KI REPORTS
KIReports.org
CLINICAL RESEARCH

Potential Benefit Associated With Delaying Initiation of Hemodialysis in a Japanese Cohort

Satoshi Higuchi[1], Izaya Nakaya[1], Kazuhiro Yoshikawa[1], Yoichiro Chikamatsu[1], Ken-ei Sada[2], Suguru Yamamoto[3], Satoko Takahashi[1], Hiroyo Sasaki[1] and Jun Soma[1]

[1]Department of Nephrology and Rheumatology, Iwate Prefectural Central Hospital, Morioka, Japan; [2]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; and [3]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Introduction: Late referral to a nephrologist, the type of vascular access, nutritional status, and the estimated glomerular filtration rate (eGFR) at the start of hemodialysis (HD) have been reported as independent risk factors of survival for patients who begin HD. The aim of this study was to clarify the influence of the HD-free interval from the time of an eGFR of 10 ml/min per 1.73 m^2 ($I_{GFR10\text{-}HD}$) on patient outcome.

Methods: We enrolled 124 patients aged older than 20 years who had HD initiated in a general hospital. The predictive factor was the HD-free $I_{GFR10\text{-}HD}$. The primary outcome was the relationship of the HD-free interval on death or the onset of a cardiovascular event. Survival analysis was performed using the Cox regression model.

Results: The median $I_{GFR10\text{-}HD}$ was 159 days (range: 2–1687 days). The median eGFR at the initiation of HD was 5.48 ml/min per 1.73 m^2. Sixty-seven of 124 patients (54.0%) reached the primary outcome. Of these, 29 died and 38 experienced a cardiovascular event. In univariate analysis, older age, a history of cardiovascular disease, nephrologic care for <6 months, higher modified Charlson comorbidity index score, poor performance status, temporary catheter, edema, diabetic retinopathy, and nonuse of erythropoiesis-stimulating agent were statistically related to the primary outcome. The unadjusted hazard ratio per log-transformed $I_{GFR10\text{-}HD}$ was 0.393 (95% confidence interval [CI]; 0.244−0.635; $P < 0.001$) and the hazard ratio adjusted for confounding factors was 0.507 (95% CI: 0.267−0.956; $P = 0.036$).

Discussion: A longer HD-free $I_{GFR10\text{-}HD}$ was associated with a lower risk of death or a cardiovascular event. The interval could be considered an independent prognostic factor for outcomes in patients on HD.

Kidney Int Rep (2017) **2,** 594–602; http://dx.doi.org/10.1016/j.ekir.2017.01.015
KEYWORDS: all-cause mortality; cardiovascular event; estimated glomerular filtration rate; hemodialysis-free interval; nephrology care; performance status

Although there has been an international trend to initiate dialysis at higher levels of the estimated glomerular filtration rate (eGFR), the benefit or harm of this trend remains unclear. Moreover, end-stage renal disease (ESRD) from diabetes mellitus and/or hypertension is increasing gradually. These patients have poorer outcomes after beginning dialysis than those with glomerulonephritis in Japan and the United States.[1–3] Predialysis management is crucial because both predialysis treatment and the clinical condition of the patient at the time of dialysis initiation influence prognosis after hemodialysis (HD) initiation. Various clinical parameters before and at the initiation of HD have been reported as independent risk factors for a poor outcome. These include late referral to a nephrologist,[4] type of vascular access,[5] nutritional status,[6] and eGFR at the start of HD.[7,8] Early referral to a nephrologist is reportedly associated with better preparation of vascular access and reduction of mortality of patients on HD.[9,10] Poor nutritional status also predicts a poor outcome for patients on HD.[6]

It was believed that the early initiation of HD might decrease uremic complications, improve survival, and decrease complications in patients undergoing HD.[11–13] Hence, some guidelines recommended initiation of dialysis at relatively high levels of eGFR.[14,15] However,

Correspondence: Izaya Nakaya, Department of Nephrology and Rheumatology, Iwate Prefectural Central Hospital, Ueda 1-4-1, Morioka 020-0066, Japan. E-mail: inakaya@chuo-hp.jp
Received 5 July 2016; revised 23 January 2017; accepted 31 January 2017; published online 10 February 2017

recent studies suggested that, with careful management of chronic kidney disease, patients could safely start dialysis at eGFR at <10 ml/min per 1.73 m^2.[16,17] A randomized trial that investigated this issue found that waiting until the eGFR was 5.0 to 7.0 ml/min per 1.73 m^2 resulted in no worse outcomes than beginning HD earlier did, at an eGFR of 10 to 14 ml/min per 1.73 m^2.[7] These results indicated that delaying HD, with a consequent savings in health care costs, would not result in a worse outcome. However, the question remains as to how long it is safe to delay HD while continuing treatment at low renal function, for example, below a threshold of an eGFR of 10 ml/min per 1.73 m^2. The aim of this study was to clarify the influence on outcome of the HD-free interval from the point at which the eGFR of 10 ml/min per 1.73 m^2 was reached until HD was initiated.

MATERIALS AND METHODS

Ethics

This study was approved by the ethics committee of Iwate Prefectural Central Hospital and was conducted in accordance with the ethical principles of the Declaration of Helsinki. We did not obtain written informed consent from the patients because the ethical guidelines for epidemiological research in Japan do not require consent for a retrospective study in which only medical records are used.

Patients

We reviewed the records of 238 patients seen at Iwate Prefectural Central Hospital, a tertiary acute care general hospital, between April 2006 and March 2011 who were older than 20 years of age and had started maintenance dialysis for the treatment of ESRD. Records were excluded if the patients had a history of HD (n = 1), underwent peritoneal dialysis (n = 11), had renal transplantation within 1 year of beginning HD (n = 1), required dialysis because of acute kidney injury (primarily secondary to postoperative complications, sequelae of cardiovascular events, or multiple organ failure) (n = 28), started HD at an eGFR >10 ml/min per 1.73 m^2 (n = 9), or those whose HD-free interval from an eGFR of 10 m/min per 1.73 m^2 ($I_{GFR10\text{-}HD}$) could not be confirmed (n = 93), who stopped HD within a year after starting (n = 2), who died in hospital after the initiation of HD (n = 12), or whose outcomes could not be obtained from their maintenance dialysis facilities (n = 2). This left 124 patients whose records were included in this study. Data from all the patients analyzed in this investigation were also included in a recent multicenter study concerning 1-year mortality after HD initiation.[18] Renal function was evaluated by eGFR using the following equation developed for Japanese patients: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$(× 0.739, if female).[19]

Predictive Factors

We estimated the point at which each patient reached an eGFR of 10 ml/min per 1.73 m^2 based on the latest point in the record that was closest (either more or less than) to that value. We presumed that eGFR declined linearly around that value. When an eGFR improved in reverse, the last point on the decline was selected. We calculated the HD-free interval as the time from an eGFR of 10 ml/min per 1.73 m^2 to the initiation of HD ($I_{GFR10\text{-}HD}$). We also calculated the rate of eGFR decline by subtracting the final predialysis eGFR from the initial eGFR divided by the time interval.

Clinical Parameters

Clinical data at the initiation of HD were obtained from medical records, including age, sex, body mass index (BMI), history of smoking, history of cardiovascular disease (CVD), medical care by nephrologists for >6 months, causes of chronic kidney disease, systolic blood pressure (SBP), diastolic blood pressure (DBP), modified Charlson comorbidity index (CCI),[20] World Health Organization Performance Status (PS),[21] laboratory data (eGFR, urea nitrogen, hemoglobin, serum albumin, sodium, potassium, calcium, phosphorus, and C-reactive protein [CRP]), type of vascular access, symptoms related to the progression of kidney disease (fatigue; peripheral and pulmonary edema; digestive symptoms such as nausea, anorexia, diarrhea, and constipation; hypertension; peripheral neuropathy; psychiatric disorder; hemorrhagic diathesis; diabetic retinopathy; and pruritus), and medication history.

Outcome

The primary outcome was the combination of all-cause death and cardiovascular events, including heart failure, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, operation for valve diseases, aortic disease, percutaneous transluminal angioplasty or limb amputation due to arteriosclerosis obliterans, or cerebrovascular disease. We obtained information on patient outcomes from maintenance dialysis facilities via a letter.

Statistical Analysis and Handling of Missing Data

We calculated the survival rate for the primary outcome with the Kaplan-Meier method and obtained hazard ratios (HRs) for each clinical parameter by the Cox proportional hazard model. Clinical parameters are shown as median (25th–75th percentiles) or percentage, as appropriate. Coefficients were calculated by Pearson

Table 1. Candidate predictors and outcome variables

Variables	Number missing	Analysis cohort (n = 124)	Event occurred (n = 67)	Event-free (n = 57)
Age, yr	0	67 (58–76)	69 (60–77)	64 (48–74)
Female sex, %	0	29.8	31.4	28.1
Body mass index, kg/m^2	2	22.4 (20.8–26.5)	23.3 (20.9–25.6)	23.7 (20.4–26.5)
Current and past smoking, %	0	47.6	52.2	42.1
History of CVD, %	0	42.7	52.2	31.6
Nephrology care >6 mo, %	0	71.0	59.7	84.2
Primary kidney disease	0			
Diabetic nephropathy, %		46.0	53.7	36.8
Chronic glomerulonephritis, %		18.6	14.9	22.8
Hypertensive nephrosclerosis, %		18.6	17.9	19.3
Other kidney disease, %		16.9	13.4	21.0
Systolic blood pressure, mm Hg	0	156 (140–178)	161 (144–184)	152 (137–166)
Diastolic blood pressure, mm Hg	0	82 (71–93)	82 (72–94)	81 (69–89)
Systolic blood pressure >160 mm Hg, %	0	42.7	50.8	33.3
eGFR, ml/min per 1.73 m^2	0	5.48 (4.74–6.80)	5.54 (4.77–7.10)	5.40 (4.51–6.53)
Urea nitrogen, mg/dl	0	89.7 (73.6–102.8)	86.0 (73.0–98.5)	93 (75.3–104.1)
Hemoglobin, g/dl	0	8.2 (7.1–9.3)	8.3 (7.1–9.2)	8.2 (7.1–9.3)
Serum albumin, g/dl	28	3.3 (2.8–3.8)	3.2 (2.7–3.7)	3.6 (2.9–3.8)
Serum sodium, mEq/L	0	139 (136–141)	139 (136–141)	139 (138–140)
Serum potassium, mEq/L	0	4.7 (4.2–5.3)	4.8 (4.3–5.4)	4.7 (4.1–5.3)
Serum calcium, mg/dl	6	7.9 (7.4–8.3)	7.8 (7.1–8.1)	8.0 (7.6–8.4)
Serum phosphorus, mg/dl	7	5.7 (4.7–6.5)	5.7 (4.6–6.8)	5.7 (4.8–6.4)
C-reactive protein, mg/dl	26	0.32 (0.13–1.89)	0.42 (0.21–2.11)	0.21 (0.08–0.9)
Interval eGFR10-HD, d	0	159 (74–345)	109 (56–286)	263 (121–447)
eGFR rate of decline, mL/min/1.73 m^2 per year	0	8.6 (4.7–17.3)	13.7 (5.3–23.6)	7.1 (3.7–10.9)
Modified Charlson Comorbidity Index[a]	0			
0/1–2 /≥3, %		46.8/46.8/6.5	34.3/58.2/7.5	61.4/33.3/5.3
Performance status	0			
0/1/2/3/4, %		5.7/41.9/24.2/17.7/10.5	4.5/31.3/25.4/23.9/14.9	7.0/54.4/22.8/10.5/5.3
Vascular access	0			
Arteriovenous fistula, %		68.6	56.7	82.5
Temporally catheter, %		31.4	43.3	17.5
Fatigue, %	0	71.0	76.1	64.9
Edema, %	0	71.0	79.1	61.4
Pulmonary edema, %	0	31.5	38.8	22.8
Nausea, %	0	37.1	34.3	40.4
Dysorexia, %	0	39.5	55.2	66.7
Diarrhea, %	0	5.7	7.5	3.5
Constipation, %	0	3.2	3.0	3.5
Other digestive symptom, %	0	0.8	0.0	1.8
CNS manifestation, %	0	2.4	4.5	0.0
Peripheral nerve abnormalities, %	0	17.7	22.4	12.3
Itch, %	0	8.9	9.0	8.8
Hemorrhagic diathesis, %	0	3.2	3.0	3.5
Diabetic retinopathy, %	0	41.1	52.2	28.1
ESA use, %	0	85.5	77.6	94.7
ACEI and/or ARB use, %	0	75.0	70.2	80.7
Vitamin D use, %	0	3.2	1.5	5.3

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CNS, central nervous system; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; HD, hemodialysis.
Continuous variables represented as median with interquartile range in parentheses.
[a]Items related to diabetes and renal disease were excluded from the original Charlson Comorbidity Index in the present study.

and Spearman correlation methods. Values were missing for 5 parameters: albumin in 22.6% (28 of 124 patients), CRP in 21.0% (26 of 124 patients), phosphorus in 6.5% (7 of 124 patients), calcium in 5.6% (6 of 124 patients), and BMI in 1.6% (2 of 124 patients). HRs for these in univariate models were estimated after 5 imputations using multiple imputations with chained equations.[18,22] We did not use these parameters as covariates in multivariate models because none had statistical significance in the univariate models.

Statistical analyses were performed using STATA version 13.1 (Stata Corp., College Station, Texas). $R > 0.20$ and $P < 0.05$ were considered statistically significant.

RESULTS

Patient Characteristics

The mean follow-up period from the initiation of HD was 882 days (range: 6–2510 days). The baseline characteristics are shown in Table 1. Median age was 67 years, and 37 patients (29.8%) were women. Fifty-three patients (42.7%) had a history of CVD, and 88 (71.0%) received nephrology care for >6 months before the initiation of HD. Fifty-seven patients (46.0%) had diabetic nephropathy, 23 (18.6%) had chronic glomerulonephritis, 23 (18.6%) had hypertensive nephrosclerosis, and 21 (16.9%) had other kidney diseases. The median SBP and DBP were 156 and 82 mm Hg, respectively. The median eGFR, hemoglobin level, and albumin levels were 5.48 ml/min per 1.73 m^2, 8.2 g/dl, and 3.3 g/dl, respectively. Eighty-five patients (68.6%) started HD with an arteriovenous fistula (AVF), and 39 (31.4%) began HD with a temporary catheter. The number of patients with a modified CCI of 0, 1 to 2, and >3 points was 58 (46.8%), 58 (46.8%), and 8 (6.5%), respectively. The number of patients with PS grades of 0, 1, 2, 3, and 4 was 7 (5.7%), 52 (41.9%), 30 (24.2%), 22 (17.7%), and 13 (10.5%), respectively. The number of patients treated with an erythropoiesis-stimulating agent (ESA), activated vitamin D3, and angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker was 106 (85.5%), 4 (3.2%), and 93 (75.0%), respectively.

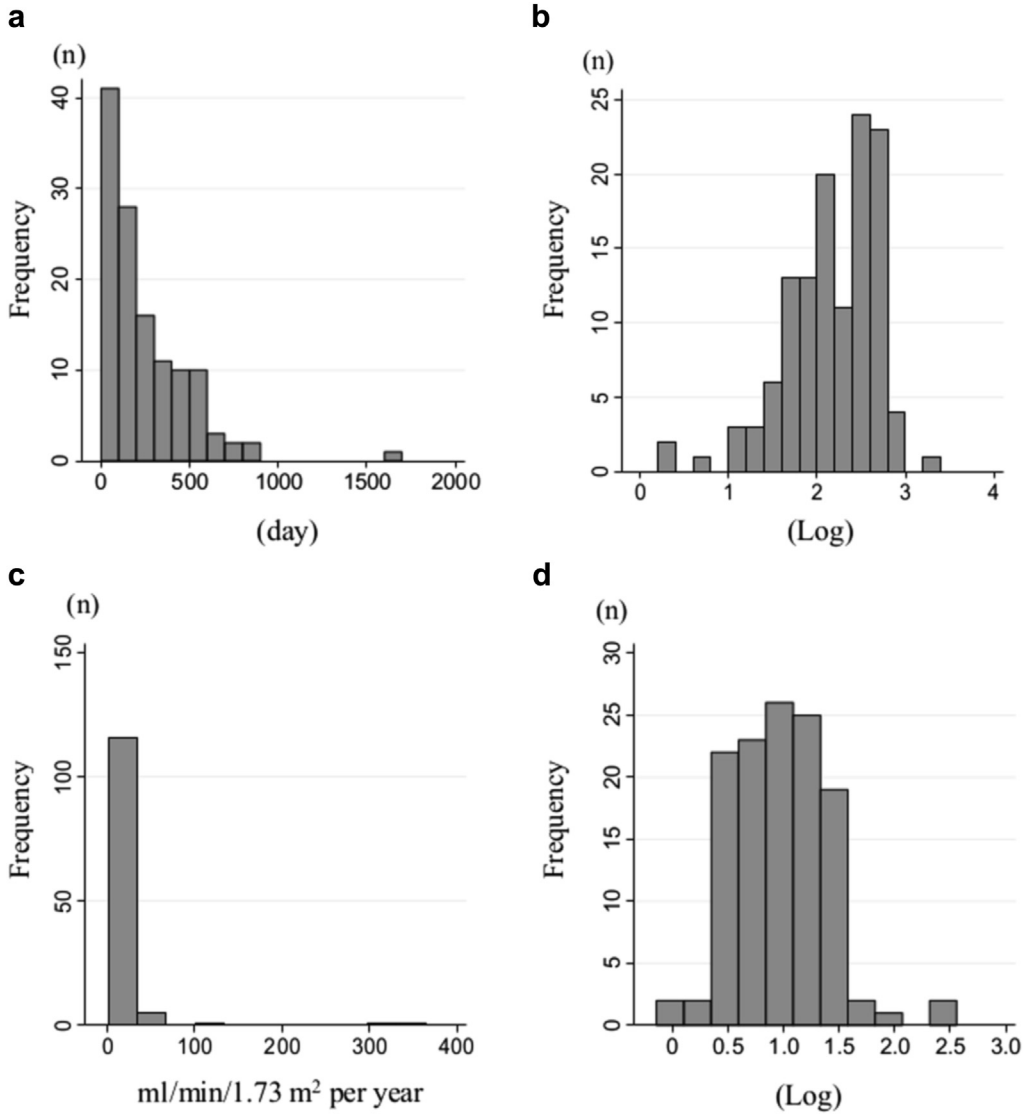

Figure 1. (a) Histogram of interval from the time of an eGFR of 10 ml/min per 1.73 m^2 ($I_{GFR10\text{-}HD}$). The median $I_{GFR10\text{-}HD}$ was 159 days (range: 2–1687 days). (b) Histogram of logarithmic $I_{GFR10\text{-}HD}$. We performed logarithmic transformation to conform to a normal distribution. (c) Histogram of estimated glomerular filtration rate (eGFR) of decline. (d) Histogram of logarithmic eGFR of decline.

HD-Free Interval From an eGFR of 10 ml/min per 1.73 m^2 and Rate of eGFR Decline During the Interval

The median $I_{GFR10\text{-}HD}$ was 159 days (range: 2–1687 days). That distribution is shown in a histogram (Figure 1a). We performed logarithmic (log) transformation to conform it to a normal distribution (Figure 1b). The median rate of eGFR decline was 8.6 ml/min per 1.73 m^2 per year. That distribution is shown in a histogram (Figure 1c). We performed log transformation to conform it to a normal distribution (Figure 1d).

Correlation of HD-Free Interval With Other Variables

eGFR at the time of HD initiation and the rate of eGFR decline from an eGFR of 10 ml/min per 1.73 m^2 showed a strong negative correlation with the interval (Table 2 and Figure 2) (R = −0.643 and −0.866, respectively). Serum albumin (R = 0.511) and potassium (R = 0.329) were positively correlated with the interval (Table 2). Sex (R = 0.228), nephrology care for >6 months (R = 0.400), AVF (R = 0.495), and ESA use (R = 0.252) were positively correlated with the interval, whereas smoking (R = −0.273), diabetic nephropathy (R = −0.352), PS (R = −0.425), pulmonary edema (R = −0.338), and diabetic retinopathy (R = −0.308) were negatively correlated with the interval according to Spearman's method (Table 2). Correlations between rates of eGFR decline and other clinical parameters were similar to those for the HD-free $I_{GFR10\text{-}HD}$ (data not shown).

Outcome and Survival Rate

Sixty-seven of 124 patients (54%) reached the primary outcome. Of these, 29 died, and 38 experienced cardiovascular events. Causes of death included cancer in 8 patients (28%), infectious disease in 4 (14%), heart failure in 3 (10%), stroke in 2 (7%), other diseases in 9 (31%), and unknown reasons in 3 (10%). Of the 38 cardiovascular events, heart failure occurred in 20 patients (53%), cerebrovascular disease in 7 (18%), acute myocardial infarction in 4 (11%), percutaneous coronary intervention in 4 (11%), and aortic disease in 3 (7%). The outcome-free survival rates at 1, 3, and 5 years for all patients were 0.73, 0.53, and 0.35, respectively (Figure 3).

HRs on Univariate and Multivariate Analysis

On univariate analysis, age, history of CVD, medical care by nephrologists for >6 months, modified CCI, PS, AVF, edema, diabetic retinopathy, and ESA use were found to be statistically related to HRs for the primary outcome (Table 3). SBP >160 mm Hg, serum albumin, log CRP, pulmonary edema, peripheral nerve abnormalities, and angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker use tended to be related to the primary outcome (Table 3). HRs for central nervous system manifestations and digestive symptoms could not be calculated because there were no observations in either the event-free group or in the group in which events occurred.

The unadjusted HR of log $I_{GFR10\text{-}HD}$ and log eGFR rate of decline were 0.393 (95% confidence interval [CI]: 0.244–0.635; $P < 0.001$) and 3.926 (95% CI: 2.128–7.245; $P < 0.001$), respectively. We adjusted these statistics in model 1, age and sex; model 2, model

Table 2. Coefficient with log-transformed interval from the time of an estimated glomerular filtration rate of 10 ml/min per 1.73 m^2

Characteristics	Number missing	Pearson's coefficient	Spearman's coefficient
Age	0	0.143	
Sex (female)	0		0.228
Body mass index, kg/m^2	2	−0.173	
Current and past smoking	0		−0.273
Nephrology care >6 mo	0		0.400
History of CVD	0		−0.135
Primary kidney disease			
Diabetic nephropathy	0		−0.352
Chronic glomerulonephritis	0		0.167
Hypertensive nephropathy	0		0.118
Others	0		0.172
Systolic blood pressure ≥160 mm Hg	0		0.009
eGFR, ml/min per 1.73 m^2	0	−0.643	
eGFR rate of decline, ml/min/1.73 m^2 per year (log)	0	−0.866	
Hemoglobin, g/dl	0	−0.031	
Serum albumin, g/dl	28	0.511	
Serum sodium, mEq/L	0	0.329	
Serum potassium, mEq/L	0	0.008	
Serum calcium, mg/dl	6	0.197	
Serum phosphorus, mg/d;	7	−0.095	
C-reactive protein, mg/dl (log)	26	−0.125	
Modified Charlson Comorbidity Index[a]	0		−0.072
Performance status	0		−0.425
Vascular access (arteriovenous fistula)	0		0.495
Fatigue	0		−0.07
Edema	0		−0.192
Pulmonary edema	0		−0.338
Nausea	0		−0.124
Dysorexia	0		−0.126
Diarrhea	0		−0.163
Constipation	0		0.000
Peripheral nerve abnormalities	0		−0.139
Itch	0		0.018
Hemorrhagic diathesis	0		0.063
Diabetic retinopathy	0		−0.308
ESA use	0		0.252
ACEI and/or ARB use	0		0.128
Vitamin D use	0		0.087

The underlined coefficients were more than 0.20.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent.
[a]Items related to diabetes and renal disease were excluded from the original Charlson Comorbidity Index in the present study.

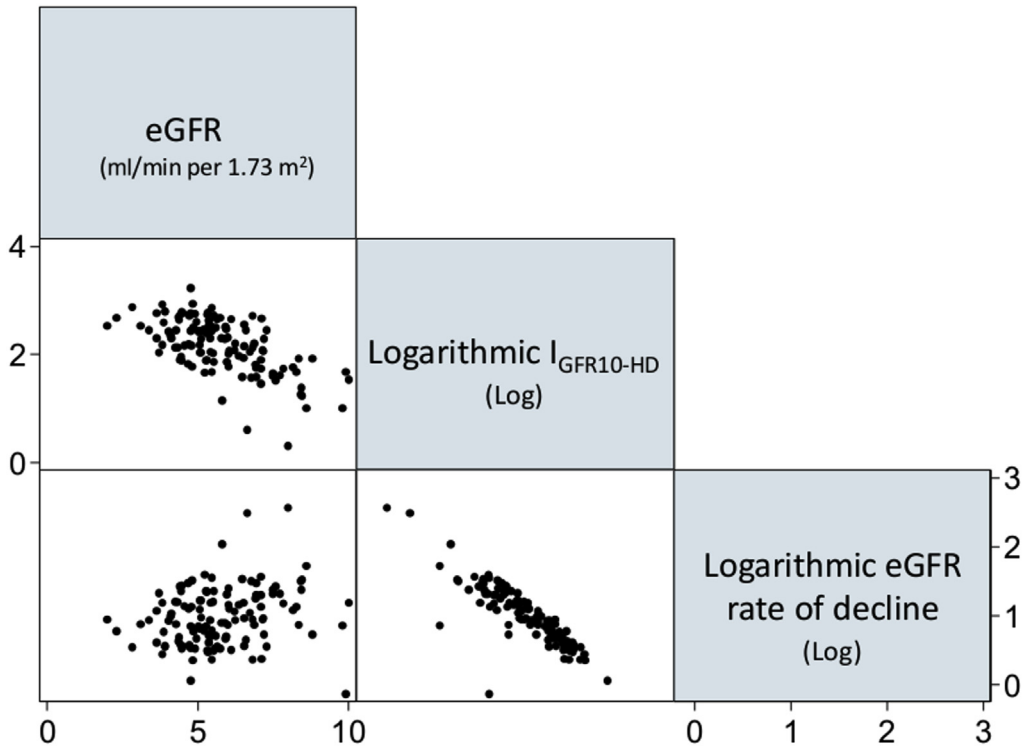

Figure 2. Scatterplots of estimated glomerular filtration rate (eGFR), logarithmic interval from the time of an eGFR of 10 ml/min per 1.73 m^2 ($I_{GFR10\text{-}HD}$), and logarithmic eGFR rate of decline. eGFR and the rate of eGFR decline from an eGFR of 10 ml/min per 1.73 m^2 showed strong negative correlation with logarithmic $I_{GFR10\text{-}HD}$ (R = −0.643 and −0.866, respectively).

1 plus nephrologist care for >6 months, PS, and AVF; and model 3, model 2 plus diabetic retinopathy and ESA use. Except for age and sex, we selected those parameters as confounding factors that were associated with both the predictive factors and the primary outcome. In models 1, 2, and 3, the HRs of log $I_{GFR10\text{-}HD}$ changed to 0.327 ($P < 0.001$), 0.471 ($P = 0.013$), and 0.507 ($P = 0.036$), respectively (Table 4). In models 1, 2, and 3, the HRs of log eGFR rate of decline changed to 5.117 ($P < 0.001$), 3.340 ($P = 0.003$), and 3.028 ($P = 0.008$), respectively (Table 5). In model 3 of log $I_{GFR10\text{-}HD}$, age (HR: 1.039; 95% CI: 1.015–1.064; $P = 0.002$), nephrology care >6 months (HR: 0.510; 95% CI: 0.282–0.925; $P = 0.027$), and PS (HR: 1.316; 95% CI: 1.003–1.728; $P = 0.048$) remained as independent risk factors. Similarly, in model 3 of eGFR rate of decline, age (HR: 1.038; 95% CI: 1.014–1.061; $P = 0.001$) and PS (HR: 1.375; 95% CI: 1.040–1.818; $P = 0.025$) remained as independent risk factors.

DISCUSSION

This study showed a longer HD-free interval from the point at which a patient's eGFR reached 10 ml/min per 1.73 m^2 was significantly correlated with a lower risk of all-cause death and cardiovascular events in patients once they started HD. This was the first report that this interval could be considered to be an independent prognostic factor for such patients. In addition, our findings might enable us to estimate the prognosis of patients based on short-term observation before HD is initiated.

Many studies worldwide focused on the ideal timing of HD initiation, especially in terms of the appropriate eGFR at which to begin dialysis. In the 1990s, early initiation of HD was recommended and believed to decrease mortality, hospitalization, and costs of treatment.[23,24] However, since the 2000s, several investigators commented on findings that early initiation of HD at a higher eGFR increased mortality.[25,26] The

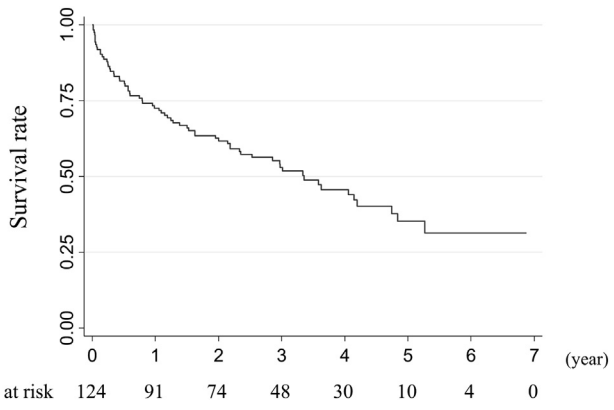

Figure 3. Survival curve for the primary outcome of death or cardiovascular events after beginning hemodialysis. The outcome-free survival at 1, 3, and 5 years for all patients was 0.73, 0.53, and 0.35, respectively.

Table 3. Hazard ratio by univariate survival analysis

Characteristics	Hazard ratio	95% confidence interval	*P* value
Age (per 1 yr)	1.028	1.008–1.048	0.007[a]
Sex (female)	0.817	0.484–1.378	0.448
Body mass index (per 1 kg/m^2)	0.987	0.936–1.040	0.623
Current and past smoking	1.289	0.797–2.084	0.301
Nephrology care >6 mo	0.405	0.248–0.662	<0.00[a]
History of CVD	1.969	1.216–3.188	0.006[a]
Primary kidney disease			
Diabetic nephropathy	1.401	0.865–2.270	0.171
Chronic glomerulonephritis	0.684	0.348–1.341	0.269
Hypertensive nephropathy	0.898	0.513–1.796	0.898
Others	0.833	0.412–1.684	0.611
Systolic blood pressure ≥160 mm Hg	1.609	0.995–2.602	0.052
eGFR (per 1 ml/min per 1.73 m^2)	1.092	0.937–1.272	0.260
Hemoglobin (per 1 g/dl)	1.081	0.911–1.282	0.374
Serum albumin, g/d; (per 1 g/dl)	0.751	0.560–1.008	0.056
Serum sodium, mEq/L (per 1mEq/L)	0.964	0.923–1.008	0.139
Serum potassium, mEq/L (per 1 mEq/L)	0.958	0.715–1.283	0.773
Serum calcium, mg/dl (per 1 mg/dl)	0.941	0.689–1.286	0.703
Serum phosphorus, mg/dL (per 1 mg/dl)	1.023	0.887–1.181	0.747
C-reactive protein, mg/dl (log)	1.302	0.981–1.729	0.068
Modified Charlson Comorbidity Index[b] (vs. 0)			
1–2	2.325	1.385–3.902	0.001[a]
≥3	2.250	0.851–5.946	0.102
Performance status (per 1)	1.549	1.252–1.916	<0.001[a]
Vascular access (vs. temporaly catheter)			
Arteriovenous fistula	0.454	0.28–0.738	0.001[a]
Fatigue	1.559	0.886–2.743	0.124
Edema	1.955	1.081–3.537	0.027[a]
Pulmonary edema	1.519	0.929–2.486	0.096
Nausea	1.029	0.620–1.708	0.912
Dysorexia	0.881	0.543–1.427	0.606
Diarrhea	1.603	0.643–3.996	0.311
Constipation	0.691	0.169–2.829	0.608
Peripheral nerve abnormalities	1.701	0.957–3.023	0.070
Itch	0.873	0.377–2.021	0.751
Hemorrhagic diathesis	1.004	0.245–4.117	0.996
Diabetic retinopathy	1.741	1.078–2.814	0.023[a]
ESA use	0.463	0.260–0.823	0.009[a]
ACEI and/or ARB use	0.614	0.364–1.039	0.069
Vitamin D use	0.354	0.049–2.550	0.302

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent.
[a]$P < 0.05$.
[b]Items related to diabetes and renal disease were excluded from the original Charlson Comorbidity Index in the present study.

previous studies recommending early initiation were all nonrandomized and subject to potential confounding factors. When a randomized controlled trial was conducted that accounted for confounding factors, including biases related to referral time, lead time, and patient selection, planned early initiation of dialysis was found not to be associated with an improvement in survival or clinical outcome.[7] In addition to the issue of the timing of HD initiation, it was reported that the rate of eGFR decline before initiating HD was associated with all-cause mortality after beginning HD.[27,28]

Table 4. Hazard ratio of logarithmic interval from the time of an estimated glomerular filtration rate of 10 ml/min per 1.73 m^2 by multivariate survival analysis

Characteristics	Hazard ratio	95% confidence interval	*P* value
Model 0	0.393	0.244–0.635	<0.001[a]
Unadjusted			
Model 1	0.327	0.204–0.523	<0.001[a]
Adjusted for age and sex			
Model 2	0.471	0.259–0.855	0.013[a]
Adjusted for Model 1 plus nephrology care >6 mo, PS, and AVF			
Model 3	0.507	0.269–0.956	0.036[a]
Adjusted for Model 2 plus diabetic retinopathy and ESA use			

AVF, arteriovenous fistula; ESA, erythropoiesis-stimulating agent; PS, performance status.
[a]$P < 0.05$.

However, to date, from what point the rate of decline might be important is uncertain.

The HD-free $I_{GFR10\text{-}HD}$ was related to already known risk factors for patients on HD, such as nephrology care, diabetic nephropathy, eGFR at HD initiation, serum albumin, PS, vascular access, and ESA use. Hsu *et al*. reported that there were differences between patients with abrupt and nonabrupt eGFR decline in terms of nephrology care, eGFR at HD initiation, serum albumin, cause of ESRD, and vascular access.[27] Of these, nephrology care before HD initiation was considered to be important, especially in older adults.[29,30] However, at which level of eGFR physicians should refer patients to nephrologists is yet to be completely elucidated. According to the Japanese dialysis initiation survey, nephrology care for ≥6 months predialysis significantly reduced the risk of 1-year mortality after HD initiation. It was reported that a higher rate of using specialized medications (e.g., ESA and sodium hydrogen carbonate) in patients who received early nephrology care might be a reason for this better outcome.[4,29,31] In the present study, nephrology care >6 months remained a strong and independent prognostic factor in the multivariate model, although most patients in our study received comprehensive treatment in our nephrology division when their eGFR was 10 ml/min per 1.73 m^2.

Table 5. Hazard ratio of logarithmic estimated glomerular filtration rate rate of decline by multivariate survival analysis

Characteristics	Hazard ratio	95% confidence interval	*P* value
Model 0	3.926	2.128–7.245	<0.001[a]
Unadjusted			
Model 1	5.117	2.638–9.925	<0.001[a]
Adjusted for age and sex			
Model 2	3.340	1.494–7.468	0.003[a]
Adjusted for Model 1 plus nephrology care >6 mo, PS and AVF			
Model 3	3.028	1.339–6.848	0.008[a]
Adjusted for Model 2 plus diabetic retinopathy and ESA use			

AVF, arteriovenous fistula; ESA, erythropoiesis-stimulating agent; PS, performance status.
[a]$P < 0.05$.

The HD-free $I_{GFR10\text{-}HD}$ was more sensitive for predicting the prognosis of HD patients than other already known risk factors. This interval correlated well with the eGFR at HD initiation, serum albumin, PS, and vascular access, all of which were reported to influence the prognosis of patients on HD.[26,32] It was possible that these factors were aggregated in the HD-free $I_{GFR10\text{-}HD}$, so that it ended up being an independent prognostic factor.

In Japan, a higher mortality was observed in patients with eGFRs >8 and <2 ml/min per 1.73 m^2 at HD initiation.[31] The guidelines of the Japanese Society for Dialysis Therapy (JSDT) therefore recommend starting HD when the eGFR is between 2 and 8 ml/min per 1.73 m^2, as long as patients have no uremic symptoms or complications, including malnutrition.[33] In this study, eGFR at the initiation of HD was found not to be a prognostic factor. Because most participants initiated HD at the time of recommended eGFR by JSDT (Table 1), we can say, at least, that eGFRs from 2 to 8 ml/min per 1.73 m^2 did not influence the prognosis once HD was initiated. In contrast, as noted previously, the rate of eGFR decline before HD initiation was reportedly associated with prognosis.[27,28] The mean levels of eGFR at HD initiation were >10 ml/min per 1.73 m^2 in these studies. In the present study, a faster rate of eGFR decline from a level of 10 ml/min per 1.73 m^2 had the expected shortening of the time to dialysis initiation. Delaying dialysis might be safe even after eGFR reaches 10 ml/min per 1.73 m^2 if a patient does not have a clear indication to start long-term dialysis.

There were 3 limitations to the present study. First, this was a retrospective single-center study, and the number of participants was insufficient for multivariate analysis. We could not completely adjust for known prognostic factors. Second, the primary outcome was the composite of all-cause mortality and cardiovascular events. Thirty-eight of 77 patients who reached the primary outcome had CVD, and 20 had heart failure. Therefore, the findings in this study, based on the outcomes we found, might not be generalizable to all patients on HD. Third, it was possible that the HD-free $I_{GFR10\text{-}HD}$ was correlated with a high starting eGFR, which might be a confounding issue. However, it was impossible to compare intervals from an eGFR 10 ml/min per 1.73 m^2 and from an eGFR >10 ml/min per 1.73 m^2 because of the unavailability of data.

In conclusion, the present study revealed that the HD-free $I_{GFR10\text{-}HD}$ might be an independent prognostic factor for patients on HD and might help in estimating a prognosis. When managing patients with ESRD, we should take this interval into consideration when discussing potential outcomes once HD is initiated.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work originated from Iwate Prefectural Central Hospital, and this study was not supported by any grant or sponsor. We are grateful for the collaboration of medical doctors and staff of the maintenance dialysis facilities who cared for the participants in this study.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: SH, IN, KS, and SY. Performed the experiments: SH, IN, KY, YC, ST, HS, and JS. Analyzed the data: SH, IN, and KS. Wrote the paper: SH, IN, and JS.

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382:260–272.
2. Collins AJ, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis*. 2010;55:S1–S420, a426–427.
3. Yamagata K, Nakai S, Iseki K, et al. Late dialysis start did not affect long-term outcome in Japanese dialysis patients: long-term prognosis from Japanese Society for [corrected] Dialysis Therapy Registry. *Ther Apher Dial*. 2012;16:111–120.
4. Chen SC, Hwang SJ, Tsai JC, et al. Early nephrology referral is associated with prolonged survival in hemodialysis patients even after exclusion of lead-time bias. *Am J Med Sci*. 2010;339:123–126.
5. Ocak G, Rotmans JI, Vossen CY, et al. Type of arteriovenous vascular access and association with patency and mortality. *BMC Nephrol*. 2013;14:79.
6. de Mutsert R, Grootendorst DC, Boeschoten EW, et al. Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr*. 2009;89:787–793.
7. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med*. 2010;363:609–619.
8. Rosansky SJ, Clark WF, Eggers P, et al. Initiation of dialysis at higher GFRs: is the apparent rising tide of early dialysis harmful or helpful? *Kidney Int*. 2009;76:257–261.
9. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: a systematic review. *Am J Med*. 2011;124:1073–1080. e1072.
10. Jungers P, Massy ZA, Nguyen-Khoa T, et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. *Nephrol Dial Transplant*. 2001;16:2357–2364.
11. Bonomini V, Feletti C, Stefoni S, et al. Early dialysis and renal transplantation. *Nephron*. 1986;44:267–271.
12. Bonomini V, Vangelista A, Stefoni S. Early dialysis in renal substitutive programs. *Kidney Int Suppl*. 1978:S112–S116.

13. Tattersall J, Greenwood R, Farrington K. Urea kinetics and when to commence dialysis. *Am J Nephrol*. 1995;15:283–289.
14. Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis*. 2006;48 Suppl 1:S2–S90.
15. Churchill DN, Blake PG, Jindal KK, et al. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. *J Am Soc Nephrol*. 1999;10 Suppl 13: S289–S291.
16. Rosansky SJ, Eggers P, Jackson K, et al. Early start of hemodialysis may be harmful. *Arch Intern Med*. 2011;171: 396–403.
17. Di Micco L, Torraca S, Pota A, et al. Setting dialysis start at 6.0 ml/min/1.73 m^2 eGFR–a study on safety, quality of life and economic impact. *Nephrol Dial Transplant*. 2009;24: 3434–3440.
18. Doi T, Yamamoto S, Morinaga T, et al. Risk score to predict 1-year mortality after haemodialysis initiation in patients with stage 5 chronic kidney disease under predialysis nephrology care. *PLoS One*. 2015;10:e0129180.
19. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992.
20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
21. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.
22. van der Heijden GJ, Donders AR, Stijnen T, et al. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol*. 2006;59: 1102–1109.
23. Hakim RM, Lazarus JM. Initiation of dialysis. *J Am Soc Nephrol*. 1995;6:1319–1328.
24. Churchill DN. An evidence-based approach to earlier initiation of dialysis. *Am J Kidney Dis*. 1997;30:899–906.
25. Traynor JP, Simpson K, Geddes CC, et al. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol*. 2002;13:2125–2132.
26. Hwang SJ, Yang WC, Lin MY, et al. Impact of the clinical conditions at dialysis initiation on mortality in incident haemodialysis patients: a national cohort study in Taiwan. *Nephrol Dial Transplant*. 2010;25:2616–2624.
27. Hsu RK, Chai B, Roy JA, et al. Abrupt decline in kidney function before initiating hemodialysis and all-cause mortality: The Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2016;68:193–202.
28. Sumida K, Molnar MZ, Potukuchi PK, et al. Association of slopes of estimated glomerular filtration rate with post-end-stage renal disease mortality in patients with advanced chronic kidney disease transitioning to dialysis. *Mayo Clin Proc*. 2016;91:196–207.
29. Hasegawa T, Bragg-Gresham JL, Yamazaki S, et al. Greater first-year survival on hemodialysis in facilities in which patients are provided earlier and more frequent pre-nephrology visits. *Clin J Am Soc Nephrol*. 2009;4:595–602.
30. Baek SH, Ahn S, Lee SW, et al. Outcomes of predialysis nephrology care in elderly patients beginning to undergo dialysis. *PLoS One*. 2015;10:e0128715.
31. Yamagata K, Nakai S, Masakane I, et al. Ideal timing and predialysis nephrology care duration for dialysis initiation: from analysis of Japanese dialysis initiation survey. *Ther Apher Dial*. 2012;16:54–62.
32. Slinin Y, Guo H, Gilbertson DT, et al. Meeting KDOQI guideline goals at hemodialysis initiation and survival during the first year. *Clin J Am Soc Nephrol*. 2010;5:1574–1581.
33. Watanabe Y, Yamagata K, Nishi S, et al. Japanese society for dialysis therapy clinical guideline for "hemodialysis initiation for maintenance hemodialysis". *Ther Apher Dial*. 2015;19 Suppl 1:93–107.