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Original Article

Aging is associated with slower renal progression in patients with chronic kidney disease

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Abstract

Objectives: Chronic kidney disease (CKD) is prevalent among the elderly. However, little is known about how the clinical course of CKD vary with age. The purpose of this study was to examine the impact of aging on the risk of end-stage kidney disease (ESKD) in patients with moderate to advanced CKD. **Materials and Methods:** A total of 454 patients with stages 3–5 CKD were prospectively followed for a median of 5.1 years. The primary outcome was ESKD needing chronic dialysis therapy or preemptive kidney transplantation. The secondary outcome was a composite of ESKD or all-cause mortality. **Results:** The mean age of the patients was 65 ± 13 years. 65.4% were men, 44.9% had diabetes mellitus, and 22.7% had cardiovascular disease. Overall, 142 participants progressed to ESKD and 63 participants died. Compared with young patients (age <65 years, n = 205), elderly patients (age ≥65 years, n = 249) were associated with a significantly decreased risk of ESKD in Cox proportional hazards models adjusted for sex, smoking history, diabetes mellitus, cardiovascular disease, systolic blood pressure, estimated glomerular filtration rate, urine protein: Creatinine ratio, use of renin-angiotensin-aldosterone blocker, hemoglobin, phosphate, interleukin-6, body mass index, and N-terminal pro-brain natriuretic peptide (hazard ratio [HR]: 0.66; 95% confidence interval [CI]: 0.45, 0.96; P = 0.028). The results remained statistically significant when death as a competing risk was taken into account (subdistribution HR: 0.65; 95% CI: 0.45, 0.95, P = 0.026). Notably, elderly did not predict a higher risk for the composite outcome (HR: 0.94; 95% CI: 0.67, 1.32; P = 0.723). **Conclusion:** Elderly confers a decreased risk of ESKD in Taiwanese patients with moderate to advanced CKD. Our findings suggest that age is an important effect modifier for CKD progression.

Keywords: *Aging, Chronic kidney disease, End-stage kidney disease, Mortality*

Introduction

More than a third of elderly people (aged ≥65 years) in Taiwan meet current diagnostic criteria for chronic kidney disease (CKD) [1]. In addition, older patients make up a large proportion of those reaching end-stage kidney disease (ESKD), with 58.6% of people starting dialysis in Taiwan being over 65 [2]. However, little is known about the clinical course of CKD in older individuals. In a large US CKD cohort with 209,622 veterans followed for a mean of 3.2 years, older patients had higher rates of death and lower rates of ESKD than younger patients with comparable levels of kidney function [3]. Whether the relative risk of ESKD is lower for older patients with CKD than for younger patients in Taiwan remains unclear.

We hypothesized that the risk of ESKD among patients with stages 3–5 CKD who were not yet on dialysis would differ substantially across age groups. In the present study, we tested this hypothesis among a CKD cohort of 454 patients who received care in the Taipei Tzu Chi Hospital by comparing the relative risk of ESKD between young (age <65 years) and elderly patients (age ≥65 years).

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Materials and Methods

Study participants

This was a prospective cohort study conducted in the outpatient clinics of the Taipei Tzu Chi Hospital, Taiwan. CKD patients >18 years of age were assessed for eligibility for inclusion between September 2011 and March 2020. CKD was defined by two separate estimated glomerular filtration rate (eGFR) values <60 mL/min per 1.73 m^2, calculated with the use of the four-variable Modification of Diet in Renal Disease (MDRD) formula [4], over an interval of 3 months. Exclusion criteria included active malignancies, acute infectious diseases, chronic inflammatory diseases, kidney injury due to reversible reasons, pregnancy, liver cirrhosis, or clinical conditions affecting body composition measurements such as amputees and patients with a cardiac pacemaker or metallic implants. Patients who were expected to enter dialysis treatment within 3 months were also ineligible. All patients received multidisciplinary CKD care plans including restriction of dietary salt and protein and avoidance of any nephrotoxic agent. Participants were followed up every 3 months during a routine clinical visit. The study fulfilled the Declaration of Helsinki and was approved by the Institutional Review Board (01-XD13-034 and 07-XD-074). Written informed consent was provided by each participant.

Data collection

Information on participant demographics, comorbidities, and medications was obtained at the time of study enrollment. Cardiovascular disease (CVD) included coronary artery disease defined by either coronary angiography or a history of myocardial infarction, New York Heart Association class III to IV heart failure, and cerebrovascular accident. Diabetes mellitus was defined as current or past use of insulin and/or oral antidiabetic drugs. Hypertension was defined as blood pressure ≥140/90 mmHg or current use of antihypertensive medications.

All blood samples were taken from the participants after overnight fasting. Serum albumin was determined with a bromocresol purple method. Plasma levels of interleukin-6 (IL-6) (RandD Systems, Minneapolis, MN) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) (Roche Diagnostics, Indianapolis, IN) were measured using the commercially available enzyme-linked immunosorbent assay kits according to the manufacturer's instructions. Proteinuria was quantified from a first-morning urine protein-to-creatinine ratio (UPCR) in g/g. Other laboratory measurements, including glucose, lipids, and electrolytes, were carried out according to routine laboratory methods.

Outcomes

The primary outcome was incident ESKD, defined as the need for chronic dialysis therapy or preemptive kidney transplantation. Death and loss to follow-up were considered censoring events. The secondary outcome was a composite of ESKD or death from any cause. Causes of death were confirmed by official death certificates. The follow-up time for each participant started at the first study visit and continued until July 2020.

Statistical analyses

Continuous data with or without a normal distribution were expressed as means ± standard deviations or medians and interquartile ranges (IQR) and compared using Student's *t*-test or Mann–Whitney *U* test, respectively. Categorical data were expressed as numbers and percentages and compared by the Chi-square test. The Cox proportional hazards models were used to determine the association between age and outcomes. Variables that were clinically relevant were considered to be adjusted in the multivariable models, and at most one variable per 10 observed events was included to avoid overfitting. Thus, Model 1 was adjusted for eGFR, and UPCR. Model 2 was additionally adjusted for sex, smoking history, diabetes mellitus, and CVD. Model 3 was additionally adjusted for use of renin-angiotensin-aldosterone blocker (RASB), systolic blood pressure, body mass index (BMI), hemoglobin, phosphate, IL-6, and NT-proBNP. Furthermore, we performed competing risk analyses according to Fine and Gray on incident ESKD, considering pre-ESKD death as a competing event [5]. Effect modification of the association between age and ESKD by 6 clinically important variables that may affect prognosis (sex, diabetes, CVD, use of RASB, BMI [<25 vs. ≥25 kg/m^2], and UPCR [<1 vs. ≥1 g/g]) was also tested by including multiplicative interaction terms in the multivariable model. A two-tailed $P < 0.05$ was considered statistically significant. Computer software Statistical Package for the Social Sciences version 20.0 (SPSS, Chicago, IL, USA) was used for all analyses.

Results

Patient characteristics

The study cohort was composed of 454 patients (157 women and 297 men; mean age 65 ± 13 years) with moderate to advanced CKD (mean eGFR 27 ± 15 mL/min per 1.73 m^2). Among them, 84.1% had hypertension (n = 382), 44.9% had diabetes mellitus (n = 204), and 22.7% had CVD (n = 103). The most common renal diagnoses in this cohort were diabetic nephropathy (44.9%) and glomerular diseases (32.4%); 22.7% of the patients had hypertensive nephrosclerosis or unknown etiology of CKD. The baseline demographic and clinical characteristics for the patient groups divided based on age <65 or ≥65 years are presented in Table 1. Compared with younger patients, older patients had a higher prevalence of CVD and a higher systolic blood pressure, IL-6, and NT-proBNP, but had a lower BMI and triglycerides. There were no significant differences in the prevalence of diabetes and the use of diuretics and statin between the two groups. As expected, a lower hemoglobin levels were observed in older patients. In addition, significant differences in baseline eGFR and UPCR were observed between both groups. For older patients, the mean eGFR values were 26 ± 14 mL/min per 1.73 m^2, and the median UPCR was 0.72 (IQR 0.30–1.98); for younger patients, the mean eGFR values was 29 ± 15 mL/min per 1.73 m^2, and the median UPCR was 1.06 (IQR 0.47–2.85).

Outcomes

During a median follow-up period of 5.1 years, there were 142 ESKD events (74 younger patients and 68 older patients) and 63 deaths from any cause (14 younger patients and 49

Table 1: Baseline characteristics of the patients stratified by age

Characteristics	Age <65 years (*n*=205), *n* (%)	Age ≥65 years (*n*=249), *n* (%)	*P*
Age (years)	53±9	75±7	<0.001
Sex	130 (63.4)	167 (67.1)	0.415
Smoking history	52 (25.4)	63 (25.3)	0.987
Hypertension	166 (81.0)	216 (86.7)	0.094
DM	89 (43.4)	115 (46.2)	0.555
CVD	31 (15.1)	72 (28.9)	<0.001
CAD	17 (8.3)	38 (15.3)	0.024
CHF	9 (4.4)	33 (13.3)	0.001
Stroke	10 (4.9)	18 (7.2)	0.300
Loop diuretics	34 (16.6)	58 (23.3)	0.077
Thiazide	31 (15.1)	31 (12.4)	0.409
CCB	100 (48.8)	131 (52.6)	0.417
RASB	138 (67.3)	140 (56.2)	0.016
Statin	80 (39.0)	77 (30.9)	0.071
Body weight (kg)	71.2±16.4	64.1±10.9	<0.001
Height (cm)	162.9±8.8	158.8±8.2	<0.001
BMI (kg/m^2)	26.6±5.0	25.4±3.5	0.002
Systolic BP (mm Hg)	134±18	140±19	0.001
Diastolic BP (mm Hg)	82±13	78±13	0.001
eGFR (mL/min/1.73 m^2)	29±15	26±14	0.020
UPCR (g/g)	1.06 (0.47-2.85)	0.72 (0.30-1.98)	0.008
Creatinine (mg/dL)	3.0±1.9	3.1±1.0	0.642
Hemoglobin (g/dL)	12.0±2.2	11.4±2.0	0.004
Sodium (mmol/L)	137 (135-139)	138 (136-140)	0.011
Potassium (mmol/L)	4.4 (4.0-4.8)	4.4 (4.0-4.8)	0.738
Calcium (mg/dL)	9.0 (8.7-9.3)	8.9 (8.6-9.2)	0.517
Phosphate (mg/dL)	3.9 (3.4-4.5)	3.8 (3.4-4.4)	0.160
Total cholesterol (mg/dL)	172 (143-203)	165 (143-190)	0.057
LDL (mg/dL)	102 (77-128)	95 (78-113)	0.117
Triglycerides (mg/dL)	144 (102-208)	122 (84-176)	<0.001
Fasting glucose (mg/dL)	106 (98-130)	109 (97-125)	0.713
IL-6 (pg/mL)	2.93 (1.73-4.82)	3.80 (2.39-7.17)	<0.001
NT-proBNP (ng/L)	132 (45-474)	342 (133-829)	<0.001

BMI: Body mass index, BP: Blood pressure, CAD: Coronary artery disease, CCB: Calcium channel blockers, CHF: Congestive heart failure, CVD: Cardiovascular disease, DM: Diabete mellitus, eGFR: Estimated glomerular filtration rate, IL-6: Interleukin-6, LDL: Low-density lipoprotein, NT-proBNP: N-terminal pro-brain natriuretic peptide, RASB: Renin-angiotensin system blocker, UPCR: Urine protein-to-creatinine ratio

older patients). The overall causes of death were infectious in 38.1%, cardiovascular in 36.5%, malignancy in 12.7%, and others in 12.7%.

Table 2 shows the results of the multivariable Cox proportional hazard analyses for the risk of ESKD in younger and older patients. In a model adjusted for eGFR and UPCR, older patients had 27% lower risk of incident ESKD compared with younger patients (hazard ratio [HR]: 0.73; 95% confidence interval [CI]: 0.52–1.03; $P = 0.070$). This risk became significantly lower after adjusting for additional demographic and clinical variables (HR: 0.66; 95% CI: 0.45–0.96; $P = 0.028$). Of note, older patients were not associated with a higher risk of the composite outcome in fully adjusted models (HR: 0.94; 95% CI: 0.67–1.32; $P = 0.723$). After the competing risk of pre-ESKD death was taken into account, older patients remained significantly associated with a lower risk of ESKD in fully adjusted models (subdistribution HR: 0.65, 95% CI: 0.45-0.95; $P = 0.026$).

Subgroup analyses are shown in Figure 1. The lower risk of ESKD associated with aging was consistent across all clinically relevant subgroups. Notably, significant interactions were observed for men versus women, with a benefit favoring men, and for the presence versus absence of diabetes at baseline, with benefit for those with diabetes.

Discussion

In this prospective cohort study, we demonstrated that aging is associated with a lower risk of ESKD in patients with stage 3–5 CKD. This association was consistent after extensive adjustment of multiple confounders and accounting for competing risk of death. Our findings were compatible with the results of previous studies from other ethnicities [3,6,7], indicating that similar levels of eGFR may have very different prognostic implications between younger and older patients.

The lower incidence of ESKD among older compared with younger patients with CKD may reflect age differences in the underlying cause of low eGFR. In older patients, perhaps low eGFR results more frequently from "normal" aging rather than from a disease process and functions more commonly

Table 2: Association of age <65 or ≥65 years and risk of end-stage kidney disease or composite outcome

	Age <65 years	Age ≥65 years	*P*
Cox model, HR (95% CI)			
ESKD			
Model 1[a]	1 (reference)	0.73 (0.52-1.03)	0.070
Model 2[b]	1 (reference)	0.72 (0.50-1.02)	0.060
Model 3[c]	1 (reference)	0.66 (0.45-0.96)	0.028
Composite outcome of ESKD or death			
Model 1[a]	1 (reference)	1.10 (0.81-1.50)	0.530
Model 2[b]	1 (reference)	1.04 (0.76-1.43)	0.803
Model 3[c]	1 (reference)	0.94 (0.67-1.32)	0.723
Competing-risk model, sHR (95% CI)			
ESKD			
Model 1[a]	1 (reference)	0.73 (0.49-1.09)	0.120
Model 2[b]	1 (reference)	0.72 (0.51-1.01)	0.057
Model 3[c]	1 (reference)	0.65 (0.45-0.95)	0.026

[a]Adjusted for eGFR, and UPCR, [b]Adjusted for covariates in Model 1, sex, smoking history, diabetes, and CVD, [c]Adjusted for covariates in Model 2, use of RASB, systolic BP, BMI, hemoglobin, phosphate, IL-6 and NT-proBNP. CI: Confidence interval, ESKD: End-stage kidney disease, HR: Hazard ratio; sHR: Subdistribution HR, eGFR: Estimated glomerular filtration rate, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, RASB: Renin-angiotensin system blocker, UPCR: Urine protein-to-creatinine ratio, CVD: Cardiovascular disease, BP: Blood pressure, BMI: Body mass index

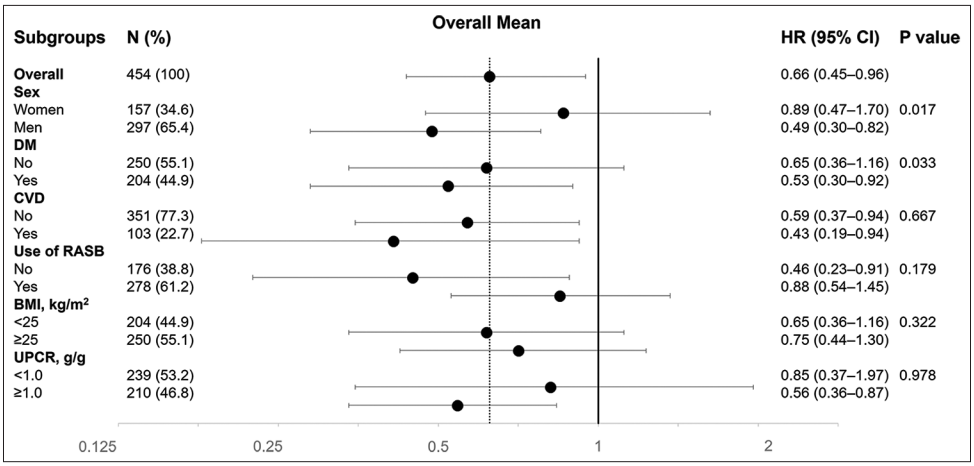

Figure 1: Association between aging and incident ESKD in different clinical subgroups. BMI: Body mass index, CI: Confidence interval, CVD: Cardiovascular disease, DM: Diabetes mellitus, HR: Hazard ratio, RASB: Renin-angiotensin system blocker, UPCR: Urine protein-to-creatinine ratio

as a "marker" for age-related coexisting comorbid conditions. In contrast, in younger patients, low eGFR results more frequently from a disease process affecting the kidney and is a better predictor of more specific renal outcomes [3]. Another possibility is that elderly patients with impaired renal function tend to die from CVD before they have lived long enough to develop ESKD [8]. However, the results of our competing risk analysis did not support the notion that lower risk of ESKD in older patients was due to a greater competing risk of death. Indeed, a recent study has shown that Taiwanese CKD patients are more likely to develop ESKD than to die [9]. Nevertheless, CVD remained the most common cause of morbidity and mortality in patients with CKD and strategies to prevent or reduce CVD risk factors should be implemented in all patients with CKD irrespective of age.

The substantial heterogeneity in ESKD outcomes between younger and older patients with CKD suggests that the uniform stage-based approach advocated in most practice guidelines is probably inadequate [3]. Current criteria for the diagnosis of CKD in adults include abnormalities of kidney structure or function such as increased proteinuria or an eGFR below 60 mL/min per 1.73 m^2 present for >3 months. However, this threshold does not separate kidney disease from kidney aging. A reasonable approach would be simply to lower the eGFR threshold for defining CKD in elderly people. It is suggested that elderly people with an eGFR of 45–60 mL/min/1.73 m^2 and no other evidence of kidney damage might not be labeled as having CKD [10]. Using an age-specific threshold for the diagnosis of CKD may help reduce not only inappropriate care but also its associated adverse effects and costs for healthy older individuals [11].

The strengths of this study include extensive adjustments for baseline characteristics associated with CKD progression in a prospective cohort with long-term follow-up. Moreover, almost all CKD patients who had indications for dialysis started on dialysis in our study. The ascertainment of incident ESKD, the primary outcome measure, was thus unbiased because the onset of ESKD is essentially a treatment decision.

However, there are a number of limitations to be considered in interpreting our results. First, as the observational nature of this study, we cannot establish the causality of the relationship between age and clinical outcomes. Second, important risk factors for CKD progression such as dietary protein intake and physical activity were not assessed at the baseline. Third, the MDRD equation has not been validated in the elderly, and there is particular concern that eGFR in the elderly may vary by changes in muscle mass. Finally, no adjustments were made for the multiplicity of exploratory outcomes.

Conclusion

In Taiwanese patients with stages 3–5 CKD, the prognostic implications of eGFR for ESKD varied greatly depending on the age of the patient. The relative risk of ESKD is much lower for an elderly patient than for a young patient with the equivalent level of kidney function. Although less likely to develop ESKD than their younger counterparts with CKD, older patients comprise a large and growing population of all new cases of ESKD in Taiwan [12]. Therefore, better prognostic tools with which to identify the small percentage but a large and growing number of older individuals who will progress to ESKD are critically needed. Future research should focus on identifying risk factors at each age and on developing strategies to best treat CKD across the full age spectrum.

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Conflicts of interest

There are no conflicts of interest.

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