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Original Article

Comparison of clinical therapeutic effects between high-flux dialysis and low-flux dialysis

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Abstract: Objective: To compare the efficacy of, as well as effects on micro-inflammatory and metabolic acidosis between high-flux and low-flux dialysis in the hemodialysis population. Methods: This multicenter retrospective cohort study, based on pre-defined blood sample data completeness criteria, screened and included treatment records of 187 patients undergoing high-flux dialysis and 189 patients undergoing low-flux dialysis from 2016 to 2018. Ultimately, 374 dialysis sessions meeting the completeness criteria from the high-flux group and 378 sessions from the low-flux group were included in the analysis. Baseline characteristics, clinical tolerance, dialysis efficiency, serum laboratory parameters, micro-inflammatory status, and metabolic acidosis indicators were compared between the two groups. Results: Both groups exhibited good biocompatibility, with effective removal of excess water and uremic toxins from the body. Contrastingly, high-flux dialysis was better than low-flux dialysis in removing moderate and small molecule toxins, maintaining blood pressure and acid-base balance in the body. Conclusions: The study provides useful insights into the comparative efficacy, micro-inflammation, and metabolic acidosis of high-flux and low-flux dialysis. These findings support the preferential use of high-flux dialysis to enhance solute clearance and correct acidosis, while affirming that both modalities are well-tolerated. The choice should be individualized based on patient characteristics and treatment goals.

Keywords: Hemodialysis, high-flux dialyzer, low-flux dialyzer, polyethersulfone membrane, clinical therapeutic effect

Introduction

Hemodialysis is the most common and effective option for patients with chronic kidney disease (CKD). Hemodialysis is based on the principle of solute removal across a semi-permeable membrane through diffusion and ultrafiltration [1, 2]. Many factors, including dialysate flow rate, dialyzer surface area, dialysis duration, and blood flow rate influence dialysis outcomes. According to differences in permeability, hemodialysis is classified into high-flux dialysis or low flux dialysis [3-5]. High-flux dialysis exhibited better than low-flux dialysis in clearing moderate-sized molecules, specifically within a molecular weight of 10,000 to 15,000 Daltons,

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such as protein β_2-microglobulin (β_2-M), protein-bound molecules, and homocysteine [6-9]. Compared to low-flux dialysis, high-flux dialysis has more advantages in alleviating the "micro-inflammatory state" in patients [10, 11], suppressing coagulation pathway activation [12, 13], improving lipid metabolism disorders [14, 15] and reducing related mortality [16, 17]. However, high-flux dialysis is not feasible for every patient with CKD. The choice of dialytic treatment for elderly patients is very complex. Further, no study has confirmed that high-flux dialysis is superior to low-flux dialysis [18-20].

We aimed at investigating whether high-flux dialysis is better than low-flux dialysis in clearance rate of globular filtration, which was assessed by determining the urea reduction ratio (URR), creatinine reduction ratio (CRR), urea clearance rate (UCR), creatinine clearance rate (CCR), Kt/V; the effects on micro-inflammatory states, presented by white blood cells (WBC), C-reactive protein (CRP), and CRP/albumin ratio; and the pH and electrolyte values.

Materials and methods

Study design and participants

This retrospective study analyzed data from 189 patients receiving low-flux dialysis and 187 patients receiving high-flux dialysis in the First Affiliated Hospital of Jinan University, the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, the Second People's Hospital of Shenzhen, and the Dongguan Kanghua Hospital between 2016 and 2018. The study protocol was approved by the Ethics Committee of the above four hospitals. Because the study was retrospective and all patient data were anonymized and de-identified before analysis, the requirement for informed consent was waived.

Inclusion and exclusion criteria

Inclusion criteria were as follows: i. Patients with acute or chronic renal failure of various causes who received stable dialysis treatment for more than 3 months; ii. Aged 18-80 years, regardless of gender; iii. Bicarbonate dialysis was administered with a dialysate flow rate of 500 mL/min; treatment frequency was 2-3 times per week (90% of patients received treatment 3 times weekly), with each session lasting 4 hours and a blood flow rate of 200-350 mL/min (adjusted based on the patient's clinical condition); iv. Dialysis access was via arteriovenous fistula or artificial vascular graft; v. At least one dialysis session record during the study period that met the predefined data completeness criteria.

Exclusion criteria were as follows: i. Patients using deep vein double-lumen catheters for dialysis access; ii. Patients undergoing acetate dialysis.

Blood sample data inclusion criteria

This analysis only included treatment data with complete serial blood sample test records. A complete record was defined as one in which arterial blood samples were collected at three time points - pre-dialysis, 15 minutes after dialysis initiation, and 1 hour after dialysis initiation - and tests for complete blood count, blood biochemistry (including renal and liver function), and blood gas analysis were completed. Meanwhile, vital signs monitoring records for these treatments were required to cover the same three time points, in addition to hourly recordings during dialysis and at the end of the session.

Equipment

Dialysis machines (Fresenius, Model 4008S/4008sv10, Germany) equipped with an online conductivity monitoring function were used in this study. Double-stage hemodialysis water treatment equipment (Hangzhou Tianchuang Environmental Technology Co., Ltd., Hangzhou, China) met the American AAMI/ASAIO standards for hemodialysis water quality. For dialysis, two types of dialyzers were used: Enttex LF Dialyzer (low-flux dialysis; ultrafiltration rate [UFR]: 21 mL/(hr·mmHg); surface area: 1.6 m^2) and Enttex HF Dialyzer (high-flux dialysis; UFR: 84 mL/(hr·mmHg); surface area: 2.0 m^2; β_2-microglobulin sieving coefficient ≥0.7; albumin sieving coefficient ≤0.01), both manufactured by Guangzhou Enttxs Medical Products Co., Ltd., Guangzhou, China. The dialyzers featured low-pass and high-pass polysulfone dialysis membranes (3M, USA), respectively, and were gamma-ray sterilized by the manufacturer.

Table 1. Comparison of patient characteristics

		Low-flux (n=189)	High-flux (n=187)
Gender	Female	63 [33%]	72 [39%]
	Male	126 [67%]	115 [61%]
Age [years old]	Minimum	22~	20~
	Maximum	77	79
	Average	46±11	45±11
Disease causes	Hypertension	59 [31%]	64 [34%]
	Diabetic nephropathy	20 [11%]	17 [9%]
	Glomerulonephritis	83 [44%]	86 [45%]
	Others	27 [14%]	24 [13%]

Study design and data extraction

This retrospective cohort study compared the efficacy of high-flux versus low-flux dialysis. Patients were assigned to the low-flux or high-flux group according to the predominant dialyzer type documented in their medical records during the observation period.

To ensure data quality and comparability, a strict predefined completeness criterion was applied: a complete record required successful blood sampling and testing at three time points - pre-dialysis, 15 minutes, and 1 hour after dialysis initiation. All historical records were screened, and only sessions meeting this criterion were included; any session with missing required samples was excluded.

The final analytical dataset comprised 378 complete sessions from 189 patients in the low-flux group and 374 complete sessions from 187 patients in the high-flux group. A post-hoc power analysis for the primary efficacy parameter (Kt/V) indicated that this sample size provided >80% power to detect a significant between-group difference at α=0.05.

The outcome measures were defined as follows: Primary efficacy outcomes: URR, CRR, Kt/V, and serum Phosphorus levels. Secondary efficacy outcomes: Micro-inflammation markers (CRP, WBC count, CRP/Albumin Ratio (CAR)) and Metabolic Acidosis parameters (serum pH, bicarbonate (HCO_3^-), Total CO_2 (TCO_2)). Safety outcomes: Vital signs (blood pressure, pulse, temperature, respiration) and the incidence of dialysis-related adverse events.

Statistical analysis

All statistical analyses were conducted using GraphPad Prism software (version 9.5.0). Data normality distribution was evaluated via the Kolmogorov-Smirnov test, D'Agostino and Pearson omnibus test, and Shapiro-Wilk test. Equality of variances was evaluated using Bartlett's test.

Quantitative data were presented as the mean ± standard error of the mean (SEM). The unpaired Student's t-test was used for normally distributed data and the Mann-Whitney U test was for non-normally distributed data. For multiple comparisons involving two treatment groups and pre- vs. post-dialysis conditions, one-way analysis of variance (ANOVA) was applied. The false discovery rate for post-hoc pairwise comparisons was controlled using the Benjamini-Hochberg procedure.

Categorical data, were expressed as counts (n) and percentages (%). Group differences were analyzed using the Chi-square test. A *p*-value ≤0.05 was considered statistically significant [21].

Results

Comparison of patient characteristics and clinical tolerability

Patient characteristics, including gender, age composition, and primary causes of CKD are presented in **Table 1**. No treatment-related adverse effects were observed. Pre- and post-dialysis changes in body temperature, pulse rate, and respiratory rate were not significant between the two treatment groups (all P> 0.05). Compared with pre-dialysis values, systolic blood pressure (SBP) decreased significantly post-dialysis in both groups (P=0.002 for the low-flux group and P<0.0001 for the high-flux group); however, no significant differences in SBP were noted between the two groups either pre- or post-dialysis (P>0.05). Diastolic blood pressure (DBP) decreased post-dialysis only in the high-flux dialysis group (P=0.0029), with no significant intergroup differences in DBP observed pre- or post-dialysis (P>0.05) (**Table 2**). Dialysis duration (P>0.05), ultrafiltra-

Table 2. Comparison of the basic vital signs of patients in this study

	Low-flux (n=189)		High-flux (n=187)	
	Pre	After	Pre	After
Body temperature [°C]	36.3±0.3	36.3±0.3	36.4±0.3*	36.4±0.2
Pulse rate [times]	77±10	78±11	77±10	79±12
Respiration rate [times]	19±1	19±1	19±2	19±1
Systolic blood pressure [mmHg]	147±21	142±23#	149±22	138±23###
Diastolic blood pressure [mmHg]	89±13	89±14	90±14	87±14##

*Significance between treatments; #significance between pre- and post-dialysis. *P=0.0189, #P=0.002, ##P=0.0029, ###P<0.0001.

Table 3. Comparison of Parameters related to dialysis

	Low-flux (n=189)	High-flux (n=187)
Dialysis duration [h]	4	4
Ultrafiltration [mL/kg/h]	10.69±4.24	11.12±3.82
Blood flow [mL/min]	243±29	241±30
Body weight pre-dialysis [kg]	61.89±11.54	60.88±11.70
Body weight post-dialysis [kg]	59.47±11.25#	58.41±11.34##
Body weight difference [%]	3.95±1.61	4.09±1.40

#significance between pre- and post-dialysis. #P=0.0177, ##P=0.0146.

tion volume (P>0.05), and blood flow rates (P>0.05) were comparable between the groups. Baseline body weights did not differ significantly between the groups (P>0.05), and the magnitude of post-dialysis weight reduction was also comparable (P>0.05) (**Table 3**).

Comparison of dialytic efficiency

Both high-flux and low-flux dialysis effectively removed serum urea, creatinine, and phosphate. Dialysis efficiency was evaluated using Kt/V, URR, and CRR. The Kt/V value was significantly higher in the high-flux dialysis group than in the low-flux group (P<0.01). Additionally, URR, CRR, and phosphorus reduction ratio (PRR) were significantly higher in the high-flux group (all P<0.05, **Figure 1**).

Comparison of serum laboratory parameters

Red blood cell, hemoglobin, and platelet levels increased post-dialysis in both groups due to blood concentration (**Table 4**). Serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), albumin, and globulin levels were also elevated post-dialysis (all P<0.01); however, there was no significant difference in serum albumin levels between the two treatment groups (P>0.05).

Comparison of micro-inflammation

In this study, CRP levels showed an increasing trend post-dialysis in both the high-flux and low-flux dialysis groups (**Figure 2A**). In the low-flux dialysis group, WBC counts tended to increase post-dialysis compared with pre-dialysis levels (**Figure 2B**). Post-dialysis, CRP and WBC levels were lower in the high-flux dialysis group than in the low-flux group. Furthermore, β_2-M levels decreased significantly post-dialysis in the high-flux group (**Table 6**, P<0.01). Correspondingly, the post-dialysis CAR was reduced in the high-flux treatment group (**Figure 2C**, P=0.0059).

Comparison of metabolic acidosis

Pre-dialysis, serum pH values were 7.35 in the high-flux dialysis group and 7.34 in the low-flux group. Post-dialysis, serum pH levels increased significantly in both groups, with a significant intergroup difference (P<0.001; **Table 5**; **Figure 3A**). Pre-dialysis serum bicarbonate concentrations were 20.82 mmol/L in the high-flux group and 20.40 mmol/L in the low-flux group (**Table 5**). Post-dialysis, serum bicarbonate levels increased significantly in both groups, with a significant intergroup difference (P=0.03; **Figure 3B**). Pre-dialysis blood TCO_2 concentrations were below 22 mmol/L in both groups and increased significantly post-dialysis (**Figure 3C**); however, the post-dialysis intergroup difference was not significant. Post-dialysis arterial CO_2 partial pressure ($PaCO_2$) levels increased in the low-flux group but showed no significant change in the high-flux group. Post-dialysis concentrations of potassium and chloride decreased, while calcium levels increased significantly in both groups, with

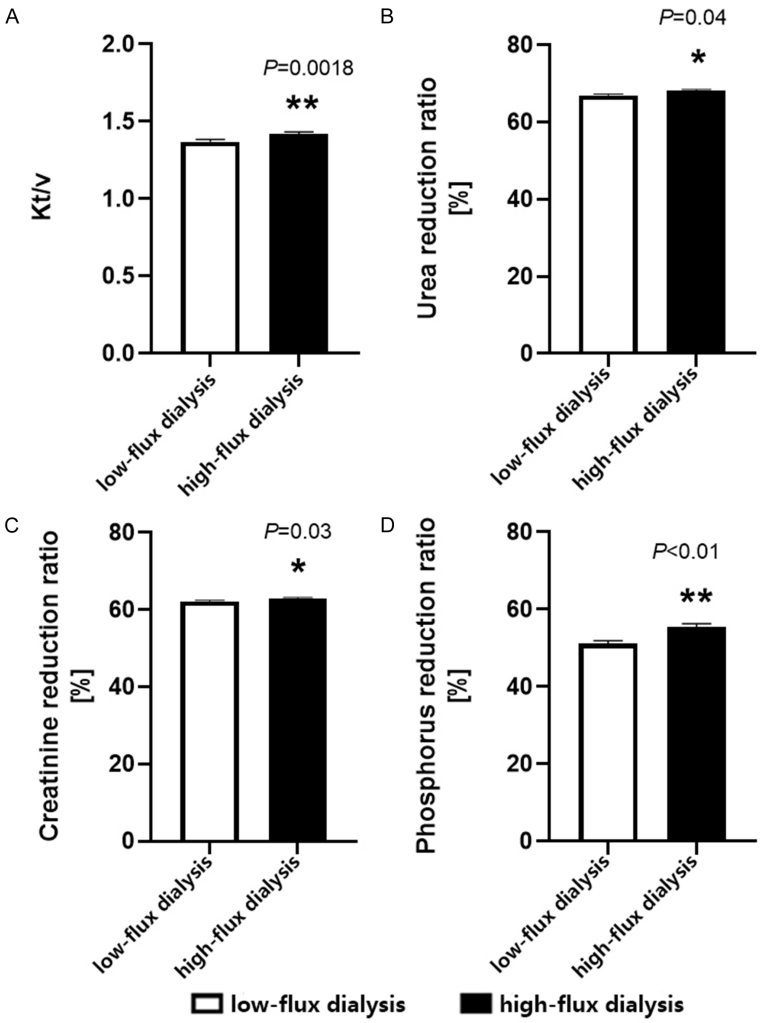

Figure 1. Comparison of Kt/v (A), urea reduction ratio (B), creatinine reduction ratio (C), and phosphorus reduction ratio (D) between low-flux dialysis and high-flux dialysis. *P<0.05, **P<0.01 for comparisons between treatments.

no significant intergroup differences observed. Sodium levels remained stable in both groups before and after dialysis.

Discussion

This study confirms that high-flux dialysis offers advantages over low-flux dialysis in clearing small and medium-sized molecular toxins and correcting metabolic acidosis. Notably, the average age of the study population was lower than that reported in most epidemiological studies, with primary diseases dominated by glomerulonephritis and hypertension - consistent with the CKD disease spectrum characteristics in China during the study period (2016-2018) [22]. While this population profile may limit the generalizability of the findings to some extent, it also provides an opportunity to observe efficacy differences attributed to the dialysis membrane itself in a relatively younger population with a lower burden of diabetic nephropathy.

Patients in both groups exhibited good clinical tolerance, with stable basic vital signs (including body temperature, heart rate, respiratory rate, and blood pressure). We specifically focused on blood pressure changes and confirmed that high-flux dialysis effectively removes excess body fluid without compromising hemodynamic stability.

Our data verify that high-flux dialysis achieves higher dialysis adequacy, as evidenced by its significantly superior efficacy in removing small-molecular solutes (e.g., urea, creatinine, and phosphorus) compared with low-flux dialysis. Although the absolute difference in Kt/V between the high-flux and low-flux groups was only 0.05, this difference was statistically significant, and Kt/V values in both groups were well above the K/DOQI guideline-recommended minimum adequacy target of 1.2. Thus, while ensuring clinically adequate dialysis, high-flux dialysis provides a statistically superior clearance rate for small-molecular solutes.

The finding of no significant difference in the impact of the two dialysis modalities on serum albumin levels has positive clinical implications. It indicates that high-flux dialysis, while enhancing the clearance of middle-molecular-weight toxins, does not cause additional depletion of core nutritional status (reflected by albu-

Table 4. Comparison of laboratory parameters

	Low-flux (n=189)			High-flux (n=187)		
	Pre	After	p	Pre	After	P
Red blood cells [10^12/L]	3.66±0.63	4.05±0.74#	#P<0.0001	3.67±0.64	4.11±0.77#	#P<0.0001
Hemoglobin [g/L]	107±14	119±18#	#P<0.0001	107±15	120±19#	#P<0.0001
Platelets [10^9/L]	188±55	195±60	#P=0.2788	190±58	196±66	#P>0.9999
ALT [U/L]	12.1±7.5	14.1±8.6#	#P=0.0002	13.5±9.2	15.4±10.1#	#P=0.0035
AST [U/L]	12.5±7.1	15.5±0.4#	#P<0.0001	13.5±0.4	16.2±0.4#	#P<0.0001
Albumin [g/L]	41.0±3.3	47.1±5.8#	#P<0.0001	41.1±3.6	47.4±6.2#	#P<0.0001
Globulin [g/L]	26.6±5.0	30.8±5.8#	#P<0.0001	25.7±4.8	29.3±5.5#,**	#P<0.0001 *P=0.005
β_2 Microglobulin [mg/L]	-	-		41.38±0.71	19.93±0.66#	P<0.01

*Significance between treatments; #significance between pre- and post-dialysis. **P=0.005.

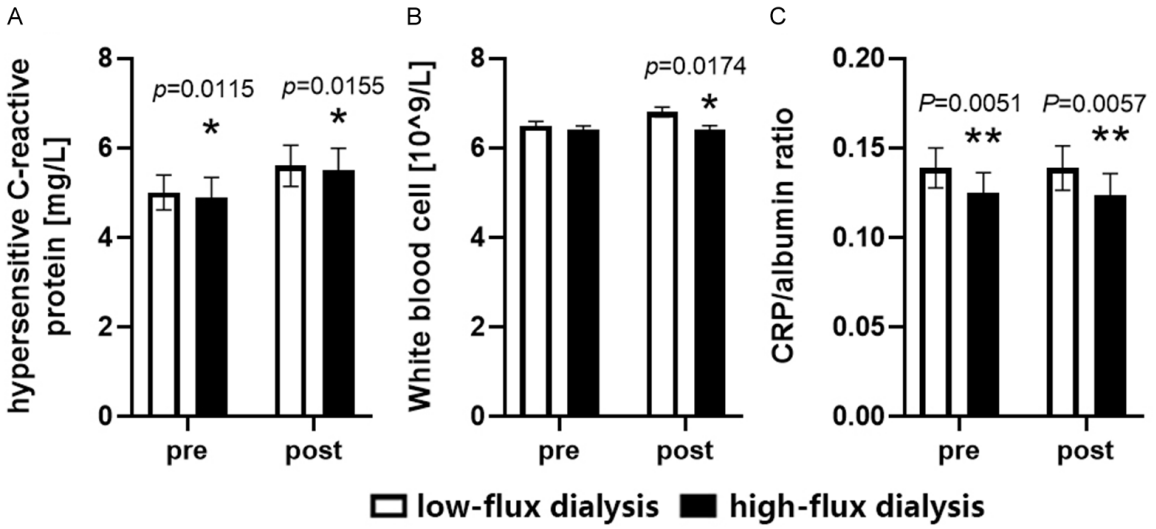

Figure 2. The effects on micro-inflammation states in low-flux dialysis and high-flux dialysis: hypersensitive C-reactive protein (CRP) level (A), white blood cell counts (B) and CRP/albumin ratio (C). *P<0.05, **P<0.01 for comparisons between treatments.

min levels). This alleviates clinicians' concerns that adopting high-flux dialysis might exacerbate nutritional risks.

Regarding the assessment of micro-inflammation, the improvement in CRP levels observed in the high-flux group is particularly significant. It should be noted that CRP is not merely an inflammatory marker; its expression is primarily regulated by upstream inflammatory cytokines such as IL-6 [23]. Therefore, the reduction in CRP levels may indirectly reflect the suppression of related inflammatory pathways (including IL-6-driven responses), providing a mechanistic explanation for how high-flux dialysis may alleviate micro-inflammation through the removal of middle-molecular-weight toxins.

High-flux dialysis is advantageous in removing moderate-sized molecular substances, such as β_2-M, inflammatory factors, cystatin C, and myoglobin [24, 25]. β_2-M stabilizes the surface expression of MHC-I molecules, plays a key role in both innate and adaptive immunity, and acts as a "trigger" for inflammatory processes, directly participating in the development of atherosclerosis [26-28]. Long-term use of high-flux dialyzers is beneficial for improving immune function, reducing micro-inflammatory states and complications induced by secondary hyperparathyroidism, enhancing quality of life, and prolonging survival in dialysis patients [29, 30]. Mohammed et al. conducted a study to evaluate the impact of high-flux versus low-flux hemodialysis on high-sensitivity CRP levels in

Table 5. Comparison of the results of blood gas analysis and electrolytes

	Low-flux (n=189)			High-flux (n=187)		
	Pre	After	P	Pre	After	P
pH	7.35±0.002	7.39±0.003$^{\#}$	<0.0001	7.34±0.002	7.45±0.003$^{\#,***}$	<0.0001
HCO_3^-	20.82±0.13	23.83±0.17$^{\#}$	<0.0001	20.40±0.12	24.52±0.19$^{\#,*}$	<0.0001
PaO_2 [mmHg]	100±0.84	105±1.20	0.0906	106±1.02**	109±1.56	>0.9999
$PaCO_2$ [mmHg]	39.3±0.25	40.7±0.24$^{\#}$	<0.0001	38.6±0.21	38.3±0.22****	0.7673
TCO_2 [mmol/L]	21.5±0.16	26.5±0.16$^{\#}$	<0.0001	21.5±0.15	26.4±0.18$^{\#}$	<0.0001
Potassium [mmol/L]	5.0±0.004	3.5±0.02$^{\#}$	<0.0001	5.1±0.04	3.5±0.02$^{\#}$	<0.0001
Sodium [mmol/L]	138.5±0.18	138.0±0.16	0.0256	138.5±0.18	138.1±0.15	0.0636
Chlorine [mmol/L]	98.4±0.24	96.7±0.20$^{\#}$	<0.0001	98.0±0.24	96.4±0.20$^{\#}$	<0.0001
Calcium [mmol/L]	2.2±0.01	2.5±0.01$^{\#}$	<0.0001	2.3±0.01	2.5±0.01$^{\#}$	<0.0001

*Significance between treatments; $^{\#}$significance between pre- and post-dialysis. HCO_3^-: bicarbonate, PaO_2: partial pressure of arterial oxygen, $PaCO_2$: partial pressure of arterial carbon dioxide, TCO_2: total carbon dioxide. *P=0.0308, **P=0.0123, ***P<0.001, ****P<0.0001.

Table 6. Comparison of the eliminating effect of β_2-M with high-flux dialysis (n=187)

	Pre-dialysis	Post-dialysis	*P* value
β_2-M [mg/L]	41.38±0.71	19.93±0.66$^{\#}$ (t-test)	<0.01

$^{\#}$Significance between pre- and post-dialysis.

maintenance hemodialysis patients. Compared with low-flux membranes, high-flux dialysis membranes resulted in a greater reduction in CRP levels and improved micro-inflammatory states, which may be attributed to the efficient removal of intact parathyroid hormone (PTH, a middle-sized uremic toxin) and reduced serum phosphorus levels [31]. In our study, high-flux dialysis showed good efficacy in removing β_2-M; however, β_2-M levels were measured before and after treatment in only over 10 patients in the low-flux dialysis group, with almost no reduction observed post-dialysis. Therefore, β_2-M levels were not assayed in the remaining low-flux group patients. These results are consistent with those from previous clinical outcome studies [32, 33].

A serum bicarbonate concentration below 22 mmol/L is a known risk factor for all-cause mortality in dialysis patients. In 2003, the K/DOQI guidelines recommended maintaining serum bicarbonate concentrations above 22 mmol/L. Consistent with this target, our study found that high-flux dialysis was superior to low-flux dialysis in correcting both pH and serum bicarbonate levels, with a significant intergroup difference. This suggests that high-flux dialysis may be more effective in correcting metabolic acidosis, which could have positive implications for improving long-term patient prognosis.

This study has several limitations. First, its retrospective design and focus on short-term parameters preclude assessment of the long-term clinical impact of high-flux dialysis on outcomes such as quality of life, cardiovascular events, or mortality. Second, the generalizability of our findings may be constrained by the sample size and its specific demographic profile - including a relatively younger population with a lower burden of diabetic nephropathy. Thus, caution is warranted when extending these results to broader groups such as pediatric or acute kidney injury patients, for whom optimal dialysis protocols remain to be established. Third, the evaluation of micro-inflammation relied on conventional biomarkers; measurement of key cytokines such as IL-6 would have strengthened the mechanistic interpretation. To address these points, future prospective studies with larger, more diverse cohorts, long-term follow-up, and extended biomarker panels are needed to comprehensively evaluate the clinical benefits of dialysis.

In summary, both low-flux and high-flux dialysis have good biocompatibility and can effectively remove excess body fluid and uremic toxins. However, high-flux dialysis is superior to low-flux dialysis in removing small and medium-sized molecular toxins, maintaining blood pressure, and correcting acid-base balance. Its applicability in specific patient populations

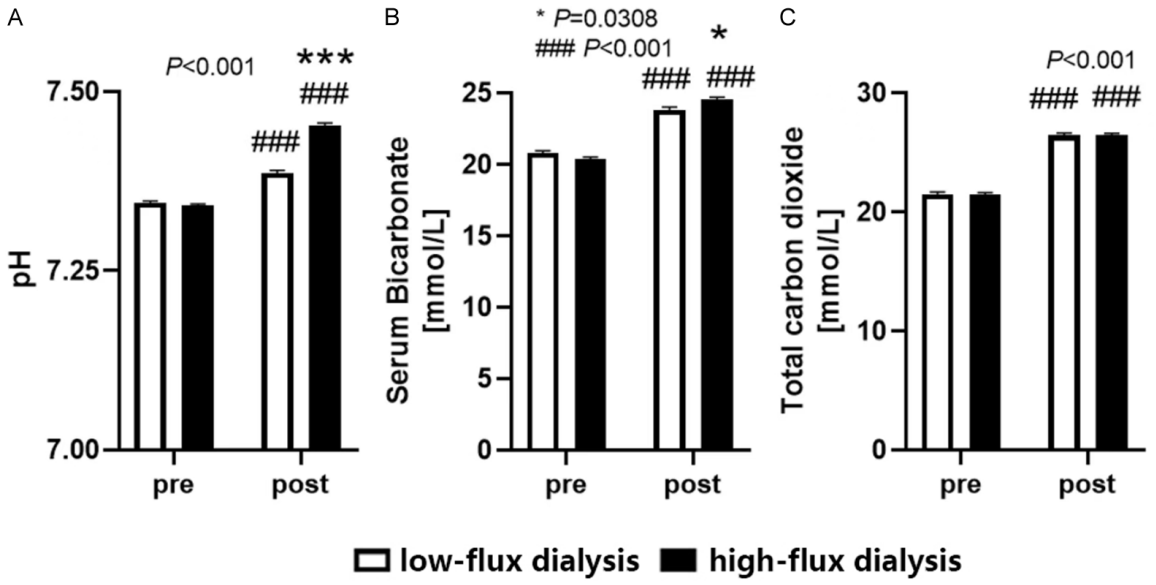

Figure 3. Improving metabolic acidosis by low-flux dialysis and high-flux dialysis: serum pH levels (A), serum bicarbonate concentrations (B) and blood Total Carbon Dioxide (TCO_2) concentrations (C). *P<0.05, ***P<0.001 for comparisons between treatments; ###P<0.001 for comparisons between pre- and post-dialysis.

requires careful consideration of individual characteristics and comorbidities. For elderly patients and those with diabetes, cardiovascular disease, or hypertension, high-flux dialysis can provide significant benefits but must be tailored to manage potential hemodynamic instability. In pediatric patients and those with acute kidney injury, high-flux dialysis may also be beneficial, but additional research is needed to establish optimal protocols. Beyond the limitations related to specific patient populations, this study is also constrained by its retrospective design, sample size, and the biomarkers used for outcome measures. Future studies will adopt a prospective design, enroll larger and more diverse patient populations, include long-term follow-up, and assess a broader range of biomarkers (especially inflammatory markers such as IL-6) to provide a more comprehensive evaluation of the clinical benefits of dialysis.

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Disclosure of conflict of interest

None.

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