Comparison of Outcomes of Chronic Kidney Disease Based on Etiology: A Prospective Cohort Study

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Abstract

Background and objectives

The cause of chronic kidney disease (CKD) affects outcomes. However, relative risks for adverse outcomes according to specific causes of CKD are not well studied.

Design, setting, participants and measurements

Prospective cohort study from KNOW-CKD cohort were analyzed using overlap propensity score weighting methods. Patients were grouped into four categories according to the cause of CKD: glomerulonephritis (GN), diabetic nephropathy (DN), hypertensive nephropathy (HTN), or polycystic kidney disease (PKD). From a total of 2,070 patients, the relative risk of kidney failure, composite of cardiovascular disease (CVD) and mortality, and the slope of the estimated glomerular filtration rate (eGFR) decline according to the cause of CKD were compared between causative groups pairwise.

Results

There were 565 cases of kidney failure and 259 cases of composite CVD and death over 6.0 years of follow-up. Hazard ratios of the PKD group for kidney failure were significantly increased at 1.82, 2.23, and 1.73 compared to GN, HTN, and DN, respectively. Hazard ratios of the DN group for the composite of CVD and death were also significantly increased at 2.07, and 1.73 compared to GN, and HTN, respectively. The adjusted eGFR decline slope for DN and PKD groups was -3.07, and -3.37 mL/min/1.73m² per year, respectively, and all of these values were significantly different than those of the GN and HTN groups (-2.16, and -1.42 mL/min/1.73m² per year, respectively).

Conclusions

Risks for renal progression were relatively higher in patients with PKD compared to other causes of CKD. However, the composite of CVD and death were relatively higher in patients with DN-related CKD than those with GN- and HTN-related CKD.

Introduction

Prevalence and incidence of chronic kidney disease (CKD) is increasing worldwide due to an increase in the number of patients at risk, namely older patients and those with diabetes, hypertension, and/or obesity.¹⁻⁴

CKD is a heterogeneous set of diseases caused by various comorbid conditions. Although the CKD patients share similar pathophysiology involved with the renal progression, the course and speed of CKD progression and associated complications differ according to the underlying causes. Therefore in the KDIGO guideline, the cause of CKD is considered one of the important predictors of the outcome, together with other variables such as glomerular filtration rate category, albuminuria category, and other comorbid conditions.⁵ Although the cause of CKD is important in predicting outcomes, the relative risk for adverse outcomes according to the specific cause of CKD has not been well studied.⁶ This might be due to the difficulty of the study design

and analysis technique since many risk factors of renal progression are related to the cause of CKD and can act as potential confounders. Direct comparison of outcomes according to the specific cause of CKD is important to understand the natural progression of CKD and characterize possible complications according to the cause of CKD. This is critical for CKD management during the predialysis period, both to slow progression and to improve long-term outcomes. In addition, this knowledge can help determine high-risk groups among the CKD population so that resources can be prioritized and therapies can be more targeted.

A few studies have investigated relative risks for adverse outcomes in the CKD population according to specific causes.⁷⁻¹⁰ *Post-hoc* study of a clinical trial showed that those participants with polycystic kidney disease (PKD) had a higher risk of kidney failure and lower risk of death than those with CKD with other etiologies.⁷ Studies of Canadian Study of Prediction of Death, Dialysis and Interim Cardiovascular Events (CanPREDDICT) cohort data reported the relative risks of adverse outcomes according to the CKD etiologies.^{8,9} CKD in Children (CKiD) study compared the rate of progression of renal disease according to the cause of CKD in children.¹⁰ However, these studies did not cover all of the major CKD etiologies or stages or address all major outcomes. Due to the limitations, the results cannot be extrapolated to the entire adult CKD population.

In this study, we analyzed the relative risks for renal progression and the composite outcome of cardiovascular disease (CVD) and all-cause mortality according to the cause of CKD in a prospective cohort. To investigate the effects of the causes of CKD on the outcomes, overlap weighted methods were used to adjust the possible confounding factors. Additionally, we analyzed annual rates of estimated glomerular filtration rate (eGFR) decline according to the cause of CKD to determine renal progression patterns according to CKD etiology.

Methods

This was a longitudinal study of a prospective cohort of CKD patients in Korea (KNOW-CKD). KNOW-CKD is a multicenter prospective cohort study that enrolled adult predialysis patients with CKD stages G1 to G5.¹¹ Patients were classified into four groups according to the specific cause of CKD at enrollment: glomerulonephritis (GN), diabetic nephropathy (DN), hypertensive nephropathy (HTN), and PKD. Group classification was determined based on pathologic diagnosis if a biopsy result was available (27.8% of total subjects and 67.0% of GN group). Otherwise, group classification was based on clinical diagnosis. GN was defined as the presence of albuminuria or glomerular hematuria with or without an underlying systemic disease causing GN. The active GN population taking immunosuppressant at enrollment was excluded. Diagnosis of DN was strictly based on albuminuria in a subject with type 2 diabetes and the presence of diabetic retinopathy and absence of glomerular hematuria. HTN was diagnosed by a history of hypertension and the absence of a systemic illness associated with renal damage. Patients with < 1.5g/day the proportion of urine albumin < 50% of urine protein were included in HTN. To diagnose PKD, unified ultrasound criteria were used.¹² Other causative diseases was categorized as 'unclassified' and excluded from our analysis. Among the total of 2,238 subjects enrolled at study entry, finally, 2,070 subjects were analyzed in this study. To determine the eGFR slope and trajectory, we included only those subjects (n =

1,952) with more than two creatinine measurements (Fig. 1). Written informed consent from each patient was collected voluntarily at the time of enrollment. The study was approved by the institutional review board of each participating hospital: Chonnam National University Hospital (CNUH-2011-092), Eulji General Hospital (201105-01), Gil Hospital (GIRBA2553), Kangbuk Samsung Medical Center (2011-01-076), Pusan Paik Hospital (11-091), Seoul National University Bundang Hospital (B-1106/129-008), Seoul National University Hospital (H-1704-025-842), Seoul St. Mary's Hospital (KC11OIMI0441), and Yonsei University Severance Hospital (4-2011-0163). This study follows the guidelines of the 2008 Declaration of Helsinki.

Demographic details and medication history were collected at enrollment. Serum creatinine was measured at each study visit by a central laboratory (Lab Genomics, Seoul, Republic of Korea) using an isotope dilution mass spectrometry-traceable method. For eGFR, the CKD Epidemiology Collaboration equation based on serum creatinine was used.¹³ After the entry visit, subjects were followed-up at 6 and 12 months and then every 1 year until death or drop-out and follow-up events were recorded. Patients who were lost to follow-up were censored at the last follow-up visit with respect to renal and CVD events. Death and the cause of death were collected using either hospital medical records or data from the National Database of Statistics Korea using the Korean resident registration number. Data were collected until whichever came first: drop-out, death, or March 31, 2020.

Both kidney failure and the composite of kidney failure and/or creatinine doubling were used as renal outcomes. Kidney failure was defined as starting maintenance dialysis (required longer than 3 months) or receiving kidney transplantation. Another outcome was the composite outcome of CVD and all-cause death. CVD was defined as any first event of the following during the follow-up: acute myocardial infarction, unstable angina, percutaneous coronary artery intervention or coronary bypass graft surgery, ischemic or hemorrhagic cerebral stroke, cerebral artery aneurysm, congestive heart failure, symptomatic arrhythmia, aggravated valvular heart, pericardial disease, abdominal aortic aneurysm, or severe peripheral arterial disease that needed hospitalization, intervention, or therapy.

The Chi-square test or t-test was used for the baseline characteristics comparison. Non-normally distributed variables were log transformed for comparison. The four groups had significant differences in baseline characteristics including age and baseline eGFR; we therefore used the overlap propensity score weighting method to minimize the effects of confounding factors on outcomes.¹⁴ Propensity scores (PS) were calculated using a generalized logit model with the following variables: age, sex, body mass index, CKD stage, mean blood pressure, CVD, hemoglobin, serum uric acid, calcium, phosphorous, albumin, total cholesterol, high-density lipid, low-density lipid, fasting blood sugar, intact parathyroid hormone, urine protein-to-creatinine ratio, high-sensitivity C-reactive protein, diuretics use, statin use, and angiotensin converting enzyme inhibitor or angiotensin receptor blocker use. The patients in the compared group were weighted by the probability reference group (1-PS) and the patients in the reference group were weighted by the probability of compared group (PS). For two groups of CKD causes, we applied the overlap weighting method on each set, resulting in a total of 6 sets. In outcome comparison analysis, a Cox proportional hazard model was used for renal outcomes, and a cause-specific hazard model was used for the composite of CVD and death. In the competing risk model for the composite of CVD and death, kidney failure was considered a competing risk since many patients who started renal replacement therapy were no longer

followed for further event thereafter. Results are presented as hazard ratio (HR) and 95% confidence interval (95%CI). To estimate annual eGFR change, generalized linear mixed models were constructed with random intercept and slope with an unstructured model for the correlation structure. The result was expressed as estimates (standard errors). In the adjusted models, the variables used in PS score calculation were further adjusted. Spaghetti plots showing the individual trajectories of eGFR during follow-up were drawn to determine patterns of eGFR decline according to cause of CKD. *P* for quadratic term was tested using polynomial mixed models with random intercept and slope. *P* < 0.05 was considered to indicate statistical significance. SAS 9.4 (SAS Institute, Cary, NC) and R version 3.5.3 (Foundation for Statistical Computing, Vienna) were used.

Results

Mean age of the population was 53.5 ± 12.2 years and 38.7% were female in a total of 2,070 subjects. At study entry, mean eGFR of total subjects was 53.2 ± 30.8 mL/min/1.73m². There were 38.6% in GN, 24.5% in DN, 19.5% in HTN, and 17.4% in PKD.

Table 1 shows the differences in baseline characteristics between the CKD etiology groups. All variables showed significant differences among groups. After overlap weighting for each set, the statistical differences disappeared and standardized mean difference was < 0.001 for all variables in all sets (**Table S1**).

Table 1
Comparison of baseline clinical characteristics according to cause of chronic kidney disease before IPTW matching

	Glomerulonephritis	Hypertensive nephropathy	Diabetic Nephropathy	Polycystic kidney disease	<i>P</i> value	<i>SMD</i>
Number	799	404	507	360		
Age, years	49.7 ± 12.1	59.7 ± 10.8	59.3 ± 9.3	47 ± 10.7	< 0.001	0.74
Female, %	44.6	27.5	31	49.2	< 0.001	0.28
BMI, kg/m²	24.2 ± 3.3	25.1 ± 3.5	25.3 ± 3.3	23.5 ± 3	< 0.001	0.32
Mean blood pressure, mmHg	91.6 ± 10.5	94.3 ± 11.8	95.3 ± 12.9	96.8 ± 10.4	< 0.001	0.25
Prevalence of cardiovascular disease, %	7.9	23.8	26.4	6.9	< 0.001	0.35
eGFR, ml/min/1.73m²	60.1 ± 31.4	42.3 ± 21.9	36.4 ± 21.8	72.7 ± 32.8	< 0.001	0.77
Chronic kidney disease stage					< 0.001	0.79
G1, %	3.7	3.7	4.1	35.0		
G2, %	13.9	13.9	7.7	26.9		
G3a, %	22.5	22.5	14.6	13.3		
G3b, %	27.2	27.2	26.0	11.9		
G4, %	26.2	26.2	35.9	9.2		
G5, %	6.4	6.4	11.6	3.6		
Hemoglobin, g/dL	13.2 ± 1.9	13.3 ± 2	11.7 ± 1.8	13.3 ± 1.7	< 0.001	0.44
Uric acid, mg/dL	7.1 ± 1.9	7.3 ± 1.8	7.4 ± 1.9	6.1 ± 1.7	< 0.001	0.39
Calcium, mg/dL	9.1 ± 0.5	9.2 ± 0.5	8.9 ± 0.6	9.3 ± 0.4	< 0.001	0.34
Phosphorous, mg/dL	3.6 ± 0.6	3.6 ± 0.6	4 ± 0.8	3.6 ± 0.6	< 0.001	0.30

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HDL, high density lipid; Hs-CRP, high sensitivity-C reactive protein; IPTW, inverse probability of treatment weighting; LDL, low density lipid; SMD; standardized mean difference

	Glomerulonephritis	Hypertensive nephropathy	Diabetic Nephropathy	Polycystic kidney disease	<i>P</i> value	<i>SMD</i>
Albumin, g/dL	4.1 ± 0.4	4.3 ± 0.3	4.0 ± 0.5	4.4 ± 0.3	< 0.001	0.63
Total Cholesterol, mg/dL	178.4 ± 38.5	169.1 ± 35.5	167.4 ± 43.8	179.0 ± 33.6	< 0.001	0.19
HDL-cholesterol, mg/dL	51.5 ± 15.6	46.7 ± 14.0	43.6 ± 14.0	54.4 ± 13.9	< 0.001	0.43
LDL-cholesterol, mg/dL	99.9 ± 32.1	94.1 ± 30.5	91.1 ± 34.0	101.6 ± 26.7	< 0.001	0.2
Fasting blood sugar, mg/dL	102.1 ± 24.7	106.7 ± 25.8	136.4 ± 59.0	96.1 ± 11.0	< 0.001	0.57
Log (parathyroid hormone, pg/mL)	3.8 ± 0.7	4.1 ± 0.7	4.3 ± 0.8	3.8 ± 0.8	< 0.001	0.35
Log (urine Protein/creatinine, g/g Cr)	-0.5 ± 1.2	-1.3 ± 1.4	0.2 ± 1.4	-2.2 ± 1.1	< 0.001	0.35
Log (hs-CRP, mg/dL)	-0.5 ± 1.3	-0.2 ± 1.4	-0.3 ± 1.3	-0.7 ± 1.4	< 0.001	0.22
Diuretics use, %	24.9	34.9	56.4	9.4	< 0.001	0.59
Statin use, %	51.6	57.4	63.9	26.9	< 0.001	0.41
ACEI or ARB use	89.7	82.2	87.0	78.6	< 0.001	0.18
Follow up duration, years	6.0 [4.4, 7.2]	5.0 [4.0, 7.0]	6.0 [4.2, 7.2]	6.6 [4.2, 8.0]		
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1C; HDL, high density lipid; Hs-CRP, high sensitivity-C reactive protein; IPTW, inverse probability of treatment weighting; LDL, low density lipid; SMD; standardized mean difference						

During the median 6.0 years of follow-up, there were a total of 565 (27.3%) kidney failure events and 723 (34.9%) composite renal events. There were a total of 259 (12.5%) events of the composite of CVD and death. Patients with PKD had a significantly increased risk for kidney failure compared to GN (HR 1.82, 95%CI 1.25–2.65), HTN (HR 2.23, 95%CI 1.47–3.38), and DN (HR 1.73, 95%CI 1.05–2.86) groups in Cox regression analysis. However, the DN, HTN, and GN groups did not show a significant difference in the risk of kidney failure or composite renal outcome compared to each other (Table 2). Results were similar for the composite renal outcome. DN groups had increased risks for the composite outcome of CVD and death than the GN (HR 2.07, 95%CI 1.23–3.46), and HTN (HR 1.73, 95%CI 1.08–2.78) groups in cause-specific regression analysis. Patients with DN did not have an increased risk of the composite of CVD and death compared to patients with PKD (*P* = 0.169). Similar results were obtained for DN in multivariate Cox

regression analyses. PKD showed increased risk of the composite of CVD and death compared to GN (HR 3.11, 95%CI 1.59–6.05) and HTN (HR 1.94, 95%CI 1.03–3.65) only in the Cox regression analysis (Table 3).

Table 2
Relative risk for renal outcomes according to the CKD causes

kidney failure			Composite renal outcome	
Cause of CKD	HR (95%CI)	P-value	HR (95%CI)	P-value
Glomerulonephritis	Reference		Reference	
Hypertensive nephropathy	0.88 (0.64–1.21)	0.429	0.80 (0.60–1.07)	0.129
Diabetic nephropathy	1.20 (0.92–1.57)	0.176	1.18 (0.93–1.49)	0.182
Polycystic kidney disease	1.82 (1.25–2.65)	0.002	2.00 (1.46–2.75)	< 0.001
kidney failure			Composite renal outcome	
Cause of CKD	HR (95%CI)	P-value	HR (95%CI)	P-value
Hypertensive nephropathy	Reference		Reference	
Diabetic nephropathy	1.28 (0.94–1.74)	0.111	1.27 (0.96–1.69)	0.093
Polycystic kidney disease	2.23 (1.47–3.38)	< 0.001	2.50 (1.71–3.66)	< 0.001
kidney failure			Composite renal outcome	
Cause of CKD	HR (95%CI)	P-value	HR (95%CI)	P-value
Diabetic nephropathy	Reference		Reference	
Polycystic kidney disease	1.73 (1.05–2.86)	0.032	1.87 (1.17–2.97)	0.008
CI, confidence interval; CKD, chronic kidney disease; HR; hazard ratio				

Table 3
Relative risk for composite outcome of CVD and all-cause death according to the CKD causes

Cox regression analysis			Cause-specific regression analysis	
Cause of CKD	HR (95%CI)	P-value	HR (95%CI)	P-value
Glomerulonephritis	Reference		Reference	
Hypertensive nephropathy	0.97 (0.59–1.59)	0.901	1.24 (0.71–2.15)	0.447
Diabetic nephropathy	1.67 (1.09–2.56)	0.019	2.07 (1.23–3.46)	0.006
Polycystic kidney disease	3.11 (1.59–6.05)	< 0.001	2.84 (1.36–5.93)	0.006
Cox regression analysis			Cause-specific regression analysis	
Cause of CKD	HR (95%CI)	P-value	HR (95%CI)	P-value
Hypertensive nephropathy	Reference		Reference	
Diabetic nephropathy	1.82 (1.19–2.79)	0.006	1.73 (1.08–2.78)	0.022
Polycystic kidney disease	1.94 (1.03–3.65)	0.041	1.41 (0.70–2.85)	0.334
Cox regression analysis			Cause-specific regression analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Diabetic nephropathy	Reference		Reference	
Polycystic kidney disease	1.84 (0.93–3.63)	0.079	1.74 (0.79, 3.84)	0.169
CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR; hazard ratio				

The eGFR slope of GN, HTN, DN and PKD groups was – 2.19, -1.44, -3.17, and – 3.45 mL/min/1.73m² per year, respectively. In the adjusted model, the rate of eGFR decline was – 2.16, -1.42, -3.07, and – 3.37 mL/min/1.73m² per year for the GN, HTN, DN and PKD groups, respectively. DN and PKD groups had faster rates of decline than GN and HTN, while the HTN group had slower rate of eGFR decline than the GN group (Table 4).

Table 4
Annual changes in estimated glomerular filtration rates according to the cause of CKD

	Annual changes of eGFR (mL/min/1.73 m ² per year)			
	Unadjusted		Adjusted [¶]	
Cause of CKD	Estimate (Standard error)	P-value	Estimate (Standard error)	P-value
		< 0.001 ¹		< 0.001 ¹
Glomerulonephritis	-2.19 (0.106)		-2.16 (0.106)	
Hypertensive nephropathy	-1.44 (0.151)	< 0.001 ²	-1.42 (0.152)	< 0.001 ²
Diabetic nephropathy	-3.17 (0.16)	< 0.001 ²	-3.07 (0.161)	< 0.001 ²
		< 0.001 ³		< 0.001 ³
Polycystic kidney disease	-3.45 (0.155)	< 0.001 ²	-3.37 (0.156)	< 0.001 ²
		< 0.001 ³		< 0.001 ³
		0.201 ⁴		0.176 ⁴
[¶] Adjusted with age, sex, body mass index, CKD stage, mean blood pressure, cardiovascular disease, hemoglobin, uric acid, calcium, phosphorous, albumin, total cholesterol, high-density lipid cholesterol, low-density lipid cholesterol, fasting blood sugar, intact parathyroid hormone, urine protein-to-creatinine ratio, high sensitivity C-reactive protein, diuretics use, statin use, and ACE inhibitor or ARB use				
¹ P-value for the interaction term between the cause of CKD and time effect in the mixed model				
² P-value for each estimated of CKD causes compared to the glomerulonephritis as reference				
³ P-value for each estimated of CKD causes compared to the hypertensive nephropathy as reference				
⁴ P-value for each estimated of CKD causes compared to the diabetic nephropathy as reference				
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate				

Rate of eGFR decline in each group was analyzed according to CKD stage at entry (Fig. 2). Fastest annual decline in eGFR was observed for those patients with PKD stages G3a and 3b (-4.94 and - 4.38 mL/min/1.73m² per year, respectively). The overall rate of eGFR decline was also fast in the DN group, ranging between - 3.87 to -2.68 mL/min/1.73m² per year for stages G1 to G4. In the HTN group, rates of eGFR decline were slow for stages G2 to G3b but eGFR declined slightly faster in stages G4 and G5. In the

GN group, rates of eGFR decline was faster in more advanced CKD stages. Trajectory patterns of eGFR decline were classified into two groups: DN (P for quadratic term = 0.608) groups showed a linear decline in eGFR while GN, HTN and PKD (P for quadratic term < 0.001, for all) showed a convex decline with acceleration of the rate of eGFR decline in advanced CKD stages (Fig. 3).

Discussion

The KDIGO Guideline states that the cause of CKD should be considered as one of the important predictors of the outcome.⁵ Evaluating the progression rate and risks of adverse outcomes according to the cause of CKD is important to predict prognosis in each individual with CKD. Besides, this could reveal further pathophysiologic characteristics of underlying CKD causes in the renal progression and other possible complications. However, not much is known about the relative risks of CKD-related adverse outcomes according to the specific cause of CKD.⁶

In the present study, we compared the relative risks of both renal outcomes and the composite outcome of CVD and death according to the cause of CKD within a prospective cohort population. Subjects were classified into GN, HTN, DN, or PKD groups based either on pathologic diagnosis or clinical judgement criteria at study entry. The baseline characteristics differed according to the cause of CKD in our study population. To overcome this limitation, we used the overlap weighting method. This is particularly advantageous when the comparator groups are initially very different from each other and this can achieve good balance and minimize the variances as shown in previous studies.^{19,20} By employing this method, we could analyze the relative risk for the outcomes between two groups of CKD causes after adjusting for potential confounders. The result showed that participants with PKD had significantly increased risks for renal outcomes compared to other CKD causes. Surprisingly, the DN group did not show an increased risk of kidney failure compared to other CKD causes. However the patients in the DN group showed the poorest outcomes regarding composite outcome of CVD and mortality among the CKD population.

We further analyzed rates of annual eGFR decline to better understand renal progression patterns according to the specific cause of CKD. Rate of GFR decline was faster in the DN and PKD groups than the GN and HTN groups. The DN and HTN population had a similar rate of eGFR decline to that shown in previous reports; however, the annual rates of decline of eGFR in the PKD groups were relatively slower in our study than those reported in previous studies.^{21–23} This could be due to differences in baseline clinical characteristics, including CKD stages, PKD genotypes and/or effects of ethnicity. About 60% of the PKD population in our cohort had early stage CKD (stage G1 or G2).

Although the eGFR declining rate in the PKD group was slightly slower than previous reports, patients in the PKD group showed the poorest renal outcomes compared to other causes of CKD. The annual rate of eGFR decline was the fastest in the PKD population. The PKD group showed an increased risk of kidney failure with the HRs at 1.73, 1.8 and 2.2 compared to the DN, GN, and HTN groups, respectively. This is a similar result to previous reports.^{9,22} These results would be due to its characteristics of genetic disorder and molecular pathogenesis. Therefore, evaluating the PKD-related risk factors and proper management would be important.

In our study results, the risk of renal outcome was not increased in the DN group, compared to other CKD cause when the confounding factors were adjusted using the overlap weighting methods. This would implicate the importance of managing the common risk factors and comorbidities in the DN population. However, the risk of CVD and mortality was significantly increased in DN compared to GN and HTN groups, suggesting that a different pathophysiology would exist between CVD or mortality and renal progression.

The CVD and mortality risk was also higher in the PKD population than the GN and HTN population. The PKD group had a similar risk of CVD and mortality to the DN group, but the outcome types were different. In the PKD population, most common composite CVD and death event was a cerebral hemorrhage or operation/interventions due to cerebral aneurysm (29.7%). Among death events, infection (30%) was the major cause of death, followed by malignancy (25%), liver failure (15%), and other causes (10%). These outcomes are different compared to those in the DN group, where, among those patients who had the composite CVD outcome and mortality, 48% had myocardial infarction, ischemic stroke, or heart failure; cerebral hemorrhagic or aneurysm events accounted for only 5.7% of total cases.

In this study, we further analyzed eGFR declining patterns according to the cause of CKD. A linear eGFR trajectory was observed in DN groups, and the rate of eGFR decline was faster in earlier CKD stages. GN, HTN, and PKD groups showed faster eGFR declining in advanced CKD stages. The renal deterioration pattern and acceleration time differed according to the cause of CKD. Therefore, patient follow-up and monitoring strategy should be individualized according to their CKD stages, comorbidities and cause of CKD. (Figs. 2 and 3)

This study has several limitations. Baseline characteristics differed among groups. Therefore we used overlap weighting method to adjust for possible confounding factors. However, there may still have been residual confounders that affected our findings. Furthermore, etiologic diagnosis of CKD was based on clinical criteria rather than pathologic diagnosis for many subjects. However, this reflects clinical practice, and we observed different outcomes based on the clinical diagnosis of CKD etiologies. In this study, we could not analyze the risk of each individual type of cardiovascular events since overall incidence of CV events were relatively lower in our cohort, compared to the Western CKD cohorts.²⁴ Since this is a result from a cohort of Asian CKD patients, the present study warrants further investigation from non-Caucasian ethnicity. Finally, our GN group comprised many different pathologic diagnoses – 40% IgA nephropathy, 7% focal segment glomerular sclerosis, 6% membranous nephropathy, 5% crescentic GN, 2.4% minimal change disease, and 1.5% lupus nephritis, among biopsy-proven GN. A group with different compositions of GN subtypes may have shown different relative risks compared to the other CKD groups evaluated in this study.

Despite these limitations, we provided basic information about the relative risks of major outcomes from four major causes of CKD within a prospective cohort followed over a long-term period. Robust and up-to-date statistical methods have been used to compare the relative risk of major outcomes by the causes of CKD after adjusting possible confounders. Individuals with PKD or GN were oversampled to ensure that we had a sufficient number of subjects for comparison. CKD patients older than 18 years with any CKD stage were enrolled to reflect the overall CKD population. We found that patients with PKD had higher risks of renal progression than patients with DN, GN and HTN. After adjustment, the DN group did not show an

increased risk of kidney failure but had a higher risk of CVD and mortality than patients with GN and HTN. This requires our individualized approach to CKD, based on specific causes of CKD, as well as the stage and albuminuria in order to improve renal and CV outcomes.

Declarations

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Disclosures

The authors have no conflicts of interest to disclose.

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Figures

Figure 1

Flowchart of enrolled study subjects.

Cause of CKD	Annual changes of eGFR (mL/min/1.73m ² per year)					
	Estimates					
	Stage G1	Stage G2	Stage G3a	Stage G3b	Stage G4	Stage G5
Glomerulonephritis	-1.38	-2.14	-2.49	-2.59	-2.76	-0.94
Hypertensive nephropathy	-2.09	-1.4	-0.91	-1.52	-1.81	-1.87
Diabetic nephropathy	-3.87	-4.22	-3.47	-2.81	-2.68	-0.45
Polycystic kidney disease	-2.45	-3.48	-4.94	-4.38	-3.16	-3.11

Figure 2

Estimated glomerular filtration rate changes according to baseline CKD stages in each CKD group. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Figure 3

Spaghetti plots (up) and trajectory of eGFR changes (down) during follow-up in patients with A) glomerulonephritis, B) hypertensive nephropathy, C) diabetic nephropathy, or D) polycystic kidney disease. eGFR, estimated glomerular filtration rate

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