KIDNEY RESEARCH AND CLINICAL PRACTICE

Preexisting comorbidities are associated with the mortality rate as well as the predialysis adverse events in incident dialysis patients

Min-Jeong Lee[1], Inwhee Park[1], Heungsoo Kim[1], Gyu-Tae Shin[1], Jong Cheol Jeong[1,2]

[1]Department of Nephrology, Ajou University School of Medicine, Suwon, Republic of Korea
[2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

Background: Optimal estimated glomerular filtration rate (eGFR) to start maintenance dialysis is controversial. Observational studies have reported that initiation of dialysis at high eGFRs is associated with worse postdialysis survival.

Methods: We retrospectively investigated 1,038 incident dialysis patients who started maintenance dialysis during 2010-2015. Patients were assessed for comorbidities and adverse events during the transitional period of dialysis initiation. Patients were classified as planned dialysis (PD) vs. unplanned dialysis (UD) according to indications for dialysis initiation.

Results: UD group comprised 352 patients (33.9%). Mean eGFR at dialysis initiation was higher in UD patients than PD patients (7.9 ± 5.1 vs. 5.9 ± 3.4 mL/min/1.73 m^2, $p < 0.001$). Mean Davies comorbidity index in the UD group was higher (vs. PD group, 1.3 ± 1.0 vs. 0.9 ± 1.0, $p < 0.001$). Patients with more comorbidities experienced more ischemic heart disease (hazard ratio [HR], 4.36; 95% confidence interval [CI], 1.71–11.14) in the medium-risk group and HR of 8.84 (95% CI, 3.06–25.55) in the high-risk group (vs. low-risk group, $p < 0.001$)) during the predialysis period. High-risk group had increased postdialysis mortality (HR, 2.48; 95% CI, 1.46–4.20; $p = 0.001$). Adjusted HR of mortality was higher in the medium-risk group of UD patients (HR, 1.72; 95% CI, 1.16–2.56; $p = 0.007$).

Conclusion: Patients with more comorbidities were at increased risk of predialysis ischemic heart disease and postdialysis mortality. UD patients in the medium-risk population had increased risk of postdialysis mortality. Dialysis start should be individualized by considering comorbidities.

Keywords: Comorbidity, Dialysis, Glomerular filtration rate, Mortality

Introduction

The number of end-stage renal disease (ESRD) patients requiring dialysis treatment has been continuously and rapidly increasing over the past few decades [1–4]. Nevertheless, the optimal estimated glomerular filtration rate (eGFR) to start renal replacement therapy (RRT) is still controversial. In the 1990s, nephrologists believed that early initiation of dialysis

could improve patient survival. Several observational cohort and case-control studies suggested that starting dialysis early may improve patients' survival, quality of life, capacity for employment, and decrease complications [5,6]. Recently, several observational studies have shown that initiation of dialysis at high eGFR is associated with worse postdialysis patient survival [7–12]. The Initiating Dialysis Early and Late (IDEAL) study, the only randomized trial to investigate the appropriate eGFR to initiate dialysis, evaluated the impact of dialysis initiation on outcomes at two different levels of kidney function. This study showed that initiation of dialysis at higher eGFR was not associated with an improvement in patient survival or clinical outcomes [13]. In that study, the decision to start dialysis was originally guided by eGFR based on serum creatinine, but the clinical profile of the patient such as uremic symptoms, signs of protein-energy wasting, or fluid overload also affected the decision to initiate dialysis. The focus of previous studies when planning the timing of dialysis initiation has primarily been on eGFR; in this study, we focused on predialysis comorbidity status in addition to eGFR. We advocate that dialysis initiation should be based on both eGFR and the comorbidities of the patient, and argue that previous studies did not capture the comorbidity profile nor capture dialysis indications accurately because most previous studies were based on administrative or claim data. Here, we investigated predialysis comorbidities and indications for dialysis initiation based on manual medical record review.

Unplanned dialysis is associated with increased patient morbidity and mortality and added health care costs [14,15]. Given the high prevalence of unplanned dialysis and its association with poor patient outcomes, it is important to identify risk factors for unplanned dialysis initiation. Therefore, we also investigated to what extent predialysis comorbidities affect dialysis initiation timing in terms of eGFR and urgency.

Methods

We performed a retrospective cohort study at Ajou University Medical Center (AUMC) in Suwon, Korea. We enrolled patients 18 years of age or older at initiation of dialysis with progressive chronic kidney disease (CKD). The study was approved by the Institutional Review Board (IRB) of Ajou University School of Medicine in Suwon, Korea (No. AJIRB-MED-MDB-15-514). Informed consent was waived due to the retrospective nature of the study. The study design followed the tenets of the Declaration of Helsinki for biomedical research.

Study populations

We retrieved a list of patients receiving their first medical order for dialysis at AUMC from the AUMC clinical data warehouse system. We reviewed medical charts of all enlisted patients. A total of 2,746 patients received conventional hemodialysis for the first time at AUMC between January 2010 and December 2015. Of these, 1,362 patients were excluded because they were predominantly hemodialysis patients. Other excluded patients included 374 who received hemodialysis for the management of acute kidney injury, 46 who switched to hemodialysis from peritoneal dialysis, 38 who returned to hemodialysis following renal allograft failure, one for whom there was insufficient data in their electrical medical record, and three who refused hemodialysis (hemodialysis prescribed but not performed). Therefore, of the original 2,746 patients, 922 patients started maintenance hemodialysis for management of ESRD between January 2010 and December 2015. Of these 922 patients, 26 were preemptive kidney transplantation cases that underwent brief hemodialysis immediately before kidney transplantation. We enrolled 14 alleged CKD stage IV patients who received continuous RRT (CRRT) as the initial dialysis modality. These patients were patients who were continuing to be treated for progressive CKD in the outpatient clinic of the nephrology department. Because we retrieved the patient list based from the data warehouse based on medical orders, we excluded other CRRT cases such as patients with acute kidney injury who needed temporary RRT or ESRD patients who needed CRRT due to unstable vital signs. Peritoneal dialysis patients were included. Over the 6-year study period, 102 patients started peritoneal dialysis for the management of ESRD. In total, the medical records of 1,038 incident dialysis patients who started maintenance dialysis between January 2010 and December 2015 were reviewed. The process for constructing the retrospective cohort is summarized in Fig. 1.
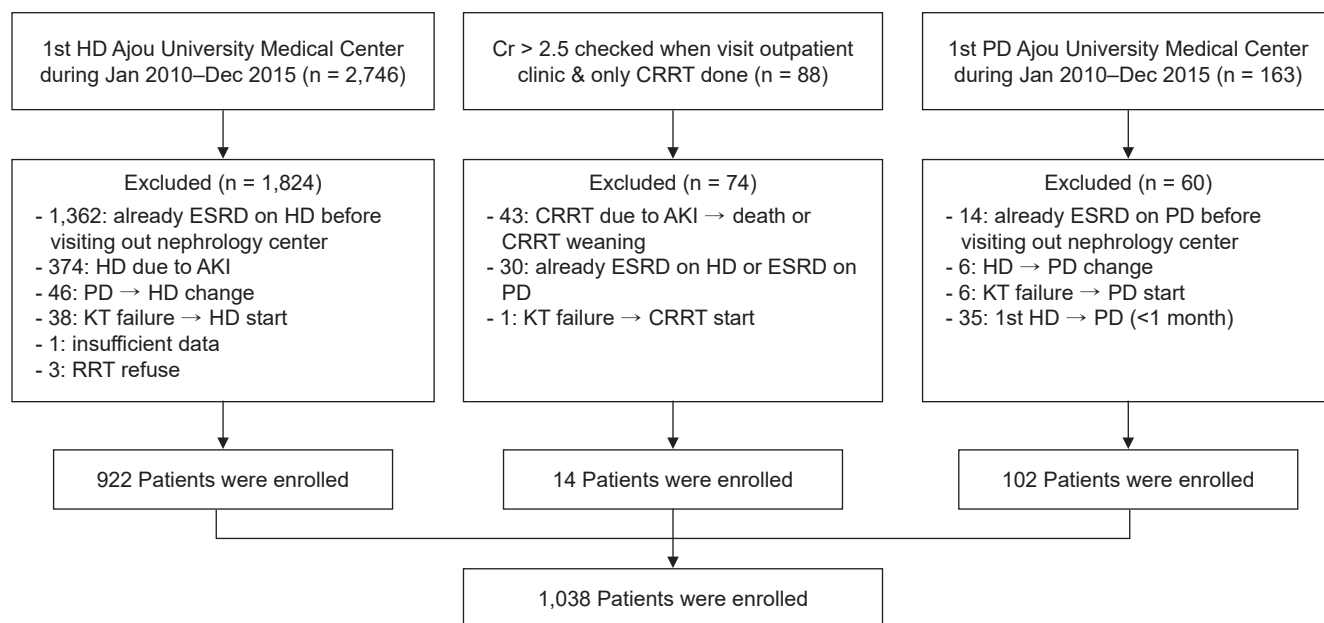
Figure 1. Patient flow diagram. Diagram shows the exclusion criteria applied to the initial dialysis order code resulting in the final cohort of 1,038 subjects.

AKI, acute kidney injury; Cr, serum creatinine; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; HD, hemodialysis; KT, kidney transplantation; PD, peritoneal dialysis; RRT, renal replacement therapy.

Data collection

Demographic, laboratory, and clinical information was collected. The presence of comorbid illnesses was assessed at the time of enrollment by complete review of inpatient and outpatient records (containing information about medical and surgical consultations and previous hospital admissions). eGFR was calculated using the Modification of Diet in Renal Disease study equation [16]. Enrollment time was defined as the first time of eGFR below 20 mL/min/1.73 m^2 referencing the criteria of other studies of patients with advanced CKD [17–19]. We reviewed predialysis adverse outcomes, such as ischemic heart disease (nonfatal myocardial infarction, new-onset angina requiring percutaneous intervention), cerebrovascular events (nonfatal stroke, transient ischemic attack), and infection requiring hospitalization from time of enrollment to dialysis initiation. Early referral and late referral were defined according to whether the patient's first encounter with a nephrologist was more than or less than 3 months prior to dialysis initiation [20]. Body mass index (BMI) was categorized according to the World Health Organization classification for Asian populations [21]. Mortality data were obtained from the time of dialysis initiation

until December 2017. When classifying the main indications for dialysis initiation, uremic symptoms were defined as following: anorexia, nausea, decreased appetite, general aches, peripheral neuropathy, pruritus, anemia despite proper medication, and other symptoms [22].

Comorbidity index

Comorbidities were defined as follows: diabetes mellitus, hypertension, ischemic heart disease (stable angina, unstable angina, and myocardial infarction), heart failure, peripheral arterial occlusive disease, cerebrovascular disease, liver cirrhosis (compensated, decompensated), chronic obstructive pulmonary disease, malignancy, acquired immune deficiency syndrome, neuromuscular disease, and systemic collagen disorder. Davies [23] comorbidity indices were calculated for each patient based on their comorbidities at enrollment. The Davies score is based on the presence or absence of seven comorbid conditions and produces three risk groups. Age is not included in this index. Patients without comorbid conditions are classified as low-risk. Patients with one or two comorbid diseases are regarded as medium-risk patients. Patients with three or more comorbid conditions are classi-

fied as high-risk patients.

Definitions of planned and unplanned dialysis

Patients were assigned to the planned dialysis group or unplanned dialysis group [14,24,25]. The unplanned dialysis group included patients who started maintenance dialysis due to a life-threatening situation regardless of a permanent access device in place. A life-threatening situation was defined as one of the following: uremic encephalopathy, uremic pericarditis, pulmonary edema on chest X-ray with consistent clinical symptoms of dyspnea, and a change in electrocardiogram rhythm with serum potassium more than 7.0 mEq/L despite proper medical treatment. The planned dialysis group was defined as the remaining cases that did not undergo unplanned dialysis.

Statistical analysis

Continuous variables are summarized as means (± standard deviation) for normally distributed data; categorical variables are presented as frequencies (percentages). The significance of differences in continuous variables between groups was assessed using the Student t test, the Mann-Whitney test, or one-way analysis of covariance (for nonnormally distributed data), while the significance of differences in categorical data among groups was evaluated using chi-square tests.

Logistic regression models were used to identify univariate and multivariable risk factors for unplanned dialysis. Comorbidity indices and predialysis adverse events between the planned dialysis group and the unplanned dialysis group were compared using Cox regression analysis. Kaplan-Meier plots were used to visualize the associations between comorbidities and predialysis adverse outcomes. We used the Cox proportional hazards model to assess factors associated with the endpoint of death from any cause. To further investigate temporal changes in the hazard ratio (HR) of different subpopulations, we applied time-varying hazard regression based on fractional polynomials [26].

All reported p-values are two-tailed, with a p-value of 0.05 indicating statistical significance. Analyses were performed using Stata software, version 15.0 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

Between Jan 2010 and Dec 2015, a total of 1,038 patients were enrolled for final analysis (Fig. 1). Table 1 shows the baseline characteristics of the patients. Four hundred 61 patients (44.4%) were female. Mean age at dialysis initiation was 58.6 ± 14.8 years old. Mean eGFR at the enrollment time was 14.1 ± 5.9 mL/min/1.73 m^2, and mean eGFR at dialysis initiation was 6.6 ± 4.2 mL/min/1.73 m^2. The proportion of early referrals was 84.2%. Common comorbidities at enrollment were hypertension (87.7%), diabetes mellitus (53.7%), previous cerebrovascular disease (12.4%), heart failure (8.9%), previous angina s/p (status post) stent insertion (7.7%), and previous myocardial infarction (5.5%). In the unplanned dialysis group, the prevalence of diabetes mellitus was higher, the duration of diabetes mellitus was longer, and insulin use was higher than in the planned dialysis group. In the unplanned dialysis group, cardiovascular disease, such as myocardial infarction and angina, heart failure, and peripheral arterial occlusive disease were more prevalent. History of chronic obstructive pulmonary disease, malignancy, neuromuscular disease, or systemic collagen disease did not differ between the two groups.

Unplanned vs. planned dialysis

There were 352 patients (33.9%) in the unplanned dialysis group and these patients were older than those in the planned dialysis group (p < 0.001). Mean eGFR at dialysis initiation in the unplanned dialysis group was higher than that in the planned dialysis group (8.0 ± 5.1 mL/min/1.73 m^2 vs. 5.9 ± 3.4 mL/min/1.73 m^2; p < 0.001). Table 2 shows in detail the main indications for dialysis and what symptoms were prevalent at the start of dialysis. In the planned dialysis group, the main indication for dialysis initiation was uremic symptoms (41.8%) while in the unplanned dialysis group, the main indication for dialysis initiation was volume overload (67.0%). The unplanned dialysis group had higher comorbidity scores than the planned dialysis group (Table 3). Logistic regression analysis showed that age at enrollment time (odds ratio [OR], 1.03; 95% confidence interval [95% CI], 1.02–1.04; p < 0.001), diabetes mellitus (OR, 1.94; 95% CI, 1.44–2.61; p < 0.001), heart failure (OR, 2.81; 95%

Table 1. Baseline characteristics of the study population

Characteristic	Total	Planned dialysis	Unplanned dialysis[a]	p-value
At the time of enrollment				
Patient	1,038 (100)	686 (66.1)	352 (33.9)	-
Male sex	577 (55.6)	383 (55.7)	195 (55.4)	0.93
Age (yr)	58.6 ± 14.8	56.1 ± 14.6	63.8 ± 13.8	<0.001
DM	557 (53.7)	325 (47.4)	235 (66.8)	<0.001
DM duration (yr)	8.8 ± 10.5	7.3 ± 9.8	11.7 ± 11.1	<0.001
Use of insulin	251 (24.2)	143 (20.8)	108 (30.7)	0.006
HTN	910 (87.7)	600 (87.5)	310 (88.1)	0.78
HTN duration (yr)	9.0 ± 9.7	8.1 ± 7.6	10.6 ± 8.5	<0.001
eGFR at enrollment time (mL/min/1.73 m^2)	14.1 ± 5.9	13.9 ± 6.0	14.4 ± 5.8	0.26
Early referral	874 (84.2)	587 (85.6)	287 (81.5)	0.09
Comorbidities at enrollment time				
Cancer	93 (9.0)	58 (8.5)	35 (10.0)	0.47
Liver cirrhosis	41 (4.0)	27 (3.9)	14 (4.9)	0.61
Cerebrovascular disease	129 (12.4)	78 (11.4)	51 (14.5)	0.18
COPD	11 (1.1)	5 (0.7)	6 (1.7)	0.15
Myocardial infarction	57 (5.5)	29 (4.2)	28 (8.0)	0.01
Angina	80 (7.7)	41 (6.0)	39 (11.1)	0.01
Heart failure	92 (8.9)	35 (5.1)	57 (16.2)	<0.001
PAOD	41 (4.0)	16 (2.3)	25 (7.1)	0.001
Neuromuscular disease	1 (0.1)	1 (0.2)	0 (0)	0.47
Systemic collagen disease	22 (2.1)	16 (2.3)	6 (1.7)	0.51
Davies comorbidity index	1.0 ± 1.0	0.9 ± 1.0	1.3 ± 1.0	<0.001
At dialysis initiation time				
Follow-up (day)[b]	434.1 ± 557.2	462.7 ± 581.9	378.4 ± 501.8	0.02
Modality, HD:PD	936:102	590:96	346:6	<0.001
Temporary catheter insertion[c]	764 (81.6)	445 (75.4)	319 (92.2)	<0.001
eGFR at dialysis initiation (mL/min/1.73 m^2)	6.6 ± 4.2	5.9 ± 3.4	8.0 ± 5.1	<0.001
Body mass index (kg/m^2)	23.1 ± 3.6	23.0 ± 3.5	23.3 ± 4.0	0.32
Predialysis adverse outcome				
Ischemic heart disease	53 (5.1)	27 (3.9)	26 (7.4)	0.02
Cerebrovascular event	33 (3.2)	15 (2.2)	18 (5.1)	0.01
Infection requiring hospitalization	112 (10.8)	65 (9.5)	47 (13.6)	0.06

Data are expressed as number (%), mean ± standard deviation, or number only.
COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HTN, hypertension; PAOD, peripheral arterial occlusive disease; PD, peritoneal dialysis.
[a]Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.
[b]Follow-up: from time of enrollment to dialysis initiation. [c]Temporary catheter insertion was analyzed only in hemodialysis patients.

CI, 1.71–4.62; p < 0.001), peripheral arterial occlusive disease (OR, 2.22; 95% CI, 1.12–4.37; p = 0.02), and late referral (OR, 0.63; 95% CI, 0.45–0.88) were independent risk factors for unplanned dialysis (Supplementary Table 1, available online). When divided into comorbidity risk index groups, the OR for unplanned dialysis was 2.43 times higher in the medium-risk group (95% CI, 1.79–3.31; p < 0.001) and 3.27 times higher in the high-risk group (95% CI, 2.03–5.26; p < 0.001) than in the low-risk group. In addition, eGFR at dialysis initiation was higher in the unplanned dialysis group than in the planned dialysis group for all comorbidity risk index groups (Table 3).

Subgroup analysis of planned and unplanned dialysis according to RRT modality is shown in Supplementary Table 2

Table 2. Main indications and prevalent symptoms at dialysis initiation

Variable	Total	Planned dialysis	Unplanned dialysis[a]	p-value
Main indication for dialysis initiation				
Azotemia without specific symptom	228 (22.0)	228 (33.2)	0 (0)	<0.001
Uremic symptom[b]	291 (28.0)	287 (41.8)	4 (1.1)	
Volume overload	351 (33.8)	115 (16.8)	236 (67.1)	
Electrolyte imbalance	89 (8.6)	18 (2.6)	71 (20.2)	
Uremic encephalopathy	30 (2.9)	2 (0.3)	28 (8.0)	
Uremic pericarditis	7 (0.7)	0 (0)	7 (2.0)	
Others	42 (4.1)	36 (5.3)	6 (1.7)	
Total	1,038 (100)	686 (100)	352 (100)	
Prevalent symptoms at dialysis initiation				
Loss of consciousness	37 (3.6)	4 (0.6)	33 (1.0)	<0.001
Delirium	63 (6.1)	14 (2.0)	49 (13.9)	<0.001
Dyspnea	420 (40.5)	161 (23.5)	259 (73.6)	<0.001
Pericardial effusion[c]	132 (12.7)	53 (7.7)	82 (23.9)	<0.001
Pulmonary edema				
Mild	171 (16.5)	132 (19.2)	39 (11.1)	<0.001
Moderate to severe	264 (25.4)	16 (2.3)	248 (70.5)	
Generalized edema	519 (50.0)	287 (41.8)	232 (65.9)	<0.001
Metabolic acidosis[d]	108 (10.4)	49 (7.1)	59 (16.8)	<0.001
Hyperkalemia[e]	153 (14.7)	70 (10.2)	83 (23.6)	<0.001
General weakness	822 (79.2)	498 (72.6)	324 (92.1)	<0.001
Anemia	82 (7.9)	58 (8.5)	24 (6.8)	0.36
Anorexia	601 (57.9)	409 (59.6)	192 (54.6)	0.12
Vomiting	303 (29.2)	220 (32.1)	83 (23.6)	0.004
General ache	37 (3.6)	23 (3.4)	14 (4.0)	0.61
Pruritus	49 (4.7)	35 (5.1)	14 (4.0)	0.42
Insomnia	47 (4.5)	33 (4.8)	14 (4.0)	0.54
Neuropathy	89 (8.6)	64 (9.3)	25 (7.1)	0.23
No symptom	69 (6.7)	68 (9.9)	1 (0.3)	<0.001
Systemic infection	40 (3.9)	15 (2.2)	25 (7.1)	<0.001

Data are expressed as number (%).

[a]Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place. [b]Uremic symptoms were defined as anorexia, nausea, decreased appetite, general aches, peripheral neuropathy, pruritus, anemia despite proper medications, and other symptoms. [c]Pericardial effusion was confirmed by echocardiogram and/or computed tomography. [d]Metabolic acidosis was defined as a serum bicarbonate level below 10 mEq/L. [e]Hyperkalemia was defined as a serum potassium level greater than 6.0 mEq/L.

Table 3. The eGFR at dialysis initiation according to comorbidity index

Davies index	Planned dialysis		Unplanned dialysis[a]		eGFR difference (unplanned − planned dialysis)	p-value[b]
	No. (%)	eGFR (mL/min/1.73 m^2)	No. (%)	eGFR (mL/min/1.73 m^2)		
Low-risk	268 (39.1)	4.9 ± 2.5	71 (20.2)	5.7 ± 3.7	0.8 ± 0.5	0.03
Medium-risk	366 (53.2)	6.5 ± 3.8	236 (67.1)	8.3 ± 5.3	1.8 ± 0.3	<0.001
High-risk	52 (7.6)	7.2 ± 2.9	45 (12.8)	10.1± 4.3	2.9 ± 0.8	<0.001

Data are expressed as number (%), mean ± standard deviation for eGFR, or contrast ± standard error for eGFR difference.

[a]Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place.
[b]We compared eGFR at dialysis initiation between the planned dialysis group and unplanned dialysis group.

(available online). In the peritoneal dialysis patients group, there was no difference in eGFR at dialysis initiation between the planned and unplanned groups (5.66 ± 5.06 mL/min/1.73 m^2 vs. 4.67 ± 0.53 mL/min/1.73 m^2, respectively; p < 0.001).

We also performed subgroup analysis of planned and unplanned dialysis based on age group (Supplementary Tabe 3, available online). There were 499 (73.4%) vs. 181 (26.6%) patients under the age of 65 years in the planned vs. unplanned dialysis groups, while there were 168 (54.4%) vs. 141 (45.6%) patients over 65 years and under 80 years in these two groups and 19 (38.8%) vs. 30 (61.2%) patients over 80 years in these two groups, respectively. In elderly patients over 80 years old, the risk of unplanned dialysis was 1.45 times higher than that of patients under 65 years of age (95% CI, 0.83–2.07; p < 0.001).

Estimated glomerular filtration rate at dialysis initiation according to comorbidity index

The higher the comorbidity index, the higher the eGFR at the initiation of dialysis (Table 3). The difference in eGFR at the start of dialysis increased as the number of comorbid conditions increased. Changes in eGFR at the start of dialysis according to the comorbidity index are shown for all patients except asymptomatic patients who started dialysis with progressive azotemia without specific symptoms (Supplementary Table 4, available online). The eGFR at dialysis according to the comorbidity index of patients showed no differences among patients except for the 14 patients with acute kidney injury on chronic kidney injury who start dialysis with CRRT (Supplementary Table 5, available online).

Predialysis adverse outcomes and comorbidity index

Analysis of the predialysis period from the time of enrollment to dialysis initiation revealed that patients with a higher comorbidity risk experienced more ischemic heart diseases such as myocardial infarction or unstable angina, and more infection events requiring hospitalization (Fig. 2). HRs of the risk groups for predialysis ischemic heart diseases were as follows: medium-risk, 4.36 (95% CI, 1.71–11.14) and high-risk, 8.84 (95% CI, 3.06–25.55) (log-rank test, global p < 0.001). HRs of each risk group for predialysis infection events were as follows: medium-risk, 2.57 (95% CI, 1.51–4.37) and high-risk,
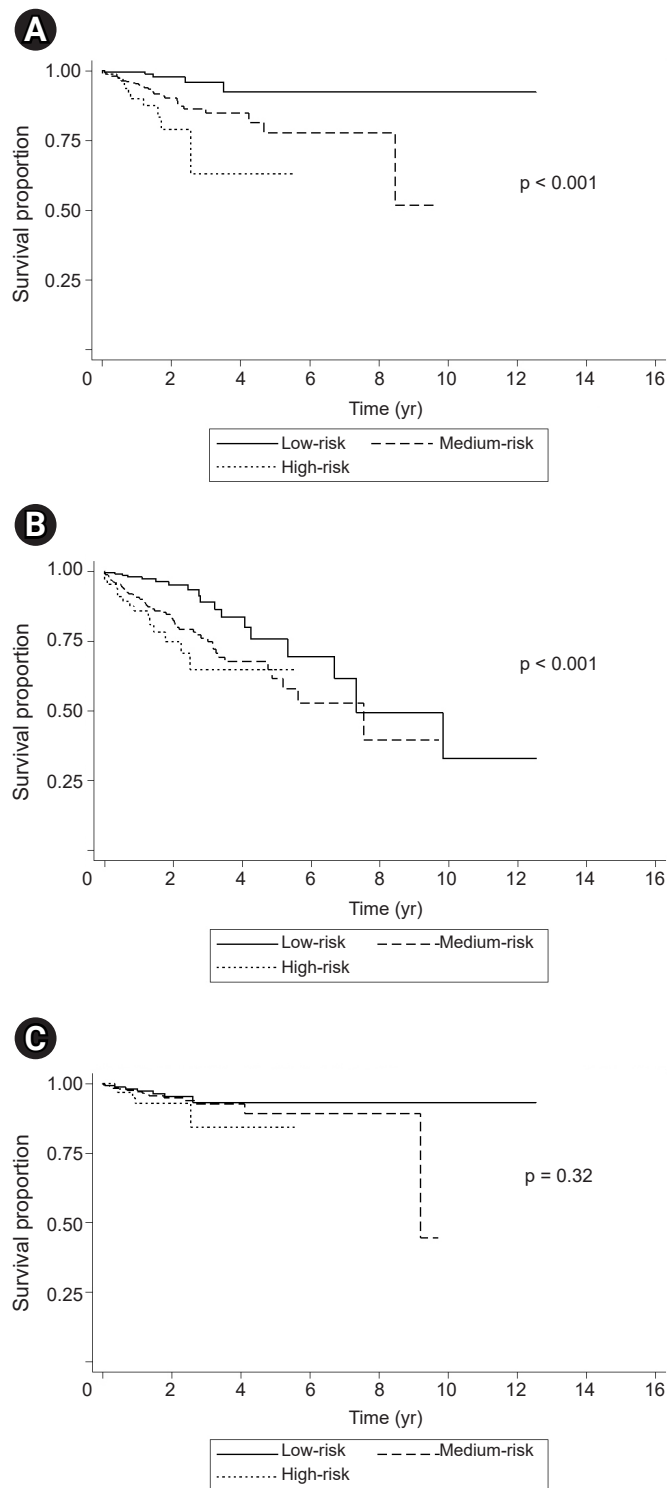
Figure 2. Predialysis adverse outcomes according to comorbidity index. (A) Ischemic heart disease-free time from study enrollment. (B) Infection-free time from study enrollment. (C) Cerebrovascular event-free time from study enrollment. X-axis represents the time (years) from the enrollment time.

3.85 (95% CI, 1.94–7.68) (log-rank test, global p < 0.001). HRs of each risk group for predialysis cerebrovascular events were as follows: medium-risk, 0.85 (95% CI, 0.36–1.99) and high-risk, 1.04 (95% CI, 0.36–1.99) (log-rank test, global p = 0.32).

Postdialysis mortality

Fig. 3 shows predicted survival after dialysis initiation based on comorbidity index and urgency of dialysis indications. Adjusted Cox regression prediction curves for comparisons of postdialysis survival show that mortality was higher with unplanned dialysis for the same comorbidity risk. As expected, patients with a high comorbidity risk who underwent unplanned dialysis had a higher mortality rate than patients at low risk who underwent planned dialysis (HR, 3.87; 95% CI, 1.85–8.09; p < 0.001), and the low-risk and planned dialysis group had the lowest mortality rate. Survival after dialysis initiation by RRT modality is shown in Supplementary Fig. 1 (available online). There was no difference in postdialysis mortality between hemodialysis patients and peritoneal dialysis patients (p = 0.10). Furthermore, the survival rate of peritoneal dialysis patients was better than that of hemodialysis patients up to about 5 years, but survival curves crossed over just before 5 years. It appears that the mortality rate in peritoneal dialysis patients increased with a longer observation period due to inaccurate death data in hemodialysis patients.

After adjustment for age, sex, eGFR at dialysis initiation,

BMI at dialysis initiation, and unplanned dialysis initiation, there was a significant increase in the risk of death as the comorbidity index increased (medium-risk vs. low-risk: HR, 1.73; 95% CI, 1.14–2.63; p = 0.01; high-risk vs. low-risk: HR, 2.50; 95% CI, 1.47–4.27; p = 0.001) (Table 4). After adjustment for age, sex, eGFR at dialysis initiation, BMI at dialysis initiation, and comorbidity indices, HR for death after dialysis initiation in the unplanned dialysis group was 1.69 (95% CI, 1.22–2.33, p = 0.001) when compared with the planned dialysis group (Table 4). Stratified analysis by comorbidity index revealed that planned dialysis was superior to unplanned dialysis in terms of postdialysis mortality in the medium-risk group.

In the unplanned dialysis group, the mortality HR compared to planned dialysis has its immediate peak in the early postdialysis period (Fig. 4A). For patients who experience predialysis ischemic heart disease, postdialysis mortality HR also peaked in the immediate postdialysis period; interestingly, the increased HR of this group was sustained until the end of follow-up after a short neutral period (Fig. 4B).

Discussion

In the present study, we found that patients with more comorbidities experienced more ischemic heart diseases such as myocardial infarction or angina, and more infection events requiring hospitalization during the predialysis period than those patients with fewer comorbidities. Patients with higher comorbidity risk were also more likely to undergo unplanned dialysis despite a higher eGFR than patients with a lower comorbidity risk. The mortality rate of patients who underwent unplanned dialysis was high even after dialysis, especially in the early postdialysis period.

Early dialysis initiation (eGFR of >10 mL/min/1.73 m^2) was not associated with morbidity or mortality benefits in the IDEAL study [13]. This randomized controlled trial influenced the development of the most recent European guidelines on the timing of dialysis initiation [27], which now place greater emphasis on the assessment of patient symptoms and signs rather than eGFR. It is suggested that in asymptomatic patients with stage V CKD, dialysis may be safely delayed until the eGFR is at least as low as 5 to 7 mL/min/1.73 m^2 if there is careful clinical follow-up and adequate patient education. In our study of 1,038 patients, mean eGFR at RRT initiation was 6.6 ± 4.2 mL/min/1.73 m^2. This result lends support to

Survival after dialysis initiation

Legend:
— Low-risk & planned dialysis
······· Low-risk & unplanned dialysis
- - - Medium-risk & planned dialysis
-·-·- Medium-risk & unplanned dialysis
— — High-risk & planned dialysis
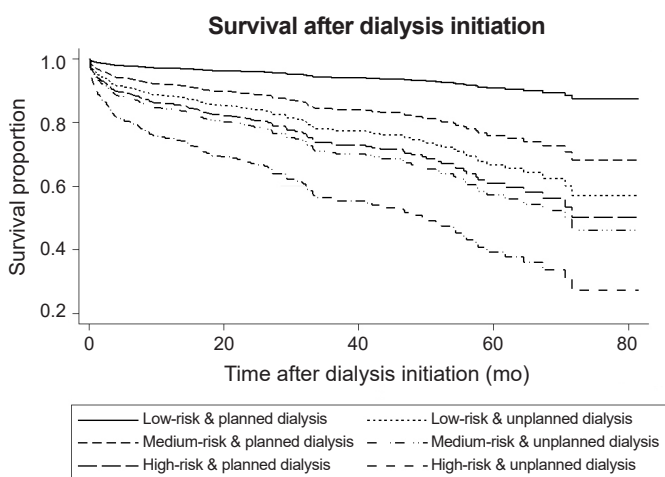- – - High-risk & unplanned dialysis

Figure 3. Adjusted Cox regression prediction curves for comparisons of postdialysis survival by comorbidity index and urgency of dialysis indications.

Table 4. Assessment of mortality after dialysis initiation based on Cox proportional hazard assumption regression analysis

Variable	Adjusted model	
	HR (95% CI)	p-value
Male sex	1.30 (0.94–1.79)	0.11
Age at dialysis initiation	1.06 (1.04–1.07)	<0.001
BMI at dialysis initiation (dry weight)	0.96 (0.91–1.01)	0.09
Unplanned dialysis[a,b]		
Planned dialysis (all risk)	Reference	-
Unplanned dialysis (all risk)	1.69 (1.22–2.33)	0.001
Planned dialysis (low-risk[c])	Reference	-
Unplanned dialysis (low-risk[c])	1.89 (0.81–4.45)	0.14
Planned dialysis (medium-risk[c])	Reference	-
Unplanned dialysis (medium-risk[c])	1.72 (1.16–2.56)	0.007
Planned dialysis (high-risk[c])	Reference	-
Unplanned dialysis (high-risk[c])	1.80 (0.80–4.04)	0.16
Comorbidity index[d]		
Low-risk[c]	Reference	-
Medium-risk[c]	1.73 (1.14–2.63)	0.01
High-risk[c]	2.50 (1.47–4.27)	0.001
Predialysis ischemic heart disease[e]		
No	Reference	-
Yes	1.74 (1.09–2.78)	0.02

BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a]Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place. [b]Adjustment for sex, age at dialysis initiation, BMI at dialysis initiation, Davies comorbidity score, and eGFR at dialysis initiation. [c]Comorbidity index was used for the Davies index and patients were divided into low, medium, and high-risk groups on the basis of this. [d]Adjustment for sex, age at dialysis initiation, unplanned dialysis, BMI at dialysis initiation, and eGFR at dialysis initiation. [e]Adjustment for sex, age at dialysis initiation, BMI at dialysis initiation Davies comorbidity score, unplanned dialysis, and eGFR at dialysis initiation.
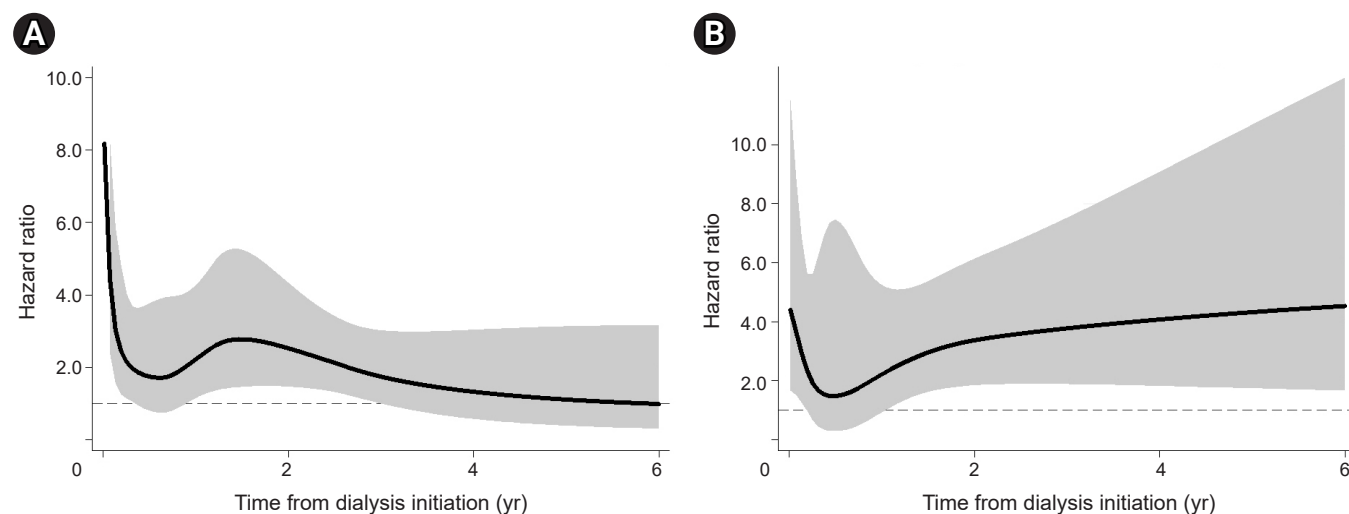

Figure 4. Time-varying hazard ratios of unplanned dialysis to postdialysis mortality. (A) Unplanned dialysis group showed an elevated hazard ratio in the early 3 years. (B) Patients who experienced predialysis ischemic heart disease had an immediate postdialysis mortality hazard ratio peak and chronically elevated hazard ratio after dialysis initiation compared to patients who did not experience predialysis ischemic heart disease. Unplanned dialysis group was defined as starting maintenance dialysis in a life-threatening situation regardless of a permanent access device in place. IHD, ischemic heart disease. Y-axis indicates the time-varying hazard ratios of risk factors of interest. Time-varying hazard ratio represents the dynamic change in hazard ratio over time.

the idea that with careful clinical management of CKD, dialysis can be delayed for some patients until the eGFR drops below 7.0 mL/min/1.73 m^2. The eGFR at dialysis initiation in our study was very low compared with 12.0 mL/min/1.73 m^2 in the early start group and 9.8 mL/min/1.73 m^2 in the late start group in the IDEAL study.

However, advanced CKD patients with a higher comorbidity burden may require early dialysis. In our study, eGFR at dialysis initiation in the unplanned dialysis group was 8.0 ± 5.1 mL/min/1.73 m^2, while eGFR at dialysis initiation in the planned dialysis group was 5.9 ± 3.4 mL/min/1.73 m^2 (p < 0.001). Therefore, knowledge of which comorbidities promote starting dialysis with a high eGFR could allow advanced dialysis planning for patients with these comorbidities. As shown previously, ischemic heart disease, such as myocardial infarction and angina, heart failure, and peripheral arterial occlusive disease were more prevalent in the unplanned dialysis group. In our study, unplanned dialysis was also associated with a significantly increased risk of postdialysis mortality after adjustment for comorbidities, which a peak in the transitional period. In other words, planned dialysis may avoid the mortality hazard during the transitional period of dialysis initiation, and could have a protective effect on survival. Therefore, in patients with these comorbidities, dialysis initiation should be planned in advance for a higher eGFR. In our study, unplanned dialysis did not increase postdialysis mortality in high-risk patients (Table 4). We believe that planned dialysis is also important in high-risk patients, but the number of patients we evaluated in our study (97 of 1,038) may have been too small to obtain statistically significant results. In addition, patients in the medium-risk and unplanned dialysis group showed an eGFR overlap with those in the high-risk and planned dialysis group (Fig. 4), suggesting that unplanned dialysis is not related to postdialysis mortality in the high-risk group. Conversely, the fact that the mortality difference between planned/unplanned dialysis patients in the medium-risk group was statistically significant suggests that it is important to closely monitor medium comorbidity risk group patients so that unplanned dialysis does not occur, and to proceed with dialysis at an appropriate time without delay.

As Table 3 shows, the higher the comorbidity index, the greater the difference in eGFR at dialysis initiation between the planned dialysis group and unplanned dialysis group. Therefore, nephrologists should be alert to the need for early

dialysis initiation in patients with many comorbidities. In addition, as shown in Table 2, symptoms related to volume overload occurred frequently in urgent patients. Therefore, it is important to emphasize the importance of a low salt diet and proper use of diuretics for volume control, especially in high-risk patients.

Cardiovascular disease is common in advanced CKD and ESRD patients and accounts for approximately 50% of deaths among dialysis patients [28,29]. Due to the retrospective nature of this study, we could not determine whether early dialysis planning can prevent predialysis ischemic heart disease. However, we showed that ischemic heart disease during the predialysis period is an important risk factor for postdialysis mortality even if other comorbidities are accounted for. Therefore, predialysis ischemic heart diseases are important risk factors for mortality after dialysis. As shown in Fig. 4, the risk of postdialysis mortality was high in the early period, and the risk of postdialysis mortality in patients who had predialysis ischemic heart disease was also high in the early period. Therefore, careful attention should be paid to the transitional period. In addition, predialysis ischemic heart disease was more common in the high-risk comorbidity group, and extra caution is required for patients with many comorbidities.

Infection is another important complication of CKD. In our study, more infection events requiring hospitalization occurred in patients with higher comorbidity indices during the predialysis period. About 50 years ago, it was assumed that general debility from chronic uremia increased the risk of infection and it was postulated that reversal of the uremic state would reduce the risk of infection [30]. Unfortunately, dialysis does not appear to reduce infection risk in patients with CKD [31]. ESRD may be considered a state of acquired immunodeficiency [32]. Increased risk for hospitalization with infection has also been observed among individuals with less severely decreased kidney function that does not require dialysis [33–35]. Some investigators have indicated that there may be a link between infectious events, which increase inflammatory mediators, and subsequent cardiovascular events, including myocardial infarction and congestive heart failure [36].

Our study has several limitations. First, this study was a retrospective, single-center study performed at a tertiary university hospital, and the results can therefore not be generalized. The classification of comorbidities for each patient was determined by clinical impression (based on docu-

mentation in electronic records) at the time of enrollment. This introduces the possibility of misclassification bias. Conversely, the data can be considered reliable as they were obtained by detailed chart reviews. In addition, our study did not include patients in the eGFR range of 20 to 30 mL/min/1.73 m^2. Furthermore, as in previous studies [7–10], we included data from only those patients who survived until initiation of dialysis therapy. RRT prevalence is used as a surrogate estimate for ESRD prevalence, but this approach ignores patients receiving conservative care. Therefore, patients with ESRD who might have experienced premature death from inadequate RRT accessibility were not analyzed in our study. Additionally, postdialysis mortality is susceptible to information censoring. Since our hospital is a tertiary university hospital, many patients transition to an outside dialysis clinic after dialysis initiation. However, early mortality during the transitional period would have had a minimal effect on information censoring bias. Another limitation of this retrospective study is the difficulty in determining a causal relationship between early planned dialysis and improved patient survival. We also did not investigate other parameters representative of nutritional status, such as serum albumin level and hsCRP, which could reflect the patient's condition at the time of dialysis initiation. Despite these limitations, our study provided several clinically relevant points. Because of a thorough electronic medical record review, we were able to capture symptoms of patients and other clinical details. We investigated comorbidities and predialysis adverse clinical outcomes preceding initiation of dialysis. Furthermore, we investigated the association between comorbidities with eGFR at dialysis initiation.

Our study provides important information for decision-making in advanced CKD patients starting dialysis. Patients with more comorbidities experienced more adverse events during the predialysis period. In particular, unplanned dialysis was more common in patients with a history of heart failure, myocardial infarction, and peripheral arterial occlusive disease. Unplanned dialysis increased the risk of postdialysis mortality in the medium-risk comorbidity index population. Together, our findings suggest that dialysis start should be individualized based on comorbidities.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors' contributions

Conceptualization: JCJ
Data curation, Formal analysis: MJL, JCJ
Investigation: MJL
Writing–original draft: All authors
Writing–review & editing: All authors
All authors read and approved the final manuscript.

ORCID

Min-Jeong Lee, https://orcid.org/0000-0002-2611-7333
Inwhee Park, https://orcid.org/0000-0002-9912-5393
Heungsoo Kim, https://orcid.org/0000-0002-9380-7457
Gyu-Tae Shin, https://orcid.org/0000-0002-1343-5332
Jong Cheol Jeong, https://orcid.org/0000-0003-0301-7644

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