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Correlation between Neutrophil-Lymphocyte-Ratio (NLR) and Clinical Severity in Acute Odontogenic Infection Patients

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Abstract: ***Introduction: Patients with facial space infections originating from odontogenic infections are at risk of experiencing life-threatening complications. Quantitative determination of serum markers can help determine the severity of odontogenic infections. Markers that have recently been introduced into clinical practice are associated with high costs which are a major limitation. Conversely, NLR is a cheap and easy to obtain parameter that does not require special equipment for NLR measurements. Neutrophils respond quickly to microbial infections and result in a drastic increase in the number of circulating neutrophils that migrate to the infected area. Conversely, an increase in lymphocyte apoptosis will result in a decrease in inflammatory effectors as well as immunosuppression. Purposes:The study wasconducted to analyze the correlation between NLR and clinical severity scale of odontogenic infection patient, and to determine the difference in the value of NLR and CSS on day 0 and day 3. Methods: This study used a prospective Cohort research method in 29 acute odontogenic infections patients who came to the Hasan Sadikin emergency department and met the inclusion criteria. Sampling was done twice, namely on day 0 (T1) and day 3 (T2). The research variables that were measured were NLR values obtained through hematologic examinations of 35 parameters, and clinical severity by summing the scores in the CSS tabel. The data obtained were then carried out by the Spearman correlation test analysis to see the correlation between the NLR and CSS values and a t-test was performed to see the differences in the NLR and CSS variable values on T1 and T2. Result: The results of the analysis using the Spearman Correlation Test show that there is a correlation between NLR and clinical severity in patients with acute odontogenic infections. On T1 the value of NLR with clinical severity has a positive correlation with the strength of moderate correlation which is statistically significant with r = 0.5 and p<0,01. At T2 the value of NLR with clinical severity has a positive correlation with the strength of a very strong correlation which is statistically significant with r = 0.8 and p<0,01. Positive correlation shows that the higher the NLR value the more severe the clinical severity in patients with acute odontogenic infection. There was a statistically significant decrease in the value of NLR between T1 and T2 with p<0,01 with an average decrease of 5.33 accompanied by a decrease in CSS with p<0,01 and an average decrease of 8.69 .***

Keywords: NLR, CSS, acuteodontogenic infection

1. Introduction

Patients with facial space infections originating from odontogenic infections are at risk of experiencing life-threatening complications due to proximity to the potential spatial anatomical structure of vital structures.[1–4]This can be anticipated and avoided by strictly adhering to clinical and laboratory parameters, because clinical signs may appear late or not enough to give a clear picture of the occurrence of the infection process.[1]The diagnosis of bacterial infection can be confirmed with culture examination, but the results of the examination tend to be slow. Therefore, the presence of a marker that can describe the presence of acute bacterial infection early in the course of the disease can greatly help reduce irrational use of antibiotics, and improve long-term outcome.[5]

Diagnostic markers currently used for bacterial etiology are not reliable enough. In addition, markers that have recently been introduced into clinical practice are associated with high costs which are a major limitation. NLR is a cheap and easy to obtain parameter that does not require special equipment for measurements.[9]The strength of NLR is that these parameters can be easily implemented using available markers because they come from very common laboratory values.[10,11]

One of the physiological responses in the immune system to systemic inflammation is an increase in the number of neutrophils and a decrease in the number of lymphocytes. This is due to changes in the dynamics and regulation of apoptosis in systemic inflammatory conditions when compared with non-inflammatory conditions. As a result of an increase in the number of neutrophils and a decrease in the number of lymphocytes, it will cause an increase in the absolute ratio of neutrophils and lymphocytes when compared to patients without a systemic inflammatory reaction.[14]

Zahorec et al. have examined the ratio of the number of neutrophils to lymphocytes as easy measurable parameters to show the degree of inflammation and sepsis in 90 oncology patients.[4,6]The population of white blood cells (lymphocytes and neutrophils) plays an important role in the systemic inflammatory response to severe infections, trauma, and shock. The immune response to endotoxemia is characterized by an increase in circulating blood neutrophils and a low lymphocyte count.[6]In the study of the immune response to the inflammatory process, in the group of patients given endotoxemia, after 4-6 hours there will be a decrease in the number of lymphocytes around 85% and

neutrophils increasing by around 300%. Changes in the value of NLR, whether the change in the initial value of NLR can be used to identify patients at high risk of having a poor prognosis.[11]The initial value of NLR examined when entering the emergency unit for patients with CAP can predict the severity and prognosis of CAP with a high degree of accuracy when compared with traditional infection markers.[12]Shinde at al. also concluded that NLR can be used as a prognostic marker in critically ill patients, at no additional cost.[12]

Bali, Rishi et al. in their research developed a scoring system that could represent the actual severity of clinical indications of infection, namely Clinical Severity Scale (CSS). The measurement scale includes 9 clinical indicators — 6 locoregional (swelling, pain, pus, related symptoms, signs involved and opening of the mouth) and 3 systemic parameters (temperature, pulse, and respiration) as indicators of the patient's clinical profile.[1]

2. Material and Methods

A prospesctive cohort of 29 patients with acute odontogenic infections patients that came to the Hasan Sadikin Hospital Emergency Department and met the inclusion criteria were assessed clinically and NLR were measured in all patients. Sampling was done twice, at the time on admission namely day 0 (T1) and day 3 (T2). The research variabels that were measured were NLR values obtained through hematologic examinations of 35 parameters, and clinical severity by summing the scores in the CSS tabel. The data obtained were then carried out by the Spearman correlation test analysis to see the correlation between the NLR and CSS values and a paired t-test was performed to see the differences in the NLR and CSS variable values on T1 and T2.

The clinical examination were performed on admission before blood test and surgical treatment. The scale of measurement covers the clinical indicator 9 — 6 lokoregional (swelling, pain, pus, related symptoms, signs involved and opening of the mouth) and 3 systemic parameters (temperature, pulse, and respiration). NLR values were obtained by dividing absolute neutrophil and lymphocytes counts. The patients characteristics were also recorded including gender, age, and the measurement results of CSS and NLR values (Table 1).

The Shapiro-Wilk's test was performed to assess data normality. The Spearman test was used for correlation analysis between NLR and clinical severity (Table 2).To compare the differences between NLR and CSS values on T1 and T2, a paired T test was used (Table 3).A p value less than 5% was considered as statistically significant.

3. Results

The distribution of most research subjects at the age of 46-59 years and 60-73 years respectively as many as 11 samples (37.9%). For gender distribution there was no difference between men and women, in men as many as 16 samples (55.17%) and women as many as 13 samples (44.83%). The absolute neutrophil count on T1 is generally at a high level, 23 samples (79.31%) with an average value of 18.55 ± 16.15.While absolute neutrophil counts on T2 are generally at the normal level, 20 samples (68.97%) with an average value of 5.57 ± 1.33. The absolute lymphocyte count in T1 was mostly in the normal level in 19 samples (65.51%) with an average of 1.99 ± 0.65; while in T2 the majority are at the normal level as many as 23 samples (79.31%) with an average value of 1.98 ± 0.58. The mean NLR value on T1 was 9.74 ± 5.28 while the mean on T2 was 5.65 ± 4.62. The clinical severity level in the T1 majority is at the weight level of 16 samples (55.17%); while for T2 the majority is at the light level, namely in 19 samples (65.52%) (Table 1).

Table 1: Subjects characteristic anddescriptive data ofneutrophil, lymphocytes, NLR, CSS

Variable		*n (%)*	*average ±SD*	*Median (min-max)*
Age	18 - 31	3 (10,34)		
	32 - 45	4 (13,8)		
	46 - 59	11 (37,93)		
	60 - 73	11 (37,93)		
Gender	Men	16 (55,17)		
	Women	13 (44,83)		
Day-0 (T1)				
Absolute neutrophil			15,94 ±15,24	
	High	23 (79,31)	18,55 ±16,15	
	Normal	6 (20,69)	5,94 ±1,04	
	Low	0	0	
Absolutely-mphocytes			1,87 ±1,21	
	Low	8 (27,58)	0,79 ±0,18	
	Normal	19 (65,51)	1,99 ±0,65	
	High	2 (6,91)	5,02 ±1,96	
NLR			9,74 ±5,28	
CSS	Moderate	13 (44,83)		13 (9-16)
	Severe	16 (55,17)		18,5 (17-25)
Day-3 (T2)			7,39±3,53	
Absolute neutrophil	High	9 (31,03)	11,43±3,56	
	Normal	20 (68,97)	5,57±1,33	
	Low	0	0	
Absolute lymphocytes			1,72±0,73	
	Low	6 (20,69)	0,71±0,09	
	Normal	23 (79,31)	1,98±0,58	
	High	0	0	
NLR			5,65±4,62	
CSS	Mild	19 (65,52)		6 (1-8)
	Moderate	9 (31,03)		11 (9-16)
	Severe	1 (3,45)		

SD = deviation standard

The results of the analysis using the Spearman Correlation Test showed that the T1 NLR value with clinical severity had a positive correlation with the strength of the medium correlation which was statistically significant with r = 0.5 and p-value 0.008. Whereas in T2 the value of NLR with clinical severity has a positive correlation with the strength of a very strong correlation which is statistically significant with r = 0.8 and p-value 0.00012 (Table 2).

Table 2: *Spearman's correlation test* of NLR andClinical severity on T1 and on T2

Variable	*Correlation coefficient*	*p-value*
NLR-*0* &CSS-*0*	0,5	0,008
NLR-*3* &CSS-*3*	0,8	0,00012

To see the differences that occur in the NLR and CSS values between T1 and T2, a paired T test is performed. In table 3, the following T-test analysis data will be presented in pairs from NLR and CSS.

Table 3: Paired T-test of NLR and CSS on T1 and T2

Variable	*n*	*average*	*SD*	*t count*	*p-value*
NLR	29	5,33	3,86	7,44	2.11E-05
CSS	29	8,69	3,8	12,32	4.02E-10

From the data in the table above shows that there are significant differences (p <0.05) NLR values between T1 and T2 with an average change of 5.33 ± 3.86. Likewise CSS on T1 and T2 also shows that there are significant differences (p <0.05) with an average change value of 8.69 ± 3.8. The NLR and CSS values both decrease between T1 and T2.

4. Discussion

From the data characteristics of the research subjects in table 4.1 illustrate that the distribution of sex in patients with acute odontogenic infections in this study is balanced between men and women (55.17% and 44.83%). This is consistent with previous studies conducted by Sánchez et al.[39]where it is also found that the distribution between the sexes is represented. While the distribution of odontogenic infections based on age, in the data in table 4.1 above, it was found that the majority of the samples in this study were at the age of 46-59 years and 60-73 years respectively 11 samples (37.9%). C. Huang et al.[40]also showed that elderly and related systemic diseases were the most important predictive factors in deep neck infection.

The absolute value of neutrophils on T1 was high in 23 samples (79.31%) with a mean of 18.55 ± 16.15. The high absolute value of neutrophils indicates that the majority of patients are in the condition of acute infection. Neutrophils respond quickly to microbial infections and result in a drastic increase in the number of circulating neutrophils that migrate to the infected area. In this situation, the production of neutrophils by bone marrow increases dramatically leading to massive recruitment of neutrophil imature into the blood circulation.[11]Decreasing the number of mature neutrophils and immature stored in the bone marrow can also stimulate the bone marrow to produce neutrophil lineages. In addition, the bone marrow continues to supply neutrophils to infected sites through the bloodstream until recovery from bacterial infections.[31]Neutrophilia is caused by the demargination of neutrophils, late apoptosis from neutrophils and stimulation of stem cells by growth factors.[12]Delaying the neutrophil apoptosis process will result in prolongation of neutrophil function in the inflammatory process while at the same time prolonging the toxic metabolic elaboration process.[14]

In this study, the absolute value of lymphocytes obtained in T1 was generally at the normal level in 19 samples (65.51%) with an average value of 1.91. A total of 8 samples (27.58%) were at a low level with an average value of 0.78. The data illustrates that in 8 subjects experienced a condition of severe bacterial infection characterized by a decrease in the absolute value of lymphocytes. Increased lymphocyte apoptosis will result in decreased inflammatory effectors as well as immunosuppression.[14]Margination of lymphocytes, redistribution of lymphocytes and accelerated apoptosis resulting in lymphocytopenia is a normal mechanism that occurs in emergency infections.[12]Lymphocytopenia may develop because of the need to suppress the adaptive immune response that supports innate immunity. This idea is supported by data showing that CD4 + T cells are the most changing lymphocyte subset during severe bacterial infections and sepsis.[9]The mechanism that leads to lymphopenia is primarily the redistribution of activated cells that leave the blood compartment to migrate to the tissues, especially to lymphatic tissue, and the occurrence of apoptosis.[42]

The absolute value of neutrophils in the majority of T2 is at the normal level of 20 samples (68.97%) with an average of 5.57 ± 1.33. This can be caused by the effect of antibiotics administration during treatment which can affect the number of neutrophils. Absolute neutrophil values that remain high at T2 in 9 samples (31.03%) indicate an infection that persists or extends because the bone marrow continues to supply neutrophils to infected sites through the bloodstream until recovery from bacterial infection.[31]While the absolute lymphocyte value in T2 is generally at the normal level in 23 samples (79.31%) with an average of 1.98 ± 0.58. While 6 samples (20.69%) are still at a low level, which means that the severe infection process is still ongoing. This might be caused by various factors including not responding to bacteria against antimicrobial drugs or it could also be due to high bacterial virulence factors such as *S. pyogenes* bacteria, or maybe it could also be caused by other factors that could influence the NLR values that were not studied in this research. This finding is consistent with the previous theory that the clinical presentation of extensive necrotic and inflammatory lesions is often associated with *S. pyogenes* infection. So that the ability of pathogens to inhibit neutrophils by either blocking apoptosis to facilitate the survival of pathogens or cause rapid lysis of neutrophils indicates the mechanism of virulence of pathogens.[32]

From the results of data analysis in Table 2 illustrates that on T1 there is a statistically significant positive correlation between the NLR value and clinical severity with r = 0.5 and p-value 0.008. Likewise at T2 where NLR and clinical severity also have a positive correlation with the strength of a very strong correlation which is very statistically significant with r = 0.8 and p-value 0.00012. Positive correlation shows that the higher the NLR value the more severe the clinical severity in patients with acute odontogenic infections and vice versa. This picture is in accordance with a previous study by Zahorec that there was a relationship between the severity of clinical conditions and the increased number of neutrophils and low lymphocytes.[6]The increasing number of neutrophils accompanied by a decrease in the number of lymphocytes in severe bacterial infections suggests that the mechanism of innate immunity provides an initial defense against infection, resulting in massive recruitment of neutrophils, while the adaptive immune response develops later and requires lymphocyte activation. The kinetics of innate and adaptive immune responses vary in different infections.[25]Dogruel, et al.[4]also stated that there was a

positive and statistically significant correlation between the ratio of neutrophil-lymphocyte counts, hospitalization period and antibiotic dose in patients with odontogenic infections.[4]Zahorec et al. has documented the ratio of neutrophil counts to lymphocytes (NLR) as an easily measured parameter that shows the severity of systemic inflammation and sepsis in 90 oncology patients. In addition, NLR is a parameter that is useful for predicting bacteremia in emergency department.[9]Nugroho in his research stated that the neutrophil lymphocyte ratio has a correlation with clinical conditions in septic patients.[14]Several studies have reported that an increase in NLR in peripheral blood flow is associated with a poor prognosis.[7]NLR has been used in the treatment of critical patients and based on the study of Hwang et al. proven to be a valuable prognostic tool.[11]

One of the physiological responses in the immune system to systemic inflammation is an increase in the number of neutrophils and a decrease in the number of lymphocytes.[34]NLR values that are mostly high at T1 and settle indicate a severe inflammatory process that is still ongoing in the presence of infection.[11]This is due to changes in the dynamics and regulation of apoptosis in systemic inflammatory conditions when compared with non-inflammatory conditions. Delaying the neutrophil apoptosis process will result in prolongation of neutrophil function in the inflammatory process and prolong the toxic metabolic elaboration, whereas increased lymphocyte apoptosis results in decreased inflammatory effectors and causes immunosuppression.[35,36]The description shows that in severe systemic inflammation, the body's immune system responds with a greater increase in the neutrophil lymphocyte ratio when compared with mild systemic inflammatory conditions or body conditions without inflammation.[14]This is consistent with the previous theory that neutrophilia and lymphocytopenia are markers of severe bacterial infection.[13]

The results in the table above support the previous theory according to Zahorec, there is a relationship between the severity of clinical conditions with increased neutrophil counts and low lymphocytes.[6]Changes in the value of NLR, whether the change in the initial value of NLR can be used to identify patients at high risk of having a poor prognosis.[11]Shinde et al. also concluded that NLR can be used as a prognostic marker in critically ill patients, at no additional cost.[12]

There are several limitations in this study: sampling was not taken on the 7th day; the culture examination results data was not recorded; unrecorded data regarding the dosage and type of antibiotics given during treatment; and the presence of other unknown comorbidities that might affect the NLR value.

5. Conclusion

There is a positive correlation between NLR and CSS both on day 0 and day 3 and there are very significant differences in the value of NLR and CSS between the 0th and 3rd day means that according to the increase in NLR, the clinical severity is also increase, and vice versa. So that NLR is expected to help clinicians in determining laboratory markers that are easier, cheaper, and valuable in determining the severity and also as a laboratory marker in evaluating the results of treatment in patients with acute odontogenic infections.

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