Predialysis trajectories of estimated GFR and concurrent trends of Chronic Kidney Disease-relevant biomarkers

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Abstract

Background: The glomerular filtration rate (GFR) decline varies in patients with advanced chronic kidney disease (CKD), and the concurrent changes in CKD-related biomarkers are unclear.

Objectives: This study aimed to examine the changes in CKD-related biomarkers along with the kidney function decline in various GFR trajectory groups.

Design: This study was a longitudinal cohort study originated from the pre-end-stage renal disease (pre-ESRD) care program in a single tertiary center between 2006 and 2019.

Methods: We adopted a group-based trajectory model to categorize CKD patients into three trajectories according to estimated glomerular filtration rate (eGFR) changes. A repeated-measures linear mixed model was used to estimate the concurrent biomarker trends in a 2-year period before dialysis and to examine the differences among trajectory groups. A total of 15 biomarkers were analyzed, including urine protein, serum uric acid, albumin, lipid, electrolytes, and hematologic markers.

Results: Using longitudinal data from 2 years before dialysis initiation, 1758 CKD patients were included. We identified three distinct eGFR trajectories: persistently low eGFR levels, progressive loss of eGFR, and accelerated loss of eGFR. Eight of the 15 biomarkers showed distinct patterns among the trajectory groups. Compared with the group with persistently low eGFR values, the other two groups were associated with a more rapid increase in the blood urea nitrogen (BUN) level and urine protein–creatinine ratio (UPCR), especially in the year before dialysis initiation, and a more rapid decline in hemoglobin and platelet counts. A rapid eGFR decline was associated with lower levels of albumin and potassium, and higher levels of mean corpuscular hemoglobin concentration (MCHC) and white blood cell (WBC). The albumin level in the group with an accelerated loss of eGFR was below the normal range.

Conclusion: Using longitudinal data, we delineated the changes in CKD biomarkers with disease progression. The results provide information to clinicians and clues to elucidate the mechanism of CKD progression.

Keywords: biomarker, chronic kidney disease, longitudinal data, trajectory

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Introduction

Chronic kidney disease (CKD), defined and staged by a decreased glomerular filtration rate (GFR) and the presence of kidney damage, such as albuminuria, is a complex disease.[1] CKD is estimated to affect 10–15% of adults and poses a public health problem worldwide.[2] Several studies have demonstrated the relationship between CKD and the risk of clinical outcomes like kidney failure, cardiovascular disease, and death.[1–3] CKD

patients, however, are highly heterogeneous in terms of clinical manifestations and disease progression. The major causes of CKD are diabetes, hypertension, and glomerulonephritis; however, others have unknown or undetermined origins.

In the past decade, several risk factors associated with CKD progression have been identified, including male sex,[4] younger age,[5] apolipoprotein L1 (*APOL1*) gene variants,[6] and uncontrolled diabetes, hypertension, and cardiovascular disease.[7,8] In addition, acute kidney injury,[9] medication non-adherence,[10] and heavy albuminuria[11] were also emphasized. Laboratory biomarkers such as uric acid,[12] serum albumin,[13] hemoglobin,[14] white blood count (WBC),[15] and potassium[16] were also mentioned. Previous studies found that serum albumin and hemoglobin were negatively related to renal function when below 4.3 g/dl and above 8.6 g/dl, respectively.[13,14] Hypokalemia/hyperkalemia and low white blood count were shown to be associated with an increased risk of CKD progression.[15,16] Zheng *et al.*[17] analyzed the multidimensional data of CKD risk factors at baseline and found that CKD patients with less favorable levels of bone mineral density, poor cardiac and kidney function markers, and inflammation had markedly increased risks of important clinical outcomes. Most of the studies regarding biomarkers for CKD progression merely analyzed baseline data, however. Few studies used longitudinal data to delineate the changes in laboratory biomarkers along with disease progression. O'Hare *et al.*[18] were the first to investigate longitudinal estimated glomerular filtration rate (eGFR) measurements before long-term dialysis and showed that an abrupt decline of kidney function was highly associated with recurrent acute kidney injury. Besides, Isakova *et al.*[19] assessed mineral metabolites spanning 8 years of CKD progression prior to end-stage renal disease (ESRD). They found that fibroblast growth factor 23 (FGF23) levels begin and continue to rapidly rise until ESRD. Bansal *et al.*[20] used baseline and follow-up data to represent the longitudinal changes in cardiac biomarkers and predicted incident heart failure and atrial fibrillation. Although predialysis eGFR trajectories were thought to be associated with renal outcomes, there are no studies so far characterizing the changing patterns of biomarkers in various eGFR trajectories.

In this study, we adopted group-based trajectory modeling to categorize CKD patients by their predialysis eGFR trajectory and then analyzed the concurrent changing trends of CKD-relevant biomarkers, including urine protein-creatinine ratio (UPCR), albumin, and uric acid. An understanding of how changes in laboratory biomarkers evolve provides critical information to clinicians and may provide clear clues to uncover the mechanisms of CKD progression.

Methods

Data sources and study population

This was a longitudinal cohort study originated from the multidisciplinary pre-ESRD care program at National Taiwan University Hospital (NTUH). The NTUH pre-ESRD care program was launched in 2006 to recruit patients with CKD stages 3b to 5 (eGFR <45 ml/min/1.73 m²) or proteinuria (UPCR >1000 mg/g) in nephrology outpatient clinics.[21] By the end of 2019, almost 8000 patients were enrolled in this program. The program participants received multidisciplinary care and were followed up until the initiation of renal replacement therapy, death, or withdrawal. The NTUH pre-ESRD database includes basic patient information, sociodemographic data, health behaviors, and biochemical tests. We excluded those aged less than 18 years, those with eGFR values ⩾60 ml/min/1.73 m², and not enrolled between 2008 and 2018 and focused on those who underwent long-term dialysis before 31 December 2018. A total of 1758 patients were included in the final analysis. The study flow chart was shown in Figure 1.

We further linked the NTUH pre-ESRD database to the NTUH–Integrated Medical Database (NTUH-IMD), a research database containing de-identified electronic medical records of NTUH, to retrieve study participants' medical records between 2006 and 2020, including administrative and demographic information, diagnoses, treatment procedures, prescriptions, laboratory tests, and hospitalization records. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines were followed.[22]

Ascertainment of trajectory

We used trajectory modeling to categorize patients according to their trends of eGFR values during a 2-year period before long-term dialysis

initiation. The long-term eGFR trajectory of each patient was characterized by the median eGFR value during each successive quarter preceding dialysis initiation. All available serum creatinine measurements within the inpatient and outpatient services in NTUH were used for eGFR trajectory modeling. The GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[23] based on the age at the time of serum creatinine measurement and sex.

The patient characteristics consisted of time-invariant and time-varying components. The time-invariant variables included baseline sociodemographic characteristics and comorbid conditions. The sociodemographic characteristics included the age at dialysis and sex. Comorbid conditions included diabetes, hypertension, congestive heart failure, ischemic heart disease, and cerebrovascular disease. The time-varying variables were CKD-relevant biomarkers, including kidney, diabetes, lipid, bone/mineral, inflammation, and cardiac-associated biochemical markers.[17] We selected a total of 46 biomarkers that were used in routine clinical practice at the NTUH (Supplementary Table S1). Biomarkers with over 10% missing data among patients were excluded. The remaining 15 biomarkers are shown in Table 1.

Ascertainment of outcomes

For each group defined by eGFR trajectory, we estimated the adjusted hazard for death after dialysis initiation. The patients were followed up from the date of dialysis initiation until death, withdrawal, or the end of 2020, whichever came first.
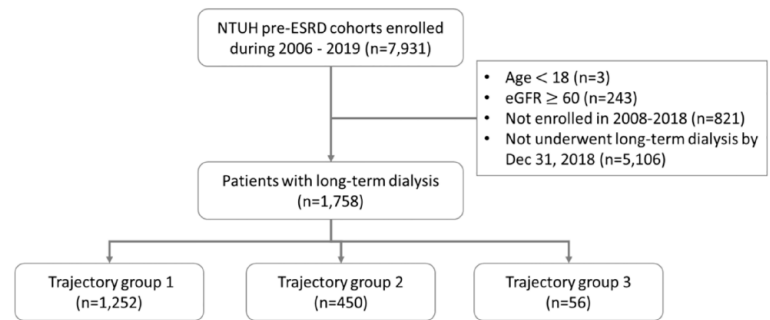

Figure 1. Flow chart of this study.

Trajectory models

Trajectory modeling is used to identify distinct changing patterns within a population and to estimate each individual's probability of assignment to each identified trajectory.[24] In this study, we first identified those who received long-term dialysis in the NTUH pre-ESRD cohort, and then extracted the eGFR measurements of each patient in the 2 years before dialysis initiation from NTUH-IMD. To accommodate trajectory modeling, we converted the eGFR measurements of each patient to median quarterly eGFR; subsequently, we performed trajectory modeling using the SAS 9.4 procedure PROC TRAJ[25,26] using a censored normal model. The number of trajectory groups can be determined on the basis of *a priori* knowledge as well as the values of Bayesian information criterion (BIC).[27] Based on previous studies and our population characteristics,[18,28–30] we finally chose to model the three eGFR trajectory groups. We assessed trajectory assignments by two means: (1) we used a repeated-measures linear mixed model to estimate the biannual mean change in the eGFR 2-year period before dialysis

Table 1. Biomarkers examined for patient characteristics.

Kidney markers	BUN	Urine protein	UPCR	Uric acid
	Urine creatinine			
Hematologic markers	Hemoglobin	MCHC		
Lipid markers	Triglyceride			
Electrolyte markers	Calcium	Phosphate	Potassium	Sodium
Inflammation markers	Albumin	Platelet	WBC	

BUN, blood urea nitrogen; MCHC: mean corpuscular hemoglobin concentration; UPCR, urine protein-creatinine ratio; WBC, white blood cell.
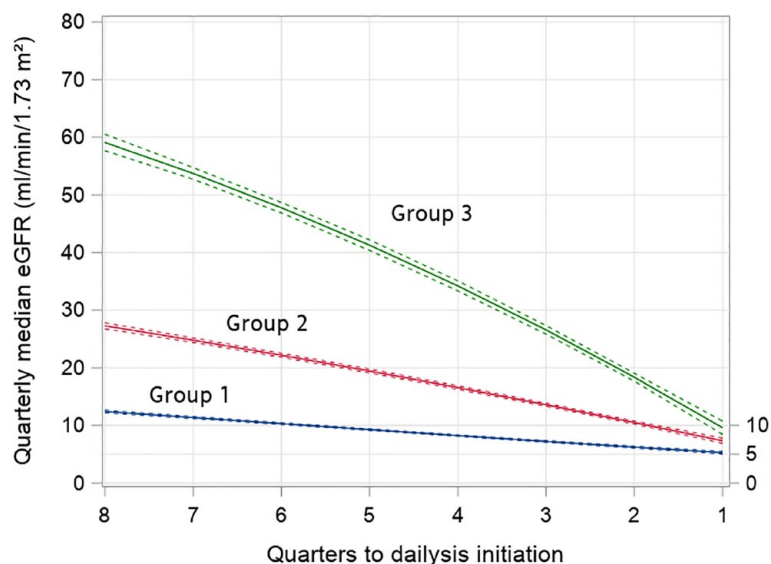
Figure 2. The eGFR trajectories 2 years before long-term dialysis initiation.
Three trajectory groups were defined by trajectory modeling. Trajectory group 1, 2 and 3 represent persistently low eGFR levels, progressive loss of eGFR, and an accelerated loss of eGFR, respectively. The solid lines and dotted lines show eGFR trajectories and 95% confidence intervals.

and (2) we fitted locally weighted scatter-plot smoothing (Lowess) curves to all eGFR measures for randomly selected patients in each trajectory group.

Statistical analysis

The continuous variables are shown as mean value ± standard deviation (SD) [or median with interquartile range (IQR)], and categorical variables are presented as counts and percentages. Log transformation was performed for the skewed data. We compared the distribution of patient characteristic variables across trajectory groups using the ANOVA test (or Kruskal–Wallis's test) and chi-square test for continuous variables and categorical variables, respectively. The Cochran–Armitage trend test was used to determine trends in mortality across trajectory groups. A repeated-measures linear mixed model was used to estimate the biomarker trends in a 2-year period before dialysis and to examine the differences among trajectory groups.

We examined the association between trajectory group, and 2-year and 5-year mortality after dialysis using Kaplan–Meier curves with log-rank tests and Cox proportional hazard models. We estimated the hazard ratios adjusted for sex, age, and diabetes. All analyses were performed using

SAS 9.4 (SAS Institute Inc., Cary, NC, USA; www.sas.com). A two-sided p value < 0.05 was considered statistically significant.

Results

Among 1758 subjects with CKD stages 3b to 5, a median of 26 (IQR = 18–39) serum creatinine levels was measured during the 2-year period before dialysis initiation. Most patients had at least one serum creatinine measurement in six out of eight quarters of 24 months. Using time-varying eGFR changes, we identified three distinct eGFR trajectories among the study participants (Figure 2 and Table 2). Trajectory group 1 accounted for 71.2% of the patients and was characterized by persistently low eGFR levels with a low initial eGFR value of $12.4 \pm 4.5 \, \text{ml/min/1.73 m}^2$ and a low decline rate of $1.0–1.3 \, \text{ml/min/1.73 m}^2$ per biannual. Trajectory group 2 accounted for 25.6% of patients and was characterized by a progressive loss of eGFR with an intermediate initial eGFR value of $27.5 \pm 6.9 \, \text{ml/min/1.73 m}^2$ and an intermediate decline rate of $2.9–3.4 \, \text{ml/min/1.73 m}^2$ per biannual. Trajectory group 3 accounted for 3.2% of patients and was characterized by an accelerated loss of eGFR with a high initial eGFR of $58.9 \pm 16.7 \, \text{ml/min/1.73 m}^2$ and a fast decline rate of $4.1–8.6 \, \text{ml/min/1.73 m}^2$ per biannual. The trajectories of median quarterly eGFR corresponded

Table 2. Patient characteristics of study samples across three trajectory groups.

	Overall (*n* = 1758)	Group 1 (*n* = 1252)	Group 2 (*n* = 450)	Group 3 (*n* = 56)	*p* value
Age (years), mean ± SD	62.39 ± 14.21	63.03 ± 13.66	61.59 ± 15.03	54.54 ± 16.93	<0.0001
Age at dialysis					<0.0001
<50 years	273 (15.53)	169 (13.50)	83 (18.44)	21 (37.50)	
50–74 years	964 (54.84)	692 (55.27)	246 (54.67)	74 (46.43)	
≥75 years	521 (29.64)	391 (31.23)	121 (26.89)	33 (16.07)	
Male sex	1005 (58.17)	638 (50.96)	334 (74.22)	33 (58.93)	<0.0001
Diabetes	882 (50.17)	593 (47.36)	260 (57.78)	29 (51.79)	<0.001
Hypertension	1211 (68.89)	873 (69.73)	305 (67.78)	33 (58.93)	0.20
CHF	85 (4.84)	55 (4.39)	27 (6.00)	3 (5.36)	0.39
IHD	162 (9.22)	110 (8.79)	46 (10.22)	6 (10.71)	0.62
CVD	51 (2.9)	34 (2.72)	17 (3.78)	0 (0)	0.22
Data at dialysis initiation					
eGFR (ml/min/1.73 m^2)	5.7 ± 3.0	4.9 ± 1.7	7.6 ± 3.8	10.1 ± 6.1	<0.0001
BUN (mg/dl)	99.2 ± 24.8	102.7 ± 24.6	90.9 ± 22.8	86.6 ± 24.3	<0.0001
UPCR (mg/g)	3805 (2153–6923)	3481 (2060–5822)	4340 (2391–8127)	7053 (2480–11036)	<0.0001
Uric acid (mg/dl)	7.7 ± 2.3	7.7 ± 2.3	7.7 ± 2.5	8.2 ± 2.7	0.39
Urine protein (mg/dl)	194 (74–399)	180 (76–356)	244 (70–468)	443 (73–622)	<0.0001
Urine creatinine (mg/dl)	70 (54–91)	68 (53–89)	73 (56–99)	70 (53–87)	<0.0001
Triglyceride (mg/dl)	139.8 ± 79.0	136.3 ± 71.8	146.7 ± 93.6	155.5 ± 90.2	0.10
Calcium (mg/dl)	8.3 ± 0.8	8.3 ± 0.9	8.2 ± 0.8	8.1 ± 0.6	0.01
Phosphate (mg/dl)	5.8 ± 1.4	5.8 ± 1.4	5.6 ± 1.4	5.7 ± 1.5	0.07
Potassium (mmol/l)	4.6 ± 0.6	4.7 ± 0.6	4.6 ± 0.6	4.3 ± 0.6	<0.0001
Sodium (mmol/l)	135.4 ± 4.8	135.3 ± 4.7	135.5 ± 4.7	135.5 ± 6.2	0.82
Albumin (g/dl)	3.6 ± 0.5	3.7 ± 0.5	3.5 ± 0.5	3.2 ± 0.5	<0.0001
WBC (k/µl)	7.1 ± 3.2	7.0 ± 3.4	7.4 ± 2.7	8.0 ± 2.9	0.01
Hemoglobin (g/dl)	9.1 ± 1.2	9.1 ± 1.2	9.1 ± 1.3	9.0 ± 1.1	0.50
MCHC (g/dl)	32.9 ± 1.2	32.8 ± 1.2	33.1 ± 1.2	33.4 ± 1.4	<0.0001
Platelet (k/µl)	182.7 ± 64.3	181.0 ± 61.5	186.8 ± 71.2	190.4 ± 66.6	0.17
Outcome					
Death	691 (39.31)	469 (37.46)	196 (43.56)	26 (46.43)	0.04
Follow-up time (years)	3.2 (1.6–5.8)	3.4 (1.7–6)	3.0 (1.1–6)	2.7 (1.3–7)	0.01

ANOVA: analysis of variance; BUN, blood urea nitrogen; CHD, congestive heart failure; CVD, cardiovascular disease; IHD, ischemic heart disease; MCHC, mean corpuscular hemoglobin concentration; SD, standard deviation; UPCR, urine protein–creatinine ratio; WBC, white blood cell.
Continuous variables are given as mean ± standard deviation or median (IQR) and analyzed by the ANOVA test and the Kruskal–Wallis test as appropriate; categorical variables are given as number (%) and analyzed by chi-square test.
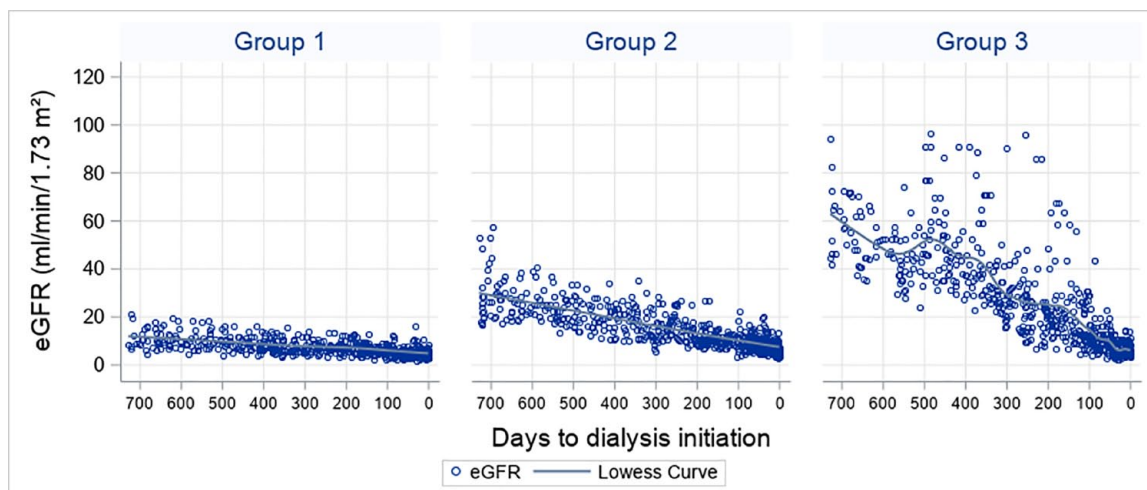
Figure 3. All eGFR measurements during the 2-year period before dialysis initiation from the 25 randomly study samples of each trajectory group.
The empty dots represent the eGFR measurements, and the solid lines shows the Lowess curves.

Table 3. Adjusted risk of death over 2-year and 5-year period after dialysis initiation by trajectory group.

Follow-up time	Group 1 (n = 1252)	Group 2 (n = 450)	Group 3 (n = 56)	*p* for trend
2 years	Reference	1.61 (1.25–2.08)	3.22 (1.94–5.34)	<0.0001
5 years	Reference	1.36 (1.12–1.66)	2.48 (1.61–3.80)	<0.0001
Until the end of 2020	Reference	1.33 (1.12–1.59)	1.77 (1.18–2.64)	<0.0001

Adjusted for sex, age, and diabetes. Cox proportional hazard model was used to estimate the association between trajectory group and mortality. The Cochran–Armitage trend test was used to assess whether a trend is present.

well with Lowess curves generated using all eGFR values from a random sample of patients in each trajectory group (Figure 3).

The patients with a progressive or accelerated loss of eGFR (groups 2 and 3) were younger, predominantly male, and more likely to have diabetes (Table 3). There were no significant differences in hypertension, congestive heart disease, ischemic heart disease, or cerebrovascular disease among the trajectory groups. At the time of dialysis initiation, biochemical markers, such as eGFR, blood urea nitrogen (BUN), UPCR, calcium, potassium, albumin, and hemograms, such as WBC and MCHC, were statistically different among the trajectory groups. Figure 4 shows a secular trend of biomarkers that were significantly different among the three trajectory groups, including biochemical markers, such as BUN, albumin, potassium, and UPCR, and hemogram markers, such as WBC, hemoglobin, MCHC, and platelets. Compared with trajectory group 1, trajectory groups 2 and 3 were associated with a more rapid increase in BUN and UPCR levels, especially in the year before dialysis initiation. Moreover, groups 2 and 3 were associated with a more rapid decline in hemoglobin and platelet counts. A rapid eGFR decline was associated with lower levels of albumin and potassium and higher levels of MCHC and WBC. The albumin level in trajectory group 3 was below the normal range (3.5 g/dl). The values of potassium, MCHC, and WBC counts were within the normal range across the 2-year period before dialysis in all three groups. Other biomarkers that did not differ among the three trajectory groups are shown in Supplementary Figure S1.

Overall, there were a total of 691 (39.3%) deaths observed during the follow-up period. In the
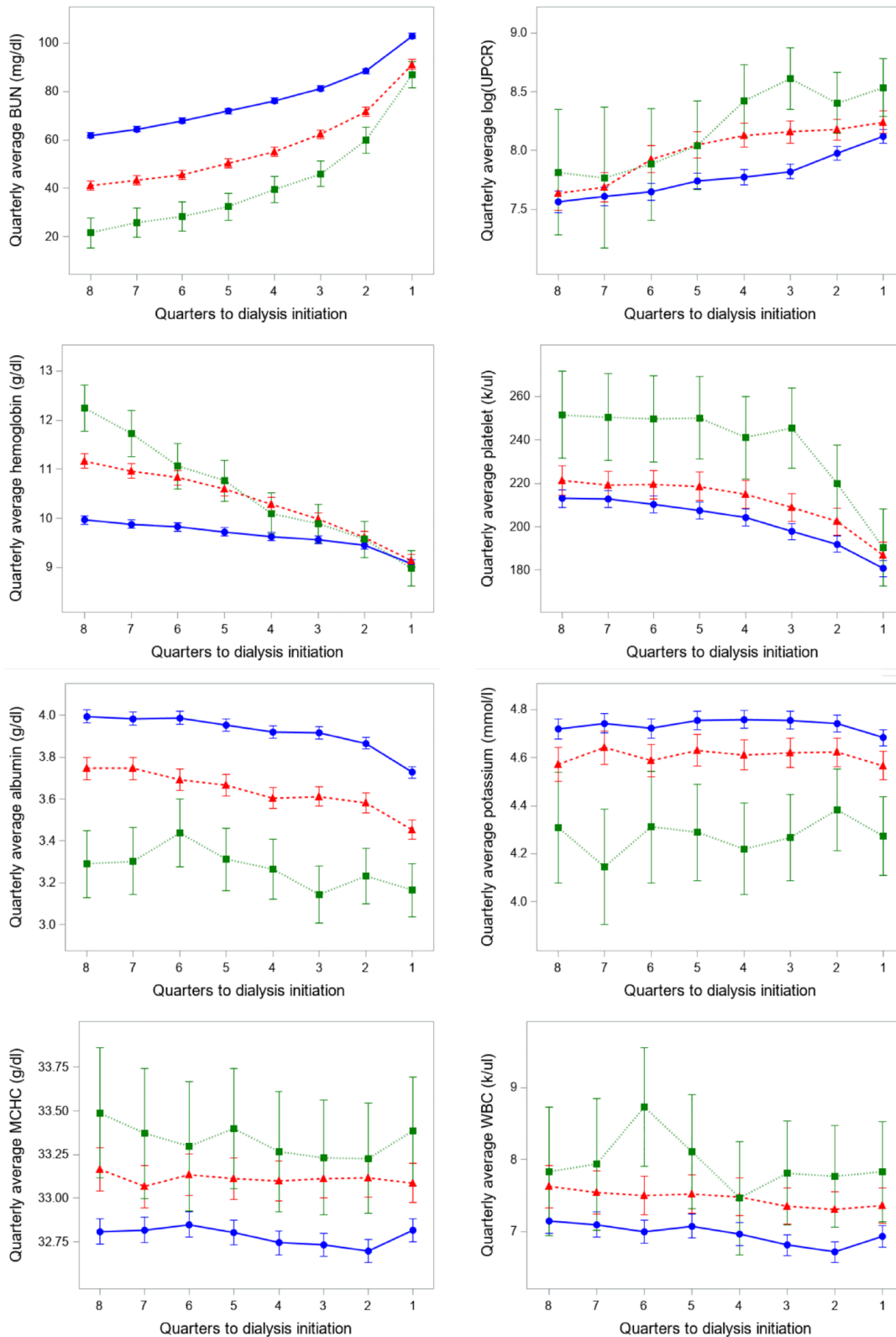
Figure 4. Changing trends of biomarkers during 2 years before dialysis initiation.
The changing trends were shown with error bars. Trajectory groups 1, 2, and 3 were shown in circles with blue lines, triangles with red lines, and squares with green lines, respectively.
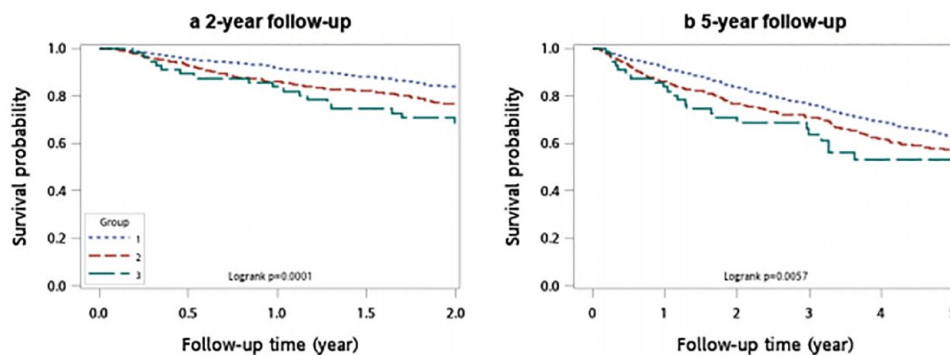
Figure 5. Kaplan–Meier curves for survival after dialysis in each trajectory group: (a) 2-year follow-up and (b) 5-year follow-up.
Trajectory groups 1, 2, and 3 were shown in blue, red lines, and green lines, respectively.

Table 4. Initial and mean changes of eGFR values before dialysis in each trajectory group.

	Initial eGFR (mean ± SD)	Mean change of eGFR* (least-square mean change ± SEM [95% CI])			
		24 m to 18 m	18 m to 12 m	12 m to 6 m	6 m to dialysis
Group 1	12.4 ± 4.5	−1.2 ± 0.1	−1.1 ± 0.1	−1.0 ± 0.1	−1.3 ± 0.1
Group 2	27.5 ± 6.9	−2.9 ± 0.2	−2.9 ± 0.2	−3.2 ± 0.1	−3.4 ± 0.1
Group 3	58.9 ± 16.7	−4.1 ± 0.7	−4.8 ± 0.5	−8.0 ± 0.4	−8.6 ± 0.3

eGFR, estimated glomerular filtration rate; CI, confidence interval; SD, standard deviation; SEM, standard error of the mean.
A repeated-measures linear mixed model was used.
*p values for mean changes of eGFR were all <0.0001.

2-year and 5-year follow-up, 302 (17.2%) and 549 (31.2%) deaths were observed, respectively. The corresponding median follow-up times were 2 years (IQR = 1.6–2.0) and 3.3 years (IQR = 1.6–5.0). Kaplan–Meier survival plots showed that the eGFR trajectory was significantly associated with the risk of mortality 2 years and 5 years after dialysis, with the log-rank test $p = 0.0057$ and $p = 0.0001$, respectively (Figure 5). After multivariate adjustment, compared with the trajectory group 1, trajectory groups 2 and 3 had a higher risk of mortality with hazard ratio (HR) and 95% confidence interval (CI) = 1.61 (1.25–2.08), 3.22 (1.94–5.34), $p < 0.0001$, respectively (Table 4).

Discussion
In this study, we applied group-based trajectory modeling and clustered three groups of patients using longitudinal eGFR measurements in the 2-year period prior to long-term dialysis initiation. Patients with accelerated loss of eGFR were younger, predominantly male, and were more likely to have diabetes. We demonstrated that the more rapid the eGFR decline, the worse the survival rate after dialysis. Along with eGFR decline, the BUN and UPCR levels significantly increased, while hemoglobin and platelet counts decreased. The changing trend was especially significant in the group with an accelerated loss of eGFR. It is worth noting that hypoalbuminemia was found to accompany the accelerated loss of eGFR, even though the level of albumin remained stable across different trajectory groups.

The predialysis eGFR trajectory has prognostic potential for postdialysis mortality. It is critical to analyze the eGFR trajectories of patients for better personalized care of patients with CKD. Previous studies that explored the association

between predialysis eGFR changes and survival after dialysis are listed in Supplementary Table S2. Among these, O'Hare *et al.*[18] first used trajectory modeling to characterize four distinct predialysis eGFR trajectories. They found patients with steeper eGFR trajectories were more likely to have been hospitalized, have experienced acute kidney injury, and had a higher risk of death in the first year after dialysis. Thereafter, Hsu *et al.*[31] classified incident hemodialysis patients into two groups based on an abrupt decline in kidney function. Abrupt onset was defined as an eGFR value $\geq 30\,\text{ml/min/1.73\,m}^2$ to ESRD in 3 months. An abrupt decline in kidney function was associated with a three-fold higher risk for death within the first year of hemodialysis. Whether using trajectory modeling or linear mixed-effects model, the subsequent studies, in general, all studies including this study concluded that the more rapid the eGFR decline, the higher the risk for postdialysis death within 2 years.[18,28–31] Regarding long-term (>2 years) mortality, the findings were inconsistent. Similar to this study, O'Hare *et al.*[18] showed that the amplitude of hazards gradually decreased over time in each trajectory group; however, Santos *et al.*[30] observed the opposite trend. This was because Santos *et al.*[30] focused on elderly patients with CKD, and this population tended to have a higher mortality rate than the younger population.

We further examined the trends of different biomarkers in the three trajectories. The trajectory of the rapid decline in eGFR had persistently lower serum albumin levels and higher UPCR compared with the other two trajectory groups throughout the follow-up period. The results showed that proteinuria was a strong determinant of CKD progression and ESRD development. Proteinuria was also a significant risk factor for cardiovascular disease and mortality, which partially explains why trajectory group 3 had the worst outcomes after dialysis. The reason for hypoalbuminemia in the accelerated eGFR loss group may be not only due to persistent urine protein loss but also due to malnutrition-inflammation status. We noticed that trajectory group 3 also had a higher WBC count and platelet levels, which implied that chronic inflammation may be more severe in the group with rapid eGFR loss. Chronic inflammation is associated with the incidence and progression of CKD. Higher c-reactive protein (CRP) and soluble tumor necrosis factor (TNF) receptor 2 levels were demonstrated to

be independently associated with faster rates of kidney function loss.[32] Elevated fibrinogen and TNF-α levels and decreased serum albumin were found to be associated with a rapid loss of kidney function in patients with CKD.[33] Our findings were consistent with those of previous studies.

The levels of some electrolytes increase while the eGFR declines, such as potassium or phosphate, some, such as sodium, remain the same, and some, such as calcium, decrease while the eGFR declines. Electrolyte imbalance, such as hyperphosphatemia, hypocalcemia, and hyperkalemia, is observed when the eGFR decreases to less than $60\,\text{ml/min/1.73\,m}^2$ and is thought to be the consequence of kidney function deterioration. The changes in serum electrolytes, however, are not risk factors for CKD progression, except for potassium levels. In a US study, hypokalemia was associated with faster CKD progression independent of race; however, hyperkalemia management may warrant race-specific consideration, as black individuals have a better tolerance to high potassium levels than white individuals. The correction of hypokalemia may slow CKD progression.[34] This study also showed that potassium was lower in the most accelerated renal loss group, and the trends of other electrolytes did not differ in the three trajectories.

Renal anemia usually develops when the eGFR decreases to less than $60\,\text{ml/min/1.73\,m}^2$.[35] Anemia is believed to play a deleterious role in kidney function. This evidence is based mostly on experimental data that imply that tubule-interstitial damage due to hypoxia is associated with CKD and, thus, the progression of renal failure.[36] On the contrary, the correction of anemia, by iron supplement or erythropoietin, alleviates the progression of CKD.[37] In this study, serum hemoglobin level decreased sharply in trajectory 3, the most accelerated renal function loss group. Our findings echo those of some previous studies, although anemia as a consequence or promoter of kidney function progression remains to be proven.

The main strength of this study is that we investigated the longitudinal trends of CKD-relevant biomarkers rather than the single time point values to clearly depict the physiological changes as the disease progresses. The biomarkers cover kidney, hematologic, lipid, electrolyte, and inflammation markers. Furthermore, the changing trends of biomarkers among three eGFR

trajectory groups were compared. Finally, the data were comprehensively obtained from an electronic medical record research database. This study had several limitations. First, the patient medication information was not incorporated. As the trajectories of biomarkers are time-varying, the effects of medications are presented in the sequential changes in data. Second, we included patients with CKD stages 3b and 5; therefore, the interpretation cannot be extended to the earlier stages of CKD. Third, we used routinely collected laboratory data from NTUH-IMD in the models, and novel CKD biomarkers were not available in this study. As stated earlier, our model is practical and can be easily replicated in most CKD cohorts. Finally, this study population was predominantly Han Chinese; therefore, the results may not be generalizable to other populations.

Conclusion

To conclude, we characterized three distinct predialysis eGFR trajectory groups in patients with advanced CKD using longitudinal data. Our results demonstrated that eGFR decline rates were associated with a higher risk of postdialysis mortality. We further delineated the changes in CKD biomarkers along with disease progression and found that abrupt eGFR decline was concurrent with the rapid increase in BUN, UPCR, and WBC count, as well as a decline in hemoglobin, platelet, albumin, and potassium levels, especially in the last year before dialysis initiation. Further studies are warranted to determine the determinants of the trajectories and their impact on renal and all-cause outcomes.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Ethics Review Board of NTUH (NTUH-REC no. 202006161RINA). Informed consent was waived due to the local regulations for research using de-identified data.

Consent for publication
Not applicable.

Author contributions
Hsiao-Mei Tsao: Conceptualization; Formal analysis; Methodology; Writing – original draft.

Tai-Shuan Lai: Conceptualization; Data curation; Funding acquisition; Writing – original draft; Writing – review & editing.

Yu-Hsiang Chou: Conceptualization; Writing – review & editing.

Shuei-Liong Lin: Conceptualization; Writing – review & editing.

Yung-Ming Chen: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials
The data that supports the findings of this study are available from the NTUH pre-ESRD and NTUH-IMD. According to the restrictions of data availability, the data can only be used under license for this study and are not publicly available.

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Supplemental material
Supplemental material for this article is available online.

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