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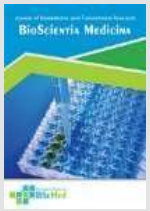

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Neutrophil-Lymphocyte Ratio as a Novel Biomarker for Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients: A Cross-Sectional Study

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A B S T R A C T

Background: Early detection of diabetic nephropathy (DN) is crucial to prevent progression to end-stage renal disease. The gold standard for diagnosing DN involves urine microalbumin testing and renal biopsy. However, the availability of these diagnostic tools is limited in many healthcare facilities across Indonesia. Consequently, there is a pressing need for an alternative examination that is readily accessible and can effectively monitor the progression of DN. **Methods:** This cross-sectional study was conducted at Dr. Mohammad Hoesin General Hospital, Palembang, from February 2024 to May 2024. The study aimed to investigate the correlation between neutrophil-lymphocyte ratio (NLR) and urinary albumin levels in type 2 diabetes mellitus (DM) patients. NLR, calculated from complete blood counts, has emerged as a potential inflammatory marker for various conditions. A total of 65 participants diagnosed with type 2 DM were enrolled in the study. Data analysis involved Spearman's correlation test to assess the relationship between NLR and urinary albumin levels. **Results:** The majority of the 65 subjects were female (58.5%). The study found that 44 subjects had normoalbuminuria, 18 had microalbuminuria, and 3 had macroalbuminuria. A significant positive correlation was observed between NLR and albuminuria levels in type 2 DM patients ($r = 0.795$; $p < 0.01$). **Conclusion:** The study's findings suggest that NLR is a potential cost-effective biomarker for the early detection of DN in type 2 DM patients, especially in resource-limited settings. Further large-scale studies are recommended to validate these findings and establish specific NLR thresholds for predicting DN progression.

1. Introduction

Diabetes mellitus (DM) is a prevalent metabolic disorder characterized by hyperglycemia and chronic inflammation, often leading to microangiopathic complications such as diabetic nephropathy (DN). This chronic disease is a global health concern that affects millions of people worldwide. It is characterized by elevated blood glucose levels resulting from defects in insulin secretion, insulin action, or both. The prevalence of DM has been steadily increasing over the past few decades, primarily due to lifestyle factors such as poor diet, lack of physical activity, and obesity. DM is associated with a low-grade chronic inflammatory state in peripheral tissues, including

adipose tissue, liver, and muscle. The persistent hyperglycemia in DM patients triggers a cascade of events, including the activation of protein kinase, increased production of reactive oxygen species (ROS), and the formation of advanced glycosylation end products (AGEs). These changes can lead to both macrovascular and microvascular complications, with diabetic nephropathy (DN) being one of the most common microvascular complications. DN is a major complication of DM and a leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide. It is estimated that approximately 50% of individuals with DM develop CKD. In Indonesia, DN ranks second only to hypertensive kidney disease as the primary cause of kidney failure. The inflammatory process associated with DM involves the activation of both innate and adaptive immune responses, along with an increase in pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-18, interferon-γ (IFN-γ), and tumor necrosis factor-alpha (TNF-α). This chronic inflammation can lead to structural damage in the kidneys, including mesangial cell hypertrophy, glomerular and tubular basement membrane thickening, glomerulosclerosis, and tubulointerstitial fibrosis. These changes ultimately impair glomerular filtration, resulting in the detection of albumin in the urine, a key indicator of kidney damage.[1-4]

Early detection of DN is essential to prevent or delay its progression. Timely intervention can significantly improve patient outcomes and reduce the risk of developing ESRD. The gold standard for diagnosing DN involves urine microalbumin testing and renal biopsy. Urine microalbumin testing is used to detect the presence of albumin in the urine, which is an early sign of kidney damage. Renal biopsy is an invasive procedure that involves removing a small tissue sample from the kidney for examination under a microscope. While renal biopsy is considered the most accurate method for diagnosing DN, it is not without risks and complications. However, these diagnostic procedures are not universally available in all healthcare facilities, particularly in resource-limited settings. The availability of these diagnostic tools is limited in many healthcare facilities across Indonesia. Therefore, there is a critical need for a simple, cost-effective, and easily accessible alternative test to identify individuals at risk of developing DN.[5-7]

The neutrophil-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count to absolute lymphocyte count from a complete blood count, has emerged as a potential marker of systemic inflammation in various conditions. NLR reflects the balance between neutrophils, key players in the innate immune response, and lymphocytes, which are central to the adaptive immune response. Neutrophils are the most abundant type of white blood cell and play a crucial role in the body's defense against infection and injury. Lymphocytes, on the other hand, are responsible for recognizing and destroying specific pathogens. Several studies have suggested that NLR may be a useful predictor of DN in type 2 DM patients. NLR has been shown to be elevated in patients with various inflammatory conditions, including cardiovascular disease, cancer, and autoimmune diseases. Recent studies have also suggested that NLR may be a useful biomarker for the early detection of DN.[8-10] This cross-sectional study aimed to investigate the correlation between NLR and urinary albumin levels in type 2 DM patients at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia.

2. Methods

This cross-sectional study was conducted at the outpatient clinic of the Department of Internal Medicine, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, from February 2024 to May 2024. Cross-sectional studies are a type of observational study that collects data at a single point in time. In this study, the cross-sectional design was chosen to investigate the correlation between NLR and urinary albumin levels in type 2 DM patients at a specific point in time. Dr. Mohammad Hoesin General Hospital is a tertiary care hospital located in Palembang, the capital city of South Sumatra province in Indonesia. The hospital serves a large population

and provides a wide range of medical services, including outpatient clinics, inpatient wards, and specialized care units. The outpatient clinic of the Department of Internal Medicine is a busy clinic that provides care to patients with a variety of medical conditions, including DM.

The study included 65 patients diagnosed with type 2 DM who met the inclusion and exclusion criteria. The inclusion criteria were; Age ≥ 18 years; Diagnosed with type 2 DM; Hyperglycemia with HbA1c > 7.5%; Willing to participate and sign the informed consent form. The exclusion criteria were; Acute coronary artery disease, acute heart failure, acute cerebrovascular disease, and uncontrolled hypertension; Conditions affecting urine protein excretion, such as nephrotic/nephritic syndrome, urolithiasis, urinary tract infection (UTI), and other acute infections; Hematologic diseases, malignancies, and medications known to alter white blood cell count (e.g., chemotherapy, long-term steroid use); Pregnancy; Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 without albuminuria or an increase in serum creatinine ≥ 1.5 times the baseline within the previous 7 days (acute kidney injury). These inclusion and exclusion criteria were established to ensure that the study population consisted of individuals with type 2 DM who were at risk of developing DN while excluding those with other medical conditions that could potentially confound the results of the study.

Data were collected through patient interviews, physical examinations, and laboratory tests. Patient interviews were conducted to gather information on demographic characteristics, medical history, and lifestyle factors. Physical examinations were performed to assess overall health status and identify any signs or symptoms of complications related to DM. Laboratory tests were conducted to measure various parameters, including blood glucose levels, lipid profile, kidney function, and inflammatory markers. The following variables were assessed; Demographic data: Age, Gender; Clinical data: Duration of DM, complications (e.g., neuropathy, retinopathy), comorbidities (e.g., hypertension, dyslipidemia); Laboratory data: Complete blood count (including neutrophil and lymphocyte counts), NLR, fasting blood glucose, HbA1c, lipid profile, serum creatinine, eGFR, urinary albumin-to-creatinine ratio (UACR).

NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from complete blood counts. The absolute neutrophil count and absolute lymphocyte count were determined from the complete blood count, which is a routine blood test that provides information on the different types of blood cells.

Urinary albumin levels were assessed using UACR from spot urine samples. UACR is a measure of the amount of albumin in the urine, normalized to the amount of creatinine. Albumin is a protein that is normally found in the blood but can leak into the urine in cases of kidney damage. Creatinine is a waste product that is produced by the muscles and excreted in the urine. UACR is considered a more accurate measure of urinary albumin levels than measuring albumin alone, as it accounts for variations in urine concentration. The following categories were used to classify albuminuria; Normoalbuminuria: UACR < 30 mg/g; Microalbuminuria: UACR 30-300 mg/g; Macroalbuminuria: UACR > 300 mg/g.

Data were analyzed using SPSS version 26.0 for Windows. SPSS is a statistical software package that is widely used in healthcare research. It provides a range of tools for data analysis, including descriptive statistics, correlation analysis, and regression analysis. Descriptive statistics were used to summarize the characteristics of the study participants. Descriptive statistics are used to describe the basic features of a dataset. They provide information on the distribution of the data, including measures of central tendency (e.g., mean, median) and measures of dispersion (e.g., standard deviation, range). The correlation between NLR and UACR was assessed using Spearman's correlation test. Spearman's correlation test is a non-parametric test that is used to assess the relationship between two variables. It is used when the data do not meet the

assumptions of a parametric test, such as the Pearson correlation test. A p-value < 0.05 was considered statistically significant. The p-value is a measure of the probability of obtaining the observed results if there is no true relationship between the variables. A p-value of less than 0.05 indicates that there is a less than 5% chance of obtaining the observed results if there is no true relationship between the variables. This is generally considered to be strong evidence of a relationship between the variables.

The study protocol was approved by the ethics committee of Dr. Mohammad Hoesin General Hospital, Palembang (FR.03/D.XVIII.1.21/20/2024). All participants provided written informed consent before enrollment in the study.

3. Results

Table 1 provides a detailed overview of the characteristics of the 65 participants enrolled in the study investigating the correlation between NLR and urinary albumin levels in type 2 DM patients. The participant pool was fairly balanced between males (41.5%) and females (58.5%), suggesting that the study captured a representative sample of the type 2 DM population in terms of gender distribution. The median age was 60 years, with a fairly even split between those above and below this age. This indicates that the study included both younger and older adults with type 2 DM, allowing for potential analysis of age-related variations in NLR and albuminuria. The median duration of diabetes was 5 years, with a larger proportion (69.2%) having had diabetes for 5 years or less. This suggests that the study primarily focused on individuals who were relatively early in their diabetes journey, which is crucial for early detection of DN. The majority of participants fell into the normal weight (44.6%) and overweight (52.3%) categories. This is consistent with the global trend of increasing obesity rates among individuals with type 2 DM. A very small percentage (3.1%) were underweight, highlighting that malnutrition is less common in this population. Diabetic neuropathy was the most prevalent complication (61.5%), followed by diabetic nephropathy (29.2%) and retinopathy (16.9%). This emphasizes the multi-systemic nature of diabetes and the potential for microvascular complications. The low prevalence of coronary artery disease (CAD) and cerebrovascular disease (CVD) (3.1% and 1.5% respectively) could be attributed to the exclusion criteria, which aimed to minimize confounding factors that could influence NLR. Dyslipidemia was the most common comorbidity (67.7%), followed by Hypertension (41.5%). These conditions are frequently associated with type 2 DM and contribute to the increased risk of cardiovascular complications. Hypertensive Heart Disease was present in a small proportion (9.2%) of participants. The provided data shows the mean and standard deviation (SD) or median and range (Min-Max) for various laboratory parameters. This information offers insights into the overall metabolic and inflammatory status of the participants. The median NLR was 1.88, with a range of 1.20 to 3.47. This provides a baseline for comparing NLR across different categories of albuminuria. Other laboratory values, such as HbA1c, Fasting Blood Glucose, Lipid profile, Serum Creatinine, and eGFR, provide a comprehensive picture of the participants' glycemic control, lipid metabolism, and kidney function.

Table 2 presents a breakdown of the distribution of participants across different NLR and albuminuria categories, offering valuable insights into the potential relationship between these two variables; NLR < 2.0: The majority of participants with NLR < 2.0 (47.7%) had normoalbuminuria, indicating normal urinary albumin levels. This suggests that a lower NLR might be associated with a lower risk of diabetic nephropathy. A small proportion (6.2%) exhibited microalbuminuria, suggesting early signs of kidney damage. No participants in this NLR category had macroalbuminuria, which is a more severe form of albuminuria; NLR 2.0 - 3.0: A smaller proportion of participants fell within this NLR range. Both normoalbuminuria (20.0%) and microalbuminuria (18.5%) were observed in this group, with

microalbuminuria being slightly more prevalent. This indicates that as NLR increases, the risk of microalbuminuria might also increase. Macroalbuminuria was present in a very small proportion (1.5%) of participants with NLR between 2.0 and 3.0; NLR > 3.0: No participants with NLR > 3.0 had normoalbuminuria. Microalbuminuria and macroalbuminuria were observed in a small proportion (3.1% each) of participants with NLR > 3.0. This suggests that higher NLR values might be associated with a higher risk of more severe albuminuria.

Table 1. Participant characteristics.

Characteristic	Frequency (Percentage); Median (Min-Max); Mean±SD
Gender	
Male	27 (41.5%)
Female	38 (58.5%)
Age (years)	
< 60	31 (47.7%)
≥ 60	34 (52.3%)
Duration of DM (years)	
≤ 5	20 (30.8%)
> 5	45 (69.2%)
BMI (kg/m²)	
Underweight (< 18.5)	2 (3.1%)
Normal weight (18.5 - 24.9)	29 (44.6%)
Overweight (25.0 - 29.9)	34 (52.3%)
Diabetic complications	
Diabetic nephropathy	19 (29.2%)
Diabetic neuropathy	40 (61.5%)
Retinopathy	11 (16.9%)
Coronary artery disease (CAD)	2 (3.1%)
Cerebrovascular disease (CVD)	1 (1.5%)
Comorbidities	
Hypertension	27 (41.5%)
Dyslipidemia	44 (67.7%)
Hypertensive heart disease	6 (9.2%)
Laboratory data	
Leukocytes (cells/mm³)	8520 (5210-10570)
Neutrophils (%)	58.87 ± 4.74
Lymphocytes (%)	31.00 (20.00-40.00)
NLR	1.88 (1.20-3.47)
HbA1c (%)	8.30 (7.60-13.10)
Fasting blood glucose (mg/dL)	181.00 (85.00-330.00)
Total cholesterol (mg/dL)	172.00 (109.00-286.00)
HDL cholesterol (mg/dL)	45.00 (11.00-57.00)
LDL cholesterol (mg/dL)	117.00 (68.00-221.00)
Triglycerides (mg/dL)	164.00 (55.00-480.00)
Serum creatinine (mg/dL)	0.94 ± 0.21
eGFR (ml/min/1.73 m²)	78.00 (45.00-110.00)
SGOT (U/L)	20.55 ± 4.21
SGPT (U/L)	23.00 (11.00-31.00)

Table 2. NLR and albuminuria.

NLR	Albuminuria category	Number (%)	Median NLR (Min-Max)
< 2.0	Normoalbuminuria	31 (47.7%)	1.73 (1.20-1.97)
	Microalbuminuria	4 (6.2%)	1.85 (1.68-1.99)
	Macroalbuminuria	0 (0%)	-
2.0 - 3.0	Normoalbuminuria	13 (20.0%)	2.38 (2.01-2.83)
	Microalbuminuria	12 (18.5%)	2.33 (2.07-2.81)
	Macroalbuminuria	1 (1.5%)	2.94
>3.0	Normoalbuminuria	0 (0%)	-
	Microalbuminuria	2 (3.1%)	3.21 (3.10-3.32)
	Macroalbuminuria	2 (3.1%)	3.28 (3.24-3.47)

Figure 1 visually represents the correlation analysis performed to assess the relationship between NLR and UACR in type 2 DM patients; Scatter Plot: Each point on the scatter plot represents an individual participant in the study, with their NLR value plotted on the x-axis and their UACR value on the y-axis. The distribution of the points suggests a positive trend, meaning that as NLR increases, UACR tends to increase as well. This indicates a potential association between higher NLR values and higher levels of albuminuria; Trend Line: The upward-sloping trend line further emphasizes the positive relationship between NLR and UACR. This line is a visual representation of the linear regression equation (y=-2.72E2+1.73E2*x) that best fits the data points. The fact that many data points cluster closely around the trend line suggests that the linear model is a good fit for the data, indicating a strong linear relationship between the two variables; Correlation Coefficient (r = 0.795): The correlation coefficient (r) quantifies the strength and direction of the linear relationship between NLR and UACR. In this case, r = 0.795 indicates a strong positive correlation. This means that higher NLR values are strongly associated with higher UACR values. The positive sign confirms the direction of the relationship observed in the scatter plot – as NLR increases, UACR also tends to increase; p-value ($p < 0.01$): The p-value represents the probability of observing such a strong correlation by chance alone if there were no true relationship between NLR and UACR. A p-value of less than 0.01 indicates that it is highly unlikely to observe this correlation by chance alone. This provides strong evidence to support the conclusion that there is a statistically significant positive correlation between NLR and UACR in type 2 DM patients; R-squared (R^2 Linear = 0.662): The R-squared value indicates the proportion of variance in UACR that can be explained by the variance in NLR. In this case, $R^2 = 0.662$ suggests that approximately 66.2% of the variability in UACR can be explained by the variability in NLR. This indicates that NLR is a significant predictor of UACR in this population.

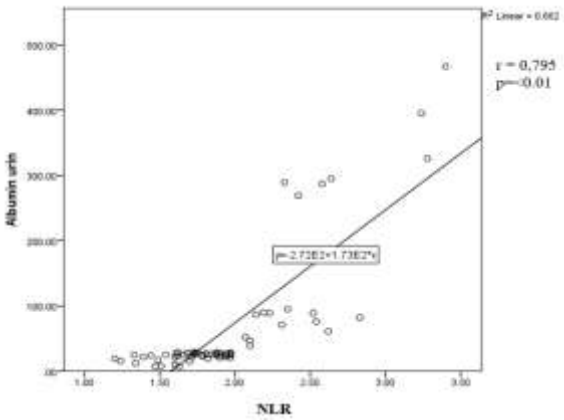

Figure 1. Correlation Analysis. Spearman's correlation analysis revealed a strong positive correlation between NLR and UACR ($r = 0.795$, $p < 0.01$).

4. Discussion

This cross-sectional study embarked on a journey to unravel the intricate relationship between the neutrophil-lymphocyte ratio (NLR) and urinary albumin levels in individuals navigating the complexities of type 2 diabetes mellitus (T2DM). The bedrock of our findings is the revelation of a robust positive correlation between NLR and urinary albumin-to-creatinine ratio (UACR) in this patient population. This correlation carries profound implications, suggesting that NLR could potentially serve as a readily accessible and cost-effective biomarker for the early detection of diabetic nephropathy (DN), a severe microvascular complication of diabetes that can ultimately culminate in end-stage renal disease (ESRD). The true significance of this finding lies in its potential to revolutionize the diagnosis and management of DN, particularly in resource-constrained environments. Currently, the gold standard for diagnosing DN involves urine microalbumin testing and renal biopsy. However, these diagnostic modalities may not be universally accessible in all healthcare settings, particularly in developing countries grappling with limited resources. In stark contrast, NLR emerges as a simple, cost-effective, and readily available test that can be seamlessly integrated into routine clinical practice. By harnessing the power of NLR as a biomarker, clinicians may be empowered to identify individuals at risk of developing DN at an earlier stage, paving the way for timely intervention and potentially delaying or even preventing the insidious progression of this debilitating disease. Our study unearthed a compelling and statistically significant positive correlation between NLR and UACR in T2DM patients. This signifies that as NLR escalates, the level of albuminuria, as meticulously quantified by UACR, also exhibits an upward trend. This observation is pivotal because it hints at a potential nexus between systemic inflammation, as mirrored by NLR, and the pathogenesis of DN, a major microvascular complication that casts a long shadow over the lives of individuals with diabetes. To truly appreciate the gravity of this finding, we must delve into the intricate pathophysiology of DN. DN is characterized by a gradual deterioration of kidney function, primarily attributed to damage to the glomeruli, the kidney's filtering units. An imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates, leading to cellular damage. A complex biological response to harmful stimuli, characterized by the activation of various inflammatory pathways and the recruitment of immune cells. A series of molecular events that amplify the inflammatory response, leading to the production of pro-inflammatory cytokines and chemokines. These processes culminate in the recruitment and activation of neutrophils, key players in the inflammatory response, leading to an elevation in NLR. Neutrophils, once activated, unleash a torrent of pro-inflammatory cytokines and reactive oxygen species, which inflict further damage upon the glomeruli and tubules, ultimately culminating in albuminuria, the leakage of albumin, a protein, into the urine. This leakage serves as an early harbinger of DN, signaling the insidious onset of kidney dysfunction. The strong positive correlation between NLR and UACR, therefore, underscores the intimate link between systemic inflammation, as reflected by NLR, and the development of DN. This correlation opens up exciting new avenues for utilizing NLR as a potential biomarker for the early detection of DN, allowing for timely intervention and potentially altering the disease's trajectory. The compelling correlation between NLR and UACR strongly advocates for the potential utility of NLR as a biomarker for the early detection of DN. A biomarker, in essence, is a measurable indicator of a biological state or condition. In the context of DN, NLR may serve as a sentinel, signaling the presence of underlying inflammatory processes that contribute to the disease's pathogenesis. Early detection of DN is of paramount importance, as it enables timely intervention and management, which can significantly delay or even prevent the relentless progression of the disease to ESRD. ESRD, the final stage of kidney failure,

necessitates dialysis or kidney transplantation for survival, underscoring the critical need for early detection and intervention. NLR, with its strong correlation with UACR, holds immense promise as a biomarker for the early detection of DN. By identifying individuals at risk of developing DN at an earlier stage, clinicians can initiate appropriate interventions. Maintaining blood glucose levels within a healthy range to minimize hyperglycemia-induced damage. Controlling blood pressure to reduce stress on the kidneys and prevent further damage. Encouraging healthy lifestyle choices, including a balanced diet, regular exercise, and weight management, to improve overall health and reduce the risk of complications. These interventions, when implemented early, can help mitigate the risk of disease progression and preserve kidney function, ultimately improving the quality of life for individuals with diabetes. The significance of NLR as a potential biomarker for DN is particularly amplified in resource-limited settings, where access to the gold standard diagnostic tools for DN, such as urine microalbumin testing and renal biopsy, may be severely constrained. These diagnostic modalities often come with a hefty price tag, necessitate specialized equipment and expertise, and may not be readily available in all healthcare facilities, particularly in developing countries grappling with limited resources and infrastructure. In these resource-constrained environments, NLR emerges as a beacon of hope, offering a simple, cost-effective, and readily available alternative that can be seamlessly incorporated into routine clinical practice. NLR can be readily calculated from a complete blood count, a routine blood test that is widely accessible in most healthcare settings, even in those with limited resources. This accessibility makes NLR an invaluable tool for the early detection and management of DN in resource-limited settings, where the burden of diabetes is often disproportionately high. By enabling early detection and intervention, NLR can play a pivotal role in mitigating the devastating consequences of DN in these vulnerable populations. The integration of NLR as a biomarker for DN holds the potential to revolutionize the diagnosis and management of this serious complication. By facilitating the identification of individuals at risk of developing DN at an earlier stage, clinicians can proactively initiate timely interventions, such as intensive glycemic control, rigorous blood pressure management, and lifestyle modifications. These interventions, when implemented early, can significantly retard the progression of DN and diminish the risk of ESRD, ultimately improving patient outcomes and quality of life.[11-13]

The findings of this study resonate with a burgeoning body of literature that points towards a compelling link between NLR and DN. Several previous studies have documented a positive association between NLR and DN in T2DM patients, reinforcing the notion that NLR is not merely an isolated marker but rather an integral player in the complex pathophysiology of DN. These studies have consistently shown that NLR is significantly higher in T2DM patients with DN compared to those without DN, underscoring its potential as a key indicator of disease presence and progression. Furthermore, NLR has demonstrated its prowess as an independent predictor of DN, suggesting that its association with DN is not merely a bystander effect but rather a significant contributor to the disease process. This predictive capability has far-reaching implications for clinical practice, as it opens up new avenues for risk stratification and early intervention in individuals with T2DM. The underlying mechanisms that weave together NLR and DN are likely intertwined with the intricate role of inflammation in the pathogenesis of DN. Chronic hyperglycemia, a defining characteristic of diabetes, sets off a chain reaction of events that fuel inflammation and contribute to the development of DN. Chronic hyperglycemia disrupts the delicate balance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms, leading to oxidative stress. ROS, when left unchecked, can wreak havoc on cellular components, including proteins, lipids, and DNA, contributing to cellular dysfunction and damage.

Hyperglycemia also activates various inflammatory pathways, setting the stage for a chronic inflammatory state. These pathways involve a complex interplay of signaling molecules, immune cells, and pro-inflammatory mediators, all of which contribute to the inflammatory milieu that characterizes DN. The inflammatory cascade culminates in the recruitment and activation of neutrophils, key players in the innate immune response. Neutrophils, when activated, release a barrage of pro-inflammatory cytokines and reactive oxygen species, further exacerbating the inflammatory response and contributing to glomerular and tubular damage. The cumulative effect of these inflammatory processes is damage to the glomeruli and tubules, the functional units of the kidneys responsible for filtration and reabsorption. This damage disrupts the integrity of the glomerular filtration barrier, leading to albuminuria, the leakage of albumin, a protein, into the urine. Albuminuria serves as an early indicator of DN, signaling the insidious onset of kidney dysfunction. NLR, as the ratio of neutrophils to lymphocytes, reflects the delicate balance between these two key players in the immune system. Neutrophils, the first responders to infection and injury, are potent mediators of inflammation. Lymphocytes, on the other hand, play a central role in the adaptive immune response, providing long-term immunity and regulating the inflammatory response. In the context of DN, an elevated NLR signifies a shift towards a pro-inflammatory state, with an increase in neutrophils and a relative decrease in lymphocytes. This imbalance reflects the chronic inflammatory processes that drive the development and progression of DN. The convergence of evidence from this study and previous research underscores the importance of NLR as a potential game-changer in the management of DN. By recognizing NLR as a reflection of systemic inflammation and a key player in the pathogenesis of DN, clinicians can leverage this readily available marker to identify individuals at risk and initiate timely interventions.[14-16]

The findings of this study have important implications for clinical practice. NLR, being a simple, cost-effective, and readily available test, can be easily integrated into routine clinical practice for the early detection of DN in T2DM patients. By identifying individuals at risk of developing DN earlier, clinicians can initiate timely interventions, such as intensive glycemic control, blood pressure management, and lifestyle modifications, to potentially delay or prevent the progression of the disease. The results of this study suggest that NLR can be a valuable tool for the early detection of DN in T2DM patients. NLR is a simple, cost-effective, and readily available test that can be easily incorporated into routine clinical practice. By using NLR as a biomarker, clinicians may be able to identify individuals at risk of developing DN earlier, allowing for timely intervention and potentially delaying or preventing the progression of the disease. Incorporate NLR calculation into routine blood tests for T2DM patients, especially during their initial assessment and follow-up visits. This can help identify individuals with elevated NLR, indicating an increased risk of DN. Determine the optimal frequency of NLR screening based on individual risk factors and disease progression. For instance, patients with existing microalbuminuria or those with multiple risk factors for DN may benefit from more frequent NLR monitoring, perhaps every 3-6 months. Conversely, patients with low risk profiles and well-controlled diabetes may only require annual screening. This frequency can be further adjusted based on the individual's response to treatment and any changes in their clinical status. Educate patients about the significance of NLR and its role in DN risk assessment. Explain how NLR reflects systemic inflammation and its potential link to kidney damage. Encourage patients to actively participate in their care by understanding their NLR values and adhering to recommended interventions. This may involve providing educational materials, such as brochures or online resources, and dedicating time during consultations to address patient questions and concerns. It is also important to emphasize the

importance of lifestyle modifications and adherence to treatment plans in managing NLR and reducing the risk of DN. Use NLR in conjunction with other risk factors, such as UACR, HbA1c, and blood pressure, to stratify patients based on their risk of developing DN. This can help prioritize patients for further investigation and management. Develop comprehensive risk assessment tools that incorporate NLR and other relevant risk factors to provide a more accurate assessment of DN risk. These tools could utilize scoring systems or algorithms to categorize patients into different risk levels based on their individual profiles. This stratification can help identify high-risk individuals who may benefit from more intensive monitoring and early intervention strategies. Use risk stratification to tailor management strategies to individual patient needs. Patients with high-risk profiles may require more aggressive interventions, such as early initiation of renin-angiotensin-aldosterone system (RAAS) inhibitors or closer monitoring for disease progression. Conversely, patients with low-risk profiles may benefit from less intensive monitoring and lifestyle interventions. This individualized approach can optimize resource allocation and improve patient outcomes. For patients with elevated NLR and other risk factors for DN, initiate timely interventions, such as intensive glycemic control, blood pressure management, and lifestyle modifications. This can help slow the progression of DN and reduce the risk of complications. Optimize glycemic control through medication adjustments, insulin therapy, and patient education on self-management strategies. Emphasize the importance of achieving and maintaining target HbA1c levels to minimize hyperglycemia-induced kidney damage. This may involve individualized medication regimens, blood glucose monitoring, and dietary counseling. Additionally, continuous glucose monitoring (CGM) can provide valuable real-time data on glucose fluctuations and help patients make informed decisions about their diabetes management. Achieve and maintain optimal blood pressure levels through lifestyle modifications and appropriate antihypertensive medications. Target blood pressure goals should be individualized based on patient characteristics and comorbidities. RAAS inhibitors are often the preferred first-line therapy for DN due to their renoprotective effects. Other antihypertensive medications, such as calcium channel blockers and beta-blockers, may also be considered based on individual needs. Encourage healthy lifestyle choices, including a balanced diet, regular exercise, and weight management, to improve overall health and reduce the risk of complications. Provide patients with practical guidance and support to implement these lifestyle changes. This may involve referral to dieticians, exercise programs, or support groups. Additionally, technology-based interventions, such as mobile health apps and wearable devices, can provide personalized support and motivation for lifestyle changes. Use NLR as a monitoring tool to assess the effectiveness of interventions and track the progression of DN. Changes in NLR over time can provide valuable information about the disease course and response to treatment. Monitor NLR trends over time to assess the impact of interventions and identify any signs of disease progression. A decreasing NLR trend may suggest a positive response to treatment and reduced inflammation, while an increasing trend may warrant further investigation and treatment adjustments. Regular monitoring of NLR can help clinicians identify subtle changes in disease activity and adjust treatment strategies accordingly. Use NLR monitoring to guide treatment adjustments and optimize patient care. For instance, if NLR remains elevated despite initial interventions, consider intensifying therapy or exploring alternative treatment options. NLR can serve as an objective measure to assess the effectiveness of different interventions and guide clinical decision-making. This can lead to more personalized and effective treatment plans. Identify individuals at risk of developing DN at an earlier stage, even before the onset of albuminuria. This allows for proactive intervention and potentially prevents irreversible kidney damage. Early detection is crucial for preserving kidney function and improving long-term

outcomes for individuals with diabetes. Stratify patients based on their risk of developing DN, allowing for personalized management strategies. This ensures that patients receive the most appropriate care based on their individual needs and risk profiles. Personalized care can lead to better treatment adherence, improved disease control, and reduced healthcare costs. Initiate timely interventions to slow the progression of DN and reduce the risk of complications. Early intervention can significantly improve long-term outcomes and prevent the need for dialysis or kidney transplantation. Timely intervention can also help preserve quality of life and reduce the economic burden associated with DN. Utilize a cost-effective and readily available test to improve the management of DN. NLR can be easily calculated from routine blood tests, making it a cost-effective tool for widespread implementation. This can be particularly beneficial in resource-constrained settings where access to specialized diagnostic tests may be limited. Potentially delay or prevent the progression of DN, improving patient outcomes and quality of life. By preserving kidney function and preventing complications, NLR integration can contribute to better overall health and well-being for individuals with diabetes. Further research is needed to establish specific NLR thresholds for predicting DN progression and guiding clinical decision-making. Optimal NLR cut-off values may vary depending on patient populations and clinical settings. Large-scale studies with diverse populations are needed to determine the most appropriate NLR thresholds for different risk categories. NLR can be influenced by various factors, such as infections, medications, and other inflammatory conditions. Clinicians need to consider these factors when interpreting NLR values and avoid attributing elevated NLR solely to DN risk. Careful clinical assessment and consideration of the patient's overall health status are crucial for accurate interpretation of NLR values. Integrating NLR into routine clinical practice may require adjustments to existing workflows and protocols. Healthcare providers may need training on NLR calculation, interpretation, and integration into clinical decision-making. This may involve developing educational programs and providing resources to support healthcare providers in implementing NLR in their practice. Ensure standardization of NLR measurement across different laboratories to ensure consistency and comparability of results. Standardized protocols for blood collection, processing, and analysis are crucial to minimize variability and ensure accurate NLR values. This may involve establishing quality control measures and inter-laboratory comparisons to ensure consistency in NLR reporting. Conduct further clinical validation studies in diverse populations to assess the generalizability of NLR as a biomarker for DN. This will help determine the applicability of NLR across different ethnicities, age groups, and disease severities. This will ensure that NLR is a reliable and valid tool for DN risk assessment in all patient populations.[17-20]

5. Conclusion

Our findings highlight a significant positive correlation between NLR and urinary albumin-to-creatinine ratio (UACR) in this patient population. This correlation holds substantial implications, suggesting that NLR could potentially function as a readily available and cost-effective biomarker for the early detection of diabetic nephropathy (DN), a severe microvascular complication of diabetes that can ultimately lead to end-stage renal disease (ESRD). The primary importance of this finding lies in its potential to transform the diagnosis and management of DN, particularly in resource-limited settings. In contrast to the current gold standard for diagnosing DN, which involves urine microalbumin testing and renal biopsy, NLR offers a simple, cost-effective, and readily available test that can be easily integrated into routine clinical practice. By utilizing NLR as a biomarker, clinicians may be able to identify individuals at risk of developing DN at an earlier stage, enabling timely intervention and potentially delaying or even preventing the progression of this serious complication. Our study revealed a strong and

statistically significant positive correlation between NLR and UACR in T2DM patients. This observation indicates a potential link between systemic inflammation, as reflected by NLR, and the development of DN. The strong positive correlation between NLR and UACR underscores the close association between systemic inflammation and the development of DN, opening up exciting possibilities for utilizing NLR as a potential biomarker for the early detection of DN. Furthermore, NLR holds significant promise as a biomarker for the early detection of DN, particularly in resource-limited settings where access to traditional diagnostic tools may be restricted. NLR's accessibility and strong correlation with UACR position it as a valuable tool for the early detection and management of DN, potentially mitigating the severe consequences of DN in vulnerable populations.

6. References

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