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ORIGINAL RESEARCH

A Novel Inflammatory Marker: Relationship Between Red Cell Distribution Width/Albumin Ratio and Vascular Complications in Patients with Type 2 Diabetes Mellitus

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Purpose: To explore the relationship between Red cell distribution width/albumin ratio (RAR) and vascular complications, including atherosclerosis of the lower limbs, diabetic nephropathy(DN), and diabetic retinopathy(DR), in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: The study included 427 patients with type 2 diabetes mellitus who were hospitalized in the Department of Endocrinology of the First Affiliated Hospital of Jinan University (Guangzhou, China) between April 1, 2022 and May 31, 2023. Baseline characteristics were displayed according to the quartiles of the RAR. Logistic regression analysis and receiver operating characteristic curves (ROC) were used to analyze the data.

Results: After adjusting for confounders, a higher RAR quartile(the fourth quartile) was associated with an increased risk of atherosclerosis of the lower limbs(OR: 2.973, 95% CI 1.281–6.906, p = 0.011), and diabetic nephropathy(OR: 2.876, 95% CI 1.315–6.287, p = 0.008) compared to the lowest RAR quartile. The patients were further divided into two groups according to urinary albumin to creatinine ratio (UACR≥30mg/g and UACR < 30mg/g) and Glomerular Filtration Rate (eGFR<60 mL·min^{-1} (1.73 m^2) $^{-1}$ and eGFR≥60 mL·min^{-1} (1.73 m^2) $^{-1}$). Similar results were observed. However, We found that RAR quartile did not significantly increase the likelihood of developing diabetic retinopathy(OR: 1.183, 95% CI 0.633–2.211, p = 0.598).

Conclusion: The RAR ratio is associated with an increased risk of atherosclerosis of the lower limbs and diabetic nephropathy in patients with T2DM. The RAR ratio may be an important clinical marker of vascular complications in T2DM.

Keywords: Type 2 diabetes mellitus, red blood cell distribution width, albumin, complications, inflammation

Introduction

Complications related to diabetes have gradually become a serious threat to human health worldwide. Diabetic vasculopathy is categorized into macrovascular and microvascular complications. Macrovascular lesion is characterized by atherosclerosis,[1] and microangiopathy is characterized by basement membrane thickening and microcirculatory disturbance, including diabetic nephropathy (DN), diabetic retinopathy (DR), and so on. Diabetics are more prone to atherosclerosis, which can lead to coronary heart disease, cerebrovascular accidents, and peripheral arterial disease (PAD).[2] Lower extremity blood vessels are the third most common site for the development of atherosclerosis after the heart and brain. Atherosclerosis of the lower limbs will lead to a gradual decrease of blood flow in the limbs,[3] and

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gradually develop into PAD, or even more serious diabetic foot.[4] Therefore, early identification of lower limb atherosclerosis is necessary. At the same time, diabetic nephropathy and diabetic retinopathy patients have a worse prognosis and financial burden. Markers of macrovascular and microvascular disease in diabetes can provide early diagnostic information that can help in prevention and treatment.

Systemic low-grade chronic inflammation is a major feature of diabetes. And increasing evidence indicates that inflammation may also be a major factor in diabetes-related complications.[1] The red blood cell distribution width/albumin ratio (RAR) is an economical and convenient inflammatory marker. It is a potential novel biomarker that is reproducible, widely used, easy to measure, and low cost. In previous studies, RAR has been considered a prognostic marker for acute and chronic inflammation in patients with diabetic ketoacidosis,[5] diabetic foot,[6] heart failure,[7] stroke,[8] etc. So far, no studies have focused on the relationship and prognostic potential of RAR with vascular complications in type 2 diabetes mellitus(T2DM). In this study, we aim to discuss the relationship between RAR and vascular complications, including atherosclerosis of the lower limbs, DN, and DR in T2DM. This may provide clinical guidance for identifying high-risk patients with poor prognosis.

Material and Methods

Study Population

The study included 427 patients with type 2 diabetes who were hospitalized in the Department of Endocrinology of the First Affiliated Hospital of Jinan University (Guangzhou, China) between April 1, 2022 and May 31, 2023. The inclusion criteria: (1) at least 18 years of age; (2) The diagnosis of T2DM conforms to the diagnostic criteria of《Standards of Care in Diabetes—2023》, published by ADA.[9] Exclusion criteria: (1) patients with severe cardiovascular and cerebrovascular diseases (transient ischemic attack (TIA), stroke, acute myocardial infarction, severe heart failure, cardiogenic shock, etc).; (2) Patients with severe liver disease (cirrhosis, liver failure, etc)., tumors, infectious diseases, and hematological disorders; (3) Patients who have recently used glucocorticoids or immunosuppressants; (4) Patients who lacked the data of RDW, ALB, lower extremity vascular arterial ultrasound and other data related to the study; (5) Patients with acute complications of diabetes, such as hypertonic hyperglycemia, diabetic ketoacidosis and/or lactic acidosis; (6) Pregnant women. The flow chart for the inclusion of the population is shown in Figure 1.

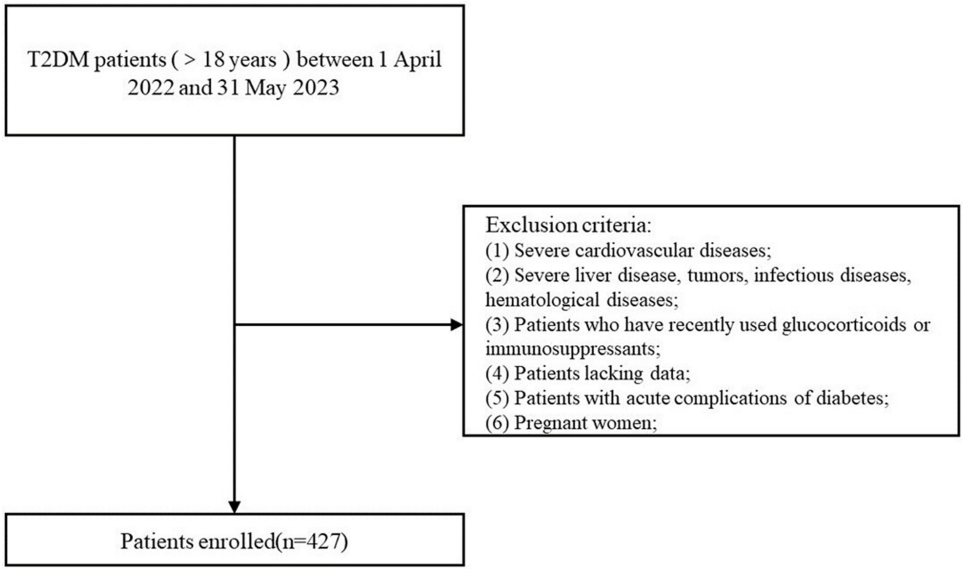

Figure 1 Flow chart for inclusion of population.

Data Collection

The sociodemographic and medical history information was collected by reviewing the medical records, including age, gender, BMI, smoking and drinking status, diabetes duration, medication history, past medical history, and medication history. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from the mean values of SBP and DBP in the three days. Fasting venous blood samples were collected from all patients after hospitalization. Strict adherence to standard laboratory protocols was maintained for quality control. Red cell distribution width (RDW), hemoglobin (HGB), lymphocyte (LYMPH), neutrophil (NEUT), and platelet (PLT) were measured by a fully automated hematology analyzer. The automatic biochemical analyzer was used to measure albumin (ALB), fasting blood glucose (FPG), total cholesterol (TC), triglycerides (TG), Human hypersensitive C Reactive Protein (HsCRP), creatinine (CREA), UREA (UREA), URIC acid. The level of glycated hemoglobin A1c(HbA1c) was measured by liquid chromatography. RDW/ALB ratio (RAR), neutrophils/lymphocytes (NLR), and platelets/lymphocytes (PLR) were calculated. Albuminuria was screened by measuring the urinary albumin-to-creatinine ratio (UACR) in urine at random points. Glomerular Filtration Rate (eGFR) is calculated using a proven formula based on the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI).[10]

Definitions

Diabetic nephropathy: Urinary albumin/creatinine ratio (UACR) ≥30 mg/g and/or estimated glomerular filtration rate (eGFR) <60 $mL \cdot min^{-1}$ $(1.73\ m^2)^{-1}$ for more than 3 months, when diabetes was identified as the cause of renal impairment and other causes of chronic kidney disease were excluded. When necessary, a complete renal biopsy is consistent with the pathological changes of DKD.[11] Diabetic retinopathy: Initial mydriasis and comprehensive eye examination (fundus photography, optical coherence tomography (OCT), fluorescein fundus angiography (FFA), etc.) are performed by a trained ophthalmologist or optometrist to look for microhemangiomas, internal retinal bleeding, rigid exudation, etc. The diagnostic criteria is 《The International Clinical Grading Standards for Diabetic Retinopathy (DR)》 released by the American Academy of Ophthalmology in 2019.[12] Atherosclerosis of the lower limbs is diagnosed by a qualified and experienced physician using an ultrasound equipment. In B-type imaging, Lower extremity arteries are scanned and imaged.

Statistical Analysis

Baseline characteristics of the total study population were shown according to the RAR quartiles. The $\chi 2$ test was used for categorical variables to compare differences among groups. We used different tests to compare the differences among groups. The *T*-test was used for the continuity values of the normal distribution. When the data presented a skewed distribution, the Kruskal–Wallis *H*-test was used. The categorical variables were represented by n(%). Numerical variables with skewed distributions were expressed as median (upper and lower quartiles, M (IQR)). The expression for data that were normally distributed was mean ± standard deviation (SD). Logistic regression was conducted after the model's collinearity was examined. Four logistic regression models were constructed to adjust for confounding factors. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the relationship between the ratios (RAR, NLR, PLR) and study outcomes as a continuity variable and a categorical variable (by quartile), respectively. Receiver operating characteristic curves (ROC) curves were used to analyze the predictive power. We calculated the corresponding area under the curve (AUC), and the sensitivity and specificity corresponding to the maximum approximate entry index. The statistical software SPSS (version 27.0; IBM, IL, USA) was used for all analyses. P value < 0.05 is considered statistically significant.

Results

Baseline Characteristics

427 patients with type 2 diabetes were included, with a median age of 60 years, and 57.8% of them were male. 59.5% of them had hypertension and 33.5% had hyperlipidemia. Among them, 333 (80.0%) patients had atherosclerosis of the lower limbs, 101 (23.7%) patients had diabetic nephropathy, and 127 (29.7%) patients had diabetic retinopathy.

According to the RAR quartile, there were four sets of participants: Q1, RAR≤ 3.28, Q2, 3.28< RAR≤3.55, Q3, 3.55< RAR<3.89, and Q4: RAR≥ 3.89. There were significant differences in Hgb, TCH, eGFR, and UACR among the four groups (P < 0.05). Hgb and eGFR decreased with the increase of RAR quartile. UACR increased with the increase of RAR quartile. Although there was a significant difference in TCH between the four groups, the relationship did not follow a linear trend. The baseline characteristics of participants were shown in Table 1.

Relationship Between RAR and the Occurrence of Any Vascular Complications

Univariate logistic regression analysis showed that age, Hgb, duration of diabetes, the use of oral hypoglycemic agents or GLP-1RA, hypertension, hyperlipidemia, the use of antihypertensive agents, and the use of lipid-lowering agents were associated with the occurrence of any vascular complications (p <0.05) (Table S1). They were added to the final regression model as potential confounder adjustments. In addition, according to previous literature, independent additional variables associated with diabetes complications or RAR were also included in the final regression model,[13] such as gender, BMI, Hb1c, HsCRP, TCH, TG, smoking, drinking, and the use of insulin. The collinearity of the model was examined. We found that the variance inflation factor (VIF) was all less than 10, and the Tolerance was much higher than 0.1 (Table S2). These findings suggested that there was no significant multicollinearity among the variables. Therefore, we further conducted multivariate logistic regression analyses (Table 2). We constructed four logistic regression models to adjust for confounding factors. Results showed that RAR was highly correlated with the risk of any vascular complications when RAR was a continuous variable (OR: 4.163, 95% CI 1.901–9.113, p < 0.001). When RAR was used as a categorical variable, the relationship between RAR and any vascular complication risk in unadjusted or adjusted models was similar to its results as a continuous variable. Q4 group were more likely to have at least one diabetes complication than Q1 group.

Relationship Between RAR and Atherosclerosis of the Lower Limbs

Q4 was significantly linked to a higher risk of lower limb atherosclerosis when Q1 was taken as a reference, and this relationship remained significant after multifactor adjustment (OR: 2.973, 95% CI 1.281–6.906, p = 0.011). Moreover, the risk increased with the increase of RAR quartile (Table 3).

Relationship Between RAR and Leukocyte-Derived Ratios and Diabetic Nephropathy

Table 4. In unadjusted or adjusted models, RAR as a categorical variable was connected to the occurrence of diabetic nephropathy and increased with RAR quartile classification (OR: 2.876, 95% CI 1.315–6.287, p = 0.008). At the same time, the OR value of NLR (OR: 5.495, 95% CI 2.277–13.264, p < 0.001) and PLR (OR: 4.450, 95% CI 1.881–10.531, p = 0.001) increased. When used as continuous variables, RAR (OR: 2.318, 95% CI 1.406–3.821, p = 0.001) and NLR (OR: 1.235, 95% CI 1.043–1.463, p = 0.014) were associated with an increased risk of diabetic nephropathy. PLR (OR: 1.008, 95% CI 1.003–1.012, p = 0.001) was not statistically significant when used as a continuity variable. Further analysis, patients were divided into two groups based on urinary albumin-to-creatinine ratio (UACR): patients with T2DM had normal albuminuria (UACR < 30mg/g), and patients with T2DM had increased albuminuria (UACR≥30mg/g). Then, patients were divided into two groups according to eGFR: eGFR<60 mL·min^{-1} (1.73 m²) $^{-1}$, and eGFR≥60 mL·min^{-1} (1.73 m²) $^{-1}$. Results showed that UACR (UACR≥30mg/g) as an outcome also observed similar outcomes to diabetic nephropathy, RAR (OR: 2.245, 95% CI 1.190–4.235, p = 0.013), NLR (OR: 2.802, 95% CI 1.449–5.417, p = 0.002), and PLR (OR: 2.992, 95% CI 1.551–5.775, p = 0.001) (Table 5). For the relationship between RAR and leukocyte-derived ratio and eGFR (eGFR<60 mL·min^{-1} (1.73 m²) $^{-1}$), when they were used as continuous variables, the results were shown as follows: RAR (OR: 1.846, 95% CI 1.122–3.039, p = 0.016), NLR (OR: 1.541, 95% CI 1.235–1.856, p < 0.001), and PLR (OR: 1.012, 95% CI 1.006–1.017, p < 0.001) (Table S3).

Relationship Between RAR and Diabetic Retinopathy

The risk of retinopathy was not significantly increased when RAR was used as either a categorical or continuous variable (OR: 1.183, 95% CI 0.633–2.211, p = 0.598) (Table S4).

Table 1 Characteristics of Participants According to RAR Quartile

Characteristics	Total (N=427)	RAR Quartiles				p value
		Q1 (n=109)	Q2 (n=106)	Q3 (n=108)	Q4 (n=104)	
Male, n (%)	247(57.8)	72(66.1)	55(51.9)	56(51.9)	64(61.5)	0.081
Age(years)	60(53, 70)	59(51, 67)	59(53, 70)	63(55, 71)	60(53, 76)	0.007
SBP(mmHg)	125(117, 135)	125(119, 132)	124(117, 131)	127(117, 136)	127(117, 139)	0.454
DBP(mmHg)	72(67, 78)	72(66, 79)	72(68, 76)	71(67, 77)	73(68, 79)	0.665
BMI(kg/m^2)	24.20(22.40, 26.55)	24.50(22.65, 27.05)	24.85(22.70, 27.03)	23.70(22.05, 26.20)	23.60(22.05, 25.95)	0.082
Hb1c(%)	8.40(7.00, 10.70)	8.80(7.20, 10.80)	7.95(6.80, 9.95)	8.45(6.83, 11.80)	8.20(6.73, 10.40)	0.177
GLU(mmol/L)	7.06(5.71, 8.85)	7.46(6.39, 9.21)	6.89(5.71, 8.47)	7.06(5.39, 9.49)	6.99(5.28, 8.90)	0.086
Hgb(g/L)	133.00(120.00, 145.00)	141.00(132.30, 150.50)	133.90(121.83, 145.93)	130.80(119.30, 141.98)	124.00(106.00, 139.20)	0.001
HsCRP(mg/L)	1.83(0.80, 4.43)	1.63(0.71, 3.26)	1.72(0.90, 4.41)	2.21(0.90, 5.20)	2.89(0.70, 5.85)	0.244
TCH(mmol/L)	4.81(3.95, 5.63)	5.02(4.14, 5.96)	4.60(4.14, 5.24)	4.85(3.72, 5.63)	4.63(3.46, 5.43)	0.036
TG(mmol/L)	1.46(1.00, 2.14)	1.63(1.13, 2.19)	1.52(1.07, 2.02)	1.33(0.99, 2.12)	1.37(0.88, 2.14)	0.219
HDL(mmol/L)	1.06(0.90, 1.30)	1.11(0.95, 1.37)	1.02(0.84, 1.25)	1.07(0.92, 1.30)	1.05(0.90, 1.34)	0.053
LDL(mmol/L)	2.70(2.13, 3.28)	2.89(2.29, 3.37)	2.63(2.37, 3.14)	2.74(1.96, 3.31)	2.60(1.80, 3.32)	0.164
eGFR(mL/min/1.73m^2)	92.90(74.00, 104.70)	96.40(82.30, 107.60)	94.90(80.35, 103.90)	90.65(71.60, 102.33)	88.10(60.35, 104.20)	0.017
URIC(umol/L)	372.70(307.00, 444.80)	380.60(314.00, 455.50)	372.85(312.95, 441.58)	355.90(281.10, 435.10)	378.31 (308.48, 456.88)	0.255
UACR(mg/g)	22.50(9.45, 99.32)	18.71(10.00, 50.71)	17.78(6.82, 61.22)	26.02(9.79, 69.40)	54.20(12.23, 471.97)	0.001
RDW(%)	13.22(12.78, 13.85)	12.80(12.40, 13.21)	13.01(12.80, 13.50)	13.40(12.93, 14.00)	14.05(13.30, 14.87)	0.001
ALB(g/dL)	3.82(3.59, 4.05)	4.16(3.97, 4.32)	3.84(3.72, 3.94)	3.68(3.55, 3.79)	3.50(3.19, 3.98)	0.001
LYMPH(×10^9/L)	1.93(1.48, 2.49)	2.07(1.53, 2.55)	2.10(1.53, 2.69)	1.92(1.58, 2.54)	1.69(1.23, 2.09)	0.001
NEUT(×10^9/L)	3.99(2.98, 5.00)	4.00(2.96, 4.71)	3.89(3.03, 5.16)	3.72(2.73, 4.81)	4.38(3.24, 5.36)	0.021
PLT(×10^9/L)	214.00(180.00, 253.00)	212.00(185.10, 249.40)	215.00(179.00, 259.13)	205.00(171.10, 243.00)	222.00(181.63, 267.58)	0.421
Duration of diabetes(years)	9.00(3.00, 14.00)	8.00(1.50, 12.50)	8.50(2.00, 14.00)	10.00(4.00, 14.00)	9.00(4.00, 15.00)	0.279
Use of insulin, n (%)	106(24.8)	22(20.2)	27(25.5)	24(22.2)	33(31.7)	0.228
Use of oral hypoglycemic agents or GLP-1RAs, n (%)	307(71.9)	77(70.6)	82(77.4)	83(76.9)	65(62.5)	0.057
Hypertension, n (%)	254(59.5)	67(61.5)	69(65.1)	58(53.7)	60(57.7)	0.362
Hyperlipidemia, n (%)	143(33.5)	45(41.3)	36(34.0)	29(26.9)	33(31.7)	0.153
Use of antihypertensive drugs, n (%)	224(52.5)	59(54.1)	61(57.5)	48(44.4)	56(53.8)	0.325
Use of lipid-lowering drugs, n (%)	79(18.5)	22(20.2)	15(14.2)	21(19.4)	21(20.2)	0.616
Smoking, n (%)	154(36.1)	40(36.7)	39(36.8)	37(34.3)	38(36.5)	0.977
Drinking, n (%)	150(35.1)	43(39.4)	30(28.3)	39(36.1)	38(36.5)	0.362
Vascular complications, n (%)						0.001
Yes	356(83.4)	75(68.8)	90(84.9)	96(88.9)	95(91.3)	
No	71(16.6)	34(31.2)	16(15.1)	12(11.1)	9(8.7)	
Atherosclerosis, n (%)						0.003
Yes	333(80.0)	72(66.1)	82(77.4)	92(85.2)	87(83.7)	
No	94(22.0)	37(33.9)	24(22.6)	16(14.8)	17(16.3)	

(*Continued*)

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Table 1 (Continued).

Characteristics	Total (N=427)	RAR Quartiles				p value
		Q1 (n=109)	Q2 (n=106)	Q3 (n=108)	Q4 (n=104)	
Diabetic nephropathy, n (%)						0.006
Yes	101(23.7)	17(15.6)	23(21.7)	24(22.2)	37(35.6)	
No	326(76.3)	92(84.4)	83(78.3)	84(77.8)	67(64.4)	
Diabetic retinopathy, n (%)						0.395
Yes	127(29.7)	33(30.3)	30(28.3)	27(25.0)	37(35.6)	
No	300(70.3)	76(69.7)	76(71.7)	81(75.0)	67(64.4)	

Abbreviations: Q1, RAR ≤ 3.28; Q2, 3.28< RAR≤3.55; Q3, 3.55< RAR<3.89; Q4:RAR≥ 3.89; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, Glycated hemoglobin A1c; HsCRP, Human hypersensitive C Reactive Protein; TCH, Total cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; URIC, Uric Acid; UACR, urinary albumin/creatinine ratio; RDW, Red blood cell distribution width; LYMPH, Lymphocyte; NEUT, Neutrophils; PLT, Platelet; RAR, Red blood cell distribution width/albumin ratio;

Table 2 Relationship Between RAR and Any Vascular Complications

Variable	Any vascular complication							
	OR (95% CI)[a]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[c]	P-value	OR (95% CI)[d]	P-value
RAR	3.620(1.894,6.921)	<0.001*	3.740(1.797,7.782)	<0.001*	4.001(1.875,8.541)	<0.001*	4.163(1.901,9.113)	<0.001*
Q1	Reference		Reference		Reference		Reference	
Q2	2.550(1.307,4.976)	0.006*	2.681(1.231,5.843)	0.013*	3.181(1.410,7.178)	0.005*	3.073(1.351,6.993)	0.007*
Q3	3.627(1.758,7.481)	<0.001*	2.823(1.231,6.473)	0.014*	3.139(1.312,7.512)	0.010*	3.013(1.261,7.202)	0.013*
Q4	4.785(2.162,10.593)	<0.001*	5.715(2.245,14.53)	<0.001*	6.661(1.513,17.656)	<0.001*	6.702(1.455,18.291)	<0.001*
P-trend		<0.001*		0.001*		0.001*		0.001*

Notes: *P < 0.05 [a]Model 1:unadjusted. [b]Model 2:Adjusted for gender, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia. [c] Model 3:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic medications or GLP-1RA, use of insulin. [d]Model 4:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic agents or GLP-1RA, use of insulin, TCH, TG, HsCRP, Hgb.
Abbreviations: Odds ratios (OR), 95% confidence intervals (95% CI), red cell distribution width/albumin ratio (RAR).

Table 3 Association Between RAR and Atherosclerosis of the Lower Limbs

Variable	Atherosclerosis of the lower limbs							
	OR (95% CI)[a]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[c]	P-value	OR (95% CI)[d]	P-value
RAR	1.787(1.092,2.924)	0.021*	1.652(0.960,2.843)	0.07	1.581(0.906,2.759)	0.107	1.690(0.947,3.016)	0.076
Q1	Reference		Reference		Reference		Reference	
Q2	1.756(0.960,3.210)	0.067	1.741(0.844,3.593)	0.134	1.948(0.925,4.104)	0.079	2.063(0.967,4.400)	0.061
Q3	2.955(1.523,5.732)	0.001*	2.178(0.997,4.759)	0.051	2.279(1.013,5.125)	0.046*	2.434(1.076,5.504)	0.033*
Q4	2.630(1.368,5.056)	0.004*	2.727(1.221,6.094)	0.014*	2.708(1.187,6.175)	0.018*	2.973(1.281,6.901)	0.011*
P-trend		0.001*		0.047*		0.072		0.044*

Notes: *P < 0.05. [a]Model 1:unadjusted. [b]Model 2:Adjusted for gender, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia. [c]Model 3:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic medications or GLP-1RA, use of insulin. [d]Model 4:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic agents or GLP-1RA, use of insulin, TCH, TG, HsCRP, Hgb.
Abbreviations: Odds ratios (OR), 95% confidence intervals (95% CI), red cell distribution width/albumin ratio (RAR).

Table 4 Association Between RAR, Leukocyte Derived Ratio and Diabetic Nephropathy

Variables	Diabetic nephropathy							
	OR (95% CI)[a]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[c]	P-value	OR (95% CI)[d]	P-value
RAR	2.335(1.551,3.516)	<0.001*	2.536(1.605,4.006)	<0.001*	2.364(1.481,3.772)	<0.001*	2.318(1.406,3.821)	0.001*
Q1	Reference		Reference		Reference		Reference	
Q2	1.500(0.750,3.001)	0.252	1.501(0.710,3.176)	0.288	1.565(0.724,3.387)	0.255	1.408(0.631,3.142)	0.403
Q3	1.546(0.777,3.077)	0.214	1.898(0.896,4.024)	0.094	1.971(0.913,4.255)	0.084	1.739(0.778,3.884)	0.177
Q4	2.989(1.553,5.753)	0.001*	3.391(1.639,7.014)	0.001*	3.197(1.513,6.755)	0.002*	2.876(1.315,6.287)	0.008*
P-trend		0.001*		<0.001*		0.001*		0.011*
NLR	1.2921(1.131,1.475)	<0.001*	1.226(1.055,1.425)	0.008*	1.230(1.053,1.437)	0.009*	1.235(1.043,1.463)	0.014*
Q1	Reference		Reference		Reference		Reference	
Q2	1.517(0.680,3.383)	0.308	1.281(0.551,2.980)	0.565	1.470(0.616,3.507)	0.386	1.821(0.733,4.521)	0.179
Q3	3.000(1.433,6.281)	0.004*	2.900(1.328,6.334)	0.008*	2.720(1.206,6.136)	0.016*	3.333(1.417,7.836)	0.006*
Q4	5.893(2.895,11.996)	<0.001*	4.395(1.987,9.723)	<0.001*	4.637(2.030,10.596)	<0.001*	5.495(2.277,13.264)	<0.001*
P-trend		<0.001*		<0.001*		<0.001*		<0.001*

(*Continued*)

Table 4 (Continued).

Variables	Diabetic nephropathy							
	OR (95% CI)[a]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[c]	P-value	OR (95% CI)[d]	P-value
PLR	1.08(1.004,1.011)	<0.001*	1.008(1.004,1.012)	<0.001*	1.008(1.004,1.012)	<0.001*	1.008(1.003,1.012)	0.001*
Q1	Reference		Reference		Reference		Reference	
Q2	2.006(0.910,4.424)	0.084	1.680(0.729,3.872)	0.224	1.685(0.711,3.994)	0.236	1.929(0.791,4.706)	0.149
Q3	2.945(1.376,6.306)	0.005*	2.686(1.203,5.997)	0.016*	2.828(1.234,6.479)	0.014*	3.033(1.290,7.133)	0.011*
Q4	5.957(2.858,12.417)	<0.001*	4.706(2.145,10.326)	<0.001*	4.619(2.051,10.402)	<0.001*	4.450(1.881,10.531)	0.001*
P-trend		0.047*		0.062		0.062		0.074

Notes: *P < 0.05. [a]Model 1:unadjusted. [b]Model 2:Adjusted for gender, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia. [c]Model 3:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic medications or GLP-1RA, use of insulin. [d]Model 4:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic agents or GLP-1RA, use of insulin, TCH, TG, HsCRP, Hgb.
Abbreviations: Odds ratios (OR), 95% confidence intervals (95% CI), red cell distribution width/albumin ratio (RAR), neutrophils/lymphocytes (NLR), platelets/lymphocytes (PLR).

Table 5 Relationship Between RAR, Leukocyte Derived Ratio and UACR (UACR≥30mg/g)

Variables	UACR							
	OR (95% CI)[a]	P-value	OR (95% CI)[b]	P-value	OR (95% CI)[c]	P-value	OR (95% CI)[d]	P-value
RAR	2.234(1.505,3.316)	<0.001*	2.362(1.533,3.640)	<0.001*	2.211(1.428,3.425)	<0.001*	2.073(1.329,3.233)	0.001*
Q1	Reference		Reference		Reference		Reference	
Q2	1.227(0.703,2.142)	0.471	1.160(0.632,2.129)	0.633	1.136(0.615,2.100)	0.683	1.094(0.589,2.032)	0.776
Q3	1.678(0.970,2.902)	0.064	1.638(0.888,3.020)	0.114	1.650(0.890,3.058)	0.112	1.554(0.832,2.903)	0.167
Q4	2.551(1.465,4.443)	0.001*	2.665(1.440,4.931)	0.002*	2.473(1.326,4.615)	0.004*	2.245(1.190,4.235)	0.013*
P-trend		<0.001*		0.001*		0.009*		<0.001*
NLR	1.454(1.250,1.693)	<0.001*	1.263(1.076,1.482)	0.004*	1.237(1.056,1.450)	0.009*	1.210(1.028,1.426)	0.022*
Q1	Reference		Reference		Reference		Reference	
Q2	1.328(0.743,2.376)	0.339	1.009(0.593,2.038)	0.764	1.129(0.604,2.110)	0.705	1.167(0.620,2.195)	0.633
Q3	2.258(1.284,3.972)	0.005*	1.961(1.075,3.577)	0.028*	1.802(0.975,3.333)	0.06	1.867(1.004,3.473)	0.049*
Q4	5.161(2.901,9.183)	<0.001*	3.004(1.588,5.680)	0.001*	2.897(1.522,5.514)	0.001*	2.802(1.449,5.417)	0.002*
P-trend		<0.001*		<0.001*		<0.001*		<0.001*
PLR	1.007(1.004,1.011)	<0.001*	1.005(1.002,1.009)	0.003*	1.005(1.001,1.009)	0.007*	1.004(1.001,1.008)	0.024*
Q1	Reference		Reference		Reference		Reference	
Q2	2.234(1.251,3.992)	0.007*	2.018(1.082,3.763)	0.027*	2.019(1.071,3.806)	0.030*	2.127(1.121,4.038)	0.021*
Q3	2.698(1.514,4.810)	0.001*	2.491(1.341,4.627)	0.004*	2.488(1.330,4.654)	0.004*	2.505(1.330,4.716)	0.004*
Q4	4.341(2.422,7.781)	<0.001*	3.303(1.763,6.189)	<0.001*	3.145(1.668,5.929)	<0.001*	2.992(1.551,5.775)	0.001*
P-trend		0.005*		0.011*		0.013*		0.005*

Notes: *P < 0.05 [a]Model 1:unadjusted. [b]Model 2:Adjusted for gender, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia. [c]Model 3:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic medications or GLP-1RA, use of insulin. [d]Model 4:Adjusted for sex, age, BMI, duration of diabetes, Hb1c, hypertension, hyperlipidemia, smoking, drinking, use of antihypertensive medications, use of lipid-lowering medications, use of oral hypoglycemic agents or GLP-1RA, use of insulin, TCH, TG, HsCRP, Hgb.
Abbreviations: Odds ratios (OR); 95% confidence intervals (95% CI); red cell distribution width/albumin ratio (RAR); neutrophils/lymphocytes (NLR); platelets/lymphocytes (PLR).

Predictive Ability in Diagnosis

In the diagnosis of any vascular complication, ROC curve analysis showed an area under the RAR curve of 0.881 (sensitivity = 83.7%, specificity = 78.9%) (Figure S1). When predicting atherosclerosis of the lower limbs, the AUC of RAR was 0.859 (sensitivity = 74.7%, specificity = 81.7%) (Figure S2). In the diagnosis of diabetic nephropathy, the predictive ability of RAR and NLR was evaluated (PLR was excluded due to its neutral effect). We used RAR, NLR, and RAR+NLR to construct the ROC curve and calculated the AUC. The AUC of RAR was 0.830 (sensitivity = 76.2%, specificity = 78.2%), higher than that of NLR, 0.824 (sensitivity = 78.2%, specificity = 76.1%) (Table 6). The AUC of RAR+NLR was 0.835 (sensitivity = 86.1%, specificity = 67.8%) (Figure 2).

Table 6 ROC Curve Analysis of RAR, NLR for Diagnosis of Diabetic Nephropathy

Variables	AUC	95% CI	Youden's index	Sensibility	Specificity	P-value
RAR	0.83	0.786–0.874	0.544	76.20%	78.20%	<0.001
NLR	0.824	0.780–0.869	0.543	78.20%	76.10%	<0.001
RAR+NLR	0.835	0.793–0.878	0.539	86.10%	67.80%	<0.001

Abbreviations: Odds ratios (OR), 95% confidence intervals (95% CI), red cell distribution width/albumin ratio (RAR), neutrophils/lymphocytes (NLR), area under the curve (AUC).

Discussion

Our study suggested that RAR may be used as a marker for vascular complications of diabetes. In our study, we adjusted for confounding factors using four models. The findings found a strong correlation between RAR and diabetic nephropathy and lower limb atherosclerosis in individuals with diabetes, but no relationship was found between diabetic retinopathy and RAR. Then, the patients were divided into two groups according to UACR and eGFR. Similar results were observed. Inflammation is closely related to the occurrence and development of diabetic nephropathy. In previous studies, NLR and PLR have been proposed as alternative markers of inflammation, and high NLR and PLR can be used as predictors and prognostic risk markers of diabetic nephropathy.[14] Therefore, we proceeded to evaluate the ability of RAR, NLR, and PLR to predict diabetic nephropathy. The findings found that the AUC of RAR was higher than that of NLR.

The red cell distribution width/albumin ratio (RAR) is a novel inflammatory marker that can be easily obtained upon admission to hospital. High RDW (The red cell distribution width) and low albumin are closely linked to enhanced inflammation. RDW is presently thought to be a unique prognostic indicator for oxidative stress and chronic inflammation.[15] Prior research has indicated a connection between RDW and conventional inflammatory biomarkers. There is a strong association between RDW and CRP and ESR. Higher RDW was independently associated with higher CRP.[16] Oxidative stress has a profound effect on erythrocyte homeostasis and survival. Low serum antioxidant concentration was negatively correlated with RDW.[17] RDW, as a hematological indicator, it reflects the degree of heterogeneity in the volume of erythrocyte. Inflammation may promote unequal red blood cell size by affecting red blood cell production, erythrocyte circulatory half-life, and erythrocyte deformability. In addition, endothelial nitric oxide

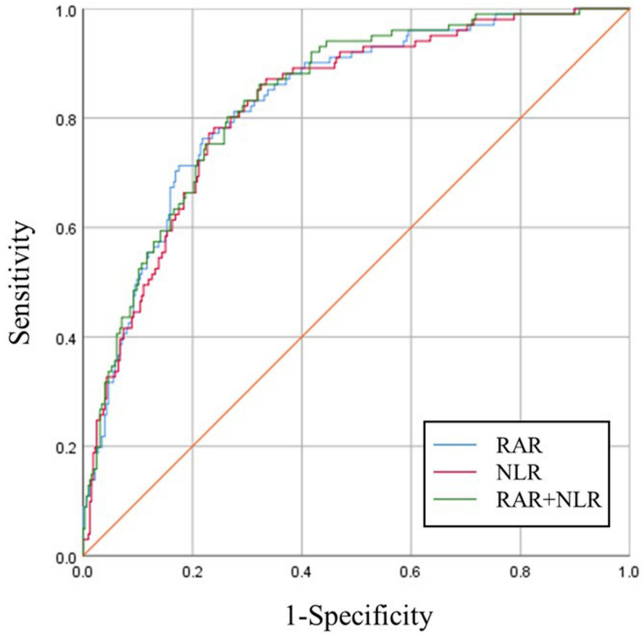

Figure 2 ROC curves of RAR and NLR for predicting diabetic nephropathy.

stimulates the proliferation of erythroid progenitor cells, while inflammatory cytokines may reduce the ability of endothelial nitric oxide production. Thus, inflammatory factors have a significant inhibitory effect on erythroid progenitor cell proliferation. At the same time, inflammation may impair red blood cell maturation through impaired iron metabolism and decreased erythropoietin. Inflammation also reduces red blood cell survival, resulting in a mix of various volumes of erythrocyte.[18] Meanwhile, serum albumin is not only a marker of nutrition but also a marker of inflammation. ALB is involved in controlling the inflammatory response, which can reduce inflammatory response by anti-oxidative stress, binding and transporting inflammatory substances and inflammatory mediators.[19]

Diabetes is a systemic, low-grade, and persistent inflammatory disease. Cytokines such as IL-1, IL-6, and TNF-α are continuously activated in diabetic patients.[20] High blood sugar induces ROS production, which leads to oxidative stress.[21] In individuals with advanced diabetes, the levels of antioxidants (such as α-lipoic acid and vitamin E) were reduced.[2,22] Meanwhile, in diabetes mellitus, increased glycosylation of cell surface proteins, reduced plasma membrane fluidity and decreased erythrocyte deformability increases the vulnerability of erythrocytes to damage.[23] Therefore, we think that RAR is closely related to diabetes. RAR is more predictive than RDW and albumin.[6,7,24] In recent years, it has been shown that RAR is related to the prognosis of diabetic ketoacidosis,[5] diabetic foot,[6] heart failure,[7] stroke,[8] chronic obstructive pulmonary disease (COPD),[25] chronic kidney disease,[24] burn surgery, and other diseases.[26] It is considered a prognostic marker for acute and chronic inflammatory diseases. In our study, we found that increased RAR was associated with diabetic nephropathy, but not with diabetic retinopathy. As stated by Malandrino, the pathogenesis of diabetic nephropathy includes both macrovascular and microvascular mechanisms, and microvascular disease is predominantly present in diabetic retinopathy. RAR as a marker of diabetic nephropathy may primarily reflect macrovascular injury.[13,27] In addition, the process of microvascular inflammation may reflect only local changes in eye tissue and may not be reflected in serum.[28] Diabetic retinopathy may have a weak or absent relationship with systemic markers of inflammation,[13] while high RAR was considered to be associated with systemic inflammation. In addition, increased tension due to high intraglomerular pressure leads to erythrocyte fragmentation, which results in increased RDW.[15] Moreover, red blood cell deformability is decreased in diabetic nephropathy patients, and this loss of deformability further leads to red blood cell fragmentation.[29,30] Meanwhile, in our study, an elevated risk of lower limb atherosclerosis was substantially correlated with RAR, and this correlation persisted even after multifactor correction. Prior research has demonstrated that high RDW is associated with the risk of carotid atherosclerosis.[31] RAR can be used as a predictor of carotid plaque formation. In a study of 107,301 patients with coronary heart disease, RAR was discovered to have a substantial correlation with carotid plaque in individuals suffering from coronary heart disease (CHD). Especially in individuals with diabetes, RAR was more associated with carotid plaque. Atherosclerosis is an inflammatory disease. Chronic high blood sugar is known to accelerate atherosclerosis by increasing oxidative stress. Diabetes accelerates atherosclerosis by inducing oxygen-free radicals and promoting inflammation.[32]

Type 2 diabetes mellitus is increasing worldwide, and its complications place a huge economic and health burden on the world's healthcare systems. RAR can be obtained simply and swiftly during a laboratory test. It can be carried out at all levels of medical care. It is repeatable, widely used, easy to measure, and low cost. RAR may help in early identification of individuals with complications of T2DM for secondary prevention. For example, early identification of the diabetic kidney without obvious symptoms allows these patients may benefit from early treatment with RAAS (renin-angiotensin-aldosterone system) drugs. Limitations of this article include: First because this is a cross-sectional study and the sample size is small, it is difficult to conclude causality. So this relationship needs to be validated in future prospective studies. Second, although we account for some potential confounders in the regression model, it is still possible to be influenced by other confounders that are not measured. Finally, our results support RAR as a clinical marker of vascular problems in T2DM even if it may not be associated with the development of these complications and cannot pinpoint the precise pathophysiological process underlying the study's findings.

Conclusion

We found that among T2DM patients, a higher RAR was linked to a higher risk of lower limb atherosclerosis and diabetic nephropathy. RAR may be significant clinical indicator of vascular complications in diabetes. This may provide

clinical guidance for identifying high-risk Individuals. Future large-scale prospective trials are needed to confirm these findings.

Data Sharing Statement

The data are not publicly available due to their containing information that could compromise the privacy of patients. All data supporting this study will be provided by the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was conducted according to the guidelines of the Declaration of Helsinki. This study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Jinan University. Informed consent was waived due to this study's retrospective nature and the anonymized processing of patient data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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