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Twice against thrice-weekly hemodialysis (TATH): a multicenter nonrandomized trial

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Abstract

Background The optimal frequency of maintenance hemodialysis remains a subject of debate. In many countries, twice-weekly hemodialysis is still commonly practiced. This trial aimed to compare the outcomes of patients undergoing twice-weekly versus thrice-weekly hemodialysis.

Methods This prospective, multicenter, nonrandomized trial included incident adult patients, with chronic kidney disease stage 5, initiating hemodialysis between January 2018 and August 2021. Patients were allocated to either a twice-weekly or thrice-weekly regimen, and monitored at 1, 3, 6, 12 and 24 months. This trial was terminated before reaching the required sample size due to the COVID-19 pandemic and economic factors. Recruitment achieved 25% of the projected number. Missing baseline factors were imputed using multiple imputation algorithms, then entered in a logistic regression model to estimate propensity scores. The primary outcome was two-year survival analyzed using a Cox regression survival model adjusted for propensity scores and baseline residual urine output. Secondary outcomes included hospitalization rates, uncontrolled hypertension and cumulative erythropoietin dose at two years, analyzed using regression models adjusted for propensity scores and baseline residual urine output. All analyses were conducted on an intention-to-treat basis.

Results A total of 132 patients on thrice-weekly hemodialysis and 71 on twice-weekly hemodialysis were included. The mean age was 67 ± 15 years and the median eGFR at dialysis initiation was 6 (4,8) mL/min/1.73 m^2. At one year, patients in the twice-weekly group had greater residual urine output. At two years, there was no significant difference in survival (HR = 0.84; 95% CI: 0.37, 1.90), hospitalization rates ($P = 0.515$) or uncontrolled hypertension ($P = 0.442$). The twice-weekly group showed a trend toward higher erythropoietin requirements ($P = 0.08$). Serum potassium levels and the number of antihypertensive medications were greater in the twice-weekly group.

Conclusions Patients on twice-weekly hemodialysis showed comparable overall survival at two years to those on thrice-weekly hemodialysis. While a twice-weekly regimen may be a viable option during the first year of dialysis, especially in low-resource settings, it carries potential risks that necessitate careful monitoring after the first year.

Trial registration The trial was registered on ClinicalTrials.gov on January 16, 2018 (Identifier NCT03415776).

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Introduction

Hemodialysis is the most commonly prescribed kidney replacement therapy for patients with kidney failure [1]. Over the past five decades, this technology-dependent treatment has undergone significant advancements, all focused on enhancing patient outcomes. These innovations have primarily focused on enhancing water purification systems, membrane permeability and biocompatibility, dialysate composition and hemodialysis dosing [2]. However, the optimal frequency of hemodialysis sessions per week remains a subject of ongoing debate, shaped by evolving scientific evidence, patient quality of life considerations, and patient concerns about increased dependence on a machine.

One of the earliest studies comparing twice- versus thrice-weekly hemodialysis was published in 1999 [3]. This retrospective analysis, which included 15,067 patients from the United States, found no significant difference in survival between the two groups [13]. Despite this, in most developed Western and Asian countries, maintenance hemodialysis is performed three times per week, following clinical practice guidelines [4]. In 2007, the European Renal Best Practice guideline recommended thrice-weekly hemodialysis with sessions lasting between three and five hours [5]. This treatment regimen is designed to achieve dialysis adequacy, typically defined as a urea reduction ratio greater than 65% and/or a single pool KT/V exceeding 1.2 [4, 6]. However, it is important to note that the widespread adoption of thrice-weekly hemodialysis occurred without supporting evidence from randomized clinical trials. The preference for thrice-weekly dialysis is primarily driven by concerns regarding dialysis adequacy and the potential risks associated with twice-weekly sessions, such as malnutrition, anemia and intradialytic hypotension [7]. Several cohort studies have also suggested a survival advantage for thrice-weekly over twice-weekly hemodialysis, particularly when the total weekly dialysis duration in the twice-weekly schedule was less than eight hours [8–10]. On the other hand, incremental hemodialysis has gained increasing attention in the past decade. This approach begins with twice-weekly dialysis for patients who still have substantial residual kidney function and transitions to a thrice-weekly schedule, typically after an average of three months, based on residual kidney function [11]. A large retrospective study from the United States found that, compared to conventional thrice-weekly hemodialysis, incremental hemodialysis was associated with improved survival in patients with a renal urea clearance ≥ 3 ml/min/1.73 m2 or urine output exceeding 600 ml/day [11]. The rationale behind incremental hemodialysis is that preserving residual kidney function can lead to better long-term outcomes [12]. However, successful implementation of this approach requires close monitoring of residual kidney function to ensure timely transition to thrice-weekly dialysis when necessary.

In both developing and some developed countries, a twice-weekly hemodialysis schedule -independent of incremental dialysis and residual kidney function- continues to be implemented. This is often due to resource limitations or, in some cases, patients' reluctance to undergo three sessions per week [7, 13, 14]. Several studies have reported that patients on twice-weekly hemodialysis without residual kidney function have lower survival rates compared to those receiving thrice-weekly treatment [7]. Furthermore, a recent observational study from Korea found that even among patients with residual kidney function, those on a twice-weekly schedule had higher mortality than those on thrice-weekly hemodialysis [10]. Given these conflicting findings, it remains uncertain whether patients should continue to have the option of twice-weekly hemodialysis. This study aimed to address this question by comparing the long-term survival outcomes of patients undergoing twice- versus thrice-weekly hemodialysis.

Methods

Study design

This is a nonrandomized multicenter clinical trial. Following extensive discussions among co-investigators, randomization was deemed unfeasible. Consequently, patient allocation was determined through shared decision-making between the nephrologist and the patient. The nephrologist informed the patient that health authorities recommended thrice-weekly hemodialysis but also highlighted that several kidney teams worldwide initiate treatment with a twice-weekly schedule. To minimize attrition, crossover between treatment schedules was permitted during follow-up.

The primary objective of this study was to assess the equivalence of the two hemodialysis schedules in terms of survival outcomes. Patients were nonrandomly assigned to one of two groups on their agreement with the treating nephrologist:

- Group 1 received three hemodialysis sessions per week.
- Group 2 received two hemodialysis sessions per week.

Study setting

Hemodialysis patients were recruited from ten Lebanese hemodialysis centers (Table S1 in Additional File 1). As of early 2018, Lebanon had approximately 4,000 patients undergoing maintenance hemodialysis across 77 dialysis units. In 2014, health authorities recommended that all patients on maintenance hemodialysis receive treatment with ultrapure water and undergo three sessions per week [15]. However, many nephrologists continued to permit the twice-weekly schedule when it was more convenient for patients, especially starting in late 2019 with the onset of the economic crisis, followed by the COVID-19 pandemic [16]. Additionally, other forms of kidney replacement therapy were not widely accessible in Lebanon; only 4% of patients were receiving peritoneal dialysis and kidney transplantation largely relied on living donors [16]. Given these circumstances, Lebanon presented a compelling setting to investigate the difference in outcomes between the two hemodialysis schedules.

Participants and eligibility criteria

We included all incident patients aged 18 years and older with stage 5 chronic kidney disease who initiated hemodialysis between January 2018 and August 2021. Patients with late-stage cancer and those who were terminally ill, defined as having an expected survival of less than three months, were excluded from the study.

Variables and data collection

Data capture was conducted using the CASTOR® eCRF (electronic case report form) (https://data.castoredc.com). All investigators had online access to the eCRF to enter baseline and follow-up variables, as well as all study outcomes.

Baseline data collection

At dialysis initiation, patient data was extracted from medical records, including demographics, comorbidities, laboratory results, medications and first dialysis prescriptions.

Demographics and comorbidities

Included age, gender, body mass index (BMI), diabetes, smoking, hypertension, hyperlipidemia, cause of kidney failure, previous cardiovascular disease, atrial fibrillation, dementia and gout.

Laboratory

Included serum creatinine (with corresponding estimated glomerular filtration rate (eGFR) using the CKD-EPI equation), phosphate (mg/dL), calcium (mg/dL), albumin (g/L), potassium (mmoL/L), sodium (mmoL/L), bicarbonate (mmoL/L), hemoglobin (g/dL), parathyroid hormone (PTH), alkaline phosphatase, ferritin (ng/mL), transferrin saturation (TSAT) (iron/total iron-binding capacity), uric acid (mg/dL), hepatitis B and hepatitis C serologies.

Residual urine output

Was assessed by collecting the 24 h-urine at dialysis initiation.

Medications

Included statins, calcium-based and non-calcium-based phosphate binders, vitamin D, antihypertensive medications, antiplatelet agents, erythropoiesis-stimulating agents (ESA) dose (mainly erythropoietin alfa), renin-angiotensin system (RAS) inhibitors and oral anticoagulants.

Dialysis prescription

Included weekly dialysis hours, blood flow and dialysate flow rates, type of vascular access (catheter, graft or arteriovenous fistula), dialysis membranes (surface area, low-flux or high-flux), dialysate potassium and calcium concentrations.

Data monitoring at 1, 3, 6, and 12 months

Laboratory measurements

At 1, 3 and 12 months: Hemoglobin, urea reduction ratio, serum calcium, phosphate, potassium and sodium.

At 3 months: Additional measurement of serum bicarbonate.

At 3 and 12 months: Serum albumin, PTH, ferritin and TSAT.

All laboratory measurements were performed using standard laboratory techniques.

Medications

Medications were adjusted to maintain serum calcium, phosphate and PTH within the target range. The cumulative erythropoietin (EPO) dose, as well as doses of alfacalcidol, cinacalcet, phosphate binders and antihypertensive treatments were recorded at 1, 3, 6 and 12 months.

Clinical data

At 1, 3, 6 and 12 months, the following clinical parameters were documented: pre-dialysis systolic and diastolic blood pressure (BP), average interdialytic weight gain, hospitalizations' number, causes of hospital admissions (myocardial infarction, angina, atrial fibrillation, pulmonary edema, hyperkalemia) and residual urine output.

Outcomes at two years

Primary outcome

- All-cause mortality at two years.

Secondary outcomes

- Cumulative number of hospitalizations at two years.
- Hospitalisations for hyperkalemia and pulmonary edema at two years.
- Uncontrolled severe hypertension at two years.
- Total cumulative ESA dose administered at two years.

Definitions

Coronary artery disease was defined as a history of myocardial infarction or obstructive coronary artery disease, managed either medically or surgically. Diabetes and hypertension were defined based on a history of treatment with antidiabetic or antihypertensive medications, respectively. Uncontrolled severe hypertension was defined as an average pre-dialysis BP exceeding 160/90 mmHg over the last three dialysis sessions. Sudden cardiac death was attributed to patients who died of an unknown cause between two dialysis sessions.

Sample size

Given that the two-year mortality rate in hemodialysis patients ranges between 10% and 40%, we estimated the required sample size using a two-sided alpha of 5%, a power of 80% and a small effect size (Cohen's d = 0.20). Based on these parameters, the total sample size needed was calculated to be 806 patients. To account for an anticipated attrition rate of 10%, the adjusted sample size was set at 896 patients, with 600 patients in the thrice-weekly hemodialysis group and 300 patients in the twice-weekly group.

Participant timeline, recruitment and study termination

Patient recruitment progressed steadily during the first two years but significantly slowed by late 2019 due to the economic and social turmoil in the country. The trial was ultimately terminated early before reaching the target sample size due to multiple challenges: 1-the COVID-19 pandemic which disrupted healthcare services and patient enrollement, 2- a severe economic crisis, limiting resources and impacting patient follow-up, 3-some dialysis units that initially approved the protocol later withdrew their participation, as they were hesitant to deviate from the health authority's recommendation for thrice-weekly hemodialysis.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 25.0. Continuous variables are presented as means ± standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if not. Categorical variables are reported as counts and percentages.

Differences between study groups were assessed using the χ^2 tests for categorical variables. The independent t-test was used for normally distributed continuous variables, while the Mann-Whitney U test was applied for non-normally distributed continuous variables. Missing baseline factors and covariates were imputed using multiple imputation (MICE, multiple imputation chained equations). Five imputed datasets were generated and analyzed. To adjust for potential confounders, propensity scores for group allocation (twice-weekly vs. thrice weekly hemodialysis) were derived using logistic regression, incorporating baseline factors and covariates as predictors. To evaluate differences in survival between the two dialysis schedules, we used a Cox-regression model including propensity score and baseline residual urine output as covariates. A logistic regression model, adjusted for propensity score and baseline residual urine output, assessed differences in severe uncontrolled hypertension at two years. A Poisson regression model, adjusted for the same covariates, was used to compare hospitalization rates between the two groups. A linear regression model, adjusted as well for propensity score and baseline residual urine output, was used to compare cumulative EPO dose requirements between the two groups.

All analyses were conducted on an intention-to-treat basis. A two-sided P-value ≤ 0.05 was considered statistically significant.

Ethical approval and consent to participate

The study was approved by the ethics committee of Hotel Dieu de France/Saint-Joseph University (CEHDF 1114) and was conducted in agreement with the Helsinki Declaration of 1975. All included patients gave their written informed consent.

Study registration

The trial was registered on ClinicalTrials.gov (Identifier NCT03415776) on January 16, 2018.

Results

Consort flow diagram

Figure 1 illustrates the flow diagram detailing patient inclusion. The loss to follow-up was 4% in the twice-weekly group and 11% in the thrice-weekly group. Loss to follow-up was primarily due to patients being transferred to another dialysis unit. Four patients in the thrice-weekly group transitioned to the twice-weekly regimen while nine patients in the twice-weekly group switched to the thrice-weekly regimen.

Baseline characteristics of patients

A total of 203 consecutive patients from 10 dialysis units were included in the study, with 132 patients in the

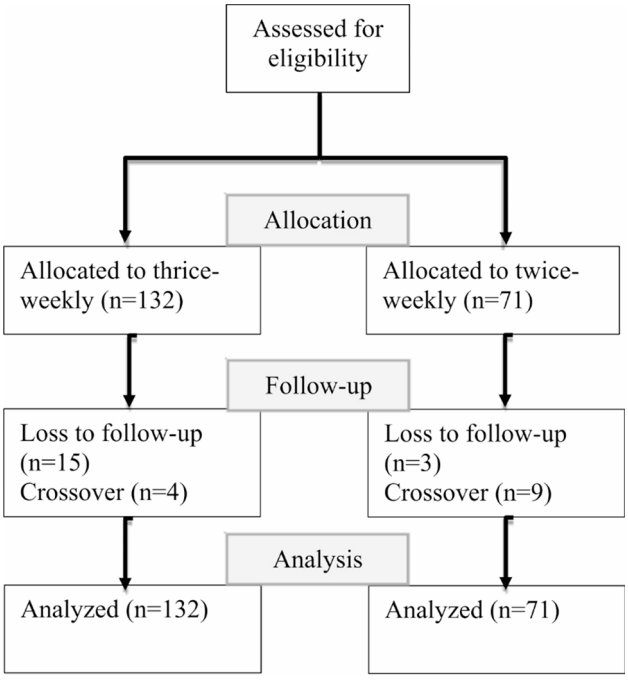

Fig. 1 CONSORT flow diagram

thrice-weekly hemodialysis group and 71 in the twice-weekly group (Table 1). The mean age of participants was 67 ± 15 years, and 54.2% were male. Notably, 41% of patients in the twice-weekly group were engaged in professional activities compared to 25.2% in the thrice-weekly group.

At dialysis initiation, median eGFR was 6 (4,8) mL/min/1.73 m^2, and median 24-hour urine output was 500 (500, 1000) mL.

Regarding dialysis treatment duration, the median weekly dialysis hours were 12 (10, 12) in the thrice-weekly group and 8 (8, 9) in the twice-weekly group.

Parameters at follow-up

Tables S2 and S3 in Additional File 1 provide a comprehensive summary of all laboratory and clinical parameters collected at one month, three months, six months and one year for both study groups. At one year, the mean hemoglobin level was 11.1 ± 1.2 g/dL in the thrice-weekly group and 11 ± 1.4 g/dL in the twice-weekly group, the median ferritin level was 496 (296, 765) ng/mL in the thrice-weekly group and 348 (202, 462) ng/mL in the twice-weekly group. At one year, the urea reduction was 73 ± 7.8% in the thrice weekly group and 73.2 ± 7.7% in the twice-weekly group. At one year, the mean inderdialytic weight gain was 2.5 ± 1.1 kg in the thrice-weekly group and 2.6 ± 1.2 kg in the twice-weekly group. At one year, the mean pre-dialysis systolic BP was 141 ± 25 mmHg in the thrice-weekly group and 145 ± 20 mmHg in the twice-weekly group while the mean diastolic BP was 74 ± 14 mmHg in the thrice-weekly group and 76 ± 14 in the twice-weekly group.

Primary outcome: survival at two years

At two years, 46 out of 203 patients had died, with 31 (23.5%) in the thrice-weekly group and 15 (21.1%) in the twice-weekly. There was no significant difference in cumulative survival between the two hemodialysis schedules (HR = 0.84, 95% CI: 0.37, 1.90) (Fig. 2). The causes of death are summarized in Table 2.

Secondary outcomes

Table 3 presents a comparison of hospitalization rates, the prevalence of uncontrolled hypertension at two years and the cumulative EPO dose between patients on twice-weekly and thrice-weekly hemodialysis, after adjusting for the propensity score and baseline residual urine output in the respective models. There was no significant difference in hospitalization rates ($P = 0.515$) or uncontrolled hypertension ($P = 0.442$) at two years. The twice-weekly group showed a trend toward higher erythropoietin requirements ($P = 0.08$). Hospitalizations for hyperkalemia were rare with one case reported in the twice-weekly group. Hospitalizations for pulmonary edema occurred in three patients - two patients in the twice-weekly group and one in the thrice-weekly group.

Post hoc analyses

Sudden cardiac death

At two years, sudden cardiac death accounted for 16.1% of deaths in the thrice-weekly group and 53.3% in the twice-weekly group (Table 2). Most of sudden cardiac deaths occurred in the second year in the twice-weekly group (7 events). However, in a multivariable logistic regression analysis adjusting for the propensity score, twice-weekly hemodialysis was not significantly associated with an increased risk of sudden cardiac death (OR = 2.84, 95% CI: 0.55, 14.72; $P = 0.211$).

Residual urine output

At two years, the median 24-hour residual urine output was 100 (0, 500) mL in the thrice-weekly group and 200 (50, 500) in the twice-weekly group ($P = 0.202$).

Serum potassium

At one year, the mean serum potassium level was 4.8 ± 0.7 mmoL/L in the thrice-weekly group and 5.2 ± 0.6 mmoL/L in the twice-weekly group (Table S2 in Additional File 1). Multivariable linear regression analysis adjusting for the propensity score confirmed that twice-weekly dialysis was significantly associated with increased serum potassium at one year (Table S4 in Additional File 1).

Table 1 Baseline characteristics of patients

Variable	Thrice-weekly *N* = 132	Twice-weekly *N* = 71	*P*
Demographics and comorbidities			
Age, years	68 ± 15	64 ± 14	0.111
Sex, M/F	71/61 (53.8/46.2)	39/32 (54.9/45.1)	0.884
Smoking	37 (30.1)	16 (24.2)	0.404
Married	113 (88.3)	54 (87.1)	0.999
Worked	31 (25.2)	25 (41)	0.041
Weight, Kgs	71.2 ± 17.4	74.3 ± 19.2	0.284
Height, cm	167 ± 9	167 ± 10	0.864
Cause of end-stage kidney disease			
Diabetes	71 (53.8)	29 (40.8)	0.105
Hypertension	25 (18.9)	28 (39.4)	0.002
Glomerulonephritis	10 (7.6)	7 (9.9)	0.601
Polycystic kidney disease	5 (3.8)	5 (7)	0.324
Chronic tubulointerstitial nephropathy	2 (1.5)	3 (4.2)	0.346
Chronic obstructive nephropathy	2 (1.5)	4 (5.6)	0.186
Other	9 (6.8)	5 (7)	0.999
Unknown	23 (17.4)	10 (14.1)	0.559
Diabetes	75 (58.1)	36 (50.7)	0.373
Hypertension	114 (88.4)	64 (90.1)	0.816
Hyperlipidemia	94 (73.4)	40 (57.1)	0.026
Dementia	9 (7)	4 (5.6)	0.775
Coronary artery disease	63 (48.5)	24 (34.8)	0.073
Atrial fibrillation	13 (10)	10 (14.5)	0.359
Hepatitis B	0 (0)	1 (1.4)	0.351
Hepatitis C	2 (1.5)	1 (1.4)	0.999
Gout	3 (2.3)	4 (5.6)	0.248
Laboratory parameters			
Serum creatinine, mg/dL	7.8 ± 3.2	8.2 ± 2.9	0.463
CKD-EPI 2012 eGFR, mL/min/1.73 m^2	6 (4.6, 8)	5.9 (4, 8)	0.680
Serum urea, mg/dL	183.7 ± 101.6	156.9 ± 84.1	0.064
Serum potassium, mmoL/L	4.5 ± 0.8	4.6 ± 1	0.744
Serum sodium, mmoL/L	135 ± 4.5	134.9 ± 5.7	0.807
Serum bicarbonate, mmoL/L	20.8 ± 4.6	20.2 ± 5.5	0.366
Hemoglobin level, g/dL	9.6 ± 1.5	9.4 ± 1.6	0.383
Ferritin, ng/mL	188 (110, 305)	211 (114, 335)	0.383
TSAT, %	18 (12, 27)	19.4 (14.3, 25)	0.765
Serum calcium, mg/dL	8.4 ± 0.8	8.4 ± 1.1	0.974
Serum phosphate, mg/dL	5.9 ± 1.9	6 ± 1.8	0.781
PTH, pg/mL	260 (139, 406)	194 (144, 540)	0.717
Serum albumin, g/L	33 (30, 37)	34 (29, 39)	0.548
Serum uric acid, mg/dL	7 (5.1, 8.4)	6.7 (5.1, 7.9)	0.448
Alkaline Phosphatase, UI	79 (60, 136)	73 (59, 105)	0.278
Clinical parameters			
24-hour urine output, mL	500 (475, 1000)	500 (500, 1000)	0.075
Pre-dialysis SBP, mmHg	143 ± 36	140 ± 36	0.643
Pre-dialysis DBP, mmHg	73 ± 19	72 ± 21	0.670
Medications			
Number of antihypertensive drugs	2 ± 1.4	2.6 ± 1.5	0.005
RAS inhibitors	10 (7.9)	7 (10)	0.792
Statins	67 (52.8)	30 (42.9)	0.234
Antiplatelets	62 (48.8)	33 (47.1)	0.882
Vitamin K Antagonists	11 (8.7)	6 (8.6)	0.999
Calcium-based phosphate binders	101 (78.9)	47 (66.2)	0.062
Non-calcium-based phosphate binders	25 (19.7)	19 (26.8)	0.286
Alfaclcidol dose per week	0.75 (0, 1.75)	1.75 (0, 3)	0.081
Epoetin alfa dose per week	4000 (4000, 12000)	8000 (2000, 12000)	0.211
Oral iron	28 (22)	10 (14.3)	0.195
Intravenous iron	48 (37.5)	24 (33.8)	0.646
Dialysis prescription			
Initiation with AV fistula	50 (38.8)	33 (47.1)	0.368
Initiation with permanent catheter	35 (27.1)	17 (24.3)	0.737
Initiation with temporary catheter	46 (35.7)	21 (30)	0.437
Total dialysis hours per week	12 (10, 12)	8 (8, 9)	< 0.001
High-flux membrane	72 (54.5)	53 (74.6)	0.006
Blood flow, mL/min	329 ± 77	292 ± 65	0.001
Dialysate calcium	18 (14.2)	35 (49.3)	< 0.001
1.25 mmoL/L	102 (80.3)	33 (46.5)	
1.5 mmoL/L	7 (5.5)	3 (4.2)	
1.75 mmoL/L			
Dialysate potassium	4 (3)	2 (2.8)	< 0.001
1 mmoL/L	2 (1.5)	0	
1.5 mmoL/L	104 (78.8)	39 (54.9)	
2 mmoL/L	16 (12.1)	28 (39.4)	
3 mmoL/L	3 (2.3)	2 (2.8)	
4 mmoL/L			
Dialysate flow	72 (54.5)	62 (87.3)	< 0.001
500 mL/min	0	2 (2.8)	
600 mL/min	42 (31.8)	4 (5.6)	
700 mL/min	16 (12.1)	3 (4.2)	
800 mL/min			

Number of antihypertensive drugs

The mean number of antihypertensive drugs was 1.57 ± 1.1 in the thrice-weekly group and 2.23 ± 1.3 in the twice-weekly group. Multivariable linear regression analysis adjusting for propensity score showed that twice-weekly dialysis was significantly associated with a higher number of antihypertensive drugs at one year (Table S5 in Additional File 1).

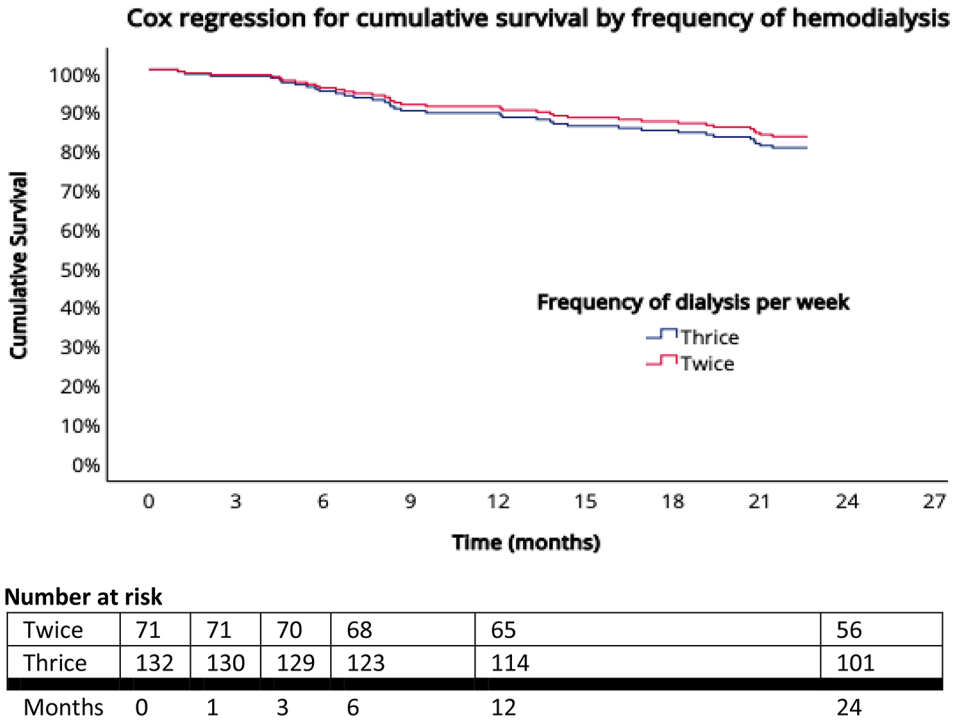

Fig. 2 Survival analysis of patients on twice- against thrice-weekly hemodialysis

Table 2 Causes of death in the two groups

Cause of death	Thrice-weekly (*n* = 31)	Twice-weekly (*n* = 15)
Cardiovascular disease	3 (9.7)	0 (0)
Sudden cardiac death	5 (16.1)	8 (53.3)
Infection	12 (38.7)	4 (26.7)
Stroke	3 (9.7)	0 (0)
Cancer	1 (3.2)	1 (6.7)
Other	3 (9.7)	1 (6.7)
Hyperkalemia	2 (6.5)	0 (0)
Unknown	2 (6.5)	1 (6.7)

Table 3 Secondary outcomes at two years

Variable	Thrice-weekly	Twice-weekly	*P**
Uncontrolled hypertension	17 (20.7)	9 (18.4)	0.442
Cumulative EPO dose	500,000 (335000, 700000)	720,000 (520000, 822000)	0.088
Hospitalization	8 (4, 14)	5 (2, 15)	0.515

(*) *P*-values are derived from multivariable models (logistic, linear, Poisson, respectively) accounting for baseline imbalance by including propensity scores and baseline residual urine output as covariates

Discussion

This trial showed that overall survival and hospitalization rates did not differ between incident patients on twice- weekly and thrice-weekly hemodialysis after two years of follow-up. These findings align with a 2022 systematic review by Moorman et al., which analyzed 21 cohort studies and found no significant difference in survival or hospitalization risk between the two dialysis schedules [17]. Notably, Moorman et al. emphasized the lack of randomized clinical trials addressing this issue and the paucity of high-quality data [17], which is surprising given that maintenance hemodialysis has been provided to over 2 million patients worldwide for more than 50 years. This raises critical questions about the feasibility of randomization when comparing long-term survival between twice- and thrice-weekly hemodialysis. Furthermore, this systematic review revealed that previous prospective studies were generally low-quality and often included prevalent rather than incident hemodialysis patients, with short follow-up periods (less than one year) and high attrition rates [17]. To our knowledge, our study is the only prospective trial that included more than 50 incident patients on twice-weekly hemodialysis with a follow-up period of two years.

Despite the similar overall survival rates in both groups, our study revealed a higher incidence of sudden cardiac death in the twice-weekly schedule during the second year of follow-up. However, when adjusted for the propensity score, the cumulative rate of sudden cardiac death was not significantly different between the two groups. In contrast, a greater proportion of patients on thrice-weekly dialysis died from infections, which is not unexpected given that patient recruitment and follow-up occurred during the COVID-19 pandemic. Importantly, sudden cardiac death accounted for 53% of all deaths in the twice-weekly group, a notably higher proportion than

previously reported in other trials [18]. The pathophysiology of sudden cardiac death is well established, involving a vulnerable myocardium triggered by arrhythmia [18]. In a 2012 analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS), Jadoul et al. identified several factors associated with sudden cardiac death in hemodialysis patients across the United States, Canada, Europe, Australia and New Zealand, and Japan [19]. One of these factors was lower Kt/V, a measure of dialysis adequacy [19]. In our study, patients on twice-weekly received 8 h of dialysis per week compared to 12 h in the thrice-weekly group, while maintaining similar urea reduction ratios at various follow-up points. Consequently, the twice-weekly dialysis patients very likely had a lower weekly Kt/V, which might have contributed to the higher incidence of sudden cardiac death observed and is consistent with the findings of the DOPPS study.

Consistent with numerous published studies, residual urine output was better preserved at one year in the twice-weekly group compared to the thrice-weekly group. However, our data collection did not include residual urea clearance or renal Kt/V. Nevertheless, based on the systematic review by Moorman et al., the preservation of residual kidney function was aligned with residual urine output and was consistently observed in patients initiated on twice-weekly hemodialysis across eight studies [17]. Preserving residual kidney function is a key therapeutic goal in both hemodialysis and peritoneal dialysis, as it helps reduce dialysis requirements and enhance patients' quality of life [20]. This principle is fundamental to the incremental dialysis approach [20–22]. A multicenter feasibility randomized trial in incident hemodialysis patients with urea clearance ≥ 3 mL/min/1.73 m^2 compared 26 thrice-weekly patients to 21 on incremental dialysis and found a higher preservation of urea clearance above 2 mL/min/1.73 m^2 at six months in the incremental dialysis group [21]. Moreover, two recent meta-analyses, including multiple cohort studies along with two to four randomized clinical trials, found no significant differences in mortality between incremental and thrice-weekly dialysis but reported lower hospitalization rates in patients receiving incremental dialysis [23, 24].

Interestingly, in our trial, patients on twice-weekly hemodialysis required a higher number of antihypertensive medications throughout the entire follow-up period. We hypothesize that less frequent dialysis may lead to greater sodium retention. However, the percentage of patients with uncontrolled hypertension at two years did not differ between the two groups. To our knwoledge, no previous prospective trial has specifically compared the number of antihypertensive drugs used in patients on twice-weekly versus thrice-weekly hemodialysis. However, the most recent systematic review comparing conventional and incremental dialysis found a reduced incidence of intradialytic hypotension in the twice-weekly group, likely reflecting the higher blood pressure levels in these patients [24]. Future trials may need to investigate the left ventricular hypertrophy in patients undergoing twice-weekly versus thrice-weekly dialysis. One possible explanation for the higher rate of sudden cardiac death observed in the second year of follow-up in our twice-weekly group of patients could be related to the left ventricular mass.

Regarding biochemical markers, our study found higher serum potassium levels in the twice-weekly group and no difference in hemoglobin levels between the two groups at one year. Unsurprisingly, serum potassium levels increase as residual urine output decreases. In studies of incremental hemodialysis, hyperkalemia has been a leading reason for patients transitioning from twice to thrice-weekly dialysis [25]. Additionally, despite similar hemoglobin levels, patients in the twice-weekly group required higher doses of erythropoietin during the two-year follow-up to maintain hemoglobin levels comparable to those in the thrice-weekly group. The literature on anemia management in twice-weekly dialysis is mixed; two out of six studies included in the meta-analysis of Moorman et al. reported lower hemoglobin levels in the twice-weekly group, though they did not provide data on cumulative erythropoietin doses [17]. Notably, patients in the twice-weekly group of our trial had consistently lower ferritin levels throughout the follow-up, which may explain the increased erythropoietin requirements in this group.

Finally, our study did not collect data on health-related quality of life. However, the baseline characteristics of our patients revealed that a higher percentage of individuals, in the twice-weekly group, maintained employment. We believe this is a significant factor influencing patients' decision to choose twice-weekly hemodialysis. By enabling a safe twice-weekly dialysis schedule, patients gain one additional working day per week or 56 extra days per year, which can greatly enhance their quality of life. This is particularly important when considering the social well-being of patients. The health system in Lebanon, like in many other countries, provides universal coverage for the cost of dialysis sessions but does not cover transportation expenses or compensate for lost productivity. Moreover, reducing the number of dialysis sessions by 56 per year per patient could have a substantial impact on the overall societal cost of hemodialysis, especially in low resource settings. The cost-saving benefit of incremental dialysis has been highlighted in a systematic review by Caton et al. [23] and further supported by a French report by Torreggiani et al., which demonstrated a 16% reduction in costs with the use of incremental dialysis [26].

The main strength of our study lies in its long follow-up duration and the substantial amount of data collected, which surpasses previous studies comparing twice-weekly and thrice-weekly hemodialysis regimens. However, there are several limitations to consider. The first limitation is the absence of randomization, which resulted from the individual preferences of both the principal investigators and the patients. To address this, we employed the propensity score analysis to mitigate the lack of randomization. Furthermore, we opted to include the propensity score as a covariate in the regression models instead of other propensity score strategies (Stratification, Matching, IPTW). This decision allowed us to retain all observations and thereby maximizing statistical power. The propensity score model included all baseline characteristics, capturing a significant portion of the baseline information and helping to address the imbalance caused by nonrandomization. Nevertheless, while the propensity score model was comprehensive, unmeasured confounding factors could not be fully accounted for. The second limitation is the early termination of the study, which prevented us from reaching the pre-specified sample size. Although we recruited 25% of the planned sample, the study experienced a low attrition rate, with only 8% of participants loss to follow-up. The third limitation pertains to patient crossovers between the two dialysis schedules. Specifically, 4 out of 132 patients in the thrice-weekly group switched to twice-weekly dialysis in the second year, primarily due to economic factors and transportation costs. Additionally, 9 out of 71 patients in the twice-weekly group switched to thrice weekly after 3 months, mainly due to dialysis inadequacy. Despite these crossovers, the pre-specified intention-to-treat analysis was applied. The fourth limitation is the presence of missing baseline data. We addressed this issue by performing multiple imputations to minimize bias and ensure the robustness of our results. Finally, the lack of data on residual kidney function and Kt/V is a notable limitation. This may have influenced the results, especially for secondary outcomes that might have been affected by the low dose of dialysis rather than the twice-weekly prescription itself.

Conclusions

In this study, patients on twice-weekly hemodialysis showed comparable overall survival and hospitalization rates at two years to those on thrice-weekly hemodialysis. Although twice-weekly hemodialysis may be a viable option in low-resource settings, it carries potential risks and requires careful monitoring of serum potassium and residual urine output after the first year. Our findings support the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference recommendations, emphasizing the importance of individualizing dialysis regimens and focusing on the patient's specific context and needs in decision-making [27].

Abbreviations

ESA	Erythropoiesis-stimulating agent
COVID-19	Coronavirus disease 2019
eCFR	Electronic case report form
BMI	Body mass index
eGFR	Estimated glomerular filtration rate
PTH	Parathyroid hormone
RAS	Renin angiotensin system
TIBC	Total iron-binding capacity
EPO	Erythropoietin
BP	Blood pressure
SPSS	Statistical Package for Social Sciences
SD	Standard deviation
IQR	Interquartile range
MICE	Multiple imputation chained equations
IPTW	Inverse probability of treatment weighting
HR	Hazard ratio
DOPPS	Dialysis Outcomes and Practice Patterns Study
KDIGO	Kidney Disease: Improving Global Outcomes

Supplementary Information

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Supplementary Material 1

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Author contributions

M.A. contributed to the conceptualization of the trial. M.A. and G.S. contributed to the methodology. M.A, D.C. and C.B. contributed to resources. M.A., C.B., S.F., R.G., N.N., J.H., J.H, S.K., C.B., A.D., R.A., B.G., S.Z., Z.M., V.H., H.A. and D.C. contributed to the data collection. G.S contributed to the data analysis. M.A., G.S., C.B., D.C. and S.F. contributed to the interpretation of results. M.A. wrote the first draft of the manuscript. All authors revised and approved the last version of the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Hotel Dieu de France/Saint-Joseph University (CEHDF 1114) and was conducted in agreement with the Helsinki Declaration of 1975. All included patients gave their written informed consent.

Consent for publication

All patients gave their consent for results' dissemination.

Study registration

The trial was registered on ClinicalTrials.gov (Identifier NCT03415776) on January 16, 2018.

Competing interests
The authors declare no competing interests.

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