

## Neutrofil-Limfosite Ratio as Marker Severity Non Proliferative Diabetic Retinopatic

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### ABSTRACT

One of the chronic microvascular complications of type 2 diabetes is diabetic retinopathy (DR). Diabetic retinopathy is assessed through fundoscopy and one type of DR is non-proliferative. Several studies have assessed the neutrophil-lymphocyte ratio in diabetic retinopathy. This study aims to determine the neutrophil-lymphocyte ratio as a marker of non-proliferative diabetic retinopathy. Cross sectional design was applied in this study. Diagnosis of type 2 diabetes is determined based on history and laboratory examination. The research was conducted at Dr. Wahidin Sudirohusodo and Hasanuddin University Hospital in Makassar from November 2018 to April 2019. The non-proliferative DR stages are based on a fundoscopic examination. In addition, blood pressure, BMI, and HbA1C were also checked. The statistical analysis performed was descriptive statistical calculations and the frequency distribution and Anova Test. A study was conducted on 36 subjects with T2DM aged 42-78 years, with a mean of  $57 \pm 9$  years. Mean NLR in Mild NPDR (2.20), Moderate NPDR (2.23), Severe NPDR (2.94). This shows an increase in the Mean NLR value followed by an increase in the severity of the NPDR-type DR, although it is not statistically significant ( $p > 0.05$ ). It was found that the corresponding increase in the NLR value was followed by an increase in the severity of the NPDR-type DR

**Keywords:** Type 2 DM, Neutrophil-Lymphocyte Ratio, Diabetic Retinopathy

### INTRODUCTION

Diabetes Mellitus (DM) type 2 is one of the main health problems where the incidence and prevalence are increasing worldwide, especially in people in Indonesia, especially in big cities (Qanita, 2011; Fong et al., 2004). This exponential increase in the incidence of type 2 diabetes will certainly be followed by an increase in the likelihood of chronic complications of type 2 diabetes. Various prospective studies clearly show an increase in diseases due to blockage of both microvascular blood vessels such as

retinopathy, nephropathy, and neuropathy as well as macrovascular diseases such as coronary artery disease and also lower leg veins (Fong et al., 2004).

Diabetic Retinopathy (DR) is one of the chronic microvascular complications of type 2 diabetes. Diabetic retinopathy is classified into non-proliferative diabetic retinopathy and proliferative diabetic retinopathy, where non-proliferative diabetic retinopathy is an early stage of diabetic retinopathy and proliferative diabetic retinopathy is an advanced stage in diabetic retinopathy (Fong et al., 2004). Research by Mei Li et.al shows that a higher NLR value is a reliable biomarker for the occurrence of DR (Li et al., 2020). This study will assess the specific neutrophil-lymphocyte ratio in non-proliferative diabetic retinopathy.

## METHODS

The research was conducted at the Wahidin Sudirohusodo Central General Hospital (RSUP) and Hasanuddin University Hospital. The research design used was analytic observational with cross sectional design with type 2 DM patients who met the inclusion criteria, namely a) Age > 18 years b) Long suffering from diabetes > 5 years c) Willing to participate in the study. With exclusion criteria a) Severe infection b). Pregnancy c) Malignancy d) Heart failure e) Urinary tract infection Approval and research ethical requirements were issued by the Biomedical Research Commission on Humans, Hasanuddin University Medical Faculty.

The results of the HbA1C examination were divided into controlled (HbA1c <7) and uncontrolled (HbA1C ≥ 7). Blood pressure assessments were classified into hypertensive and non-hypertensive. Body mass index (BMI) is categorized into normal, overweight, obese I, and obesity II. The statistical test used is the Chi-Square test and significant test if  $p < 0.05$ . Minimum sample size of 30.

## RESULTS

Data analysis was performed on 36 subjects with T2DM aged 42-78 years, with a mean of  $57 \pm 9$  years. Table 1 describes the characteristics of the subjects of this study, consisting of gender, BMI, blood pressure, HbA1C, and funduscopy. Subjects consisted of men (36.1%) and women (63.9%).

Table 1. Characteristics of Research Subjects

variable		n	%
gender	man	13	36,1
	woman	23	63,9
IMT	Normal	7	19,4
	Overweight	10	27,8
	Obese 1	17	47,2
	Obese 2	2	5,6
Hypertension	already	17	47,2
	do not	19	52,8
age	< 65	30	83,3
	≥ 65	6	16,7
HbA1c	< 7	7	8,3
	≥ 7	75	91,7

NLR	0.75 – 1.40	8	22,2
	1.41 – 1.96	10	27,8
	1.97 – 2.68	7	29,4
	2.69 – 7.56	11	20,6
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	Funduscopy	Mild NPDR	5
Moderate NPDR		13	36,1
Severe NPDR		18	50,0
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Mean NLR is lowest in Mild NPDR (2.20), and highest seen in Severe NPDR (2.94), although statistically insignificant ( $p > 0.05$ )

Table 2. Correlation of Funduscopy with NLR

Funduscopy	N	Mean	SD	P
Mild NPDR	5	2,20	0,837	
Moderate NPDR	13	2,23	1,166	0,174
Severe NPDR	18	2,94	1,162	

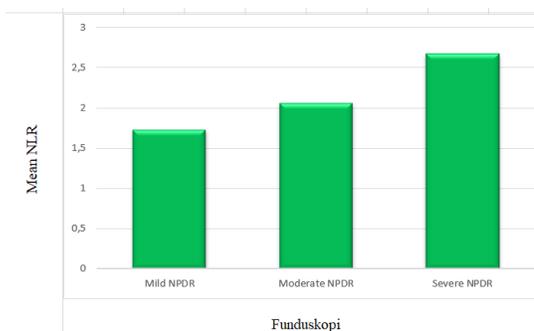


Figure 1. Mean NLR Comparison by Funduscopy

Table 3 shows no significant differences in the severity of non-proliferative diabetic retinopathy according to sex, BMI, blood pressure and HbA1c levels ( $p > 0.05$ ). This table also shows a significant relationship between age and an increase in the degree of non-proliferative diabetic retinopathy where the percentage of p value  $< 0.05$

Table 3. Sex, Age, Blood Pressure, BMI, and HbA1c Relationship with Diabetic Grading Retinopathy

NPDR			Total	P
Mil	Mo	Se		
<hr/>				

		d	der	ver		
		ate	e			
gender	man	2 5,6 %	3 8,3 %	8 22, 2 %	13 36, 1 %	0,46
	woman	3 8,3 %	10 27, 8 %	10 27, 8 %	23 64, 6 %	
age	< 65 years old	5 13, 9 %	8 22, 2 %	17 47, 2 %	30 83, 3 %	0,03
	≥ 65 years old	0 0,0 %	5 13, 9 %	1 2,8 %	6 16, 7 %	
IMT	Normal	0 0,0 %	5 13, 9 %	2 5,6 %	7 19, 4 %	0,42
	Overwe ight	2 5, 6 %	2 5, 6 %	6 16 ,7 %	10 27 ,8 %	
	Obese 1	3 8, 3 %	5 13 ,9 %	9 25 ,0 %	17 47 ,2 %	
	Obese 2	0 0, 0 %	1 2, 8 %	1 2, 8 %	2 5, 6 %	
Hyperte nsion	already	2 5, 6 %	5 13 ,9 %	10 27 ,8 %	17 67 ,2 %	0,60
	do not	3 8, 3 %	8 22 ,2 %	8 22 ,2 %	19 52 ,8 %	
HbA1C	< 7	1 2, %	0 0, %	2 5, %	3 8, %	0,32

	8	0	6	3
	%	%	%	%
>=7	4	13	18	75
	11	36	44	91
	,1	,1	,4	,7
	%	%	%	%

## DISCUSSION

In this study, it was found that more women suffer from diabetes (63.9%) than men (36.1%) which is in accordance with the characteristics of diabetics where if it is related to body mass index, the more suffering is women. (obese 1 = 47.2%), this is in accordance with what was explained by (Kautzky-Willer et al., 2016).

Another characteristic is that the incidence of both proliferative and non-proliferative diabetic retinopathy is more common in patients with type 2 diabetes who have HbA1c more than 7%. In this study it was also found that patients with diabetic retinopathy had an HbA1c level of more than 7% as determined by the American Diabetic Association (ADA) and this has been studied by Cho et al., (2013) that the HbA1c threshold above 6.5% allows the correct detection of diabetic retinopathy. The UK Prospective Diabetes Study (UKPDS) shows that improved blood glucose control reduces the risk of retinopathy and nephropathy events and reduces neuropathy. The overall rate of microvascular complications was decreased by 25% in patients receiving intensive therapy compared to conventional therapy. Epidemiological analysis of the UKPDS data shows a continuing association between the risk of microvascular complications and glycemia, so that for every percentage point decrease in HbA1c (e.g. from 8 to 7%), there is a 35% reduction in the risk of microvascular complications (Fong et al., 2004)

In this study, it was found that the higher the mean of NLR, the higher the severity of non-proliferative diabetic retinopathy even though it was not statistically significant ( $P > 0.05$ ). This is in line with a study by Mei Li, et.al. where they observed that the NLR in patients with diabetic retinopathy was higher than that of patients without diabetic retinopathy. And in line with research Cagri Ilhan et.al. where getting the NLR cut off with a value of 2.11 or more is a sign of severe NPDR or PDR. In Memnune Ulu Sena et.al's study, the results were in line where the NLR value was correlated with the incidence of DR and DR severity itself ( $r = 0.466$ ,  $P < 0.001$ ; and  $r = 0.630$ ,  $P < 0.001$ , in their respective categories) Li et al., 2020; Ulu et al., 2013).

In this study, it is also found in Table 3 that the NLR value correlates with the patient's age when suffering from DR, where those under 65 years of age have a tendency to experience DR more frequently. Several literature reviews suggest that the effect of age on the prevalence and severity of diabetic retinopathy is unclear, and varies with the population studied. The UKPDS study reported that older age ( $> 58$  years) was a risk factor for the incidence of diabetic retinopathy (RR 2.1, 95% CI 1.5 to 2.7) but not the incidence. A study conducted on patients with diabetic retinopathy in Singapore found those who were aged 65 and under had a higher risk of developing diabetic retinopathy (multivariate OR 2.2,  $p < 0.001$ ).

Other studies have also identified younger age as a risk factor for DR. The Wisconsin Epidemiological Study of Diabetic Retinopathy reported a younger severity of age-related retinopathy when the diagnosis of DR was made. The same study found that the incidence of retinopathy, progression of retinopathy, and progression to proliferative retinopathy was highest in the group diagnosed before age 30 years. A clinical-based cross-sectional study in Singapore reported that younger age of the patient was a risk factor for DR. (multivariate OR 0.97,  $p < 0.00$ ) (Namperumalsamy et al., 2009; Stratton et al., 2001; Tan et al., 2010; Klein et al., 1994; Lim et al., 2008).

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