

# Comparison of Neutrophil to Lymphocyte Ratio (NLR) and Lymphocyte to Monocyte Ratio (LMR) values in controlled and uncontrolled Type 2 Diabetes Mellitus (T2DM) patient



Putu Yudi Adnyani<sup>1\*</sup>, Ni Nyoman Mahartini<sup>2</sup>, Sianny Herawati<sup>2</sup>, Ni Kadek Mulyantari<sup>2</sup>, Anak Agung Wiradewi Lestari<sup>2</sup>

## ABSTRACT

**Background:** Inflammation is related to insulin resistance. Neutrophil to Lymphocyte Ratio (NLR) and Lymphocyte to Monocyte Ratio (LMR) are used as inflammation markers and predictors of complications associated with diabetes. This study aims to determine the differences of NLR and LMR values in controlled and uncontrolled type 2 diabetes mellitus (DM) patients.

**Methods:** A cross-sectional was conducted in this study at Sanglah General Hospital. Research data were taken from the Laboratory Information System (LIS) and medical records. NLR is obtained from the absolute neutrophils divided by absolute lymphocytes, LMR is obtained from absolute lymphocytes divided by absolute monocytes. Data were analyzed using SPSS version 25 for Windows.

**Results:** Type 2 diabetes mellitus mainly was male (58.3%) with the highest proportion at the age of 46-55 years (50.0%). The mean leukocyte count was significantly higher in the uncontrolled group ( $8.45 \pm 1.58$  cells/ $\mu$ L) ( $p < 0.05$ ). NLR showed a significant difference in the two groups ( $p < 0.05$ ). However, there was no significant difference in LMR between groups ( $p > 0.05$ ).

**Conclusion:** NLR in uncontrolled type 2 DM was significantly higher than in controlled type 2 DM. Meanwhile, the LMR did not show a significant difference between the two groups.

**Keywords:** NLR, LMR, DM type 2.

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<sup>1</sup>Clinical Pathology Specialist Programme, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;

<sup>2</sup>Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;

\*Corresponding author:

Putu Yudi Adnyani;  
Clinical Pathology Specialist Programme, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;  
[yudismaradayita@gmail.com](mailto:yudismaradayita@gmail.com)

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## INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia caused by abnormalities in insulin secretion, insulin action or both.<sup>1</sup> Currently, DM is a health problem around the world. The incidence has increased significantly. The World Health Organization predicts an increase in the number of DM patients in Indonesia from 8.4 million in 2000 to 21.3 million in 2030.<sup>1</sup>

DM has serious microvascular and macrovascular complications.<sup>2</sup> Microvascular complications include diabetic nephropathy, diabetic retinopathy and diabetic neuropathy. Macrovascular complications include stroke,

cardiovascular disease, and peripheral vascular disease.<sup>2</sup> Poorly controlled glycemia levels in DM patients could cause chronic inflammation, which accelerates the development of macrovascular and microvascular complications.<sup>2,3</sup>

Inflammation has a close relationship with insulin resistance.<sup>4</sup> Epidemiological studies have shown that leukocytes, an indicator of inflammation, can predict diabetes risk. The total number of leukocytes is a sensitive indicator of inflammation and can be easily done in the laboratory routinely and cost-effectively.<sup>4</sup> Neutrophil to Lymphocyte Ratio (NLR) and Lymphocyte to Monocyte Ratio (LMR) are used as markers of

inflammation, predictors of heart disease, malignancy, and complications associated with diabetes.<sup>5,6</sup>

Based on those mentioned above, this study aims to determine the differences of NLR and LMR values in patients with type 2 diabetes mellitus in the control group and the uncontrolled group at Sanglah General Hospital Denpasar.

## METHODS

The design of this study is an analytic observational study with a cross-sectional approach to determine the difference of NLR and LMR values in patients with type 2 diabetes mellitus control and uncontrolled groups. This research was

**Table 1. General characteristics patient with DM type 2**

Characteristics	Subjects (N=60)	Groups (N=60)	
		Controlled DMT2 group (N=30)	Uncontrolled DMT2 group (N=30)
Gender, n (%)			
Male	35 (58.3)	15 (50.0)	20 (66.7)
Female	25 (41.7)	15 (50.0)	10 (33.3)
Age (years), n (%)			
< 45	9 (15.0)	4 (13.3)	5 (16.7)
46-55	30 (50.0)	15 (50.0)	15 (50.0)
56-65	14 (23.3)	5 (16.7)	9 (30.0)
≥ 65	7 (11.7)	6 (20.0)	1 (3.3)
DM therapy given, n (%)			
Insulin	39 (65.0)	29 (96.7)	10 (33.3)
Antidiabetic drug	21 (35.0)	1 (3.33)	20 (66.7)
Duration of DM (years), n (%)			
< 5	58 (96.7)	30 (100.0)	28 (93.3)
> 5	2 (3.3)	0 (0.0)	2 (6.7)

DM: Diabetes Mellitus; DMT2: Diabetes Mellitus Type-2

**Table 2. Characteristics laboratory data of patients with DM type 2**

Parameter	Groups (N=60)		P
	Controlled DMT2 group (N=30)	Uncontrolled DMT2 group (N=30)	
HbA1C (%), median (min-max)	5.20 (4.20-6.40)	9.05 (6.70-19.30)	0.000 <sup>a□</sup>
FBG (mg/dL), median (min-max)	90.00 (47.00-99.00)	178.00 (128.00-410.00)	0.000 <sup>a□</sup>
Leukocytes (cells/μL) (Mean±SD)	7.48±2.04	8.45±1.58	0.045 <sup>b□</sup>
Neutrophil (cells/μL) (Mean±SD)	4.25±1.57	4.98±1.32	0.054 <sup>b</sup>
Lymphocyte (cells/μL) (Mean±SD)	2.46±0.59	2.36±0.64	0.564 <sup>b</sup>
Monocyte (cells/μL) (Mean±SD)	0.48±0.12	0.55±0.18	0.093 <sup>b</sup>

FBG: Fasting Blood Glucose; Min: Minimum; Max: Maximum; SD: Standard Deviation; <sup>a</sup>: Mann-Whitney U Test; <sup>b</sup>: Independent T-Test; <sup>□</sup>: Statistically significant if p-value less than 0.05

**Table 3. Value difference of NLR and LMR in controlled and uncontrolled DM type 2.**

Parameter	Groups		Mean Difference	CI 95%	p
	Controlled DMT2	Uncontrolled DMT2			
NLR (Mean±SD)	1.77±0.62	2.32±1.08	0.550±0.460	-1.009 – (-0.094)	0.019
LMR (Mean±SD)	5.38±1.86	4.75±1.90	0.630±0.048	-0.342 – 1.601	0.200

NLR: Neutrophil to Lymphocyte Ratio; LMR: Lymphocyte to Monocyte Ratio; DMT2: Diabetes Mellitus Type 2; <sup>\*</sup>Independent T-test: statistically significant if p-value less than 0.05.

conducted in September 2020 at the Clinical Pathology Laboratory of Sanglah Hospital Denpasar.

The target population in this study were patients with type 2 diabetes who visited the polyclinic and performed blood tests at the Clinical Pathology Laboratory of Sanglah Hospital, Denpasar. Study participants have met the inclusion and exclusion criteria, selected by consecutive sampling techniques. The inclusion criteria in this study were all type 2 diabetes

mellitus patients who were at least 18 years old, did HbA1c, fasting blood glucose, and complete blood counts examination simultaneously. The exclusion criteria in this study were typed 2 DM patients with complications of heart disease, chronic renal failure, infection, inflammation, hematological malignancy and pregnancy.

Laboratory examination data were taken from the Laboratory Information System (LIS), while patient demographic data, medical history, duration of illness,

and drugs consumed were taken from medical record data. Furthermore, the NLR and LMR values were recorded for the NLR value obtained from the absolute neutrophils divided with absolute lymphocytes. In contrast, the LMR value was obtained from absolute lymphocytes divided by absolute monocytes.

Study participants were divided into two groups, controlled type 2 DM, if Fasting Blood Glucose (FBG) < 100 mg/dL and HbA1C < 6.5%, and uncontrolled

type 2 diabetes mellitus. Univariate and bivariate analysis were performed on research data. The Kolmogorov-Smirnov normality test was used on data with a numerical measuring scale to determine whether the data is normally distributed with a  $p$  value  $> 0.05$ . Univariate analysis was used for demographic data in order to obtain a characteristic distribution of study participants. Bivariate analysis was used to determine the mean difference between NLR and LMR values in controlled and uncontrolled type 2 diabetes mellitus groups using an Independent T-test for normally distributed data and Mann-Whitney U test for data that were not normally distributed. The test result is significant if the  $p$ -value is  $< 0.05$  on the SPSS version 25 software for Windows.

## RESULTS

The study participants were 60 patients with type 2 diabetes who met the inclusion and exclusion criteria, consisting of 30 patients with controlled type 2 diabetes with levels of HbA1c  $< 6.5\%$  and GBF  $< 100$  mg/dL, in the uncontrolled group composed of 30 patients with type 2 diabetes with levels of HbA1c  $\geq 6.5\%$  and FBG  $\geq 126$  mg/dL. General characteristics data and laboratory examination results can be seen in Tables 1 and 2.

In this study, men are the most common gender with type 2 diabetes mellitus patients and shown in Table 1 compared to women. The most common age range is 46-55 years, both in the controlled (50.0%) and uncontrolled (50.0%) groups. A total of 39 patients (65.0%) used insulin as therapy for type 2 diabetes. The proportion of insulin use was higher in the control group (96.7%). In both groups, it was found that patients with type 2 DM for less than 5 years (96.7%) were higher than patients who had type 2 diabetes for more than 5 years (3.3%) (Table 1).

The HbA1c and fasting blood glucose levels in the uncontrolled type 2 DM group were higher than in the controlled type 2 DM group, with median values of 9.05% and 178 mg/dL. The number of leukocytes, neutrophils, and monocytes showed a higher mean tendency in the uncontrolled type 2 DM group ( $8.45 \pm 1.58$  cells/ $\mu$ L;  $4.98 \pm 1.32$  cells/ $\mu$ L;  $0.55 \pm 0.18$  cells/ $\mu$ L) compared to the controlled type

2 DM group ( $7.48 \pm 2.0$  cells/ $\mu$ L;  $4.25 \pm 1.57$  cells/ $\mu$ L;  $0.48 \pm 0.12$  cells/ $\mu$ L) (Table 2). However, only significant differences were found in the number of leukocytes ( $p < 0.05$ ). The number of lymphocytes showed a higher mean tendency in the controlled type 2 DM group ( $2.46 \pm 0.59$  cells/ $\mu$ L) than the uncontrolled type 2 DM group ( $2.36 \pm 0.64$  cells/ $\mu$ L) (Table 2).

The next step was to determine the difference of NLR and LMR values in controlled and uncontrolled type 2 diabetes mellitus patients. The NLR value showed a significant difference between the two groups with type 2 diabetes ( $p = 0.019$ ). The LMR values did not show a significant difference between the two groups ( $p = 0.200$ ) (Table 3).

## DISCUSSION

Type 2 diabetes is characterized by a chronic inflammatory state which is part of the activation of the natural immune system. This condition is caused by the formation of pro-inflammatory mediators and an increase in the formation of the end result of excess glycation. Increased oxidative stress also exacerbates the inflammatory process in diabetic patients. Prolonged hyperglycemia is the main factor that causes vascular changes in DM type 2.<sup>7,8</sup> NLR and LMR are used as markers of inflammation, a predictor of heart disease, malignancy, and complications associated with diabetes.<sup>5,6</sup>

This study found that from all type 2 DM patients, the proportion of male patients was higher than females. This is because men are more susceptible to oxidative stress than women, so it disrupts the antioxidant system and can be a factor in developing type 2 diabetes complications. The greatest proportion range age group for controlled and uncontrolled type 2 DM was 46-55 years. The use of insulin therapy was higher in the controlled group, while the uncontrolled group used more anti-diabetic oral treatment.

The study of leukocyte parameters showed higher results on the mean number of leukocytes, neutrophils, and monocytes in the uncontrolled type 2 DM group. At the same time, the lymphocyte count was higher in the controlled type 2 DM group. A significant difference was only found in the number of leukocytes ( $p$

$< 0.05$ ). These results are consistent with Sefil F et al., and Hussain M et al., which shows a significant difference in the higher number of leukocytes in uncontrolled type 2 diabetes mellitus patients.<sup>9,10</sup> The results of this study are different from a study conducted by Mendes BB et al., which showed that there was no significant difference in the number of leukocytes between the two groups.<sup>4</sup>

Type 2 diabetes is an inflammatory condition that can lead to increased production of monocytes and neutrophils. Acute and chronic inflammation can increase NLR in DM patients. Hyperglycemic conditions produce excessive glycation products and cause vascular changes. This condition causes neutrophil activation due to the release of Reactive Oxygen Species (ROS). Neutrophil activation includes changes in neutrophil morphology and the appearance of immature neutrophils in the circulation. Higher neutrophils are associated with thrombus formation processes and ischemic injury caused by hyperglycemia.<sup>7,8,11</sup>

In chronic inflammation, there is usually an increase in lymphocytes, but in patients with type 2 diabetes, the lymphocyte value is lower due to Insufficiency of Lymphocyte Proliferation (IPL), so the lymphocyte value in uncontrolled type 2 DM patients is lower than in controlled type 2 DM patients. The decrease in lymphocyte proliferation is caused by decreased expression of interleukin-2 receptors (IL-2) due to Clusters of Differentiation Antigen 25 (CD25) deficiency. This condition causes a decrease in the value of lymphocytes and an increase in the value of neutrophils.<sup>9,11</sup>

This study indicates a significant difference between the NLR value of the controlled type 2 diabetes group and the uncontrolled type 2 diabetes mellitus group. These results support previous research conducted by Sefil F et al., and Devamsh GN et al., who showed that NLR was higher in uncontrolled type 2 DM patients.<sup>9,12</sup>

Hyperglycemia accompanied by hypercholesterolemia triggers progenitor cells to produce monocytes. Increasing the number of monocytes in the circulation will increase the recruitment of monocytes

to the injured tissue.<sup>13</sup> Monocytes and macrophages have an important role in all stages of atherosclerosis and diabetes complications such as diabetic kidney disease and diabetic retinopathy. Because monocytes are circulating cells that can enter all injured tissue and are associated with atherogenesis.<sup>13</sup> LMR is a marker of inflammation that compares the value of lymphocytes and monocytes. Study on differences in LMR values in controlled and uncontrolled type 2 DM patients is still limited. A study on LMR has more to do with prognostic factors in the incidence of DM complications. The prognostic value of LMR has been described in a previous study on tumors and diabetic retinopathy.<sup>14</sup> In this study, the LMR values in the two groups did not show significant differences. Several factors such as body mass index, lipid profile, and duration of suffering from diabetes may be confounding factors.

The limitation in this study is the sample is taken from secondary data, so the accuracy is questionable. There is very limited information about the type of therapy and other clinical conditions.

## CONCLUSION

Neutrophil to lymphocyte ratio (NLR) in the uncontrolled type 2 DM group was significantly higher than in the controlled type 2 DM group. Meanwhile, the lymphocyte to monocyte ratio (LMR) did not significantly differ between the two groups. Further research that did not use secondary data is expected so the patient's body mass index, lipid profile, length of diabetes, and type of therapy can be evaluated.

## CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

## ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Faculty of Medicine, Sanglah General Hospital, Bali, Indonesia, with number 1818/UN14.2.2.VII.14/LT/2020.

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None.

## AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the study results through publication.

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