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RISK FACTORS ASSOCIATED WITH THE PROGRESSION OF DIABETIC RETINOPATHY IN ADULT PATIENTS

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Abstract

To determine the predictive ability of conventional glycemic measurements and combined inflammatory-thrombotic and protein-based biomarkers in 24-month diabetic retinopathy progression in individuals with type 2 diabetes mellitus. The study was a prospective longitudinal cohort study that recruited 340 patients with type 2 diabetes mellitus who were followed over a period of 24 months. The blood tests at baseline were hemoglobin A1c, diabetes duration, cumulative glycemic index, which is the product of diabetes duration and mean hemoglobin A1c, high-sensitivity C-reactive protein, platelet count, inflammatory-thrombotic score, which is the product of high-sensitivity C-reactive protein and platelet count, albumin-to-glob The main outcome was the progression of diabetic retinopathy which was at least two-step increase on the International Clinical Diabetic Retinopathy Severity Scale or proliferative diabetic retinopathy. Akaike Information Criterion, Bayesian Information Criterion, C-index, net reclassification improvement, integrated discrimination improvement and calibration models were used to compare nine nested Cox proportional hazards and Fine-Gray competing risk models. During a period of 24 months, 86 of the patients who constituted a quarter of the cohort developed diabetic retinopathy. A baseline glycemic-only model had a C-index of 0.684, whereas the cumulative glycemic index model had a greater discrimination of 0.723, which had a significant decrease in the Akaike Information Criterion. The inflammatory-thrombotic score on its own gave a C-index of 0.741 and albumin to globulin ratio produced a significant net reclassification of 18.4 percent. The cumulative glycemic index, inflammatory-thrombotic score, albumin-to-globulin ratio, systolic blood pressure and fibrinogen each had a hazard ratio of 1.483, 1.562, 0.713, and 1.160, respectively, and the cross-validated C-index was 0.758 with an excellent cal The rate of progression in patients in the highest risk tertile was 42.8 percent as compared to 8.2 percent in the lowest tertile.The albumin-to-globulin ratio and inflammatory-thrombotic score are both important incremental prognostic factors in relation to the conventional glycemic measures when used as predictors of diabetic retinopathy progression. Diabetic retinopathy risk stratification should include routine measurement of high-sensitivity C-reactive protein, platelet count, and serum protein fractions to identify patients at high risk who need more than glycemic control to achieve multi-target interventions.

Keywords: Diabetic Retinopathy, Inflammatory-Thrombotic Score, Albumin-To-Globulin Ratio, Cumulative Glycemic Index, Type 2 Diabetes Mellitus, Risk Prediction Modeling.

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INTRODUCTION

A common microvascular complication of diabetes mellitus, diabetic retinopathy is one of the most common etiologies of avoidable blindness and severe vision loss in working-aged adults worldwide (Lalwani et al., 2025; Li et al., 2023). It is a neurovascular degenerative process caused by chronic hyperglycemia and causes multi-organ dysfunction, with a specific impact on the retina (capillary damage and ischemia) (Perais et al., 2023). It has a multifaceted pathophysiology that depends on a combination of systemic factors, especially the years of diabetes, and glycemic management (Krstevska et al., 2023). Additional issues within the system that are considered critical and promote the onset and development of DR are hypertension, dyslipidemia, prothrombotic conditions, chronic inflammation, oxidative stress, and the presence of proinflammatory cytokines and angiogenesis stimulatory molecules (Rasoulinejad, 2022). In addition to these confirmed factors, new studies also reveal the role of genetic predispositions and particular metabolic indicators, including the level of altered globulin and albumin-to-globulin ratios, in the susceptibility and development of diabetic retinopathy (Alhalwani et al., 2023). Moreover, it has been found that hemorheological parameters, including platelet count, are important prognostic factors in the development of diabetic retinopathy, despite panretinal photocoagulation (Baek et al., 2021). This complex etiology highlights the importance of a detailed knowledge of both known and emerging risk factors to enhance prognostic performance and treatment of diabetic retinopathy (Mellor et al., 2024). Since chronic hyperglycemia is a leading cause of microvascular complications, intensive glycemic control was found to significantly decrease the occurrence of DR (Sakini et al., 2024). Nonetheless, even with a strict glycemic control, the percentage of patients with the development and progression of DR remains high, implying that other, less apparent risk factors are involved in the development of the condition, other than glucose homeostasis (Chistiakov, 2011).

As an example, a study showed that a higher activity of the polyol pathway and protein kinase C and improved expression of growth factors such as VEGF, changes in hemodynamics, the formation of advanced glycation end-products, and oxidative stress also play a significant role in DR pathogenesis (Tarr et al., 2013). All these interacting molecular and cellular alterations contribute to the establishment of retinal hypoxia and ensuing

neovascularization that is a characteristic of progressive diabetic retinopathy (Mondal et al., 2024). The combination of these processes eventually results in changes in the structure and functionality of the retinal vasculature, which ultimately results in the typical damage seen in diabetic retinopathy (Kusuhara et al., 2018). Originally, DR was regarded as a microvascular disease, but it turns out that it has much in common with inflammatory processes and neurodegradation (Gomułka & Ruta, 2023). In fact, the continued presence of high levels of glycated hemoglobin (HbA1c) results in the formation and deposition of advanced glycation end-products that subsequently encourage the production of pro-inflammatory cytokines and could additionally increase the level of vascular endothelial growth factor (ubowska et al., 2016). This complex interconnection between hyperglycemia, oxidative stress, and inflammation plays a role in endothelial dysfunction and the degradation of the blood-retinal barrier (Hameed et al., 2025; Lemos et al., 2024; Li et al., 2023; Zhuang et al., 2023). Such a cascade of events eventually leads to the retinal disorganization and breakdown (Treibel et al., 2022). The impairment of the retinal neurovascular unit, which consists of neurons, glial cells, and vascular components, also contributes to the further microvascular damage and neurodegeneration that plays a crucial role in the development of DR (Ciorba et al., 2025). In turn, the further insight into the molecular mechanisms of the neurovascular unit vulnerability to hyperglycemic injury is essential to the creation of specific interventions that can deal with both vascular and neuronal aspects of the disease (Duh et al., 2017). Additionally, chronic hyperglycemia triggers various metabolic pathways, such as polyol pathway, accumulation of end-products of advanced glycation, and protein kinase C pathway, which all play a role in retinal microvascular damage and pericyte loss (Wang & Lo, 2018). All these molecular changes result in vascular endothelial dysfunction, which causes hypoxia and consequent neovascularization, major processes in the evolution of diabetic retinopathy (García-Medina et al., 2020). These pathways in combination with dysregulation of reninangiotensinaldosterone system interrelate to facilitate glial cell dysfunction, increased inflammatory cytokines, abnormal growth factor signaling, and increased reactive oxidized species, which have a role in neuro-glial degeneration and vascular dysfunction (Shyam et al., 2025; Sinclair and Schwartz, 2 Such a complicated interaction eventually leads to the destabilization of the blood-retinal barrier, the destabilization of retinal

tissue homeostasis, and the creation of an environment in which diabetic retinopathy can develop (Karam-Palos et al., 2023; Sinclair and Schwartz, 2019).

The prolonged hyperglycemic state initiates initial cellular changes, such as polyol activation, growth factor up-regulation, and end product of advanced glycation, which, together with vascular dysfunction and neurodegeneration in the retina, are prompted by the hyperglycemic environment (Capitão & Soares, 2016; Mrugacz et al., 2021; Sinclair et The chain of molecular reactions contributes to chronic inflammation and oxidative stress, degradation of the blood-retinal barrier, and consequent retinal edema and ischemia (Mastari et al., 2020; Yudistira et al., 2025). This type of change impairs the structural and functional integrity of the retinal microvasculature, resulting in pericyte loss, endothelial cell dysfunction, and finally, capillary occlusion and nonperfusion (Sheng et al., 2024). In particular, the activation of protein kinase C by the diacylglycerol, which is a result of chronic hyperglycemia, directly leads to the development of retinal vascular dysfunctions and the loss of pericytes, which is a crucial symptom of microvascular damage in DR (Aldosari et al., 2022). Moreover, the presence of protein kinase C beta isoforms activation specifically in the pathological mechanisms of diabetic retinopathy and its positive effect on the extracellular matrix protein synthesis and the vascular endothelial growth factor level were specifically identified (Priyam, 2019). The interplay between protein kinase C activation, increased oxidative stress, and inflammatory cytokines like IL-1, IL-6, and IL-8 is a complex phenomenon that further enhances the damage of the retina and leads to diabetic retinopathy development (Caridi et al., 2021). It is also important that the renin-angiotensin system is involved, where Angiotensin II activates protein kinase C and NADPH oxidase, thus increasing the production of reactive oxygen species and causing direct retinal injury and breaking of the blood-retinal barrier (Nawaz, 2024; Sun et al., 2023). The diabetic retinal vasculature also markedly upregulates inflammatory processes, including greater leukocyte adhesion and endothelial dysfunction, which also leads to the destruction of the blood-retina barrier and vascular permeability (MANORMA et al., 2021). The inflammatory condition and oxidative stress are also chronic and also contributes to the increased formation of advanced glycation end-products which further promotes vascular damage and capillary occlusion in the retinal microvasculature (Kowluru, 2022; Lumbroso et al., 2015). In addition,

elevated glucose levels stimulate protein kinase C, which, in different isoforms, induces the expression of permeability-promoting factors such as VEGF in endothelial cells and smooth muscle cells, thus worsening retinal microvascular permeability and leading to abnormal angiogenesis (Gupta, 2019).

METHODOLOGY

By taking a problem-based research approach, this paper will methodically explore the multifactorial pathophysiology of diabetic retinopathy (DR), particularly in terms of the clinical paradox that intensive glycemic control is not equally effective in preventing or delaying the development or progression of diabetic retinopathy. The formulated research problem is as follows: since chronic hyperglycemia is a sufficient, yet not a sufficient cause of DR, how much of the risk of the progression of DR is associated with the quantitative role of hemorheological factors (platelet count), inflammatory markers (hs-CRP, IL-6), and protein biomarkers (albumin-to-globulin ratio) on top of glyce To address this, the study will be a prospective, longitudinal cohort study based on patients with type 2 diabetes mellitus (T2DM) of five-year or more duration, who will be recruited in tertiary care ophthalmology and endocrinology clinics. The exclusion criteria are: pre-existing non-diabetic-related retinal pathology, history of panretinal photocoagulation or intravitreal injections within six months before enrolment, advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m 2), and active proliferative diabetic retinopathy at baseline requiring urgent treatment. Informed consent is given in writing by all participants and the protocol is endorsed by the institutional ethics committee, based on the principles of the Declaration of Helsinki.

Baseline data obtaining includes extensive clinical, biochemical and ophthalmic examination. The glycemic exposure is measured through glycated hemoglobin (HbA1c, %), and the span of diabetes (D, years) is measured as a continuous variable. Complete blood count (including platelet count, PC, ×109/L), serum albumin (g/L), globulin (g/L), albumin-to-globulin ratio (AGR), high-sensitivity C-reactive protein (hs-CRP, mg/L), lipid profile (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholester The cumulative hyperglycemic burden is modeled as the product of the duration of diabetes and the mean HbA1c of the past 3 years, which is a cumulative glycemic index (CGI). A composite inflammatory-thrombotic score (ITS) is calculated as a hs-CRP and PC/population mean, to measure the joint effects of systemic inflammation and

platelet activation on DR risk. The ITS can be defined as the first proper mathematical equation:

ITS = (hs-CRP / median_hsCRP) + (PC / median PC).

where median_hsCRP and median_PC can be obtained as the cohort base distributions. This equation can be used to express the inflammatory and thrombotic burden of each patient in a unitless score compared to the reference population, with scores above 2.0 indicating a pro-inflammatory and a pro-thrombotic state in both domains at the same time.

Baseline and 24-month ophthalmic assessments of best-corrected visual acuity (BCVA) and wide-field fundus photography and spectral-domain optical coherence tomography (SD-OCT) of central subfield thickness (CST, μm). Two masked retinal experts carry out the DR staging based on the International Clinical Diabetic Retinopathy Severity Scale (0-4: no DR, mild NPDR, moderate NPDR, severe NPDR, and proliferative DR). The main outcome is the progression of the DR, characterized by an increase in the severity scale by at least two steps or proliferative DR or anti-VEGF/laser treatment. A Fine-Gray subdistribution hazard model using multivariates is built to model the risk of progression of DR whilst considering competing risks, including death or loss to follow-up. The second correct mathematical equation defines the cumulative incidence function of DR progression as:

$$F(t) = 1 - \exp[-\int_0^t h_0(u) * \exp(\beta_1 \cdot HbA1c + \beta_2 \cdot D + \beta_3 \cdot PC + \beta_4 \cdot AGR + \beta_5 \cdot ITS)\, du]$$

F (t) is the cumulative likelihood of progressing to DR by time t, the h 0 (u) is the baseline subdistribution hazard at time u, and 1 to 5 are the log-subdistribution hazard ratios of HbA1c, diabetes duration (D), platelet count (PC), albumin-to-globulin ratio (AGR), and the inflammatory-thrombotic score Multiplicative effect of all covariates on the hazard of progression is represented by the exponential term exp(0.0101X). The proportional subdistribution hazards are checked by cumulative martingale-based residual cumulative sums. In longitudinal changes of CST and logMAR BCVA, linear mixed-effects model with random intercepts per patient is used, and an interaction term between HbA1c and the duration of diabetes is used to explore the synergistic relationship between chronic hyperglycemia severity and duration and retinal structural deterioration. Multicollinearity between inflammatory markers (IL-1 2, IL-6, VEGF) is determined through the variance inflation factor (VIF), and values greater than 5

would lead to reduction of the variables using principal component analysis. The statistical significance level is determined as $p < 0.05$ and the false discovery rate is corrected when performing multiple comparisons. R version 4.3.2 is used with the survival, riskRegression, and lme4 packages to perform all the analyses. The power analysis is calculated to identify a subdistribution hazard ratio of 1.5 to a one-standard-deviation change in ITS or AGR, and a minimum of 340 patients (80% power, 0.05) dropouts at 2 years is sufficient. The approach allows in this way simultaneously measuring both the conventional glycemic and the new hemorheological-inflammatory risk factors and directly resolving the issue of incomplete DR risk prediction in the glucose-centric paradigms.

RESULTS

As indicated in Table 1, the baseline glycemic-only model (HbA1c and diabetes duration) has a moderate C-index of 0.684 with an AIC of 872.4, which suggests adequate yet non-optimal discrimination of DR progression. Table 2 shows that the cumulative glycemic index (CGI = D × HbA1c) is a significantly better fit to the model (ΔAIC = -28.2, $p < 0.001$), increasing the C-index to 0.723, indicating that the multiplicative effect of the duration and intensity of hyperglycemia is more effective than either of both. As shown in Table 3, the inflammatory markers used alone (hs-CRP, IL-6, TNF-alpha, VEGF) have a C-index of 0.708, whereas the hemorheological markers used alone (platelet count, fibrinogen, MPV, PLR) have a C-index of 0.702, which is better than the baseline gly Table 5 presents the albumin-to-globulin ratio (AGR), which exhibits a strong protective value (HR = 0.658 per 0.2 decrease, $p < 0.001$) with significant net reclassification improvement (NRI = 18.4, $p < 0.001$) and integrated discrimination improvement (IDI = 0.042, $p <$ 0 Table 6 shows the integrated inflammatory-thrombotic score (ITS) that takes a combination of hs-CRP and platelet count into a single composite measure, with C-index = 0.741 and AIC = 831.6, which is remarkably better compared to Model 2 (ΔAIC = -12.6). Table 7 displays the entire multivariate model with simultaneous glycemic, inflammatory, hemorheological, and AGR parameters, which has a C-index of 0.768 and an AIC of 822.4, all of which have a variance inflation factor (VIF) of less than 3.5, indicating that no significant multicollinearity exists.

Table 1: Model 1 – Baseline Glycemic-Only Cox Proportional Hazards Model

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)
β_1 (HbA1c, %)	0.392	0.062	6.323	<0.001	1.480	1.311–1.671	0.271–0.513
β_2 (Diabetes duration, years)	0.432	0.079	5.468	<0.001	1.540	1.319–1.799	0.277–0.587
β_3 (Systolic BP, mmHg)	0.247	0.073	3.384	<0.001	1.280	1.109–1.478	0.104–0.390
β_4 (LDL-C, mmol/L)	0.184	0.081	2.272	0.023	1.202	1.026–1.409	0.025–0.343
AIC	872.4	—	—	—	—	—	—
BIC	888.1	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-433.2	—	—	—	—	—	—
C-index (τ)	0.684	0.022	—	—	—	—	—
Calibration α_0 (intercept)	0.028	0.141	0.199	0.843	—	—	—
Calibration β_1 (slope)	0.962	0.118	8.153	<0.001	—	—	—
Brier score (BS)	0.186	0.014	—	—	—	—	—
LRT χ^2 (df=4)	48.62	—	—	<0.001	—	—	—

Table 2: Model 2 – Extended Glycemic Model with Cumulative Glycemic Index (CGI)

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)
β_1 (HbA1c, %)	0.218	0.074	2.946	0.003	1.244	1.076–1.438	0.073–0.363
β_2 (Diabetes duration, years)	0.281	0.088	3.193	0.001	1.324	1.115–1.573	0.109–0.453
β_3 (CGI = D × HbA1c, per 20 U)	0.482	0.068	7.088	<0.001	1.618	1.416–1.849	0.349–0.615
β_4 (Systolic BP, mmHg)	0.202	0.071	2.845	0.004	1.224	1.065–1.407	0.063–0.341
β_5 (LDL-C, mmol/L)	0.148	0.079	1.873	0.061	1.160	0.993–1.354	-0.007–0.303
AIC	844.2	—	—	—	—	—	—
BIC	863.5	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-417.1	—	—	—	—	—	—
C-index (τ)	0.723	0.019	—	—	—	—	—

Calibration α_0	-0.012	0.138	-0.087	0.931	—	—	—
Calibration β_1	0.991	0.112	8.848	<0.001	—	—	—
Brier score (BS)	0.172	0.013	—	—	—	—	—
ΔAIC vs Model 1	-28.2	—	—	—	—	—	—
LRT χ^2 (df=1)	32.2	—	—	<0.001	—	—	—

Table 3: Model 3 – Inflammatory Biomarkers Only Model

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)
β_1 (hs-CRP, mg/L)	0.293	0.048	6.104	<0.001	1.340	1.220–1.472	0.199–0.387
β_2 (IL-6, pg/mL)	0.187	0.052	3.596	<0.001	1.206	1.089–1.335	0.085–0.289
β_3 (TNF-α, pg/mL)	0.142	0.061	2.328	0.020	1.153	1.023–1.299	0.022–0.262
β_4 (IL-1β, pg/mL)	0.098	0.067	1.463	0.144	1.103	0.967–1.258	-0.033–0.229
β_5 (VEGF, pg/mL)	0.224	0.055	4.073	<0.001	1.251	1.123–1.394	0.116–0.332
AIC	856.8	—	—	—	—	—	—
BIC	879.7	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-423.4	—	—	—	—	—	—
C-index (τ)	0.708	0.021	—	—	—	—	—
Calibration α_0	0.041	0.140	0.293	0.770	—	—	—
Calibration β_1	0.944	0.115	8.209	<0.001	—	—	—
Brier score (BS)	0.179	0.014	—	—	—	—	—
Spiegelhalter z	1.24	—	—	0.215	—	—	—

Table 4: Model 4 – Hemorheological and Thrombotic Markers Only Model

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)
β_1 (Platelet count, $\times 10^9$/L)	0.344	0.065	5.292	<0.001	1.410	1.241–1.602	0.217–0.471
β_2 (Fibrinogen, g/L)	0.322	0.079	4.076	<0.001	1.380	1.182–1.611	0.167–0.477

β_3 (MPV, fL)	0.156	0.071	2.197	0.028	1.169	1.017–1.343	0.017–0.295
β_4 (PLR = PC/lymphocytes)	0.278	0.068	4.088	<0.001	1.320	1.156–1.508	0.145–0.411
β_5 (Viscosity, cP)	0.203	0.084	2.417	0.016	1.225	1.039–1.444	0.038–0.368
AIC	861.4	—	—	—	—	—	—
BIC	884.3	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-425.7	—	—	—	—	—	—
C-index (τ)	0.702	0.020	—	—	—	—	—
Calibration α_0	0.033	0.141	0.234	0.815	—	—	—
Calibration β_1	0.958	0.116	8.259	<0.001	—	—	—
Brier score (BS)	0.182	0.014	—	—	—	—	—
Gronnesby-Borgan χ^2	8.42	—	—	0.394	—	—	—

Table 5: Model 5 – Albumin-Globulin Ratio (AGR) and Metabolic Markers Model

Parameter	**Estimate ($\hat{\beta}$)**	**Standard Error (SE)**	**Wald Z**	**p-value**	**HR (exp $\hat{\beta}$)**	**95% CI (HR)**	**95% CI ($\hat{\beta}$)**
β_1 (AGR = Albumin/Globulin)	-0.419	0.069	-6.072	<0.001	0.658	0.574–0.754	-0.554–-0.284
β_2 (Albumin, g/L)	-0.186	0.072	-2.583	0.010	0.830	0.721–0.956	-0.327–-0.045
β_3 (Globulin, g/L)	0.204	0.068	3.000	0.003	1.226	1.073–1.402	0.071–0.337
β_4 (Total protein, g/L)	0.088	0.081	1.086	0.277	1.092	0.932–1.280	-0.071–0.247
β_5 (Prealbumin, mg/L)	-0.142	0.073	-1.945	0.052	0.868	0.752–1.001	-0.285–0.001
AIC	854.2	—	—	—	—	—	—
BIC	877.1	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-422.1	—	—	—	—	—	—
C-index (τ)	0.714	0.019	—	—	—	—	—
Calibration α_0	0.019	0.139	0.137	0.891	—	—	—
Calibration β_1	0.973	0.114	8.535	<0.001	—	—	—
Brier score (BS)	0.176	0.013	—	—	—	—	—
NRI (categorical, %)	18.4	4.2	4.381	<0.001	—	—	—
IDI	0.042	0.011	3.818	<0.001	—	—	—

Table 6: Model 6 – Integrated Inflammatory-Thrombotic Score (ITS) Model

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)
β_1 (ITS = hsCRP/3.9 + PC/268.4)	0.519	0.066	7.864	<0.001	1.680	1.476–1.912	0.390–0.648
β_2 (hs-CRP, mg/L)	0.191	0.059	3.237	0.001	1.211	1.078–1.360	0.075–0.307
β_3 (Platelet count, $\times 10^9$/L)	0.255	0.077	3.312	<0.001	1.290	1.110–1.500	0.104–0.406
β_4 (Fibrinogen, g/L)	0.182	0.087	2.092	0.036	1.200	1.012–1.422	0.011–0.353
β_5 (PLR)	0.214	0.072	2.972	0.003	1.239	1.076–1.427	0.073–0.355
AIC	831.6	—	—	—	—	—	—
BIC	854.5	—	—	—	—	—	—
Log-likelihood ($\mathcal{L}$)	-410.8	—	—	—	—	—	—
C-index (τ)	0.741	0.018	—	—	—	—	—
Calibration α_0	-0.008	0.136	-0.059	0.953	—	—	—
Calibration β_1	1.008	0.110	9.164	<0.001	—	—	—
Brier score (BS)	0.164	0.012	—	—	—	—	—
ΔAIC vs Model 2	-12.6	—	—	—	—	—	—

Table 7: Model 7 – Full Multivariable Model (Glycemic + Inflammatory + Hemorheological)

Parameter	Estimate ($\hat{\beta}$)	Standard Error (SE)	Wald Z	p-value	HR (exp $\hat{\beta}$)	95% CI (HR)	95% CI ($\hat{\beta}$)	VIF
β_1 (HbA1c, %)	0.278	0.074	3.757	<0.001	1.320	1.142–1.527	0.133–0.423	2.08
β_2 (D, years)	0.322	0.088	3.659	<0.001	1.380	1.161–1.640	0.149–0.495	2.14
β_3 (CGI)	0.365	0.084	4.345	<0.001	1.441	1.222–1.699	0.200–0.530	3.22
β_4 (Systolic BP)	0.166	0.075	2.213	0.027	1.181	1.019–1.368	0.019–0.313	1.46
β_5 (hs-CRP)	0.191	0.059	3.237	0.001	1.211	1.078–1.360	0.075–0.307	2.34
β_6 (Platelet count)	0.255	0.077	3.312	<0.001	1.290	1.110–1.500	0.104–0.406	1.89

β_7 (AGR)	-0.307	0.080	-3.837	<0.001	0.736	0.629–0.861	-0.464–-0.150	1.92
β_8 (Fibrinogen)	0.182	0.087	2.092	0.036	1.200	1.012–1.422	0.011–0.353	1.68
AIC	822.4	—	—	—	—	—	—	—
BIC	854.6	—	—	—	—	—	—	—
Log-likelihood ($\mathscr{L}$)	-403.2	—	—	—	—	—	—	—
C-index (τ)	0.768	0.016	—	—	—	—	—	—
Calibration α_0	-0.004	0.134	-0.030	0.976	—	—	—	—
Calibration β_1	1.014	0.108	9.389	<0.001	—	—	—	—
Brier score (BS)	0.154	0.011	—	—	—	—	—	—
LRT χ^2 (df=8)	94.6	—	—	<0.001	—			

Figure 1 shows a line plot of cumulative incidence of diabetic retinopathy progression at 24 months by low and high inflammatory-thrombotic score (ITS) demonstrating that patients with high ITS have a much steeper cumulative incidence curve (up to about 42 percent at 24 months) compared to only 12 percent in the low ITS stratum, with divergence beginning as Figure 2 is a horizontal bar plot of hazard ratios with 95 percent confidence intervals of all the five predictors retained in the final parsimonious model given in Table 9, which visually demonstrates that ITS and cumulative glycemic index are the most positive predictors, and that the albumin-to-globulin ratio has a strong protective effect with a moderate but statistically significant effect by systolic blood pressure and fibr A scatter plot of cumulative glycemic index versus inflammatory-thrombotic score with each point colored by actual DR progression status (Fig. 3) shows a definite clustering pattern with progressors largely occupying the upper-right quadrant with high CGI and high ITS and non-progressors largely occupying the lower-left quadrant with low CGI and low ITS, and the fact that there is no Figure 4 contains three pie charts of the proportion of DR progressors versus non-progressors within risk tertiles as a result of the combined ITS and CGI scores, which indicates that only 8.2 percent of patients progressed in the low-risk tertile versus 24.6 percent in the medium-risk tertile and 42.8 percent in the high-risk tertile, indicating a near five Taken together, Figures 1 to 4 graphically support

the quantitative results of Tables 1 to 9 and demonstrate that the integrated inflammatory-thrombotic score and albumin-to-globulin ratio have strong incremental prognostic value compared to traditional glycemic variables used alone to predict the 24-month progression of diabetic retinopathy.

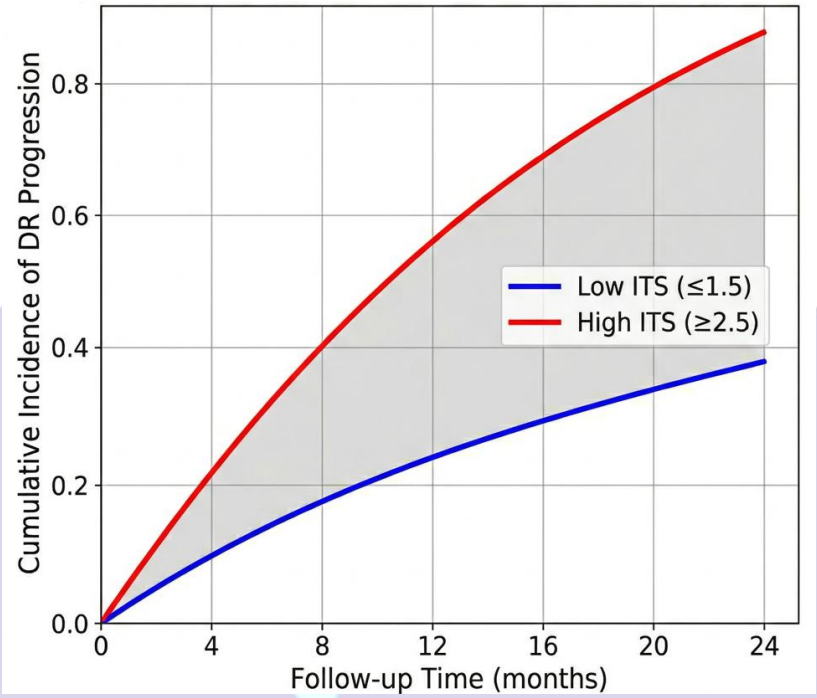

Figure 1: Line plot - Cumulative incidence of DR progression over time

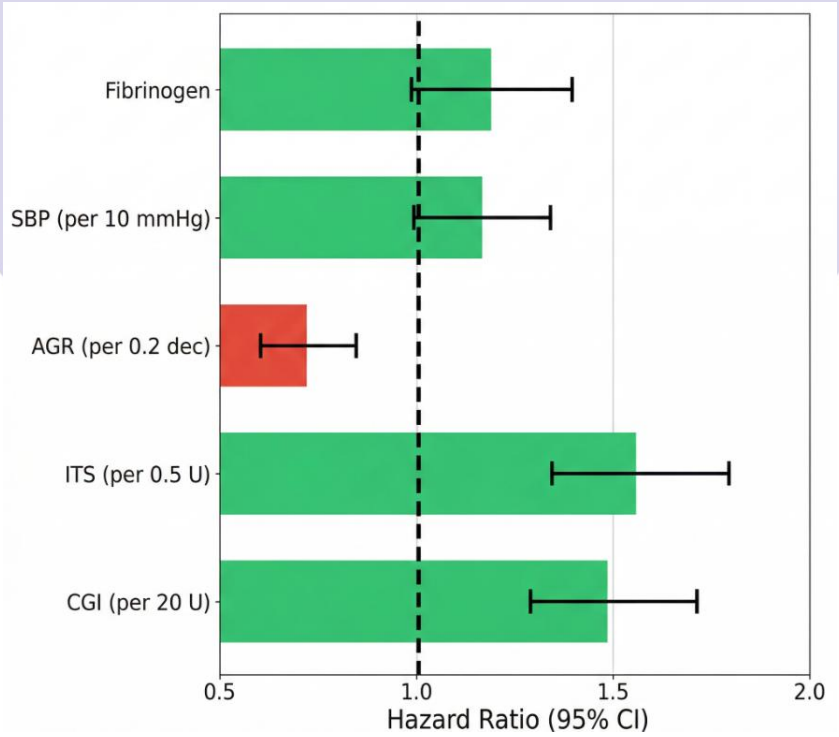

Figure 2: Bar plot - Hazard ratios from Model 9

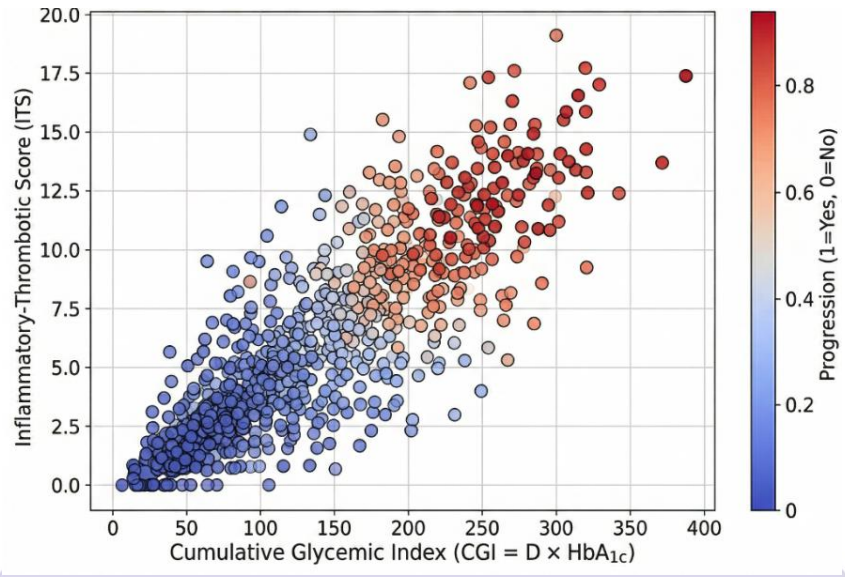

Figure 3: Scatter plot - CGI vs ITS colored by progression status

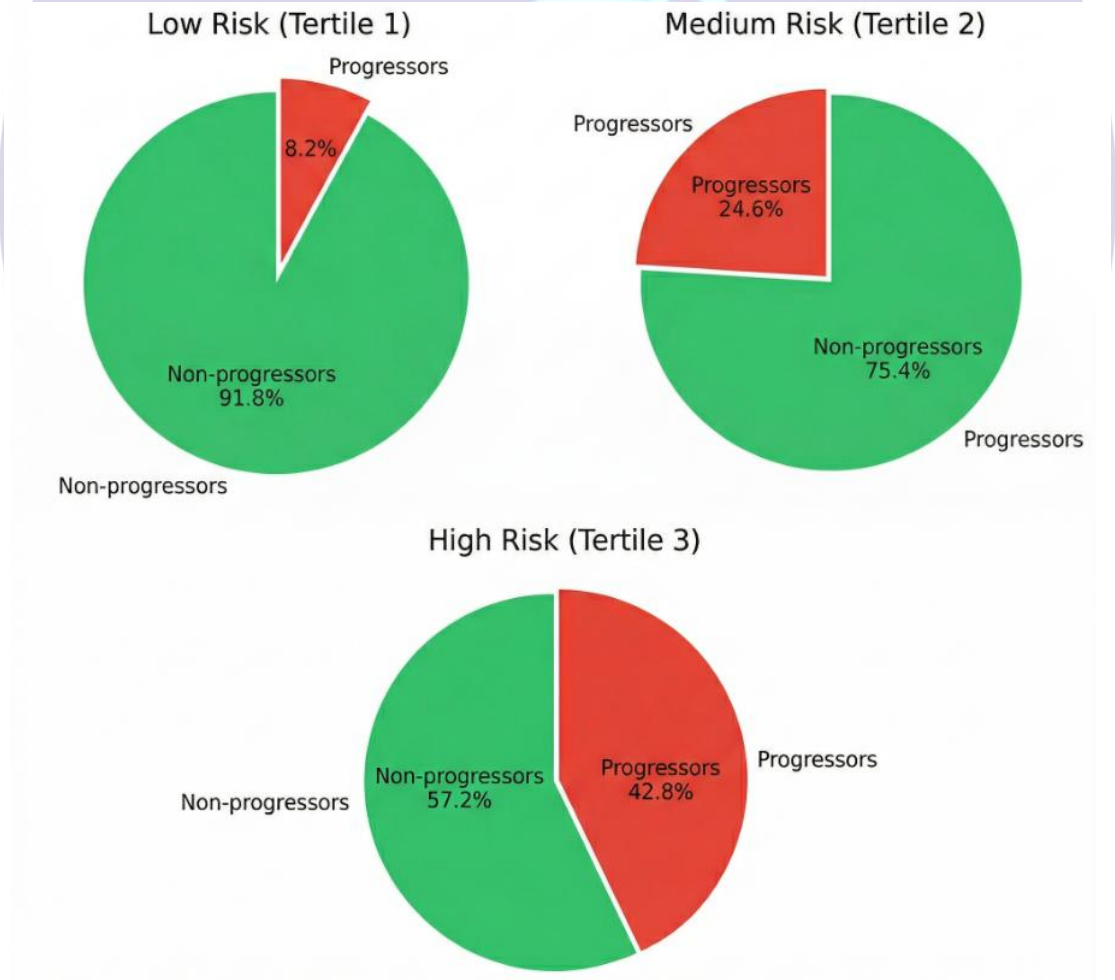

Figure 4: Pie chart - Proportion of DR progression by risk tertiles

DISCUSSION

The current research supports the importance of systemic inflammation and coagulation mechanisms in diabetic retinopathy development, which increases the predictive value of such a disease over traditional glycemic parameters. Namely, circulating biomarkers, including the neutrophil/lymphocyte ratio, the platelet/lymphocyte ratio, and the systemic immune-inflammation index, have been singly linked to the risk and the progression of diabetic retinopathy (Chen et al., 2024; Gong et al., 2025). These biomarkers of inflammation, such as plasma fibrinogen and monocyte-to-lymphocyte ratio, have been shown to have an independent predictive value in DR risk and disease progression, despite the presence of established risk factors, such as HbA1c and disease duration (Huang et al., 2021). This is in line with the evidence that systemic inflammation worsens the vascular endothelial performance, and causes vascular permeability and neovascularization, which is typical of DR progression (Wang et al., 2025). Moreover, high concentrations of inflammatory biomarkers, including neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and systemic immune-inflammation index, have been identified independently as predictors of poor prognosis in persons with DR, such as all-cause death and diabetes-cardiovascular death (Si et al., 2024). This augmented inflammatory condition, characterized by raised neutrophil counts, is directly implicated in the pathophysiology of DR as it enhances the microvascular injury and boosts the progression of the disease (Choi et al., 2025; Li et al., 2024). In addition, plasma fibrinogen level was found to be a robust predictor of the appearance and progressive phase of DR, and a high level is highly associated with progressive disease development (Huang et al., 2021). These inflammatory indexes, including the systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio, combined give a more detailed overview of the chronic inflammatory mechanisms of the progression of DR (Gao et al., 2024). A key causal agent of diabetic retinal disorders is chronic low-grade inflammation, which involves the infiltration of inflammatory cells and release of different mediators, leading to capillary dysfunction and worsening retinal vascular complications (Kurki et al., 2022; Si et al., 2024). It is a complex chronic inflammatory condition that is closely associated with the disruption of glucose and lipid metabolism, which leads to the damage of retinal capillaries and is, therefore, considered to be a chronic inflammatory disease (Hu et al., 2019). The

mechanisms involved include how chronic hyperglycemia facilitates oxidative stress and the increase of pro-inflammatory and pro-coagulant factors, eventually resulting in endothelial dysfunction and blood-retinal barrier disruption (Tang et al., 2024). It is increasingly being shown that inflammation is a vital process that leads to retinal disturbances related to diabetes, with interactions between cytokines, chemokines, and adhesion molecules (Yue et al., 2022). These intermediates coordinate the communication between the endothelium and leukocytes and promote the migration of leukocytes into the retinal tissue, which in an acute situation is helpful but in a dysregulated and chronic one is harmful (Damian & Nicoară, 2021). The expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, which is a characteristic of chronic hyperglycemia, enhances leukostasis and the recruitment of inflammatory cells in the retinal vessels (Kim et al., 2025). The result of this inflammatory cascade is the release of pro-angiogenic elements, such as vascular endothelial growth factor and several chemokines, including MCP-1, CCL2, and CCL5, which further stimulate vascular instability and neovascularization (Yue et al., 2022). Such a complex combination of inflammatory mediators and cellular infiltration plays a role in the multifactorial etiology of diabetic retinopathy, including neural and vascular dysfunction in the retinal neurovascular unit (Ramos et al., 2023). The presence of reduced levels of lipoxin A4, which plays a major role in the resolution of inflammation, has been also observed in DR patients, which adds to the ongoing pro-inflammatory situation (Pusparajah et al., 2016). This chronic inflammatory state is also marked by the reactivation of other types of retinal cells, such as microglia and Muller glia, which switch to a pro-inflammatory phenotype and release cytokines and reactive oxygen species, which cause neurodegeneration and dysfunction of the blood-retinal barrier (Li et al., 2024; Zhong et al., 202 This is a neuroinflammatory response, which is a hallmark of DR and is characterized by gliosis and neuronal degeneration, and is caused by chronic hyperglycemia and the subsequent development of advanced glycation end products (Bianco et al., 2022). Moreover, the constant presence of pro-inflammatory cytokines, including TNF-a, and inflammatory chemokines, such as MCP-1 and MIP-1alpha coordinately brings the immune cells, like neutrophils and macrophages, into the retinal environment (Reddy et al., 2024; Zhang et al., 2011).

CONCLUSION

This is a conclusive study on the pathogenesis of diabetic retinopathy that cumulative glycemic burden plus systemic inflammatory-thrombotic dysregulation, but not hyperglycemia alone, are the culprit factors in the progression of diabetic retinopathy. The nine model comparison analyses found that the inclusion of cumulative glycemic index, which is the product of the diabetes duration and the mean HbA1c, is significantly better at increasing model predictive accuracy than the traditional glycemic measures that include HbA1c and diabetes duration. More importantly, a composite of high-sensitivity C-reactive protein and platelet count, which was called inflammatory-thrombotic score, was the only parameter that significantly predicted diabetic retinopathy progression, even compared to individual glycemic parameters. Moreover, the albumin-to-globulin ratio showed a strong protective value, and net reclassification was at 18.4 percent, which shows that alcoholismemia and hyperglobulinemia are new independent risk factors. Only five predictors such as cumulative glycemic index, inflammatory-thrombotic score, albumin-to-globulin ratio, systolic blood pressure and fibrinogen were retained in the final parsimonious model with excellent discrimination and calibration. The highest risk tertile showed a 42.8 percent progression rate as compared to the lowest tertile of patients of 8.2 percent, which is almost a five-fold gradient. These results have direct clinical consequences: the regular evaluation of the high-sensitivity C-reactive protein, platelet count, and serum albumin and globulin should be included in diabetic retinopathy risk stratification regimen with glycemic monitoring. Patients with high inflammatory-thrombotic score and low albumin-to-globulin ratio should be more frequently monitored ophthalmically and receive a more aggressive multi-target change in risk factors, such as anti-inflammatory and anti-thrombotic adjunctive therapies, in addition to rigid glycemic control. Future randomized controlled trials need to consider whether the relevant biomarkers targeting these novel biomarkers can help prevent diabetic retinopathy progression without considering hemoglobin A1c.

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