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One-year estimated glomerular filtration rate decline as a risk factor of cardiovascular and renal end-points in high-risk Japanese patients

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Keywords
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ABSTRACT

Aims/Introduction: As estimated glomerular filtration rate (eGFR) progression might correlate with cardiovascular prognosis, the correlation between 1-year decline in eGFR and cardiovascular incidences and renal outcome was investigated.

Materials and Methods: The 1-year percentage decline in eGFR at the first observation year was calculated in a cohort of the standard versus intEnsive statin therapy for hypercholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) trial participants. The primary end-point was the composite cardiovascular end-point including the renal end-point. The associations between the incidence of each end-point and clinical markers were analyzed using the Cox proportional hazards regression model.

Results: A total of 4,461 patients were analyzed. The mean observation period was 765.3 ± 363.1 days. The best cut-off value of 1-year eGFR decline was 0.099 in the first year for renal end-point prediction by receiver operating characteristic curve analysis. The area under the curve of the model including the 1-year eGFR decline of the first year was significantly larger than the model without it (0.943, 95% confidence interval 0.915–0.971 to 0.967, 95% confidence interval 0.950–0.983, $P = 0.019$). Primary end-point incidences and the renal end-point were much higher in rapid eGFR decliners compared with non-decliners ($P < 0.0001$). The cardiovascular end-point incidence, except for the renal end-point, was not different between the groups. According to Cox regression analysis, 1-year eGFR decline during the first year was a significant risk factor for the end-points, including the renal end-point, independent of albuminuria and eGFR at baseline.

Conclusions: The 1-year eGFR decline rate provided useful information for cardiovascular end-point predictions, including the renal end-point, in addition to the conventional risk factors.

INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) worldwide. It is a public health problem and a major financial burden for healthcare systems[1]. Conventionally, kidney disease as a result of diabetes is called diabetic nephropathy and is diagnosed based on albuminuria; however, DKD diagnosis does not necessitate the presence of albuminuria and is based on the decreased absolute value of the estimated glomerular filtration rate (eGFR). The National Kidney Foundation and Kidney Disease Outcomes Quality Initiative have described the clinical course of DKD, and its complex pathogenesis involving hypertension, dyslipidemia, obesity and atherosclerosis[1]. Albuminuria was used as the primary end-point in earlier studies, whereas, in recent, large clinical studies, eGFR decline has now been accepted as a surrogate end-point[2,3]. Although albuminuria increases the risk of ESRD and cardiovascular (CV) disease, it is unclear whether reduction in albuminuria contributes to improved clinical outcomes. Clinically significant renal end-points, such as kidney replacement, do not frequently occur during the observation period of clinical trials, which makes it difficult to determine whether medical

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treatment really prevents significant kidney outcomes. A recent study concluded that a 30–40% decline in eGFR over a period of 2 years was a surrogate outcome equivalent to clinically significant renal end-points[2]. Therefore, early identification of a declining eGFR might help clinicians identify patients at a high risk for ESRD. Patients who lose renal function at a rate faster than the average age-related decline in eGFR tend to progress to ESRD. The slope of the eGFR decline is not consistent during the course of diabetes, but usually increases with the progression of albuminuria. However, the slope becomes steeper in some patients before the onset of albuminuria, or even without albuminuria in others. Extensive research has been carried out to identify a new clinical marker to detect early eGFR decliners[4,5]. We reported that a maximum 1-year eGFR decline >7.5% could identify patients with a high risk for renal outcome if the eGFR values were mathematically smoothed and the noise was reduced[6], this was nearly equivalent to a 20% eGFR reduction over a period of 1–2 years if the eGFR slope was not mathematically smoothed.

The standard versus intEnsive statin therapy for hypercholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study was a multicenter randomized controlled trial in Japan that compared intensive and standard statin therapy, as the primary prevention modality, in patients with hypercholesterolemia and diabetic retinopathy. The results have been reported elsewhere[7]. Briefly, the primary end-point of the combined CV outcome in the intervention and control groups was not significantly different. However, the occurrence of stroke was significantly decreased with intensive statin treatment. Post-hoc analysis showed that achieving a low-density lipoprotein cholesterol target of <1.81 mmol/L reduced the occurrence of CV events more effectively than achieving a target between 2.59 mmol/L and < 3.10 mmol/L[8]. Renal outcomes, defined as the need for renal replacement therapy or doubling of serum creatinine levels, did not differ between the groups. The effect of eGFR was not assessed in the study and was not used as a predictive marker for renal disease.

The current study, thus, investigated the predictive value of the 1-year eGFR decline rate in the first year of observation for CV incidence and the renal end-point in an EMPATHY study cohort[9].

METHODS

The present study conforms with the provisions of the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. The protocol was reviewed and approved by the institutional review board of the Keio University School of Medicine, Tokyo, Japan.

EMPATHY trial

The EMPATHY trial had a multicenter, prospective, randomized, open-label, blinded end-point (PROBE) design, and enrolled patients from hospitals and family practice clinics across Japan (clinical trial registration number: UMIN000003486). Patients with elevated low-density lipoprotein cholesterol and diabetic retinopathy, and without a history of coronary artery disease were considered eligible and provided written informed consent before enrollment by the investigators. Patients were randomly assigned in equal numbers to oral intensive treatment with a low-density lipoprotein cholesterol target of < 70 mg/dL or standard treatment with a target of 100–120 mg/dL. Medical histories and physical and laboratory evaluations were obtained at the beginning of the run-in period. Bodyweight, blood pressure, pulse rate and laboratory data were measured every 6 months during the treatment period[9]. Laboratory assays included assessment of levels of blood lipids, glycated hemoglobin, blood glucose and insulin, serum electrolytes, and creatinine kinase, as well as hematology, liver and renal function tests, and urinalysis. The levels of lipids, B-type natriuretic peptide, high-sensitivity C-reactive protein, high molecular weight adiponectin and serum creatinine were assayed at a central laboratory (SRL Inc., Tokyo, Japan). The primary outcome was the composite incidence of CV events, including cardiac, cerebral, renal and vascular events, or CV-associated death. Secondary outcomes included death from any cause, study-defined CV events for the primary end-point, stroke and safety. Renal events included initiation of chronic dialysis or at least a twofold increase in serum creatinine level (>1.5 mg/dL). The mean follow-up duration was 37 ± 13 months. The incidence of the primary end-points with intensive treatment was not significantly different from that with conservative treatment. Cerebral events, including ischemic stroke, were significantly fewer with the intensive treatment than with the standard treatment. The occurrence of renal events in the two groups was not significantly different.

Calculation of 1-year eGFR decline rate in the first year after enrollment

eGFR was calculated using the formula provided by the working group of the Japanese Chronic Kidney Disease Initiative: eGFR, mL/min/1.73 m^2 = 194 × (serum creatinine, μg/L) − 1.094 × (age) − 0.287 (×0.739 for women)[10]. At 1 year after the enrollment in the study, the 1-year eGFR decline rate was calculated as $(eGFR_{at\ baseline} - eGFR_{at\ 12\ months}) / eGFR_{at\ baseline}$ (Figure 1).

End-points

The primary and secondary end-points of the EMPATHY study have been previously described[9]. Additionally, the composite incidence of the CV end-point, except for the renal end-point, was analyzed.

Clinical stage of albuminuria

The clinical stage of albuminuria was described based on the urinary albumin/creatinine ratio at baseline as none (<30 mg/g·Cr), microalbuminuria (30–299 mg/g·Cr) or macroalbuminuria (≥300 mg/g·Cr)[11].

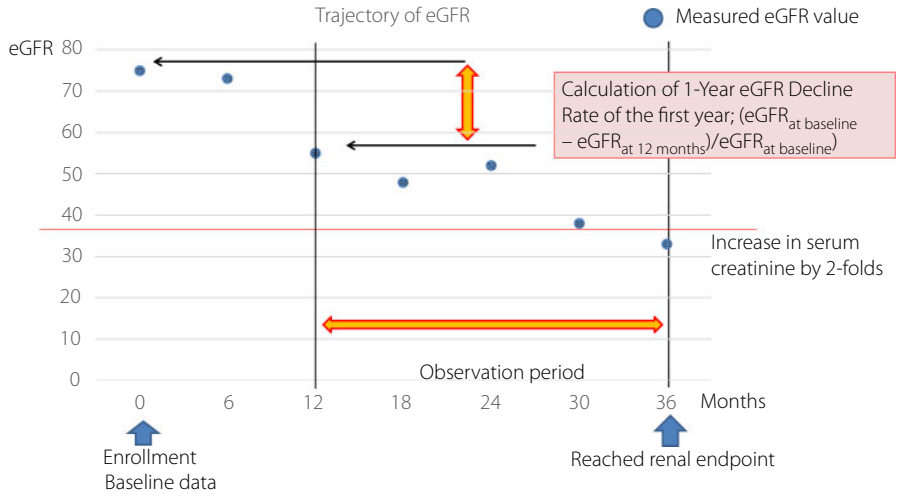

Figure 1 | An example calculation of 1-year estimated glomerular filtration rate (eGFR) decline during the first year and determination of the renal end-point.

Statistical analysis

Statistical analysis was carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Data are reported as the mean ± standard deviation or interquartile range. The level of significance was $P < 0.05$. We carried out receiver operating characteristic curve (ROC) analysis, and the best cut-off value of 1-year eGFR decline in the first year for prediction of the renal end-point was estimated by calculating the minimum Euclidean distance between the ROC curve and the upper left corner of the graph. To estimate the predictive value of the 1-year eGFR decline in the first year, we verified the area under the curve of the ROC analysis by the Mann–Whitney test for two different models of logistic regression analysis. Model 1 consisted of age, sex, body mass index, the presence of hypertension, smoking, clinical stage of albuminuria at baseline and eGFR at baseline as covariates. In model 2, the 1-year eGFR decline rate of the first year was added as a covariate to model 1.

Patients with an eGFR decline greater than the best cut-off value for the renal end-point in the first year of the observation were defined as 'fast decliners,' and the others were defined as 'non-decliners.' Differences in the baseline characteristics between the groups were examined by non-parametric Mann–Whitney *U*-test for continuous variables, and the χ^2-test for categorical variables. Time-to-event analysis for each end-point was carried out by the log-rank test. Cox regression analysis was carried out to determine the hazard ratio (HR) for the end-points of risk factors, such as age, sex, body mass index, the presence of hypertension, smoking, clinical stage of albuminuria at baseline, eGFR at baseline and 1-year eGFR decline in the first year. HR was calculated with 95% confidence intervals (CI).

RESULTS

Patient inclusion and baseline characteristics

In the present study, 4,461 patients of the EMPATHY study, whose 1-year eGFR decline rate in the first year was available, were analyzed. The mean observation period from 1 year after enrollment was 785.1 ± 349.3 days. A total of 81 patients reached a renal end-point (1 for dialysis and 80 for the twofold increase in serum creatinine level).

ROC analysis of the 1-year eGFR decline rate of the first year for the renal event and the best cut-off point

The ROC analysis of the renal end-point showed that the area under the curve of the 1-year eGFR decline rate in the first year was 0.880, and its best cut-off point was 0.099. Sensitivity and specificity were 0.851 and 0.744, respectively.

The area under the curve of model 2, to which the 1-year eGFR decline in the first year greater than cut-off was added to model 1, significantly increased from 0.943 (95% CI 0.915–0.971) to 0.967 (95% CI 0.950–0.983; $P = 0.019$; Figure 2). Baseline characteristics according to the best cut-off of the 1-year eGFR decline rate (0.099) in the first year are shown in Table 1. The mean 1-year eGFR decline rate in the first year was 18.2 ± 8.7 in fast decliners and −2.2 ± 10.4 in non-decliners ($P < 0.0001$).

The fast decliners were younger; had higher prevalence of smoking, hypertension and advanced retinopathy; had slightly, but significantly higher glycated hemoglobin; had a higher prevalence of advanced albuminuria; and had higher eGFR at baseline compared with non-decliners (Table 1).

The number of the patients who met the end-points in each group is shown in Table 2. Primary and renal end-point incidences were significantly more frequently seen in the fast

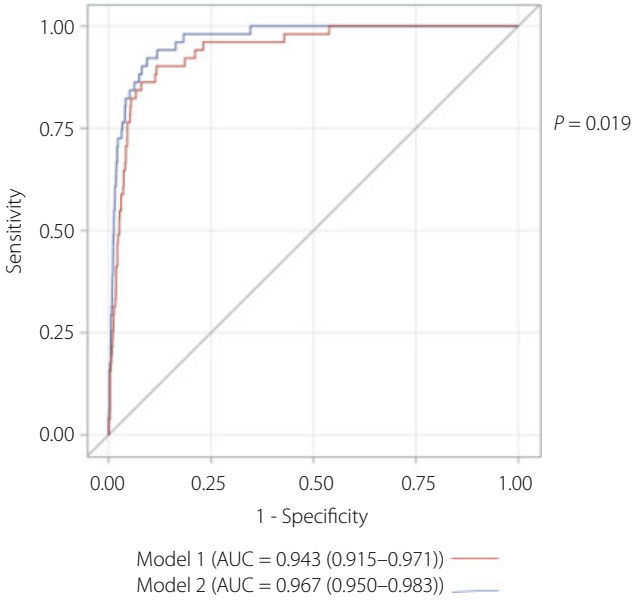

Figure 2 | Receiver operating characteristic curve analysis of renal end-point occurrence. Model 1 includes covariates of age, sex, body mass index, the presence of hypertension, smoking, clinical stage of diabetic nephropathy at baseline and estimated glomerular filtration rate at baseline. Model 2 adds the presence of maximum 1-year estimated glomerular filtration rate decline rate of >20% as a covariate to model 1. AUC, area under the curve.

decliners in time-to-event analysis (Table 2, Figure 3a,c, $P< 0.0001$, respectively). The incidence of the CV end-point, except for the renal end-point, was not different between the groups (Table 2, Figure 3b).

Incidences of the primary end-point, CV end-point, except for the renal end-point, and the renal end-point were significantly different among the clinical stages of albuminuria (Table 2, Figure 4a–c, $P < 0.0001$).

Cox regression analysis

The results of the Cox regression analysis are shown in Table 3. The HRs of the clinical stage of albuminuria were significant irrespective of the renal end-point. The eGFR at baseline and 1-year eGFR decline greater than the cut-off were significant for the primary end-point and the renal end-point, but not for the composite CV end-point, except for the renal end-point.

DISCUSSION

The present study investigated the predictive value of the 1-year eGFR decline rate in the first observation year in the EMPATHY study cohort for specific end-points. Patients with 1-year eGFR decline >9.9% reached a renal end-point more frequently than those without. The ROC analysis confirmed that the model that used the 1-year eGFR decline greater than the cut-off led to an improvement in the predictability of the renal end-point compared with the model not using it. The 1-year eGFR decline rate was a significant risk factor for the end-points that included the renal end-point. The clinical stage of albuminuria was significant for the CV end-point irrespective of the inclusion of the renal end-point. In diabetes, the rate of eGFR decline is not constant, so the timely identification of a change to a sudden, steep eGFR decline during the medical follow up can be crucial in preventing the worsening of kidney function. In the present study, the eGFR of the fast decliners at baseline was significantly higher than that of the non-decliners. Information on 1-year eGFR decline proved to be a useful predictive value in addition to the conventional risk factors. Therefore, clinicians should be cautious and take note of the eGFR trajectory, as well as albuminuria or the absolute eGFR value itself, to help identify patients at a high risk of ESRD.

Originally, Krolewski *et al.*[12] had defined progressive renal decline as an eGFR loss of ≥3.3%/year. Additionally, the Kidney Disease: Improving Global Outcomes guidelines defined rapid progression as the rate of eGFR decline of <–5 mL/min/year. Fast eGFR decliner had no concrete definition until now, partly because the high instability of the eGFR value on measurement and the observational study period to evaluate renal outcomes largely varied among studies. Krolewski *et al.*[13] reviewed the fast eGFR decline in diabetes patients in 2017. They divided their cohort into four categories with respect to the quartile of the annual eGFR decline rate. The eGFR decline rate of the fast decliner in the present study was nearly equivalent to the "very fast decliner." We supposed that the "very fast decliner" could only achieve the renal outcome in the short observation period, because the fast decliner in the present study was defined based on the result of the ROC analysis for the renal end-point. Previously, we reported that a maximum 1-year eGFR decline of >7.5% predicted an increased risk of renal outcome if the eGFR values were mathematically smoothed and the noise reduced[6]. In that study, the average time taken for participants to reach a renal end-point was 98 months, which is different from the result in the present study. In this study, data were not sufficient for smoothing, and the observation period was shorter, 2.2 years versus 9.1 years. Longer observation durations can help distinguish the effect of small changes in the eGFR slope on late renal dysfunction, and noise reduction also reduces the occurrence of false positive results. The lack of data smoothing and the shorter observation period could explain the difference of the threshold for the prediction of renal end-points between the studies. If we can use the eGFR data of longer duration of medical follow up, we can discriminate the subtle, but significant, change in eGFR to distinguish patients at a high risk for ESRD.

Some studies reported that fast eGFR decliners are at high risk for CV disease[14–16]. In the present study, there was no association between fast eGFR decliners and CV end-points, except for the renal end-point. One possible explanation is that the observation period after calculation of annual eGFR decline in the first year might not be a sufficiently long duration to

Table 1 | Baseline characteristics according to 1-year estimated glomerular filtration rate decline rate in the first year

Characteristics	All participants (n = 4,461)	Non-decliner (n = 3,275)	Fast decliner (n = 1,186)	P-value
Male sex	2,118 (47.7)	1,551 (47.4)	567 (47.8)	0.817
Age (years)	63.1 ± 10.5	63.4 ± 10.4	62.2 ± 10.9	0.001
BMI	25.7 ± 4.3	25.7 ± 4.2	25.8 ± 4.4	0.626
Abdominal circumference (cm)	90.5 ± 10.8	90.4 ± 10.8	90.8 ± 10.8	0.228
Smoking	824 (18.5)	575 (17.6)	249 (21.0)	0.010
Duration of diabetes (years)	13.1 ± 8.8	13.2 ± 8.7	121.7 ± 7.9	0.087
Hypertension	3,168 (71.0)	2,286 (69.8)	882 (72.4)	0.003
Funduscopy				<0.0001
Simple retinopathy	2,979 (66.9)	2,252 (68.9)	727 (62.6)	
Preproliferative retinopathy	812 (18.2)	568 (17.4)	244 (20.7)	
Proliferative retinopathy	640 (14.4)	432 (13.2)	208 (17.6)	
Other	21 (0.5)	19 (0.6)	2 (0.2)	
HbA1c, % (mmol/mol)	7.6 (59.1) ± 1.2 (13.0)	7.6 (58.6) ± 1.1 (12.5)	7.7 (60.4) ± 1.3 (14.2)	0.001
LDL cholesterol (mg/dL)	106.0 ± 26.2	105.9 ± 25.8	106.2 ± 27.0	0.908
Blood pressure (mmHg)				
Systolic	134.6 ± 16.5	133.8 ± 16.3	136.7 ± 16.8	<0.001
Diastolic	74.8 ± 11.3	74.5 ± 11.2	75.7 ± 11.5	0.006
eGFR (mL/min/1.73 m^2)	74.4 ± 20.1	73.6 ± 18.8	76.6 ± 23.2	<0.001
1-year eGFR decline rate of the first year (%)	3.2 ± 13.4	−2.2 ± 10.4	18.2 ± 8.7	<0.0001
Urinary ACR, mg/g × Cr (IQR)	219.0 (102.4)	142.7 (75.6)	436.2 (271.0)	<0.0001
Clinical stage of albuminuria				<0.0001
None	1,639 (36.7)	1,297 (55.3)	342 (41.5)	
Microalbuminuria	1,088 (24.3)	806 (34.3)	282 (34.2)	
Macroalbuminuria	445 (10.0)	244 (10.4)	201 (24.4)	
Lack of data	1,289 (28.9)	928 (28.3)	361 (30.4)	

ACR, albumin/creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IQR, interquartile range; LDL, low-density lipoprotein.

Table 2 | Number and percentage of each end-point according to the annual estimated glomerular filtration rate decline and clinical stage of albuminuria

Estimated glomerular filtration rate	Fast decliner	Non-decliner	P-value
Primary end-point	95 (8.13%)	87 (2.68%)	<0.0001
CV end-point, except for renal end-point	31 (2.65%)	73 (2.25%)	0.573
Renal end-point	67 (5.74%)	14 (0.43%)	<0.0001

Clinical stage of albuminuria	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	P-value
Primary end-point	20 (1.23%)	45 (4.15%)	54 (12.47%)	<0.0001
CV end-point except for renal end-point	18 (1.10%)	38 (3.51%)	19 (4.39%)	<0.0001
Renal end-point	2 (0.12%)	8(0.74%)	36 (8.31%)	<0.0001

CV, cardiovascular.

evaluate the CV risk. The second explanation is that a considerable number of patients encountered a renal end-point, which was the primary end-point of the present study, before a CV event, and thus terminated the study. Therefore, for such individuals, the study was ended before a possible CV event, except for the renal event, would occur. However, the clinical stage of albuminuria was also a significant risk factor for the occurrence of a CV event irrespective of the occurrence of a renal event. Studies in Japan have found that renal and cardiovascular outcomes were much more frequent in patients with albuminuria, and that those with a reduced eGFR without albuminuria had a relatively benign status[17–20]. Yokoyama *et al.*[21] reported that non-albuminuric DKD patients did not have a high risk of mortality, CVD events or renal function decline when non-albuminuric DKD was not accompanied by previous macrovascular complication. We could not simply compare their study

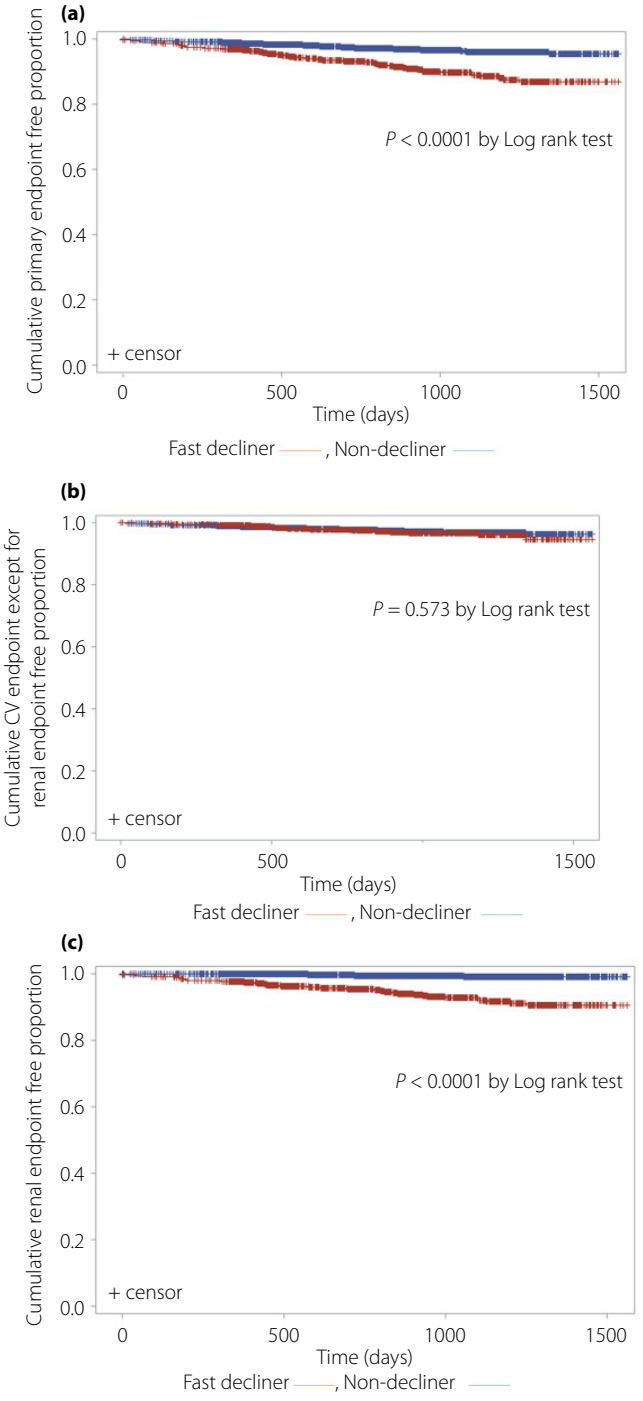

Figure 3 | Cox regression analysis for the cumulative end-point-free proportion of patients in the fast estimated glomerular filtration rate decliners versus non-decliners group. (a) Primary end-point, (b) cardiovascular (CV) end-point, except for renal end-point, and (c) renal end-point.

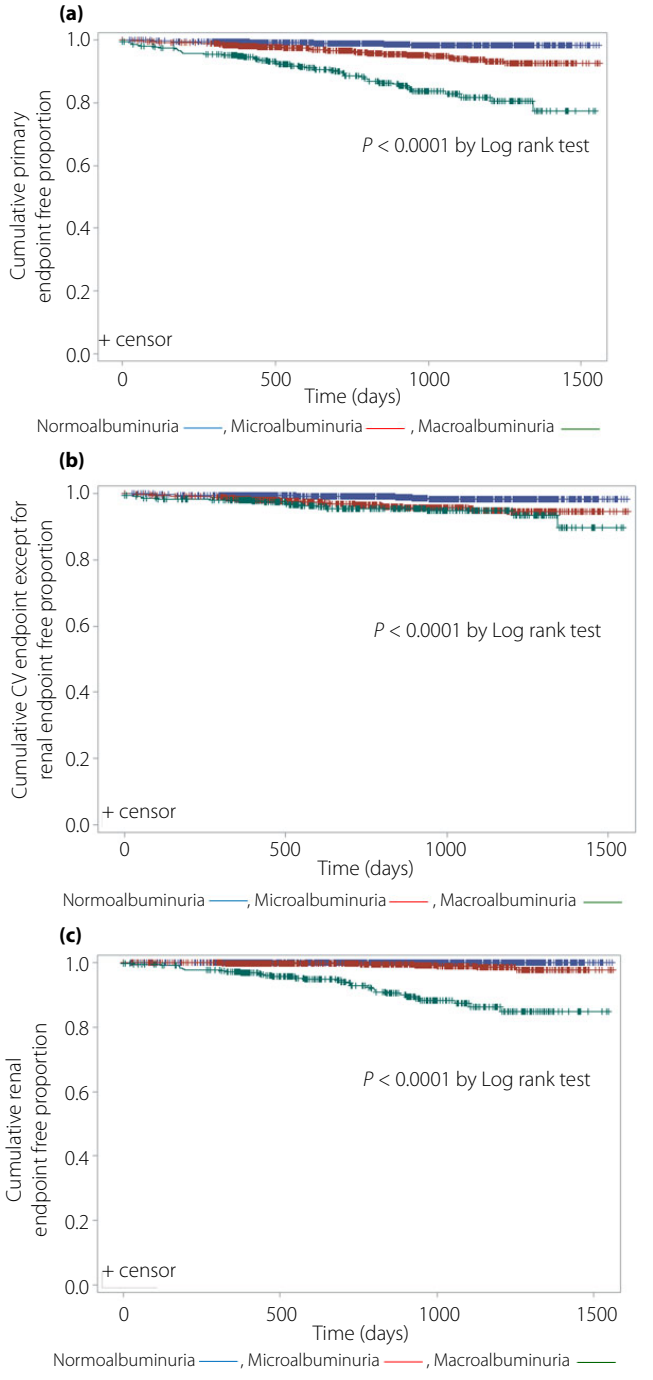

Figure 4 | Cox regression analysis for the cumulative end-point-free proportion of patients according to the clinical stage of albuminuria. (a) Primary end-point, (b) cardiovascular (CV) end-point, except for renal end-point, and (c) renal end-point.

with the present study, as the background of the study population and the observation period differed between the two studies. However, the present study confirmed the importance of albuminuria in type 2 diabetes patients both for renal outcome and for CVD. This result highlights the importance of the albuminuria for the prediction of prognosis in this population.

Table 3 | Cox regression analysis for each end-point

	Primary end-point			Cardiovascular end-point except for renal end-point			Renal end-point		
Variables	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age	1.016	0.995–1.037	0.141	1.058	1.028–1.089	<0.001	0.962	0.932–0.998	0.020
Sex	0.591	0.392–0.890	0.012	0.591	0.357–0.979	0.041	0.507	0.243–1.058	0.070
BMI	1.017	0.969–1.066	0.498	1.038	0.980–1.099	0.201	0.968	0.888–1.055	0.456
Hypertension	1.894	1.015–3.534	0.26	1.541	0.787–3.012	0.207	4.808	0.637–37.037	0.128
LDL cholesterol	1.000	0.994–1.007	0.968	0.998	0.989–1.006	0.586	1.003	0.994–1.012	0.540
Smoking	1.305	0.831–2.050	0.248	1.394	0.777–2.500	0.266	1.346	0.665–2.723	0.409
Microalbuminuria at baseline	2.611	1.528–4.462	<0.001	2.641	1.492–4.674	<0.001	3.110	0.640–15.112	0.160
Macroalbuminuria at baseline	5.071	2.879–8.932	<0.001	3.223	1.604–6.675	<0.001	10.479	2.347–46.796	0.002
eGFR at baseline	0.975	0.965–0.986	<0.001	0.997	0.984–1.011	0.688	0.945	0.927–0.964	<0.0001
1-year eGFR decline more than cut-off	2.086	1.427–3.049	<0.001	0.955	0.569–1.606	0.864	9.948	4.124–23.996	<0.0001

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

The present study had some limitations, such as the enrollment of participants with type 2 diabetes and retinopathy. This is a population at extremely high risk for classical diabetic nephropathy. Therefore, the results might not apply to the general diabetes population. However, the results of this study implied that only an approximately 10% decrease in raw eGFR value in a year could be a clinically meaningful change in patients with diabetes with retinopathy. The other limitation was that because eGFR data before study entry were not available, some participants might have experienced a steep eGFR decline before enrollment in the study. As each eGFR measurement is very different, it can be challenging to identify at-risk participants from a single eGFR value. Furthermore, renal function deteriorated very rapidly in some patients, especially those with macroalbuminuria. Calculation of eGFR decline is a simple and convenient way for the evaluation of ESRD risk, as it uses already available data. However, a single evaluation of eGFR after an interval of 12 months is not sufficient to identify patients at high risk of such progressive renal deterioration; therefore, more frequent measurements of eGFR are necessary. The present results also suggest that the eGFR trajectory requires careful monitoring, with frequent calculation of eGFR, to identify the patients at high risk of CV disease and ESRD.

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DISCLOSURE

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