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ORIGINAL RESEARCH

Fibrinogen to Albumin Ratio as an Independent Risk Factor for Type 2 Diabetic Kidney Disease

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Purpose: Diabetic kidney disease (DKD) is an inflammatory disease. This study aimed to investigate the association of fibrinogen to albumin ratio (FAR) with DKD.

Patients and Methods: A total of 1022 type 2 diabetes mellitus (T2DM) patients with DKD and 1203 T2DM patients without DKD were enrolled in this study. Laboratory values including blood cell count, hemoglobin A1c, biochemical parameters, and fibrinogen and albumin creatinine ratio were recorded. Patients were classified according to tertile of admission FAR. Clinical parameters were compared between groups. Logistic regression, linear regression, ROC analysis and spline regression were carried out.

Results: FAR in the DKD group was significantly higher than that in the non-DKD group. FAR had the highest odds ratio as an independent risk factor for the development of DKD and the highest area under ROC curve for predicting DKD compared with albumin (ALB) or fibrinogen (FIB) alone. Simple linear regression analyses revealed a significant and linear correlation of FAR with neutrophil and neutrophil-to-lymphocyte ratio. FAR was an independent risk factor for development of DKD. Spline regression showed that there was a significant linear association between DKD incidence and continuous FAR value when it exceeded 67.3mg/g.

Conclusion: FAR is a stronger independent predictor of DKD than FIB and ALB. FAR is an independent risk factor for DKD development when it exceeded 67.3mg/g. FAR might be one of novel diagnostic biomarkers to predict and prevent DKD progression. However, a prospective study to validate the prognostic model is still needed.

Keywords: type 2 diabetes mellitus, diabetic kidney disease, inflammation, fibrinogen to albumin ratio

Introduction

Diabetic kidney disease (DKD) is the most prevalent chronic renal disease.[1] Around 35–40% of patients with type 2 diabetes mellitus (T2DM) will go on to develop DKD.[2] DKD is characterized by albuminuria and reduced estimated glomerular filtration rate (eGFR), both of which are independent risk factors for end-stage kidney disease (ESKD), cardiovascular events, and death.[3,4] DKD accounts for a significant increase in mortality among diabetic patients and is a grave threat to their clinical outcome.

Inflammation plays a major role in the development of DKD.[5,6] Serum fibrinogen (FIB) is a biomarker of coagulation and inflammation.[7–9] Elevated serum FIB is an independent risk factor of DKD progression to ESKD in patients with T2DM.[10] Albumin (ALB) has anti-inflammatory functions and antioxidant properties.[11,12] Hypoalbuminemia is associated with a poorer renal prognosis in patients with

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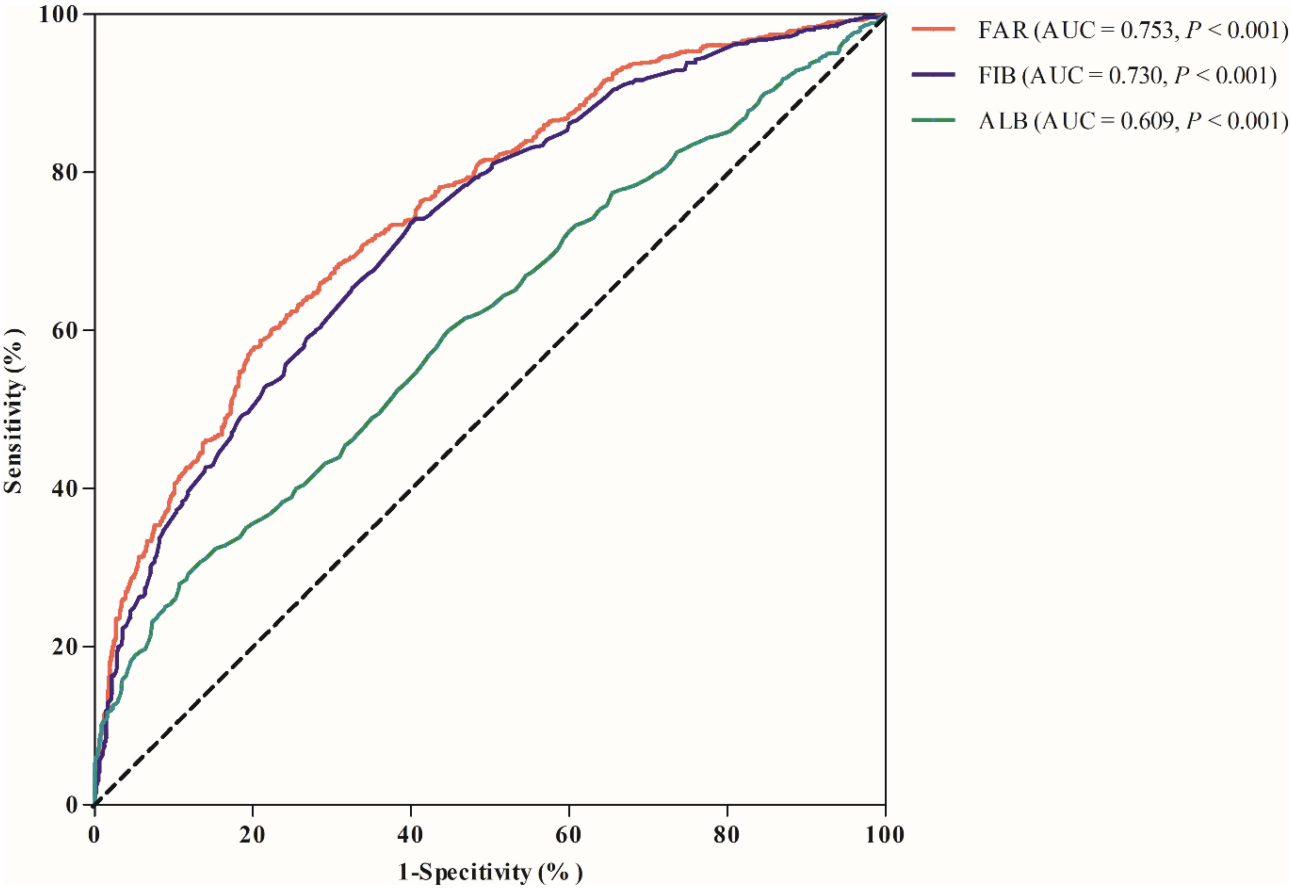
Graphical Abstract



T2DM and DKD.[13] Fibrinogen to albumin ratio (FAR) is a more significant prognostic marker than each single marker itself in cancer study.[14–16] We speculated that FAR is also closely related to DKD.

To date, the prognostic role of FAR in patients with DKD has not been determined. Our study aimed to investigate this association.

Patients and Methods

Study Participants

The study complied with the Declaration of Helsinki and all subjects gave written informed consent. The study was approved by the ethics committees of Shanghai Fifth People's Hospital (No.2018–213) and Zhejiang Kaihua County Hospital of Chinese Medicine (No.2019–002).

Between January 2018 and December 2020, 2602 patients with T2DM, diagnosed according to the American Diabetes Association (ADA) criteria,[17] were recruited from the Department of Endocrinology, Shanghai Fifth People's Hospital and the Department of Nephrology, Zhejiang Kaihua County Hospital of Chinese Medicine.

DKD was defined as the presence of macro-albuminuria or micro-albuminuria in association with diabetic retinopathy according to the diagnostic criteria of KDOQI clinical practice guidelines.[18] Macroalbuminuria was defined as an albumin creatinine ratio (ACR) > 300 mg/g and micro-albuminuria as an ACR 30 to 300 mg/g in two of three urine samples.

Patients were excluded from study if they had any of the following: ESKD (defined as requirement of dialysis, renal transplantation, or eGFR<15mL/min/1.73 m^2 at baseline), manifest cardiovascular disease (CVD), acute infectious disease, history of hepatitis and HIV virus infection or carrier, diabetic ketoacidosis, any kind of cancer, unstable thyroid function, undergoing steroid therapy, or established autoimmune disease. The retrospective

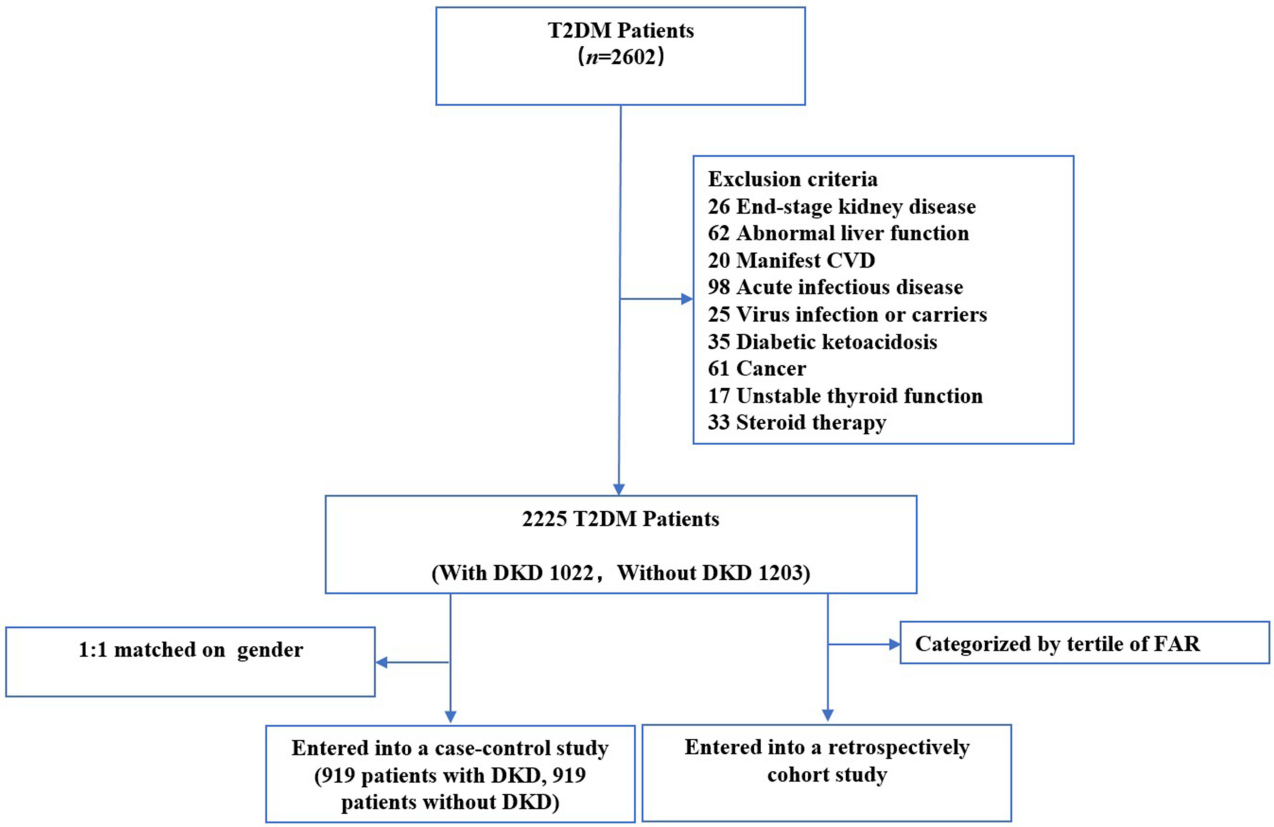


Figure 1 The flowchart of this study.
Abbreviations: DKD, diabetic kidney disease; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; FAR, fibrinogen to albumin ratio.

analysis is described in Figure 1. After exclusions, data from 1022 patients with DKD and 1203 patients without DKD were analyzed.

Data Collection and Laboratory Assessments

Patient's age and medical history, duration of disease, hypertension, body mass index (BMI), and systolic (SBP) and diastolic blood pressure (DBP) were recorded. After a 12-hour overnight fast, blood was collected for measurement of full blood count (XN9000, Sysmex, Japan) and hemoglobin A1c (HbA1c, Variant II, Bio-Rad, USA), biochemical parameters (Cobas 8000, Roche, Switzerland), and FIB (CS5100, Sysmex Corporation, Japan). A urine sample was collected for measurement of ACR (Turbidimetry Hitachi system, Roche, Germany). eGFR was calculated using the modification of diet in renal disease (MDRD) equation developed for the Chinese population: eGFR (mL/min/1.73m^2) = 186 × (Crea×0.011)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female/1 if male) ×1.233, where creatinine (Crea) was in μmol/L and 1.233 was the adjusting coefficient for Chinese patients.[19]

Statistical Analysis

A case control matching analysis was performed to avoid the potential bias of an uneven distribution of covariates between individuals with and without DKD. Data with normal distribution are expressed as mean ± standard deviation and were analyzed by student *t* test or ANOVA test. Non-normally distributed variables are expressed as median and interquartile range (IQR) and were analyzed by nonparametric tests (Mann–Whitney or Kruskal–Wallis). Categorical variables are presented as frequencies and proportions and were analyzed by χ^2 test. Pearson correlation analysis was used to determine the biochemical parameters that showed significant changes in the case control matching analysis. To determine the risk factors for development of DKD, logistic regression analysis (enter method) was used in the matched case-control analysis and cohort study. Statistical descriptions for logistic regression analysis are presented as regression coefficient (standard error) and odds ratio (95% confidence interval). Continuous association of FAR with DKD incidence was determined by spline regression analysis. All data were

analyzed using SPSS 24.0 software (IBM, Armonk, NY) and R software (version R 4.0.1). A two-tailed P value < 0.05 was considered statistically significant.

Results

Demographics of Patients with and without DKD in the Matched Case-Control Study

Demographics and clinical data of all subjects were shown in Table 1. There were significant differences on clinical characteristics, including gender (male/female) (736:467 vs 452:570, P<0.001), age, disease duration, BMI and SBP between the patients with or without DKD. Meanwhile, significant differences were also observed on laboratory parameters, including neutrophil (NEU), lymphocyte (LYM), neutrophil-to-lymphocyte ratio (NLR), fasting plasma glucose (FPG), triglyceride (TG), urea nitrogen (UN), uric acid (UA), creatinine (Crea), eGFR, ACR, alanine aminotransferase (ALT), FIB (2652.7 ± 711.1 mg/L vs 3112.8 ± 992.7 mg/L, P<0.001) between the patients with or without DKD. Notably, patients with DKD had a higher level of FAR than individuals without DKD (62.8 ± 19.9 mg/g vs 78.1 ± 33.6 mg/g, P<0.001) (Table 1).

To avoid the statistical bias, which may cause uneven distribution of covariates between the individuals with and without DKD, a 1:1 case-control matching analysis was performed. After covariates matching, significant differences were still remained on age, disease duration, BMI, SBP, NEU, LYM, NLR, FPG, TG, UN, UA, Crea, eGFR, ACR, ALT, ALB (42.3 ± 4.0 g/L vs 40.9 ± 5.2 g/L, P<0.001), FIB (2840.3 ± 696.7 mg/L vs 3227.2 ± 979.7 mg/L, P<0.001), FAR (67.9 ± 19.8 mg/g vs 81.5 ± 33.7 mg/g, P<0.001) (Table 1).

Table 1 Demographics of the Study Population

Variable	All Subjects			Matched Case-Control Study		
	Non-DKD	DKD	*P*	Non-DKD	DKD	*P*
n (Male/Female)	1203 (736:467)	1022 (452:570)	**<0.001**	919 (452:467)	919 (452:467)	1.000
Age (years)	59 ± 11	64 ± 10	**<0.001**	60 ± 10	64 ± 10	**<0.001**
Duration (years)	8.6 ± 7.1	12.0 ± 8.0	**<0.001**	8.9 ± 7.1	12.2± 8.0	**<0.001**
BMI (kg/m^2)	24.8 ± 3.7	25.3 ± 4.1	**0.032**	24.8 ± 3.9	25.3 ± 4.0	**0.028**
SBP (mmHg)	129 ± 16	134 ± 20	**<0.001**	129 ± 16	135 ± 20	**<0.001**
DBP (mmHg)	79 ± 10	78 ± 11	0.493	79 ± 10	79 ± 11	0.879
NEU (×10^9/L)	3.56 ± 1.12	3.81 ± 1.20	**<0.001**	3.58 ± 1.13	3.89 ± 1.19	**<0.001**
LYM (×109/L)	1.76 ± 0.61	1.62 ± 0.61	**<0.001**	1.73 ± 0.60	1.61 ± 0.62	**<0.001**
NLR	2.12 ± 1.14	2.64 ± 1.68	**<0.001**	2.25 ± 1.18	2.71 ± 1.72	**<0.001**
HbA1c (%)	9.1 ± 2.4	9.0 ± 2.3	0.726	9.2 ± 2.4	9.1 ± 2.4	0.668
FPG (mmol/L)	7.95 ± 2.84	8.24 ± 3.17	**0.030**	7.94 ± 2.84	8.23 ± 3.16	**0.047**
TC (mmol/L)	4.43 ± 1.22	4.53 ± 1.42	0.079	4.43 ± 1.20	4.54 ± 1.45	0.090
TG (mmol/L)	1.41 (0.98, 2.07)	1.62 (1.13, 2.28)	**0.004**	1.38 (0.98, 2.02)	1.61 (1.13, 2.27)	**<0.001**
HDL-C (mmol/L)	1.11 ± 0.34	1.12 ± 0.36	0.434	1.12 ± 0.34	1.11 ± 0.36	0.674
UN (mmol/L)	5.14 ± 1.40	6.31 ± 2.51	**<0.001**	5.02 ± 1.37	6.39 ± 2.55	**<0.001**
UA (μmol/L)	287 ± 83	327 ± 103	**<0.001**	279 ± 82	330 ± 104	**<0.001**
Crea (μmol/L)	63 ± 16	81 ± 35	**<0.001**	60 ± 15	83 ± 34	**<0.001**
eGFR (mL/min/1.73m^2)	93.7 ± 24.5	68.9 ± 32.4	**<0.001**	90.3 ± 23.4	70.1 ± 33.4	**<0.001**
ACR (mg/g)	7.0 (4.0, 14.0)	67.1 (30.0, 250.8)	**<0.001**	7.0 (4.0, 14.0)	75.0 (32.0, 296.9)	**<0.001**
ALT (U/L)	24.1 ± 16.4	20.4 ± 13.6	**<0.001**	23.4 ± 16.3	20.2 ± 13.7	**<0.001**
ALB (g/L)	42.8 ± 4.0	41.3 ± 5.1	**<0.001**	42.3 ± 4.0	40.9 ± 5.2	**<0.001**
FIB (mg/L)	2652.7 ± 711.1	3112.8 ± 992.7	**<0.001**	2840.3 ± 696.7	3227.2 ± 979.7	**<0.001**
FAR (mg/g)	62.8 ± 19.9	78.1 ± 33.6	**<0.001**	67.9 ± 19.8	81.5 ± 33.7	**<0.001**

Notes: Data with normal distribution are expressed as mean ± standard deviation or median with interquartile range. Bold indicates statistical significance (P<0.05).
Abbreviations: DKD, diabetic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; HbA1c, glycated hemoglobin A1c; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; UN, urea nitrogen; UA, uric acid; Crea, creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; ALT, alanine aminotransferase; ALB, albumin; FIB, fibrinogen; FAR, fibrinogen to albumin ratio.

Higher FAR Outperformed ALB and FIB as an Independent Risk Factor and Diagnostic Predictive Factor for DKD in the Matched Case-Control Study

Logistic regression analysis with enter selection was performed separately in the matched case-control study to compare the predictive ability of FAR, ALB and FIB for development of DKD. Results revealed that FAR had the highest odds ratio (OR) value as an independent risk factor for the development of DKD in the middle (OR: 1.395; 95% CI:1.089–1.788; vs the lowest tertile, P= 0.008) and highest tertile of patients (OR: 2.879; 95% CI: 2.239, 3.700; vs the lowest tertile, P <0.001) regardless of age or TG compared with ALB (OR: 0.754; 95% CI: 0.590, 0.963 in the middle tertile vs the lowest tertile, P= 0.024; OR: 0.648; 95% CI: 0.504–0.832 in the highest tertile vs the lowest tertile, P=0.001) and FIB (OR: 1.343; 95% CI: 1.047–1.724 in the middle tertile vs the lowest tertile, P= 0.020; OR: 2.624; 95% CI: 2.040–3.375 in the highest tertile vs the lowest tertile, P<0.001) (Table 2).

In addition, FAR had the highest area under receiver operating characteristic curve (AUC) for prediction of DKD compared with ALB and FIB (0.753, 0.730 and 0.609 respectively) (Figure 2). The optimal value of FAR as an indicator for monitoring the development of DKD was 71.7 mg/g, which yielded a sensitivity of 58.8% and a specificity of 79.9%.

Comparison of Clinical Parameters Among Three Groups Categorized by Tertile of FAR in the Cohort Study

Subjects were divided into three groups according to tertile of FAR, lowest group (below 61.2 mg/g), middle group (61.2 to 75.4 mg/g), and highest group (above 75.4 mg/g). Significant

Table 2 Logistic Regression Analysis (Enter Method) to Determine Risk Factors for Development of DKD in the Case-Control Study

Variable	β (SE)	OR (95% CI)	*P*
Tertile of FAR			
Lowest	Reference	Reference	
Middle	0.333 (0.126)	1.395 (1.089, 1.788)	**0.008**
Highest	1.057 (0.128)	2.879 (2.239, 3.700)	**<0.001**
Age (years)	0.037 (0.131)	1.037 (1.027, 1.048)	**<0.001**
TG (mmol/L)			
< 2.3	Reference	Reference	
≥ 2.3	0.566 (0.131)	1.762 (1.364, 2.275)	**<0.001**
Tertile of ALB			
Lowest	Reference	Reference	
Middle	−0.282(0.125)	0.754 (0.590, 0.963)	**0.024**
Highest	−0.434 (0.128)	0.648 (0.504, 0.832)	**0.001**
Age (years)	0.038 (0.005)	1.038 (1.028, 1.049)	**<0.001**
TG (mmol/L)			
< 2.3	Reference	Reference	
≥ 2.3	0.544 (0.130)	1.723 (1.335, 2.222)	**<0.001**
Tertile of FIB			
Lowest	Reference	Reference	
Middle	0.295 (0.127)	1.343 (1.047, 1.724)	**0.020**
Highest	0.965 (0.128)	2.624 (2.040, 3.375)	**<0.001**
Age (years)	0.038 (0.005)	1.038 (1.028, 1.049)	**<0.001**
TG (mmol/L)			
< 2.3	Reference	Reference	
≥ 2.3	0.622 (0.129)	1.862 (1.446, 2.398)	**<0.001**

Notes: Data are presented as regression coefficient (standard error), odds ratio (95% confidence interval) and *P* value. Bold indicates statistical significance (P< 0.05).
Abbreviations: DKD, diabetic kidney disease; FAR, fibrinogen to albumin ratio; TG, triglyceride; ALB, albumin; FIB, fibrinogen.

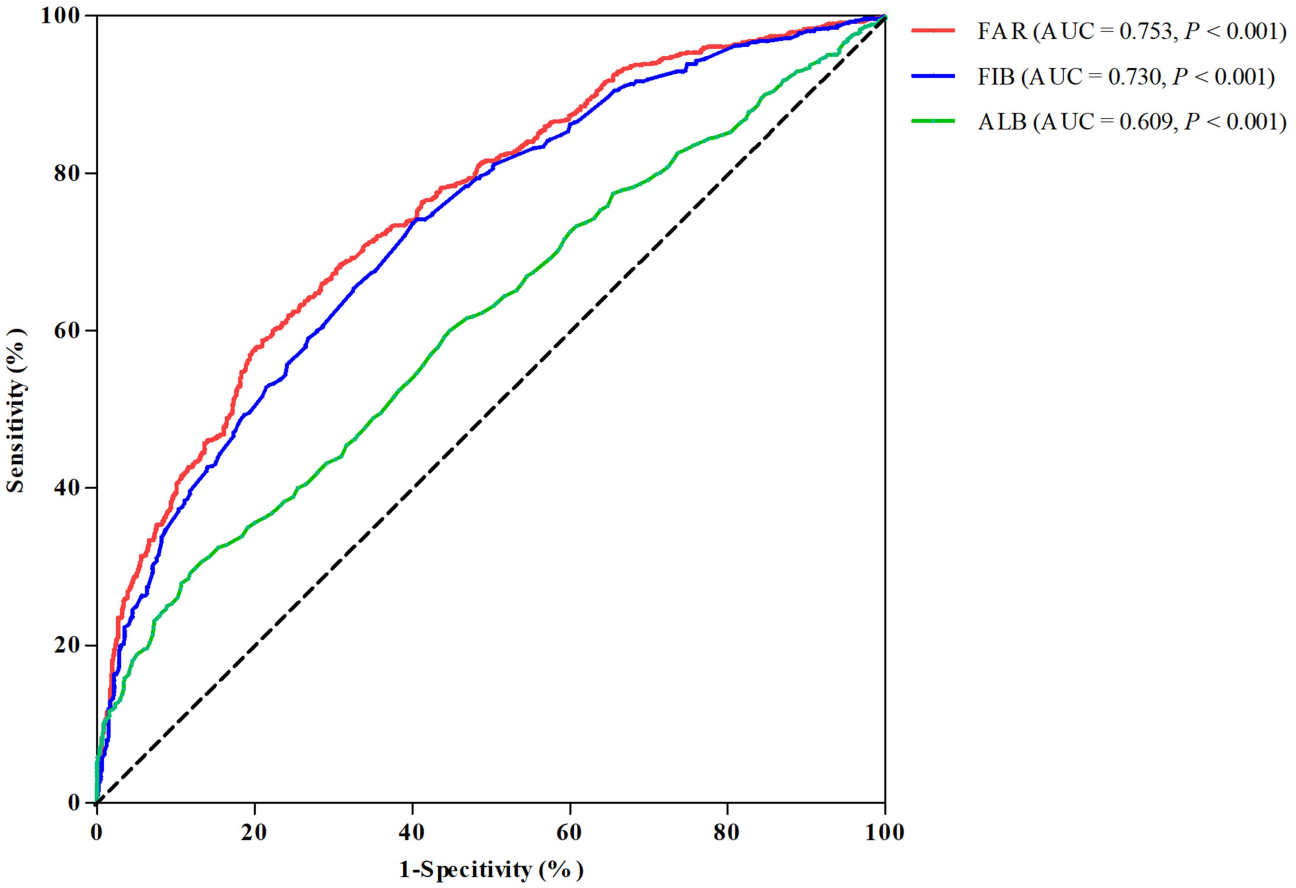


Figure 2 ROC curve of FAR, FIB and ALB for diagnosing DKD.
Abbreviations: FAR, fibrinogen to albumin ratio; FIB, fibrinogen; ALB, albumin; AUC, area under ROC curve.

differences were observed on age, disease duration, SBP, NEU, NLR, HbA1c, UN, UA, Crea, eGFR, ACR, ALT, ALB (43.5 ± 3.7 g/L vs 42.4 ± 3.8 g/L vs 39.0 ± 5.1 g/L, P<0.001), FIB (2337.0 ± 301.7 mg/L vs 2857.0 ± 293.7 mg/L vs 3906.2 ± 909.7 mg/L, P<0.001) cross the lowest, middle, and highest groups, respectively (Table 3).

FAR Was Closely Associated with NEU and NLR

Linear regression and correlation analysis revealed a significant and linear correlation of FAR with NEU (adjusted R^2 = 0.070; P<0.001) (Figure 3A) and NLR (adjusted R^2 = 0.078; P<0.001) (Figure 3B).

FAR Was an Independent Risk Factor for the Development of DKD in the Cohort Study

To determine independent risk factors for the development of DKD in the cohort study, tertile of FAR, age, disease duration, and tertile of NLR, HbA1c, FPG, TG and ALT were entered into logistic regression analysis with enter selection. Age, disease duration, SBP, and TG were identified as significant risk factors. Of note, FAR (OR: 1.334; 95% CI: 0.878–2.027 in the middle tertile vs the lowest tertile, P=0.176; OR: 2.403; 95% CI: 1.566–3.686 in the highest tertile vs the lowest tertile, P<0.001) remained a risk factor for development of DKD independent of these factors (Table 4).

Continuous FAR Was Closely Associated with the Incidence of DKD in the Cohort Study

After adjusting for age, disease duration, SBP and TG, a spline model showed a significant relationship between continuous FAR and DKD incidence. The risk of developing DKD increased when FAR exceeded 67.3 mg/g (Figure 4).

Table 3 Comparison of Parameters Among Three Groups Categorized by Tertile of FAR in the Cohort Study

Variable	Lowest Group	Middle Group	Highest Group	*P*
FAR (mg/g)	Below 61.2	61.2 to 75.4	Above 75.4	
n (Male/Female)	610 (296:314)	616 (300:316)	612 (308:304)	0.785
Age (years)	61 ± 10	62 ± 11*	63 ± 10***	**<0.001**
Duration (years)	9.6 ± 7.3	9.9 ± 7.8	12.1 ± 7.9***	**<0.001**
BMI (kg/m^2)	24.9 ± 3.8	25.4 ± 4.1	24.7 ± 4.0	1.000
SBP (mmHg)	130 ± 18	133 ± 18	133 ± 20*	**0.047**
DBP (mmHg)	78 ± 9.9	79 ± 10	78 ± 11	0.794
NEU (×10^9/L)	3.49 ± 1.03	3.63 ± 1.12	4.07 ± 1.26***	**<0.001**
LYM (×10^9/L)	1.71 ± 0.61	1.69 ± 0.59	1.63 ± 0.62	0.113
NLR	2.22 ± 1.07	2.33 ± 1.21	2.85 ± 1.92***	**<0.001**
HbA1c (%)	8.8 ± 2.2	9.1 ± 2.3	9.5 ± 2.5***	**<0.001**
FPG (mmol/L)	7.95 ± 2.82	8.14 ± 3.06	8.16 ± 3.13	0.674
TC (mmol/L)	4.45 ± 1.23	4.51 ± 1.38	4.49 ± 1.38	1.000
TG (mmol/L)	1.49 (1.03, 2.15)	1.46 (1.11, 2.17)	1.45 (1.06, 2.13)	0.585
HDL-C (mmol/L)	1.14 ± 0.33	1.11 ± 0.34	1.10 ± 0.38	0.088
UN (mmol/L)	5.43 ± 1.77	5.50 ± 1.74	6.18 ± 2.73***	**<0.001**
UA (μmol/L)	294 ± 90	305 ± 95	315 ± 105***	**<0.001**
Crea (μmol/L)	65 ± 21	68 ± 23	81 ± 39***	**<0.001**
eGFR (mL/min/1.73m^2)	85.2 ± 27.5	81.4 ± 29.9	73.9 ± 33.0***	**<0.001**
ACR (mg/g)	11.1 (4.0, 34.1)	15.4 (6.0, 49.0) *	42.0 (9.0, 384.8) ***	**<0.001**
ALT (U/L)	24.1 ± 16.1	22.4 ± 15.2	18.8 ± 13.5***	**<0.001**
ALB (g/L)	43.5 ± 3.7	42.4 ± 3.8***	39.0 ± 5.1***	**<0.001**
FIB (mg/L)	2337.0 ± 301.7	2857.0 ± 293.7***	3906.2 ± 909.7***	**<0.001**

Notes: Data with normal distribution are expressed as mean ± standard deviation or median with interquartile range. *P<0.05, ***P<0.001, versus lowest group. Bold indicates statistical significance (P<0.05).

Abbreviations: FAR, fibrinogen to albumin ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NEU, neutrophil; LYM, lymphocyte; NLR, neutrophil- to-lymphocyte ratio; HbA1c, glycated hemoglobin A1c; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; UN, urea nitrogen; UA, uric acid; Crea, creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin creatinine ratio; ALT, alanine aminotransferase; ALB, albumin; FIB, fibrinogen.

Discussion

In this study, we have shown that FAR is significantly higher in patients with DKD. The diagnostic efficacy of FAR is higher than that of FIB and ALB. FAR may be considered an independent risk factor and help to predict the development of DKD.

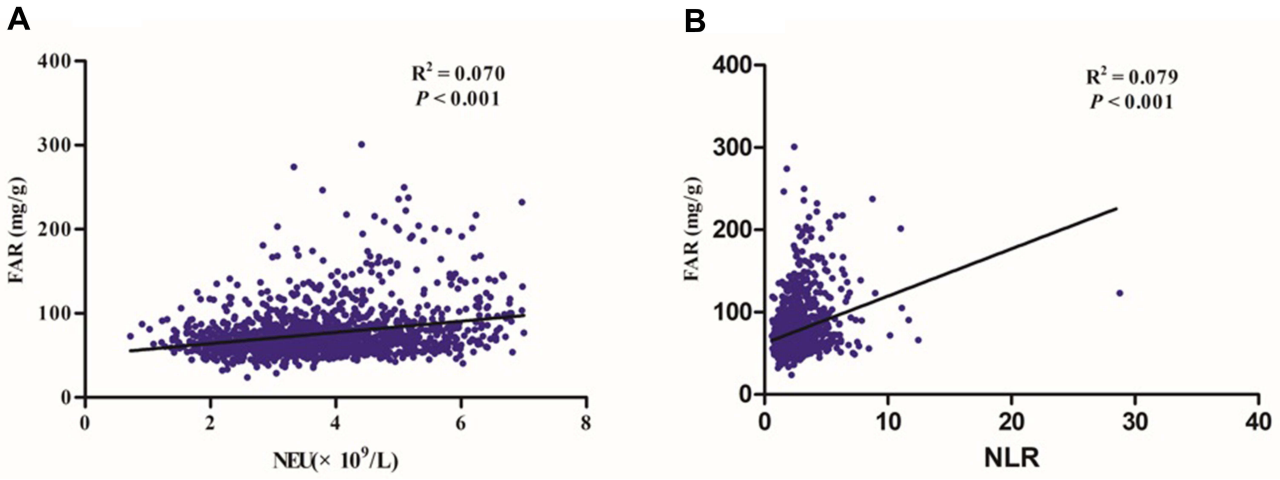


Figure 3 Simple linear regression analysis among FAR, NEU (**A**) and NLR (**B**).

Abbreviations: FAR, fibrinogen to albumin ratio; NEU, neutrophil; NLR, neutrophil-to-lymphocyte ratio.

Table 4 Logistic Regression Analysis (Enter Method) to Determine the Risk Factors for Development of DKD in the Cohort Study

Variable	β (SE)	OR (95% CI)	*P*
Tertiles of FAR (mg/g)			
Lowest	Reference	Reference	
Middle	0.288 (0.213)	1.334 (0.878, 2.027)	0.176
Highest	0.877 (0.218)	2.403 (1.566, 3.686)	**<0.001**
Age (years)	0.022 (0.010)	1.022 (1.002, 1.042)	**0.026**
Duration (years)	0.045 (0.012)	1.046 (1.021, 1.071)	**<0.001**
SBP (mmHg)	0.010 (0.005)	1.010 (1.001, 1.020)	**0.027**
Tertile of NLR			
Lowest	Reference	Reference	
Middle	0.276 (0.214)	1.318 (0.867, 2.005)	0.197
Highest	0.353 (0.224)	1.423 (0.917, 2.208)	0.115
HbA1c (%)			
≤ 7.0	Reference	Reference	
> 7.0	−0.067 (0.224)	0.935 (0.603, 1.449)	0.763
FPG (mmol/L)			
≤ 7.0	Reference	Reference	
> 7.0	−0.163 (0.186)	0.850 (0.590, 1.224)	0.383
TG (mmol/L)			
< 2.3	Reference	Reference	
≥ 2.3	0.733 (0.211)	2.082 (1.377, 3.150)	**0.001**
ALT (U/L)			
< 40	Reference	Reference	
≥ 40	−0.246 (0.292)	0.782 (0.441, 1.385)	0.399

Notes: Data are presented as regression coefficient (standard error), odds ratio (95% confidence interval) and *P* value. Bold indicates statistical significance ($P<0.05$).
Abbreviations: DKD, diabetic kidney disease; FAR, fibrinogen to albumin ratio; SBP, systolic blood pressure; NLR, neutrophil lymphocyte ratio; HbA1c, glycated hemoglobin A1c; ALT, alanine aminotransferase.

FIB is a soluble glycoprotein that plays a vital role in coagulation and inflammation.[20,21] It has been shown to be significantly elevated in DKD[22,23] and a powerful predictor of DKD occurrence.[24,25] Elevated serum levels of FIB have been associated with diabetic ESRD in patients with T2DM.[10] ALB, the most prevalent plasma protein, is synthesized in the liver and secreted into the vascular space for distribution to all body tissues.[26] It has anti-inflammatory functions and antioxidant properties[11,12] and is associated with a poor renal prognosis in patients with T2DM and DKD.[13] Synthesis of FIB and ALB is upregulated in T2DM patients with increased urinary albumin excretion.[27] In our case-control study, after matching the possible confounding factors, FIB and ALB were all associated with the development of DKD, consistent with previous studies.[10,13]

Fibrinogen to albumin ratio (FAR) could be a more significant prognostic marker than each single marker itself in cancer study.[14–16] Previous studies showed that FAR could predict severity of coronary artery disease and all-cause mortality in patients with myocardial infarction.[28–31] Patients with exaggerated metabolic syndrome had a higher FAR and FAR may be a better predictor than FIB and ALB of exaggerated metabolic syndrome.[32] Similarly, in cancer studies, FAR was a valuable marker that could predict progression-free survival and overall survival and a stronger prognostic factor than FIB and ALB alone in breast, gallbladder, renal and gastric cancer and in glioblastoma.[14–16,33,34] In accordance with these results, we also found that FAR had the highest OR and possessed the most predictive value in DKD and was superior to FIB and ALB. Moreover, fully adjusted spline regression showed a significant correlation of continuous FAR with DKD incidence and the risk abruptly increased when FAR exceeded 67.3mg/g.

Although NEU and NLR are classic inflammatory indicators, studies have suggested that NEU level is

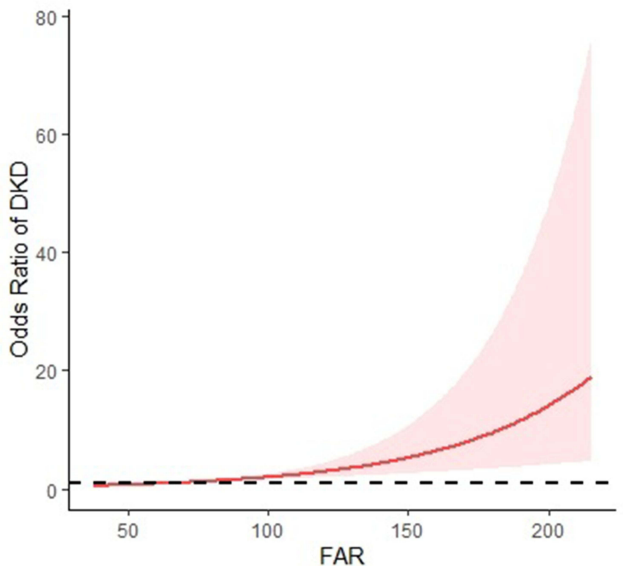


Figure 4 Continuous association of FAR with the incidence of DKD. Adjusted for age, disease duration, SBP and TG.
Abbreviations: FAR, fibrinogen to albumin ratio; DKD, diabetic kidney disease; SBP, systolic blood pressure; TG, triglyceride.

associated with the incidence of DKD.[35,36] A higher NLR level has been associated with an increased prevalence of DKD in diabetic adults.[37–42] In our study, the differences in NEU and NLR among subjects with DKD were monitored separately. NEU and NLR were significantly higher in the highest tertile FAR group compared with the lowest. FAR was positively correlated with NEU and NLR. We speculate that FAR may participate in the pathogenesis of DKD by affecting inflammation.

Clinical diagnosis of DKD allows us to identify a group of patients at very high cardiorenal risk, for whom care is really difficult.[43] At the same time, by using FAR as a potential indicator for predicting and preventing the progress of DKD in early stage, multifactorial intensive therapy is applied and induces a remarkable benefit on the risk of major adverse cardiovascular events (MACEs) and mortality in high-risk DKD patients.[44]

This study also has some limitations. First, enrolled patients were only from two hospitals and may lack representativeness, which could lead to biased results. Second, the two study groups, despite our efforts to match them, were different in age, eGFR and disease duration etc. Third, the two study groups have relatively poor glycemic control, which could make the study results non-generalizable to diabetic subjects with relatively good glycemic control. Finally, although we have indicated that the pathophysiological role of FAR in DKD development could be associated with an inflammatory state, it is unclear whether these changes are a cause or consequence of DKD development. Future longitudinal studies may provide further clarification.

Conclusion

FAR is significantly higher in patients with DKD. The diagnostic efficacy of FAR is higher than that of FIB and ALB. FAR may be a stronger independent predictor of the presence of DKD than FIB and ALB. FAR is an independent risk factor for DKD development when it exceeded 67.3mg/g. FAR might be one of novel diagnostic biomarkers to predict and prevent DKD progression. However, a prospective study to validate the prognostic model is still needed.

Data Sharing Statement

The experimental data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

The study complied with the Declaration of Helsinki, and all subjects gave written informed consent. The study was approved by the ethics committees of Shanghai Fifth People's Hospital (No.2018-213) and Zhejiang Kaihua County Hospital of Chinese Medicine (No.2019-002).

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Disclosure

The authors report no conflicts of interest in this work.

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