Research article

Platelet to Lymphocyte Ratio in Diabetic Patients with Foot Ulcers and without Foot Ulcers

Dr. Yennam Pranav Reddy[1] Dr. Rajeshwara K[2] & Dr. Prajwal Chandrashekhara[3]

[1]MBBS, Final Year Post Graduate, Dept. of General Surgery, K S Hegde Medical Academy, NITTE University, Mangaluru.
[2]MBBS, MS (General Surgery) Professor, Dept. of General Surgery, K S Hegde Medical Academy, NITTE University, Mangaluru.
[3]MBBS, DNB (General Surgery) Assistant Professor, Dept. of General Surgery, K S Hegde Medical Academy, NITTE University, Mangaluru.

HIGHLIGHTS

1. Platelet to lymphocyte ratio indicates inflammation levels.

2. Higher ratios suggest severe diabetic foot ulcers.

3. Lower ratios may indicate better healing potential.

4. Monitoring can guide treatment strategies effectively.

5. Ratio differences highlight underlying health issues.

ARTICLE INFO

ABSTRACT

Introduction: Diabetes mellitus (DM) is a widespread chronic disease, often leading to complications like diabetic foot ulcers (DFU), which can result in infections, osteomyelitis, or amputations. The platelet-to-lymphocyte ratio (PLR), an inflammatory marker may predict adverse outcomes in various conditions. This study investigates the relationship between PLR and DFU severity in type 2 diabetes mellitus (T2DM) patients, focusing on its potential to predict ulcer severity and patient outcomes. **Objective:** The primary objective of this study was to assess the association between PLR and diabetic foot ulcers in T2DM patients, and to evaluate PLR as a prognostic marker for outcomes such as wound severity, reamputation, and mortality. **Methods:** This hospital-based, prospective observational study included 118 participants, divided into two groups: 59 patients with DFU and 59 controls without DFU. Peripheral venous blood samples were collected to measure PLR, and HbA1c levels were recorded for glycemic control assessment. Data were analyzed using multivariate logistic regression to determine the relationship between PLR and DFU severity based on Wagner's classification. **Results:** The mean PLR was significantly higher in patients with DFU (192.14 ± 95.77) compared to controls (144.15 ± 75.25), $p < 0.001$. HbA1c levels were also elevated in the DFU group (10.03 ± 2.19 vs. 8.06 ± 2.14, $p < 0.001$). PLR was positively correlated with Wagner's DFU grade ($p = 0.038$), indicating its potential as a marker for assessing ulcer severity. **Conclusion:** PLR is a simple, costeffective marker that could help predict the severity of diabetic foot ulcers and identify patients at higher risk of adverse outcomes. Its inclusion in routine diagnostic workups may improve the early detection and management of diabetic complications.

INTRODUCTION

Diabetes mellitus (DM) is a significant global health issue, particularly prevalent among individuals from lower socioeconomic backgrounds. This chronic condition has a profound impact on patients' quality of life, as it often leads to severe complications if not properly managed (1). Approximately 10% of the population is affected by DM and its related complications, which can worsen over time, especially in poorly controlled cases. Among the most common complications are peripheral neuropathy, vasculopathy, and foot abnormalities, which tend to occur in the advanced stages of the disease (2).

Peripheral neuropathy and vasculopathy are two major issues that significantly affect individuals with DM. These complications can result in the development of treatmentresistant chronic ulcers, diabetic arthropathies, and osteomyelitis (3). As these conditions progress, they become harder to manage and often lead to severe consequences such as limb amputation. Early intervention in the form of wound care, debridement, and the use of tissue flaps can sometimes prevent these outcomes, but once the disease reaches a critical stage, amputation may be the only option for preserving the patient's health and quality of life (4).

Determining the appropriate level of amputation in diabetic patients is a challenging task for healthcare providers. Several factors need to be carefully considered, including the patient's overall health, the vascular health of the affected limb, and the presence of chronic sores or infections (5). The complexity of these cases makes it difficult to predict outcomes and choose the best treatment option. Despite numerous studies exploring the prevalence and mortality associated with amputations in diabetic patients, predicting the best course of action remains difficult. In this context, researchers have begun exploring various biomarkers that might help predict patient outcomes (6).

One of these biomarkers is the platelet to lymphocyte ratio (PLR), a simple and cost effective measure that has been used in several clinical settings. PLR is an indicator of inflammation, and its elevation is associated with poor outcomes in conditions such as cardiovascular diseases and cancer (7). However, its potential role in DM, particularly in relation to diabetic complications and surgical outcomes, has not been widely studied. In this study, we aim to investigate the relationship between elevated preoperative PLR and key outcomes such as mortality, reamputation rates, and wound complications in

patients with DM (8).

Patients with type 2 diabetes mellitus (T2DM) often exhibit elevated PLR levels, which may be attributed to the underlying inflammatory burden of the disease. T2DM is characterized by a chronic lowgrade inflammatory state, which worsens as blood sugar control deteriorates (9). Inadequate management of the disease leads to an increase in various inflammatory markers, including CRP (C-reactive protein) and interleukin-6, both of which are associated with disease progression and severity. As inflammation increases, patients are more likely to experience complications, making PLR a potentially useful marker for identifying patients at higher risk of poor outcomes (10).

The connection between inflammation and T2DM is wellestablished in the literature. Numerous studies have demonstrated that elevated levels of inflammatory markers precede the development of diabetes and may even predict its onset (11). For instance, research by Pradhan et al. indicated that elevated CRP and interleukin-6 levels are linked to an increased risk of developing diabetes (12). Additionally, studies have shown that chronic inflammation is associated with a higher risk of mortality in T2DM patients, especially in those with longstanding complications. This chronic inflammatory state may exacerbate the risk of developing severe diabetic complications, such as neuropathy and vasculopathy (13).

In particular, persistent diabetic complications have been closely associated with elevated inflammation. For example, Navarro et al. found that albuminuria, a marker of kidney damage in diabetic patients, is strongly correlated with inflammatory markers like CRP and tumor necrosis factor-alpha (14). Diabetic patients with proteinuria exhibited higher PLR levels compared to those without proteinuria, suggesting that PLR could serve as an indicator of more severe disease. However, the study's small sample size limited its ability to establish significant associations between PLR and other complications, such as diabetic neuropathy or retinopathy (15).

PLR has been studied as an inflammatory marker in various conditions, including coronary artery disease, rheumatoid arthritis, psoriasis and malignancies where elevated levels are linked to worse outcomes, particularly in cancer patients (16). This suggests its potential as a valuable marker across multiple diseases, including diabetes. Our study expands on this by examining PLR in diabetic patients undergoing surgery for severe complications, revealing a positive correlation between PLR and HbA1c, an indicator of long-term blood sugar control (17). As poor glycemic control .

heightens inflammation and increases complications, PLR may help identify diabetic patients at higher risk of adverse outcomes due to inadequate management (18)

While this study provides promising insights into the potential of the platelet-to-lymphocyte ratio (PLR) as a prognostic marker in diabetic patients, its retrospective design and small sample size limit the generalizability of the findings. As one of the first to explore the link between PLR and surgical outcomes in diabetes, further research, particularly larger prospective studies, is necessary to confirm these results. Elevated PLR, an indicator of inflammation, may be associated with higher mortality, increased risk of re-amputation, and wound complications. Despite the need for more studies, PLR shows promise as a simple, cost-effective tool for guiding treatment decisions in diabetes management.

MATERIAL AND METHODS

This hospitalbased, prospective, observational study utilizes an analytical crosssectional design conducted at Justice K.S. Hegde Charitable Hospital, Mangaluru. The study employs convenient sampling, following patients with Diabetes Mellitus (DM) and classifying them into those with and without diabetic foot ulcers. Peripheral venous blood samples will be collected in EDTA vacutainers during routine blood work. Inclusion criteria include patients aged 18 and above with DM, with or without foot ulcers. Exclusion criteria consist of patients with acute infections, hepatic or renal failure, autoimmune diseases, or malignancies, which could affect platelet and lymphocyte counts.

RESULTS

The mean age for cases is 59.29 years, slightly older than controls at 55.42 years. The age ranges are 28-87 for cases and 34-80 for controls, with interquartile ranges of 16 and 14, respectively. The 95% confidence intervals suggest cases are generally older. Regarding sex distribution, males dominate both groups, with 50 males and 9 females in cases, and 46 males and 13 females in controls, indicating a higher proportion of males in both groups.

Table : 1 Diagnosis of cases of study participants

Diagnosis case	Frequency
Diabetic foot ulcer-Right Foot	30
Diabetic foot ulcer-Left Foot	29
Total	59
Invalid	0
Total	59

The distribution of diabetic foot ulcers by foot involvement among 59 patients. Of these, 30 cases (50.8%) have a diabetic foot ulcer on the right foot, ulcer on the left foot. There are no invalid cases, and the total number of patients is 59. This data shows an
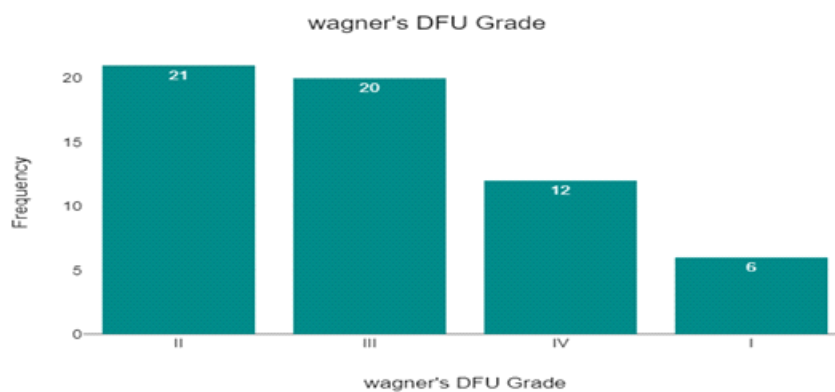
Figure: 1 Graph Denoting Distribution of Cases Based on Wagner's DFU Grade

The distribution of Wagner's Diabetic Foot Ulcer (DFU) grades among 59 patients. Grade II is the most common, with 35.59% of cases, followed by Grade III at 33.9%, and Grade IV at 20.34%. Grade I account for 10.17% of cases. There are no invalid cases, and the total number of patients is 59, indicating a full dataset. This data highlights that moderate to severe DFU grades (II-IV) are more prevalent in the study population.

Table : 2 Comparison of PLR of cases and control groups

	n	Mean	Std. Deviation	Std. Error Mean
PLR-case	59	192.14	95.77	12.47
PLR-controls	59	144.15	75.25	9.8

The comparison of the platelet to lymphocyte ratio (PLR) between cases and controls. The mean PLR for cases is 192.14 with a standard deviation of 95.77 and a standard error of 12.47, indicating higher variability. In contrast, the controls have a mean PLR of 144.15 with a standard deviation of 75.25 and a standard error of 9.8, showing less variability. This suggests that the PLR is higher in cases compared to controls, with greater dispersion in the case group.

Figure: 2 Box and Whisker plot Showing the Distribution of HbA1C of Cases and Control Groups

The HbA1c levels between cases and controls. The mean HbA1c for cases is 10.03 with a standard deviation of 2.19 and a standard error of 0.29, indicating higher blood sugar levels. In contrast, controls have a mean HbA1c of 8.06, with a standard deviation of 2.14 and a standard error of 0.28. This suggests that the cases have significantly higher HbA1c levels compared to the controls, reflecting poorer glycemic control in the case group.

Table: 3 Correlation of PLR, HbA1C of Cases and Control Groups

	n	Mean	Std. Deviation
PLR-case	59	192.14	95.77
HbA1C-case	59	10.03	2.19
PLR-controls	59	144.15	5.25
HbA1C-controls	59	8.06	2.14
Total	236	88.59	101.53

The table compares PLR and HbA1c levels between cases and controls. Cases have a higher mean PLR (192.14) and HbA1c (10.03), with standard deviations of 95.77 and 2.19, indicating more inflammation and poorer glycemic control. Controls show lower mean PLR (144.15) and HbA1c (8.06), with standard deviations of 75.25 and 2.14. Overall, the data averages to 88.59 with a standard deviation of 101.53 across all groups.
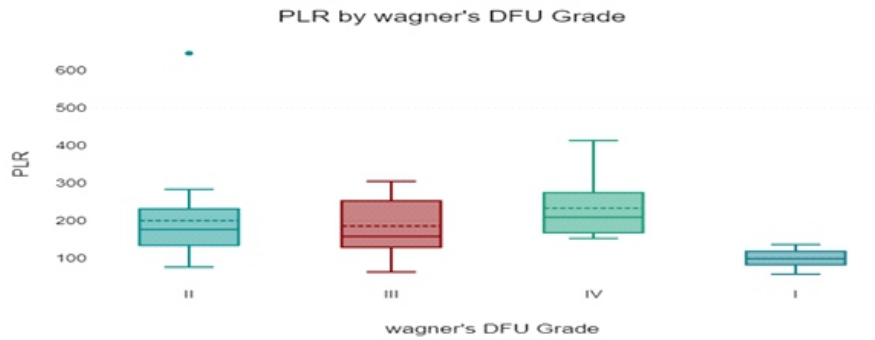
Figure : 3 Box and Whisker plot showing the Comparison of PLR of different Wagner's DFU grades of cases

The mean PLR across different Wagner's Diabetic Foot Ulcer (DFU) grades. Grade IV has the highest mean PLR at 233.72 with a standard deviation of 80.71, followed by Grade II with a mean of 200.45 and a standard deviation of 117.6. Grade III has a mean PLR of 186.35 (SD 74.28), while Grade I shows the lowest mean PLR at 99.19 (SD 28.9). The overall mean PLR across all grades is 192.14 with a standard deviation of 95.77.

Table: 4 Showing Variables of Wagner's DFU Grades of Cases

	Sum of Squares	df	Mean Square	F	p
Wagner's DFU Grade	74710.96	3	24903.65	3	.038
Residual	457259.07	55	8313.8		
Total	531970.03	58			

The p-value of 0.038 is less than the commonly used significance level of 0.05, indicating a significant difference between the groups II, III, IV, and I.

Table: 5 Table Showing the Comparison of Variables of HbA1c, PLR of Cases and Control Groups

		Mean diff.	Std. Error	f	p	95% CI lower limit	95% CI upper limit
PLR-case	HbA1C-case	182.11	11.216	16.24	<.001	151.46	212.76
PLR-case	PLR-controls	47.99	11.216	4.28	<.001	17.34	78.64
PLR-case	HbA1C-controls	184.08	11.216	16.41	<.001	153.43	214.73
HbA1C-case	PLR-controls	134.12	11.216	11.96	<.001	-164.77	-103.48
HbA1C-case	HbA1C-controls	1.97	11.216	0.18	1	-28.68	32.62
PLR-controls	HbA1C-controls	136.09	11.216	12.13	<.001	105.44	166.74

The table compares mean differences between PLR and HbA1c in cases and controls. Significant differences (p < .001) were found in all comparisons except between HbA1c levels in cases and controls (p = 1), showing no significant difference. The mean PLR difference between cases and controls was 47.99, while the difference between PLR in cases and HbA1c in controls was 184.08. The 95% confidence intervals confirm the statistical differences in significant results.

DISCUSSION

Diabetic patients often experience reduced quality of life and increased morbidity and mortality due to foot ulcers and the need for amputations, which also impose significant financial burdens. Identifying diabetic neuropathy and peripheral arterial disease (PAD) is crucial for preventing foot ulcers. Various studies highlight several risk factors for diabetic foot ulceration, and early identification and management of these risks can mitigate adverse outcomes. This cross-sectional study identified a significant correlation between high risk diabetic foot ulcers and the Platelet to Lymphocyte Ratio (PLR) in type 2 diabetes patients. Multivariate logistic regression confirmed this connection, marking it as the third study to examine this relationship (19).

In this study, cases had a higher average age than controls, though the difference was not statistically significant. A multivariate analysis found no correlation between age, diabetic foot severity, or PLR. Mineoka et al. (Japan) reported a significant age difference between groups with and without diabetic foot, while Zhang et al. observed no significant age variation among different groups, consistent with our findings (20,21).

In the current investigation, no gender distribution disparity was observed between the two groups. Similarly, Mineoka et al. reported a distribution of 273 males and 180 females, aligning with our findings. Zhang et al. studied three groups: the first had 90 participants (50 males, 40 females), the second had 102 participants (58 males, 44 females), and the third had 104 participants (63 males, 41 females), reflecting comparable gender distributions across groups (20, 21).

In this investigation, HbA1c levels were significantly higher in the cases compared to the controls. HbA1c and PLR were used as independent variables in the multivariate logistic regression analysis for diabetic foot ulcers (DFU). Mineoka et al. reported HbA1c levels of 7.5 ± 0.9% in individuals with a history of DFU and 7.8 ± 1.5% in those with active DFU, showing no

significant difference. Zhang et al. found HbA1c levels of 5.51 ± 0.50 in individuals without DFU, 8.10 ± 1.75 in those with DFU, and 9.58 ± 2.64 in individuals with type 2 diabetes. Binary logistic regression analysis identified PLR, smoking status, and HbA1c as independent risk factors for DFU (p < 0.05) (20, 21).

The current study revealed that patients had a significantly higher Platelet to Lymphocyte Ratio (PLR) compared to controls, with a weak negative correlation between the groups' PLR values. This suggests PLR could be a useful marker for assessing outcomes in diabetic foot ulcers (DFU). Calculating PLR is simple, requiring only a routine peripheral blood count during clinic visits. Recent research supports PLR's predictive value for diabetes related complications. Multivariate logistic regression showed a strong association between PLR and high risk DFU, even after adjusting for other factors. Prior studies, such as those by Zhang et al., Mineoka et al., Atak et al., and Serban et al., found PLR to be significantly associated with DFU severity and progression. These findings highlight PLR's potential in predicting atherosclerosis in the lower extremities and aiding in the early assessment of DFU risk (20, 21, 22, 23).

CONCLUSION

Patients with diabetic foot infections (DFI) who had elevated platelet to lymphocyte ratios (PLR) showed a strong association with osteomyelitis, higher risk of amputation, and increased likelihood of septic complications. PLR is significantly elevated in individuals with diabetic foot ulcers (DFU) and correlates with Wagner's DFU grade, suggesting its potential as a useful marker for assessing the severity of DFU. The PLR, easily calculated from a routine peripheral blood count, offers a cost effective diagnostic tool that can aid in the early detection and prevention of DFU, providing a new perspective in patient care.

REFERENCES

1. Arokiasamy P, Salvi S, Selvamani Y. Global burden of diabetes mellitus. In Hand book of global health 2021 May 4 (pp. 1-44). Cham: Springer International Publishing.

2. Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: a mini review. Current diabetes reviews. 2017 Feb 1;13(1):3-10.

3. Tracy JA, Dyck PJ. Managing inflammatory diabetic neuropathies. Diabetes Management. 2014 Sep 1;4(5):437.

4. Frykberg Robert G. Challenges in the treatment of chronic wounds. Advances in wound care. 2015 Aug 3.

5. Schaper NC, Apelqvist J, Bakker K. Reducing lower leg amputations in diabetes: a challenge for patients, healthcare providers and the healthcare system. Diabetologia. 2012 Jul;55:1869-72.

6. Bouwmeester W, Zuithoff NP, Mallett S, Geerlings MI, Vergouwe Y, Steyerberg EW, Altman DG, Moons KG. Reporting and methods in clinical prediction research: a systematic review. PLoS medicine. 2012 May 22;9(5):e1001221.

7. Kriplani A, Pandit S, Chawla A, de la Rosette JJ, Laguna P, Jayadeva Reddy S, Somani BK. Neu-trophil–lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR) in predicting systemic inflammatory response syndrome (SIRS) and sepsis after percutaneous nephrolithotomy (PNL). Uroli-thiasis. 2022 Jun;50(3):341-8.

8   Koliaki C, Liatis S, Le Roux CW, Kokkinos A. The role of bariatric surgery to treat diabetes: current challenges and perspectives. BMC endocrine disorders. 2017 Dec;17:1-2.

9. Serban D, Papanas N, Dascalu AM, Kempler P, Raz I, Rizvi AA, Rizzo M, Tudor C, Silviu Tudosie M, Tanasescu D, Pantea Stoian A. Significance of neutrophil to lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) in diabetic foot ulcer and potential new therapeutic targets. The International Journal of Lower Extremity Wounds. 2024 Jun;23(2):205-16.

10 Ansar W, Ghosh S, Ansar W, Ghosh S. Inflammation and inflammatory diseases, markers, and mediators: Role of CRP in some inflammatory diseases. Biology of C reactive protein in health and disease. 2016:67-107.

11. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes research and clinical practice. 2014 Aug 1;105-(2):141-50.

12. Zohmangaihi D, Sharma SB, Madhu SV. Adip-onectin, IL-6 and hsCRP: Interplay of inflammation with obesity and type 2 diabetes in Indian population. J Diabetes Metab. 2019;-10(822):2.

13. Lowe G, Woodward M, Hillis G, Rumley A, Li Q, Harrap S, Marre M, Hamet P, Patel A, Poulter N, Chalmers J. Circulating inflammatory markers and the risk of vascular complications and mortality in people with type 2 diabetes and cardiovascular disease or risk factors: the ADVANCE study. Diabetes. 2014 Mar 1;63(3):1115-23.

14. Donate-Correa J, Luis-Rodriguez D, Martin Nunez E, Tagua VG, Hernandez-Carballo C, Ferri C, Rodr-iguez-Rodriguez AE, Mora-Fernandez C, Navarro-Gonzalez JF. Inflammatory targets in diabetic nephropathy. Journal of Clinical Medicine. 2020 Feb 7;9(2):458.

15. Jaaban M, Zetoune AB, Hesenow S, Hessenow R. Neutrophil-lymphocyte ratio and platelet-lymp-hocyte ratio as novel risk markers for diabetic nephropathy in patients with type 2 diabetes. Heliyon. 2021 Jul 1;7(7).

16. Gasparyan AY, Ayvazyan L, Mukanova U, Yess-irkepov M, Kitas GD. The platelet-to-lymph-ocyte ratio as an inflammatory marker in rheu-matic diseases. Annals of laboratory medicine. 2019 Jul 1;39(4):345-57.

17. Wu JH, Marklund M, Imamura F, Tintle N, Korat AV, De Goede J, Zhou X, Yang WS, de Oliveira Otto MC, Kroger J, Qureshi W. Omega-6 fatty acid bio-markers and incident type 2 diabetes: pooled analysis of individual-level data for 39 740 adults from 20 prospective cohort studies. The lancet Diabetes & endocrinology. 2017 Dec 1;5(12):965-74.

18. Amalia M, Saputri FC, Sauriasari R, Widyantoro B. Complete blood count, lipid profiles, and inflam-matory markers associated with atherosclerotic cardiovascular disease in patients with diabetes. F1000Re search. 2023 Nov 14;12:1470.

19. Moore Z, Avsar P, Wilson P, Mairghani M, O'Connor T, Nugent L, Patton D. Diabetic foot ulcers: trea-tment overview and cost considerations. Journal of Wound Care. 2021 Oct 2;30(10):786-91.

20. Mineoka Y, Ishii M, Hashimoto Y, Yamashita A, Nakamura N, Fukui M. Platelet to lymphocyte ratio correlates with diabetic foot risk and foot ulcer in patients with type 2 diabetes. Endocr J. 2019.

21 Zhang K, Ding S, Lyu X, Tan Q, Wang Z. Correlation between the platelet-to-lymphocyte ratio and diabetic foot ulcer in patients with type 2 diabetes mellitus. J Clin Lab Anal. 2021;35(4) doi:10-.1002/jcla.23719

22. Atak B, Aktas G, Duman TT, Erkus E, Kocak MZ, Savli H. Diabetes control could through plate-let-to-lymphocyte ratio in hemograms. Rev Assoc Med Bras (1992). 2019;65(1):38-42.

23. Serban D, Papanas N, Dascalu AM, et al. Sign-ificance of Neutrophil to Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in Diabetic Foot Ulcer and Potential New Thera-peutic Targets. Int J Low Extrem Wounds. 2024;23(2):205-216. doi:10.1177/15347346211057742