

Utilization of NLR and PLR Data in Determining Prognosis of Diabetic Ulcer Patient

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Abstract

Diabetes mellitus is a disease of blood sugar control. This can be caused by problematic insulin production or loss of sensitivity of the insulin receptor. Diabetes mellitus especially type 2 has many fatal consequences, one of which is diabetic ulcer. Diabetic ulcers are one of the complications of type 2 diabetes mellitus that could cause decrease of productivity, increase in cost, amputation, even death. Research shows that approximately 0.03% -1.5% of diabetic foot patients require amputation which can reduce productivity and increase costs for treatment. So, studies related to risk factors and determining factor of prognosis need to be conducted for example, NLR and PLR are closely related to inflammation and infection. This article briefly explains various use of NLR and PLR value in determine the prognosis of diabetic patients.

Keyword: Diabetes Mellitus, NLR, PLR, Prognosis

1. Introduction

Diabetes mellitus is a disease of blood sugar control. This can be caused by problematic insulin production or loss of sensitivity of the insulin receptor (Sapra and Bhandari, 2021). It has so many negative impact on a person's quality of life and can even lead to death. International Diabetes Federation (IDF) states that currently there are more than 90 million adults living with diabetes and 747 thousand cases deaths occur due to diabetes in the world. The prevalence of diabetes cases that occur in Indonesia also has quite a lot, namely around 19.5 million people living with diabetes (International Diabetes Federation, 2021). This thing is quite serious, especially because diabetes mellitus has several complications, one of which is diabetic foot.

Diabetic feet occur in approximately 6 percent of people with diabetes, including infections, wounds, and tissue damage. Some symptoms that can be experienced in Diabetic feet are sensory impairment due to peripheral neuropathy and ischemia due to peripheral arterial problems (Mishra *et al.*, 2017). If these two things happen at the same time and not treated immediately, it can progress to diabetic ulcers. This can lead to decrease of productivity, increase in cost, amputation, even death . Research shows that approximately 0.03% - 1.5% of foot patients diabetes requires amputation which can reduce productivity, increased costs for treatment. Apart from that, the impact of diabetic ulcers too very big on a person because it can also end in

death so research regarding risk factors and prognosis is very necessary one of which is infection and inflammation

NLR and PLR is a value that is closely related to the presence of inflammation and infection. NLR consists of the neutrophil value divided by the patient's lymphocyte value while PLR consist of the platelet value divided by the patient's lymphocyte value. NLR and PLR is now studied quite often, especially in relation to the severity and prognosis of a disease. Apart from its relation to disease, the NLR value is often studied because the value is quite easy to obtain just by looking at a complete blood test which is routinely carried out, especially in inpatients. This review was conducted with the aim of evaluating the usefulness of NLR and PLR in predicting the prognosis and outcome of diabetic ulcer patients..

2. Neutrophil Lymphocyte Ratio (NLR)

Neutrophils are part of white blood cells (leukocytes) characterized by having a dense nucleus with 2-5 lobes (Hoffbrand and Moss, 2016). These neutrophil cells are often found in the peripheral bloodstream but can also be found in the bone marrow. These cells are a very important part of the body's immunity. These neutrophils are the first line of defense to respond to an infection and go to the site of the infection. On the other hand, lymphocytes are also one of the cells that provide an immune response originating from the bone marrow. B lymphocytes make antibodies and T lymphocytes help kill tumor cells and control the immune response. These two components can be combined in the form of a ratio, namely the Neutrophil Lymphocyte Ratio (NLR) to be used to determine inflammatory conditions.

Neutrophil Lymphocyte Ratio (NLR) is a marker of the inflammatory process that can be used as a marker of inflammation (Martins *et al.*, 2019). This NLR consists of the number of neutrophils divided by the number of lymphocytes. Neutrophils represent non-specific mediators of inflammation which are the first line of defense for the body while lymphocytes represent regulators or protectors of inflammatory components (Moursy *et al.*, 2015). This NLR is quite stable because it is not easily influenced by physiological, pathological or physical factors.

2.1 NLR in diabetes mellitus patients

In recent years, the use of the NLR has begun to be widely researched, especially in relation to determining inflammation. In diabetes patients, research conducted by Mertoglu and Gunay, (2017) shows that the PLR value can be used to determine the possible severity of blood sugar control problems that lead to diabetes in patients with comorbid obesity. This is known because the lowest NLR value was higher in patient that previously diagnosed with diabetes followed by patient that newly diagnosed with impaired glucose tolerance and the lowest values were obtained in patients with normal glucose tolerance. NLR was also found to be higher in patients who experienced complications such as retinopathy, nephropathy, and peripheral neuropathy which could also increase the patient's chance of death. Currently, it is found that these complications can be considered as a possible occurrence of generalized inflammation (Moursy *et al.*, 2015).

In other cases, this NLR was found to be a predictor of coronary sluggish flow (CSF) because the value was found to be high in diabetes mellitus patients with CSF and the difference was found to have moderate to high significance (Elsanan *et al.*, 2023). Another study conducted by Joshi *et al.*, (2023) also found that NLR could be a predictor of stable ischemic heart disease (SIHD) in diabetes mellitus patients with a sensitivity of 50% and a specificity of 73%. This shows the many benefits of using NLR and PLR, especially in the case of diabetes mellitus patients

2.2 The use of NLR in determining the prognosis of diabetic ulcer patients

Other research states that this NLR can be used to indicate the severity of diabetic foot events. Research conducted by Altay *et al.*, (2019) stated that patients with higher NLR values were found to require more vascular intervention, had a higher risk of amputation, longer treatment duration, and longer IV treatment. Although a relationship was found between the NLR value and the severity of diabetic ulcer patients, the relationship with the severity of infection, which is closely related to the incidence of diabetic ulcers is still unclear (Altay *et al.*, 2019). In some cases, an increase in the NLR value is a marker of a poor prognosis in patients. An increase in neutrophils as an inflammatory response can inhibit the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, T cells, and NK cells (Templeton *et al.*, 2014). In addition, previous research was found that NLR could be a marker for patients with peripheral arterial problems, especially in patients requiring amputation, especially major amputation (Chen *et al.*, 2021)

All the things that have been mentioned from the start are also in line with the study conducted by Serban *et al.*, (2021) which found that there was a significant correlation between NLR with risk for DFU, the severity of lesions, the risk for amputation, and short and midterm mortality. The high value of this biomarker is closely related to chronic hyperglycemia and low-grade systemic inflammation, atherosclerotic and vascular complications, and also the associated septic factor so that regular follow-up of patients is highly recommended (Serban *et al.*, 2021). With the correlation between leukocytes and inflammatory processes, their use especially as inflammatory markers is highly desirable. However, the use of each leukocyte component itself is said to be less stable compared to the use of NLR. Although NLR levels can also be influenced by several things such as dehydration, over-hydration, watery blood specimens, and in-vitro blood specimen handling (Balta, Hastanesi and Ozturk, 2016). Apart from that, NLR calculation data can also be obtained through a complete blood test so it is relatively easy and cheap to do

3. Platelet Lymphocyte ratio (PLR)

Platelets or also called thrombocyte are one of the cells in the blood produced in the bone marrow from fragmentation of megakaryocyte cytoplasm (Hoffbrand and Moss, 2016). These cells function to form clots and stop or slow down bleeding during the wound healing process. Lymphocytes, as in the previous definition, are one of the cells that provide an immune response originating from the bone marrow. These lymphocytes consist of B lymphocytes which make antibodies and T lymphocytes which help kill tumor cells and control the immune response. These two components can be combined in the form of a ratio, namely the Platelet Lymphocyte Ratio (PLR) to be used to determine inflammatory conditions. In the event of infection and inflammation. Platelet levels in the blood will increase in response to this. This condition is called secondary thrombocytosis (Rokkam and Kotagiri, 2022). Meanwhile, lymphocyte levels will decrease, especially in conditions of prolonged sepsis (Mims, 2018). This condition is called lymphocytopenia. On this basis, PLR, which consists of the number of platelets divided by the number of lymphocytes, can be used as a marker of infection and inflammation, and disease severity marker.

3.1 PLR in diabetes mellitus patients

Same like NLR, the use of the PLR has begun to be widely researched, especially in relation to determining inflammation. Specifically in patients with diabetes, research conducted by Mertoglu and Gunay, (2017) shows that the PLR value can be used to determine the possible severity of blood sugar

control problems that lead to diabetes in patients with comorbid obesity. This is known because the lowest PLR value was found in the group of patients diagnosed with diabetes mellitus using the OGTT test, followed by patients with impaired glucose tolerance, and the highest in the normal glucose tolerance group. (Elsanan *et al.*, 2023). Another study conducted by Joshi *et al.*, (2023) also found that PLR could be a predictor of stable ischemic heart disease (SIHD) in diabetes mellitus patients with a sensitivity sensitivity of 73% and a specificity of 46% (Joshi *et al.*, 2023).

In wider clinical use, previous studies stated that this PLR value could be associated with the progression of rheumatoid arthritis (RA) in several groups with different characteristics. This is important because a study conducted found that rheumatoid arthritis is a risk factor for diabetes (Tian *et al.*, 2021). However, this study found that the use of NLR still had more significant benefits in determining disease progression than the use of PLR (Gasparyan *et al.*, 2019). In other studies, it also found that the PLR value had a relationship with systemic lupus erythematosus. PLR values were found to be much higher in patients with SLE. This value can be used as an emerging inflammatory biomarker to be used to assess disease activity and predict it. In this study, it was stated that PLR is a very valuable component in the assessment and prediction of SLE disease activity (El-Said, Adle and Fathi, 2022). Although DM and SLE rarely occur together, information related to this is important because the management of SLE patients accompanied by Diabetes mellitus becomes more complex, especially related to other complications that occur such as renal, peripheral neuropathy and retinal disease (Cortes *et al.*, 2008). In addition, patients with SLE and Diabetes mellitus will have two major risk factors for atherosclerosis.

3.2 The use of PLR in determining the prognosis of diabetic ulcer patients

In the case of diabetic ulcer, PLR values was found to be increased in diabetic foot patients with osteomyelitis and patients undergoing amputation. However, this PLR was not found to be significant in patients who required major amputation. In other studies, it was found that PLR was found to increase significantly in patients with diabetic feet, identified as an independent risk factor for diabetic feet, and could also indicate the severity of diabetic feet using the Wagner grading (Zhang *et al.*, 2021). The pre-amputation PLR value was also found to be higher in patients who died after amputation compared to those with low values, although no statistically significant difference was found. This can be used as a consideration to be more careful in providing action and treatment to patients with high PLR (Gocer *et al.*, 2017)

Apart from these things, an increase in PLR was found to be associated with an increase in medical costs for a patient. However, this increase in PLR is not related to the length of a patient's treatment period (Eren *et al.*, 2020). Several studies also give information that the Platelet Lymphocyte Ratio (PLR) is also a marker that can also be used as a marker for inflammation in several diseases. All the things that have been mentioned from the start are also in line with the study conducted by Serban *et al.*, (2021) which found that there was a significant correlation between NLR and PLR risk for DFU, the severity of lesions, the risk for amputation, and short and midterm mortality. The high value of this biomarker is closely related to chronic hyperglycemia and low-grade systemic inflammation, atherosclerotic and vascular complications, and also the associated septic factor so this study recommend to do the serial dynamic follow up to the patients (Serban *et al.*, 2021). A lot of research has been done on PLR and its significance has been found, but it is not yet widely used. PLR data can also be obtained from complete blood tests which are often carried out in clinical settings. So this PLR examination can be said to be relatively easy and cheap to carry out

4. Conclusion

NLR and PLR are markers of inflammation and infection that are currently widely studied, especially because they are cheap and quite easy to obtain. In diabetic ulcer patients, this NLR can be used to predict the severity of complications, the possibility of amputation, duration and cost of treatment, and also the outcome of patients with diabetic ulcer complications. Similar to NLR, PLR can also be used to predict the possibility of amputation, treatment costs, and severity of diabetic ulcers based on Wagner staging, although it is not related to the length of patient care. Based on several literatures found, these two markers can be used to determine the prognosis of diabetic ulcer patients so that serial follow up is highly recommended and they can be taken into consideration in providing action and treatment to patients.

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