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The correlation between the neutrophil-to-lymphocyte ratio and random blood glucose in patients with type 2 diabetes mellitus in Prof. Dr. I G. N. G. Ngoerah Hospital

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ABSTRACT

Background: Diabetes mellitus and complications related to this disease have become a great problem affecting one in eleven adults. Pathophysiologically, this disease occurs due to impaired insulin secretion, resulting from systemic dysfunction in metabolic homeostasis involving inflammatory processes. One marker that can be used to measure such chronic inflammation is the neutrophil-lymphocyte ratio. Therefore, this study aims to evaluate the association between the neutrophil-to-lymphocyte ratio (NLR) with random blood glucose in patients with type 2 diabetes mellitus in Prof. Dr. I G. N. G. Ngoerah Hospital

Methods: Our study is a cross-sectional study with secondary data from medical records and involved 155 type 2 diabetes mellitus patients who received inpatient or outpatient care at Prof. Dr. I G. N. G. Ngoerah Hospital in the period of 2021-2022.

Results: Our analysis found a significant correlation between the neutrophil-lymphocyte ratio with random blood sugar levels ($r = 0.228$; $p = 0.004$). Additionally, the analysis also found a significant difference in random blood sugar level between the normal with the high neutrophil-lymphocyte ratio groups ($p = 0.023$; median difference = 39.5 mg/dL).

Conclusion: It can be inferred that there is a weak and significant correlation between NLR with random blood glucose level in type 2 diabetes mellitus patients.

Keywords: diabetes, neutrophil-to-lymphocyte ratio, random blood glucose.
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INTRODUCTION

Diabetes mellitus and complications related to this disease have become a great problem worldwide. International data in 2018 estimates that approximately 415 million patients aged 20 to 79 years suffer from diabetes mellitus representing one in eleven adults.[1] Diabetes mellitus can be the result of insufficient insulin production and impaired insulin function. Pathophysiologically, this disease occurs due to impaired insulin secretion, resulting from systemic dysfunction in metabolic homeostasis involving inflammatory processes. Various other pathophysiological processes are also associated with T2DM, some of which are inflammation, immune system, incretin effects, adipose dysregulation, liver damage, and several other etiologies.[2]

Immune dysregulation and inflammation are some of the pathways in the pathophysiology of DM according to the egregious eleven theory.[3] Inflammation found in T2DM is chronic and low grade. This is thought to be based on the expansion of fat tissue without the formation of capillaries which causes it to undergo necrosis, remodeling, and hypoxia. Several other factors also contribute to chronic inflammation in diabetes, namely vitamin D deficiency, inflammatory reflexes by the vagus nerve, gut microbiota, periodontitis, genetics, and air pollution.[4–6] Overall, the development of diabetes has been observed to be associated with an increase in inflammatory markers.[7]

The neutrophil-lymphocyte ratio (NLR) has been used to evaluate various diseases' progress and complications and has been studied focus, especially in biomedical research, in the past 10 years. Although the exact cut-off value has yet to be determined, the role of this ratio in describing the homeostatic condition of the immune system has been proven. This ratio describes the comparison of two sides of the immune response system, namely innate or nonspecific immunity which is represented by neutrophil, and adaptive or acquired (specific) immunity which is represented by lymphocytes. As part of the innate immune system, neutrophils will work to inhibit pathogen invasion by releasing pro-inflammatory cytokines and increase the stress oxidative on the targeted cell by increasing the reactive oxygen species releases. Lymphocytes, on the other hand, play a role in adaptive immunity that has specific responses to

pathogens. Several studies show that high NLR is associated with an imbalanced inflammatory and systemic inflammatory response state.[8] This ratio has been established as one of the indices that can indicate chronic systemic inflammation. With its wide availability and routine checking, this ratio can be applied as a marker of chronic inflammatory processes, especially in diabetes and its glycemic control condition.[9,10] Previous studies have shown a correlation of this ratio to chronic inflammation, DM incidence as well as blood sugar control in DM patients.[9–12] Therefore, this study aims to evaluate the association between the NLR with random blood glucose in patients with type 2 diabetes mellitus in Prof. Dr. I G. N. G. Ngoerah Hospital

METHODS

An observational study using medical records was conducted in a cross-sectional manner with an analytic approach. Subject selection was carried out using a random sampling technique to determine the value of glucose during and the neutrophil lymphocytes ratio of the patients with type 2 diabetes mellitus at Prof. Dr. I. G. Ngoerah Hospital during the period of 2021-2022. Data collection was conducted in August – October 2023. High NLR was classified as NLR > 3.13 based on the instrument's guideline.

All medical records containing diagnoses of type 2 DM at Prof. Dr. I. G. Ngoerah Hospital, Denpasar for the period of 2021-2022 were collected and pooled into a list. Medical record numbers were randomly selected until an adequate sample size was achieved. The formula of Bujang and Baharum (2016) was used as a power analysis to determine the minimal sample.[13] Since the hypothesis is tested two-tailed, the accepted type 2 error is 0.1 (β=0.1) and the accepted type 1 error is 0.05 (α=0.05). From there, a statistical power of 90% and a confidence interval of 95% can be determined. With the null hypothesis of no correlation found (r0=0), and the anticipated correlation strength is 0.3 the minimum sample table shows a minimum sample of one hundred and twelve samples.[14]

The data that has been collected will be confirmed for completeness again. After that, the data will be processed using computer software. Data analysis began with an examination of sample characteristics, namely gender and age frequencies. Next, numerical data will be characterized by descriptive analysis that includes mean, median, and standard deviation. Bivariate data analysis will be performed to gauge the relationship of NLR with random blood glucose levels. If the data distribution is found to be normal, this relationship will be measured using the Pearson correlation test. If the data distribution is found to be abnormal, the relationship will be measured using the Spearman correlation test. An association with p-value < 0.05 is considered a statistically significant association.

RESULTS

A total of 7,186 medical records were pooled. After employing a simple random sampling method, as many as 155 patients were included in the analysis process, of which 83 (53.5%) were male and 72 (46.5%) were female. The subject's age range was 21 years to 64 years old. And the median age was 55 years old. The result of the descriptive analysis of subject characteristics is reported below.

Kolmogorov-Smirnov analysis found abnormal distribution across all collected variables (p < 0.001). There was no effect of age and gender on the dependent variable of interest, i.e. blood glucose level. Our Spearman Correlation Test reported there is no significant relationship between age with blood glucose level (r = -0.127; p = 0.114). In addition, the Mann-Whitney U test also reported there is an insignificant difference in patients' fasting blood sugar levels between the two genders (p = 0.383).

The evaluation of NLR association with random blood sugar level was reported in Table 2. The Spearman Correlation Test reported a weak correlation with a statistically significant value between the NLR dan blood sugar level (r = 0.228; p = 0.004). In addition, the Mann-Whitney U Test also reported a significant mean difference (MD) in blood sugar level in patients with NLR above the normal limit compared to patients with NLR in the normal limit (p = 0.023; median difference = 39.5). This indicates that NLR levels influence the current blood sugar levels of patients with type II diabetes.

DISCUSSION

Neutrophil lymphocyte ratio (NLR) is an inflammatory marker that can simply be measured, accessible, validated, and used in various diseases. It can reflect the condition of cellular immunity holistically by describing the interaction of the innate and adaptive immune systems[15]. Literature studies have shown that NLR has a better ability to detect subclinical inflammation than the absolute values of neutrophils and lymphocytes.[16] Moreover, the correlation between NLR and cardiometabolic disease risk and their complications and mortality has been consolidated through many studies.[8,17]

This study found a significant association with a weak correlation between NLR with blood sugar levels. Significant differences were also found in

Table 1. Characteristics of the study population

Characteristics	Result (n=155)
Sex, n (%)	
Male	83 (53.54%)
Female	72 (46.45%)
Median age (IQR)	55 (12)
Neutrophil Lymphocyte Ratio, median (IQR)	3.95 (9)
Blood Sugar, mg/dL, median (IQR)	202.00 (132.00)

Abbreviations: IQR, interquartile range.

Table 2. Association between the NLR and random blood glucose of the subject involved

		Random Blood Sugar
Neutrophil-to-lymphocyte ratio	r	0.228
	p	0.004
	n	115

the blood sugar levels of the normal NLR and high NLR groups. This finding is in line with a study by Hussain, *et al* which found a strong association between NLR values and blood sugar control based on HbA1c levels ($p < 0.001$).[16] Similarly, Shiny, *et al* found that individuals with glucose intolerance had higher NLR values than individuals with normal glucose tolerance, and DM patients had higher NLR values than both. The study by Sefil, *et al* found significant differences in NLR levels in good and poor blood sugar control patients with diabetes mellitus ($p < 0.001$). In addition, this study mentioned a correlation between NLR and HbA1c levels ($r = 0.577$; $p < 0.001$).[17] Similar results have also been found in several other studies.[9–12] These findings come from decreased lymphocyte production because of a decrease in interleukin-2 receptor expression and increased neutrophils that have been observed in conjunction with increased ROS under hyperglycemic conditions.[17] The absolute and relative decrease of insulin is involved in increasing the NLR level due to its decreased lymphocyte proliferation promotion activity.[19] In addition, the increase in NLR also occurs due to the high number of neutrophils as a result of hyperglycemia through the interaction of glucose with the receptor for advanced glycation end products (RAGE) and increased protein kinase C activity, indirectly inhibiting neutrophil performance.[20,21]

Some findings have contradictory results to this study. A study done in the Korean population found no association between NLR and fasting blood sugar levels and explained that this difference stemmed from the population being healthy individuals, rather than DM patients like previous studies.[19] In addition, a study conducted on the elderly in Surabaya found no association between NLR and fasting blood sugar, HbA1c levels, or post-prandial (after 2-hour after meal) blood sugar[22]. Both studies were not conducted in patients with DM, indicating the increasing significance of the relationship between NLR and blood sugar control with disease progression and insulin resistance.[18]

Inflammation is a by-product of hyperglycemia and insulin resistance, and a cause of both. Endothelial cells have a dynamic and adaptive immune-metabolism phenotype, where cellular metabolic activity undergoes reprogramming in response to inflammatory stimulation.[23] In the face of inflammation, the body needs to facilitate increased proliferation and activity to fight pathogens and prevent increased damage. In endothelial cells, the inflammatory stimulus increases glycolysis as its main source of energy needed to facilitate leukocyte activity and migration.[24,25]

However, to focus glucose utilization for the immune system, glucose consumption in muscle is reduced through decreased blood flow to the muscle due to the inflammatory response. In addition, pro-inflammatory cytokines, including IL-1, IL-6, IL-1b, TNF-a, and interferons have been found to reduce insulin sensitivity in body tissues, reducing glucose consumption.[26] The induced insulin resistance also reduces insulin's activity in increasing peripheral blood flow, one of which is to the muscles, thus exacerbating the low glucose utilization. Furthermore, proinflammatory cytokines such as IL-6 can also increase glucagon secretion by interacting with the central nervous system and pancreatic alpha cells directly.[27]

A hyperglycemic environment alters gene expression in pro-inflammatory cells.[28] Diabetes can increase oxidative stress due to increased activity of NADPH oxidase and advanced glycation end products, triggering an inflammatory response in the endothelium.[29] This observation is consistent with clinical findings revealing that an elevated NLR, a recognized marker of inflammatory condition, was found in individuals with an extended duration of type 2 DM.[30] Chronic hyperglycemia also leads to increased oxidative stress, indicated by increased levels of malondialdehyde as the product of lipid peroxidation, which can result in elevated inflammation.[31] This study has not controlled for confounding variables that could influence the research results so improvements are needed in future studies.

CONCLUSION

Our study concludes that there is a weak but significant association between neutrophil-to-lymphocyte ratio and random blood glucose level in type 2 diabetes mellitus patients.

CONFLICT OF INTEREST

There is no conflict of interest in all of the processes of our research and study publication.

ETHICAL CLEARANCE

This study has been granted an ethical exemption by the Ethical Committee of the Faculty of Medicine, Udayana University with ethical clearance No. 54/UN.14.2.2.VII.14/LT/2023 has obtained research permission from Prof. Dr. I.G.N.G Ngoerah Hospital with the research ID 230706.266.

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AUTHOR CONTRIBUTION

All authors have fully contributed to the research and formulation of the paper.

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