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Outcomes of Stage 3–5 Chronic Kidney Disease before End-Stage Renal Disease at a Single Center in Taiwan

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Key Words
Cardiovascular disease · Chronic kidney disease progression · End-stage renal disease

Abstract
Background: Taiwan has the highest incidence of end-stage renal disease (ESRD) in the world, but little is known about the outcomes of patients with chronic kidney disease (CKD) before ESRD in Taiwan. This study investigated the rate of renal progression and predictors for ESRD and death in a prospective cohort of patients under usual nephrologic care at a single center. ***Methods:*** A total of 433 patients at CKD stage 3–5 short of dialysis were recruited from nephrology clinics. Patients were monitored for up to 36 months or until ESRD, death or loss to follow-up. Glomerular filtration rates (GFR) were calculated by the Modification of Diet in Renal Disease abbreviated formula. ***Results:*** At baseline, mean age was 65.6 years, 61.7% were male, 33.3% were diabetic and 29.1% had cardiovascular diseases (CVD). At the end of follow-up, 123 patients (28.4%) had advanced to ESRD and 41 (9.5%) had died. Mean annual declines in GFR were 2.24, 4.22, and 3.23 ml/min/1.73 m^2 for stages 3, 4, and 5, respectively. By Cox regression model, patients with CVD, lower BMI and higher systolic BP were more likely to develop ESRD. Older patients with CVD and lower systolic BP were more likely to die. ***Conclusion:*** In this CKD cohort, patients were more likely to develop ESRD than cardiovascular death. The rate of GFR decline and predictors of ESRD were comparable to those reported in Western countries. Thus, the high incidence of ESRD in Taiwan may be attributed, at least in part, to lower cardiovascular mortality.

Introduction

Chronic kidney diseases (CKD) frequently advances to end-stage renal disease (ESRD), and the number of patients affected is steadily increasing worldwide. Taiwan has the highest incidence of treated ESRD in the world [1], despite stringently regulated initiation of renal replacement therapy (RRT) according to local practice guidelines. In the past decade, many important studies identified therapeutic strategies to retard the progression and reduce the mortality of CKD patients, including stringent control of blood pressure and hyperglycemia, use of renin-angiotensin system blockers and reduction of proteinuria [2–6]. These treatments could impact the progression and outcomes of CKD patients greatly, but regretfully angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are frequently under-

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utilized [7] and blood pressure is not optimally controlled [8]. On the other hand, while it had also been suggested that renal failure patients should be referred to nephrologists early [9], no contemporary study has been conducted to study the progression and clinical outcomes of renal failure patients under routine care provided by nephrologists.

Besides, the reasons for Taiwan's ESRD endemic remain largely unknown. Recent epidemiological data estimate the prevalence of stage 3–5 CKD to be around 6.4%, representing 1.5 million individuals [10]. This figure is not so different from that of industrialized countries with a similarly high incidence of ESRD, such as Japan (6.7%) [11] and the United States (4.6%) [12] but is appreciably lower than that of Australia (11.2%) where ESRD incidence and prevalence are one-half that of Taiwan [13]. Hence, Taiwan's high incidence of ESRD cannot be explained by the size of the CKD pool. One recent study shows similar CKD prevalence rates in the United States and Norway, but the relative risk for progression from CKD stage 3 or 4 to ESRD in US white patients was 2.5 times that of Norwegian patients [14]. Given similar rates of cardiovascular death in the two countries, it was suggested that a slower rate of CKD progression in Norway have contributed to its lower incidence of ESRD. However, the progression rate and mortality of Taiwanese pre-ESRD CKD patients have never been reported. This study was thus initiated to investigate the rate and predictors of renal progression and pre-ESRD mortality in a Taiwanese CKD cohort under nephrologists' care.

Methods

Subjects and CKD Stratification

National Taiwan University Hospital is a major medical center located in northern Taiwan that serves as a referral center for more than 2 million residents of metropolitan Taipei area. From September 2003 to March 2004, we consecutively screened persons with stage 3–5 CKD short of ESRD from the nephrologic outpatient clinic. Taiwanese adults >20 years old with stable renal function for at least 3 months and not expecting to start dialysis or undergo renal transplantation within 6 months were included. Patients with active infection or decompensated liver cirrhosis at the time of screening were excluded. A total of 433 patients were enrolled and received regular clinic follow-up. GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula: $186 \times Scr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 if African-American. Because no participant was of African descent, the last factor was ignored. CKD stage was determined as described by the National Kidney Foundation of the United States. At the time of entry, GFRs of 30–59, 29–15 and <15 ml/min/1.73 m^2 for more than 3 months were classified as CKD stages 3, 4 and 5, respectively. The study protocol was approved by the Research and Ethics Committee of the Hospital (No. 9461701018).

Baseline Data

Diabetes was documented by the presence of elevated fasting blood sugar levels or hypoglycemic therapy. Glomerulonephritis, hypertensive nephrosclerosis, or polycystic kidney disease were diagnosed based on clinically relevant medical history or examinations. CVD included five categories: (1) sudden death, (2) coronary heart disease, (3) congestive heart failure, (4) cerebrovascular infarcts or hemorrhage, and (5) peripheral arterial disease. Coronary heart disease was diagnosed by a cardiologist according to a prior history of myocardial infarction, positive cardiac thallium scan or coronary angiography. All laboratory measurements were carried out by the Department of Laboratory Medicine, National Taiwan University Hospital. The body mass index (BMI) was measured by calculating the individual's weight divided by the square of the height and expressed as kg/m^2. Dipstick urinalysis was performed with spontaneously voided fresh urine and the result interpreted as (–), (±), (1+), (2+), and (3+). We defined (–) as no proteinuria, (±) to (2+) as mild proteinuria, and (3+) as heavy proteinuria.

Outcome Data

The observation period of each patient was defined to start immediately after the registered measurement of serum creatinine satisfying the above criteria (designated as the index date) and lasted for 36 months or until ESRD, death or loss to follow-up. ESRD was defined as initiation of RRT, i.e. chronic dialysis or renal transplantation. The timing to initiate RRT follows the regulations by the Bureau of National Health Insurance, including creatinine clearance <15 ml/min or serum Cr >6 mg/dl, plus any of the following conditions: (1) blood urea nitrogen >100 mg/dl, (2) refractory heart failure, lung edema, metabolic acidosis, or hyperkalemia, (3) pericarditis, (4) bleeding tendency, (5) uremic encephalopathy or neuropathy, and (6) uncontrolled nausea, vomiting, or cachexia. Patients lost to regular clinic follow-up or transferred to other health care facilities were contacted by telephone to monitor and record their renal function.

Statistical Analyses

Continuous variables are presented as mean ± SD. Comparison of continuous variables between stages of CKD were performed using one-way ANOVA. Categorical and nominal data were compared using the χ^2 test. To calculate the rate of GFR decline, the first and latest available serum creatinine data were used. To study CKD stage transition, event rates were calculated using the cumulative rate approach, and the result expressed as the cumulative rates over 36 months. The starting time for survival analysis was the index date of each patient. Differences in baseline demographic data, underlying diseases and laboratory data were calculated by ANOVA for continuous data and by the χ^2 test for nominal data. The difference in morbidity rate of dialysis or mortality rate between stages 3, 4 and 5 were tested by the Poisson regression model. The univariate and multivariate association of presumed risk factors with RRT or death was performed by Cox proportional hazards model. All analyses were performed with SPSS, version 13.0 (SPSS Inc., Chicago, Ill., USA). $p < 0.05$ was considered significant.

Table 1. Baseline characteristics of patients by CKD staging

Variable	All (n = 433)	Stage 3 (n = 184)	Stage 4 (n = 142)	Stage 5 before RRT (n = 107)	p value
Age, years	65.6 ± 14.1	65.7 ± 13.7	66.2 ± 15.0	64.5 ± 13.6	0.626
Gender					
Male, % (n)	61.7 (267)	74.5 (137)	57.0 (81)	45.8 (49)	<0.001
Female, % (n)	38.3 (166)	25.5 (47)	43.0 (61)	54.2 (58)	<0.001
Past medical history					
Diabetes, % (n)	33.3 (144)	30.4 (56)	39.4 (56)	29.9 (32)	0.162
Glomerulonephritis, % (n)	22.4 (97)	22.8 (42)	23.2 (33)	20.6 (22)	0.868
Hypertensive nephrosclerosis, % (n)	4.6 (20)	6.0 (11)	3.5 (5)	3.7 (4)	0.542
Polycystic kidney disease, % (n)	1.4 (6)	0.1 (1)	1.4 (2)	2.8 (3)	0.188
CVD, % (n)	29.1 (126)	27.2 (50)	31.0 (44)	29.9 (32)	0.688
Hyperlipidemia, % (n)	26.6 (115)	31.5 (58)	29.6 (42)	14.0 (15)	0.003
Systolic BP, mm Hg	136.0 ± 18.6	133.7 ± 17.3	135.1 ± 18.9	141.2 ± 19.7	0.003
Diastolic BP, mm Hg	78.4 ± 11.5	79.2 ± 10.9	77.2 ± 12.2	78.8 ± 11.5	0.285
BMI	24.4 ± 4.4	24.5 ± 3.6	25.0 ± 5.5	23.4 ± 3.9	0.029
Hemoglobin, g/dl	10.5 ± 2.2	12.6 ± 1.9	10.4 ± 1.8	9.1 ± 1.6	<0.001
Serum albumin, g/dl	4.1 ± 0.9	3.9 ± 0.5	4.2 ± 1.4	4.1 ± 0.6	0.597
Serum creatinine, mg/dl	3.1 ± 2.0	1.7 ± 0.3	2.9 ± 0.6	5.8 ± 2.1	<0.001
GFR, ml/min/1.73 m^2	27.2 ± 14.3	41.2 ± 8.1	21.9 ± 4.4	9.9 ± 2.9	<0.001
Proteinuria					
No proteinuria, % (n)	17.6 (76)	29.3 (54)	10.6 (15)	6.5 (7)	<0.001
Mild proteinuria (± to 2+), % (n)	47.3 (205)	47.8 (88)	45.1 (64)	49.5 (53)	0.773
Heavy proteinuria (3+), % (n)	35.1 (152)	22.8 (42)	44.4 (103)	43.9 (47)	<0.001
Medications					
ACE inhibitors or angiotensin receptor blockers, % (n)	54.3 (235)	64.1 (118)	57.0 (81)	34.6 (36)	<0.001
Lipid-lowering agents, % (n)	22.9 (99)	28.8 (53)	26.1 (37)	8.4 (9)	<0.001

Values shown as mean ± SD. For comparison between 3 patient groups, p values were calculated by ANOVA for continuous data and by Pearson χ^2 test for nominal data.

CVD = Presence of cardiovascular disease at baseline, including coronary artery disease, peripheral artery disease, cerebrovascular disease and congestive heart failure; BP = blood pressure; GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme.

Results

Baseline Demographic Characteristics

A total of 433 patients with a mean age of 65 years were enrolled. Their baseline demographic characteristics are summarized in table 1. At the start of the study, 184 (42.5%) patients were at stage 3, 142 (32.8%) at stage 4, and 107 (24.7%) at stage 5 short of RRT. Most were male (267, or 61.7%) and 144 (33.3%) were diabetic. More male patients were at stage 3 CKD, but percentages became more balanced at later stages. The most common primary etiology of CKD at all stages was likely related to diabetes, followed by glomerulonephritis, hypertensive nephrosclerosis, and polycystic kidney disease. In 3.9% of patients, the primary etiology of CKD was not clear, but presumably could be ascribed to chronic tubulointerstitial disease. The prevalence of CVD was similar across all three CKD stages. Patients with stage 3 CKD had significantly lower systolic blood pressure (BP), higher hemoglobin, less severe proteinuria, higher BMI, and more frequently used angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and lipid-lowering drugs, when compared to patients at stage 4 or 5. As CKD progressed, BMI gradually decreased but serum albumin levels remained the same.

Patient Outcomes

Nearly all, or 411 (94.9%) patients completed the 3-year follow-up or were followed until they reached ESRD or death. Only 22 (5.1%) patients were lost to follow-up.

Table 2. Clinical outcomes of patients by baseline CKD stages

Variable	All (n = 433)	Stage 3 (n = 184)	Stage 4 (n = 142)	Stage 5 (n = 107)	p value
Annual GFR decline, ml/min/1.73m^2					
Diabetes	5.38 ± 0.50	4.98 ± 1.00	5.10 ± 0.60	6.52 ± 1.00	0.233
Non-diabetes	2.77 ± 0.33	2.05 ± 0.42	3.77 ± 0.76	2.83 ± 0.59	0.028
All	2.99 ± 0.20	2.24 ± 0.30	4.22 ± 0.36	3.23 ± 0.32	0.002
ESRD, % (n)	28.41 (123)	3.80 (7)	33.10 (47)	64.49 (69)	<0.001
ESRD rate %/100 patient-years	12.29	1.35	14.61	42.78	<0.001
Death[b] % (n)	9.46 (41)	5.98 (11)	11.97 (17)	12.15 (13)	<0.001
Death rate %/100 patient-years	4.09	2.12	5.28	8.05	<0.001
Cause of death[1]					
Cardiovascular disease, % (n)	43.90 (18)	27.27 (3)	47.06 (8)	53.85 (7)	
Infectious disease, % (n)	29.27 (12)	36.36 (4)	29.41 (5)	23.08 (3)	
Other etiology, % (n)	26.83 (11)	36.36 (4)	23.53 (4)	23.08 (3)	

GFR = Glomerular filtration rate. Values shown as mean ± SE. For comparison between three patient groups, p values were calculated by ANOVA for continuous data and by Pearson χ^2 test for nominal data.

ESRD = End-stage renal disease: including outcomes of patients transferred to other hospital facilities.

[1] Data expressed as percent of cases of death within each group.

The median period of observation was 27.8 months. Table 2 summarizes the progression rates and clinical outcomes for patients by CKD stage. The mean annual declines in glomerular filtration rates (GFR) were 2.24, 4.22, and 3.23 ml/min/1.73 m^2 for stages 3, 4 and 5, respectively. By ANOVA analyses, the annual decline in GFR was significantly greater for patients in stage 4 or 5 compared to those in stage 3 (p = 0.002). This trend was statistically significant in non-diabetic but not in diabetic patients. At the end of the study, 123 patients (28.4%) had started RRT (102, hemodialysis; 19, peritoneal dialysis; 2, renal transplantation), and 41 patients had died (9.5%). Compared to patients in stage 3 CKD, patients in stage 4 or 5 were more susceptible to death from any cause, although the difference did not reach statistical significance. The major cause of death was CVD (n = 18), which included sudden death (n = 4), acute coronary syndromes (n = 9), heart failure (n = 4), and cerebrovascular events (n = 1).

Three-year cumulative outcomes grouped by baseline stages of CKD are depicted in figure 1. The risk for CKD stages 3, 4 and 5 to reach ESRD was 3.8, 33.1 and 64.5%, and to die from any cause, 6.0, 12.0 and 12.1%, respectively. Patients with stage 3 CKD had a slightly higher risk of dying than of developing ESRD. Conversely, patients with stage 4 or 5 CKD were appreciably more likely to develop ESRD than to die. A significant portion of patients remained alive and dialysis free (90.2%, stage 3; 54.9%, stage 4; 22.8%, stage 5). The Kaplan-Meier curves for the combined end point of ESRD and death in patients with different stages of CKD are depicted in figure 2.

Predictors for RRT

Univariate logistic regression shows that diabetes (OR, 1.92; 95% CI, 1.35–2.74), higher systolic BP (per 5 mm Hg; OR, 1.12; 95% CI, 1.07–1.16), mild proteinuria (OR, 4.03; 95% CI, 1.44–11.28), and heavy proteinuria (OR, 14.25; 95% CI, 5.22–38.92) were associated with a higher risk of ESRD (table 3). Higher baseline GFR (OR, 0.88; 95% CI, 0.86–0.90), higher hemoglobin level (OR, 0.753; 95% CI, 0.67–0.85) and use of angiotensin II blockers (OR, 0.50; 95% CI, 0.35–0.71) were associated with a lower risk for ESRD. Compared to those with BMI less than 20, higher BMI levels were associated with lower risk of ESRD (BMI 20.01–24.99, OR, 0.56; 95% CI, 0.34–0.94; BMI 25.00–29.99, OR, 0.53; 95% CI, 0.30–0.91; BMI 30, OR, 0.41; 95% CI, 0.17–0.96).

By age-adjusted multivariate Cox survival analysis, being male (OR, 1.82; 95% CI, 1.20–2.78), having diabetes (OR, 2.00; 95% CI, 1.31–3.06), presence of CVD at baseline (OR, 1.77; 95% CI, 1.15–2.73), higher systolic BP (per 5 mmHg; OR, 1.09; 95% CI, 1.03–1.14), lower baseline GFR (OR, 0.86; 95% CI, 0.81–0.87), and heavy proteinuria (OR, 5.12; 95% CI, 1.80–14.52) were independent predictors for ESRD (table 4). Compared to BMI <20, BMI

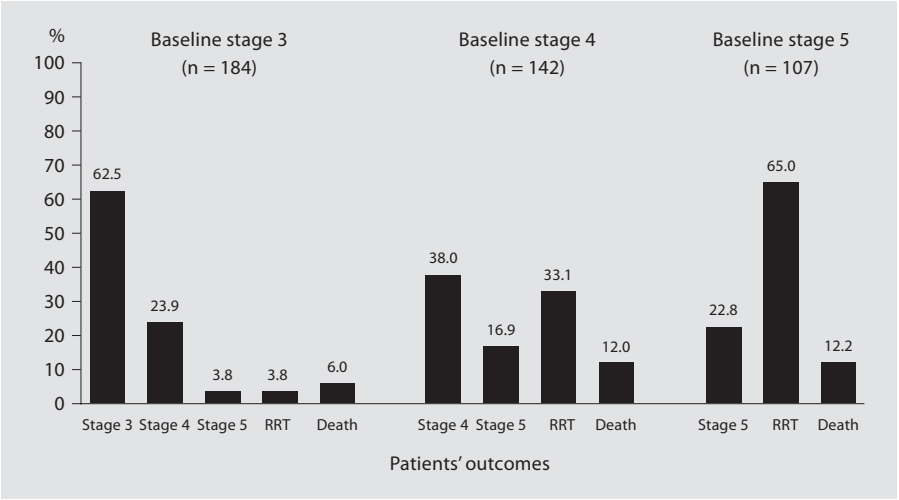

Fig. 1. Three-year cumulative outcomes grouped by baseline stages of CKD. Collectively, more patients develop ESRD than death from any cause, and the probability of stage progression or death is higher in patients with more severe CKD.

25.00–29.99 (OR, 0.52; 95% CI, 0.29–0.94) and BMI >30 (OR, 0.16; 95% CI, 0.06–0.42) were independent protectors from ESRD.

Predictors for Mortality

Being older (OR, 1.10; 95% CI, 1.06–1.13), presence of CVD at baseline (OR, 3.44; 95% CI, 1.86–6.38), lower systolic BP (OR, 0.92; 95% CI, 0.85–0.92), lower diastolic BP (OR, 0.77; 95% CI, 0.67–0.90), lower serum hemoglobin level (OR, 0.81; 95% CI, 0.68–0.96), lower serum albumin level (OR, 0.42; 95% CI, 0.20–0.87) and lower baseline GFR level (OR, 0.96; 95% CI, 0.93–0.98) were associated with all-cause mortality. Compared with BMI less than 20, BMI 20.01–24.99 (OR, 0.31; 95% CI, 0.13–0.73) and BMI 25.00–29.99 (OR, 0.39; 95% CI, 0.16–0.95) were associated with less mortality risk (table 5).

In multivariate Cox survival analysis, being older (OR, 1.09; 95% CI, 1.05–1.13), baseline presence of CVD (OR, 2.13; 95% CI, 1.15–4.03), lower baseline GFR (OR, 0.95; 95% CI, 0.83–0.99), and lower systolic BP (per 5 mm Hg; OR, 0.91; 95% CI, 0.83–0.99) remained independent predictors of mortality before the development of ESRD (table 6).

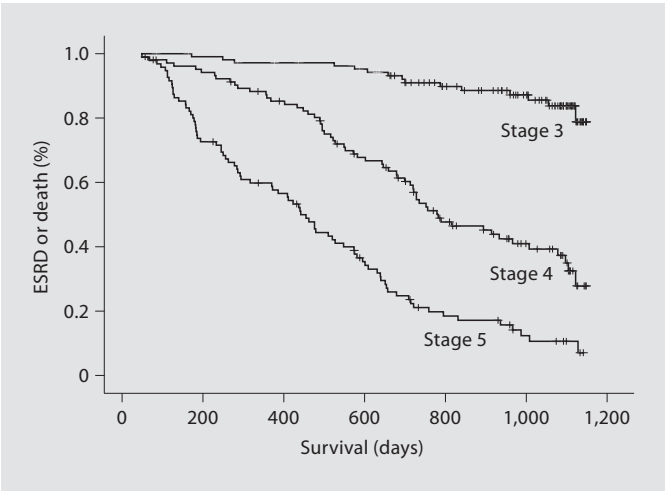

Fig. 2. Kaplan-Meier curves showing the combined end point of ESRD and death in patients with different stages of CKD (log-rank tests indicate $p < 0.001$ between any 2 of the 3 groups).

Discussion

This study is the first to demonstrate renal progression and stage transition in a prospective cohort of moderate-to-severe CKD patients over a period of 3 years in Taiwan where ESRD is endemic. The annual GFR decline of 2.99 ml/min in this cohort was no faster than that reported in major renal clinical trials (2–6 ml/min per year), which were conducted mostly in patients with milder CKD, i.e. stage 2–3 [3, 15–17]. A recent report by Hou et al. [18] shows an annual GFR decline of 3.2–5 ml/min in Chinese non-diabetic patients with stage 4 CKD, which is comparable to similar patients in our study (3.77 ml/min/year) (table 2). At the end of study, a significant portion of patients remained alive and dialysis free (fig. 1).

Patients with CKD in Western countries frequently die of CVD before developing ESRD [19–21]. By contrast, this study shows that Taiwanese patients are more likely

Table 3. Univariate analyses of baseline variables in association with risk of ESRD

Variable	Hazard ratio	95% CI	p value
Age	0.99	0.98–1.00	0.169
Male gender	0.86	0.98–1.24	0.423
Diabetics	1.92	1.35–2.74	<0.001
Glomerulonephritis	0.87	0.56–1.33	0.511
CVD	1.25	0.86–1.83	0.247
Hyperlipidemia	0.61	0.39–0.95	0.027
Systolic BP, per 5 mm Hg increase	1.12	1.07–1.16	<0.001
Diastolic BP, per 5 mm Hg increase	1.06	0.97–1.16	0.255
BMI			
≤20.00	reference		
20.01–24.99	0.56	0.34–0.94	0.028
25.00–29.99	0.53	0.30–0.91	0.023
≥30.00	0.41	0.17–0.96	0.04
Hemoglobin, g/dl	0.75	0.67–0.83	<0.001
Serum albumin, g/dl	0.78	0.49–1.23	0.292
Baseline GFR, ml/min/1.73 m^2	0.88	0.86–0.90	<0.001
Level of proteinuria			
No proteinuria	reference		
Mild proteinuria (± to 2+)	4.03	1.44–11.28	0.008
Heavy proteinuria (3+)	14.25	5.22–38.92	<0.001
ACE inhibitors or angiotensin receptor blockers	0.45	0.35–0.71	<0.001
Lipid-lowering agents	0.59	0.37–0.95	0.028

CVD = Presence of cardiovascular disease at baseline, including coronary artery disease, peripheral artery disease, cerebrovascular disease and congestive heart failure; BP = blood pressure; GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme.

Table 4. Age-adjusted multivariate Cox proportional model for the effect of baseline variables on risk of ESRD

Variable	Hazard ratio	95% CI	p value
Gender			
Female	1.00		
Male	1.82	1.20–2.78	0.005
Diabetics	2.00	1.31–3.06	0.001
Systolic BP, per 5 mm Hg increase	1.09	1.03–1.14	0.001
BMI			
≤20.00	reference		
20.01–24.99	0.77	0.45–1.33	0.330
25.00–29.99	0.52	0.29–0.94	0.032
≥30.00	0.16	0.06–0.42	<0.001
CVD	1.77	1.15–2.73	0.01
Baseline GFR, ml/min/1.73 m^2	0.86	0.81–0.87	<0.001
Level of proteinuria			
No proteinuria	reference		
Mild proteinuria (± to 2+)	1.06	0.37–3.06	0.921
Heavy proteinuria (3+)	5.12	1.80–14.52	0.001

CVD = Presence of cardiovascular disease at baseline, including coronary artery disease, peripheral artery disease, cerebrovascular disease and congestive heart failure; BP = blood pressure; GFR = glomerular filtration rate.

Table 5. Univariate analyses of baseline variables in association with risk of death

Variable	Hazard ratio	95% CI	p value
Age	1.10	1.06–1.13	<0.001
Male gender	0.70	0.38–1.30	0.260
Diabetics	1.42	0.76–2.66	0.277
Glomerulonephritis	0.45	0.18–1.15	0.094
CVD	3.44	1.86–6.38	<0.001
Hyperlipidemia	0.68	0.33–1.43	0.314
Systolic BP, per 5 mm Hg increase	0.92	0.85–0.98	0.047
Diastolic BP, per 5 mm Hg increase	0.77	0.67–0.90	0.001
BMI			
≤20.00	reference		
20.01–24.99	0.31	0.13–0.73	0.007
25.00–29.99	0.39	0.16–0.95	0.038
≥30.00	0.32	0.02–1.09	0.060
Hemoglobin, g/dl	0.81	0.68–0.96	0.016
Serum albumin, g/dl	0.42	0.20–0.87	0.02
Baseline GFR, ml/min/1.73 m^2	0.96	0.93–0.98	0.001
Level of proteinuria			
No proteinuria	reference		
Mild proteinuria (± to 2+)	2.07	0.79–5.40	0.138
Heavy proteinuria (3+)	1.49	0.52–4.30	0.460
ACE inhibitors or angiotensin receptor blockers	0.49	0.26–0.92	0.491
Lipid-lowering agents	0.60	0.27–1.36	0.220

CVD = Presence of cardiovascular disease at baseline, including coronary artery disease, peripheral artery disease, cerebrovascular disease and congestive heart failure; BP = blood pressure; GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme.

to develop ESRD than to die. Death rates from any cause were appreciably lower in this cohort than in those in industrialized countries [20, 22]. Reasons for this differential mortality are not clear but may be related to racial disparities. Indeed, the prevalence of coronary heart disease or heart failure in association with CKD varies substantially between racial populations [23]. Wong et al. [24] have reported a survival advantage of Asian American dialysis patients compared with Caucasian Americans. Further, based on United State Renal Data System (USRDS) data for 1995–2000, Young et al. [25] have shown that Asian and Hispanic American ESRD patients exhibit lower rates of myocardial infarction compared with Caucasians. Since progression of CKD toward ESRD is a continuous process, a cardiovascular survival advantage could explain the high incidence of ESRD in Taiwan. It is important to note that CVD remained the most common cause of death in this cohort. Hence, strategies to prevent or reduce CV risk factors should be implemented in all patients with CKD irrespective of stage.

Table 6. Multivariate Cox proportional model for the effect of baseline variables on risk of death

Variable	Hazard ratio	95% CI	p value
Age	1.09	1.05–1.13	<0.001
Male gender	0.75	0.40–1.43	0.387
Diabetes	1.49	0.77–2.88	0.237
CVD	2.13	1.15–4.03	0.018
Systolic BP, per 5 mm Hg increase	0.91	0.83–0.99	0.037
Baseline GFR, ml/min/1.73 m^2	0.95	0.92–0.98	0.001

CVD = Presence of cardiovascular disease at baseline, including coronary artery disease, peripheral artery disease, cerebrovascular disease and congestive heart failure; BP = blood pressure; GFR = glomerular filtration rate.

Very few studies had investigated the role of CVD as an independent risk factor for CKD progression and ESRD development. In this cohort, presence of CVD at baseline is a strong predictor for ESRD, even after multivariable adjustment for other established risk factors. This finding is reminiscent of that reported by Levin et al. [26], which showed that presence of CVD at baseline increased the probability of progression to ESRD by 50% in a Canadian cohort of patients with stage 2–5 CKD short of dialysis. Interestingly, CVD has also been associated with decline of renal function and development of kidney disease in a large community-based population with normal baseline renal function [27].

Accumulating evidence indicates that higher BMI is a risk factor for CKD in apparently healthy persons [28, 29], and graft loss in kidney transplantation recipients [30]. The result of a recent study from Taiwan [31] also supports this notion. By contrast, our study identifies lower BMI as an independent predictor for ESRD in patients with stage 3–5 CKD. This seemingly paradoxical finding could be reminiscent of the 'reverse epidemiology' seen in the dialysis population where low BMI and the associated malnutrition were liable for an augmented hazard of death worse than for those with high BMI [32–34].

Our observation that systolic BP was a stronger predictor for progression than diastolic BP is consistent with that reported in the AIPRD (ACE inhibition in Progressive Renal Disease) [15] and RENAAL (Reduction of End Points in NIDDM with the Angiotensin II Receptor Antagonist Losartan) studies [5]. In addition, we found that lower systolic BP was closely associated with higher all-cause mortality, and similar observation had been reported by Kovesdy et al. [35]. It is assumed that lower systolic BP may reflect worsening cardiovascular function or a consequence of increasing uremic burden during progression, such as autonomic neuropathy and diffuse calcification.

There are several limitations in this study. First, potential selection bias exists since patients prone to the development of ESRD might be preferentially recruited given the high prevalence of proteinuria. However, proteinuria is also a risk factor for CVD [36]; yet most patients in this cohort, unlike Western counterparts, develop ESRD rather than cardiovascular death. This suggests that other factors such as racial disparities may play a more important role in the differential evolution of ESRD and CVD. Secondly, there is a controversy about adjustment for racial coefficient while using the modified MDRD formula in Asian people. Ma et al. [37] have constructed a modified MDRD formula for the Chinese. However, the formula was derived mainly from non-diabetic patients with very mild CKD, and its applicability to diabetic, advanced CKD persons still awaits verification. Nevertheless, when our data were calculated by using Ma's formula, the trend of GFR decline among different stages of CKD remain the same (data not shown). Finally, since this was an observational study, the presence of confounding factors such as nonrandomized use of erythropoietin, ACE inhibitors, angiotensin receptor blockers or statins cannot be excluded. In spite of that, this study was designed to follow individual patient's renal function under routine nephrologists' care; thus, many of our findings could be valuable for physicians and health personnel while taking care of CKD patients. Further multicenter prospective studies are needed to confirm the external validity of the findings accrued from this study.

In conclusion, this study shows the current status of CKD progression and stage transition in a single-center cohort under daily nephrologic care over a period of 3 years. It is not clear to what extent our cohort represents the general CKD population in Taiwan. The nationwide CKD education program endorsed by the Bureau of Health Promotion in Taiwan was launched in 2005, but longitudinal CKD registry data are not likely available for analysis before 2010. For now, suffice it to say that CKD patients in this cohort were more likely to develop ESRD than cardiovascular death. Because the rate of GFR decline and predictors of ESRD were comparable to those reported in Western countries, it is surmised that the high incidence of ESRD in Taiwan may be attributed, at least in part, to lower cardiovascular mortality.

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