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# STUDY OF NEUTROPHIL/LYMPHOCYTE AND PLATELET/LYMPHOCYTE RATIOS IN TYPE 2 DIABETES MELLITUS

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## Abstract

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are potential inflammatory biomarkers for prognostic analysis in several diseases, such as type 2 diabetes mellitus (T2DM). This study analyzed NLR and PLR as possible T2DM biomarkers. A cross-sectional study was conducted with a secondary database that included laboratory test results from two healthcare units in Goiânia, GO, Brazil, between 2015 and 2016. The participants were normoglycemic (NG), prediabetic (preDM), and had controlled DM (CDM) and uncontrolled DM (UDM). NLR and PLR were compared between study groups according to sex and age group. NLR was higher in group UDM than preDM (1.88 vs. 1.62, p <0.05) and lower in group preDM than NG (1.62 vs. 1.80, p <0.05). NG women aged ≥65 years were six times more likely to present PLR ≤91.83 than preDM ones (OR: 6.34; CI: 1.98 - 20.55; sensitivity = 41.5%, PPV = 84.6, and LR + = 4.15). NG men aged <65 years were almost four times more likely to present PLR ≤120 (OR: 3.64; CI: 1.21 - 10.89; sensitivity = 80%, PPV = 37.7, and LR + 1.53) than preDM ones. NLR and PLR increases are directly proportional to DM severity, except for group preDM compared to NG for NLR values. These biomarkers can help estimate T2DM prognosis.

**Keywords:** Chronic disease. Comorbidity. Diabetes mellitus. Health planning. Severity of illness index.

## 1. Introduction

Diabetes mellitus (DM) comprises metabolic disorders involving several clinical, epidemiological, and physiopathogenic aspects (American Diabetes Association 2019). The main feature of this disorder is persistent hyperglycemia due to the dysfunctions in insulin production or action and the metabolism of carbohydrates, lipids, and proteins (Rodacki et al. 2022).

The chronicity of high blood glucose levels is strongly related to microvascular tissue damage, increasing the risk of macrovascular complications and potentially compromising the normal physiology of organs and body systems (WHO 2016). The pathophysiology of type 2 diabetes mellitus (T2DM) is directly linked to the inflammation triggered by glucotoxicity, lipotoxicity, oxidative stress, glycation products, and advanced glycation end products (AGEs) (Herder et al. 2013). The molecules circulating in inflammatory cells can decrease beta-cell function by causing their dysfunction or uncontrolled apoptosis (Agrawal 2014).

Hematological parameters, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are potential inflammatory markers used for the prognostic analysis of the inflammatory state of several clinical conditions, such as tumors, cardiovascular problems, and diabetes (Acmaz et al. 2014; Afari and Bhat 2018). As the name implies, these prognostic reasons are mathematical ratios between the absolute number of blood cells and platelets from the same blood sample. The relationship between these inflammatory biomarkers and DM has been demonstrated and can be explained by biochemical processes involved in the pathophysiology of the disease (Shiny et al. 2014; Demirtas et al. 2015; Lou et al. 2015; Mertoğlu and Günay 2016; Yingli Lu et al. 2020).

These studies significantly show that NLR and PLR values can be reliable prognostic biomarkers, as NLR increases proportionally to glucose intolerance severity, while PLR reduces in prediabetes (preDM) and the early stages of the disease and increases in later stages (Shiny et al. 2014; Demirtas et al. 2015; Lou et al. 2015; Mertoğlu and Günay 2016). However, further studies with more extended series and different groups of patients are required to confirm these findings. Therefore, this study analyzed neutrophil/lymphocyte and platelet/lymphocyte ratios in type 2 diabetes mellitus patients.

## 2. Material and Methods

### Study design

It was a cross-sectional study based on a secondary database of laboratory test results of patients treated at the Clinics Hospital of the Federal University of Goiás (HC/UFG/EBSERH) and the Military Police Hospital of Goiás (HPM), both in Brazil, between 2015 and 2016. The results included in the database were blood cell counts and glycated hemoglobin (HbA1c) tested on the same date.

### Eligibility criteria

The patients whose laboratory test results were included in this research were treated at the two referred hospitals, were ≥40 years old, and underwent the three tests of interest. Thus, the study included 13,207 participants. Pregnant women and individuals with HIV, tuberculosis, hepatitis, hematologic disease, lung disease, autoimmune disease, or any malignant neoplasm were excluded from the study, resulting in 695 participants.

After calculating hematological ratios, participants with results above or below the interquartile limits (outliers) for NLR and PLR were excluded, totaling 621 study participants.

### Study population

HbA1c values were considered for creating the following groups: normoglycemic (NG) (HbA1c<5.7%), prediabetics (preDM) (5.7%≤HbA1c<6.5%), controlled DM (CDM) (6.5%≤HbA1c<7%), and uncontrolled DM (UDM) (HbA1c≥7%). Subsequently, the four groups were stratified according to sex and age group (<65 years old and ≥65 years old).

### Data analysis

Prognostic ratio calculations considered the absolute value of blood components and occurred with simple divisions between neutrophils per lymphocyte (NLR) and platelets per lymphocyte (PLR). A variability estimate that allowed the measurement of NLR and PLR limits (upper and lower) for each participant was calculated to remove outliers from the interquartile range.

The data were tabulated in Excel® spreadsheets and primarily analyzed in the SPSS® program. The study performed the normality test (Kolmogorov-Smirnov with Lilliefors correction) and the comparative analysis between the groups (Kruskal-Wallis and post-hoc). The receiver operating characteristic (ROC) curve was analyzed with the MedCalc® program by calculating cut-offs and odds ratios for NLR and PLR according to the Youden index. The sensitivity and specificity values of the cut-offs were presented with

95% confidence intervals (95% CI). The graphs were constructed in the GraphPad Prism® program. Values of p <0.05 were statistically significant in all tests.

The UDM group presented the worst outcome, the NG group represented the control, and the preDM and CDM groups were time control cases for group comparisons. The variables were compared intergroup: NG x UDM/CDM/preDM, preDM x CDM/UDM, and CDM x UDM.

**Ethical considerations**

This study was approved by the Ethics Committee of the Federal University of Goiás (UFG), under CAAE #21377413.7.0000.5078, and the Ethics Committee of the Military Police Hospital (HPM), under CAAE #08254212.5.0000.0037.

## 3. Results

The study included 621 patients with a mean age of 61 years (40 to 96 years old), of which 60.2% (n=374) were <65 years old and 61.8% (n=384) were women. According to HbA1c levels, 230 (37%) patients were NG, 140 (22.5%) were preDM, 22 (3.6%) had CDM, and 229 (36.9%) had UDM.

**Table 1.** Sociodemographic and laboratory data of the participants divided into groups according to HbA1c levels (N= 621).

| | NG | preDM | CDM | UDM | Total |
|---|---|---|---|---|---|
| Sex n (%) | n=230 | n=140 | n=22 | n=229 | n=621 |
| Female | 131 (57.0) | 97 (69.3) | 13 (59.1) | 143 (62.4) | 384 (61.8) |
| Male | 99 (43.0) | 43 (30.7) | 09 (40.9) | 86 (37.6) | 237 (38.2) |
| Age group n (%) | | | | | |
| <65 years | 156 (67.8) | 72 (51.4) | 09 (40.9) | 137 (59.8) | 374 (60.2) |
| ≥65 years | 74 (32.2) | 68 (48.6) | 13 (59.1) | 92 (40.2) | 247 (39.8) |
| LABORATORY DATA | | | | | P-value* |
| Neutrophils[a] Median (min-max) | 3438.5 (990-7383) | 3530.5 (1768.5-7259) | 3863 (1620-7316) | 3850 (1353-8162.7) | 0.014 |
| Lymphocytes[a] Median (min-max) | 1976.4 (932.5-4107) | 2133.95 (1089-4187) | 2079 (1188-3626) | 2100 (1050-5324) | 0.004 |
| Platelet count[a] Median (min-max) | 226000 (57000-380000) | 229500 (100000-434000) | 219000 (89000-348000) | 230000 (83000-520000) | 0.986 |
| HbA1c[b] Median (min-max) | 5.3 (3.8-5.6) | 5.9 (5.7-6.4) | 6.7 (6.5-6.9) | 8.7 (7-17.1) | 0.000 |
| RATIOS | | | | | |
| NLR Median (min-max) | 1.80 (0.56-3.50) | 1.62 (0.55-3.43) | 1.81 (0.88-3.33) | 1.88 (0.55-3.45) | 0.006 |
| PLR Median (min-max) | 119.99 (52.67-193.67) | 107.11 (45.56-195.29) | 114.64 (51.67-180.75) | 112.32 (40.38-191.27) | 0.062 |

NG: normoglycemic; preDM: prediabetic; CDM: controlled DM; UDM: uncontrolled DM. a: measurement in $mm^3$; b: measure in percentage (%); c: measurement in mg/dL. *Kruskal-Wallis test and post-hoc analysis showed that total neutrophil values significantly differed between NG and UDM while absolute lymphocyte values differed between NG and preDM patients. HbA1c values were significantly different when comparing almost all groups, except between preDM and CDM patients. NLR was different between groups NG and preDM and when comparing preDM and UDM

The absolute neutrophil count was higher for group UDM than NG (3850/$mm^3$ vs. 3438.5/$mm^3$, p <0.05), the absolute lymphocyte count was higher for group preDM than NG (2133.95/$mm^3$ vs. 1976.4/$mm^3$, p <0.05). NLR was higher in group UDM than preDM (1.88 vs. 1.62, p <0.05) but lower for

group preDM than NG (1.62 vs. 1.80, p <0.05). The absolute platelet count did not show differences between the studied groups. Table 1 presents demographic and laboratory data of the study population.

Study groups were stratified according to age group and sex. Women aged <65 years with CDM had lower PLR than NG ones (75.47 vs. 125.61, p <0.05). Among men, PLR values were not significantly different between groups. NLR was not different in stratified group comparisons (Table 2).

**Table 2.** Laboratory data of participants according to HbA1c levels, sex, and age group.

| Sex | FEMALE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Study group (n) | NG (93) | preDM (48) | CDM (05) | UDM (83) | *p*-value# | NG (38) | preDM (49) | CDM (08) | UDM (60) | *p*-value# |
| Age group (years) | <65 | <65 | <65 | <65 | | ≥65 | ≥65 | ≥65 | ≥65 | |
| NLR Median (min-max) | 1.73 (0.82-3.55) | 1.54 (0.80-3.00) | 1.34 (0.88-3.00) | 1.76 (0.55-3.40) | 0.67 | 2.00 (0.98-3.23) | 1.61 (0.55-3.43) | 1.84 (1.02-2.83) | 1.87 (0.87-3.23) | 0.052 |
| PLR* Median (min-max) | 125.61* (58.75-193.67) | 112.84 (54.71-183.39) | 75.47* (60.12-104.36) | 112.16 (40.38-189.30) | 0.012* | 126.57 (57.66-190.57) | 104.69 (45.56-195.29) | 147.40 (114.58-180.75) | 116.62 (63.09-163.52) | 0.032 |
| Sex | MALE | | | | | | | | |
| Study group (n) | NG (63) | preDM (24) | CDM (04) | UDM (54) | *p*-value# | NG (36) | preDM (19) | CDM (05) | UDM (32) | *p*-value# |
| Age group (years) | <65 | <65 | <65 | <65 | | ≥65 | ≥65 | ≥65 | ≥65 | |
| NLR Median (min-max) | 1.85 (0.56-3.14) | 1.84 (0.64-3.14) | 1.99 (0.88-3.33) | 1.98 (0.78-3.45) | 0.371 | 1.94 (0.87-3.25) | 1.81 (1.02-3.19) | 1.81 (1.08-3.26) | 2.12 (0.69-3.09) | 0.730 |
| PLR Median (min-max) | 116.80 (61.13-180.35) | 100.74 (59.95-167.63) | 105.91 (82.12-119.69) | 106.82 (44.87-191.27) | 0.182 | 100.76 (52.67-192.02) | 117.09 (79.33-181.20) | 90.91 (51.67-151.65) | 112.18 (45.28-176.17) | 0.374 |

NG: normoglycemic; preDM: prediabetic; CDM: controlled DM; UDM: uncontrolled DM. NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; #Kruskal Wallis test and post-hoc analysis, *showing that PLR values significantly differed between NG and CDM women aged <65 years.

The cut-off was investigated from the ROC curve of each ratio. The UDM group presented the worst clinical outcome. Forty-eight (48) curves were generated, of which four obtained a robust area under the curve (AUC): two referring to NLR for women of both age groups and two referring to PLR for both sexes (Figure 1).

Women with UDM, regardless of being younger or older than 65 years, were almost three times more likely (OR: 2.93; CI: 1.35 – 6.37) to show NLR above 1.82 (sensitivity = 49.4%, PPV = 78.2, and LR+ = 1.98) or (OR: 2.86; CI: 1.28 – 6.37) with NLR above 2.03 (sensitivity = 46.8%, PPV = 70.7, and LR+ = 2.07) respectively, than preDM ones. NG women aged ≥65 years were six times more likely (OR: 6.34; CI: 1.98 – 20.55) to present PLR ≤91.83 (sensitivity = 41.5%, PPV = 84.6, and LR+ = 4.15) than preDM ones. NG men under 65 years old were almost four times more likely (OR: 3.64; CI: 1.21 – 10.89) to show PLR ≤120 (sensitivity = 80%, PPV = 37.7, and LR+ of 1.53) than preDM ones. Table 3 details these findings.

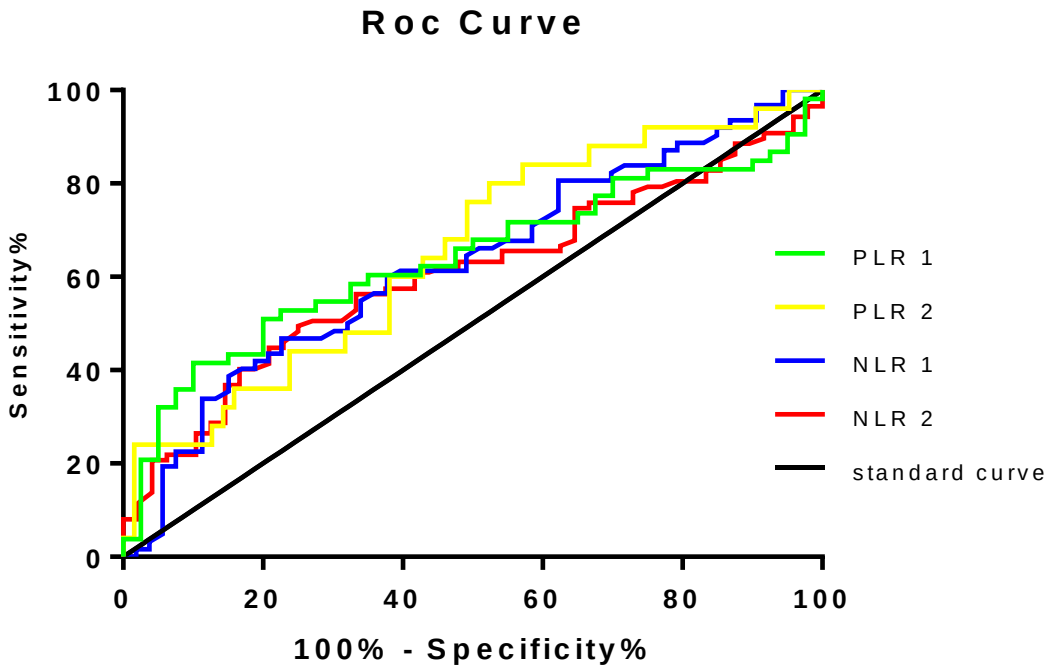


**Figure 1.** Representation of the studied ROC (receiver operating characteristic) curves**.** PLR 1: ROC curve for PLR for women aged ≥65 years, comparing normoglycemic (NG) and prediabetic (preDM) groups; PLR 2: ROC curve for PLR for men aged <65 years, comparing NG and preDM groups; NLR 1: ROC curve for NLR for women aged <65 years, comparing UDM and preDM groups; NLR 2: ROC curve for women aged ≥65 years, comparing UDM and preDM groups.

**Table 3.** ROC analysis and efficiency measures for NLR and PLR as prognostic reasons. *

| | Ratio | Age group (years) | Sex | Study groups | AUC | *p*-value | Cut-off | Sensitivity | Specificity | OR | PPV (CI 95%) | NPV (CI 95%) | LR+ (CI 95%) | LR- (CI 95%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | NLR | <65 | F | UDM x preDM (83)x(48) | 0.60 | 0.03 | >1.818 | 49.43 | 75.00 | 2.93 (1.35-6.37) | 78.2 (67.7-85.9) | 45.0 (38.6-51.6) | 1.98 (1.2-3.4) | 0.67 (0.5-0.9) |
| 2 | NLR | ≥65 | F | UDM x preDM (60)x(49) | 0.63 | 0.01 | >2.034 | 46.77 | 77.36 | 2.86 (1.28-6.37) | 70.7 (57.9-80.9) | 55.4 (48.6-62.1) | 2.07 (1.2-3.6) | 0.69 (0.5-0.9) |
| 3 | PLR | ≥65 | F | NG x preDM (38)x(49) | 0.64 | 0.01 | ≤91.827 | 41.51 | 90.00 | 6.34 (1.98-20.55) | 84.6 (67.3-93.6) | 53.7 (47.5-59.8) | 4.15 (1.6-11.1) | 0.65 (0.5-0.8) |
| 4 | PLR | <65 | M | NG x PreDM (63)x(24) | 0.65 | 0.02 | ≤120 | 80.00 | 47.62 | 3.64 (1.21-10.89) | 37.7 (30.9-45.2) | 85.7 (72.4-93.2) | 1.53 (1.1-2.1) | 0.42 (0.2-1.0) |

NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; F: female; M: male; NG: normoglycemic; AUC: area under the curve; OR: odds ratio; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; CI: confidence interval. * Four of 48 curves generated according to group stratifications by age group and sex showed a significant AUC.

## 4. Discussion

This study identified that neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios differ according to the clinical outcome of type 2 diabetes mellitus (T2DM). The glycemic index above reference values triggers inflammatory responses that progress by increasing total neutrophils and decreasing total lymphocytes in the long term. That may explain the higher NLR in group UDM (uncontrolled diabetes) compared to preDM (prediabetic) and the higher absolute value of neutrophils in group UDM than NG (normoglycemic). Moghanjoughi et al. (2022) suggest a relationship between NLR and metabolic syndrome, Shiny et al. (2014) found a higher NLR for diabetic than premenopausal diabetic patients (2.2

±1.12 vs. 1.82 ±0.63, p <0.05), and Mertoğlu & Günay (2016) found a higher NLR (2.07 ±0.95 vs. 1.6 ±0.85, p <0.05) for diabetic than preDM patients.

Participants with UDM are likely to have prolonged immune and inflammatory responses, inducing the hypersecretion of inflammatory agents, such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), which in turn, produce consistently high amounts of neutrophils (Von Vietinghoff and Ley 2008; Tabák et al. 2010). Regarding lymphocyte reduction, studies have shown a relationship between prolonged insulin resistance and decreased T-cell counts (Nishimura et al. 2009; Lorenzo et al. 2014).

NLR was lower in group preDM than NG because of the higher absolute number of lymphocytes. Increased insulin resistance drives inflammatory processes in the early stages of the disease. However, these events still unfold mildly and follow the regulatory mechanisms of the organism, increasing lymphocyte numbers and decreasing NLR (Azab et al. 2012). A lower NLR (higher lymphocyte count) when diagnosing type 1 diabetes mellitus may indicate a low daily insulin requirement in the 3$^{rd}$ month of the disease (Erbas et al. 2022), suggesting a good prognosis.

Age group, sex, and T2DM evolution may influence peripheral blood cell dynamics. Researchers have evaluated the impact of work stress on T2DM development and found that a heavy workload can decrease the risk for men while having the opposite effect on women (Eriksson et al. 2013). The pairing of this study minimizes biases related to differences in pathophysiology, lifestyle, and comorbidities inherent to sex. However, the NLR cut-off value seems to increase among diabetic patients with advanced age, showing that the inflammatory process caused by diabetes is clinically relevant and requires follow-up.

As in other studies, the present one identified the lowest PLR among diabetic women with CDM and younger than 65 years compared to NG ones (Shiny et al. 2014; Demirtas et al. 2015; Lou et al. 2015; Mertoğlu and Günay 2016). A cohort study in China analyzed the platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, and their dynamic changes with T2DM in more than 40,000 individuals, concluding that a higher PLR may reduce the risk of T2DM and a higher NLR may increase such risk (Zhang et al. 2022). Oxidative stress from hyperglycemia, added to other pro-inflammatory events, causes platelet dysfunction and the release of signals that work to maintain it. That may justify platelet changes in T2DM patients that alter PLR and increase lymphocytes (Langsenlehner et al. 2015).

Factors such as the epidemiological transition, which show an increase in life expectancy, indicate immunosenescence and the coexistence of other comorbidities that also alter the immunoinflammatory system (Prattichizzo et al. 2018). As mentioned, men and women present relevant differences. Hormonal heterogeneity causes different inflammatory responses for each sex, which may explain the significant results found for women but not men (Kautzky-Willer et al. 2016).

This research has limitations, such as the non-homogeneous distribution between the groups and the evaluation of a single laboratory test. Nonetheless, besides investigating probable differences in prognostic ratios according to HbA1c levels, sex, and age, this study calculated cut-offs for NLR and PLR. Thus, this investigation helped to elucidate the reasons applied to the follow-up of patients with chronic diseases that progress with inflammation, considering the satisfactory sensitivity and specificity obtained by effectively studying classified groups, allowing the distinction between the clinical conditions of participants.

## 5. Conclusions

The UDM group exhibited a significantly higher NLR (1.9), and NG showed NLR around 1.8, but it was lower for participants in the early stages of the disease (preDM). Diabetic women with UDM were more likely to present NLR above the cut-off (1.8 for women under 65 years old and 2.0 for older ones). PLR was lower (91.8 for women and 120 for men) in group NG.

This study found cut-offs for NLR and PLR with good AUC (~0.6), good sensitivity (41 - 80%), and very good specificity (47 - 90%), indicating that these biomarkers may help assess the prognosis of diabetic patients. Study follow-ups, such as a prospective cohort investigation, might confirm that these reasons increase as a poor prognosis develops and the disease worsens.

**Authors' Contributions:** MARTINS, I.J.: acquisition of data, analysis and interpretation of data, drafting the article, and critical review of important intellectual content; JUNQUEIRA, I.C.: analysis and interpretation of data, drafting the article, and critical review of important

intellectual content; NASCIMENTO, T.C.: drafting the article and critical review of important intellectual content; COSTA, S.H.N.: conception and design, drafting the article, and critical review of important intellectual content; ALCÂNTARA, K.C.: conception and design, drafting the article, and critical review of important intellectual content. All authors have read and approved the final version of the manuscript.

**Conflicts of Interest:** The authors declare no conflicts of interest.

**Ethics Approval:** This study was approved by the Ethics Committee of the UFG under the CAAE number 21377413.7.0000.5078, and by the Ethics Committee of the HPM under the CAAE number 08254212.5.0000.0037.

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