Nonalbuminuric Diabetic Kidney Disease and Risk of All-Cause Mortality and Cardiovascular and Kidney Outcomes in Type 2 Diabetes: Findings From the Hong Kong Diabetes Biobank

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Rationale & Objective: Nonalbuminuric diabetic kidney disease (DKD) has become the prevailing DKD phenotype. We compared the risks of adverse outcomes among patients with this phenotype compared with other DKD phenotypes.

Study Design: Multicenter prospective cohort study.

Settings & Participants: 19,025 Chinese adults with type 2 diabetes enrolled in the Hong Kong Diabetes Biobank.

Exposures: DKD phenotypes defined by baseline estimated glomerular filtration rate (eGFR) and albuminuria: no DKD (no decreased eGFR or albuminuria), albuminuria without decreased eGFR, decreased eGFR without albuminuria, and albuminuria with decreased eGFR.

Outcomes: All-cause mortality, cardiovascular disease (CVD) events, hospitalization for heart failure (HF), and chronic kidney disease (CKD) progression (incident kidney failure or sustained eGFR reduction ≥40%).

Analytical Approach: Multivariable Cox proportional or cause-specific hazards models to estimate the relative risks of death, CVD, hospitalization for HF, and CKD progression. Multiple imputation was used for missing covariates.

Results: Mean participant age was 61.1 years, 58.3% were male, and mean diabetes duration was 11.1 years. During 54,260 person-years of follow-up, 438 deaths, 1,076 CVD events, 298 hospitalizations for HF, and 1,161 episodes of CKD progression occurred. Compared with the no-DKD subgroup, the subgroup with decreased eGFR without albuminuria had higher risks of all-cause mortality (hazard ratio [HR], 1.59 [95% CI, 1.04-2.44]), hospitalization for HF (HR, 3.08 [95% CI, 1.82-5.21]), and CKD progression (HR, 2.37 [95% CI, 1.63-3.43]), but the risk of CVD was not significantly greater (HR, 1.14 [95% CI, 0.88-1.48]). The risks of death, CVD, hospitalization for HF, and CKD progression were higher in the setting of albuminuria with or without decreased eGFR. A sensitivity analysis that excluded participants with baseline eGFR <30 mL/min/1.73 m^2 yielded similar findings.

Limitations: Potential misclassification because of drug use.

Conclusions: Nonalbuminuric DKD was associated with higher risks of hospitalization for HF and of CKD progression than no DKD, regardless of baseline eGFR.

Visual Abstract online

Complete author and article information (including information on the members of the Hong Kong Diabetes Biobank Study Group) provided before references.

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Diabetic kidney disease (DKD) develops in approximately 40% of people with type 2 diabetes mellitus (T2DM),[1] and is the leading cause of kidney failure globally,[2] contributing to half of new kidney failure cases.[3] Despite advancements in therapies and improvement in risk management, the incidence of kidney failure has been increasing in Asian and other populations,[4] highlighting the need for earlier risk stratification and treatment to prevent development and progression of DKD.

Traditionally, based on studies in type 1 diabetes, the natural course of DKD is believed to progress from normoalbuminuria to moderate and then severe albuminuria in an approximately linear pattern, with subsequent development of decreased glomerular filtration. However, this model has been challenged because accumulating studies have reported significant heterogeneity in the manifestations of DKD in T2DM: a decreased estimated glomerular filtration rate (eGFR; to <60 mL/min/1.73 m^2) develops in the absence of albuminuria in a proportion of individuals.[5-9] Moreover, this group with decreased eGFR without albuminuria has become the prevailing DKD phenotype.[10] In a previous analysis, we also found heterogeneous trajectories in the progression to kidney failure in individuals with T2DM.[11]

In the context of DKD, some clinicopathological characteristics of individuals with decreased eGFR without albuminuria are distinct from those with albuminuria, including a higher proportion of women and nonsmokers,

PLAIN-LANGUAGE SUMMARY

Nonalbuminuric diabetic kidney disease (DKD) has become the prevailing DKD phenotype, and distinct clinicopathological characteristics have been reported. We assessed the risks of adverse outcomes (all-cause mortality, cardiovascular disease, heart failure hospitalization, and kidney disease progression) among patients with nonalbuminuric DKD compared with patients with other DKD phenotypes in a multicenter prospective cohort study of type 2 diabetes that included 19,025 individuals. We found that patients with nonalbuminuric DKD had increased risks of death, hospitalization for heart failure, and chronic kidney disease progression compared with those without DKD, and the risks of all adverse outcomes were higher among individuals with albuminuric DKD after adjustment for a wide range of confounders. Further studies are warranted to explore possible mechanisms explaining these observations that will help to tailor the clinical management of nonalbuminuric DKD.

better risk factor profile, and normal or mild diabetic renal structural lesions on biopsy.[5,12-15] With this group now becoming the prevailing DKD phenotype[10] and an upward trend in mortality reported in this group,[16] more studies on the prognosis of this phenotype are warranted. However, current studies are limited and have reported mixed results.[12,14-17] In some studies, patients with decreased eGFR without albuminuria have been found to be at increased risks of mortality[15,17] and cardiovascular disease (CVD);[15] by contrast, a study reported comparable risks of mortality, CVD, and kidney failure among individuals with decreased eGFR without albuminuria and people without DKD.[14] eGFR and urinary albumin-creatinine ratio (UACR) have been reported to be associated with heart failure (HF),[18] but, to the best of our knowledge, the risk of HF across different DKD phenotypes has not been well investigated. Accordingly, in a multicenter prospective cohort of Chinese patients with T2DM, we aimed to assess the risks of all-cause mortality, CVD, hospitalization for HF, and CKD progression in the subgroup of patients with decreased eGFR without albuminuria in comparison with other DKD phenotypes.

Methods

Study Design and Participants

The Hong Kong Diabetes Biobank (HKDB) is a multicenter prospective cohort study coordinated by the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong. A total of 11 diabetes centers at major public hospitals across Hong Kong participated in the study. The HKDB used enrollment and assessment methods similar to those of the Hong Kong Diabetes Registry, established at the Prince of Wales Hospital since 1995 as a quality-improvement program, incorporating comprehensive and structured assessment of risk factors and diabetes complications.[19] A territory-wide diabetes risk assessment program was subsequently set up by the Hong Kong Hospital Authority in 2000 by establishing hospital-based diabetes centers and adopting a similar structured assessment of diabetes complications.[20] The HKDB was initiated in 2014 to establish a multicenter diabetes registry and biobank for identification of novel biomarkers of diabetes and diabetes-related complications. Briefly, all participants were invited to take part in the study when attending a scheduled and standardized diabetes complication assessment based on the modified European DIABCARE protocol.[21] The recruitment methods, collection of anthropometrics and lifestyle factors, and biochemical investigations have been detailed previously.[19,22] When enrolled, the participant is followed until death. A total of 19,789 Chinese patients with T2DM were enrolled consecutively from 2014 to 2019 (Table S1). After exclusion of 460 participants with missing baseline eGFR or UACR and 304 participants with prevalent kidney failure, 19,025 participants were included in the analysis (Fig S1). All participants provided written informed consent at the time of enrollment. Approvals were obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee and the clinical research ethics committee of each participating hospital.

Measurements

Anthropometrics, clinical examination, and laboratory investigations were performed at enrollment, and sociodemographic data and medical and medication history were also documented during face-to-face interviews.[22] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure (in millimeters of mercury) was measured in both arms after at least 5 minutes of sitting, and a mean value was taken for the analysis. Blood samples after at least 8-hour overnight fasting were measured for glycated hemoglobin, serum creatinine, and lipid profile with certificated routine assays at local laboratories. Creatinine was measured using the Jaffe kinetic method,[19] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for eGFR calculation.[23] A random spot urine sample was used for urinary albumin measurement using the immunoturbidimetry method.[19]

Eye examination included visual acuity and retinal photography, and the images were reviewed by diabetologists. Retinopathy was defined by typical changes due to diabetes, laser scars, or a history of vitrectomy. History of CVD was defined as coronary heart disease, stroke, and/or peripheral vascular disease.

According to the status of albuminuria (UACR ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women)[11] and decreased eGFR (<60 mL/min/1.73 m^2), participants were categorized into 4 DKD phenotypes: no DKD (no albuminuria or decreased eGFR), albuminuria without decreased eGFR, decreased eGFR without albuminuria, and albuminuria with decreased eGFR.

Outcomes

The end points of this study were all-cause mortality, CVD, hospitalization for HF, and a CKD progression end point (incident kidney failure or sustained ≥40% reduction in eGFR vs baseline) defined by discharge or diagnostic codes based on the *International Classification of Diseases, Ninth Revision* (Table S2). CVD was defined as the first occurrence of coronary heart disease (myocardial infarction, ischemic heart disease, or angina pectoris), stroke (ischemic stroke except transient ischemic attack, hemorrhagic stroke, or acute but ill-defined cerebrovascular disease), or peripheral vascular disease (amputation, gangrene, or peripheral revascularization). Incident kidney failure was defined as the first occurrence of long-term dialysis, kidney transplant, or sustained (90 days apart) eGFR ≤15 mL/min/1.73 m^2. Sustained eGFR reduction was defined as a ≥40% reduction in eGFR compared with baseline based on 2 eGFR values during follow-up that were 90 days apart. Participants were censored at the time of the study outcome of interest, death, or December 31, 2019, whichever came first.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and differences were compared by analysis of variance or Kruskal-Wallis test as appropriate. Categorical variables are presented as number (percentage) and compared by χ^2 test. Median follow-up time was estimated using the reverse Kaplan-Meier method based on time to mortality.[24]

With no DKD as the reference group, risks of all-cause mortality across DKD phenotypes were estimated using Cox proportional hazards models, and risks of CVD, hospitalization for HF, and CKD progression were estimated using cause-specific hazards models. Two models were built for each outcome: the unadjusted model and the fully adjusted model adjusting for age, sex, smoking at any time, diabetes duration, systolic blood pressure, BMI, glycated hemoglobin, triglyceride level (natural log–transformed), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, oral antihyperglycemic drugs, insulin, antihypertensive drugs, lipid-lowering drugs, renin-angiotensin system (RAS) blockers, statins, diabetic retinopathy, and history of CVD and heart failure.

Missing baseline covariates were imputed with multiple imputation by chained equations using all variables in Table 1. Imputation was performed separately for each outcome to create 5 imputed datasets. Predictive mean matching was used for continuous variables, and logistic regression was used for binary variables.[25] Parameter estimates were obtained by Rubin's formula.[26] Cumulative incidences were estimated with the Kaplan-Meier method (all-cause mortality) or cumulative incidence function (the remaining outcomes), and differences across DKD phenotypes were compared by the log-rank or the Gray test, respectively. Corresponding survival curves were generated from the fully adjusted Cox proportional (all-cause mortality) or subdistribution (the remaining outcomes) hazards models in the first imputed dataset. A 2-tailed P value <0.05 was considered statistically significant. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing). R packages "mice" and "survival" were used for multiple imputation and Cox proportional or cause-specific hazards models, respectively.

Sensitivity Analysis

To explore the potential influence of baseline eGFR on the rates of progressing to the outcomes, we repeated the analyses after further excluding participants with baseline eGFR <30 mL/min/1.73 m^2 without performing imputation.

Results

Baseline Characteristics

Table 1 summarizes the baseline characteristics of the 19,025 participants included in the study. The mean age was 61.1 ± 11.2 (standard deviation) years, 58.3% were male, and the mean diabetes duration was 11.1 ± 8.8 years. The frequencies of DKD phenotypes were 51% for no DKD, 29% for albuminuria without decreased eGFR, 5% for decreased eGFR without albuminuria, and 15% for albuminuria with decreased eGFR. Participants with decreased eGFR without albuminuria had lower systolic blood pressure, BMI, and glycated hemoglobin and lower prevalence of diabetic retinopathy compared with participants with albuminuric DKD (ie, albuminuria with or without decreased eGFR). Moreover, participants with decreased eGFR without albuminuria were older, more likely to be female and to have prevalent CVD, and less likely to have ever been a smoker, and had lower levels of diastolic blood pressure, total cholesterol, and low-density lipoprotein cholesterol than the 3 other DKD phenotypes. The use of RAS blockers was similar among the groups with decreased eGFR without albuminuria, albuminuria without decreased eGFR, and albuminuria with decreased eGFR.

Risk of All-Cause Mortality

During a median of 3.06 (interquartile range, 1.76-4.24) years of follow-up, 438 (event rate, 2.30%) participants died, corresponding to a mortality rate of 7.83 (95%

Table 1. Baseline Characteristics of Study Population Stratified by DKD Phenotypes

Variable	Overall (N = 19,025)	No DKD (n = 9,713; 51%)	Albuminuria Without Decreased eGFR (n = 5,457; 29%)	Decreased eGFR Without Albuminuria (n = 1,044; 5%)	Albuminuria With Decreased eGFR (n = 2,811; 15%)	*P*
Demographic						
Age, y	61.1 ± 11.2	58.6 ± 10.6	59.9 ± 11.0	69.3 ± 8.4	68.6 ± 9.6	<0.001
Male sex	11,084 (58.3%)	5,280 (54.4%)	3,440 (63.0%)	546 (52.3%)	1,818 (64.7%)	<0.001
Smoking, ever	6,452 (33.9%)	3,026 (31.1%)	2,055 (37.6%)	308 (29.5%)	1,063 (37.8%)	<0.001
Missing	8 (0.04%)	4 (0.02%)	3 (0.1%)	0	1 (0.03%)	
Clinical and laboratory						
Diabetes duration, y	11.1 ± 8.8	9.2 ± 8.0	11.1 ± 8.6	14.7 ± 9.5	16.2 ± 9.4	<0.001
Missing	55 (0.3%)	19 (0.2%)	17 (0.3%)	7 (0.7%)	12 (0.4%)	
SBP, mm Hg	134.8 ± 17.8	130.8 ± 16.4	138.2 ± 17.8	133.8 ± 16.4	142.4 ± 18.9	<0.001
Missing	17 (0.1%)	5 (0.1%)	9 (0.2%)	1 (0.1%)	2 (0.1%)	
DBP, mm Hg	74.8 ± 11.4	74.3 ± 10.8	77.1 ± 11.7	71.0 ± 10.7	73.8 ± 12.1	0.004
Missing	9 (0.1%)	1 (0.01%)	6 (0.1%)	1 (0.1%)	1 (0.04%)	
Hemoglobin, g/dL	13.5 ± 1.5	13.8 ± 1.4	13.7 ± 1.5	12.8 ± 1.5	12.7 ± 1.7	<0.001
Missing	1,174 (6.2%)	653 (6.7%)	360 (6.6%)	52 (5.0%)	109 (3.9%)	
BMI, kg/m^2	26.4 ± 4.6	25.8 ± 4.3	27.2 ± 5.1	26.3 ± 4.3	26.8 ± 4.3	<0.001
Missing	52 (0.3%)	14 (0.1%)	22 (0.4%)	1 (0.1%)	15 (0.5%)	
FPG, mmol/L	7.8 ± 2.6	7.6 ± 2.3	8.3 ± 2.9	7.5 ± 2.4	8.0 ± 3.0	<0.001
Missing	179 (0.9%)	106 (1.1%)	39 (0.7%)	13 (1.2%)	21 (0.7%)	
HbA_{1c}, %	7.6 ± 1.5	7.4 ± 1.3	7.9 ± 1.6	7.5 ± 1.2	7.9 ± 1.6	<0.001
HbA_{1c}, mmol/L	59.9 ± 16.0	57.6 ± 14.7	62.5 ± 17.3	58.8 ± 13.4	63.0 ± 17.4	<0.001
Missing	1,185 (6.2%)	554 (5.7%)	359 (6.6%)	65 (6.2%)	207 (7.4%)	
eGFR, mL/min/1.73 m^2	79.6 ± 23.0	90.0 ± 14.3	86.5 ± 15.2	48.9 ± 9.2	41.6 ± 11.8	<0.001
UACR, mg/mmol	2 [0.7-9.4]	0.8 [0.5-1.4]	8.8 [4.7-23.4]	1 [0.6-1.8]	34.5 [9.9-123.8]	<0.001
Triglycerides, mmol/L	1.3 [0.9-2.0]	1.2 [0.9-1.7]	1.4 [1.0-2.1]	1.4 [1.0-1.9]	1.6 [1.1-2.3]	<0.001
Missing	294 (1.5%)	190 (2.0%)	65 (1.2%)	10 (1.0%)	29 (1.0%)	
TC, mmol/L	4.3 ± 0.9	4.3 ± 0.9	4.3 ± 1.0	4.1 ± 1.0	4.2 ± 1.0	<0.001
Missing	291 (1.5%)	188 (1.9%)	65 (1.2%)	10 (1.0%)	28 (1.0%)	
HDL-C, mmol/L	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	<0.001
Missing	295 (1.6%)	188 (1.9%)	70 (1.3%)	10 (1.0%)	27 (1.0%)	
LDL-C, mmol/L	2.3 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	2.1 ± 0.7	2.2 ± 0.8	<0.001
Missing	440 (2.3%)	224 (2.3%)	139 (2.5%)	13 (1.2%)	64 (2.3%)	
Medical history						
Diabetic retinopathy	4,259 (22.4%)	1,634 (16.9%)	1,473 (27.0%)	253 (24.2%)	899 (31.9%)	<0.001
CVD	4,657 (24.5%)	1,856 (19.1%)	1,327 (24.3%)	405 (38.8%)	1,069 (38.0%)	<0.001
CHD	3,268 (17.2%)	1,346 (13.9%)	883 (16.2%)	310 (29.7%)	2,082 (74.1%)	
Stroke	1,623 (8.5%)	582 (6.0%)	496 (9.1%)	131 (12.5%)	414 (14.7%)	
PVD	236 (1.2%)	42 (0.4%)	73 (1.3%)	23 (2.2%)	98 (3.5%)	
CHF	706 (3.7%)	173 (1.8%)	193 (3.5%)	82 (7.9%)	258 (9.2%)	<0.001
Medication history						
Oral antihyperglycemic drugs	13,781 (72.4%)	6,862 (70.6%)	4,165 (76.3%)	756 (72.4%)	1,998 (71.1%)	<0.001
Missing	3,767 (19.8%)	2,068 (21.3%)	1,010 (18.5%)	198 (19.0%)	491 (17.5%)	
Insulin	5,985 (31.5%)	2,304 (23.7%)	1,820 (33.4%)	376 (36.0%)	1,485 (52.8%)	<0.001
Missing	143 (0.8%)	80 (0.8%)	38 (0.7%)	6 (0.6%)	19 (0.7%)	
Lipid-lowering drugs	13,039 (68.5%)	6,180 (63.6%)	3,768 (69.0%)	819 (78.4%)	2,272 (80.8%)	<0.001

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Study Population Stratified by DKD Phenotypes

Variable	Overall (N = 19,025)	No DKD (n = 9,713; 51%)	Albuminuria Without Decreased eGFR (n = 5,457; 29%)	Decreased eGFR Without Albuminuria (n = 1,044; 5%)	Albuminuria With Decreased eGFR (n = 2,811; 15%)	*P*
Missing	106 (0.6%)	61 (0.6%)	28 (0.5%)	6 (0.6%)	11 (0.4%)	
Antihypertensive drugs	13,618 (71.6%)	5,666 (58.3%)	4,425 (81.1%)	900 (86.2%)	2,627 (93.5%)	<0.001
Missing	92 (0.5%)	58 (0.6%)	23 (0.4%)	5 (0.5%)	6 (0.2%)	
RAS blockers	10,009 (52.6%)	3,702 (38.1%)	3,558 (65.2%)	662 (63.4%)	2,087 (74.2%)	<0.001
Missing	1 (0.01%)	1 (0.01%)	0	0	0	
Statins	12,268 (64.5%)	5,696 (58.6%)	3,562 (65.3%)	794 (76.1%)	2,216 (78.8%)	<0.001
Missing	1 (0.01%)	1 (0.01%)	0	0	0	

Data are expressed in mean ± standard deviation, median [interquartile rage], or number (percentage) as appropriate. *P* values for differences across DKD phenotypes were obtained by one-way analysis of variance, Kruskal-Wallis test, or χ^2 test as appropriate. Abbreviations: BMI, body mass index; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; RAS, renin-angiotensin system; SBP, systolic blood pressure; TC, total cholesterol; UACR, urinary albumin-creatinine ratio.

confidence interval [CI], 7.12-8.60) per 1,000 person-years. The crude incidence was lowest for people with no DKD and highest for people with albuminuria with decreased eGFR (Fig 1; Table 2). The unadjusted Cox model showed a similar pattern (Table 2). In the fully adjusted Cox model, compared with people with no DKD, hazard ratios (HRs) for all-cause mortality for participants with decreased eGFR without albuminuria, albuminuria without decreased eGFR, and albuminuria with decreased eGFR were 1.59 (95% CI, 1.04-2.44), 2.00 (95% CI, 1.52-2.63), and 3.26 (95% CI, 2.43-4.38), respectively (Table 2).

Risk of CVD and Hospitalization for HF

During the observation period, CVD developed in 1,076 (5.66%) participants and 298 (1.57%) participants were hospitalized for HF, corresponding to incidence rates of 19.91 (95% CI, 18.73-21.13) and 5.38 (95% CI, 4.78-6.02) per 1,000 person-years, respectively. The crude incidences and HRs for CVD and hospitalization for HF were lowest for participants with no DKD and highest for participants with albuminuria with decreased eGFR (Fig 1; Table 2). For CVD, compared with participants with no DKD and after adjusting for confounders, HRs were significantly higher for participants with albuminuria without or with decreased eGFR (1.19 [95% CI, 1.02-1.40] and 1.47 [95% CI, 1.23-1.76], respectively), but not significantly different for participants with decreased eGFR without albuminuria (1.14 [95% CI, 0.88-1.48]; Table 2; Fig S2). HRs for hospitalization for HF exhibited similar patterns to those for mortality (Table 2; Fig S2).

Risk of CKD Progression

A total of 1,161 (6.10%) participants reached the CKD progression outcome during follow-up (incidence rate, 21.74 [95% CI, 20.50-23.02] per 1,000 person-years), including 414 kidney failure events and 899 participants with sustained ≥40% reduction in eGFR. People with decreased eGFR without albuminuria had a lower incidence of CKD progression compared with those with albuminuria with or without decreased eGFR, but a higher incidence than those with no DKD (Fig 1; Table 2). After accounting for confounders, similar results were found (Table 2; Fig S2).

Sensitivity Analyses

After further excluding participants with baseline eGFR <30 mL/min/1.73 m^2 (n = 18,425 included in the analyses), the patterns of risks remained unchanged for hospitalization for HF and for CKD progression (Table 3). For mortality and CVD, compared with people with no DKD, HRs for participants with decreased eGFR without albuminuria were rendered nonsignificantly different (1.45 [95% CI, 0.86-2.42] and 1.24 [95% CI, 0.90-1.70], respectively), whereas the HR remained significantly higher for mortality for participants with albuminuria with or without decreased eGFR (Table 3).

Discussion

In a well-characterized prospective cohort of T2DM, we assessed the prognosis of people with different DKD phenotypes. Compared with people without DKD, those with decreased eGFR without albuminuria exhibited nonsignificantly increased risks of CVD and death when baseline eGFR was >30 mL/min/1.73 m^2; however, people in this group were at increased risks of hospitalization for HF and of CKD progression regardless of baseline CKD stage.

People with decreased eGFR without albuminuria appear to have some shared clinical characteristics across ethnicities that are different from other DKD phenotypes.[14,15,17] People with decreased eGFR without albuminuria tend to be older and are more likely to be female and nonsmokers compared with people with the other DKD phenotypes. Moreover, people with decreased eGFR without albuminuria have been reported to have a lower prevalence of diabetic retinopathy than those with albuminuric DKD and a higher prevalence of CVD than those with albuminuria without decreased eGFR.[14,17] In the

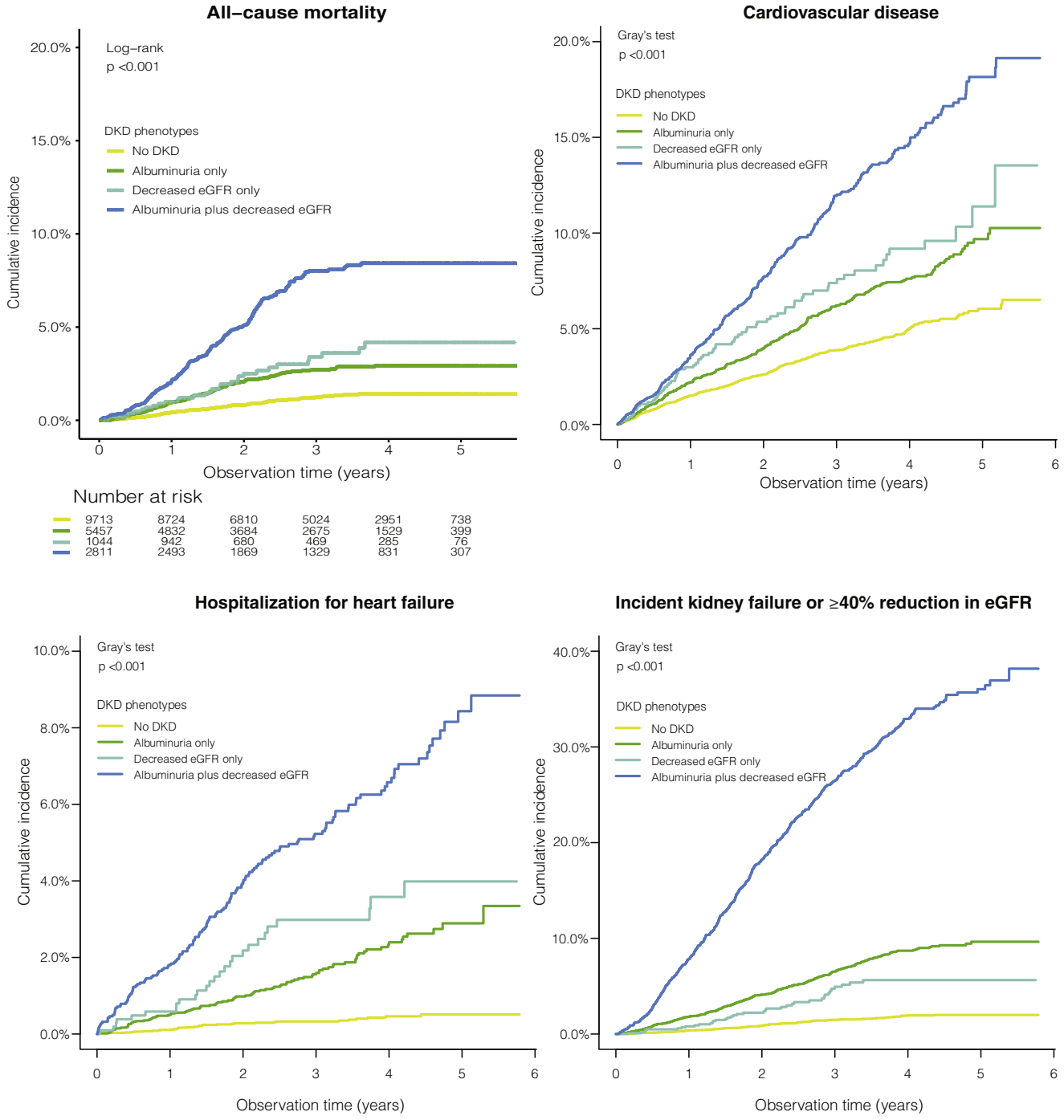

Figure 1. Cumulative incidence curves for all-cause mortality, cardiovascular disease, hospitalization for heart failure, and chronic kidney disease progression according to 4 diabetic kidney disease (DKD) phenotypes. Abbreviation: eGFR, estimated glomerular filtration rate. Please note the *y*-axis of each graph has been zoomed in.

present study, we found better blood pressure and lipid control and more prevalent CVD in people with decreased eGFR without albuminuria versus other DKD phenotypes, including no DKD.

In line with previous studies,[15,17] people with decreased eGFR without albuminuria had a higher risk of death than those without DKD, with this risk mainly concentrated in those with baseline eGFR <30 mL/min/1.73 m^2. Data from the RIACE (Renal Insufficiency and Cardiovascular Events) study found a higher risk of death in people with decreased eGFR without albuminuria (HR, 1.58 [95% CI, 1.43-1.75]) than in those with no DKD.[17] Similarly, results from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study suggested higher risks of mortality (HR, 1.42 [95% CI, 1.14-1.78]) and major cardiovascular events

Table 2. Event/Incidence Rates and Risks of Mortality, CVD, Hospitalization for HF, and CKD Progression Across 4 DKD Phenotypes

Outcome	Overall (N = 19,025)	No DKD (n = 9,713; 51%)	Albuminuria Without Decreased eGFR (n = 5,457; 29%)	Decreased eGFR Without Albuminuria (n = 1,044; 5%)	Albuminuria With Decreased eGFR (n = 2,811; 15%)
All-cause mortality					
Events	438 (2.30%)	103 (1.06%)	124 (2.27%)	30 (2.87%)	181 (6.44%)
Incidence per 1,000 p-y	7.83 (7.12-8.60)	3.56 (2.90-4.31)	7.83 (6.51-9.33)	10.21 (6.89-14.58)	22.14 (19.03-25.61)
Unadjusted HR	–	1.00 (reference)	2.19 (1.69-2.84)	2.83 (1.88-4.25)	6.28 (4.93-8.00)
Adjusted HR	–	1.00 (reference)	2.00 (1.52-2.63)	1.59 (1.04-2.44)	3.26 (2.43-4.38)
CVD					
Events	1,076 (5.66%)	369 (3.80%)	318 (5.83%)	73 (6.99%)	316 (11.24%)
Incidence per 1,000 p-y	19.91 (18.73-21.13)	13.05 (11.76-14.46)	20.79 (18.57-23.21)	25.88 (20.28-32.54)	41.21 (36.79-46.02)
Unadjusted HR	–	1.00 (reference)	1.59 (1.37-1.85)	1.98 (1.54-2.54)	3.15 (2.71-3.66)
Adjusted HR	–	1.00 (reference)	1.19 (1.02-1.40)	1.14 (0.88-1.48)	1.47 (1.23-1.76)
Hospitalization for HF					
Events	298 (1.57%)	33 (0.34%)	90 (1.65%)	27 (2.59%)	148 (5.27%)
Incidence per 1,000 p-y	5.38 (4.78-6.02)	1.14 (0.79-1.60)	5.73 (4.61-7.04)	9.32 (6.14-13.56)	18.71 (15.82-21.98)
Unadjusted HR	–	1.00 (reference)	5.02 (3.37-7.48)	8.14 (4.89-13.53)	16.36 (11.22-23.87)
Adjusted HR	–	1.00 (reference)	3.14 (2.09-4.73)	3.08 (1.82-5.21)	5.50 (3.63-8.34)
CKD progression[a]					
Events	1,161 (6.10%)	128 (1.32%)	327 (5.99%)	38 (3.64%)	668 (23.76%)
Incidence per 1,000 p-y	21.74 (20.50-23.02)	4.46 (3.72-5.31)	21.59 (19.31-24.06)	13.27 (9.39-18.22)	99.29 (91.90-107.11)
Unadjusted HR	–	1.00 (reference)	4.85 (3.95-5.94)	2.99 (2.08-4.29)	22.53 (18.64-27.22)
Adjusted HR	–	1.00 (reference)	3.77 (3.05-4.66)	2.37 (1.63-3.43)	14.01 (11.31-17.36)

Ranges in parentheses are 95% CIs. Adjustments were made for age, sex, smoking at any time, diabetes duration, systolic blood pressure, body mass index, glycated hemoglobin, natural log–transformed triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, oral antihyperglycemic drugs, insulin, lipid-lowering drugs, antihypertensive drugs, renin-angiotensin system blockers, statins, diabetic retinopathy, and history of CVD and congestive heart failure. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; p-y, person-years.
[a]Defined as incident kidney failure or sustained eGFR reduction ≥40%.

(myocardial infarction, stroke, and cardiovascular death; HR, 1.44 [95% CI, 1.13-1.84]) in people with decreased eGFR without albuminuria versus those without DKD.[15] In the present study, we found a higher risk of hospitalization for HF in those with decreased eGFR without albuminuria. Because baseline eGFR is associated with death and CVD in patients with diabetes,[18,27] to address the possible influence of eGFR on the risk of outcomes, we further excluded participants with baseline eGFR <30 mL/min/1.73 m^2 and found nonsignificantly different risks of death and CVD in people with decreased eGFR without albuminuria versus people with no DKD; however, participants with this DKD phenotype were still at increased risk of hospitalization for HF. In keeping with our result, an analysis from the JDDM (Japan Diabetes Clinical Data Management) study that included Japanese participants with baseline eGFR ≥30 mL/min/1.73 m^2 reported no significant differences in the risks of death (HR, 1.46 [95% CI, 0.73-2.92]) and CVD (coronary heart disease, stroke, peripheral vascular disease, and cardiovascular death; HR, 1.06 [95% CI, 0.63-1.79]) between people with decreased eGFR without albuminuria and those with no DKD.[14]

There are several potential explanations for a nonsignificantly different risk of CVD between the subgroup with decreased eGFR without albuminuria and the subgroup with no DKD. First, studies have found that there is a higher proportion of women, fewer smokers, and better glycemic and blood pressure control in patients with T2DM with decreased eGFR without albuminuria,[14,15,17] suggesting that reduced eGFR in the absence of albuminuria may represent a distinct DKD phenotype with a more favorable clinical characteristic profile that responds better to risk-factor management. This phenotype may be enriched with people whose condition regressed to normoalbuminuria because of RAS blockers, giving them a lower likelihood of CKD progression. However, our results showed that people with decreased eGFR without albuminuria had a higher risk of CKD progression, even after

Table 3. Event/Incidence Rates and Risks of Mortality, CVD, Hospitalization for HF, and CKD Progression Across 4 DKD Phenotypes After Further Excluding Participants With Baseline eGFR <30 mL/min/1.73 m^2

	Overall (N = 18,425)	No DKD (n = 9,713; 52.7%)	Albuminuria Without Decreased eGFR (n = 5,457; 29.6%)	Decreased eGFR Without Albuminuria (n = 1,000; 5.4%)	Albuminuria With Decreased eGFR (n = 2,255; 12.2%)
All-cause mortality					
Events	376 (2.04%)	103 (1.06%)	124 (2.27%)	27 (2.70%)	122 (5.41%)
Incidence per 1,000 p-y	6.94 (6.26-7.68)	3.56 (2.90-4.31)	7.83 (6.51-9.33)	9.56 (6.30-13.91)	18.61 (15.45-22.22)
Unadjusted HR	–	1.00 (reference)	2.19 (1.69-2.84)	2.65 (1.74-4.05)	5.27 (4.05-6.85)
Adjusted HR	–	1.00 (reference)	1.88 (1.36-2.59)	1.45 (0.86-2.42)	2.78 (1.93-3.99)
CVD					
Events	993 (5.39%)	369 (3.80%)	318 (5.83%)	69 (6.90%)	237 (10.51%)
Incidence per 1,000 p-y	18.93 (17.77-20.15)	13.05 (11.76-14.46)	20.79 (18.57-23.21)	25.42 (19.78-32.17)	38.42 (33.69-43.64)
Unadjusted HR	–	1.00 (reference)	1.59 (1.37-1.85)	1.94 (1.50-2.51)	2.94 (2.49-3.46)
Adjusted HR	–	1.00 (reference)	1.15 (0.95-1.40)	1.24 (0.90-1.70)	1.30 (1.03-1.64)
Hospitalization for HF					
Events	255 (1.38%)	33 (0.34%)	90 (1.65%)	25 (2.50%)	107 (4.75%)
Incidence per 1,000 p-y	4.74 (4.18-5.36)	1.14 (0.79-1.60)	5.73 (4.61-7.04)	8.97 (5.81-13.25)	16.80 (13.77-20.30)
Unadjusted HR	–	1.00 (reference)	5.02 (3.37-7.48)	7.86 (4.67-13.21)	14.74 (9.97-21.77)
Adjusted HR	–	1.00 (reference)	3.69 (2.15-6.31)	3.61 (1.84-7.09)	4.83 (2.75-8.50)
CKD progression[a]					
Events	908 (4.93%)	128 (1.32%)	327 (5.99%)	37 (3.70%)	416 (18.45%)
Incidence per 1,000 p-y	17.38 (16.26-18.54)	4.46 (3.72-5.31)	21.59 (19.31-24.06)	13.43 (9.46-18.52)	73.26 (66.39-80.65)
Unadjusted HR	–	1.00 (reference)	4.86 (3.96-5.96)	3.03 (2.10-4.37)	16.67 (13.67-20.32)
Adjusted HR	–	1.00 (reference)	3.34 (2.52-4.44)	2.30 (1.38-3.82)	10.00 (7.42-13.46)

Ranges in parentheses are 95% CIs. Adjustments were made for age, sex, ever smoking, diabetes duration, systolic blood pressure, body mass index, glycated hemoglobin, natural log–transformed triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, oral antihyperglycemic drugs, insulin, lipid-lowering drugs, antihypertensive drugs, renin-angiotensin system blockers, statins, diabetic retinopathy, and history of CVD and congestive heart failure. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; p-y, person-years.
[a]Defined as incident kidney failure or sustained eGFR reduction ≥40%.

adjustment for RAS blockers. Furthermore, after excluding participants taking RAS blockers at baseline from the group of participants with decreased eGFR without albuminuria, we found a similar result: people with decreased eGFR without albuminuria had a higher risk of CKD progression (Table S3). The second possible explanation is the underlying pathological features. Among patients with biopsy-proven DKD, those without proteinuria typically have less advanced and typical glomerular classifications as well as less severe interstitial and vascular lesions.[12] Albuminuria is a biomarker of endothelial dysfunction and inflammation and has been associated with CVD in T2DM[28]; therefore, people with decreased eGFR without albuminuria may have less atherosclerotic burden. It has been reported that the risk of CVD is not significantly increased in those with decreased eGFR without albuminuria compared with those with no DKD in the East Asian population,[14] but that this risk is significantly higher in the Western population.[15] This can be attributed to differences in the prevalence of comorbidities, especially higher rates of obesity, hypertension, and CVD, in the Western population. Although BMI, systolic blood pressure, and history of CVD have been controlled for in the analysis from the ACCORD study[15] and in our analysis, the mean BMI, systolic blood pressure, and prevalence of CVD were lower in our cohort (32.2 vs 26.4 kg/m^2, 136.3 vs 134.8 mm Hg, and 35.2% vs 24.5%, respectively).

Diabetes is a major risk factor for heart failure,[29] and the consistent results of a reduced risk of hospitalization for HF in patients receiving a sodium/glucose cotransporter 2 (SGLT2) inhibitor[30-32] highlights the cardioprotective effect of an SGLT2 inhibitor beyond its role in glucose lowering. A secondary analysis of the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction) randomized clinical trial found no heterogeneity in the effect on hospitalization for HF across DKD markers (eGFR <60 mL/min/1.73 m^2 and albuminuria) and reported a larger effect in patients with albuminuria with decreased eGFR.[33] The present study demonstrated that participants with decreased eGFR without albuminuria had a higher risk of hospitalization for HF than participants without DKD, and the finding remained unchanged after excluding participants with baseline eGFR <30 mL/min/1.73 m^2. Because

the secondary analysis of DECLARE-TIMI 58 combined patients with reduced eGFR or albuminuria into one group,[33] it remains to be confirmed how much patients with reduced eGFR in the absence of albuminuria would benefit from an SGLT2 inhibitor.

In contrast to our result that participants with decreased eGFR without albuminuria had a higher risk of kidney failure or ≥40% eGFR reduction compared with people without DKD, results from the ACCORD study reported that the risk of kidney failure in decreased eGFR without albuminuria was not increased compared with patients with no DKD[15]; however, both studies found that the highest risk of kidney disease progression occurred in people with albuminuria with decreased eGFR. An analysis of participants with baseline eGFR ≥30 mL/min/1.73 m^2 from the JDDM study also found no significant increase in risk of ≥30% eGFR decrease compared with those without DKD.[14] However, our result is not without support. Higher risk of progression to kidney failure has been found in people with decreased eGFR without albuminuria versus those without albuminuria and decreased eGFR in a large population-based study.[34] An analysis from the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation) study found that, among patients with normoalbuminuria, the risk of renal events (death from kidney causes, incident kidney replacement therapy, or doubling of serum creatinine level to >200 μmol/L) was higher in patients with eGFR <60 versus ≥60 mL/min/1.73 m^2.[35] Previous randomized trials testing potential renoprotective drugs in T2DM mostly excluded patients with reduced eGFR without albuminuria,[30,31,36,37] making the treatment for this phenotype less clear. Findings in the present study suggest that this phenotype is at risk of CKD progression; hence, more randomized trials including people with decreased eGFR without albuminuria are needed.

The major strengths of the present study include a large sample size and a sufficient number of events to facilitate the analyses. However, interpretations should be made in the context of some limitations. Because our study included only Chinese participants, further investigations in different populations are warranted to examine the generalizability of our findings. Given the observational nature of the study, residual confounding cannot be ruled out. Information on the use of SGLT2 inhibitors was not considered. Therefore, we were not able to compare the differences in SGLT2 inhibitor prescriptions among DKD phenotypes or their possible influence on the outcomes, especially hospitalization for HF and CKD progression. However, evidence that SGLT2 inhibitors prevent hospitalization for HF and progression of CKD is mainly from patients with overt albuminuria,[30,31,36,38] and studies in participants with decreased eGFR without albuminuria are limited. Further, a recent territory-wide analysis from Hong Kong indicated that the use of SGLT2 inhibitors was quite low overall, at 0.4% in 2016[39]; however, the rates of use within the HKDB would likely be higher given the setting of specialized diabetes clinics. The definition of DKD was based on eGFR and UACR, rather than requiring biopsy-proven DKD. We acknowledge that the renal lesions of clinically defined DKD may be attributable to nondiabetic kidney disease, as a proportion of patients can have kidney biopsy results suggestive of nondiabetic kidney disease.[40] However, a study in people with biopsy-proven DKD found similar results: persons without proteinuria (UACR <300 mg/g) had a lower risk of mortality than people with proteinuria.[12]

In conclusion, in a prospective cohort of Chinese patients with T2DM, we demonstrated that decreased eGFR without albuminuria was associated with higher risks of hospitalization for HF and subsequent progression of CKD compared with people without DKD. Currently, therapeutic strategies and targets for this phenotype are less well defined.[37] With this group becoming the prevailing DKD phenotype and showing distinct clinicopathological features as well as risks of adverse outcomes, more studies are needed to explore possible mechanisms and to tailor management and interventions for this phenotype.

Supplementary Material

Supplementary File (PDF)

Figure S1: Analysis flow in the Hong Kong Diabetes Biobank.

Figure S2: Adjusted survival curves for all-cause mortality, CVD, hospitalization for HF, and CKD progression according to the 4 DKD phenotypes.

Item S1: Members of the Hong Kong Diabetes Biobank Study Group.

Table S1: Baseline characteristics of the Hong Kong Diabetes Biobank, the overall DKD group, and those excluded.

Table S2: Definitions of outcomes based on diagnosis and procedure codes.

Table S3: Event/incidence rates and risks of mortality, CVD, hospitalization for HF, and CKD progression in non-RAS blocker users at baseline among patients with decreased eGFR without albuminuria.

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