https://doi.org/10.48047/AFJBS.6.14.2024.4254-4260

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

A STUDY TO ANALYSE AND ASCERTAIN SYSTEMIC IMMUNE INFLAMMATION INDEX – A POTENTIAL RISK PREDICTOR OF DIABETIC RETINOPATHY IN TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN SOUTH INDIAN POPULATION

Dr. Dhanvanth Rajesh B [1], Dr. V.M. Jyotsnaa Grace [2], Dr.Chevuri Mounika [3] Dr. V.R.Mohan Rao [4]

[1]Postgraduate , Department of General Medicine, Chettinad Hospital and Research Institute, Chennai, India.
[2] Fellow, Department of Hematology & Blood Transfusion, Dr.Rela Institute and Medical center, Chennai, India.
[3]Assistant Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Chennai, India.
[4]Professor & Head, Department of General Medicine, Chettinad Hospital and Research Institute, Chennai, India.
Email: [1] dhanvanthrajesh27@gmail.com
Orchid Id number:
[1]0009-0004-7969-6852, [2]0009-0007-4761-9547, [3]0009-0000-2323-6823, [4]0009-0004-4973-0431
Corresponding Author*: Dhanvanth Rajesh B

Volume 6, Issue 14, Aug 2024

Received: 09 June 2024

Accepted: 19 July 2024

Published: 08 Aug 2024

doi: 10.48047/AFJBS.6.14.2024.4254-4260

ABSTRACT :

Aim: This study aims to investigate Systemic Immune Inflammation Index (SII) as a predictor of Diabetic Retinopathy (DR) in type II Diabetic Mellitus in a tertiary care centre in South Indian population.

Method: In this study, 104 patients with type 2 Diabetes Mellitus (DM) were included and divided into three groups: without retinopathy (NDR), Non-Proliferative DR (NPDR), and Proliferative DR (PDR) based on their fundoscopic findings during their ophthalmic examination. After obtaining complete blood counts, SII , NLR, PLR & LMR were computed and compared.

Result: In our study , SII (p value – 0.03) & PLR (p value – 0.04) were statistically significant in diabetic retinopathy group compared to NDR group. Among DR group, SII & PLR were more elevated in moderate NPDR group compared to severe NPDR and PDR.

Conclusion: White cell inflammatory biomarkers such as SII & PLR can serve as a simple, cost effective, reliable predictors of DR, but severity of DR cannot be determined based on their elevated values.

Keywords: Diabetic Retinopathy, Inflammation, Systemic Immune Inflammation index, Neutrophil-Lymphocyte ratio, Platelet-Lymphocyte ratio, Lymphocyte-Monocyte ratio.

INTRODUCTION: Diabetes mellitus (DM) is a global health problem, approximately there are 537 million cases worldwide and is expected to reach 700 million by 2045. (1)(2) Type 2 DM is associated with chronic inflammatory changes and oxidative stress resulting in neurodegeneration and destruction of blood vessels, causing damage to multiple organs. Many studies have proposed that inflammatory pathways are the principal pathogenetic mechanism in the course of diabetes mellitus under the stimulus of various risk factors. (3)

Diabetic retinopathy (DR) is an important microvascular complication of Diabetes Mellitus and a major cause of visual impairment worldwide. The prevalence of Diabetic Retinopathy was recently estimated to be 34.6% globally. It is estimated that 27.0% of diabetic individuals have diabetic retinopathy, resulting in 0.4 million cases of blindness worldwide. (4)(5) The presence of DR can also serve as an indicator for other diabetic microvascular and macrovascular complications. Thus, early detection through DR screening and timely treatment can prevent visual impairment and blindness.

Landmark clinical trials such as The DCCT Research Group, 1993, and UKPDS Group, 1998, have stated that hyperglycemia is the decisive risk factor for the development of DR. (6) The metabolic effects of hyperglycemia result in microvascular damage of the retina that lead to vascular leakage - Non-proliferative DR (NPDR) and ischemia-induced retinal neovascularization - Proliferative DR (PDR).

Vascular, immunological, and neurological pathways are some of the proposed mechanisms in the pathogenesis of DR. However, recent studies have identified chronic inflammation as an important molecular mechanism in the development and progression of DR. Pathophysiology of DR include numerous cytokines, including interleukin-6, interleukin-1β, and tumor necrosis factor-α, stimulate the onset of inflammation and lead to disease progression. Early Non-proliferative Diabetic Retinopathy (NPDR) is characterized by the presence of vascular abnormalities such as selective loss of pericytes, formation of acellular capillaries, basement membrane thickening, and increased vascular permeability. Retinal leukostasis is an early event that occur in retinal capillaries, it is associated with areas of vascular non-perfusion and the development of diabetic retinopathy. In response to capillary non-perfusion, there is dilation of neighbouring capillaries. Due to ischemia, there is increased production of growth factors which lead to the growth of new blood vessels hence there is development of Proliferative Diabetic Retinopathy (PDR), resulting in severe and irreversible visual loss. (7)

White cell inflammatory biomarkers, such as Neutrophil-to-Lymphocyte Ratio (NLR), Platelet- to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR), and Systemic Immune Inflammation index (SII) showed good predictive value for several inflammatory conditions.(8)
The Systemic Immune Inflammation index (SII) is a prognostic score that depicts the systemic inflammation and is based on platelet, neutrophil, and lymphocyte counts. (9)

Evidence regarding the significance of these inflammatory biomarkers in the prediction of DR is still uncertain. Hence the present study was undertaken to evaluate the role of SII as a potential predictor of DR.

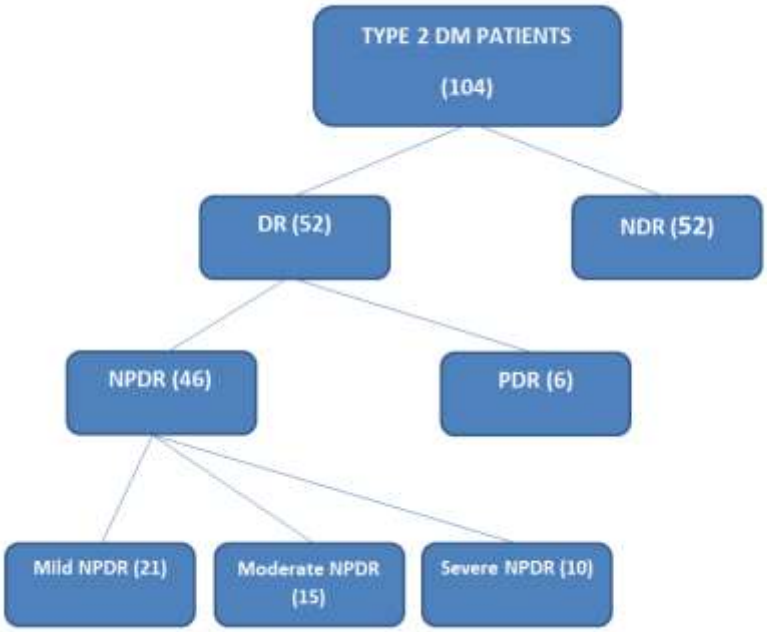
METHODOLOGY:

After obtaining IHEC approval, a retrospective study was conducted on 104, Type 2 DM patients admitted in Chettinad Hospital and Research Institute from January 2023 to January 2024. Data from the patients who met the inclusion & exclusion criteria were collected for the study. Type 2 DM patients of age range between 18 to 65 years were included in study while patients with systemic or ocular inflammatory conditions, cancer patients, previously diagnosed hematological conditions, systemic infections such as Pulmonary Tuberculosis, bronchiectasis, bronchiolitis, ocular infections, patients on antiplatelet drugs, steroid, immunosuppressants, anti-inflammatory drugs and patients who had recent surgery were excluded in this study.

Type 2 DM patients were divided into three groups: without retinopathy (NDR), Non-Proliferative DR (NPDR), and Proliferative DR (PDR) based on their fundoscopic findings during their ophthalmic examination. Again the Non-Proliferative DR (NPDR) group was divided into mild NPDR, moderate NPDR and severe NPDR. Totally there were 21 patients with mild NPDR, 15 patients with moderate

NPDR, 10 patients with severe NPDR, 6 patients with PDR and 52 patients in NDR group as mentioned in Figure 1.

Figure 1: Number of Type 2 DM patients in DR & NDR group.



Data pertaining to gender, age, medical history, comorbid illness, regular medications and laboratory investigation were collected. Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR) and Systemic Immune Inflammation index (SII) was calculated from their complete blood count and compared.

Systemic Immune Inflammation index (SII) is calculated as :

$$SII = P \times N / L$$

where P– Platelet count, N – Neutrophil count and L– Lymphocyte count. (9)

All counts are determined from the same automated blood sample measurement and expressed as a value in cells/Litre. Data analysis was done using SPSS software and p-value <0.05 was considered statistically significant.

RESULT:

A total of 104 patients were included in the study and were divided into 2 groups - 52 patients with Diabetic Retinopathy and 52 patients without Diabetic retinopathy.

Table 1 :- Types of DR and socio-demographic characteristics

	DR				NDR	p-value
	NPDR			PDR		
	Mild NPDR	Moderate	Severe			

			NPDR	NPDR			
AGE		48.80 ±1.30	55.06 ±6.43	54.60 ±7.63	47.33 ±7.03	50.90 ±9.95	0.325
SEX	Males	10	8	7	3	24	0.842
	females	11	7	3	3	28	

Baseline characteristics such as age and gender among the groups were recorded and mentioned in Table 1.

Table 2:- NLR, PLR, LMR and SII distribution in the study groups.

	DR				NDR	p-value
	NPDR			PDR		
	Mild NPDR	Moderate NPDR	Severe NPDR			
NLR	2.81±1.50	4.09±3.09	2.49±1.16	2.32±0.75	2.38±1 .26	0.74
PLR	182.89±74.6 4	184.60±10.1 2	125.60±38. 38	155.61±4 4.98	129.70 ±47.05	0.04*
LMR	4.07±1.97	3.54±2.72	4.67±2.75	3.49± 0.61	4.88±3 .01	0.063
SII	1002.8±638. 80	1172.6±989. 10	660.01±30 6.23	715.17±3 35.81	662.57 ±367.8 1	0.03*

White cell indices like NLR, PLR, LMR & SII were calculated and compared among the study groups as depicted in Table 2.

In our study, SII (p value – 0.03) & PLR (p value – 0.04) were statistically significant in diabetic retinopathy group compared to NDR group. Among DR group, SII & PLR were more elevated in moderate NPDR group compared to severe NPDR and PDR.

DISCUSSION:

Diabetic retinopathy (DR) is an important microvascular complication of Diabetes Mellitus and a major cause of visual impairment worldwide. DR is listed as a priority eye disease in the 2030 IN SIGHT strategy (10)

Rajiv Raman, MS et al. in his study has stated that at least 3 million people are at risk or already have vision loss due to Vision Threatening DR (VTDR) in India hence there is a urgent need to identify and treat Vision Threatening DR in India. (11) Vision loss due to late diagnosis of VTDR can lead to loss of productivity and increase in DALYs (Disability-adjusted life years) (12) Hence finding new biomarkers with potential predictive value may serve as a valuable tool in early identification of those at risk of developing sight-threatening complications. Nowadays there is more emphasis on the role of ocular and systemic inflammation in the pathogenesis of diabetic retinopathy which is confirmed by many previous articles. (13)(14)(15)

Van Hecke MV et al. has stated in their study that both inflammatory and endothelial function markers were strongly associated with the presence of diabetic retinopathy. (16) Chronic hyperglycemia due to

impairment in glucose metabolism, leads to pro-inflammatory changes in the retina, resulting in microvascular retinal damages, this involves multiple pathways such as activation of aldose-reductase and polyol pathway, activation of the protein kinase C (PKC) pathway, accumulation of free radicals - reactive oxygen species (ROS), nitric oxide deficiency. (17)(18)

In recent studies, White cell inflammatory biomarkers, such as Neutrophil-to-Lymphocyte ratio (NLR), Platelet-to-Lymphocyte (PLR), Lymphocyte-to-Monocyte ratio (LMR), and Systemic Immune Inflammation index (SII), have showed good predictive value for several inflammation associated disease conditions including cancer and cardiovascular disease. (19) Thus the predictive value of these indices for DR was assessed in our study. Hu et al. first proposed SII, which has shown a higher predictive value for prognosis in the cancer field than other inflammatory predictors, such as NLR and PLR (20)

Yiqi Nie et al. have emphasized that SII levels are strongly related to diabetes.(21) Systemic Immune Inflammation Index (SII) is a new and reliable indicator which is calculated as platelet count multiplied by the neutrophil count divided by the lymphocyte count. (22) Calculation of SII is simple & cost-effective as it can be easily obtained from complete blood count, which is the most commonly performed test in clinical practice.

In our study, SII (p value – 0.03) was found to be statistically significant in diabetic retinopathy group compared to without DR group. These findings were consistent with the study conducted by Shuqi Wang et al. which stated that SII level in the DR group were higher than those in the NDR group and SII hold significant diagnostic value for identifying Diabetic Retinopathy in T2DM patients, Thus SII may serve as a valuable biological indicators of early DR screening. (23)

However, retrospective study done by Ana Maria Dascalu et al. on 129 T2DM patients, investigated the predictive value of the NLR, PLR, LMR, and SII for diabetic retinopathy (DR) and its severity. They found that there was no statistical difference between NDR and NPDR groups for any of the white cell inflammatory biomarkers. Systemic white cell inflammatory biomarkers did not predict DR in their study group. (9)

Several studies has shown higher values of NLR and PLR that were found to be predictive for diabetic microvascular and macrovascular complications. One such study by Zeng et al. has stated that in patients with DR, the median NLR, PLR, were significantly higher than in patients without DR ($p = 0.012$, $p < 0.001$ respectively). In the post hoc analysis, there was no correlation between the severity of retinopathy and the increase in NLR or PLR. Also PLR may be used as an independent risk factor for evaluating DR in type 2 diabetes mellitus patients. (24) In our study PLR (p value – 0.04) was statistically significant in diabetic retinopathy group compared to NDR group. But both NLR and LMR did not show any statistical significance as shown in table 2.

Similar to some studies, our study also analysed the correlation between the severity of DR & higher values of white cell biomarkers and found that SII & PLR were more elevated in moderate NPDR group compared to severe NPDR and PDR group. Cagri Ilhan et al. in his study has stated that the NLR of the PDR and severe NPDR groups was statistically significant & greater than that of the control group ($p=0.002$ and $p=0.048$, respectively), but there was no statistically significant difference between the PDR and severe NPDR groups ($p=0.083$). PLR was also similar in all 3 groups (all p values >0.05). Hence concluded that NLR value of 2.11 or more predicted DR (PDR or severe NPDR) with a sensitivity of 76% and a specificity of 80%. (25). Another study by Juxiang Liu et al. in their metanalysis included a total of 48 studies and concluded that NLR has a positive association with DN and DR. NLR could be recommended as inexpensive diagnostic markers for DN and DR. (26)

CONCLUSION:

In our study, SII (p value – 0.03) & PLR (p value – 0.04) were statistically significant in diabetic retinopathy group compared to NDR group. Among DR group, SII & PLR were more elevated in moderate NPDR group compared to severe NPDR and PDR. Thus, White cell inflammatory biomarkers such as PLR and SII can serve as simple, cost effective, reliable predictors of DR, but severity of DR cannot be

determined based on their elevated values. However, our study results are limited to a specific local population, with a relatively small sample size. Thus, further large, multicentric prospective studies are required to examine the precise connection between SII and other white cell inflammatory markers with that of Diabetic Retinopathy.

REFERENCES:

1. Saeedi, P. et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res. Clin. Pract. 2019, 157, 107843.
2. Serban, D. et al. Significance of Neutrophil to Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in Diabetic Foot Ulcer and Potential New Therapeutic Targets. Int. J. Low. Extrem. Wounds 2021, 18, 15347346211057742.
3. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, Deftereos S, Tousoulis D. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. Eur Cardiol. 2019 Apr;14(1):50-59. doi: 10.15420/ecr.2018.33.1. PMID: 31131037; PMCID: PMC6523054
4. Thomas R, Halim S, Gurudas S, Sivaprasad S, Owens D. IDF Diabetes Atlas: a review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. Diabetes Res Clin Pract. 2019;157:107840.
5. Zegeye, A.F.; Temachu, Y.Z.; Mekonnen, C.K. Prevalence and factors associated with diabetes retinopathy among type 2 diabetic patients at Northwest Amhara Comprehensive Specialized Hospitals, Northwest Ethiopia 2021. BMC Ophthalmol. 2023, 23, 9.
6. Sampathkumar Rangasamy et al. Diabetic Retinopathy and Inflammation: Novel Therapeutic Targets. Middle East Afr J Ophthalmol. 2012 Jan-Mar; 19(1): 52–59
7. Rakesh Chibber et al. Leukocytes in diabetic retinopathy. Curr Diabetes Rev. 2007 Feb;3(1):3-14.
8. Dascalu, A.M.; Serban, D.; Tanasescu, D.; Vancea, G.; Cristea, B.M.; Stana, D.; Nicolae, V.A.; Serboiu, C.; Tribus, L.C.; Tudor, C.; et al. The Value of White Cell Inflammatory Biomarkers as Potential Predictors for Diabetic Retinopathy in Type 2 Diabetes Mellitus (T2DM). Biomedicines 2023, 11, 2106. https://doi.org/10.3390/ biomedicines11082106
9. Hu, B.; Yang, X.-R.; Xu, Y.; Sun, Y.-F.; Sun, C.; Guo,W.; Zhang, X.;Wang,W.-M.; Qiu, S.-J.; Zhou, J. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin. Cancer Res. 2014, 20, 6212–6222
10. Katie Curran et al. Inclusion of diabetic retinopathy screening strategies in national-level diabetes care planning in low- and middle-income countries: a scoping review.Health Research Policy and Systems volume 21, Article number: 2 (2023)
11. Rajiv Raman, MS et al. Prevalence of Diabetic retinopathy in India stratified by known and undiagnosed diabetes, urban-rural locations, and socioeconomic indices: results from SMART india population-based cross-sectional screening study. The Lancet. VOLUME 10, ISSUE 12, E1764-E1773, DECEMBER 2022
12. Burton MJ Ramke J Marques AP et al.The Lancet Global Health Commission on Global Eye Health: vision beyond 2020.Lancet Glob Health. 2021; 9: e489-e551
13. Kuo, C.Y.J.; Murphy, R.; Rupenthal, I.D.; Mugisho, O.O. Correlation between the progression of diabetic retinopathy and inflammasome biomarkers in vitreous and serum—A systematic review. BMC Ophthalmol. 2022, 22, 238.
14. Gomułka, K.; Ruta, M. The Role of Inflammation and Therapeutic Concepts in Diabetic Retinopathy—A Short Review. Int. J. Mol. Sci. 2023, 24, 1024.
15. Semeraro, F.; Cancarini, A.; dell'Omo, R.; Rezzola, S.; Romano, M.R.; Costagliola, C. Diabetic Retinopathy: Vascular and Inflammatory Disease. J. Diabetes Res. 2015, 2015, 582060.
16. van Hecke M V et al. Inflammation and endothelial dysfunction are associated with retinopathy: the Hoorn Study. Diabetologia 48:1300–1306
17. Rübsam, A.; Parikh, S.; Fort, P.E. Role of Inflammation in Diabetic Retinopathy. Int. J. Mol. Sci. 2018, 19, 942
18. Aldosari, D.I.; Malik, A.; Alhomida, A.S.; Ola, M.S. Implications of Diabetes-Induced Altered Metabolites on Retinal Neurodegeneration. Front. Neurosci. 2022, 16, 938029

19. Zhen Ye et al. Systemic immune-inflammation index as a potential biomarker of cardiovascular diseases: A systematic review and meta-analysis. Front Cardiovasc Med. 2022; 9: 933913
20. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. (2014) 20:6212–22. 10.1158/1078-0432.CCR-14-0442
21. Yiqi Nie et al. Association between systemic immune-inflammation index and diabetes: a population-based study from the NHANES. Front. Endocrinol., 31 October 2023.Sec. Clinical Diabetes Volume 14 – 2023
22. Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et al. Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. Sci Rep (2019) 9:3284. doi: 10.1038/s41598-019-39150-0
23. Shuqi Wang et al. Exploring the Correlation Between the Systemic Immune Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Type 2 Diabetic Retinopathy. Diabetes Metab Syndr Obes. 2023; 16: 3827–3836.
24. Zeng, J.; Chen, M.; Feng, Q.; Wan, H.; Wang, J.; Yang, F.; Cao, H. The Platelet-to-Lymphocyte Ratio Predicts Diabetic Retinopathy in Type 2 Diabetes Mellitus. Diabetes Metab. Syndr. Obes. 2022, 15, 3617–3626
25. Ilhan, C.; Citirik, M.; Uzel, M.M.; Tekin, K. The Optimal Cut-off Value of Neutrophil/Lymphocyte Ratio for Severe Grades of Diabetic Retinopathy. Beyoglu Eye J. 2019, 4, 76–81.
26. Juxiang Liu et al. The association of neutrophil to lymphocyte ratio, mean platelet volume, and platelet distribution width with diabetic retinopathy and nephropathy: a meta-analysis. Biosci Rep. 2018 Jun 29; 38(3): BSR20180172