Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Correlation Between the Ratio of Uric Acid to High-Density Lipoprotein Cholesterol (UHR) and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus:A Cross-Sectional Study

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Background/Objective: Considering the uncertain relationship between high-density lipoprotein cholesterol (HDL-C) and uric acid (UA) with diabetic retinopathy (DR),this study investigates the link between Uric Acid to High-Density Lipoprotein Cholesterol (UHR) and DR in T2DM patients, evaluating its potential for DR diagnosis and early prediction.

Study Design and Data Collection: This retrospective study analyzed 1450 type 2 diabetes patients, divided into NDR and DR groups by retinal exams. We gathered demographic and clinical data, calculated UHR, and explored its correlation with DR development.

Outcomes: Individuals diagnosed with diabetic retinopathy (DR) exhibited a markedly elevated uric acid to high-density lipoprotein cholesterol (UHR) ratio when contrasted with those without DR (NDR), achieving statistical significance with a P-value below 0.001. The Mantel-Haenszel chi-square test for linear association validated a pronounced positive correlation between the UHR ratio and the incidence of DR ($P<0.001$). Binary logistic regression analysis revealed that age, glycated hemoglobin (HbA1c), uric acid (UA), high-density lipoprotein cholesterol (HDL-C), and the UHR ratio were all independent risk factors for the development of DR in patients with type 2 diabetes. Furthermore, the receiver operating characteristic (ROC) curve analysis indicated that the UHR ratio was the most precise predictor for diagnosing DR, with an area under the ROC curve (AUC) of 78.4%, a sensitivity of 87%, and a specificity of 60.6%.

Conclusion: Our research has found that the UHR ratio is an independent risk factor for diabetic retinopathy (DR) in patients with type 2 diabetes and can serve as a readily available indicator that takes into account both metabolic status and inflammatory status for the early detection of DR.

Keywords: uric acid to high-density lipoprotein cholesterol ratio, UHR, Type 2 diabetes mellitus, diabetic retinopathy

Introduction

In Asia, diabetes is transforming into a widespread and increasingly serious health challenge at an alarming rate.[1] It is projected that by February 2045, the number of people with diabetes worldwide may reach 693 million, a figure that reflects the increasing threat of diabetes to global health.[2] Diabetic retinopathy (DR) is a prevalent complication associated with type 2 diabetes, posing a significant risk to patients' eyesight. Initially, DR is characterized by harm to the blood vessel lining and the development of microaneurysms. As the disease advances, it can cause the neovascularization and the overgrowth of fibrous tissue. If untreated, DR can escalate to proliferative diabetic retinopathy (PDR), which, in extreme cases, may culminate in retinal detachment and loss of vision.[3] Given the unique pathological features

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of diabetic retinopathy (DR), retinal examination is essential for the early detection and risk assessment of the condition.[4] Nevertheless, constrained by the scarcity of medical resources and the challenges in patient adherence, the implementation of fundus examinations has not been universally embraced, resulting in a low prevalence of early DR detection. Consequently, a significant number of individuals fail to receive timely treatment, which can lead to permanent impairment of their vision.[5] Therefore, discovering more effective biomarkers is crucial for improving the early screening rate and intervention outcomes of DR.

Hyperlipidemia, considered a possible contributor to the onset of diabetic retinopathy (DR), might be linked to compromised lipid clearance mechanisms within the retina of diabetic patients. This impairment can lead to heightened non-enzymatic oxidation, intensified glycation, and the triggering of inflammatory responses. These processes collectively cause an increase in vascular permeability and a breach in the integrity of the blood-retinal barrier.[6] While high-density lipoprotein cholesterol (HDL-C) is often viewed as a beneficial factor against diabetic retinopathy (DR) because of its potential to counteract oxidative stress and inflammation, the precise nature of its connection to DR is still a subject of debate. There is evidence from certain research suggesting that higher levels of HDL-C are linked to a reduced severity of DR,[7] while others suggest a positive correlation or an inverted U-shaped relationship,[8] which may be related to differences in study design, sample selection, and control of confounding variables.

Serum uric acid (UA), being the principal byproduct of purine metabolism, has a significant association with the development and advancement of cardiovascular diseases and diabetes.[9,10] A multitude of studies have demonstrated that increased levels of uric acid (UA) are associated with a higher degree of diabetic retinopathy (DR), indicating that hyperuricemia might contribute to the risk of developing DR.[11] Furthermore, a comprehensive meta-analysis has uncovered a substantial link between hyperuricemia and a heightened risk of developing diabetic peripheral neuropathy (DPN).[12] While hyperuricemia is associated with diabetic complications, the actual impact of uric acid in these conditions is still a matter of significant debate.[13,14] Considering the intricate interplay between high-density lipoprotein cholesterol (HDL-C) and uric acid (UA) with diabetic retinopathy (DR), we suggest a holistic approach to evaluating uric acid levels and lipid metabolism in individuals with type 2 diabetes mellitus (T2DM). By determining the ratio of uric acid to high-density lipoprotein cholesterol (UHR), we can derive a novel biomarker that reflects both metabolic and inflammatory states. Research has established that the UHR is correlated with poor glycemic control, heightened susceptibility to diabetic kidney disease (DKD), and the development of diabetic peripheral neuropathy.[15–17] Nevertheless, there is a scarcity of studies examining the link between the uric acid to high-density lipoprotein cholesterol ratio (UHR) and diabetic retinopathy (DR). Consequently, deeper investigation into the role of UHR in the development of DR is anticipated to yield fresh perspectives and strategies for the early detection and management of DR.

Materials and Methods

Inclusion and Exclusion Criteria

The participants in this study consisted of 1450 individuals with type 2 diabetes mellitus who were admitted to the Affiliated Lu'an Hospital of Anhui Medical University between January 1, 2021, and November 31, 2023. The criteria for participant inclusion were as follows: (1) individuals with a diagnosis of type 2 diabetes in accordance with the 2020 diagnostic and classification criteria for diabetes, and (2) those who underwent a funduscopic examination using the non-mydriatic fundus camera CR-2AF by Canon Japan and were assessed by a qualified clinical ophthalmologist for the presence or absence of diabetic retinopathy. The exclusion criteria encompassed: (1) individuals with a prior diagnosis of DR, (2) those with liver, gallbladder, hematopoietic system, or systemic inflammatory diseases, (3) patients with media opacities that impeded fundus visualization, and (4) individuals under the age of 18. To ensure that our research results have sufficient statistical power, we calcula ted the required sample size based on the expected proportion p, the allowable margin of error ε, and a 95% confidence level, using the following formula: n = (1-p) * Z_(1-α/2) / (ε^2 * p).Here, Z_(1-α/2) corresponds to the Z-score for a 95% confidence level, which is typically 1.96. Our sample size is larger than the minimum sample size calculated using the sample size formula.

Data Cleaning

Because data stored and retrieved from computer systems are prone to issues like missing information, inaccuracies, duplicates, and inconsistencies, these problems can severely impede the analysis process. Thus, it is crucial to cleanse the data before conducting any analysis. In this research, the primary data cleaning tasks focused on dealing with missing data and anomalies.

Addressing missing values in data cleaning pertains to instances where data was not recorded due to human error, technical failures, or oversight of the importance of the data. The presence of missing data can significantly skew the results of data analysis, possibly introducing bias into numerical outcomes. There are several strategies to manage missing data, such as disregarding the issue, removing the entries with missing values, or filling in the missing values. Given the distinct nature of each patient's data in this study and the lack of a clear pattern or sequence in the data, we chose a meticulous experimental approach by deciding to exclude the data. For data entries with unit errors, like the duration of diabetes, we conducted unit conversions to ensure uniformity in measurements. Through measures such as strict inclusion and exclusion criteria, DR screening performed by qualified clinical ophthalmologists, and stringent data cleaning, we were able to compile a refined sample of subjects (Figure 1).

The ethical aspects of this study were scrutinized and granted approval by the Ethics Committee of the Affiliated Lu'an Hospital of Anhui Medical University, with the ethical approval number being 2024LLKS-KY-039. The research was carried out in compliance with the principles outlined in the Declaration of Helsinki. All participant data was gathered in an anonymous manner, and written consent was secured from each participant. The samples and participant data were furnished by our hospital's Information Department.

Clinical Data Collection

A total of 1450 patients were selected based on the criteria mentioned, of which 484 had diabetic retinopathy (DR), representing about 33.3% of the entire patient cohort. Demographic details such as age, gender, duration of diabetes

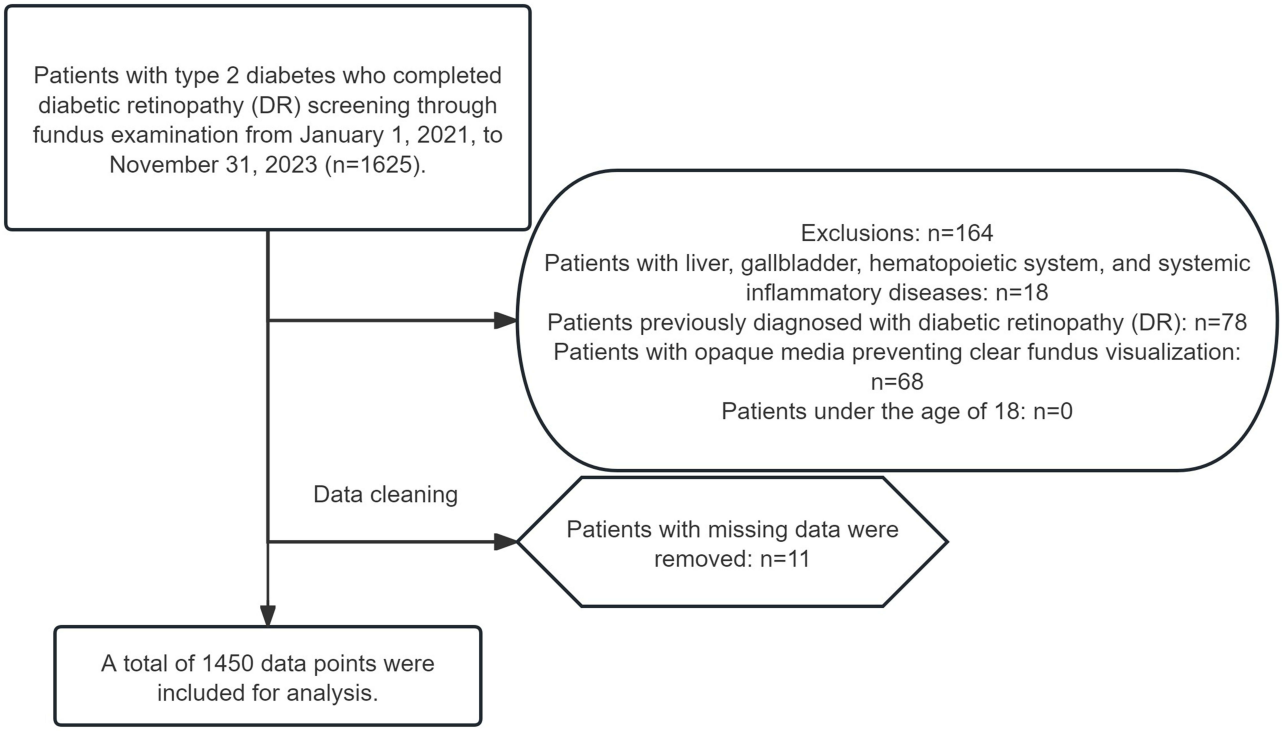

Figure 1 Flowchart of Data Acquisition Process.

Notes: Patients with Incomplete Data: Any samples lacking one or more variables are excluded; DR Diagnostic Criteria: A diagnosis of DR is made if patients exhibit any of the following characteristic lesions: microaneurysms, hard exudates, intraretinal hemorrhages, soft exudates, venous beading, intraretinal microvascular abnormalities, neovascularization, preretinal hemorrhages, or vitreous hemorrhages.

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(DC), and body mass index (BMI) were gathered. Additionally, fasting blood test results taken the day after admission were collected, encompassing the following parameters: (K+, potassium ion concentration; CR, creatinine; BUN, blood urea nitrogen; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; GLB, globulin; TCH, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GLU, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin concentration; WBC, white blood cell count; PLT, platelet count; RDW-CV, red blood cell distribution width; C-P (fasting), fasting C-peptide; C-P (1 hour postprandial), C-peptide 1 hour after a meal), and urine test results (UP, urine protein). Binary scoring was applied to urine protein (positive = 1, negative = 0) and gender (female = 2, male = 1). All biochemical analyses were carried out by the laboratory department of the Affiliated Lu'an Hospital of Anhui Medical University. Routine collection of 2mL peripheral blood samples from all inpatients in EDTA tubes was conducted, and a complete blood count analysis was performed within 30 minutes of collection using a hematology analyzer (Mindray BC5500, China). Glycated hemoglobin levels were determined using a glycated hemoglobin analyzer (MQ6000, China) within 2 hours after collecting 2mL blood samples in EDTA-containing tubes. A 4mL blood sample drawn into a test tube with a clotting agent was utilized for the assessment of biochemical-related indicators.

Data Analysis

The collected data underwent statistical analysis using SPSS 21.0 software, and graphical representations were generated with R 4.3.1 software. Data that were normally distributed are presented as the mean ± standard deviation, with group comparisons conducted using two independent sample t-tests. Non-normally distributed measurement data are depicted as medians and interquartile ranges [M (P25%, P75%)], and group comparisons were performed using the Mann–Whitney *U*-test. Trend analysis was executed with the chi-square trend test alongside Mantel-Haenszel analysis. Binary logistic regression analysis was utilized to identify the independent risk factors for DR in patients with T2DM. The diagnostic efficacy of UHR for DR in patients with T2DM was assessed by examining the receiver operating characteristic (ROC) curve, which included the calculation of the area under the curve (AUC). A P-value of less than 0.05 was set as the threshold for statistical significance in all analyses.

Results

Comparison of General Information and Laboratory Indicators Between the Two Groups

When comparing the general demographics and laboratory data between the two groups, it was observed that among all patients with T2DM, those with DR had a markedly higher UHR value compared to those without DR (NDR), with a statistically significant difference (P<0.001) as detailed in Table 1 and illustrated in Figure 2. DR patients were also found to be older than NDR patients, with a significant difference (P<0.001). Certain laboratory measurements were elevated in the DR group, such as uric acid (UA) and glycated hemoglobin (HbA1c), while high-density lipoprotein cholesterol (HDL-C) levels were lower (P<0.05 for all comparisons). However, there were no significant differences detected between the DR and NDR groups in terms of disease duration, gender, body mass index (BMI), serum potassium, creatinine (CR), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, globulin, total cholesterol (TCH), triglycerides (TG), low-density lipoprotein (LDL), fasting blood glucose (GLU), hemoglobin concentration (Hb), white blood cell count (WBC), platelet count (PLT), red blood cell distribution width (RDW-CV), fasting C-peptide, one-hour postprandial C-peptide, or urine protein positivity (Table 1).

Trend Test of UHR Quartiles and DR Risk in T2DM Patients

We categorized the patients into four groups based on the quartiles of the uric acid to high-density lipoprotein cholesterol ratio (UHR), treating UHR as an ordered polycategorical variable. Specifically, First, the UHR values were sorted in ascending order, and then the quartiles were determined: the first quartile (Q1) marks the point below which 25% of the values fall, the second quartile (Q2) indicates the median, with 50% of the values falling below it,

Table 1 Comparison of General Information Between Non-DR Patients and DR Patients

General Information	DR (n=484)	NDR (n=966)	$\chi^{2/z/t}$	p
Gender [n(%)]			2.216	0.137
Male	301(62.190)	639(66.149)		
Female	183(37.810)	327(33.851)		
Age	59.496±9.379	54.516±13.057	8.321	0.000**
Disease Course (Year)	8.320±6.288	7.864±5.992	1.345	0.179
BMI(kg/m2)	24.626±3.302	24.934±3.586	−1.586	0.113
K+(mmol/L)	3.991±0.444	3.952±0.387	1.634	0.103
CR (umol/L)	64.050(52.375,78.275)	64.300(54.375,75.925)	−0.254	0.799
BUN (mmol/L)	6.567±2.303	6.466±2.157	0.8	0.424
UA (umol/L)	3501.450±63.473	292.197±95.664	12.333	0.000**
AST (u/L)	18.000(15.000,23.000)	19.000(15.000,25.000)	−1.209	0.227
ALT (u/L)	19.000(14.000,27.000)	20.000(14.000,32.000)	−1.93	0.054
Albumin (g/L)	42.637±4.881	42.915±4.062	−1.079	0.281
Globulin (g/L)	24.150(21.325,27.600)	24.000(21.300,26.900)	−0.686	0.492
TCH (mmol/L)	4.785(3.993,5.555)	4.835(4.100,5.670)	−1.318	0.188
TG (mmol/L)	1.410(0.923,2.130)	1.360(0.930,2.232)	−0.562	0.574
LDL (mmol/L)	2.982±1.035	2.934±0.926	0.892	0.373
HDL (mmol/L)	1.299±0.342	1.705±0.647	−15.627	0.000**
GLU (mmol/L)	10.086±4.618	10.156±4.340	−0.284	0.776
HbA1c (%)	10.694±2.001	9.559±2.201	9.535	0.000**
Hb (g/L)	134.512±18.300	135.609±15.989	−1.121	0.263
WBC (109/L)	6.302±1.777	6.447±1.830	−1.438	0.151
PLT (109/L)	207.200±62.409	208.029±61.563	−0.241	0.81
RDW-CV	12.500(12.100,13.000)	12.500(12.100,12.900)	−1.036	0.3
Fasting C-Peptide (ng/mL)	1.060(0.620,1.528)	1.010(0.530,1.590)	−0.99	0.322
C-peptide 1 hour after a meal (ng/mL)	1.975(1.330,2.840)	2.040(1.188,3.322)	−0.689	0.491
UHR	394.959±112.951	277.630±129.698	16.941	0.000**
Urine Protein [n(%)]			2.21	0.137
Negative	380(78.512)	790(81.781)		
Positive	104(21.488)	176(18.219)		

Notes: P < 0.05 indicated statistical significance, **p<0.01.

Abbreviations: DR, Diabetic retinopathy; NDR, No diabetic retinopathy;BMI, Body mass index;K+, Serum potassium;CR, Creatinine; BUN, Blood urea nitrogen; UA, Uric acid; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TCH, Total cholesterol; TG, Triglycerides; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; GLU, Fasting blood glucose; HbA1c, Glycated hemoglobin; Hb, Hemoglobin concentration; WBC, White blood cell count; PLT, Platelet count; RDW-CV, Red blood cell distribution width;UHR, Uric acid to high-density lipoprotein cholesterol ratio.

and the third quartile (Q3) signifies that 75% of the values are below this point. Subsequently, the dataset was divided into four groups based on these quartiles: Group A includes data points below Q1 (0% - 25%), Group B encompasses data points between Q1 and Q2 (25% - 50%), Group C consists of data points between Q2 and Q3 (50% - 75%), and Group D comprises data points above Q3 (75% - 100%). The results indicate that Group A comprises patients with UHR less than 214.773, Group B includes patients with UHR between 214.773 and 301.963, Group C consists of patients with UHR between 301.963 and 396.700, and Group D contains patients with UHR greater than 396.700.All four groups underwent the Mantel-Haenszel chi-square trend test. The analysis revealed a distinct linear relationship between UHR and diabetic retinopathy (DR), indicating a positive correlation ($P<0.001$, $\chi2=322.614$). The incidence of DR rose with increasing UHR quartile levels, with rates of 1.033% in Group A, 18.182% in Group B, 37.603% in Group C, and 43.182% in Group D (Table 2).

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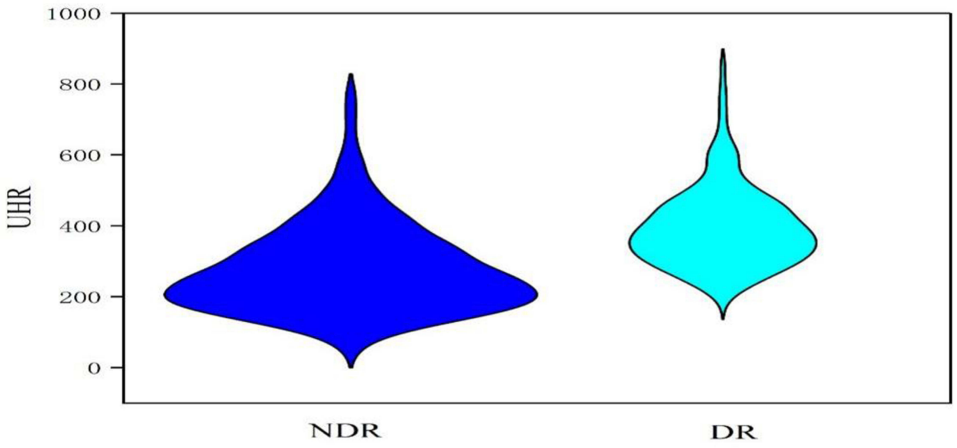

Figure 2 Patient Corresponding UHR Values.
Notes: UHR, Uric Acid to High-Density Lipoprotein Cholesterol Ratio.

Multivariate Regression Analysis of Diabetic Retinopathy (DR) in Type 2 Diabetes Patients

Using diabetic retinopathy (DR) as the dependent variable, potential predictor variables were filtered, and those with a P-value less than 0.05—namely, age, uric acid (UA), glycated hemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), and urinary albumin excretion rate (UHR)—were selected for inclusion in the binary logistic regression model. The regression analysis identified age, HbA1c, UA, HDL-C, and UHR as independent risk factors for DR. It was found that for each one-unit increment in UHR, the likelihood of DR developing in patients with type 2 diabetes mellitus (T2DM) increases by a factor of 0.004 (Table 3).

Table 2 UHR Quartile Ranges and DR Risk

Indicator	Group	DR	NDR	Total	χ^2	*p*
UHR	A	5(1.033)	358(37.060)	363(25.034)	322.614	0.000**
	B	88(18.182)	274(28.364)	362(24.966)		
	C	182(37.603)	180(18.634)	362(24.966)		
	D	209(43.182)	154(15.942)	363(25.034)		
Total		484	966	1450		

Notes: P < 0.05 indicated statistical significance, **p<0.01.
Abbreviations: DR, Diabetic retinopathy; NDR, No diabetic retinopathy; UHR, Uric acid to high-density lipoprotein cholesterol ratio.

Table 3 Results of Binary Logistic Regression Analysis

Indicator	Regression Coefficient	Standard Error	z-value	Wald χ^2	*p*	Odds Ratio	95% Confidence Interval (CI) for the Odds Ratio (OR)
HDL (mmol/L)	−0.841	0.236	−3.559	12.668	0.000**	0.431	0.272 ~ 0.685
HbA1c (%)	0.314	0.032	9.707	94.228	0.000**	1.369	1.285 ~ 1.459
Age	0.058	0.006	9.793	95.903	0.000**	1.060	1.047 ~ 1.072
UA (umol/L)	0.004	0.002	2.355	5.544	0.019*	1.004	1.001 ~ 1.007
UHR	0.004	0.001	2.976	8.858	0.003**	1.004	1.002 ~ 1.007
Intercept	−8.659	0.721	−12.016	144.386	0.000**	0.000	0.000 ~ 0.001

Notes: P < 0.05 indicated statistical significance, *p<0.05, **p<0.01.
Abbreviations: HDL, High-density lipoprotein; HbA1c, Glycated hemoglobin; UA,Uric acid;UHR, Uric acid to high-density lipoprotein cholesterol ratio.

Table 4 Results of ROC Curve Analysis

Indicator	AUC	Optimal Cutoff Value	Sensitivity	Specificity	Cut-off
Age	0.624	0.264	0.667	0.596	57.000
UA (umol/L)	0.720	0.521	0.932	0.589	301.600
HDL (mmol/L)	0.683	0.039	0.835	0.204	0.980
HbA1c (%)	0.652	0.282	0.475	0.806	11.500
UHR	0.784	0.475	0.870	0.606	282.266

Abbreviations: HDL, High-density lipoprotein; HbA1c, Glycated hemoglobin; UA,Uric acid;UHR, Uric acid to high-density lipoprotein cholesterol ratio;AUC,Area Under the Curve.

ROC Curve Analysis of the Diagnostic Value of UHR

The receiver operating characteristic (ROC) curve analysis demonstrated that the uric acid to high-density lipoprotein cholesterol ratio (UHR) had the greatest accuracy in assessing diabetic retinopathy (DR), with an area under the curve (AUC) of 0.784, a sensitivity of 87%, and a specificity of 60.6%. UHR proved to be a more precise indicator than either uric acid (UA) or high-density lipoprotein cholesterol (HDL) alone. The AUC for UA was 0.72, which was higher than that for HDL.The study results indicate that the uric acid to high-density lipoprotein cholesterol ratio (UHR) is an independent risk factor for the development of diabetic retinopathy (DR) in patients with type 2 diabetes. On the basis of being easily accessible, compared to uric acid and high-density lipoprotein cholesterol levels alone, UHR takes into account both metabolic status and inflammatory conditions, serving as a biomarker for the early detection of DR (Table 4 and Figure 3).

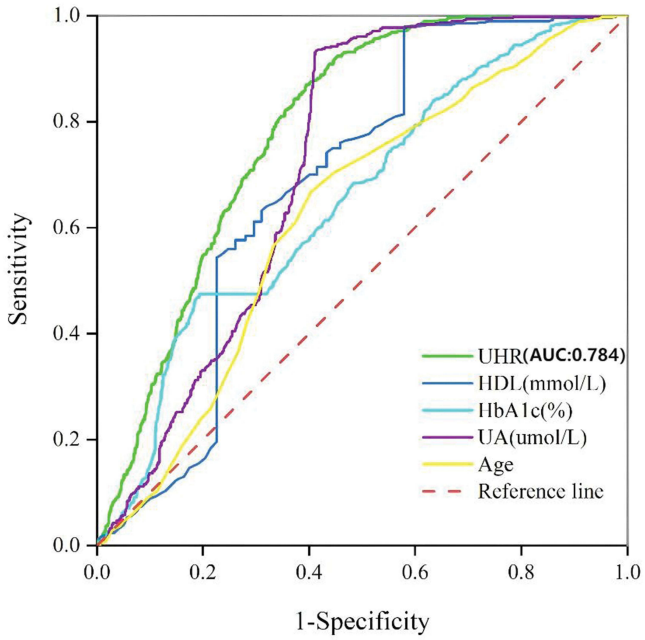

Figure 3 ROC Curves for Each Indicator.

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Discussion

Diabetic retinopathy (DR) is a prevalent eye complication associated with diabetes, impacting roughly 30% to 40% of individuals with diabetes.[18,19] Globally, more than 100 million individuals are affected by DR, making it a primary contributor to blindness and vision loss, particularly among adults of working age.[18,20] It is anticipated that the global prevalence and impact of diabetic retinopathy (DR) will rise considerably in the next few decades, increasing from approximately 103 million individuals in 2020 to 130 million by 2030, and further escalating to 161 million by 2045.[21] The steep rise of more than 25% in the disease burden of DR within a mere decade could potentially place additional pressure on healthcare systems and resources that are already stretched thin. The economic burden associated with DR management is substantial, and the findings show that the direct and indirect costs associated with DR are considerable and difficult to control.[22]

Previous studies have established that abnormal lipid metabolism, oxidative stress, and the triggering of inflammatory responses are significant contributors to the progression of diabetic retinopathy (DR).[8,23,24] High-density lipoprotein cholesterol (HDL-C) is a complex substance made up of various triglycerides, lipoproteins, and cholesterol. Research has indicated that HDL-C plays a role in numerous vascular pathological mechanisms, with one of the most prominent being the migration and proliferation of vascular cells. It has been observed that elevated levels of HDL-C can negatively impact blood vessels and are linked to vascular conditions, including coronary heart disease, nephropathy, and diabetic complications.[25–28] Nonetheless, the connection between high-density lipoprotein cholesterol (HDL-C) and diabetic retinopathy (DR) remains ambiguous. Morton et al investigated the relationship between HDL-C and DR and concluded that there was no significant association.[29–31] On the other hand, Sasso et al identified a substantial positive link between the severity of diabetic retinopathy (DR) and higher concentrations of high-density lipoprotein cholesterol (HDL-C).[32,33] Popescu et al observed an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and the occurrence of diabetic retinopathy (DR), a finding that aligns with our own results.[34,35] There are also perspectives indicating a positive correlation or an inverted U-shaped relationship between the two variables.[8] HDL-C could potentially serve as a modifiable risk factor for DR. These insights imply that HDL-C might be a target for intervention to reduce the risk of DR, and that there might be an optimal HDL-C level for patients with DR. This serves as a reminder in clinical practice to be cautious about not over-correcting HDL-C levels in patients with DR.Several studies have demonstrated that elevated uric acid (UA) levels are linked to a heightened risk of diabetic retinopathy (DR), suggesting that high UA could be a potential risk factor for the advancement of DR,[36] This aligns with our findings. Uric acid (UA) might be involved in the development of diabetic retinopathy (DR). A growing body of experimental and clinical evidence suggests that oxidative stress and inflammation triggered by UA can result in damage to the microvasculature associated with DR.[37,38] Uric acid in the bloodstream is capable of scavenging superoxide and hydroxyl radicals, which could potentially result in an escalation of reactive oxygen species (ROS) formation, consequently leading to disturbances in microcirculatory coagulation.[39] These factors together contribute to the occurrence and development of DR.

Prolonged hyperglycemia and inadequate glycemic control are widely acknowledged as significant risk factors for the development of diabetic retinopathy (DR).[40] Hemoglobin A1c (HbA1c) serves as a prevalent biomarker for assessing blood glucose control. Our research findings indicate a positive correlation between HbA1c levels and the incidence of diabetic retinopathy (DR). This association might stem from chronic hyperglycemia, which can activate several pathways: the polyol pathway, the hexosamine pathway, and protein kinase C (PKC), as well as increase the formation of advanced glycation end products (AGEs). These factors contribute to the development of oxidative stress, which in turn promotes the onset of DR.[41] The stimulation of these pathways leads to the generation of substantial quantities of reactive oxygen species (ROS). When these ROS accumulate in the body, they can inflict damage on blood vessels, ultimately contributing to the onset and progression of diabetic retinopathy.[42–44]

In clinical settings, patients may have glycated hemoglobin, uric acid, and blood lipid levels that fall within the normal range, yet they still advance to diabetic retinopathy (DR). To better evaluate patients' conditions, we have been exploring additional biological markers to aid in the diagnosis of DR. The uric acid to high-density lipoprotein cholesterol ratio (UHR), as a novel inflammatory marker, is closely associated with conditions characterized by chronic low-grade inflammation, such as diabetic nephropathy and hypertension. This chronic low-grade inflammation is pivotal

in the onset and progression of DR.[45,46] This study's findings indicate that the uric acid to high-density lipoprotein cholesterol ratio (UHR) is significantly associated with diabetic retinopathy (DR). The receiver operating characteristic (ROC) curve analysis demonstrates that UHR is the most accurate in assessing DR, with an area under the curve (AUC) of 0.784, a sensitivity of 87%, and a specificity of 60.6%. With each one-unit increment in UHR, the likelihood of DR in patients with type 2 diabetes mellitus (T2DM) rises by a factor of 0.004. The ROC curve analysis suggests that UHR has a larger AUC than either uric acid (UA) or high-density lipoprotein (HDL) alone, making it a potentially valuable diagnostic tool for DR and possibly a new biological marker for early DR screening. The composition of UHR—where HDL-C is inversely related to the occurrence of DR and UA is directly related—aligns with our findings. Additionally, Mehmet Ali Kosekli et al have noted that UHR values correlate with glycemic control in T2DM patients. Prolonged poor glycemic control can lead to oxidative stress through several mechanisms, including the activation of the polyol pathway, the induction of the hexosamine pathway, the activation of protein kinase C (PKC), and an increase in advanced glycation end products (AGEs).[41] The stimulation of these pathways results in the generation of substantial quantities of reactive oxygen species (ROS), which in turn activate further ROS. The buildup of ROS within the body can inflict damage on retinal vascular endothelial cells and the surrounding tissues. Intracellular ROS can also harm retinal mitochondria, inducing the apoptosis of capillary cells. This mitochondrial damage leads to an increased production of ROS, perpetuating a vicious cycle that continues to amplify, ultimately contributing to the onset and progression of diabetic retinopathy.[42–44] The use of the UHR ratio is simple and cost-effective, and its link to diabetic retinopathy (DR) and its predictive capabilities enable medical professionals to detect complications early in their practice. This can aid in delaying or even preventing the onset of DR, thereby improving patients' quality of life and treatment outcomes, and leading to economic savings. Looking ahead, machine learning methods might be employed to select key predictive variables, which could further enhance the performance of DR prediction models that incorporate UHR. However, it's important to note that different ethnicities and genetic backgrounds may respond differently to UHR, potentially impacting its predictive value as a risk factor for DR. Moreover, the lifestyle and dietary habits of various populations can influence the levels of uric acid and high-density lipoprotein cholesterol, which in turn affect the clinical significance of UHR. Lastly, in healthcare settings with limited resources, UHR testing may not be as accessible as in wealthier environments, potentially restricting its use as an early detection tool.

This study, however, is not without its limitations. Firstly, a cross-sectional design such as ours does not allow for the establishment of a causal link between the UHR ratio and diabetes-related complications; therefore, additional prospective studies are needed to validate our results. Secondly, the fact that our study sample is drawn exclusively from the People's Hospital of Lu'an City may introduce selection bias. Lastly, given that all participants are of Chinese ethnicity, the generalizability and practical application of UHR in other racial or ethnic groups remain uncertain.

Conclusion

Our study finds that the Uric Acid to High-Density Lipoprotein Cholesterol ratio (UHR) is an independent risk factor for Diabetic Retinopathy (DR) in patients with type 2 diabetes. This discovery is innovative and provides new evidence for the study of changes in uric acid levels and dyslipidemia in microvascular complications of diabetes. As a potential biomarker, UHR is significant for the early detection of DR, which may help intervene at an early stage of the disease, thereby delaying or preventing the progression of DR, However, we need to conduct multicenter prospective studies to further clarify the relationship between UHR and DR, ultimately incorporating it into existing clinical guidelines.

Data Sharing Statement

Appropriate databases will be made available as required.

Ethical Statement

The ethical considerations for this research project have been scrutinized and approved by the ethics committee at Lu'an Hospital, which is affiliated with Anhui Medical University in China (Approval Number: 2024LLKS-KY-039). All participants have provided their informed consent, and the research is conducted in accordance with the principles outlined in the Declaration of Helsinki.

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Disclosure

During the composition of the paper, there was no influence from interested parties, and no conflicts of interest were identified.

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