Received: 10 February 2022 | Revised: 3 March 2022 | Accepted: 6 March 2022

DOI: 10.1002/jcla.24351

RESEARCH ARTICLE

WILEY

Association between red blood cell distribution width-to-albumin ratio and diabetic retinopathy

Fengping Zhao[1] | **MengYun Liu**[2] | **Lingzhen Kong**[3]

[1]Department of Ophthalmology, Mingsheng Eye Hospital, Yiwu, China

[2]Department of Ophthalmology, The Affiliated People's Hospital of Ningbo University, Ningbo, China

[3]Department of Ophthalmology, Zhuji Central Hospital, Zhuji, China

Correspondence
Lingzhen Kong, Department of Ophthalmology, Zhuji Central Hospital, Zhuji, Zhejiang 311800, China.
Email: 13587389718@163.com

Abstract

Background: Diabetes mellitus (DM) has shown a trend of reaching pandemic levels in the world. Chronic inflammation is a key factor in the development of diabetic retinopathy (DR). Red blood cell distribution width-to-albumin ratio (RA) is used to assess immune status and the immune response. Our study was conducted to assess the association between DR and RA levels to determine the value of RA in predicting DR.

Methods: The data came from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2006, The RA was calculated as the Red Blood Cell Distribution Width/Albumin Ratio. Multivariable logistic regression and propensity score-matched analysis were used to examine the association between RA and DR levels.

Results: The clinical and demographic features of the 1,751 patients with DM. The eligible participants included 874 females and 870 males with mean age 62.2 ± 14.0 years, and mean RA 3.2 ± 0.5. RA ≥ 2.9659 was a risk factor for DR (OR = 1.66 95% CI: 1.31–2.11, $p < 0.0001$). After adjusting for age, sex, race, education, marital status, ratio of family income to poverty, body mass index, fasting glucose, hypertension, and coronary heart disease, RA ≥ 2.9659 was an independent risk factor for DR (OR = 1.64, 95% CI: 1.23–2.19, $p = 0.0008$). The propensity score-matched analysis also showed that high RA was an independent risk factor for DR.

Conclusions: Our study shows that RA is a risk factor for patients with DR. The findings of this study should be validated the role of RA in DR in diabetic patients.

KEYWORDS
diabetes mellitus, diabetic retinopathy, National Health and Nutrition Examination Survey, red blood cell distribution width-to-albumin ratio

1 | INTRODUCTION

Diabetes mellitus (DM) has shown a trend of reaching pandemic levels in the world.[1–3] It has rapidly become a global health problem. Diabetic retinopathy (DR) is the most common microvascular complication of type 2 diabetes mellitus (T2D) and the most frequent.[4] DR is one of the major eye diseases causing blindness in people aged 50 years and above.[5] Its basic pathological changes are destruction of blood retinal barrier (BRB) and the formation of retinal neovascularization.[6] Studies[7] on the prevalence of DR in China show that between 9.4% and 43.1% of patients with diabetes are diagnosed with DR. In addition, DR is always asymptomatic before entering the later stage because DR seriously harms human health and the economic sustainability of the national health system, both for individual vision

and society.[6,8,9] Early detection of predictors of the occurrence of DR allows doctors to identify high-risk patients earlier for early prevention and quality treatment.

Chronic inflammation is the non-specific response of body to injury or stress.[10,11] There is growing evidence that chronic inflammation is a key factor in the development of DR.[12,13] Pathological manifestations of chronic retinal inflammation, such as increased retinal blood flow, abnormal stasis of white blood cells, infiltration of neutrophils and macrophages, activation of complement and microglia, up-regulation of cytokines, and increased vascular permeability and tissue edema, have been confirmed in animal models as well as in patients with DR during the development of chronic retinal inflammation.[14] Red blood cell distribution width (RDW) is a parameter that reflects the heterogeneity of red blood cells (RBC) measured using hematology analyzer.[15] The normal range of RDW in human is between 11 and 15%. The larger the RDW value, the greater the difference of red blood cell shape and size. This suggests that there is poor blood and various hematopoietic abnormalities. It was evident that RDW was generally elevated in patients with diabetes and its complications.[16,17] Moreover, elevated RDW is associated with severe imbalance of RBC homeostasis, abnormal RBC production and survival. This may be associated with oxidative stress, vascular inflammation, and malnutrition such as iron, vitamin $B_{12,}$ and folic acid deficiencies. In addition, excessive RDW may increase mortality from diabetes mellitus and macrovascular as well as microvascular diseases. Recent studies[18,19] have shown that albumin is involved in inflammation. The RA is an integrated and novel inflammatory biomarker based on RDW and albumin. Its index was originally used to assess the outcomes in patients with solid stroke[19] and ARDS[20] and is believed to accurately reflect inflammation. However, the role of RA in patients with diabetic retinopathy is still unclear. In the present study, it was hypothesized that patients with DM and higher levels of inflammation were at higher risk of developing retinopathy as measured by RA. Therefore, a cross-sectional study was conducted to assess the association between diabetic retinopathy and RA levels to determine the value of RA in predicting DR.

2 | METHODS

2.1 | Data and sample sources

The data came from the National Health and Nutrition Examination Survey (NHANES). NHANES was a 2-year cross-sectoral, hierarchical and multi-stage probability cluster survey. It aimed to gather information on a variety of potential risk factors and nutrition in the non-institutionalized, democratized and U.S. population. The NHANES was approved by the Institutional Review Board of the National Centre for Health Statistics with the informed consent of all participants. The National Center for the Health Statistics Ethics Review Board also approved the NHANES, and all participants gave written informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed in this study. The Medical Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital approved our study (ethical review batch number: 20211090).

2.2 | Study variables

Definition of DM: the selection criteria for diabetes included self-reported diabetes, on anti-diabetes drugs, taking insulin, fasting glucose ≥110 mg/dl, or glycohemoglobin (HbA1c) ≥6.5%. Definition of DR: using the Canon CR6-45NM ophthalmic digital imaging system and Canon EOS 10D digital camera (Canon), or has a doctor ever told that diabetes has affected eyes or that had retinopathy. Demographic characteristics included age, sex, race, marital status, education level, body mass index (BMI), C-reactive protein (CRP), RDW, Albumin, Insulin use, fasting glucose, ratio of family income to poverty (PIR), hypertension, and coronary heart disease.

2.3 | Statistical analyses

Continuous data were expressed as mean ± standard deviation, and categorical variables were expressed as frequency. Differences in baseline characteristics were compared via an independent sample t test in continuous variables and $\chi 2$ tests in categorical variables. For the current study, receiver operating characteristic curve analysis was used to determine the optimal cutoff value for the RA. A multivariable logistic regression analysis was performed to examine the association between RA and diabetic DR thus calculating 95% confidence intervals (CI) and odds ratios (OR). In model 1, there was no adjustment any confounding factors. Age, sex, race, education, marital status, PIR, BMI, fasting glucose chronic conditions including hypertension and CHD was adjusted in model 2. To avoid potential bias, propensity score matching (PSM) was also determined in this study. This study ensured that all reported selection factors for DR were included in the model covariation to further reduce potential confusion. The PSM was performed at a ratio of 1:1, using the 0.05 caliper width of the SD by the propensity score log. After PSM, model 3 was analyzed. All analyses were conducted using R software (version 4.01, http://www.r-project.org). The double-sided significant difference was set at $p < 0.05$.

3 | RESULTS

3.1 | Subject characteristics

The clinical and demographic features of the 1,751 patients with DM were as presented in Table 1. However, it was found that the data of some patients were partly incomplete. The eligible participants included 874 female and 870 males with mean age 62.2 ± 14.0 years, and mean RA 3.2 ± 0.5. The outcomes of this study showed that there was no statistical difference in the age, sex, race, marital status,

BMI, and CRP. Patients with DR had high levels of RA, RDW, albumin, fasting glucose insulin using hypertension and CHD ($p < 0.05$).

3.2 | RA was an independent risk factor for DR

Smooth curve fitting was used to assess the effects of RA and DR (Figure 1). We constructed various models to assess the independent effects of RA and DR, after adjusting for other potential confounders. Results of logistic regression analysis found that shows effect sizes (OR) and 95% CI (Table 2). In univariate analysis, RA ≥ 2.9659 was a risk factor for diabetic DR (OR = 1.66 95% CI: 1.31–2.11, $p < 0.0001$). After adjusting for age, sex, race, education, marital status, PIR, BMI, fasting glucose chronic conditions including hypertension (yes/no) and CHD (yes/no), RA ≥ 2.9659 was an independent risk factor for DR (OR = 1.64, 95% CI: 1.23–2.19, $p = 0.0008$).

TABLE 1 Basic characteristics of study population

	All	No DR	DR	*p*
Sample size, N	1751	1309	442	
Age (years)	62.2 ± 14.0	62.1 ± 14.5	62.6 ± 12.4	0.957
Female (%)	874 (49.9)	656 (50.1)	218 (49.3)	0.773
Race (%)				
Non-Hispanic White	674 (38.5)	516 (39.4)	158 (35.7)	0.450
Black	448 (25.6)	326 (24.9)	122 (27.6)	
Mexican American	485 (27.7)	356 (27.2)	12 (2.6)	
Other Hispanic	75 (4.3)	60 (4.6)	12 (2.6)	
Other	69 (3.9)	60(3.9)	9 (2.0)	
Education level (%)				
Primary school	812 (46.4)	586 (44.8)	226 (51.1)	0.041
High school	378 (21.6)	284 (21.7)	94 (21.3)	
Above	559 (32.0)	437 (33.4)	122 (27.6)	
PIR	2.2 ± 1.5	2.3 ± 1.5	1.9 ± 1.4	<0.001
Marital status (%)				
Married/living with partner	1036 (60.8)	779 (60.9)	257 (60.3)	0.202
Widowed/divorced	552 (32.4)	405 (31.7)	147 (34.5)	
Never married	117 (6.9)	95 (7.4)	22 (5.2)	
BMI (kg/m^2)	31.3 ± 7.0	31.2 ± 6.8	31.7 ± 7.6	0.373
Waist circumference (cm)	106.6 ± 15.2	106.2 ± 14.8	107.7 ± 16.1	0.187
RDW (%)	13.2 ± 1.3	13.1 ± 1.3	13.3 ± 1.4	0.016
Albumin (g/dl)	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.4	<0.001
RA	3.2 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	<0.001
Fasting glucose (mg/dl)	164.9 ± 73.2	161.5 ± 71.3	176.1 ± 77.9	0.012
HDL (mg/dl)	47.9 ± 14.0	47.7 ± 14.0	48.3 ± 14.0	0.429
LDL (mg/dl)	110.2 ± 36.0	111.1 ± 36.6	107.4 ± 33.8	0.608
Insulin use (%)	163 (9.3)	93 (7.1)	70 (15.8)	<0.001
CRP (mg/dl)	0.7 ± 1.4	0.7 ± 1.4	0.7 ± 1.4	0.440
Chronic conditions				
Coronary heart disease (%)				
Yes	1307 (74.9)	1007 (77.3)	300 (67.9)	<0.001
No	438 (25.1)	296 (22.7)	142 (32.1)	
Hypertension (%)				
Yes	621 (35.5)	483 (37.0)	138 (31.3)	0.031
No	1126 (64.5)	823 (63.0)	303 (68.7)	

Note: Data are weighted estimates, and values are presented as means ± standard deviation or means (percentage).

Abbreviations: BMI, body mass index; CRP, C-reactive protein; PIR, ratio of family income to poverty; RA, red blood cell distribution width-to-albumin ratio; RDW, red blood cell distribution width.

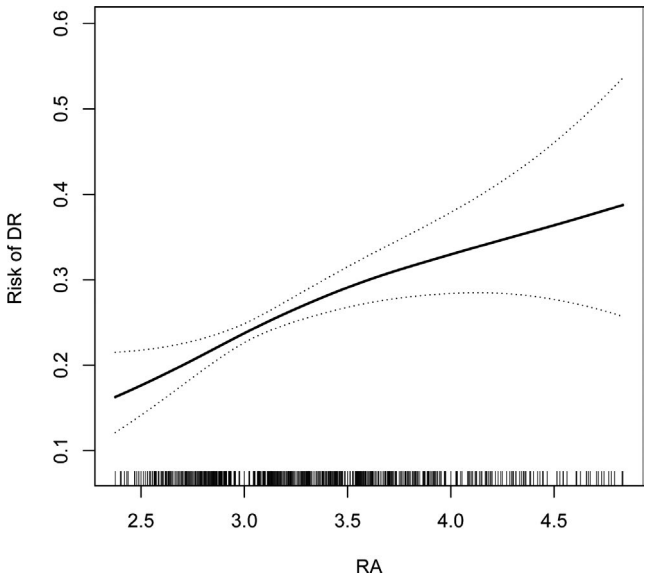

FIGURE 1 Association between RA and risk of DR. Abbreviation: DR, diabetic retinopathy; RA, red blood cell distribution width-to-albumin ratio

TABLE 2 Association between RA and diabetic retinopathy

RA	OR	95% CI	*p*
Before propensity score			
<2.9659	Reference	1.31–2.11	<0.00001
≥2.9659	1.66		
Before propensity score[a]			
<2.9659	Reference	1.23–2.19	0.0008
≥2.9659	1.64		
After propensity score			
<2.9659	Reference	1.26–2.40	0.0008
≥2.9659	1.74		

Abbreviations: CI, confidence interval; OR odds ratio; RA, red blood cell distribution width-to-albumin ratio.

[a]Adjusted for age, sex, race, education, marital status, ratio of family income to poverty, body mass index, fasting glucose, hypertension, and coronary heart disease.

3.3 | Propensity score-matched analysis

The propensity score-matched analysis was also performed to further verify the relationship between RA and DR. After propensity score-matched analysis, the baseline characteristics of patients in different RA groups were not significantly different (Table 3). Results of logistic regression analysis showed that RA ≥ 2.9659 was an independent risk factor for DR (OR = 1.74, 95% CI: 1.26–2.40, $p = 0.0008$).

4 | DISCUSSION

This is the first study which has shown that RA is an independent risk factor for DR. Further results revealed that patients with DR had higher levels of RA than those without DR.

Diabetes is a chronic, low-grade and persistent inflammatory disease.[21,22] Normal tissue immune cells, such as regulatory T cells, macrophages, and eosinophils, exert anti-inflammatory effects by synthesis of cytokines such as IL-3, IL-10, and IL-4 thereby maintaining microenvironmental homeostasis.[23,24] When diabetes and its complications occur, the AGEs, lipid metabolism disorders and OS induce monocytes, macrophages as well as natural killer cells to infiltrate into the non-inflammatory tissues such as fat and muscle, resulting in changes in the number and types of immune cells and the release of inflammatory factors which causes chronic inflammation.[25] The serum and vitreous and aqueous humor tissue of patients with diabetes contain a variety of inflammatory cytokines and chemokines. A variety of eye tissue of patients with NPDR also contains inflammatory cytokines IL-1 beta, IL-6, IL-8, TNF alpha, and mononuclear cells chemokine (monocyte chemotactic protein, MCP-1) such as add.[26] Recent studies have reported that Il-8 and TNF - α levels were even higher in patients with active PDR.[27] In ischemia mice models, some cytokines such as macrophage inflammatory protein 1 (MIP), IL–1, and IL-3 of these inflammatory mediators. First, the formation of new blood vessels is considered to be the early diabetic retinal nerve cells, the cause of death, activated microglia and endothelial cells, glial cells even later these cytokines increase of neuron, illustrates this some inflammatory cytokines lead to inflammation in the development of early DR and the DR has always been.

Inflammatory response may promote the heterogeneity of RBC volume and lead to the increase of RDW[28,29] by affecting RBC genesis, RBC circulating half-life and RBC deformability. Red cells with 1/4 higher RDW have higher IL-6 levels. Inflammatory factors in DR patients have serious damage to endothelial cells and glomerular permeability. The TNF-α and IL-6 are related to proteinuria and reflect the level of inflammation. Further, RDW is positively correlated with proteinuria. In addition, the nuclear factor κB (NF-κB) signaling pathway plays an important role in the early pathogenesis of diabetes mellitus and its complications. In inflammatory response, this pathway is mainly involved in the expression of inflammatory cytokines and is a key nuclear factor in the initiation and regulation of inflammatory response in diabetes mellitus. In addition, NF-κB-mediated inflammation may lead to cell damage through increased production of active oxygen clusters (ROS). Albumin is negative acute phase protein with antioxidant properties in contrast to CRP.[30] Inflammatory activities are inversely associated with albumin synthesis rate which raises blood viscosity, aggregation, and platelet activation.[31] Earlier studies have shown that decreased albumin increases the general population risk for cardiovascular events. In our research, the levels of albumin in patients with higher RDW were considerably lower.

HbA1c is produced in red blood cells through a slow and irreversible reaction between hemoglobin and glucose.[32] It reflects the average blood glucose level of body in recent 3 months, with no obvious short-term fluctuation, which is suitable for long-term[33] monitoring. HbA1c is mainly determined by blood glucose concentration and the lifespan of RBC. In addition to promoting the formation of HbA1c, hyperglycemia also changes the mechanical properties of

TABLE 3 Characteristics of patients before and after PSM

	Before propensity score		After propensity score	
	<2.9659	≥2.9659	<2.9659	≥2.9659
Sample size, N	553	1198	432	432
Age, years	60.2 ± 14.0	63.1 ± 13.9*	61.7 ± 13.2	61.1 ± 13.4
Sex, n (%)		*		
Male	339 (61.3)	538 (44.9)	250 (57.9)	244 (56.5)
Female	214 (38.7)	660 (55.1)	182 (42.1)	188 (43.5)
Ethnicity, n (%)		*		
Non-Hispanic White	236 (42.7)	438 (36.6)	186 (43.1)	142 (32.9)
Black	65 (11.8)	383 (32.0)	48 (11.1)	132 (30.6)
Mexican American	192 (34.7)	293 (24.5)	156 (36.1)	119 (27.5)
Other Hispanic	29 (5.2)	46 (3.8)	19 (4.4)	24 (5.6)
Other	31 (5.6)	38 (3.2)	23 (5.3)	15 (3.5)
Education level (%)				
Primary school	250 (45.2)	562 (47.0)	191 (44.2)	192 (44.4)
High school	107 (19.3)	271 (22.7)	84 (19.4)	101 (23.4)
Above	196 (35.4)	363 (30.4)	157 (36.3)	139 (32.2)
PIR	2.3 ± 1.5	2.2 ± 1.4	2.4± 1.5	2.4± 1.5
Marital status (%)		*		
Married/living with partner	365 (69.1)	671 (57.0)	292 (67.6)	293 (67.8)
Widowed/divorced	132 (25.0)	420 (35.7)	120 (27.8)	119 (27.5)
Never married	31 (5.9)	86 (7.3)	20 (4.6)	20 (4.6)
BMI (kg/m^2)	29.0 ± 5.2	32.4 ± 7.5*	29.4 ± 5.0	29.8± 6.0
Waist circumference (cm)	102.4 ± 12.8	108.6 ± 15.8*	103.7± 12.4	104.3 ± 15.1
RA	2.8 ± 0.1	3.4 ± 0.5*	2.8± 0.1	3.3 ± 0.4*
RDW (%)	12.3 ± 0.5	13.6 ± 1.4*	12.3 ± 0.5	13.4± 1.3*
Albumin (g/dl)	4.5 ± 0.2	4.0 ± 0.3*	4.5± 0.2	4.1± 0.3*
Fasting glucose (mg/dl)	164.0 ± 71.6	165.4 ± 73.9	162.6 ± 67.1	160.9 ± 71.3
CRP (mg/dl)	0.3 ± 0.4	0.9 ± 1.6*	0.4± 0.4	0.4± 0.4
HDL (mg/dl)	46.9 ± 13.2	48.4 ± 14.4	46.6 ± 13.2	47.02± 14.3
LDL (mg/dl)	117.3 ± 33.4	107.0 ± 36.8	117.8 ± 34.0	110.0 ± 36.0
Insulin use (%)	32 (5.8)	131 (10.9) *	24 (5.6)	28 (6.5)
CHD (%)		*		
Yes	84 (15.3)	354 (29.6)	75 (17.4)	72 (16.7)
No	466 (84.7)	841 (70.4)	357 (82.6)	360 (83.3)
Hypertension (%)		*		
Yes	293 (53.2)	833 (69.6)	246 (56.9)	240 (55.6)
No	258 (46.8)	363 (30.4)	186 (43.1)	192 (44.4)
DR		*		*
Yes	105 (19.0)	337 (28.1)	79 (18.3)	121 (28)
No	448 (81.0)	861 (71.9)	353 (81.7)	311 (72)

Note: $^*p < 0.05$.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DR, diabetic retinopathy; PIR, ratio of family income to poverty; RA, red blood cell distribution width-to-albumin ratio; RDW, red blood cell distribution width.

red blood cells, such as increased osmotic brittleness of red blood cells, enhanced adhesion, and increased density of red blood cells, erythrocyte membrane rearrangement and deficiency of oxygen-binding activity of hemoglobin. In addition, hyperglycemia also has an impact on RBC lifespan, resulting in highly variable RBC volume, which may affect RDW machine.

Some studies have found that RDW is correlated with the increase of HbA1c concentration, but not with blood glucose

concentration. This indicates that RDW may be related to HbA1c through non-glucose pathway. The RBC survival time increases with decrease in rate of RBC renewal and the small RBC in the circulation is delayed, resulting in uneven RBC size. Further, it was found the increase of RBC survival time increased HbA1c concentration, suggesting that the correlation between RDW and HbA1c was caused by an increase in RBC survival time and high RDW. It was evident that the level of RDW was positively correlated with HbA1c and negatively correlated with blood glucose.[33,34]

Serum albumin is only synthesized in the liver and is a biochemical marker of nutritional status and a major component of colloidal osmotic pressure. Albumin is a negative acute phase protein whose synthesis rate is negatively correlated with inflammatory activity.

Currently, there are no effective biomarkers to monitor the DR or to effectively classify patients in order to best assess the efficacy of treatment, and our study has several advantages. The sample size of this study was large enough to determine a significant association between RA and patients with DR. In addition, analysis of detailed covariant data allowed the adjustment for potential confounding factors that might influence the association between RA and DR. However, there are some limitations to the current study. First, cross-sectional study design means causality could not be determined. Prospective studies are thus needed to determine the cause and effect. Second, the data used in this study were extracted from a single blood test. Furthermore, a continuous testing may be more informative than admission testing because of the short life span of the blood cells. Third, RA is easily measured in clinical practice, but the loss of RDW and albumin is common.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (Lingzhen Kong).

REFERENCES

1. Dieren SV, Beulens J, Schouw Y, Grobbee DE, Neal BJ. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil*. 2010;17(1_Suppl):s3-s8.
2. Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: clinical considerations and management. *Nat Rev Endocrinol*. 2021;17(9):534-548. doi:10.1038/s41574-021-00512-2
3. Katulanda P, Sheriff M, Matthews DR. The diabetes epidemic in Sri Lanka – a growing problem. *Ceylon Med J*. 2006;51(1):26-28.
4. Skyler JS, Oddo C. Diabetes trends in the USA. *Diabetes Metab Res Rev*. 2002;18(S3):S21-S26.
5. Flugelman M. Compositions and methods for treating ophthalmic disorders; 2008.
6. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124-136.
7. Cui J, Ren JP, Chen DN, et al. Prevalence and associated factors of diabetic retinopathy in Beijing, China: a cross-sectional study. *BMJ Open*. 2017;7(8):e015473.
8. Lin T, Gubitosi-Klug RA, Channa R, Wolf RM. Pediatric Diabetic Retinopathy: Updates in Prevalence, Risk Factors, Screening, and Management. *Curr Diab Rep*. 2021;21(12):56. doi:10.1007/s11892-021-01436-x
9. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med*. 1994;331(22):1480-1487.
10. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Investig*. 2003;112(12):1821-1830.
11. Festa A, D'Agostino R, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome. *Circulation*. 2000;102(1):42-47.
12. Li J, Wang JJ, Qiang Y, Min W, Zhang SX. Endoplasmic reticulum stress is implicated in retinal inflammation and diabetic retinopathy. *FEBS Lett*. 2009;583(9):1521-1527.
13. Joussen AM, Poulaki V, Le ML, et al. A central role for inflammation in the pathogenesis of diabetic retinopathy. *FASEB J*. 2004;18(12):1450-1452.
14. Grigsby JG, Cardona SM, Pouw CE, et al. The role of microglia in diabetic retinopathy. *J Ophthalmol*. 2014;2014:705783.
15. Vaya A, Hernández J, Zorio E, Bautista D. Association between red blood cell distribution width and the risk of future cardiovascular events. *Clin Hemorheol Microcirc*. 2012;50(3):221-225.
16. Ma Y, Li S, Zhang A, et al. Association between red blood cell distribution width and diabetic retinopathy: a 5-year retrospective case-control study. *J Ophthalmol*. 2021;2021:1-9. doi:10.1155/2021/6653969
17. Magri CJ, Fava S. Red blood cell distribution width and diabetes-associated complications. *Diabetes Metab Syndr Clin Res Rev*. 2014;8(1):13-17.
18. Long J, Xie X, Xu D, et al. Association between red blood cell distribution width-to-albumin ratio and prognosis of patients with aortic aneurysms. *Int J Gen Med*. 2021;14:6287-6294.
19. Zhao N, Hu W, Wu Z, et al. The red blood cell distribution width–albumin ratio: a promising predictor of mortality in stroke patients. *Int J Gen Med*. 2021;14:3737-3747.
20. Yoo J, Ju S, Lee S, Cho Y, Lee J, Kim HC. Red cell distribution width/albumin ratio is associated with 60-day mortality in patients with acute respiratory distress syndrome. *Infect Dis*. 2020;52(4):266-270.
21. Bendek M, Canedo-Marroquín G, Realini O, et al. Periodontitis and gestational diabetes mellitus: a potential inflammatory vicious cycle. *Int J Mol Sci*. 2021;22:(21):11831. doi:10.3390/ijms222111831
22. Frühbeck G, Gómez-Ambrosi J, Ramírez B, et al. Increased levels of interleukin-36 in obesity and type 2 diabetes fuel adipose tissue inflammation by inducing its own expression and release by adipocytes and macrophages. *Front Immunol*. 2022;13:832185.
23. Zychowska M, Rojewska E, Kreiner G, Nalepa I, Przewlocka B, Mika J. Minocycline influences the anti-inflammatory interleukins and enhances the effectiveness of morphine under mice diabetic neuropathy. *J Neuroimmunol*. 2013;262(1-2):35-45. doi:10.1016/j.jneuroim.2013.06.005
24. Liu H, Jin F, Li Q, Gao Y, Liu X, Hou R. IL-34 and coronary heart disease complicated with diabetes mellitus. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2021;46(12):1409-1414.
25. Cabrera S, Coren A, Pant T, et al. Probiotic normalization of systemic inflammation in siblings of type 1 diabetes patients: an open-label pilot study. *Sci Rep*. 2022;12(1):3306.
26. Khairul-Anwar I, Wan-Nazatul-Shima S, Siti-Lailatul-Akmar Z, Siti-Azrin A, Zunaina E. Evaluation of TNF-α and IL-6 in saliva among diabetic retinopathy patients in East Coast Malaysia. *Trop Med Int Health*. 2022;27(3):310-316. doi:10.1111/tmi.13724
27. Lu L, Zou G, Chen L, Lu Q, Wu M, Li C. Elevated NLRP3 inflammasome levels correlate with vitamin D in the vitreous of proliferative diabetic retinopathy. *Front Med*. 2021;8:736316.
28. Lucijanić M, Jordan A, Jurin I, et al. Red cell distribution width is a potent prognostic parameter for in-hospital and post-discharge

mortality in hospitalized coronavirus disease 2019 patients: a registry-based cohort study on 3941 patients. *Croat Med J*. 2022;63(1):44-52.
29. Katamreddy A, Kokkinidis D, Miles J, Siasos G, Giannakoulas G. Faillace RT. Elevated red cell distribution width and cardiovascular mortality in ASCVD risk cohorts: National Health and Nutrition Examination Survey (NHANES III). *Rev Cardiovasc Med*. 2022;23(2):51.
30. Don BR, Kaysen G. Serum albumin: relationship to inflammation and nutrition. *Semin Dial*. 2004;17(6):432-437.
31. LeFevre ML. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161(4):281-290.
32. Delanghe J, Lambrecht S, Fiers T. Speeckaert MM. Labile glycated hemoglobin: an underestimated laboratory marker of short term glycemia. *Clin Chem Lab Med*. 2022;60(3):451-455.
33. Gu L. Xue S. The association between red blood cell distribution width and the severity of diabetic chronic kidney disease. *Int J Gen Med*. 2021;14:8355-8363.
34. Tsilingiris D, Makrilakis K, Barmpagianni A, et al. The glycemic status determines the direction of the relationship between red cell distribution width and HbA1c. *J Diabetes Complications*. 2021;35(10):108012.

How to cite this article: Zhao F, Liu M, Kong L. Association between red blood cell distribution width-to-albumin ratio and diabetic retinopathy. *J Clin Lab Anal*. 2022;36:e24351. doi:10.1002/jcla.24351