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# CORRELATION OF HBA1C WITH NEUTROPHIL-LYMPHOCYTE RATIO AND MONOCYTE-LYMPHOCYTE RATIO AS MARKERS OF INFLAMMATION IN TYPE 2 DIABETES MELLITUS PATIENTS AT SANJIWANI HOSPITAL FROM 2021 TO 2023

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## ABSTRACT

Chronic inflammation in type 2 diabetes mellitus (T2DM) is the main link between hyperglycemia and immune system dysfunction. Chronic inflammation that cannot be controlled can increase the risk of complications. This inflammatory state is caused by growing glycemic levels as assessed by HbA1c examination. Previous studies have shown that the neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) are inflammatory markers that can indicate immune system dysfunction. This study aims to determine the correlation of HbA1c with NLR and MLR as markers of inflammation in T2DM patients at Sanjiwani Regional Hospital for the 2021–2023 period. This research utilized a cross-sectional method. The study sample size was 73 T2DM patients who met the research criteria. The correlation of HbA1c with NLR and MLR was analyzed using the Spearman correlation test. Of the 73 research samples, it was found that 43 people (58.9%) were men, and 30 people (41.1%) were women, with an average ± SD age of 57.88 ± 9.98 years. The median HbA1c value was 8.80% (6.5%–14.5%), the median NLR value was 2.64 (0.89–6.78), and the median MLR value was 0.22 (0.02–0.57). The results of Spearman's correlation analysis between HbA1c and NLR showed no significant correlation ($r = 0.195$, $p = 0.098$), and the correlation between HbA1c and MLR was also not significant ($r = 0.146$, $p = 0.217$). So, it can be concluded that there is no significant correlation between HbA1c with NLR and MLR.

**Keywords:** type 2 diabetes mellitus., chronic inflammation., HbA1c., neutrophil-to-lymphocyte ratio., monocyte-to-lymphocyte ratio

## INTRODUCTION

Diabetes mellitus (DM) is a multifactorial chronic metabolic disorder characterized by hyperglycemia.[1] One of the top 10 killers in the world, DM is still a significant concern in public health today. According to data from the World Health Organization (WHO) and the International Diabetes Federation (IDF), the prevalence of diabetes mellitus (DM) among adults (those aged 20-79) was 10.5% (537 million) in 2021 and is anticipated to reach 12.2% (783 million) by 2045.[2,3] Of the total DM cases, 90–95% are type 2 DM (T2DM), which primarily affects adults (over 40 years).[4] In 2018, almost 20.4 million people in Indonesia were living with diabetes. By 2045, experts predict the figure will climb to 28.57 million, making it the top cause of death in the country.[5] In Bali Province, the number of DM cases in 2018 ranked 14th out of 34 provinces in Indonesia, with 67,172 cases.[6] The incidence of DM continues to rise annually due to the increasing urban population, poor lifestyle choices, and genetic risk factors.[7]

Diabetes mellitus (DM) occurs due to pancreatic beta-cell damage, insulin resistance, or a combination of both conditions. Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other forms of diabetes are categorized according to their cause.[1] Insulin resistance is a hallmark of type 2 diabetes, a metabolic disorder. In this condition, there is a process of relative insulin deficiency that progresses to absolute insulin deficit due to beta cell dysfunction, leading to hyperglycemia, which has the potential to trigger various complications.[8] The pathophysiology of T2DM involves pancreatic beta cells. Early in the disease process, pancreatic beta cells still produce insulin and are well-regulated by alpha cells, but the body develops insulin resistance.[9] As the disease progresses, damage to pancreatic beta cells occurs, with an imbalance in the production of beta and alpha cells, causing persistent low-grade chronic inflammation.[10]

Chronic inflammation is vital in the pathophysiology of T2DM, causing abnormal metabolic changes and immune system dysfunction. It increases pro-inflammatory cytokine levels in the circulation and leukocytosis, including neutrophils, lymphocytes, and monocytes. Neutrophils and monocytes are innate immune cells that increase during inflammation, while lymphocytes are adaptive immune cells that respond to inflammation. This condition contributes to the progression of T2DM complications, both macrovascular and microvascular.[11,12] Previous research showed that the most common microvascular complication was diabetic nephropathy, affecting 38.8% of patients.[13] Meanwhile,

macrovascular complications, such as cardiovascular disease, experience a high rate of illness and death.[7]

Hyperglycemia in T2DM is used to evaluate and diagnose DM, and glycated hemoglobin (HbA1c) testing is one of the signs.[14] HbA1c is a component of adult hemoglobin (HbA) used to diagnose DM, with a value of ≥6.5% indicating DM.[15] Since it displays the typical blood glucose levels over the past two to three months, HbA1c is now thought to be the most significant predictor for long-term glycemic control.[14] When gauging the likelihood of diabetic problems, HbA1c is a fantastic indicator.[16] However, HbA1c does not indicate ongoing inflammatory conditions, whereas chronic inflammation is integral to the pathophysiology of DM and the development of complications.[11]

Various inflammatory markers are associated with DM complications, including several interleukins, TNF-α, TGF-β1, C-reactive protein, and procalcitonin. However, these tests are costly and not performed routinely.[17] The neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) are now recognized as reliable, accessible, cost-effective inflammatory markers that indicate immune dysfunction based on complete blood counts.[18,19] NLR and MLR are systemic inflammatory markers used in various clinical conditions. NLR is the absolute ratio of neutrophils to lymphocytes. In chronic inflammatory conditions due to DM with poor glycemic control, neutrophil counts are elevated at the onset of inflammation, and lymphocyte counts are low, indicating a failure of the body's defense system.[20,21] MLR is calculated as the absolute ratio of monocytes to lymphocytes, with monocyte numbers increasing during chronic inflammation. These two inflammatory markers are more stable than independent monocyte, lymphocyte, or leukocyte counts.[22]

Based on the description above, it is known that HbA1c, NLR, and MLR influence chronic inflammatory conditions in T2DM. Although several previous studies have clarified the correlation between HbA1c and NLR, few studies have examined HbA1c and MLR, and no similar research has investigated the correlation between HbA1c with NLR and MLR at Sanjiwani Hospital. Therefore, this study aims to analyze the correlation between HbA1c levels and inflammatory markers, specifically NLR and MLR, in patients with T2DM at Sanjiwani Hospital from 2021 to 2023. This study seeks to provide further insights into the role of these markers in assessing inflammation in T2DM patients.

## LITERATURE REVIEW

### Chronic Inflammation as a Link between Hyperglycemia and Immune Dysfunction in Type 2 Diabetes Mellitus

Chronic inflammation is a high contributor to the progression of T2DM, acting as a bridge between hyperglycemia and immune system dysfunction. It can affect various organs and tissues, beta cells, skeletal muscle, the intestines, the liver, adipose tissue, and the hypothalamus in the neurological system. Together, these effects increase circulating pro-inflammatory factors. However, the literature suggests that inflammation in adipose tissue and beta cells plays a more significant role in immune dysfunction.[12]

Adipose tissue is responsible for storing energy reserves such as triglycerides. Also, it functions as an endocrine organ, producing various inflammatory mediators known as adipocytokines, including IL-1, IL-6, IL-8, IFN-γ, TNF-α, leptin, and resistin. Production of these adipocytokines is associated with adipocyte cell destruction. In T2DM, the increase in adipocyte size further influences fatty tissue to produce adipocytokines, triggering a series of inflammatory processes, including infiltrating neutrophils, lymphocytes, and monocytes into adipose tissue. As a result of this invasion, adipocytes produce more adipokines, chemokines, and pro-inflammatory cytokines.[9,24]

Beta cell inflammation also contributes to immune dysfunction. This begins with lipotoxicity, where beta cells are continuously stimulated to work despite the body's resistance, inducing inflammatory stress in beta cells. This stress activates the beta cell apoptosis pathway via the unfolded protein response (UPR) pathway, stimulating inflammatory mediators, including IL-1. This cycle disrupts insulin signal transduction.[25] Additionally, oxidative stress in beta cells generates reactive oxygen species (ROS), cytokines, and other pro-inflammatory chemokines, which impair blood flow and cause organ damage.[9]

## OBJECT AND METHOD

This cross-sectional study was conducted from January to September 2024. Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Medicine, Udayana University (Ethical Clearance No. 2727/UN14.2.2.VII.14/LT/2023). Electronic medical records from the Medical Records Installation of Sanjiwani Hospital were used as secondary data. This study focused on individuals diagnosed with type 2 diabetes mellitus (T2DM) at Sanjiwani Hospital from 2021 to 2023.

A total of 1108 patient records were initially reviewed. After applying the inclusion and exclusion criteria, a final sample of 73 eligible T2DM patients was selected. The inclusion criteria consisted of patients aged 18–80 years, diagnosed with T2DM by an internal medicine specialist at Sanjiwani Hospital between 2021 and 2023, whose medical records contained data on HbA1c, NLR, and MLR. The exclusion criteria included incomplete medical records and comorbidities affecting immunity, such as cancer, immunodeficiency, sepsis, COVID-19, and other infections. From the initial 1108 records, 1035 were excluded due to the following reasons: incomplete data (952 cases), other infection diseases (65 cases), sepsis (11 cases), and COVID-19 (7 cases).

This study employed a consecutive sampling technique, in which all available electronic medical records of T2DM patients from 2021 to 2023 at Sanjiwani Hospital were screened, with samples selected sequentially until the minimum required number was reached. A thorough screening was conducted, and records were cross-checked to maintain data integrity. The minimum sample size was determined using a numerical correlative analysis formula with a one-way hypothesis to achieve sufficient statistical power. Data extraction was performed manually by the researcher to maintain precision. The extracted data underwent a double-checking process to confirm completeness and minimize errors, thus improving overall validity.

This study's independent variable was HbA1c, while the dependent variables were NLR and MLR. Age and sex were controlled and analyzed through stratification. HbA1c was classified into three groups: good control (6.5%–<7%), poor

control (7%–9%), and very poor control (>9%).[23] NLR was categorized into three groups: normal (0.7–<2), low inflammatory (2–<3), and low to moderate inflammatory (3–7).[21] MLR was categorized into two groups: increased (>0.19) and not increased (≤0.19).[22] Age was categorized into ages: 18–25 years, 26–45 years, 46–65 years, and 66–80 years.[19] Sex was classified into two categories: male and female.

All study data were analyzed using SPSS 26.0. Descriptive analysis was carried out to characterize the study's variables. Numerical data were presented in line with the findings of the Kolmogorov-Smirnov test for normality, while categorical data were presented in tables with percentages and absolute values. Mean ± standard deviation (SD) was used to represent a normal distribution of numerical variables. In contrast, median values (minimum-maximum) were utilized for variables not in line with a normal distribution. The correlation between HbA1c with NLR and MLR was analyzed using the Spearman correlation test.

## RESULT

### Characteristics of Basic Research Data

The results deemed a sample size of 73 participants adequate for the study. **Table 1** displays the characteristics of the research data.

**Table 1.** Characteristics of basic research data

| Variable | N (%) | Mean ± SD | Median (min-max) | p-Value |
|---|---|---|---|---|
| **Sex** | | | | |
| **Female** | 30 (41.1%) | | | |
| **Male** | 43 (58.9%) | | | |
| **Age (year)** | | 57.88 ± 9.98 | | 0.200* |
| **HbA1c (%)** | | | 8.80 (6.5–14.5) | 0.001 |
| **NLR** | | | 2.64 (0.89–6.78) | 0.000 |
| **MLR** | | | 0.22 (0.02–0.57) | 0.012 |

P-value: significance value of Kolmogorov-Smirnov normality test
*: normally distributed data (p-value>0.05)

**Table 1** shows that there were more male patients than female patients. Male patients totaled 43 (58.9%), while female patients totaled 30 (41.1%). There was an average age of 57.88 years among the participants. With a range of 6.5% to 14.5%, the median HbA1c was 8.80%. With values ranging from 0.89 to 6.78, the median NLR was 2.64. With a range from 0.02 to 0.57, the median MLR was 0.22. **Table 1** displays the findings of the normalcy test and shows that the age variable was the only one that followed a normal distribution (p-value>0.05 at a 95% confidence level). However, the HbA1c, NLR, and MLR variables were not normally distributed.

### Correlation Between HbA1c and Neutrophil-to-Lymphocyte Ratio

The correlation of HbA1c and NLR was analyzed utilizing the Spearman correlation test, as non-normality was observed in both variables. The Spearman correlation test findings for HbA1c and NLR are stated in **Table 2.**

**Table 2.** Spearman correlation test results for HbA1c and NLR

| | HbA1c | |
|---|---|---|
| | Correlation Coefficient (r) | p-Value |
| **NLR** | 0.195 | 0.098 |

Correlation is significant if the p-value<0.05

**Table 2** states a correlation coefficient of 0.195, indicating a very weak positive correlation between HbA1c and NLR. The positive correlation coefficient (r = 0.195) suggests a positive relationship between the two variables; as HbA1c increases, NLR also tends to increase. The significance value is p = 0.098 (p>0.05), indicating that the correlation is not statistically significant. This means the correlation is not strong enough to be recognized as significant.

### Correlation Between HbA1c and Monocyte-to-Lymphocyte Ratio

The correlation of HbA1c and MLR was also analyzed utilizing the Spearman correlation test, as non-normality was observed in both variables. The findings of the Spearman correlation test for HbA1c and MLR are stated in **Table 3.**

**Table 3.** Spearman correlation test results for HbA1c and MLR

| | HbA1c | |
|---|---|---|
| | Correlation Coefficient (r) | p-Value |
| **NLR** | 0.146 | 0.217 |

Correlation is significant if the p-value<0.05

**Table 3** shows the correlation coefficient of 0.146, indicating a very weak positive correlation between HbA1c and MLR. The positive correlation coefficient (r = 0.146) suggests a positive relationship between the two variables; as HbA1c increases, MLR also tends to increase. The significance value is p = 0.217 (p>0.05), indicating that the correlation is not statistically significant. This means the correlation is not strong enough to be recognized as significant.

## DISCUSSION

A more significant proportion of male patients than female patients were reported to have T2DM in the research. This study's

findings corroborate Varma et al.'s (2021) and Suguna and Kusumadevi (2019) research.[19,23] The stage of reproductive life has an inverse relationship with the sex difference in the prevalence of diabetes. Men tend to develop diabetes at an earlier age, before puberty, while women are more likely to be affected during menopause or postmenopause. Women have the hormone estrogen, which aids illness prevention in various ways, although women tend to increase body mass index (BMI).[26] In fact, women of menopausal age who undergo estrogen therapy may still be protected from the development of diabetes.[22] Furthermore, men are also at a higher risk of developing atherosclerotic plaques than women. Regarding lifestyle and nutrition, women tend to adopt healthier diets, although they are less physically active than men.[26]

The participants' ages varied from 30 to 78, with 57.88 being the average. There were 51 patients in the 46–65 age bracket, making it the largest age group. These results are consistent with what has been found in studies by Ahmad et al. (2022), Mahankali et al. (2021), and Suguna and Kusumadevi (2019).[4,19,27] T2DM typically develops in adulthood (after age 40), as the aging process is often accompanied by chronic systemic inflammation, which accelerates cellular aging and organ dysfunction, resulting in increased adiposity, particularly central obesity. Additionally, factors related to heredity interact to cause type 2 diabetes and poor lifestyle choices at a younger age.[28,29]

This study found that 91.8% (67/73) of T2DM patients had elevated HbA1c levels, with 36 patients classified as having poor control and 31 with very poor control. The distribution of HbA1c values in this study included: good control (HbA1c 6.5–7%) in 6 patients (8.2%), poor control (HbA1c 7–9%) in 36 patients (49.3%), and very poor control (HbA1c>9%) in 31 patients (42.5%). These findings are consistent with previous studies, which also observed elevated HbA1c levels in the study samples. Some of these studies include those by Anggoro (2019) and Mahankali et al. (2021).[27,30] Higher HbA1c values indicate worsening T2DM conditions. HbA1c reflects blood glucose regulation; hence, the risk of type 2 diabetes complications increases when HbA1c levels rise.[31]

This research demonstrated that 64.4% (47/73) of T2DM patients had elevated NLR values, with 15 patients falling into the low inflammation category and 32 in the low to moderate inflammation category. The distribution of NLR values in this study included normal NLR (0.7–<2) in 26 patients (35.6%), low inflammation (2–<3) in 15 patients (20.6%), and low to moderate inflammation (3–7) in 32 patients (43.8%). This study's findings contradict those of Anggoro (2019), who used a reference range for normal NLR values between 0.78–3.53, finding that 72.91% (35/48) of the samples showed normal NLR values.[30] However, the results of Varma et al. (2021), who also used the reference range of 0.78–3.53 for NLR, align with this study, showing an increase in NLR in 75.23% (79/105) of the samples.[23] Additionally, research by Chandra et al. (2023) and Kartadinata et al. (2023) have similar results to this study, showing that increased HbA1c levels were associated with a rise in NLR.[31,32]

An increased NLR indicates a chronic inflammatory condition. Chronic inflammation is present in T2DM and links hyperglycemia and immune system dysfunction through elevated pro-inflammatory cytokines and leukocytosis. In chronic inflammatory states, neutrophils increase while lymphocytes decrease, leading to a higher NLR.[33] Additionally, activated neutrophils interact with other immune cells, such as lymphocytes and monocytes, increasing MLR.[17,21] Elevated NLR in T2DM patients can also serve as a predictor of complication risk.[34] Therefore, T2DM is linked to elevated NLR and complications due to the rise in neutrophils and reduced lymphocytes in chronic inflammation.

This study showed that 57.5% (42/73) of T2DM patients had elevated MLR values, and 42.5% (31/73) had low MLR values. The MLR value is influenced by the chronic inflammatory process, which leads to an increase in monocytes and a decrease in lymphocytes.[35] A literature review did not find studies describing MLR values in T2DM patients. However, MLR can serve as a marker of chronic inflammation in T2DM, and elevated MLR values can help assess disease progression associated with inflammatory reactions.[22]

This study found a weak positive correlation between HbA1c and NLR ($r = 0.195$; $p = 0.098$), which was not statistically significant. These results differ from previous studies by Anggoro (2019), Varma et al. (2021), and Mahankali et al. (2021).[23,27,30] The differences may be attributed to variations in sample size, study location, duration, sampling methods, and data sources. Furthermore, this study's correlation strength ($r = 0.195$) is categorized as weak. The study did not account for several confounding factors, which may have influenced the results. A study by Mendes et al. (2019) found similar results, reporting no relationship between NLR and changes in HbA1c.[36] This study also did not exclude comorbidities in T2DM, consider the duration of the disease, or account for medication use in patients.

This study found a weak positive correlation between HbA1c and MLR ($r = 0.146$; $p = 0.217$), which was also not statistically significant. These findings align with previous studies but contradict the theoretical expectations. Research by Suguna and Kusumadevi (2019) supports these findings, though it did not consider the potential confounding effect of drug consumption.[19] Alfhili et al. (2022) also found no relationship between MLR and HbA1c. HbA1c reflects long-term glycemic control (approximately 2–3 months), with reasonable specificity but less sensitivity to early-phase inflammatory responses. The interindividual variation in this marker likely explains the lack of association between HbA1c and MLR.[22]

NLR and MLR are inflammatory markers associated with various conditions involving systemic inflammation or immune system dysregulation. Several factors can influence the chronic inflammatory process, including biological/genetic factors (race, age, sex), lifestyle and social factors (lack of physical activity, poor diet, sleep disorders, circadian rhythm disruptions, psychological stress), pharmacological factors (medications consumed), and environmental factors or xenobiotic exposure (industrial toxins, pollution, hazardous chemicals).[37,38] Since the patient's medical records did not wholly document these confounding circumstances, this investigation did not consider them. This may have affected the HbA1c values, NLR, MLR, and the correlations between variables.

Systemic inflammation is closely related to infectious and non-infectious diseases, which can further increase NLR and MLR values.[22,38] This occurs because the initial inflammatory response activates neutrophils, which, in turn, trigger the local inflammatory process. This process produces pro-inflammatory cytokines and other inflammatory cells, such as lymphocytes and monocytes, leading to increased NLR.[39] Conversely, the increase in monocytes and decrease in lymphocytes contribute to elevated MLR values.[22] Some of these comorbidities were not fully controlled for in the patients involved in the study, which could act as confounding factors affecting the significance of the correlation between HbA1c, NLR, and MLR.

Age and sex were two sample variables that may have contributed to this study's lack of statistical significance. Stratification was used to evaluate the data after controlling for these two factors. No significant correlation was found after looking at the link between HbA1c, NLR, and MLR for the sample (73 people). But when we separated the data by sex, we got a different picture. In men, the correlation between HbA1c and NLR was moderately positive ($r = 0.402$; $p = 0.008$), while the link between HbA1c and MLR was weakly positive ($r = 0.317$; $p = 0.039$). The weak negative correlation between HbA1c and NLR in female individuals was statistically significant ($r = -0.151$; $p = 0.426$), while the moderate negative correlation between HbA1c and MLR was not statistically significant ($r = -0.042$; $p = 0.825$). The negative correlation in females that differed from the correlation in the overall sample may be due to differences in sample characteristics and other confounding factors not controlled for in this study. This suggests that sex is a confounding variable that can influence study results because men and women have different characteristics, especially hormonal factors.[26] Jebbor et al. (2024) also found that NLR values differed significantly between men and women ($p<0.05$) due to sex dimorphism in disease processes related to inflammation and immunosenescence, which occurs differently in men and women.[40]

This study included a broad age range of 18 to 80 years, which may have introduced considerable variability within the sample. No significant correlation was found between HbA1c and the NLR or MLR across the entire sample (73 participants), regardless of age group. When stratified by age category, similar results were observed. No significant correlation was found in any age group, including those aged 26–45, 46–65, or 66–80. Therefore, the age variable does not appear to confound the correlation between HbA1c and NLR/MLR. Research by Yun et al. (2023) reported that younger people's lower HbA1c readings may result from their increased knowledge of type 2 diabetes and their more diligent treatment of the disease.[41] In contrast, older individuals generally have higher HbA1c levels, possibly attributable to age-related changes and comorbidities. In addition, Jebbor et al. (2024) found that NLR values differed significantly across age groups in both sexes ($p<0.05$). Their study indicated a positive relationship between NLR and age, with older individuals showing relatively higher NLR values than younger individuals due to increased granulocytes and decreased lymphocytes with age. Furthermore, chronic diseases and malignancies are more commonly observed in older adults in clinical settings.[40]

## CONCLUSIONS AND SUGGESTIONS

This study concludes that there was no significant correlation between HbA1c with the neutrophil-lymphocyte ratio and monocyte-lymphocyte ratio as an inflammatory marker in patients with type 2 diabetes mellitus at Sanjiwani Hospital from 2021 to 2023.

The authors recommend a bigger sample size for future research. It should consider various confounding variables that may influence the research results, such as biological/genetic factors (e.g., race, age, sex), lifestyle and social factors (e.g., insufficient exercise, unhealthy eating, sleep disorders, circadian rhythm disturbances, psychological stress), pharmacological factors (e.g., medications), environmental factors or xenobiotic exposure (e.g., toxins, industrial waste, pollution, or other hazardous chemicals), and comorbidities (e.g., infectious or non-infectious diseases). Consequently, future studies will yield more significant correlation results with stronger associations.

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