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Correlation between Neutrophil to Lymphocyte Ratio (NLR) and D-Dimer in Patients Covid-19 with Diabetes

Dharma Lindarto[1]*, Franciscus Ginting[2]

[1]*Division of Endocrinology and Metabolism, H. Adam Malik Hospital, Faculty of Medicine, Universitas Sumatra Utara, Medan, Indonesia.*
[2]*Division of Tropical and Infectious Diseases, H. Adam Malik Hospital, Faculty of Medicine, Universitas Sumatra Utara, Medan, Indonesia*

ABSTRACT

Background: The neutrophil-to-lymphocyte ratio (NLR) has been proposed as an inflammatory biomarker. The study aimed to assess the association between NLR and D-dimer in Covid-19 patients with diabetes.

Method: This is a retrospective descriptive and analytical study carried out at NLR, blood rutin and D-dimer, FPG, and PPG levels of COVID-19 patients with comorbid in H. Adam Malik Medan, Indonesia, from May 19, 2020, to June 08, 2021. The data were collected by cheek list, using electronic medical records. The data included age, gender, medical history, comorbidity with diabetics, and ward and ICU admission. All these cases of COVID-19 have been confirmed in the laboratory by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR).

Results: There were 163 COVID-19 patients with diabetes consisting FPG 241.65±122.23 mg/dl, PPG 286.01±123.92 mg/dl, and HbA1c 9.49±2.41%. There is a significant correlation between NRL and hemoglobin, white blood cells, platelets, neutrophils, and D-dimers (all, $p<0.001$*).

Conclusion: Diabetes is the commonest comorbidity in COVID-19 patients, and NLR and other inflammatory assessments have reliable parameters for assessing and evaluating the prognosis of COVID-19 patients as well as an accurate and practical coagulation parameter for predicting mortality.

*Corresponding author at: Division of Endocrinology and Metabolism, H. Adam Malik Hospital, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

E-mail address: dharmalindarto22@gmail.com

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Keywords: Covid-19, Diabetes, D-dimer, Neutrophil to Lymphocyte Ratio (NLR)

ABSTRAK

Latar Belakang*: Rasio neutrofil terhadap limfosit (NLR) telah diusulkan sebagai biomarker inflamasi. Penelitian ini bertujuan untuk menilai hubungan antara NLR dan D-dimer pada pasien Covid-19 dengan diabetes.*

Metode*: Ini adalah studi deskriptif dan analitik retrospektif yang dilakukan pada NLR, rutin darah dan kadar D-dimer, FPG, dan PPG pasien COVID-19 dengan komorbid di H. Adam Malik Medan, Indonesia, dari 19 Mei 2020 hingga 08 Juni 2021. Data dikumpulkan oleh cheek list, menggunakan rekam medis elektronik. Data termasuk usia, jenis kelamin, riwayat medis, komorbiditas dengan penderita diabetes, dan masuk bangsal dan ICU. Semua kasus COVID-19 ini telah dikonfirmasi di laboratorium oleh Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR).*

Hasil: *Terdapat 163 pasien COVID-19 dengan diabetes yang terdiri dari FPG 241,65± 122,23 mg/dl, PPG 286,01 123,92 mg/dl±, dan HbA1c 9,49 2,41±%. Ada korelasi yang signifikan antara NRL dan hemoglobin, sel darah putih, trombosit, neutrofil, dan D-dimer (semua, p<0,001*).*

Kesimpulan: *Diabetes adalah komorbiditas paling umum pada pasien COVID-19, dan NLR dan penilaian inflamasi lainnya memiliki parameter yang dapat diandalkan untuk menilai dan mengevaluasi prognosis pasien COVID-19 serta parameter koagulasi yang akurat dan praktis untuk memprediksi kematian.*

Kata kunci*: Covid-19, Diabetes, D-dimer, Rasio Neutrofil terhadap Limfosit (NLR)*

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1 Introduction

The inflammatory response is a key mechanism in the pathogenesis of atherosclerosis and its progression.[1] Neutrophils secrete inflammatory mediators that can cause vascular wall degeneration. Conversely, lymphocytes regulate the inflammatory response and thus have an antiatherosclerotic role. Therefore, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as an inflammatory biomarker,[2] and a potential predictor of risk and prognosis in CVD.

Insulin resistance (IR), glucotoxicity, and lipotoxicity may cause systemic chronic low-grade inflammation and can be related to AS and lipo hyalinosis.[3,4] Chronic inflammation also leads to the release of proinflammatory and immunomodulatory mediators, such as cytokines and chemokines, which attract leukocytes and create a microenvironment favorable to the development and progression of tumors. Neutrophils and other myeloid cells take part in the inflammatory

response. Activated neutrophils stimulated by tumor necrosis factor-alpha release pro-angiogenic factors, such as vascular endothelial growth.[5]

The neutrophil-to-lymphocyte ratio (NLR) serves as the cheap, facile, widely accessible, and highly stable factor reflecting systemic inflammation, which is less susceptible to physiological states, such as hemoconcentration.[6] An increased NLR is related to serious stress, inflammation, trauma, injury, cancer, or major surgery, which can also predict a poor prognostic outcome in terms of incidence and mortality[6] NLR is a new indicator of subclinical inflammation in diabetes.[7] An increased NLR was significantly associated with IR,[8] and its value acted as a predictive marker, indicating the risk and severity of diabetic complications, such as diabetic retinopathy,[9] diabetic nephropathy,[10] diabetic peripheral neuropathy,[11] and coronary microvascular dysfunction.[12] The NLR shows positive relation to 3-month mortality risk post-stroke.[13] An increasing number of studies have reported the sensitivity of NLR in predicting stroke severity and short-term prognosis.[14-16] However, there are few studies on the role of NLR in cerebrovascular complications of diabetes, that NLR is an independent risk factor for cerebral hemorrhage in patients with type 2 diabetes (T2DM).[17] However, the role of NLR in ischemic stroke patients with diabetes is rarely investigated.

2 Method

2.1 Study Population

This is a retrospective descriptive and analytical study carried out at NLR, blood rutin and D-dimer, FPG, and PPG levels of COVID-19 patients with comorbid in H Adam Malik Medan, Indonesia, from May 19, 2020, to June 08, 2021. The data were collected by cheek list, using electronic medical records. The data included age, gender, medical history, comorbidity with diabetics, and ward and ICU admission. All these cases of COVID-19 have been confirmed in the laboratory by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR). Exclusion criteria were age <18 years, patients who were on anticoagulants or had a history of venous thromboembolism and pregnancy, and only patients who received a D-dimer assay were included in this study. In the assessment of disease severity, critical illness was identified if satisfying at least one of the following criteria: 1) respiratory failure requiring mechanical ventilation; 2) shock performance; 3) multiple organ failure requiring intensive care unit (ICU) monitoring. COVID-19 severity disease divided by 4: 1). Mild; 2). Moderate; 3). Severe; and 4). Critical,[18] and Guidelines for The Prevention and Control of Coronavirus Disease (COVID-19) of The Indonesian Ministry of Health.[19] Examination of D-dimer values with ELFA (Enzyme-Linked Fluorescent Assay)

2.2 Statistical Analysis

The data were entered and analyzed into SPSS software by first performing a descriptive analysis of the various data; Quantitative variables were described by means and standard deviation. we used the Spearman correlation test in an abnormal distribution test between two variables. The difference is considered to be statistically significant when $p< 0.05$. The Institutional Ethics Committee gave its approval to this report.

3 Results

There were 163 COVID-19 patients with diabetes consisting FPG 241.65±122.23 mg/dl, PPG 286.01±123.92 mg/dl, and HbA1c 9.49±2.41 % (Tabel-1).

Table 1 Characteristic Data of Covid-19 Patients with Diabetes

Variable	Mean±SD, n=163
Age (yr)	56.94±10.36
Blood Routine	
Hemoglobin, $x10^9$/L	13.05±2.34
White blood cells, $x10^9$/L	11.11±6.23
Platelets, $x10^9$/L	270.01±128.85
Neutrophils, $x\ 10^9$/L	75.56±14.56
Lymphocytes, $x10^9$/L	15.46±10.83
FPG (mg/dl)	241.65±122.23
PPG (mg/dl)	286.01±123.92
HbA1c (%)	9.49±2.41
D-dimer (ng/ml)	1067.50±1254.56
CRP	0.95±0.50
LDH	362.53 ±202.35
NLR	10.29±11.65

Based on Table 2, there is a significant correlation between NRL and hemoglobin, white blood cells, platelets, neutrophils, and D-dimers (all, $p<0.001$*)

Table 2 Correlation between NLR and marker inflammation

Variable	r	p
Age (yr)	0.134	0.087
Blood Rutin		
Hemoglobin, $x10^9$/L	-0.219	0.005*
White blood cells, $x10^9$/L	0.677	0.001*
Platelets, $x10^9$/L	0.279	0.001*
Neutrophils, x 10^9/L	0.945	0.001*
Lymphocytes, $x10^9$/L	-0.979	0.001*
FPG (mg/dl)	0.142	0.070
PPG (mg/dl)	0.099	0.209
HbA1c (%)	-0.008	0.921
D-dimer (ng/ml)	0.376	0.001*
CRP	-.041	0.605
LDH	0.214	0.006*

4 Discussion

In humans, neutrophils account for 40 to 70% of total white blood cells under physiological conditions. They are the most prevalent circulating polymorphonuclear (PMN) leukocytes. Their main role is to eliminate pathogenic agents at the sites of infectious or non-infectious inflammation. They also play roles in a variety of physiological and pathological processes and are endowed with a plethora of surface receptors for immunological and pathological mediators [20,21]. Neutrophils are responsible for the first line of host immune response against invading pathogens, through different mechanisms, including chemotaxis, phagocytosis, release of reactive oxygen species (ROS), granular proteins, and the production and liberation of cytokines.[22] Neutrophils also play an important regulatory role in adaptive immunity and are the main effector cells during the systemic inflammatory response (SIRS). As regulators of innate immunity, neutrophils recruit, activate, and program other immune cells, secreting an array of pro-inflammatory and immunomodulatory cytokines and chemokines capable of enhancing the recruitment and effector functions of other immune cells, such as dendritic cells (DCs), B cells, NK cells, CD4, CD8, and γδ T cells, as well as mesenchymal stem cells.[23] An isolated rise in neutrophil count, and, consequently, an elevated NLR, can be observed in several conditions: bacterial or fungal infection,[24,25] acute stroke [24], myocardial infarction [25], atherosclerosis [26], severe trauma [27], cancer [28], post-surgery complications [29] and any condition characterized by tissue damage that activates SIRS. This is because the early hyperdynamic phase of infection is characterized by a proinflammatory state, mediated by neutrophils and other inflammatory cells [30]. SIRS is associated with the suppression of neutrophil apoptosis, which augments neutrophil-mediated killing as part of the innate response [30]. Thus, NLR is often characterized by an increase in neutrophils and a decline in lymphocytes. In this study, we found a significant correlation between NRL and hemoglobin, white blood cells, platelets, neutrophils, D-

dimers, and LDH (all, p<0.001*). Thus, NLR may be used as an alternative inflammatory test against Covid-19 infection in diabetic patients.

5 Conclusion

Diabetes is the commonest comorbidity in COVID-19 patients, and NLR and other inflammatory assessments have reliable parameters for assessing and evaluating the prognosis of COVID-19 patients as well as an accurate and practical coagulation parameter for predicting mortality.

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