diastolic blood pressure, mean arterial blood pressure (MAP; mmHg), pulse pressure (PP; mmHg), dialysis dose (Kt/V), protein catabolic rate (PCRn; g/kg BW/day).

During the entire study period the number and causes of death were recorded. Causes of renal failure were: chronic glomerulonephritis 20%, tubulointerstitial nephritis 18%, angiosclerosis 18%, polycystic kidney disease 6%, diabetes 16%, unknown 22%. Biochemical parameters were measured by standard laboratory methods.

Definitions used in the study

Cardiovascular diseases (CVD). Cardiovascular diseases included the presence of ischaemic heart disease, peripheral vascular disease, and cerebral vascular disease.

Ultrafiltration rate. The rate of volume removal at dialysis, expressed in ml/h/kg BW, measured by the weight change per duration of HD treatment using the post HD weight as denominator. The value of UFR used in the analysis was the mean UFR for each patient over a one-month period (13 HD sessions). UFR was determined with the same modality at the end of the study.

Body weight (BW). Body weight was clinically determined, and reflects the lowest weight the patient can tolerate without intradialytic symptoms and hypotension in the absence of overt fluid overload and was modified by the attending doctor as needed.

Dialysis dose (Kt/V). Urea kinetic modelling was performed midweek at the start of the study and every 4 months until the end of the study. BUN samples were drawn from the arterial side of the AV fistula at the start, 15 min after the end, and at the beginning of the next dialysis session. Kt/V was calculated according to Daugirdas [11]. Protein catabolic rate (PCRn) was calculated according to the NKF-K/DOQI Clinical Practice Guidelines for nutrition in chronic renal failure [12].

Pre-HD systolic, diastolic blood pressure, MAP, PP. These were the mean values for each patient over the first month of observation (13 HD sessions).

All patients were advised to eat a salt-restricted (mean salt intake 4–5 g/day), normal-high protein (1–1.2 g/kg BW/day) diet and to drink no more than their thirst indicated. Meals during dialysis were not allowed.

Data analysis

Continuous data are reported as mean $\pm$ SD or median and interquartile range (IQR). Comparisons between patients were performed using Student's *t*-test for paired and unpaired data for normally distributed data, Mann-Whitney test for median data, χ^2 test for categorical data. Univariate analysis was performed by mean of log-rank test and graphically plotting time vs a suitable transformation of Kaplan-Meier [$\log(-\log(S(t)))$]. These plots were used to check the assumption of proportionality. Given the good ratio between number of predictors and number of events (quite 1–20) and that no predictor failed the test for proportionality, all parameters: UFR, age, sex, dialytic vintage, CVD, diabetes, dialysis modality, duration of HD, BW, IWG, BMI, MAP, PP, Kt/V, PCRn, were inserted in a multivariate Cox proportional hazards regression model. The Variance Inflation Factors (VIF) were evaluated to uncover possible collinearity among the parameters in the Cox model, since collinear parameters contain highly redundant information. Parameters with VIF > 5 , index of a remarkable collinearity with the other parameters in the model, were discarded to avoid biased estimations. The Akaike Information Criterion was applied as a selection approach in the Cox proportional hazards regression model. We have also applied the approach of Heagerty *et al.* [13] to evaluate the prediction power of UFR in relation to death at 5 years using the receiver operating characteristic (ROC) curves for time dependent outcomes. Significant differences were defined by $P < 0.05$. All statistical analyses were performed using R Language.

Results

Population description

There were 165 men and 122 women, mean age 66 ± 13 years (range 20–90 years), in dialysis treatment for a median of 48 months (range 6–372 months). Table 1 shows the main demographic and biochemical data of the whole population. During the 5 years of follow-up, 149 patients (52%) died, and 37 patients were lost to follow-up for renal transplantation. The main causes of death were: cardiac 49%, vascular 20%, infectious diseases 7%, other causes 24%. As a whole, cardiovascular events accounted for 69% of deaths.

Table 2 shows the comparison of clinical and biochemical data taken at the start of the study (time 0) for patients that survived (group A), and patients who died (group B). Age, CVD, diabetes,

and IWG were significantly higher in group B as compared to group A. Sex distribution, dialytic age, dialysis modality, duration of dialysis, Kt/V, MAP and PP did not show any difference between the two groups. BW, BMI, PCRn were significantly lower in group B as compared to group A.

Table 3 shows the behaviour over time of the parameters studied in patients that completed the study (Survivors) and patients who died (Died). No significant change over time was observed in both groups of patients. In 'Died patients', parameters were evaluated at the start of observation and just before death (mean 35 ± 16 days before death).

UFR and survival

Figure 1 shows UFR (ml/h/kg BW) between patients who survived (group A) and patients who died (group B). UFR was significantly higher in group B than group A (group B: 13.9 ± 3.4 ml/h/kg BW; group A: 11.5 ± 3.1 ml/h/kg BW; $P < 0.00001$). In order to exclude the possible effect of diabetes on the levels of UFR, we performed the same analysis excluding the 55 patients with diabetes. Again, UFR was significantly higher in patients who died compared to patients who survived (14.1 ± 3.5 ml/h/kg BW vs 11.4 ± 3.1 ml/h/kg BW; $P < 0.00001$), so we considered all the patients as a whole group.

Table 4 shows Cox regression analysis. We included in the model: UFR, age, sex, dialytic vintage, CVD, diabetes, dialysis modality, duration of HD, BW, BMI, MAP, PP, Kt/V, PCRn and IWG. The IWG was eliminated as it had a VIF equal to 8.12 and, moreover, it was not statistically significant ($P = 0.10$). It is worthwhile to underline the good correlation between UFR and IWG ($r = 0.52$, $P < 0.01$). After selection by mean of Akaike Information Criterion factors reaching statistical significance for death were: age, PCRn, diabetes, UFR and CVD.

Table 1. Demographic and biochemical data of the whole population studied

Cardiovascular disease	47% (135)
Diabetes	19% (55)
Bicarbonate dialysis	85% (244)
HDF	15% (43)
Duration of HD (min). median; (range)	240; (180–300)
Kt/V (range)	1.27 ± 0.13 ; (0.92–1.81)
Body weight (kg)	62 ± 13 ; (38–127)
BMI (kg/m ²)	23 ± 4 ; (15–42)
Interdialytic BW gain (kg) ^a	3.0 ± 0.6 ; (1.1–7.3)
UFR (ml/kg BW/h) ^a	12.7 ± 3.5 ; (5.2–27.8)
PCRn (g/kg/day)	1.11 ± 0.20 ; (0.6–1.9)
Mean arterial blood pressure (mmHg) ^a	99 ± 9 ; (61–137)
Pulse pressure (mmHg) ^a	65 ± 12 ; (27–110)

Data are mean $\pm$ SD and range. Numbers after percents are frequencies.

^aMean values for each patient over 13 dialysis sessions.

HDF, haemodiafiltration; BMI, body mass index; UFR, ultrafiltration rate; PCRn, protein catabolic rate.

Table 2. Clinical and biochemical data between patients at the start of the study (group A, patients who survived; group B, patients who died)

Parameter	Group A <i>n</i> = 138	Group B <i>n</i> = 149	<i>P</i>
Age (years)	58 ± 14	72 ± 8	0.00001
Sex (men/women) ^a	80/58 (58%)	88/61 (59%)	NS
Dialytic vintage (months)	74 ± 72	61 ± 59	NS
Cardiovascular diseases ^a	41/138 (30%)	94/149; (63%)	0.0001
Diabetes ^a	12% (17)	38/149; (25%)	0.007
BicHD/HDF ^a	Bic: 84% (117) HDF: 15% (21)	Bic: 84% (127) HDF: 15% (22)	NS
Duration of HD (min)	237 ± 19	235 ± 19	NS
Kt/V	1.26 ± 0.13	1.28 ± 0.13	NS
Body weight (kg)	66 ± 13	61 ± 12	0.0001
BMI (kg/m ²)	24 ± 5	23 ± 4	0.0001
Interdialytic BW gain (kg)	2.9 ± 0.6	3.2 ± 0.6	0.0005
PCRn (g/kg/day)	1.17 ± 0.21	1.04 ± 0.17	0.00001
MAP (mmHg)	101 ± 11	99 ± 8	NS
Pulse pressure (mmHg)	65 ± 13	65 ± 10	NS

Data are mean $\pm$ SD. Numbers after percents are frequencies.

^a χ^2 test for categorical data. All other correlations are Student's *t*-test for unpaired data.

Bic HD, bicarbonate dialysis; HDF, haemodiafiltration; BMI, body mass index; PCRn, protein catabolic rate; MAP, mean arterial pressure.

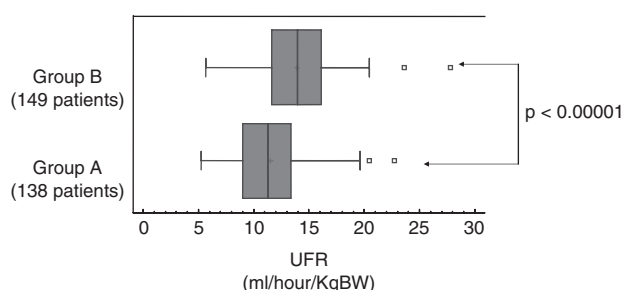
Table 3. Behaviour over time of the parameters studied in patients that completed the study (Survivors) and patients who died (Dead)

	Survivors ^a (n = 101)			Dead ^a (n = 149)		
	2000	2005	P	2000	End	P
Kt/V	1.26 ± 0.13	1.27 ± 0.14	NS	1.28 ± 0.13	1.27 ± 0.13	NS
BW (kg)	66 ± 13	67 ± 15	NS	61 ± 12	62 ± 13	NS
BMI (kg/m ²)	24 ± 5	24 ± 5	NS	23 ± 4	23 ± 5	NS
IWG (kg)	2.9 ± 0.6	3.0 ± 0.6	NS	3.2 ± 0.6	3.3 ± 0.4	NS
UFR (ml/h/kgBW)	11.5 ± 3.1	11.2 ± 3.1	NS	13.9 ± 3.4	13.5 ± 3.5	NS
PCRn (g/kg/day)	1.17 ± 0.21	1.14 ± 0.18	NS	1.04 ± 0.17	1.02 ± 0.15	NS
MAP (mmHg)	101 ± 11	100 ± 11	NS	99 ± 8	100 ± 10	NS
PP (mmHg)	65 ± 13	65 ± 14	NS	65 ± 10	64 ± 13	NS

Data are mean ± SD.

^aStudent's *t*-test for paired data.

BW, body weight; BMI, body mass index; IWG, interdialytic weight gain; UFR, ultrafiltration rate; PCRn, protein catabolic rate; MAP, mean arterial pressure; PP, pulse pressure.

**Fig. 1.** UFR in patients who survived (Group A) and patients who died (Group B).**Table 4.** Survival analysis: predicting mortality by the Cox proportional hazards regression model after adjustment for multiple medical and demographic covariates^a

	HR	CI 95%	P
UFR	1.22	1.16 – 1.28	<0.0001
PCRn	0.17	0.07 – 0.43	<0.0001
Age	1.06	1.04 – 1.08	<0.0001
CVD	1.86	1.32 – 2.642	=0.007
Diabetes	1.81	1.24 – 2.47	=0.007

Model adjusted for: UFR, age, sex, dialytic vintage, CVD, diabetes, dialysis modality, duration of HD, BW, BMI, IWG, MAP, PP, Kt/V, PCRn.

UFR, ultrafiltration rate; PCRn, protein catabolic rate; CVD, cardiovascular diseases.

We estimated the discrimination potential of UFR, evaluated at baseline, in predicting death at 5 years, calculating the relative receiver operating characteristic (ROC) curve and the cut-off that minimize the absolute difference between sensitivity and specificity. Figure 2 shows the ROC curve for UFR, the area under the curve and its confidence intervals. The UFR cut-off threshold for mortality was 12.37 ml/h/kg BW that gave 73% sensitivity and 73% specificity.

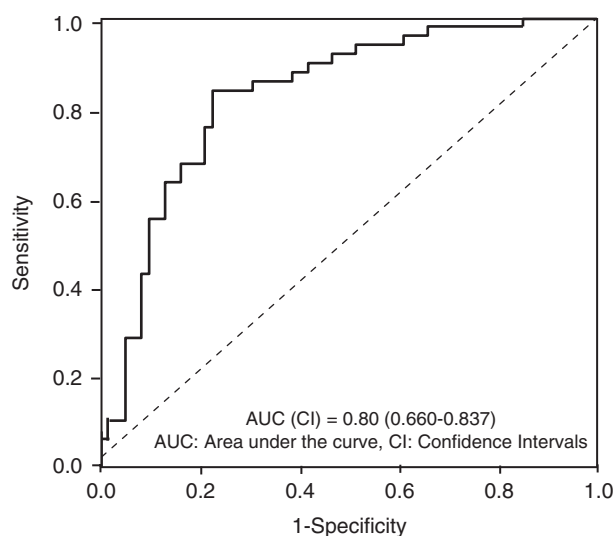
**Fig. 2.** Receiver operating characteristic (ROC) curve for UFR and mortality.

Figure 3 shows the survival curves adjusted for significant predictors at Cox analysis by using UFR as categorical variable defined according to the ROC derived UFR threshold of 12.37 ml/h/kg BW. A significant greater mortality for patients with $UFR \geq 12.37$ ml/h/kg BW was observed ($P < 0.0001$).

Discussion

The main finding from this study is that an excessive UFR (≥ 12.37 ml/h/kg BW) in patients on regular thrice weekly HD treatment is independently associated with an increased long-term risk of death. The effect of UFR on patient outcome has received very little attention in HD literature mainly because of its complex interrelations with IWG, duration of dialysis session and efficiency of dialysis. IWG is primarily

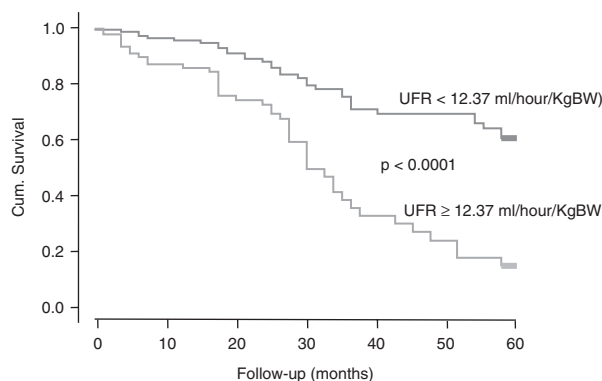


Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

determined by the HD patient's fluid and sodium intake, but other factors, such as hyperglycaemia, residual renal function, and extent of urinary output, may affect IWG [14].

Patients included in this study were on regular HD treatment for at least 6 months, with negligible urinary outputs, so it is extremely unlikely that this factor could have influenced the amount of IWG. Comparison between patients who survived and patients who died (Table 2) showed that patients who died were significantly older, had lower BW and PCRn, a higher incidence of diabetes and CVD, and higher IWG than patients who survived. Moreover, patients who died showed higher levels of UFR compared to patients who survived (Figure 1). The higher UFR in patients who died could suggest a possible direct role of the duration of HD treatment on survival.

Many investigators have stressed the importance of the duration of treatment time in HD [7,15]. Held *et al.* [16] investigated the relationship over a 3-year period of mortality and duration of HD session in a sample of 600 HD patients from 36 dialysis units in the USA, and found that a treatment time <3.5 h was associated with a significantly higher mortality. However, that study, although adjusted for a great variety of patient, provider, and geographical covariates, was not adjusted for dialysis adequacy, and authors could not exclude the effect of a reduced delivered Kt/V on mortality in patients dialysing for shorter periods. In our study, Kt/V for the whole group of patients was 1.27 ± 0.13 , well above the minimum suggested dose for dialysis adequacy (Table 1) [17]. Moreover, no significant differences in Kt/V levels between patients who survived and patients who died (Table 2) were observed, and, more importantly, they did not change over time (Table 3), thus excluding that efficiency of dialysis could have played any significant role in survival. Moreover, in our population, the duration of HD session was never less than 210 min (3.5 h) (with the exception of only two patients) with a median treatment time of 240 min (Table 1), and it

was not different between patients who survived and patients who died (Table 2). This could be the reason why the duration of HD treatment had no independent influence on patient survival in Cox regression model analysis. In fact, after adjustment for multiple covariates, duration of HD treatment and Kt/V did not exert any significant effect on patient survival (Table 4). On the contrary, a clear independent significant role for UFR was evident. The HR of death, adjusted for age, sex, dialytic vintage, diabetes, CVD, UFR, BW, IWG, BMI, MAP, PCRn, showed a 22% increase for each ml/h/kg BW increase in UFR. Of note is the fact that although IWG and UFR were significantly correlated, only UFR emerged as independent significant predictor for death at Cox regression model analysis.

The discrimination potential of UFR, evaluated at baseline, in predicting death at 5 years, studied by ROC curve (Figure 2), detected the cut-off threshold that minimizes the absolute difference between sensitivity and specificity at 12.37 ml/h/kg BW. The survival curves of the predictive role of UFR for death, adjusted for significant predictors at Cox analysis, using the ROC derived threshold for UFR (Figure 3) confirmed the role of increasing UFR values on mortality, with the higher mortality risk in patients with $\text{UFR} \geq 12.37 \text{ ml/h/kg BW}$, and the lower in patients with UFR below this limit. As expected, other significant predictors for mortality were age, PCRn, CVD and diabetes. Excessive increase in intravascular volume is a major pathogenic factor for hypertension in chronic renal failure. Interdialytic expansion of blood volume is not linear but exponential [18], and correlates directly with the left ventricular diameter in HD patients and left ventricular hypertrophy. Hypertension, left ventricular hypertrophy, peripheral and cerebral vascular disease are all well known mortality risk factors [2] and in fact CVD was confirmed as a significant independent mortality risk factor in the Cox analysis of our study (Table 4) as well as increasing age and presence of diabetes.

An interesting finding is the fact that despite patients who died were older with lower BW, BMI and PCRn than patients who survived (Table 2), thus suggesting a bad nutritional status and a reduced nutritional intake, they still had greater UFR than patients who survived. Various studies have found a positive correlation between IWG and nutritional parameters [19]. Sherman *et al.* [20] have shown a direct correlation between IWG, PCRn and serum albumin concentrations, thus suggesting that higher body weight gains might be associated with a better nutritional status. A recent study from Lopez-Gomez *et al.* [21] noted that IWG as a percentage of dry weight was directly correlated with predialysis systolic and diastolic blood pressure as well as serum creatinine, urea, PCRn, and BMI. These authors concluded that the positive effect of IWG on nutrition outweighs its negative effect on blood pressure, but cautioned that the results of the study should not deter from imposing salt restriction for blood pressure control. Our data do not agree with these observations, as patients who died showed larger

BW gains and UFRs but lower BW and BMI. A possible explanation for these findings is that patients who died, being older with a greater incidence of diabetes and CVD, had reduced protein-energy intakes, as suggested by their reduced PCRn and BMI levels, while still maintaining elevated fluid intakes, thus resulting in elevated UFR. Fluid intake in HD patients varies from subject to subject and it is related to dietary sodium intake, dialysate Na concentration, psychological reasons and probably hyperglycaemia in diabetic patients. Moreover, it tends to remain rather constant over time [22]. High dialysate Na concentrations are associated with thirst, larger IWGs, and higher predialysis blood pressure due to chronic positive Na balance [19]. This should not be the case in our patients since dialysate Na concentration for all patients was 140 mmol/l, and we did not find any significant difference in UFR related to the dialysis modality (HD or HDF), thus excluding that the dialysis procedure could cause different Na balance among patients. Moreover, since exclusion of diabetic patients did not change the association between UFR and mortality, it is extremely unlikely that diabetes per se could have played any specific role in the amount of fluid ingestion and UFR. On the other hand, our data confirm the relative stability over time of fluid intake either in patients who survived or patients who died (Table 3) in spite of the continuous warnings by the dialysis team about the danger of excessive water and salt ingestion.

In conclusion, within the well-known limits of an observational study, we show that high UFRs are independently associated with an increased mortality risk in patients on HD treatment. Better survival was observed in patients with mean UFR < 12.37 ml/h/kg BW. For patients with higher body weight gains, longer or more frequent dialysis sessions should be considered in order to prevent the deleterious consequences of too high UFR.

Conflict of interest statement. None declared.

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