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ORIGINAL ARTICLE

Super high-flux membrane dialyzers improve mortality in patients on hemodialysis: a 3-year nationwide cohort study

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ABSTRACT

Introduction. In Japan, dialyzers are classified based on β_2-microglobulin clearance. Type I dialyzers are classified as low-flux dialyzers (<10 mL/min clearance), type II and III as high-flux dialyzers (≥10 to <30 mL/min and ≥30 to <50 mL/min clearance, respectively), and type IV and V as super high-flux dialyzers (≥50 to <70 mL/min and ≥70 mL/min clearance, respectively). Super high-flux dialyzers are commonly used, but their superiority over low-flux dialyzers is controversial.

Methods. In this nationwide prospective cohort study, we analyzed Japanese Society for Dialysis Therapy Renal Data Registry data collected at the end of 2008 and 2011. We enrolled 242,467 patients on maintenance hemodialysis and divided them into five groups by dialyzer type. We assessed the associations of each dialyzer type with 3-year all-cause mortality using Cox proportional hazards models and performed propensity score matching analysis, adjusting for potential confounders.

Results. By the end of 2011, 53,172 (21.9%) prevalent dialysis patients had died. Mortality significantly decreased according to dialyzer type. Hazard ratios (HRs) were significantly higher for type I, II and III compared with type IV (reference) after adjustment for basic factors and further adjustment for dialysis-related factors. HR was significantly higher for type I, but significantly lower for type V, after further adjustment for nutrition- and inflammation-related factors. These significant findings were also evident after propensity score matching.

Conclusions. Hemodialysis using super high-flux dialyzers might reduce mortality. Randomized controlled trials are warranted to clarify whether these type V dialyzers can improve prognosis.

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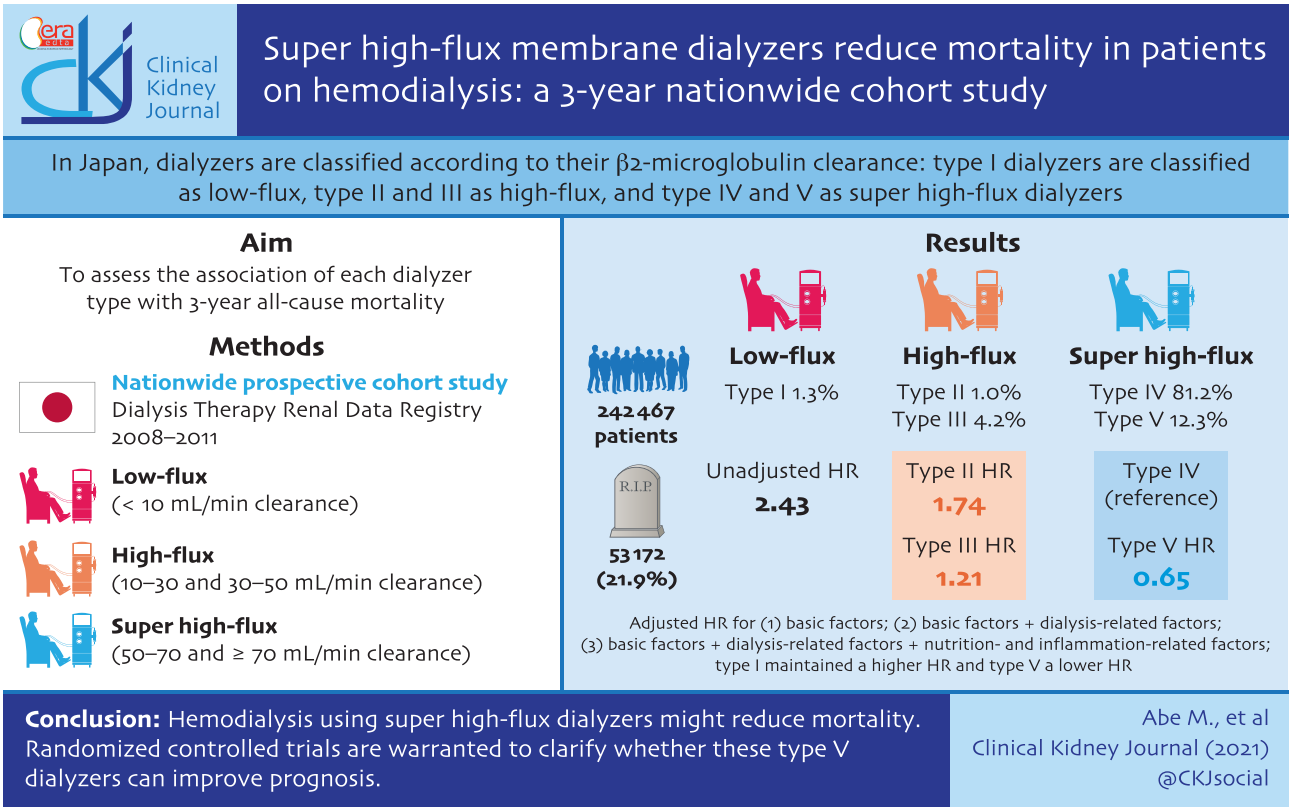
GRAPHICAL ABSTRACT



Keywords: β_2-microglobulin, hemodialysis, high-flux dialyzer, low-flux dialyzer, super high-flux dialyzer

INTRODUCTION

Hemodialysis is the main modality of renal replacement therapy (RRT) for the increasing number of patients with end-stage kidney disease (ESKD) worldwide [1, 2]. Dialysis removes uremic toxins that accumulate in patients' bodies, and these toxins are classified as small sized (<500 Da), middle sized (500 Da–15 kDa) or protein bound [3, 4]. Starting in the 1980s, middle-sized toxins and large molecular weight substances (>5000 Da) were targeted for removal [5]. Subsequently, when β_2-microglobulin (β2MG) was identified as the amyloid precursor protein in dialysis-related amyloidosis [6], low-molecular-weight proteins and albumin-bound toxins also started being targeted for removal.

In the past decade, the dialyzers used most often internationally have been low-flux membrane dialyzers [7]. With an ultrafiltration rate of <15 mL/mmHg/h and β2MG clearance of <15 mL/min [8], they remove small solutes effectively through diffusion, but only negligible amounts of middle-sized solutes, which are considered more toxic and more difficult to remove by diffusion [9]. This limitation led to the development of high-flux membrane dialyzers, which are defined as having an ultrafiltration rate of ≥15 mL/mmHg/h and β2MG clearance rate of ≥15 mL/min [8]. High-flux membranes have high hydraulic permeability and higher solute permeability for middle-sized solutes than low-flux membrane dialyzers. In 2005, to address the problem of albumin leakage, super high-flux membranes with a large pore size were developed in Japan [10]. In 2008, more than 90% of Japanese patients on hemodialysis were being treated with this type of dialyzer [9, 11].

Despite the successful use of super high-flux membrane dialyzers in Japan for more than 15 years, it is unclear whether this type of dialyzer improves prognosis compared with other dialyzer types in use. In Japan, dialyzers are classified into five types based on their clearance of β2MG with a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min [12, 13]: type I are classified as low-flux membrane dialyzers (<10 mL/min clearance); type II and III as high-flux membrane dialyzers (≥10 to <30 mL/min and ≥30 to <50 mL/min clearance, respectively); and type IV and V as super high-flux membrane dialyzers (≥50 to <70 mL/min and ≥70 mL/min clearance, respectively). Type IV and V dialyzers are also classified as high-performance membrane (HPM) dialyzers due to their high flux rate, permeability and biocompatibility. In this prospective 3-year cohort study using data from a nationwide registry of hemodialysis patients in Japan, we sought to clarify the association between each of the five types of dialyzers and mortality rate.

MATERIALS AND METHODS

Source of data

All data analyzed in this study were extracted from the database of the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR). The data were collected in surveys conducted by

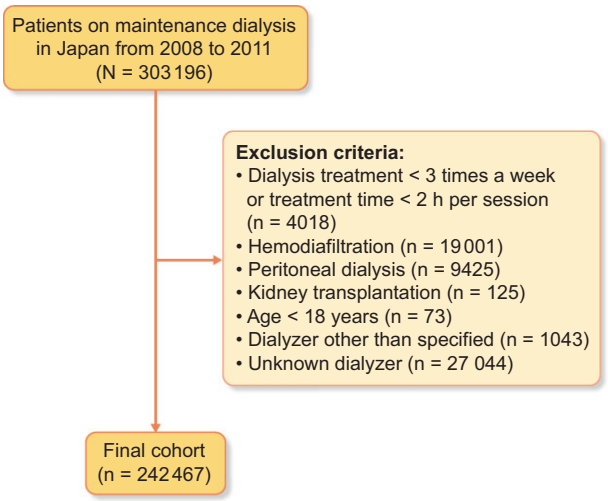


FIGURE 1: Flowchart of study participants.

volunteers from the Japanese Society for Dialysis Therapy (JSDT), as described previously [9, 11, 14]. Briefly, data for 2008 covered 282 622 patients undergoing dialysis therapy at 4072 facilities, and subsequent surveys covered 290 675 patients at 4125 facilities in the 2009 survey, 297 126 patients at 4152 facilities in the 2010 survey and 304 592 patients at 4205 facilities in the final 2011 survey [15, 16].

In this study, we analyzed data that were already de-identified. The study protocol was approved by the Medicine Ethics Committee of JSDT, with the need for informed consent waived due to the use of de-identified information. The study was conducted according to the principles of the declaration of Helsinki, Japanese privacy protection laws, and Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Education, Science and Culture, and the Ministry of Health, Labour and Welfare in 2015. This study is registered with the University Hospital Medical Information Network (UMIN000025728).

Study design

In this 3-year prospective cohort study, we used JRDR data collected as of 31 December 2008 (baseline) and 31 December 2011 [15, 16]. Eligibility criteria were undergoing maintenance dialysis at the end of 2008 and treatment with a type I, II, III, IV or V dialyzer (see Supplementary data, Table S1 for dialyzer classification details and Table S2 for the names of the dialyzers and their materials). Exclusion criteria were receiving dialysis fewer than three times per week or for less than 2 h per day, having undergone organ transplantation, receiving hemodiafiltration or peritoneal dialysis, aged <18 years, and incomplete records for date of birth, dialysis initiation, dialyzer type being used or outcome. Follow-up ended at death, withdrawal, kidney transplantation or as of 31 December 2011 (whichever occurred first).

Of the 303 196 patients registered at the end of 2008, 242 467 patients remained after exclusions (Figure 1). Among the baseline patient and laboratory data extracted from the JRDR database for analysis were age, sex, body mass index (BMI; calculated using the following formula: post-hemodialysis body weight in kilograms/height in meters squared), dialysis vintage, cause of ESKD, presence of diabetes mellitus (DM), pre-hemodialysis levels of serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone (PTH), β2MG, and C-reactive protein (CRP), and past history of cardiovascular diseases (CVD; myocardial infarction, cerebral hemorrhage, cerebral infarction and limb amputation). Single-pool Kt/V, normalized protein catabolic rate (nPCR) and percent creatinine generation rate (%CGR) were calculated using Shinzato's formula [17, 18].

Statistical methods

Data were summarized as proportions, with means ± standard deviation (SD) or median (interquartile range) as appropriate. Categorical variables were analyzed using the Chi-square test, and continuous variables were compared using Student's t-test, as appropriate. Categorical data between groups were compared using repeated measures ANOVA and Tukey's honestly significant difference test or the Kruskal–Wallis test, as appropriate.

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 (e.g. age, sex, primary kidney disease, CVD comorbidity and dialysis vintage) predicted survival for up to 3 years of follow-up, survival analyses with Cox proportional hazards regression were performed. To examine the dose–response association between dialysis vintage categories and mortality, patients were divided into seven *a priori* dialysis vintage categories. Additional analyses were performed with adjustment for dialysis dose and β2MG. To examine the dose–response association between Kt/V categories and mortality, patients were divided into eight *a priori* single-pool Kt/V categories (<0.8 and ≥2.0, in 0.2 increments). Additional analyses were done with adjustment for nutrition- and inflammation-related factors (e.g. BMI, serum albumin, hemoglobin, phosphate, calcium, intact-PTH, and CRP levels, nPCR and %CGR). To examine the dose–response association between categories of these nutrition- and inflammation-related factors and mortality, patients were divided into six *a priori* categories based on nPCR (<0.5 to ≥1.3 g/kg/day, in 0.2 g/kg/day increments), on serum albumin levels (<3.0 to ≥4.5 g/dL, in 0.5 g/dL increments), on BMI (<16 and ≥28 kg/m^2, in 2 kg/m^2 increments) and on %CGR (<60% and ≥140%, in 20% increments). In the analyses, age, β2MG, 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. Patients were divided into five dialyzer groups, and analysis was performed with adjustment for the above-mentioned basic factors, as well as dialysis dose and nutritional- and inflammation-related factors measured at baseline. The reference group was the type IV dialyzer group because it is the most widely used dialyzer in Japan [15].

Last, propensity score matching was used to adjust significant baseline covariates. The above-mentioned basic factors, dialysis dose, and nutritional- and inflammation-related factors were used to calculate propensity scores, which were then used in univariate Cox proportional hazards regression analysis. Patients with a type IV dialyzer (reference group) were matched in a 1:1 ratio with the other types of dialyzers, resulting in 1661, 1186, 5733 and 18 676 matched pairs (I, II, III and V, respectively). All-cause mortality was also compared in propensity score-matched patients.

When appropriate, missing covariate data were imputed by a conventional method for multivariate regression. All analyses

Table 1. Demographic, clinical, and laboratory values at baseline for 242 467 hemodialysis patients included in this study

Variable	
N (female %)	242 467 (38.5)
Age (years)	65.6 ± 15.9
Dialysis vintage (years)	6 (3–11)
Comorbid CVD (%)	24.5
Coronary artery disease	7.3
Ischemic stroke	14.6
Hemorrhagic stroke	4.7
Limb amputation	2.9
Primary kidney disease (%)	
Glomerulonephritis	41.5
Diabetic nephropathy	34.4
Nephrosclerosis	7.6
Other	16.5
Smoking (%)	14.0
Body mass index (kg/m^2)	21.2 ± 3.5
Hemoglobin, g/dL	10.4 ± 1.3
Calcium, mg/dL	8.9 ± 0.8
Phosphate, mg/dL	5.3 ± 1.5
Intact-PTH, pg/mL	119 (60–202)
C-reactive protein, mg/dL	0.12 (0.05–0.40)
β2MG, mg/L	26.6 ± 7.1
Total cholesterol, mg/dL	157 ± 35
HDL-cholesterol, mg/dL	48 ± 16
Albumin, g/dL	3.7 ± 0.5
Kt/V	1.39 ± 0.30
nPCR, g/kg/day	0.89 ± 0.17
%CGR, %	94.9 ± 28.1

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. HDL, high-density lipoprotein.

were conducted using JMP® version 13.0 (SAS Institute, Cary, NC, USA) and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

As shown in Table 1, the characteristics of the 242 467 hemodialysis patients included in this study can be summarized as follows: mean age 65.6 ± 15.9 years, 38.5% female, 21.2 ± 3.5 kg/m^2 BMI, mean dialysis vintage 6 years (range 3–11 years), 24.5% with CVD history, albumin levels 3.7 ± 0.5 g/dL and hemoglobin levels 10.4 ± 1.3 g/dL. The most common cause of ESKD was glomerulonephritis (41.5%), followed by diabetic nephropathy (34.4%) and nephrosclerosis (7.6%). Supplementary data, Tables S3 and S4 show the number of missing values among the study participants and proportions of categorical variables, respectively. During observation, 53 172 deaths were recorded (22 911 cardiovascular-related deaths, 10 665 infection-related deaths, 4738 cancer-related deaths and 14 858 other deaths).

Associations of all-cause mortality with basic factors, dialysis dose, and nutritional- and inflammation-related factors

Table 2 shows the hazard ratios (HRs) for variables that were evaluated as potential predictors of mortality in hemodialysis patients. Significant predictors of mortality were male sex, increasing age, dialysis vintage, comorbid CVD and causes of ESKD other than glomerulonephritis. Lower mortality risk was

Table 2. HRs and 95% CIs for variables evaluated as potential predictors of mortality among all patients

Factors	HR	95% CI	P-value
Sex			
Male	1.000	Reference	–
Female	0.914	0.898–0.930	<0.0001
Age, years			
1-year increase	1.003	1.002–1.003	<0.0001
Dialysis vintage, years			
<2	0.992	0.968–1.016	0.553
≥2–5	1.000	Reference	–
≥5–10	1.008	0.985–1.031	0.465
≥10–15	0.892	0.867–0.918	<0.0001
≥15–20	0.764	0.735–0.795	<0.0001
≥20–25	0.682	0.647–0.719	<0.0001
≥25	0.837	0.797–0.878	<0.0001
Primary kidney disease			
Glomerulonephritis	1.000	Reference	–
Diabetic nephropathy	1.504	1.475–1.533	<0.0001
Nephrosclerosis	1.562	1.515–1.611	<0.0001
Other	1.215	1.185–1.245	<0.0001
Comorbid CVD			
No	1.000	Reference	–
Yes	2.037	1.999–2.076	<0.0001
Kt/V			
<0.8	4.105	3.901–4.319	<0.0001
≥0.8–1.0	1.394	1.347–1.442	<0.0001
≥1.0–1.2	1.164	1.134–1.194	<0.0001
≥1.2–1.4	1.000	Reference	–
≥1.4–1.6	0.939	0.916–0.963	<0.0001
≥1.6–1.8	0.856	0.829–0.882	<0.0001
≥1.8–2.0	0.807	0.772–0.834	<0.0001
≥2.0	0.791	0.745–0.838	<0.0001
β2MG, mg/L			
<15	1.029	0.992–1.068	0.119
≥15–20	1.026	0.991–1.063	0.141
≥20–25	0.996	0.969–1.023	0.408
≥25–30	1.000	Reference	–
≥30–35	1.242	1.209–1.276	<0.0001
≥35–40	1.550	1.495–1.607	<0.0001
≥40	1.924	1.846–2.006	<0.0001
CRP			
1 mg/dL increase	1.082	1.081–1.084	<0.0001
Hemoglobin			
1 g/dL increase	0.831	0.825–0.837	<0.0001
BMI, kg/m^2			
<16	2.920	2.814–3.029	<0.0001
≥16–18	1.699	1.650–1.749	<0.0001
≥18–20	1.231	1.199–1.265	<0.0001
≥20–22	1.000	Reference	–
≥22–24	0.849	0.822–0.875	<0.0001
≥24–26	0.765	0.732–0.793	<0.0001
≥26–28	0.718	0.685–0.737	<0.0001
≥28	0.743	0.684–0.806	<0.0001
Serum albumin, g/dL			
<3.0	4.548	4.429–4.669	<0.0001
≥3.0–3.5	2.104	2.061–2.148	<0.0001
≥3.5–4.0	1.000	Reference	–
≥4.0–4.5	0.587	0.570–0.603	<0.0001
≥4.5	0.527	0.478–0.581	<0.0001

Table 2. Continued

Factors	HR	95% CI	P-value
nPCR, g/kg/day			
<0.5	7.187	6.782–7.616	<0.0001
≥0.5–0.7	2.917	2.847–2.989	<0.0001
≥0.7–0.9	1.000	Reference	–
≥0.9–1.1	0.789	0.773–0.807	<0.0001
≥1.1–1.3	0.739	0.713–0.766	<0.0001
≥1.3	0.899	0.834–0.968	0.005
%CGR, %			
<60	3.846	3.741–3.954	<0.0001
≥60–80	2.103	2.046–2.162	<0.0001
≥80–100	1.527	1.487–1.569	<0.0001
≥100–120	1.000	Reference	–
≥120–140	0.703	0.676–0.732	<0.0001
≥140	0.751	0.701–0.805	<0.0001

associated with higher dialysis dose (assessed by single-pool Kt/V) and lower β2MG levels. Furthermore, higher mortality was associated with poor nutritional status, indicated by lower hemoglobin, serum albumin, BMI, nPCR and %CGR values, and with increased inflammatory status, indicated by higher CRP levels.

Associations of clinical and demographic characteristics with dialyzer type

Table 3 shows the patient demographics and characteristics in each dialyzer group: most patients received hemodialysis with type IV dialyzers (81.2%), followed by type V (12.3%), type III (4.2%), type I (1.3%) and type II (1.0%). Patients treated using type I dialyzers were characterized as older, more likely to be female, have higher rates of comorbid CVD and DM, and lower BMI. In contrast, patients treated using type V dialyzers were characterized as younger, more likely to be male, have lower rates of comorbid CVD and DM, and higher Kt/V, nPCR and %CGR.

Associations of all-cause mortality with dialyzer type

Kaplan–Meier analysis showed that survival deteriorated steadily as dialyzer type increased (log-rank test, $P < 0.0001$; Figure 2), except for type V. Compared with the type IV group (reference), the type I, II and III groups showed unadjusted HRs [95% confidence intervals (CIs)] for all-cause mortality of 2.43 (2.31–2.56), 1.74 (1.63–1.86) and 1.21 (1.16–1.25), respectively. The type V group had a significantly lower HR of 0.65 (0.63–0.67).

Figure 3 shows the adjusted HRs for all-cause mortality in each group. After adjustment for basic factors, the HRs for the type I, II and III groups, compared with the type IV group (reference), were 2.31 (2.18–2.44), 1.59 (1.47–1.72) and 1.20 (1.15–1.25), respectively. The type V group had a significantly lower HR of 0.68 (0.66–0.70).

After adjustment for basic factors, dialysis dose and β2MG, the HRs for the type I, II and III groups, compared with the type IV group, were 1.89 (1.76–2.01), 1.39 (1.26–1.52) and 1.12 (1.05–1.17), respectively. The type V group had a significantly lower HR of 0.70 (0.67–0.73).

Lastly, after adjustment for basic factors, dialysis dose, and nutritional- and inflammation-related factors, the HRs for the type III groups did not differ significantly compared with the type IV group, but the type I and II groups had significantly higher HRs of 1.30 [(1.20–1.41), $P < 0.0001$] and 1.18 [(1.06–1.31), $P = 0.004$], and a lower HR for type V group [0.85 (0.81–0.89), $P < 0.0001$] remained (Supplementary data, Table S5).

Propensity score matching analysis

Table 4 shows patient characteristics and clinical data at baseline in the type IV group and each corresponding group after propensity score matching. There were no significant differences in any variables. Figure 4 shows that, compared with the type IV group, the type I group had a significantly higher HR [1.13 (1.02–1.26), $P = 0.018$], the type II and III groups showed no significant difference, and the type V group had a significantly lower HR [0.90 (0.785–0.95), $P = 0.0015$].

DISCUSSION

Two new findings were revealed in this study. First, 3-year mortality was significantly dependent on dialyzer performance, which was classified according to β2MG clearance in prevalent dialysis patients. Second, when mortality was compared between the five types of dialyzers after final adjustment for multiple predicting factors, the HR for the type I group was significantly higher and the type V group was significantly lower compared with the type IV reference group. Furthermore, the same results were evident after propensity score matching. Thus, this is the first study to suggest that dialyzer types might affect mortality risk in hemodialysis patients and that super high-flux membrane dialyzers might improve outcomes. These findings underscore the need to carefully consider the dialyzer selected for patients on hemodialysis.

It was reported that a new generation of dialysis membrane made available since 2017 in European countries suppresses platelet adhesion to the dialyzer membrane and maintains its adsorption properties [19, 20]. This novel class of membranes—the super high-flux membranes or medium cut-off (MCO) membranes, as they are known in Europe—have recently been designed and incorporated into clinical practice to remove middle and large molecules during hemodialysis treatments [21]. However, the concept behind HPM dialyzers using these membranes was developed in Japan as early as 2005 to ameliorate comorbidities associated with long-term dialysis therapy and to improve outcomes [12]. In fact, more than 90% of the hemodialysis patients included in the present study were treated with HPM dialyzers (as of 2008), in accordance with JSDT recommendations for HPM dialyzer use [12]. HPM dialyzers are defined as having high hydraulic permeability, high solute permeability (especially for middle molecules and uremic toxins with molecular weights of 10 000–30 000 Da), high biocompatibility and β2MG clearance >50 mL/min [11]. HPMs have larger pores than low- and high-flux membranes, which means they can remove small, middle and large molecules, including low-molecular-weight proteins and small amounts of albumin [22]. The optimal pore size should prevent the loss of >3 g of albumin per session with the standard hemodialysis procedure in Japan of a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min [10, 12, 22]. Therefore, HPM dialyzers, super-flux membrane dialyzers and MCO membrane dialyzers belong to the same class of dialyzer, and these membranes can be used only in the modality of hemodialysis. In addition, the albumin leakage of many type V dialyzers used in the present study does not exceed 3 g [10]. The patients in the type V dialyzer group had the

Table 3. Demographic, clinical, and laboratory values in 242 467 hemodialysis patients according to dialyzer type

	I	II	III	IV	V	P-value
n (%)	3172 (1.3)	2416 (1.0)	10 189 (4.2)	196 779 (81.2)	29 911 (12.3)	
Age (years)	74.3 ± 11.0	70.9 ± 12.2	67.9 ± 12.5	65.8 ± 12.4	61.1 ± 12.3	<0.0001
Sex (female %)	53.0	46.8	40.5	38.8	31.5	<0.0001
Dialysis vintage (years)	3 (1–6)	3 (1–6)	5 (2–10)	6 (3–11)	7 (4–13)	<0.0001
Presence of DM (%)	47.7	43.2	42.4	40.9	35.3	<0.0001
Comorbid CVD (%)	32.7	32.0	26.4	25.1	19.9	<0.0001
Coronary artery disease	8.6	9.5	7.4	7.4	6.2	
Ischemic stroke	21.4	20.4	16.8	14.9	11.0	
Hemorrhagic stroke	6.0	6.1	4.8	4.8	3.7	
Limb amputation	3.7	3.5	3.1	2.9	2.4	
BMI (kg/m^2)	20.0 ± 3.6	20.4 ± 3.6	20.9 ± 3.5	21.1 ± 3.5	21.6 ± 3.5	<0.0001
Hemoglobin (g/dL)	9.9 ± 1.5	10.0 ± 1.4	10.3 ± 1.3	10.4 ± 1.3	10.5 ± 1.3	<0.0001
Serum albumin (g/dL)	3.4 ± 0.5	3.5 ± 0.5	3.6 ± 0.5	3.7 ± 0.4	3.7 ± 0.4	<0.0001
Calcium (mg/dL)	8.6 ± 0.9	8.8 ± 0.9	8.9 ± 0.8	8.9 ± 0.8	9.0 ± 0.8	<0.0001
Phosphate (mg/dL)	4.9 ± 1.5	5.1 ± 1.5	5.2 ± 1.5	5.2 ± 1.5	5.5 ± 1.5	<0.0001
Intact-PTH (pg/mL)	106 (52–186)	112 (55–177)	119 (59–202)	118 (59–202)	126 (65–208)	0.0064
β2MG (mg/L)	28.7 ± 10.6	27.6 ± 9.2	27.3 ± 7.9	26.4 ± 7.0	26.9 ± 6.8	<0.0001
CRP (mg/dL)	0.20 (0.06–0.85)	0.19 (0.08–0.70)	0.15 (0.06–0.50)	0.12 (0.05–0.40)	0.10 (0.05–0.30)	<0.0001
Kt/V	1.22 ± 0.31	1.24 ± 0.30	1.35 ± 0.30	1.39 ± 0.30	1.43 ± 0.30	<0.0001
nPCR (g/kg/day)	0.84 ± 0.20	0.84 ± 0.17	0.87 ± 0.17	0.89 ± 0.17	0.90 ± 0.17	<0.0001
%CGR (%)	75.3 ± 29.4	79.7 ± 29.5	90.2 ± 28.4	94.6 ± 27.8	101.6 ± 27.2	<0.0001

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated.

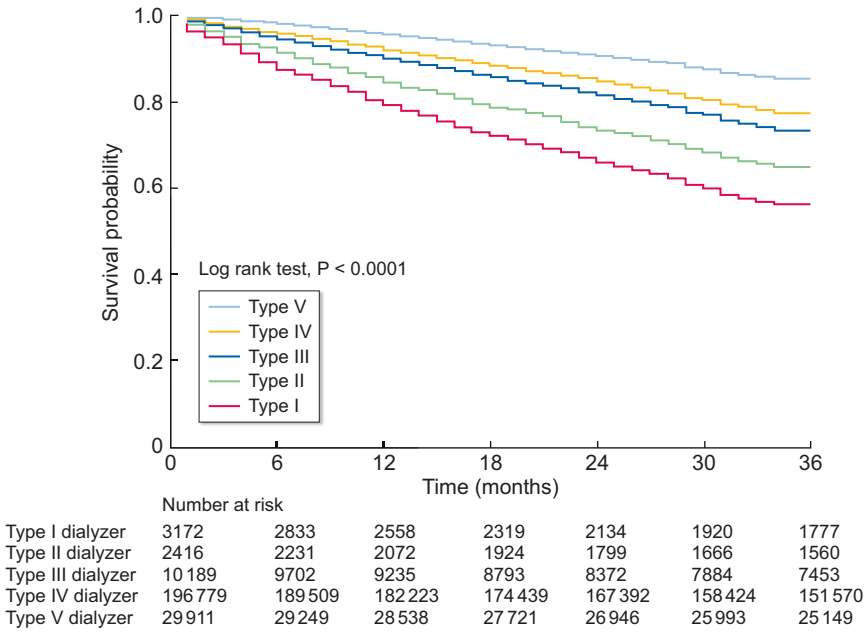


FIGURE 2: Kaplan–Meier survival curve for all-cause mortality in the five dialyzer type groups.

highest serum albumin levels among the dialyzer groups, and therefore large amounts of albumin leakage, which would lead to hypoalbuminemia, did not occur. Furthermore, this study included some dialyzers that had adsorption capacity, such as polymethylmethacrylate (PMMA) membranes, and many of the patients treated with a PMMA membrane were classified into the type IV group. We could not evaluate adsorption capacity of dialyzers in the present study, and further studies are therefore needed to clarify whether adsorptive dialyzers have clinical advantages.

Previously, no significant difference in mortality was found between high-flux and low-flux dialyzer groups in the Hemodialysis Study, a large randomized controlled trial [8], indicating that increased dialysis dose, with increased clearance of traditional small uremic solutes, was not associated with improved patient outcome. However, other studies and analyses have shown superiority of high-flux over low-flux dialyzers. A subgroup analysis of patients who had been receiving hemodialysis for more than 3.7 years revealed significantly better survival in the high-flux dialyzer group and a relative risk

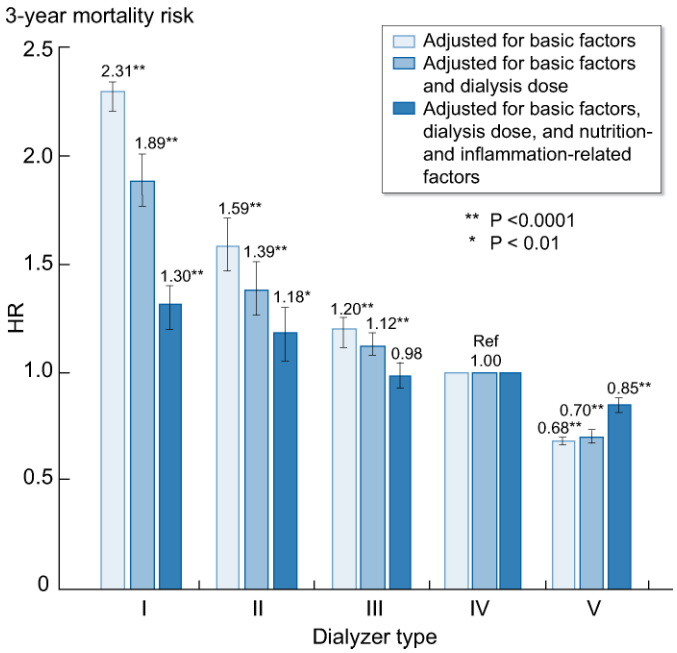


FIGURE 3: HR of all-cause mortality among the five dialyzer types in 242 467 patients undergoing hemodialysis, determined using standard Cox proportional hazards regression. Light blue bars are adjusted for basic factors including age, sex, dialysis vintage, primary causes of ESKD and presence/absence of cardiovascular complications. Blue bars are adjusted for dialysis dose as assessed by Kt/V and β2MG levels in addition to basic factors. Dark blue bars are adjusted for basic factors, dialysis dose, and nutrition- and inflammation-related factors, including BMI, levels of CRP, hemoglobin, calcium, phosphate, intact-PTH and serum albumin, nPCR and %CGR. **P < 0.0001, *P < 0.01 versus type IV dialyzer group (reference). Error bars correspond to 95% confidence intervals.

reduction of 32% [23]. Also, after adjustment for residual kidney function and dialysis vintage, middle molecule concentrations, which include β2MG, were found to be an independent predictor of mortality. In a *post hoc* analysis, the relative risk of death was found to increase by 11% for every 10-mg/L increase in pre-hemodialysis β2MG concentrations [24]. In the Membrane Permeability Outcome Study, where 657 incident dialysis patients were randomly allocated to treatment with high-flux or low-flux dialyzers, high-flux membranes resulted in improved β2MG clearance, which with associated with a 37% reduction in mortality risk in patients with serum albumin levels <4.0 g/dL [25]. Hemodialysis patients with diabetes were also found to have significantly longer survival in a high-flux group compared with a low-flux group, with a subgroup analysis showing a relative risk reduction of 38% [25]. A meta-analysis suggested that cardiovascular mortality was reduced in patients treated with high-flux membranes [26], and a Cochrane Database systematic review showed significant benefits of high-flux dialyzers on all-cause mortality for certain prespecified conditions, such as serum albumin levels <4 g/dL, undergoing maintenance hemodialysis for >3.7 years, or having DM or arterio-venous fistula [27]. Based on these results, the Kidney Disease Outcomes Quality Initiative guidelines updated in 2015 recommend the use of biocompatible high-flux hemodialysis membranes for hemodialysis [28].

To improve prognosis, protein-bound uremic toxins and middle-sized substances, such as β2MG and α1-microglobulin, are now being targeted for removal in hemodialysis patients [29, 30]. The removal of middle-sized substances depends on both dialyzer permeability and treatment modality. Recently, the use of novel hemodialysis devices, sterile ultrapure solutions and high-quality water treatment [31] have allowed for the development of convective therapies, particularly online hemodiafiltration. Convective therapies require large volumes of substitution fluid and sophisticated volume-control systems to maintain fluid balance, and online hemodiafiltration, which uses high-flux dialyzers, ultrapure dialysis fluid and extensive convective fluid exchanges [32], is currently considered the new standard for highly efficient RRT. It offers the best clearance of small- and middle-sized molecules and is widely used in Japan and some European countries. Furthermore, high-volume post-dilution online hemodiafiltration, which is defined as a convective volume of ≥23 L/session, has shown greater removal of both uremic toxins and improved survival [33, 34]. Unfortunately, however, online hemodiafiltration cannot be the treatment of choice for all maintenance hemodialysis patients, and it tends not to be widely available in many countries.

Recent investigations have reported that super high-flux hemodialysis is noninferior to high-volume post-dilution online hemodiafiltration for removing protein-bound, middle-molecule, and small-molecule uremic toxins and albumin [35–37], and it could therefore be an option for long-term hemodialysis patients. However, these were short-term studies and they compared solute clearance, so outcomes were not investigated. Blood flow rate is significantly lower in patients on hemodialysis in Japan compared with other countries because more than 90% of Japanese patients have an arterio-venous fistula for vascular access [38]. However, arterio-venous fistula placement is known to improve patient survival compared with arterio-venous graft or central venous catheter [39]. In 2008, the percentage of patients who used a native vessel arterio-venous fistula was 89.7% in the JRDR [15]. Furthermore, the JSDT standard for endotoxin level in dialysis fluid (<0.050 EU/mL) was achieved in 91.8% of facilities in Japan in 2010, and the JSDT standard for bacterial cell counts in dialysis fluid (<100 c.f.u./mL) was achieved in 98.2% in 2010 [40]. Therefore, excellent water

Table 4. Baseline characteristics after propensity score matching between the type IV dialyzer (reference) and other dialyzer types

	Matched			Matched			Matched			Matched		
	I	IV	P-value	II	IV	P-value	III	IV	P-value	V	IV	P-value
n	1661	1661	–	1 186	1 186	–	5733	5733	–	18 676	18 676	–
Age (years)	74.1 ± 10.9	74.2 ± 10.3	0.944	70.7 ± 11.9	70.8 ± 11.6	0.841	67.7 ± 12.2	67.8 ± 11.9	0.684	60.9 ± 12.7	60.9 ± 12.2	0.573
Sex (female %)	54.4	54.6	0.916	49.2	49.7	0.805	40.5	40.0	0.391	31.2	31.5	0.423
Dialysis vintage (years)	3 (1–7)	3 (1–6)	0.311	3 (1–7)	4 (2–7)	0.931	5 (2–9)	5 (2–10)	0.786	7 (4–13)	7 (4–13)	0.421
Presence of DM (%)	48.5	47.9	0.781	46.7	46.6	0.779	43.2	43.8	0.559	34.6	34.5	0.752
Comorbid CVD (%)	33.2	33.5	0.854	29	27.1	0.293	25.0	25.0	0.863	18.9	19.1	0.460
BMI (kg/m^2)	20.0 ± 3.3	20.0 ± 3.3	0.557	20.5 ± 3.5	20.5 ± 3.5	0.967	21.0 ± 3.5	21.0 ± 3.5	0.761	21.7 ± 3.5	21.7 ± 3.5	0.918
Hb (g/dL)	10.0 ± 1.4	10.0 ± 1.4	0.583	10.1 ± 1.3	10.2 ± 1.3	0.795	10.3 ± 1.3	10.3 ± 1.3	0.250	10.6 ± 1.2	10.6 ± 1.2	0.969
Albumin (g/dL)	3.5 ± 0.5	3.5 ± 0.5	0.731	3.5 ± 0.5	3.5 ± 0.5	0.695	3.7 ± 0.4	3.7 ± 0.4	0.934	3.7 ± 0.4	3.7 ± 0.4	0.596
Calcium (mg/dL)	8.6 ± 0.9	8.7 ± 0.8	0.425	8.7 ± 0.8	8.8 ± 0.8	0.122	8.9 ± 0.8	8.9 ± 0.8	0.553	9.0 ± 0.8	9.0 ± 0.8	0.906
Phosphate (mg/dL)	5.0 ± 1.4	4.9 ± 1.4	0.068	5.0 ± 1.4	5.0 ± 1.4	0.146	5.2 ± 1.4	5.2 ± 1.4	0.850	5.5 ± 1.4	5.5 ± 1.4	0.931
Intact-PTH (pg/mL)	109 (53–193)	106 (54–185)	0.634	110 (54–176)	106 (56–183)	0.386	119 (59–202)	112 (57–188)	0.379	122 (62–207)	125 (64–206)	0.619
β2MG (mg/L)	25.7 ± 7.7	25.3 ± 7.6	0.089	27.2 ± 9.1	26.8 ± 8.3	0.177	26.0 ± 6.5	25.9 ± 6.4	0.408	26.1 ± 5.7	26.1 ± 5.8	0.581
CRP (mg/dL)	0.18 (0.06–0.62)	0.16 (0.08–0.58)	0.562	0.12 (0.06–0.45)	0.15 (0.06–0.60)	0.490	0.12 (0.05–0.39)	0.13 (0.06–0.40)	0.398	0.10 (0.05–0.31)	0.10 (0.05–0.30)	0.140
Kt/V	1.23 ± 0.29	1.24 ± 0.28	0.370	1.24 ± 0.28	1.24 ± 0.28	0.775	1.35 ± 0.29	1.36 ± 0.29	0.469	1.43 ± 0.30	1.43 ± 0.29	0.094
nPCR (g/kg/day)	0.84 ± 0.18	0.84 ± 0.17	0.541	0.83 ± 0.16	0.83 ± 0.16	0.630	0.87 ± 0.17	0.87 ± 0.16	0.121	0.91 ± 0.17	0.91 ± 0.16	0.819
%CGR (%)	76.7 ± 28.7	76.8 ± 27.8	0.942	80.2 ± 29.4	80.0 ± 26.8	0.613	90.9 ± 28.4	91.0 ± 28.1	0.920	101.5 ± 25.2	101.7 ± 24.8	0.371

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. Hb, hemoglobin.

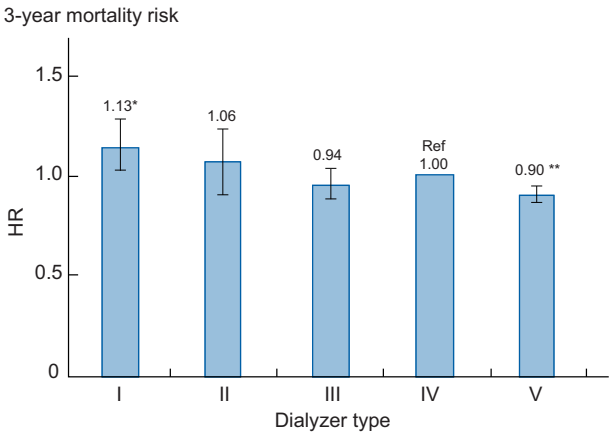


FIGURE 4: HRs of all-cause mortality after propensity score matching for four types of dialyzers compared with the type IV dialyzer (reference), determined using Cox proportional hazards regression. **P < 0.01, *P < 0.05 versus type IV dialyzer. Error bars correspond to 95% confidence intervals.

quality might be an important factor that improves the prognosis of hemodialysis patients in Japan, and might have contributed to the lower CRP levels in the present study. A major strength of the present study is its large sample size and use of all current types of low-flux, high-flux and super high-flux membrane dialyzers. Also, given that data were collected in a nationwide survey of Japanese dialysis facilities, the findings should be broadly generalizable to the Japanese dialysis population and may be helpful in other countries where low-flux membrane dialyzers are used.

There are several limitations in this study. First, the numbers of the patients differed among the five dialyzer groups because of data collection via annual surveys and the observational cohort study design. Second, mortality rates could have varied between the participating facilities due to differences in practice and patient populations, and therefore selection bias might have occurred. Also, selection bias could be present in this study because the type I dialyzer group had poor nutritional status, and the number of patients in the type I and II groups was small. However, to reduce potential confounding and treatment selection bias, we performed propensity score matching analysis and then could confirm the superiority of the type V dialyzer over the type I dialyzer after propensity score matching analysis. Third, we had no information about residual kidney function, which could be a possible confounder. However, given that the reported loss of kidney function after starting dialysis is approximately 2.0 mL/min/year [41] and the mean estimated glomerular filtration rate at dialysis initiation was 6.52 mL/min/1.73 m^2 in 2007 throughout Japan [42], the impact of residual kidney function on our cohort may have been negligible because the median dialysis duration was 6 years in our cohort. Finally, we excluded patients treated with hemodiafiltration to eliminate modality bias and account for the small number of these patients in Japan in 2008 [15]. However, hemodiafiltration is considered more efficient than hemodialysis when using high-flux dialyzers, and the number of the patients treated with hemodiafiltration is growing in Japan. Therefore, further investigations are needed to evaluate differences in the use of high-flux dialyzers across treatment modalities.

In conclusion, dialyzer type, classified by β2MG clearance, was significantly associated with 3-year mortality in this large national cohort study of Japanese dialysis patients. Based on our findings, super high-flux dialyzers might be beneficial for hemodialysis patients. Although type IV and V dialyzers are classified as super high-flux membrane dialyzers, this study indicated the superiority of type V dialyzers. The present study is an observational cohort study. To determine whether higher β2MG clearance with super high-flux membrane dialyzers provides improved outcomes for hemodialysis patients, randomized controlled studies are necessary.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.A., S.N. and I.M. conceived and designed the experiments; M.A. performed the experiments; A.W. and M.A. analyzed the data; M.A. and I.M. contributed reagents/materials/analysis tools; M.A. wrote the paper; and K.N. and H.N. contributed supervision.

STATEMENT OF ETHICS

This work, based on existing data, was performed in accordance with Japanese laws concerning privacy protection, the tenets of the Declaration of Helsinki, and the 2015 Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Japanese Ministries of Education, Culture, Sports, Science and Technology and of Health, Labour, and Welfare. The Medicine Ethics Committee of the Japanese Society for Dialysis Therapy approved the protocol of the study and waived the need for informed consent due to the use of de-identified data.

CONFLICT OF INTEREST STATEMENT

None declared.

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