

# Impact of twice- or three-times-weekly maintenance hemodialysis on patient outcomes

## A multicenter randomized trial

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### Abstract

**Aim:** Maintenance hemodialysis (MHD) frequency is associated with survival and complication rates. Achieving the optimal balance between healthcare, quality of life (QOL), and medical costs is challenging. We compared complications, inflammatory status, nutritional status, and QOL between patients with different MHD frequencies.

**Material and Methods:** This was a multicenter randomized trial of patients treated between May 2011 and August 2017 at 3 tertiary hospitals in Wenzhou. Patients were grouped according to their treatment schedule over 1 year: twice-weekly or 3-times-weekly. Complications, biochemistry parameters, and QOL (KDQOL-SFTM 1.3 scale) were assessed.

**Results:** One hundred forty patients were included aged 29 to 68 years (mean age,  $50.9 \pm 4.3$  years). There were no significant differences in infection, heart failure, or cerebral hemorrhage complications between the 2 groups ( $P = .664$ ). Pre-dialysis hemoglobin, high-sensitivity C-reactive protein, serum albumin, total cholesterol, triglyceride, calcium, phosphate, parathyroid hormone, and ejection fraction were similar in both groups ( $P > .05$ ). After 1 year of MHD, both groups exhibited significant improvements in these parameters (all  $P < .05$ ) with no significant differences between groups. Serum creatinine, blood urea nitrogen (BUN), and weekly standard hemodialysis treatment adequacy did not improve after treatment (all  $P > .05$ ), although a difference in BUN was observed between the 2 groups ( $P < .001$ ). QOL was superior in the twice-weekly group than in the 3-times-weekly group (all  $P < .05$ ), except for social support, which was slightly better in the 3-times-weekly group than in the twice-weekly group.

**Conclusions:** Twice- and 3-times-weekly MHD resulted in comparable inflammatory and nutritional clinical outcomes and adverse events. QOL was better for the twice-weekly schedule. Even for patients with economic constraints, twice- or 3-times-weekly MHD should be selected with caution after consideration of BUN levels at baseline.

**Abbreviations:** CHO = total cholesterol, EF = ejection fraction, ESRD = end-stage renal disease, HD = hemodialysis, MHD = maintenance hemodialysis, PD = peritoneal dialysis, QOL = quality of life, RRT = renal replacement therapy, TG = triglyceride.

**Keywords:** calcium-phosphorus metabolism, complications, dialysis frequency, maintenance hemodialysis, nutritional status

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The authors have no conflicts of interest to disclose.

The study was approved by the ethics committee of Rui'an People's Hospital. Each participant provided written informed consent. This study is registered at the Chinese Clinical Trial Registry (ChiCTR1800014496).

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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## 1. Introduction

End-stage renal disease (ESRD) is a symptomatic decrease in renal function for >3 months requiring renal replacement therapy (RRT).<sup>[1,2]</sup> The incidence of ESRD is increasing worldwide, attributable in part to a lengthening of lifespan in many countries as well as poorer health behaviors associated with a Western lifestyle and nutrition.<sup>[2–4]</sup> In the USA, the incidence of ESRD varies from 2.2% in white women to 8.5% in black men.<sup>[5]</sup> Based on a study of 47,204 Chinese adults, the prevalence of chronic kidney disease between 2007 and 2010 was 10.8%.<sup>[3]</sup> In 2013, the prevalence of ESRD in China was 579 per million population, and the annual mortality rate was 6.4%.<sup>[6]</sup> There is wide geographic variation in China, probably due to different levels and rates of economic development among regions.<sup>[7–10]</sup> Nevertheless, ESRD remains a major public health issue in China.

The primary management for ESRD is RRT, including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplant.<sup>[2]</sup> HD is the most commonly used RRT for ESRD due to a limited supply of donor kidneys and restricted application of PD.<sup>[2]</sup> HD brings blood into contact with dialysates in a dialysis machine through a semipermeable membrane, thereby allowing the exchange of substances along concentration gradients and

clearance of waste products and excessive electrolytes.<sup>[2]</sup> Maintenance HD (MHD) has an optimal therapeutic effect in kidney failure.<sup>[2,11]</sup> Some studies reported that the frequency of MHD was associated with patient survival.<sup>[11–13]</sup> Nevertheless, long-term dialysis impacts on nutritional status, and different dialysis frequencies likely lead to divergent incidence rates of complications.<sup>[2,11]</sup> The most serious complications relating to MHD involve cardiovascular disease, which has a high mortality rate.<sup>[14]</sup> However, unlike the general population the risk factors for cardiovascular events in MHD are markers of protein-energy malnutrition and inflammation.<sup>[14]</sup> Another important complication is infection that most often occurs in relation to the vascular access.<sup>[15]</sup> In addition, in many centers, equipment availability has to be taken into account.<sup>[11]</sup>

After new health insurance policies were issued in China, most patients have access to medical care.<sup>[16,17]</sup> Nevertheless, the annual costs of treatment prevent many patients with ESRD from receiving therapy and those that can afford treatment need to ensure that they are achieving the maximum clinical benefit for their money. Hence, these patients need to consider an optimal balance between their healthcare outcomes, quality of life (QOL), and medical costs.

Studies about dialysis frequency suffer from a number of limitations. Although some studies suggest that an increase in dialysis frequency reduces microinflammation, malnutrition, and the incidence of long-term complications and improves QOL, there remains debate about the optimal frequency.<sup>[2,11–13]</sup> Therefore, this randomized trial aimed to analyze the complications, inflammatory status, nutritional status, and QOL of patients with different MHD frequencies.

## 2. Materials and methods

### 2.1. Study design

This was a multicenter randomized trial of patients treated between May 2011 and August 2017 at the HD centers of 3 tertiary hospitals in Wenzhou: Rui'an People's Hospital, Yueqing People's Hospital and Wenzhou Hospital of Integrated TCM and Western Medicine. The study was approved by the ethics committee of Rui'an People's Hospital. Each participant provided written informed consent. This study is registered at the Chinese Clinical Trial Registry (ChiCTR1800014496).

### 2.2. Patients

The inclusion criteria were:

1. diagnosed with chronic renal failure<sup>[2]</sup>;
2. >18 years of age; and
3. regular twice- or 3-times-weekly dialysis for at least 1 year.

The exclusion criteria were:

1. diagnosed with acute renal failure;
2. once-weekly or more than 3-times-weekly dialysis for 1 year;
3. variation in HD frequency during the previous year; or
4. participation in another interventional clinical trial at the same time.

### 2.3. Randomization and blinding

The patients were randomized to twice- or 3-times-weekly MHD using a random number table prepared by an independent

statistician. Each grouping scheme was printed on carbon free copy paper and placed into an envelope. The code was written on the envelope, and the envelope was sealed and handed over to the researcher. When a subject was enrolled into the study, the patient was numbered if he/she met the inclusion criteria and exclusion criteria. Then the corresponding numbered envelope was opened, and the intervention was conducted according to the grouping scheme in the envelope. Blinding was not possible because of the nature of the intervention.

### 2.4. Dialysis

Dialysis was performed using a Rapido BLS17SD hemodialyzer (Sorin Group Italia, Mirandola, Italy) and a Polyflux 14L membrane (Baxter Healthcare, Deerfield, IL). Patients in the twice-weekly group received dialysis on Monday and Thursday, Tuesday and Friday, or Wednesday and Saturday. Patients in the 3-times-weekly group received dialysis on Monday, Wednesday and Friday, or Tuesday, Thursday and Saturday. Dialysate A contained sodium chloride, potassium chloride, calcium chloride, magnesium chloride, glacial acetic acid, and an appropriate amount of dialysis water, and dialysate B contained sodium bicarbonate with an appropriate amount of dialysis water. The dialysate flow rate was 500 mL/min, the blood flow rate was 200 to 280 mL/min, and the dialysis duration was 4 hours each time. During dialysis, the following medications were administered: oral folic acid 5 mg tid (Lisheng Pharma, Tianjin, China); calcitriol 0.25 µg daily orally or by pulse therapy (Shanghai Roche Pharmaceuticals, Shanghai, China); a phosphate binder: oral calcium acetate 0.667 g tid (Bangyu Pharmaceutical, Kunming, China), oral lanthanum carbonate 0.5 g tid (Shire Pharmaceuticals Ltd, Basingstoke, UK) or oral sevelamer 800 mg or 1600 mg tid depending on the patient's condition (Genzyme, Cambridge, MA); erythropoietin 10,000 U qw by subcutaneous injection (Epiabo injection, 3SBio Inc., Shenyang, China); and nifedipine 150 mg bid (Kremers Urban Pharmaceuticals, Seymour, IN) or intravenous injection of iron sucrose 100 mg tiw (Pude Pharmaceutical, Shanxi, China). Concomitant hypertension was treated with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-adrenoceptor blocker, clonidine, or calcium channel blocker. Concomitant hyperglycemia was managed with basen tablets (Takeda Pharmaceuticals, Tianjin, China) or novorapid flexpen 30R (Novo Nordisk (China) Pharmaceutical Co. Ltd., Beijing, China).

### 2.5. Outcomes

The primary outcomes were the occurrence of complications relating to cardiovascular events, cerebral hemorrhage, infection, and heart failure. The secondary outcomes included inflammatory status, nutritional status, MHD adequacy, and QOL of patients.

### 2.6. Adverse events

Adverse events included HD catheter-related infection and internal fistula-related bloodstream infection. The diagnostic criteria for catheter-related bacteremia were:

1. blood culture yielded positive results for both the catheter and a peripheral vein;
2. the same microorganism was detected from the catheter tip and at least 1 percutaneously drawn blood sample;

3. the same microorganism was detected from blood samples taken from 2 different peripheral veins, and no other infected foci were found.

Active prophylactics were given as needed. If infection occurred, the pathogenic bacteria were identified, and targeted antibacterial therapy was given.

### 2.7. Data collection

The doctors in the department collected the data for the study from the HD system using the patient's electronic medical record number, the data were collected from the hospital test reports from the 3 research centers at the start of the study. All data were collected during the first week of each month. HD adequacy was estimated by Kt/V every 3 months, the renal function before and after HD was collected and evaluated in the HD system. For measures of nutritional status, we evaluated the patient's hemoglobin, albumin, blood phosphorus, and other indicators in blood samples. The patient's inflammation status was obtained through monthly blood collection to evaluate CRP, and blood cell counts, and catheter blood culture was taken when the patient presented with fever and the infection results and fever were recorded. QOL was collected and assessed at the end of the study.

The following data were collected during the monthly follow-up visits during 1 year of HD: complications (death, cerebral hemorrhage, infection, and heart failure), hemoglobin level (Hb; cetyltrimethylammonium bromide method), high-sensitivity C-reactive protein (hs-CRP; immunoturbidimetry method), serum albumin (ALB), total cholesterol (CHO), triglyceride (TG), calcium and phosphate (automatic biochemical analyzer, Hitachi, Tokyo, Japan), parathyroid hormone (PTH; double antibody assay), ejection fraction (EF) based on echocardiography (DW-500 B-ultrasound machine, Dawei Medical, Jiangsu, China). The Chinese version of the KDQOL-SFTM 1.3 scale,

which has been validated,<sup>[18]</sup> was used to evaluate and dialysis-related QOL. HD treatment adequacy was evaluated by calculation of Kt/V using the equation:

$$Kt/V = -\ln(R - 0.008T) + (4 - 3.5R) \times (\Delta BW/BW)$$

where R = blood urea nitrogen (BUN) after dialysis/BUN before dialysis, T = dialysis time (h),  $\Delta BW$  = change in body weight from before to after dialysis (kg), and BW = dry body weight (kg).

### 2.8. Calculation of sample size

The incidence of cardiovascular events was the primary endpoint of this study, and calculation of the sample size was made based on a previous investigation that reported incidences of 12% for 3-times-weekly HD and 32% for twice-weekly HD.<sup>[19]</sup> Based on  $\alpha$  and  $\beta$  values of 0.05 and 0.20, respectively, and an equal number of patients in each group, it was calculated that a total of 63 patients per group were needed. Assuming a loss to follow-up of 10%, the required sample size was 70 patients in each group.

### 2.9. Statistical analysis

SPSS 19.0 (IBM Corp., Armonk, NY) was used for data analysis. Categorical data are expressed as percentages and were analyzed using the chi-squared test. Continuous data are expressed as mean  $\pm$  standard deviation and were analyzed using Student *t* test. Two-sided *P* values < .05 were considered statistically significant.

## 3. Results

### 3.1. Characteristics of the patients

A total of 428 patients were screened for inclusion between May 2011 and August 2017, but 288 patients were excluded because

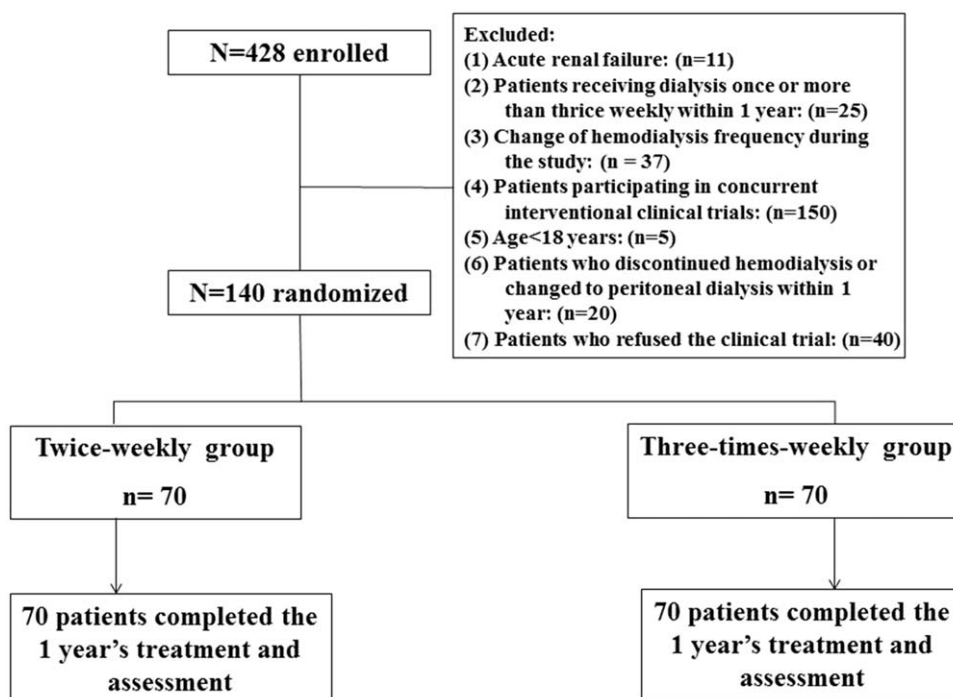


Figure 1. Flow chart showing patient enrolment.

**Table 1**  
**Characteristics of the patients before dialysis and medical costs.**

Characteristic	Twice weekly (n = 70)	Three times weekly (n = 70)	P
Age (years), mean $\pm$ SD	50.9 $\pm$ 4.3	50.6 $\pm$ 4.9	.701
Female sex, n (%)	31 (44.3%)	28 (40.0%)	.608
Body mass index (kg/m <sup>2</sup> ), mean $\pm$ SD	18.5 $\pm$ 1.7	18.4 $\pm$ 1.8	.691
Weight after dialysis (kg), mean $\pm$ SD	53.9 $\pm$ 10.1	54.6 $\pm$ 9.9	.688
Disease course (years)	6.9	9.2	<.001
Duration of end-stage renal disease, n (%)			.325
<2 yr	15 (21.4%)	10 (14.3%)	
2–5 yr	38 (54.3%)	36 (51.4%)	
>5 years	17 (24.3%)	24 (34.3%)	
Employment status, n (%)			.813
Employed	4 (5.8%)	3 (4.9%)	
Unemployed	66 (94.2%)	67 (95.1%)	
Health insurance policy, n (%)			.849
New rural cooperatives	48 (68.3%)	49 (69.9%)	
Insurance in cities and towns	21 (30.7%)	20 (29.2%)	
Cause of end-stage renal disease, n (%)			.805
Diabetic nephropathy	27 (38.6%)	26 (37.1%)	
Glomerulonephritis	29 (41.4%)	31 (44.3%)	
Hypertensive nephrosclerosis	11 (15.7%)	9 (12.9%)	
Polycystic kidney disease	1 (1.4%)	3 (4.3%)	
Other	2 (2.9%)	1 (1.4%)	
Coexisting medical conditions, n (%)			
Hypertension	61 (87.1%)	67 (95.7%)	.070
Heart failure	25 (35.7%)	24 (34.3%)	.859
Atrial fibrillation	1 (1.4%)	5 (7.1%)	.950
Stroke	3 (4.3%)	7 (10.0%)	.144
Dementia	0 (0.0%)	2 (2.9%)	.154
Diabetes and complications of diabetes	29 (41.4%)	30 (42.9%)	.181
Hemiplegia	2 (2.9%)	5 (7.1%)	.245
Chronic pulmonary disease	4 (5.7%)	9 (12.9%)	.145
Moderate or severe liver disease	1 (1.4%)	3 (4.3%)	.310
Residual kidney function, n (%)			.002
Anuria	35 (50.0%)	53 (75.7%)	
>0–1 mL/min	23 (32.9%)	15 (21.4%)	
>1–3 mL/min	12 (17.1%)	2 (2.9%)	
Diastolic blood pressure (mmHg)	158	161	.061
Dialysis access, n (%)			.604
Fistula	42 (60.0%)	45 (64.3%)	
Synthetic graft	0 (0.0%)	1 (1.4%)	
Catheter	28 (40.0%)	24 (34.3%)	
Direct medical expenses over the year (CNY), mean $\pm$ SD	83586.43 $\pm$ 62551.42	108531.72 $\pm$ 89453.21	<.001
Medical insurance payments over the year (CNY), mean $\pm$ SD	60155.25 $\pm$ 49853.15	83644.43 $\pm$ 61356.23	<.001

of acute kidney failure (n = 11), a dialysis frequency of once per week or more than 3 times weekly within the past 1 year (n = 25), changes in HD frequency during the trial (n = 37), participation in another interventional study at the same time (n = 150), age < 18 years (n = 5), discontinuation of HD or switch to PD within 1 year after starting the trial (n = 20), or unwillingness to participate in a clinical trial (n = 40). Therefore, this study included 140 patients treated between May 2011 and August 2017 (Fig. 1). The age range of the patients was 29 to 68 years (mean age, 50.9  $\pm$  4.3 years). There were 70 patients in each group with no significant differences between the 2 groups in gender, age, body mass index, weight after dialysis, employment status, health insurance, cause of ESRD, comorbidities, blood pressure, and dialysis access (all  $P > .05$ ; Table 1). Health insurance policies included new rural cooperatives and insurance in cities and towns, although a small number of patients self-paid. The cost in terms of both direct medical expenses and medical insurance over the 1 year of the

study were significantly less in the twice-weekly group compared to the 3-times-weekly group ( $P < .001$ ; Table 1).

### 3.2. MHD complications

Table 2 shows the complications of the 2 groups. There were no significant differences in complications between the 2 groups ( $P = .664$ ).

### 3.3. Nutritional and inflammation status, cardiac function, and MHD adequacy in both groups before dialysis and after 1 year of dialysis

There were no significant differences between groups in pre-dialysis nutritional markers: Hb, ALB, CHO, TG, calcium, phosphate, or PTH or the inflammation marker hs-CRP ( $P > .05$ ). After 1 year of dialysis, significant improvements in the

**Table 2**  
Cardiovascular events and adverse reactions.

	Twice weekly (n = 70)	Three times weekly (n = 70)	P
Infection	9 (12.9%)	8 (11.4%)	.796
Heart failure	2 (2.9%)	2 (2.9%)	1.000
Cerebral hemorrhage	3 (4.3%)	2 (2.9%)	1.000
Total	14 (20.0%)	12 (17.1%)	.664

Data are presented as n (%).

above parameters were observed in both groups (all  $P < .05$ ), but there were no differences between the 2 groups (all  $P > .05$ ). The pre-dialysis EF of the 2 groups was also similar ( $P > .05$ ). After 1 year of dialysis both groups showed a significant improvement in EF ( $P < .05$ ). Both groups showed no improvements in serum creatinine, BUN, or weekly standard Kt/V after treatment (all  $P > .05$ ), although a difference in BUN was observed between the 2 groups ( $P < .001$ ; Table 3).

### 3.4. Quality of life

Compared with males, females had higher scores for somatic pain, somatic function (Table 4), social support, cognitive function, and social relationship quality and lower scores for sexual function, influence on daily life, the burden of life, overall health expectation and self-evaluation of health. The twice-weekly group had higher scores than the 3-times-weekly group for all QOL items (all  $P < .05$ ) except for social support, which was slightly higher for the 3-times-weekly group than for the twice-weekly group.

## 4. Discussion

The frequency of MHD is associated with patient survival and the incidence of complications.<sup>[11–13]</sup> The optimal balance between healthcare, QOL, and medical costs is challenging to achieve.<sup>[2,11]</sup> Therefore, the present study aimed to analyze the complications, inflammatory status, nutritional status, and QOL

**Table 4**  
Quality of life.

	Twice weekly (n = 70)	Three times weekly (n = 70)	P
Somatic pain score			
Males	63.8 ± 20.2	69.4 ± 19.3	.099
Females	68.3 ± 16.6	74.7 ± 20.0	.043
Somatic function			
Males	60.2 ± 19.9	47.3 ± 14.7	<.001
Females	68.4 ± 16.4	54.6 ± 19.9	<.001
Quality of social relations	67.8 ± 14.6	66.2 ± 13.7	.518
Sexual function	51.3 ± 5.0	32.3 ± 28.7	<.001
Cognitive function	78.4 ± 16.7	67.8 ± 21.6	.002
Influence on daily life	58.5 ± 12.5	44.7 ± 13.5	<.001
Burden of life	47.3 ± 6.0	61.3 ± 7.0	<.001
Social support	94.2 ± 11.0	95.2 ± 12.0	.607
Overall health expectation	64.0 ± 27.7	59.4 ± 29.0	.345
Self-evaluation of health	59.2 ± 23.4	45.4 ± 27.0	.002
Total KDQOL score	61.0 ± 8.9	53.5 ± 9.0	<.001

Data are presented as mean ± standard deviation.  
KDQOL = Kidney Disease Quality of Life Instrument.

of patients with different dialysis frequencies. The results suggest that twice-weekly and 3-times-weekly MHD have comparable clinical outcomes and adverse event profiles. QOL was better with the twice-weekly schedule and costs were lower. The present study strongly suggests an equivalent efficacy between twice-weekly and 3-times-weekly dialysis. Nevertheless, the relevant clinical guideline recommends 3-times-weekly MHD.<sup>[2,20,21]</sup> The absence of a difference in efficacy between the 2 dialysis frequencies in the present study might be attributable to 2 factors:

1. residual renal function was better in the twice-weekly group, likely due to a randomization artifact; and
2. the included patients were younger than those usually undergoing dialysis in China (50 years in the present study vs 60 years in China).<sup>[3,6,10]</sup>

Hence, additional studies are necessary to determine the adequate dialysis frequency in a wider range of patients.

**Table 3**  
Nutritional and inflammation status, cardiac function, and maintenance hemodialysis adequacy before dialysis and at 1-year post-dialysis.

	Twice weekly (n = 70)			Three times weekly (n = 70)			P <sup>†</sup>
	Pre-dialysis	Post-dialysis	P	Pre-dialysis	Post-dialysis	P	
Hemoglobin (g/L)	72.19 ± 9.54	105.83 ± 6.56*	<.001	72.41 ± 9.56	106.32 ± 6.99*	<.001	.852
hs-CRP (mg/L)	15.78 ± 2.35	12.22 ± 2.39*	<.001	15.69 ± 2.45	11.67 ± 2.51*	<.001	.287
Albumin (g/L)	31.3 ± 4.6	38.8 ± 5.1*	<.001	31.4 ± 4.6	39.5 ± 4.9*	<.001	.467
Cholesterol (mmol/L)	3.99 ± 0.29	4.41 ± 0.34*	<.001	3.93 ± 0.25	4.55 ± 0.31*	<.001	<.001
Triglycerides (mmol/L)	0.87 ± 0.13	1.32 ± 0.12*	<.001	0.86 ± 0.12	1.45 ± 0.13*	<.001	<.001
Calcium (mmol/L)	1.46 ± 0.45	2.19 ± 0.31*	<.001	1.46 ± 0.47	2.23 ± 0.33*	<.001	.580
Phosphate (mmol/L)	2.19 ± 0.22	1.32 ± 0.27*	<.001	2.14 ± 0.25	1.39 ± 0.26*	<.001	.008
Parathyroid hormone (pg/mL)	389.3 ± 29.5	149.3 ± 12.6*	<.001	386.4 ± 28.8	149.5 ± 12.5*	<.001	.469
Serum creatinine (μmol/L)	937.5 ± 259.3	932.7 ± 377.5	.931	926.4 ± 261.4	859.8 ± 302.1	.165	.414
Blood urea nitrogen (mg/dL)	25.7 ± 6.8	27.1 ± 6.7	.213	21.5 ± 5.7	20.7 ± 5.8	.425	<.001
Weekly standard Kt/V	1.54 ± 0.03	1.53 ± 0.04	.760	1.50 ± 0.03	1.53 ± 0.05	.529	.899
Ejection fraction (%)	54.9 ± 5.6	65.2 ± 2.4*	<.001	54.7 ± 5.3	65.4 ± 2.4*	<.001	.596
Body mass index (kg/m <sup>2</sup> )	18.5 ± 1.7	17.9 ± 2.9*	.185	18.4 ± 1.8	18.5 ± 1.3*	.791	.106

Data are presented as mean ± standard deviation.

hs-CRP = high-sensitivity C-reactive protein.

\* Difference is significant between the pre and post-dialysis levels within the same group.

† Intergroup comparison of differences between pre/post-dialysis in each group.

In China, about 26% of patients on HD take the twice-weekly scheme. According to DOPPS data, China has more patients receiving twice-weekly dialysis than other countries, which might be related to their social situation.<sup>[22]</sup> This schedule is particularly common in patients who have recently started dialysis, mild disease, and unfavorable economic status and insurance coverage.<sup>[22]</sup> Twice-weekly dialysis is associated with a number of advantages such as preservation of residual kidney function,<sup>[22–24]</sup> preservation of vascular access longevity,<sup>[23]</sup> and improvement of medical resource utilization.<sup>[23]</sup> Some studies have reported a higher survival rate for a twice-weekly scheme than for a 3-times-weekly schedule.<sup>[24,25]</sup> One study from Shanghai showed that survival was similar overall for both schemes but was better in patients with a twice-weekly scheme and <5 years of dialysis.<sup>[26]</sup> On the other hand, twice-weekly HMD is associated with some disadvantages compared with a 3-times-weekly schedule (eg, inadequacy of dialysis, malnutrition, anemia, interdialytic weight gain, interdialytic hypotension, and electrolyte imbalance<sup>[23]</sup>). Other studies have observed better survival for the 3-times-weekly scheme than for the twice-weekly schedule.<sup>[27–29]</sup> An increase in dialysis frequency may give rise to more thorough and adequate dialysis, thereby improving the clinical effect. For example, a superior clinical effect was found for 3- or 4-times-weekly dialysis vs twice-weekly dialysis.<sup>[11]</sup> The present study found no differences in Hb, hs-CRP, ALB, CHO, TG, calcium, phosphate, PTH, and EF between the 2 groups before and after therapy, but each parameter improved after treatment in each group. During therapy, complications occurred in both groups, but without any differences between the 2 groups. Further analysis showed similar outcomes for twice-weekly vs 3-times-weekly HD. The exact reasons for discrepancies between studies requires additional study.

The present study found that QOL was better for twice-weekly MHD than for a 3-times-weekly schedule. This is supported by a number of studies, as reviewed by Yan et al,<sup>[23]</sup> Rhee et al<sup>[30]</sup> and Kalantar-Zadeh et al.<sup>[31]</sup> On the other hand, Bieber et al<sup>[22]</sup> showed no differences between the 2 schemes. Additional studies are necessary to address this issue. Discrepancies may be due to a number of factors, including the study population, questionnaires used, and insurance coverage.

Importantly, the results of this study show that twice-weekly MHD will lead to smaller financial burdens on patients, their families, and society in general, as compared with 3-times-weekly MHD, particularly for developing countries such as China where access to equipment may be a limitation.<sup>[11]</sup> Some patients could start on a twice-weekly scheme and be switched to a 3-times-weekly scheme when required, as suggested by Obi et al.<sup>[32]</sup> This would save money and resources for the time period during which the patients do not require more frequent treatment. Kalantar-Zadeh et al<sup>[31]</sup> suggested 10 criteria to select patients for twice-weekly HMD. For patients meeting the appropriate criteria, a twice-weekly scheme would be more appropriate than a 3-times-weekly schedule due to similar clinical outcomes but better QOL and lower medical costs.

Regarding BUN, the results suggest that although there was no significant change in BUN within each group, there was a significant difference between the changes in the 2 groups, highlighting that the BUN levels showed a rising trend in the twice-weekly group and a slight decrease in the 3-times-weekly group. So while, from a clinical point of view, short-term (1 year), twice-weekly HD did not lead to an increased

cardiovascular disease rate in the twice-weekly group, this may need further investigation. Therefore, when taking into consideration BUN levels twice-weekly HD may only be suitable in the short term.

The present study is not without limitations. The sample size was relatively small. Only a limited panel of indicators was examined, and the impact of the treatment scheme on inflammation and immune function may be interesting. In the present study, only 2 schemes were compared. The Frequent HD Network studies suggest good outcomes with MHD 6-times-weekly.<sup>[33,34]</sup> The patients from the 3 centers were treated as 1 group for randomization and we did not perform subgroup analysis to determine differences in outcomes at the different centers, so this may have included some bias in the study. Additional studies are necessary to determine the optimal MHD scheme in patients with ESRD.

The strengths of the study include the inclusion of patients from 3 different hospitals in China, the randomization of the patients to the groups, and the 1 year follow up. The clinical implications of the study suggest that using twice weekly HD can be considered for patients with financial constraints.

In conclusion, the results suggest that twice- and 3-times-weekly MHD had comparable outcomes in terms of nutritional and inflammation status, cardiac function, MHD adequacy, and adverse event profiles. However, QOL was better with the twice-weekly schedule. Nevertheless, even for patients with economic constraints, twice- or 3-times-weekly HD should be selected with caution, and BUN levels at baseline should be taken into consideration.

## Author contributions

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