Renal Replacement Therapy

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Super high-flux dialyzers improve survival in patients on hemodialysis: a cohort study of the Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry

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Abstract

Background In Japan dialyzers are classified as type I, II, III, IV, or V on the basis of the β_2-microglobulin clearance. In 2023, Type V dialyzers were defined as super high-flux membrane dialyzers. Herein, we investigate the association between dialyzer type and mortality.

Methods A cohort study was conducted using the Japanese Society for Dialysis Therapy Renal Data Registry database from 31 December 2017, to 31 December 2019. We enrolled 181,879 patients on hemodialysis who were divided into type I–V groups per the Japanese classification. We assessed the associations of each group with 2-year all-cause mortality using Cox proportional hazard models. Furthermore, propensity score matching analysis was performed.

Results By the end of 2019, 34,196 patients (18.8%) had died. The hazard ratio (95% confidence interval) was significantly higher in the type I (1.25 [1.12–1.39]), type II (1.21 [1.13–1.31]), and type III (1.07 [1.02–1.13]) groups and significantly lower in the type V group (0.86 [0.80–0.92] $P < 0.0001$) than in the IV group as a reference after adjusting for all confounders. The type V group had a significantly lower adjusted mortality risk regardless of Kt/V and was robust in several sensitivity analyses. Furthermore, the findings remained significant after propensity score matching.

Conclusions This observational study revealed that hemodialysis performed using super high-flux dialyzers may reduce mortality rates regardless of Kt/V. However, to establish the efficacy of super high-flux dialyzers in improving outcomes, randomized controlled trials should be conducted.

Trial registration number: UMIN000018641.

Keywords Cumulative survival, Dialyzer, Hemodialysis, Kt/V, Super high-flux membrane

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Background

Dialyzers are commonly classified as low-flux or high-flux membrane dialyzers. Low-flux membrane dialyzers are characterized by an ultrafiltration rate of < 12 mL/mmHg/h and a β_2-microglobulin (β2MG) clearance of < 10 mL/min [1, 2]. Although they effectively remove small solutes through diffusion, a few medium-sized molecules, which are considered more toxic, are more difficult to remove via diffusion [3]. This limitation led to the development of high-flux membrane dialyzers, defined by an ultrafiltration rate of ≥ 15 mL/mmHg/h and a β2MG clearance of ≥ 15 mL/min at a blood flow rate of 200 mL/min, dialysate flow rate of 500 mL/min, and membrane surface area of 1.5 m^2 [4]. High-flux membranes have high hydraulic permeability and greater solute permeability for middle molecules than low-flux membrane dialyzers. Furthermore, to remove several medium-to-large molecules, super high-flux membrane dialyzers with large pores were developed in Japan [5]. More than 90% of Japanese patients on hemodialysis (HD) were being treated with super high-flux dialyzers in 2008 [6, 7]. In Japan, dialyzers were categorized into the following five types on the basis of β2MG clearance: types I, II, III, IV, and V, with β2MG clearance of < 10, ≥ 10–30, ≥ 30–50, ≥ 50–70, and ≥ 70 mL/min, respectively, at a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min from 2005 to 2012 [8]. Currently, super high-flux dialyzers are defined as those with β2MG clearance of ≥ 70 mL/min in Japan. Therefore, only type V dialyzers are classified as super high-flux dialyzers. HD using type IV and type V dialyzers reduces mortality rates compared with high-flux dialyzers [9, 10]. However, these studies were conducted in 2010. Considering the worldwide increase in the number of patients undergoing HD, we conducted a nationwide cohort study to confirm the reproducibility of the prognostic improvement effects of super high-flux dialyzers in patients on HD.

Methods

Study design

This is a prospective cohort study conducted using data from the Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry (JRDR) system, a nationwide cohort of patients on dialysis in Japan. Detailed information about the JRDR has been previously published [11–13]. The JSDT conducts a survey of all dialysis facilities in Japan at the end of each year, with response rates consistently above 95% throughout the study period. These national registry data were provided by 4360 out of 4413 centers (98.8%) in 2017, 4402 out of 4458 centers (98.7%) in 2018, and 4411 out of 4487 centers (98.3%) in 2019. Therefore, this registry can be considered representative of the entire population of Japanese patients on dialysis [11–13].

The study protocol was approved by the medicine ethics committee of JSDT (Approval No. 53), and the study was conducted per the principles outlined in the Declaration of Helsinki. The ethics committee also waived consent for the use of JRDR data. The database has been completely deidentified to ensure the privacy of human subjects, and any secondary or unofficial use (i.e., any distribution to a third party, unauthorized replication or manipulation of the database, and deviation from the proposal accepted by the Committee of JRDR) has been strictly prohibited under the agreement between the principal investigators and JSDT, which reserves all rights regarding the database. This study was registered with the University Hospital Medical Information Network (UMIN000018641).

Setting and participants

In this study, we included patients undergoing maintenance HD at the end of 2017, with the observation period ending at the end of 2019. Patients who underwent maintenance HD three times a week and who had undergone maintenance dialysis for at least 6 months at the end of 2017 were included. However, patients were excluded if they were treated less than three times a week or for < 3 h per session, had undergone hemodiafiltration (HDF) or peritoneal dialysis, had a history of kidney transplantation, were less than 18 years old, and had missing data on date of birth, dialysis initiation, type of dialyzer, or outcome. The main outcome measure of this study was the time to all-cause mortality during the 2-year observation period. Patients were divided into five dialyzer groups; i.e., the type I–V groups, according to the Japanese dialyzer classification based on β2MG clearance.

Definition of the dialyzer type

In Japan, the dialyzer type is defined on the basis of β2MG clearance, and based on this definition, dialyzers are classified into five categories—types I to V—according to JSDT guidelines [4]. Type I, II, III, IV, and V dialyzers correspond to β2MG clearance of < 10, ≥ 10–30, ≥ 30–50, ≥ 50–70, and ≥ 70, respectively, at a blood flow rate of 200 mL/min, dialysate flow rate of 500 m/min, ultrafiltration rate of 15 mL/min, and membrane surface area of 1.5 m^2 [4]. Type I and type II dialyzers are defined as low-flux dialyzers, type III dialyzers as high-flux dialyzers, and type IV and type V dialyzers as protein-leaking dialyzers per the ultrafiltration rate and β2MG clearance in the international classification [1]. In particular, type V dialyzers are defined as super high-flux dialyzers in Japan (see Supplementary Table 1 for dialyzer classification details).

Statistical methods

Data are summarized using proportions, means with standard deviations, percentages, or medians with interquartile ranges, as appropriate. Categorical variables were analyzed using the chi-squared test, whereas continuous variables were compared using Student's *t*-test or the Mann–Whitney U test as appropriate. Comparisons of continuous data were performed using the repeated-measures analysis of variance with Tukey's honestly significant difference test or the Kruskal–Wallis test, as appropriate.

Baseline patient and laboratory data were collected from the JRDR database in 2017. These variables included age, sex, dialysis duration, modality, body mass index (BMI; calculated as post-HD body weight (kg)/height $(m)^2$), cause of end-stage kidney disease, systolic and diastolic blood pressure (BP), heart rate, single-pool Kt/V for urea (Kt/V), and laboratory measures including pre-HD hemoglobin, serum albumin, urea nitrogen (UN), creatinine (Cr), phosphate, calcium, intact parathyroid hormone (i-PTH), β2MG, and C-reactive protein (CRP) levels, normalized protein catabolic rate (nPCR), and history of myocardial infarction, cerebral hemorrhage, cerebral infarction, and limb amputation. Kt/V was measured using Daugirdas' equation [14].

Survival according to dialyzer type was estimated using the Kaplan–Meier method and compared using the log-rank test. To examine whether baseline basic factors, including age, sex, cause of end-stage kidney disease, and dialysis duration, predicted survival for up to 2 years of follow-up, we performed survival analyses with Cox proportional hazards regression. Additional analyses were performed after adjusting for dialysis-related factors assessed by Kt/V, β2MG levels, and systolic and diastolic BPs. Analyses were also performed with adjustments for nutrition- and inflammation-related factors, including BMI, serum albumin, UN, Cr, hemoglobin, phosphate, calcium, i-PTH, nPCR, and CRP levels. In the analyses, age, CRP levels, and hemoglobin levels were treated as continuous variables. In the final analysis, associations were examined between all-cause mortality and the five dialyzer types according to the β2MG clearance. The reference group was the Type IV dialyzer because it is the most widely used dialyzer in Japan.

To assess the robustness of the main results, several sensitivity analyses were performed. First, an age-stratified subgroup analysis was conducted, with the categories being < 70 years and ≥ 70 years (the median value served as the threshold). Second, a subgroup analysis was performed on the basis of each patient's history of cardiovascular disease (CVD) and diabetes mellitus (DM) status, given that dialyzers with a large surface area are unlikely to be used in patients with impaired cardiac function and the higher rate of comorbid CVD in patients with DM. Third, a subgroup analysis was conducted by BMI < 21 and ≥ 21 (the median value was used as the threshold). Fourth, a stratified analysis was conducted according to serum β2MG and albumin levels. Finally, considering that the dialyzer types might be associated with Kt/V, a subgroup analysis was performed according to the Kt/V quartile.

Propensity score matching was used to adjust for significant baseline covariates. The abovementioned basic factors, dialysis-related factors, and nutrition- and inflammation-related factors were used to calculate propensity scores, which were then used in univariate Cox proportional hazards regression analysis. Patients with the type IV dialyzer (reference group) were matched in a 1:1 ratio with patients with the other types of dialyzers. Propensity scores were derived from age, sex, dialysis vintage, comorbid CVD and DM, systolic and diastolic BPs, heart rate, BMI, Kt/V, β2MG, serum albumin, UN, Cr, hemoglobin, phosphate, calcium, i-PTH, CRP levels, and nPCR values. All-cause mortality was also compared in propensity score-matched patients.

When appropriate, missing covariate data were imputed using a conventional method for multivariate regression. All analyses were performed using JMP® version 13.0 (SAS Institute, Cary, NC). The significance threshold was set at $P < 0.05$.

Results

Baseline characteristics of patients

At the end of 2017, 365,809 patients were initially registered for the study. In the end, 181,879 of them were eligible for the analysis (Fig. 1). Table 1 shows the baseline characteristics of the 181,879 patients (age, 69.5 ± 12.2 years; male, 64.9%; median dialysis duration, 67 months) with dialyzer type data. The underlying conditions comprised diabetic nephropathy in 39.7%, chronic glomerulonephritis in 29.8%, nephrosclerosis in 12.1%, and other conditions in 18.4% of cases. In the type I and type II groups, there were older patients, more female patients, a shorter dialysis vintage, higher rates of comorbid CVDs, lower BMI, lower Cr, lower serum albumin, lower Kt/V values, lower phosphate, and lower nPCR values. During the 2-year observation period from January 2018 to December 2019, 34,196 patients (18.8%) died, whereas 147,683 patients (81.2%) survived.

Predictors of all-cause mortality in 181,879 patients undergoing hemodialysis

The hazard ratios (HRs) and 95% confidence intervals for variables that were evaluated as potential predictors of mortality in hemodialysis patients are shown in Supplementary Table 2. Statistically significant predictors

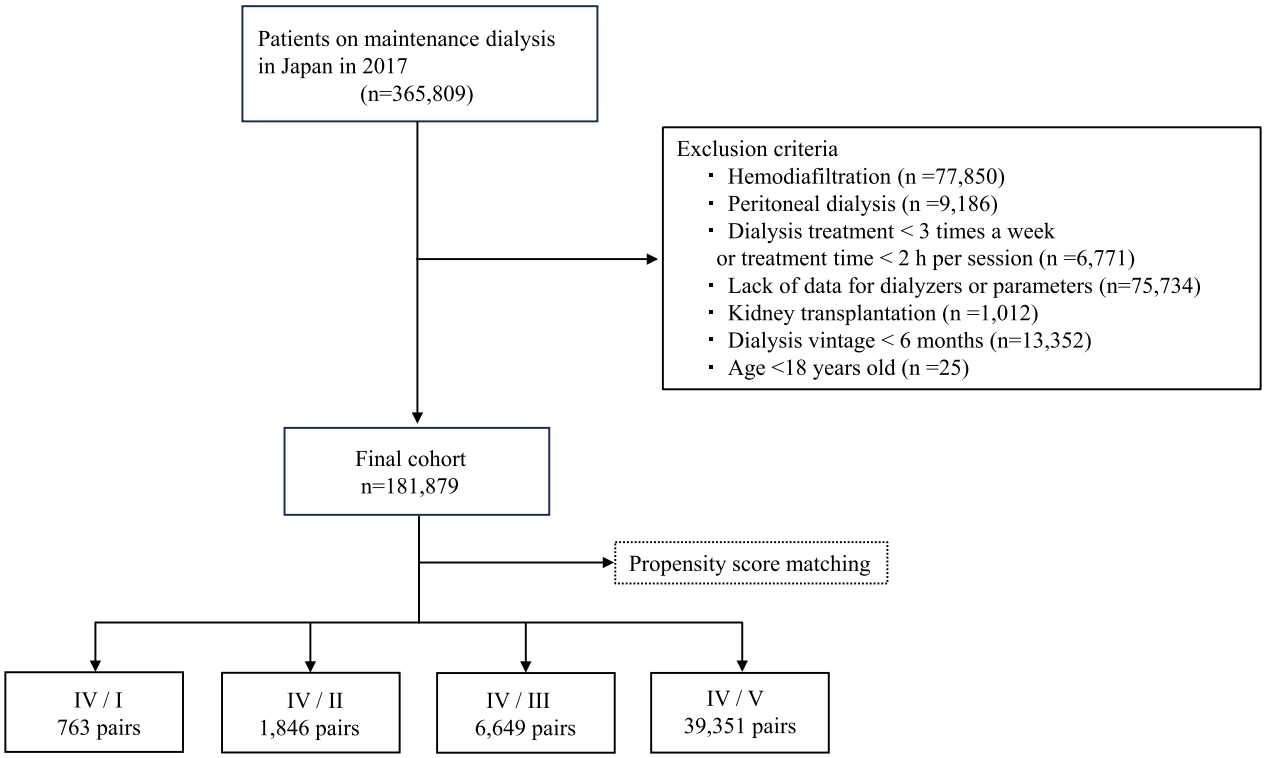


Fig. 1 Flow diagram of the patient selection process

of mortality among the basic factors were the male sex, older age, longer dialysis duration, comorbid CVD, and presence of DM. Regarding dialysis-related factors, a lower mortality risk was associated with higher Kt/V and lower β2MG levels. Furthermore, for nutrition- and inflammation-related factors, higher mortality was associated with poor nutritional status, as indicated by lower hemoglobin, serum albumin, BMI, and nPCR values, and with increased inflammatory status, as indicated by higher CRP levels.

Associations of the five dialyzer groups with all-cause mortality

Kaplan–Meier analyses revealed that survival varied steadily depending on the dialyzer type (log-rank test, $P < 0.0001$; Fig. 2). Compared with the IV group (reference), the types I, II, and III groups had a higher unadjusted HR (95% confidence interval) for all-cause mortality of 2.47 (2.28–2.69), 2.17 (2.04–2.31), and 1.31 (1.26–1.37), respectively. In contrast, the V group showed a lower unadjusted HR for all-cause mortality 0.62 (0.61–0.64). (Supplementary Table 3).

The adjusted HRs for all-cause mortality in each group are shown in Fig. 3. After adjustment for basic factors, including age, sex, dialysis duration, history of CVD, and presence or absence of DM, the types I, II, and III groups had a higher HR (95% confidence interval) for all-cause mortality of 1.88 (1.72–2.05), 1.61 (1.51–1.71), and 1.17 (1.12–1.22), respectively. In contrast, the type V group showed a lower HR for all-cause mortality of 0.77 (0.75–0.79; Supplementary Table 3). After adjustment for basic factors and dialysis-related factors (including Kt/V, β2MG levels, and systolic and diastolic BPs), the types I, II, and III groups had a higher HR (95% confidence interval) for all-cause mortality of 1.38 (1.25–1.52), 1.25 (1.16–1.34), and 1.10 (1.04–1.15), respectively. In contrast, the type V group showed a lower HR for all-cause mortality of 0.81 (0.78–0.83; Supplementary Table 3). Finally, after adjustment for basic factors, dialysis-related factors, and nutrition- and inflammation-related factors, including BMI, serum albumin, UN, Cr, hemoglobin, phosphate, calcium, i-PTH, nPCR, and CRP levels, the types I, II, and III groups had a higher HR (95% confidence interval) for all-cause mortality of 1.25 (1.12–1.39), 1.21 (1.13–1.31), and 1.07 (1.02–1.13), respectively. In contrast, the V group showed a lower HR for all-cause mortality of 0.86 (0.80–0.92). (Supplementary Table 3).

The sensitivity analysis yielded similar results. After adjusting for all covariates, the risk of all-cause death was lower in the type V group regardless of age, comorbid CVD or DM, BMI, β2MG, or serum albumin levels (Fig. 4 and Supplementary Table 4). Analyses performed

Table 1 Demographic, clinical, and laboratory values of 181,879 hemodialysis patients according to dialyzer type

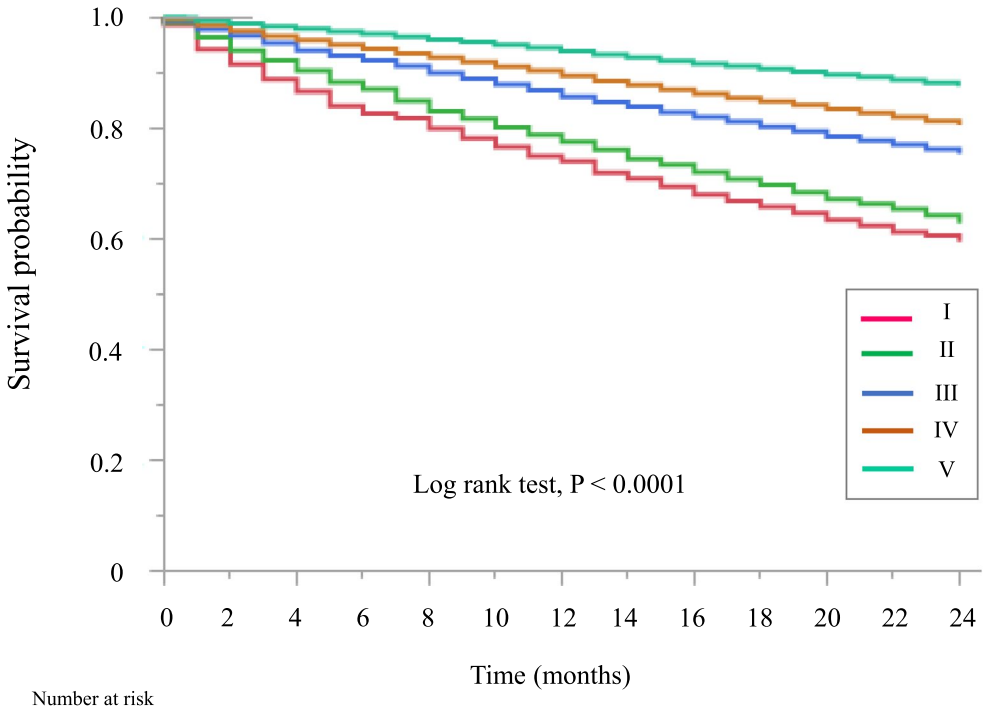
Variable	I	II	III	IV	V	*P* value
n (%male)	1506 (47.0)	3277 (49.6)	10,689 (56.8)	97,927 (62.1)	68,480 (71.2)	< 0.0001
Age, years	77.8 ± 9.8	77.4 ± 10.1	73.3 ± 11.5	70.9 ± 11.8	66.2 ± 12.1	< 0.0001
Vintage, months	46 (19–101)	46 (21–98)	53 (23–109)	61 (28–121)	79 (38–145)	< 0.0001
Cause of ESKD, %						< 0.0001
Diabetic nephropathy	38.9	38.2	40.3	39.9	39.5	
Chronic glomerulonephritis	26.8	24.1	26.7	29.0	31.8	
Nephrosclerosis	15.3	15.1	13.9	12.6	10.8	
Others	19.0	22.6	19.1	18.5	17.9	
Diabetes mellitus, %	56.8	57.2	56.3	54.2	53.9	< 0.0001
Comorbid CVD, %	41.2	42.7	35.7	35.2	31.7	< 0.0001
Systolic BP, mmHg	146 ± 27	147 ± 27	149 ± 25	150 ± 25	152 ± 24	< 0.0001
Diastolic BP, mmHg	73 ± 15	73 ± 15	75 ± 14	76 ± 14	79 ± 15	< 0.0001
Heart rate, bpm	74 ± 13	73 ± 13	74 ± 13	74 ± 13	75 ± 13	< 0.0001
Body mass index, kg/m^2	19.4 ± 3.5	19.7 ± 3.5	20.8 ± 3.8	21.3 ± 3.9	22.3 ± 4.2	< 0.0001
Serum urea nitrogen, mg/dL	56.4 ± 18.7	55.5 ± 17.5	59.6 ± 16.5	59.6 ± 15.8	61.4 ± 15.4	< 0.0001
Creatinine, mg/dL	7.0 ± 2.7	7.4 ± 2.7	8.7 ± 2.7	9.4 ± 2.8	10.6 ± 2.7	< 0.0001
β_2-microglobulin, mg/L	31.1 ± 11.6	30.1 ± 9.9	27.5 ± 7.4	26.9 ± 6.9	27.3 ± 6.3	< 0.0001
Kt/V	1.31 ± 0.31	1.35 ± 0.31	1.46 ± 0.31	1.47 ± 0.31	1.49 ± 0.30	< 0.0001
Serum albumin, g/dL	3.1 ± 0.6	3.2 ± 0.6	3.5 ± 0.5	3.5 ± 0.5	3.6 ± 0.4	< 0.0001
Hemoglobin, g/dL	10.4 ± 1.5	10.5 ± 1.4	10.7 ± 1.3	10.8 ± 1.3	10.9 ± 1.3	< 0.0001
C-reactive protein, mg/dL	0.30 (0.09–1.15)	0.25 (0.08–0.90)	0.19 (0.07–0.60)	0.16 (0.06–0.50)	0.14 (0.05–0.41)	< 0.0001
Calcium, mg/dL	8.5 ± 0.8	8.5 ± 0.8	8.6 ± 0.8	8.7 ± 0.7	8.7 ± 0.7	< 0.0001
Phosphate, mg/dL	4.8 ± 1.7	4.8 ± 1.5	5.0 ± 1.5	5.1 ± 1.4	5.3 ± 1.5	< 0.0001
Intact-PTH, pg/mL	108 (54–194)	110 (57–188)	126 (67–205)	127 (69–205)	136 (77–215)	< 0.0001
nPCR, g/kg/day	0.77 ± 0.20	0.77 ± 0.19	0.84 ± 0.18	0.84 ± 0.18	0.86 ± 0.17	< 0.0001

Data are shown as frequencies (percentages), mean ± standard deviation, or median (interquartile range). *BP*, blood pressure; *CVD*, cardiovascular disease; *ESKD*, end-stage kidney disease; *nPCR*, normalized protein catabolic rate; *PTH*, parathyroid hormone

using the Cox proportional hazards model revealed that both dialyzer types and Kt/V were significantly and independently associated with all-cause mortality after adjusting for covariates. Adjusted associations between Kt/V and mortality varied across the dialyzer type groups (*P* interaction = 0.001). The type V group had a significantly lower adjusted mortality risk regardless of Kt/V (Fig. 5 and Supplementary Table 5).

Propensity score matching analysis

Patients treated with Type IV dialyzers were matched with those treated with other types of dialyzers in a 1:1 ratio according to their propensity scores. After propensity score matching, 763, 1846, 6649, and 39,351 patient pairs were matched in the type I, II, III, and V groups, respectively. Table 2 shows the patient characteristics and clinical data at baseline in type IV and I groups before and after propensity score matching. There were no significant differences in any of the variables. As shown in Fig. 6a, compared with the type IV group, the type I group had a higher HR (HR 1.20, 95% CI 1.03–1.40, $P = 0.024$). Table 3 shows the patient characteristics and clinical data at baseline in the type IV and II groups before and after propensity score matching. Although there were no significant differences in any variables, compared with the type IV group, the type II group had a higher HR (HR 1.13, 95% CI 1.01–1.27, $P = 0.028$; Fig. 6b). Table 4 shows the patient characteristics and clinical data at baseline in the type IV and III groups before and after propensity score matching. There were no significant differences in any variables. As shown in Fig. 6c, compared with the type IV group, the Type III group had a higher HR (HR 1.10, 95% CI 1.02–1.18, $P = 0.012$). Table 5 shows the patient characteristics and clinical data at baseline in the type IV and V groups before and after propensity score matching. There were no significant differences in any variables. As shown in Fig. 6d, compared with the type IV group, the type V group had a lower HR (HR 0.91, 95% CI 0.87–0.94, $P < 0.0001$).



Number at risk

I	1,385	1,231	1,135	1,040	963	897	841
II	3,075	2,838	2,615	2,427	2,260	2,106	1,978
III	10,534	10,054	4,202	9,162	8,743	8,373	8,038
IV	96,227	93,111	90,076	87,015	83,773	81,118	78,353
V	67,926	66,790	65,494	64,135	62,544	61,170	59,800

Fig. 2 Kaplan–Meier survival curve for all-cause mortality in the five dialyzer type groups

Discussion

This cohort study provides reproducibility that supports improved survival associated with super high-flux dialyzers. This study analyzed data from a large-scale registry of 181,879 Japanese patients on HD, with a 2-year follow-up period. The results demonstrate a significant association between type V group and lower all-cause mortality. Mortality rates were compared among the five groups, considering predictive factors and adjusting for confounders. After adjusting for predictive factors and using propensity score matching, HR was significantly lower in the type V group than in the type IV group (reference). Furthermore, HRs for the type V group were consistently, significantly lower regardless of age, history of CVD, presence or absence of DM, BMI, serum albumin levels, and β2MG levels. In addition, this study revealed the superiority of super high-flux dialyzers as indicated by a higher β2MG clearance regardless of Kt/V. Although our previous studies were conducted in 2008–2010, some dialyzers have been discontinued, and others were newly released in 2017. The major strengths of this study include its large sample size and the inclusion of all current dialyzer types used in Japan.

Recently, not only small and medium-sized molecules (such as β2MG with a molecular weight of 11.8 kDa) but also medium-sized and large molecules, such as α_1-microglobulin (molecular weight: 33.0 kDa) and protein-bound uremic toxins, have been targeted for removal in patients on HD, which might improve prognosis [3, 15, 16]. Patients in the type I and II groups were characterized as elderly and malnourished. However, HRs for the type I and II groups were higher, even after adjusting for nutritional- and inflammation-related factors. Therefore, the performance of the dialyzers has been improved to achieve great removal of medium-middle to large-middle molecules. The medium cutoff dialyzer is defined by a β2MG clearance of > 80 mL/min, a high ultrafiltration coefficient (i.e., 40–60 mL/h/mmHg/m^2), and a sieving coefficient of albumin < 0.01 at a blood flow rate of 300–400 mL/min, dialysate flow rate of 500 mL/min, and membrane surface area of 1.7 m^2 [1, 17]. Protein-leaking dialyzers are characterized by not only a higher β2MG clearance of > 80 mL/min but also a higher ultrafiltration coefficient of > 40 mL/h/mmHg/m^2 and a sieving coefficient of albumin < 0.03 [1, 9]. Super high-flux dialyzers are also characterized by a higher β2MG clearance

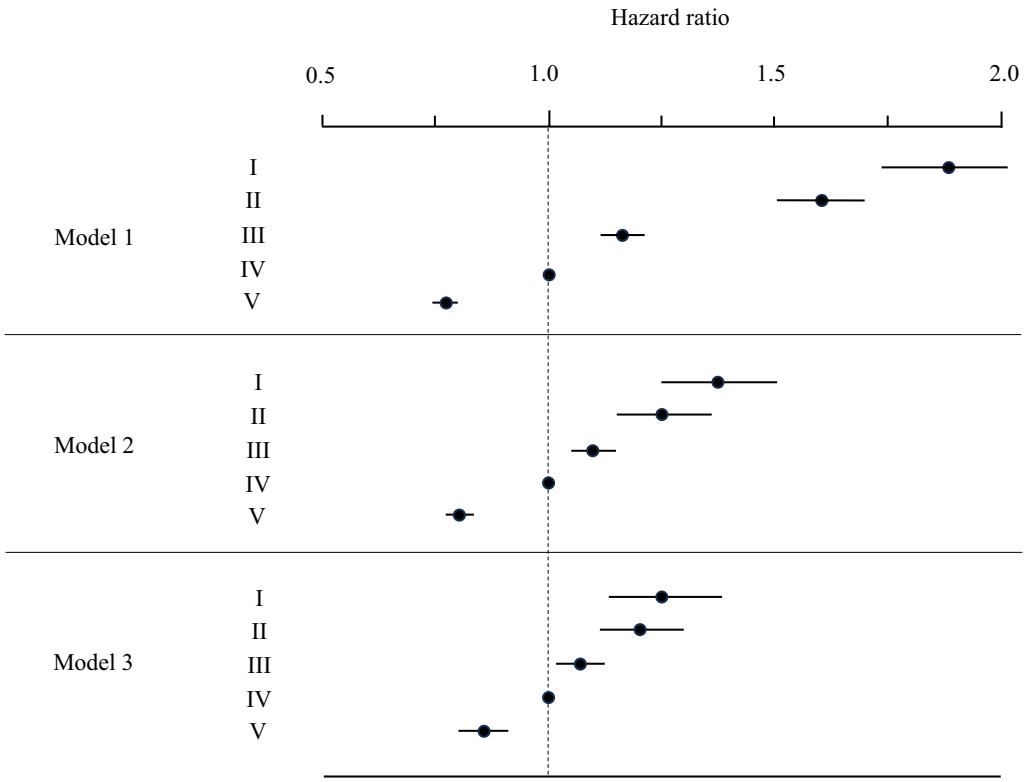


Fig. 3 Comparison of all-cause mortality among the five dialyzer type groups using Cox proportional hazards regression. The circles indicate the hazard ratios, and the bars correspond to 95% confidence intervals. Model 1 was adjusted for basic factors, including age, sex, dialysis vintage, the presence or absence of diabetes mellitus, and the presence or absence of cardiovascular complications. Model 2 was adjusted for dialysis-related factors, including Kt/V values, β2-microglobulin levels, and systolic and diastolic blood pressure values, in addition to basic factors. Model 3 was adjusted for basic factors, dialysis-related factors, and nutrition- and inflammation-related factors, including body mass index, serum albumin, urea nitrogen, creatinine, hemoglobin, phosphate, calcium, intact parathyroid hormone, normalized protein catabolic rate, and C-reactive protein levels

of > 70 mL/min and a higher ultrafiltration coefficient of > 40 mL/h/mmHg/m^2. This study demonstrated that type V groups, which are super high-flux dialyzers have the best prognosis. Furthermore, super high-flux dialyzers might have a higher back filtration rate than conventional low-flux dialyzers to remove uremic toxins. Therefore, dialysate purification is essential for using super high-flux dialyzers. The JSDT standard for endotoxin level in dialysate (< 0.050 EU/mL) was achieved in 96.6% of facilities in Japan in 2017, and the JSDT standard for bacterial cell counts in dialysis fluid (< 100 cfu/mL) was achieved in 99.0% in 2017 [18]. Therefore, excellent water quality might be an important factor that improves the prognosis of hemodialysis patients in Japan and contributed to the lower CRP levels in this study.

Mortality did not differ significantly between low-flux and high-flux dialyzers in the HEMO study, which was a large randomized controlled study [19]. Increments in the dialysis dose and clearance of small molecules were not associated with improved outcomes in patients on HD in the HEMO study. However, in patients with a longer dialysis duration (more than 3.7 years), high-flux dialyzers were associated with significantly better survival than low-flux dialyzers in a subgroup analysis [2]. In addition, after adjusting for residual kidney function and dialysis duration, the pre-HD β2MG level was found to be an independent predictor of mortality [20]. Meanwhile, the β2MG level in the Type V group was higher than that in the Type IV group. Most patients in the Type V group were younger males, which means they had high uremic toxin accumulation. The type V dialyzer may have been selected to improve removal efficiency in these patients. However, in stratified analyses, the prognosis was better for the type V group regardless of the β2MG level at pre-HD. Therefore, the evaluation of post-HD β2MG levels and removal rates may also be necessary in the future. Another large randomized controlled study (the Membrane Permeability Outcome study) revealed that high-flux dialyzers were associated with significantly better survival than low-flux dialyzers in patients with diabetes or serum albumin levels of < 4.0 g/dL [21]. A systematic review also found significant benefits of high-flux

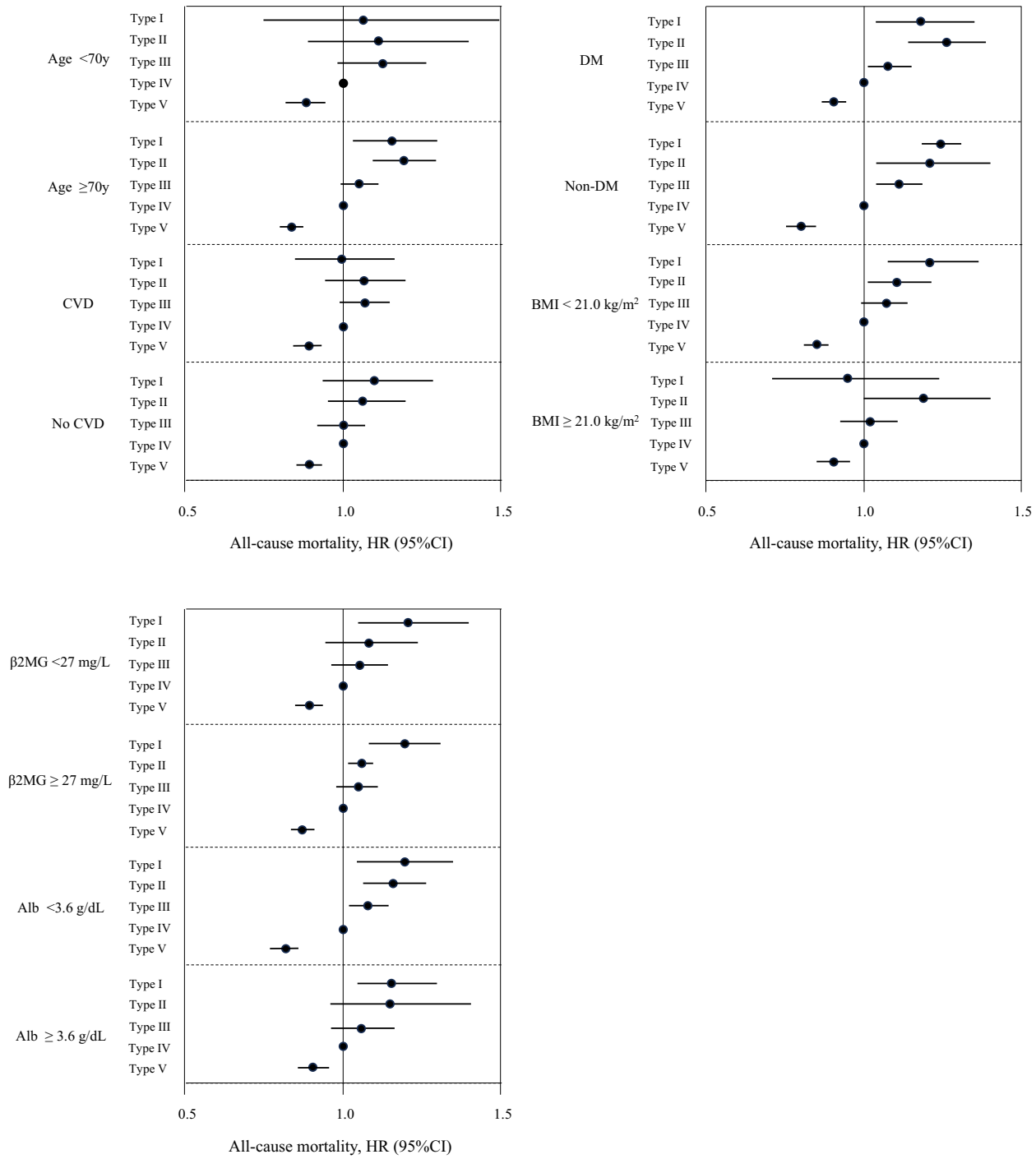


Fig. 4 Comparison of hazard ratios (95% confidence intervals) for all-cause mortality according to dialyzer type and stratified by median values of age, body mass index, β_2-microglobulin, and serum albumin levels, and comorbid cardiovascular disease or diabetes mellitus at baseline. β2MG, β_2-microglobulin; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio

dialyzers on all-cause mortality for certain prespecified conditions, such as a serum albumin level of < 4 g/dL, a maintenance HD duration of > 3.7 years, and the presence of diabetes or arteriovenous fistula [22]. However, in the present study, super high-flux dialyzers improved survival consistently, regardless of serum albumin and β2MG levels at baseline, comorbid CVD, and presence or absence of DM.

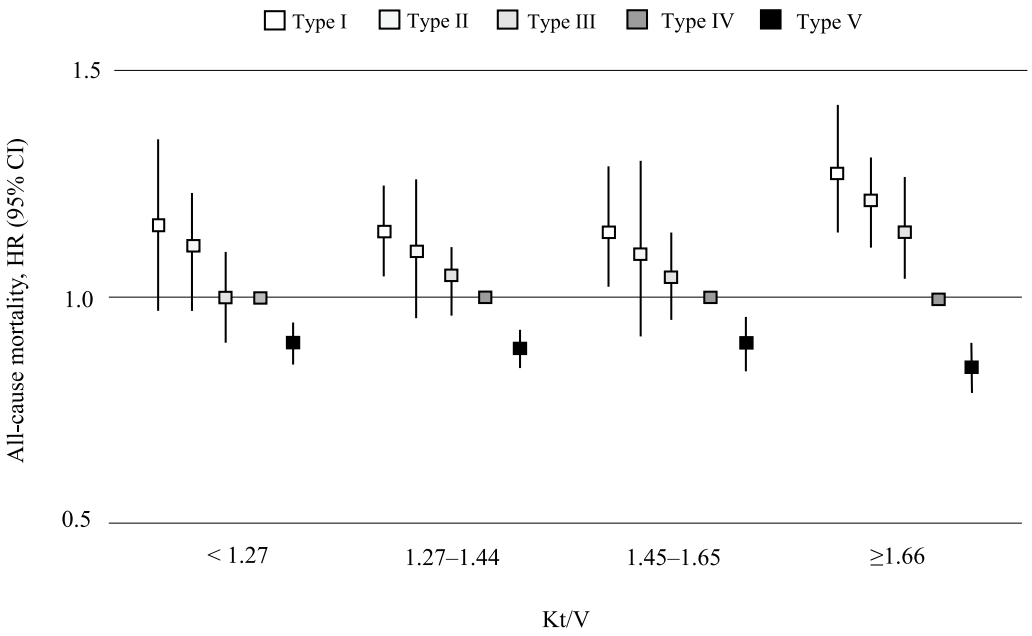


Fig. 5 Hazard ratios (95% confidence intervals) for all-cause mortality according to dialyzer type and all-cause mortality stratified by Kt/V. CI, confidence interval; HR, hazard ratio

Table 2 Comparison of variables before and after propensity score matching in type IV and type I groups

Variable	Before matching			After matching		
	IV	I	*P* value	IV	I	*P* value
n (%male)	97,927 (62.1)	1506 (47.0)	< 0.0001	763 (42.6)	763 (44.9)	0.353
Age, years	70.9 ± 11.8	77.8 ± 9.8	< 0.0001	77.9 ± 9.7	78.1 ± 9.7	0.768
Vintage, months	61 (28–121)	46 (19–101)	< 0.0001	44 (17–100)	44 (19–99)	0.712
Diabetes mellitus, %	54.2	56.8	0.078	51.3	52.9	0.505
Comorbid CVD, %	35.2	41.2	< 0.0001	45.2	47.2	0.441
Systolic BP, mmHg	150 ± 25	146 ± 27	< 0.0001	148 ± 27	149 ± 27	0.605
Diastolic BP, mmHg	76 ± 14	73 ± 15	< 0.0001	73 ± 15	74 ± 14	0.886
Heart rate, bpm	74 ± 13	74 ± 13	0.791	73 ± 13	73 ± 13	0.580
BMI, kg/m^2	21.3 ± 3.9	19.4 ± 3.5	< 0.0001	19.3 ± 3.5	19.3 ± 3.5	0.871
Serum UN, mg/dL	59.6 ± 15.8	56.4 ± 18.7	< 0.0001	56.4 ± 16.0	55.9 ± 17.3	0.519
Creatinine, mg/dL	9.4 ± 2.8	7.0 ± 2.7	< 0.0001	6.9 ± 2.5	7.0 ± 2.5	0.417
β2MG, mg/L	26.9 ± 6.9	31.1 ± 11.6	< 0.0001	30.6 ± 10.7	31.3 ± 11.5	0.203
Kt/V	1.47 ± 0.31	1.31 ± 0.31	< 0.0001	1.33 ± 0.30	1.32 ± 0.29	0.269
Serum albumin, g/dL	3.5 ± 0.5	3.1 ± 0.6	< 0.0001	3.2 ± 0.5	3.2 ± 0.5	0.871
Hemoglobin, g/dL	10.8 ± 1.3	10.4 ± 1.5	< 0.0001	10.5 ± 1.4	10.5 ± 1.4	0.501
CRP, mg/dL	0.16 (0.06–0.50)	0.30 (0.09–1.15)	< 0.0001	0.25 (0.08–0.80)	0.24 (0.08–0.93)	0.456
Calcium, mg/dL	8.7 ± 0.7	8.5 ± 0.8	< 0.0001	8.5 ± 0.8	8.5 ± 0.8	0.570
Phosphate, mg/dL	5.1 ± 1.4	4.8 ± 1.7	< 0.0001	4.7 ± 1.5	4.8 ± 11.6	0.362
Intact-PTH, pg/mL	127 (69–205)	108 (54–194)	0.001	107 (54–186)	110 (54–189)	0.689
nPCR, g/kg/day	0.84 ± 0.18	0.77 ± 0.20	< 0.0001	0.78 ± 0.17	0.77 ± 0.18	0.217

Data are shown as frequencies (percentages), mean ± standard deviation, or median (interquartile range). *β2MG*, β_2-microglobulin; *BMI*, body mass index; *BP*, blood pressure; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *nPCR*, normalized protein catabolic rate; *UN*, urea nitrogen; *PTH*, parathyroid hormone

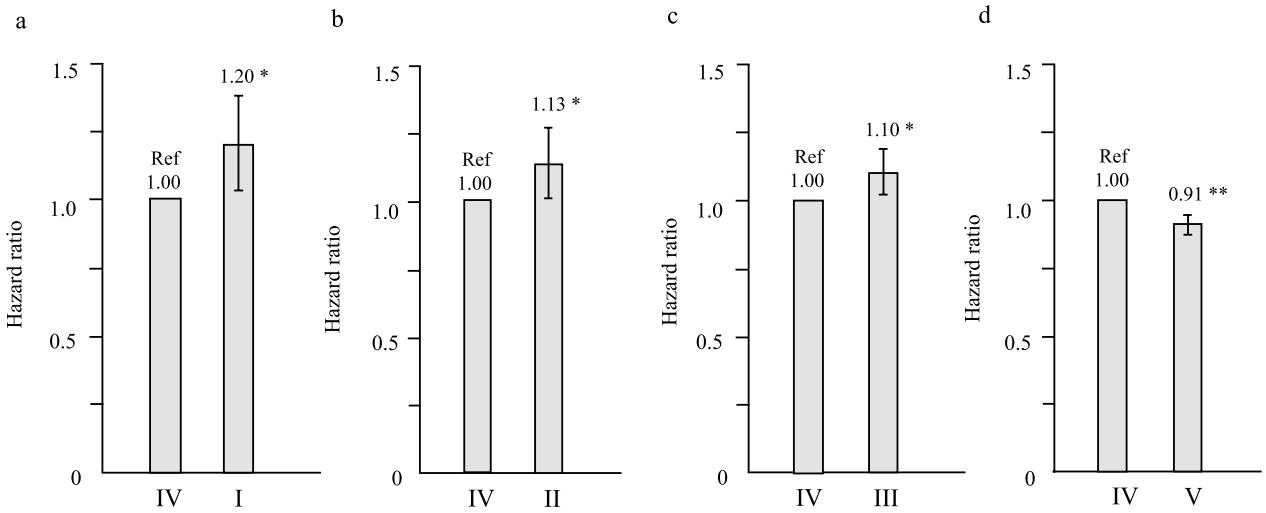


Fig. 6 **a** Hazard ratios for all-cause mortality after propensity score matching determined using Cox proportional hazard regression. **a** The type I group against the type IV group (reference); **b** the type II group against the type IV group (reference); **c** the type III group against the type IV group (reference); **d** the type V group against the type IV group (reference). *$P < 0.05$, **$P < 0.0001$ versus the type IV group. Error bars correspond to 95% confidence intervals

Table 3 Comparison of variables before and after propensity score matching in type IV and type II groups

Variable	Before matching			After matching		
	IV	II	P value	IV	II	*P* value
n (%male)	97,927 (62.1)	3277 (49.6)	< 0.0001	1846 (51.7)	1846 (49.7)	0.223
Age, years	70.9 ± 11.8	77.4 ± 10.1	< 0.0001	77.3 ± 9.8	77.0 ± 10.1	0.396
Vintage, months	61 (28–121)	46 (21–98)	< 0.0001	47 (21–90)	47 (21–95)	0.120
Diabetes mellitus, %	54.2	57.2	0.003	54.3	56.9	0.105
Comorbid CVD, %	35.2	42.7	< 0.0001	42.6	44.8	0.185
Systolic BP, mmHg	150 ± 25	147 ± 27	< 0.0001	149 ± 25	149 ± 26	0.870
Diastolic BP, mmHg	76 ± 14	73 ± 15	< 0.0001	74 ± 14	74 ± 14	0.214
Heart rate, bpm	74 ± 13	73 ± 13	0.006	73 ± 13	73 ± 13	0.298
BMI, kg/m^2	21.3 ± 3.9	19.7 ± 3.5	< 0.0001	19.9 ± 3.6	19.8 ± 3.6	0.373
Serum UN, mg/dL	59.6 ± 15.8	55.5 ± 17.5	< 0.0001	60.7 ± 15.3	60.8 ± 15.2	0.088
Creatinine, mg/dL	9.4 ± 2.8	7.4 ± 2.7	< 0.0001	10.1 ± 2.7	10.2 ± 2.7	0.739
β2MG, mg/L	26.9 ± 6.9	30.1 ± 9.9	< 0.0001	29.8 ± 9.6	30.0 ± 9.9	0.135
Kt/V	1.47 ± 0.31	1.35 ± 0.31	< 0.0001	1.37 ± 0.32	1.36 ± 0.31	0.363
Serum albumin, g/dL	3.5 ± 0.5	3.2 ± 0.6	< 0.0001	3.6 ± 0.4	3.6 ± 0.4	0.546
Hemoglobin, g/dL	10.8 ± 1.3	10.5 ± 1.4	< 0.0001	10.6 ± 1.3	10.6 ± 1.3	0.587
CRP, mg/dL	0.16 (0.06–0.50)	0.25 (0.08–0.90)	< 0.0001	0.21 (0.07–0.66)	0.21 (0.07–0.69)	0.637
Calcium, mg/dL	8.7 ± 0.7	8.5 ± 0.8	< 0.0001	8.5 ± 0.8	8.5 ± 0.8	0.329
Phosphate, mg/dL	5.1 ± 1.4	4.8 ± 1.5	< 0.0001	4.8 ± 1.4	4.8 ± 1.4	0.773
Intact-PTH, pg/mL	127 (69–205)	110 (57–188)	< 0.0001	112 (60–193)	111 (54–187)	0.567
nPCR, g/kg/day	0.84 ± 0.18	0.77 ± 0.19	< 0.0001	0.77 ± 0.18	0.77 ± 0.17	0.303

Data are shown as frequencies (percentages), mean ± standard deviation, or median (interquartile range). *β2MG*, β_2-microglobulin; *BMI*, body mass index; *BP*, blood pressure; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *nPCR*, normalized protein catabolic rate; *UN*, urea nitrogen; *PTH*, parathyroid hormone

Table 4 Comparison of variables before and after propensity score matching in type IV and type III groups

Variable	Before matching			After matching		
	IV	III	*P* value	IV	III	*P* value
n (%male)	97,927 (62.1)	10,689 (56.8)	< 0.0001	6,649 (56.9)	6,649 (57.4)	0.559
Age, years	70.9 ± 11.8	73.3 ± 11.5	< 0.0001	72.9 ± 10.9	73.0 ± 11.4	0.545
Vintage, months	61 (28–121)	53 (23–109)	< 0.0001	52 (23–107)	52 (23–107)	0.856
Diabetes mellitus, %	54.2	56.3	0.0003	55.4	55.3	0.616
Comorbid CVD, %	35.2	35.7	0.291	38.1	38.7	0.487
Systolic BP, mmHg	150 ± 25	149 ± 25	< 0.0001	150 ± 25	150 ± 24	0.919
Diastolic BP, mmHg	76 ± 14	75 ± 14	< 0.0001	75 ± 14	75 ± 14	0.564
Heart rate, bpm	74 ± 13	74 ± 13	0.003	73 ± 13	73 ± 13	0.092
BMI, kg/m^2	21.3 ± 3.9	20.8 ± 3.8	< 0.0001	20.9 ± 3.7	20.9 ± 3.8	0.903
Serum UN, mg/dL	59.6 ± 15.8	59.6 ± 16.5	0.670	60.0 ± 15.7	60.0 ± 15.9	0.442
Creatinine, mg/dL	9.4 ± 2.8	8.7 ± 2.7	< 0.0001	8.8 ± 2.6	8.8 ± 2.6	0.636
β2MG, mg/L	26.9 ± 6.9	27.5 ± 7.4	< 0.0001	27.4 ± 7.3	27.5 ± 7.3	0.905
Kt/V	1.47 ± 0.31	1.46 ± 0.31	0.039	1.47 ± 0.31	1.47 ± 0.30	0.757
Serum albumin, g/dL	3.5 ± 0.5	3.5 ± 0.5	< 0.0001	3.5 ± 0.4	3.5 ± 0.4	0.375
Hemoglobin, g/dL	10.8 ± 1.3	10.7 ± 1.3	< 0.0001	10.7 ± 1.3	10.7 ± 1.2	0.952
CRP, mg/dL	0.16 (0.06–0.50)	0.19 (0.07–0.60)	< 0.0001	0.16 (0.06–0.48)	0.17 (0.06–0.55)	0.786
Calcium, mg/dL	8.7 ± 0.7	8.6 ± 0.8	0.015	8.6 ± 0.7	8.6 ± 0.7	0.289
Phosphate, mg/dL	5.1 ± 1.4	5.0 ± 1.5	< 0.0001	5.0 ± 1.4	5.0 ± 1.4	0.832
Intact-PTH, pg/mL	127 (69–205)	126 (67–205)	0.494	124 (69–201)	128 (69–205)	0.428
nPCR, g/kg/day	0.84 ± 0.18	0.84 ± 0.18	0.144	0.84 ± 0.18	0.84 ± 0.18	0.997

Data are shown as frequencies (percentages), mean ± standard deviation, or median [interquartile range]. *β2MG*, β_2-microglobulin; *BMI*, body mass index; *BP*, blood pressure; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *nPCR*, normalized protein catabolic rate; *UN*, urea nitrogen; *PTH*, parathyroid hormone

The Kt/V for urea is used as an indicator of dialysis efficiency because it is correlated with treatment outcomes in patients on HD [23]. Because urea accumulation determines the need for dialysis and its removal determines the efficiency of the former, the Kt/V for urea is a suitable marker for patients on HD. To increase uremic toxin removal, the Renal Association recommends the use of high-flux dialyzers and a minimum HD time of 12 h per week for patients treated thrice weekly [24]. Furthermore, the Kidney Disease Outcomes Quality Initiative (KDOQI) and JSDT guidelines recommended a dialysis dose assessed by Kt/V of 1.4 per hemodialysis session and a minimum delivered Kt/V of 1.2 [4, 25]. Kt/V can be increased by increasing the blood or dialysate flow rate, dialyzer surface area, and treatment time. Although treatment time and membrane flux determine the Kt/V, prolonged HD treatment time and membrane surface area were found to be associated with lower mortality risk even with the same Kt/V level [26, 27]. In addition, this study revealed that the super high-flux dialyzer group had the best prognosis, even at the same Kt/V in the analysis stratified by Kt/V. Therefore, predictors of prognosis other than Kt/V may exist for patients on HD. Thus, in patients who can tolerate super high-flux dialyzers, low mortality rates may be achieved even when the Kt/V is low. However, further studies are needed to confirm whether super high-flux dialyzers are associated with better prognoses because of the removal of larger amounts of small-, medium-, and large-sized molecules, as we could not assess the clearance of these toxins.

This study has several limitations that should be considered. First, the number of patients differed among the five groups, which is inherent to the use of the annual survey and the observational cohort study design employed. The number of patients in the type I and II groups was small. However, after conducting a propensity score matching analysis, the superiority of type V dialyzers was confirmed. Second, important information regarding the facility effects or practice patterns of the dialysis unit was unavailable. These factors could act as potential confounders and may contribute to variations in mortality rates among different centers because of differences in center practices and patient populations. Third, we could not evaluate the cost-effectiveness of super high-flux dialyzers. Costs of dialyzers may differ from country to country. However, the cost difference is not much in Japan. The costs of type I–III, IV, and V dialyzers are 14.4, 14.5, and 15.2 USD, respectively. Our findings should be broadly generalizable to the Japanese dialysis population and may be helpful in other countries

Table 5 Comparison of variables before and after propensity score matching in type IV and type V groups

Variable	Before matching			After matching		
	IV	V	*P* value	IV	V	*P* value
n (%male)	97,927 (62.1)	68,480 (71.2)	< 0.0001	39,351 (69.4)	39,351 (69.4)	0.914
Age, years	70.9 ± 11.8	66.2 12.1	< 0.0001	67.5 ± 11.8	67.5 ± 11.3	0.465
Vintage, months	61 (28–121)	79 (38–145)	< 0.0001	74 (36–140)	76 (37–141)	0.272
Diabetes mellitus, %	54.2	53.9	0.063	52.8	53.1	0.443
Comorbid CVD, %	35.2	31.7	< 0.0001	34.1	34.1	0.988
Systolic BP, mmHg	150 ± 25	152 ± 24	< 0.0001	152 ± 24	152 ± 24	0.547
Diastolic BP, mmHg	76 ± 14	79 ± 15	< 0.0001	79 ± 14	79 ± 14	0.548
Heart rate, bpm	74 ± 13	75 ± 13	< 0.0001	75 ± 13	75 ± 13	0.656
BMI, kg/m^2	21.3 ± 3.9	22.3 ± 4.2	< 0.0001	22.1 ± 3.9	22.1 ± 3.9	0.766
Serum UN, mg/dL	59.6 ± 15.8	61.4 ± 15.4	< 0.0001	61.0 ± 15.2	61.0 ± 15.2	0.486
Creatinine, mg/dL	9.4 ± 2.8	10.6 ± 2.7	< 0.0001	10.3 ± 2.6	10.3 ± 2.6	0.749
β2MG, mg/L	26.9 ± 6.9	27.3 ± 6.3	< 0.0001	27.2 ± 6.4	27.2 ± 6.4	0.709
Kt/V	1.47 ± 0.31	1.49 ± 0.30	< 0.0001	1.49 ± 0.29	1.49 ± 0.30	0.557
Serum albumin, g/dL	3.5 ± 0.5	3.6 ± 0.4	< 0.0001	3.6 ± 0.4	3.6 ± 0.4	0.612
Hemoglobin, g/dL	10.8 ± 1.3	10.9 ± 1.3	< 0.0001	10.9 ± 1.2	10.9 ± 1.2	0.860
CRP, mg/dL	0.16 (0.06–0.50)	0.14 (0.05–0.41)	< 0.0001	0.14 (0.06–0.41)	0.13 (0.05–0.40)	0.922
Calcium, mg/dL	8.7 ± 0.7	8.7 ± 0.7	< 0.0001	8.7 ± 0.7	8.7 ± 0.7	0.120
Phosphate, mg/dL	5.1 ± 1.4	5.3 ± 1.5	< 0.0001	5.3 ± 1.4	5.3 ± 1.4	0.226
Intact-PTH, pg/mL	127 (69–205)	136 (77–215)	< 0.0001	133 (74–210)	135 (77–212)	0.114
nPCR, g/kg/day	0.84 ± 0.18	0.86 ± 0.17	< 0.0001	0.86 ± 0.17	0.86 ± 0.17	0.270

Data are shown as frequencies (percentages), mean ± standard deviation, or median [interquartile range]. *β2MG*, β_2-microglobulin; *BMI*, body mass index; *BP*, blood pressure; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *nPCR*, normalized protein catabolic rate; *UN*, urea nitrogen; *PTH*, parathyroid hormone

where low- or high-flux membrane dialyzers are used. However, cost-effectiveness analyses might be needed in the future. Finally, patients treated with HDF were excluded from the present study to eliminate modality bias. However, the number of patients undergoing predilution online HDF has been increasing in Japan, and it is considered to be a highly efficient technique for using high-flux membranes. It might achieve higher clearance of small solutes, such as urea, and small-, medium-, and large-middle molecules, such as β2MG and α_1-microglobulin, compared with high-flux HD [28, 29]. Therefore, more clinical trials should be conducted in the future to investigate the impact of this modality on mortality outcomes.

Conclusions

This large national cohort study of Japanese patients undergoing dialysis has provided valuable insights into the association between dialyzer type (classified by β2MG clearance) and the 2-year mortality rate. These findings suggest that super high-flux dialyzers (which have a β2MG clearance rate of more than 70 mL/min) may be beneficial for patients undergoing HD, regardless of Kt/V. Further randomized controlled studies are warranted to determine whether the higher β2MG clearance of super high-flux dialyzers truly improves outcomes for patients on HD.

Abbreviations

β2MG	β_2-Microglobulin
BMI	Body mass index
BP	Blood pressure
CRP	C-reactive protein
Cr	Creatinine
CVD	Cardiovascular disease
DM	Diabetes mellitus
HD	Hemodialysis
HDF	Hemodiafiltration
HR	Hazard ratio
i-PTH	Intact parathyroid hormone
JSDT	Japanese Society for Dialysis Therapy
JRDR	JSDT Renal Data Registry
nPCR	Normalized protein catabolic rate
UN	Urea nitrogen

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-024-00567-7.

Supplemetary Material 1

Supplemetary Material 2

Supplemetary Material 3

Supplemetary Material 4

Supplemetary Material 5

Acknowledgements
We thank all members of the committee of the JSDT Renal Data Registry for their efforts and the staff of all the participating dialysis facilities.

Author contributions
M.A. wrote the manuscript and analyzed the data; K.K., E.K., and N.H. were cosupervisors, designed the study, and revised the manuscript; A.W. and S.N. contributed to data collection; M.A., K.K., and N.H. discussed the results and contributed to the final manuscript. All authors have read and approved the final manuscript.

Funding
Not applicable.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of the Japanese Society for Dialysis Therapy. The need for informed consent was waived because of the use of deidentified information. This study was registered at the University Hospital Medical Information Network (UMIN000018641).

Consent for publication
Not applicable.

Availability of data and materials
The data used in this study are available from the corresponding author.

Competing interests
M.A. is the deputy editor of Renal Replacement Therapy, and N.H. is the associate editor of Renal Replacement Therapy. The other authors declare that they have no other relevant financial interests. The publication of this report was not supported by any grants. No financial support was provided for this study.

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Received: 30 April 2024 Accepted: 1 August 2024
Published online: 22 August 2024

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