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RESEARCH

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Systemic immune-inflammatory index and systemic inflammation response index in predicting renal impairment in children with type 1 diabetes mellitus

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Abstract

Background The aim of this study was to investigate the role of systemic immune-inflammatory index and systemic inflammation response index in predicting early renal impairment in children with type 1 diabetes mellitus (T1DM).

Methods This is a retrospective cohort study which searched the electronic medical records of patients consecutively admitted to Pediatric Endocrinology Unit with the diagnosis of type 1 diabetes mellitus between August 2022 and July 2023.

Results A total of 100 children with the diagnosis of T1DM were enrolled in the study. Early stage diabetic nephropathy (DN) was found in 34 patients. Patients with DN showed significantly higher HbA1C, microalbuminuria, cholesterol, TLC, platelet, neutrophil count, NLR, PLR, SII, and SIRI than the DM without DN. It was discovered that DN was independently correlated with NLR, PLR, SII, and SIRI.

Conclusions SIRI and SII are easily available and affordable inflammatory markers that may serve as independent early predictors of diabetic nephropathy in individuals with type 1 diabetes.

Keywords Systemic immune-inflammatory index, Systemic inflammation response index, Diabetic nephropathy, Diabetes mellitus

Background

Type 1 diabetes mellitus is becoming more widespread, and diabetic complications are frequent. Premature death and type 1 diabetes (T1D) are still linked. It is critical to identify those people who are more likely to die in order to assess the prognosis of any type 1 diabetic and guide preventative treatments [1].

A frequent consequence of T1D that affects up to 30% of patients is diabetic nephropathy (DN) [2]. Chronic renal disease has been linked to T1D mortality risk factors in earlier research [3, 4].

Microalbuminuria is widely regarded as a risk factor for cardiovascular disease and DN, as well as the first sign of renal impairment. It was formerly believed that individuals with diabetes would acquire renal problems and ultimately end-stage renal disease in a linear fashion, starting with the onset of microalbuminuria and ending with frank proteinuria [5].

Four main pathogenic pathways are identified by DN: oxidative stress, inflammation, tubular damage, and glomerular damage [6]. Research has demonstrated the significance of immunological and inflammatory responses in the development of DN, as well as chronic inflammation of the renal tissue and circulatory system. It has been

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demonstrated that inflammatory factors that are raised in blood, such as IL-6, TNF-α, TGF-β1, and IL-18, are involved in the onset and progression of DKD [7].

Emerging indicators that have been highlighted in many clinical circumstances are the systemic immune-inflammation index (SII), which is computed using platelets, neutrophils, and lymphocytes, and the systemic inflammatory response index (SIRI), which is computed using neutrophils, monocytes, and lymphocytes. The SII was first created as a prognostic marker for a variety of malignancies, cardiovascular illnesses, and inflammatory disorders. It was intended to represent the equilibrium of the host's inflammatory and immunological status, which might predict the outcome in patients with various diseases [8].

As far as we know, this is the first study to investigate the role of systemic immune-inflammatory index and systemic inflammation response index in predicting early renal impairment in children with T1D.

Methods

This is a retrospective cohort study which searched the electronic medical records of patients consecutively admitted to Pediatric Endocrinology Unit with the diagnosis of type 1 diabetes mellitus between August 2022 and July 2023.

Inclusion criteria included children and adolescents aged 1–18 years who met the clinical and laboratory criteria of type 1 diabetes mellitus. The following conditions precluded study participation: (a) inflammatory bowel illnesses; (b) other autoimmune disorders such as Hashimoto thyroiditis, celiac disease, or autoimmune hepatitis; (c) patients on steroids or other immune modulatory medications; and (d) patients with insufficient medical records.

We searched the medical records of the patients and the following data was extracted: full history with special emphasis on the age and sex, age at diagnosis and diabetes duration, and history and frequency of acute diabetic complications. Thorough clinical examination included anthropometric measurements and systolic and diastolic blood pressure.

Laboratory investigations included CBC, CRP, HbA1C, serum albumin, serum urea and creatinine, cholesterol, triglycerides, and microalbumin (microalbuminuria was defined by a urinary albumin excretion (UAE) of 30–299 μg/min, macroalbuminuria by a UAE > 300 [9], and eGFR was calculated by bed-side Schwartz's formula: 0.413 × height (cm)/serum creatinine (mg/dl) [10]).

Systemic inflammatory ratios

Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic immune-inflammatory index (SII) ((neutrophil count × platelet count)/lymphocyte count) [11], and systemic inflammation response index (SIRI) ((neutrophil count × monocyte count)/lymphocyte count) [12].

Statistical analysis

Statistical analysis was carried out using SPSS version 23. Normally distributed data were expressed as mean ± standard deviation, while abnormally distributed data were expressed as median and interquartile range (IQR). Student's *t*-test was used to compare between normally distributed data. The Mann–Whitney test was used to compare between abnormally distributed data. The association between microalbuminuria and inflammatory ratios was found using Spearman's correlation. In order to evaluate the usefulness of inflammatory ratios in predicting early stage DN in children with DM, binary logistic regression analysis was conducted. Utilizing a receiver operating characteristic (ROC) curve, the predictive ability of NLR, PLR, SII, and SIRI for microalbuminuria was evaluated. *P* value was considered significant at level < 0.05.

Results

Clinical characteristics

A total of 100 children with the diagnosis of type 1 DM were enrolled in the study (Fig. 1). Early stage diabetic nephropathy (DN) was found in 34 patients.

Regarding to the duration of DM, weight, height, BMI, and BMI Z-score, there were no statistically significant difference noted between the two groups. Conversely, it

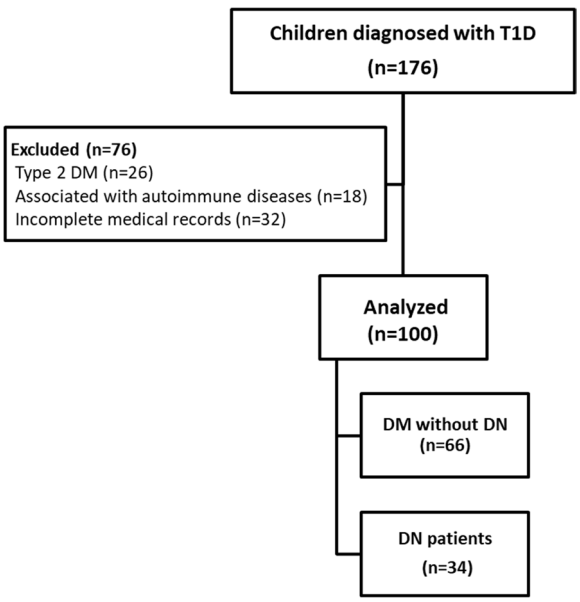

Fig. 1 Flow chart of the study

was observed that diabetic individuals with DN exhibited notably elevated diastolic blood pressure compared to those without DN, as illustrated in Table 1.

Laboratory characteristics

The laboratory findings were summarized in Table 2. Patients with DN exhibited notably elevated levels of HbA1C, microalbuminuria, cholesterol, TLC, platelets, neutrophil count, NLR, PLR, SII, and SIRI compared to those with DM but without DN.

A logistic regression analysis was conducted to predict early DN by examining the significant inflammatory ratios, as presented in Table 3. The results revealed that NLR, PLR, SII, and SIRI were independently associated with DN.

Table 1 Demographic and clinical characteristics of the studied patients

	DM without DN (*n* = 66)	DM with DN (*n* = 34)	*P* value
Sex			
Male	35 (53.0%)	13 (38.2%)	0.206
Female	31 (47.0%)	21 (61.8%)	
Age (years)	11.27 ± 4.11	12.09 ± 4.39	0.356
Duration of DM (years)	3.32 ± 2.21	3.47 ± 2.19	0.757
Weight (kg)	42.36 ± 18.58	46.59 ± 19.19	0.289
Height (cm)	141.27 ± 20.53	144.41 ± 20.15	0.468
BMI (kg/m^2)	20.03 ± 4.65	21.27 ± 4.89	0.218
BMI Z-score	−0.01 (−0.85–0.80)	−0.18 (−0.63–0.53)	0.925
SBP (mm Hg)	104.09 ± 11.96	107.21 ± 12.00	0.221
DBP (mm Hg)	66.29 ± 9.42	71.76 ± 11.21	0.011*

**P* value significant if < 0.05

DM diabetes mellitus, *DN* diabetic nephropathy, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Laboratory findings of the studied patients

	DM without DN (*n* = 66)	DM with DN (*n* = 34)	*P* value
HbA1C %	7.75 (6.57–8.50)	9.15 (8.50–11.00)	< 0.001*
CRP (mg/l)	0.00 (0.00–6.00)	0.00 (0.00–1.50)	0.253
Albumin (gm/dl)	4.17 (3.70–4.50)	4.15 (3.68–4.30)	0.093
eGFR (ml/min/1.73 m^2)	83.90 (74.86–93.52)	83.15 (69.36–105.32)	0.636
Creatinine (mg/dl)	0.7 (0.6–0.8)	0.7 (0.59–0.8)	0.994
Microalbuminuria (µg/min)	10.0 (5.8–14.7)	47.35 (36.75–96.25)	< 0.001*
Cholesterol (mg/dl)	150.0 (129.25–179.25)	167.5 (160.0–192)	0.003*
Triglycerides (mg/dl)	94.5 (75.0–127.75)	91.50 (79.25–130.00)	0.864
HB (gm/dl)	12.0 (11.0–12.85)	12.25 (11.03–13.00)	0.455
TLC (10^3/µl)	6.9 (5.48–8.60)	8.05 (6.28–11.53)	0.030*
PLT (10^3/µl)	262.00 (214.75–322.25)	280.0 (252.25–386.0)	0.030*
Lymphocytes (10^3/µl)	3.39 (2.70–4.19)	3.00 (1.92–4.01)	0.102
Neutrophils (10^3/µl)	2.69 (1.97–3.88)	4.38 (3.66–6.44)	< 0.001*
Monocytes (10^3/µl)	0.25 (0.12–0.38)	0.23 (0.08–0.53)	0.954
NLR	0.88 (0.56–1.07)	1.76 (1.16–2.54)	< 0.001*
PLR	80.82 (50.75–105.41)	108.75 (72.11–157.46)	0.002*
MLR	0.07 (0.04–0.11)	0.08 (0.02–0.15)	0.270
SII	224.4 (132.2–307.6)	508.4 (311.4–827.3)	< 0.001*
SIRI	0.17 (0.08–0.26)	0.34 (0.12–0.65)	0.003*

**P* value significant if < 0.05

DM diabetes mellitus, *DN* diabetic nephropathy, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *HB* hemoglobin, *TLC* total leukocytic count, *PLT* platelet, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *MLR* monocyte/lymphocyte ratio, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index

Table 3 Logistic regression analysis of significant inflammatory ratios associated with DN

	OR (95% CI)	*P* value
NLR	16.87 (5.276–53.907)	< 0.001*
PLR	1.02 (1.009–1.033)	0.001*
SII	1.01 (1.005–1.012)	< 0.001*
SIRI	12.16 (2.298–64.351)	0.003*

**P value significant if <0.05, OR* odds ratio, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index

Table 4 ROC analysis of significant inflammatory ratios as predictors of DN

	Cut-off	AUC	*P* value	Sensitivity	Specificity
NLR	1.05	0.886	< 0.001	91.2%	72.7%
PLR	109.5	0.694	0.002	50.0%	81.8%
SII	274.4	0.886	< 0.001	91.2%	71.2%
SIRI	0.28	0.684	0.003	64.7%	78.8%

AUC area under the curve, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index

ROC curve analysis was conducted to predict DN using NLR, PLR, SII, and SIRI. NLR and SII exhibited the greatest AUC of 0.886 ($P<0.001$). PLR showed the second-highest AUC of 0.694 ($P=0.002$), while SIRI displayed the lowest AUC of 0.684 ($P=0.003$) (Table 4, Fig. 2).

Significant positive correlations were found between microalbuminuria and NLR, PLR, SII, and SIRI as shown in Fig. 3.

Discussion

Out of the 100 children with T1D that were included in our study, 34 patients were diagnosed with DN. The DN patients exhibited a notably higher diastolic blood pressure compared to the other group ($P=0.011$). This finding aligns with the research conducted by Huang et al. and Abo El-Asrar et al. [13, 14]. However, our results did not show a significant difference in systolic blood pressure between the two groups, which contrasts with their studies. This discrepancy could potentially be attributed to the older age and longer duration of diabetes observed in their studies.

An increased diastolic blood pressure in children poses a threat of developing microalbuminuria and advancing chronic kidney disease, while effective management of hypertension can mitigate this risk [15–18].

In the current study, HbA1C levels were notably elevated in the DN group, aligning with prior research

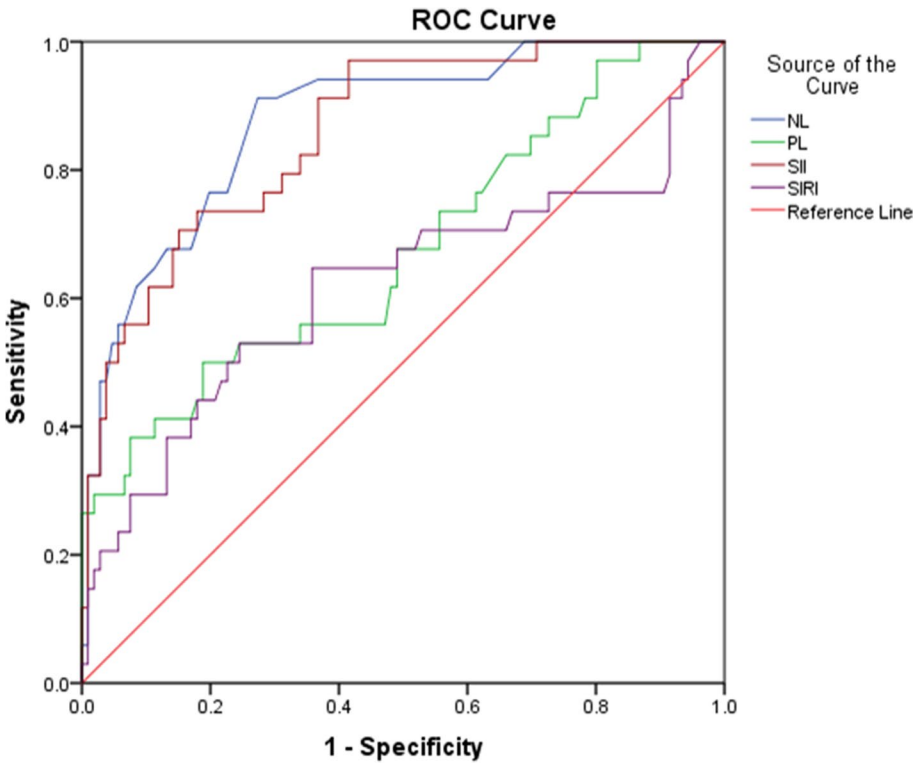

Fig. 2 ROC curve analysis of NLR, PLR, SII, and SIRI for predicting microalbuminuria

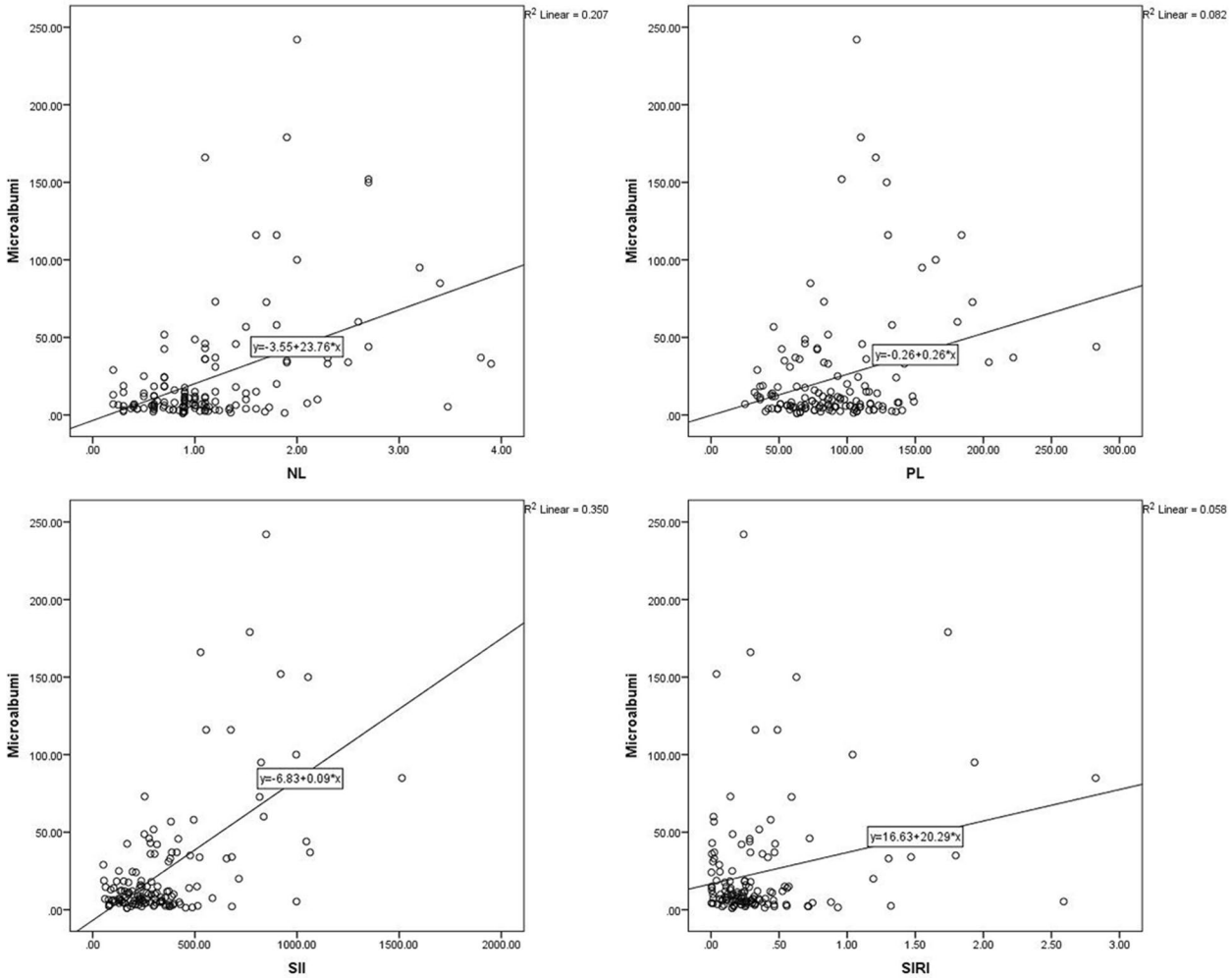

Fig. 3 Correlations between microalbuminuria and NLR, PLR, SII, and SIRI

findings that link DN with the degree of glycemic regulation indicated by HbA1C [13, 19–22].

A significant part of the pathophysiology of vascular complications of T1D is immunological dysfunction and chronic inflammation [23]. Among various WBC parameters, the NLR has recently gained attention [24]. Leucocyte dysregulation is commonly regarded as an inflammatory marker in numerous disorders, such as cancers, collagen diseases, and diabetes mellitus [25, 26]. Although NLR and PLR are increasingly recognized as dynamic inflammatory markers, there is limited evidence linking these markers to diabetic vascular complications [27–29].

In the current study, NLR and PLR were significantly elevated in patients with DN. In concordance with our study, Salah et al. concluded that children with T1D had significantly higher NLR but lower PLR in children with diabetic microvascular complications than those without [25]. They explained that the reduced PLR could be attributed to increased platelet activation, aggregation, and oxidative stress in diabetic patients. Likewise, Khandare et al. explored the NLR as an indicator for DN in type 2 diabetes and established a significant correlation between NLR and DN [24].

The logistic regression analysis showed that NLR is an independent risk factor for DN in T1D; this result is in agreement with that done by Yu et al., which also identified high neutrophil count as an independent risk factor for DN in TID. Furthermore, the study revealed a statistically significant positive connection between NLR and albuminuria [30].

A novel inflammatory marker called SII has been researched in conditions where there is ongoing inflammation [31]. In our study, SII was an independent predictor of DN and was substantially greater in children with DN compared to the other group. These findings align with previous research conducted on adults diagnosed with type 2 diabetes (T2D) by Taslamacioglu

et al. and Guo et al., where they observed that SII holds predictive value for diabetic kidney injury in individuals with diabetes [32, 33].

MLR exhibited no statistically significant difference between the two groups in the current study; nevertheless, patients with DN had greater values than the other group. This contradicts the findings of Huang et al., who observed significantly elevated MLR in patients with DN compared to those without complications, albeit within the context of type 2 diabetes [34].

To the best of our knowledge, there is little research on SII and SIRI in diabetic children [35, 36]. These inflammatory markers, which can be easily calculated from a complete blood count and do not incur any additional costs, hold potential for utilization in clinical settings. In our study, we observed a significant correlation between SII and DN.

The limitations of this study are its retrospective nature and it is a single center study with relatively small size. To validate the preliminary findings, larger prospective multicenter investigations are required in the future.

Conclusions

SIRI and SII are easily available and affordable inflammatory markers that may serve as independent early predictors of diabetic nephropathy in patients with type 1 diabetes. Furthermore, they have good sensitivity and specificity in diagnosing diabetic nephropathy.

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Not applicable.

Authors' contributions
All authors contributed to the study conception and design. Material preparation and data collection were performed by MHE. Data analysis and the first draft of the manuscript were performed by RE. The methodology was written by MZA. The discussion was written by SE. All authors read, revised, and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the research ethics committee of the Faculty of Medicine, Tanta University, under the number 36264PR328/9/23. The need for informed consent was waived by the ethics committee of the Faculty of Medicine, Tanta University, because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors have no potential conflicts of interest regarding the research, authorship, and/or publication of this article.

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