ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Correlation of newer inflammatory markers in patients with type 2 diabetes mellitus: A cross-sectional study

Swetha Akkina[1], Srikanth Akula[2], Rajeev Gandham[3], Preethi Batakala[4], Bhagyalakshmi Atla[5], Divija Reddy Bonthu[6], Sunkara Uha Priya[7]

[1,2]Associate Professor, [6,7]Postgraduate Resident, Department of General Medicine, [3]Assistant Professor, [4]Professor and Head, Department of Biochemistry, [5]Professor and Head, Department of Pathology, NRI Institute of Medical Sciences, Visakhapatnam, Andhra Pradesh, India

Submission: 12-11-2024 Revision: 03-01-2025 Publication: 01-02-2025

ABSTRACT

Background: Globally, diabetes mellitus (DM) is a major health concerns and has reached alarming levels. DM is a group of metabolic disorders characterized by hyperglycemia leading to micro- and macro-vascular complications. Chronic low-grade inflammation is associated with the pathophysiology of DM. **Aims and Objectives:** The present study aimed to assess the levels of neutrophil-to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and other inflammatory markers in T2DM patients and their correlation with blood sugar and HbA1c. **Materials and Methods:** This cross-sectional study was conducted in Department of Biochemistry in association with Department of General Medicine and Pathology, NRI Institute of Medical Sciences (NRIIMS), Visakhapatnam, Andhra Pradesh, India. In this study, 90 T2DM patients and 90 non-diabetic subjects were recruited. Fasting and post-prandial blood samples were collected and used for the estimation of blood sugar, urea, creatinine, and lipid profile parameters. Whole blood (EDTA) samples were used for analysis of complete blood count (CBC) and HbA1c. NLR, PLR, SII, SIRI, MHR, NHR, LHR, and PHR were calculated from CBC values. Demographic details were collected. **Results:** In this study, significant increase in blood pressure (systolic [120.4 ± 8.1 mmHg], diastolic [80.2 ± 4.8 mmHg]), fasting blood sugar (FBS) (162.5 ± 53.7 mg/dL), post-prandial blood sugar (238.3 ± 78.8 mg/dL), HbA1c (8.5 ± 2.2%), urea (28.6 ± 8.6 mg/dL), creatinine (1.1 ± 0.2 mg/dL), total cholesterol (186.8 ± 46.1 mg/dL), triglycerides (168.9 ± 61.2 mg/dL), LDLC (115.0 ± 36.3 mg/dL), VLDL (33.8 ± 12.4 mg/dL), and neutrophil count (66.6 ± 11.4%) was observed in T2DM cases. Inflammatory markers such as NLR (4.2 ± 1.1), PLR (0.17 ± 0.01), SII (12.6 ± 3.6), SIRI (25.7 ± 5.2), MHR (0.15 ± 0.08), NHR (1.9 ± 0.72), and PHR (0.07 ± 0.02) were significantly increased in T2DM cases than non-diabetic subjects. FBS was positively correlated with SIRI (r = 0.180), MHR (r = 0.257), NHR (r = 0.418), and PHR (r = 0.212). Similarly, HbA1c positively correlated with NHR (r = 0.353) and PHR (r = 0.177) in T2DM subjects. In this study, HDLC level and lymphocyte count was significantly decreased in T2DM cases. **Conclusion:** The study may conclude that increased levels of NLR, PLR, SII, SIRI, MHR, NHR, and PHR in T2DM and their positive correlation with blood sugar and HbA1c may serve as alternate markers of inflammation and are useful to assess the impact of systemic inflammatory response in T2DM patients.

Key words: Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Systemic immune inflammation index; Systemic inflammation response index

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i2.4396

E-ISSN: 2091-0576

P-ISSN: 2467-9100

Address for Correspondence:
Dr. Rajeev Gandham, Department of Biochemistry, NRI Institute of Medical Sciences, Visakhapatnam, Andhra Pradesh, India.
Mobile: +91-8892551401. **E-mail:** gandhamrajeev33@gmail.com

INTRODUCTION

Globally, diabetes mellitus (DM) is a major health concern and has reached alarming levels. DM is a group of metabolic disorders characterized by hyperglycemia leading to micro- and macrovascular complications. In 2021, it is estimated that 537 million people have diabetes, and this number is projected to increase 643 million by 2030 and 783 million by 2045. In India, the prevalence of DM is 77 million in 2019, projected to increase 134 million by 2045. The reported prevalence of diabetes in Andhra Pradesh is 8.4%. Population aging, urbanization, sedentary lifestyle, and unhealthy dietary habits are proposed to be the major contributing factors for this increasing prevalence.[1,2]

Chronic low-grade inflammation is associated with the pathophysiology of DM and inflammatory markers may lead to insulin resistance (IR) by inhibiting β-cell function and by accelerating apoptosis.[3] Therefore, monitoring of blood glucose levels in the early stage can delay the onset of diabetic vascular complications. Patients with type 2 diabetes mellitus (T2DM) are more prone to developing cardiovascular diseases. Chronic low-grade inflammation due to IR may lead to cardiac and other vascular complications of diabetes. Inflammatory markers such as CRP (C-reactive protein), total white blood cell count, interleukin (IL)-6, IL-1, IL-18, and tumor necrosis factor-α (TNF-α) are well established. However, these markers are not done routinely due to their cost and technical difficulties.[4]

Recently, neutrophil-lymphocyte ratio (NLR) has been proposed as a novel biomarker for inflammation in diabetic kidney disease, heart failure, and SARS-COV-2 infection.[5-7] Neutrophils are concerned with the release of inflammatory mediators that can cause vascular wall degeneration, whereas lymphocytes are involved in the regulation of inflammatory response and thus play a role as an anti-atherosclerotic. Therefore, the ratio of neutrophil to lymphocyte may serve as a surrogate marker for inflammation.[8]

Similarly, platelet-to-lymphocyte ratio (PLR) has also been reported as a novel biomarker for inflammation in liver diseases and cancer.[9,10] PLR indicates increased platelet count that leads to platelet aggregation and thus promotes vascular complications and decreased lymphocytes, suggestive of inflammation. Recently, systemic immune-inflammatory index (SII) and systemic inflammatory response index (SIRI) have been proposed as a complete blood count (CBC) derived inflammatory markers, and the levels were reported in coronary artery disease (CAD) and malignancies.[11,12]

Furthermore, new inflammatory markers are calculated from CBC values related to HDL-C, which includes monocyte/HDL-C ratio (MHR), neutrophil/HDL-C ratio (NHR), lymphocyte/HDL-C ratio (LHR), and platelet/HDL-C ratio (PHR). A few studies have reported their role in stroke, cardiovascular diseases, and diabetic kidney disease.[13-15]

Although NLR, PLR, SII, SIRI, and other CBC-derived inflammatory markers have been proposed as novel biomarkers in various conditions, there are limited studies available on the use of these markers in DM. In addition, this study included all the CBC-derived inflammatory and their correlation with blood sugar and HbA1c.

Aims and objectives

The present study aimed to assess the levels of NLR, PLR, SII, SIRI, and other inflammatory markers in T2DM patients and their correlation with blood sugar and HbA1c.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Biochemistry in association with Department of General Medicine and Pathology, NRIIMS, Visakhapatnam, Andhra Pradesh, India. After obtaining the Institutional Ethics Committee (IEC/NRI/114/2024) and informed consent from all the study subjects, a total of 180 subjects were recruited into the study using simple random sampling method. Out of 180, T2DM patients were 90 and non-diabetic subjects were 90. Sample size was calculated with a power of 80% and with type I error of 5% using the formula: $[Z1-\alpha/2]^2$ [b] [1-b]/$d^{2,3}$

Inclusion criteria

Diabetic and non-diabetic subjects willing to participate in the study, age of ≥18 years, both male and females were included. T2DM was diagnosed based on the American Diabetes Association criteria.

Exclusion criteria

Patients refused to participate in the study, patients with immunosuppressive therapy, autoimmune diseases, cardiovascular diseases, diabetes other than T2DM, liver diseases, renal diseases, thyroid diseases, gestational diabetics, epilepsy, hypertensive encephalopathy, malignancy conditions, and pregnant women were excluded from the study.

Sample collection

Under aseptic conditions, after 8–12 h fasting, 5 mL of venous blood samples and 2 mL post-prandial samples were collected from all study subjects, visiting to Department of General Medicine. The collected blood samples were

allowed to stand for 1 h and centrifuged at 3000 rpm for 10 min to separate serum sample. The obtained serum sample was used for the estimation of fasting and post-prandial glucose by GOD-POD, urea (urease), creatinine (Jaffe's), total cholesterol (cholesterol oxidase/peroxidase), triglycerides (glycerol phosphate oxidase/peroxidase), and HDLC (HDLC-Direct) were estimated using Biosystems BA-200 Biochemistry fully autoanalyzer. LDLC and VLDLC were calculated by Friedewald's formula. EDTA samples were used for the measurement of HbA1c using BIORAD D-10 analyzer and CBC using Mindray BC 780 Hematology analyzer. NLR, PLR, SII, SIRI, MHR, NHR, LHR, and PHR were calculated from CBC values using the following formulas.

NLR=Neutrophil-to-lymphocyte ratio
PLR=Platelet-to-lymphocyte ratio
SII=Platelet × Neutrophil-to-lymphocyte ratio
SIRI=Monocyte × Neutrophil-to-lymphocyte ratio
MHR=Monocyte-to-HDLC ratio
NHR=Neutrophil-to-HDLC ratio
LHR=Lymphocytes-to-HDLC ratio
PHR=Platelets-to-HDLC ratio

Detailed physical and clinical examination was done for all the study subjects. Body mass index was calculated and blood pressure was measured in addition to the family history and lifestyle parameters.

Statistical analysis

The data were represented in mean and standard deviation and categorical data were expressed in percentages. The difference observed if any in quantitative measurement was tested by applying Mann–Whitney U test. Spearman's rho correlation was applied to correlate inflammatory markers with blood sugar and HbA1c. The P value ($P<0.05$) was considered as statistically significant. Data analysis was done using SPSS 22.0.

RESULTS

In the present study, among T2DM subjects males were 48 (53.3%) and females were 42 (46.7%). In non-diabetic subjects, males were 49 (54.5%) and females were 41 (45.5%). In this study, mean age (56.9±10.4 years) was significantly high in T2DM cases than non-diabetics. Significant increase in systolic blood pressure (120.4±8.1 mmHg), diastolic blood pressure (80.2±4.8 mmHg), FBS (162.5±53.7 mg/dL), post-prandial blood sugar (238.3±78.8 mg/dL), HbA1c (8.5±2.2%), urea (28.6±8.6 mg/dL), creatinine (1.1±0.2 mg/dL), total cholesterol (186.8±46.1 mg/dL), triglycerides (168.9±61.2 mg/dL), LDLC (115.0±36.3 mg/dL), VLDL (33.8±12.4 mg/dL), and neutrophil count (66.6±11.4%) was observed in T2DM cases than non-diabetic subjects. Significant decrease in HDLC and lymphocytes was observed in T2DM subjects as shown in Table 1.

In the current study, inflammatory markers such as NLR (4.2±1.1), PLR (0.17±0.01), SII (12.6±3.6), SIRI (25.7±5.2), MHR (0.15±0.08), NHR (1.9±0.72), and PHR (0.07±0.02) were significantly increased in T2DM cases than non-diabetic subjects, LHR statistically not significant as shown in Table 2.

In this study, FBS was significantly correlated (positive) with SIRI (r=0.180), MHR (r=0.257), NHR (r=0.418), MHR (r=0.257), and PHR (r=0.212). Similarly, HbA1c positively correlated with NHR (r=0.353) and PHR (r=0.177). Other inflammatory markers also showed positive correlation but not reached statistical significance (Table 3).

DISCUSSION

DM is a complex and multifactorial disease associated with IR, oxidative stress, and inflammation. Chronic inflammation plays an important role in the initiation and progression of T2DM and further accelerates micro- and macrovascular complications. Accelerated inflammation and elevated immune response can lead to the upregulation of pro-inflammatory cytokines and chemokines, such as IL-1β, TNF-α, and vascular endothelial growth factor, which can cause endothelial dysfunction and leukocyte infiltration.[16]

In this study, significant elevation of inflammatory markers such as NLR, PLR, SII, SIRI, MHR, NHR, and PHR was observed in T2DM cases compared to non-diabetic controls. Inflammatory markers showed positive correlation with blood sugar and HbA1c. Neutrophils are associated with inflammation, whereas lymphocytes indicate immunoregulation. These can indicate the systemic inflammation and also innate and adaptive immuneresponses. Inflammation caused by hyperglycemia may cause changes in the peripheral blood cell levels.[17] Previous studies have evidenced that peripheral blood leukocytes and their subgroups are associated with micro and macrovascular complications in T2DM patients.[18,19] More specifically, peripheral blood leukocytes include neutrophils, lymphocytes, monocytes, eosinophils, and basophils, each type of which holds a unique biological function in systemic inflammation.[20]

In this study, increased NLR may be a manifestation of an increased number of neutrophils, which adhere to the endothelial cell, leading to vascular endothelial cell damage

Table 1: Comparison of demographic details, biochemical, and hematological parameters in T2DM patients and non-diabetic subjects

Parameters	T2DM cases (Mean±SD) (n=90)	Non-diabetic subjects (Mean±SD) (n=90)	P-value
Demographic Details			
Age (years)	56.9±10.4	49.7±12.8	0.000*
Males (n,%)	53.3	54.5	-
Females (n,%)	46.7	45.5	-
Body mass index (kg/m^2)	25.1±2.6	22.9±1.3	0.000*
Systolic blood pressure (mmHg)	120.4±8.1	116.3±4.8	0.001*
Diastolic blood pressure (mmHg)	80.2±4.8	70.1±3.2	0.047*
Biochemical parameters			
Fasting blood sugar (mg/dL)	162.5±53.7	91.8±10.4	0.000*
Post-prandial blood sugar (mg/dL)	238.3±78.8	127.3±21.2	0.000*
HbA1c	8.5±2.2	5.3±0.26	0.000*
Serum urea	28.6±8.6	21.5±7.8	0.000*
Serum creatinine	1.1±0.2	0.8±0.2	0.000*
Serum total cholesterol	186.8±46.1	153.0±20.9	0.000*
Serum triglycerides	168.9±61.2	142.8±40.1	0.028*
Serum HDLC	38.2±10.2	47.3±8.8	0.000*
Serum LDLC	115.0±36.3	77.3±18.1	0.000*
Serum VLDL	33.8±12.4	28.4±7.9	0.020*
Hematological parameters			
Hemoglobin (%)	11.2±1.9	11.5±2.3	0.733
Packed cell volume	31.9±4.5	33.8±4.9	0.008*
White blood cell count	8970.±2472.5	8362.4±2352.4	0.190
Platelets	2.8±0.68	2.8±0.55	0.900
Neutrophils (%)	66.6±11.4	60.4±10.1	0.004*
Lymphocytes (%)	24.1±10.9	29.4±8.8	0.006*
Monocytes (%)	5.6±2.7	5.4±1.9	0.951

*Significant (P<0.05). SD: Standard deviation

Table 2: Comparison of inflammatory markers in T2DM patients and non-diabetic subjects

Parameters	T2DM cases (Mean±SD) (n=90)	Non-diabetic subjects (Mean±SD) (n=90)	P-value
Neutrophil-to-lymphocyte ratio (NLR)	4.2±1.1	2.3±1.0	0.009*
Platelet-to-lymphocyte ratio (PLR)	0.17±0.01	0.10±0.04	0.046*
systemic immune inflammation index (SII)	12.6±3.6	6.7±3.7	0.028*
Systemic inflammation response index (SIRI)	25.7±5.2	12.4±7.0	0.006*
Monocyte-to-HDLC ratio (MHR)	0.15±0.08	0.12±0.05	0.002*
Neutrophil-to-HDLC ratio (NHR)	1.9±0.72	1.3±0.27	0.000*
Lymphocyte-to-HDLC ratio (LHR)	0.66±0.32	0.64±0.24	0.807
Platelet-to-HDLC ratio (PHR)	0.07±0.02	0.06±0.01	0.000*

*Significant, (P<0.05). SD: Standard deviation

Table 3: Correlation of inflammatory markers with FBS and HbA1c

Parameters	FBS		HbA1c	
	r-value	P-value	r-value	P-value
Neutrophil-to-lymphocyte ratio	0.133	0.120	0.154	0.072
Platelet-to-lymphocyte ratio	0.066	0.442	0.044	0.607
Systemic immune inflammation index	0.106	0.217	0.083	0.335
Systemic inflammation response index	0.180*	0.034	0.127	0.136
Monocyte-to-HDLC ratio	0.257**	0.002	0.147	0.086
Neutrophil-to-HDLC ratio	0.418**	0.000	0.353**	0.000
Lymphocyte-to-HDLC ratio	0.095	0.268	0.044	0.611
Platelet-to-HDLC ratio	0.212*	0.013	0.177*	0.037

FBS: Fasting blood sugar
**Correlation is significant at the 0.01 level (2-tailed)
*Correlation is significant at the 0.05 level (2-tailed)

and in turn causing extensive chronic inflammation.[21] Hence, the elevated NLR might indicate increased microvascular inflammation in patients with T2DM. Lymphocytes serve as a major part of the body's immuneresponse. They are involved in the regulation of inflammatory responses and have a relatively higher proportion of CD4 T cells that were proved to be anti-atherosclerotic.[22]

Similarly, PLR is significantly increased in T2DM patients. Studies have reported the role of PLR in predicting diabetes-associated lower limb vascular disease, atherosclerosis, and diabetic foot ulcers.[23,24] It has been well documented that platelets participate in thrombosis. Many studies have reported that platelets play a significant role in the immuno-inflammatory response. Specifically, platelets can release a variety of immune-regulating cytokines, chemokines, and other mediators, thus regulating the inflammation response in blood vessels in an autocrine or paracrine manner.[25] Meanwhile, platelets could also regulate neutrophils, endothelial cells, and lymph directly, allowing them to recruit toward injured tissue. Therefore, because of this regulatory function of platelets, elevated PLR might indicate the relatively active inflammatory response of platelets among T2DM patients.[26]

The SII and SIRI are proposed as novel CBC-derived inflammatory markers. Studies have reported the association between SII, SIRI, and diabetic complications.[15,27] The association between SII and diabetic vascular complications is unsurprising given some of the mechanisms underlying the development of diabetes and its complications. Inflammation and immune response play important roles in the pathophysiology and progression of diabetes. Especially, chronic low-grade inflammation contributes to organ dysfunction and tissue damage, which can promote IR and impaired insulin secretion.[28] Our results are in accordance with the studies conducted by Mann[29] and Yang et al.,[30]. In addition, Elbeyli et al., reported that increased SII was strongly associated with the development of diabetic macular edema.[31] In 2022, a study conducted by Guo et al., reported that elevated SII was associated with diabetic kidney disease.[15] In 2023 Lin et al., reported that elevated SIRI has been independently associated with the risk of diabetic CVDs.[32]

MHR is reported to be a novel biomarker with integration of pro-inflammatory and anti-inflammatory indices. Monocytes play a significant role in the development of diabetic vascular complications. Monocyte counts have been shown to be correlated with IR, T2DM, and vascular complications.[18,33] On the other hand, emerging data indicate that reduced HDL-C is an important contributor to accelerate atherosclerosis in diabetic patients. Therefore, the integrated maker, MHR, may serve as better marker to indicate vascular inflammatory changes in diabetic patients. In addition to the above inflammatory markers, NHR and PHR were also significantly elevated in T2DM patients.

Limitations of the study

The present study has the following limitations. (1) Sample size and (2) established inflammatory markers such as CRP and IL-6 were not assessed.

CONCLUSION

The study may conclude that increased levels of NLR, PLR, SII, SIRI, MHR, NHR, and PHR in T2DM and their positive correlation with blood sugar and HbA1c may serve as alternate markers of inflammation. These markers are easily calculated from CBC values and are less expensive. Therefore, these simple and inexpensive markers are useful to assess the impact of systemic inflammatory response in T2DM patients. Further, studies are recommended with large sample size.

ACKNOWLEDGMENT

We would like to thank the authorities of NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam, Andhra Pradesh, India.

REFERENCES

1. Sinha R, Priya A, Sinha A and Hifz Ur Rahman M. Prevalence of diabetes distress among type 2 diabetes mellitus patients in India: A systematic review and meta-analysis. Health Psychol Behav Med. 2024;12(1):2324091.
   https://doi.org/10.1080/21642850.2024.2324091
2. Pradeepa R and Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021;69(11):2932-2938.
   https://doi.org/10.4103/ijo.ijo_1627_21
3. Sahu JK, Kalita R, Gandham R and Medikonda R. Assessment of neutrophil and platelet-to-lymphocyte ratio as inflammatory markers in type 2 diabetes mellitus patients. Asian J Med Sci. 2023;14(4):50-53.
   https://doi.org/10.3126/ajms. v14i4.51515
4. Jaaban M, Zetoune AB, Hesenow S and Hessenow R. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as novel risk markers for diabetic nephropathy in patients with type 2 diabetes. Heliyon. 2021;7(7):e07564.
   https://doi.org/10.1016/j.heliyon.2021.e07564
5. Li L, Shen Q and Rao S. Association of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic kidney disease in Chinese patients with type 2 diabetes: A cross-sectional study. Ther Clin Risk Manag. 2022;18:1157-1166.
   https://doi.org/10.2147/tcrm.s393135
6. Boralkar KA, Kobayashi Y, Amsallem M, Ataam JA, Moneghetti KJ, Cauwenberghs N, et al. Value of neutrophil to lymphocyte ratio and its trajectory in patients hospitalized with acute heart failure and preserved ejection fraction. Am J Cardiol.

2020;125(2):229-235.

https://doi.org/10.1016/j.amjcard.2019.10.020

7. Khalid A, Ali Jaffar M, Khan T, Abbas Lail R, Ali S, Aktas G, et al. Hematological and biochemical parameters as diagnostic and prognostic markers in SARS-COV-2 infected patients of Pakistan: A retrospective comparative analysis. Hematology. 2021;26(1):529-542.

https://doi.org/10.1080/16078454.2021.1950898

8. Angkananard T, Anothaisintawee T, McEvoy M, Attia J and Thakkinstian A. Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. Biomed Res Int. 2018;2018:2703518.

https://doi.org/10.1155/2018/2703518

9. Hirahara T, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer. 2019;19(1):672.

https://doi.org/10.1186/s12885-019-5903-y

10. Kosekli MA. Mean platelet volume and platelet to lymphocyte count ratio are associated with hepatitis B-related liver fibrosis. Eur J Gastroenterol Hepatol. 2022;34(3):324-327.

https://doi.org/10.1097/meg.0000000000002219

11. Dziedzic EA, Gąsior JS, Tuzimek A, Paleczny J, Junka A, Dąbrowski M, et al. Investigation of the associations of novel inflammatory biomarkers-Systemic Inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI)-with the severity of coronary artery disease and acute coronary syndrome occurrence. Int J Mol Sci. 2022;23(17):9553.

https://doi.org/10.3390/ijms23179553

12. Saroul N, Puechmaille M, Lambert C, Hassan AS, Biau J, Lapeyre M, et al. Prognosis in head and neck cancer: Importance of nutritional and biological inflammatory status. Otolaryngol Head Neck Surg. 2022;166(1):118-127.

https://doi.org/10.1177/01945998211004592

13. Lin KB, Fan FH, Cai MQ, Yu Y, Fu CL, Ding LY, et al. Systemic immune inflammation index and system inflammation response index are potential biomarkers of atrial fibrillation among the patients presenting with ischemic stroke. Eur J Med Res. 2022;27(1):106.

https://doi.org/10.1186/s40001-022-00733-9

14. Xia Y, Xia C, Wu L, Li Z, Li H and Zhang J. Systemic Immune Inflammation Index (SII), System Inflammation Response Index (SIRI) and risk of all-cause mortality and cardiovascular mortality: A 20-year follow-up cohort study of 42,875 US adults. J Clin Med. 2023;12(3):1128.

https://doi.org/10.3390/jcm12031128

15. Guo W, Song Y, Sun Y, Du H, Cai Y, You Q, et al. Systemic immune-inflammation index is associated with diabetic kidney disease in type 2 diabetes mellitus patients: Evidence from NHANES 2011-2018. Front Endocrinol (Lausanne). 2022;13:1071465.

https://doi.org/10.3389/fendo.2022.1071465

16. Dascalu AM, Georgescu A, Costea AC, Tribus L, El Youssoufi A, Serban D, et al. Association between Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) with diabetic retinopathy in type 2 diabetic patients. Cureus. 2023;15(11):e48581.

https://doi.org/10.7759/cureus.48581

17. Azab B, Daoud J, Naeem FB, Nasr R, Ross J, Ghimire P, et al. Neutrophil-to-lymphocyte ratio as a predictor of worsening renal function in diabetic patients (3-year follow-up study). Ren Fail. 2012;34(5):571-576.

https://doi.org/10.3109/0886022x.2012.668741

18. Tong PC, Lee KF, So WY, Ng MH, Chan WB, Lo MK, et al. White blood cell count is associated with macro-and microvascular complications in Chinese patients with type 2 diabetes. Diabetes Care. 2004;27(1):216-222.

https://doi.org/10.2337/diacare.27.1.216

19. Wang JR, Chen Z, Yang K, Yang HJ, Tao WY, Li YP, et al. Association between neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and diabetic retinopathy among diabetic patients without a related family history. Diabetol Metab Syndr. 2020;12:55.

https://doi.org/10.1186/s13098-020-00562-y

20. Mertoglu C and Gunay M. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diabetes Metab Syndr. 2017;11(Suppl 1):S127-S131.

https://doi.org/10.1016/j.dsx.2016.12.021

21. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, et al. Usefulness of neutrophil to lymphocyte ratio in predicting short-and long-term mortality after non-ST-elevation myocardial infarction. Am J Cardiol. 2010;106(4):470-476.

https://doi.org/10.1016/j.amjcard.2010.03.062

22. Wang RT, Zhang JR, Li Y, Liu T and Yu KJ. Neutrophil-lymphocyte ratio is associated with arterial stiffness in diabetic retinopathy in type 2 diabetes. J Diabetes Complications. 2015;29(2):245-249.

https://doi.org/10.1016/j.jdiacomp.2014.11.006

23. Liu N, Sheng J, Pan T and Wang Y. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with lower extremity vascular lesions in Chinese patients with type 2 diabetes. Clin Lab. 2019;65(3).

https://doi.org/10.7754/clin.lab.2018.180804

24. Mineoka Y, Ishii M, Hashimoto Y, Yamashita A, Nakamura N and Fukui M. Platelet to lymphocyte ratio correlates with diabetic foot risk and foot ulcer in patients with type 2 diabetes. Endocr J. 2019;66(10):905-913.

https://doi.org/10.1507/endocrj.ej18-0477

25. Chatterjee M and Geisler T. Inflammatory contribution of platelets revisited: New players in the arena of inflammation. Semin Thromb Hemost. 2016;42(3):205-214.

https://doi.org/10.1055/s-0035-1570081

26. Jenne CN, Urrutia R and Kubes P. Platelets: Bridging hemostasis, inflammation, and immunity. Int J Lab Hematol. 2013;35(3): 254-261.

https://doi.org/10.1111/ijlh.12084

27. Wang J, Zhou D, Dai Z and Li X. Association between systemic immune-inflammation index and diabetic depression. Clin Interv Aging. 2021;16:97-105.

https://doi.org/10.2147/cia.s285000

28. Wada J and Makino H. Innate immunity in diabetes and diabetic nephropathy. Nat Rev Nephrol. 2016;12(1):13-26.

https://doi.org/10.1038/nrneph.2015.175

29. Mann CJ. Observational research methods. Research design II: Cohort, cross sectional, and case-control studies. Emerg Med J. 2003;20(1):54-60.

https://doi.org/10.1136/emj.20.1.54

30. Yang C, Yang Q, Xie Z, Peng X, Liu H and Xie C. Association of systemic immune-inflammation-index with all-cause and cause-specific mortality among type 2 diabetes: A cohort study base on population. Endocrine. 2024;84(2):399-411.

https://doi.org/10.1007/s12020-023-03587-1

31. Elbeyli A, Kurtul BE, Ozcan SC and Ozarslan Ozcan D. The diagnostic value of systemic immune-inflammation index in

diabetic macular oedema. Clin Exp Optom. 2022;105(8): 831-835.
https://doi.org/10.1080/08164622.2021.1994337

32. Lin K, Lan Y, Wang A, Yan Y and Ge J. The association between a novel inflammatory biomarker, systemic inflammatory response index and the risk of diabetic cardiovascular complications. Nutr Metab Cardiovasc Dis. 2023;33(7):1389-1397.
https://doi.org/10.1016/j.numecd.2023.03.013

33. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C and Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002;51(2):455-461.
https://doi.org/10.2337/diabetes.51.2.455

Authors Contribution:
SA- Definition of intellectual content, Data collection, data analysis, concept, design, clinical protocol, literature survey, implementation of study protocol**;** **SA-** Data collection, data analysis, concept, design, clinical protocol, implementation of study protocol**; RG-** Prepared first draft of manuscript, data analysis, statistical analysis and Interpretation, manuscript preparation and submission of article, coordination and Manuscript revision**; PB-** Review manuscript**;** **BA-** Review Manuscript**; DRB-** Design, clinical protocol, Literature survey, data collection, data analysis**; SUP-** Design, clinical protocol, Literature survey, data collection, data analysis.

Work attributed to:
NRI Institute of Medical Sciences, Sangivalasa, Visakhapatnam - 531 162, Andhra Pradesh, India.

Orcid ID:
Dr. Swetha Akkina - https://orcid.org/0009-0006-8097-0331
Dr. Srikanth Akula - https://orcid.org/0009-0006-3386-6259
Dr. Rajeev Gandham - https://orcid.org/0000-0002-5288-486X
Dr. Preethi Batakala - https://orcid.org/0009-0005-8690-8814
Dr. Bhagyalakshmi Atla - https://orcid.org/0009-0007-0606-7301
Dr. Divija Reddy Bonthu - https://orcid.org/0009-0000-9108-9829
Dr. Sunkara Uha Priya - https://orcid.org/0009-0003-5286-9891

Source of Support: Nil, **Conflicts of Interest:** None declared.