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*Original Article*

# Impact of high-flux vs. conventional hemodialysis on clinical efficacy in patients with chronic renal failure (uremic stage) using real-world data

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**Abstract:** Objective: Based on real-world data, this retrospective investigation discusses the impact of high-flux hemodialysis (HFHD) versus conventional hemodialysis (HD) on clinical outcomes in patients with chronic renal failure (CRF) of the uremic stage. Methods: We selected 192 CRF (uremic stage) cases and conducted grouping based on intervention schemes: the HFHD group (n=100) received HFHD, while the HD group (n=92) received HD. We then conducted comparative analyses between the groups, with the dimensions covering: clinical efficacy; dialysis adequacy; toxin clearance efficiency; complications; inflammation; nutrition; bone metabolism (serum calcium [Ca], serum phosphorus [P], intact parathyroid hormone [iPTH]); and all-cause mortality. Results: HFHD was associated with markedly higher therapeutic efficacy than HD. While demonstrating a dialysis adequacy equivalent to that of HD group, HFHD showed superior toxin clearance efficiency, induced fewer complications, and led to markedly lower one-year all-cause mortality rates. In addition, the post-interventional inflammatory markers, P, and iPTH of HFHD group displayed greater reductions compared to the control group, along with more pronounced increases in nutritional indices and Ca. Conclusion: HFHD outperforms conventional HD in clinical efficacy in managing uremic-stage CRF patients.

**Keywords:** High-flux hemodialysis, conventional hemodialysis, chronic renal failure, uremic stage, clinical efficacy

## Introduction

Chronic kidney disease (CKD), a progressive and fatal condition, has posed a negative threat to over 10% of the world's population, with a ~42% increase in mortality across all age groups [1]. Defined as chronic renal insufficiency persisting over 3 months, CKD can eventually progress to chronic renal failure (CRF), increasing treatment difficulty and incurring great costs [2, 3]. With a lengthy disease duration, CRF can be classified into the compensatory, failure, and uremic (most advanced) stages based on kidney function impairment severity [4]. Patients with CRF in the uremic stage (also known as CKD stage 5 or end-stage renal disease [ESRD]) have more serious conditions, as various organs in the body accumulate metabolic wastes (e.g., urea, creatinine, uric acid) that are difficult to excrete, possibly inducing multi-organ failure and even death [5]. Meanwhile, a series of uncomfortable symptoms are common in such patients, including nausea, vomiting, fatigue, anorexia, muscle spasm, and mental abnormality, seriously impacting their quality of life and elevating mortality risk [6]. At present, uremic patients with CRF are primarily intervened by hemodialysis (HD). Conventional HD is generally of a low-flux type, which utilizes low-flux membranes and relies on the diffusion transport of solutes across the semi-permeable membrane to exert therapeutic effects. It shows efficacy in removing small solutes like urea and correcting electrolyte, acid-base, and fluid imbalances [7]. Although conventional HD remains the most commonly used renal replacement therapy for ESRD, there are still persistent risks of high morbidity and mortality [8]. High-flux HD (HFHD), as an extensively employed renal replacement

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therapy, effectively clears small and medium molecules like β2-microglobulin (β2-MG). Yet, its limitation lies in the difficulty of removing >15 kDa molecules that are closely related to vascular calcification, chronic inflammation, cardiovascular complications, and mortality risk [9]. In elderly patients with maintenance HD, evidence has linked HFHD to a reduced cardiovascular death risk compared to conventional HD [10].

Considering the dearth of comparative analysis on the clinical efficacy of routine HD vs. HFHD in uremic patients with CRF, this study conducts validation and reports the results in detail.

## Information and methodology

### *Patient data*

Eligibility requirements: a CRF diagnosis [11]; age 18-80 years; primary or secondary renal disease-induced glomerular filtration rate (GFR) <60 mL•min$^{-1}$, persisting at least 3 months; disease progression to the uremia stage (stage 5 CKD; GFR <15 mL•min$^{-1}$ accompanied by corresponding symptoms), with indications of HFHD or conventional HD [12]; first-time HFHD or routine HD recipients; intact case data. Ineligibility requirements: other infections and use of antibiotics; allergies to dialysis membranes; immune function diseases such as rheumatoid arthritis, tuberous sclerosis, and Kawasaki disease; surgical treatment within the past 3 months; cognitive/neurological disorders; abnormal blood pressure or blood sugar levels; secondary nephropathy; serious heart disease; renal tumors or other neoplastic diseases. Following approval by the Nanjing Drum Tower Hospital Ethics Committee and screening based on the above selection criteria, this study enrolled 192 cases of uremia patients with CRF (March 2022-March 2024). Intervention schemes guided patient allocation, with 100 cases receiving HFHD assigned to the HFHD group and 92 cases undergoing routine HD included in the HD group. Group comparability was confirmed by the absence of statistical difference in general data (P>0.05).

### *Sample size and power calculations*

This study adopts a retrospective design. The sample size was determined based on all consecutive cases that met the eligibility and ineligibility requirements in a specific period. Although no prior sample size calculation was conducted during the research design stage, we performed a post hoc power analysis for the primary endpoint “total efficacy rate”. Setting α=0.05 (two-tailed) and based on the observed total effective rate of the HFHD and HD groups (90.00% vs. 72.83%), as well as the actual sample size, the statistical power (1-β) of this study was calculated to be 94%. This indicates that the current sample size is sufficient to detect the inter-group differences observed.

### *Methods*

All cases underwent HD with a Fresenius 4008B hemodialysis machine. Before dialysis, an arteriovenous fistula was established in the patient’s forearm. All patients received routine basic treatments such as antihypertensive treatment, correction of calcium-phosphate metabolism, and anemia amelioration. Comparative efficacy analysis was performed one month after the dialysis.

HFHD parameters: A high-flux polysulfone dialyzer (FX60) was used, with a mass transfer area coefficient (KoA) of 750 mL/min, a ultrafiltration coefficient (Kuf) of 50 mL/mmHg/h, an effective membrane surface area of 1.5 m$^2$, a blood flow rate of 280 mL/min, and a dialysate flow rate of 450-500 mL/min. Dialysis, lasting 4.5 hours per session, was conducted 3 times per week.

In the HD group, HD was carried out with a low-flux polysulfone dialyzer (F6; KoA: 700 mL/min, Kuf: 10 mL/mmHg/h, surface area: 1.2 m$^2$, blood flow: 280 mL/min, dialysate flow: 450-500 mL/min) with the same frequency and treatment time per session as the HFHHD group.

### *Outcome measures*

Curative effects [13]: Efficacy was evaluated one month post-dialysis as follows: Marked effectiveness: complete disappearance of clinical symptoms and signs post-dialysis, plus a >60% improvement in renal function-related indexes. Effectiveness: great alleviation of clinical symptoms and signs post-treatment with a 30-60% improvement in renal function-associ-

ated indices. Ineffectiveness: no changes in clinical symptoms and signs post-therapy, a <30% improvement in renal function parameters, or even illness deterioration. Total effective rate = (markedly effective cases + effective cases)/total number of cases.

Dialysis adequacy: It was assessed by recording the urea clearance index (KT/V), time-average concentration of urea (TACurea), and standard protein catabolic rate (nPCR).

Toxin clearance efficiency: Serum was separated from elbow venous blood draws (5 mL) collected from patients pre- and post-dialysis via centrifugation. An automatic biochemical analyzer measured serum urea nitrogen (BUN) and serum creatinine (SCr) levels, while the electrochemiluminescence method determined β2-MG contents in serum.

Complications: The number of patients suffering from skin itching, restless legs syndrome, gastrointestinal symptoms, and hypotension was recorded.

Inflammation: We conducted enzyme-linked immunosorbent assays (ELISAs) to quantify serum C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α concentrations.

Nutritional status: Serum hemoglobin (Hb) and albumin (Alb) measurements were carried out pre- and post-treatment with an automatic biochemical analyzer.

Bone metabolism: Pre- and post-dialysis measurements of serum calcium (Ca) and phosphorus (P) levels (via the automatic biochemical analyzer), as well as electrochemiluminescence-based serum intact parathyroid hormone (iPTH), were performed.

All-cause mortality: All patients were followed up quarterly by telephone, QQ, WeChat, email, etc. The 6- and 12-month all-cause mortality rates were computed and statistically compared.

*Statistical processing and analysis*

This study used the number of cases/percentage (n/%) to describe the counting data and the $\chi^2$ test to identify between-group differences. Measurement data, if confirmed to have homogeneity of variance by the Bartlett test and normality by the Kolmogorov-Smirnov test, were shown as mean ± standard deviation (SD) and compared by the t-test (between groups) or the paired t-test (within-groups pre- and post-treatment); if not, the data were represented by the median (interquartile range) [M (Q1, Q3)] and compared between groups with the Mann-Whitney U test. Ordinal multinomial Logistic regression analysis was employed for efficacy assessment, with the potential confounders adjusted. For repeated measurement data like inflammatory markers, nutritional indices, and bone metabolism parameters, repeated measures analysis of variance (ANOVA) was utilized to simultaneously analyze the treatment effect, time effect, and the interaction between groups and time, and to control the influence of the baseline level. Data analyses were performed in SPSS 20.0, with differences considered statistically significant when $P<0.05$.

## Results

*General data*

We found no notable between-group differences in sex, age, disease duration, or primary disease ($P>0.05$; **Table 1**).

*Curative effects*

The HFHD group had a total effective rate of 90.00%, higher than the 72.83% reported in the HD group, with the difference reaching statistical significance ($P=0.002$; **Table 2**).

Ordinal logistic regression analysis showed that after adjusting for sex, age, disease duration, and primary disease, the advantage of HFHD-treated patients in obtaining better clinical efficacy was 4.87 times that of HD-managed cases (OR = 4.873, 95% CI: 2.718-8.737, $P<0.001$). None of the other covariates showed statistical significance ($P>0.05$; **Table 3**).

*Dialysis adequacy*

The dialysis adequacy of the two groups was evaluated to verify the clinical advantages of the two treatment schemes. The HFHD and HD groups were found to exhibit similar KT/V, TACurea, and nPCR values ($P>0.05$; **Figure 1**).

**Table 1.** General data of HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | $\chi^2$/t/Z | P |
|---|---|---|---|---|
| Sex | | | 0.465 | 0.495 |
| Male | 56 (56.00) | 47 (51.09) | | |
| Female | 44 (44.00) | 45 (48.91) | | |
| Age (years) | 51.74±7.07 | 51.32±6.87 | 0.417 | 0.677 |
| Disease duration (years) | 8.00 (6.00, 10.00) | 8.00 (6.00, 10.00) | -0.632 | 0.527 |
| Primary disease | | | 2.019 | 0.364 |
| Glomerulonephritis | 41 (41.00) | 43 (46.74) | | |
| Hypertensive nephropathy | 27 (27.00) | 28 (30.43) | | |
| Diabetic nephropathy | 32 (32.00) | 21 (22.83) | | |

Note: HFHD, high-flux hemodialysis; HD, hemodialysis.

**Table 2.** Curative effects of HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | $\chi^2$ | P |
|---|---|---|---|---|
| Markedly effective | 60 (60.00) | 21 (22.83) | | |
| Effective | 30 (30.00) | 46 (50.00) | | |
| Ineffective | 10 (10.00) | 25 (27.17) | | |
| Overall effectiveness | 90 (90.00) | 67 (72.83) | 9.481 | 0.002 |

Note: HFHD, high-flux hemodialysis; HD, hemodialysis.

**Table 3.** Ordinal logistic regression evaluation of clinical efficacy in HFHD and HD groups

| Indicators | B | Standard error | Wald | P | OR | 95% CI for OR |
|---|---|---|---|---|---|---|
| Treatment modality | 1.584 | 0.298 | 28.254 | <0.001 | 4.873 | 2.718-8.737 |
| Sex | 0.160 | 0.284 | 0.318 | 0.573 | 1.174 | 0.673-2.047 |
| Age (years) | -0.017 | 0.020 | 0.654 | 0.419 | 0.983 | 0.945-1.024 |
| Disease course (years) | -0.006 | 0.053 | 0.012 | 0.914 | 0.994 | 0.896-1.104 |
| Primary disease | -0.265 | 0.171 | 2.387 | 0.122 | 0.767 | 0.549-1.074 |

Note: OR, odds ratio; CI, confidence interval.

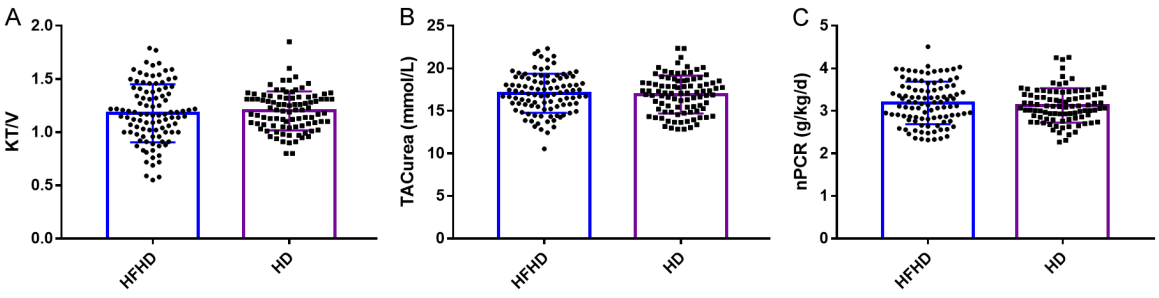


**Figure 1.** Comparative dialysis adequacy between HFHD and HD groups. A. Comparative KT/V analysis. B. Comparison of TACurea. C. Comparative nPCR analysis. Note: HFHD, high-flux hemodialysis; HD, hemodialysis; KT/V, urea clearance index; TACurea, time-average concentration of urea; nPCR, standard protein catabolic rate.

*Toxin clearance efficiency*

Baseline BUN, SCr, and β2-MG did not differ markedly across the groups (P>0.05). A statistical post-interventional reduction in all these indexes was observed in both cohorts, especially in the HFHD group (P<0.05). Meanwhile, the main effect of group/time as well as the group × time interaction of each index were statistically significant (P<0.001; **Figure 2**).

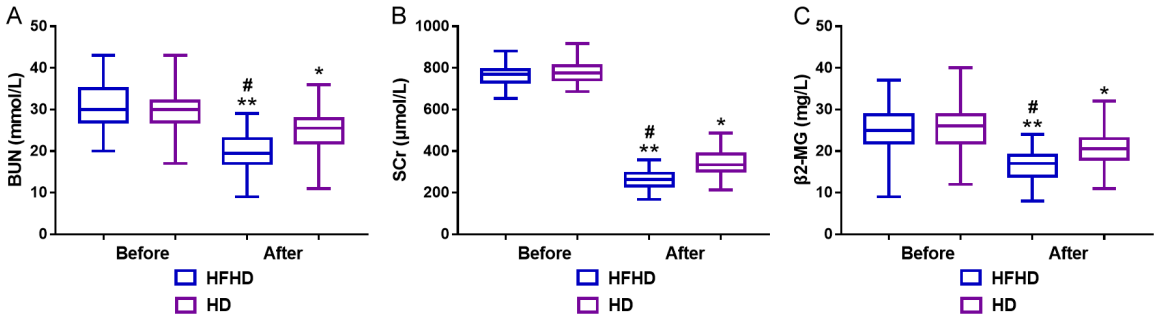


**Figure 2.** Toxin clearance efficiency of HFHD and HD groups. A. Pre- and post-interventional BUN. B. SCr pre- and post-intervention. C. β2-MG before and after intervention. Note: *P<0.05, **P<0.01 (intra-group comparison vs. pre-intervention). #P<0.05, compared with the control group at the same time point. HFHD, high-flux hemodialysis; HD, hemodialysis; BUN, blood urea nitrogen; SCr, serum creatinine; β2-MG, β2-microglobulin.

**Table 4.** Complications between HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | $\chi^2$ | P |
|---|---|---|---|---|
| Skin itching | 3 (3.00) | 7 (7.61) | | |
| Restless legs syndrome | 2 (2.00) | 5 (5.43) | | |
| Gastrointestinal symptoms | 1 (1.00) | 5 (5.43) | | |
| Hypotension | 3 (3.00) | 3 (3.26) | | |
| Total | 9 (9.00) | 20 (21.74) | 6.064 | 0.014 |

Note: HFHD, high-flux hemodialysis; HD, hemodialysis.

*Complications*

Skin itching, restless legs syndrome, gastrointestinal symptoms, and hypotension were the complications tracked. The above adverse events occurred at an overall incidence of 9.00% in the HFHD group and 21.74% in the HD group, showing statistical significance (P<0.001). All the recorded complications were relieved after symptomatic treatment (antihistamines, dry weight adjustment, iron supplementation, etc.), and did not cause treatment suspension or hospitalization (**Table 4**).

*Inflammatory markers*

Based on ELISA detection of inflammatory indexes, the two groups were similar in pre-treatment CRP, IL-6, and TNF-α levels (P>0.05). Despite a marked decrease in these markers across groups post-intervention (P<0.05), lower inflammatory marker levels were determined in the HFHD (P<0.05). Repeated measures ANOVA showed that the main effects of group, time, and the interaction between group and time for the three indicators (CRP, IL-6, TNF-α) all reached statistical significance (P<0.01; **Table 5**).

*Nutritional indices*

Evaluation of Hb and Alb showed no notable inter-group differences at baseline (P>0.05). Both interventions induced an increase in Hb and Alb (P<0.05), with HFHD treatment causing greater elevations than HD therapy (P<0.05). Additionally, the main effect of group (Hb: P=0.042; Alb: P<0.001) and time (Hb: P<0.001; Alb: P<0.001) of both nutritional indices, as well as the group × time interaction (Hb: P=0.044; Alb: P=0.002), were statistically significant (**Figure 3**).

*Bone metabolic parameters*

According to the evaluation of bone metabolism indexes, Ca, P, and iPTH were not statistically different between the groups at baseline (P>0.05). Ca in both groups increased post-intervention, while P and iPTH decreased (P< 0.05). The inter-group comparison of post-interventional bone metabolism further revealed higher Ca and lower P and iPTH in the HFHD group (P<0.05). According to repeated measures ANOVA, the main effect of group and time for Ca was statistically significant (all P<0.01), but with no significant group × time interaction

**Table 5.** Inflammatory markers of HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | t | P |
|---|---|---|---|---|
| CRP (mg/L) | | | | |
| Before intervention | 7.44±2.07 | 7.55±1.78 | 0.393 | 0.695 |
| After intervention | 4.62±1.91** | 5.85±1.72* | 4.674 | <0.001 |
| Group main effect *P*-value | 0.001 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | 0.003 | | | |
| IL-6 (ng/L) | | | | |
| Before intervention | 39.16±5.98 | 40.60±6.84 | 1.556 | 0.121 |
| After intervention | 24.87±5.48** | 30.04±4.25* | 7.260 | <0.001 |
| Group main effect *P*-value | <0.001 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | 0.003 | | | |
| TNF-α (ng/L) | | | | |
| Before intervention | 534.03±75.16 | 536.98±70.29 | 0.280 | 0.780 |
| After intervention | 393.29±74.05** | 459.84±70.81* | 6.353 | <0.001 |
| Group main effect *P*-value | <0.001 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | <0.001 | | | |

Note: *P<0.05, **P<0.01 (intra-group comparison vs. pre-intervention). HFHD, high-flux hemodialysis; HD, hemodialysis; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

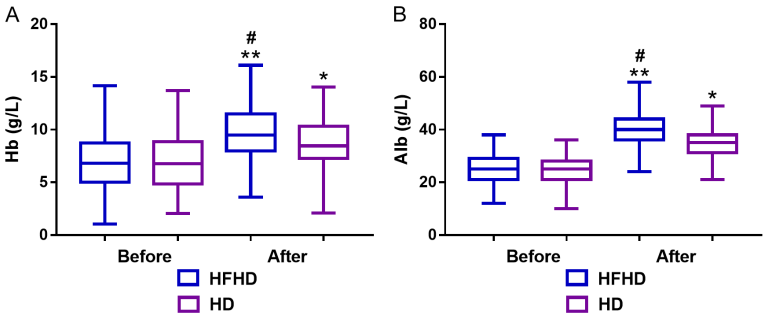


**Figure 3.** Nutritional indicators in the HFHD and HD groups. A. Hb levels before and after intervention in both groups. B. Alb levels before and after intervention in both groups. Note: *P<0.05, **P<0.01 (intra-group comparison vs. pre-intervention). #P<0.05, compared with the control group at the same time point. HFHD, high-flux hemodialysis; HD, hemodialysis; Hb, hemoglobin; Alb, albumin.

observed (P>0.05). For P, the time main effect and group × time interaction were statistically significant (all P<0.01), but the main effect of group was not (P>0.05). The main effects of group and time, as well as the group × time interaction, all showed statistically significant results for iPTH (P<0.01; **Table 6**).

*Short-term prognosis*

The one-year follow-up outcomes indicated an equivalent 6-month all-cause mortality (P>0.05) but a lower one-year all-cause mortality in the HFHD group versus the HD group (12.00% vs. 23.91%, P=0.031). Meanwhile, we plotted Kaplan-Meier survival curves, with the Log-rank test demonstrating consistent results, namely the HFHD group had a lower one-year all-cause mortality (P=0.030) and an equivalent half-year all-cause mortality (P>0.05) than the HD group (**Table 7**; **Figure 4**).

## Discussion

This study first found higher clinical efficacy in uremia patients with CRF undergoing HFHD. Besides, HFHD contributed to considerable dialysis adequacy compared with conventional HD. HFHD treatment also displayed more prominent toxin clearance efficiency, evidenced by greater BUN and SCr (small molecular toxins) down-regulation as well as lower β2-MG (a medium molecular toxin). The high-flux dialyzers used in HFHD have a higher ultrafiltration coefficient and a larger membrane pore diameter, which

**Table 6.** Bone metabolic parameters of HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | t | P |
|---|---|---|---|---|
| Ca (mmol/L) | | | | |
| Before intervention | 1.95±0.51 | 1.85±0.54 | 1.320 | 0.189 |
| After intervention | 2.37±0.53** | 2.14±0.42* | 3.314 | 0.001 |
| Group main effect *P*-value | 0.001 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | 0.231 | | | |
| P (mmol/L) | | | | |
| Before intervention | 2.33±0.51 | 2.20±0.57 | 1.668 | 0.097 |
| After intervention | 1.79±0.43** | 2.02±0.51* | 3.387 | <0.001 |
| Group main effect *P*-value | 0.336 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | 0.001 | | | |
| iPTH (pg/mL) | | | | |
| Before intervention | 710.62±203.25 | 685.39±179.58 | 0.908 | 0.365 |
| After intervention | 370.46±139.56** | 521.77±186.46* | 6.398 | <0.001 |
| Group main effect *P*-value | 0.001 | | | |
| Time main effect *P*-value | <0.001 | | | |
| Time × Group interaction *P*-value | <0.001 | | | |

Note: *P<0.05, **P<0.01 (intra-group comparison vs. pre-intervention). HFHD, high-flux hemodialysis; HD, hemodialysis; Ca, serum calcium; P, serum phosphorus; iPTH, intact parathyroid hormone.

**Table 7.** Short-term prognosis of HFHD and HD groups

| Indicators | HFHD group (n=100) | HD group (n=92) | $\chi^2$ | P |
|---|---|---|---|---|
| 6-month all-cause mortality | 5 (5.00) | 8 (8.70) | 1.037 | 0.309 |
| 1-year all-cause mortality | 12 (12.00) | 22 (23.91) | 4.667 | 0.031 |
| Cardiovascular mortality | 7 (7.00) | 13 (14.13) | | |
| Infection-related death | 3 (3.00) | 6 (6.52) | | |
| Other cause mortality | 2 (2.00) | 3 (3.26) | | |

Note: HFHD, high-flux hemodialysis; HD, hemodialysis.

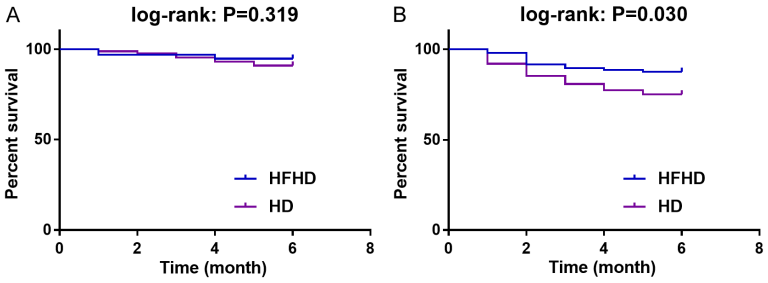


**Figure 4.** Kaplan-Meier survival curves. A. Kaplan-Meier curves of patients' half-year survival. B. Kaplan-Meier curves of patients' one-year survival. Note: HFHD, high-flux hemodialysis; HD, hemodialysis.

results in higher hydraulic permeability compared to conventional HD. This enables them to remove large, medium, and small molecular toxins more efficiently while increasing the ultrafiltration volume [14, 15]. According to a subsequent safety assessment, HFHD was associated with a lower total complication rate in uremic patients with CRF, indicating that HFHD is beneficial in complication prevention. ELISA further showed more efficient suppression of serum inflammation (significantly down-regulated CRP, IL-6, and TNF-α) under HFHD treatment. CRP, IL-6, and TNF-α, typical inflammatory factors, reflect the micro-inflammatory state of CKD patients [16, 17].

Furthermore, HFHD-managed patients exhibited a better nutritional status, as reflected by

higher Hb and Alb levels. Uremic toxins not only exert pro-inflammatory effects, but also stimulate muscle protein decomposition, affecting the gastrointestinal tract of patients and causing anorexia and nausea. The removal of small and medium molecule uremic toxins by HFHD helps reduce the decomposition of proteins by these substances and improve appetite, which is beneficial to improving patients' nutritional status [18, 19]. In the research of Chi et al. [20], the application of HFHD in elderly maintenance HD patients aids in enhancing the molecular toxin clearance effect while correcting malnutrition by increasing Hb levels, aligning with our findings. Similarly, HFHD was found to be effective in enhancing the body's bone metabolism by significantly up-regulating Ca and inhibiting P and iPTH levels. This is related to the more effective anti-inflammatory effect of HFHD on patients, which is conducive to alleviating bone absorption abnormalities in patients and improving their bone metabolism [21-23].

Finally, the one-year follow-up data indicated a lower one-year all-cause mortality in uremic patients with CRF under HFHD treatment, despite a six-month all-cause mortality equivalent to conventional HD. This outcome suggests the short-term survival benefit of HFHD for such patients. This may be related to the conventional HD using a low-flux dialyzer with a small membrane pore size. Although it shows efficacy in removing small molecular uremic toxins, it has a limited effect on medium-sized toxin clearance, which can cause the retention of some toxic substances related to metabolism in patients' serum, thus hindering the improvement of patients' one-year survival outcome [24, 25]. In the study of Liu et al. [26], switching to HFHD for patients on long-term routine HD is instrumental in extending their 1-to-4-year survival, similar to our findings. A meta-analysis further points to the advantages of HFHD over hemodiafiltration in preventing infection-related mortality in uremic patients with CRF, while demonstrating non-inferiority regarding all-cause mortality and cardiovascular mortality [27]. Similarly, Abe et al. [28] pointed out the benefits of super high-flux membrane dialyzers in maintenance HD patients in reducing the risk of three-year all-cause death. This evidence complements the results of the present study. Additionally, narrative nursing has been indicated to assist in further enhancing clinical safety and nursing satisfaction in CRF patients, as well as alleviate negative emotions and improve the quality of life [29]. This suggests that narrative nursing can be incorporated to further strengthen the clinical effectiveness of HFHD in treating patients with CRF in the uremic stage. Zhao et al. [30] conducted a meta-analysis and pointed out that expanded HD, as an emerging dialysis method, can validly enhance the clearance effect of medium and large-molecular-weight uremic toxins compared to HFHD, suggesting its potential as an alternative therapy to HFHD in the future. However, its efficacy and prognostic implications still require further evaluation in the future. Besides, repeated measures ANOVA was used to evaluate toxin clearance efficiency, inflammation, nutrition, and bone metabolism. Except for serum Ca, the group × time interaction of all indicators was significant, revealing that the HFHD regimen enables patients to achieve more significant improvements in indicators within the same treatment cycle.

This study shows room for improvement: First, the limited geographical space of patient recruitment and the single-center design may affect the representativeness of the sample and the extrapolation of the conclusions, making the application effectiveness of HFHD in a wider range of people questionable. In the future, multi-center samples distributed across regions should be included to improve the universality of the research results. Second, no analysis at the cellular level was conducted, and the lack of mechanism analysis imposes certain limitations on the interpretation of the conclusions. The inclusion of relevant mechanism analysis would help to further clarify HFHD's mechanism of action and the pathological mechanism underlying CRF. Third, the key confounders that may affect the results (e.g., dialysis duration, ultrafiltration volume, combined medication like statins+anti-inflammatory drugs, patient compliance) are not included in the statistical model for adjustment, which may lead to deviated results. Thus, more relevant indicators should be added prospectively to address this issue. Fourth, the failure to record the specific occurrence time and detailed complication grading standards limits the in-depth analysis of related complications.

In the future, a prospective analysis should be conducted for a detailed evaluation. Finally, it is difficult to evaluate the application value and economic burden of the two therapies from the level of health decision-making without a comparative analysis of their medical costs and economic benefits. The supplement and verification of relevant data are instrumental in promoting the transformation of research findings into clinical practice and policies.

In our cohort of uremic patients with CRF, HFHD contributes to superior clinical outcomes compared to conventional HD. With non-inferior dialysis adequacy, it significantly improves clinical effects, improves toxin clearance efficiency, prevents complications, inhibits serum inflammation, and enhances nutritional status, bone metabolism, and one-year prognosis. Moreover, HFHD is especially suitable for patients presenting clinical characteristics such as medium molecular toxin accumulation, micro-inflammation, or abnormal bone and mineral metabolism.

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## Disclosure of conflict of interest

None.

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