ORIGINAL ARTICLE

NEUTROPHIL-TO-LYMPHOCYTE AND PLATELET-TO-LYMPHOCYTE RATIOS AS PREDICTIVE BIOMARKERS FOR DECREASED GLOMERULAR FILTRATION RATE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Highlights:

(1) Inflammatory biomarkers predict decreased glomerular filtration. (2) Neutrophil-to-lymphocyte ratio, inflammation, and development of kidney injury. (3) Platelet-to-lymphocyte ratio indicates the severity of diabetic nephropathy.

PRE-PROOF
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ABSTRACT

Diabetes mellitus is considered one of the major public health problems of the 21st century and is one of the most important risk factors for chronic kidney disease. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are biomarkers associated with systemic inflammation, measured through complete blood count, and have been investigated as biomarkers for other inflammatory diseases, showing promising results. In this context, diabetic nephropathy is associated with chronic low-grade inflammation. Therefore, the present study aimed to evaluate the correlation between leukocyte parameters and renal function biomarkers in patients with type 2 diabetes mellitus (T2DM). A total of 33 male patients with T2DM, with a mean age of 65 years, underwent clinical and laboratory assessment to evaluate hematological and biochemical parameters. Descriptive statistical analysis was performed using the Kolmogorov-Smirnov test for normality, Pearson's test (for parametric data), or Spearman's test (for nonparametric data), with statistical significance set at $P \leq 0.05$. NLR and PLR were inversely correlated with decreased glomerular filtration rate and positively correlated with increased urea and creatinine concentrations. The use of NLR and PLR proved to be predictive biomarkers for reduced glomerular filtration rate in patients with T2DM, representing a low-cost tool in patient care.

Keywords: Diabetic Nephropathy, Glomerular Filtration, Biomarkers, Hematological Parameters.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a clinical condition characterized by partial or complete failure of insulin production in the pancreas or by resistance to insulin action, leading to chronic hyperglycemia. This state is associated with complications such as kidney injury and consequent impairment of renal function[1]. In this context, diabetic nephropathy (DN) is the most common chronic complication related to T2DM, affecting approximately 40% of patients.

In about one-fifth of these cases, a decline in the efficiency of functional renal units (nephrons) is observed due to reduced glomerular filtration rate (GFR)[1,2].

T2DM is the leading cause of progression to end-stage renal disease (ESRD)[4]. Moreover, the development of this chronic injury is associated with a 100-fold higher risk of death compared to the non-diabetic population, and a 50-fold higher risk compared to diabetic patients without nephropathy[5]. It is estimated that by 2040, the number of individuals with diabetes will exceed 642 million worldwide[6]. Furthermore, life expectancy in diabetic patients is reduced by 5 to 10 years[6]. According to Batista et al[7],68% of patients with diabetes and/or hypertension present a significant decline in renal function (GFR < 30 mL/min/1.73 m²), with diabetes currently representing the main cause of chronic kidney disease (CKD)[8]. The development of DN represents the leading cause of morbidity and mortality in patients with T2DM[8].

CKD is defined as the presence of kidney injury or reduced GFR, which can be estimated using the Cockcroft-Gault equation based on serum creatinine values and other formulas[9]. In the pathophysiology of CKD, the inflammatory process plays a central role, with changes observed in different blood cells. Neutrophils adhere to endothelial cells and migrate into the interstitium, leading to alterations in vascular and endothelial permeability and in the integrity of renal tubular cells. In addition, neutrophils release proteases and cytokines, exacerbating the inflammatory response. Capillary obstruction may also occur due to accumulation of neutrophils together with platelets, ultimately impairing the structure and function of the renal tissue[10]. Given the role of these cells in inflammatory and hemodynamic responses, the biomarkers neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which reflect immuno-inflammatory disturbances, show potential for detecting tissue damage, including renal injury[11].

Therefore, the aim of the present study was to evaluate the association of NLR and PLR with hematological and biochemical parameters assessed as biomarkers of renal function in patients with T2DM.

MATERIALS AND METHODS

Study design and population

This was a cross-sectional study that evaluated biochemical and hematological parameters in patients with T2DM. The study population consisted of patients enrolled in diabetes care programs provided by Family Health Strategy (FHS) teams in the municipality of Santo Ângelo, Rio Grande do Sul, Brazil (medication data are presented in Supplementary Table 1). Participation in the study was voluntary and all participants signed an informed consent form prior to enrollment. Patients were selected according to predefined inclusion and exclusion criteria.

Inclusion criteria

Male patients with T2DM who were under medical follow-up through diabetes patient groups of the FHS in Santo Ângelo were included.

Exclusion criteria

Patients who did not agree to participate or who initially consented but did not undergo laboratory assessment were excluded. Additionally, patients with autoimmune diseases, acute infections, or a previous diagnosis of cancer were excluded.

Procedures

Initial contact was made with the Municipal Health Secretariat and Primary Health Care Units (PHCUs) of Santo Ângelo to present the project. Following approval, the research protocol was submitted to the Research Ethics Committee of UNIJUÍ for ethical clearance. Before any procedures were performed, patients were fully informed about the objectives and steps of the study, and those who agreed signed the informed consent form.

Researchers attended the monthly meetings of diabetic patient groups at the PHCUs, where patients usually receive their medications and multiprofessional care, to present the study. Participants who agreed to join scheduled a date for biological sample collection and anthropometric measurements. All procedures were performed in designated rooms that ensured biosafety standards and patient privacy. During the interview, personal information (name, telephone number, residential address, occupation, date of birth, age, sex, and attending

physician) was collected. Blood pressure, weight, height, waist, and hip circumference were measured.

All laboratory procedures, from collection to reporting, were carried out by trained professionals, researchers, and fellows. Blood samples were collected on scheduled dates by an experienced research team at the PHCUs. Samples were transported under biosafety standards to the laboratory, where they were processed and separated for hematological and biochemical analyses.

Blood collection

A 10-mL venous blood sample was collected from each patient after a 10-hour fasting period by venipuncture. Of this volume, 4 mL was collected in EDTA tubes (whole blood) and 6 mL in clot activator tubes, with serum obtained by centrifugation (15 minutes at 3,500 rpm).

Laboratory assessments

Hematology: Complete blood count (whole blood with EDTA) was performed using ABX Micros 60 automation followed by microscopic evaluation of Giemsa–May–Grünwald–stained blood smears.

- Platelet-to-lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count (Platelets/Lymphocytes).
- Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (Neutrophils/Lymphocytes).
- Monocyte-to-lymphocyte ratio (MLR) was calculated by dividing the absolute monocyte count by the absolute lymphocyte count (Monocytes/Lymphocytes).

Biochemistry: Fasting glucose, creatinine, and urea were measured in serum samples using automated kinetic and colorimetric methods (BS200 Mindray). The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault equation:

- *Creatinine Clearance (mL/min)* = [140 − Age(years) × Weight(kg) / 72 × Plasma Creatinine (mg/dL)] × 1.00 (for males)

Anthropometric assessment

Body weight was measured in kilograms using calibrated scales available at the PHCUs, and height in centimeters (stadiometer/scale). The body mass index (BMI) was calculated as weight/height² (kg/m²).

Statistical analysis

Descriptive analysis was expressed as mean ± standard deviation. The normality of quantitative variables was assessed using the Kolmogorov–Smirnov test. Associations between variables were analyzed using Pearson's correlation (parametric data) or Spearman's correlation (nonparametric data) coefficients. A P-value < 0.05 was considered statistically significant.

Ethical considerations

The study was conducted in accordance with the Guidelines and Regulatory Standards for Research Involving Human Beings (Resolution 466/2012 of the Brazilian National Health Council). The protocol was approved by the Research Ethics Committee of UNIJUÍ (approval number: 1.173.158).

RESULTS AND DISCUSSION

The 33 male patients evaluated had a mean age of 65.88 ± 12.07 years. Eleven patients (33.33%) presented urea levels above the reference value, 25 (75.75%) had decreased GFR values, and the mean fasting glucose was 135.60 ± 64.4 mg/dL, which is consistent with a population of patients with T2DM. Regarding BMI, 17 patients (51.51%) were classified as class I obese and 9 (27.27%) as overweight.

Table 1.Parameters evaluated in patients

Parameter	Results (mean ± SD)	Reference values
Age	65.88 ± 12.07	-
BMI	29.40 ± 4.69	18.5 to 24.9 kg/m^2
Fasting glucose	137.75 ± 64.43	60 to 99 mg/dL
Urea	36.34 ± 14.32	16 to 40 mg/dL
Creatinine	1.19 ± 0.28	0.7 to 1.3 mg/dL
Estimated GFR	71.27 ± 23.03	90 to 120 mL/min
RBC	4.87 ± 0.53	4.2 to 5.9 millions/uL
HGB	14.60 ± 1.67	13 to 18 g/dL
HTC	42.33 ± 7.14	38 to 52 %
MCV	89.14 ± 5.88	80 to 100 fL
RDW	14.31 ± 0.89	11 to 15 %
MCH	29.65 ± 2.34	27 to 32 pg
MCHC	33.27 ± 0.95	31 to 36 %
WBC	7657.57 ± 1905.09	40000 to 10000 /uL
Segmented neutrophils	4991.33 ± 1701.63	1600 to 8000 /uL
Band neutrophils	144.81 ± 137.15	0 to 800 /uL
Eosinophils	168.87 ± 94.86	0 to 500 /uL
Basophils	0	0 to 200 /uL
Monocytes	337.36 ± 99.23	100 to 1000 /uL
Lymphocytes	2027.57 ± 590.91	900 to 4000 /uL
NLR	2.89 ± 1.55	-
MLR	0.17 ± 0.046	-
PLR	119.39 ± 40.87	-

Legend: BMI, body mass index; RBC, red blood cell count; HGB, hemoglobin concentration; HCT, hematocrit; MCV, mean corpuscular volume; RDW, red cell distribution width; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

Urea and creatinine levels were within the reference ranges, but estimated GFR was reduced (Table 1). GFR is considered a more sensitive marker than creatinine and urea, since reductions in GFR precede increases in serum creatinine, urea, and uric acid concentrations. Calculation of GFR is recommended for all patients at risk of CKD. At-risk patients should undergo serum creatinine testing and have their GFR estimated. Creatinine clearance remains one of the most widely used markers for assessing renal function[9].

The *Program for Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes, and Cardiovascular Disease in Developing Countries* recommends early diagnosis through blood sampling to determine serum creatinine concentration for calculating estimated GFR, as this is a sensitive and low-cost measure for monitoring the development of renal complications[12].

According to BMI reference values, the patients evaluated were overweight (BMI 25–29.9 kg/m²), with a predominance of class I obesity (Table 1). Furthermore, fasting glucose levels were elevated, which was expected for T2DM patients. In T2DM, insulin secretion is insufficient to suppress hepatic glucose production or promote adequate glucose uptake by skeletal muscle[13]. Kiya et al.[14]observed that increased fasting glucose was associated with higher BMI, a finding related to insulin resistance (IR) and dyslipidemia. Thus, increased glycemia is closely associated with elevated BMI.

Obesity induces chronic low-grade inflammation, and adipokines derived from adipose tissue are directly linked to insulin resistance and the pathophysiology of metabolic syndrome (MS). This inflammatory environment hinders glycemic control and contributes to comorbidities such as hypertension and diabetic nephropathy[15]. Consequently, T2DM patients present a state of chronic low-grade inflammation characterized by hypersecretion of inflammatory factors such as CRP, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and MCP-1, resulting in persistently elevated neutrophil counts[16]. The association between inflammatory activity, MS, and impaired renal function has also been reported[17]. These findings are consistent with our results, in which reduced GFR was associated with overweight and diabetes, as demonstrated by leukocyte parameters.

Figure 1 shows the correlations between renal function markers and leukocyte parameters. NLR was negatively correlated with estimated GFR, which in turn was associated with increased serum creatinine (Figure 1A, C). Thus, NLR can be considered a good biomarker

because it was able to detect reductions in GFR even before elevations in creatinine and urea were observed (Table 1). Similarly, PLR was negatively correlated with reduced estimated GFR (Figure 1B) and positively correlated with increased serum urea (Figure 1D). Therefore, PLR also proved to be a good biomarker, showing sensitivity in detecting reductions in GFR.

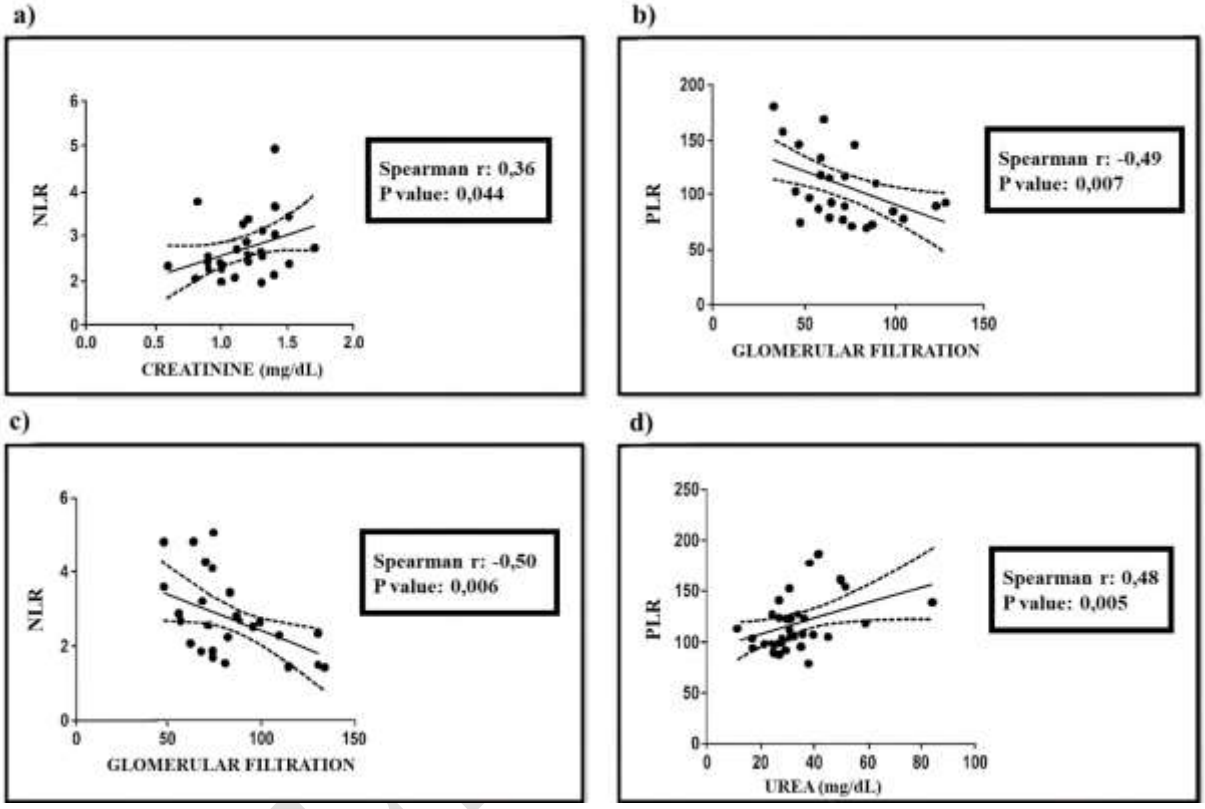

Figure 1 – Correlation between hematological parameters and renal function.
Legend: a) Spearman correlation coefficient between serum creatinine and neutrophil-to-lymphocyte ratio (NLR); b) Pearson correlation coefficient between estimated glomerular filtration rate (eGFR) and platelet-to-lymphocyte ratio (PLR); c) Spearman correlation coefficient between eGFR and NLR; d) Spearman correlation coefficient between serum urea and PLR.

The NLR has been recently used as a marker of chronic inflammation. This marker reflects two components: neutrophils - the active nonspecific mediators initiating the first line of defense - and lymphocytes - a regulatory or protective component of the inflammatory response[18]. Recent studies have demonstrated a direct role of T lymphocytes in the early development of acute kidney injury (AKI) and a possible modulatory role of B lymphocytes during the progression of renal damage[19].

The immune-inflammatory profile associated with the development and progression of DN can be assessed by NLR, what is important for evaluating the prognosis of patients with this condition[20]. Previous studies have shown that both NLR and PLR are positively associated with the development of renal disease in diabetic patients, highlighting NLR as an important predictor of DN and vascular complications[21,22,23]. Furthermore, NLR has been correlated with end-stage CKD[24]

According to Huang et al., increased NLR is significantly associated with DN and may serve as a reliable predictive marker for early-stage DN, which is consistent with our findings showing a correlation between elevated NLR, reduced GFR, and increased creatinine levels[18]. Our findings contribute to the body of evidence indicating that NLR can be considered both a predictor and a prognostic marker for DN risk, given its association with chronic inflammation and vascular complications[22].

PLR is an inflammatory marker that, in combination with NLR and other hematologic indices, may assist in diagnosing and evaluating the activity and severity of various diseases, including DN and predicting the progression of T2DM, aiding prognostic evaluation and clinical decision-making[25].

Akdoğan et al. introduced PLR as a novel biomarker of systemic inflammatory response and predictor of microvascular complications in T2DM, such as DN[26]. Additionally, PLR provides insight into platelet aggregation and inflammatory pathways, making it valuable for estimating inflammatory burden [27] and serving as a prognostic factor in several diseases[28,29,30].

There is evidence that platelets are key mediators in initiating and sustaining a chronic pro-inflammatory environment through direct interactions with endothelial and inflammatory cells[31]. The positive correlation between PLR and leukocyte count indicates that this inflammatory marker gradually increases and is associated with leukocytosis resulting from neutrophilia, further reflecting the chronic low-grade inflammation observed in T2DM patients[32].

Elevated PLR has also been associated with poorer prognosis in diseases such as cancer and coronary artery disease (CAD)[33,34]. Sunbul, Gerin, and Durmus reported that PLR is a significant predictor of non-adherence in hypertensive patients[35]. Additionally, older patients have been shown to have higher mean PLR values compared to younger individuals[36]. PLR

may therefore complement traditional risk factors by providing information about platelet aggregation and inflammatory pathways, particularly in older adults.

According to European and Japanese guidelines, NLR in CKD patients improves diagnostic accuracy and therapeutic management, thereby reducing mortality[37]. Investigating inflammatory biomarkers is crucial in non-communicable chronic diseases such as diabetes, as it allows the monitoring of pathological mechanisms and disease-related complications[38]. There are few studies in Brazil correlating NLR and PLR with hyperglycemic states. Therefore, our results are relevant because T2DM prevalence in Brazil is high and has significant demand for healthcare resources. NLR and PLR are low-cost, easily accessible markers that allow simpler monitoring and management strategies[39].

Overall, the use of NLR and PLR as potential adjunctive prognostic markers in T2DM and renal impairment represents a simple, rapid, and low-cost approach that can support patient care, aid prognostic assessment, and inform clinical decision-making regarding therapeutic interventions.

CONCLUSION

NLR and PLR are novel, low-cost hematological parameters used to evaluate immune-inflammatory status. In our study, we demonstrated that these markers correlate with reduced GFR, a more sensitive indicator of renal disease, and are also associated with increased serum urea and creatinine concentrations. Therefore, they may serve as important predictive biomarkers for the development of renal complications in diabetic patients.

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SUPPLEMENTARY

Table 1: List of medications used by study participants

Medication	Main pharmacological effect	Participants using it (%)
Acetylsalicylic acid (ASA)	Analgesic and antiplatelet	56
Alendronate sodium	Osteoporosis treatment	4
Atenolol	Antihypertensive	4
Biperiden	Anticholinergic	8
Captopril	Antihypertensive	24
Cinarzine	Antihistamine	8
Potassium diclofenac	Anti-inflammatory, analgesic, antipyretic	4
Enalapril	Antihypertensive	24
Fluoxetine	Antidepressant	4
Glibenclamide	Antidiabetic	8
Haloperidol	Antipsychotic	8
Aluminum hydroxide	Antacid	4
Insulin	Antidiabetic	8
Levothyroxine	Synthetic thyroid hormone	4
Losartan	Antihypertensive	8
Metformin	Antidiabetic	16
Omeprazole	Antacid	24
Propranolol	Antihypertensive	8
Simvastatin	Antihyperlipidemic	24