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Assessment of Systemic Immune-Inflammatory (SII) Index, Systemic Inflammatory Response (SIR) Index, Neutrophil to HDL-C ratio (NHR), Monocyte to HDL-C ratio (MHR) and Lymphocyte to HDL-C ratio (LHR) as markers of Inflammation in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus (DM), a chronic metabolic disease with increasing prevalence in India. Type 2 diabetes mellitus (T2DM) and its associated vascular complications are major contributors to mortality and morbidity worldwide. Inflammation and immune response play a significant role in the pathogenic mechanism and progression of DM. Chronic low-grade inflammation contributes to organ dysfunction and tissue damage, promoting insulin resistance (IR) by inhibiting β-cell function, impairing insulin secretion, and accelerating apoptosis.

Aim: The present study aimed to assess the systemic immune inflammation (SII) index and systemic inflammation response (SIR) Index in patients with T2DM.

Materials and Methods: This retrospective study was conducted in the Department of Biochemistry in association with the Department of Pathology, Gayatri Vidhya Parishad Institute of Health Care & Medical Technology (GVPIHC&MT), Visakhapatnam, Andhra Pradesh, India. After obtaining the Institutional Ethics Committee, a total 280 subject's data was collected. Among them, 140 were type 2 diabetes mellitus patients and 140 were non-diabetic subjects. Necessary details were collected from medical records including demographic details like age, sex, BMI and blood pressure. Details of biochemical parameters such as fasting and post-prandial glucose, urea, creatinine, total cholesterol, Triglycerides, and high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and HbA1c. Hematological parameters like complete blood count (CBC) values were collected. The SII index, SIR index, NHR, MHR and LHR were calculated by using the formulas.

Results: In the present study, significant increase in blood pressure [(systolic 120.2±6.2 mmHg), (diastolic 80.2±2.2 mmHg)], fasting blood sugar (FBS) (155.2±50.1 mg/dl), post-prandial blood sugar (PPBS) (211.5±58.4 mg/dl), HbA1c (8.1±2.5 %), urea (30.4±7.1 mg/dl), creatinine (1.2±0.2 mg/dl), total cholesterol (196.7±56.7 mg/dl), triglycerides (178.5±68.5 mg/dl), LDL-C (130.6±31.5 mg/dl), VLDL-C (35.6±13.7 mg/dl) and neutrophil count (64.6±11.4 %) was

observed in T2DM cases than non-diabetic subjects. Significant decrease in HDL-C (30.5±11.5 mg/dl), and lymphocytes (26.5±10.9%) observed in T2DM subjects. Concerned with inflammatory markers such as SII index (12.6±3.6), SIR index (25.7±5.2), NHR (1.9±0.72), MHR (0.15±0.08), PHR (0.07±0.02), NLR (4.2±1.1) and PLR (0.17±0.01) were significantly increased in T2DM cases than non-diabetic subjects. In this study, FBS significantly correlated (positive) with SII index (r=0.367), SIR index (r=0.199), NHR (r=0.524), MHR (r=0.368), PHR (r=0.225), and NLR (r=0.289). HbA1c also showed a positive correlation with SII index (r=0.253), SIR index (r=0.199), NHR (r=0.462), and PHR (r=0.198).

Conclusion: The present study results may conclude significant elevation of inflammatory markers such as SII index, SIR index, NHR, MHR, PHR, NLR, and PLR and a significant positive correlation with blood sugar and HbA1c.

Keywords: *Inflammation, Lymphocyte to HDL-C ratio (LHR), Monocyte to HDL-C ratio (MHR), Neutrophil to HDL-C ratio (NHR), Systemic Immune-Inflammatory (SII) Index, Systemic Inflammatory Response (SIR) Index*

1. INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic disease with increasing prevalence in India. In India, the reported prevalence in 2001 was 72 million, and by 2045 projected to increase 125 million. [1] DM has a significant impact on human life as well as healthcare expenditures. Type 2 diabetes mellitus (T2DM) and its associated vascular complications are major contributors to mortality and morbidity worldwide. Diabetic patients have twice the risk of mortality as compared to non-DM patients. [2]

Inflammation and immune response play a significant role in the pathogenic mechanism and progression of diabetes. Chronic low-grade inflammation contributes to organ dysfunction and tissue damage, can promote insulin resistance (IR) by inhibiting β-cell function, and impairs insulin secretion and accelerates apoptosis. [3] Inflammation has been considered a key factor in the development and progression of atherosclerotic cardiovascular diseases (CVDs). Many inflammatory markers were reported to be associated with T2DM, these include interleukin-1 (IL-1), IL-6, transforming growth factor (TGF-β1), and Tumor necrosis factor - α (TNF-α). The assessment of these markers is not done routinely. [4,5]

Therefore, there is a need to establish simple and inexpensive markers. Recently, systemic immune inflammation (SII) index and systemic inflammatory response (SIR) index were proposed as novel markers of inflammation and were integrated into various subgroups in white blood cells (WBCs).

A few recent studies have reported the association of the SII index with diabetic nephropathy, hepatic steatosis, cardiovascular disease, and cancer. [6-9] However, the SIR index was not explored much. In 2023 a study conducted by Lin K et al. indicated that increased SIR index was independently associated with the risk of CVDs in diabetic patients. [10] A study conducted by Liu W et al., in 2024 demonstrated an association between SII index, SIR index, and renal function in patients with T2DM. A high SIR index was an independent risk factor for diabetic kidney disease (DKD), while an elevated SII index was associated with an increased risk of kidney disease progression in biopsy-confirmed DKD cases. [11]

Further, decreased levels of high-density lipoprotein cholesterol (HDL-C) are commonly seen in patients with DM, and metabolic syndrome (MetS). Low levels of HDL-C accelerate the proinflammatory and prothrombotic states during atherogenesis. [12.] Functionally, HDLC is considered anti-atherogenic, protective, and has an antioxidant role, inhibiting cytokine-induced expression of endothelial cell adhesion molecules. [13] However, in individuals with low HDL-C levels, the protective effect is compromised and increases inflammation and atherosclerosis. [14] Furthermore, new hematological parameters related to HDL-C and complete blood count (CBC) have been proposed as novel inflammatory biomarkers [15]. These include the neutrophil/HDL-C ratio (NHR), monocyte/HDL-C ratio (MHR), lymphocyte/HDL-C ratio (LHR) and platelet/HDL-C ratio (PHR).

In 2023, a study conducted by Song Y et al. reported that levels of NHR, MHR, PHR, SII index, SIR index, and aggregate index of systemic inflammation (AISI) were higher in T2DM- peripheral arterial disease (PAD) patients and they were independently linked with its clinical severity. The combination of NHR and SIR index was most valuable for predicting T2DM – PAD. [16] In 2023, Zhang H et al., reported that MHR was independently associated with endothelial dysfunction in T2DM patients. It could be a new biomarker for vascular endothelial function assessment. [17] Although the SII index, SIR index, and new hematological parameters related to HDL-C and complete blood count (CBC) have been proposed as novel biomarkers of inflammation, limited studies were conducted in India.

Aim:

The present study was conducted to assess the systemic immune inflammation (SII) index and systemic inflammation response (SIR) index in patients with T2DM.

2. MATERIALS AND METHODS

This retrospective study was conducted in the Department of Biochemistry in association with the Department of Pathology, Gayatri Vidhya Parishad Institute of Health Care & Medical Technology (GVPIHC&MT), Visakhapatnam, Andhra Pradesh, India. After obtaining the Institutional Ethics Committee (GVPIHC&MT/IEC/20250106/01), a total of 280 subjects' data was collected. Among them, 140 were type 2 diabetes mellitus patients and 140 were non-diabetic subjects.

Inclusion Criteria:

Age of study subjects ≥18 years, both male and females, T2DM, non-diabetic subjects.

Exclusion criteria:

Patients with autoimmune diseases, immunosuppressive therapy, diabetes other type 2, diabetes with micro-and macrovascular complications, hypertensive encephalopathy, malignancy, and pregnant women were excluded from the study.

Data collection:

Necessary details were collected from medical records including demographic details like age, sex, BMI and blood pressure were recorded. Details of biochemical parameters such as fasting and post-prandial glucose by (GOD-POD method), urea (urease), creatinine (Jaffe's), total cholesterol (cholesterol oxidase/peroxidase), Triglycerides (glycerol phosphate oxidase/peroxidase), HDL-C (HDLC- Direct). LDL-C, VLDL-C and HbA1c. Hematological parameters such as complete blood count (CBC) details were collected. The SII index, SIR index, NHR, MHR, LHR, and PHR were calculated using the following formulas:

SII index: Platelet x Neutrophil to lymphocyte ratio

SIR index: Monocyte x Neutrophil to lymphocyte ratio

NHR = Neutrophil/HDL-C

MHR = Monocyte/HDL-C

LHR = Lymphocyte/HDL-C

PHR = Platelet /HDLC

Statistical Analysis:

The data was represented in Mean±SD. Categorical variables were expressed in percentages. Mann-Whitney *U* test was used for continuous non-normally distributed variables. P value of <0.05 is considered statistically significant. Data analysis was performed using SPSS software, version 22.0.

3. RESULTS

In the present study, among T2DM subjects' males were 80 (57.2%) and females were 60 (42.8%). In non-diabetic subjects, males were 71 (52.7%) and females were 69 (49.3%). A significant increase in mean age (54.2±9.2 years) and BMI (26.1±1.9 kg/m^2) was observed in T2DM cases than in non-diabetics. Significant increase in blood pressure [(systolic 120.2±6.2 mmHg), (diastolic 80.2±2.2 mmHg)], fasting blood sugar (FBS) (155.2±50.1 mg/dl), post-prandial blood sugar (PPBS) (211.5±58.4mg/dl), HbA1c (8.1±2.5 %), urea (30.4±7.1 mg/dl), creatinine (1.2±0.2 mg/dl), total cholesterol (196.7±56.7 mg/dl), triglycerides (178.5±68.5 mg/dl), LDL-C (130.6±31.5 mg/dl), VLDL-C (35.6±13.7 mg/dl) and neutrophil count (64.6±11.4 %) was observed in T2DM cases than non-diabetic subjects. Significant decrease in HDL-C (30.5±11.5 mg/dl), and lymphocytes (26.5±10.9%) observed in T2DM subjects. Concerned with inflammatory markers such as SII index (12.6±3.6), SIR index (25.7±5.2), NHR (1.9±0.72), MHR (0.15±0.08), PHR (0.07±0.02), NLR (4.2±1.1) and PLR (0.17±0.01) were significantly increased in T2DM cases than non-diabetic subjects as shown in table 1.

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)	54.2±9.2	48.2±11.7	0.000*

Males (n, %)	80 (57.2%)	60 (42.8%)	-
Females (n, %)	71 (50.7%)	69 (49.3%)	-
Body mass index (BMI) (kg/m^2)	26.1±1.9	21.2±1.4	0.000*
Systolic blood pressure (SBP) (mmHg)	120.2±6.2	118.1±3.2	0.001*
Diastolic blood pressure (DBP) (mmHg)	80.2±2.2	70.8±2.5	0.047*
Biochemical parameters			
Fasting blood sugar (FBS) (mg/dl)	155.2±50.1	90.2±11.3	0.000*
Post-prandial blood sugar (PPBS) (mg/dl)	211.5±58.4	122.5±19.5	0.000*
HbA1c	8.1±2.5	5.2±0.3	0.000*
Serum urea	30.4±7.1	20.4±5.4	0.000*
Serum creatinine	1.2±0.2	0.7±0.1	0.000*
Serum total cholesterol	196.7±56.7	151.5±35.5	0.000*
Serum triglycerides	178.5±68.5	130.7±22.8	0.028*
Serum HDL-C	30.5±11.5	45.4±15.9	0.000*
Serum LDL-C	130.6±31.5	80.1±15.1	0.000*
Serum VLDL-C	35.6±13.7	26.1±4.5	0.020*
Hematological parameters			
Hemoglobin (Hb) (%)	11.3±2.1	11.7±2.6	0.733
Packed cell volume (PCV)	30.9±3.8	34.6±5.1	0.008*
White blood cell count (WBC)	8869.1±2569.7	8362.4±2352.4	0.190
Platelets	2.5±0.59	2.9±0.57	0.801
Neutrophils (%)	64.6±11.4	57.6±10.1	0.004*
Lymphocytes (%)	26.5±10.9	31.5±8.8	0.006*
Monocytes (%)	7.9±2.7	7.5±1.9	0.951
Inflammatory markers			
Systemic immune inflammation (SII) index	13.4±3.9	5.9±3.9	0.028*
Systemic inflammation response (SIR) index	28.6±4.9	14.5±8.0	0.006*
Neutrophil to HDL-C ratio (NHR)	2.1±0.94	1.8±0.21	0.000*
Monocyte to HDL-C ratio (MHR)	0.26±0.07	0.19±0.05	0.002*
Lymphocyte to HDL-C ratio (LHR)	0.88±0.31	0.95±0.24	0.807
Platelet to HDL-C ratio (PHR)	0.08±0.05	0.06±0.01	0.000*
Neutrophil to lymphocyte ratio (NLR)	2.4 ±1.0	1.8±1.1	0.009*
Platelet to lymphocyte ratio (PLR)	0.09±0.05	0.09±0.06	0.089

In this study, FBS was significantly correlated (positive) with SII index (r=0.367), SIR index (r=0.199), NHR (r=0.524), MHR (r=0.368), PHR (r=0.225) and NLR (r=0.289). HbA1c also showed a positive correlation with SII index (r=0.253), SIR index (r=0.199), NHR (r=0.462), and PHR (r=0.198) as shown in Table 2.

Table: 2 Correlation of inflammatory markers with FBS and HbA1c

Parameters	FBS		HbA1c	
	r-value	p-value	r-value	p-value
Systemic immune inflammation (SII) index	0.367**	0.017	0.253*	0.012
Systemic inflammation response (SIR) index	0.199*	0.034	0.199*	0.019
Neutrophil to HDL-C ratio (NHR)	0.524**	0.000	0.462**	0.000
Monocyte to HDL-C ratio (MHR)	0.368**	0.002	0.151	0.079
Lymphocyte to HDL-C ratio (LHR)	0.089	0.281	0.051	0.721
Platelet to HDL-C ratio (PHR)	0.225*	0.015	0.198*	0.031
Neutrophil to lymphocyte ratio (NLR)	0.289*	0.013	0.114	0.083
Platelet to lymphocyte ratio (PLR)	0.066	0.442	0.052	0.712

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

4. DISCUSSION

Diabetes mellitus, a chronic metabolic disorder associated with micro- and macrovascular complications. The present study was undertaken to evaluate the various inflammatory markers and their correlation with fasting blood sugar and HbA1c in T2DM patients. The study findings showed a significant increase in SII index, SIR index, NHR, MHR, PHR, NLR, and PLR in T2DM and their correlation with blood sugar and HbA1c.

During an inflammatory response, the body activates a series of events involving circulating white blood cells (i.e., neutrophils), which may stimulate the secretion of cytokines and proteolytic enzymes, can lead to tissue damage by activating the coagulation cascade and disrupting the integrity of the endothelial cells. A decrease in lymphocyte count is often observed during inflammatory conditions and is linked to poor prognosis in coronary artery disease (CAD). Monocytes are also activated during inflammation and can trigger the production of inflammatory cytokines. [18]

Moreover, in patients with T2DM, the amount of HDL-C is reduced [19]. In healthy persons, the HDL-C molecule is responsible for removing cholesterol from cells and exerting anti-inflammatory, antioxidant, and antithrombotic effects. [13] They are also highly effective in inhibiting the expression of adhesion molecules on endothelial cells, thus preventing monocyte recruitment to the artery wall. Therefore, a lower HDL-C count and higher monocyte count may indicate inflammation [20].

A study by Marra A et al., reported elevated CBC-derived inflammatory indexes in patients with metabolic syndrome. [18] A study by Wang S et al., reported that the SII index and SIR index are independent risk factors for diabetic retinopathy (DR) and suggested that SII combined with SIR index may serve as early biological indicators for DR diagnosis. [21]

Liu W et al., a study reported an association between SII index, SIR index, and renal function in patients with T2DM. Significantly increased SIR index was an independent risk factor for diabetic kidney disease (DKD) and SII index was correlated with an increased risk of kidney disease progression in biopsy-confirmed DKD cases. They suggested that for monitoring DKD in primary care settings the SII index and SIR index serve as inflammatory indicators. [11]

Another study by Alhalwani AY et al., reported that increased SII index was associated with increased HbA1c in T2DM-dry eye disease (DED) patients. The potential of the SII index and HbA1c as early diagnostic indicators for ocular problems associated with diabetes is highlighted by a favourable connection in diagnosing DM2-DED. [22]

A recent study by Yan P et al., reported that an increased SII index is independently associated with an increased risk of presence and severity of diabetic kidney disease (DKD). [23] A study by Elmeazawy R et al., reported that SIR index and SII index may be considered inflammatory markers and may serve as independent early predictors of diabetic nephropathy in individuals with type 1 diabetes. [24] In a study by Scutca AC et al., emphasized the potential utility of the SIR index as a prognostic marker in identifying patients at increased risk during T1DM hospital admissions. [25]

A study by Zhang H et al., reported that MHR was independently associated with endothelial dysfunction in T2DM patients and suggested that it may serve as a new biomarker for assessment of vascular endothelial function. [17] A study by Çallı Ü et al., reported that MHR is considered a potential biomarker of inflammation and significantly increased in diabetic

retinopathy (DR) patients compared with diabetic patients without DR and healthy subjects. [26] A study by Tang X et al., suggested that the MHR can be used as a marker to indicate the prevalence of diabetic retinopathy (DR) in patients with T2DM. [27] Amouzegar A et al., reported an association between MHR and carotid intima-media thickness (CIMT) in patients with diabetes mellitus. Suggested that MHR may serve as a predictor of CIMT. [28]

A study by Chen H et al., reported that LHR may be a useful marker of inflammation to assess the presence and severity of metabolic syndrome (MetS). [29] A study by Guo J et al., reported that increased LHR was positively correlated with the prevalence of insulin resistance and metabolic syndrome, indicating its promising role in early screening and disease prevention. [30] A study conducted by Chen HL et al., reported that an elevated neutrophil-to-lymphocyte ratio (NLR) is associated with a higher risk of T2DM. [31]

Another study by Xu T et al., reported that significant elevation of NLR in patients with diabetic peripheral neuropathy (DPN) and NLR showed a significant correlation with DPN, suggesting that NLR may be an independent risk factor of DPN. [32] A study Madhavi Kemba et al., reported that unregulated diabetic patients have a higher neutrophil-lymphocyte ratio (NLR) and are at a higher risk of cardiovascular complications. [33] A study by Zhang K et al., reported that PLR is significantly elevated in patients with diabetic foot ulcer (DFU) and suggested that PLR may be a valuable marker for early diagnosis and assessment of severity of DFU. [34]

5. CONCLUSION

The present study results may conclude that significant elevation of inflammatory markers such as SII index, SIR index, NHR, MHR, PHR, NLR, and PLR and their significant positive correlation with blood sugar and HbA1c. Further studies with large sample sizes are recommended.

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