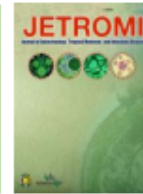




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The Association of the Neutrophil-Lymphocyte Ratio with Diabetes Mellitus and Diabetic Foot Ulcer: A Review Article

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ABSTRACT

Introduction: Diabetes mellitus (DM) is inappropriately elevated blood glucose levels. Diabetic foot ulcer (DFU) is the most common complication of diabetes mellitus. Many research studies found that the neutrophil-lymphocyte ratio (NLR) has a positive correlation with HbA1C, blood glucose, and the outcome of diabetic foot ulcers. **Methods:** The literature searches using online databases such as PubMed, ScienceDirect Elsevier, and Google Scholar. **Result:** After doing an online search, we found 39 articles were relevant to this review topic. **Analysis:** Many research studies have found that increased HbA1C ($\geq 6,5$) and increased blood glucose (random blood glucose ≥ 200 mg/dL and/or fasting blood glucose ≥ 126 mg/dL) in patients with diabetes mellitus have a positive correlation with increased NLR. There were increased NLR values in patients with diabetic foot ulcers and NLR values were higher ($NLR \geq 6$) in non-healing ulcers than in healing ulcers. **Conclusion:** NLR can be used as a screening tool for determining the evaluation of diabetes mellitus and as a screening tool for determining the outcome of diabetic foot ulcers

Keywords: Diabetes Mellitus, Diabetic Foot Ulcer, Neutrophil Lymphocyte Ratio.

ABSTRAK

Pendahuluan: Diabetes melitus (DM) adalah peningkatan kadar glukosa darah secara tidak wajar. Ulkus kaki diabetik (UKD) merupakan komplikasi diabetes melitus yang paling umum. Banyak penelitian menemukan bahwa rasio neutrofil limfosit (RNL) mempunyai korelasi positif dengan HbA1C, glukosa darah, dan hasil keluaran dari ulkus kaki diabetik. **Metode:** Pencarian literatur menggunakan database online seperti PubMed, ScienceDirect Elsevier, dan Google Scholar. **Hasil:** Setelah melakukan pencarian online, kami menemukan 39 artikel yang relevan dengan topik review ini. **Analisis:** Banyak penelitian yang menemukan peningkatan HbA1C ($\geq 6,5$) dan peningkatan glukosa darah (glukosa darah sewaktu ≥ 200 mg/dL dan/atau glukosa darah puasa ≥ 126 mg/dL) pada pasien diabetes melitus mempunyai korelasi positif dengan peningkatan RNL. Dan terjadi peningkatan nilai RNL pada pasien ulkus kaki diabetik dan nilai RNL lebih tinggi ($RNL \geq 6$) pada ulkus yang tidak sembuh dibandingkan dengan ulkus yang sudah sembuh. **Kesimpulan:** RNL dapat

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digunakan sebagai alat skrining untuk menentukan evaluasi diabetes melitus dan sebagai alat skrining untuk menentukan outcome ulkus kaki diabetik

Kata Kunci: *Diabetes Mellitus, Rasio Neutrofil Limfosit, Ulkus Kaki Diabetik.*

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1 Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by inappropriately elevated blood glucose levels or what we usually call hyperglycemia due to impairment of insulin secretion, defective insulin action, or both.[1]-[4] Diabetic foot ulcer (DFU) is the most common complication of diabetes, which is due to microvascular damage. Diabetic foot ulcers are a prevalent cause of osteomyelitis of the foot and amputation of lower limbs. It has been found that >50% of all nontraumatic amputations of the lower extremities that occur in patients with diabetes are related to diabetic ulcers.[5]-[10]

Triad pathologic mechanisms of diabetic foot ulcers are neuropathy, vascular insufficiency, and secondary infection. Hyperglycemia produces oxidative stress on nerve cells and leads to neuropathy. Motor neuron dysfunction may lead to an imbalance of flexors and extensors, anatomic deformities, and eventual skin ulcerations. Damage to autonomic nerves impairs sweat gland function, and the foot may develop decreased ability to moisturize skin, leading to epidermal cracks and skin breakdown. In sensory neuropathy, diabetes induces neuronal autonomic dysfunction that results in impaired sweat production, leaving the foot susceptible to dryness, skin cracking, and fissuring, patients may not notice foot wounds because of decreased peripheral sensation. In vascular insufficiency, hyperglycemia induces changes in the peripheral arteries of the foot and begins on the cellular level. Endothelial cell dysfunction leads to a decrease in vasodilators, plasma thromboxane A₂ levels become elevated. The result is vasoconstriction and plasma hypercoagulation in peripheral arteries leading to ischemia and increased risk of ulceration. Secondary infection is usually due to trauma of the foot.[11]-[14]

Diabetic foot ulcers are characterized by an increase in the number of leukocytes in the blood as a physiological response to stress in the circulation. Neutrophils are active inflammatory mediators, which serve as the first line of defense and a high neutrophil count is a nonspecific marker of the inflammatory process. Lymphocytes can control and regulate the inflammatory response as well as anti-atherosclerosis. Systemic inflammatory conditions in diabetic patients, especially in patients with diabetic foot ulcers can be assessed by inflammatory markers such as the neutrophil-lymphocyte ratio (NLR).[11]-[14]

Many research studies found that increased HbA_{1C} has a positive correlation with increased neutrophil-lymphocyte ratio (NLR) and increased fasting blood glucose in patients with diabetes mellitus.[15]-[18] Some studies showed that NLR has been associated with microvascular and

macrovascular complications in diabetes. One of the macrovascular complications is peripheral arterial disease which NLR values increase, the combined effect of peripheral arterial disease with neuropathy is the most common cause of diabetic foot ulcers.[15],[19]-[23]

Many studies have shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher in non-healing ulcers than in healing ulcers.[6][7][14]

This review article will provide a review of the NLR between healing and non-healing ulcers and then also aims to determine the association of the NLR with the outcome of diabetic foot ulcer and determine the association of the NLR with evaluation of diabetes mellitus.

2 Methods

This review article uses a Mixed Methods Review. Mixed Methods Review refers to a combination of review approaches for example combining quantitative with qualitative research or outcome with process studies. Requires either a very sensitive search to retrieve all studies or separately conceived quantitative and qualitative strategies.[24]

The literature searches using online databases such as PubMed, ScienceDirect Elsevier, and Google Scholar. Published literature relating to DM and NLR was obtained using the keywords “diabetes mellitus”, “diabetic foot ulcer”, “neutrophil-lymphocyte ratio”, “complication of diabetes mellitus”, “neutrophil-lymphocyte ratio” in association with “diabetes mellitus” and “neutrophil-lymphocyte ratio” in association with “diabetic foot ulcer”. The articles must be in English and published in 10 years (2014 until 2023). Studies in non-English language and performed on animals were excluded from this review. The selected articles were carefully reviewed and analyzed to extract essential insights about the topic under discussion.

3 Results

Table 1 Total number of articles applying inclusion criteria

Online Database	Keyword	Number of Result
PubMed	Diabetes Mellitus	133.235
	Complications of Diabetes Mellitus	682
	Diabetic Foot Ulcer	1283
	Neutrophil Lymphocyte Ratio	2774
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	122
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	2
Science Direct Elsevier	Diabetes Mellitus	229.541
	Complications of Diabetes Mellitus	2.593
	Diabetic Foot Ulcer	4.870
	Neutrophil Lymphocyte Ratio	3.651
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	733
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	6
google scholar	Diabetes Mellitus	1.460.000
	Complications of Diabetes Mellitus	12.000
	Diabetic Foot Ulcer	20.200
	Neutrophil Lymphocyte Ratio	19.800
	Neutrophil Lymphocyte Ratio, Diabetes Mellitus	12.000
	Neutrophil Lymphocyte Ratio, Diabetic Foot Ulcer	173

After doing an online search on PubMed, ScienceDirect Elsevier, and Google Scholar. We found that 42 articles were relevant to this review topic. The articles were reviewed and analyzed to extract essential insights about the topic under discussion.

4 Discussion

4.1 Diabetes Mellitus

Diabetes mellitus is taken from the Greek word diabetes, meaning siphon - to pass through, and the Latin word mellitus meaning sweet. Diabetes mellitus is a metabolic disorder characterized by inappropriately elevated blood glucose levels or what we usually call hyperglycemia due to impairment of insulin secretion, defective insulin action, or both. Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress. These states affect b-cell mass and/or function such that insulin levels are eventually unable to respond sufficiently to insulin demands, leading to hyperglycemia levels sufficient to diagnose diabetes. In some cases, genetic and environmental risk factors and gene-environment interactions can directly impact b-cell mass and/or function. Regardless of the pathophysiology of diabetes, chronic high blood glucose levels are associated with microvascular and macrovascular complications that increase morbidity and mortality for people with diabetes. This model positions b-cell destruction and/or dysfunction as the necessary common factor to all forms of diabetes. DM is classified as Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gestational Diabetes Mellitus, monogenic diabetes mellitus, and other less common conditions, such as diabetes related to pancreatic disease, drug-induced, or rare insulin resistance, and mitochondrial syndromes. [1]-[4]

4.2 Diabetic Foot Ulcer

Diabetic foot ulcer is the most common complication of diabetes, which is due to microvascular damage. This can lead to both morbidity as well as mortality. Diabetic foot ulcers are one of the most prevalent consequences of poorly treated diabetes mellitus. Diabetic foot ulcers are a prevalent cause of osteomyelitis of the foot and amputation of lower limbs. A diabetic foot ulcer is a localized foot ulcer that is associated with neuropathy and/or peripheral arterial disease of the lower limb in patients with diabetes. It has been found that >50% of all nontraumatic amputations of the lower extremities that occur in patients with diabetes are related to diabetic ulcers. [1],[5]-[10]

Diabetic foot ulcers frequently result from a person with diabetes simultaneously having two or more risk factors, with diabetic peripheral neuropathy and peripheral artery disease usually playing a central role. The neuropathy leads to an insensitive foot, loss of protective sensation, foot deformities, and limited joint mobility can result in mechanical trauma in some areas which usually causes thickened skin (callus). Finally, frequent trauma of the callus results in subcutaneous hemorrhage and eventually becomes an ulcer. In diabetic microenvironments neutrophils dysregulated release granular molecules to kill foreign pathogens in ulcers, causing a proinflammation and overproduction of cytokines and superoxide, which delay wound healing. [8][13][25] - [27]

Table 2 Wagner's classification of diabetic foot ulcers[13][27]

Grade	Characteristic
Wagner grade 0	No ulcer but high-risk foot
Wagner grade 1	Partial or full-thickness ulcer (superficial)
Wagner grade 2	Deep ulcer extending to ligament, tendon, joint capsule, bone, or deep fascia without abscess or osteomyelitis
Wagner grade 3	Deep abscess, osteomyelitis, or joint sepsis
Wagner grade 4	Partial/localized foot gangrene e.g. toe, heel, etc
Wagner grade 5	Extensive gangrene involving the whole foot

4.3 Neutrophil Lymphocyte Ratio with Diabetes Mellitus and Diabetic Foot Ulcer

NLR is the ratio of the absolute neutrophil count to the absolute lymphocyte count. It is regarded as a marker of the body's immune response to offending agents. It is also regarded as a rapid and simple parameter indicative of systemic inflammation and stress. Neutrophilia or lymphopaenia results in high NLR while lymphocytosis or neutropaenia results in low NLR. Overall the normal range of NLR is in the range of 0.8–3. The values above 3.0 and below 0.7 in adults are pathological. However, NLR in the grey zone of the range of 2.3–3 may serve as a warning that there is a pathological process present in organisms, such as cancer, atherosclerosis or ischemic heart disease, psychiatric disorders, subclinical infection, and/or inflammation.[28]-[31]

Many research studies have found that increased HbA1C (≥ 6.5) and increased blood glucose (Random Blood Glucose ≥ 200 mg/dL and/or Fasting Blood Glucose ≥ 126 mg/dL) in patients with

diabetes mellitus have a positive correlation with increased NLR. NLR has been found higher in uncontrolled diabetes mellitus than in controlled diabetes mellitus.[15]-[19][32]-[42]

Some studies showed that NLR has been associated with microvascular and macrovascular complications in diabetes, most importantly in disease progression and metabolic impairment.[15][19]-[22][42]-[44] One of the macrovascular complications is a peripheral arterial disease in which NLR values definitely increased and also found increased NLR values in diabetic peripheral neuropathy, the combined effect of peripheral arterial disease with neuropathy is the most common cause of diabetic foot ulcers.[45]-[49]

Many studies have shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher ($NLR \geq 6$) in non-healing ulcers than in healing ulcers.[6][7][14][37][50]-[52] NLR significantly increased in patients with diabetic foot ulcer, compared with type 2 diabetes mellitus patients without diabetic foot ulcer and higher NLR values were an independent factor for wound healing. And the NLR value was significantly higher in grade 5 and lowest in grade 2 indicating that there was a significant relationship between NLR and Wagner's classification.[14][32]

Elevated NLR in patients with diabetic foot infections increased the risk of amputation and sepsis.[32][53] NLR has high specificity and sensitivity in predicting the prognosis of patients with diabetic foot, increased NLR value was found to be a reliable predictive biomarker of mortality in diabetic foot ulcer patients following amputation.[52][54]-[58] A correlation has been found between the degree of diabetic foot ulcers according to Wagner's classification with NLR, patients with high NLR values have a higher degree of diabetic foot ulcer, and the need for vascular treatment and amputation is much higher than patients with low NLR value.[59][60]

5 Conclusion

In these articles, we found many studies had shown increased NLR values in uncontrolled diabetes mellitus ($HbA1C \geq 6,5$ and/or Random Blood Glucose ≥ 200 mg/dL and/or Fasting Blood Glucose ≥ 126 mg/dL). In these review articles, we also found many studies had shown a significant association between diabetic foot ulcers and NLR, there was an increased NLR value in patients with diabetic foot ulcers and NLR values were higher ($NLR \geq 6$) in non-healing ulcers than in healing ulcers. So, NLR can be used as a screening tool for determining the evaluation of diabetes mellitus and NLR can be used as a screening tool for determining the outcome of diabetic foot ulcers.

REFERENCE

- [1] A. Sapra, P. Bhandari, NCBI Bookshelf: Diabetes, StatPearls Publishing LLC, 2023. [Online]. <https://www.ncbi.nlm.nih.gov/books/NBK551501/?report=printable>. [Accessed: Oct. 19, 2023]
- [2] Z. Punthakee, R. Goldenberg, P. Katz, Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome, *Canadian Journal of Diabetes*, vol. 42, pp. S10–S15. 2018.
- [3] M. Z. Banday, A. S. Sameer, S. Nissar, Pathophysiology of diabetes: An overview, *Avicenna Journal of Medicine*, vol. 10, issue 4, pp. 174–188. 2020.
- [4] L. Blonde, G. E. Umpierrez, S. S. Reddy, J. B. McGill, et al, American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update, *Endocrine Practice*, vol 28, issue 10, pp. 923-1049. 2022.
- [5] T. Gary, M. Pichler, K. Belaj, F. Hafner, et al, Neutrophil-to-Lymphocyte Ratio and Its Association with Critical Limb Ischemia in PAOD Patients. *PLoS ONE*, vol. 8, issue 2. 2013.
- [6] N. Vatankhah, Y. Jahangiri, G. J. Landry, R. B. McLafferty, et al, Predictive Value Of Neutrophil-To-Lymphocyte Ratio In Diabetic Wound Healing. *Journal of Vascular Surgery*, vol. 65, no. 2, pp. 478–483. 2017.
- [7] C. Kahraman, G. Yumun, M. K. Kahraman, N. D. Namdar, et al, Neutrophil-To-Lymphocyte Ratio In Diabetes Mellitus Patients With And Without Diabetic Foot Ulcer, *European Journal of Medical Sciences*, vol. 1, issue 1, pp. 8–13. 2014.
- [8] B. Ren, B. Li, T. Pan, E. Zhao, et al, Risk Factors For At-Risk Foot And Peripheral Artery Disease Among The Population With Diabetes: A Multicommunity-Based Cross-Sectional Study, *Diabetes Research and Clinical Practice*, vol. 203. 2023.
- [9] K. Alexiadou, J. Doupis, Management of Diabetic Foot Ulcers. *Diabetes Therapy*, vol. 3, issue 1, pp. 1–15. 2012.
- [10] A. F. Mavrogenis, P. D. Megaloikononimos, T. Antoniadou, V. G. Igoumenou, et al, Current Concepts For The Evaluation And Management of Diabetic Foot Ulcers. *EFORT Open Reviews*, vol. 3, issue 9, pp. 513–525. 2018.
- [11] W. D. Aumiller and H. A. Dollahite, Pathogenesis and Management of Diabetic Foot Ulcers, *Journal of American Academy of Physician Assistants*, vol 28, no 5, pp. 28-33. 2015.
- [12] S. Syafril, Pathophysiology Diabetic Foot Ulcer, *IOP Conf. Series: Earth and Environmental Science*, vol 125, no 012161, pp. 1-5. 2018.
- [13] J. M. Raja, M. A. Maturana, S. Kayali, A. Khouzam, et al, Diabetic Foot Ulcer: A Comprehensive Review of Pathophysiology and Management Modalities, *World Journal of Clinical Cases*, vol. 11, issue 8, pp. 1684–1693. 2023.
- [14] R. Ulandari, L. B. Kurniawan, D. Muhadi, Analysis of NLR in Type 2 Diabetes Mellitus with and without Diabetic Foot Ulcer, *Indonesian Journal of Clinical Pathology and Medical Laboratory*, vol 29, issue 2, pp. 185-188. 2023.
- [15] F. Sefil, K. T. Ulutas, R. Dokuyucu, A. T. Sumbul, et al. Investigation of Neutrophil Lymphocyte Ratio and Blood Glucose Regulation in Patients with Type 2 Diabetes Mellitus, *Journal of International Medical Research*, vol 42, issue 2, pp. 581–588. 2014.
- [16] T. Adane, M. Melku, Y.B. Worku, A. Fasil, et al, The Association between Neutrophil-to-Lymphocyte Ratio and Glycemic Control in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis, *Journal of Diabetes Research*, vol. 2023, pp. 1-9. 2023.
- [17] T. T. Duman, G. Aktas, B. M. Atak, M. Z. Kocak, et al, Neutrophil to Lymphocyte Ratio as An Indicative of Diabetic Control Level in Type 2 Diabetes Mellitus, *African Health Sciences*, vol. 19, issue 1, pp. 1602–1606. 2019.

- [18] E. Palella, R. Cimino, S. A. Pullano, A. S. Fiorillo, et al, Laboratory Parameters of Hemostasis, Adhesion Molecules, and Inflammation in Type 2 Diabetes Mellitus: Correlation with Glycemic Control, *International Journal of Environmental Research and Public Health*, vol. 17, issue 1, pp. 1-7. 2020.
- [19] B. B. Mendes, A. C. R. Oliveira, K. C. Alcântara, Comparison of The Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Normoglycemic and Hyperglycemic Subjects, *Einstein*, vol. 17, issue 1, pp. 1-5. 2019.
- [20] I. Paulus, K. A.S. Palguna, J. Wirasugianto, I. G. Supadmanaba, et al, Neutrophil Lymphocyte Ratio (NLR) was Significantly Associated with Diabetic Nephropathy at Sanglah General Hospital, Denpasar, Bali, Indonesia: A Case-Control Study, *World Journal of Current Medical and Pharmaceutical Research*, vol. 3, issue 3, pp. 50–54. 2021.
- [21] A. Shiny, Y. S. Bibin, C. S. Shanthirani, B. S. Regin, et al, Association of Neutrophil-Lymphocyte Ratio with Glucose Intolerance: An Indicator of Systemic Inflammation in Patients with Type 2 Diabetes, *Diabetes Technology, and Therapeutics*, vol. 16, issue 8, pp. 524–530. 2014.
- [22] H. Wan, Y. Wang, S. Fang, Y. Chen, et al, Associations between the Neutrophil-to-Lymphocyte Ratio and Diabetic Complications in Adults with Diabetes: A Cross-Sectional Study, *Journal of Diabetes Research*, vol. 2020, pp. 1-8. 2020.
- [23] J. I. Spark, J. Sarveswaran, N. Blest, P. Charalabidis, et al, An Elevated Neutrophil-Lymphocyte Ratio Independently Predicts Mortality In Chronic Critical Limb Ischemia, *Journal of Vascular Surgery*, vol. 52, issue 3, pp. 632–636. 2010.
- [24] M. J. Grant and A. Booth, A Typology of Reviews: An Analysis of 14 Review Types and Associated Methodologies, *Health Information and Libraries Journal*, vol 26, pp.91–108. 2009.
- [25] T. I. Oliver, M. Mutlioglu, NCBI Bookshelf: Diabetic Foot Ulcer, StatPearls Publishing LLC, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK537328/?report=printable>. [Accessed: Oct. 31, 2023]
- [26] M. C. Schaper, J. J. van Netten, J. Apelqvist, S. A. Bus, et al, *IWGDF Guidelines on The Prevention and Management of Diabetic Foot Disease*. The International Working Group on the Diabetic Foot, 2019. Available: www.iwgdfguidelines.org.
- [27] P. Shah, R. Inturi, D. Anne, D. Jadhav, et al, Wagner’s Classification as a Tool for Treating Diabetic Foot Ulcers: Our Observations at a Suburban Teaching Hospital, *Cureus*, vol. 14, no. 1, pp. 1-11. 2022.
- [28] J. S. Lee, N. Y. Kim, S. H. Na, Y. H. Youn, et al, Reference Values of Neutrophil-Lymphocyte Ratio, Lymphocyte-Monocyte Ratio, Platelet-Lymphocyte Ratio, and Mean Platelet Volume in Healthy Adults in South Korea, *Medicine*, vol. 97, issue 26. 2018.
- [29] R. Zahorek, Neutrophil-to-lymphocyte ratio, past, present and future perspectives, *Bratisl Med J*, vol. 122, no. 7, pp. 474 – 488. 2021.
- [30] P. Forget, C. Khalifa, J. P. Defour, D. Latinne, et al, What is The Normal Value of The Neutrophil-to-Lymphocyte Ratio?, *BMC Research Notes*, vol. 10, issue 1, pp. 1–4. 2017.
- [31] N. I. Alexander, Reference Values of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio and Mean Platelet Volume in Healthy Adults in North Central Nigeria, *Journal of Blood & Lymph*, vol. 6, issue 1, pp. 1-3. 2016.
- [32] D. Serban, N. Papanas, A. M. Dascalu, P. Kempler, et al, 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*, pp. 1-9. 2021.
- [33] Nurahmi, B. Mulyono, Windarwati, The Relationship of Nutrophil-Lymphocyte Ratio and Glycemic Control in Type 2 Diabetes Mellitus Patients, *Indonesian*

- Journal of Clinical Pathology and Medical Laboratory*, vol. 28, issue 1, pp. 14–16. 2021.
- [34] P. Y. Adnyani, N. N. Mahartini, S. Herawati, N. K. Mulyantari, et al, Comparison of Neutrophil to Lymphocyte Ratio (NLR) and Lymphocyte to Monocyte Ratio (LMR) Values in Controlled and Uncontrolled Type 2 Diabetes Mellitus (T2DM) Patient, *Bali Medical Journal*, vol. 10, no. 2, pp. 798–801. 2021.
- [35] M. A. Alfhili, J. Alsughayyir, A. Basudan, H. K. Ghneim, et al, Isolated and Combined Effect of Age and Gender on Neutrophil–Lymphocyte Ratio in the Hyperglycemic Saudi Population. *Medicina (Lithuania)*, vol. 58, no. 8. 2022.
- [36] Z. I. Y. Salduz, A. Ozder, Neutrophil Lymphocyte Ratio as Useful Predictive Tool for Glycaemic Control in Type 2 Diabetes: Retrospective, Single Centre Study in Turkey, *Journal of the Pakistan Medical Association*, vol. 72, no. 6, pp. 1097–1100. 2022.
- [37] M. K. Umarani, K. Sahi, M. Bharatih, Study of Neutrophil-Lymphocyte Ratio (NLR) in Diabetes Mellitus. *Tropical Journal of Pathology and Microbiology*, vol. 6, no. 4, pp. 298–302. 2020.
- [38] M. Hussain, M. Z. M. Babar, L. Akhtar, M. S. Hussain, Neutrophil Lymphocyte Ratio (NLR): A Well Assessment Tool of Glycemic Control in Type 2 Diabetic Patient, *Pak J Med Sci*, vol. 33, no. 6, pp. 1366-1370. 2017.
- [39] G. Chen, C. Tan, X. Liu, Y. Chen, Association Between the Neutrophil-To-Lymphocyte Ratio and Diabetes Secondary to Exocrine Pancreatic Disorders. *Frontiers in Endocrinology*, vol. 13. 2022.
- [41] U. P. Singh, B. V. Singh, P. Jain, M. Garg, Association of HbA1c and Neutrophil-To-Lymphocyte Ratio in Type 2 Diabetic Patients: An Observational Study, *European Journal of Cardiovascular Medicine*, vol. 13, issue 2, pp. 1020-1024. 2023.
- [42] E. N. Almatin, E. D. Woelansari, Suhariyadi, Neutrophil Lymphocyte Ratio (NLR) Value As Inflammation Marker In Ulcer Diabetic Patients With Variation Of Blood Glucose, *The 4th International Conference On Health Polytechnics Of Surabaya (ICOHPS)*, pp. 100-103. 2021.
- [43] A. Fawwad, A. M. Butt, I. A. Siddiqui, M. Khalid, et al, Neutrophil-to-Lymphocyte Ratio and Microvascular Complications in Subjects with Type 2 Diabetes: Pakistan’s Perspective. *Turkish Journal of Medical Sciences*, vol. 48, no. 1, pp. 157–161. 2018.
- [44] M. Mahajan, M. K. Prasad, C. Ashok, R. T. Guria, et al, The Correlation of the Neutrophil-to-Lymphocyte Ratio With Microvascular Complications in Patients With Diabetes Mellitus. *Cureus*, vol. 15, no. 9. 2023.
- [45] T. Xu, Z. Weng, C. Pei, S. Yu, et al, The Relationship between Neutrophil-to-Lymphocyte Ratio and Diabetic Peripheral Neuropathy in Type 2 Diabetes Mellitus. *Medicine (United States)*, vol. 96, no. 45. 2017.
- [46] M. Chen, Y. Zhu, J. Wang, G. Wang, et al, The Predictive Value of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio Levels of Diabetic Peripheral Neuropathy. *Journal of Pain Research*, vol. 14, pp. 2049–2058. 2021.
- [47] J. Teperman, D. Carruthers, Y. Guo, M. P. Barnett, et al, Relationship Between Neutrophil-Lymphocyte Ratio and Severity of Lower Extremity Peripheral Artery Disease. *International Journal of Cardiology*, vol. 228, pp. 201–204. 2017.
- [48] A. R. Shahrabi, G. Arsenault, S. A. Nabipoorashrafi, B. Lucke-Wold, et al, Relationship Between Neutrophil to Lymphocyte Ratio and Diabetic Peripheral Neuropathy: A Systematic Review and Meta-Analysis. *European Journal of Medical Research*, vol. 28, no. 1. 2023.
- [49] M. Sathvik, K. Vuppuluri, P. Dulipala, The Association of the Neutrophil-Lymphocyte Ratio With the Outcome of Diabetic Foot Ulcer. *Cureus*, vol. 15, no. 1. 2023.

- [50] Sanganabasappa, “Neutrophil-To-Lymphocyte Ratio In Diabetes Mellitus Patients With Foot Ulcer-A Case-Control Study”, Dissertation, Rajiv Gandhi University of Health Sciences, Karnataka, Bengaluru, 2018.
- [51] C. Kahraman, G. Yumun, N. K. Kahraman, N. D. Namdar, et al, Neutrophil-to-Lymphocyte Ratio in Diabetes Mellitus Patients With And Without Diabetic Foot Ulcer. *European Journal of Medical Sciences*, vol. 1 no. 1, pp. 8-13. 2014.
- [52] T. M. Zaid, D. R, N. Maheshwari, V. S, Role of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Diabetic Ulcer Patients, *International Journal of Science and Research*, vol. 12, issue 1, pp. 802-806. 2022.
- [53] B. Sun, Y. Chen, Y. Ma, Y. Fu, et al, Clinical Value of Neutrophil-to Lymphocyte Ratio and Prognostic Nutritional Index on Prediction of Occurrence and Development of Diabetic Foot-Induced Sepsis. *Frontiers in Public Health*, vol. 11, no. 1181880, pp. 1-7. 2023.
- [54] T. Demirdal, P. Sen, The Significance Of Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio And Lymphocyte-Monocyte Ratio In Predicting Peripheral Arterial Disease, Peripheral Neuropathy, Osteomyelitis And Amputation In Diabetic Foot Infection, *Diabetes Research and Clinical Practice*, vol. 144, pp. 118–125. 2018.
- [55] W. Chen, K. Chen, Z. Xu, Y. Hu, Y., et al, Neutrophil-To-Lymphocyte Ratio and Platelet-To-Lymphocyte Ratio Predict Mortality In Patients With Diabetic Foot Ulcers Undergoing Amputations, *Diabetes, Metabolic Syndrome and Obesity Target and Therapy*, vol. 14, pp. 821–829. 2021.
- [56] W. S. Pierre-Louis, J. Bath, S. Mikkilineni, M. C. Scott, et al, Neutrophil to Lymphocyte Ratio as a Predictor of Outcomes after Amputation, *Annals of Vascular Surgery*, vol. 54, pp. 84–91. 2019.
- [57] S. Xu, Y. Wang, Z. Hu, L. Ma, et al, Effects Of Neutrophil-To-Lymphocyte Ratio, Serum Calcium, And Serum Albumin On Prognosis In Patients With Diabetic Foot, *International Wound Journal*, vol. 20, issue 5, pp. 1638–1646. 2023.
- [58] M. A. Eren, A. E. Güneş, İ. Kırhan, T. Sabuncu, The Role Of The Platelet-To-Lymphocyte Ratio And Neutrophil-to-Lymphocyte Ratio In The Prediction Of Length And Cost Of Hospital Stay In Patients With Infected Diabetic Foot Ulcers: A Retrospective Comparative Study, *Acta Orthop et Traumatol Turc*, vol. 54, issue 2, pp. 127–131. 2020.
- [59] D. Syauta, Mulawardi, Prihantono, J. Hendarto, et al, Risk Factors Affecting The Degree of Diabetic Foot Ulcers According to Wagner Classification in Diabetic Foot Patients, *Medicina Clinica Practica*, vol. 4, pp. 1-3. 2021.
- [60] Y. Zhu, H. Xu, Y. Wang, X. Feng, et al, Risk factor analysis for diabetic foot ulcer-related amputation including Controlling Nutritional Status score and neutrophil-to-lymphocyte ratio. *International Wound Journal*, vol. 20, pp. 4050-4060. 2023.