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Research Article

Association of NLR, MLR, PLR, SII, and SIRI with the stages of chronic kidney disease - A cross-sectional study

Deepalakshmi Elangovan, Sowmya Krishnamoorthy, Sowmiya Thiyagarajan, Santhi Silambanan

Department of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Chennai, India

Abstract

Objectives: Chronic Kidney Disease (CKD) is a long-standing metabolic disease manifested by renal impairment, high morbidity and mortality, and causing a huge financial burden. Systemic inflammation and local intrarenal inflammation are found to exacerbate this irreversible condition. White blood cells, platelets, and their derived indices may aid in the assessment of the progression of CKD. This study aimed to assess the alterations of complete blood count and their derived indices in the various stages of chronic kidney disease.

Methods: The retrospective cross-sectional study was conducted in the Department of Biochemistry at a tertiary care hospital, Chennai, India. The data were collected from the Medical Records Department from July 2022 to June 2023. The study included chronic kidney disease patients aged 35 to 70 years of both genders. Children, pregnant women, and patients with heart and liver diseases were excluded. The data of the renal profile and complete blood count were collected. Statistical analysis was performed using SPSS software version 16. A $p \leq 0.05$ was considered statistically significant.

Results: Among the study participants, 65% were male and were more than 50 years of age. All the derived inflammation index parameters, such as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lympho- cyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). were significantly increased in stage 5 of CKD. Also, SII and SIRI were found to be correlated with other inflammatory variables.

Conclusion: Chronic inflammation is considered to be prevalent among CKD patients. Inflammatory markers such as SII and SIRI are simple and cost-effective parameters to routinely assess the staging of CKD and thus initiate appropriate management to improve the quality of life.

Keywords: Chronic kidney disease, eGFR, MLR, NLR, PLR, SII, SIRI

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Chronic kidney disease (CKD) affects more than 850 million adults across the globe. CKD refers to the gradual loss of kidney function to the extent that the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2; this pathology should have been present for at least three months, without regard to the etiology [1]. In India, the prevalence of CKD is 1–13% across different regions of the country. The prevalence as given by the International Society of Nephrology's Kidney Disease Data Centre Study is 17% [2]. CKD is insidious in nature and is asymptomatic. CKD equally involves developed and developing countries. In a developing country where the literacy rate is poor, people are unaware of the disease. Hence, early diagnosis of CKD is rarely done, and it is highly challenging. By the time they are diagnosed, the disease has almost reached an irreversible state.

Many factors are found to contribute to the initiation of inflammation, including increased synthesis and release of proinflammatory mediators, release of reactive oxygen

Address for correspondence: Santhi Silambanan, MD. Department of Biochemistry, Sri Ramachandra Institute of Higher Education and Research, Chennai, India
Phone: 044-24768027 **E-mail:** santhisilambanan@gmail.com **ORCID:** 0000-0003-0720-6063
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species and reactive nitrogen species from oxidative stress, metabolic acidosis, alteration in gut microbiota, and altered metabolism of adipose tissue [3]. Risk factors of CKD include diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, and prolonged use of certain medications [4]. GFR is considered to be the marker for the assessment of the extent of kidney damage. Many equations are available to calculate GFR, called eGFR, but the one which has gained wide acceptance is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Based on eGFR, CKD is classified into various stages [5].

In CKD, chronic inflammation is associated with increased levels of proinflammatory markers such as C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α). Additionally, there is increased malondialdehyde (MDA), which is an oxidative stress marker [6]. Cells such as neutrophils, monocytes, T lymphocytes, and B lymphocytes are part of the immune system. All the immune cells, upon activation, release various inflammatory mediators [7]. Platelets participate in hemostasis, thrombosis, and wound healing, thus contributing to the pathological processes in CKD and associated cardiac complications [8]. In addition to individual white blood cells (WBCs) in circulation, composite inflammatory indices calculated based on the individual WBC counts and platelets serve as easy and cost-effective tools in assessing systemic inflammation. These indices include neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). SII and PLR values are higher in low-grade inflammation patients who have elevated CRP. Additionally, the platelets reflect a systemic inflammatory response [9]. All the indices—NLR, SIRI, SII, PLR, and MLR—independently have positive predictive values for inflammation [10]. The current study was designed to elucidate the association between eGFR and the inflammatory markers in the various stages of CKD.

Materials and Methods

Study design and site

The retrospective cross-sectional study was conducted in the Department of Biochemistry, SRIHER, Chennai, India. The data were collected from the Medical Records Department from July 2022 to June 2023. Two milliliters each of fluoride, citrate, and EDTA plasma and serum samples were collected for the analysis of glucose, glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), creatinine, and complete blood count (CBC). Plasma glucose was analyzed by hexokinase, serum blood urea nitrogen by urease, and serum creatinine by the modified Jaffe's method (Beckman Coulter AU 5800, Beckman Coulter, Inc., California, USA) and HbA1c by ion exchange chromatography method (Tosoh Automated Glycohemoglobin Analyzer HLC-723 G8, Tosoh Corporation, Japan). Among CBC, hemoglobin (Hb) was analyzed by spectrophotometry; white blood cell (WBC), red blood cell (RBC), and platelet counts were analyzed by the impedance method; and differential count by fluorescence flow cytometry (Sysmex XN-3100 six-part CBC analyzer, Sysmex Corporation, Japan). Derived indices were calculated as follows:

NLR = Neutrophil count / Lymphocyte count

MLR = Monocyte count / Lymphocyte count

PLR = Platelet count / Lymphocyte count

SII = (Platelet × Neutrophil) / Lymphocyte [10]

SIRI = (Monocyte × Neutrophil) / Lymphocyte [10]

The laboratory data were obtained from the patient records at the Medical Records Department. eGFR was calculated using the CKD-EPI formula. CKD-EPI stands for Chronic Kidney Disease Epidemiology Collaboration. CKD-EPI formula:

$eGFRcr=142\times\min(Scr/\kappa, 1)\alpha\times\max(Scr/\kappa, 1)^{-1.200}\times0.9938\text{^}Age\times 1.012$ [if female]

Inclusion criteria

The study included chronic kidney disease individuals aged 35 to 70 years of both genders. Individuals with hypertension, type 2 diabetes mellitus, and obesity were included. Since all the patients were either diabetic or hypertensive, they were on regular antidiabetic or antihypertensive drugs. In addition, they were on maintenance hemodialysis in stage 5 of CKD.

Exclusion criteria

Children, pregnant women, and patients with heart and liver diseases were excluded.

Ethics committee approval

Ethics approval was obtained from the Institutional Ethics Committee of the institute (CSP-MED/23/NOV/96/288, dated 28-11-2023). The study was carried out according to the principles outlined in the Declaration of Helsinki. A waiver of informed consent was obtained since the patients were treated and discharged from the hospital.

Statistics

The obtained data were subjected to checking for normality of distribution. Since the data were found to follow a normal distribution, the continuous variables were expressed as mean and standard deviation. One-way ANOVA with Tukey's HSD post-hoc test was used to compare the variables across the groups. The Pearson correlation coefficient was used to compare the variables. Statistical analysis was performed using SPSS software version 16. A $p\leq0.05$ was considered statistically significant.

Results

The retrospective study was conducted among 418 CKD patients belonging to stages 1 to 5. Around 65% were male, and 35% were female. Approximately 34.2% of study participants were 61–70 years old, and 34.9% of study partici-

Table 1. Demographic details of the study participants

Variables	Frequency	
	n	%
Gender		
Male	272	65.1
Female	146	34.9
Age (years)		
35–40	41	9.8
41–50	88	21.1
51–60	146	34.9
61–70	143	34.2
Distribution of participants according to CKD stages		
CKD 1	6	1.4
CKD 2	2	0.4
CKD 3a	12	2.8
CKD 3b	16	3.9
CKD 4	100	23.9
CKD 5	282	67.6
Duration of T2DM (years)		
0–5	215	51.4
6–10	94	22.5
11–15	64	15.3
16–20	30	7.2
>20	15	3.6
Duration of HTN (years)		
0–5	241	57.7
6–10	107	25.6
11–15	36	8.6
16–20	24	5.7
>20	10	2.4

Expressed as frequency and percentage. CKD: Chronic kidney disease; T2DM: Type 2 diabetes mellitus; HTN: Hypertension.

pants were 51–60 years old. Around 51.1% and 57.7% of the individuals had T2DM and HTN, respectively, for less than five years (Table 1).

The biochemical variables were compared from stages 3a to stage 5 of CKD. Renal parameters were significantly altered across the stages of CKD. There was a consistent decrease in blood hemoglobin level from stage 3a to stage 5. There were statistically significant alterations among the groups. The inflammatory indices, such as NLR, MLR, PLR, SII, and SIRI, were significantly increased in stage 5 compared to other stages of CKD (Table 2).

The study participants were grouped into five based on the duration (in years) of T2DM and HTN: group A (0–5 years), group B (6–10 years), group C (11–15 years), group D (16–20 years), and group E (>20 years) (Tables 3, 4). There was a statistically significant increase in creatinine across the groups based on the duration of T2DM. When compared among groups, there was a statistically significant difference between groups D and E. eGFR was statistically significant in both diabetes mellitus and hypertension (Table 3).

There was a statistically significant difference in the total WBC count across the duration of T2DM. Within the groups, statistically significant differences were obtained between groups D (16–20 years) and E (>20 years). There was a statistically significant difference in absolute neutrophil count (ANC) across the duration of T2DM. Among the groups, there was a statistically significant difference between groups A (<5 years) and B (6–10 years) as well as between groups D (16–20 years) and E (>20 years) (Table 4).

All the composite indices showed a consistent increase in levels across the groups with increasing duration of either T2DM or HTN. NLR showed a statistically significant increase with the advancing duration of T2DM and HTN. MLR showed a statistically significant increase with the advancing duration of T2DM and HTN. Among diabetics, MLR showed a statistically significant difference between groups A (<5 years) and E (>20 years) as well as between groups B (6–10 years) and E (>20 years). Among hypertensives, MLR showed statistically significant differences between groups B (6–10 years) and E (>20 years). PLR showed statistically significant differences across the groups of duration of T2DM and HTN. SII showed statistically significant differences across the groups of duration of T2DM and HTN. Among the diabetics, there were statistically significant differences between groups A and E as well as between groups B and E. SIRI showed statistically significant differences across the groups of duration of T2DM and HTN. Among the diabetics, there were statistically significant differences between groups A and B as well as between groups A and E (Table 5).

BUN was positively correlated with SII. Hb was positively correlated with ALC and negatively correlated with NLR, PLR, and SII. MLR was positively correlated with NLR. PLR was positively correlated with NLR and MLR. SII was positively correlated with NLR, MLR, and PLR. SIRI was positively correlated with NLR, MLR, PLR, and SII (Table 6).

Discussion

The present retrospective study was conducted among 418 CKD patients belonging to stages 1 to 5 to assess the association of inflammatory markers with the progression of CKD. Since the number of participants in CKD stages 1 and 2 was few, only stages 3a to 5 were included for further analysis and discussion. Similar to other studies, most of the participants were male. This could probably be due to the high predisposition of males to comorbid conditions such as hypertension or diabetes mellitus. Approximately 34.2% of study participants were 61–70 years old, and 34.9% of study participants were 51–60 years old. Around 51.1% and 57.7% of the individuals had T2DM and HTN, respectively, for less than five years (Table 1). The findings in the present study were similar to the study by Aneez et al. [4], where around

Table 2. Distribution of biomarkers according to the stages of CKD

Markers	Stages of CKD				p
	Stage 3a (n=12)	Stage 3b (n=16)	Stage 4 (n=100)	Stage 5 (n=282)	
BUN (mg/dL)	20.16 (7.94)	25.86 (13.96)	29.87 (12.38)	50.19 (20.79)	<0.001**
Creatinine (mg/dL)	1.55 (0.12)	2.19 (0.35)	3.38 (0.69)	7.56 (2.89)	<0.001**
eGFR (mL/min)	50.5 (4.12)	34.06 (4.11)	19.81 (4.34)	8.15 (2.98)	<0.001**
Hb (g/dL)	11.08 (3.43)	9.17 (2.76)	9.05 (1.97)	8.45 (1.85)	0.001**
	Significance between groups: p1=0.004, p2=0.002, p3=0.003**				
FPG	162.1 (70.1)	189.2 (66.2)	154.9 (80.3)	153.2 (72.8)	0.33
HbA1c	7.3 (1.3)	7.0 (1.7)	6.8 (1.6)	6.8 (1.6)	0.72
PLT (10^5 cells/ µL)	2.39 (1.18)	2.37 (1.03)	2.49 (0.97)	2.29 (1.03)	0.431
WBC-total (cells/µL)	7367.5 (1261.99)	7705.33 (1914.22)	9147.45 (3636.08)	8955.60 (3554.19)	0.201
ANC (cells/µL)	4833.83 (1060.75)	5434.06 (1851.93)	6869.07 (3520.71)	6744.39 (3290.36)	0.093
AMC (cells/µL)	503.25 (143.87)	393.6 (139.12)	426.33 (195.56)	473.11 (267.85)	0.249
ALC (cells/µL)	1687.33 (481.12)	1467.53 (730.04)	1468.82 (669.12)	1347.66 (710.74)	0.198
NLR	3.05 (0.98)	4.11 (2.30)	5.79 (4.58)	6.67 (5.88)	0.033*
MLR	0.26 (0.06)	0.27 (0.11)	0.35 (0.21)	0.45 (0.39)	0.018*
PLR	114.61 (35.65)	138.86 (38.89)	191.35 (107.05)	216.06 (163.75)	0.037*
SII	123.2 (30.76)	129.70 (38.76)	248.44 (92.08)	385 (123.76)	0.036*
SIRI	134.91 (47.60)	139.44 (69.27)	232.12 (95.40)	308.62 (99.14)	0.005**

Expressed as mean and SD, ANOVA and Tukey post-hoc tests were used. p: p value for comparing between the studied groups; p1: Groups 3a & 3b; p2: Groups 3a & 4; p3: Groups 3a & 5; p4: Groups 3b & 4; p5: Groups 3b & 5; p6: Groups 4 & 5. *: p value statistically significant; **: p value statically highly significant. CKD: Chronic kidney disease; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; FPG: Fasting plasma glucose; HbA1c: Glycated haemoglobin; PLT: Platelet; WBC: White blood cell; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index; SD: Standard deviation.

Table 3. Distribution of renal markers according to the duration of T2DM and HTN among CKD patients

Markers	T2DM/HTN	Duration (years)					p
		Group A (0–5)	Group B (6–10)	Group C (11–15)	Group D (16–20)	Group E (>20)	
BUN (mg/dL)	T2DM	41.86 (21.00)	44.85 (23.44)	46.06 (22.30)	33.56 (17.24)	49.38 (19.93)	0.052
	HTN	42.09 (21.50)	44.74 (21.99)	42.83 (22.83)	40.25 (20.38)	45.4 (17.73)	0.807
Creatinine (mg/dL)	T2DM	6.44 (3.41)	5.98 (3.56)	5.71 (2.74)	4.46 (2.19)	5.66 (2.36)	0.027*
		Significance between groups: p9=0.001**					
	HTN	5.95 (3.34)	6.61 (3.45)	4.98 (2.21)	6.18 (2.89)	6.13 (3.01)	0.119
eGFR (mL/min)	T2DM	14.13 (12.70)	11.83 (6.46)	10.37 (4.69)	9.08 (2.02)	8.14 (2.47)	0.04*
	HTN	15.16 (14.54)	12.16 (10.40)	11.61 (4.55)	8.90 (3.79)	7.85 (3.48)	0.037*

Expressed as mean and SD, ANOVA and Tukey post-hoc tests were used. p: p value for comparing between the studied groups, p1: Groups A & B; p2: Groups A & C; p3: Groups A & D; p4: Groups A & E; p5: Groups B & C; p6: Groups B & D; p7: Groups B & E; p8: Groups C & D; p9: Groups C & E; p10: Groups D & E. *: p value statistically significant, **: p value statically highly significant. T2DM: Type 2 diabetes mellitus; HTN: Hypertension; CKD: Chronic kidney disease; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate.

59% were male, with a mean age of 58.1 years. In the present study, based on the CKD stages, 68% were in stage 5, 24% were in stage 4 CKD, and the rest of the participants were in lower CKD stages (Table 1). As per Aneez et al. [4], 34% of the study participants are in stage 4 CKD. The present study results are in alignment with the study by Swartling et al. [11], which showed that men have a high rate of mortality, an increased risk of CKD progression, and a rapid decline in eGFR.

In the present study, Table 2 shows the comparison of biomarkers across the groups—stages 3a, 3b, 4, and 5—classified based on eGFR by the CKD-EPI equation. Since the study participants were classified based on eGFR, statistically high significance was expected across the stages of CKD with regard to BUN, creatinine, and eGFR (Table 2). According to Suriyong et al. [12], the major predisposing factors in Asia include an increasing elderly population, low literacy rate, increased preva-

Table 4. Distribution of CBC markers according to the duration of T2DM and HTN among CKD patients

CBC markers	T2DM/ HTN	Duration (years)					p
		Group A (0–5)	Group B (6–10)	Group C (11–15)	Group D (16–20)	Group E (>20)	
Hb (g/dL)	T2DM	8.80 (2.26)	8.72 (1.97)	8.46 (1.81)	8.86 (1.58)	8.89 (1.59)	0.835
	HTN	8.62 (2.10)	8.73 (2.12)	8.92 (1.76)	9.54 (2.04)	8.67 (0.90)	0.329
WBC-total (cells/µL)	T2DM	8652.55 (3282.64)	8528 (2966.71)	10122.7 (4652.07)	8369 (2439.86)	10739.23 (4176.37)	0.006**
		Significance between groups: p10=0.031*					
	HTN	8851.73 (3591.32)	8920.18 (3032)	9198.05 (4118.09)	8137.5 (2402.60)	10006 (4626.30)	0.649
ANC (cells/µL)	T2DM	6405.42 (3035.86)	6372.55 (2723.74)	7840.32 (4547.17)	5901.9 (2170.40)	8324.38 (4068.10)	0.004**
		Significance between groups: p1=0.001**, p10=0.014*					
	HTN	6656.54 (3403.12)	6537.78 (2692.88)	7011.33 (4020.15)	5845.33 (2158.78)	7845.9 (4467.49)	0.499
AMC (cells/ µL)	T2DM	446.01 (203.02)	457.51 (345.33)	465.43 (210.21)	490.8 (200.57)	548.61 (246.22)	0.577
	HTN	455.36 (265.74)	450.32 (204.82)	443.83 (193.61)	503.25 (222.83)	539.6 (300.98)	0.701
ALC (cells/ µL)	T2DM	1395.98 (739.61)	1360.27 (658.93)	1418.25 (626.97)	1549.23 (626.97)	1499.76 (744.80)	0.741
	HTN	1365.50 (700.37)	1479.25 (754.70)	1428.27 (599.14)	1403.83 (596.07)	1332.2 (528.55)	0.713
PLT (10^5 cells/ µL)	T2DM	2.27 (0.98)	2.409 (1.07)	2.63 (1.18)	2.22 (1.107)	2.52 (0.84)	0.15
	HTN	2.31 (1.01)	2.58 (1.14)	2.28 (1.12)	2.14 (0.64)	2.13 (0.59)	0.133

Expressed as mean and SD, ANOVA and post-hoc tests were used. p: p value for comparing between the studied groups, p1: groups A & B, p2: groups A & C, p3: groups A & D, p4: groups A & E, p5: groups B & C, p6: groups B & D, p7: groups B & E, p8: groups C & D, p9: groups C & E, p10: groups D & E. *: p value statistically significant; **: p value statically highly significant. T2DM: Type 2 diabetes mellitus; HTN: Hypertension; CKD: Chronic kidney disease, CBC: Complete blood count; Hb: Hemoglobin; WBC: White blood cell; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; ALC: Absolute lymphocyte count; PLT: platele; SD: Standard deviation.

lence of comorbidities, and inappropriate use of nonsteroidal anti-inflammatory drugs. In the present study, when compared among the stages of CKD, hemoglobin (Hb) showed statistically significant differences between the stages of CKD, with a consistent decrease in Hb levels as CKD advanced. As kidney disease advances, there is decreased erythropoietin synthesis leading to decreased Hb levels. Additionally, other factors contribute, such as repeated infections, decreased food intake due to loss of appetite, and blood loss during hemodialysis (Table 2). A similar finding was obtained by Kutuby et al. [13] and Akinsola et al. [14] in their studies. In the present study, Hb concentration was 8.45 g/dL in CKD stage 5. Anemia is one of the risk factors for cardiovascular diseases in patients with CKD. According to a study by Pan et al. [15], CKD patients with Hb less than 8.6 g/dL show an increased risk of CKD progression. Demir et al. [16] have demonstrated that CKD with decreasing Hb along with increasing serum creatinine is a risk factor for the occurrence of coronary artery disease.

The kidney is highly vulnerable to inflammatory damage because it receives around 25% of blood circulation, lacks antioxidant activity, has altered gut microbiota along with the loss of the intestinal barrier, and altered intrarenal perfusion distribution [3]. Inflammatory markers such as CRP, pentraxin 3 (PTX3), serum component of amyloid A (SAA), and procalcitonin (PCT) are found to be useful in assessing cardiac complications in CKD patients with eGFR close to normal [17]. According to Alves et al. [18], markers of subclinical CKD include TNF-α, monocyte chemoattractant protein-1 (MCP-1), and E-selectin. However, these inflammatory markers are not easily accessible in countries with a low economic background. Also, since CKD is an asymptomatic disease, frequent screening of individuals, especially those with comorbidities who have the potential to develop CKD, is not feasible. Hence, relying on the composite CBC markers, which are derived from the routine hemogram, will be of use to clinicians in the regular management of CKD.

In the present study, analysis of CBC across the stages of CKD showed that individual WBC counts did not show any statistical significance. However, the inflammatory indices such as NLR, MLR, and PLR were significantly increased across the stages of CKD, with the highest levels in stage 5 compared to other stages of CKD. During inflammation, neutrophils, monocytes, and platelets increase, and they contribute to inflammation by free radical production and thrombosis. Lymphocytes play a protective role in cellular function, but their counts decrease, impairing their function. This is reflected by the alterations in the ratios, indicating disease activity and risk for increased mortality and morbidity in CKD due to cardiac and non-cardiac events. High NLR indicates increased inflammation and worse prognosis in CKD (Table 2). A similar finding was obtained by Yoshitomi et al. [6]. Zhang et al. [7] concluded that MLR is an early indicator of CKD, especially in individuals with GFR closer to normal. NLR and PLR show positive correlations with the urine protein-creatinine ratio (UPCR) and serum creatinine only in the advanced CKD stages [19]. According to Okyay et al. [19],

Table 5. Distribution of derived inflammatory indices according to the duration of T2DM and HTN among CKD patients

Derived inflammatory indices	T2DM/ HTN	Duration (years)					p
		Group A (0–5)	Group B (6–10)	Group C (11–15)	Group D (16–20)	Group E (>20)	
NLR	T2DM	5.73 (4.48)	6.15 (5.85)	7.19 (6.31)	7.90 (6.07)	8.82 (5.99)	0.048*
	HTN	4.95 (2.86)	5.70 (4.80)	6.64 (3.43)	6.73 (2.17)	7.18 (5.94)	0.029*
MLR	T2DM	0.35 (0.19)	0.36 (0.17)	0.41 (0.28)	0.44 (0.24)	0.50 (0.33)	0.022*
		Significance between groups: p4=0.039*, p7=0.049*					
	HTN	0.38 (0.21)	0.39 (0.21)	0.41(0.18)	0.46 (0.20)	0.55 (0.25)	0.022*
		Significance between groups: p7=0.011*					
PLR	T2DM	186.12 (100.93)	189.99 (98.78)	214.73 (134.15)	234.35 (87.74)	264.02 (202.47)	0.035*
	HTN	191.98 (102.67)	198.42 (118.05)	249.18 (146.74)	245.74 (77.79)	272.99 (230.08)	0.045*
SII	T2DM	116.15 (91.42)	123.33 (91.03)	131.08 (97.29)	138.42 (60.03)	192.00 (133.84)	0.038*
		Significance between groups: p4=0.01*, p7=0.027*					
	HTN	109.57 (70.31)	125.89 (89.99)	130.44 (60.53)	147.25 (55.52)	193.11 (137.55)	0.013*
		Significance between groups: p4=0.007**, p7=0.048*					
SIRI	T2DM	216.96 (163.96)	215.15 (162.22)	265.37 (218.58)	294.85 (169.49)	356.74 (261.46)	0.008**
		Significance between groups: p1=0.01*, p4=0.013*					
	HTN	214.20 (150.69)	219.26 (165.43)	245.79 (146.39)	312.97 (173.30)	346.97 (176.13)	0.025*

Expressed as mean and SD, ANOVA and post-hoc tests were used. p: p value for comparing between the studied groups; p1: Groups A & B; p2: Groups A & C; p3: Groups A & D; p4: Groups A & E; p5: Groups B & C; p6: Groups B & D; p7: Groups B & E; p8: Groups C & D; p9: Groups C & E; p10: Groups D & E. *: p value statistically significant; **: p value statically highly significant. T2DM: Type 2 diabetes mellitus; HTN: Hypertension; CKD: Chronic kidney disease; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammation index; SIRI: Systemic inflammation response index.

CKD patients on dialysis have high NLR, IL-6, and high-sensitivity CRP (hs-CRP) [20]. According to Chen et al. [21], CKD patients with high NLR show an increased risk of poor renal outcomes. Macrophages within adipocytes also produce various pro-inflammatory cytokines [22]. Uduagbamen et al. [23] and Yuan et al. [24] suggest that NLR is higher in CKD patients compared to healthy controls; moreover, NLR is used in the risk assessment of CKD stage 4 patients with replacement therapies.

In the present study, inflammatory indices such as SII and SIRI were significantly increased in stage 5 compared to the other stages of CKD. Both SII and SIRI involve neutrophil and lymphocyte counts along with either platelet or monocyte counts. Hence, these composite indices could be better indicators of inflammation than NLR, PLR, and MLR (Table 2). In the study by Ustundag et al. [9], SII and PLR values are elevated in patients with low-grade inflammation, as indicated by a mild increase in CRP. High PLR predicts the onset of cardiovascular complications. The systemic inflammation response index (SIRI) has a high independent positive predictive value for those individuals with high-risk scores for cardiac diseases [10]. SII and SIRI are associated with CKD prevalence, especially in the US population [25]. There is a strong linkage between SII and CKD in older patients with HTN or T2DM [26]. Screening for CKD is mandatory for older individuals with hypertension or diabetes mellitus [27]. SII levels have a strong association with diabetic nephropathy (DN). According to Li et al. [28], decreased eGFR and urinary albumin excretion are associated with SIRI. SIRI is used to evaluate the risk of mortality in patients with CKD who are subjected to maintenance peritoneal dialysis (PD) [29].

In the present study, the study participants were grouped into five based on the duration of T2DM and HTN. There was no significant alteration in Hb and BUN across the groups with regard to the duration of T2DM or HTN. There was a statistically significant increase in serum creatinine levels across the groups based on the duration of T2DM. However, there was no statistically significant difference with regard to HTN. eGFR was statistically significant across the groups with the duration of either T2DM or HTN. Irrespective of the presence of hypertension or diabetes, the magnitude of kidney damage was almost similar (Table 3). T2DM and HTN are the primary risk factors for CKD and its complications [30]. According to Kaneyama et al. [31], HTN has a higher influence than T2DM on the progression of CKD in Japanese individuals. As per the present study, the minimum duration of hypertension or T2DM was five years. According to Gembillo et al. [32], diabetics show an average time for the onset of CKD of seven to ten years. The risk of progression of CKD to end-stage renal disease (ESRD) and cardiac complications is much higher in T2DM. According to Wang et al. [33], in China, the prevalence of CKD is 10.8%; among them, around 40% and 60% have T2DM and HTN, respectively.

Table 6. Shows the correlation among the variables in CKD patients

	BUN	Creat	Hb	WBC total	eGFR	ANC	AMC	PLT	ALC	NLR	MLR	PLR	SII
WBC-total													
r	0.131	-0.025	0.018										
p	0.007	0.617	0.719										
eGFR													
r	-0.486	-0.631	0.249	-0.035									
p	<0.001	<0.001	<0.001	0.473									
ANC													
r	0.165	-0.023	-0.053	0.964	-0.066								
p	0.001	0.638	0.280	<0.001	0.178								
AMC													
r	0.019	0.044	0.064	0.431	-0.040	0.355							
p	0.701	0.365	0.191	<0.001	0.411	<0.001							
PLT													
r	0.029	-0.093	0.087	0.333	0.119	0.271	0.154						
p	0.553	0.058	0.076	<0.001	0.015	<0.001	0.002						
ALC													
r	-0.136	-0.088	0.288	0.250	0.157	0.010	0.177	0.303					
p	0.005	0.074	<0.001	<0.001	0.001	0.842	<0.001	<0.001					
NLR													
r	0.169	0.008	-0.223	0.393	-0.098	0.556	0.041	-0.027	-0.568				
p	0.001	0.878	<0.001	<0.001	0.046	<0.001	0.396	0.581	<0.001				
MLR													
r	0.100	0.069	-0.182	0.162	-0.111	0.258	0.527	-0.039	-0.490	0.646			
p	0.052	0.185	<0.001	0.001	0.028	<0.001	<0.001	0.526	<0.001	<0.001			
PLR													
r	0.170	0.026	-0.220	0.046	-0.062	0.188	-0.039	0.372	-0.544	0.659	0.551		
p	<0.001	0.595	<0.001	0.347	0.207	<0.001	0.428	<0.001	<0.001	<0.001	<0.001		
SII													
r	0.224	0.008	-0.210	0.498	-0.069	0.622	0.113	0.423	-0.398	0.794	0.531	0.805	
p	<0.001	0.863	<0.001	<0.001	0.161	<0.001	0.021	<0.001	<0.001	<0.001	<0.001	<0.001	
SIRI													
r	0.125	0.034	-0.165	0.488	-0.099	0.572	0.565	0.061	-0.362	0.735	0.903	0.481	0.668
p	0.011	0.489	0.001	<0.001	0.044	<0.001	<0.001	0.214	<0.001	<0.001	<0.001	<0.001	<0.001

BUN: Blood urea nitrogen; Hb: Hemoglobin; WBC: White blood cell; eGFR: Estimated glomerular filtration rate; ANC: Absolute neutrophil count; AMC: Absolute monocyte count; PLT: Platelet; ALC: Absolute lymphocyte count; NLR: Neutrophil to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune inflammation index.

In the present study, there was a statistically significant difference in total WBC count and absolute neutrophil count (ANC) according to the duration of T2DM. There was a significant increase in counts when T2DM existed for more than 20 years. There was a statistically significant difference in patients with T2DM with regard to ANC. ANC seemed to be a better marker than total WBC count since there were statistically significant changes in the early stages of CKD (Table 4). There were statistically significant differences in all the composite markers (NLR, MLR, PLR, SII, and SIRI) in CKD patients with either T2DM or HTN (Table 5). Similar findings were reported by other studies [34, 35]. There is an association between MLR and the risk of all-cause death in patients with DN [27]. Turkmen et al. [36] showed that PLR is superior to NLR in assessing inflammation in ESRD patients. T2DM patients with DN have high SII levels [37]. SII and CKD are high in individuals with HTN or T2DM [26]. Low eGFR and albuminuria are positively correlated with SIRI [29].

In the present study, Table 6 shows the correlation among the biochemical variables. With advancing renal disease, hemoglobin and lymphocyte counts decreased. Due to the increase in neutrophils, monocytes, and platelets and the decrease in lymphocytes, the composite indices also showed a similar pattern. All the composite markers showed positive correlations among themselves. However, as individual WBC counts, this type of association was not seen. In T2DM, neu-

trophils have a high predilection to move to the glomerular basement membrane and initiate a sequence of inflammatory reactions, causing further damage to the kidney (Table 6). Neutrophil esterase (NE) is toxic to glomerular cells, thus damaging renal cells [38]. Elderly CKD patients may not present with leukocytosis, unlike younger individuals [39]. The findings of the present study were similar to other studies [40–42]. According to Xiong et al. [43], NLR, MLR, and PLR have the capacity to be strong predictors of 30-day mortality in ESRD patients requiring renal replacement therapy. Thus, the derived composite indices are valid, and appropriate markers can assess the extent of systemic inflammation, especially in resource-limited settings.

Limitations

The data regarding urine albumin excretion, ESR, and peripheral smears were not obtained. Comparison with well-known inflammatory markers such as IL-6 and hs-CRP could not be done. The drug histories of the participants were not complete enough to analyze the effect of confounders. Also, the confounding effects of diabetes mellitus, hypertension, and obesity were not assessed. A cohort study would have helped in assessing the markers associated with the progression of CKD. Since this was a retrospective study, data on CKD in the earlier stages could not be obtained.

Conclusion

The study included CKD patients from stage 3a to stage 5, with most of them being male and more than 50 years old. NLR, MLR, PLR, SII, and SIRI are significantly elevated in CKD stage 5 compared to other CKD stages. All the composite indices showed a correlation with renal parameters, hemoglobin, and inflammatory markers. Hence, the inflammatory markers are potential markers for the diagnosis and prognosis of the various stages of CKD. Thus, they can be used to monitor the progression of CKD, especially in individuals with metabolic diseases.

Ethics Committee Approval: The study was approved by The Sri Ramachandra Institute of Higher Education and Research Institutional Research Ethics Committee (No: CSP-MED/23/NOV/96/288, Date: 28/11/2023).

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