REVIEW

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Neutrophil-to-lymphocyte ratio (NLR) in dermatology perspective: a review

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ABSTRACT

The neutrophil-to-lymphocyte ratio (NLR) is the ratio between the number of neutrophils and lymphocytes in the peripheral blood. Neutrophils are responsible for an initial immune response to pathogens that enter the body through the mechanisms of chemotaxis, phagocytosis, the release of reactive oxygen species (ROS), granular proteins, production and release of cytokines. Neutrophils also have an important role in the occurrence of the systemic inflammatory response (SIRS). There are several types of diseases in the field of dermatology that are also related to NLR. It is associated with the presence of an inflammatory process. In addition, NLR is considered an easy, inexpensive, and reproducible parameter associated with clinical outcomes and disease severity. Several diseases in the field of dermatology found to be associated with NLR include leprosy, Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN), psoriasis, vitiligo, atopic dermatitis, systemic sclerosis, and skin cancer. In recent years, its role as an independent prognostic factor for neoplasms and as an inflammatory biomarker in various acute and chronic diseases has been increasingly established in the dermatology field. However, not all studies have found significant results. One of them is vitiligo which still finds controversial results. For this reason, this literature review will discuss specifics related to several diseases in dermatology associated with NLR.

Keywords: Neutrophil-to-lymphocyte ratio, NLR, systemic inflammatory response, dermatology.
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INTRODUCTION

The neutrophil-to-lymphocyte ratio (NLR) is a simple ratio calculation between the number of neutrophils and lymphocytes in peripheral blood. Neutrophils are responsible for the host's initial immune response against pathogens that enter the body through chemotaxis, phagocytosis, release of reactive oxygen species (ROS), granular protein, production, and release of cytokines. Neutrophils are also important in developing the systemic inflammatory response (SIRS). As immune regulators, neutrophils will recruit, activate, and program other immune cells and secrete various proinflammatory cytokines and immunomodulators that can increase immune cells' recruitment and other effector functions. Neutrophil-to-lymphocyte ratio (NLR) is a simple indicator systemic inflammatory status of patients. Research shows that NLR is a good marker for predicting mortality in the population of diseases, including cancer, infectious diseases and inflammation.[1]

Although many studies show the predictive value of NLR in many dermatoses as signs of inflammation in current literature, several disorders in the field of dermatology can be identified by the neutrophil-to-lymphocyte ratio, leprosy, SJS/TEN, psoriasis, and vitiligo.[1,2]

Leprosy is a chronic granulomatous infectious disease caused by *Mycobacterium leprae*, which usually influences the skin and peripheral nervous system. If not treated properly, this infection will result in permanent nerve damage and progressive disability. Leprosy reactions have 2 classifications, namely type 1 and type 2. An active cellular immune system causes type 1 reactions due to infection with the *M. leprae* antigen, characterized by increased symptoms of inflammation from pre-existing skin lesions and neuritis intense that can cause sensory neuronal and motor disturbances of the affected area. Furthermore, the type 2 leprosy reaction or erythema nodusum leprosum (ENL) is an acute inflammation of the skin, blood vessels, subcutaneous and other tissues characterized by painful and sudden pain in most of the erythematous nodules throughout the body.[3]

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe skin adverse reactions caused by drug reactions. This disease is characterized by blistering mucocutaneous lesions that cause necrosis and exfoliation of the epidermis of the skin and mucosa. This disease has sequelae such as blindness and a high mortality rate, so parameters are needed to determine the severity prediction.[3]

Psoriasis is a chronic and systemic disorder due to immune disorders triggered by genetic and environmental factors.[3-8] Characteristics of this disorder are the increased proliferation of the epidermis.[9] It can be known that psoriasis is associated with increased risk factors for cardiovascular disorders because they have the same inflammatory pathway. Therefore, defining the severity of the disease in psoriasis is important to plan appropriate, safe, and effective treatment.[10]

Vitiligo is a disorder that can be caused by depigmentation of the skin. This occurs because of the loss of melanocytes.[11]

Several hypotheses suggest that vitiligo is a genetic, neurohormonal, oxidative stress and autoimmune predisposition as the pathophysiology of vitiligo.[12] This review will discuss the association between NLR to several disease in dermatology field.

NEUTROPHIL-TO-LYMPHOCYTE RATIO IN THE FIELD OF DERMATOLOGY

Leprosy

Neutrophilic leukocytosis as an indicator of systemic inflammation is one of the earliest features noted in ENL patients. Among various parameters for monitoring neutrophil counts, the NLR has been recognized as a unique, stable marker reflecting underlying acute inflammatory response. Neutrophil-to-lymphocyte ratio is an easy, inexpensive, reproducible parameter associated with clinical outcomes and disease severity. In recent years, its role has been increasingly established as an independent prognostic factor for neoplasms and as an inflammatory biomarker in various acute and chronic cardiovascular/ metabolic/ infectious/ inflammatory diseases.[8,13–15]

A study by Gomes et al. reported a higher mean NLR in patients with leprosy reactions than those without (p<0.001). The NLR was also higher between patients with type 2 reactions and those with type 1 reactions or those without leprosy reactions (p<0.001). The mean NLR in multibacillary leprosy was higher (5.7 + 10.2) than in paucibacillary leprosy (2.0 + 0.9) (p0.002). NLR can diagnose leprosy reactions with a sensitivity of 61.0%, specificity of 92.0% and accuracy of 77.0%). To diagnose type 2 leprosy reaction with a sensitivity of 81.0%, specificity of 74.0% and accuracy of 78.0%. To diagnose type 1 leprosy, the NLR is not accurate enough.[2]

Tanojo et al. describe the results of the NLR study in patients with type 2 leprosy (ENL). It was found that patients with ENL had a higher NLR than patients without ENL (p<0.001). The results of the further analysis showed that the NLR value had a positive relationship with the incidence of ENL (p 0.45; p <0.05). The diagnostic value using the NLR was found to have a cut-off value 4.99, with a sensitivity of 86.4%, specificity of 82.5%, and accuracy of 82.97%.[16]

Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)

In research by Wang et al., results showed the NLR in patients with SCORTEN >3 was higher than in patients with SCORTEN <3 (p 0.014). The NLR can reflect the severity and degree of inflammation of SJS/TEN and predict the risk of death. NLR > 5.79 was associated with a significantly increased risk of death (p 0.014).[17]

Primisawitri et al. reported that the NLR in SJS/TEN patients had a significantly higher value of 6.6 than the threshold for SCORTEN>3, with a sensitivity of 61% and specificity of 51%. NLR has a predictive value for mortality with a limit value of 5.79 (p<0.05), a specificity of 63.6%, and a sensitivity of 85.7%.[18]

A study by Takayoshi *et al.* in Japan in 2017 reports that NLR in SJS/TEN is significantly higher than in other skin lesions such as maculopapular exanthema and positively correlates with the chemokine level regulated by thymus (TARC), which is related to the early stage of the disease. It indicates that NLR can reflect the inflammation condition of SJS/TEN in the early onset and can help the clinicians establish the diagnosis faster the predicting the potential severity.[19]

Psoriasis

NLR has been identified as a potential diagnostic and prognostic marker in chronic inflammatory diseases, psoriasis. The results of research by Wang et al. showed that patients with psoriasis had a high NLR (p < 0.05). Compared with other psoriasis subtypes, the lowest NLR value was found in the psoriasis vulgaris group (p<0.001) and the highest NLR value in the generalized pustular psoriasis group (p<0.001).[20] Polat et al. reported that psoriasis patients had a high NLR correlated with PASI.[9]

A study by Karabay et al. reported that NLR values were significantly higher in moderately severe psoriasis patients compared to mild psoriasis and healthy controls (p=0.024). In this study, there was a positive correlation between the PASI score and the NLR value (p 0.009) and no correlation was found between the NLR value and the disease duration (p 0.190).[10] Meanwhile, from the research by Ataseven et al., there was an increase in NLR in patients with psoriasis (p=0.011), and there was no correlation between NLR and PASI score (p>0.05).[21]

A meta-analysis by Palogiannis et al. found that NLR was significantly associated with the incidence of psoriasis. NLR levels were generally higher in psoriasis patients (SMD = 0.69; 95% CI = 0.53–1.85; p<0.001).[22] The NLR is an index that measures the number of white blood cells involved in the pathogenesis of several chronic diseases, including psoriasis. Lymphocytes produce tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine that plays a central role in the cross-path between innate and adaptive immunity.[23] TNF-α is also produced by dermal plasmacytoid dendritic cells after stimulation by cathelicidin, keratinocytes, and endothelial cells.[24] In addition, Th17 cells which are part of lymphocytes, produce interleukin-17 (IL-17), also produced by neutrophils, mast cells, and macrophages.[25] Both TNF-α and IL-17 stimulate keratinocyte proliferation and the production of inflammatory mediators, thereby increasing cell involvement.[22]

These results are also supported by the study of Nawaz et al, who found that patients with psoriasis had a higher neutrophil count and a lower lymphocyte count than healthy controls. NLR is significantly increased in patients with psoriasis and is a potential diagnostic biomarker. This increase in NLR is an indicator of systemic inflammation.[26] The psoriasis activity and severity index (PASI) score correlates positively with NLR and is significantly higher in moderate to severe psoriasis patients (PASI≥10) compared to mild patients (PASI<10). Neutrophil-to-lymphocyte ratio is the strongest predictor of psoriatic arthritis, specifically in multivariate analysis (OR= 3.351; p= 0.005).[8] NLR is even a potential marker that can predict cardiovascular risk in psoriasis patients.[27]

Vitiligo

Vitiligo is a disease whose exact cause is unknown but is thought to occur due to genetic, autoimmune, and biochemical disorders.[12] Research conducted by Solak et al. showed that patients with generalized vitiligo significantly increased NLR values. This appears to be related

to increased systemic inflammation.[11] However, it differs from Sarac et al.'s study that there was no significant increase in NLR in patients with vitiligo compared to controls.[12]

Atopic dermatitis

Atopic dermatitis (AD) or atopic eczema is a skin disease that involves a chronic inflammatory process and is most common in young age groups (infants and children). Several studies have reported the association of systemic inflammation parameters, including NLR, with AD cases.[28] A retrospective study by Jiang and Ma involving 80 AD patients and 45 control subjects reported that NLR values in AD patients were significantly higher compared to the control group (p<0.001). In addition, the NLR value also has a positive correlation with the Scoring Atopic Dermatitis Index (SCORAD). The NLR value with a cut-off>1.75 was reported as the predictive limit value for severe AD (SCORAD ≥51) (sensitivity 94.7%, specificity 58.6%, AUC 0.778, p=0.001).[29]

A case-control study that evaluated the parameters of AD severity in 66 pediatric AD patients reported that NLR values were significantly higher in patients with severe AD than in mild-grade AD patients. In addition, the NLR value also correlates with the severity of AD. However, there was no difference in NLR values between the AD patient and control groups (p>0.05).[30]

A study by Inokuchi-Sakata et al. evaluated subjective parameters related to AD severity, including a visual analog scale for itching, eczema measurement, 5-D itch scale, dermatology quality of life index, eczema area index and severity, body surface area, and the Investigator Global Assessment of 55 AD patients reported that the NLR value correlated with the level of inflammation and the area of AD, as well as the severity of the disease.[31]

Systemic sclerosis

Systemic sclerosis (SS) is a chronic autoimmune disease that involves a multisystem inflammatory process due to autoimmunity, vasculopathy, and tissue fibrosis, leading to a poor prognosis. The pathogenesis of systemic sclerosis can cause clinical manifestations in skin tissue, such as Raynaud's phenomenon, digital ulcers, and tissue fibrosis due to excessive accumulation of extracellular matrix.[32] A few previous studies have reported the relationship between immune parameters, especially NLR levels, with the development and clinical outcome of the disease. A cross-sectional study by Yayla et al.) involving 69 SS patients and 50 control patients reported that the neutrophil count was higher (p=0.004) and the lymphocyte count was lower (p<0.001) in SS patients compared to controls. In addition, logistic regression showed that NLR levels were significantly different between groups (regression coefficient= 3.49, p=0.031; Cox and Snell R2= 0.243; Nagelkerke R2= 0.337, p<0.001). Neutrophil-to-lymphocyte ratio also positively correlated with the Modified Rodnan Skin Score (mRSS), the European Scleroderma Trials and Research Group (EUSTAR) score, and c reactive protein (CRP) levels. The mRSS score is a parameter for the spread of skin fibrosis. The EUSTAR score is used as a parameter of activity level and disease severity. The study concluded that NLR has an association with vascular and skin manifestations, as well as the level of disease activity and severity of SS.[33]

A cohort study by Wareing et al. involving 447 SS patients also reported that higher neutrophil counts and NLRs correlated with increased mRSS scores (p<0.001). In addition, neutrophil count and NLR were reported to predict an increased risk of long-term death (neutrophil HR 1.42; p = 0.02; and NLR HR 1.48; p <0.001).[34] On the other hand, the study by Kim et al. (2020), who evaluated 114 female patients with SS, reported that there was no significant association between NLR levels and the incidence of digitalis ulcers and the modified Rodnan skin score regardless of the difference in NLR levels between the SS and control groups.[32] Despite these findings, the immune component, including neutrophils and lymphocytes, has been reported to play a significant role in the pathogenesis of the immune system in SS, reflecting the disease's development, modulation, and prognosis.[35]

Skin cancer

Various types of cancer are closely related to the inflammatory process. Therefore, various types of inflammatory markers were further investigated to determine these biomarkers' role in response to therapy and survival rates. One of the biomarkers being studied is the neutrophil-lymphocyte ratio (NLR). This parameter has a systemic inflammatory index (SII) so that it can be used to predict the risk of developing cancer. There are several types of cancer in the field of dermatology related to NLR, such as basal cell carcinoma (BCC), squamous skin cell carcinoma (SCC), malignant myeloma (MM), and adnexal skin tumors. A study conducted by Derebaşınlıoğlu H et al., who evaluated the role of NLR as SII in BCC, SCC, and MM, found that the difference in mean NLR levels in SCC, MM and BB was statistically significant (p=0.003). This indicates a link between NLR and the three types of skin cancer. From this mean difference, the highest mean NRL value was found in SCC, which was 4.41 ± 5.25, followed by MM (3.25 ± 3.19) and BCC (2.53 ± 1.54). In addition, this study also showed a relationship between NLR and SII, which had a fairly good sensitivity score of 80 but did not have a good specificity score of only 64.1, with a cut-off of ≥414 (p=0.028). For this reason, it can be concluded that NLR, as a determinant of SII, is quite sensitive in identifying a person's risk of developing the three types of cancer above but is not specific.[36] The role of NLR in MM as a prognostic factor has been discussed in the literature review by Cohen JT et al., which summarizes five related studies. All of the studies show that NLR can significantly be used as a potential parameter in determining the prognosis of melanoma patients.[37]

The results obtained above are certainly motivated by several basic theories. In general, neutrophils can play a protumorigenic role. Even neutrophilia in the tumor microenvironment can confer a poor prognosis in most cases of melanoma. Neutrophils in the form of neutrophil extracellular traps (NETs) assist in the metastatic process.[37] Fridlender et al. have previously shown in a mouse model of human mesothelioma

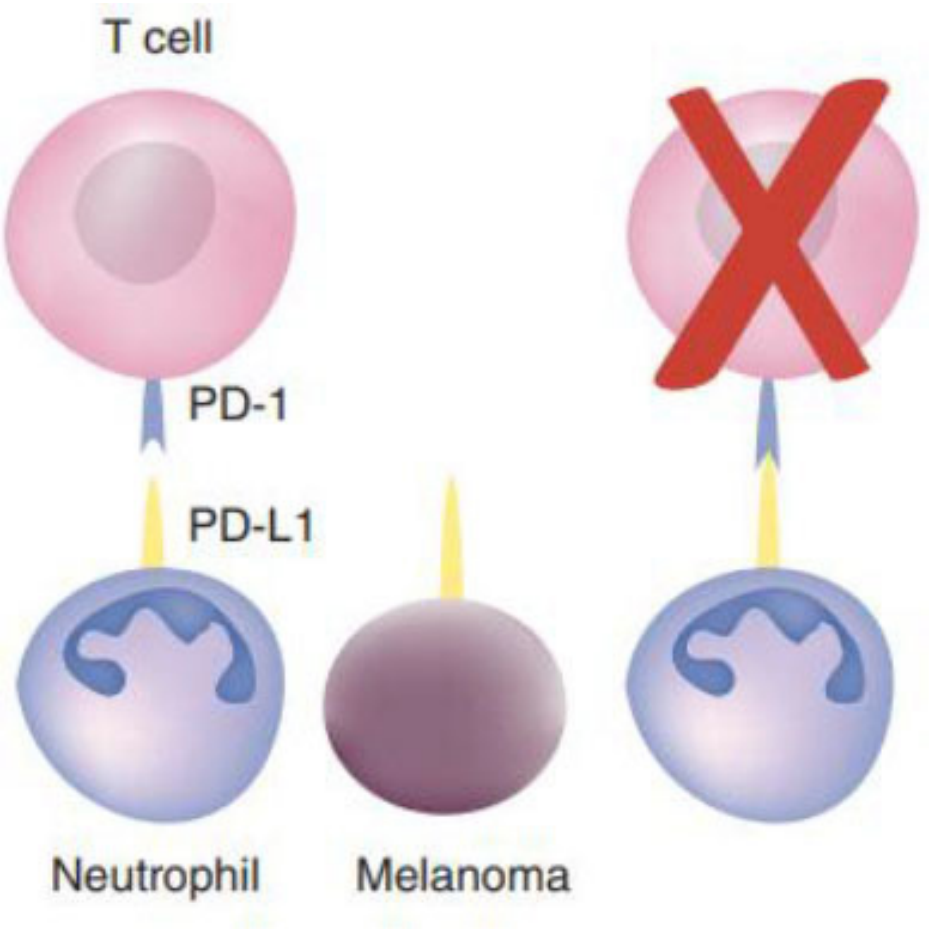

Figure 1. The apoptosis mechanism of neutrophil and tumor PD-L1 through activation T-cell apoptosis.[36]

that depletion of neutrophils from the tumor microenvironment leads to an increased proportion of cytotoxic T cells in the infiltrating tumor, resulting in increased killing of malignant cells.[38] These neutrophils can also modulate the adaptive immune system through multiple mechanisms. Neutrophils can suppress T-cell proliferation by releasing hydrogen peroxide into immunological synapses.[39] In addition, suppression of T-cell proliferation is induced by neutrophils expressing arginase-1, which depletes the microenvironment of L-arginine, a conditionally essential amino acid required for synthesizing T-cell receptors. Finally, neutrophils can directly induce T-cell apoptosis via the neutrophil PD-L1 interaction with its receptor, PD-1 (Figure 1).[37]

Cellulitis

Cellulitis is a non-necrotizing inflammation of the skin and subcutaneous tissue caused by Staphylococcus or Streptococcus bacteria. Cellulitis occurs most frequently in the lower extremities and usually unilaterally. Changes in the ratio of peripheral blood leukocytes, such as NLR, is a simple, fast, and potential examination as a parameter of inflammation, including cellulitis. There was a significant difference ($p<0.001$) between NLR levels in cellulitis patients [8.65 (1.70-34.36)] and controls [1.76 (0.71-17.93)].[40] These results were also supported by another study which found a significant difference ($p=0.001$) between patients with induced fever, including infectious cellulitis [8 (3.00-15.00)] and patients with non-infectious induced fever [5 (3.00-9)].[41]

NLR levels are higher in cellulitis patients. This can be explained because infection increases the NLR level, which indicates systemic inflammation.[40] Neutrophil-to-lymphocyte ratio is more effective than leukocyte levels in predicting inflammation, proving its superiority as a diagnostic marker in disease.[42] Neutrophil-to-lymphocyte ratio is significantly lower in patients <65 years ($p=0.032$).[40] Sakarozi's study showed that the survival rate of patients with high NLR was significantly lower than patients with low NLR ($p=0.009$).[43] Neutrophil-to-lymphocyte ratio levels were positively correlated with body temperature. In addition, a significant positive correlation ($p<0.05$) was found between length of stay and NLR, showing the highest coefficient. Neutrophil-to-lymphocyte ratio is a parameter that helps to evaluate the severity and prognosis of disease in patients with cellulitis.[44,45]

CONCLUSION

The NLR is an inexpensive, easy-to-obtain, and safe parameter that can be used as a marker for diagnosis, assessing severity, predicting risk of death, prognosis and therapeutic effects. In patients with leprosy, NLR can be used as a diagnostic marker to assess the leprosy reaction's severity. In the case of SJS/NET, the NLR value can be used to reflect the severity of the disease and predict the risk of death. NLR in psoriasis cases can assess the severity of psoriasis and cardiovascular risk in psoriasis patients. In atopic dermatitis, NLR can be used to determine the severity of the disease. The NLR value in systemic sclerotic disease can be used to determine the severity and predict the long-term risk of death. NLR is a sensitive examination to identify a person's risk of developing skin cancer (BCC, SCC, and MM). In cases of cellulitis, the NLR value can be used as a diagnostic marker, determining the severity and prognosis. However, cases of vitiligo still find controversial results.

DISCLOSURE

Conflict of Interest

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