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Relationship of Neutrophil Lymphocyte Ratio and Glomerulus Filtration Rate in Diabetic Nephropathy Patients at H. Adam Malik Hospital, Medan, Indonesia

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ABSTRACT

Background: Diabetic nephropathy is a serious complication of diabetes mellitus (DM). The neutrophil-lymphocyte ratio is the result of the relative count of neutrophils divided by the relative number of lymphocytes in diabetic nephropathy patients in % units obtained from routine hematology results using EDTA blood samples and measured by flow cytometry with Sysmex XN-1000, glomerular filtration rate was measured according to the Cockroft-Gault formula. This study aimed to determine the relationship between neutrophil lymphocyte ratio (NLR) and glomerular filtration rate in diabetic nephropathy patients.
Subjects and Method: This was a cross sectional study conducted at H. Adam Malik Hospital, Medan, North Sumatera, Indonesia, from November 2022 – January 2023. 30 diabetic nephropathy patients were selected for this study consecutively. The dependent variable was the glomerular filtration rate. The independent variable was the NLR. Blood sample was taken for a complete blood count and creatinine examination. Data were analyzed using the Spearman test.
Results: NLR was negatively associated with eGFR in patients with diabetic nephropathy, but it was statistically non significant (r= -0.25; p= 0.186).
Conclusion: NLR is negatively associated with eGFR in patients with diabetic nephropathy, but it is statistically non significant.

Keywords: neutrophil lymphocyte ratio, glomerular filtration rate, diabetic nephropathy

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BACKGROUND

Diabetic nephropathy is a serious complication of diabetes mellitus (DM) such as cardiovascular disease, and progression to End Stage Renal Disease (ESRD) which is associated with an increased risk of death (Chewcharat A, et al, 2020). The process of changing kidney function begins with a state

of progressive hyperglycemia which stimulates kidney cell hypertrophy, extracellular matrix synthesis and changes in capillary permeability. Hyperglycemia will also cause non-enzymatic glycation of amino acids and proteins to form Advanced Glycation End Products (AGEs). The formation of AGEs causes thickening of the glomerular basement membrane and tubulointerstitial fibrosis resulting in renal sclerosis. This process causes glomerular filtration to be disrupted and microalbuminuria occurs which ends in diabetic nephropathy (Park HC, et.al, 2019). This neutrophil-lymphocyte ratio is also used as a marker of inflamation in diabetic nephropathy. The neutrophil-lymphocyte ratio is the result of the relative count of neutrophils divided by the relative number of lymphocytes in diabetic nephropathy patients in % units obtained from routine hematology results using EDTA blood samples and measured by flow cytometry with a Sysmex XN-1000. The glomerular filtration rate is measured according to the Cockroft-Gault formula (Khandare et al., 2017).

A study by Azikin et al. (2018), examined the relationship between NLR and eGFR in the diabetic nephropathy group with Chronic Kidney Diseases (CKD). The NLR value increased by (Mean= 3.19; SD= 1.83) and GFR decreased by (Mean= 30.54; SD= 16.45). There is a negative and significant relationship between NLR and GFR (r= -0.635; p< 0.001). There is a significant relationship between increased NLR and decreased GFR in patients with diabetic nephropathy (Azikin et al, 2018).

A study by Fawwad et al. (2018) reported the NLR improvement (Mean= 3.19; SD= 1.83) was followed GFR reduction (Mean= 30.54; SD= 16.45) in the diabetic nephropathy with CKD group. The results of the research show that there is a relationship between the neutrophil-lymphocyte ratio and a decrease in GFR with a correlation coefficient of r=-0.635 and a coefficient of determination of 0.403, meaning that every increase in the neutrophil-lymphocyte ratio will be followed by a decrease in GFR of 40%. (Fawwad et al, 2018) .

From previous research data, it has never been carried out at H. Adam Malik General Hospital, Medan. Therefore, research on the relationship between neutrophil lymphocyte ratio (NLR) and a decrease in glomerular filtration rate in diabetic nephropathy patients is a predictor to help in the severity of diabetic nephropathy patients. This research was carried out at H. Adam Malik General Hospital, Medan.

SUBJECTS AND METHOD

1. Study Design

This was a cross sectional study conducted at H. Adam Malik Hospital, Medan, North Sumatera, Indonesia, from November 2022-January 2023.

2. Population and Sample

The subjects in this study were 30 diabetic nephropathy patients, using a consecutive sampling technique who met the criteria, namely Type 2 DM sufferers with chronic kidney disease and aged >40 years and were willing to take part in the study and the exclusion criteria were patients who had Hypertension Nephropathy, obstructive renal failure, Acute renal failure, patients with kidney tumors, sufferers of type 1 diabetes, gestational and other types.

3. Study Variables

The dependent variable is the neutrophil lymphocyte ratio, the independent variable is the glomerular filtration rate.

4. Operational Definition of Variables

Diabetic nephropathy is a complication that often occurs in people with type 2 DM. In this disease there is damage to the kidney filter or what is known as the glomerulus with kidney damage ≥3 months with protein

≥+1 found in the morning urine specimen or regular urine with high serum creatinine ≥2.0 mg/dl, then characterized by a decrease in eGFR <60ml/min/1.73m².

NLR is the result of the relative neutrophil count divided by the relative lymphocyte count in diabetic nephropathy patients in % units obtained from routine hematology results.

Glomerular filtration rate is the best test to measure the level of kidney function and determine the stage of kidney disease.

5. Instrument

Patients were analyzed using interviews to obtain data on subject characteristics including age, gender, duration of suffering from Type 2.

Diabetes Mellitus and laboratory examinations including examination of neutrophils, lymphocytes, urea, creatinine in diabetic nephropathy patients in accordance with the research inclusion criteria.

6. Data Analysis

Data were analyzed using the Statistical Program and Service Solution (SPSS) software program, for analysis using the Spearman Correlation test with all statistical tests with a p value < 0.05 considered significant.

7. Research Ethics

This research has received approval from the Ethics Commission of the Faculty of Medicine, University of North Sumatra with No. 24/KEPK/USU/2023 and research permission from the R&D Installation of H. Adam Malik Hospital Medan with No. LB.02.02/XV.III.2.2.2/260/ 2023.

RESULTS

This study was attended by 30 type 2 DM patients with diabetic nephropathy who were treated at H. Adam Malik General Hospital, Medan. All subjects met the inclusion criteria. Demographic characteristics are presented in Table 1. The majority of the study were men, namely 19 people (63.3%) with an average age of research subjects of 58 years, with a long history of suffering from Type 2 DM >10 years, namely 21 people (70%) .

Table 1. Characteristics of study subjects

Variable	Characteristics	N= 30	%
Gender	Male	19	63.3
	Female	11	36.7
Illness duration	<10 years	9	30
	>10 years	21	70

Laboratory characteristics are presented in table 2. It was found that the mean of age was 58 years old and mean of body weight was 63.73 kg. NLR and eGFR values were found to be not normally distributed. The median creatinine level was 3.06 mg/dL (1.37 - 4.24). The median neutrophil value was 76.20% (60.40% - 96.60%), the median lymphocyte value was 14.20% (2.50% - 31.00%), the median NLR value was 5.36 (2.11 - 23.68) and the median eGFR value was 22.50 mg/dL (14 – 46).

Table 2. Laboratory results of research subjects

Variable	N	Mean	Median	SD	Min.	Max.
Age (years old)	30	58.4	58	6.36	46	69
Weight (kg)	30	63.73	64	5.8	56	77
Ureum, mg/dL	30	135.7	148	43.15	43	188
Kreatinin, mg/dL	30	3.19	3.06	0.76	1.37	4.24
Neutrofil	30	77.47	76.2	10.63	60.4	96.6
Limfosit	30	4.54	14.2	8.31	2.5	31

NLR	30	7.89	5.36	5.63	2.11	23.68
eGFR , mg/dL	30	22.33	22.5	6.71	14	46

Table 3 showed the results of Spearman correlation. Table 3 reported that NLR was negatively associated with eGFR in patients with diabetic nephropathy, but it was statistically non significant (r= -0.25; p= 0.186).

Table 3. Correlation between Neutrophil Lymphocyte Ratio (NLR) and Glomerular Filtration Rate (eGFR) in Type 2 DM Subjects with Diabetic Nephropathy

Variable	r	p
NLR	-0.25	0.186

DISCUSSION

This study was attended by 30 type 2 DM patients who were treated at H. Adam Malik General Hospital, Medan. All subjects met the inclusion criteria. In table 1 there are more male patients than female (36.7% vs 63.3%). The results of this study are in line with research conducted by Azikin et al during February 2015 to February 2016 when there were more male patients than female patients (50.4% vs 49.6%) (Azikin et al., 2018). Apart from that, this research is in line with other research by Ren et al, the trigger is more in men where smoking is a risk factor for diabetic nephropathy in diabetic men in China (Ren et al, 2022) This is different from research conducted by Heng et al, where this research found more female patients, amounting to 72.20% (Heng et al, 2020). The results of this study also contradict research conducted by Adnyani et al which stated that there are more women and are the main cause of type 2 diabetes mellitus due to a decrease in the hormone estrogen, especially during menopause. Another influencing factor is womens body weight, which is often not ideal, so this can reduce insulin response sensitivity. This is what makes women more likely to suffer from diabetes than men (Adnyani et al, 2021).

In this study, 21 people (70%) also found a long history of suffering from Type 2 DM >10 years. This is not in line with Erny's research. K, et al where in this study, 65 patients with chronic complications of diabetic nephropathy and peripheral vascular disease were found, 42 patients had suffered from DM for ≤ 5 years (64.6%) and 23 patients had suffered from DM for >5 years. years (35.4%) (Erny et al., 2020). A study by Kothai et al. (2020) found that the majority of patients had suffered from diabetes between 6-15 years, 40% (Kothai et al., 2020).

The average age of this study subjects was 58.08 years. Heng et al. (2020) also reported the similar results (Mean of age= 56 years old). Apart from that, another study by Adnyani et al, 2021 where the largest number of subjects experienced diabetes mellitus in the 45-60 year age group. The hormones estrogen and progesterone have the ability to increase the insulin response in the blood. When menopause occurs, the insulin response decreases due to low estrogen and progesterone hormones. According to theory, it is stated that age ≥ 60 years is associated with chronic complications of diabetic nephropathy in diabetes mellitus sufferers because in old age, physiological body function decreases due to the aging process, there is a decrease in insulin secretion or resistance so that the body's ability to control high blood glucose is less than optimal. 42

In laboratory characteristics in this study, the mean neutrophil lymphocyte ratio (NLR) value was 7.89 with the lowest value being 2.11 and the highest being 23.68. The mean glomerular filtration rate (eGFR) was 22.33 mg/dL with the lowest value being 14 mg/dL and the highest being 46 mg/dL. The results of this study are in line with research conducted by He et al. They conducted a study on 50 type 2 DM patients, 30 of whom were 60% subjects with CKD with an average fasting KGD of 224 mg/dl. Mean HbA1c was 7.9%. The mean urea was 98 mg/dL. The mean creatinine was 2.24 mg/dL with the lowest level being 0.43 mg/dL. The mean neutrophil was 73.4%. The average lymphocyte count was 17.26%. The mean neutrophil lymphocyte ratio (NLR) value was 4.99. The mean glomerular filtration rate (eGFR) was 46.45 mg/dL (He et al, 2022).

A study by Yoshitomi et al. (2019) NLR values ranged from 0.51 to 1.86 in the low NLR group, and from 1.87 to 5.92 in the high NLR group. For all subjects, the median eGFR value was 33.6 mL/min/1.73 m^2. An increase in the number of neutrophils reflects oxidative stress and a lower number of lymphocytes reflects a decrease in nutritional status, oxidative stress is involved in the development of kidney disease in CKD (Yoshitomi et al. 2019).

The simplest way to assess kidney functional status in type 2 DM patients is to examine serum urea and creatinine and calculate the Glomerular Filtration Rate. Urea is the end product of protein metabolism which is excreted through the kidneys. Elevated blood urea nitrogen is an indication of dehydration and prerenal failure or kidney failure. Creatinine is the end product of muscle metabolism which is filtered by the glomerulus and secreted in the urine. Disturbances in the glomerular filtration system are indicated by an increase in creatinine levels. Examination of serum urea and creatinine levels is a good indicator for assessing kidney function in type 2 DM patients (Dabla PK, 2019).

This findings showed that there was no significant correlation between NLR and eGFR. Kothai (2020) had similar findings that there is a negative relationship between eGFR and NLR (r= -0.21, p=0.006). Using the ROC curve, it was found that NLR with 7 cutoffs had a sensitivity and specificity of 88.89% and 94.9% respectively in predicting diabetic nephropathy (AUC= 93.7%) with a positive likelihood ratio of 17.48 and negative likelihood ratio of 0.11.

Meanwhile, these results contradict a study by Azikin et al. (2018). The NLR value of diabetic nephropathy sufferers increased by (Mean= 3.19; SD= 1.83) and GFR decreased by (Mean= 30.54; SD= 16.45). The Spearman test showed a negative and significant relationship between NLR and GFR (r= -0.64, p<0.001).

This study obtained slightly different results from other studies showing that hyperglycemia promotes an increase in the number of circulating neutrophils, and the migration of neutrophils via chemokines to the site of glomerular basement membrane injury promotes an inflamatory cascade through further chemotaxis from mononuclear macrophages (Zhang et al., 2022).

While the results of this study did not show a significant association between high neutrophil counts or low lymphocyte counts and poor renal outcomes, the high NLR group had predictive value for outcomes. These results indicate that NLR itself, rather than absolute neutrophil or lymphocyte counts, is a useful marker for predicting the development of kidney disease (Yoshitomi, 2019).

The results of the study have limitations, including several factors that can

influence the results which are not significant, such as the influence of inflammatory factors, obesity, infection, immune disorders, etc. and in samples from previous studies, research samples were taken with stage V chronic kidney disease patients, whereas In this study, we tried to take research samples from patients with stage III – IV chronic kidney disease. So further research is needed using better methods and paying attention to the factors of receiving hemodialysis and not having hemodialysis on patients which can influence the results of this study. This study showed that in diabetic nephropathy patients a weak correlation was found where an increase in the neutrophil lymphocyte ratio was followed by a decrease in the glomerular filtration rate but no statistically significant relationship was found. Further research is needed in type 2 DM patients with kidney failure and patients who have not received hemodialysis and who have received hemodialysis to analyze the comparison of the neutrophil lymphocyte ratio value with the glomerular filtration rate to prevent the process of diabetic nephropathy earlier.

AUTHOR CONTRIBUTIONS

Jelita Siregar and Santi Syafril as supervisors and providers of input regarding literature reviews and research methods. Asrii Merlin is a writer and thinker who analyzes data and discusses results.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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