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ORIGINAL RESEARCH

Effect of Urinary Albumin Creatinine Ratio on Cardiovascular Morbidity and Mortality in Diabetes Patients with Atherosclerotic Disease

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Background: Diabetes mellitus (DM) patients with increased urinary albumin creatinine ratio (uACR) have higher risk of mortality, while it is unclear in DM patients with atherosclerotic cardiovascular disease (ASCVD).

Methods: We analysed 2832 DM patients with ASCVD in this multi-center registry cohort study Cardiorenal ImprovemeNt II (CIN-II) in 5 Chinese tertiary hospitals from 2007 to 2020. Patients were divided into 3 groups according to their uACR level (normal group: uACR <30mg/g, moderately increased group: 30mg/g≤ uACR <300mg/g, severely increased group: 300mg/g≤ uACR). The main outcome of the study was cardiovascular mortality and all-cause mortality.

Results: During a median follow-up of 2.1 years, among 2832 patients (mean age: 63.3 ± 9.9 years, 29.1% women), 434 patients (15.3%) had moderately increased uACR, and 203 patients (7.2%) had severely increased uACR. Compared to patients in normal group, patients had higher cardiovascular mortality in moderately increased group and severely increased group (2.5% vs 9.9% vs 16.7%, P < 0.001), as well as all-cause mortality. After adjusting confounders, the risk of cardiovascular mortality remained higher in moderately increased group (adjusted hazard ratio [aHR]: 3.13; 95% confidence interval [CI]: 2.04–4.81) and severely increased group (aHR: 4.54; 95% CI: 2.58–8.01) than in normal group, as well as all-cause mortality.

Conclusion: In our study, we found nearly a quarter of DM patients with ASCVD had increased uACR, and they have over 2- or 3-fold risk of cardiovascular mortality than those with normal uACR. UACR is a helpful indicator for risk stratification and treatment target for DM patients with ASCVD.

Keywords: diabetes mellitus, atherosclerotic cardiovascular disease, urinary albumin creatinine ratio, cardiovascular mortality

Introduction

Diabetes mellitus (DM) is a strong risk factor for cardiovascular disease.[1] Patients diagnosed with DM have a two-thirds chance of developing some form of cardiovascular disease (CVD) in their lifetime, of which 85.8% are classified as atherosclerotic CVD (ASCVD) and even as high as 94.9% in China.[2,3] In addition, DM patients with ASCVD also had high prevalence of

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comorbidities, especially hyperlipidemia, chronic kidney disease (CKD), and congestive heart failure (CHF) than those without.[4,5]

Previous study suggests that persistent microalbuminuria is a risk marker of cardiovascular morbidity and mortality in DM patients,[6] while persistent micro- or macroalbuminuria are considered as the markers of generalised vascular endothelial damage, which is early event in development of ASCVD.[7]

As a common indicator to reflect urinary albumin levels, urine Albumin Creatinine Ratio (uACR) is a recommended indicator for detecting early renal injury and the primary screening tool for diabetic nephropathy according to the guideline,[8,9] and it can be easily measured through urinalysis and widely used in clinical work.[10,11] Previous study shows that uACR is associated with cardiovascular events and all-cause mortality.[12] In patients with DM, uACR is also a powerful predictor of mortality.[1]

However, the effect of increased uACR on cardiovascular risk in DM patients with ASCVD was unclear. Therefore, we aimed to investigate the relationship between the level of uACR and long-term cardiovascular mortality and all-cause mortality among DM patients with ASCVD.

Methods

Study Design and Population

This multi-center, retrospective study was based on the registry of Cardiorenal ImprovemeNt II (CIN-II, NCT05050877) cohort from January 2000 to December 2020 in five south Chinese regional central tertiary teaching hospitals. Considering the time consistency among different centers, we included the patients from 2007 to 2020.[13] Patients not hospitalised for the first time were excluded, as well as patients without discharge status reporting. Patients without records of uACR were excluded. Finally, 2832 DM participants with ASCVD in CIN-II were included in our study (see Figure 1).

The study protocol was approved by the Guangdong Provincial People's Hospital ethics committee (No.GDREC2019-555H-2), all participating sites received institutional review board approval from their own ethics committees, and the study was performed according to the declaration of Helsinki.

Data Collection

The follow-up information was obtained by matching the survival information of patients with Centers for Disease Control and Prevention. The hospital patient data was collected from the Electronic Clinical Management System (ECMS). Urinary albumin excretion was measured on spot urine specimens by immunoturbidimetry with goat anti-human albumin antiserum with a coefficient of variation <10%. Urinary creatinine was measured by using a colorimetric dye-binding technique based on its reaction with picric acid with a coefficient of variation <6%.[14] Both tests were performed on a laboratory analyser with standard reagents (Beckman Coulter AU5800, Beckman Coulter, Inc., Brea, CA). UACR values were calculated as mg albumin/g creatinine. The data was mainly included from six sections: demographics, discharge diagnosis, laboratory examinations, treatment (procedures), medication use, and discharge status. All statistical analyses were performed using R, version 4.1.0 software (R Foundation for Statistical Computing, Vienna, Austria).

Senior cardiologists were responsible for the data quality control and periodically carried out database checking. Finally, the accuracy of diagnosis and other variables underwent random on-site audits, and the error rate among 5000 patients was below 2%.

Outcomes and Definitions

The main outcome of the study was all-cause mortality and cardiovascular mortality. DM was accessed according to the discharge diagnosis, or glycated hemoglobin (HbA1c) >6.5%, or treatment with a hypoglycemic agent or insulin. ASCVD was defined as a diagnosis of coronary artery disease (CAD) or stroke, peripheral arterial disease (PAD).[15] CAD was confirmed by CAG and discriminated according to the 10th Revision Codes of the International Classification of Diseases. Hypertension (HT) was defined according to the 10th Revision Codes of the International Classification of Diseases (I10.xxx-I12.xxx, I15.xxx and I67.400). Chronic kidney disease (CKD) was defined as the discharge diagnosis and estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula.[16] Congestive heart failure (CHF) was defined as the discharge diagnosis and New York Heart Association class >2 or Killip class >1. Anemia was defined using World Health Organisation criteria: baseline hematocrit value <39% for men and <36% for women.[17,18] The key variables included

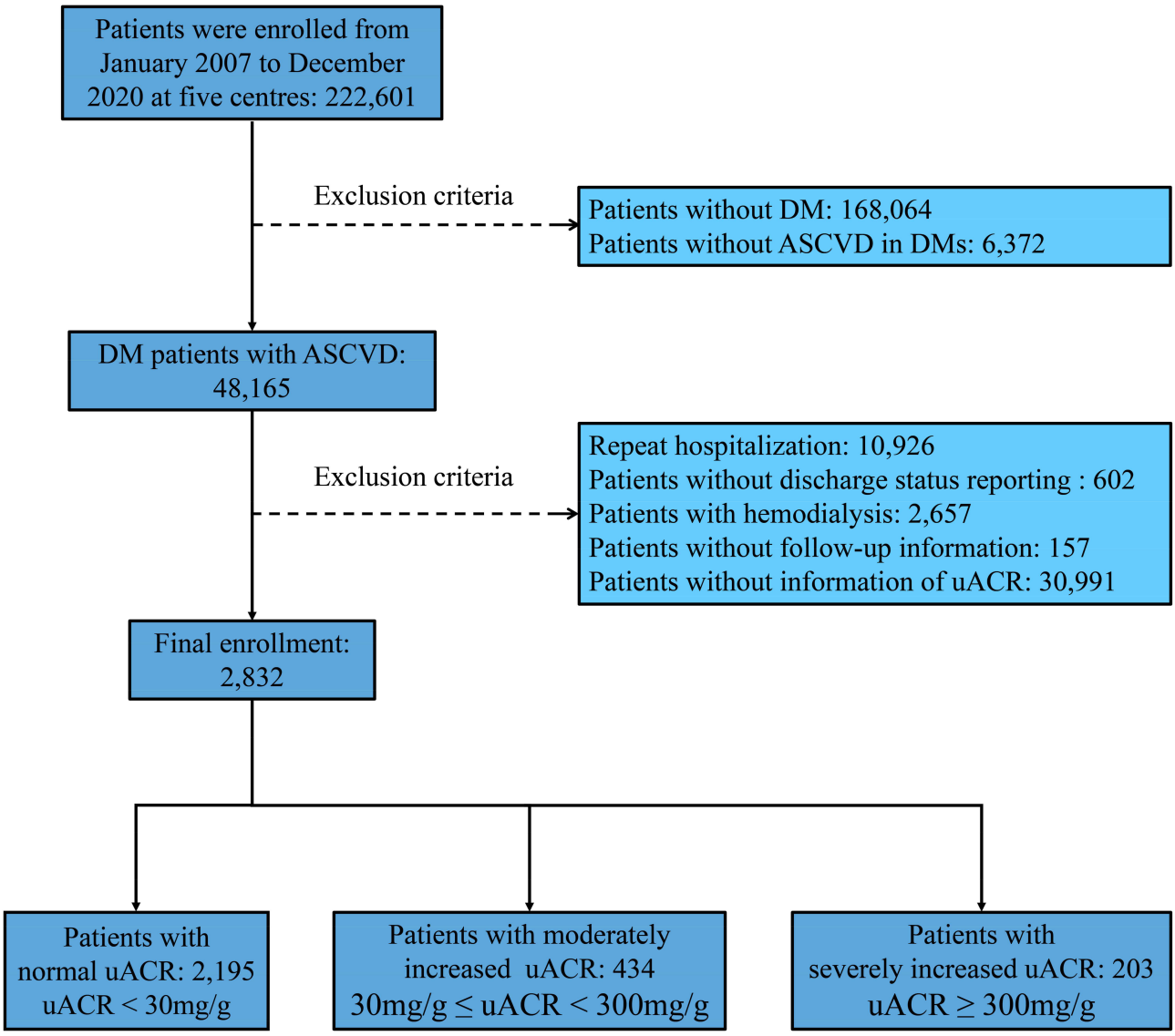

Figure 1 Flow diagram.

demographic characteristics (age, gender), medical comorbidities (acute myocardial infarction [AMI], HT, CAD, percutaneous coronary intervention [PCI], CKD and CHF), laboratory examinations (HbA1c, low-density lipoprotein cholesterol [LDLC], high-density lipoprotein cholesterol [HDLC], hemoglobin [HGB], prior serum creatinine [SCr], uric acid [URIC]), medication (Dual antiplatelet therapy [Aspirin/Clopidogrel or Ticagrelor], Statins, Aspirin, Angiotensin converting enzyme inhibitors or angiotensin receptor blocker [ACEI/ARB], Spironolactone and β-blockers).

Statistical Analysis

The study included 2832 DM patients with ASCVD. These patients were divided into 3 groups according to their level of uACR:[8]

- Group 1: uACR <30 mg/g (normal)
- Group 2: 30 mg/g ≤ uACR < 300 mg/g (moderately increased)
- Group 3: uACR ≥300 mg/g (severely increased)

The continuous variables were summarised as mean ± standard deviation (SD) or median [interquartile ranges (IQRs)], and categorical variables were presented as counts and proportions. Characteristics were compared between groups using ANOVA, Kruskal Wallis tests and χ^2 tests as appropriate. Kaplan–Meier method (KM) and Log rank test

were used to analyse cumulative hazard of all-cause mortality. In addition, cumulative incidence function (CIF) was used to calculate cardiovascular mortality, and Gray's (1988) test was used to investigate their group differences. Cox regression models were used to assess the association between the level of uACR and all-cause mortality, and Fine-Gray competing risks models were used in cardiovascular mortality. Characteristic variables with significant baseline differences or clinical significance were used as candidate predictors in the multivariate Cox regression model. Model 1 is unadjusted, model 2 is adjusted for age and gender, and model 3 is adjusted for age, gender, AMI, HT, CKD, CHF, anemia, HbA1c, LDLC, HDLC and PCI. Adjusted hazards ratios with 95% confidence intervals were calculated for each variable. The relationship between logarithmic uACR and all-cause mortality was investigated through restricted cubic splines.

Results

Clinical Characteristics

This study included 2832 DM patients with ASCVD (mean age: 63.3 ± 9.9 years, 29.1% women). Patients were divided into three groups according to their uACR value: normal group (Group 1) (uACR <30mg/g, n = 2195), moderately increased group (Group 2) (30mg/g ≤ uACR < 300mg/g, n = 434), severely increased group (Group 3) (300mg/g ≤ uACR, n = 203). Totally 585 (20.7%) patients were diagnosed with CKD, and 430 patients (15.2%) had CHF.

In addition, compared with Group 1, patients in increased uACR groups (Group 2 and Group 3) had higher prevalence of CKD (14.2% vs 31.8% vs 66.5%, P < 0.001) and CHF (12.1% vs 23.3% vs 31.5%, P < 0.001). Detailed patients' clinical characteristics are listed in Table 1.

Main Outcomes

During the median follow-up of 2.1 years (interquartile range: 1.2–3.1 years), a total of 212 patients (7.5%) experienced all-cause mortality. Among them, 132 patients (4.7%) experienced cardiovascular mortality. Compared to patients in Group 1, patients had higher cardiovascular mortality in Group 2 and Group 3 (2.5% vs 10.1% vs 16.9%, P < 0.001), as

Table 1 Demographic and Clinical Characteristics of DM Patients with ASCVD

Characteristics	Overall	uACR < 30mg/g	30~ 300mg/g	uACR≥ 300mg/g	P value
	N=2832	N=2195	N=434	N=203	
Demographic characteristics					
Age, year	63.3 (9.9)	63.0 (9.8)	65.0 (10.0)	63.9 (10.2)	<0.001
Women, n(%)	823 (29.1)	593 (27.0)	164 (37.8)	66 (32.5)	<0.001
Comorbidities					
AMI, n(%)	432 (15.3)	298 (13.6)	85 (19.6)	49 (24.1)	<0.001
HT, n(%)	1927 (68.0)	1408 (64.1)	344 (79.3)	175 (86.2)	<0.001
CAD, n(%)	2579 (91.1)	1985 (90.4)	398 (91.7)	196 (96.6)	0.012
CKD, n(%)	585 (20.7)	312 (14.2)	138 (31.8)	135 (66.5)	<0.001
CHF, n(%)	430 (15.2)	265 (12.1)	101 (23.3)	64 (31.5)	<0.001
Anemia, n(%)	1047 (37.9)	711 (33.2)	208 (49.5)	128 (64.3)	<0.001
Laboratory tests					
HbA1c, %	7.6 (1.5)	7.5 (1.5)	8.0 (1.7)	8.1 (1.8)	<0.001
LDLC, mmol/L	2.8 (0.9)	2.8 (0.9)	2.9 (0.9)	3.2 (1.1)	<0.001
HDLC, mmol/L	0.9 (0.2)	1.0 (0.2)	0.9 (0.2)	1.0 (0.3)	0.029
HGB, g/L	130.7 (18.3)	133.1 (16.2)	126.3 (19.5)	114.1 (25.3)	<0.001
Prior SCr, umol/L	0.9 [0.7, 1.1]	0.9 [0.7, 1.1]	1.0 [0.7, 1.2]	1.4 [0.9, 2.3]	<0.001
URIC, umol/L	411.9 (122.7)	404.2 (116.9)	426.5 (136.7)	466.7 (137.2)	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Overall	uACR < 30mg/g	30~ 300mg/g	uACR≥ 300mg/g	P value
	N=2832	N=2195	N=434	N=203	
Medication					
Statins, n(%)	1746 (96.3)	1380 (96.6)	244 (94.2)	122 (96.8)	0.172
Aspirin, n(%)	2452 (87.4)	1912 (87.7)	368 (86.0)	172 (87.3)	0.616
ACEI/ARB, n(%)	1313 (72.4)	1022 (71.5)	208 (80.3)	83 (65.9)	0.003
Spironolactone, n(%)	425 (15.2)	269 (12.3)	107 (25.0)	49 (24.9)	<0.001
β-blockers, n(%)	1525 (84.1)	1186 (83.0)	229 (88.4)	110 (87.3)	0.053
DAPT, n(%)	1345 (74.1)	1047 (73.3)	195 (75.3)	103 (81.7)	0.103
Procedure					
PCI, n(%)	2016 (71.2)	1528 (69.6)	325 (74.9)	163 (80.3)	0.001

Abbreviations: AMI, Acute myocardial infarction; HT, Hypertension; CAD, Coronary artery disease; CKD, Chronic kidney disease; CHF, Congestive heart failure; HbA1c, Glycated hemoglobin; LDLC, Low density lipoprotein cholesterol; HDLC, High density lipoprotein cholesterol; HGB, Hemoglobin; Prior SCr, Prior serum creatinine; URIC, Uric acid; eGFR, Estimated glomerular filtration rate epidemiology collaboration equation; ACEI/ARB, Angiotensin converting enzyme inhibitors or angiotensin receptor blocker; DAPT, Dual-antiplatelet therapy; PCI, Percutaneous coronary intervention.

well as all-cause mortality (5.0% vs 13.8% vs 21.2%, P < 0.001). After the adjustment for age, gender, AMI, HT, CKD, CHF, anemia, HbA1c, LDLC, HDLC, PCI, multivariate Cox analysis showed that patients had a higher risk of cardiovascular mortality in Group 2 (aHR: 3.08, 95% CI 2.00–4.76; P < 0.001) and Group 3 (aHR: 4.61, 95% CI 2.60–8.17; P < 0.001) than patients in Group 1. Similarly, patients also had a higher risk of all-cause mortality in Group 2 (aHR: 2.35, 95% CI 1.67–3.30; P < 0.001) and Group 3 (aHR: 3.02, 95% CI 1.96–4.65; P < 0.001) than patients in Group 1 after adjusting for confounders (Table 2). The results of Cumulative hazard (Kaplan-Meier) of all-cause mortality were shown in Figure 2. The restricted cubic splines curves showed a linear relationship between ln(uACR) and the risks of all-cause mortality (P for nonlinearity = 0.77) and cardiovascular mortality (P for nonlinearity = 0.73). (Figures 3 and 4) Especially, we found the angiotensin converting enzyme inhibitors or angiotensin receptor blocker (ACEI/ARB) can significantly affect the mortality of DM patients with ASCVD, but did not include them in the final multivariate analysis due to its excessive data loss. (Supplement Tables S1 and S2)

Discussion

Our study evaluated the relationship between the level of uACR and long-term cardiovascular mortality and all-cause mortality among DM patients with ASCVD. In this study, we found that nearly a quarter of DM patients with ASCVD had increased uACR, and they have 1- or 2-fold higher risk of all-cause mortality and over 2- or 3-fold higher risk of cardiovascular mortality than those with normal uACR. Patients with increased uACR were associated with an increased risk of mortality.

Table 2 Multivariate Risk Regression of Different Groups

	Groups	Events, n(%)	Model 1	Model 2	Model 3
			HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular mortality	Group 1	55 (2.5)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Group 2	43 (10.1)	4.33 (2.90–6.46)**	4.12 (2.76–6.15)**	3.08 (2.00–4.76)**
	Group 3	34 (16.9)	7.49 (4.87–11.53)**	7.28 (4.70–11.27)**	4.61 (2.60–8.17)**
All-cause mortality	Group 1	109 (5.0)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
	Group 2	60 (13.8)	3.05 (2.22–4.18)**	2.95 (2.15–4.05)**	2.35 (1.67–3.30)**
	Group 3	43 (21.2)	4.95 (3.47–7.05)**	5.01 (3.51–7.14)**	3.02 (1.96–4.65)**

Notes: Group 1: uACR < 30mg/g; Group 2: 30mg/g ≤ uACR < 300mg/g; Group 3: uACR ≥ 300mg/g; Model 1: unadjusted; Model 2: adjusted for age, gender; Model 3: adjusted for age, gender, AMI, HT, CKD, CHF, anemia, HbA1c, LDLC, HDLC, PCI. **P < 0.001.

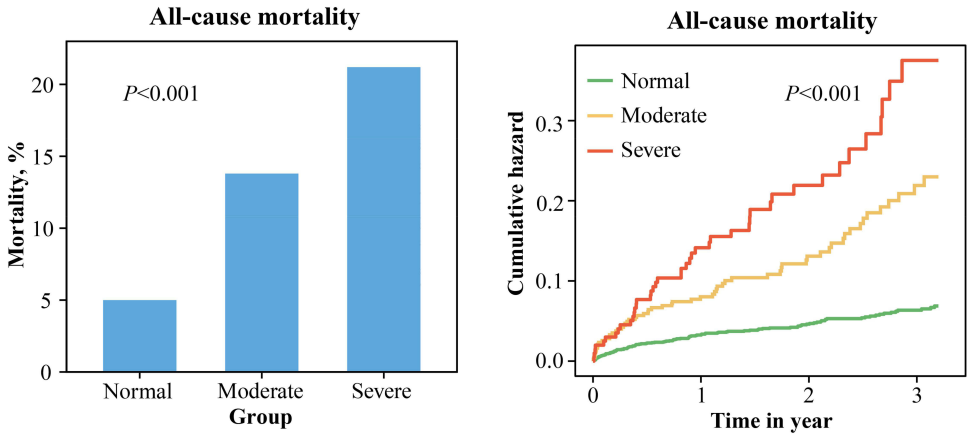

Figure 2 All-cause mortality and cumulative hazard (Kaplan-Meier).

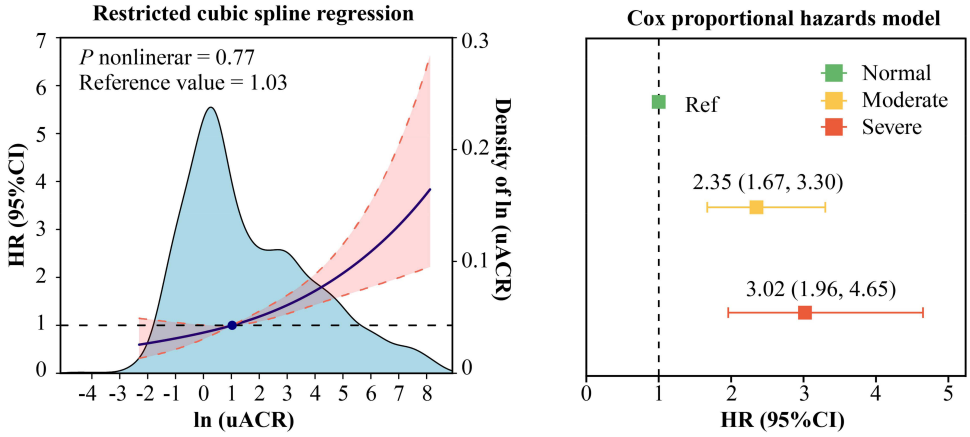

Figure 3 Restricted spline curve and cox proportional hazards model of all-cause mortality.

UACR was an effective urinalysis indicator for indicating renal function, and was widely used in patients with DM or CKD. In our study, we found the increased uACR was associated with the risk of long-term mortality in DM patients with ASCVD, especially cardiovascular mortality. Similar to our study, Cao et al conducted a study to assess the association between urinary albumin excretion and CVD and all-cause mortality in an elderly cohort aged 68–102 years.[12] They found that comparing with the normal urinary albumin excretion patients (uACR <30 g/mg), CVD incidence and all-cause mortality were 2- to 3-fold higher in those with macroalbuminuria (uACR >30 g/mg). Since the study cohort was not limited to the DM population, even though the mean age of patients was much higher than in our cohort, the risk of mortality in patients in this study was lower than in our cohort after adjusting for confounders. In addition, previous studies have confirmed the uACR values can diagnose the microalbuminuria (MA) which is reported to be associated with the increased risk of cardiovascular events and all-cause mortality by numerous prospective epidemiologic studies.[19–22] In DM patients, elevated uACR levels were also independently associated with an increased risk of all-cause mortality[23] Therefore, uACR, as an easily available and valuable prognostic indicator, deserves attention in such high-risk patients (DM patients with ASCVD).

DM, as a strong risk factor for CVD, is often complicated with other cardio and renal diseases like CAD and CKD.[1,24] The pathogenesis of CVD in DM is complex and has been largely attributed to the toxic cardiovascular effects of hyperglycemia and relevant metabolic abnormalities (diabetic cardiomyopathy) as well as the frequently coexisting morbidities such as HT, CAD and diabetic nephropathy.[25] Meanwhile, DM impairs the generation of nitric oxide (NO) and the increase of reactive oxygen species, resulting in endothelial dysfunction, further progression to

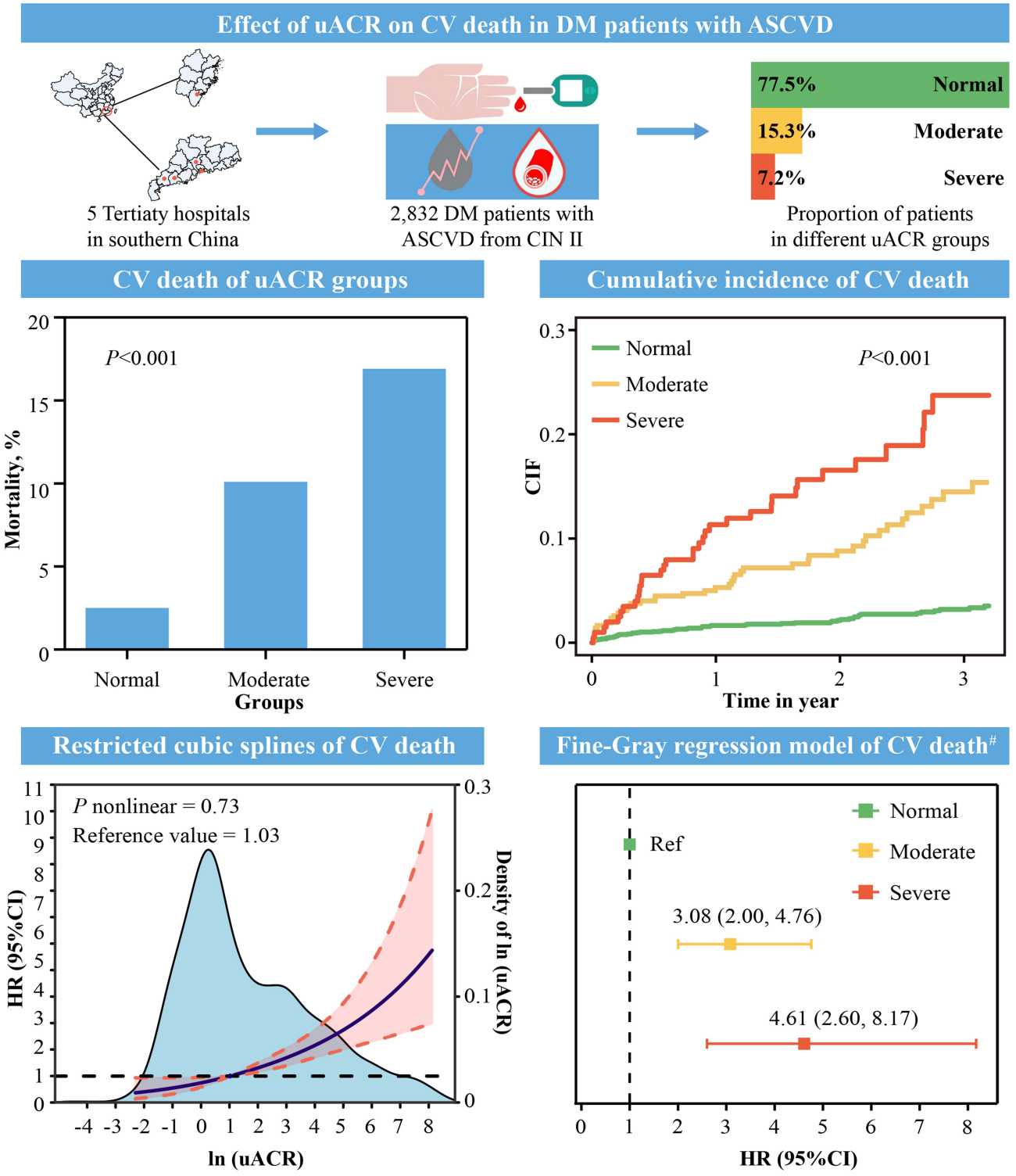

Figure 4 Centre illustrations. Normal group: uACR < 30mg/g; Moderately increased group: 30mg/g < uACR < 300mg/g; Severely increased group: 300mg/g<uACR. #Adjusted for age, gender, AMI, HT, PCI, CKD, CHF, anemia, LDLC, HDLC, HbA1c.

Abbreviations: CIN II, Cardiorenal ImprovemeNt II; uACR, Urinary albumin creatinine ratio; CV, Cardiovascular; DM, Diabetes mellitus; ASCVD, Atherosclerotic cardiovascular disease; AMI, Acute myocardial infarction; HT, Hypertension; CKD, Chronic kidney disease; CHF, Congestive heart failure; HbA1c, Glycated hemoglobin; LDLC, Low-density lipoprotein cholesterol; HDLC, High-density lipoprotein cholesterol; PCI, Percutaneous coronary intervention.

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CKD.[26–28] In addition, patients with clinical ASCVD represent the highest risk population for adverse cardiovascular events.[29] Persistent micro- or macroalbuminuria are contemporary considered as the markers of generalised vascular endothelial damage, reflecting increased vascular wall permeability for albumin, which is early event in development of ASCVD.[6,7] Therefore, DM complicated with ASCVD can further aggravate endothelial dysfunction. Increased uACR, as the result of endothelial dysfunction is associated with an increase in the severity of CVD and results in much greater atherosclerotic burden.[30,31] In our study, uACR is related to long-term cardiovascular mortality and all-cause mortality in DM patients with ASCVD. Screening for uACR is a good way to diagnose the risk of DM patients with ASCVD.

Our study suggests that increased uACR is an independent predictor of cardiovascular and all-cause mortality among DM patients with ASCVD. However, its predictive value for cardiovascular mortality risk among such high-risk individuals is often ignored in the clinical practice of the department of cardiology. It reminded clinicians that once DM patients with ASCVD have a uACR value ≥30mg/g, he has a higher risk for cardiovascular and all-cause mortality. In addition, a routine urinalysis may provide useful information for cardiologists and nephrologists to identify the high risk of DM patients with ASCVD.

Limitation

There were several limitations in this study. First, this is a retrospective study, but our study is a large multicenter cohort study to investigate the relationship between the level of uACR and cardiovascular mortality and all-cause mortality in DM patients with atherosclerotic cardiovascular disease (ASCVD). Second, our study was conducted in teaching hospitals in southern China, and cannot be extended to DM patients with ASCVD throughout China for the time being. However, the study population is distributed in urban and rural areas, which is representative to some extent. In addition, the end points of our study are cardiovascular and all-cause mortality but do not include the major adverse cardiovascular events. Therefore, more high-quality studies about the level of uACR on incidence of major adverse cardiovascular events among DM patients with ASCVD are needed to confirm our findings.

Conclusion

In our study, we found nearly a quarter of DM patients with ASCVD had increased uACR, and they have 1- or 2-fold higher risk of all-cause mortality and over 2- or 3-fold higher risk of cardiovascular mortality than those with normal uACR. Increased uACR is an independent predictor of all-cause mortality and cardiovascular mortality among DM patients with ASCVD. It is necessary to perform uACR measurement for risk stratification and can provide therapeutic direction for the management of DM patients with ASCVD.

Abbreviations

DM, Diabetes mellitus; uACR, urinary albumin creatinine ratio; ASCVD, Atherosclerotic cardiovascular disease; CVD, Cardiovascular disease; CAD, Coronary artery disease; HT, Hypertension; CKD, Chronic kidney disease; CHF, Congestive heart failure; AMI, Acute myocardial infarction; PCI, Percutaneous coronary intervention; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; ACEI/ARB, Angiotensin converting enzyme inhibitors or angiotensin receptor blocker; CI, Confidence interval.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Guangdong Provincial People's Hospital ethics committee (No.GDREC2019-555H-2), all participating sites received institutional review board approval from their own ethics committees, and the study was performed according to the declaration of Helsinki. All the data used in this study were anonymized before its use. Since our study included retrospective cases, there was no additional intervention, and all patient information was

desensitized, and no informed consent was required. The need of informed consent was waived by Guangdong Provincial People's Hospital ethics committee (No.GDREC2019-555H-2).

Author Contributions

All authors made a significant contribution to the work reported in terms of the conception, study design, execution, acquisition of data, analysis and interpretation. They took part in drafting, revising or reviewing the article; gave final approval of the final manuscript to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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