

## Original Article

## Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis

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**SUMMARY:**

**Aim:** Patients with end-stage renal disease (ESRD) often start long-term haemodialysis (HD) thrice weekly, regardless of the level of residual renal function (RRF). In this study, we investigated whether ESRD patients having sufficient RRF can be maintained on twice-weekly HD, and how they fare compared to patients without RRF on thrice-weekly HD.

**Methods:** We analyzed 74 patients who had undergone long-term HD and maintained on the same dialysis frequency from February 1998 to July 2005, and followed until December 2005. We compared the clinical variables between twice-weekly and thrice-weekly HD patients and a second analysis testing the residual urine output as an independent predictor for twice-weekly HD.

**Results:** After a mean follow up of 18 months, twice-weekly HD patients ( $n=23$ ) had lower serum  $\beta_2$ -microglobulin than thrice-weekly HD patients ( $n=51$ ). Moreover, the twice-weekly group had a slower decline of RRF, as indicated by their higher urine output and creatinine clearance, fewer intradialytic hypotensive episodes, and required less frequent hospitalization. There was no difference between the two groups in cardiothoracic ratio or indices of nutrition and inflammation. Multivariable logistic regression identified age (odds ratio (OR), 1.866; 95% CI, 1.093–3.183), dry body mass index (OR, 0.790; 95% CI, 0.625–0.999), and urine output (OR, 1.093; 95% CI, 1.026–1.164) as predictors for maintaining twice-weekly HD.

**Conclusion:** Our data suggest that when patients who have sufficient urine output are given twice-weekly HD, they maintain dialysis adequacy and exhibit better preservation of RRF than patients on thrice-weekly HD.

**KEY WORDS:** end-stage renal disease, haemodialysis, residual renal function.

Patients with end-stage renal disease (ESRD) often start long-term haemodialysis (HD) on a thrice-weekly schedule, even if they have appreciable residual renal function (RRF). RRF is crucial for the maintenance of fluid balance and adequacy of long-term peritoneal dialysis, and has been

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recognized as a powerful predictor of survival in ESRD patients.<sup>1–4</sup> However, the clinical benefit of RRF in long-term HD remains controversial.<sup>5</sup> At present, there are no clinical practice guidelines concerning the optimal frequency of long-term HD based on levels of RRF. It is possible that ESRD patients on thrice-weekly HD may experience accelerated loss of RRF due to intradialytic complications, notably hypotensive events.

In this study we investigated whether ESRD patients with sufficient RRF have a better chance of preserving RRF by undergoing twice-weekly HD and the effect of this twice-weekly schedule on dialysis adequacy and clinical outcomes.

**METHODS****Study population**

We screened 197 ESRD patients on long-term HD at the National Taiwan University Hospital (NTUH), a medical centre in North

Taiwan. These patients had begun long-term HD at least 3 months previously and maintained the same dialysis schedule between February 1998 and July 2005. They were treated at the same unit by the same team of physicians and nurses who used biocompatible membranes (Polysulfone, F-series; Fresenius Medical Care AG & Co. KGaA, Homburg, Germany) for dialysis, including high-flux membranes (Helixone, FX-class; Fresenius Medical Care AG&Co. KGaA) once a week. All patients received ultrapure bicarbonate buffered dialysis fluid for dialysis. Ninety-eight patients were excluded for the following reasons: being bed-ridden ( $n=24$ ), using catheter-based vascular accesses ( $n=35$ ), having advanced liver cirrhosis (class C by Child's classification) ( $n=16$ ), experiencing an active infection ( $n=18$ ) or experiencing acute myocardial infarction ( $n=5$ ). Another 25 patients refused to participate. Finally, a total of 74 persons (44 men, 30 women) were enrolled and followed until December 2005. The initial frequency of HD was determined according to patients' clinical conditions by attending nephrologists. Among them, 23 were on twice-weekly HD (all used arteriovenous fistula (AVF) for vascular accesses) and 51 were on thrice-weekly HD (47 used AVF and four used arteriovenous graft (AVG)). This study was approved by the National Taiwan University Hospital research ethics committee (no. 9461701007), and written consents were obtained from all individuals or their next of kin.

### Data collection and outcome measurements

We recorded biochemical data at the beginning and the end of the study period. We collected interdialytic 3 day urine samples during non-dialysis days for measurement of RRF. Single-pool Kt/V (SpKt/V) and normalized protein catabolic rates were calculated using the second-generation kinetic urea model.<sup>6</sup> The residual glomerular filtration rate (GFR) was calculated as the arithmetic mean of urea and creatinine clearances.<sup>7,8</sup> SpKt/V was converted to equivalent urea clearance (eKru) by the Gotch adjusted model.<sup>9</sup> The weekly total Kt/V was calculated as  $(eKru + Kru)/V$ , where V was estimated by the Watson method.<sup>10</sup> Intradialytic hypotensive episodes during the study were recorded according to the following criteria: a drop of systolic blood pressure greater than 30–40 mm Hg or 25% of basal, or systolic blood pressure lower than 100 mm Hg that required a nursing intervention with i.v. fluids. We obtained baseline cardiothoracic ratios of all patients from chest radiographs, and traced any events of vascular access dysfunction and hospitalization during the follow-up period. Vascular access dysfunction was defined as inadequate flow to support the prescribed dialysis or haemodynamically significant venous stenosis requiring interventions. Serum  $\beta_2$ -microglobulin was quantified by the Latex nephelometry method (N Latex  $\beta_2$ -microglobulin; Dade Behring Marburg, Marburg, Germany; reference range, 0.7–1.8 mg/L) on the BN II systems. A highly sensitive method for C-reactive protein (CRP) measurement was performed by Latex nephelometry (N-Latex CRPII, Seiken, Tokyo, Japan).

### Statistics

Continuous variables are given as mean  $\pm$  standard deviation and compared using the Student's *t*-test. Pearson's correlation was used to examine associations between two groups. Discrete variables are presented as percentages and analyzed using the  $\chi^2$ -test. Multiple logistic regression analysis with the backward variable selection method was performed to identify predictors for maintaining twice-weekly HD at the end of observation. The explanatory variables included age, sex, body mass index (BMI), dialysis duration, residual GFR, 3 day urine output, interdialytic weight gain (IDWG), diabetes mellitus history, angiotensin II receptor blockers usage and obstructive uropathy history. Sequential elimination of variables was performed by the likelihood

ratio method to develop a final parsimonious model. We assessed calibration of the model by Cg, a goodness-of-fit statistical test described by Hosmer–Lemeshow,<sup>11</sup> and evaluated discrimination capability for dialysis frequency prediction by determination of the area under the receiver–operator curve (ROC).<sup>12</sup> All statistical analyses were performed using SPSS software, ver. 14.0 (SPSS Software, Chicago, IL, USA) and STATA statistical software, ver. 9.0 (StataCorp, College Station, TX, USA).  $P < 0.05$  was considered significant.

## RESULTS

### Study population

The baseline characteristics, comorbid illnesses and use of antihypertensive drugs of the 74 patients enrolled in this study are shown in Table 1. All twice-weekly patients and 47 (92.2%) thrice-weekly patients underwent long-term HD via the AVF, while four patients (7.8%) in the thrice-weekly group received dialysis via the AVG. The mean age of twice-weekly group was greater than that of the thrice-weekly group (72 vs 63 years old,  $P = 0.002$ ), but there were no differences between the groups in sex ( $P = 0.461$ ) and dialysis duration ( $P = 0.236$ ). Obstructive uropathy was more common in the twice-weekly group. In the twice-

**Table 1** Baseline demographics, comorbidities, and use of anti-hypertensive drugs in patients on twice-weekly (BIW) and thrice-weekly (TIW) haemodialysis

| Variable                      | BIW               | TIW               | P      |
|-------------------------------|-------------------|-------------------|--------|
| <b>Demographics</b>           |                   |                   |        |
| No. of patients               | 23                | 51                |        |
| Mean age (years)              | 72.39 $\pm$ 8.69  | 63.11 $\pm$ 15.31 | 0.007* |
| Sex (% female)                | 35                | 44                | 0.461  |
| Shunt (%AVG)                  | 0                 | 7.8               | 0.303  |
| Follow-up duration (months)** | 15.91 $\pm$ 14.86 | 20.57 $\pm$ 16.90 | 0.236  |
| <b>Comorbidities</b>          |                   |                   |        |
| Diabetes mellitus             | 17.39%            | 39.22%            | 0.106  |
| Hypertension                  | 82.61%            | 78.43%            | 0.764  |
| Severe CHF (NYHA IV)          | 8.69%             | 5.88%             | 0.643  |
| Obstructive uropathy          | 21.74%            | 1.96%             | 0.027* |
| <b>Medication use</b>         |                   |                   |        |
| Beta-blocker                  | 26.09%            | 29.41%            | 1.000  |
| $\alpha$ -blocker             | 30.43%            | 21.57%            | 0.559  |
| CCB                           | 43.47%            | 45.09%            | 1.000  |
| Diuretics                     | 13.04%            | 3.92%             | 0.170  |
| ACEI                          | 0%                | 5.88%             | 0.548  |
| ARB                           | 30.43%            | 17.65%            | 0.236  |

Data are expressed as number (%) of patients or mean  $\pm$  standard deviation for continuous variables. Discrete variables are presented as percentages and analyzed using a  $\chi^2$ -test. \* $P < 0.05$  was considered statistically significant. \*\*Follow-up duration: duration (months) since inception of dialysis. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; AVG, arterial-venous graft; BMI, body mass index; BW, bodyweight; CCB, calcium channel blocker; CHF, chronic heart failure; NYHA, New York Heart Association Classification.

**Table 2** Indices of blood chemistry, residual renal function, and dialysis adequacy in patients on twice-weekly (BIW) and thrice-weekly (TIW) haemodialysis at the end of the study

| Variable                     | BIW             | TIW             | P      |
|------------------------------|-----------------|-----------------|--------|
| Dry BMI (Kg/m <sup>2</sup> ) | 21.24 ± 2.65    | 23.03 ± 3.41    | 0.020* |
| Dry BW (Kg)                  | 53.89 ± 14.84   | 60.95 ± 10.91   | 0.049* |
| Albumin (mg/dL)              | 3.99 ± 0.25     | 4.06 ± 0.30     | 0.266  |
| nPCR (g/Kg BW/day)           | 1.37 ± 0.27     | 1.45 ± 0.25     | 0.222  |
| Cholesterol (mg/dL)          | 170.31 ± 33.73  | 177.77 ± 43.54  | 0.427  |
| Triglyceride (mg/dL)         | 133.90 ± 76.51  | 194.09 ± 173.57 | 0.039* |
| Calcium (meq/dL)             | 2.29 ± 0.22     | 2.34 ± 0.22     | 0.456  |
| Phosphorus (mg/dL)           | 5.09 ± 1.46     | 5.25 ± 1.62     | 0.667  |
| iPTH (pg/dL)                 | 230.78 ± 159.14 | 201.56 ± 172.67 | 0.480  |
| Potassium (mg/dL)            | 4.81 ± 0.78     | 4.75 ± 0.81     | 0.754  |
| Haematocrit (%)              | 32.48 ± 4.07    | 31.92 ± 3.11    | 0.561  |
| Ferritin (mg/dL)             | 382.55 ± 412.37 | 478.48 ± 578.57 | 0.414  |
| Iron (mg/dL)                 | 53.91 ± 30.01   | 58.90 ± 18.94   | 0.466  |
| TIBC (µg/dL)                 | 192.69 ± 54.42  | 208.37 ± 25.47  | 0.213  |
| hsCRP (mg/dL)                | 0.77 ± 1.51     | 0.53 ± 1.09     | 0.430  |
| β2-microglobulin (mg/L)      | 21.79 ± 8.26    | 28.71 ± 8.20    | 0.002* |
| URR                          | 77.77 ± 5.44    | 75.47 ± 6.27    | 0.114  |
| Pre-HD MAP (mmHg)            | 93.2 ± 3.3      | 114.2 ± 10.1    | 0.001* |
| Post-HD MAP (mmHg)           | 93.9 ± 1.1      | 97.2 ± 4.4      | 0.035* |
| IDWG (Kg)                    | 1.89 ± 1.20     | 2.89 ± 1.22     | 0.002* |
| Urine output (mL/3-day)      | 1667 ± 1104     | 613 ± 994       | 0.001* |
| Renal GFR (mL/min)           | 1.88 ± 1.29     | 0.71 ± 1.16     | 0.001* |
| Dialysis spKt/V              | 1.53 ± 0.26     | 1.45 ± 0.25     | 0.194  |
| Weekly dialysis Kt/V         | 2.99 ± 0.45     | 3.37 ± 0.42     | 0.002* |
| Weekly renal Kt/V            | 0.45 ± 0.35     | 0.17 ± 0.29     | 0.002* |
| Weekly Total Kt/V†           | 3.44 ± 0.66     | 3.54 ± 0.47     | 0.533  |

Data are expressed as mean ± standard deviation for continuous variables. To convert creatinine in mg/dL to µmol/L, it was multiplied 88.4; to convert BUN in mg/dL to mmol/L, it was multiplied by 0.357. \* $P < 0.05$  was considered statistically significant. †Weekly total Kt/V: sum of weekly dialysis Kt/V and weekly renal Kt/V. BUN, blood urea nitrogen; Cre, creatinine; GFR, glomerular filtration rate; HD, haemodialysis; hsCRP, highly sensitive chronic reactive protein; IDWG, interdialytic weight gain; iPTH, intact-parathyroid hormone; MAP, mean arterial pressure; nPCR, normalized protein catabolic rate; TIBC, total iron binding capacity; URR, urea reduction rate.

weekly group, two patients suffered from malignancy-related hydronephrosis and three had obscure aetiologies. In the thrice-weekly group, one patient had malignancy-related kidney disease and the other had unknown aetiology. There was no difference in the classes of antihypertensive drugs used.

## Outcomes

Table 2 shows that the twice-weekly group had lower serum β2-microglobulin ( $P = 0.002$ ), lower triglyceride ( $P = 0.039$ ), higher residual urine output ( $P = 0.001$ ), higher residual GFR ( $P = 0.001$ ) and higher weekly renal Kt/V ( $P = 0.002$ ). There was no difference between the two groups in weekly total (dialysis and renal) Kt/V, CRP, normalized protein catabolic rate, urea reduction rate, serum albumin, serum electrolytes or haematocrit. The thrice-weekly group had higher IDWG, and higher pre- and post-HD mean arterial pressure. Furthermore, patients on thrice-weekly HD experienced a faster decline in urine volume ( $P = 0.022$ ) and renal creatinine clearance/month

( $P = 0.035$ ). Chest radiographs indicated there was no difference between the two groups in changes of cardiothoracic ratio (CTR)/month (Table 3).

During the follow-up period, patients on twice-weekly HD suffered from significantly fewer intradialytic hypotensive episodes (twice-weekly group,  $0.26 \pm 0.49$  times/month; thrice-weekly group,  $1.10 \pm 1.21$  times/month;  $P < 0.001$ ). There was no difference between the two groups in the incidence of AVF dysfunction (17.39% vs 12.77%,  $P = 0.719$ ). We also found a higher incidence of AVG thrombosis in the thrice-weekly HD group (average of once/3 months). More thrice-weekly HD patients were hospitalized due to infections from any cause (thrice-weekly group, 62.71%; twice-weekly group, 31.82%;  $P = 0.012$ ) (data not shown).

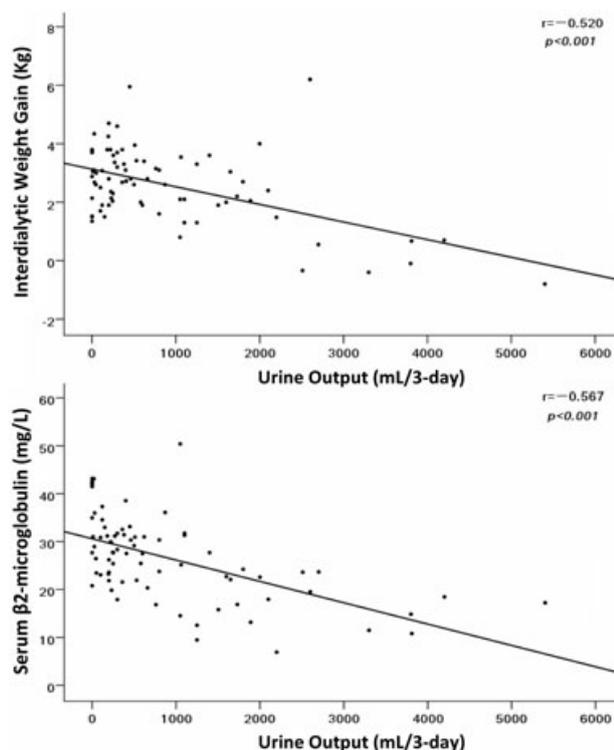
## Predictors for twice-weekly HD

The 3-day urine volume on non-dialysis days was inversely correlated with IDWG ( $r = -0.520$ ,  $P < 0.001$ ) and serum β2-microglobulin level ( $r = -0.567$ ,  $P < 0.001$ ) (Fig. 1). The independent predictors for twice-weekly HD were older age

**Table 3** Changes of creatinine clearance, urine volume, and cardiothoracic ratio in patients on twice-weekly (BIW) and thrice-weekly (TIW) haemodialysis

| Variable                | Time               | BIW             | TIW            | P       |
|-------------------------|--------------------|-----------------|----------------|---------|
| Ccr (mL/min)            | At basal           | 3.42 ± 1.36     | 4.07 ± 2.02    | 0.127   |
|                         | At the end         | 2.5 ± 1.79      | 0.96 ± 1.41    | <0.001* |
|                         | Changes per month† | -0.057 ± 0.103  | -0.355 ± 0.266 | 0.035*  |
| Urine volume (mL/3-day) | At basal           | 1072.2 ± 699.9  | 1047.7 ± 703.3 | 0.901   |
|                         | At the end         | 1551.4 ± 1094.6 | 659.5 ± 1106.0 | 0.005*  |
|                         | Changes per month† | 160.4 ± 442.2   | -20.8 ± 101.7  | 0.022*  |
| CTR (%)                 | At basal           | 52.47 ± 7.16    | 53.89 ± 7.52   | 0.451   |
|                         | At the end         | 51.31 ± 6.35    | 50.62 ± 6.89   | 0.684   |
|                         | Changes per month† | -0.15 ± 1.59    | -0.47 ± 0.95   | 0.387   |

Data are expressed as mean ± standard deviation for continuous variables and analyzed using the Student's *t*-test test. †Changes per month, the average changes/month during the follow up. \**P* < 0.05 was considered statistically significant. Ccr, residual creatinine clearance; CTR, cardiothoracic ratio.



**Fig. 1** Correlations between 3-day urine output and interdialytic weight gain (top), and serum  $\beta$ 2-microglobulin levels (bottom).

(OR, 1.866; 95% CI, 1.093–3.183; *P* = 0.022), lower dry BMI (OR, 0.790; CI, 0.625–0.999; *P* = 0.049), and higher 3 day urine volume (OR, 1.093; CI, 1.026–1.164; *P* = 0.006) (Table 4). The log odds for receiving twice-weekly HD based on the multivariable logistic regression equation was:  $(0.624) \times (\text{age/decades}) + (0.089) \times (3 \text{ days urine amount/dL}) - (0.236) \times (\text{dry BMI}) - 0.847$ . This model had a good calibration, as estimated by the Hosmer–Lemeshow goodness-of-fit test (Cg, 6.974; *P* = 0.539).

## DISCUSSION

This study shows that ESRD patients undergoing twice-weekly HD have a slower decline of RRF and less hospitalization rates, and fare similarly to thrice-weekly HD patients in terms of blood pressure and fluid control, indices of nutrition, inflammation, dialysis adequacy and vascular access dysfunction. Further analysis showed that the 3 day interdialytic urine volume correlates inversely with serum  $\beta$ 2-microglobulin levels, and is an independent predictor for maintaining twice-weekly HD.

Most studies that have addressed the issue of RRF have focused on patients undergoing long-term peritoneal dialysis (PD) rather than HD. RRF is a well-known and important predictor of mortality in patients undergoing PD.<sup>1,3,7,13–17</sup> Apart from removal of small molecular toxins, RRF contributes significantly to the clearance of middle and large molecular weight substances in PD patients.<sup>18</sup> Indeed, patients on PD with RRF have lower levels of  $\beta$ 2-microglobulin than those without RRF.<sup>19</sup>

There are fewer studies of RRF in patients on long-term HD, perhaps because that RRF tends to decline more quickly in these patients.<sup>7,8,20,21</sup> However, the presence of RRF is certainly important for patients undergoing HD. Network registry data from the USA and the Netherlands Cooperative Study on the Adequacy of Dialysis both indicate the importance of RRF for survival of HD patients.<sup>22,23</sup> HD patients with RRF are also known to have lower levels of  $\beta$ 2-microglobulin, better nutritional status and better quality of life.<sup>24–27</sup> Consistent with these studies, compared with our thrice-weekly HD group, our twice-weekly HD group had a significantly lower level of serum  $\beta$ 2-microglobulin at the end of the follow-up period. We believe this may be attributable to the higher RRF in the twice-weekly group.

From our study, patients with higher RRF on twice-weekly HD were found to experience a slower decline of residual GFR than patients having lower RRF on thrice-weekly HD. The reason for this phenomenon is not clear.<sup>7</sup> Given the detrimental effect of ischaemia on RRF, one plausible explanation is that this is related to the lower

**Table 4** Predictors for maintaining twice-weekly haemodialysis using multivariable logistic regression model

| Factor                   | Univariate |             |       | Backward logistical regression |             |       |
|--------------------------|------------|-------------|-------|--------------------------------|-------------|-------|
|                          | OR         | 95% CI      | P     | OR                             | 95% CI      | P     |
| Age (per decade)         | 1.906      | 1.162–3.124 | 0.011 | 1.866                          | 1.093–3.183 | 0.022 |
| Sex (male)               | 1.626      | 0.566–4.666 | 0.366 | –                              | –           | –     |
| BMI (Kg/m <sup>2</sup> ) | 0.813      | 0.671–0.986 | 0.035 | 0.790                          | 0.625–0.999 | 0.049 |
| Residual GFR (mL/min)    | 2.074      | 1.314–3.272 | 0.002 | –                              | –           | –     |
| Urine output (dL/3-day)  | 1.093      | 1.034–1.156 | 0.002 | 1.093                          | 1.026–1.164 | 0.006 |
| IDWG (Kg)                | 0.498      | 0.309–0.803 | 0.004 | –                              | –           | –     |
| Diabetes mellitus        | 1.171      | 0.231–5.944 | 0.849 | –                              | –           | –     |
| ARB use                  | 3.024      | 0.635–14.40 | 0.165 | –                              | –           | –     |
| Obstructive uropathy     | 0.092      | 0.010–0.844 | 0.045 | –                              | –           | –     |

ARB, angiotensin II receptor blockers; BMI, body mass index; GFR, glomerular filtration rate; IDWG, interdialytic weight gain; OR, odds ratio; 95% CI, 95% confidence interval.

incidence of intradialytic hypotensive episodes in our study.<sup>28</sup> It may also be related to the lower rate of hospitalization in our study, and consequently less exposure to nephrotoxic drugs or agents during diagnosis and treatment.<sup>20</sup>

There was no difference between the twice-weekly and thrice-weekly groups in blood pressure control, cardiothoracic ratio (chest radiographs), indices of nutrition (albumin, normalized protein catabolic rate), inflammation (CRP), dialysis adequacy (weekly total Kt/V,  $\beta_2$ -microglobulin) and vascular access dysfunction. This suggests that for a subset of patients with sufficient urine volume (and thereby RRF), long-term biweekly HD maybe sufficient to achieve a dialysis target comparable to that observed in patients with minimal RRF on thrice-weekly HD. Because biweekly HD patients receive fewer venipunctures, one might expect they would also suffer fewer events of vascular access stenosis and/or thrombosis. This, however, was not the case in our study. This may be due to the small number of cases, the limited time of observation, and/or the high level of venipuncture expertise.

Most clinical practice guidelines recommend initiating long-term renal replacement therapy for patients with chronic kidney disease when their GFR drops below 10 mL/min. However, most patients still have relatively high urine volume (i.e. RRF) even at this stage. To our knowledge, no randomized clinical trials have evaluated the optimal HD frequency for these patients. In this study, we found that the 3 day interdialytic urine volume was a powerful predictor for twice-weekly HD. Given the global epidemic of chronic kidney disease and the heavy financial burden imposed by reimbursement for long-term dialysis, our data provide preliminary evidence in support of prescribing long-term HD at a lower-than-routine frequency wherever appropriate, such as in the presence of RRF.

There were some limitations in this study. First, we only included prevalent ESRD patients, so HD frequency was not assigned randomly and the results may be biased. Moreover, this was an observational study with a small number of participants and limited follow-up period without measurement of impact on mortality. Nevertheless, our study raises the possibility that long-term HD at a lower frequency does

not jeopardize the adequacy of dialysis or affect short-term outcomes. This is consistent with the concept of 'incremental dialysis' proposed by Tattersall *et al.*<sup>29</sup> Furthermore, our study suggests that urine output on non-dialysis days is a good indicator for establishing dialysis frequency and fluid status monitoring. Further multicenter prospective randomized control trials are needed to confirm our findings.

In conclusion, our data suggest that ESRD patients with sufficient urine output may undergo twice-weekly HD without suffering from dialysis inadequacy, and that they maintain better RRF than patients on thrice-weekly HD. Given the escalating financial burden of renal replacement therapy, our results have important clinical implications.

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