



Correlation of HbA1c levels and neutrophil-to-lymphocyte ratio (NLR) with wagner grade of diabetic foot ulcers in type ii diabetes mellitus patients undergoing treatment at Ibnu Sina Hospital in 2023

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ABSTRACT

Diabetes Mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or insulin resistance. HbA1c levels can reflect long-term glycemic control, while the neutrophil-to-lymphocyte ratio (NLR) serves as an inflammatory biomarker associated with disease severity in type II DM, including diabetic foot. This study is a descriptive analytic observational study with a cross-sectional design aimed at analyzing the relationship between HbA1c levels and NLR with Wagner's grading of diabetic foot ulcers in type II diabetes mellitus patients. Among 34 diabetic foot patients, the majority were over 50 years old (94.1%), with a higher proportion of females (55.9%), an average HbA1c level of 9.33, and an average NLR of 9.31, indicating variations in glycemic control and systemic inflammation in Ibnu Sina Hospital in January until September 2023. Wagner's ulcer grade ranged from 2 to 4, with an average of 2.82, reflecting moderate to severe severity. Correlation analysis showed that HbA1c levels ($r = 0.523$, $p = 0.002$) and NLR ($r = 0.602$, $p = 0.000$) had a significant and positive relationship with diabetic ulcer severity. The study results indicate a significant correlation between HbA1c levels and NLR with Wagner's grading of diabetic foot ulcers, where higher ulcer severity is associated with increased HbA1c and NLR levels due to greater insulin resistance.

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1. Introduction

Diabetes Mellitus (DM) is an endocrine disorder characterized by relative or absolute insulin deficiency due to dysfunction or damage to pancreatic β -cells. DM is a global health issue, with the number of cases among individuals aged 20-79 estimated at 536.6 million (10.5% of the global population) in 2021, projected to rise to 783.2 million (12.2%) by 2045 (Fan et al., 2022). Indonesia ranks 7th among the 10 countries with the highest number of DM cases, with approximately 10.7 million affected individuals (Indriyani et al., 2023). DM is classified into several categories, including type I DM, type II DM, maturity-onset diabetes of the young (MODY), gestational diabetes, and neonatal diabetes. Type II DM is more

commonly found in adults and the elderly, often resulting from chronic hyperglycemia influenced by lifestyle and poor dietary choices (Sapra & Bhandari, 2023).

One of the most concerning chronic complications of DM is diabetic foot, which occurs due to prolonged hyperglycemia leading to neuropathy and vascular abnormalities. These abnormalities cause changes in the skin and muscles, as well as uneven pressure distribution on the soles, making ulcer formation more likely (Waspadji, 2015). These ulcers are prone to infection and can progress to severe complications. The severity of diabetic foot ulcers can be classified using the Wagner grading system, which categorizes ulcers into six levels (0 to 5) based on infection, ischemia, and depth of the wound (Nisak, 2021).

HbA1c measurement plays a crucial role in assessing a patient's glycemic control over the past 1-3 months, as HbA1c forms through a non-enzymatic glycation process with hemoglobin in red blood cells, which have a lifespan of 90-120 days. Meanwhile, the neutrophil-to-lymphocyte ratio (NLR) is an inflammatory parameter used to evaluate disease severity, including type II DM. NLR has been proven to be a biomarker associated with glycemic control and systemic inflammation, which plays a role in the pathogenesis and progression of DM complications, including diabetic foot ulcers (Kartadinata et al., 2023). Research conducted by (Liu et al., 2023) through systematic review obtained the final model included data from 95,604 patients with Type 2 Diabetes Mellitus (T2DM) across 18 cohorts. The factors considered in the analysis were age, smoking status, body mass index, duration of diabetes, hemoglobin A1c levels, low HDL cholesterol, high triglycerides, hypertension, as well as the presence of diabetic retinopathy, diabetic kidney disease, and cardiovascular disease. Based on this background, this study aims to analyze the relationship between HbA1c levels and the neutrophil-to-lymphocyte ratio (NLR) with Wagner's grading of diabetic foot ulcers in type II DM patients treated at Ibnu Sina Hospital in 2023.

2. Methods

Tools And Materials

This study is a descriptive analytical observational (non-experimental) study with a cross-sectional approach, aiming to analyze the correlation between HbA1c levels and Neutrophil/Lymphocyte Ratio (NLR) with Wagner's grade of diabetic foot ulcers in type II diabetes mellitus patients receiving treatment used medical record data containing data on DM patient at Ibnu Sina Hospital Makassar.

Design

The cross-sectional study design was used to measure variables at a single point in time. The study sample was determined using the total sampling method, where all type II diabetes mellitus patients with diabetic foot ulcers who met the inclusion criteria were included. The inclusion criteria consisted of: (1) type II diabetes mellitus patients with diabetic foot ulcers receiving treatment at Ibnu Sina Hospital Makassar, (2) patients newly diagnosed with diabetic foot ulcers upon hospital admission, and (3) diabetic foot patients without other complications.

Data Analysis

Data analysis was conducted through univariate and bivariate analyses. The univariate analysis aimed to describe the characteristics of the study variables, such as frequency distribution, mean values, and standard deviation. The Shapiro-Wilk test was performed before correlation analysis to determine whether the data were normally distributed. If the data did not meet normality assumptions, the Spearman's rank correlation test was used to assess the relationship between HbA1c levels and NLR with Wagner's grade of diabetic foot ulcers. Statistical test results were interpreted based on a probability value with a significance level of $\alpha = 0.05$, where Sig. < 0.05 indicated a significant correlation, while Sig. > 0.05 indicated no significant correlation.

3. Results and Discussion

3.1. Results

This study was conducted at Ibnu Sina Hospital Makassar from August to September 2024, using secondary data from medical records covering the period of January to December 2023. The study had a total sample of 115 patients, with 34 research samples meeting the inclusion criteria.

Characteristics of DM Patients at Ibnu Sina Hospital

Table 1.
Characteristics of DM Patients

Variables	Frequency	Percentage(%)
Age		
< 50 years	2	05,90
> 50 years	32	94,10
Gender		
Male	15	44,10
Female	19	55,90
Total	34	100

Based on the table 1. presents the demographic characteristics of diabetes mellitus (DM) patients based on age and gender. Most of patients (94.1%) were aged over 50 years, while only 5.9% were under 50 years old, indicating that DM predominantly affects older individuals in this study. In terms of gender distribution, female patients (55.9%) outnumbered male patients (44.1%), suggesting a slightly higher prevalence of DM among women.

Measurement of several parameters, including HbA1c levels, Neutrophil/Lymphocyte Ratio (NLR), and diabetic foot ulcers based on the Wagner classification

Table 2.
Characteristics of including HbA1c levels, Neutrophil/Lymphocyte Ratio (NLR), and diabetic foot ulcers based on the Wagner classification

Variabels	N	Minimum	Maximum	Mean	Std. Deviation
HbA1c	34	1,87	14,00	9,33	2,79
Neutrofil/Limfosit Ratio (NLR)	34	1,92	23,81	9,31	6,74
Wagner Grade	34	2	4	2,82	0,83

Table 2 presents the characteristics of HbA1c levels, Neutrophil/Lymphocyte Ratio (NLR), and Wagner grade classification of diabetic foot ulcers in 34 patients. The HbA1c levels ranged from 1.87 to 14.00, with a mean of 9.33 and a standard deviation of 2.79. The NLR values varied between 1.92 and 23.81, with an average of 9.31 and a standard deviation of 6.74. Regarding the Wagner classification of diabetic foot ulcers, the severity ranged from grade 2 to grade 4, with a mean Wagner grade of 2.82 and a standard deviation of 0.83. These findings indicate variations in glycemic control, inflammatory response, and ulcer severity among the study participants.

The relationship between HbA1c and NLR variables with the Wagner grade variable

Table 3.
Correlation test between HbA1c and NLR variables with the Wagner grade variable

Bivariate Analysis		HbA1c	NLR	Wagner Grade	
Spearman's rho	HbA1c	Correlation Coefficient	1000	0,083	0,523**
		Sig. (2-tailed)	-	0,641	0,002
		N	34	34	34
NLR	NLR	Correlation Coefficient	0,083	1000	0,604**
		Sig. (2-tailed)	0,641	-	0,000
		N	34	34	34
Derajat Wagner	Derajat Wagner	Correlation Coefficient	0,523**	0,604**	1000
		Sig. (2-tailed)	0,002	0,000	-
		N	34	34	34

Based on the table above, first, the Sig. (2-tailed) value, which corresponds to the p-value for the HbA1c variable, is 0.002, which is smaller than the significance level of 0.05. This indicates a significant relationship between HbA1c and the Wagner grade. Additionally, the correlation coefficient (r) of 0.523, which is positive, suggests a moderate and direct relationship, meaning that the more severe a person's diabetic ulcer, the higher their HbA1c level.

Second, the Sig. (2-tailed) value, which corresponds to the p-value for the NLR variable, is 0.000, which is smaller than the significance level (r) of 0.05. This indicates a significant relationship between NLR and the Wagner grade. Additionally, the correlation coefficient of 0.602, which is positive, suggests a moderate and direct relationship, meaning that the more severe a person's diabetic ulcer, the higher their NLR value.

3.2. Discussion

Characteristics of DM Patients

Based on Table 4.1, the univariate analysis showed that among Type II diabetes mellitus (DM) patients with diabetic foot ulcers classified by Wagner's system, only 2 patients (5.9%) were under 50 years old, while 32 patients (94.1%) were over 50 years old. This finding aligns with (Farhan, 2024), which reported that patients under 50 years old experienced fewer diabetic foot ulcers compared to those over 50. Similarly, (Sukmana et al., 2019) found that two out of three respondents with diabetic foot ulcers were over 50 years old. The degenerative process in aging reduces the body's ability to metabolize glucose, increasing the risk of diabetes mellitus and glucose intolerance, particularly in individuals over 45 years old. Prolonged diabetes exposure can lead to complications such as diabetic foot ulcers, influenced by factors beyond just age.

Aging is a key risk factor for diabetes mellitus and diabetic ulcers, as organ function declines with age. This includes reduced pancreatic beta-cell activation and decreased insulin sensitivity, leading to insulin resistance and impaired blood sugar regulation (Wahyuni, 2023). Consequently, older individuals experience slower wound healing due to reduced cells regeneration. This study supports Singh's theory, which states that aging reduces insulin secretion and resistance, affecting lower limb blood circulation and increasing the risk of diabetic ulcers. (Kirana Dela Rosa et al., 2019) also found that individuals over 55 years old have a 1.8 times higher risk of developing diabetic gangrene.

From the 34 patients analyzed in Table 4.1, more females (19 patients or 55.9%) suffered from diabetic foot ulcers than males (15 patients or 44.1%). This result is consistent with (Farhan, 2024), who reported a higher prevalence in females (57.9%) than males (42.1%). Similarly, (Wahyuni, 2023) found that the majority of diabetic foot ulcer patients were female (58.8%). Menopause leads to a decline in estrogen and progesterone levels, contributing to blood sugar regulation issues and increasing susceptibility to diabetic foot ulcers. Additionally, women tend to have a higher percentage of body fat (20-25%) compared to men (15-20%), with hormonal fluctuations further influencing fat accumulation and increasing body mass index (BMI) (Speksnijder et al., 2023).

Although gender differences exist, their influence on blood glucose levels in diabetic foot ulcer patients is minimal. Both men and women face similar risks of developing diabetes mellitus, with blood sugar variations primarily influenced by other factors rather than gender itself. Therefore, while women may have a slightly higher prevalence of diabetic foot ulcers due to hormonal and physiological differences, the overall risk of diabetes complications remains significant in both genders (Hu et al., 2024).

Correlation Between HbA1c Levels and Wagner Grade of Diabetic Foot Ulcers

The Spearman-rho correlation test showed a significant relationship between HbA1c levels and diabetic foot ulcers based on Wagner's classification ($p = 0.002 < 0.05$). This result aligns with previous studies by (Kalsum et al., 2024), (Zulri et al., 2023), and (Salsabila K & Kamila Salsabila B, 2023), all of which found a strong correlation between HbA1c levels and diabetic ulcers. However, it contradicts studies by (Aulia Cahyani et al., 2024) and (Suastidewi & Dwipayana, 2020), which found no significant correlation, possibly due to confounding factors such as BMI, cholesterol levels, triglycerides, and other metabolic parameters. Theoretically, uncontrolled blood glucose in diabetes patients increases bacterial

colonization and impairs wound healing. Elevated HbA1c levels can disrupt red blood cell function, reducing oxygen release, causing hypoxia, and leading to tissue necrosis, which exacerbates diabetic foot ulcers.

Diabetic foot ulcers result from neuropathy, peripheral artery disease, and prolonged hyperglycemia, which induce oxidative stress, vasoconstriction, inflammation, and thrombosis. Chronic hyperglycemia triggers immune and inflammatory responses, leading to platelet deposition, macrophage accumulation, fibrosis, and vascular smooth muscle proliferation. Various conditions, including hemoglobinopathies, kidney disease, and certain medications, can influence HbA1c levels. Despite high HbA1c levels, the severity of diabetic foot ulcers can be mitigated with proper wound care and appropriate footwear, making HbA1c a useful predictor for diabetic foot complications (Farooque et al., 2020).

Correlation Between Neutrophil/Lymphocyte Ratio (NLR) and Wagner Grade of Diabetic Foot Ulcers

The study results show a significant correlation between the Neutrophil/Lymphocyte Ratio (NLR) and Wagner grade of diabetic foot ulcers, with a p-value of 0.000 (<0.05) and a correlation coefficient of 0.602, indicating a moderate, positive relationship. This means that the more severe a patient's diabetic foot ulcer, the higher their NLR score. This finding aligns with research by (Syauta et al., 2021), which found a significant correlation between Wagner classification and NLR ($p=0.028$, $r=0.34$), albeit with a weaker correlation. However, it contradicts the study by (Raharjo et al., 2020), which found no significant correlation between NLR and diabetic foot ulcers ($p=0.14$). The relationship between NLR and diabetic complications, particularly vascular and metabolic diseases, has been well-documented. An increased NLR is commonly found in diabetic peripheral neuropathy and peripheral artery disease, both of which contribute to diabetic foot ulcers. Higher NLR values in diabetic foot infections indicate an increased risk of amputation and sepsis, making NLR a valuable predictive biomarker for disease severity and prognosis.

In Type 2 Diabetes Mellitus (T2DM), hyperinsulinemia and insulin resistance lead to chronic hyperglycemia, which increases the risk of complications such as diabetic foot ulcers. The immune response to chronic inflammation is marked by elevated neutrophils and reduced lymphocytes. Neutrophils, as part of the nonspecific immune system, initiate inflammatory responses and remain elevated due to persistent inflammation. Chronic inflammation induces hypersecretion of pro-inflammatory cytokines like IL-6 and TNF- α , causing a sustained increase in neutrophils. Conversely, lymphocytes represent the protective component of the immune response. The decline in lymphocyte count, known as lymphocytopenia, occurs due to apoptosis, delayed clearance, and increased stimulation of stem cells by G-CSF, leading to elevated neutrophil levels. This neutrophil dominance reflects a nonspecific, destructive inflammatory process within the body (Nurdin N et al., 2021).

NLR serves as a biomarker to assess immune system activity and balance. A high NLR indicates endothelial dysfunction and increased neutrophil activity, which exacerbates tissue damage and leads to more severe complications. The rise in NLR aligns with existing theories suggesting that chronic inflammation in diabetic foot ulcers results from an overactive neutrophil response and decreased lymphocyte function. Since cytokines continuously stimulate bone marrow to produce leukocytes, lymphocytopenia is usually transient (Sylvana & Santi Syafril, 2024). However, persistent inflammation in diabetes can sustain this imbalance, further contributing to complications. This makes NLR a critical indicator for predicting diabetic foot ulcer severity and the likelihood of poor outcomes.

4. Conclusion

Based on the findings of this study, it can be concluded that most diabetic foot ulcer patients treated at RS Ibnu Sina in 2023 were over 50 years old and predominantly female. There was a significant correlation between HbA1c levels and the Neutrophil/Lymphocyte Ratio (NLR) with the Wagner grade of diabetic foot ulcers in Type II Diabetes Mellitus (DM) patients. The study also found that the higher the severity of diabetic foot ulcers, the higher the NLR value, which is linked to increased insulin resistance and elevated HbA1c levels. For future research, it is recommended to use primary data from Type II DM patients with diabetic foot ulcers to further validate these findings. The findings of this study have

several important clinical implications. Since most diabetic foot ulcer patients treated at RS Ibnu Sina in 2023 were over 50 years old and predominantly female, screening and preventive strategies should prioritize this population. The significant correlation between HbA_{1c} levels, the Neutrophil/Lymphocyte Ratio (NLR), and the Wagner grade of diabetic foot ulcers suggests that these parameters can serve as useful indicators for assessing ulcer severity and disease progression. Furthermore, the observation that higher NLR values are associated with more severe ulcers highlights its potential as a simple, cost-effective inflammatory marker to guide early intervention, monitor treatment response, and predict adverse outcomes. The relationship between increased ulcer severity, insulin resistance, and elevated HbA_{1c} underscores the importance of strict glycemic control to prevent further complications. Overall, incorporating HbA_{1c} and NLR into routine clinical evaluation could enhance risk stratification and support individualized management of patients with diabetic foot ulcers.

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