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ORIGINAL ARTICLE

Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes

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Abstract
Background The number of patients suffering from diabetic nephropathy resulting in end-stage kidney disease is increasing worldwide. In clinical settings, there are limited data regarding the impact of the urinary albumin-to-creatinine ratio (UACR) and reduced estimated glomerular filtration rate (eGFR) on renal and cardiovascular outcomes and all-cause mortality.
Methods We performed a historical cohort study of 4328 Japanese participants with type 2 diabetes from 10 centers. Risks for renal events (requirement for dialysis or transplantation, or half reduction in eGFR), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), and all-cause mortality were assessed according to UACR and eGFR levels.
Results During follow-up (median 7.0 years, interquartile range 3.0–8.0 years), 419 renal events, 605 cardiovascular events and 236 deaths occurred. The UACR levels increased the risk and the adjusted hazard ratios for these three events. In addition to the effects of UACR levels, eGFR stages significantly increased the adjusted hazard ratios for renal events and all-cause mortality, especially in

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patients with macroalbuminuria. Diabetic nephropathy score, based on the prognostic factors, well predicted incidence rates per 1000 patient/year for each event.
Conclusions Increased UACR levels were closely related to the increase in risks for renal, cardiovascular events and all-cause mortality in Japanese patients with type 2 diabetes, whereas the association between high levels of UACR and reduced eGFR was a strong predictor for renal events.

Keywords Diabetic nephropathy · Chronic kidney disease · Albuminuria · Cardiovascular disease · Mortality · Glomerular filtration rate

Introduction

Diabetic nephropathy is a leading cause of end-stage kidney (renal) disease (ESKD or ESRD) worldwide [1]. In addition, cardiovascular diseases and deaths increase in patients with diabetic nephropathy before and after dialysis [2–4]. Therefore, to determine and manage risk factors for progression of renal and cardiovascular outcomes and mortality is of importance to prolong the life expectancy of diabetic patients.

A high urinary albumin-to-creatinine ratio (UACR) and low estimated glomerular filtration rate (eGFR) have been believed to be predictors for diabetic ESKD and death [5–7]. Kidney Disease Improving Global Outcomes (KDIGO) provided a new classification for chronic kidney disease (CKD) by adding stages that stratified urinary albumin excretion as well as eGFR and emphasizing clinical diagnosis [8]. This new classification, mainly based on the collaborative meta-analysis of general population cohorts [8], has shed light on prognosis assigned by clinical diagnosis, stage, and other key factors relevant to renal and cardiovascular outcomes. However, the clinical impact of UACR levels in combination with eGFR on outcomes in Japanese patients with diabetic nephropathy needs to be confirmed. Therefore, deeper clinical insights of UACR along with GFR are required to provide a key for the pathogenesis and outcomes of progressive renal complications, and associated cardiovascular events in type 2 diabetic patients.

Here we examined the prognostic value of UACR and eGFR for renal events, cardiovascular events and all-cause mortality in Japanese patients with type 2 diabetes. Furthermore, we proposed a diabetic nephropathy score for predicting prognosis in diabetic patients.

Subjects and methods

Subjects

This study was a historical cohort consisting of 4814 Japanese patients with type 2 diabetes who were treated by trained physicians at 10 centers between 1985 and 2010. Four hundred and fifty-nine patients were excluded because of age <18 ($n = 6$), follow-up <1 year ($n = 151$) and no measurement of urinary albumin or HbA1c or blood pressure (BP) ($n = 329$), leaving 4328 Japanese patients to be enrolled in this study. Patients with secondary diabetes, renal transplantation or dialysis were also excluded.

This study was conducted according to the ethical guidelines for epidemiological research designed by the Japanese Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour, and Welfare (http://www.lifescience.mext.go.jp/files/pdf/n796_01.pdf).

The study design was included in a comprehensive protocol of retrospective study at the Division of Nephrology, Kanazawa University Hospital approved by Kanazawa University ethical committee (approval number 815).

Follow-up and assessments

Type 2 diabetes was defined according to the Japan Diabetes Society (JDS) criteria [9]. In this historical cohort study, UACR and eGFR were also determined. Measurement of UACR, by a turbidimetric immunoassay at each laboratory, was performed on spot urine samples at baseline. Serum creatinine was measured at baseline, at subsequent yearly intervals, and at the end of follow-up. Serum and urinary concentrations of creatinine were measured by an enzymatic method, and eGFR was estimated using the equation proposed by the Japanese Society of Nephrology [10]. Both UACR and serum creatinine were measured at local laboratories. At each study visit, blood pressure (BP) was measured in the sitting position. Hypertension was defined as BP $\geq$ 140/90 mmHg or

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current use of antihypertensive drugs. Non-fasting blood samples were obtained for measurements of HbA1c and lipid levels at local laboratories. HbA1c was measured and standardized by the JDS (normal range 4.3–5.8 %) and certified by the US National Glycohemoglobin Standardization Program (National Glycohemoglobin Standardization Program, NGSP; NGSP = JDS + 0.4) [9].

UACR and GFR categories

Based on the new classification of CKD [8], the albuminuria category was classified at baseline as normoalbuminuria (<30 mg/g), microalbuminuria (≥30 and <300 mg/g), and macroalbuminuria (≥300 mg/g). In addition, baseline eGFR levels were divided into six categories: ≥90, 60–89, 45–59, 30–44, 15–29 and <15 ml/min per 1.73 m^2. Patients examined in this study were categorized and assessed based on the above classifications.

Outcomes

The main outcomes of this study were renal events (requirement for dialysis or transplantation, or half reduction in eGFR), cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), and all-cause mortality death. These conditions corresponded to the International Classification of Diseases, 11th version (http://www.who.int/classification/icd/en/). Definitions for nonfatal myocardial infarction and nonfatal stroke are given elsewhere [11]. Patients were referred to cardiologists, neurosurgeons, neurologists or else to confirm diagnoses. Only the first event of the relevant outcome type was included in each analysis and the last day of the observation period was also noted if there were no incidences.

Statistical analysis

Data are expressed as mean ± SD or median (interquartile range). Incidence rates of renal events, cardiovascular events, and all-cause death for different categories were calculated. Cox proportional hazards analysis was used to compute hazard ratios and 95 % confidence intervals (CI) to assess the impact of albuminuria and eGFR on the outcomes by using the group with eGFR ≥60 ml/min per 1.73 m^2 and/or the group with normoalbuminuria (<30 mg/g) as the reference [8]. In multivariate analysis, adjustment for risk factors for renal events, cardiovascular events, or all-cause mortality included age, gender, HbA1c, and systolic BP. A p value <5 % was considered significant. p values for trend tests examined whether UACR and eGFR levels were associated with increased hazard ratios. Trend tests across increasing risks for renal, cardiovascular events and all-cause mortality are stratified by factors for diabetic nephropathy score.

All analyses were performed with the statistical software package SPSS (SPSS Japan, Tokyo, Japan).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of patients examined in this study. The 4328 patients were distributed according to CKD stage and were followed until the onset of the first event or the end of the observation period (Table 1).

Incidence of numbers of patients of each event

During a median follow-up of 7.0 years (interquartile range 3.0–8.0 years), 419 renal events, 605 cardiovascular events and 236 deaths occurred, which were stratified by stages of renal function and levels of UACR with each event (Table 2). The incidence rates of each outcome per 1000 person-years were 19.8 for renal events, 23.3 for cardiovascular events and 8.4 for all-cause mortality. The incidence of each event increased with worsening of UACR levels and eGFR stages. Of importance, high incidence rates were noted in patients with macroalbuminuria plus reduced eGFR, especially for renal events (Table 2).

Risk for renal events, cardiovascular events, and all-cause mortality stratified by albuminuria and eGFR

Risks for renal events, cardiovascular events and all-cause mortality were evaluated by Cox proportional hazards analysis. The estimates were adjusted for age, gender, HbA1c, and systolic BP. The adjusted hazard ratios for renal events were 3.21 (95 % CI 2.31–4.47) for microalbuminuric patients and 21.86 (95 % CI 16.15–29.59) for macroalbuminuric patients as compared to normoalbuminuric patients as reference. Similarly, the adjusted hazard ratios for cardiovascular events and all-cause mortality were 1.38 (95 % CI 1.14–1.67) and 1.37 (95 % CI 0.99–1.89) for microalbuminuric patients and 2.05 (95 % CI 1.61–2.58) and 3.60 (95 % CI 2.53–5.20) for macroalbuminuric patients as compared to reference, respectively. Interestingly, UACR levels had the most significant impact on renal events. In addition to the effects of UACR levels, eGFR stages significantly increased the adjusted hazard ratios for renal events in patients with macroalbuminuria (Table 3). In Table 3, hazard ratios for cardiovascular events increased in patients with a higher UACR. In

Table 1 Baseline characteristics of participants ($n = 4328$)

Variable	All	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	*p* For trend
N	4328	2679	1115	534	
Age (years; mean [SD])	60.2 (11.6)	59.5 (11.4)	61.9 (11.5)	59.8 (12.0)	<0.001
Male (*n* [%])	2546 (58.8)	1531 (57.1)	656 (58.8)	359 (67.2)	<0.001
Kidney factors					
UACR (mg/g; median [IQR])	18.2 (8.6–66.6)	10.2 (6.5–16.4)	66.6 (42.6–121.3)	994.8 (518.5–2272.5)	<0.001
eGFR (ml/min/1.73 m^2; mean [SD])	77.0 (25.9)	81.3 (23.8)	76.4 (25.3)	56.9 (28.0)	<0.001
eGFR ≥90 (*n* [%])	1201 (27.7)	839	297	65	
eGFR 60–89 (*n* [%])	2051 (47.4)	1371	530	150	
eGFR 45–59 (*n* [%])	642 (14.8)	345	174	123	
eGFR 30–44 (*n* [%])	311 (7.2)	109	100	102	
eGFR 15–29 (*n* [%])	117 (2.7)	15	14	88	
eGFR <15 (*n* [%])	6 (0.1)	0	0	6	
BP (mmHg)					
Systolic BP (mean [SD])	131.0 (18.6)	127.2 (16.6)	134.2 (18.4)	143.0 (22.0)	<0.001
Diastolic BP (mean [SD])	74.3 (18.0)	73.3 (20.7)	74.8 (11.8)	78.1 (13.1)	<0.001
Other major risk factors					
HbA1c (%; mean [SD])	7.6 (1.7)	7.5 (1.7)	7.8 (1.7)	7.9 (1.8)	<0.001
Total cholesterol (mg/dL; mean [SD])	205.2 (35.9)	205.3 (34.1)	202.2 (33.9)	214.2 (50.2)	0.925
Body mass index (kg/m^2; mean [SD])	25.3 (4.2)	25.1 (4.2)	25.5 (4.2)	25.4 (4.8)	0.098

Table 2 Number of patients and incidence rates of each outcome stratified by stages of eGFR and albuminuria

UACR	eGFR (ml/min/1.73 m^2)					
	>90	60–89	45–59	30–44	15–29	<15
Renal events (RRT or halving reduced eGFR)						
Normoalbuminuria	58 (4.2)		4 (2.3)	3 (6.9)	1 (21.3)	0
Microalbuminuria	31 (17.2)	41 (13.1)	15 (18.0)	10 (21.0)	1 (25.6)	0
Macroalbuminuria	20 (59.5)	62 (87.7)	56 (126.7)	54 (193.5)	61 (309.6)	2 (250.0)
Cardiovascular events						
Normoalbuminuria	229 (16.2)		40 (23.1)	14 (33.0)	1 (18.9)	0
Microalbuminuria	31 (16.1)	95 (28.7)	33 (32.6)	28 (56.1)	2 (43.5)	0
Macroalbuminuria	7 (17.2)	41 (44.6)	30 (44.3)	30 (64.2)	23 (57.9)	1 (100.0)
All-cause mortality						
Normoalbuminuria	70 (4.7)		26 (13.8)	4 (8.2)	4 (67.8)	0
Microalbuminuria	11 (5.4)	32 (8.9)	13 (11.9)	5 (8.5)	6 (117.6)	0
Macroalbuminuria	6 (14.4)	13 (12.3)	19 (24.6)	13 (23.6)	12 (26.8)	2 (142.9)

Number of patients (incidence rates per 1000 person-years)

RRT renal replacement therapy

addition, our results showed that there was a slight increase in the hazard ratios of cardiovascular events based on UACR levels plus co-existing reduced eGFR, especially in patients with microalbuminuria based on *p* for trend. In contrast, all-cause mortality was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2, and the presence of macroalbuminuria even with preserved eGFR. The present study also revealed that normoalbuminuric renal insufficient diabetic patients did not have relatively poor outcomes for renal events. Table 4 highlights the impact of low GFR and/or UACR on three distinct outcomes.

The clinical significance of diabetic nephropathy score in predicting the prognoses of renal events, cardiovascular events, and all-cause mortality

Considering the results of univariable and multivariable analyses, weighted arbitrary scores were allocated to each

Table 3 Hazard ratios based on CKD stages for each outcome

UACR	eGFR (ml/min/1.73 m^2)						*p* for trend (eGFR)
	>90	60–89	45–59	30–44	15–29	<15	
Renal events (RRT or halving reduced eGFR)							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	0.69 (0.24–1.98)	1.83 (0.53–6.31)	11.59 (1.43–93.78)	NA	0.85
Microalbuminuria	3.31 (2.07–5.28)	3.04 (1.98–4.68)	3.36 (1.63–6.93)	3.10 (1.41–6.83)	3.60 (0.42–31.28)	NA	0.60
Macroalbuminuria	11.14 (5.87–21.17)	15.64 (10.30–23.74)	33.37 (20.58–50.91)	41.36 (25.09–68.16)	71.58 (40.41–126.80)	NA	<0.01
p for trend (albuminuria)	<0.01	<0.01	<0.01	<0.01	0.06	NA	
Cardiovascular events							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	1.05 (0.73–1.49)	1.30 (0.74–2.28)	0.42 (0.06–3.06)	NA	0.46
Microalbuminuria	1.01 (0.69–1.49)	1.48 (1.15–1.90)	1.33 (0.89–2.00)	1.85 (1.20–2.85)	0.47 (0.11–1.97)	NA	0.04
Macroalbuminuria	1.28 (0.56–2.94)	2.10 (1.46–3.02)	1.85 (1.23–2.78)	2.37 (1.55–3.63)	2.09 (1.26–3.45)	12.76 (0.95–171.19)	0.20
p for trend (albuminuria)	0.81	<0.01	0.09	0.45	0.17	NA	
All-cause mortality							
Normoalbuminuria	1.00 (Reference)	1.00 (Reference)	1.67 (1.02–2.74)	1.22 (0.43–3.46)	8.19 (2.65–25.34)	NA	<0.01
Microalbuminuria	1.51 (0.78–2.95)	1.44 (0.92–2.24)	1.22 (0.63–2.35)	0.84 (0.31–2.26)	8.36 (2.81–24.90)	NA	0.04
Macroalbuminuria	4.37 (1.70–11.24)	1.92 (0.97–3.79)	4.84 (2.72–8.62)	4.09 (2.00–8.34)	6.16 (2.80–13.56)	70.57 (3.65–1363.68)	0.06
p for trend (albuminuria)	0.01	0.01	0.01	0.02	0.80	NA	

The estimates are adjusted for age, gender, HbA1c, systolic BP

RRT renal replacement therapy, *NA* not available

Table 4 Hazard ratios based on levels of UACR and eGFR for each outcome

UACR	eGFR (ml/min/1.73 m^2)		
	>60	30–59	<30
Renal events (RRT or halving reduced eGFR)			
Normoalbuminuria	1.00 (Reference)		49.82 (29.9–83.0)
Microalbuminuria	3.26 (2.34–4.55)		
Macroalbuminuria	13.6 (9.3–20.0)	33.0 (22.7–48.2)	
Cardiovascular events			
Normoalbuminuria	1.00 (Reference)		1.54 (1.00–2.39)
Microalbuminuria	1.40 (1.16–1.69)		
Macroalbuminuria	1.90 (1.36–2.65)	2.09 (1.54–2.84)	
All-cause mortality			
Normoalbuminuria	1.00 (Reference)		7.08 (4.16–12.05)
Microalbuminuria	1.30 (0.93–1.81)		
Macroalbuminuria	2.34 (1.35–4.04)	4.59 (2.90–7.25)	

The estimates are adjusted for age, gender, HbA1c, systolic BP

selected variable on the basis of each odds ratio (OR), and we defined a summation of scores as a new risk scoring system as the diabetic nephropathy score. We evaluated the diabetic nephropathy score for predicting the prognoses of renal events, cardiovascular events, and all-cause mortality. Each prognostic factor has a score and the maximum score is 6—microalbuminuria = 1, macroalbuminuria = 2, eGFR <45 ml/min per 1.73 m^2 = 1, age ≥60 years = 1, systolic BP >130 mmHg = 1, and HbA1c (NGSP) ≥6.9 % = 1. This score put stress on amounts of UACR. Importantly, this simple score well predicted the incidence rates per 1000 patient/year for each event (Table 5).

Discussion

In this study we examined the clinical impact of UACR as well as the evaluation of GFR on outcomes in diabetic patients. We now report that increased urinary albumin excretion was strongly associated with risks for renal

Table 5 Diabetic nephropathy score reflects diabetic outcomes

Score	Renal events (RRT or halving reduced eGFR)				Cardiovascular events				All-cause mortality			
	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI	Number of patients	Number of incidents	Rate per 1000 patient-years	95 % CI
0	204	0	0.0		204	2	1.4	0.2–5.1	204	0	0.0	
1	902	18	3.1	1.9–5.0	954	58	9.7	7.4–12.6	954	13	2.1	1.1–3.6
2	1228	54	6.9	5.2–9.0	1,310	174	21.4	18.4–24.9	1310	71	8.1	6.3–10.3
3	952	96	16.6	13.4–20.0	1,017	161	26.2	22.3–30.6	1017	62	9.4	7.2–12.0
4	471	118	46.6	38.5–56.0	532	116	39.0	32.2–46.8	532	45	13.4	9.8–18.0
5	213	93	103.8	83.8–127.0	238	71	60.5	47.3–76.3	238	35	25.5	17.7–35.4
6	61	40	216.2	154.5–294.0	73	23	80.4	51.0–120.7	73	10	28.1	13.5–51.7
p for trend			<0.001				<0.001				<0.001	

events, cardiovascular events and deaths in Japanese patients with type 2 diabetes. Of note, eGFR stages significantly increased the adjusted hazard ratios for renal events, especially when co-existing with macroalbuminuria, while patients with normoalbuminuria had relatively low risks for renal events. All-cause mortality was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2 and the presence of macroalbuminuria even with preserved eGFR. However, the association between normoalbuminuria and reduced eGFR showed relatively low risks for cardiovascular events in the cohort of the Japanese population with type 2 diabetes. These findings suggested that diabetic patients with macroalbuminuira and low GFR had risks for adverse outcomes, even though UACR levels and eGFR had distinct clinical impacts on each event, respectively. Finally, the diabetic nephropathy score based on our present study may be useful for predicting the prognoses of outcomes in diabetic patients.

The present study has clearly shown that renal insufficiency plus the presence of macroalbuminuria accelerated risks for adverse outcomes, especially renal events. Recently, KDIGO reported the definition, classification and prognosis of CKD based both on estimated GFR and urinary levels of albumin excretion, emphasizing that a decrease in GFR as well as macroalbuminuria is important for renal outcomes of CKD [8]. In addition, the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study reported that reduced eGFR with macroalbuminuria was associated with a higher risk for renal events [6]. Interestingly, the Casale Monferrato study revealed that macroalbuminuira was the main predictor of mortality, independently of both eGFR and cardiovascular risk factors [12]. In contrast, reduced eGFR did not increase the adjusted hazard ratio for renal events even in patients with microalbuminuria. This may be partly because the number of microalbuminuric patients with reduced GFR having renal events was relatively small as shown in Table 2. Collectively, these findings suggest that the assessment of macroalbuminuria as well as levels of eGFR may enable us to predict high risk for renal events.

The association between UACR and reduced eGFR showed relatively low risks for cardiovascular events, even though the incidence rate of cardiovascular events was 23.3, which was almost comparable to that observed in the Japan Diabetes Complications Study (JDCS) [13]. Our results also demonstrated that UACR was closely associated with cardiovascular events in patients with eGFR 60–89 ml/min per 1.73 m^2 and that reduced eGFR was important in microalbuminuric patients based on *p* values for trend. Of note, Yokoyama et al. recently reported that the risk for cardiovascular events was associated with progression of UACR stage in type 2 Japanese diabetic

patients [14]. In contrast, reduced eGFR was a high risk for developing cardiovascular endpoints (cardiovascular death, new admissions due to to angina, myocardial infarction, stroke, revascularization or heart failure) and all-cause mortality independent of UACR [15]. Interestingly, the Second Nord-Trøndelag Health (HUNT II) study [16] reported that reduced eGFR with higher UACR was associated with a higher risk for cardiovascular events. This discrepancy compared to our present study may be partly because the number of patients with cardiovascular events in the present study was relatively small as shown in Table 2. Further studies will be required to examine this discrepancy.

This study also revealed that normoalbuminuric renal insufficient diabetic patients did not have relatively poor renal outcomes. In fact, the percentage of diabetic patients with normoalbuminuria and low eGFR is supposed to be relatively common in clinical settings. In this aspect, Yokoyama et al. [17] described that the proportion of subjects with low eGFR (<60 ml/min per 1.73 m^2) and normoalbuminuria was 11.4 % of type 2 diabetic patients examined (262/2,298). Supporting our notion, Rigalleau et al. [18] reported that risk for renal progression in such patients with type 1 or type 2 diabetes is lower. On the contrary, all-cause mortality, not cardiovascular events, was strongly associated with reduced eGFR <30 ml/min per 1.73 m^2 in normoalbuminuric diabetic patients in this present study. Supporting this notion, hazard ratios for all-cause mortality as well as cardiovascular mortality increased in normoalbuminuric diabetic patients with low GFR [19]. The FIELD study also revealed that normoalbuminuric patients with eGFR 30–59 ml/min per 1.73 m^2 had a higher risk of cardiovascular events, cardiovascular death, non-coronary heart disease deaths, death from any cause than normoalbuminuric patients with eGFR ≥60 ml/min per 1.73 m^2 [7]. Interestingly, in the ADVANCE study, patients with normoalbuminuria and eGFR <60 ml/min/1.73 m^2 had a 3.95-fold higher risk for renal events, a 1.33-fold higher risk for cardiovascular events and a 1.85-fold higher risk for cardiovascular death [6]. In contrast, Vlek et al. [20] reported that eGFR <60 ml/min per 1.73 m^2 without UACR mainly influenced the risk of vascular events (hazard ratio 1.50; 1.05–2.15), but did not affect all-cause mortality. Furthermore, in type 2 diabetic patients, eGFR provided no further information for all-cause mortality and cardiovascular mortality in normoalbuminuric patients [14]. Therefore, further studies are needed to determine renal outcomes as well as all-cause mortality in normoalbuminuric diabetic patients with low eGFR.

We proposed a novel diabetic nephropathy score to predict incidence rates per 1000 patient/year for each event. To date, few studies have addressed individual prognostic factors/scores to predict outcomes of diabetic complications in clinical settings. Couchoud et al. [21] reported development and validation of a prognostic score for 6-month mortality in elderly patients starting dialysis for ESKD. Nine risk factors were selected and points assigned for the score were body mass index <18.5 kg/m^2 (2 points), diabetes (1 point), congestive heart failure stages III to IV (2 points), peripheral vascular disease stages III to IV (2 points), dysrhythmia (1 point), active malignancy (1 point), severe behavioral disorder (2 points), total dependency for transfers (3 points) and unplanned dialysis (2 points). These scores effectively predict short-term prognosis among elderly patients, in which approximately 20 % of the patients had diabetic nephropathy. In contrast to this previous study, our simple prognostic scoring system may clearly predict cardiovascular events and all-cause mortality as well as renal events for patients of any age. Even though validation of this score system will be required for other cohorts, this system seems simple and useful for predicting clinical aspects.

To date, UACR levels and reduced eGFR have independently been reported to predict cardiovascular and real outcomes in diabetes [6]. Previously, diabetic patients with microalbuminuria/macroalbuminuira had a risk for adverse outcomes, including cardiovascular events, cardiovascular death, and renal events as reported by the ADVANCE study [6]. Importantly, the present study, consisting of 4328 Japanese patients with type 2 diabetes, was critically different from the ADVANCE study in terms of (1) being a historical cohort study consisting of 10 centers, (2) longer observation period (median 7.0 years), (3) including the assessment of all-cause mortality, (4) including assessment of each event based on the new classification CKD stages, and (5) providing a diabetic nephropathy score to predict the prognoses of renal events, cardiovascular events, and all-cause mortality. Therefore, our present study further revealed the clinical significance of UACR and eGFR on adverse outcomes in diabetic patients.

There are several limitations to this study. First, the lack of histologically proven diabetic nephropathy should be discussed, even though diabetic nephropathy is clinically diagnosed by the presence of microalbuminuria. Second, the low incidence of cardiovascular events may result in a relatively weak statistical power. Furthermore, the lack of data regarding whether enrolled patients have predisposing cardiovascular diseases must be considered. However, this multicenter observational study of 4328 diabetic patients over 7 years may strengthen the present results and increase the accuracy of risk estimation and establishment of a prognostic diabetic nephropathy score.

In conclusion, these results conclude that the presence of microalbuminuria/macroalbuminuria is closely related to the increase in risks for adverse outcomes in Japanese diabetic patients, whereas the association between

macroalbuminuria and reduced eGFR was a strong predictor for renal events. Further studies will be required to validate the prognostic factors and related diabetic nephropathy score by using other cohorts together with future perspectives.

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