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Comparison of survival for super high-flux hemodialysis (SHF-HD) with high albumin leakage versus online hemodiafiltration or SHF-HD with low albumin leakage: the SUPERB study

Kazuyoshi Okada[1*], Manabu Tashiro[1], Hiroyuki Michiwaki[2], Tomoko Inoue[1], Hisato Shima[1], Jun Minakuchi[1] and Shu Kawashima[1]

Abstract

Background Survival is equivalent between super high-flux hemodialysis (SHF-HD) and online hemodiafiltration (OHDF) with similar albumin leakage. According to the 2013 Japanese dialyzer performance classification, survival on HD is optimal when a type II dialyzer (β_2-microglobulin clearance ≥ 70 mL/min) is used. Here, we investigated whether survival could be improved by SHF-HD using a type II-b dialyzer (sieving coefficient for albumin ≥ 0.03) with high albumin leakage compared with OHDF or SHF-HD using a type II-a dialyzer (sieving coefficient for albumin < 0.03) with low albumin leakage.

Methods This 3-year retrospective observational propensity score-matched study included 738 patients receiving SHF-HD (*n* = 310) or OHDF (*n* = 428) with a type II dialyzer at our institution between April 1 and July 1, 2017. Three-year all-cause mortality was compared for SHF-HD with high estimated albumin leakage (EAL) versus OHDF and SHF-HD with low EAL. Kaplan–Meier survival curves were compared using the log-rank test and hazard ratios were calculated by Cox regression analysis.

Results Mortality in SHF-HD with high EAL was significantly lower than OHDF with low EAL (each *n* = 52 after matching; *P* = 0.007, log-rank test). All the dialyzers used a polyethersulfone (PES) membrane, whereas none of the hemodiafilters had a PES membrane. In SHF-HD, mortality was significantly lower when EAL was ≥ 3.0 g/session than when EAL was < 3.0 g/session (each *n* = 115 after matching, *P* = 0.004, log-rank test) and when the dialyzer used was type II-b rather than type II-a (each *n* = 133 after matching, *P* = 0.001, log-rank test).

Conclusions These findings suggest that survival is better on SHF-HD using a type II-b dialyzer with high albumin leakage than on OHDF with low albumin leakage or SHF-HD using a type II-a dialyzers. The PES used in the type II-b dialyzer may also have a beneficial effect on survival.

Keywords Albumin leakage, Super high-flux, Hemodialysis, Online hemodiafiltration, Polyethersulfone

*Correspondence:
Kazuyoshi Okada
kokada@ckdjapan.jp
Full list of author information is available at the end of the article

Introduction

Hemodialysis (HD) using a high-flux membrane has limited ability to remove medium-middle and large-middle molecules. Therefore, online hemodiafiltration (OHDF), which has a high substitution volume, has been developed to remove these molecules by increasing the convection volume. In Europe, high-volume post-dilution OHDF (post-OHDF) using low-permeability membranes for albumin is the norm with albumin leakage not exceeding 3.4–5.0 g/session [1, 2]. In Japan, predilution OHDF (pre-OHDF) with a substitution volume of 24–84 L using membranes with low-to-high permeability for albumin is the norm, with albumin leakage set at no more than 5 g/session in many facilities; post-OHDF with a substitution volume of 6–16 L has also been performed although not often [3].

A prospective randomized controlled trial demonstrated that survival was significantly better in high-volume post-OHDF than in HD whether a high-flux membrane or a low-flux membrane was used [4]. However, three prospective randomized controlled trials using a high-flux [5, 6] or low-flux [7] membrane and a prospective observational study using both high-flux and low-flux membranes [8] have failed to demonstrate a survival advantage of high-volume post-OHDF over HD.

In 2004, the Ministry of Health, Labour and Welfare of Japan classified dialyzers into the following five functional types according to the β_2-microglobulin (β_2MG) clearance runder set conditions of membrane surface area 1.5 m^2, blood flow rate (QB) 200 mL/min, dialysate flow rate (QD) 500 mL/min, and filtration flow rate 15 mL/min: type I, < 10 mL/min; type II, ≥ 10 and < 30 mL/min; type III, ≥ 30 and < 50 mL/min; type IV, ≥ 50 and < 70 mL/min; and type V, ≥ 70 mL/min) [9]. Subsequently, type I was defined as a low-flux membrane, types II and III as high-flux membranes, and types IV and V as super high-flux (SHF) membranes [10]. In 2013, the Japanese Society for Dialysis Therapy (JSDT) extended these five types of dialyzer to include a further four types determined by β_2MG clearance and the sieving coefficient (SC) for albumin (type I-a, < 70 mL/min and < 0.03; type I-b, < 70 mL/min and ≥ 0.03; type II-a, ≥ 70 mL/min and < 0.03; type II-b, ≥ 70 mL/min and ≥ 0.03) and a type S (a dialyzer membrane with special features, such as those made from ethylene vinyl alcohol or polymethylmethacrylate) as shown in Additional file 1: Table S1 [11]. Although the JSDT allowed albumin leakage with SC ≥ 0.03, the basis for setting reference SC values for albumin and β_2MG clearance was not clear.

In a 7-year observational study using dialyzers with β_2MG clearance ≥ 10 mL/min (types II–V in the 2004 classification), Nagai et al. found that prognosis was better when the estimated albumin leakage (EAL) was ≥ 3.0 g/session than when it was < 3.0 g/session [12]. Abe et al. reported that mortality was significantly lower with SHF membranes that have β_2MG clearance of ≥ 50 and < 70 mL/min than with those that have β_2MG clearance of < 10 mL/min and was also significantly lower when β_2MG clearance was ≥ 70 mL/min (type V in the 2004 classification and type II in the 2013 classification) than when it was ≥ 50 and < 70 mL/min (type IV in the 2004 classification and type I in the 2013 classification) [10, 11]. We have recently reported that survival is better with high albumin leakage than with low albumin leakage regardless of whether patients are receiving SHF-HD or OHDF, that survival is equivalent between these two dialysis modalities at a similar level of albumin leakage, and that survival in patients on OHDF is influenced by albumin leakage rather than substitution volume [13].

Based on these considerations, we hypothesized that survival would be better in SHF-HD using a dialyzer with β_2MG clearance ≥ 70 mL/min and high albumin leakage than in either OHDF or SHF-HD with low albumin leakage. The aim of this study was to determine whether or not survival is better on SHF-HD with a type II-b dialyzer than on OHDF with low albumin leakage or SHF-HD with a type II-a dialyzer.

Methods

Patient selection

As shown in Fig. 1, 738 of 944 previously described patients undergoing maintenance dialysis with SHF-HD or OHDF at our institution and registered in our records database as of July 1, 2017 [14], were recruited to prepare a propensity score-matched (PSM) model. The patients were divided into those on SHF-HD with β_2MG clearance ≥ 70 mL/min (n = 310) and those on OHDF (n = 428). The exclusion criteria were dialysis with β_2MG clearance < 70 mL/min, a type S dialyzer, age younger than 20 years, a blood purification method other than HD or OHDF, dialysis frequency of fewer than 3 sessions/week, dialysis time less than 3 h, substitution volume for pre-OHDF < 60 L and post-OHDF < 8 L, missing covariate values, and pregnancy or lactation. Patients whose dialysis conditions (dialysis method, dilution method, substitution volume, and/or membrane material) at the start of the study on July 1, 2017, were different from those on April 1, 2017, were also excluded. Patients receiving SHF-HD or OHDF were defined as those confirmed annually to have received the same dialysis method for 3 years (July 1, 2017 to July 1, 2020). Switching between groups was censored in the Kaplan–Meier survival curve. The dialysis modality was chosen at the physician's discretion. Blood test results were extracted from the medical records.

Preparation of propensity score-matched pairs

Patients with EAL corresponding to the third quartile or higher for SHF-HD vs. those corresponding to within the first quartile for OHDF and patients with EAL corresponding to the seventh octile or higher for SHF-HD vs. those corresponding to within the first octile for OHDF were used to investigate all-cause mortality between SHF-HD with high albumin leakage and OHDF with low albumin leakage. The propensity scores were matched for 117 pairs of patients receiving SHF-HD and 52 pairs of patients receiving OHDF. The following 14 items were used to calculate the propensity score for comparing patient survival outcomes: presence or absence of diabetes mellitus, age, dialysis vintage, body mass index, normalized protein catabolism rate, serum albumin, corrected calcium, phosphorus, hemoglobin, high-sensitivity C-reactive protein, Kt/V, systolic blood pressure, QB, and membrane surface area. The duration of each dialysis session was 4 h and both QD in HD and total QD (QD plus the substitution volume) in OHDF were fixed at 500 mL/min.

Next, patients with EAL $\geq$ 3.0 g/session vs. those with EAL $<$ 3.0 g/session and patients treated using a type II-b dialyzer vs. a type II-a dialyzer were selected for investigation of all-cause mortality in SHF-HD according to whether albumin leakage was high or low; propensity scores were matched in 115 pairs and 133 pairs, respectively. The following 11 items were used to calculate the propensity score for comparing patient survival outcomes: presence or absence of diabetes mellitus, age, dialysis vintage, body mass index, normalized protein catabolism rate, serum albumin, corrected calcium, phosphorus, hemoglobin, high-sensitivity C-reactive protein, and Kt/V.

To calculate the propensity score for each patient, multivariable logistic regression analysis was performed using the treatment group as the dependent variable and 14 covariates as independent variables, followed by logit transformation. The propensity scores were calculated to 14 decimal places. Regardless of the number of cases, patients in the two groups were paired by nearest available matching at a ratio of 1:1 within a caliper (0.348014 for SHF-HD with high albumin leakage vs. OHDF with low albumin leakage; 0.173634 for EAL $\geq$ 3.0 g/session vs. EAL $<$ 3.0 g/session in SHF-HD, and 0.144746 for type II-b dialyzers vs. type II-a dialyzers in SHF-HD) of $0.2 \times$ SD of the logit values for all patients in both groups [15].

Estimation of amount of albumin leakage

The amount of albumin leakage was measured for each dialyzer or hemodiafilter by collecting whole dialysis waste liquid for 4 h; the average value was assigned according to the substitution volume. QB was 250 mL/min for HD and 280 mL/min for OHDF, and both QD in HD and total QD in OHDF were 500 mL/min. The substitution volumes were 60 L, 72 L, and 84 L for pre-OHDF and 8 L, 10 L, 12 L, and 16 L for post-OHDF. The dialyzers and hemodiafilters used in this study and the average EAL values are listed in Additional files 2 and 3: Tables S2 and S3. The albumin level was measured using a turbidimetric immunoassay for the dialysate and a photometric method using bromocresol green for serum.

Statistical analysis

Survival was determined from the medical records, which include information on deaths and transfers to other hospitals. A daily survival analysis was performed for the two groups, including censored cases, using the Kaplan–Meier method. Between-group differences were examined for statistical significance using the log-rank test. Cox regression analysis was used to calculate hazard ratios (HRs). All analyses were performed using SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). A two-tailed P-value $<$ 0.05 was considered statistically significant.

Results

Effect of SHF-HD with high EAL and OHDF with low EAL on survival

Variables for SHF-HD with EAL at or above the third quartile and OHDF with EAL within the first quartile and after PSM are compared in Table 1a. After PSM, there was a significant increase in the hemoglobin level and a significant decrease in the membrane surface area in SHF-HD compared with OHDF. EAL of 3.0 g/session corresponded to the third quartile for SHF-HD, and EAL of 3.4 g/session corresponded to the first quartile for OHDF. As shown in Fig. 2a, there was no significant difference in 3-year all-cause mortality ($P = 0.477$, log-rank test) despite a significant difference in EAL between SHF-HD and OHDF (3.9 $\pm$ 0.9 g/session vs. 2.7 $\pm$ 0.5 g/session, $P < 0.001$). All dialyzers with EAL $\geq$ 3.0 g/session were type II-b (Additional file 2: Table S2).

Variables for SHF-HD with EAL at or above the seventh octile and OHDF with EAL within the first octile before and after PSM are compared in Table 1b. All significant differences in covariates between SHF-HD and OHDF disappeared after PSM. EAL of 4.1 g/session corresponded to the seventh octile for SHF-HD and EAL of 2.4 g/session corresponded to the first octile for OHDF. Three-year all-cause mortality was significantly lower in SHF-HD than in OHDF ($P = 0.007$, log-rank test; Fig. 2b). However, the HR and 95% confidence interval (CI)

Table 1 Comparison of variables before and after propensity score matching between SHF-HD with high EAL and OHDF with low EAL

Item	Before matching			After matching		
	SHF-HD	**OHDF**	***P*-value**	**SHF-HD**	**OHDF**	***P*-value**
(a) SHF-HD with EAL at the third quartile or above vs. OHDF with EAL within the first quartile						
n	117	127		117	117	
Sex, male/female, %	71.7/28.3	61.4/38.6	0.104	71.8/28.2	59.8/40.2	0.073
Diabetes mellitus, % with/without	39.3/60.7	40.2/59.8	0.897	39.3/60.7	41.0/59.0	0.894
Age, years	68.5 ± 10.3	70.4 ± 10.0	0.199	68.5 ± 10.3	70,2 ± 9.8	0.279
Dialysis vintage, months	108.5 ± 90.9	133.5 ± 126.4	0.292	108.5 ± 90.9	135.9 ± 128.6	0.247
Body mass index, kg/m^2	22.6 ± 4.2	22.1 ± 3.7	0.407	22.6 ± 4.2	22.2 ± 3.8	0.475
Normalized protein catabolism rate, g/kg/day	0.8 ± 0.2	0.8 ± 0.2	0.688	0.8 ± 0.2	0.8 ± 0.2	0.626
Albumin, g/dL	3.4 ± 0.3	3.4 ± 0.3	0.836	3.4 ± 0.3	3.4 ± 0.3	0.836
Corrected calcium, mg/dL	9.1 ± 0.7	9.2 ± 0.6	0.278	9.1 ± 0.7	9.2 ± 0.6	0.364
Phosphorus, mg/dL	5.1 ± 1.5	5.2 ± 1.4	0.381	5.1 ± 1.5	5.2 ± 1.3	0.518
Hemoglobin, g/dL	11.2 ± 1.2	10.8 ± 1.1	0.031	11.2 ± 1.2	10.9 ± 1.1	0.042
High-sensitivity C-reactive protein, mg/dL	0.337 ± 0.617	0.403 ± 1.199	0.122	0.337 ± 0.617	0.415 ± 1.242	0.168
Kt/V value	1.66 ± 0.28	1.60 ± 0.29	0.065	1.66 ± 0.28	1.61 ± 0.29	0.090
Systolic blood pressure, mmHg, predialysis	145 ± 21	140 ± 26	0.140	145 ± 21	140 ± 26	0.153
Blood flow rate, mL/min	275.7 ± 15.7	272.3 ± 17.3	0.139	275.7 ± 15.7	272.9 ± 17.4	0.253
Membrane surface area, m^2	2.17 ± 0.15	2.24 ± 0.19	0.003	2.17 ± 0.15	2.23 ± 0.19	0.007
Variable	**Before matching**			**After matching**		
	SHF-HD	**OHDF**	***P*-value**	**SHF-HD**	**OHDF**	***P*-value**
(b) SHF-HD with EAL at or above the seventh octile vs. OHDF with EAL within the first octile						
n	72	83		52	52	
Sex, male/female, %	75.0/25.0	59.0/41.0	0.042	69.2/30.8	55.7/44.3	0.224
Diabetes mellitus, % with/without	41.7/58.3	34.9/65.1	0.411	42.3/57.7	46.2/53.8	0.844
Age, years	66.4 ± 10.9	72.4 ± 9.5	0.001	67.9 ± 10.1	71.3 ± 10.2	0.084
Dialysis vintage, months	111.1 ± 95.8	150.5 ± 138.3	0.129	112.9 ± 96.5	106.8 ± 104.8	0.723
Body mass index, kg/m^2	23.3 ± 4.4	21.1 ± 3.0	0.002	23.0 ± 4.6	21.6 ± 3.1	0.298
Normalized protein catabolism rate, g/kg/day	0.8 ± 0.2	0.9 ± 0.2	0.563	0.8 ± 0.2	0.8 ± 0.2	0.777
Albumin, g/dL	3.4 ± 0.2	3.4 ± 0.3	0.917	3.5 ± 0.2	3.4 ± 0.3	0.930
Corrected calcium, mg/dL	9.1 ± 0.6	9.3 ± 0.6	0.069	9.1 ± 0.6	9.2 ± 0.7	0.358
Phosphorus, mg/dL	5.2 ± 1.5	5.2 ± 1.2	0.839	5.1 ± 1.2	5.2 ± 1.1	0.904
Hemoglobin, g/dL	11.2 ± 1.2	10.8 ± 1.1	0.025	11.2 ± 1.1	10.8 ± 1.0	0.077
High-sensitive C-reactive protein, mg/dL	0.337 ± 0.643	0.229 ± 0.403	0.117	0.236 ± 0.300	0.211 ± 0.289	0.483
Kt/V value	1.64 ± 0.26	1.63 ± 0.26	0.785	1.66 ± 0.27	1.65 ± 0.26	0.805
Systolic blood pressure, mm Hg, predialysis	147 ± 22	139 ± 25	0.082	144 ± 21	143 ± 25	0.876
Blood flow rate, mL/min	275.7 ± 17.9	274.8 ± 14.7	0.612	273.9 ± 17.5	275.2 ± 14.2	0.774
Membrane surface area, m^2	2.22 ± 0.18	2.10 ± 0	< 0.001	2.12 ± 0.09	2.10 ± 0.0	0.080

EAL estimated albumin leakage; *OHDF* online hemodiafiltration; *SHF-HD* super high-flux hemodialysis

could not be calculated because there were no deaths in SHF-HD. EAL was significantly higher in SHF-HD than in OHDF (4.2 ± 0.3 g/session vs. 2.3 ± 0.1 g/session, $P < 0.001$). All the dialyzers with EAL ≥ 4.2 g/session were type II-b and had a polyethersulfone (PES) membrane (Additional file 2: Table S2). None of the hemodiafilters with an EAL < 2.3 g/session had a PES membrane (Additional file 3: Table S3).

Comparison of SHF-HD according to whether EAL was high or low

Table 2a compares the variables recorded before and after PSM according to whether EAL was ≥ 3.0 g/session or < 3.0 g/session. After PSM, the corrected calcium level was significantly lower and the hemoglobin level was significantly higher when EAL was ≥ 3.0 g/session (mean 3.9 ± 0.8 g/session) than when it was < 3.0 g/session (mean

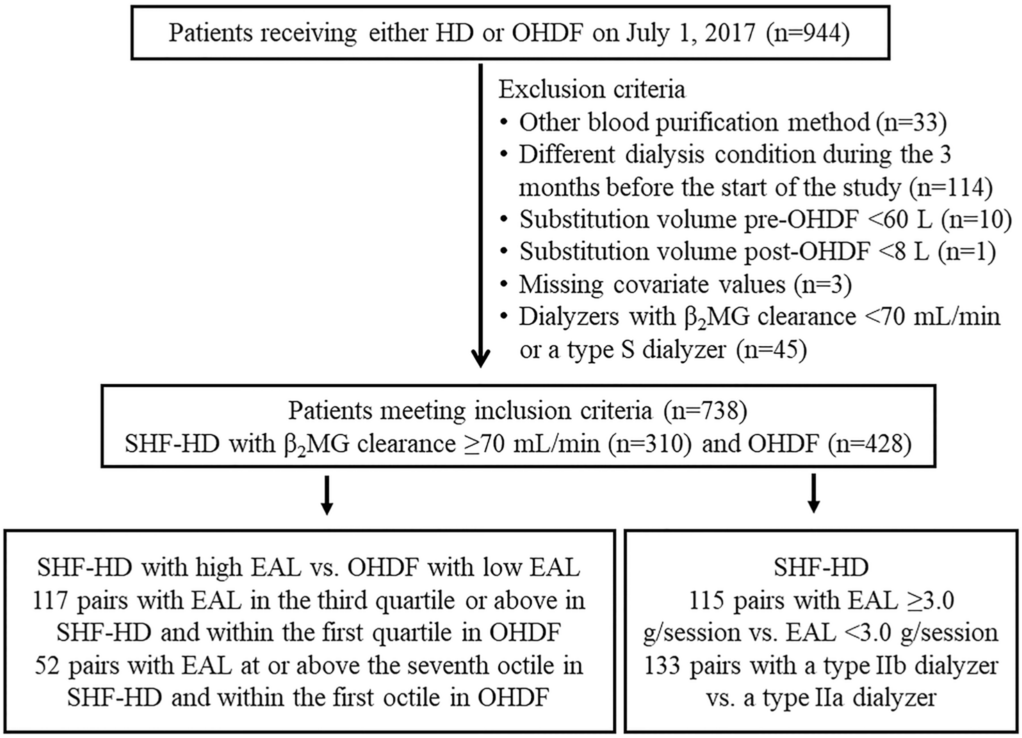

Fig. 1 Flow diagram of patients in the study *β_2MG* β_2-microglobulin; *EAL* estimated albumin leakage; *HD* hemodialysis; *OHDF* online hemodiafiltration; *post-OHDF* post-dilution online hemodiafiltration; *pre-OHDF* predilution online hemodiafiltration; *SHF-HD* super high-flux hemodialysis

1.5 ± 0.2 g/session) (P < 0.001). Furthermore, 3-year all-cause mortality was significantly lower when the EAL was ≥ 3.0 g/session (*P* = 0.004, log-rank test; HR 0.37, 95% CI 0.18–0.75; Fig. 3a). Dialyzers with EAL ≥ 3.0 g/session were type II-b only while those with EAL < 3.0 g/session included type II-b and type II-a (Additional file 2: Table S2).

Variables measured before and after PSM are compared between type II-b and type II-a dialyzers in Table 2b. After PSM, the patient age and Kt/V level were significantly lower and dialysis vintage and serum albumin were significantly higher with a type II-b dialyzer (mean EAL 3.7 ± 1.0 g/session) than with a type II-a dialyzer (mean EAL 1.4 ± 0.2 g/session) (P < 0.001). The 3-year all-cause mortality rate was significantly lower for type II-b dialyzers than for type II-a dialyzers (*P* = 0.001, log-rank test; HR 0.34; 95% CI 0.17–0.68; Fig. 3b).

Discussion

This observational study is the first to suggest that survival on SHF-HD using a type II-b dialyzer (β_2MG clearance ≥ 70 mL/min and SC for albumin ≥ 0.03) with high EAL is better than that on OHDF using a hemodiafilter with low EAL, that survival on SHF-HD using a type II dialyzer (β_2MG clearance ≥ 70 mL/min) with EAL ≥ 3.0 g/session is better than that with EAL < 3.0 g/session, and that survival is better on SHF-HD using a type II-b dialyzer (SC for albumin ≥ 0.03) than on SHF-HD using a type II-a dialyzer (SC for albumin < 0.03). Moreover, it is possible that the PES membrane material itself, which allows high albumin leakage, contributes to the improvement in survival.

Albumin is a classic nutritional marker associated with mortality, and malnutrition, which can trigger hypoalbuminemia, may increase mortality in patients on HD [16]. Although high albumin leakage may induce hypoalbuminemia that worsens survival, it is possible that hypoalbuminemia resulting from excessive removal of albumin with degraded antioxidant activity by high albumin leakage leads to production of new albumin with normal antioxidant activity in the liver [17]. We have recently reported that high albumin leakage can improve survival to a similar extent on OHDF and SHF-HD even in the presence of mild-to-moderate hypoalbuminemia [13]. Of note is that in the European studies where no difference in mortality was found between patients on HD and those on OHDF, the mean serum albumin levels did not indicate hypoalbuminemia at baseline or during follow-up in any group [5–7], which suggests low albumin leakage. Endogenous uremic toxins have recently been

Table 2 Comparison of variables before and after propensity score matching between high and low EAL on super high-flux hemodialysis

Variable	Before matching			After matching		
	EAL ≥ 3.0 g/session	EAL < 3.0 g/session	*P*-value	EAL ≥ 3.0 g/session	EAL < 3.0 g/session	*P*-value
(a) EAL ≥ 3.0 g/session vs. EAL < 3.0 g/session						
n	117	193		115	115	
Sex, male/female, %	71.8/29.2	42.5/57.5	0.109	71.3/28.7	60.0/40.0	0.095
Diabetes mellitus, % with/without	39.3/60.7	40.2/59.8	0.635	39.1/60.9	40.9/59.1	0.893
Age, years	68.5 ± 10.3	73.9 ± 10.4	< 0.001	68.9 ± 10.1	71.3 ± 11.1	0.067
Dialysis vintage, months	108.5 ± 90.9	89.6 ± 91.3	0.019	107.9 ± 90.2	127.8 ± 97.5	0.102
Body mass index, kg/m^2	22.6 ± 4.2	21.3 ± 3.5	0.009	22.6 ± 4.1	21.7 ± 3.5	0.160
Normalized protein catabolism rate, g/kg/day	0.8 ± 0.2	0.8 ± 0.2	0.253	0.8 ± 0.2	0.8 ± 0.2	0.905
Albumin, g/dL	3.4 ± 0.3	3.3 ± 0.4	0.027	3.4 ± 0.3	3.4 ± 0.4	0.487
Corrected calcium, mg/dL	9.1 ± 0.7	9.3 ± 0.7	0.0496	9.1 ± 0.7	9.4 ± 0.8	0.002
Phosphorus, mg/dL	5.1 ± 1.5	4.9 ± 1.4	0.282	5.1 ± 1.5	5.0 ± 1.4	0.723
Hemoglobin, g/dL	11.2 ± 1.2	10.9 ± 1.1	0.042	11.1 ± 1.2	10.8 ± 1.2	0.019
High-sensitivity C-reactive protein, mg/dL	0.337 ± 0.617	0.664 ± 1.546	0.282	0.338 ± 0.622	0.432 ± 0.807	0.695
Kt/V value	1.66 ± 0.28	1.73 ± 0.37	0.019	1.66 ± 0.28	1.72 ± 0.35	0.077
Variable	**Before matching**			**After matching**		
	Type II-b dialyzers	**Type II-a dialyzers**	***P*-value**	**Type II-b dialyzers**	**Type II-a dialyzers**	***P*-value**
(b) Type II-b dialyzers vs. type II-a dialyzers						
n	133	177		133	133	
Sex, male/female, %	71.4/28.6	62.1/37.9	0.091	71.4/28.6	62.4/37.6	0.152
Diabetes mellitus, % with/without	39.1/60.9	42.9/57.1	0.560	39.1/60.9	43.6/56.4	0.534
Age, years	68.8 ± 10.4	74.3 ± 10.3	< 0.001	68.8 ± 10.4	74.4 ± 10.3	< 0.001
Dialysis vintage, months	108.3 ± 90.4	88.0 ± 91.6	0.008	108.3 ± 90.4	88.1 ± 87.6	0.018
Body mass index, kg/m^2	22.5 ± 4.2	21.3 ± 3.5	0.025	22.5 ± 4.2	21.4 ± 3.4	0.060
Normalized protein catabolism rate, g/kg/day	0.9 ± 0.2	0.8 ± 0.2	0.013	0.9 ± 0.2	0.8 ± 0.2	0.058
Albumin, g/dL	3.4 ± 0.3	3.3 ± 0.4	0.009	3.4 ± 0.3	3.3 ± 0.4	0.020
Corrected calcium, mg/dL	9.1 ± 0.7	9.3 ± 0.7	0.094	9.1 ± 0.7	9.2 ± 0.7	0.236
Phosphorus, mg/dL	5.1 ± 1.5	4.9 ± 1.5	0.084	5.1 ± 1.5	4.9 ± 1.5	0.167
Hemoglobin, g/dL	11.1 ± 1.2	10.9 ± 1.1	0.097	11.1 ± 1.2	10.9 ± 1.1	0.246
High-sensitivity C-reactive protein, mg/dL	0.480 ± 1.337	0.585 ± 1.248	0.181	0.480 ± 1.337	0.492 ± 0.887	0.221
Kt/V value	1.67 ± 0.28	1.73 ± 0.38	0.041	1.67 ± 0.28	1.74 ± 0.37	0.025

EAL estimated albumin leakage

classified as small, small-middle, medium-middle, large-middle, and large molecules [18]. The improved survival with high albumin leakage suggests the importance of removing not only large-middle molecules (25–58 kDa) but also large molecules (58–170 kDa), such as albumin-bound uremic toxins. In the present study, survival was better in patients on SHF-HD with a type II-b dialyzer and high albumin leakage than in those on OHDF with low albumin leakage. Therefore, aggressive albumin leakage may be important in patients on SHF-HD or OHDF, except for those with malnutrition or inflammation. Our present findings indicate that survival is improved by using a dialyzer with EAL ≥ 3.0 g/session or a type II-b dialyzer. SC for albumin of ≥ 0.03 corresponds to mean EAL of ≥ 3.0 g/session (Additional file 2: Table S2). However, there was a type II-b dialyzer that had mean EAL as low as 2.1 ± 1.1 g/session. For this reason, we should consider the effect of ultrafiltration volume and variation in performance when measuring albumin leakage.

In Europe, with QB set at 300–400 mL/min, low-flux membranes are defined as dialyzers having β_2MG clearance of < 10 mL/min and SC for albumin of 0, high-flux membranes are defined as those having β_2MG clearance of ≥ 20 and ≤ 40 mL/min and SC

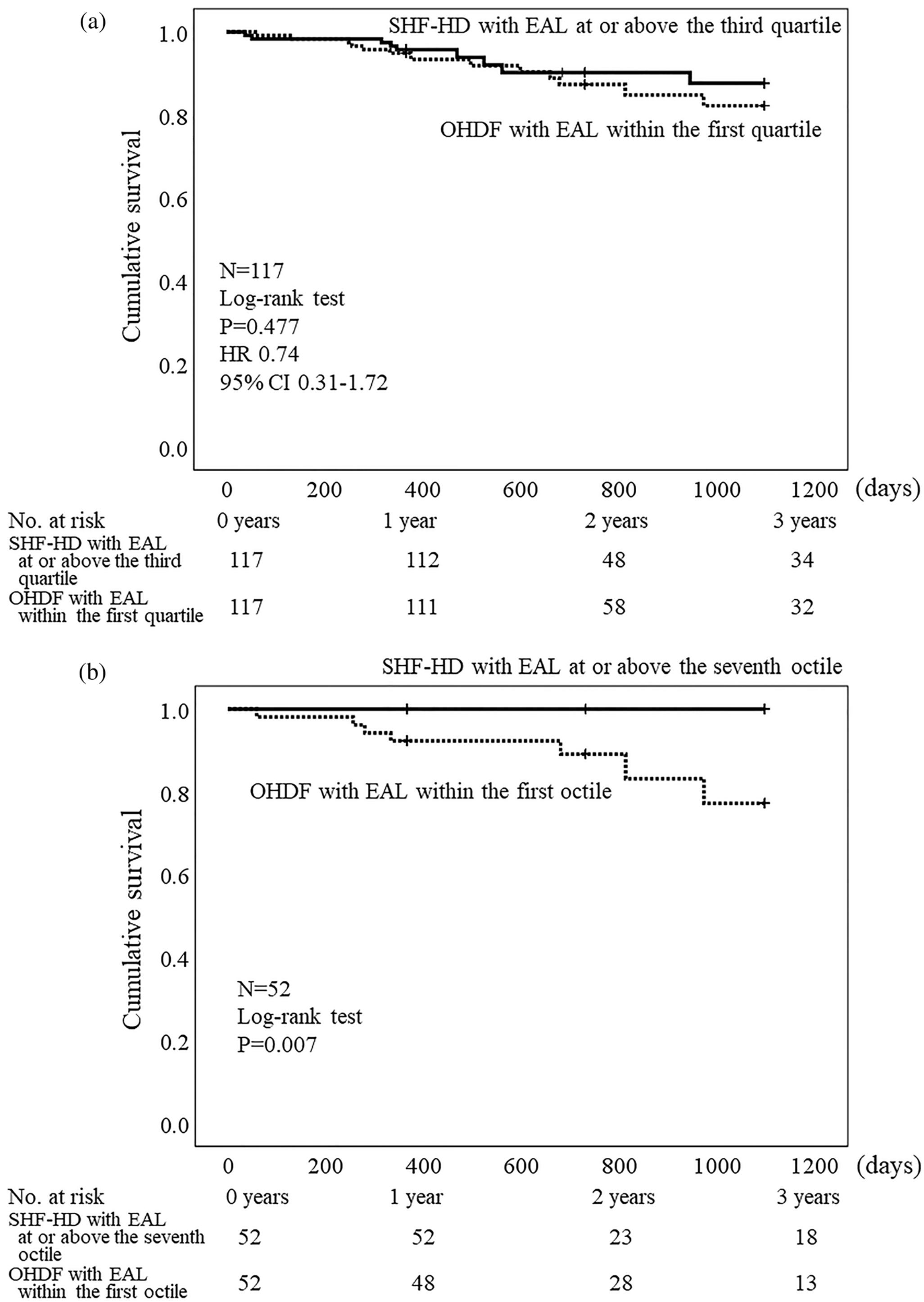

Fig. 2 Comparison of patient survival outcomes between hemodialysis using SHF-HD) with high EAL and OHDF with low EAL. **a** SHF-HD with EAL at the third quartile or above versus OHDF with EAL within the first quartile. **b** SHF-HD with EAL at or above the seventh octile versus OHDF with EAL within the first octile. *CI* confidence interval; *EAL* estimated albumin leakage; *HR* hazard ratio; *OHDF* online hemodiafiltration; *SHF-HD* super high-flux hemodialysis

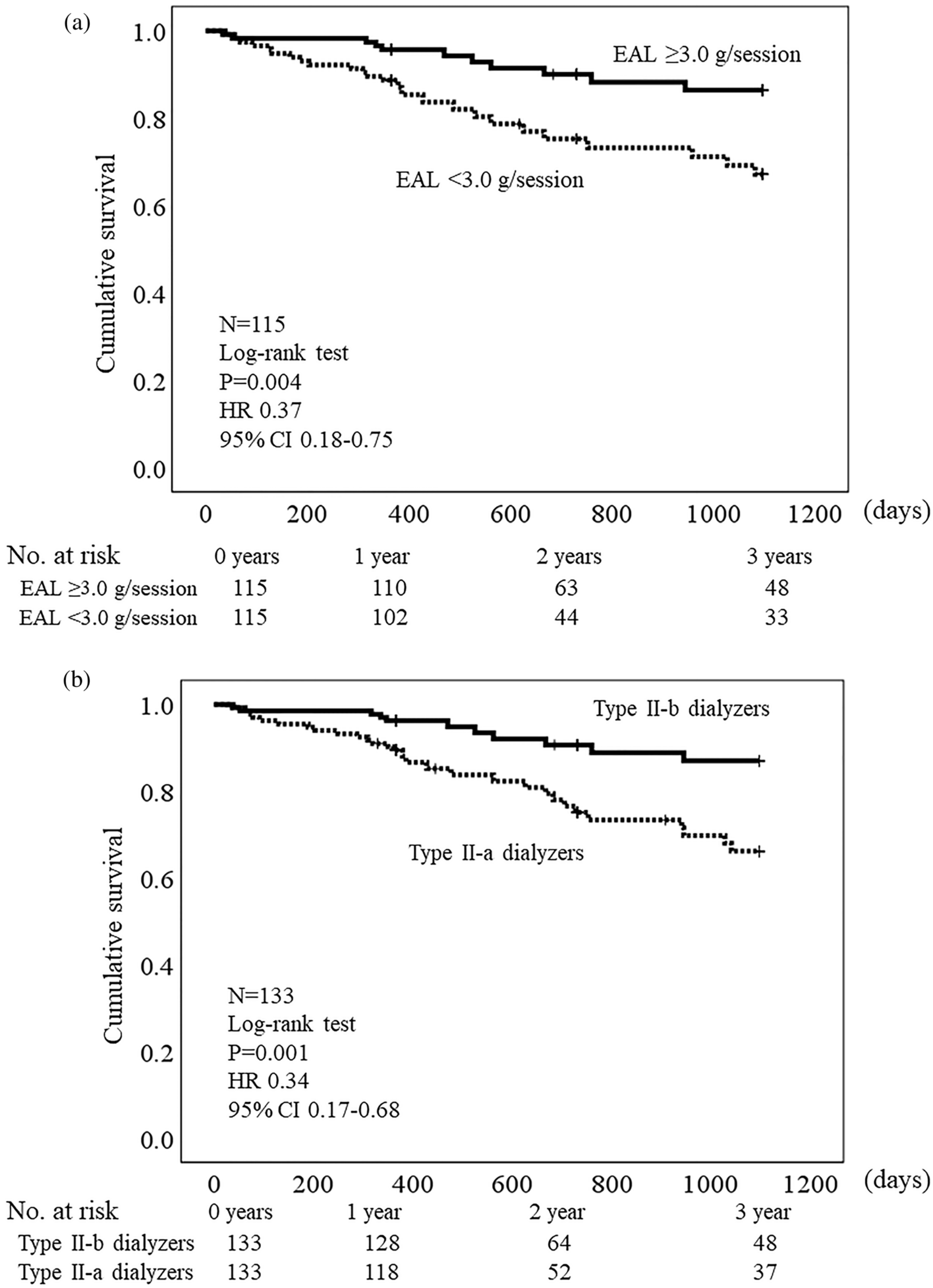

Fig. 3 Comparison of patient survival outcomes in SHF-HD according to whether EAL was high or low. **a** EAL ≥ 3.0 g/session vs. EAL < 3.0 g/session. **b** Type II-b dialyzers vs. type II-a dialyzers. *CI* confidence interval; *EAL* estimated albumin leakage; *HR* hazard ratio

for albumin of < 0.01, medium cutoff membranes are defined as those having β_2MG clearance > 80 mL/min and SC for albumin of < 0.01, and high cutoff membranes are defined as those having no β_2MG clearance and SC for albumin of < 0.2 [19]. In 2013, the JSDT reclassified the dialyzers now used in clinical practice into five types as shown in Additional file 1: Table S1 [11]. Considering the findings of this study, we recommend use of a type II-b dialyzer in patients on HD who do not have malnutrition or an inflammatory condition. Considering that Japan and other countries use different dialysis conditions when measuring β_2MG clearance and SC for albumin, a global dialyzer classification with measurements obtained under the same conditions is needed to compare the performance of dialyzers internationally. However, the JSDT has adopted a single classification for hemodiafilters in which β_2MG clearance is ≥ 70 mL/min.

The only membrane material used in SHF dialyzers with EAL at or above the seventh octile is PES, which is not included in hemodiafilters that have EAL within the first octile. In 2017, Abe et al. reported a cohort PSM study in which they investigated the effects of dialysis membrane materials on the prognosis in 136,676 patients on dialysis in Japan [20]. They compared PES, cellulose triacetate, polyester polymer alloy, polymethyl-methacrylate, polyacrylonitrile, and ethylene vinyl alcohol membranes with polysulfone (PS) membranes for 2 years from 2009 and found that the survival was significantly better when a PES membrane was used rather than a PS membrane. This finding has prompted consideration of differences in biocompatibility arising from differences in membrane materials.

Although the removal of protein-bound and large-middle molecule uremic toxins by SHF-HD using a PES membrane was similar to that achieved by high-volume post-OHDF [21], it is not known whether this would improve survival. We have previously reported that SHF-HD improves survival to the same extent as OHDF with a similar level of albumin leakage [13]. However, in the present study, we found that survival was better for SHF-HD using a type II-b dialyzer with high albumin leakage than for OHDF with low albumin leakage.

The main limitation of this study was the accuracy of the EAL and its fluctuation, especially for hemodiafilters, as indicated previously [13]. The patient characteristics were different in three of the four groups, even after PSM, because of the small number of patients. Unlike in the nationwide database, there are no significant differences in unobserved background factors, such as quality of medical management or dialysis conditions, at our facilities [14]. Therefore, we consider it reliable to set a caliper value of 0.2 multiplied by the standard deviation of the logit transformed value of the propensity score for all cases [15]. We do not have data on residual kidney function, although the dialysis vintage for patients receiving SHF-HD or OHDF was more than 3 months. A randomized controlled trial is needed to confirm our findings.

Conclusions

This study is the first to suggest that better survival is achieved by SHF-HD using a type IIb dialyzer with high albumin leakage than by OHDF using a hemodiafilter with low albumin leakage, that survival is better for SHF-HD using a type II dialyzer with albumin leakage ≥ 3.0 g/session that with albumin leakage < 3.0 g/session, and that survival is improved on SHF-HD when a type II-b dialyzer is used. A PES membrane with high albumin leakage may also have a beneficial effect on patient survival.

Abbreviations

β_2MG	β_2-Microglobulin
BSA	Bisphenol A
CI	Confidence interval
EAL	Estimated albumin leakage
HD	Hemodialysis
HR	Hazard ratio
JSDT	Japanese Society for Dialysis Therapy
MCO	Medium cutoff
OHDF	Online hemodiafiltration
PES	Polyethersulfone
post-OHDF	Post-dilution online hemodiafiltration
pre-OHDF	Predilution online hemodiafiltration
PS	Polysulfone
PSM	Propensity score matching
QB	Blood flow rate
QD	Dialysate flow rate
RCT	Randomized controlled trial
SC	Sieving coefficient
SHF	Super high-flux

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-023-00490-3.

Additional file 1: Table S1. Functional classification of dialyzers 2013 developed by the Japanese Society for Dialysis Therapy [11]

Additional file 2: Table S2. Super high-flux dialyzers, mean estimated albumin leakage (EAL) and functional classification of dialyzers 2013 developed by the Japanese Society for Dialysis Therapy (JSDT).

Additional file 3: Table S3. Hemodiafilters and mean estimated albumin leakage (EAL).

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Author contributions

KO interpreted the results of statistical analysis and was the major contributor to drafting the manuscript, and MT, HM, TI, HS, JM, and SK performed data collection. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. Data supporting the results of the study are kept at Japan Institute of Statistical Technology (https://www.jiost.com/).

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of Kawashima Hospital and registered in the UMIN Clinical Trials Registry (UMIN000047948 registered on June 4, 2022—retrospectively registered, https://center6.umin.ac.jp/cgi-bin/ctr/ctr_view_reg.cgi?recptno=R000054664, and UMIN000050068 registered on January 18, 2023—retrospectively registered, https://center6.umin.ac.jp/cgi-bin/ctr/ctr_view_reg.cgi?recptno=R000056883). All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All patients gave informed consent for their data to be included in this study.

Consent for publication
Not applicable.

Competing interests
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Author details
[1]Department of Nephrology, Kawashima Hospital, 6-1 Kitasakoichiban-cho, Tokushima-shi, Tokushima 770-0011, Japan. [2]Department of Clinical Engineering, Kawashima Hospital, Tokushima, Japan.

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