Meditory
(The Journal of Medical Laboratory)
Volume 14 Issue 1 Page 38-44 – June 2026
https://doi.org/10.33992/meditory.v13i1.4056

ANALYSIS OF PLATELET-LYMPHOCYTE RATIO IN TYPE 2 DIABETES MELLITUS AS A SYSTEMIC INFLAMMATION BIOMARKER

Fathul Hidayatul Hasanah [1*], Sri Wahyuni[1], Danny Meganingdyah Primartati[1], Aulia Risqi Fatmariza[1], Fita Sari[1]

[1]Institut Ilmu Kesehatan Bhakti Wiyata Kediri, Jl.K.H.Wahid Hasyim No 65, Kediri, East Java 64114, Indonesia

Article History
Received, May 20th, 2025
Revised, September 18th , 2025
Reviewed, May 25th , 2026
Posted, July 17th, 2026

Editor
Wimbuh Tri Widodo

***Corresponding author**
Fathul Hidayatul Hasanah
e-mail:
fathul.hidayatul@iik.ac.id

Keywords
Diabetes Mellitus, Platelet Lymphocyte Ratio, Inflammation Biomarker

Abstract

Background: Chronic hyperglycemia in type 2 DM causes chronic low-grade systemic inflammation, which triggers complications. The body responds with an increase in proinflammatory cytokines and changes in blood cell hemostasis. The platelet lymphocyte ratio (PLR) is a new inflammatory marker that has clinical prognostic value.

Objective: Comparison of PLR values in type 2 DM without complications with the cardiovascular and nephropathy complication groups.

Methods: The study employed a retrospective research design and included a total of 617 respondents with type 2 DM. The respondents were divided into three groups: 162 with uncomplicated type 2 DM, 291 with cardiovascular complications, and 164 with nephropathy. The data was collected from Mojowarno Christian General Hospital in Jombang.

Results: The mean value of PLR in uncomplicated type 2 DM was 238.4 ± 225, in cardiovascular 327.11 ± 162, and in nephropathy 449.52 ± 107. The difference test yielded a statistically significant result $p < 0.001$, indicating that there were notable differences in PLR values across the three type 2 DM groups.

Conclusions: There is a difference in PLR values in type 2 DM between the group without complications and the group with complications (cardiovascular and nephropathy).

Cite this Article
Hasanah FH, Wahyuni S, Primartati DM, Fatmariza AR, Sari F. Analysis Of Platelet-Lymphocyte Ratio In Type 2 Diabetes Mellitus As A Systemic Inflammation Biomarker. Meditory J Med Lab. 2026;14(1):38–44.

INTRODUCTION

According to the World Health Organization (WHO), 422 million people worldwide have diabetes mellitus (DM), and diabetes causes 1.5 million deaths every year (1). Indonesia ranks fifth in the number of people with DM, with around 19.5 million people affected and 236,000 deaths in 2021 (2). Hyperglycemia in people with diabetes can lead to microvascular and macrovascular complications (3). Researchers have put forward various hypotheses about the mechanism of these complications, including chronic low-grade systemic inflammation. This condition is characterized by an increase in inflammatory biomarkers, such as pro-inflammatory cytokines (interleukin 1 [IL-1], interleukin 1β [IL-1β], interleukin 2 [IL-2], interleukin 6 [IL-6], interleukin 8 [IL-8], tumor necrosis factor-α [TNF-α], and transforming growth factor-β1 [TGF-β1]) and C-reactive protein (CRP) in type 2 DM) (4,5)

Increased proinflammatory cytokines have been demonstrated to affect the immune response, immune regulation, and various physiological and pathological mechanisms. For instance, increased Interleukin 6 has been shown to stimulate platelet production by affecting the performance of thrombopoetin. Similarly, Interleukin 1β has been demonstrated to play a role in the differentiation and maturation of megakaryocyte cells and to induce thrombopoiesis. Finally, Interleukin 2 has been shown to influence platelet viability (6). CRP has been demonstrated to play a pivotal role in the progression of atherosclerosis by virtue of its pro-inflammatory effects. These effects include the promotion of platelet activation and thrombus formation, which, in turn, increases the risk of blood vessel blockage (7). The immune response to inflammation can manifest as immunosuppression, which is typified by a lymphocyte count of less than 500/μL, indicative of a poor prognosis (8). Inflammatory conditions are known to induce an increase in platelet count due to the action of proinflammatory cytokines, while concurrently leading to a decrease in leukocyte count, indicative of diminished immune function. The platelet-lymphocyte ratio (PLR) is the value obtained by dividing the absolute number of platelets by the absolute number of lymphocytes. Previous studies have demonstrated the clinical prognostic value of the PLR (9).

The PLR value was found to be elevated in type 2 DM patients with retinopathy in comparison to the type 2 DM control group without retinopathy ($p = 0.012$). A prior study reported that the PLR value was elevated in type 2 DM patients with retinopathy compared to type 2 DM patients without retinopathy ($p = 0.012$) (10). A significant correlation has been demonstrated between increased PLR and the incidence of diabetic nephropathy. Therefore, PLR has the potential to serve as a predictor of diabetic nephropathy complications. Abnormal insulin action in diabetes mellitus (DM) has been demonstrated to induce augmented platelet adhesion. Hyperglycemia has been shown to stimulate increased platelet metabolism, coagulation, and anticoagulation imbalances, which can result in thrombosis, atherogenesis, and microcirculation disorders (11). PLR has been demonstrated to increase in patients with type 2 DM, and its correlation with HbA1c has been established (12).

According to the provided background information, the researcher's objective is to investigate the discrepancy in PLR values among individuals with three distinct clinical presentations: uncomplicated type 2 DM, type 2 DM accompanied by cardiovascular complications, and type 2 DM s associated with nephropathy. This investigation aims to

address a significant gap in knowledge by conducting original research in this area, as no prior studies have systematically examined this particular topic. The findings of this study offer novel insights into the significance of PLR in various diabetic complications that have not been previously examined. These findings serve to bolster the evidence supporting the utilization of PLR as a straightforward and cost-effective alternative to inflammatory biomarkers, such as CRP and interleukin 6.

MATERIALS AND METHODS

The research design employed was retrospective. Secondary data were obtained from the laboratory examination results of type 2 DM patients from the laboratory information system (LIS) from January to December 2023 at the Mojowarno Christian General Hospital, Jombang. The study respondents were type 2 DM patients who had received outpatient treatment or had stayed overnight at Mojowarno Christian General Hospital in Jombang and met the inclusion and exclusion criteria. The following exclusion criteria were applied to respondents who were pregnant and to those with comorbidities, which included, but were not limited to, the following conditions: 1) severe acute respiratory syndrome (SARS-CoV-2); 2) tuberculosis; 3) typhoid; 4) dengue fever; 5) hepatitis; and 6) cancer. A total of 617 patients with type 2 DM were included in the study, which was further subdivided into three groups: 162 patients without complications, 291 patients with cardiovascular complications, and 164 patients with nephropathy complications. This research has been approved by the ethics commission of IIK Bhakta with letter number 05/FTMK/EP/IV/2023.

The PLR calculation is derived from the ratio of platelet count to lymphocyte count. This data is typically obtained from routine blood test results. Routine blood tests utilize whole blood samples preserved in lavender vacutainer tubes (K3EDTA anticoagulant). The instrumentation employed is the Sysmex XN series 1000 automatic hematology analyzer. Internal quality control is ensured through the utilization of XN CHECK Bf blood control checks, in accordance with the specifications outlined in the XN-Series haematology system recommendations. Serum blood glucose levels were examined in accordance with the Gluc-DH FS* Diasys insert kit, and serum specimens were obtained in Serum Separator Tube (SST). The data underwent rigorous scrutiny through a series of analytical procedures, including a thorough examination for normality date, a two-way analysis of variance (ANOVA) test and Mann-Whitney test. These meticulous analyses were conducted using the SPSS 25.0 software, with a significance level set at P = 0.05..

RESULTS AND DISCUSSIONS

The present study was conducted at Mojowarno Christian General Hospital in Jombang. The study population included type 2 DM patients without complications (n = 162), patients with cardiovascular complications (n = 291), and patients with nephropathy complications (n = 164). The results of the comparison test of all research variables are shown in Table 1. The findings of the study demonstrated that patient age did not have a statistically significant impact on the prevalence of complications in individuals diagnosed with type 2 DM. This conclusion was supported by the results of the Mann-Whitney test, which yielded a p-value greater than 0.05 (p=0.799). The mean age of individuals diagnosed with type 2 DM in the uncomplicated group was 58.43 years. This finding was observed to

be similar in the cardiovascular group, with a mean age of 58.28 years, and in the nephropathy group, where the mean age was 59.47 years. This finding aligns with the conclusions of related publications, reported that the age of type 2 DM is predominantly concentrated in the 56–71 age group. This phenomenon is associated with impaired glucose tolerance, which is predicted to diminish with advancing age. In 2021, impaired glucose tolerance was observed in the 45-69 age group. Projections indicate a likelihood of an escalation in prevalence among younger demographics by 2045 (2).

Table 1. Comparison of Laboratory Examination Results

Variabel	Without Complications (n=162) Mean	Cardiovascular Complications (n=291) Mean	Nephropathy Complications (n=164) Mean	*P Value*
Age (year)	58.43	58.28	59.47	0.799
Male/Female	49/113	127/164	58/106	<0.001**
Random blood sugar (mg/dl)	273.7±97	227±190	293.8±285.6	0.002**
PLR	238.4±225	327.11±162	449.52±107	<0.001**

The present study revealed that type 2 DM is more prevalent among women. The data demonstrated that the proportion of women in each type 2 DM group with complications was as follows: without complications (113 [69.7%] cases), cardiovascular complications (164 [56.3%] cases), and nephropathy (106 [64.6%] cases). The study also indicated a tendency for complications, with a p-value of less than 0.05. Women diagnosed with type 2 DM exhibit a cardiometabolic risk profile characterized by elevated blood pressure, obesity, and lipid targets that are associated with an increased risk of complications when compared to male patients (13).

A statistically significant discrepancy was observed in the comparison ANOVA test of blood glucose levels among the type 2 DM groups ($p = 0.002$). The mean glucose level in each group exceeded the established cutoff value of ≤135 mg/dl. The findings revealed that intermittent blood glucose levels in the respondents indicated uncontrolled blood glucose. This observation was also noted in the uncomplicated type 2 DM group, where the levels reached 273 mg/dl.

In this study, the mean value of PLR was found to be significantly different in the type 2 DM group ($p<0.001$) with ANOVA test. The type 2 DM group with complications exhibited a higher mean PLR value compared to the group without complications. The mean PLR value for the complication-free group was 238.4 ± 225, while the mean PLR value for the cardiovascular group was 327.11 ± 162 and for the nephropathy group was 449.52 ± 107. The present findings contradict those of previous publications (14), which indicated that there was no statistically significant difference between PLR in diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar (HH) states, with an average PLR value of 234.29 (DKA) and 237.42 (HH), respectively. This discrepancy can be attributed to the varying sample sizes of the studies, with the Hariogie and Chess study having a sample size of 71, and the other studies having smaller sample sizes. Nevertheless, there are also several publications that support the results of this study. These publications state that PLR

increases in heart and oncological diseases, so it can be used as a potential inflammatory biomarker in heart and chronic kidney disease (15). Moreover, PLR has been documented as a cost-effective predictor of microvascular complications in diabetes mellitus (DM) (16) . This finding aligns with the observations reported for NLR. Another study found that PLR can be used as a biomarker to assess the risk of foot ulcers in patients with type 2 diabetes (17).

The increase in PLR of type 2 DM is attributable to a state of chronic hyperglycemia, which has been demonstrated to result in elevated levels of proinflammatory cytokines (e.g., interleukin 1, interleukin 1β, interleukin 2, interleukin 6, interleukin 8, tumor necrosis factor-α, and transforming growth factor-β1) and C-reactive protein (CRP) in type 2 DM (4);(5). Increased levels of Interleukin 6 have been shown to affect the performance of thrombopoetin, resulting in an increase in the rate of thrombopoiesis (6). In addition to its role as a stimulator of megakaryocyte differentiation and maturation, and its induction of thrombopoiesis, Interleukin 2 has been demonstrated to influence platelet viability. This mechanism suggests that the number of platelets will increase in chronic hyperglycemia. The increase in PLR is found to be strongly influenced by the number of lymphocytes.

CLINICAL IMPLICATION

Our findings indicate that the PLR value exhibits a substantial increase in type 2 DM cases accompanied by complications, specifically nephropathy and cardiovascular disease. This observation underscores the potential of PLR as a valuable predictor of complications and inflammatory biomarkers, particularly in type 2 DM contexts.

LIMITATIONS

A notable limitation of the present study is the absence of platelet index parameters in the utilized tools. A comprehensive evaluation of platelet activity in individuals with type 2 DM necessitates a multifaceted approach, encompassing the measurement of mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), and platelet activation index (PAI). This comprehensive approach facilitates a nuanced comparison of platelet activity across diverse type 2 DM groups, thereby enhancing our understanding of the risk of thromboembolism in this populations.

CONCLUSIONS

PLR values were found to vary significantly between the type 2 DM group with complications and the group without complications. Specifically, PLR values in type 2 DM patients with cardiovascular complications and nephropathy were higher than in those without such complications.

CONFLICT OF INTEREST

The authors affirm that the investigate was conducted within the nonattendance of any commercial or financial relationships that may well be interpreted as a potential strife of intrigued.

AUTOR CONTRIBUTIONS

Fathul was responsible for the conceptualization, methodology, data analysis, original draft, and revision of the text. Sri, Danny, and Aulia were responsible for the investigation, data collection, and validation. Fita's role was to review and edit the text.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to all those who have contributed to this research, including all authors and Mojowarno Christian Hospital Jombang as a research site and Bhakti Wiyata Institute of Health Sciences Kediri.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DECLARATION OF ARTIFICIAL INTELLIGENCE USE

The authors used Deepl Translator to assist in improving the language and grammar of the manuscript. The authors reviewed and verified the content to ensure accuracy and integrity.

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