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Risk factors of gender for renal progression in patients with early chronic kidney disease

Po-Ya Chang, PhD[a], Li-Nien Chien, PhD[b], Yuh-Feng Lin, MD, PhD[c], Mai-Szu Wu, MD, PhD[d], Wen-Ta Chiu, MD, PhD[e,*], Hung-Yi Chiou, PhD[a,*]

Abstract

Risk factors for chronic kidney disease (CKD), such as hypertension, hyperglycemia, albuminuria, renal structure, and sex hormones, have been reported to have different effects on males and females. Thus, CKD progression may differ depending on sex. In addition to CKD management, treatment at earlier stages can reduce complications and prevent disease progression as well as high medical expenses at late stages. We examined the differences in predictive risk factors for renal progression between male and female patients with early CKD.

This case–cohort study recruited patients aged 18 years or older treated in the outpatient departments of 8 hospitals in Taiwan between August 2008 and September 2014. In total, 1530 patients were included in the analysis. Renal progression was defined as ≥25% decline based on baseline estimated glomerular filtration rate. To examine the predictive risk factors for renal progression, we constructed a subset multivariate logistic model with stepwise variable selection by using $P < 0.10$ for variable retention.

The numbers of male and female patients with CKD exhibiting renal progression were 100 (11.64%) and 84 (12.52%), respectively. After adjusting for all the potential confounders, stepwise logistic regression analysis showed that main independent predictive risk factors for the male patients– (C statistic = 0.72) were proteinuria (odds ratio [OR] 2.20; 95% confidence interval [CI] 1.26–3.84), age (OR 1.04; 95% CI 1.02–1.06), anemia (OR 2.75; 95% CI 1.20–6.30), and poor control of blood pressure (OR 1.84; 95% CI 1.05–3.22). However, the main independent predictive factors for the female patients were (C statistic = 0.75) poor glycemic control (OR 2.28; 95% CI 1.22–4.25), poor blood pressure control (OR 1.93; 95% CI 1.06–3.50), and family income (OR 2.51; 95% CI 1.01–6.20).

In conclusion, this study demonstrated that proteinuria was the most crucial risk factor for male patients, whereas poor glycemic control was the main risk factor for female patients. Poor blood pressure control was a shared risk factor for male and female patients.

Abbreviations: BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, HbA1c = glycated hemoglobin, OR = odds ratio, SBP = systolic blood pressure, SCr = serum creatinine.

Keywords: chronic kidney disease, early stage, sex, progression

1. Introduction

The prevalence of chronic kidney disease (CKD) is high and rapidly increasing worldwide. In the United States, the percentage of patients with CKD increased from 11.96% (1988–1994) to 13.65% (2007–2012), accounting for >20 million people.[1] In addition, CKD is associated with an increased risk of end-stage renal disease (ESRD), dialysis, renal transplantation, and cardiovascular comorbidity. Thus, effectively preventing or delaying CKD progression improves survival and quality of life.[2,3]

CKD progression may differ depending on sex.[4,5] Male patients show a substantially higher prevalence of CKD and incidence rate of ESRD than those observed in female patients.[6,7] A survey conducted by the Japanese Society for Dialysis Therapy indicated sex differences in mean age at the start of dialysis.[8] Men with diabetes have a higher risk of nephropathy than women with diabetes do.[9] By contrast, women have a higher risk of accelerated disease progression than do men.[10] Furthermore, a survey conducted in the United States reported that the percentages of male and female patients with CKD were 21.42% and 27.11% among those with an estimated glomerular filtration rate (eGFR) ≥90, 32.95% and 29.12% among those with an eGFR 60 to 89, 10.95% and 5.68% among

Editor: Sanket Patel.

Funding: This study was supported by a grant from the Health Promotion Administration, Ministry of Health and Welfare, Taiwan, Republic of China (DOH101-HP-1103, DOH102-HP-1103, MOHW103-HPA-H-114-134101, MOHW104-HPA-H-114-134101).

The authors report no conflicts of interest.

[a] School of Public Health, [b] School of Health Care Administration, [c] Graduate Institute of Clinical Medicine, [d] School of Medicine, [e] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan. .

[*] Correspondence: Hung-Yi Chiou, PhD, School of Public Health, Taipei Medical University, No. 250, Wu-Hsing Street, Taipei 110, Taiwan (e-mail: hychiou@tmu.edu.tw); Wen-Ta Chiu, Graduate Institute of Injury Prevention and Control, Taipei Medical University, No. 250, Wu-Hsing Street, Taipei 110, Taiwan (e-mail: wtchiu@tmu.edu.tw).

Medicine (2016) 95:30(e4203)

Received: 19 December 2015 / Received in final form: 14 May 2016 / Accepted: 13 June 2016

http://dx.doi.org/10.1097/MD.0000000000004203

those with stage 3, 0.70% and 0.31% among those with stage 4, and 0.12% and 0.04% among those with stage 5, respectively.[11]

Sex differences in CKD progression are influenced by various risk factors such as hypertension,[12,13] hyperglycemia,[14] albuminuria,[15] dyslipidemia,[16] body mass index,[17,18] lifestyle factors,[19,20] and renal structure and sex hormones.[21] Duru et al[12] demonstrated that African-American men have a higher risk of CKD progression than African-American women do because of the poorly controlled hypertension among these males.[12] Women with hyperglycemia might experience more vascular and renal target organ damage than men do.[14] Albuminuria incidence and decreases in the eGFR might be greater among men with diabetes than among women with diabetes.[14,15,22]

Previous studies have used a few specific risk factors for evaluating sex differences. By contrast, we explored the differences in predictive risk factors for CKD progression between male and female patients. In addition, we focused on early CKD because CKD management and treatment at earlier stages can reduce complications[23] and prevent disease progression as well as high medical expenses at later stages.[24] However, monitoring and providing intervention to all patients with early CKD can result in high expenses on healthcare resources. Thus, identifying male and female patients with a high risk of renal progression is essential. Because diseases can effectively be managed and controlled, medical costs for CKD will substantially decrease. To the best of our knowledge, sex differences in the risk factors for renal progression among patients with early CKD have not been discussed. Therefore, this study examined the predictive risk factors for renal progression among male and female patients with early CKD.

2. Methods

2.1. Study design and participants

This case–cohort study recruited 16,434 participants aged 18 years or older treated in the outpatient departments of 8 hospitals in Taiwan, namely Tri-Service General Hospital, Cardinal Tien Hospital, Shuang Ho Hospital, China Medical University Hospital, Kaohsiung Medical University Chung-Ho Memorial Hospital, National Cheng Kung University Hospital, Changhua Christian Hospital, and Kaohsiung Chang Gung Memorial Hospital between October 2008 and September 2014. The same medical laboratory criteria and protocol be used in our studying hospitals, and the value of serum creatinine derived from different hospital can be compared and standardized with each other. In this study, we measured the change of CKD progression at the individual level. In addition, the patients were reexamined in the same hospital to control the individual variation. All patients provided informed consent before data collection. The study was approved by the Taipei Medical University Joint Institutional Review Board (No. 201204036).

For this study, we excluded the following criteria: renal function cannot be assessed (n = 623); SCr was measured only once (n = 6921); follow-up periods were <12 months (n = 1798); non-CKD patients (n = 2607); missing proteinuria data (n = 1969). In total, 2516 patients with CKD were enrolled, with 1530 and 986 having early and late CKD, respectively. Early CKD refers to the patients of CKD stage 1, stage 2, and stage 3a, whereas late CKD refer to the patients of CKD stage 3b, stage 4, and stage 5. In the present study, we examined the risk factors for renal progression in the patients with early CKD. Therefore, the final total number of patients included in the analysis was 1530 (Fig. 1). Patients were followed from the baseline date for examination to the end of the study period (June 18, 2015). Total renal progression cases are 184 (male, n = 100; female, n = 84). In this study, the case group refers to the patients with renal progression; the control group refers to the patients who have no renal progression in the study period. Renal progression was defined as ≥25% decline based on baseline eGFR.[25]

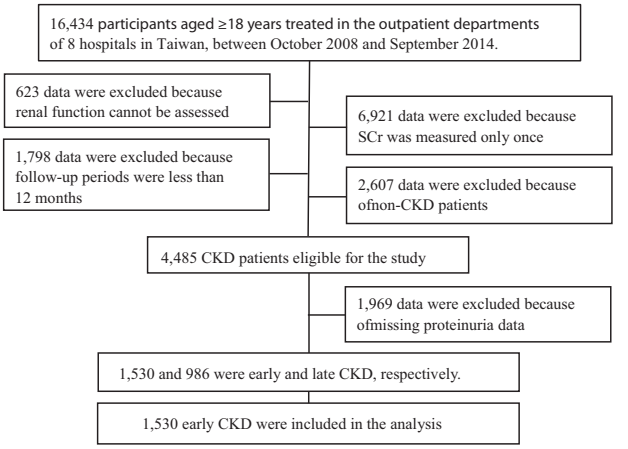

Figure 1. Flowchart of participants analyzed in this study.

CKD was defined according to the Kidney Disease Outcomes Quality Initiative guidelines[26] and was evaluated using eGFR, which was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, eGFR (mL/min/1.73 m^2) = 141 × min (SCr/κ, 1)$^{\alpha}$ × max(serum creatinine/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) and × 1.159 (if black), where SCr is serum creatinine (mg/dL), κ = 0.7 (female) and 0.9 (male), α = −0.329 (female) and −0.411(male), min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.[27]

CKD was classified as follows: CKD stage 1, eGFR ≥90 mL/min/1.73 m^2 and the presence of kidney damage (i.e., proteinuria dipsticks ≥1+, urine protein-to-creatinine ratio [UPCR] ≥150, or urine albumin-to-creatinine ratio [UACR] ≥30); CKD stage 2, eGFR = 60–89 mL/min/1.73 m^2 and the presence of kidney damage (i.e., proteinuria dipsticks ≥1+, UPCR ≥150, or UACR ≥30); CKD stage 3a, eGFR = 45–59 mL/min/1.73 m^2; CKD stage 3b, eGFR = 30–44 mL/min/1.73 m^2; CKD stage 4, eGFR = 15–29 mL/min/1.73 m^2; and CKD stage 5, eGFR <15 mL/min/1.73 m^2.[2]

2.2. Measurements and variable definitions

Baseline variables were demographic characteristics, namely age, years of education, and family income; clinical variables were diabetes, hypertension, dyslipidemia, gout, cardiovascular disease, and anemia; physical examination variables were the waist circumference, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP); laboratory test variables were the levels of serum creatinine, blood urea nitrogen (BUN), uric acid, glycated hemoglobin (HbA1C), triglyceride, total cholesterol, and proteinuria; and health-related behaviors were cigarette smoking and alcohol consumption. The demographic, clinical, and health-related behavior data were collected using a structured questionnaire. The physical examination and

laboratory variables were obtained through medical chart reviews.

Glycemia, blood pressure, and lipid control conditions were classified as intensive and poor. Intensive control refers to glycemia (HbA1C <7%),[28,29] blood pressure (SBP <130 mmHg),[30] and lipid (total cholesterol < 200 mg/dL).[31,32] On the other hand, poor control refers to glycemia (HbA1C ≥7%), blood pressure (SBP ≥130 mmHg), and lipid (total cholesterol ≥200 mg/dL).

The waist circumference was classified as normal (<90 and <80 cm for males and females, respectively) and abnormal (≥90 and ≥80 cm for males and females, respectively). The BMI was classified as <18.5, 18.5 to 23.9, and ≥24 kg/m^2. Proteinuria status was determined using the urine dipstick test, which yielded 3 levels of none, trace, and ≥1+. A urine dipstick test score ≥1+ indicated proteinuria. Cigarette smoking was dichotomized as smoking (smoking ≥100 cigarettes during the patient lifetime) and never smoking, and alcohol consumption was dichotomized as current and noncurrent drinking.

2.3. Statistical analysis

The differences between male and female patients with early CKD were examined using the χ^2 and Student t tests for categorical and continuous variables, respectively. All variables were evaluated for bivariate associations with renal progression. A logistic regression model was used for exploring the risk factors affecting renal progression. The potential confounders were selected from demographic characteristics,[33,34] clinical variables,[13,35,36] physical examination variables,[17,37,38] laboratory test variables,[39,40] and health-related behaviors[19,20,41] associated with renal progression. Stepwise logistic regression analysis was performed to adjust for potential confounders. To examine the predictive risk factors for renal progression, we constructed a subset multivariate logistic model with stepwise variable selection, using $P < 0.10$ for variable retention. All analyses and calculations were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Demographic characteristics of the patients

The mean follow-up duration was 25.67 ± 7.28 months, and the mean patient age was 59.18 ± 14.48 years. Of the 1530 patients, 859 (56.14%) and 671 (43.86%) were male and female, respectively. In addition, 38.50%, 67.58%, and 36.14% had diabetes mellitus, hypertension, and dyslipidemia, respectively. Furthermore, 19.29%, 49.33%, and 33.74% had poor control of glycemia, blood pressure, and lipid, respectively. At the baseline, the male patients had more years of education, higher income, and a significantly higher percentage of hypertension, gout, cardiovascular disease, cigarette smoking, and alcohol consumption than did the female patients. The variables of glycemia and blood pressure control did not show significant differences. Table 1 lists the baseline clinical characteristics of the included patients.

Table 1

Baseline characteristics of the study cohort.

Variable	Total (n = 1530)	Male (n = 859)	Female (n = 671)	P
Demographic characteristics				
Age, mean ± SD	59.18 ± 14.48	59.73 ± 15.25	58.46 ± 13.41	0.083
Years of education, y				<0.001
<6	34.20	27.39	42.86	
6–12	39.16	37.80	40.88	
≥13	26.64	34.81	16.26	
Family income, NT dollars				<0.001
<40,000	70.81	66.86	75.86	
≥40,000	29.19	33.14	24.14	
Clinical variables				
Diabetes	38.50	37.60	39.64	0.447
Hypertension	67.58	70.55	63.79	0.006
Dyslipidemia	36.14	36.09	36.21	0.959
Glycemia control				0.980
Intensive control	80.71	80.68	80.74	
Poor control	19.29	19.32	19.26	
Blood pressure control				0.322
Intensive control	50.67	49.50	52.14	
Poor control	49.33	50.50	47.86	
Lipid control				<0.001
Intensive control	66.26	70.84	60.30	
Poor control	33.74	29.16	39.70	
Gout	18.69	25.49	9.99	<0.001
Cardiovascular disease	22.22	25.84	17.59	<0.001
Anemia	8.04	6.64	9.84	0.029
Physical examination variables				
Waist circumference				<0.001
Normal	57.06	61.82	50.97	
Abnormal	42.94	38.18	49.03	
BMI, kg/m^2				0.010
<18.5	32.22	29.80	35.32	
18.5–23.9	14.38	13.39	15.65	
≥24	53.40	56.81	49.03	
SBP, mmHg, mean ± SD	130.86 ± 17.08	131.41 ± 16.44	130.16 ± 17.83	0.187
DBP, mmHg, mean ± SD	77.25 ± 11.11	77.59 ± 11.14	76.83 ± 11.06	0.211
Laboratory variables				
Baseline eGFR, mL/min/1.73 m^2, mean ± SD	85.64 ± 24.29	75.57 ± 20.06	98.53 ± 23.12	<0.001
BUN, mg/dL, mean ± SD	16.68 ± 6.18	16.93 ± 5.72	16.34 ± 6.73	0.088
Uric acid, mg/dL, mean ± SD	6.21 ± 1.54	6.56 ± 1.48	5.75 ± 1.48	<0.001
HbA1c, %, mean ± SD	7.35 ± 3.68	7.38 ± 4.66	7.32 ± 1.94	0.837
Total cholesterol, mg/dL, mean ± SD	188.97 ± 43.85	185.17 ± 44.50	193.90 ± 42.53	<0.001
Triglyceride, mg/dL, mean ± SD	133.48 ± 75.70	134.90 ± 72.85	131.66 ± 79.22	0.439
Proteinuria				0.887
None	48.04	47.61	48.58	
Trace	14.31	14.20	14.46	
≥1+	37.65	38.18	36.96	
Health-related behaviors				
Cigarette smoking	22.96	38.00	3.75	<0.001
Alcohol consumption	11.26	17.87	2.86	<0.001

Data are expressed as mean ± SD or percentage. BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, SBP = systolic blood pressure, SD = standard deviation.

3.2. Risk factors for renal progression in male and female patients

Table 2 details that the numbers of male and female patients with renal progression were 100 (11.64%, mean follow-up duration was 27.43 ± 6.09 months) and 84 (12.52%, mean follow-up duration was 26.81 ± 7.53 months), respectively. The differences in the eGFR slopes between the male and female patients were significant ($P = 0.03$). The mean eGFR slopes for the male and female patients were −2.03 ± 7.23 and −2.89 ± 7.86 mL/min/1.73 m^2 per year, respectively. Compared with the male and female patients without progression, both groups with progression had lower family income, higher percentage of poor glycemic and blood pressure control, higher SBP, higher BUN, and higher proteinuria. Compared with the male patients without progression, those with progression were older and had higher percentage of anemia. Compared with the female patients without progression, those with progression have higher percentage of gout, lower baseline eGFR, and higher uric acid.

Table 2

Characteristics of early CKD patients according to renal progression status.

Variable	Male (n = 859)		P	Female (n = 671)		P
	Progression (n = 100)	Nonprogression (n = 759)		Progression (n = 84)	Nonprogression (n = 587)	
Follow-up duration (month), mean ± SD	27.43 ± 6.09	25.72 ± 7.32	0.01	26.81 ± 7.53	25.13 ± 7.34	0.05
Demographic characteristics						
Age, mean ± SD	64.20 ± 15.55	59.15 ± 15.13	0.002	59.48 ± 15.16	58.32 ± 13.15	0.459
Years of education, y			0.148			0.056
<6	29.29	27.14		50.62	41.77	
6–12	44.44	36.91		41.98	40.73	
≥13	26.26	35.96		7.41	17.5	
Family income, NT dollars			0.016			0.008
<40000	78.00	65.39		88.10	74.11	
≥40000	22.00	34.61		11.90	25.89	
Clinical variables						
Diabetes	47.00	36.36	0.051	53.57	37.65	0.008
Hypertension	76.00	69.83	0.248	73.81	62.35	0.055
Dyslipidemia	26.00	37.42	0.034	38.10	35.95	0.793
Glycemia control			0.003			<0.001
Intensive control	68.48	82.36		65.38	83.04	
Poor control	31.52	17.64		34.62	16.96	
Blood pressure control			0.001			0.002
Intensive control	33.33	51.72		35.44	54.53	
Poor control	66.67	48.28		64.56	45.47	
Lipid control			0.243			0.675
Intensive control	76.67	70.09		63.16	59.89	
Poor control	23.33	29.91		36.84	40.11	
Gout	25.00	25.56	0.904	17.86	8.86	0.017
Cardiovascular disease	32.00	25.03	0.169	20.24	17.21	0.597
Anemia	13.00	5.80	0.012	17.86	8.69	0.015
Physical examination variables						
Waist circumference			0.773			0.439
Normal	60.00	62.06		46.43	51.62	
Abnormal	40.00	37.94		53.57	48.38	
BMI, kg/m^2			0.264			0.352
<18.5	35.00	29.12		41.67	34.41	
18.5–23.9	9.00	13.97		11.90	16.18	
≥24	56.00	56.92		46.43	49.40	
SBP, mmHg, mean ± SD	137.06 ± 16.95	130.65 ± 16.24	0.001	134.63 ± 18.22	129.50 ± 17.70	0.018
DBP, mmHg, mean ± SD	76.44 ± 11.30	77.74 ± 11.12	0.304	76.70 ± 12.37	76.85 ± 10.87	0.913
Laboratory variables						
Baseline eGFR, mL/min/1.73 m^2, mean ± SD	72.46 ± 19.47	75.97 ± 20.12	0.100	82.96 ± 23.38	100.76 ± 22.23	<0.001
BUN, mg/dL, mean ± SD	18.60 ± 7.06	16.71 ± 5.49	0.003	20.95 ± 8.65	15.62 ± 6.08	<0.001
Uric acid, mg/dL, mean ± SD	6.80 ± 1.69	6.53 ± 1.45	0.140	6.43 ± 1.58	5.65 ± 1.44	<0.001
HbA1c, %, mean ± SD	7.58 ± 1.92	7.34 ± 5.01	0.564	7.74 ± 1.90	7.23 ± 1.94	0.114
Total cholesterol, mg/dL, mean ± SD	178.24 ± 38.78	186.07 ± 45.14	0.080	193.83 ± 52.22	193.91 ± 41.00	0.990
Triglyceride, mg/dL, mean ± SD	136.61 ± 79.06	134.68 ± 72.06	0.815	148.51 ± 97.14	129.34 ± 76.24	0.112
Proteinuria			<.001			0.001
None	41.00	48.48		33.33	50.77	
Trace	4.00	15.55		11.90	14.82	
≥1+	55.00	35.97		54.76	34.41	
Health-related behaviors						
Cigarette smoking	38.00	38.00	1.000	4.76	3.61	0.831
Alcohol consumption	14.00	18.39	0.349	2.38	2.93	0.779

Data expressed as mean SD or percentage. BMI = body mass index, BUN = blood urea nitrogen, CKD, chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, SBP = systolic blood pressure, SD = standard deviation.

Table 3 shows the risk factors for renal progression in the male and female patients. According to the univariate analysis results, age (odds ratio [OR] 1.03; 95% confidence interval [CI] 1.01–1.05), family income (OR 1.88; 95% CI 1.07–3.31), poor glycemic control (OR 1.99; 95% CI 1.18–3.35), poor blood pressure control (OR 2.03; 95% CI 1.23–3.34), anemia (OR 2.76; 95% CI 1.32–5.75), BUN (OR 1.05; 95% CI 1.02–1.10), and proteinuria (OR 1.81; 95% CI 1.11–2.95) were positively associated with renal progression in the male patients. However, years of education (OR 4.28; 95% CI 1.28–14.35), family income (OR 2.43; 95% CI 1.13–5.26), poor glycemic control (OR 2.90; 95% CI 1.66–5.06), poor blood pressure control (OR 2.35; 95% CI 1.37–4.05), gout (OR 2.26; 95% CI 1.11–4.58), BUN (OR 1.08; 95% CI 1.04–1.12), uric acid (OR 1.39; 95% CI 1.17–1.65), and proteinuria (OR, 2.19; 95% CI 1.24–3.88) were positively associated with renal progression in the female patients.

Table 3

Univariate analyses of associations between risk factors and renal progression.

Variable	Male OR (95% CI)	Female OR (95% CI)
Demographic characteristics		
Age	1.03 (1.01–1.05)	1.01 (0.99–1.03)
Years of education, y		
<6	1.64 (0.88–3.07)	4.28 (1.28–14.35)
6–12	1.70 (0.95–3.06)	3.36 (0.98–11.46)
≥13	Reference	Reference
Family income, NT dollars		
<40000	1.88 (1.07–3.31)	2.43 (1.13–5.26)
≥40000	Reference	Reference
Clinical variables		
Glycemia control		
Intensive control	Reference	Reference
Poor control	1.99 (1.18–3.35)	2.90 (1.66–5.06)
Blood pressure control		
Intensive control	Reference	Reference
Poor control	2.03 (1.23–3.34)	2.35 (1.37–4.05)
Lipid control		
Intensive control	1.00 (Reference)	1.00 (Reference)
Poor control	0.81 (0.48–1.40)	0.67 (0.38–1.17)
Gout	1.10 (0.64–1.88)	2.26 (1.11–4.58)
Cardiovascular disease	1.49 (0.89–2.50)	1.20 (0.62–2.31)
Anemia	2.76 (1.32–5.75)	1.56 (0.72–3.39)
Physical examination variables		
Waist circumference		
Normal	Reference	Reference
Abnormal	1.06 (0.65–1.70)	1.71 (0.99–2.94)
BMI, kg/m^2		
<18.5	1.15 (0.42–3.19)	2.52 (0.73–8.70)
18.5–23.9	Reference	Reference
≥24	0.96 (0.36–2.56)	2.89 (0.86–9.74)
Laboratory variables		
Baseline eGFR, mL/min/1.73 m^2	0.99 (0.98–1.00)	0.97 (0.96–0.98)
BUN, mg/dL	1.05 (1.02–1.10)	1.08 (1.04–1.12)
Uric acid, mg/dL	1.16 (0.99–1.36)	1.39 (1.17–1.65)
Proteinuria		
None	Reference	Reference
Trace	0.21 (0.05–0.88)	1.24 (0.53–2.93)
≥1+	1.81 (1.11–2.95)	2.19 (1.24–3.88)
Health-related behaviors		
Cigarette smoking	0.99 (0.61–1.61)	1.43 (0.40–5.12)
Alcohol consumption	0.84 (0.45–1.58)	1.20 (0.26–5.56)

BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, OR = odds ratio, SBP = systolic blood pressure.

3.3. Predictive risk factors for renal progression

The predictive risk factors for renal progression in the male and female patients were established through stepwise selection (Fig. 2). After adjusting for several potential confounders, stepwise logistic regression analysis showed that main independent predictive risk factors for the male patients were proteinuria (OR 2.20; 95% CI 1.26–3.84), age (OR 1.04; 95% CI 1.02–1.06), anemia (OR 2.75; 95% CI 1.20–6.30), and poor blood pressure control (OR 1.84; 95% CI 1.05–3.22) (C statistic = 0.72). The main independent predictive factors for the female patients were poor glycemic control (OR 2.28; 95% CI 1.22–4.25), poor blood pressure control (OR 1.93; 95% CI 1.06–3.50), and family income (OR 2.51; 95% CI 1.01–6.20) (C statistic = 0.75).

Proteinuria ($\chi^2 = 14.18$, $P < 0.001$) and poor glycemic control ($\chi^2 = 11.64$, $P = 0.001$) were the most significant risk factors for the male and female patients, respectively, and were included in the logistic regression model. In addition, poor blood pressure control was a significant shared risk factor among the male and female patients.

4. Discussion

This is the first study to examine the risk factors for renal progression in male and female patients with early CKD. The male and female patients have the common factors: family income, poor control of glycemia and blood pressure, BUN, and proteinuria. The results were consistent with previous studies. For example, hyperglycemia has been reported as a crucial risk factor for microvascular complications, including nephropathy, retinopathy, and neuropathy.[42,43] High–normal blood pressure were the independent risk factor for the development of ESRD.[44] Annual income has been reported as potential risk factors for CKD.[33] However, our results showed that poor lipid control did not influence the risk of renal progression. In agreement with previous studies, lipid control parameters, namely total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and serum triglycerides, were not associated with severe renal progression outcomes.[45,46] Furthermore, dyslipidemia was not an independent predictor of CKD[47] or ESRD.[35] Our results indicated that poor lipid control was not positively associated with renal progression in both the male and female patients with early CKD.

To examine the predictive risk factors for renal progression, we further constructed a subset multivariate logistic model with stepwise variable selection. Figure 2 shows the significant level of risk factors for renal progression. Proteinuria, age, anemia, and poor blood pressure control were the significant risk factors for the male patients, whereas poor control of glycemia and blood pressure and family income were the significant risk factors for the female patients. Especially, proteinuria and glycemic control were very important for male and female patients, respectively. Proteinuria has been recognized to relate to chronic glomerular disease because urinary proteins themselves may develop tubulointerstitial inflammation and fibrosis effects, which in turn directly contribute to renal damage.[39,48] Patients with hyperglycemic lead to onset of kidney progression because hyperglycemic may elicit glomerular and renal hypertrophy, which in turn lead to the increased urinary albumin, tubulointerstitium fibrosis, and tubular atrophy.[49]

According to the univariate analysis results, poor control of glycemia and proteinuria was significantly associated with renal progression for both male and female. As we further used stepwise logistic regression with poor control of glycemia and proteinuria being forced to entry the model, the results showed that male patients were sensitive to proteinuria rather than poor control of glycemia, whereas female patients were sensitive to poor control of glycemia rather than proteinuria. Based on the analysis results, there were significantly different between the risk factors of male and female patients. As proteinuria dipstick test used in this study mainly detected urinary albumin, our findings were consistent with previous studies reported urinary albumin excretion as a risk factor for male patients.[45] In addition, pervious cohort studies indicated that the poor glycemic control affected subsequent clinical outcomes for female patients, which were consistent with our findings.[42,43] The plausible explanations for the sex differences in progression risk factors include

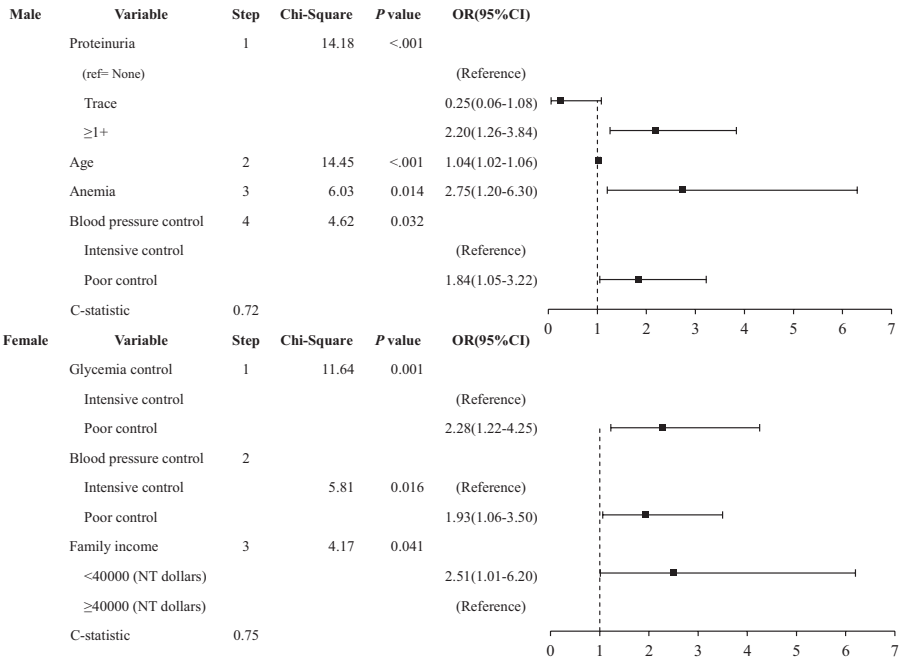

Figure 2. Predictive risk factors associated with renal progression among the male and female patients.

cultural and social environmental differences (e.g., differences in treatment prescriptions or disease perceptions) and biologically influences (e.g., hormonal and genetic factors).[4,5,8,10] Further investigations are encouraged to investigate the effect of mechanism of sex difference on renal progression.

In addition, poor blood pressure control was a shared risk factor for renal progression in the male and female patients in our study. SBP in male and female patients is an independent risk factor for renal progression.[45] Tozawa et al[44] also argued that controlling blood pressure within normal levels can prevent development of ESRD in both male and female patients.[44]

This study had several advantages. First, we had a large cohort that included patients from multicenter around Taiwan. Second, we provided sex-specific data, showing different indecently specific risk factors for renal progression in sex. Third, information on demographic characteristics and health-related behaviors was collected through face-to-face interviews by well-trained interviewers to ensure data quality.

However, there are some limitations in our study. First, because patients voluntarily enrolled in the study, a potential selection bias was unavoidable. Second, variables of clinical disease were collected using a structured questionnaire, introducing underestimation of certain test results. Third, this study did not contain the information of potential factors, including medication (e.g., H2 blocker and Lipanthyl). However, Taiwan's clinical drug guideline indicated that H2 blocker and Lipanthyl should be carefully used for renal disease patients. Thus, the medication might have insignificant influence on renal progression in our studying patients.

In conclusion, this study determined sex-specific prediction models for risk factors for renal progression. Moreover, we revealed proteinuria as the most crucial risk factor for male patients and poor glycemic control as the crucial risk factor for female patients. Poor blood pressure control was a mutual risk factor for male and female patients. Thus, we suggest that while monitoring and providing intervention to patients with early CKD, clinicians should focus on sex-specific risk factors. The male patients refer to those who are aging and have poor control of blood pressure, anemia, and proteinuria; the female patients refer to those who have poor control of glycemia, blood pressure, and lower income. Therefore, effectively monitoring the major risk factors for renal progression among male and female patients is essential for reducing the incidence rate of ESRD.

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