• Investigation •

Association between blood urea nitrogen to albumin ratio and diabetic retinopathy: insights from the US National Health and Nutrition Examination Survey

Fei-Fei Dai, Jian-Dong Pan, Xiao-Jie He

National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China

Correspondence to: Xiao-Jie He. National Clinical Research Center for Ocular Diseases, Eye Hospital, Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China. hexj@eye.ac.cn

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Abstract

● **AIM:** To investigate whether blood urea nitrogen to serum albumin ratio (BAR) influences the onset and progression of diabetic retinopathy (DR) in diabetic patients.

● **METHODS:** The diabetic individuals were extracted from the National Health and Nutrition Examination Survey (NHANES) database spanning 1999 to 2018. The BAR was calculated as the ratio of blood urea nitrogen to serum albumin. To evaluate the association between BAR levels and DR, a generalized additive model and multivariate logistic regression analysis were performed. Additionally, subgroup analyses were conducted to determine whether other factors modified this association.

● **RESULTS:** The number of eligible individuals in the current research endeavor equaled 5798. The resulting data were indicative of the existence of a nearly linearly positive relationship between BAR levels and DR. Following confounding variable adjustment (age, gender, marital status, red blood cell, hemoglobin, lactate dehydrogenase, uric acid, creatinine, gender, red cell distribution width, high-density lipoprotein, glucose, sodium, glycated hemoglobin, hypertension, and total cholesterol), the multivariate investigation implied that an elevated DR risk correlated with elevated levels of BAR (OR: 1.46, 95%CI: 1.20-1.79). This relationship was noted to be reliable and stable across diverse analyses, following the conduction of sensitivity analysis (*P* for trend: 0.0002). Subgroup analysis showed no statistically significant interactions between BAR and most other risk factors for DR.

● **CONCLUSION:** The study provides evidence of a positive association between elevated BAR levels and an increased risk of DR in diabetic individuals.

● **KEYWORDS:** blood urea nitrogen to albumin ratio; diabetic retinopathy; diabetes mellitus; National Health and Nutrition Examination Survey

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INTRODUCTION

Diabetic retinopathy (DR) is a significant global health issue that arises as a complication of diabetes. This condition profoundly impacts the quality of life of affected individuals, as it remains the leading cause of impaired vision and blindness worldwide[1]. The prevalence of DR varies significantly across different regions, ranging from 18% in India to 40% in the United States[2], highlighting substantial disparities in the burden of this disease among diabetic populations globally. On a global scale, approximately 34.6% of individuals with diabetes are affected by DR, with nearly 1 in 10 at risk of developing sight-threatening complications[3]. The far-reaching consequences of DR, including vision loss and associated financial burdens, classify it as a critical public health concern[3]. Projections indicate a rising trend, with DR cases expected to reach 16 million by 2050, accompanied by an annual economic burden of approximately $500 million[4]. Given the global burden of diabetes and the anticipated rise in DR prevalence, identifying risk factors for DR development is essential for early intervention to prevent visual impairment and blindness.

Research has established associations between DR and multiple metabolic and inflammatory markers in individuals with type 2 diabetes mellitus (DM). These markers include serum vitamin D levels[5], the uric acid-to-high-density lipoprotein cholesterol ratio[6], and omentin levels[7]. Inflammatory parameters such as the platelet-to-lymphocyte ratio[8] and the C-reactive protein-to-

serum albumin ratio[9] have also been linked to DR progression. Pathological mechanisms underlying DR involve complex interactions, including diabetic macular edema, intraocular neovascularization, and proliferative vitreoretinopathy[10-11]. Among these mechanisms, inflammation and microangiopathy play pivotal roles in DR pathogenesis[12-13]. Over the past few decades, substantial research efforts have been directed toward developing therapeutic strategies to prevent and slow the progression of DR.

Biochemical indicators are routinely used to assess clinical status, with blood urea nitrogen (BUN) being one such critical marker. BUN levels reflect key physiological states, including dehydration, low cardiac output, neurohumoral activation, and renal hypoperfusion[14-16]. In elderly populations, elevated BUN levels have been identified as independent predictors of mortality[17]. Albumin, the primary serum protein, is integral to numerous physiological processes, serving as a marker of nutritional status and organ function across diverse clinical scenarios[18-19]. Low serum albumin levels have been associated with increased risks of hospital readmission and all-cause mortality, particularly in elderly populations[20-21]. Recently, the blood urea nitrogen to serum albumin ratio (BAR) has emerged as a novel biomarker, combining two important predictors—urea nitrogen and albumin. Studies have demonstrated the predictive value of BAR in diverse diseases, including aspiration pneumonia, acute pulmonary embolism, among others[22-24]. However, the potential role of BAR in predicting the onset and progression of DR remains largely unexplored. Therefore, the primary objective of the present study is to evaluate the utility of BAR as a predictive biomarker for DR onset and progression in individuals with diabetes.

PARTICIPANTS AND METHODS

Ethical Approval The protocols for the conduct of NHANES were approved by the NCHS institutional review board. The Johns Hopkins Medical Institutions Institutional Review Board reviewed and approved the study (NCHS IRB/ERB Protocol Number: #98-12, #2005-06, #2011-17, #2018-01). Informed written consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

Data Source The National Health and Nutrition Examination Survey (NHANES) database is a comprehensive resource, offering a meticulously designed, clustered, stratified, multistage, cross-sectional probability sample. This sample is intentionally restricted to non-institutionalized U.S. civilians and is conducted under the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention (CDC). Between the years 1988 and 1994, the NHANES III survey was carried out, whereas the recent NHANES survey spanned from 1999 to 2020, with the data released in a 2-year interval. The survey follows a specific procedure. Initially, the participants are required to give an in-home interview, after which their health assessment is performed at mobile examination centers. The process encompasses an evaluation of the clinical and physiological parameters, with subsequent laboratory assessment. This research dealt with the 1999 to 2018 NHANES DM data. To ensure data integrity and relevance, the following criteria were applied for exclusion: participants under 18 years of age, no BUN or albumin measured, and having more than 5% missing data.

Study Variables The data isolated in this research encompassed marital status, gender, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), BUN, albumin, total cholesterol, high-density lipoprotein, triglycerides, white blood cell (WBC), neutrophil percentage, lymphocyte percent, monocyte percent, red blood cell (RBC), hemoglobin, hematocrit, red cell distribution width (RDW), platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase, globulin, total bilirubin, bicarbonate, glutamyl transpeptidase (GGT), glucose, glycated hemoglobin, uric acid, total calcium, potassium, iron, chloride, creatinine, sodium, hypertension, phosphorus, and DR. BAR was expressed as BUN/albumin.

Statistical Analysis In this analysis, the χ^2 test was employed to comparatively assess the variation in baseline characteristics between the DR and non-DR groups for categorical variables, while the independent-sample *t*-test was utilized for continuous variables. Further assessment of the association of BAR with DR was done *via* multivariate logistic regression analysis. Quantification of the odds ratio (OR) and calculation of the 95% confidence intervals (CI) were executed. To adhere to the guidelines outlined in the STROBE statement[25], both the fully and minimally adjusted results were presented. Notably, the matched OR experienced an alteration exceeding 10% when covariates were introduced into this model[26]. Generalized additive models were utilized for the determination of linear relationships between BAR and the incidence of DR. Furthermore, subgroup analysis was conducted *via* a stratified linear regression model in order to ascertain the impact of BAR levels on DR. $P<0.05$ (two-sided) was deemed to represent statistical significance. The analyses were conducted utilizing EmpowerStats (http://www.empowerstats.com/en/, X&Y Solutions, Inc., Boston, MA, USA) and R language (http://www.R-project.org) software.

RESULTS

Characteristics of the Subjects In total, 5798 individuals with diabetes who fit the study requirements were retrieved. The study involved classifying the finalized individuals into

tertiles per their BAR scores. Among the total individuals under study, men were 2991 in number while 2807 participants were women. Overall, 1278 of the individuals were diagnosed with DR (22.04%). An overview of the baseline features is provided in Table 1. Individuals with higher BAR (BAR ≥157.7 mmol/kg) were generally older and had higher values of SBP, neutrophil percentage, monocyte percent, RDW, LDH, alkaline phosphatase, globulin, uric acid, creatinine, sodium, potassium, and chloride.

BAR's Relation to the Risk of DR The association of BAR levels with DR was nearly positive linear (Figure 1). The correlation between BAR and the risk of DR was investigated through a logistic multivariate regression model (Table 2). In model I, following correction (age, gender, and marital status), elevated BAR levels were linked to the increase in the risk of DR (OR: 2.12, 95%CI: 1.79-2.51, P<0.0001). In model II, after accounting for confounding variables (age, gender, marital status, RBC, hemoglobin, LDH, uric acid, creatinine, gender, RDW, high-density lipoprotein, glucose, sodium, glycated hemoglobin, hypertension, total cholesterol), increased BAR levels were noted to be linked to elevation in the risk of DR (OR: 1.46, 95%CI: 1.20-1.79). The relationship was noted to be stable and consistent following sensitivity analysis (P for trend: 0.0002).

Subgroup Analyses As shown in Table 3, the test for interactions was statistically significant in several strata (P for interaction <0.05). Notably, across these strata, it was noted that individuals with elevated BARs had an independent relationship with DR in RBC<4.6×10^{12}/L, hemoglobin <13.8 g/dL, hematocrit <40.8%, RDW ≥13.3%, and creatinine ≥79 μmol/L.

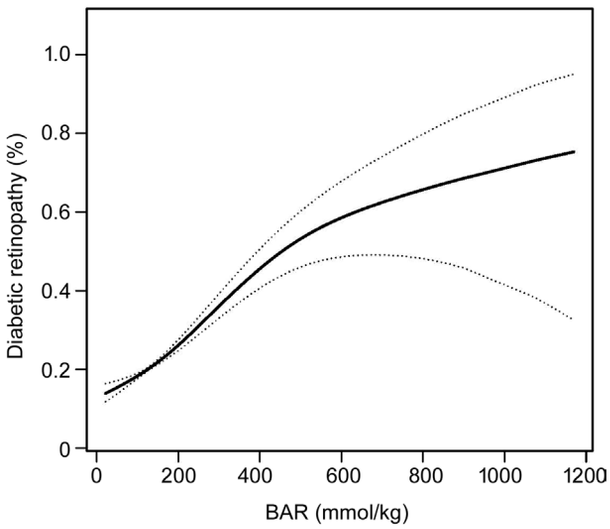

Figure 1 Incidence of DR across different levels of the BAR The X-axis represents BAR levels, while the Y-axis represents the incidence rate of DR among diabetic patients. The solid black line indicates the mean incidence rate, and the dotted lines represent the 95% confidence intervals.

DISCUSSION

Our study observed a nearly linear positive association between BAR levels and the risk of DR. In fully adjusted models, higher BAR levels remained significantly associated with an increased risk of DR. To our knowledge, this appears to be the initial step toward measuring the association between BAR and the risk of DR in diabetic individuals.

Previous research has explored the potential association between BUN levels and DR, with findings supporting a positive relationship. Wu *et al*[27] conducted a multifactorial logistic regression analysis involving 298 patients and demonstrated that BUN was independently associated with DR risk, even after adjusting for covariates. Similarly, Zhang *et al*[28] reported a positive correlation between BUN levels and DR prevalence in patients with type 2 diabetes. However, the underlying mechanisms linking BUN levels to DR remain incompletely understood. Elevated BUN levels are commonly observed in patients with diabetic nephropathy, suggesting that BUN may reflect impaired renal function and glucose dysregulation[29]. Chronic hyperglycemia can trigger increased oxidative stress, inflammation, and endothelial dysfunction, which are common pathological mechanisms underlying both diabetic nephropathy and DR[30-31]. Notably, these two conditions frequently coexist[32-33]. Increased BUN levels may therefore serve as an indirect marker for oxidative stress and a hypercoagulable state, both of which contribute to DR pathogenesis[34]. Microvascular hypoperfusion and oxidative stress are pivotal processes in DR development[35], which may explain the observed elevation in BUN levels in DR patients.

Serum albumin, on the other hand, exhibits well-recognized protective properties, including anti-inflammatory, antioxidant, and immune-modulating effects[36]. Inflammation is believed to play a critical role in every stage of vascular sclerosis, contributing to the progression of microvascular complications in diabetes[37-38]. Albumin has been shown to inhibit tumor necrosis factor-α-induced expression of vascular cell adhesion molecule-1 and reduce monocyte adhesion to endothelial cells, demonstrating its anti-inflammatory potential[39]. Additionally, albumin acts as a key extracellular antioxidant, and hypoalbuminemia has been associated with increased free radical and reactive oxygen species levels[40]. Additionally, albumin serves as a protective factor for endothelial cell function and the maintenance of vascular integrity[41]. These aspects are strongly linked to microvascular complications in type 2 DM[42].

The BAR serves as a combined biomarker that integrates the predictive potential of both BUN and albumin, offering a simple, cost-effective, and rapid assessment tool. This makes it particularly valuable in resource-limited healthcare settings. Our findings demonstrated that the association between BAR and DR risk remained statistically significant after adjusting

Table 1 Characteristics of the study patients according to BAR

Characteristics	BAR, mmol/kg			
	<109.8 (*n*=1932)	≥109.8, <157.7 (*n*=1933)	≥157.7 (*n*=1933)	*P*
Age, y	54.90±14.22	61.79±12.60	68.20±10.74	<0.001
Gender, *n* (%)				<0.001
Female	1045 (54.09)	879 (45.47)	883 (45.68)	
Male	887 (45.91)	1054 (54.53)	1050 (54.32)	
Marital status, *n* (%)				0.002
Married	1037 (53.67)	1131 (58.51)	1038 (53.70)	
Other	895 (46.33)	802 (41.49)	895 (46.30)	
SBP, mm Hg	130.76±19.60	132.58±19.52	136.36±23.38	<0.001
DBP, mm Hg	71.81±13.13	68.97±14.07	64.30±16.24	<0.001
BMI, kg/m^2	31.92±7.35	31.91±7.07	32.38±7.82	0.258
BAR, mmol/kg	85.72±16.74	132.00±13.58	237.46±101.08	<0.001
Blood urea nitrogen, mmol/L	3.60±0.76	5.48±0.68	9.33±3.55	<0.001
Albumin, g/dL	4.20±0.34	4.15±0.32	3.98±0.38	<0.001
Total cholesterol, mmol/L	4.92±1.17	4.80±1.17	4.64±1.17	<0.001
High density lipoprotein, mmol/L	1.26±0.38	1.24±0.35	1.24±0.37	0.340
Triglycerides, mmol/L	2.13±1.85	2.15±1.74	2.08±1.43	0.523
WBC, 10^9 /L	7.58±2.21	7.47±2.06	7.69±2.61	0.162
Neutrophil percentage, %	57.91±9.62	58.97±8.88	61.24±9.84	<0.001
Lymphocyte percent, %	31.20±8.86	29.56±8.18	26.72±9.02	<0.001
Monocyte percent, %	7.49±2.27	7.89±2.18	8.20±2.35	<0.001
RBC, 10^{12}/L	4.73±0.49	4.67±0.49	4.39±0.57	<0.001
Hemoglobin, g/dL	14.08±1.53	13.95±1.48	13.16±1.63	<0.001
Hematocrit, %	41.66±4.21	41.35±4.21	39.18±4.73	<0.001
RDW, %	13.40±1.43	13.47±1.25	13.95±1.63	<0.001
Platelet, 10^9/L	256.51±75.20	242.54±68.47	234.37±72.84	<0.001
ALT, U/L	26.82±19.01	26.10±24.67	23.18±34.00	<0.001
AST, U/L	26.13±16.81	25.55±23.90	24.39±18.17	<0.001
LDH, U/L	132.40±30.58	137.82±41.32	149.49±38.90	<0.001
Alkaline phosphatase, U/L	77.66±30.00	77.21±32.88	80.79±37.52	0.008
Globulin, g/L	30.54±4.93	30.46±4.96	31.36±5.40	<0.001
Total bilirubin, μmol/L	10.98±4.81	10.70±4.94	10.46±5.09	<0.001
Bicarbonate, mmol/L	25.06±2.41	25.00±2.41	24.71±2.73	<0.001
GGT, U/L	39.10±55.89	35.13±46.29	34.91±46.79	<0.001
Glucose, mmol/L	8.52±4.17	8.56±4.19	8.62±4.30	0.552
Glycated hemoglobin, %	7.49±1.92	7.49±1.83	7.38±1.68	0.689
Uric acid, μmol/L	306.23±78.66	329.29±84.51	382.03±104.34	<0.001
Creatinine, μmol/L	68.34±17.25	79.23±26.04	129.71±111.35	<0.001
Sodium, mmol/L	138.68±2.82	138.85±2.82	139.11±3.01	<0.001
Potassium, mmol/L	3.99±0.35	4.07±0.36	4.26±0.46	<0.001
Chloride, mmol/L	102.14±3.39	102.10±3.42	102.45±4.00	0.001
Phosphorus, mmol/L	1.20±0.17	1.18±0.19	1.22±0.22	<0.001
Total calcium, mmol/L	2.37±0.10	2.36±0.10	2.35±0.12	<0.001
Iron, μmol/L	14.25±5.86	14.22±5.82	13.15±5.15	<0.001
Hypertension, *n* (%)				<0.001
No	1141 (59.06)	1300 (67.25)	1479 (76.51)	
Yes	791 (40.94)	633 (32.75)	454 (23.49)	
Diabetic retinopathy, *n* (%)				<0.001
No	1604 (83.02)	1543 (79.82)	1373 (71.03)	
Yes	328 (16.98)	390 (20.18)	560 (28.97)	

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; BAR: Blood urea nitrogen-to-albumin ratio; WBC: White blood cell; RBC: Red blood cell; RDW: Red cell distribution width; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; GGT: Glutamyl transpeptidase.

Table 2 ORs (95%CIs) for DR across groups of BAR level

BAR (tertiles), mmol/kg	Model I		Model II	
	OR (95%CIs)	*P*	OR (95%CIs)	*P*
<109.8	1.0 (ref)		1.0 (ref)	
≥109.8, <157.7	1.28 (1.08, 1.51)	0.0038	1.17 (0.98, 1.40)	0.0762
≥157.7	2.12 (1.79, 2.51)	<0.0001	1.46 (1.20, 1.79)	0.0002
P trend	<0.0001		0.0002	

OR: Odds ratio; CI: Confidence interval; BAR: Blood urea nitrogen to serum albumin ratio; DR: Diabetic retinopathy. Models were derived from logistic multivariate regression models. Adjust I model adjust for: age, gender and marital status. Adjust II model adjust for: age, gender, marital status, red blood cell, hemoglobin, lactate dehydrogenase, uric acid, creatinine, gender, red cell distribution width, high density lipoprotein, glucose, sodium, glycated hemoglobin, hypertension, total cholesterol.

Table 3 Subgroup analysis of the associations between BAR and DR

Characteristic	BAR, mmol/kg			*P* for interaction
	<109.8	≥109.8, <157.7	≥157.7	
Age, y				0.9446
<62	1.0 (ref)	1.24 (1.00, 1.53)	2.26 (1.79, 2.85)	
≥62	1.0 (ref)	1.28 (0.98, 1.67)	2.01 (1.58, 2.56)	
Gender				0.0516
Female	1.0 (ref)	1.35 (1.06, 1.70)	2.41 (1.94, 3.01)	
Male	1.0 (ref)	1.12 (0.89, 1.40)	1.65 (1.33, 2.05)	
Marital status				0.0350
Married	1.0 (ref)	1.03 (0.82, 1.28)	1.87 (1.52, 2.31)	
Other	1.0 (ref)	1.56 (1.23, 1.99)	2.15 (1.71, 2.70)	
SBP, mm Hg				0.8150
<128	1.0 (ref)	1.35 (1.06, 1.74)	2.14 (1.68, 2.73)	
≥128	1.0 (ref)	1.18 (0.93, 1.50)	1.77 (1.41, 2.21)	
DBP, mm Hg				0.2837
<69	1.0 (ref)	1.32 (1.01, 1.72)	2.09 (1.65, 2.67)	
≥69	1.0 (ref)	1.22 (0.97, 1.54)	1.72 (1.35, 2.18)	
BMI, kg/m^2				0.6457
<30.8	1.0 (ref)	1.21 (0.96, 1.52)	1.83 (1.47, 2.28)	
≥30.8	1.0 (ref)	1.23 (0.97, 1.56)	2.08 (1.67, 2.60)	
Total cholesterol, mmol/L				0.4302
<4.64	1.0 (ref)	1.46 (1.14, 1.86)	2.21 (1.76, 2.78)	
≥4.64	1.0 (ref)	1.08 (0.87, 1.35)	1.85 (1.49, 2.30)	
High density lipoprotein, mmol/L				0.6696
<1.18	1.0 (ref)	1.18 (0.93, 1.48)	1.89 (1.52, 2.35)	
≥1.18	1.0 (ref)	1.30 (1.03, 1.63)	2.09 (1.68, 2.60)	
Triglycerides, mmol/L				0.7557
<1.7	1.0 (ref)	1.16 (0.92, 1.46)	1.93 (1.55, 2.40)	
≥1.7	1.0 (ref)	1.31 (1.04, 1.64)	2.06 (1.66, 2.56)	
WBC, 10^9 /L				0.1352
<7.2	1.0 (ref)	1.36 (1.08, 1.72)	2.29 (1.83, 2.86)	
≥7.2	1.0 (ref)	1.13 (0.90, 1.42)	1.76 (1.42, 2.18)	
Neutrophil percentage, %				0.8528
<59.8	1.0 (ref)	1.34 (1.08, 1.67)	1.85 (1.48, 2.32)	
≥59.8	1.0 (ref)	1.12 (0.88, 1.43)	2.08 (1.68, 2.59)	
Lymphocyte percent, %				0.5998
<28.5	1.0 (ref)	1.12 (0.88, 1.44)	2.03 (1.62, 2.53)	
≥28.5	1.0 (ref)	1.33 (1.08, 1.66)	1.90 (1.52, 2.38)	
Monocyte percent, %				0.4911
<7.6	1.0 (ref)	1.16 (0.93, 1.46)	1.91 (1.54, 2.38)	
≥7.6	1.0 (ref)	1.32 (1.04, 1.67)	2.09 (1.68, 2.61)	
RBC, 10^{12}/L				0.0112
<4.6	1.0 (ref)	1.60 (1.25, 2.05)	2.31 (1.84, 2.91)	
≥4.6	1.0 (ref)	0.99 (0.80, 1.23)	1.63 (1.30, 2.05)	
Hemoglobin, g/dL				0.0020
<13.8	1.0 (ref)	1.50 (1.17, 1.92)	2.29 (1.83, 2.86)	
≥13.8	1.0 (ref)	1.04 (0.84, 1.30)	1.56 (1.24, 1.96)	
Hematocrit, %				0.0034
<40.8	1.0 (ref)	1.53 (1.20, 1.96)	2.30 (1.84, 2.88)	
≥40.8	1.0 (ref)	1.03 (0.83, 1.28)	1.59 (1.27, 2.00)	

Table 3 Subgroup analysis of the associations between BAR and DR (continued)

Characteristic	BAR, mmol/kg			*P* for interaction
	<109.8	≥109.8, <157.7	≥157.7	
RDW, %				0.0176
<13.3	1.0 (ref)	1.25 (1.00, 1.56)	1.64 (1.30, 2.06)	
≥13.3	1.0 (ref)	1.25 (0.98, 1.59)	2.36 (1.90, 2.94)	
Platelet, 10^9/L				0.5969
<236	1.0 (ref)	1.25 (0.98, 1.59)	2.07 (1.65, 2.59)	
≥236	1.0 (ref)	1.24 (0.99, 1.54)	1.96 (1.58, 2.43)	
ALT, U/L				0.1499
<21	1.0 (ref)	1.34 (1.05, 1.71)	2.21 (1.77, 2.77)	
≥21	1.0 (ref)	1.16 (0.93, 1.44)	1.74 (1.40, 2.17)	
AST, U/L				0.3056
<22	1.0 (ref)	1.19 (0.94, 1.52)	2.05 (1.64, 2.57)	
≥22	1.0 (ref)	1.27 (1.02, 1.59)	1.91 (1.55, 2.37)	
LDH, U/L				0.4103
<135	1.0 (ref)	1.23 (0.97, 1.55)	1.72 (1.35, 2.19)	
≥135	1.0 (ref)	1.24 (0.97, 1.60)	2.10 (1.67, 2.63)	
Alkaline phosphatase, U/L				0.0570
<73	1.0 (ref)	1.36 (1.06, 1.74)	1.76 (1.38, 2.25)	
≥73	1.0 (ref)	1.16 (0.92, 1.47)	2.23 (1.80, 2.76)	
Globulin, g/L				0.0639
<30	1.0 (ref)	0.96 (0.75, 1.24)	1.75 (1.38, 2.23)	
≥30	1.0 (ref)	1.48 (1.19, 1.83)	2.17 (1.77, 2.66)	
Total bilirubin, μmol/L				0.3578
<10.26	1.0(ref)	1.14 (0.89, 1.46)	1.99 (1.59, 2.50)	
≥10.26	1.0(ref)	1.31 (1.05, 1.63)	1.97 (1.60, 2.43)	
Bicarbonate, mmol/L				0.5844
<25	1.0 (ref)	1.18 (0.91, 1.53)	1.85 (1.45, 2.34)	
≥25	1.0 (ref)	1.27 (1.03, 1.57)	2.11 (1.72, 2.58)	
GGT, U/L				0.4921
<24	1.0 (ref)	1.38 (1.08, 1.75)	2.08 (1.66, 2.61)	
≥24	1.0 (ref)	1.13 (0.91, 1.41)	1.97 (1.59, 2.43)	
Glucose, mmol/L				0.8774
<7.33	1.0 (ref)	1.13 (0.88, 1.44)	1.89 (1.50, 2.37)	
≥7.33	1.0 (ref)	1.33 (1.07, 1.65)	2.08 (1.69, 2.56)	
Glycated hemoglobin, %				0.6619
<7	1.0 (ref)	1.30 (1.01, 1.68)	2.06 (1.62, 2.62)	
≥7	1.0 (ref)	1.20 (0.97, 1.48)	1.97 (1.61, 2.42)	
Uric acid, μmol/L				0.5115
<325	1.0 (ref)	1.22 (0.98, 1.51)	1.95 (1.55, 2.45)	
≥325	1.0 (ref)	1.29 (1.00, 1.65)	2.11 (1.68, 2.65)	
Creatinine, μmol/L				0.0319
<79	1.0 (ref)	1.21 (0.98, 1.48)	1.39 (1.05, 1.84)	
≥79	1.0 (ref)	1.43 (1.07, 1.92)	2.57 (1.97, 3.36)	
Sodium, mmol/L				0.7885
<139	1.0 (ref)	1.36 (1.07, 1.72)	2.27 (1.79, 2.86)	
≥139	1.0 (ref)	1.15 (0.92, 1.43)	1.84 (1.50, 2.26)	
Potassium, mmol/L				0.6849
<4.1	1.0 (ref)	1.13 (0.90, 1.41)	1.88 (1.49, 2.38)	
≥4.1	1.0 (ref)	1.35 (1.06, 1.72)	2.06 (1.65, 2.56)	
Chloride, mmol/L				0.9487
<102.2	1.0 (ref)	1.18 (0.94, 1.46)	1.88 (1.52, 2.33)	
≥102.2	1.0 (ref)	1.31 (1.02, 1.67)	2.16 (1.72, 2.70)	
Phosphorus, mmol/L				0.1062
<1.19	1.0 (ref)	1.27 (1.01, 1.59)	1.78 (1.42, 2.23)	
≥1.19	1.0 (ref)	1.20 (0.95, 1.51)	2.18 (1.77, 2.69)	
Total Calcium, mmol/L				0.0508
<2.34	1.0 (ref)	1.10 (0.86, 1.43)	2.15 (1.70, 2.70)	
≥2.34	1.0 (ref)	1.33 (1.08, 1.65)	1.81 (1.47, 2.24)	
Iron, μmol/L				0.3188
<13.08	1.0 (ref)	1.30 (1.03, 1.65)	2.17 (1.75, 2.69)	
≥13.08	1.0 (ref)	1.17 (0.94, 1.47)	1.77 (1.42, 2.22)	
Hypertension				0.0747
No	1.0 (ref)	1.11 (0.91, 1.36)	1.95 (1.62, 2.35)	
Yes	1.0 (ref)	1.47 (1.12, 1.94)	1.78 (1.33, 2.38)	

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WBC: White blood cell; RBC: Red blood cell; RDW: Red cell distribution width; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; GGT: Glutamyl transpeptidase; BAR: Blood urea nitrogen to serum albumin ratio; DR: Diabetic retinopathy.

for multiple covariates, including age, sex, marital status, RBC, hemoglobin, LDH, uric acid, creatinine, RDW, high-density lipoprotein, glucose, sodium, glycated hemoglobin, hypertension, and total cholesterol. The robustness of this association across sensitivity analyses suggests the reliability of our results. The simplicity of BAR as an indicator also allows for individualized risk assessment and supports tailored treatment strategies, enabling more efficient allocation of healthcare resources. As a marker reflecting both inflammation and nutritional status, BAR holds promise as a novel and independent predictor for DR development.

Nevertheless, this study has several limitations. First, the inherent constraints of observational studies make it challenging to eliminate residual confounding factors completely, despite statistical adjustments. Second, data extraction was challenging and labor-intensive, and the exclusion of numerous variables due to incomplete data may have introduced bias. Third, the cross-sectional design of this study prevents the establishment of a causal relationship between BAR levels and DR risk. Prospective cohort studies are required to confirm these findings and elucidate causal pathways. At last, our analysis relied on a single blood test measurement of BAR, whereas longitudinal assessments with repeated measurements could provide more robust insights.

In conclusion, in diabetic individuals, it was noted that elevated BAR is correlated with a higher risk of suffering from DR. Nevertheless, these findings require validation through prospective multicenter studies to establish BAR as a reliable predictive biomarker for DR.

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Data Availability Statement: The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. All data were downloaded from the NHANES website (http:// www.cdc.gov/nchs/Nhanes).

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REFERENCES

1 Lin KY, Hsih WH, Lin YB, *et al*. Update in the epidemiology, risk factors, screening, and treatment of diabetic retinopathy. *J Diabetes Investig* 2021;12(8):1322-1325.

2 Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet* 2010;376(9735):124-136.

3 Wang LZ, Cheung CY, Tapp RJ, *et al*. Availability and variability in guidelines on diabetic retinopathy screening in Asian countries. *Br J Ophthalmol* 2017;101(10):1352-1360.

4 Nagda D, Mitchell W, Zebardast N. The functional burden of diabetic retinopathy in the United States. *Graefes Arch Clin Exp Ophthalmol* 2021;259(10):2977-2986.

5 Pittas AG, Kawahara T, Jorde R, *et al*. Vitamin D and risk for type 2 diabetes in people with prediabetes. *Ann Intern Med* 2023;176(3):355-363.

6 Aktas G, Kocak MZ, Bilgin S, *et al*. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. *Aging Male* 2020;23(5):1098-1102.

7 Kazemzadeh K, Bayani M, Khademi R, *et al*. Association of serum omentin levels with microvascular complications of type 2 diabetes mellitus: a systematic review and meta-analysis. *J Diabetes Metab Disord* 2024;23(1):239-249.

8 Liu Y, Wang X, Wang L, *et al*. Platelet-to-lymphocyte ratio predicts the presence of diabetic neurogenic bladder. *Diabetes Metab Syndr Obes* 2022;15:7-13.

9 Bilgin S, Kurtkulagi O, Atak Tel BM, *et al*. Does C-reactive protein to serum albumin ratio correlate with diabetic nephropathy in patients with type 2 diabetes mellitus? The CARE TIME study. *Prim Care Diabetes* 2021;15(6):1071-1074.

10 Kutlutürk Karagöz I, Allahverdiyev A, Bağırova M, *et al*. Current approaches in treatment of diabetic retinopathy and future perspectives. *J Ocul Pharmacol Ther* 2020;36(7):487-496.

11 Lechner J, O'Leary OE, Stitt AW. The pathology associated with diabetic retinopathy. *Vision Res* 2017;139:7-14.

12 Sorour OA, Levine ES, Baumal CR, *et al*. Persistent diabetic macular edema: Definition, incidence, biomarkers, and treatment methods. *Surv Ophthalmol* 2023;68(2):147-174.

13 Yue T, Shi Y, Luo SH, *et al*. The role of inflammation in immune system of diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. *Front Immunol* 2022;13:1055087.

14 Richter B, Sulzgruber P, Koller L, *et al*. Blood urea nitrogen has additive value beyond estimated glomerular filtration rate for prediction of long-term mortality in patients with acute myocardial infarction. *Eur J Intern Med* 2019;59:84-90.

15 Emami A, Javanmardi F, Rajaee M, *et al*. Predictive biomarkers for acute kidney injury in burn patients. *J Burn Care Res* 2019;40(5):601-605.

16 Zhao DM, Liu YL, Chen SH, *et al*. Predictive value of blood urea nitrogen to albumin ratio in long-term mortality in intensive care unit patients with acute myocardial infarction: a propensity score matching analysis. *Int J Gen Med* 2022;15:2247-2259.

17 Park HJ, Woo SH, Kim DH, Seol SH, Lee JY, Lee WJ, Hong S, Cha K, Youn CS, Park S. Efficacy of blood urea nitrogen and the neutrophil-to-lymphocyte ratio as predictors of mortality among elderly patients with genitourinary tract infections: a retrospective multicentre study. *J Infect Chemother* 2021;27(2):312-318.

18 Wiedermann CJ, Wiedermann W, Joannidis M. Causal relationship between hypoalbuminemia and acute kidney injury. *World J Nephrol* 2017;6(4):176-187.

19 Amri F, Rahaoui M, Aissaoui H, *et al*. Is serum albumin a pivotal biomarker in anticipating acute pancreatitis outcomes? *BMC Gastroenterol* 2024;24(1):234.

20 Wu CY, Hu HY, Huang N, *et al*. Albumin levels and cause-specific mortality in community-dwelling older adults. *Prev Med* 2018;112:145-151.

21 Choi SU, Rho JH, Choi YJ, *et al*. Postoperative hypoalbuminemia is an independent predictor of 1-year mortality after surgery for geriatric intertrochanteric femoral fracture: a retrospective cohort study. *Medicine* (*Baltimore*) 2021;100(51):e28306.

22 Ryu S, Oh SK, Cho SU, *et al*. Utility of the blood urea nitrogen to serum albumin ratio as a prognostic factor of mortality in aspiration pneumonia patients. *Am J Emerg Med* 2021;43:175-179.

23 Küçükceran K, Ayrancı MK, Girişgin AS, *et al*. The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. *Am J Emerg Med* 2021;48:33-37.

24 Fang JH, Xu B. Blood urea nitrogen to serum albumin ratio independently predicts mortality in critically ill patients with acute pulmonary embolism. *Clin Appl Thromb Hemost* 2021;27:10760296211010241.

25 Vandenbroucke JP, von Elm E, Altman DG, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12(12):1500-1524.

26 Agoritsas T, Merglen A, Shah ND, *et al*. Adjusted analyses in studies addressing therapy and harm: users' guides to the medical literature. *JAMA* 2017;317(7):748-759.

27 Wu YB, Wang CG, Xu LX, *et al*. Analysis of risk factors for progressive fibrovascular proliferation in proliferative diabetic retinopathy. *Int Ophthalmol* 2020;40(10):2495-2502.

28 Zhang GH, Chen HY, Chen WQ, *et al*. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. *Br J Ophthalmol* 2017;101(12):1591-1595.

29 Koppe L, Nyam E, Vivot K, *et al*. Urea impairs β cell glycolysis and insulin secretion in chronic kidney disease. *J Clin Invest* 2016;126(9):3598-3612.

30 Yang J, Liu Z. Mechanistic pathogenesis of endothelial dysfunction in diabetic nephropathy and retinopathy. *Front Endocrinol (Lausanne)* 2022;13:816400.

31 Goldney J, Sargeant JA, Davies MJ. Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy. *Diabetologia* 2023;66(10):1832-1845.

32 Yamanouchi M, Mori M, Hoshino J, *et al*. Retinopathy progression and the risk of end-stage kidney disease: results from a longitudinal Japanese cohort of 232 patients with type 2 diabetes and biopsy-proven diabetic kidney disease. *BMJ Open Diabetes Res Care* 2019;7(1):e000726.

33 Hsieh YT, Hsieh MC. Time-sequential correlations between diabetic kidney disease and diabetic retinopathy in type 2 diabetes - an 8-year prospective cohort study. *Acta Ophthalmol* 2021;99(1):e1-e6.

34 Coull BM, Beamer N, de Garmo P, *et al*. Chronic blood hyperviscosity in subjects with acute stroke, transient ischemic attack, and risk factors for stroke. *Stroke* 1991;22(2):162-168.

35 Hammes HP. Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. *Diabetologia* 2018;61(1):29-38.

36 Mazzaferro EM, Edwards T. Update on albumin therapy in critical illness. *Vet Clin North Am Small Anim Pract* 2020;50(6):1289-1305.

37 Kong P, Cui ZY, Huang XF, *et al*. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. *Signal Transduct Target Ther* 2022;7(1):131.

38 Pedro-Botet J, Climent E, Benaiges D. Atherosclerosis and inflammation. new therapeutic approaches. *Med Clínica Engl Ed* 2020;155(6):256-262.

39 Zhang W. Albumin selectively inhibits TNFα-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. *Cardiovasc Res* 2002;55(4):820-829.

40 Lapenna D, Ciofani G, Ucchino S, *et al*. Serum albumin and biomolecular oxidative damage of human atherosclerotic plaques. *Clin Biochem* 2010;43(18):1458-1460.

41 Aldecoa C, Llau JV, Nuvials X, *et al*. Role of albumin in the preservation of endothelial glycocalyx integrity and the microcirculation: a review. *Ann Intensive Care* 2020;10(1):85.

42 Zhu Y, Cai X, Liu Y, *et al*. Serum albumin, but not bilirubin, is associated with diabetic chronic vascular complications in a Chinese type 2 diabetic population. *Sci Rep* 2019;9(1):12086.