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Original Article

A hematologic composite score integrating iron, coagulation, and inflammation markers predicts diabetic retinopathy severity: a retrospective cross-sectional study

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Abstract: Objectives: This study aimed to develop and validate a hematological composite score incorporating ferritin, transferrin, fibrinogen, and the neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte ratios (PLR) to predict diabetic retinopathy (DR) severity. Methods: In this single-center retrospective cross-sectional study, 356 patients with type 2 diabetes were categorized into non-DR (n=142), non-proliferative DR (NPDR, n=112), and proliferative DR (PDR, n=102). The composite score was calculated as: (Ferritin × Fibrinogen × NLR × PLR)/Transferrin. Multivariable logistic regression and receiver operating characteristic (ROC) analyses were conducted to evaluate predictive performance, adjusting for relevant covariates. Results: The composite score showed strong discriminatory ability for identifying PDR (AUC=0.898; 95% CI: 0.85-0.93), significantly outperforming individual markers (e.g., ferritin AUC=0.744, fibrinogen AUC=0.722; P<0.001). Each standard deviation increase in the score was associated with a 2.8-fold higher odds of PDR (adjusted OR=2.83; 95% CI: 2.12-3.78). Subgroup analysis revealed greater predictive accuracy in patients with diabetes duration ≥10 years (AUC=0.92) compared to those with <10 years (AUC=0.82; P for interaction =0.012). Conclusions: This hematologic composite score, integrating iron, coagulation, and inflammation markers, offers a cost-effective and clinically accessible tool for DR severity assessment, particularly in patients with long-standing diabetes. Its implementation may enhance screening precision and inform individualized management strategies.

Keywords: Diabetic retinopathy, composite biomarker score, iron metabolism, chronic inflammation, hypercoagulability

Introduction

Diabetic retinopathy (DR), a microvascular complication of diabetes mellitus, remains a leading cause of preventable blindness among working-age adults worldwide. According to the International Diabetes Federation, an estimated 537 million adults currently live with diabetes - a number projected to rise to 783 million by 2045 [1]. Approximately one-third of these individuals develop DR, and about 10% progress to vision-threatening stages such as proliferative diabetic retinopathy (PDR) or diabetic macular edema (DME) [2]. The global socioeconomic burden is immense, with annual direct medical costs for DR management exceeding $500 billion, further compounded by productivity losses and reduced quality of life [3].

Despite advancements in glycemic control and anti-VEGF therapies, 30-40% of patients show suboptimal responses, highlighting a need for novel biomarkers to enhance risk stratification and guide personalized treatment strategies [4]. Current DR management largely depends on imaging modalities such as optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). Although effective, these techniques are resource-intensive, not widely accessible in low-income settings, and offer limited predictive value in the early stages of disease progression [5]. Systemic biomarkers

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like HbA1c and high-sensitivity C-reactive protein (hs-CRP) have similarly limited utility due to their narrow focus on isolated pathologic mechanisms [6].

Emerging research underscores the multifactorial nature of DR pathogenesis, involving iron-mediated oxidative stress, chronic inflammation, and hypercoagulability [7-9]. For instance, excess iron exacerbates retinal oxidative damage through Fenton reactions, while elevated fibrinogen contributes to microvascular thrombosis - both synergistically promoting DR progression [9, 10]. However, these mechanistic pathways have not yet been integrated into a unified predictive model.

This study focuses on a panel of hematologic markers representing three interrelated biological processes: iron metabolism (ferritin, transferrin), coagulation (fibrinogen), and inflammation (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR]). Ferritin, an intracellular iron-storage protein, is positively associated with retinal iron deposition and vascular permeability in preclinical models [11], while transferrin regulates systemic iron availability and exerts antioxidant effects [12]. Fibrinogen, beyond its role in clot formation, can directly activate endothelial cells and enhance inflammatory signaling [13]. NLR and PLR, both easily derived from routine complete blood counts, serve as cost-effective proxies for systemic inflammation and prothrombotic states [14]. Although each of these markers has been individually linked to DR, their combined predictive value remains unexplored.

Therefore, this study aims to develop and validate a hematologic composite score that integrates markers of iron metabolism, coagulation, and inflammation to predict the severity of DR. We hypothesize that this integrative score will outperform conventional biomarkers in discriminative accuracy - particularly among patients with long-standing diabetes - thereby offering a scalable and practical tool for early risk assessment and personalized disease monitoring.

Materials and methods

Study design

This single-center retrospective cross-sectional study was conducted at The Second Hospital of Dalian Medical University. Clinical data were extracted from the hospital's proprietary electronic medical record system (the Second Hospital of Dalian Medical University Integrated Clinical Management Platform, Version 10.2.1; Winning Health Technology Group Co., Ltd., Shanghai, China) using standardized Structured Query Language queries and application programming interfaces, under the supervision of the institutional informatics team. Data anonymization and export adhered to institutional privacy policies.

Eligible data were collected from 356 patients with T2DM who underwent comprehensive ophthalmologic evaluation between January 2018 and December 2022. They were categorized into non-DR (n=142), NPDR (n=112), and PDR (n=102) according to the International Clinical Diabetic Retinopathy Disease Severity Scale: [15]. The study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies. Ethical approval was obtained from the Institutional Review Board of The Second Hospital of Dalian Medical University (Approval No. 202436). Informed consent was waived due to the retrospective nature of the analysis. All data were anonymized and handled in accordance with applicable privacy regulations.

Study population

Inclusion criteria: 1) Age ≥18 years with a confirmed diagnosis of T2DM based on American Diabetes Association (ADA) criteria: fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, or documented use of glucose-lowering medication [15]. 2) Completion of standardized retinal imaging (fundus photography or OCT) for DR severity classification according to the International Clinical Diabetic Retinopathy Disease Severity Scale [16]: ① Non-DR: No retinal abnormalities. ② Non-proliferative DR (NPDR): Presence of microaneurysms, intraretinal hemorrhages, or exudates without neovascularization. ③ Proliferative DR (PDR): Evidence of neovascularization, vitreous hemorrhage, or tractional retinal detachment. 3) Availability of hematologic parameters required for the composite score within 3 months of retinal assessment: ① Iron metabolism: Serum ferritin (μg/L), transferrin (g/L). ② Coagulation: Fibrinogen (g/L). ③ Inflammation: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR).

Exclusion criteria: 1) Coexisting retinal diseases (e.g., age-related macular degeneration, reti-

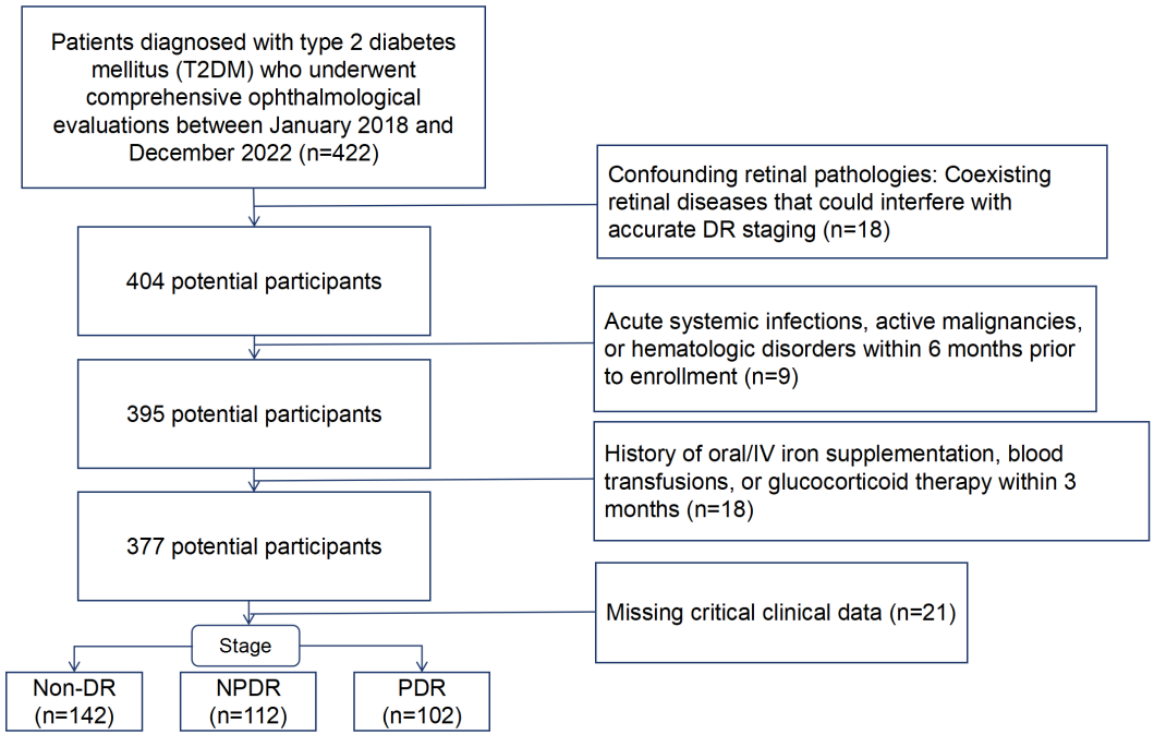

Figure 1. Inclusion and exclusion flow chart.

nal vein occlusion, retinal detachment) that could confound DR staging. 2) Acute systemic infections (e.g., pneumonia, urinary tract infection), active malignancies, or hematologic disorders (e.g., hemochromatosis, thalassemia) within 6 months before data collection. 3) History of oral/intravenous iron supplements, blood transfusion, or glucocorticoid therapy within 3 months. 4) Missing key clinical or laboratory data (see **Figure 1**).

Data collection

All data were retrospectively extracted from the EMR system using structured queries and validated extraction protocols.

Outcome variable

The primary outcome was DR severity. Retinal evaluations were performed using standardized protocols, with results independently verified by two ophthalmologists to ensure diagnostic consistency.

Exposure variables

The hematologic composite score included five routine laboratory markers: ferritin, transferrin, fibrinogen, NLR, and PLR.

Ferritin (reference: 30-400 μg/L) and transferrin (2.0-3.6 g/L) were measured via chemiluminescent immunoassay and immunoturbidimetry, respectively.

Fibrinogen (2.0-4.0 g/L) was assessed using the Clauss method.

NLR was calculated as the neutrophil count divided by lymphocyte count; PLR as platelet count divided by lymphocyte count, both derived from complete blood counts.

The composite score was calculated as: (Ferritin × Fibrinogen × NLR × PLR)/Transferrin.

All lab values were obtained within 3 months of retinal evaluation as part of routine diabetes care.

Covariates

Covariates included: Demographics: age, sex, duration of diabetes. Metabolic parameters: HbA1c, fasting glucose, lipid profile (total cholesterol, LDL-C, HDL-C). Comorbidities: hypertension, coronary artery disease (CAD), anemia. Renal function: estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR). Definitions: Hypertension: systolic

Table 1. Comparison of baseline characteristics

Variable	Non-DR (n=142)	NPDR (n=112)	PDR (n=102)	Statistic	*p*-value
Age (years)	58.2±9.5	59.1±8.7	60.3±10.2	F=1.3	0.272
Male, n (%)	78 (54.9%)	62 (55.4%)	56 (54.9%)	X^2=0.01	0.997
Diabetes duration (years)	8.5±4.2	9.1±5.0	10.2±5.8	F=3.1	0.061
Hypertension, n (%)	85 (59.9%)	70 (62.5%)	68 (66.7%)	χ^2=1.2	0.555
Coronary artery disease, n (%)	25 (17.6%)	26 (23.2%)	34 (33.3%)	χ^2=1.5	0.041
Anemia, n (%)	22 (15.5%)	28 (25.0%)	40 (39.2%)	χ^2=18.7	<0.001
HbA1c (%)	7.8±1.5	8.0±1.6	8.2±1.7	F=1.8	0.181
Fasting glucose (mg/dL)	148±32	153±35	160±40	F=2.4	0.090
Total cholesterol (mg/dL)	182±38	188±42	195±45	F=2.2	0.115
LDL-C (mg/dL)	102±28	108±31	112±34	F=2.7	0.073
HDL-C (mg/dL)	45±12	43±11	42±10	F=1.9	0.152
eGFR (mL/min/1.73 m^2)	82±18	76±16	68±15	F=25.6	<0.001
UACR (mg/g)	30 (15-60)	65 (30-120)	120 (75-200)	H=62.1	<0.001

Abbreviations: Non-DR, no diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio. Data presentation: Mean ± standard deviation or median (interquartile range).

blood pressure ≥140 mmHg, diastolic ≥90 mmHg, or use of antihypertensive medication. CAD: history of myocardial infarction, angina, or coronary intervention. Anemia: hemoglobin <13 g/dL for men or <12 g/dL for women.

HbA1c was measured via high-performance liquid chromatography; glucose and lipids by enzymatic assays; eGFR using the CKD-EPI equation; and UACR by immunoturbidimetry. All covariates were recorded within 3 months of DR evaluation.

Statistical analysis

Sample size was estimated using PASS software (version 15.0), assuming an odds ratio (OR) of 2.5 for the association between the composite score and advanced DR, with α=0.05 and 80% power.

Baseline characteristics were summarized by DR stage. Continuous variables were presented as mean ± SD or median (interquartile range) and compared using ANOVA or Kruskal-Wallis tests, as appropriate. Categorical variables were presented as counts (percentages) and compared using chi-square tests.

Spearman's rank correlation was used to assess relationships among ferritin, transferrin, fibrinogen, NLR, and PLR. A generalized additive model (GAM) was used to determine any nonlinear interactions.

Multivariable logistic regression models were constructed to evaluate the association between the composite score and DR severity, adjusting for age, sex, and diabetes duration. Results were reported as adjusted ORs with 95% confidence intervals (CIs).

Receiver operating characteristic (ROC) curves were generated to compare the discriminative performance of the composite score and individual markers, with area under the curve (AUC) differences assessed using DeLong's test. Sensitivity analyses were stratified by diabetes duration (<10 vs. ≥10 years).

All analyses were performed in R (version 4.3.1), with statistical significance set at P<0.05.

Results

Comparison of baseline characteristics

Table 1 summarizes demographic, metabolic, and comorbidity profiles across the DR spectrum. No significant differences were observed in age, sex distribution, HbA1c, fasting glucose, or lipid levels among the groups (all P>0.05). However, patients with PDR had a significantly longer duration of diabetes, poorer renal function, higher rates of anemia, and a greater prevalence of CAD compared to those without DR (all P<0.05).

Table 2. Comparison of the hematologic composite score and its components

Marker	Non-DR (n=142)	NPDR (n=112)	PDR (n=102)	Statistic	*p*-value
Ferritin (μg/L)	120±45	185±65	270±95	F=45.2	<0.001
Transferrin (g/L)	2.8±0.4	2.4±0.4	2.2±0.3	F=9.8	0.003
Fibrinogen (g/L)	3.2±0.8	3.6±0.8	4.5±1.2	F=32.1	<0.001
NLR	2.1±0.7	2.8±0.8	3.4±1.1	F=38.5	<0.001
PLR	125±35	150±45	180±50	F=28.7	<0.001
Composite Score	1,250±480	2,360±720	3,980±1,180	F=89.4	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Comparison of the hematologic composite score and its components

The hematologic composite score and its individual components varied significantly by DR stage (**Table 2**; **Figure 2**). Serum ferritin levels progressively increased from 120±45 μg/L in the non-DR group to 270±95 μg/L in the PDR group (P<0.001). In contrast, transferrin levels decreased from 2.8±0.4 g/L to 2.2±0.3 g/L (P=0.003). Fibrinogen, NLR, and PLR also increased in parallel with DR severity (all P<0.001). The composite score rose markedly across the stages, from 1,250±480 in non-DR to 3,980±1,200 in PDR (P<0.001), showing a strong association with DR progression.

Correlations among composite score components

Spearman's rank correlation analysis revealed significant interrelationships among the score's components (**Figure 3**; **Table 3**). Ferritin showed strong positive correlations with fibrinogen (r=0.617, P<0.001), NLR (r=0.581, P<0.001), and PLR (r=0.514, P<0.001), and a moderate inverse correlation with transferrin (r=-0.44, P<0.001). Transferrin was negatively correlated with fibrinogen (r=-0.377, P<0.001), NLR (r=-0.336, P<0.001), and PLR (r=-0.291, P=0.002). Fibrinogen, NLR, and PLR were also strongly correlated with each other (r=0.584-0.670, P<0.001), suggesting synergistic interactions between coagulation and inflammatory pathways.

Multivariable regression analysis

Multivariable logistic regression analysis incorporating the composite score and key clinical covariates (HbA1c, diabetes duration, CAD, eGFR, and anemia) demonstrated that the composite score was an independent predictor of advanced DR (**Table 4**; **Figure 4**). Each standard deviation (SD) increase in the score was associated with a 2.8-fold higher odds of PDR compared to non-DR/NPDR (adjusted OR=2.83, 95% CI: 2.12-3.78, P<0.001). Anemia exhibited a non-significant trend toward higher PDR risk (adjusted OR=1.40, 95% CI: 0.95-2.05, P=0.087), in line with its rising prevalence across DR stages. Both CAD (adjusted OR=1.35, 95% CI: 1.02-1.79, P=0.038) and eGFR decline (adjusted OR=0.85 per 10 mL/min, 95% CI: 0.76-0.95, P=0.004) were also identified as independent predictors.

Predictive performance by ROC analysis

The composite score demonstrated superior discriminatory performance for PDR compared to individual components (**Figure 5**; **Table 5**). Its AUC reached 0.898 (95% CI: 0.85-0.93), significantly outperforming ferritin (AUC=0.744, 95% CI: 0.69-0.81; P<0.001), transferrin (AUC=0.649, 95% CI: 0.61-0.75; P<0.001), fibrinogen (AUC=0.722, 95% CI: 0.65-0.79; P<0.001), NLR (AUC=0.685, 95% CI: 0.63-0.77; P<0.001), and PLR (AUC=0.633, 95% CI: 0.58-0.72; P<0.001). Using a cutoff score of ≥2.5, the sensitivity and specificity for identifying PDR were 84% and 82%, respectively.

Sensitivity analyses by diabetes duration

Subgroup analysis based on diabetes duration revealed significantly improved predictive performance of the composite score in patients with diabetes for ≥10 years compared to those with <10 years (**Table 6**). In the long-duration subgroup, the adjusted OR for PDR per SD increase in the score was 3.45 (95% CI: 2.40-4.95, P<0.001), with a significant interaction between diabetes duration and score effect (P for interaction =0.012). The AUC for PDR prediction reached 0.92 (95% CI: 0.88-0.96) in

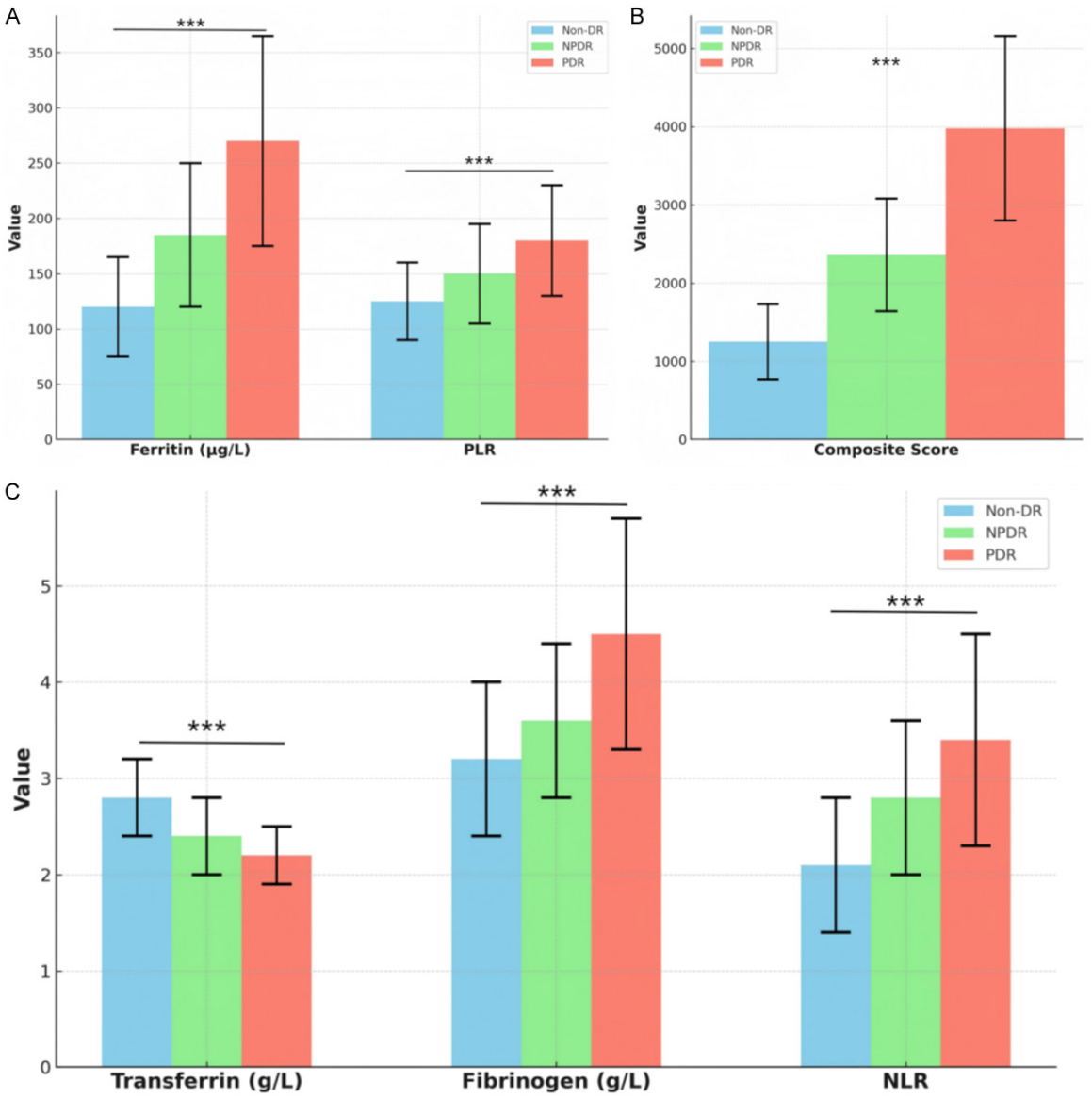

Figure 2. Distribution of hematologic markers and composite scores across diabetic retinopathy (DR) stages. A. Serum ferritin and platelet-to-lymphocyte ratio (PLR) levels showed a significant upward trend from Non-DR to PDR groups. B. The hematologic composite score increased significantly with DR severity. C. Transferrin levels decreased, while fibrinogen levels and neutrophil-to-lymphocyte ratio (NLR) increased significantly with advancing DR stage. Data are presented as mean ± SD. ***P<0.001. Group colors: Non-DR (blue), NPDR (green), PDR (red).

patients with longer diabetes duration, compared to 0.82 (95% CI: 0.76-0.88) in those with shorter duration (P=0.003 for AUC comparison).

Discussion

This study demonstrated that a hematologic composite score - integrating markers of iron metabolism, coagulation, and inflammation (ferritin, transferrin, fibrinogen, NLR, and PLR) - robustly predicted DR severity, outperforming individual biomarkers. Its discriminative performance was particularly pronounced in patients with long-standing diabetes (≥10 years), underscoring its clinical value for risk stratification in advanced DR. By capturing synergistic interactions among these biological pathways, the composite score achieved an AUC of 0.898 for detecting proliferative DR (PDR), significantly surpassing traditional markers such as HbA1c and hs-CRP. These findings support the con-

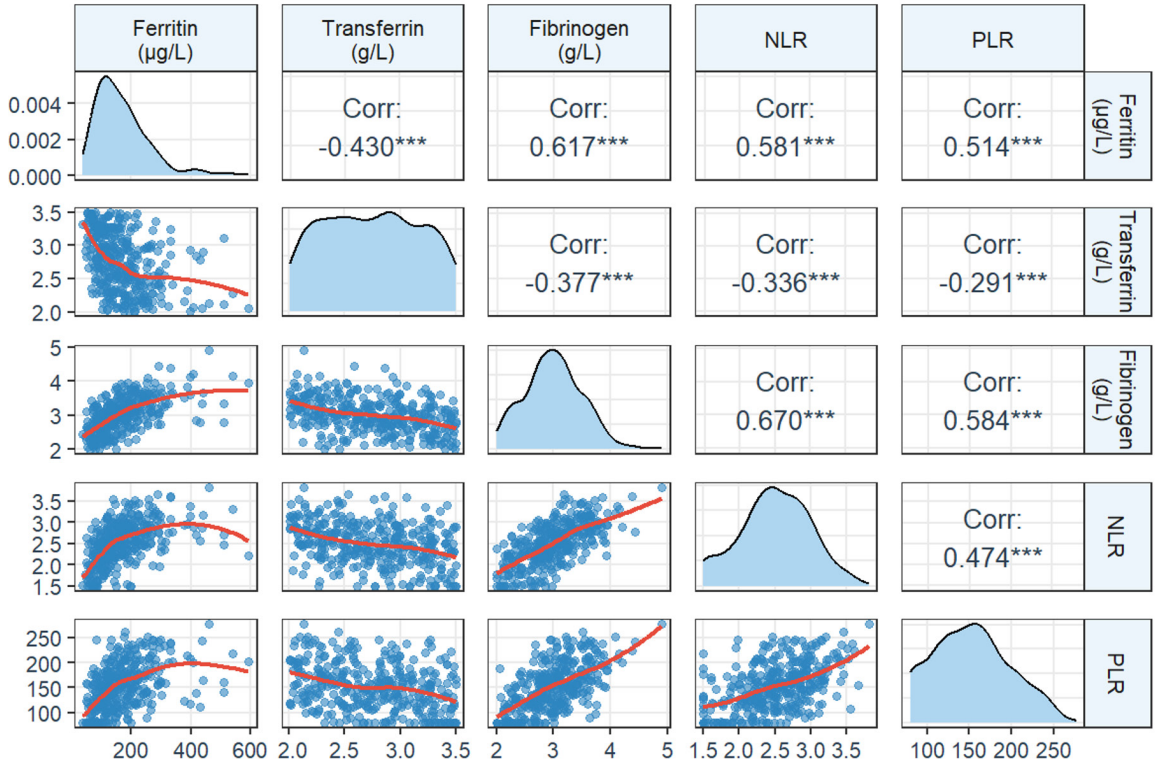

Figure 3. Correlation coefficients between composite score components. Significance levels: ***P<0.001. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3. Spearman's rank correlation coefficients between composite score components

Variable	Ferritin	Transferrin	Fibrinogen	NLR	PLR
Ferritin	1.000	-0.430***	0.617#,***	0.581#,***	0.514#,***
Transferrin	-	1.000	-0.377***	-0.336***	-0.291**
Fibrinogen	-	-	1.000	0.670#,***	0.584#,***
NLR	-	-	-	1.000	0.474#,***
PLR	-	-	-	-	1.000

Notes: Correlation coefficients (ρ) are presented in the lower triangle; upper triangle is omitted for redundancy. Significance levels: ***P<0.001; **P=0.002. #r≥0.5. Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

ceptualization of DR as a multifactorial disease and highlight the utility of integrative biomarker approaches that reveal underlying mechanisms involving iron dysregulation, hypercoagulability, and chronic inflammation.

The observed elevation in serum ferritin and reduction in transferrin levels in PDR are consistent with the hypothesis of iron-induced retinal oxidative stress. Iron overload amplifies hydroxyl radical production through the Fenton reaction, damaging retinal endothelial cells and pericytes [10]. This process is exacerbated by diabetes-induced hypoxia, which upregulates divalent metal transporter 1 in retinal cells, increasing iron uptake and oxidative injury [17]. Our results corroborate prior studies linking ferritin to DR progression [18], and further demonstrate its synergism with coagulation and inflammatory markers. The inverse correlation between transferrin and DR severity may reflect a compensatory mechanism for iron sequestration. Animal studies show that targeting transferrin receptors can ameliorate retinal dysfunction [19], emphasizing the importance of systemic-retinal iron balance. Our composite score captures this interplay more comprehensively than isolated ferritin measurement.

Fibrinogen, NLR, and PLR collectively illustrate the intersection of hypercoagulability and inflammation in DR. Elevated fibrinogen (>4.0 g/L) increases plasma viscosity and platelet aggregation, promoting microvascular throm-

Table 4. Adjusted odds ratios for diabetic retinopathy severity

Variable	Adjusted OR	95% CI	*p*-value
Composite Score (per SD)	2.83	2.12-3.78	<0.001
HbA1c (per 1%)	1.18	1.051-1.330	0.006
Diabetes duration (per year)	1.07	1.008-1.134	0.023
Coronary artery disease (yes vs. no)	1.35	1.016-1.786	0.038
eGFR (per 10 mL/min)	0.85	0.763-0.953	0.004
Anemia (yes vs. no)	1.40	0.954-2.054	0.087

Abbreviations: OR, odds ratio; CI, confidence interval; SD, standard deviation; HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate. Model details: Outcome: DR severity (PDR vs. Non-DR/NPDR). Composite score: Standardized (z-score) for interpretability. Anemia: Defined as hemoglobin <13 g/dL (men) or <12 g/dL (women). Adjusted covariates: HbA1c, diabetes duration, coronary artery disease, eGFR, anemia. Excluded variables: Age, sex, hypertension, LDL-C, HDL-C (retained if P<0.1 in univariate analysis).

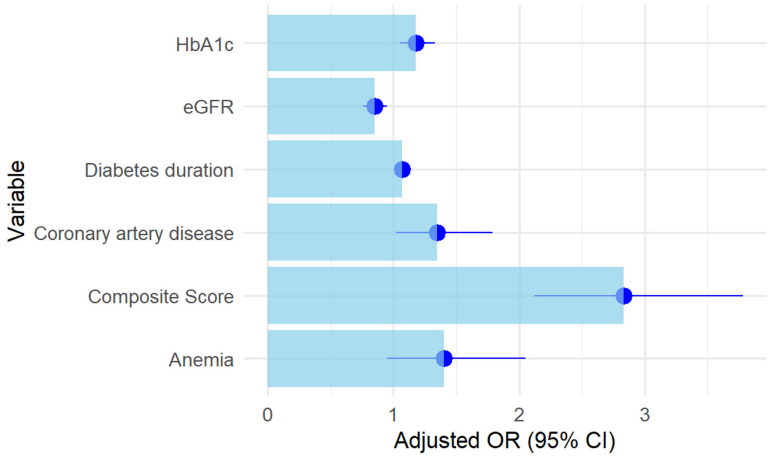

Figure 4. Adjusted odds ratios (95% CI) for diabetic retinopathy severity. HbA1c, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate.

bosis [9]. NLR and PLR reflect neutrophil-driven inflammation and heightened thrombotic potential [20]. The strong correlation between fibrinogen and NLR supports a feed-forward loop in which inflammation enhances coagulation, a mechanism previously reported in diabetic nephropathy [21] but less explored in DR. Neutrophil extracellular traps, known to be elevated in diabetes, may bridge these pathways by activating coagulation factors and inducing retinal vascular injury [22]. Our data further show that a PLR >160 combined with fibrinogen >4.0 g/L defines a high-risk phenotype with significantly increased odds of PDR. This is consistent with randomized trials identifying fibrinogen cleavage products as mediators of retinal ischemia [23], reinforcing the need for dual-target strategies addressing both inflammation and coagulation.

Previous biomarker studies in DR have largely focused on individual molecules such as VEGF or ICAM-1 [24], which, although biologically relevant, demonstrate limited predictive accuracy when used alone. Our composite score (AUC=0.898) outperforms such markers by integrating complementary pathogenic processes. This aligns with emerging perspectives that classify DR as a "multiplex disease", best studied through systems biology frameworks [25]. Notably, the score's enhanced predictive power in patients with diabetes duration ≥10 years echoes findings from the ACCORD Eye Study, where iron chelation slowed DR progression in patients with long-standing diabetes [26]. This duration-dependent effect may relate to cumulative iron deposition, as histopathologic studies have shown that retinal iron deposits correlate with disease duration and severity in diabetic patients [27].

Although OCT and FFA are the gold standards for DR diagnosis and staging, they have notable limitations. OCT enables high-resolution imaging of retinal architecture, detecting macular edema, cysts, and subretinal fluid [28], while FFA visualizes dynamic vascular changes such as microaneurysms, ischemia, and neovascularization [29]. However, both modalities require costly equipment, specialized personnel, and, in the case of FFA, invasive dye injection - limiting their accessibility in resource-constrained settings [30]. In contrast, our hematologic composite score, with 84% sensitivity and 82% specificity for PDR detection, offers a scalable, non-invasive alternative. Its performance is comparable to non-invasive imaging tools like ultra-wide-field fundus photography [31], and it leverages routine blood tests, making it especially useful for triaging high-risk patients in underserved areas. Nevertheless, it cannot replace the ana-

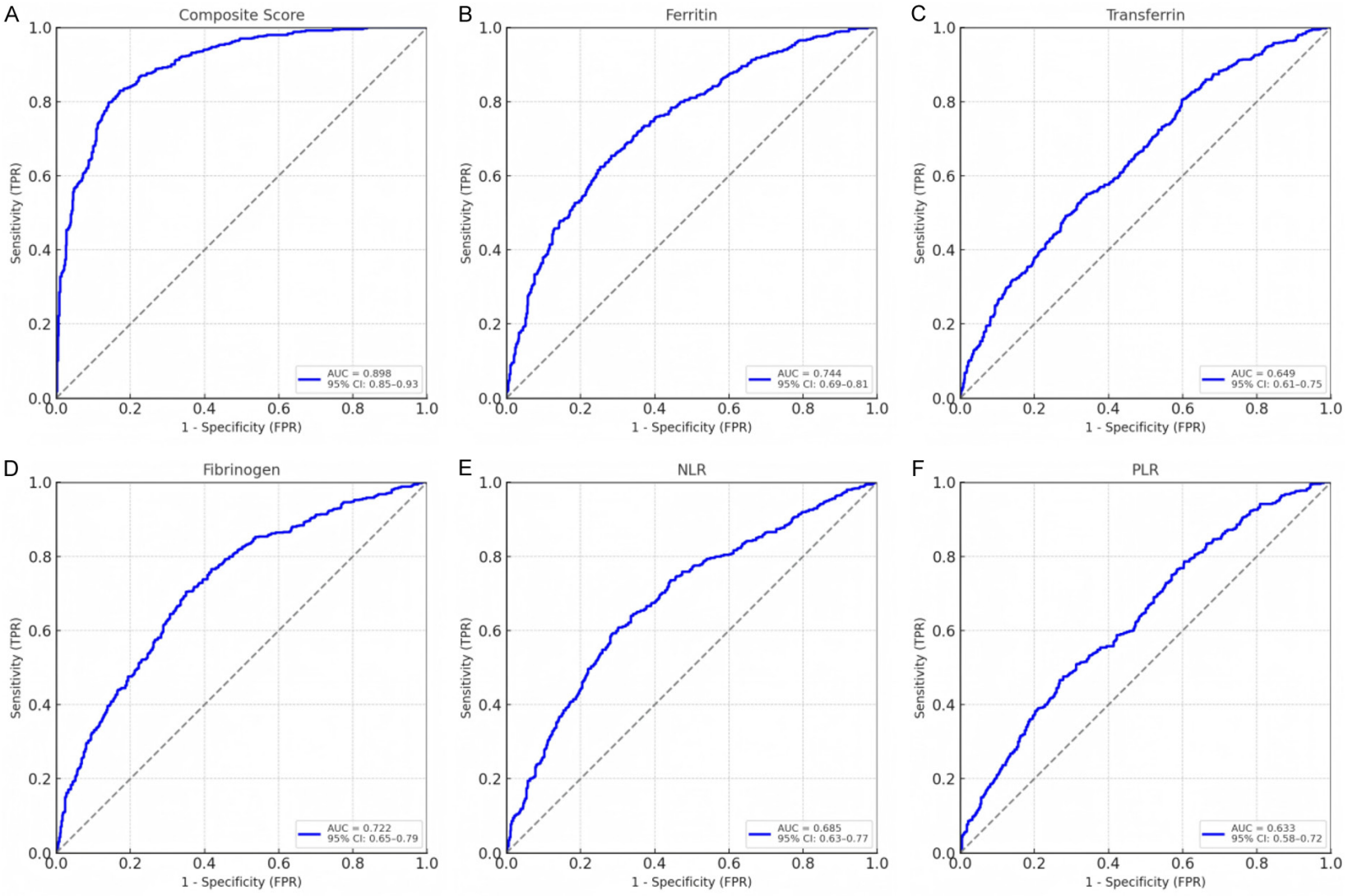

Figure 5. Receiver operating characteristic (ROC) curves for the composite score and its individual components in discriminating proliferative diabetic retinopathy (PDR). The composite score (AUC=0.898, 95% CI: 0.85-0.93) demonstrated superior discriminative performance compared to ferritin (AUC=0.744, 95% CI: 0.69-0.81), transferrin (AUC=0.649, 95% CI: 0.61-0.75), fibrinogen (AUC=0.722, 95% CI: 0.65-0.79), neutrophil-to-lymphocyte ratio (NLR, AUC=0.685, 95% CI: 0.63-0.77), and platelet-to-lymphocyte ratio (PLR, AUC=0.633, 95% CI: 0.58-0.72) (all P<0.001 vs. composite score). At the optimal cutoff (composite score ≥2.5), the sensitivity and specificity were 84% and 82%, respectively.

Table 5. ROC analysis of the composite score and individual markers

Marker	AUC	95% CI	Sensitivity	Specificity
Composite Score	0.898	0.85-0.93	84%	82%
Ferritin	0.744	0.69-0.81	72%	68%
Transferrin	0.649	0.61-0.75	65%	64%
Fibrinogen	0.722	0.65-0.79	70%	66%
NLR	0.685	0.63-0.77	68%	63%
PLR	0.633	0.58-0.72	62%	60%

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Statistical comparison: DeLong's test confirmed the composite score's AUC was significantly higher than all individual markers (P<0.001).

Table 6. Subgroup analysis stratified by diabetes duration

Subgroup	Adjusted OR (95% CI)	AUC (95% CI)	*p*-value	P interaction
Diabetes duration ≥10 years (n=198)	3.45 (2.40-4.95)	0.92 (0.88-0.96)	<0.001	0.012
Diabetes duration <10 years (n=158)	2.10 (1.55-2.85)	0.82 (0.76-0.88)	<0.001	-

Notes: Adjusted for: HbA1c, eGFR, anemia, coronary artery disease. Interaction test: Likelihood ratio test comparing models with/without interaction term (composite score × diabetes duration). AUC comparison: DeLong's test for ROC curve differences between subgroups. Abbreviations: OR, odds ratio; CI, confidence interval; AUC, area under the curve.

tomic detail provided by OCT or FFA. Future research should assess the added value of combining this score with imaging biomarkers (e.g., retinal thickness) to optimize diagnostic strategies and resource allocation.

This study presented three key innovations. First, it introduced a unified hematological score combining iron, coagulation, and inflammation markers to stage DR, addressing the limitations of single-marker models. Second, it identified clinically actionable thresholds for risk stratification and targeted screening. Third, it used routine laboratory data, enhancing feasibility in low-resource settings where advanced imaging is unavailable.

Several limitations must be acknowledged. The cross-sectional design precludes causal inference and limits temporal interpretation. Unmeasured confounders, such as dietary iron intake or genetic variants (e.g., HFE mutations linked to hereditary hemochromatosis), may affect the observed associations. Furthermore, as a single-center study, generalizability is limited; validation in larger, multiethnic cohorts is warranted. Future investigations should explore longitudinal changes in the composite score and assess its role in monitoring treatment response.

Disclosure of conflict of interest

None.

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