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Original Research Article

ASSOCIATION BETWEEN SYSTEMIC IMMUNE-INFLAMMATION INDEX AND SEVERITY OF DIABETIC RETINOPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Diabetic retinopathy (DR) is a major microvascular complication of Type 2 Diabetes Mellitus (T2DM), and chronic systemic inflammation plays a crucial role in its pathogenesis. The Systemic Immune-Inflammation Index (SII) has emerged as a novel biomarker reflecting systemic inflammatory status. The objective is to evaluate the association between the Systemic Immune-Inflammation Index and the severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus.

Materials and Methods: This hospital-based analytical cross-sectional study included 150 patients with T2DM who underwent detailed clinical evaluation, laboratory investigations, and comprehensive ophthalmic examination. SII was calculated using the formula: platelet count × neutrophil count/lymphocyte count. Diabetic retinopathy was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification. Statistical analysis was performed using SPSS version 25.0.

Results: The mean age of participants was 56.9 ± 10.8 years, and 58.7% were males. Diabetic retinopathy was present in 81.3% of patients. Mean SII increased progressively with increasing severity of diabetic retinopathy, from 402.5 ± 92.4 in patients without retinopathy to 1024.5 ± 214.3 in those with proliferative diabetic retinopathy ($p<0.001$). Higher SII values were significantly associated with longer duration of diabetes, elevated HbA1c, diabetic macular edema, hypertension, and advanced stages of diabetic retinopathy. Patients with SII ≥700 had significantly greater frequencies of severe non-proliferative and proliferative diabetic retinopathy compared with those having lower SII values ($p<0.001$).

Conclusion: Elevated Systemic Immune-Inflammation Index is significantly associated with increasing severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus. SII is an inexpensive, readily available inflammatory biomarker that may assist in early risk stratification and identification of patients requiring closer ophthalmic surveillance and timely intervention.

Keywords: Type 2 diabetes mellitus; diabetic retinopathy; systemic immune-inflammation index; inflammation; proliferative diabetic retinopathy; biomarker; diabetic macular edema.

INTRODUCTION

Diabetes mellitus (DM) is one of the fastest-growing non-communicable diseases worldwide and poses a major public health challenge due to its increasing prevalence and long-term microvascular and macrovascular complications. Type 2 diabetes mellitus (T2DM) accounts for nearly 90–95% of all

diabetes cases and is a leading cause of visual impairment, cardiovascular disease, renal failure, and premature mortality.[1,2]

Diabetic retinopathy (DR) is one of the most common microvascular complications of T2DM and remains a leading cause of preventable blindness among the working-age population. Chronic hyperglycemia induces retinal microvascular damage through oxidative stress, endothelial dysfunction, inflammation, and increased vascular permeability, resulting in progressive retinal ischemia and neovascularization.[3,4]

Growing evidence suggests that chronic low-grade inflammation plays a pivotal role in the pathogenesis and progression of diabetic retinopathy. Persistent activation of inflammatory pathways promotes leukocyte adhesion, endothelial injury, capillary occlusion, and breakdown of the blood-retinal barrier, thereby accelerating retinal damage. In addition, neuroinflammatory mechanisms contribute to retinal neuronal degeneration even before clinically apparent vascular changes develop.[5]

The Systemic Immune-Inflammation Index (SII), calculated as platelet count × neutrophil count / lymphocyte count, is a novel inflammatory biomarker that reflects the balance between host immune response and systemic inflammation. Compared with individual hematological parameters, SII provides a more comprehensive assessment of inflammatory status and has been investigated in several inflammatory, cardiovascular, and malignant disorders.[6,7]

Although inflammation is recognized as an important contributor to diabetic retinopathy, limited studies have evaluated the relationship between SII and the severity of diabetic retinopathy in patients with T2DM. Identification of an inexpensive, readily available inflammatory biomarker may facilitate early risk stratification and timely intervention in patients at higher risk of progressive retinal disease. Therefore, the present study was undertaken to evaluate the association between the Systemic Immune-Inflammation Index and the severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus.

MATERIALS AND METHODS

Study Design: This was a hospital-based analytical cross-sectional study conducted to evaluate the association between the Systemic Immune-Inflammation Index (SII) and the severity of diabetic retinopathy among patients with Type 2 Diabetes Mellitus.

Study Setting: Study was conducted in department of ophthalmology in tertiary care hospital.

Study Duration: The study was conducted over a period of 18 months.

Sample Size: A total of 150 patients with Type 2 Diabetes Mellitus were enrolled consecutively during the study period.

Study Population: Adult patients with previously diagnosed or newly diagnosed Type 2 Diabetes Mellitus attending the medicine and ophthalmology outpatient departments or admitted to the hospital were screened for diabetic retinopathy.

Inclusion Criteria

- Patients aged ≥18 years.
- Diagnosed cases of Type 2 Diabetes Mellitus according to the American Diabetes Association (ADA) criteria.
- Patients willing to provide written informed consent.
- Patients undergoing complete ophthalmic evaluation with fundus examination.

Exclusion Criteria

- Type 1 diabetes mellitus.
- Gestational diabetes mellitus.
- Active systemic infection or inflammatory disease.
- Autoimmune disorders.
- Hematological malignancies or active cancer.
- Chronic liver disease or end-stage renal disease.
- Current corticosteroid or immunosuppressive therapy.
- Previous retinal laser photocoagulation or vitreoretinal surgery.
- Other retinal diseases such as retinal vein occlusion, age-related macular degeneration, hypertensive retinopathy, or uveitis.
- Incomplete clinical or laboratory data.

Study Procedure: After obtaining informed consent, demographic details including age, sex, duration of diabetes, body mass index (BMI), smoking status, hypertension, and current antidiabetic treatment were recorded. A detailed clinical examination was performed.

Laboratory investigations included:

- Complete blood count with differential leukocyte count
- Fasting blood glucose
- Postprandial blood glucose
- Glycated hemoglobin (HbA1c)
- Serum creatinine
- Blood urea
- Lipid profile
- Urine albumin

The Systemic Immune-Inflammation Index (SII) was calculated using the following formula:

SII = Platelet Count × Neutrophil Count / Lymphocyte Count

All participants underwent comprehensive ophthalmic evaluation including:

- Best-corrected visual acuity (BCVA)
- Slit-lamp biomicroscopy
- Intraocular pressure measurement
- Dilated fundus examination using indirect ophthalmoscopy and slit-lamp biomicroscopy with a 90D lens
- Fundus photography, where available

Diabetic retinopathy was classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification into:

- No diabetic retinopathy
- Mild non-proliferative diabetic retinopathy (NPDR)
- Moderate NPDR
- Severe NPDR
- Proliferative diabetic retinopathy (PDR)

Diabetic macular edema was documented whenever present.

Outcome Measures

Primary Outcome

- Association between the Systemic Immune-Inflammation Index and the severity of diabetic retinopathy.

Secondary Outcomes

- Correlation of SII with HbA1c and duration of diabetes.
- Association between SII and stages of diabetic retinopathy.
- Relationship of SII with diabetic macular edema.
- Identification of independent predictors of severe diabetic retinopathy.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Differences between groups were analyzed using the independent Student's t-test or one-way ANOVA for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Pearson's correlation coefficient was used to assess correlations between SII and continuous clinical variables. Multivariate logistic regression analysis was performed to identify independent predictors of severe diabetic retinopathy. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 150 patients with Type 2 Diabetes Mellitus were included in the study. The mean age of the participants was 56.9 ± 10.8 years (range: 34–79 years). Males constituted 88 (58.7%) of the study population, while 62 (41.3%) were females. The mean duration of diabetes was 9.4 ± 4.6 years, and the mean HbA1c was 8.5 ± 1.4%.

Based on fundus examination, 28 (18.7%) patients had no diabetic retinopathy (DR), whereas 122 (81.3%) had varying grades of DR. Moderate NPDR was the most common stage, followed by severe NPDR and proliferative diabetic retinopathy. The mean Systemic Immune-Inflammation Index (SII) increased progressively with increasing severity of diabetic retinopathy.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (n = 150)

Variable	Value
Age (years)	56.9 ± 10.8
Gender	
Male	88 (58.7%)
Female	62 (41.3%)
Duration of diabetes (years)	9.4 ± 4.6
HbA1c (%)	8.5 ± 1.4
Body Mass Index (kg/m²)	27.3 ± 3.8
Hypertension	82 (54.7%)
Dyslipidemia	69 (46.0%)
Mean SII	645.7 ± 238.6

The study population consisted predominantly of middle-aged to elderly patients with longstanding Type 2 Diabetes Mellitus. More than half had hypertension, and the average SII suggested a moderate degree of systemic inflammation.

Table 2: Distribution of Patients According to Severity of Diabetic Retinopathy and Mean Systemic Immune-Inflammation Index

Severity of Diabetic Retinopathy	Number (%)	Mean SII (Mean ± SD)	p-value
No diabetic retinopathy	28 (18.7)	402.5 ± 92.4	
Mild NPDR	34 (22.7)	531.8 ± 118.6	
Moderate NPDR	42 (28.0)	668.9 ± 146.5	
Severe NPDR	26 (17.3)	834.7 ± 175.8	
Proliferative DR	20 (13.3)	1024.5 ± 214.3	<0.001

The Systemic Immune-Inflammation Index increased significantly with advancing stages of diabetic retinopathy. Patients with proliferative diabetic retinopathy had the highest mean SII values, indicating a strong association between systemic inflammation and retinal disease severity.

Table 3: Association of High Systemic Immune-Inflammation Index (≥700) with Clinical Parameters

Variable	SII <700 (n=92)	SII ≥700 (n=58)	p-value
Duration of diabetes >10 years	28 (30.4%)	36 (62.1%)	<0.001
HbA1c ≥8%	45 (48.9%)	46 (79.3%)	<0.001
Severe NPDR/PDR	18 (19.6%)	28 (48.3%)	<0.001
Diabetic macular edema	14 (15.2%)	24 (41.4%)	<0.001

Hypertension	44 (47.8%)	38 (65.5%)	0.036

Patients with a high Systemic Immune-Inflammation Index (≥700) had significantly longer duration of diabetes, poorer glycemic control, more advanced diabetic retinopathy, higher prevalence of diabetic macular edema, and a greater frequency of hypertension compared with those having lower SII values.

DISCUSSION

The present study evaluated the association between the Systemic Immune-Inflammation Index (SII) and the severity of diabetic retinopathy (DR) in patients with Type 2 Diabetes Mellitus (T2DM). The study demonstrated a significant progressive increase in SII with advancing stages of diabetic retinopathy. Patients with proliferative diabetic retinopathy exhibited the highest SII values, and elevated SII was significantly associated with longer duration of diabetes, poor glycemic control, diabetic macular edema, and advanced retinal disease.

The Systemic Immune-Inflammation Index has recently emerged as a comprehensive inflammatory biomarker that reflects the balance between innate immune activation and adaptive immune response. Hu et al,[8] first demonstrated the clinical utility of SII as a reliable indicator of systemic inflammatory status and prognosis in chronic diseases. Since chronic inflammation is a key mechanism underlying diabetic microvascular complications, SII has gained increasing attention as a potential marker for diabetic retinopathy.

The findings of the present study are consistent with those of Wang et al,[9] who reported a significant positive correlation between SII and the severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus. They observed that patients with proliferative diabetic retinopathy had markedly higher SII values than those with non-proliferative disease, suggesting that increasing systemic inflammation parallels progressive retinal microvascular damage. Similar results were observed in our study, where mean SII increased significantly from patients without diabetic retinopathy to those with proliferative diabetic retinopathy.

Similarly, Tabakoglu and Celik,[10] demonstrated that elevated SII independently predicted poor clinical outcomes and disease progression among patients with diabetic retinopathy during long-term follow-up. Their findings indicate that SII reflects persistent inflammatory activity responsible for endothelial dysfunction, capillary occlusion, and retinal ischemia. The present study also showed that patients with higher SII had significantly more severe retinal disease and diabetic macular edema.

The large multicenter study by Deng et al,[11] evaluated several inflammatory biomarkers and found SII to be one of the strongest predictors of diabetic retinopathy severity. They demonstrated a gradual increase in inflammatory markers from mild non-proliferative diabetic retinopathy to proliferative diabetic retinopathy, supporting the hypothesis that chronic systemic inflammation contributes to retinal vascular injury. Our findings closely parallel these observations.

Li et al,[12] further demonstrated that SII, together with neutrophil-to-lymphocyte ratio and systemic inflammation response index, showed excellent diagnostic performance in identifying patients with advanced diabetic retinopathy and predicting disease progression. Likewise, in the present study, elevated SII was significantly associated with severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular edema, indicating its usefulness as a simple screening biomarker.

More recently, Guo et al,[13] analyzed a large NHANES cohort and reported that higher SII levels were associated with increased mortality among individuals with diabetic retinopathy. Their findings emphasize that systemic inflammation not only reflects retinal disease severity but also represents generalized vascular injury and increased cardiovascular risk. Although the present study did not evaluate long-term mortality, the strong association between elevated SII and advanced retinopathy supports its prognostic significance.

A comprehensive review by Ziaei et al,[14] concluded that systemic inflammatory indices, including SII, are inexpensive, reproducible, and readily available biomarkers that may improve risk stratification in diabetic retinopathy when used alongside routine ophthalmic evaluation. The present study reinforces this concept by demonstrating a significant association between elevated SII and increasing severity of retinal disease.

Overall, the findings suggest that chronic systemic inflammation plays an important role in the pathogenesis and progression of diabetic retinopathy. The Systemic Immune-Inflammation Index, derived from a routine complete blood count, may serve as a practical and cost-effective biomarker for identifying patients at increased risk of severe diabetic retinopathy. Larger prospective multicenter studies are recommended to validate its predictive value and determine appropriate clinical cut-off values for routine use.

CONCLUSION

The present study demonstrated a significant association between the Systemic Immune-Inflammation Index and the severity of diabetic retinopathy in patients with Type 2 Diabetes Mellitus. Higher SII values were associated with longer duration of diabetes, poor glycemic control, diabetic macular edema, and advanced stages of diabetic retinopathy, including proliferative disease.

Since SII is inexpensive, readily available, and calculated from routine hematological parameters, it may serve as a valuable adjunctive biomarker for early identification of patients at risk of severe diabetic retinopathy. Incorporating SII into routine clinical assessment may facilitate timely ophthalmic referral, closer monitoring, and early intervention. Further large-scale prospective studies are required to establish standardized cut-off values and confirm its role in predicting disease progression.

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