Risk associated with estimated glomerular filtration rate and albuminuria for PAD among patients with type 2 diabetes

Chi-Feng Pan,[1,2,3] Shih-Ming Chuang ,[2,3,4] Kuan-Chia Lin,[5,6] Ming-Chieh Tsai,[3,4] Wei-Tsen Liao,[4] Yi-Hong Zeng,[3,4] Chun-Chuan Lee[3,4]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jim-2021-001786).

For numbered affiliations see end of article.

Correspondence to
Chun-Chuan Lee, Mackay Memorial Hospital, Number 92, Section 2, Zhongshan North Road, Zhongshan District, Taipei 10449, Taiwan;
lee5957.5957@mmh.org.tw

C-FP and S-MC contributed equally.

Accepted 31 March 2021

To cite: Pan C-F, Chuang S-M, Lin K-C, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2021-001786

ABSTRACT

Chronic kidney disease (CKD) is significantly associated with peripheral arterial disease (PAD) in some studies, but data on the association of the risk of PAD across a broad range of kidney function in patients with type 2 diabetes are limited. Between October 17, 2013 and February 7, 2015, all consecutive outpatients with type 2 diabetes underwent ankle-brachial index (ABI) examination. We investigated the association of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) with the risk of PAD. A total of 1254 patients were cross-classified into 12 groups based on ACR category (normoalbuminuria, microalbuminuria and macroalbuminuria) and eGFR stage (≥90, 60–89, 30–59 and <30 mL/min/1.73 m^2). Logistic regression analysis was used to investigate the association of eGFR and ACR with PAD. Within each ACR category, a lower eGFR stage was associated with PAD. Similarly, within each eGFR group, a higher ACR category was also associated with PAD. The OR for PAD was highest in patients with eGFR <30 mL/min/1.73 m^2 and macroalbuminuria (OR 14.42, 95% CI 4.60 to 45.31) when compared with the reference group of subjects with eGFR ≥90 mL/min/1.73 m^2 and normoalbuminuria. Our study found that cross-classification of eGFR with ACR revealed a more comprehensive association with risk of PAD than eGFR or ACR alone.

Significance of this study

What is already known about this subject?

- Peripheral artery disease (PAD) is one of the macrovascular complications of diabetes and is associated with an increased risk of cardiovascular disease, limb-related damage and amputations.
- Identifying kidney disease by measurement of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) was a standard routine for diabetes management and intervention to identify the development of diabetic kidney disease and avoid progression.
- Although either reduced eGFR or elevated ACR is associated with an increased risk of PAD, studies evaluating the combined effect of reduce eGFR and elevated ACR on risk of PAD in patients with type 2 diabetes mellitus are rare.

What are the new findings?

- The prevalence of PAD increased with increasing ACR category: normoalbuminuria, microalbuminuria and macroalbuminuria, and with de-escalating stage of eGFR ≥90, 60–89, 30–59 and <30 (mL/min/1.73 m^2).
- The association between reduced eGFR and risk of PAD was stronger in participants with macroalbuminuria compared with those with microalbuminuria.
- The OR for PAD was highest in patients with macroalbuminuria and eGFR <30 mL/min/1.73 m^2 (OR 14.42, 95% CI 4.60 to 45.31) when compared with the reference group of subjects with eGFR ≥90 mL/min/1.73 m^2 and normoalbuminuria.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is thought to be an independent risk factor for cardiovascular disease (CVD) and its equivalents, including peripheral artery disease (PAD). PAD is one of the common diffuse atherosclerotic CVD in subjects with T2DM.[1] According to some related studies from Taiwan, PAD is prevalent in more than half of the patients with lower limb amputations and about one-third to one-half of these amputated patients have T2DM.[2] Besides, PAD is associated with diabetic macrovascular complications and increased prevalence of CVD, limb-related damage and amputations.[3] Diabetic kidney disease (DKD) has been well recognized as the main cause of end-stage renal disease and is significantly associated with increasing the risk of CVD and death.[4] As a result, measurement of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) was a standard routine for diabetes management and intervention to identify the development of DKD and avoid progression. Elevated ACR was thought to be due to glomerular hemodynamic disturbances and endothelial

Significance of this study

How might these results change the focus of research or clinical practice?

- Cross-classification categories of eGFR with ACR revealed a more comprehensive association for risk of PAD than eGFR or ACR alone.

impairment in the glomerulus, and to be even related to systemic endothelial dysfunction.[5] Reduced eGFR, the stage of chronic kidney disease (CKD), is also associated with a high risk of incident CVD.[6] Previous studies have confirmed that either elevated ACR or reduced eGFR was closely related to PAD in patients with diabetes.[7 8] With the development of diabetes, the association between albuminuria and PAD may be affected by kidney function, or the predicted value of proteinuria reduced after adjusting for kidney function.[9] Therefore, previous research results might have underestimated their degree of association in patients with T2DM using either eGFR or ACR alone. Both criteria for DKD should be used simultaneously to better investigate and characterize the association between kidney disease and PAD. The current study aimed to explore the association of cross-classification categories of eGFR with ACR and risk of PAD among patients with T2DM.

METHODS

All 1623 subjects with T2DM, ranging from 20 to 91 years of age, were consecutively recruited from the endocrinology outpatient department of a Taipei Medical Center between October 17, 2013 and February 7, 2015. We excluded patients with infection (especially urinary tract infection), malignant diseases or previous operations of lower extremities. Patients with incomplete laboratory data were also excluded. Since all enrolled patients had to receive comprehensive renal function evaluation which included serum creatinine, urine creatinine and urine albumin, if even one of these data missing it was regarded as incomplete data. Finally, a total of 1254 subjects who fulfilled all the criteria participated in our study. All study participants were enrolled from the diabetes shared care program, which provides complete and comprehensive diabetes care for patients with diabetes. All enrolled subjects received intensive treatment for T2DM and hypertension at the outpatient clinic, and blood samples were taken every 2–3 months. We recorded the duration of diabetes, gender, waist circumference and related comorbidity such as atherosclerotic cardiovascular disease and laboratory data from medical records. The following data were obtained during routine physical examination: age, blood pressure and body mass index (BMI) and laboratory data using venous samples collected 10 hours after an overnight fasting included fasting plasma glucose, postprandial plasma glucose, glycated hemoglobin (HbA1c), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, liver enzymes, serum creatinine, eGFR and urinary ACR. Additionally, the participant's medical history including smoking and alcohol consumption was also acquired from medical records. Smoking history was defined as current, never or past. Hypertension was defined as a history of hypertension as indicated in the medical records, or systolic blood pressure (SBP) ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg. With the patient in a sitting position, a trained nurse used an automatic oscilloscope monitor to measure blood pressure and the average of the two blood pressure readings was reported as the blood pressure. Hyperlipidemia was defined as a history of hyperlipidemia as indicated in the medical records, or total cholesterol >200 mg/dL or LDL-C >130 mg/dL. Additionally, individual drug history regarding routine regimens, including lipid-lowering, antihypertensive agents, anticoagulants and insulin use was acquired from medical records. For collection of accurate information, all anthropometric and laboratory measurements were garnered between 2 months before and 1 month after the time of performance of ankle-brachial index (ABI).

Outcomes

Ankle-brachial index measurements

The operator measured the blood pressures of both upper and lower extremities to determine the ABI; and ABI<0.9 was considered diagnostic for PAD.[10] The SBP of bilateral brachial arteries, posterior tibial arteries and dorsal pedal arteries were estimated by Colin VP-1000 Doppler ultrasound device (Colin Medical Technology Company, Komaki, Japan) while the patient was in a supine position after resting for 20 min. We placed a 26×13 cm occluding cuff over the malleolus to measure the ankle pressure. ABI is the ratio calculated by the instrument automatically and obtained by dividing the SBP at the ankle by the SBP in the arm. Right or left ABI was calculated by dividing the highest right or left ankle pressure (at the dorsal pedal or posterior tibial) by the higher brachial pressure on either side, respectively.

The measurement of eGFR and albuminuria

Early morning spot urine sample was collected for urine albumin excretion, indicated as ACR, and calculated by dividing albumin concentration in milligrams by creatinine concentration in grams. The study population was further divided into three ACR categories based on the following: <30, 30–299 and >300 mg/g indicative of normoalbuminuria, microalbuminuria and macroalbuminuria, respectively. The eGFR was estimated using the Modification of Diet in Renal Disease equation Study formula as follows: $175 \times Scr^{-1.154} \times age^{-0.203} \times (0.742$ if female).

The same study population was further divided into four groups based on eGFR: ≥90, 60–89, 30–59 and <30 mL/min/1.73 m^2, respectively. In our study, since only 16 (1.3%) patients had eGFR <15 mL/min/1.73 m^2, those with 15–29 and <15 mL/min/1.73 m^2 were combined as eGFR <30 mL/min/1.73 m^2. Thus, we reclassified the stages of eGFR into four different stages and albuminuria into three different stages. For comparison of different interactions, ACR <30 mg/g and/or eGFR ≥90 mL/min/1.73 m^2 were defined as the reference group. All enrolled subjects were subsequently cross-classified into different categories depending on these ACR and eGFR.

Table 1 Characteristics of patients with type 2 DM (n=1254)

Variable	Mean±SD	Count (%)
Age (years)	65.1±10.0	
BMI (kg/m^2)	25.9±4.2	
DM duration (years)	11.0±7.3	
HbA1c (%)		7.6 (3.2)
Gender (male)		582 (46.4)
Hyperlipidemia		875 (69.8)
Hypertension		820 (65.4)
Smoking status		
Non		877 (69.9)
Active		107 (8.5)
Past		10 (0.8)
Drinking		52 (4.1)
Urine ACR category (mg/g)		
<30		794 (63.3)
30–299		297 (23.7)
>300		163 (13.0)
eGFR (mL/min/1.73 m^2)	78.87±30.53	
CKD stage (mL/min/1.73 m^2)		
eGFR ≥90		389 (31.0)
eGFR 60–89		548 (43.7)
eGFR <30–59		258 (20.6)
eGFR <30		59 (4.7)
Insulin use		265 (21.1)
ABI <0.9		94 (7.5)

Normoalbuminuria ACR <30 mg/g; microalbuminuria ACR 30–299 mg/g, macroalbuminuria ACR >300 mg/g.
ABI, ankle-brachial index; ACR, albumin-to-creatinine ratio; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.

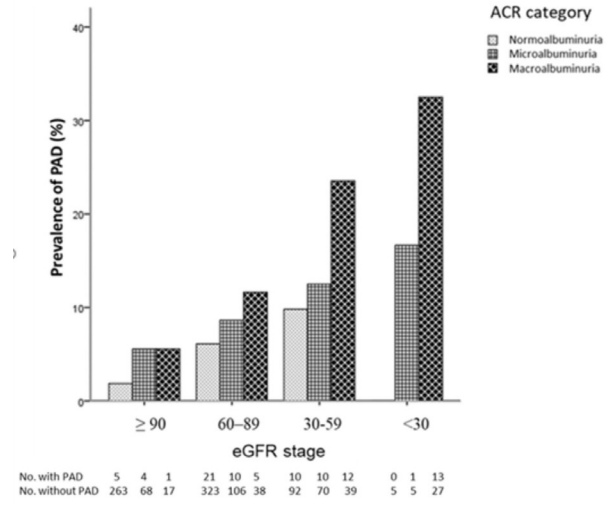

Figure 1 Prevalence of peripheral arterial disease (PAD) (ankle-brachial index <0.9) in different cross-categories of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR).

Analytical methods

Quantitative or qualitative baseline data for the study participants were expressed as a percentage or mean±SD for normally distributed variables or median (IQR) for skewed variables. Logistic regressions were used to investigate the association between PAD and different variables. The degree of the association between PAD and the characteristics of the participants were presented as OR and 95% CI. Apart from multicollinearity, multiple logistic regression analyses were further used to determine the association of eGFR with ACR and risk of PAD after adjusting statistically significant variables. Adequacy of the logistic regression models was assessed by validation of C-statistics. The C-statistics provides the variable probability of risk score for PAD depending on different models. All assessments were considered significant when the probability (p value) was <0.05 (two-sided). Statistical analysis was performed using IBM SPSS V.23.0 (IBM, Armonk, New York, USA).

RESULTS

The baseline clinical and biochemical characteristics of 1254 patients with T2DM ranging from 20 to 91 years of age are summarized in table 1. The average age of the patients was 65.1±10.0 years, average BMI was 25.9±4.2 kg/m^2 and the male:female ratio was 1:1.15. Mean ABI of the overall population was 1.08±0.12. In our study, 794 (63.3%) had normoalbuminuria, 297 (23.7%) had microalbuminuria and 163 (13.0%) had macroalbuminuria. The mean eGFR was 78.87±30.53 mL/min/1.73 m^2. With regard to eGFR, there were 389 (31.0%) patients with eGFR ≥90 mL/min/1.73 m^2, 548 (43.7%) patients with eGFR: 60–89 mL/min/1.73 m^2, 258 (20.6%) patients with eGFR: 30–59 mL/min/1.73 m^2 and 59 (4.7%) patients with eGFR <30 mL/min/1.73 m^2. Among the 1254 patients, 7.5% (94/1254) of the participants had an ABI <0.9.

Figure 1 shows the prevalence of patients with PAD (ABI <0.9) in the different cross-classifications of eGFR and ACR. The prevalence of PAD increased with increasing ACR category: normoalbuminuria, microalbuminuria and macroalbuminuria, and with de-escalating stage of eGFR ≥90, 60–89 and 30–59 mL/min/1.73 m^2. However, for those with eGFR <30 mL/min/1.73 m^2, none had normoalbuminuria, while 1 patient (16.7%) had microalbuminuria and 13 (32.5%) patients had macroalbuminuria, respectively.

We performed univariate and multivariate analyses to investigate the association between the different eGFR and ACR categories and PAD and the results are depicted in table 2. Using univariate logistic regression analysis, when compared with those with normoalbuminuria; the OR for the presence of PAD progressively increased with increasing ACR category. Compared with those with eGFR ≥90 mL/min/1.73 m^2, a lower eGFR was also significantly associated with increasing risk of PAD. After performing multivariate logistic regression analyses with adjustments for covariables including age, gender, hypertension, coronary artery disease, DM duration, smoking, hyperlipidemia and HbA1c; both high albuminuria and low eGFR were associated with risk of PAD (table 2).

We defined patients with eGFR ≥90 mL/min/1.73 m^2 or normalbuminuria as the reference group and cross-classification of different ranges of eGFR and ACR resulted in seven groups, as shown in table 3. We performed logistic regression analysis to further compare the association of renal function and PAD. As shown in table 3, there was a

Table 2 Multivariate logistic regression analysis for PAD associated with independent effect of eGFR and ACR

	Model I		Model II	
Variable	**OR 95% CI**	**P value**	**OR 95% CI**	**P value**
eGFR stage				
eGFR ≥90	1 (reference)		1 (reference)	
eGFR 60–89	2.52 (1.23 to 5.16)	0.012	2.41 (1.17 to 4.96)	0.017
eGFR <30–59	4.24 (2.00 to 9.00)	<0.001	3.69 (1.73 to 7.88)	0.001
eGFR <30	6.40 (2.41 to 17.03)	<0.001	5.39 (2.00 to 14.48)	0.001
ACR category				
<30	1 (reference)			
30–299	1.57 (0.91 to 2.71)	0.100	1.37 (0.79 to 2.39)	0.260
>300	2.83 (1.55 to 5.17)	0.001	2.29 (1.24 to 4.25)	0.008
Age	1.03 (1.01 to 1.06)	0.017	NS	
Hypertension	2.78 (1.42 to 5.45)	0.003	2.16 (1.18 to 3.96)	0.012
Coronary artery disease	2.77 (1.49 to 5.14)	0.001	2.60 (1.48 to 4.56)	0.001

Model I: univariate analysis, and model II: adjusted for age, hypertension, coronary artery disease and other variables included: gender, DM duration, smoking, hyperlipidemia and HbA1c.
ABI, ankle-brachial index; ACR, albumin-to-creatinine ratio; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; NS, not significant; PAD, peripheral arterial disease.

strong association for a higher risk of PAD at a lower GFR in subjects with macroalbuminuria (p=0.074 at eGFR 60–89 mL/min/1.73 m^2, p<0.001 at eGFR 30–59 mL/min/1.73 m^2 and p<0.001 at eGFR <30 mL/min/1.73 m^2). At microalbuminuria levels, there was less association for increased presence of PAD with decreasing eGFR (p=0.125 at eGFR 60–89 mL/min/1.73 m^2, p=0.009 at eGFR 30–59 mL/min/1.73 m^2 and p=0.235 at eGFR <30 mL/min/1.73 m^2). Although the ORs of cross-classification of ACR and eGFR for PAD were attenuated by other relative covariables, the association between reduced eGFR and risk of PAD still tended to be stronger in participants with macroalbuminuria compared with those with microalbuminuria.

For further comparison, we redefined patients with eGFR ≥90 mL/min/1.73 m^2 and normalbuminuria as the reference group, resulting in 12 groups according to ACR and eGFR. Logistic regression analysis was performed to assess the association of the cross-classified categories of eGFR and ACR with PAD and the results are shown in figure 2. The analyses are complimentary and provide a comprehensive description of the synergistic interaction of these two variables with the risk of PAD. The associations for PAD are presented as color patterns (figure 2) for all outcomes. Four different categories, from low to high risk for PAD are indicated in figure 2 by different colors. Within each ACR category, eGFR decline was associated with a higher risk of PAD. Similarly, within each eGFR stage, increased ACR was associated with a progressively increased risk of PAD. After adjustment for covariables, patients with macroalbuminuria and eGFR <30 mL/min/1.73 m^2 had the highest risk association for risk of PAD (OR 14.42, 95% CI 4.60 to 45.31) as compared with the reference group of subjects with eGFR ≥90 mL/min/1.73 m^2 and normalbuminuria. When examining the associations with risk of PAD, the C-statistic was higher for cross-classificaton into 12 categories by ACR and eGFR compared with other models (C-statistic 0.75, p<0.001) (online supplemental table S1).

DISCUSSION

Several studies have shown that the prevalence of PAD increased in individuals with CKD. The association between

Table 3 Multivariate logistic regression analysis for PAD associated with interaction cross-classified by eGFR and ACR

	Model I		Model II	
Cross-classification of ACR and eGFR	OR 95% **CI**	**P value**	**OR 95% CI**	**P value**
ACR <30 or eGFR ≥90	(reference)			
ACR 30–299 plus eGFR 60–89	1.76 (0.86 to 3.61)	0.125	1.47 (0.71 to 3.07)	0.300
ACR 30–299 plus eGFR <30–59	2.66 (1.28 to 5.54)	0.009	1.81 (0.84 to 3.87)	0.129
ACR 30–299 plus eGFR <30	3.73 (0.43 to 32.64)	0.235	1.90 (0.21 to 17.19)	0.568
ACR >300 plus eGFR 60–89	2.45 (0.92 to 6.56)	0.074	1.98 (0.73 to 5.38)	0.181
ACR >300 plus eGFR <30–59	5.73 (2.79 to 11.77)	<0.001	3.89 (1.84 to 8.23)	<0.001
ACR >300 plus eGFR <30	9.97 (3.31 to 18.66)	<0.001	5.58 (2.58 to 12.06)	<0.001
Age			1.03 (1.01 to 1.05)	0.019
Hypertension			2.15 (1.18 to 3.94)	0.013
Coronary artery disease			2.58 (1.46 to 4.55)	0.001

Model I: univariate analysis and model II: adjusted for age, hypertension, coronary artery disease, gender, DM duration, smoking, hyperlipidemia and HbA1c.
ABI, ankle-brachial index; ACR, albumin-to-creatinine ratio; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PAD, peripheral arterial disease.

eGFR	ACR		
	<30	30-299	≧300
≧90	Ref	2.83 (0.74-10.91)	2.70 (0.29-24.94)
60-89	3.02 (1.11-8.19)	3.73 (1.23-11.33)	4.97 (1.35-18.28)
30-59	4.11 (1.33-12.69)	4.68 (1.50-14.61)	9.91 (3.22-30.49)
<30	NA	5.04 (0.47-53.64)	14.42 (4.60-45.31)

Figure 2 Categorical analysis of association for peripheral artery disease in different estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) categories. Panels show ORs adjusted for age, hypertension, coronary artery disease, gender, diabetes mellitus duration, smoking, hyperlipidemia and HbA1c. Color coding is based on the following cut-off values: green indicates <1.5, yellow indicates 1.5 to <5, orange indicates 5 to <10 and red indicates 10 or higher. NA, not available.

CKD and PAD has been reported before, but the difference is that our study focused on patients with diabetes.[11] In our cross-sectional study on 1254 subjects with T2DM with age ranging from 20 to 91 years, the overall prevalence of PAD was 7.5%. Based on ACR category, elevated ACR was associated with increased risk of PAD. Similarly, based on eGFR stage, reduced eGFR was also significantly associated with increased risk of PAD. Therefore, both reduced eGFR and elevated ACR were confirmed to be highly associated with PAD.

It has been reported that kidney damage clinically manifests in different ways as albuminuria or reduced eGFR.[12] Some studies demonstrated that albuminuria was independently associated with the metabolic syndrome. The components of metabolic syndrome which were widely recognized as cardiovascular risk factors included atherogenic dyslipidemia, hypertension and hyperglycemia.[13] Albuminuria was also thought to be one of the components of the metabolic syndrome. As the prevalence of microalbuminuria increases significantly, the number of metabolic syndrome components increases simultaneously.[14] Albuminuria also served as a surrogate maker for the progression of kidney disease and vascular damage due to the possible pathophysiology of hyperinsulinemia, widespread atherosclerosis and endothelial injury.[15] CVD arising from impaired renal function may be attributed to decreased nephrons and progressive fibrosis due to the accumulation of uremic toxins, volume loss, blood pressure fluctuation and metabolic abnormalities. While CVD is caused by different mechanisms of albuminuria or impaired renal function, there may be some interactions between them,[16] thus requiring distinct interventions which have not yet been determined. Based on these previous results, it is recommended to routinely evaluate albuminuria and eGFR during the clinical care of patients with T2DM.

A study by Lee *et al* found that macroalbuminuria is a stronger indicator for PAD than low eGFR.[17] However, our research performed a more comprehensive comparison than their study.[17] In our study, we found that in the group with macroalbuminuria, presence of a low eGFR increased the risk of PAD more than other subgroups. Due to the strong association between eGFR change and albuminuria, the relationship between albuminuria and PAD may be affected by kidney function. With diabetes progression, it was thought that the predictive effect of albuminuria on PAD gradually declined after adjusting for the effect of renal function.[9] Therefore, the intensity of these associations may be underestimated according to conclusions from a previous study.[18] In brief, the risk of PAD was not just emphasized by the presence of albuminuria alone, especially in patients in the advance stage of DKD.

In the present study, we found that among patients in the mild eGFR stage, the prevalence of PAD significantly increased in those with microalbuminuria or macroalbuminuria (figure 1). This implies that albuminuria could be an independent risk factor for PAD. Besides, the prevalence of PAD was highest in those with macroalbuminuria plus low eGFR. Previous studies found that the prevalence of PAD was significantly increased when accompanied by both abnormalities, reduced eGFR and elevated ACR.[19] The results were consistent with our study, but diabetes accounted for only a minority of the study population, while in our study all subjects had diabetes. As we know, the development of low eGFR and albuminuria are both hallmarks of atherosclerotic CVD, but the pathophysiological mechanisms between PAD and both abnormalities have not been fully elucidated.

Analysis of the association between PAD and its related risk factors were investigated but were occasionally limited by classification using either ACR or eGFR.[9 20] Actually, depending on whether elevated ACR or reduced eGFR exists or not, there can be different categories of CKD, but in our report only 78.9% of patients with elevated ACR had eGFR reduction, while only 43.7% of patients with eGFR reduction had elevated ACR. We hypothesized that many cases with pre-existing kidney disease may be missed due to reliance on only a single criterion instead of cross-classified criteria. Therefore, we analyzed the synergistic interaction of different categories of both ACR and eGFR for the risk of PAD in our study. Both criteria for DKD should be used simultaneously to better investigate and characterize the association between renal disease and PAD.

We explored the combined effects of ACR and eGFR further to find a more effective relationship between CKD and PAD, which was the main feature of our study. Some previous studies disclosed that individuals with CKD are more likely to develop atherosclerotic CVD.[7 21 22] Besides, some experts have demonstrated that the clinical physiopathology of lower extremity PAD was a part of systemic atherosclerosis and the related prevalence of PAD was also thought to increase the risk of CVD.[23] Figure 1 demonstrated that patients with macroalbuminuria and eGFR <30 mL/min/1.73 m^2 have the highest prevalence of PAD. Additionally, the prevalence of PAD in patients with normoalbuminuria plus eGFR ≥90 mL/min/1.73 m^2 was 1.9% and increased to 32.5% in patients with macroalbuminuria plus eGFR <30 mL/min/1.73 m^2.

Finally, in figure 2, we attempted to confirm the cumulative effect of eGFR and ACR on the increase risk of PAD by performing logistic regression analysis based on cross-classification into 12 groups. Different cross-classifications of eGFR and ACR were significantly associated with the

presence of PAD. A relatively high risk for PAD was demonstrated in the following three combined categories: eGFR: 30–59 mL/min/1.73 m^2 with ACR >300 mg/g, eGFR <30 mL/min/1.73 m^2 with microalbuminuria and eGFR <30 mL/min/1.73 m^2 with macroalbuminuria. These two criteria (ACR and eGFR) are distinct and complementary, and may be a reflection of their pathophysiological differences in the different stages of renal disease.

Unquestionably, as illustrated in figures 1 and 2, the highest frequency and ORs for PAD were in patients with macroalbuminuria and eGFR <30 mL/min/1.73 m^2. In our study, 76.6% of participants had either reduced eGFR or albuminuria, which were defined as having CKD. Therefore, our study evaluated ACR and GFR simultaneously, and we specifically combined these two in different staging systems of DKD to find the association of CKD and PAD in patients with T2DM.

There are several limitations to our study. First, it is a cross-sectional research, and we only focused on its association rather than causality, hence further longitudinal observational researches are needed to determine its outcome or directionality. Second, the misclassification of outcomes arising from transient reduced eGFR or temporary progression of albuminuria could not be completely excluded. Third, although some researches proved that early morning urinary ACR ≥30 mg/g was correlated with an albumin excretion rate ≥30 mg/min with high sensitivity and specificity, the presence of albuminuria was calculated and defined from only a single spot urine sample in our study.[24] Fourth, it is possible to misclassify PAD as the golden standard tool for diagnosis is angiography instead of a non-invasive tool such as ABI. However, due to the risk of adverse effects, clinicians rarely perform angiography on elderly patients solely for the purpose of diagnosis. Finally, another limitation of our study is the issue of generalisability as it is a single-center study from a single clinic.

CONCLUSION

PAD is a common diabetic macrovascular complication and an important risk factor for lower limb amputation in the diabetic population. Through this cross-classification method, we found that even mild CKD in the presence of albuminuria can increase the risk of PAD. In addition, normoalbuminuria may also increase the risk of PAD if accompanied by reduced eGFR. Therefore, both criteria of CKD, eGFR and ACR should be used simultaneously to extensively explore the association of the risk of PAD and kidney disease in patients with T2DM.

Author affiliations
[1]Department of Internal Medicine, Division of Nephrology, Mackay Memorial Hospital, Taipei, Taiwan
[2]Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan
[3]Department of Medicine, Mackay Medical College, New Taipei City, Taiwan
[4]Department of Internal Medicine, Division of Endocrinology and Metabolism, Mackay Memorial Hospital, Taipei, Taiwan
[5]Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan
[6]Community Medicine Research Center, Preventive Medicine Research Center, National Yang-Ming University, Taipei, Taiwan

Acknowledgements The authors would like to thank Dr Ming-Chieh Tsai (from Mackay Memorial Hospital) for conceptualization of the study. The authors would also like to thank all of the physicians, educators and nurses who helped in this study.

Contributors Conceptualization, C-FP; data curation, M-CT, W-TL and Y-HZ; formal analysis, K-CL; methodology, S-MC; project administration, M-CT; resources, K-CL and M-CT; software, W-TL; supervision, C-CL; validation, Y-HZ; writing—original draft, C-FP and S-MC; Writing—review and editing, C-CL.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All aspects of this study were carried out in accordance with relevant guidelines and regulations (Declaration of Helsinki) and Good Clinical Practice. Data were analyzed anonymously as this study was done retrospectively without informed consent. All protocols were approved by the Institutional Ethics Committee of Mackay Memorial Hospital on March 5, 2015 (15MMHIS055e).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data used to support the findings of this study are available from the corresponding author upon request.

ORCID iD
Shih-Ming Chuang http://orcid.org/0000-0002-8622-1968

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