ORIGINAL ARTICLE

Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study

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To examine the clinical significance of hypertensive nephropathy (HN) among non-diabetic chronic kidney disease (CKD) patients. The study comprised 2692 CKD patients recruited from 11 outpatient nephrology clinics; these included 1306 patients with primary renal disease (PRD), 458 patients with HN, 283 patients with diabetic nephropathy (DN) and 645 patients with other nephropathies (ONs). All patients fulfilled the criteria of CKD, with a persistent low estimated glomerular filtration rate (eGFR) $<60 \text{ ml min}^{-1} \text{ per } 1.73 \text{ m}^2$ or proteinuria as determined by a urine dipstick test. The risk factors for cardiovascular disease (CVD), such as ischemic heart disease, congestive heart failure and stroke; all-cause mortality; and progression to end-stage renal failure (dialysis induction) were analyzed using a Cox proportional hazards model in each group. During a mean follow-up period of 22.6 months from recruitment, 100 patients were lost to follow-up and 192 patients began chronic dialysis therapy. A total of 115 CVD events occurred (stroke in 37 cases), and 44 patients died. Regarding CVD events and death, there were significant differences in the hazard ratios (HRs) for the groups of patients with different underlying renal diseases as determined by both univariate and multivariate analysis adjusted for confounding factors including estimated glomerular filtration rate: PRD, 1.0 (reference); HN, 3.33 (95% confidence interval, 1.82–6.09); DN, 5.93 (2.80–12.52); and ON, 2.22 (1.22–4.05). However, there were no differences in the hazard ratio for dialysis induction for the groups of patients with different underlying renal diseases. HN is associated with an increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.

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INTRODUCTION

Chronic kidney disease (CKD)¹ is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure and all-cause mortality in the general population.^{2–8}

The relation between excess CVD morbidity and mortality, and decreased kidney function has been well demonstrated in diabetic patients^{9,10} in specific sub-populations with preexisting heart disease,^{11,12} hypertension¹³ and dyslipidemia,¹⁴ and in the elderly.¹⁵

Patients with primary or secondary kidney diseases are exposed to several unique factors that increase the frequency of CVD events. These factors include hyperlipidemia and coagulopathy due to nephritic syndrome, systemic inflammation-associated vasculitides, underlying collagen or infectious disease, and the use of therapeutic agents such as steroids.^{16–18} Even though patients with hypertensive nephropathy (HN, nephrosclerosis) are believed to be at high risk for

progression to kidney failure,¹⁹ the impact of HN on the frequency of CVD events compared with the impact of other nephropathies (ONs) has not been clearly demonstrated.

Accordingly, in terms of risk stratification of patients, it is crucially important to clarify the clinical outcomes of CKD with respect to the underlying renal diseases, especially for CKD cases that are not the result of diabetes. Only a few reports have examined this issue, including our preliminary report.^{20–22}

The present study aimed to address this issue in a cohort of patients from nephrology clinics.

METHODS

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of the patient characteristics and outcomes of individuals who visit outpatient nephrology clinics in the Miyagi Prefecture (Northeast area of Japan), the details of which have been

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reported elsewhere.²² Eleven affiliated hospitals with Tohoku University, including one university hospital (Tohoku University Hospital), are participating in the project. Patient registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of the Tohoku University School of Medicine and by the respective participating hospitals.

Registration was conducted from May 2006 to November 2008, and 4015 patients were registered. Among the original registered patients, certain subjects were excluded from the present analysis—150 cases lacking data on serum creatinine levels and 241 cases with unknown underlying renal diseases. Among patients with essential hypertension and estimated glomerular filtration rates (eGFRs) above 60 ml min⁻¹ per 1.73 m², those who did not have positive proteinuria findings at registration (*n*=836) and those lacking urinary testing results (*n*=96) were excluded. As a result, 2692 patients with complete CKD criteria were selected¹ and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to one of four underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): primary renal disease (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including biopsy-proven cases (81%); HN, defined by a history of hypertension and the absence of other possible disorders, including cases of biopsy-proven nephrosclerosis (20.8%); diabetic nephrop-

athy, defined by a history of diabetes accompanying nephropathy and the absence of other possible renal disorders or presenting with nephropathy with diabetic retinopathy and the absence of other possible renal disorders, including biopsy-proven diabetic nephropathy (24.9%); and ONs, defined by ONs not included in the other three groups, including biopsy-proven cases (24.9%). The HN cases included in the present classification were in those patients who had an eGFR below 60 ml min⁻¹ per 1.73 m² or positive proteinuria as determined by a dipstick test.

The primary outcomes of this survey included CVD events, such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes within 12 months after registration were surveyed using the medical records of the hospitals, death certificates and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (International Classification of Disease, 10th revision: I00 to I99), and the number of patients with angina pectoris or acute myocardial infarction included those who had received coronary stenting, angioplasty or bypass surgery, or who had a definite clinical course of acute myocardial infarction. In patients with congestive heart failure, only those who were admitted for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke,²³ and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Table 1 Patient characteristics

	All	PRD	ONs	HN	DN
<i>n</i>	2,694	1,306	643	462	283
Age (years)	60.0 ± 16.2	55.7 ± 16.6	58.6 ± 15.7	70.3 ± 11.4	66.5 ± 12.6
Gender (male)	1441 (53.5%)	716 (54.8%)	275 (42.8%)	262 (56.7%)	188 (66.4%)
BMI	23.5 ± 3.8	23.4 ± 3.8	22.9 ± 3.7	24.2 ± 3.8	24.1 ± 3.8
<i>Blood pressure (mmHg)</i>					
Systolic	130.95 ± 16.2	129.21 ± 15.1	129.33 ± 15.8	134.68 ± 17.4	136.64 ± 17.5
Diastolic	76.7 ± 10.9	77.3 ± 10.4	76.7 ± 10.7	76.4 ± 11.8	74.0 ± 11.6
<i>CKD stage (%)</i>					
Stage 1+2	40.3	49.1	47.4	17.7	20.4
Stage 3	37.6	35.7	31.1	57.6	28.3
Stage 4	13.4	10.3	14.5	15.8	21.6
Stage 5	8.7	4.9	7.0	8.9	29.7
<i>Comorbidities (%)</i>					
Cardiac disease	12.8	7.5	12.3	21.2	24.7
Stroke	6.5	3.5	5.9	11.9	12.7
Diabetes	27.4	15.5	18.0	34.2	100.0
Hypertension	77.1	72.8	70.6	93.7	89.4
Hyperlipidemia	42.6	44.6	36.8	42.2	51.6
<i>Pharmacotherapy (%)</i>					
ARB/ACEI	62.7	62.1	52.6	70.1	76.3
Statin	34.7	36.1	30.0	32.3	43.1
ESA	6.5	3.6	4.8	7.8	21.9
Steroid	25.3	32.9	36.2	2.8	2.1
Proteinuria (%)	49.6	47.3	41.2	49.8	78.9
Hemoglobin (g dl ⁻¹)	12.8 ± 2.1	13.2 ± 1.9	12.6 ± 2.0	12.7 ± 2.1	11.6 ± 2.3
Total cholesterol (mg dl ⁻¹)	197.6 ± 38.7	198.7 ± 35.9	203.5 ± 41.3	190.99 ± 39.9	190.4 ± 41.4
Smoker (%)	16.2	15.8	14.6	16.2	21.6
Renal biopsy proven (%)	62.7	81.0	53.5	20.8	24.9
					mean ± s.d.

Abbreviations: ARB/ACEI, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; BMI, body mass index; DN, diabetic nephropathy; ESA, erythropoiesis stimulating agent; HN, hypertensive nephropathy; ONs, other nephropathies; PRD, primary renal disease.

Data collection

Serum creatinine levels were measured using the enzyme assay method. Kidney function was determined using the formula for eGFR for Japanese individuals.²⁴ Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Patients were considered to be positive for macroalbuminuria when the dipstick result was positive or greater, corresponding to a urinary protein level $> 30 \text{ mg dl}^{-1}$.²⁵ Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the subject in a seated position. Information on medications at baseline and each patient's history of CVD, diabetes mellitus, hypertension and hyperuricemia were obtained from the medical records or from the results of blood examinations at registration. Subjects receiving lipid-lowering drugs or displaying serum cholesterol levels $> 220 \text{ mg dl}^{-1}$ were considered to have hypercholesterolemia. Subjects with fasting glucose levels $> 126 \text{ mg dl}^{-1}$ or non-fasting glucose levels $> 200 \text{ mg dl}^{-1}$ or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and either baseline kidney function or underlying renal disease were examined using Cox proportional hazard model analysis adjusted for confounding factors.

Data are shown as means $\pm$ s.d. A *P*-value < 0.05 indicated statistical significance. All statistical analyses were conducted using STATA version 10.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

During an observation period of 22.6 ± 11.9 months, 100 patients were lost because of a switch to other medical services or to the patient quitting due to social reasons, and the follow-up of 192 patients was ended because of the initiation of maintenance dialysis therapy. There were 115 cases of CVD events (37 cases of stroke) and 44 cases of all-cause death (Table 2).

Table 2 Number of events

CKD stage	CVD	Stroke	Death	ESRD
<i>Primary renal disease</i>				
CKD1+2	2	1	1	—
CKD3	7	2	6	2
CKD4	2	1	2	8
CKD5	—	—	1	40
<i>Hypertensive nephropathy</i>				
CKD1+2	4	—	1	1
CKD3	12	8	6	—
CKD4	7	4	3	6
CKD5	3	2	3	24
<i>Diabetic nephropathy</i>				
CKD1+2	4	3	—	1
CKD3	7	1	3	1
CKD4	8	—	5	18
CKD5	10	3	4	54
<i>Other nephropathies</i>				
CKD1+2	2	7	2	—
CKD3	3	4	3	3
CKD4	6	1	4	9
CKD5	1	—	—	25

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease (dialysis induction).

In terms of CVD events and all-cause mortality, significant increases in hazard ratios were seen with increasing CKD stage using univariate analysis (Figure 1); however, these trends disappeared after multivariate adjustment (Table 3a). Significant differences in hazard ratios were seen with respect to underlying renal diseases using univariate analysis, and these differences were significant even after adjusting for confounding factors including eGFR (Table 3b).

Dialysis was started only for those patients who had a CKD stage 4 to 5 at the time of entry (Figure 2; CKD1+2: 0.2%, CKD3: 0.6%,

Figure 1 Event-free survival for cardiac disease, apoplexy and all cause of death for patients at different chronic kidney disease (CKD) stages.

Table 3a Risk for endpoints of CVD, stroke and death by CKD stage in all patients

CKD stage	CVD	Stroke	Death	Univariate analysis		Multivariate analysis ^a	
				HR	95% CI	HR	95% CI
CKD 1+2	12	11	4	1.00		1.00	
CKD 3	29	15	18	2.21	1.37–3.55	1.06	0.64–1.77
CKD 4	23	6	14	4.39	2.62–7.36	1.76	1.00–3.12
CKD 5	14	5	8	7.47	4.22–13.24	2.29	1.17–4.49

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease (such as angina pectoris, acute myocardial infarction and congestive heart failure); HR, hazard ratio.

^aAdjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin-angiotensin system) inhibitors.

Table 3b Risk for endpoints of CVD, stroke and death by underlying renal diseases in all patients

Underlying renal disease	CVD	Stroke	Death	Univariate analysis		Multivariate analysis ^a	
				HR	95% CI	HR	95% CI
PRD	11	4	10	1.00		1.00	
ONs	12	12	9	3.17	1.78–5.62	2.22	1.22–4.05
HN	26	14	13	7.12	4.18–12.14	3.33	1.82–6.09
DN	29	7	12	10.88	6.29–18.84	5.93	2.80–12.52

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DN, diabetic nephropathy; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.

^aAdjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin-angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

Figure 2 Event-free survival for progression to end-stage renal disease (dialysis induction) for patients at different chronic kidney disease (CKD) stages.

Table 4 Risk of progression to ESRD (dialysis induction) by underlying renal disease

Underlying Renal disease	ESRD	Univariate analysis		Multivariate analysis ^a	
		HR	95% CI	HR	95% CI
PRD	50	1.00		1.00	
ONs	37	1.43	0.94–2.19	1.11	0.70–1.76
HN	31	1.09	0.70–1.71	1.13	0.69–1.88
DN	74	5.25	3.66–7.53	1.25	0.68–2.28

Abbreviations: CI, confidence interval; DN, diabetic nephropathy; ESRD, end-stage renal disease; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.

^aAdjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin-angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

CKD4: 11.4%, CKD5: 61.1%), and no significant differences were observed with respect to underlying renal diseases after adjusting for confounding factors, including eGFR (Table 4).

DISCUSSION

This study aimed to clarify the impact of underlying renal diseases on CVD events and death before the initiation of dialysis treatment by analyzing the outcomes of 2692 CKD outpatients from 11 nephrology clinics. After 22.6 months of follow-up, there was a significant difference in the frequencies of CVD events and mortality among groups of patients with different underlying renal diseases, even after adjusting for possible confounding factors including kidney function. These findings showed that patients with HN represent a high-risk group, except for diabetic nephropathy patients, followed by ONs and PRD. In contrast, in terms of chronic dialysis induction, no significant differences were observed based on underlying renal diseases.

Both traditional and non-traditional mechanisms underlie the increased risk of CVD among CKD patients. Traditional factors include hypertension, diabetes, hyperlipidemia and smoking, whereas non-traditional factors include specific factors related to the uremic milieu, such as fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, enhanced inflammation and oxidative stress, and the accumulation of uremic toxins.^{26–34} Therefore, subjects with vasculopathy demonstrated by traditional factors are thought to undergo accelerated vascular damage along with progression of the CKD stage. Hypertension is a predominant risk factor for CVD in the general population, and it is logical that long-standing exposure to

pathological conditions such as hypertension may have resulted in an increased frequency of CVD and mortality among non-diabetic subjects with HN. Several factors could have contributed to the better CVD outcomes in the group with PRD. First, half of the patients with PRD had immunoglobulin A nephropathy; glucocorticoid therapy does not increase the risk of CVD for these patients.³⁴ Blood pressure was also more adequately controlled in these patients than in patients in the other groups (Table 1). In addition, prevalent vasculopathy was not predominant in pre-dialysis PRD patients, as has been indicated for pediatric patients.^{35,36} These results indicate that CKD staging cannot be applied on its own to predict which subjects are at high risk of CVD without taking into account the type of underlying renal disease. These results also suggest that individuals with HN should be the primary targets of CVD prevention measures among non-diabetic CKD patients.

In contrast, the present study revealed that the differences among underlying renal diseases did not have any influence on the frequency of the induction of dialysis after adjusting for confounding factors, including eGFR. In addition, dialysis induction was limited to subjects with CKD5. This result may confirm the clinical notion that CKD5 is the primary criterion for dialysis induction, as recommended in published guidelines.^{37–39}

In the present study, several clinical issues that might have biased the analytical results must be considered. First, because all of the included patients were recruited from nephrology clinics, our patient selection may have introduced a bias toward relatively better medical compliance among those patients with modifiable factors, including the uremic milieu and blood pressure. Second, among patients with hypertension or diabetes, patients who had presented with proteinuria before entry into the study and who had responded to medical treatment thereafter were excluded from the study unless their eGFR was $<60 \text{ ml min}^{-1}$ per 1.73 m^2 . Thus, the patients with diabetes or HN included in the present study may have been relatively resistant to conventional therapies. This resistance may have made their outcomes relatively worse, even though we adjusted for positive findings for proteinuria. Finally, data on microalbuminuria were not available in the present study. Because the clinical significance of microalbuminuria has been well demonstrated, further study is needed to determine the effect of microalbuminuria in these patients.

In conclusion, the present study demonstrated that patients with HN are at increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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