Renal Replacement Therapy

RESEARCH

Open Access

Intermittent infusion hemodiafiltration is associated with improved survival compared to hemodialysis

Masanori Abe[1,2*], Kan Kikuchi[1,3], Atsushi Wada[1,4], Shigeru Nakai[1,5] and Norio Hanafusa[1,6]

Abstract

Background Approximately 16.4% of patients on hemodialysis (HD) in Japan are treated with intermittent infusion hemodiafiltration (I-HDF). However, large-scale data on clinical outcomes with this modality are lacking. This study aimed to compare the outcomes of I-HDF with those of conventional HD.

Methods A cohort study was conducted using the Japanese Society for Dialysis Therapy Renal Data Registry database from December 31, 2017 to December 31, 2019. The subjects were 210,574 patients on maintenance HD. The exposure of interest was I-HDF treatment versus conventional HD. The I-HDF group was divided into two subgroups based on substitution: low-volume (< 1.2 L per session) and high-volume (≥ 1.2 L per session). Outcomes included 2-year all-cause and cardiovascular mortality. The data were analyzed using Cox regression models after adjusting for potential confounders.

Results I-HDF was associated with improved all-cause mortality compared to HD (hazard ratio: 0.94, 95% confidence interval: 0.90–0.99) after adjusting for all covariates. However, there was no significant difference in cardiovascular mortality between the two groups. In patients treated with I-HDF, the high-volume I-HDF group had improved all-cause and cardiovascular mortality compared to low-volume I-HDF or HD groups. Propensity score matching analysis revealed that the high-volume I-HDF group had better survival rates than the HD group.

Conclusions This observational study suggests that I-HDF, especially with high- volumes substitution, may improve all-cause and cardiovascular mortality. However, to establish a causal relationship and further evaluate the efficacy of I-HDF in improving outcomes and reducing cardiovascular events in patients on dialysis, randomized controlled trials are warranted.

Trial registration UMIN000018641.

Keywords Cardiovascular event, Cumulative survival, Hemodialysis, Intermittent infusion hemodiafiltration, Substitution volume

*Correspondence:
Masanori Abe
abe.masanori@nihon-u.ac.jp
Full list of author information is available at the end of the article

Introduction

Hemodiafiltration (HDF) is a blood purification therapy that combines both diffusive and convective transport. Studies have demonstrated that HDF is more effective than conventional hemodialysis (HD) in removing β_2-microglobulin (β2MG) and various cytokines [1]. In Japan, there are currently over 186,000 patients undergoing online HDF, with 69.0% of them utilizing predilution online HDF [2]. Recently, there has been a significant increase in the number of patients receiving intermittent infusion HDF (I-HDF) in Japan. Approximately 55,000 patients, accounting for 29.7% of online HDF cases, are currently undergoing I-HDF [2]. In I-HDF, ultrapure dialysis fluid is infused at a volume of 200 mL and a rate of 150 mL/min by back filtration every 30 min during treatment. Additionally, the same volume of body fluid is filtered after each infusion to remove excess water. The first infusion is performed 30 min after the start of treatment, and the last is performed 30 min before the end of treatment. Therefore, the total infusion volume is estimated to be 1.4 L/session, calculated by multiplying the infusion volume (200 mL) by the number of infusions (7 infusions) [3]. I-HDF is considered a type of online HDF with a negligible replacement volume. As I-HDF involves a closed system in which infusion and ultrafiltration occur, it is accepted as HDF by Japanese medical insurance if the equipment requirements are met.

I-HDF was developed to prevent rapid decreases in blood pressure (BP) during treatment and improve peripheral circulation. This is achieved through repeated intermittent infusions of ultrapure dialysis fluid or sterile nonpyrogenic substitution fluids, which increase the circulating blood volume [4, 5]. The main aims of intermittent infusion are to reduce the risk of BP drops during treatment by preventing a rapid drop in blood volume due to excess water removal and to enhance the transport of water and solutes from the extravascular space to the intravascular space by improving the peripheral circulation in patients. By using I-HDF, the number of interventions for intradialytic hypotension can be reduced [6]. Furthermore, I-HDF is expected to alleviate the fouling effect caused by protein deposition on the membrane due to ultrafiltration by using membrane backlashing with purified dialysate [4, 5]. Although some observational studies and small clinical trials have reported the clinical benefits of I-HDF, there is a lack of large-scale studies analyzing the clinical effects of I-HDF on patient survival outcomes [7, 8]. Therefore, we conducted a cohort study using a nationwide registry of patients on dialysis in Japan to clarify the survival outcomes of I-HDF. In the present study, survival outcomes, such as 2-year all-cause mortality and cardiovascular mortality, were compared between the HD and I-HDF groups.

Methods

Study design

This is a prospective cohort study using data from the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) system, a nationwide cohort of patients on dialysis in Japan. Detailed information about JRDR has been previously published [9–11]. The Japanese Society for Dialysis Therapy (JSDT) conducts a survey of all dialysis units in Japan at the end of every year, with response rates consistently above 95% throughout the study period. The study protocol was approved by the Medicine Ethics Committee of JSDT (Approval No. 39), and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The ethics committee also granted a waiver of consent for the use of JRDR data. The database has been completely de-identified 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 Renal Data Registry) has been strictly prohibited under the agreement between the principal investigators and JSDT, which reserves all rights regarding the database. This study was registered at the University Hospital Medical Information Network (UMIN000018641).

Setting and participants

The inclusion criteria for this study were patients undergoing HD and I-HDF at the end of 2017, with the observation period ending at the end of 2019. The patients receiving I-HDF were then divided into two groups based on the median substitution volume. The low-volume substitution group consisted of patients with a substitution volume of < 1.2 L per session (low-volume I-HDF), while the high-volume substitution group consisted of patients with a substitution volume of ≥ 1.2 L per session (high-volume I-HDF). Patients who underwent maintenance HD and I-HDF three times a week and had received maintenance dialysis for at least 1 year at the end of 2017 were included. However, patients were excluded if they were dialyzed less than three times a week or for less than three hours per session, received long-time HD (i.e., more than six hours per session), had received conventional HDF or peritoneal dialysis, had a history of organ transplantation, were under 18 years old, had a dialysis vintage of less than 1 year, and had incomplete records regarding date of birth, dialysis initiation, dialyzer usage, or outcomes.

Exposure of interest and outcomes

The exposure of interest was I-HDF therapy versus HD therapy. The primary outcome variable was all-cause mortality, while the secondary outcome was

cardiovascular (CV) mortality. CV mortality was defined as death from a myocardial infarction, valvular heart disease, cardiomyopathy, arrhythmia, pulmonary edema, sudden cardiac arrest, endocarditis, pericarditis, or stroke.

Statistical methods

Data were summarized using proportions, means with standard deviations, percentages, or medians with interquartile ranges, as appropriate. Categorical variables were analyzed using the chi-squared test, while continuous variables were compared using the Student's *t*-test, as appropriate. The categorical data were compared between groups using repeated-measures analysis of variance with Tukey's honestly significant difference test or Kruskal–Wallis test, as appropriate.

To compare the effects of HD, low-volume I-HDF, and high-volume I-HDF on survival outcomes, survival analysis was estimated using the Kaplan–Meier method and compared using the log-rank test. Survival analyses using Cox proportional hazards regression were used to determine whether baseline factors, including gender, age, cause of end-stage kidney disease, duration of dialysis, and comorbid cardiovascular disease (CVD) predicted survival for up to 2 years of follow-up. Additional analyses were performed after adjusting for dialysis-related factors as assessed by Kt/V and β2MG levels. Further analyses included adjusting for nutrition- and inflammation-related factors, including body mass index (BMI), serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, C-reactive protein (CRP) levels, systolic and diastolic BP values and heart rate at predialysis, normalized protein catabolic rate (nPCR), and percentage of creatinine generation rate (%CGR). In these analyses, age, CRP, and hemoglobin levels were all treated as continuous variables. In addition, subgroup analyses were performed. First, a subgroup analysis was conducted and stratified by gender and age (using the median values of age < 70 and ≥ 70 years). Second, a subgroup analysis was performed based on dialysis therapy vintage, CVD history, and diabetes mellitus (DM) status. Third, a subgroup analysis was conducted and stratified by the median values of BMI (< 22 and ≥ 22) and serum albumin levels (< 3.6 and ≥ 3.6 g/dL). Finally, a subgroup analysis was conducted and stratified by the median systolic BP levels at predialysis (< 150 and ≥ 150 mmHg).

Finally, propensity score matching was used to adjust for significant baseline covariates. The dialysis-related and nutrition- and inflammation-related factors were used to calculate propensity scores, which were then used in univariate Cox proportional hazard regression analysis. Patients in the HD group (reference group) were matched in a 1:1 ratio to those in the low- and high-volume I-HDF groups. Propensity scores were derived from gender, age, duration of dialysis, presence or absence of diabetes, comorbid CVD, Kt/V, β2MG, BMI, serum albumin, hemoglobin, CRP levels, systolic and diastolic BPs, heart rate, nPCR, and %CGR value. All-cause and CV mortality were compared in propensity score-matched patients.

Missing covariate data were imputed using the conventional multivariate regression method, as appropriate. All analyses were conducted using JMP® Version 13.0 (SAS Institute, Cary, NC, USA), and a p value < 0.05 was considered statistically significant.

Results

Patients' characteristics

At the end of 2017, a total of 365,809 patients were initially registered for the study. After applying the exclusion criteria, 210,574 patients remained for analysis (Fig. 1). The baseline characteristics of the patients in the HD and I-HDF groups are summarized in Table 1. In the I-HDF group, there were more female patients, a shorter dialysis period, a higher ratio of diabetic nephropathy, a higher BMI, higher serum albumin, nPCR, and %CGR values, higher rates of comorbid CVD, and lower Kt/V values. During the 2-year observation period from January 2018 to December 2019, a total of 51,458 patients (24.4%) died, while 159,116 patients (75.6%) survived.

Predictors of all-cause mortality in 210,574 patients with HD and I-HDF

The hazard ratios (HRs) for variables evaluated as potential predictors of mortality in all patients are presented in Additional file 1. Male gender, increasing age, longer dialysis duration, the presence of DM, and comorbid CVD were significant predictors of mortality. A higher dialysis dose, as assessed by single-pool Kt/V, was associated with a lower mortality risk. Furthermore, poor nutritional status and increased inflammatory status, as evidenced by lower hemoglobin levels, higher CRP levels, lower nPCR, lower serum albumin levels, lower BMI, and lower %CGR, were also associated with a higher mortality rate in patients undergoing HD and I-HDF.

Comparison of patient survival outcomes between the HD and I-HDF groups

The 2-year all-cause mortality rate in the I-HDF group was found to be significantly lower than in the HD group, as determined by Cox regression analysis (log-rank test: $p < 0.0001$; HR: 0.84, 95% confidence interval [CI]: 0.81–0.87; Fig. 2). These findings indicate a significant improvement in the 2-year all-cause mortality associated with I-HDF. After adjusting for basic factors, including age, gender, dialysis vintage, history of CVD, and

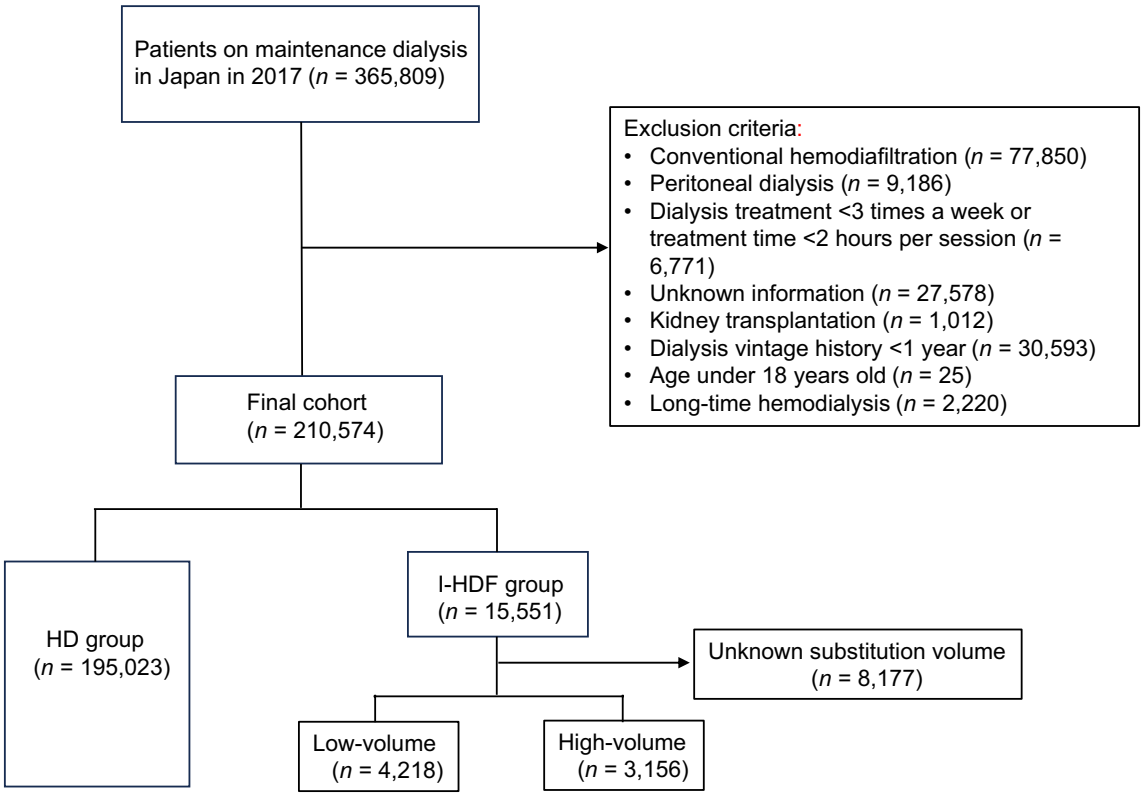


Fig. 1 Flow diagram for patient selection HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

presence or absence of DM, the I-HDF group still had a significantly lower 2-year all-cause mortality rate than the HD group (HR: 0.87, 95% CI: 0.84–0.91; Table 2). After adjusting for basic and dialysis-related factors, including Kt/V and β2MG values, the I-HDF group still had a significantly lower 2-year all-cause mortality rate than the HD group (HR: 0.91, 95% CI: 0.87–0.96). Finally, after adjusting for basic, dialysis-related, nutrition- and inflammation-related factors including BMI, serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, CRP levels, systolic and diastolic BPvalues and heart rate at predialysis, nPCR, and %CGR, the I-HDF group had a significantly lower 2-year all-cause mortality rate than the HD group (HR: 0.94, 95% CI: 0.90–0.99, $p=0.016$). After adjusting for all covariates, the risk of all-cause death was lower in the I-HDF group than in the HD group in patients who were female, older in age, had a longer dialysis vintage, no history of DM or CVD, lower BMI, serum albumin levels, and systolic BP levels at predialysis (Fig. 3).

Comparison of cardiovascular outcomes between the HD and I-HDF groups

The 2-year CV mortality rate in the I-HDF group was found to be significantly lower than in the HD group, as determined by Cox regression analysis (log-rank test: $p<0.0001$; HR: 0.59, 95% CI: 0.56–0.63; Fig. 4). After adjusting for basic factors, the I-HDF group still had a significantly lower 2-year CV mortality rate than the HD group (HR: 0.70, 95% CI: 0.66–0.74; Table 3). However, there was no significant difference in the 2-year CV mortality rate between the two groups after adjusting for basic and dialysis-related factors (HR: 0.93, 95% CI: 0.88–1.00, $p=0.062$), as well as after adjusting for basic, dialysis-related, nutrition- and inflammation-related factors (HR: 0.94, 95% CI: 0.88–1.00, $p=0.069$).

Comparison of patient outcomes among the HD, low-volume I-HDF, and high-volume I-HDF groups

In the I-HDF group, the HR for a 0.1-L increase in substitution volume was 0.78 (95% CI: 0.72–0.85, $p<0.0001$). Survival analysis was performed for the HD, low-volume I-HDF, and high-volume I-HDF groups (median substitution volume of 1.1 [1.0–1.4] per session). The baseline characteristics of patients in the HD, low-volume I-HDF, and high-volume I-HDF groups are summarized in Table 4.

According to the Kaplan–Meier analysis, the 2-year all-cause mortality rate in the low-volume I-HDF and high-volume I-HDF groups was significantly lower than in the

Table 1 Comparison of the baseline characteristics in hemodialysis (HD) and intermittent infusion hemodiafiltration (I-HDF) groups

Variables	HD	I-HDF	*P* value
n, male (%)	195,023 (64.4)	15,551 (62.7)	< 0.0001
Age, years	70.1 ± 12.1	70.0 ± 12.0	< 0.0001
HD duration, months	73 (37–136)	71 (36–132)	0.0004
Primary causes of ESKD, %			< 0.0001
Diabetic nephropathy	40.2	42.0	
Chronic glomerulonephritis	28.6	27.9	
Nephrosclerosis	12.4	12.6	
Others	18.8	17.5	
Diabetes mellitus, %	56.6	56.6	0.971
Smoking, %	10.6	10.1	0.102
Body mass index, kg/m^2	21.6 ± 4.0	21.8 ± 4.0	< 0.0001
Serum UN, mg/dL	60.0 ± 16.1	60.1 ± 15.8	< 0.0001
Creatinine, mg/dL	9.6 ± 2.9	9.7 ± 2.8	< 0.0001
β_2-microglobulin, mg/L	27.0 ± 7.0	27.1 ± 6.7	0.009
Serum albumin, g/dL	3.5 ± 0.5	3.6 ± 0.4	< 0.0001
Total cholesterol, mg/dL	156 ± 36	156 ± 35	0.037
HDL cholesterol, mg/dL	48.3 ± 16.5	48.4 ± 16.8	0.646
C-reactive protein, mg/dL	0.16 (0.06–0.50)	0.16 (0.06–0.50)	0.098
History of CVD, %	31.0	33.2	< 0.0001
Ischemic heart disease	15.3	15.9	0.028
Hemorrhagic stroke	5.3	5.3	0.441
Ischemic stroke	15.0	16.9	< 0.0001
Limb amputation	3.2	3.3	0.468
Systolic BP, mmHg	151 ± 24.8	152 ± 25.6	< 0.0001
Diastolic BP, mmHg	77.2 ± 14.6	77.5 ± 14.8	0.014
Heart rate, bpm	74.4 ± 12.9	74.4 ± 12.7	0.989
Calcium, mg/dL	8.6 ± 0.7	8.7 ± 0.7	< 0.0001
Phosphate, mg/dL	5.2 ± 1.5	5.2 ± 1.4	< 0.0001
Intact PTH, pg/mL	132 (73–212)	129 (73–208)	0.001
Hemoglobin, g/dL	10.8 ± 1.3	10.9 ± 1.2	< 0.0001
Kt/V	1.45 ± 0.31	1.44 ± 0.30	< 0.0001
nPCR, g/kg/day	0.84 ± 0.18	0.85 ± 0.17	< 0.0001
% CGR	90.6 ± 29.1	91.7 ± 27.7	< 0.0001
Substitutional volume, L	–	1.1 (1.0–1.4)	–

Data are presented as means ± standard deviations, percentages, or medians (interquartile range). BP, blood pressure; CGR, creatinine generation rate; CVD, cardiovascular disease; ESKD, end-stage kidney disease; HDL, high-density lipoprotein; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; UN, urea nitrogen.

HD group (log-rank test: $p < 0.0001$; Fig. 5). Compared to the HD group, the low-volume and high-volume I-HDF groups had significantly lower unadjusted all-cause mortality rates (HR: 0.74, 95% CI: 0.69–0.79 and HR: 0.55, 95% CI: 0.50–0.60, respectively; Fig. 6, Additional file 2). After adjusting for basic factors, the low-volume and high-volume I-HDF groups still had significantly lower all-cause mortality rates (HR: 0.82, 95% CI: 0.76–0.88 and HR: 0.63, 95% CI: 0.57–0.68, respectively). After adjusting for basic and dialysis-related factors, the high-volume I-HDF group still had a significantly lower all-cause mortality rate (HR: 0.81, 95% CI: 0.73–0.90, $p = 0.001$), while the low-volume I-HDF and HD groups had no significant differences. Finally, after adjusting for basic, dialysis-related, nutrition-related, and inflammation-related factors, the high-volume I-HDF group still had a significantly lower all-cause mortality rate (HR: 0.82, 95% CI: 0.74–0.91, $p = 0.0003$).

According to the Kaplan–Meier analysis, the 2-year CV mortality rates in the low-volume and high-volume I-HDF groups were significantly lower than in the HD group (log-rank test: $p < 0.0001$; Fig. 7). Compared to the HD group, the low-volume and high-volume I-HDF groups had significantly lower unadjusted CV mortality (HR: 0.55, 95% CI: 0.48–0.62 and HR: 0.74, 95% CI: 0.67–0.82, respectively; Fig. 8, Additional file 3). After adjusting for basic factors, the low-volume and high-volume I-HDF groups still had significantly lower CV mortality (HR: 0.63, 95% CI: 0.55–0.72 and HR: 0.81, 95% CI: 0.73–0.90, respectively). After adjusting for basic and dialysis-related factors, the high-volume I-HDF group had significantly lower CV mortality (HR: 0.83, 95% CI: 0.73–0.93, $p = 0.015$), while the low-volume I-HDF group had no significant difference. Finally, after adjusting for basic, dialysis-related, nutrition- and inflammation-related factors, the high-volume I-HDF group had significantly lower CV mortality (HR: 0.85, 95% CI: 0.73–0.98, $p = 0.025$).

The survival analysis was performed for the low-volume I-HDF (median substitution volume of 1.0 [0.7–1.0] L per session) and high-volume I-HDF (median substitution volume of 1.4 [1.4–1.5] L per session) groups. According to Cox regression analysis after adjusting for all covariates, the high-volume I-HDF group had a significantly lower 2-year all-cause mortality rate (HR: 0.84, 95% CI: 0.75–0.93, $p = 0.002$; Additional file 4) and 2-year CV mortality rate (HR: 0.82, 95% CI: 0.71–0.94, $p = 0.004$; Additional file 5) than in the low-volume I-HDF group.

Propensity score matching analysis

Patients treated with HD were matched with those treated with low- and high-volume I-HDF in a 1:1 ratio based on propensity scores. After propensity score matching, 2260 and 2030 patient pairs were matched in the low- and high-volume I-HDF groups, respectively. Additional file 6 shows the patient characteristics and clinical data at baseline in the HD group and low-volume I-HDF group after propensity score matching. No significant differences were observed in any variables. As shown in Fig. 9, no significant difference in HRs of

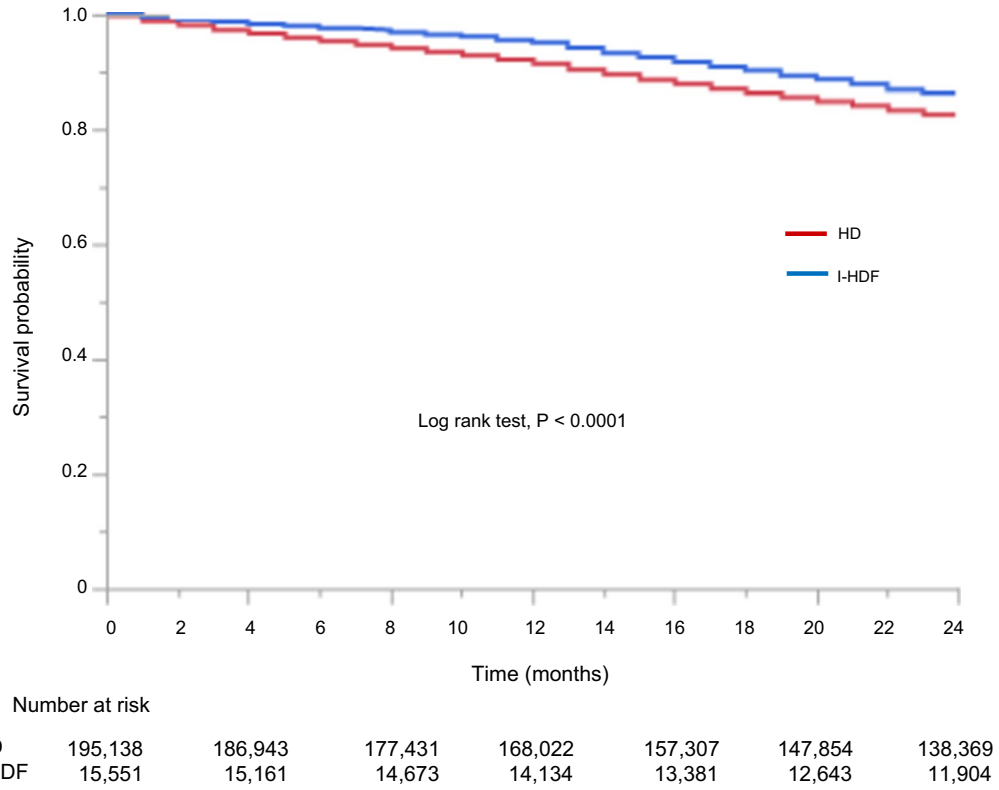


Fig. 2 Comparison of patient survival outcomes between the hemodialysis (HD) and intermittent infusion hemodiafiltration (I-HDF) groups HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

Table 2 Comparison of all-cause mortality between the intermittent infusion hemodiafiltration (I-HDF) and hemodialysis (HD) groups using the Cox proportional hazards regression model

Group	Unadjusted			Adjusted for basic factors[a]			Adjusted for basic and dialysis-related factors[b]			Adjusted for basic, dialysis-related, and nutrition/inflammation-related factors[c]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
HD	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
I-HDF	0.84	0.81–0.87	< 0.0001	0.87	0.84–0.91	< 0.0001	0.91	0.87–0.96	0.003	0.94	0.90–0.99	0.016

[a] Adjusted for gender, age, duration of dialysis, presence or absence of diabetes, and cardiovascular disease. [b]Adjusted for basic factors and dialysis-related factors, including Kt/V and β_2-microglobulin levels. [c]Adjusted for basic and dialysis-related factors, and nutrition- and inflammation factors, including body mass index, systolic and diastolic blood pressures and heart rate at predialysis, serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, C-reactive protein levels, normalized protein catabolic rate, and % creatinine generation rate. CI, confidence interval; HD, hemodialysis; HR, hazard ratio; I-HDF, intermittent infusion hemodiafiltration

all-cause and CV mortalities was observed between the two groups. Additional file 7 shows the patient characteristics and clinical data at baseline in the HD group and high-volume I-HDF group after propensity score matching. Although no significant differences were observed in any variables, compared with the HD group, the high-volume I-HDF group had lower HRs of all-cause mortality (0.83 [0.73–0.94], $p = 0.0002$) and CV mortality (0.84 [0.72–0.98], $p = 0.027$) (Fig. 10).

Discussion

In this study, we first confirmed that I-HDF was superior to standard HD in terms of all-cause mortality. In addition, the I-HDF modality may be more beneficial

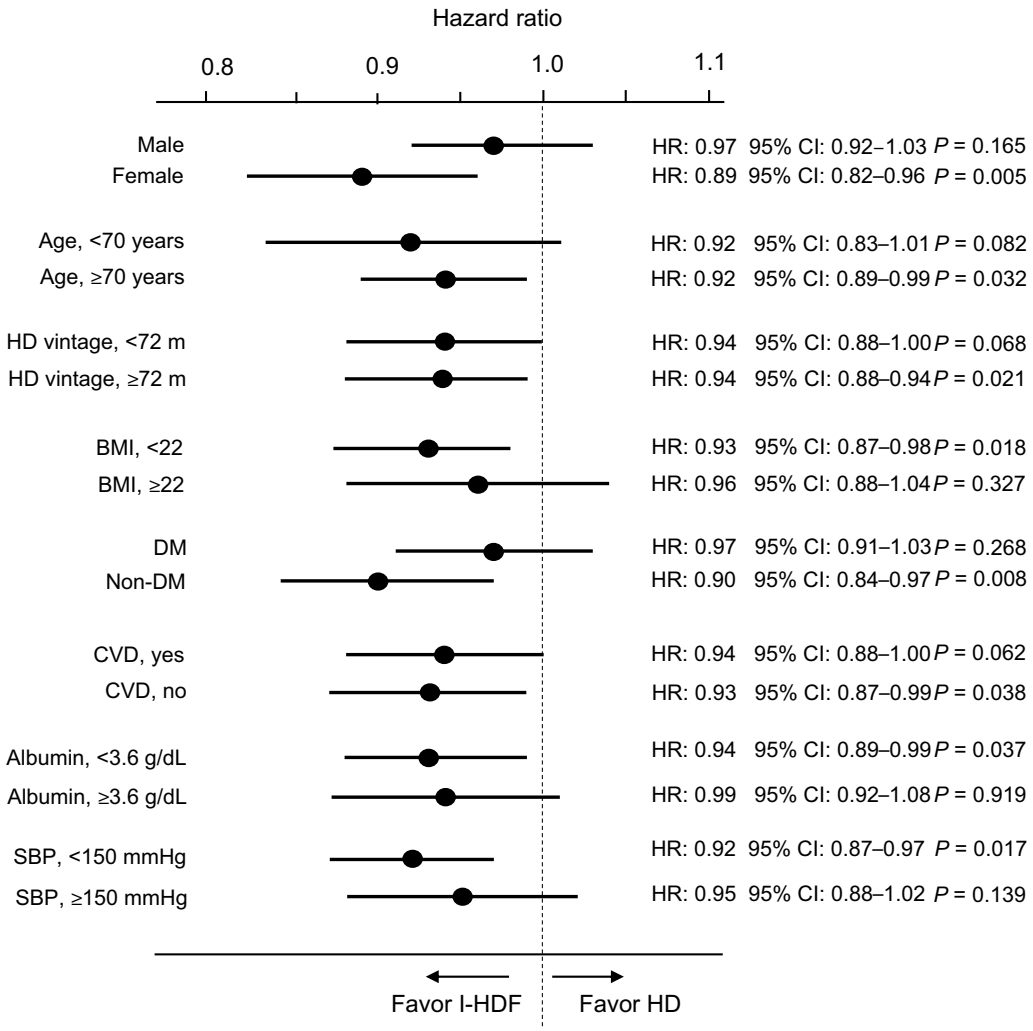


Fig. 3 Subgroup analyses for the association between intermittent infusion hemodiafiltration (I-HDF) therapy and mortality BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration; SBP, systolic blood pressure

than standard HD in patients who are older females, have a longer dialysis vintage, have no history of diabetes or CVD, and have lower BMI, serum albumin, and systolic BP levels at predialysis. Furthermore, among patients treated with I-HDF, those receiving high substitution volumes (≥ 1.2 L per session) showed improved all-cause mortality and CV mortality compared to those receiving low substitution volumes (< 1.2 L per session) or those on standard HD. In addition, via propensity score matching analysis, the present study revealed that the I-HDF with high substitution volumes was superior to the standard HD. A major strength of this study was the large sample size, which allowed for the identification of patient characteristics suitable for I-HDF. This study is the first to indicate the potential for improvement in mortality risk through the use of I-HDF.

Intradialytic hypotension has several negative consequences, including a reduction in dialysis efficiency, increased patient discomfort, such as loss of consciousness, and the potential development of cardiac dysfunction with myocardial stunning [12, 13]. Furthermore, intradialytic hypotension is recognized as an independent predictor of survival in patients on HD [13, 14]. During HD, fluids accumulated in the body need to be removed during each dialysis session, which is usually performed three times a week. This process of removing and adding blood volume repeatedly can lead to nonphysiological fluctuations, causing stress-induced BP instability. Intradialytic hypotension occurs when the cardiovascular system fails to compensate for the hypovolemia resulting from excessive or rapid fluid removal. In addition to the decreased quality of life, intradialytic hypotension can rapidly decrease coronary and cerebral blood flow.

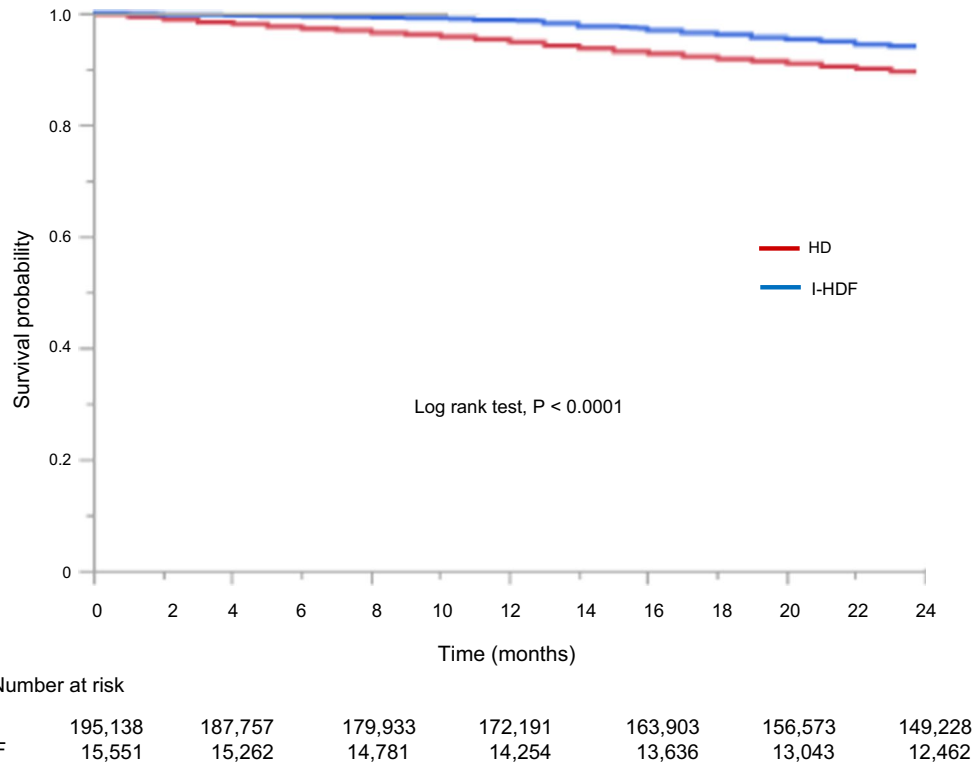


Fig. 4 Comparison of cardiovascular survival between the hemodialysis (HD) and intermittent infusion hemodiafiltration (I-HDF) groups HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

Table 3 Comparison of cardiovascular mortality between the intermittent infusion hemodiafiltration (I-HDF) and hemodialysis (HD) group using Cox proportional hazards regression model

Group	Unadjusted			Adjusted for basic factors[a]			Adjusted for basic factors and dialysis-related factors[b]			Adjusted for basic, dialysis-related, and nutrition/inflammation-related factors[c]		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
HD	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–	1.00	Reference	–
I-HDF	0.59	0.56–0.63	< 0.0001	0.70	0.66–0.74	< 0.0001	0.93	0.88–1.00	0.062	0.94	0.88–1.00	0.069

[a] Adjusted for gender, age, duration of dialysis, presence or absence of diabetes, and cardiovascular disease. [b]Adjusted for basic factors and dialysis-related factors, including Kt/V and β_2-microglobulin levels. [c]Adjusted for basic and dialysis-related factors, and nutrition- and inflammation factors, including body mass index, systolic and diastolic blood pressures and heart rate at predialysis, serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, C-reactive protein levels, normalized protein catabolic rate, and % creatinine generation rate. CI, confidence interval; HD, hemodialysis; HR, hazard ratio; I-HDF, intermittent infusion hemodiafiltration

Therefore, preventing intradialytic hypotension remains a major challenge in intermittent renal replacement therapy. A crossover study comparing HD to I-HDF in 68 patients who experienced a tendency for decreased BP during HD was conducted. The study revealed that intradialytic BP increased, and the intervention rate for intradialytic hypotension during I-HDF was lower compared to that during HD [6]. Furthermore, the heart rate was lower during I-HDF than during HD, indicating less sympathetic stimulation during I-HDF. Elderly patients and those with higher interdialytic weight gain were considered suitable candidates for I-HDF. Subgroup analysis also revealed that I-HDF was preferable for elderly patients and those with lower SBP at predialysis. However, the present study could not evaluate hemodynamics during dialysis sessions; therefore, further investigation is required to determine whether I-HDF may contribute to the prevention of intradialytic hypotension.

Table 4 Comparison of baseline characteristics in the hemodialysis (HD), low-volume intermittent infusion hemodiafiltration (I-HDF), and high-volume I-HDF groups

	HD	Low-volume I-HDF	High-volume I-HDF	*P* value
n, male (%)	195,023 (64.4)	4,218 (62.7)	3,156 (65.0)	0.010
Age, years	70.1 ± 12.1	69.4 ± 12.4	68.7 ± 12.1	< 0.0001
HD duration, months	73 (37–136)	66 (34–128)	79 (39–145)	< 0.0001
Diabetes mellitus, %	56.6	55.4	53.3	0.0004
Body mass index, kg/m^2	21.6 ± 4.0	21.7 ± 4.0	22.0 ± 4.1	< 0.0001
β_2-microglobulin, mg/L	27.0 ± 7.0	27.2 ± 7.3	27.2 ± 6.5	0.066
Serum albumin, g/dL	3.5 ± 0.5	3.6 ± 0.4	3.6 ± 0.4	< 0.0001
C-reactive protein, mg/dL	0.16 (0.06–0.50)	0.16 (0.06–0.49)	0.15 (0.06–0.46)	0.098
History of CVD, %	31.0	37.1	37.5	< 0.0001
Systolic BP, mmHg	151 ± 24.8	152 ± 25	151 ± 26	< 0.0001
Diastolic BP, mmHg	77.2 ± 14.6	78.2 ± 14.9	78.2 ± 14.7	< 0.0001
Heart rate, bpm	74.4 ± 12.9	74.8 ± 12.8	74.2 ± 12.4	0.059
Hemoglobin, g/dL	10.8 ± 1.3	10.9 ± 1.3	10.9 ± 1.2	< 0.0001
Kt/V	1.45 ± 0.31	1.40 ± 0.29	1.47 ± 0.28	< 0.0001
nPCR, g/kg/day	0.84 ± 0.18	0.84 ± 0.17	0.86 ± 0.17	< 0.0001
%CGR	90.6 ± 29.1	89.4 ± 28.4	96.1 ± 26.5	< 0.0001
Substitutional volume(L)	–	1.0 (0.7–1.0)	1.4 (1.4–1.5)	< 0.0001*

Data are expressed as mean ± standard deviation or median (interquartile range). * Low-volume I-HDF group vs. high-volume I-HDF group. BP, blood pressure; CGR, creatinine generation rate; CVD, cardiovascular disease; HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration; nPCR, normalized protein catabolic rate

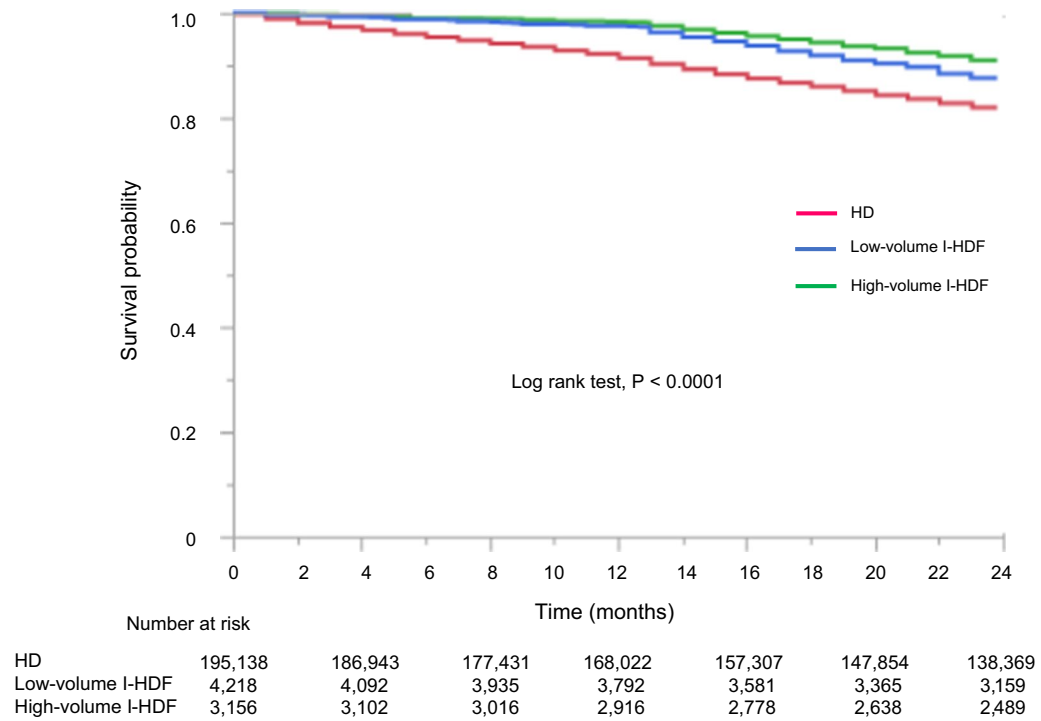


Fig. 5 Comparison of patient survival outcomes between the hemodialysis (HD), low-volume intermittent infusion hemodiafiltration (I-HDF), and high-volume I-HDF groups HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

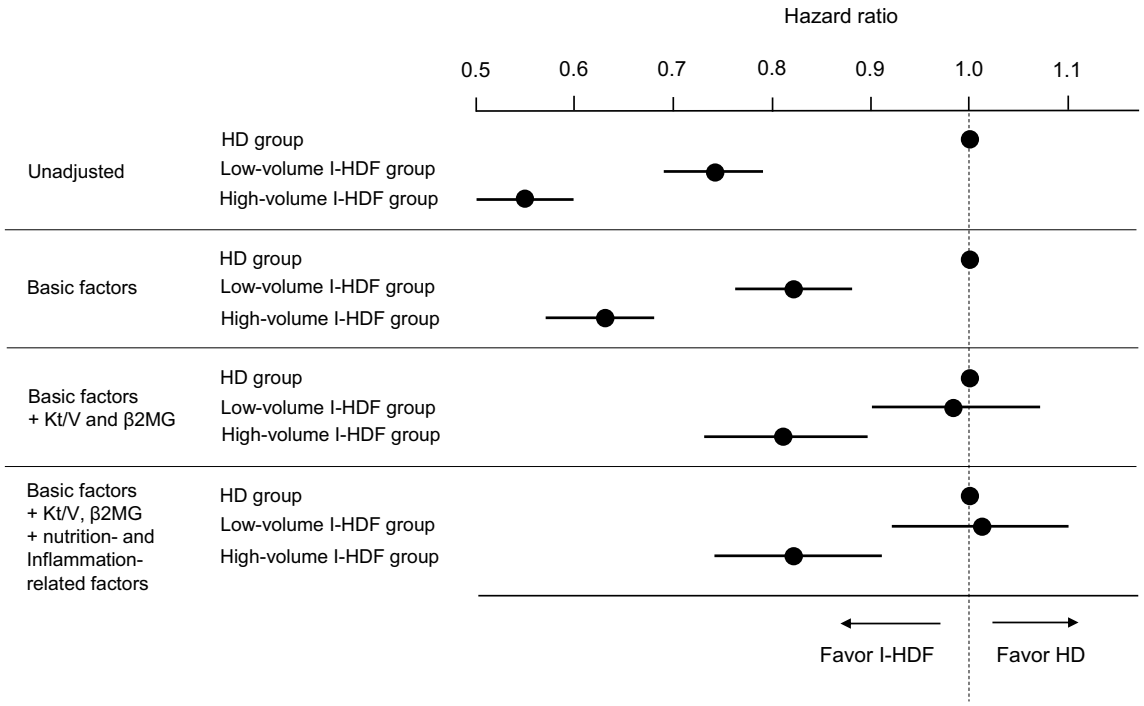
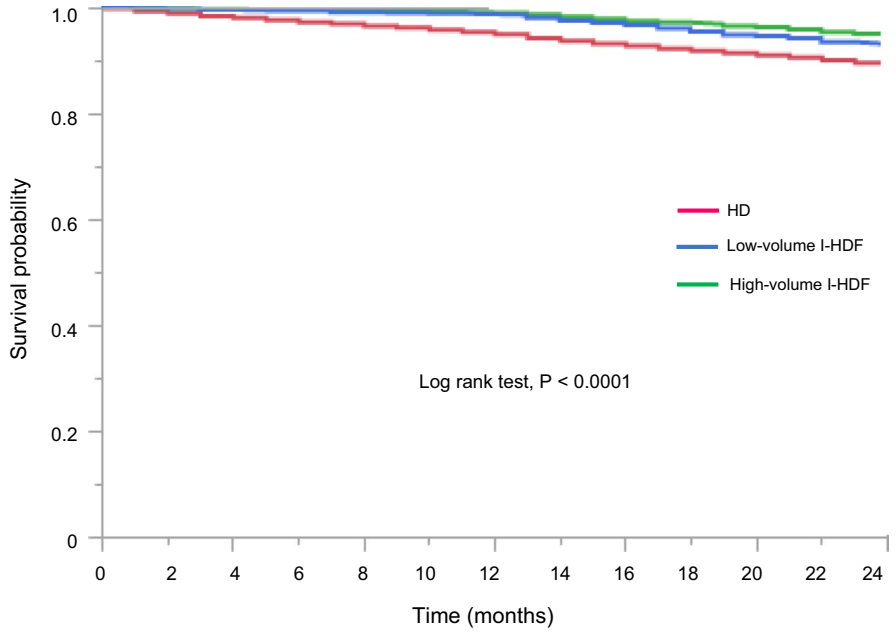


Fig. 6 Comparison of all-cause mortality between the hemodialysis (HD), low-volume intermittent infusion hemodiafiltration (I-HDF), and high-volume I-HDF groups using Cox proportional hazards regression. The circle indicates the hazard ratio, and the bars correspond to 95% confidence intervals. Basic factor includes gender, age, duration of dialysis, presence or absence of diabetes, and cardiovascular disease. Nutrition- and inflammation-related factors include body mass index, systolic and diastolic blood pressures and heart rate at predialysis, serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, C-reactive protein levels, normalized protein catabolic rate, and percentage of creatinine generation rate. β2MG, β_2-microglobulin; HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

I-HDF has been reported as an effective treatment option due to its association with increased plasma refilling rates [3, 4]. A comparative study was conducted to evaluate the total water removal amount and time-averaged blood volume reduction rate between HD and I-HDF [3]. Although there was no significant difference in the total volume of water removal between HD and I-HDF, I-HDF demonstrated a significantly lower rate of time-averaged blood volume decline than HD. This indicates that the plasma refilling rate during I-HDF was greater than that during HD. A higher plasma refilling rate during I-HDF may contribute to improved peripheral circulation, which could potentially reduce the rate of CV events, particularly limb amputation. However, there was no significant difference in CV mortality between the HD and I-HDF groups after adjusting for all covariates. It has been reported that patients with mild or more severe valvular heart disease or Grade IIb or higher severe lower extremity arterial disease (LEAD), according to the Fontaine classification [15], did not respond well to I-HDF. Furthermore, all patients with LEAD also had concomitant CVD, suggesting that I-HDF may be ineffective in patients with severe LEAD and valvular heart disease [15]. However, subgroup analysis in our study revealed that I-HDF was effective in patients without a history of CVD. In addition, our findings suggest that high-volume I-HDF may improve CV mortality. Although the difference in substitution volume between the low- and high-volume I-HDF groups was small, our result suggests that an appropriate amount of substitution volume may be required to obtain the effects of I-HDF. Furthermore, the plasma refilling rate and peripheral circulation might not improve with a low substitution volume. Therefore, long-term prospective studies are necessary to confirm whether I-HDF can prevent the development of new CVD by suppressing intradialytic hypotension and improving peripheral circulation in patients on dialysis who have no history of CVD. The appropriate substitution volume that can effectively suppress CV events should be considered.

The solute removal properties of I-HDF may differ from those of conventional HD under similar conditions, including blood flow rate, dialysate flow rate, and treatment time. The urea and creatinine removal rates during treatment were found to be significantly lower in I-HDF than in HD, while the β2MG and α_1-microglobulin (α1MG) removal rates were significantly higher in I-HDF than in HD [8]. Furthermore, a comparative



Number at risk

HD	194,088	187,741	179,922	172,184	163,898	156,568	149,223
Low-volume I-HDF	3,821	3,710	3,570	3,445	3,295	3,178	2,998
High-volume I-HDF	2,931	2,883	2,802	2,714	2,605	2,503	2,391

Fig. 7 Comparison of cardiovascular survival between the hemodialysis (HD), low-volume intermittent infusion hemodiafiltration (I-HDF), and high-volume I-HDF groups HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

study between I-HDF and predilution online HDF also reported interesting findings [7]. The average substitution volumes for the I-HDF and predilution online HDF groups were found to be 1.4 L and 44.9 ± 4.0 L, respectively. The I-HDF group had significantly lower albumin leakage than the predilution online HDF group. In Japan, HD aims to improve the removal of middle molecules ranging from β2MG to α1MG, and a small amount of protein leakage is allowed during HD to prevent the induction of malnutrition [16, 17]. I-HDF is considered to be suitable for malnourished patients and the elderly due to its minimal albumin leakage.

This study has several limitations that should be considered. First, the number of patients differed between the two groups, which is inherent to an annual survey and observational cohort study design. In addition, important information regarding hypotensive episodes, blood flow rate, convection volume, vascular access, and facility effects or practice patterns of the dialysis unit was unavailable. Therapeutic selection bias and substitution volumes in differences in center practice and patient population could not yet be adequately corrected in this statistical analysis. Second, the study did not investigate the purity of the dialysate used in patients on I-HDF. The JSDT standard for endotoxin level in dialysis fluid (< 0.050 EU/mL) was achieved in 96.6% of patients in 2017, and the JSDT standard for bacterial cell counts in dialysis fluid (< 100 cfu/mL) was achieved in 99.0% of patients in 2017 [18]. Therefore, it is important to consider the role of excellent water quality in improving the prognosis of patients on chronic dialysis in Japan, as it may contribute to the lower CRP levels observed in the present study. Third, the study could not determine the optimal substitution volume for I-HDF. Although the study suggested the superiority of high-volume I-HDF, the optimal substitution volume and infusion pattern for I-HDF may vary for each individual patient. Continuous monitoring of blood volume during treatment can help determine the optimal infusion pattern, as the plasma refilling rate can be continuously monitored during treatment. In recent years, commercially available dialysis machines in Japan are typically equipped with an intermittent infusion mode, which allows the infusion volume, cycle, and flow rate to be customized for each patient. To clarify the optimal infusion pattern for I-HDF, further detailed studies are required. Finally, patients treated with predilution online HDF were excluded from the present study to eliminate modality bias. However, the number of patients receiving predilution online HDF

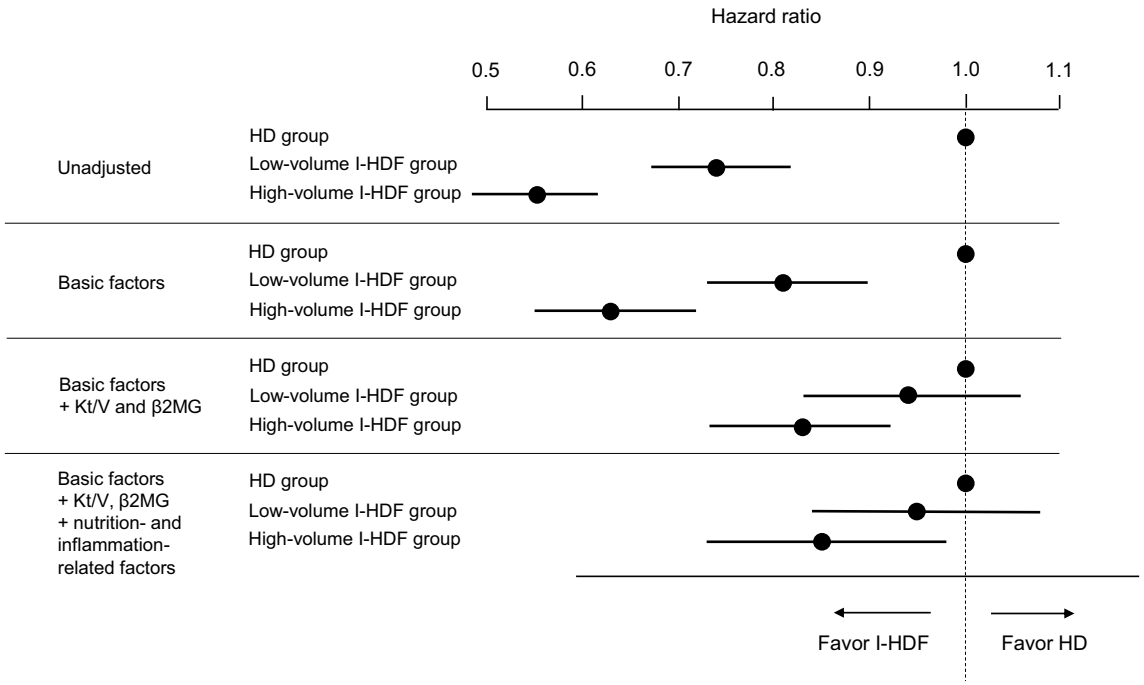


Fig. 8 Comparison of cardiovascular mortality between the hemodialysis (HD), low-volume intermittent infusion hemodiafiltration (I-HDF), and high-volume I-HDF groups using Cox proportional hazards regression. The circle indicates the hazard ratio, and the bars correspond to 95% confidence intervals. Basic factor includes gender, age, duration of dialysis, presence or absence of diabetes, and cardiovascular disease. Nutrition- and inflammation-related factors include body mass index, systolic and diastolic blood pressures and heart rate at predialysis, serum albumin, hemoglobin, phosphate, calcium, intact parathyroid hormone, C-reactive protein levels, normalized protein catabolic rate, and percentage of creatinine generation rate. β2MG, β_2-microglobulin; HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration

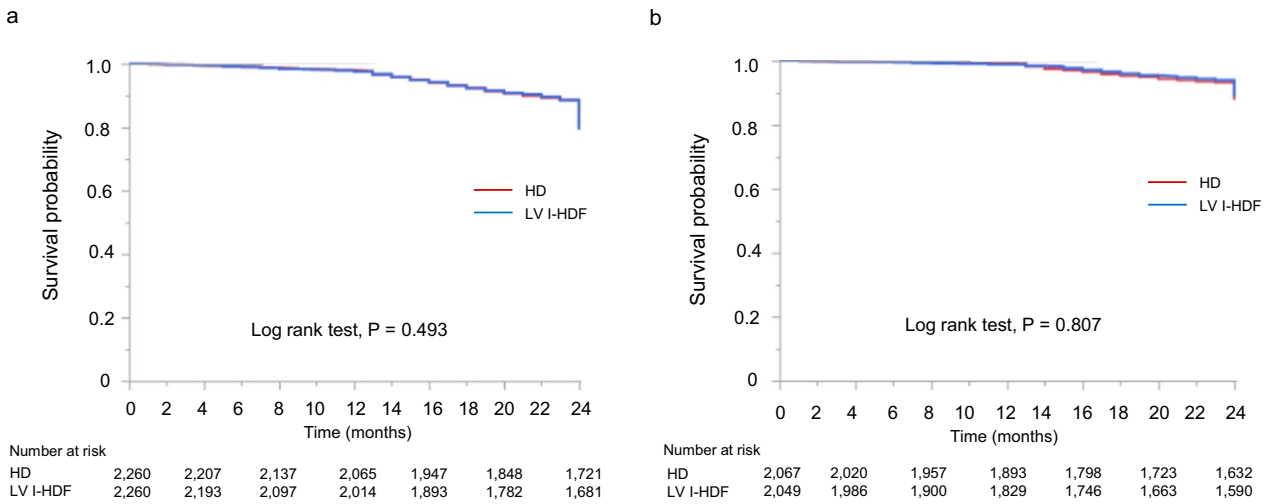


Fig. 9 Comparison of patient survival outcomes between the HD and low-volume I-HDF groups. **a** Comparison of cumulative survival. **b** Comparison of cumulative cardiovascular survival. HD, hemodialysis; I-HDF, intermittent infusion hemodiafiltration; LV, low-volume

has recently been increasing, and it is considered to be the most efficient technique for using high-flux membranes, as it achieves higher clearance of small solutes like urea and middle-molecular solutes like β2MG compared to high-flux HD [19]. In 2017, the number of patients treated with HD, predilution online HDF, and I-HDF was 68.2%, 21.8%, and 5.3% of all dialysis patients, respectively. However, in 2022, the number

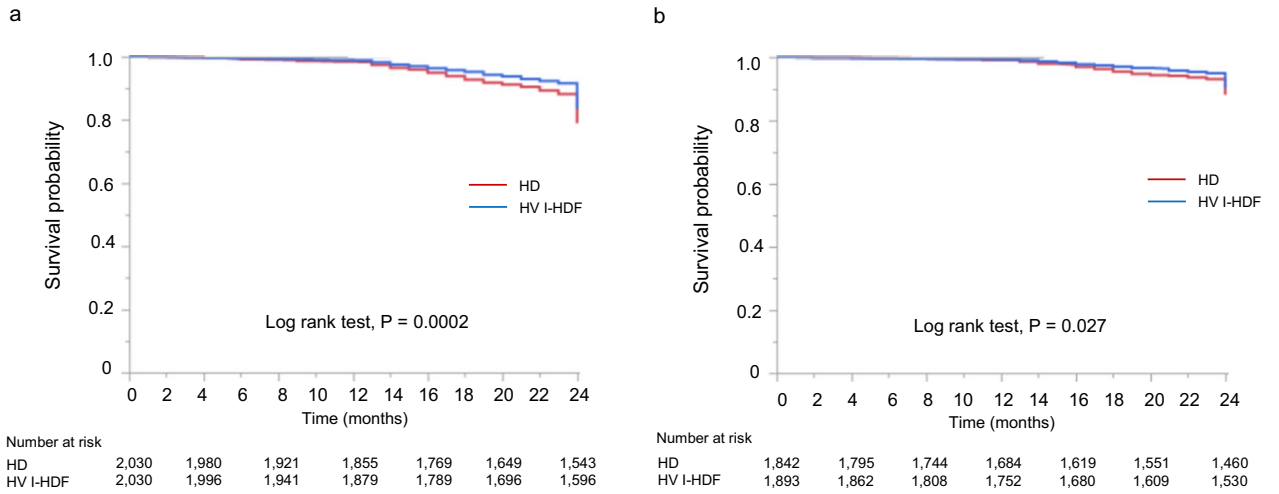


Fig. 10 Comparison of patient survival outcomes between the HD and high-volume I-HDF groups. **a** Comparison of cumulative survival. **b** Comparison of cumulative cardiovascular survival. HD, hemodialysis; HV, high-volume; I-HDF, intermittent infusion hemodiafiltration.

of patients treated with predilution online HDF and I-HDF has increased to 38.0% and 16.4% of all dialysis patients, respectively, while that of HD has decreased to 41.5%. Therefore, further clinical trials are required to compare these three modalities, HD, I-HDF, and predilution online HDF, on mortality outcomes.

In conclusion, this large nationwide cohort study of Japanese patients on dialysis found that I-HDF was significantly associated with improved 2-year all-cause and CV mortality compared to standard HD. Based on our findings, high-volume I-HDF with a substitution volume of 1.2 L per session or higher may be beneficial for these patients. However, the optimal substitution volume and infusion pattern for I-HDF may vary for each patient. Therefore, further detailed studies are required to determine the optimal infusion pattern and volume for individual patients. In addition, randomized controlled studies are warranted to determine whether I-HDF can improve survival outcomes and reduce the incidence of CVD in patients on dialysis.

Abbreviations

α1MG	α_1-Microglobulin
β2MG	β_2-Microglobulin
BMI	Body mass index
BP	Blood pressure
CGR	Creatinine generation rate
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes mellitus
HD	Hemodialysis
HDF	Hemodiafiltration
I-HDF	Intermittent infusion hemodiafiltration
JSDT	Japanese Society for Dialysis Therapy
JRDR	JSDT renal data registry
LEAD	Lower extremity arterial disease
nPCR	Normalized protein catabolic rate
SBP	Systolic blood pressure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-024-00540-4.

Additional file 1. **Table S1.** Hazard ratios (95% confidence intervals) for variables evaluated as potential predictors of mortality among all patients.

Additional file 2. **Table S2.** Comparisons of all-cause mortality between the low-volume and high-volume intermittent infusion hemodiafiltration (I-HDF) groups and the hemodialysis (HD) group using the Cox proportional hazards regression model.

Additional file 3. **Table S3.** Comparisons of cardiovascular mortality between the low-volume and high-volume intermittent infusion hemodiafiltration (I-HDF) groups and the hemodialysis (HD) group using Cox proportional hazards regression model.

Additional file 4. Figure S1.

Additional file 5. Figure S2.

Additional file 6. Table S4. Comparison of variables after propensity score matching between the HD and low-volume I-HDF groups.

Additional file 7. Table S5. Comparison of variables after propensity score matching between the HD and high-volume I-HDF groups.

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
MA wrote the manuscript and analyzed the data. KK and NH were co-supervisors, designed the study, and revised the manuscript. AW and SN contributed to data collection. MA, KK, and NH discussed the results and contributed to the final manuscript. All authors have read and approved the final manuscript.

Funding
Not applicable.

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

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 de-identified information. This study was registered at the University Hospital Medical Information Network (UMIN000018641).

Consent for publication
Not applicable.

Competing interests
MA is the deputy editor of Renal Replacement Therapy, and NH 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.

Author details
[1]The Committee of Renal Data Registry, The Japanese Society for Dialysis Therapy, Tokyo, Japan. [2]Division of Nephrology, Hypertension and Endocrinology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan. [3]Division of Nephrology, Shimoochiai Clinic, Tokyo, Japan. [4]Department of Nephrology, Kitasaito Hospital, Asahikawa, Japan. [5]Department of Clinical Engineering, Fujita Health University, Aichi, Japan. [6]Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan.

Received: 15 January 2024 Accepted: 17 March 2024
Published online: 29 March 2024

References

1. Rosner MH, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, Blankestijn PJ, Cozzolino M, Juillard L, Kashani K, Kaushik M, Kawanishi H, Massy Z, Sirich TL, Zuo L, Ronco C. Classification of uremic toxins and their role in kidney failure. Clin J Am Soc Nephrol. 2021;16(12):1918–28.
2. Japanese Society for Dialysis Therapy. https://www.jsdt.or.jp/dialysis/2227.html.
3. Mineshima M, Eguchi K. Development of intermittent infusion hemodiafiltration using UltraPure dialysis fluid with an automated dialysis machine. Blood Purif. 2013;35(Suppl 1):55–8.
4. Mineshima M, Eguchi K. Validity of intermittent infusion hemodiafiltration. Blood Purif. 2019;48(Suppl 1):7–10.
5. Koda Y, Aoike I. Prevention of intradialytic hypotension with intermittent back-filtrate infusion haemodiafiltration: insights into the underlying mechanism. Blood Purif. 2019;48(Suppl 1):1–6.
6. Koda Y, Aoike I, Hasegawa S, Osawa Y, Nakagawa Y, Iwabuchi F, Iwahashi C, Sugimoto T, Kikutani T. Feasibility of intermittent back-filtrate infusion hemodiafiltration to reduce intradialytic hypotension in patients with cardiovascular instability: a pilot study. Clin Exp Nephrol. 2017;21(2):324–32.
7. Mineshima M, Eguchi K, Shishido K, Takahashi S, Kubo T, Kawaguchi H, Shitomi K, Shibagaki K, Suga K, Nagao H, Takada M, Taoka M, Sato T. Clinical effectiveness of intermittent infusion hemodiafiltration using Backfiltration of UltraPure dialysis fluid compared with predilution on-line hemodiafiltration. Contrib Nephrol. 2017;189:24–9.
8. Mineshima M, Takahashi S, Tomo T, Kawanishi H, Kawaguchi H, Minakuchi J, Nakanishi T, Sato T, Nitta K, Tsuchiya K, Masakane I, Itami N. A clinical significance of intermittent infusion hemodiafiltration using backfiltration of ultrapure dialysis fluid compared to hemodialysis: a multicenter randomized controlled crossover trial. Blood Purif. 2019;48(4):368–81.
9. Abe M, Masakane I, Wada A, Nakai S, Nitta K, Nakamoto H. Dialyzer classification and mortality in hemodialysis patients: a 3-year nationwide cohort study. Front Med (Lausanne). 2021;8:740461.
10. Abe M, Masakane I, Wada A, Nakai S, Nitta K, Nakamoto H. Dialyzer surface area is a significant predictor of mortality in patients on hemodialysis: a 3-year nationwide cohort study. Sci Rep. 2021;11(1):20616.
11. Hanafusa N, Abe M, Joki N, Ogawa T, Kanda E, Kikuchi K, Goto S, Taniguchi M, Nakai S, Naganuma T, Hasegawa T, Hoshino J, Miura K, Wada A, Takemoto Y. Annual dialysis data report 2019, JSDT renal data registry. Ren Replace Ther. 2023;9(1):47.
12. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4(5):914–20.
13. Henderson LW. Symptomatic intradialytic hypotension and mortality: an opinionated review. Semin Dial. 2012;25(3):320–5.
14. Shoji T, Tsubakihara Y, Fujii M, Imai E. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int. 2004;66(3):1212–20.
15. Eiki K, Otake T. Factors affecting intermittent infusion hemodiafiltration. Blood Purif. 2019;48(Suppl 1):17–21.
16. Abe M, Masakane I, Wada A, Nakai S, Kanda E, Nitta K, Nakamoto H. High-performance dialyzers and mortality in maintenance hemodialysis patients. Sci Rep. 2021;11(1):12272.
17. Abe M, Masakane I, Wada A, Nakai S, Nitta K, Nakamoto H. Super high-flux membrane dialyzers improve mortality in patients on hemodialysis: a 3-year nationwide cohort study. Clin Kidney J. 2022;15(3):473–83.
18. Nitta K, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, Goto S, Wada A, Hamano T, Hoshino J, Joki N, Abe M, Yamamoto K, Nakamoto H. Annual dialysis data report 2017, JSDT renal data registry. Ren Replace Ther. 2019;5(1):53.
19. Kikuchi K, Hamano T, Wada A, Nakai S, Masakane I. Predilution online hemodiafiltration is associated with improved survival compared with hemodialysis. Kidney Int. 2019;95(4):929–38.

Publisher's Note