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Subnormal Estimated Glomerular Filtration Rate Strongly Predict Incident Cardiovascular Events in Type 2 Diabetic Chinese Population With Normoalbuminuria

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Abstract: No study has evaluated whether subnormal estimated glomerular filtration rate (eGFR) (between 61 and 90 mL/min) and high normal albumin–creatinine ratio (ACR) (<30 mg/g) are associated with cardiovascular (CV) events and mortality in type 2 diabetic (T2DM) patients with normoalbuminuria.

We observed a longitudinal cohort study of 1291 T2DM patients with normoalbuminuria who were receiving intensified multifactorial treatment from 2004 to 2008. Cox regression models were used to evaluate eGFR and ACR as the risk factors of major CV events (nonfatal myocardial infarction and stroke) and mortality.

During the 4-year period, 56 patients died and 159 patients developed major CV events. We found eGFR, but not ACR, to be associated with major CV events. Compared to those with eGFR higher than 90 mL/min, patients with subnormal eGFR (HR: 3.133, 1.402–7.002, $P = 0.005$) were at greater risk of incident major CV events. Extremely low eGFR (<30 mL/min) was associated with mortality only in patients under 65 years old.

Subnormal eGFR was a strong predictor of major CV events in diabetic patients with normoalbuminuria. Normoalbuminuric diabetic patients with subnormal eGFR may need intensive CV risk factor intervention to prevent and treat CV events.

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Abbreviations: A1C = glycosylated hemoglobin, ACR = albumin–creatinine ratio, ADA = American Diabetes Association, BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CV = cardiovascular, CVD = cardiovascular disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL-Chigh-density = lipoprotein cholesterol, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, SBP = systolic blood pressure, T2DM = type 2 diabetes, TG = triglyceride.

INTRODUCTION

Microalbuminuria, a prognostic factor for cardiovascular (CV) morbidity and mortality, is defined as having a urinary albumin–creatinine ratio (ACR) ranging from 30 to 300 mg/g.^{1–4} American Diabetes Association (ADA) position statement⁵ announced that microalbuminuria and macroalbuminuria were no longer used but rather referred to as persistent albuminuria at levels 30 to 299 mg/24 hours and levels ≥ 300 mg/24 hours. The new nomenclature was intended to emphasize the continuous nature of albuminuria as a risk factor. Recent studies have found an association between elevated urinary albumin excretion levels, even within the normal range (ACR < 30 mg/g) (defined as high normal ACR) and greater risk of cardiovascular disease (CVD).^{1,6,7}

Chronic kidney disease (CKD), defined as having an estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m², has also been found to be a major risk factor for CV morbidity and mortality.^{8–10} This increased CKD-CV risk, however, appears to diminish when there is no microalbuminuria or proteinuria.^{11–13} Studies have found decreased GFR in the absence of increased urine albumin excretion in a substantial percentage of adults with diabetes.¹⁴ Ninomiya et al¹⁵ have recently reported high albuminuria and low eGFR to be independent risk factors for CV events in patients with type 2 diabetes (T2DM). However, there is no study to evaluate the association between subnormal eGFR (between 61 and 90 mL/min) and CVD and mortality risk particularly in diabetic patients with normoalbuminuria. One of our latest studies¹⁶ has reported that diabetic nephropathy can be delayed by helping patients reach many of the treatment goals outlined by ADA at the same time. In this observational study, we investigate the possible association between subnormal eGFR and high normal ACR and the risk of CV events and mortality in patients who have T2DM and normoalbuminuria.

METHODS

Population

This study included all patients with T2DM who visited the diabetic clinic in the Metabolism Division at Kaohsiung

Medical University Hospital and Changhua Christian Hospital between January 2004 and April 2005. The follow-up period lasted until December 2008. We included patients¹ who had been diagnosed with T2DM with no history of acute myocardial infarction (MI), heart failure, or stroke within 1 year, and had been followed up regularly every 3 to 6 months at the outpatient departments of the 2 hospitals and² who had normoalbuminuria (defined as having a least 2 times of urinary ACR < 30 mg/g). The protocol for this study was approved by the Human Research Ethics Committees at both hospitals, and informed consent was obtained from each patient.

Baseline Investigation

An interview with all-inclusive appraisal of risk factors, complications, and disease status were accomplished in each patient. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained as the average of 2 mensurations in sitting positions after 10 minutes of relaxation. We estimated body mass index (BMI) by using body weight divided by body height squared (kg/m^2) from each patient. We obtained blood samples of each patient at early morning after overnight fast. The plasma glucose, total cholesterol (Chol), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and creatinine levels were interpreted by using a biochemistry automatic analyzer (Bechman-Coulter Inc. Fullerton, CA). We used ion exchange high-performance liquid chromatography (Bio-Rad, Varianttm II Turbo, CA) to figure out HbA1c in whole blood. All patients were followed up regularly and took part in a strict intervention program aimed to meet the treatment goals recommended by ADA: HbA1c < 7%, SBP < 130 mmHg, DBP < 80 mmHg, LDL-C < 100 mg/dL, TG < 150 mg/dL, HDL-C > 40 mg/dL for men, and > 50 mg/dL for women. A diabetes care team consisted of physicians, nurses, and dietitians modified patients' behavior through counseling and educational programs, and various pharmacologic regimens in order to assist the patient achieve the goals.

Kidney Function Tests

Fasting venous blood and an overnight first-void urine sample were collected to measure creatinine and urine albumin in the clinic. The urinary ACR was calculated from urine albumin and creatinine levels. The definition of normoalbuminuria was as an ACR of < 30 mg/g. All cases in this study had normoalbuminuria at baseline and the baseline ACR levels were divided into 4 quartiles. The GFR was estimated by using the equations recommended the National Kidney Foundation in the Modified Diet in Renal Disease (MDRD)¹⁷ and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).¹⁸

Outcome Assessment

During the follow-up, we collected information major CV endpoints and all-cause mortality until December 2008. The major CV endpoint was defined as the incidence of nonfatal MI or stroke. Death by any cause was identified from the Data File of Death Causes which published by Department of Health in Taiwan, based on the International Classification of Disease 9th revision.

Statistical Analysis

The baseline clinical and biochemical features of the population are presented as mean \pm SD, or percentages. Cox regression analysis was used to examine the eGFR and ACR that

might predict major CV endpoints and all-cause mortality. The eGFR levels were divided into groups >90 mL/min, 61 to 90 mL/min, 46 to 60 mL/min, 30 to 45 mL/min, and <30 mL/min; the ACR levels were divided into 4 quartiles. Variables including sex, age, durations of diabetes, SBP, DBP, BMI, glycosylated hemoglobin (A1C), Chol, TG, LDL-C, and HDL-C at baseline were used for adjustment in Cox regression models by forward selection. A *P* value of 0.2 or less was used to determine whether a variable would be entered into the analysis, and a *P* value of 0.05 or less was used to determine whether the variable would remain in the models. Because the distribution of TG was highly right skewed, it was natural log-transformed for analyses. Results are described as hazard ratios (HRs) and their 95% confidence intervals (CIs). All statistical operations were performed using SAS 9.4 (SAS Institute, Cary, NC) except that XLSTAT (Addinsoft, New York, NY) was performed for calculation of power in estimating HRs.

RESULTS

Initially, we enrolled 1303 patients. Twelve patients were lost to follow-up in the initial 6 months and were excluded from our study. After exclusion, we had a total of 1291 diabetic patients with normoalbuminuria (578 men and 713 women). The mean age of the cohort was 59.8 years. Clinical and biochemical characteristics of the patients at baseline are shown in Table 1. Compared to patients who did not receive antihypertensive medication, those who did had a higher mean ACR (11.5 ± 7.6 vs 10.5 ± 7.4 , $P = 0.013$) and a lower mean eGFR (67.1 ± 19.1 vs 76.8 ± 16.8 , $P < 0.001$). During the follow-up period, 56 patients died (4.3%) and 159 patients (12.3%) developed major CV events, including acute MI in 100 patients (7.7%) and stroke in 81 patients (6.3%). By the end of the study period, our patient population had a mean HbA1c of 7.3%, SBP of 129.3 mmHg, DBP of 74.4 mmHg, LDL-C of 98.6 mg/dL, HDL-C of 53.6 mg/dL, and TG of 116.0 mg/dL.

Major CV Endpoints

Table 2 summarizes the results of Cox regression analysis for major CV events with baseline eGFR and ACR as risk factors. Diabetic patients with low baseline eGFR were found to be at increased risk of major CV events. After adjusting for sex, age, and baseline data including BMI, A1C, cholesterol, LDL-C, HDL-C, and TG, we found that, compared to those with eGFR calculated by MDRD more than 90 mL/min, patients with subnormal eGFR (between 61 and 90 mL/min) (HR: 3.740, 1.478–9.465, $P = 0.005$), eGFR between 46 and 60 mL/min (HR: 5.394, 2.019–14.408, $P < 0.001$), eGFR between 30 and 45 mL/min (HR: 6.348, 2.175–18.523, $P < 0.001$), and eGFR less than 30 mL/min (HR: 9.168, 2.458–34.195, $P = 0.001$) were at greater risk of incident major CV event. The subnormal eGFR was significantly associated with elevated risk of incident MI but not stroke after adjusting for sex, age, and baseline data including BMI, A1C, cholesterol, LDL-C, HDL-C, and TG (Table 2). Using another often used method of calculating eGFR known as the CKD-EPI produced similar results. Neither baseline ACR nor mean follow-up ACR was associated with major CV events, MI, or stroke.

All-Cause and CV Mortality

Table 3 showed the results of Cox regression analysis for all-cause mortality with eGFR and ACR as risk factors. Patients with eGFR less than 30 mL/min (HR: 6.985, 1.747–27.930, $P = 0.006$) were associated with all-cause mortality as

TABLE 1. Baseline Characteristics of Participants

Characteristics	Baseline Data (n = 1291)
Age, year	59.8 (12.0)
Sex, female	713 (55.2%)
Duration of diabetes, year	15.1 (7.0)
Smoking	186 (14.4%)
BMI	25.4 (3.4)
Waist circumference, cm	89.6 (38.2)
SBP, mm Hg	132.3 (17.3)
DBP, mm Hg	76.9 (10.6)
HBA1c, %	7.5 (1.6)
Fasting glucose, mg/dL	145.8 (50.6)
Total cholesterol, mg/dL	183.3 (35.8)
LDL-C, mg/dL	103.5 (27.3)
HDL-C, mg/dL	50.4 (13.3)
Triglycerides, mg/dL	140.4 (103.1)
Creatinine, mg/dL	1.0 (0.3)
Estimated GFR, mL/min/1.73 m ²	72.1 (18.6)
ACR, mg/g	11.0 (7.6)
Glucose-lowering drug	
Oral hypoglycemic agent	821 (63.6%)
Insulin	144 (11.6%)
Insulin plus oral hypoglycemic agent	176 (13.6%)
Diet control only	150 (11.2%)
Antihypertensive treatment	625 (48.4%)
ACEI or ARB	565 (43.8%)
Diuretics	267 (20.7%)
CCB	176 (13.6%)
β-Blocker	136 (10.5%)
Statin	363 (28.1%)
Fibrate	38 (2.9%)
Anti-platelet drug	8 (0.6%)

Data are shown as mean (SD) or number (percentage). ACEI = angiotensin converting enzyme inhibitor, ACR = albumin/creatinine ratio, ARB = angiotensin II receptor blocker, BMI = body mass index, CCB = calcium channel blocker, DBP = diastolic blood pressure, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, SBP = systolic blood pressure, TG = triglyceride.

compared to those with eGFR more than 90 mL/min calculated by MDRD in simple regression analysis, though the result was not significant in multiple regression after adjusted for other factors. The findings remained similar when calculated eGFR by CKD-EPI. Neither baseline ACR nor mean follow-up ACR was associated with mortality in patients with T2DM. The results of Cox regression analysis for CV mortality with eGFR and ACR as risk factors are shown in Supplementary Table 1, <http://links.lww.com/MD/A597>. Neither eGFR nor ACR was significantly associated with CV mortality in patients with T2DM. The statistical power for CV mortality, however, was low because the number of CV mortality was small in this cohort, and in some categories of eGFR or quartiles of ACR there was even no CV mortality.

Older Patients Versus Younger Patients

We analyzed major CV events and mortality by eGFR in older patients (≥ 65 years old) and younger patients (< 65 years old), respectively. Figures 1 and 2 showed the results of Cox regression analysis with adjustment of confounding factors in 2

different age groups. The risk of major CV events increased with decreasing eGFR in both older and younger subjects after adjusted for confounding factors, with even higher magnitude of HR in the younger groups (Figure 1A). Low eGFR was significantly associated with MI in younger patients, while this relationship was not as strong in older ones (Figure 1B). Younger patients with eGFR less than 45 mL/min were at significantly higher risk for stroke (Figure 1C). Younger patients, not older ones, with extremely low eGFRs (< 30 mL/min) were found to be at significantly high risk for all-cause mortality (Figure 2). ACR was not related to CV events or all-cause mortality in either the older subjects or the younger ones.

DISCUSSION

Our study found subnormal eGFR but not high normal ACR to be a powerful predictor of major CV events in T2DM patients with normoalbuminuria. Low eGFR was significantly associated with incidental major CV events both in older and younger patients with T2DM, the association being more obvious in younger patients.

Ishani et al¹⁹ reported the association of eGFR with risk of CVD to be limited in the absence of microalbuminuria. The Prevention of Renal and Vascular End-stage Disease study¹³ also found subjects with stage 3 CKD who had a urinary albumin excretion rates < 30 mg/24 hours to have a CV risk comparable to those with stage 1 and 2 CKD. The second Nord-Trondelag Health Study¹¹ found no significant trend for increased CV risk in patients with decreased eGFR and lower ACR levels. However, So et al²⁰ found that T2DM Chinese patients with no albuminuria but eGFRs < 60 mL/min to be at significant CV risk. Drury et al²¹ reported that diabetic patients with an eGFR less than 60 mL/min and normoalbuminuria had higher risk of CV events in a low-risk population mainly of European ancestry. Knobler et al²² also reported an eGFR less than 60 mL/min to predict increased risk for cardiac events independent of albuminuria. However, there has been no study to evaluate the association between subnormal eGFR and major CV events in the absence of microalbuminuria. We studied this association and we found a significant association between eGFR and major CV events in diabetic patients with normoalbuminuria. Patients with eGFRs between 61 and 90 mL/min were at significantly higher risk of incidental major CV events (HR: 2.617, 1.246–5.496, $P = .01$) than those with normal renal function after adjustment for age and multiple known risk factors. Besides, we also found that there was a strong progressive relationship between lower eGFR and major CV events. Our results suggested eGFR to be a strong predictor of major CV events in normoalbuminuria diabetic patients receiving treatment for multiple factors.

van der Velde et al²³ recently reported that most GFR estimates and age together could significantly predict CV outcomes, and eGFR measurement was associated with the risk of CV events in younger subjects but not in the elderly. Two previous studies^{24,25} reported that as people age, the less influence decreasing eGFR has on the risk of mortality. O'Hare et al²⁶ also found a lower association between eGFR and risk for mortality in older population. Our study revealed that the risk of major CV events increased with decreasing eGFR both in older and younger patients, while the correlation was stronger in younger group. As to the association between eGFR and all-cause mortality, it was found only in younger patients but not in older patients. The possible reason for this decreased risk in the

TABLE 2. Hazard Ratio of Major Cardiovascular Events, Myocardial Infarction, and Stroke in Patients With Type 2 Diabetes Stratified by eGFR and ACR Categories

	(a) Major Cardiovascular Events						
	Unadjusted			Adjusted*			
	HR	95% CI	P	HR	95% CI	P	Power
>90 (208 cases)	1			1			
61–90 (753 cases)	4.909	1.989–12.114	<0.001	3.740	1.478–9.465	0.005	0.999
46–60 (248 cases)	8.525	3.386–21.462	<0.001	5.394	2.019–14.408	<0.001	1
30–45 (66 cases)	11.143	4.102–30.268	<0.001	6.348	2.175–18.523	<0.001	0.976
<30 (16 cases)	17.969	5.194–62.158	<0.001	9.168	2.458–34.195	0.001	0.735
eGFR (mL/min per 1.73 m ²) by CKD-EPI							
>90 (250 cases)	1			1			
61–90 (703 cases)	4.057	1.870–8.801	<0.001	3.124	1.398–6.983	0.006	0.994
46–60 (235 cases)	7.458	3.363–16.539	<0.001	4.870	2.045–11.596	<0.001	0.999
30–45 (83 cases)	8.204	3.437–19.578	<0.001	5.050	1.947–13.099	<0.001	0.957
<30 (20 cases)	17.659	6.183–50.434	<0.001	9.296	2.938–29.413	<0.001	0.987
Quartiles of ACR (mg/g)							
1st quartile (≤4.6) (325 cases)	1			1			
2nd quartile (4.7–9.4) (322 cases)	1.102	0.700–1.736	0.68	0.905	0.572–1.433	0.67	0.064
3rd quartile (9.5–16.2) (323 cases)	0.964	0.611–1.521	0.87	0.912	0.578–1.439	0.69	0.059
4th quartile (≥16.3) (320 cases)	1.185	0.760–1.847	0.45	0.993	0.635–1.553	0.98	0.027
Mean follow-up ACR (mg/g)							
<30 (1258 cases)	1			1			
≥30 (33 cases)	1.744	0.916–3.321	0.091	1.678	0.894–3.150	0.11	0.180
	(b) Myocardial Infarction						
	Unadjusted			Adjusted*			
	HR	95% CI	P	HR	95% CI	P	Power
eGFR (mL/min per 1.73 m ²) by MDRD							
>90 (208 cases)	1			1			
61–90 (753 cases)	4.947	1.542–15.886	0.007	4.828	1.501–15.532	0.008	1
46–60 (248 cases)	9.416	2.864–30.957	<0.001	9.566	2.899–31.565	0.002	1
30–45 (66 cases)	14.215	4.027–50.117	<0.001	14.233	3.942–51.396	<0.001	0.996
<30 (16 cases)	11.226	1.870–67.383	0.008	11.832	1.951–71.737	0.007	0.657
eGFR (mL/min per 1.73 m ²) by CKD-EPI							
>90 (250 cases)	1			1			
61–90 (703 cases)	4.282	1.542–11.891	0.005	4.146	1.489–11.547	0.007	0.999
46–60 (235 cases)	8.624	3.028–24.562	<0.001	8.757	3.064–25.031	<0.001	1
30–45 (83 cases)	11.626	3.779–35.765	<.001	12.094	3.875–37.742	<0.001	1
<30 (20 cases)	10.303	2.526–42.021	0.001	9.864	2.365–41.136	0.002	0.758
Quartiles of ACR (mg/g)							
1st quartile (≤4.6) (325 cases)	1			1			
2nd quartile (4.7–9.4) (322 cases)	1.492	0.847–2.626	0.17	1.347	0.759–2.390	0.31	0.182
3rd quartile (9.5–16.2) (323 cases)	1.095	0.616–1.948	0.76	1.121	0.628–2.004	0.70	0.058
4th quartile (≥16.3) (320 cases)	1.328	0.737–2.391	0.35	1.154	0.636–2.092	0.64	0.071
Mean follow-up ACR (mg/g)							
<30 (1258 cases)	1			1			
≥30 (33 cases)	2.093	0.935–4.687	0.073	1.455	0.771–2.744	0.25	0.087
	(c) Stroke						
	Unadjusted			Adjusted*			
	HR	95% CI	P	HR	95% CI	P	Power
eGFR (mL/min per 1.73 m ²) by MDRD							
>90 (208 cases)	1			1			
61–90 (753 cases)	6.192	1.498–25.595	0.01	3.862	0.911–16.370	0.07	0.947

(Continued)

	(c) Stroke						
	Unadjusted			Adjusted*			
	HR	95% CI	P	HR	95% CI	P	Power
46–60 (248 cases)	7.538	1.761–32.270	<0.001	3.578	0.789–16.216	0.10	0.807
30–45 (66 cases)	10.001	2.071–48.283	0.004	4.515	0.880–23.152	0.07	0.611
<30 (16 cases)	34.411	6.293–188.15	<0.001	13.823	2.315–82.526	0.004	0.569
eGFR (mL/min per 1.73 m ²) by CKD-EPI							
>90 (250 cases)	1			1			
61–90 (703 cases)	4.0882	1.509–15.789	0.008	3.134	0.940–10.448	0.06	0.898
46–60 (235 cases)	5.725	1.689–19.406	0.005	2.822	0.775–10.268	0.12	0.666
30–45 (83 cases)	7.810	2.100–29.040	0.002	3.674	0.918–14.702	0.07	0.566
<30 (20 cases)	28.090	6.701–117.74	<0.001	11.184	2.361–52.983	0.002	0.574
Quartiles of ACR (mg/g)							
1st quartile (≤4.6) (325 cases)	1			1			
2nd quartile (4.7–9.4) (322 cases)	1.084	0.579–2.027	0.80	0.915	0.485–1.726	0.78	0.047
3rd quartile (9.5–16.2) (323 cases)	1.000	0.523–1.914	0.99	1.040	0.545–1.985	0.91	0.033
4th quartile (≥16.3) (320 cases)	0.935	0.494–1.770	0.94	0.800	0.418–1.531	0.50	0.104
Mean follow-up ACR (mg/g)							
<30 (1258 cases)	1			1			
≥30 (33 cases)	0.959	0.363–2.530	0.93	0.666	0.246–1.801	0.42	0.085

ACR = albumin/creatinine ratio, CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, HR = hazard ratio.

* Sex, age, duration of diabetes, HbA1c, BMI, SBP, DBP, cholesterol, TG, LDL-C, and HDL-C were adjusted in these models by forward selection.

older group is that traditional risk factors have reduced predictive power for CV events and mortality in the elderly.^{27–29} Danziger et al³⁰ reported that the age-associated decline in GFR is not modulated by changes in blood pressure or CV performance. Of course, the elderly might have many comorbid

disorders which can have an influence on the decline rate of GFR over the age-associated decline. However, it may be difficult to sort out the effects of aging per se and the effect of comorbid conditions commonly accompanying the aging process.³¹ Age itself is not a direct cause of CV events but rather

TABLE 3. Hazard Ratios of All-Cause Mortality in Patients with Type 2 Diabetes Stratified by eGFR and ACR Categories

	All-Cause Mortality						
	Unadjusted			Adjusted*			
	HR	95% CI	P	HR	95% CI	P	Power
eGFR (mL/min per 1.73 m ²) by MDRD							
>90 (208 cases)	1			1			
61–90 (753 cases)	1.238	0.509–3.009	0.64	0.768	0.304–1.940	0.58	0.085
46–60 (248 cases)	2.332	0.912–5.961	0.08	1.006	0.353–2.865	0.99	0.026
30–45 (66 cases)	2.710	0.827–8.881	0.10	1.086	0.293–4.019	0.90	0.032
<30 (16 cases)	6.985	1.747–27.930	0.006	2.311	0.498–10.731	0.28	0.084
eGFR (mL/min per 1.73 m ²) by CKD-EPI							
>90 (250 cases)	1			1			
61–90 (703 cases)	1.149	0.491–2.691	0.75	0.761	0.308–1.878	0.55	0.092
46–60 (235 cases)	2.521	1.037–6.128	0.04	1.154	0.409–3.260	0.79	0.045
30–45 (83 cases)	3.621	1.313–9.986	0.01	1.631	0.504–5.273	0.41	0.097
<30 (20 cases)	5.817	1.504–22.499	0.01	1.867	0.388–8.993	0.44	0.066
Quartiles of ACR (mg/g)							
1st quartile (≤4.6) (325 cases)	1			1			
2nd quartile (4.7–9.4) (322 cases)	0.985	0.442–2.193	0.97	0.933	0.419–2.080	0.87	0.038
3rd quartile (9.5–16.2) (323 cases)	1.435	0.685–3.005	0.34	1.376	0.657–2.883	0.40	0.132
4th quartile (≥16.3) (320 cases)	1.237	0.579–2.644	0.58	1.215	0.567–2.601	0.62	0.072
Mean follow-up ACR (mg/g)							
<30 (1258 cases)	1			1			
≥30 (33 cases)	1.461	0.356–5.995	0.28	1.015	0.245–4.196	0.98	0.026

ACR = albumin/creatinine ratio, CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, HR = hazard ratio.

* Sex, age, duration of diabetes, HbA1c, BMI, SBP, DBP, cholesterol, TG, LDL-C, and HDL-C were adjusted in these models by forward selection.

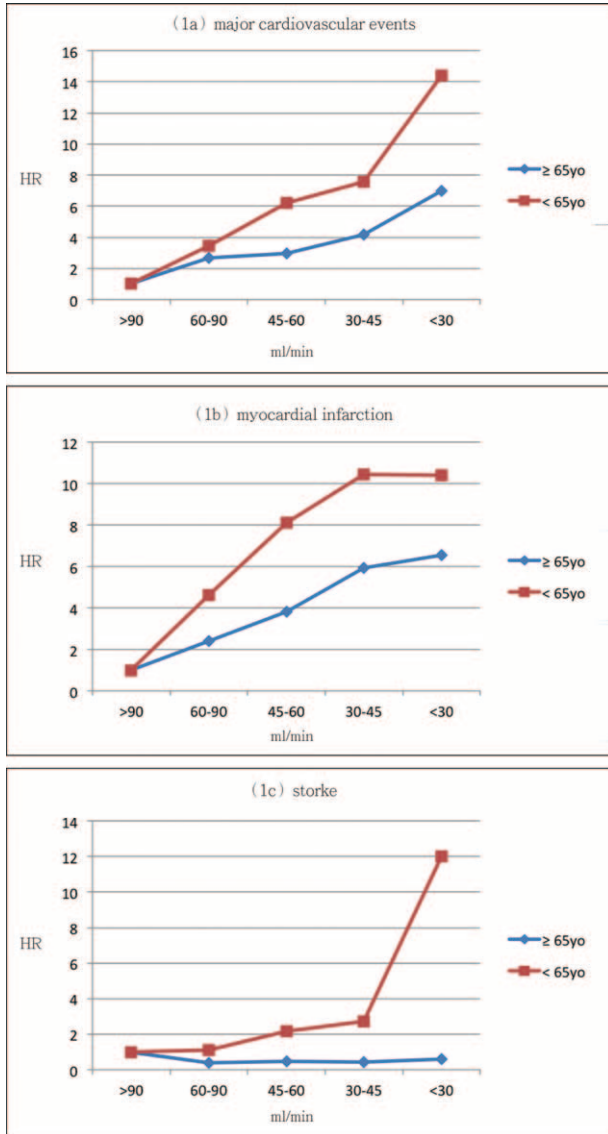


FIGURE 1. HR for risk of major cardiovascular events (A), myocardial infarction (B), and stroke (C) with eGFR category after adjusting for sex, age, cholesterol, triglyceride, LDL-C, HDL-C, BMI, and ACR in elderly and young patients. Group 1: eGFR > 90 mL/min, Group 2: eGFR 61 to 90 mL/min, Group 3: eGFR 46 to 60 mL/min, Group 4: eGFR 30 to 45 mL/min, and Group 5: eGFR < 30 mL/min. HR = 1 set at reference for Group 1. ACR = albumin-creatinine ratio, BMI = calculated body-mass index, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol.

reflects the progression of atherosclerosis. Recently, Hallan et al¹¹ reported that reduced renal function and albuminuria were both risk factors for CV death particularly in the elderly persons.

In a pooled analysis of 4 studies (the Atherosclerosis Risk in Communities, Cardiovascular Health, Framingham Heart, and Framingham Offspring studies),³² it was found that CKD was a risk factor for all-cause mortality in the general population. Another meta-analysis study³⁵ found that diabetic

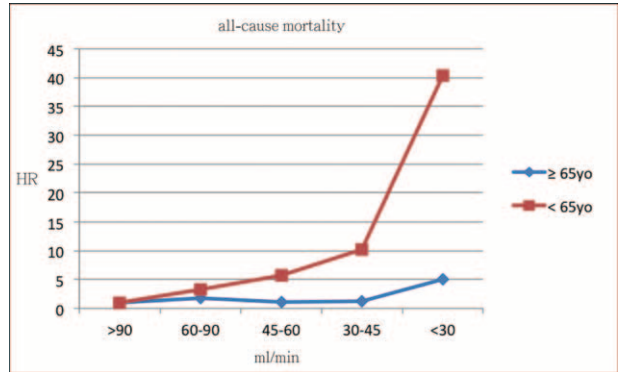


FIGURE 2. HR for risk of all-cause mortality with eGFR category after adjusting for sex, age, cholesterol, triglyceride, LDL-C, HDL-C, BMI, and ACR in elderly and young patients. Group 1: eGFR > 90 mL/min, Group 2: eGFR 61 to 90 mL/min, Group 3: eGFR 46 to 60 mL/min, Group 4: eGFR 30 to 45 mL/min, and Group 5: eGFR < 30 mL/min. HR = 1 set at reference for Group 1. ACR = albumin-creatinine ratio, BMI = calculated body-mass index, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol.

patients with low eGFR (<60 mL/min) and normoalbuminuria had significantly higher all-cause mortality but not CV mortality than those with normal eGFR (≥60 mL/min) and normoalbuminuria. One large study³⁴ of 1,102,581 individuals (75% Asians, 21% Whites, and 4% Blacks) found that low eGFR was independently associated with an increased risk of all-cause mortality and CV mortality in the three major races. However, the National Health and Nutrition Examination Survey (NHANES) I study³⁵ reported that moderate renal insufficiency was not associated with all-cause mortality and CV mortality after adjustment for traditional CV risk factors. The Framingham Heart Study³⁶ did not find baseline kidney disease to be associated with CV mortality in multivariable analyses. Our study also did not find there to be an association between low eGFR and all-cause mortality or CV mortality, although there was a trend toward increased all-cause mortality as the eGFR decreased. Although the first three studies³²⁻³⁴ were very large and had sufficient statistical power to investigate the relationship between CKD and CV and all-cause mortality, they each had their own definition of normal eGFR as the reference category in the meta-analysis studies. These differences in the definition may have influenced their results. One of them³³ evaluated the association between low eGFR and mortality in patients with diabetes, and this meta-analysis concluded that the patient numbers investigating the association between low eGFR and mortality were small. Our study found that eGFR was significantly associated with major CV events but not with CV mortality and all-cause mortality. Therefore, eGFR may be a specific predictor of major CV events but not an unspecific marker of health status.

The traditional definition of microalbuminuria, based on the level of urinary albumin excretion in patients with diabetes, predicts the development of clinical diabetic nephropathy. Although microalbuminuria has been known to be a predictor of CV morbidities and mortality,¹⁻⁴ it was not until it was discovered that there was an association between low-grade albuminuria and CV events that much attention was paid to it. Gerstein et al¹ found any degree of albuminuria, starting well

below the microalbuminuria cutoff, to be a risk factor for CV events in individuals with or without diabetes. Klausen et al^{16,37} reported urinary albumin excretion $>4.8 \mu\text{g}/\text{min}$ to be a strong and independent determinant of coronary artery disease and death in the general population and hypertensive subjects. Recently, Huang et al³⁸ found an association between low grade albuminuria, which is below the current cutoff point of microalbuminuria, and carotid intima-media thickness (IMT) in Chinese T2DM. Our current study, however, did not find an association between high normal ACR and incidental major CV events or death in Chinese with normoalbuminuria. The difference between 2 of the previous studies and our current one might be explained by the fact that the subjects of previous studies^{6,37} came from the general population or were hypertensive subjects with a low prevalence of diabetes. The other study³⁸ focused on the association between albuminuria and carotid IMT, but was not designed to follow progression. Our study evaluated the effect of multiple factorial interventions in a 5-year cohort of normoalbuminuric T2DM patients. Therefore, the difference in our results and those of others may be related in differences in study populations and design. We did not find an association between high normal ACR and risk for major CV events or mortality in normoalbuminuric T2DM Chinese.

A reduced eGFR may be associated with retention of urotoxins and an increased occurrence of nontraditional risk factors of CV events, including chronic inflammation, hyperhomocysteinemia, and increased oxidative stress, all of which could lead to atherosclerosis.^{39,40} Albuminuria can indicate damage to glomerular basement membranes and may reflect endothelial dysfunction.⁴¹ Recently, Drury et al²¹ reported reduced eGFR and albuminuria to be independent risk factors for CV events and mortality in patients with T2DM. One collaborative meta-analysis⁴² has also concluded that low eGFR and high ACR were independent predictors of mortality in the general population. Our prospective cohort has clearly demonstrated an inverse relationship between eGFR and major CV events in diabetic patients with normoalbuminuria. This association was obvious even in subjects with eGFR between 61 and 90 mL/min. On the other hand, we found no association between high normal ACR and major CV events. It is likely that reduced eGFR and albuminuria are markers of different pathologic processes. Our findings are in agreement with the ADA recommendation⁵ that albuminuria and renal function, as estimated by eGFR, be used to assess CV risk in diabetic patients.

This study has several limitations. First, we have not examined the contribution of nontraditional risk factors, which are complex and not routinely measured in daily clinical practice. Nontraditional risk factors such as oxidant stress, elevated inflammatory markers, and homocystine are associated with atherosclerosis and may be additional contributors to high risk of CV events in CKD.^{43,44} Second, we did not find an association between ACR and adverse outcomes. This could be due to several possible reasons. One possibility is that there is a threshold effect at or near the ACR decision point of 30 mg/g. Another is that the correlations between ACR and adverse outcomes are small and continuous. The inability to show that small changes in ACR within the reference interval are predictive of an adverse outcome could be due to the small size of our sample and the short follow-up time. A third limitation is that we did not demonstrate a relationship between eGFR and CV mortality or all-cause mortality, possibly also due to the small number of CV mortalities and all-cause mortalities. A large cohort study with a longer follow-up time may be necessary to clarify the association between eGFR and mortality. The

strengths of the present study should be acknowledged as well. First, this is the first study to evaluate whether subnormal eGFR and high normal ACR are independently associated with CV events and mortality in T2DM with normoalbuminuria under multifactorial intervention. Second, eGFR was calculated by both MDRD and CKD-EPI equations in this study. Third, our study clarifies the important role of renal function, as estimated by eGFR, showing it can be used in the assessment of CV risk in diabetic patients with normoalbuminuria. Although the ADA recommends that albuminuria and renal function, as estimated by eGFR, to be used to assess CV risk in diabetic patients,⁵ the awareness of CKD by general practitioners is low in diabetic population.⁴⁵ One study also reported the low rates of CKD detection at a large hospital.⁴⁶ Furthermore, some studies reported that eGFR was not a strong predictor of CV events in the absence of microalbuminuria. It is reasonable to hypothesize that unawareness of CKD is common especially in diabetic patients with normoalbuminuria in the real world practice.

In conclusion, this study found subnormal eGFR to be a strong predictor of major CV events in diabetic patients with normoalbuminuria. Renal function, as estimated by eGFR, can be used to assess CV risk in diabetic patients with normoalbuminuria. Normoalbuminuric diabetic patients with subnormal eGFR are at higher risk of CV events and may need intensive CV risk factor intervention to prevent and treat CV events.

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