The use of Neutrophil – Lymphocyte Ratio (NLR) as a potential biomarker to predict the prognosis of Ludwig's angina patients

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The use of Neutrophil – Lymphocyte Ratio (NLR) as a potential biomarker to predict the prognosis of Ludwig's angina patients

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ABSTRACT

Background: Ludwig's angina is an infection of the submandibular cavity in the form of cellulitis that is rapidly progressive and potentially life-threatening. Neutrophils and lymphocytes play an important role in this infection process. Neutrophil-lymphocyte Ratio (NLR) is a simple biomarker to evaluate systemic inflammation. We aimed to determine the association between NLR and various prognostic parameters in patients with Ludwig's Angina.

Methods: A retrospective cohort study was conducted using medical records of Ludwig's Angina patients treated at Dr. Soetomo General Hospital, Surabaya, Indonesia, between January 2018 – December 2021. The NLR cut-off value was calculated using the receiver operating characteristics (ROC) curve. The association between NLR with severity, length of stay (LoS), and mortality were analyzed using SPSS version 23 for Windows.

Results: We recruited a total of 96 patients. NLR values are divided categorically into low NLR and high NLR using a cut-off value of 16.86. There were 49 patients (51%) with low NLR and 47 (49%) with high NLR. There was a significant relationship between NLR with severity, LoS, and mortality in Ludwig's angina patients (p=0.032, p=0.002, and p=0.026, respectively). According to a survival study, the high NLR group's survival rate was significantly lower than the low NLR group's (p=0.009).

Conclusion: There was a significant relationship between NLR severity grading, survival, and the length of stay in patients with Ludwig's Angina.

Keywords: Ludwig's Angina, neutrophil-lymphocyte ratio, prognostic predictor, survival
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INTRODUCTION

Ludwig's angina is a rapidly progressive and potentially life-threatening cellulitis of the submandibular cavity. The mortality rate for this disease exceeded 50% in the pre-antibiotic era.[1] This figure has decreased significantly since the 1940s with the introduction of antibiotics, improvements in oral and dental hygiene, and aggressive surgical approaches.[2] Ludwig's angina is described as a rapidly progressing gangrenous cellulitis with soft tissue edema of the neck and floor of the mouth.[2] One of the severe complications of this disease is airway obstruction which becomes the main cause of death. The diagnosis of this condition is based on the clinical criteria proposed by Grodinsky, which include: bilateral infection in more than one compartment in the submandibular space, serosanguinous gangrenous infiltrate with or without pus, the effects on connective tissue, fascia, and muscle but not glandular structures which spreads faster continuously than lymphatic.[3]

Most Ludwig's angina cases originated as an odontogenic infection. The causative organisms are usually consisting of normal floras in the oral cavity. Patients present with classic symptoms: fever, malaise, sudden edema of the floor of the mouth, dysphagia, dyspnea, and drooling. Some patients with a delay in diagnosis and delay in getting proper therapy may present with trismus. Physicians should be aware of respiratory distress in these patients, and intubation should be considered immediately. Complications other than airway obstruction include the spreading into the chest cavity, which can lead to mediastinitis, empyema, or even lung abscess.[4,5]

Ludwig's angina patients show a host response and humoral immunity, such as activation of complement, acute phase proteins, cytokines, monocytes, macrophages, and anti-inflammatory mediators. Neutrophils and lymphocytes play an important role in the infectious process compared to other leukocytes. In the infection process, the increase in neutrophils is a response from leukocytes to microbes that enter the body. Neutrophils play an important role in the process of infectious disease. Neutrophils and lymphocytes play important roles in the infectious process among leukocyte subpopulations. In infection, an increase in neutrophils is a typical response of leukocytes. The neutrophil-lymphocyte ratio (NLR) is more sensitive to indicating the extension of systemic infection than other WBC subpopulations.[6]

Recent studies have shown that the neutrophil-lymphocyte ratio has been introduced clinically to evaluate systemic inflammation. This ratio has been studied

for its predictability in various diseases, including death from cardiovascular disease, pulmonary arterial hypertension, testicular germ cell tumor and survival in malignancy.[7,8] To the best of our knowledge, no studies have investigated the relationship between the neutrophil-lymphocyte ratio in patients with Ludwig's angina in Indonesia. Therefore, this study aimed to assess the pre-therapy NLR and analyze its relationship with prognostic factors such as length of stay, severity, and mortality in terms of recovery time and disease progression in patients with Ludwig's angina.

METHODS

A retrospective cohort study was conducted at Dr. Soetomo General Hospital, Surabaya, Indonesia. The inclusion criteria in this study were the medical record of Ludwig's Angina patients treated at Dr. Soetomo General Hospital between January 2018 and December 2021. In addition, we excluded patients with incomplete medical records. Following the inclusion and exclusion criteria, we reviewed 96 medical records of all patients diagnosed with Ludwig's Angina who received treatment at the Department of Surgery at Dr. Soetomo General Hospital.

The diagnosis of Ludwig's Angina is determined based on the history, physical examination, and laboratory and radiological examinations. The length of stay is the number of days the patients spend in a single episode of hospitalization. The severity of the disease was determined based on the scoring previously reported, based on several parameters such as systemic inflammatory response syndrome (SIRS), trismus condition, dysphagia, affected facial cavity, signs of dehydration and comorbidities.[9] The disease severity divided into: 0 = Normal; 1-8 = Mild severity score; 9-16 = Moderate severity score; and >16 = Severe severity score. Mortality is the incidence of death during treatment at Dr. Soetomo General Hospital, as written in the medical record. Total neutrophil and lymphocyte values were obtained from complete blood medical record data when patients were admitted at Dr. Soetomo General Hospital. This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, following the guidelines of the Declaration of Helsinki.

The laboratory parameters measurement was performed at the Clinical Pathology Laboratory of Dr. Soetomo General Hospital. The Dimension Chemistry System (Siemens, USA) was used to measure albumin, SGOT, SGPT, blood urea nitrogen (BUN), serum creatinine, and serum electrolytes. The Sysmex XN-3000 was used to measure the complete blood count, PPT, and APTT parameters. The complete blood count parameters used in this study were neutrophils and lymphocyte.

Medical record data of patients with Ludwig's angina who received treatment and met the inclusion and exclusion criteria of the study were collected from January 2018 to December 2021. The particular period to collect the NLR data was admission before the patient received the surgical treatment. Furthermore, general data about the subject, such as name, age, gender, address and telephone number, were recorded. The length of stay and the comorbidities of the subject were also recorded. The results of the pre-therapy complete blood count were recorded for further analysis. The NLR was calculated by dividing the neutrophil by the lymphocyte value.

Statistical analysis was performed using the SPSS statistical software package version 23 for Windows. The variables were analyzed and presented as frequency distribution and cross-tabulation. We examined to determine the association between NLR and prognostic predictor in Ludwig's Angina using Chi-squared (χ^2) test. Receiver operating characteristic (ROC) curve analysis was performed to calculate an optimal cut-off value for NLR to prognostic predictor in Ludwig's Angina. In this study, a p-value less than 0.05 was considered statistically significant. We also calculated the likelihood of survival as a function of time using Kaplan-Meier analysis. We measure the survival of Ludwig's Angina patients based on the severity level and NLR value.

RESULTS

Our study sample was 96 patients in Dr. Soetomo General Hospital, Surabaya, Indonesia, between January 2018 and December 2021, that met the inclusion and exclusion criteria, consisting of 36 females and 60 males. There were 19 samples of severe severity (19.8%) and 8 mild severity (8.3%). The length of stay in this study was divided into several categories, namely 0-7 days (58.3%), 8-14 days, 8-14 days (31.3%), 15-21 days (7.3%), 22- 28 days (2.1%), and 36-42 days (1%). The sample had a live outcome of 72 samples (75%), and only 26 samples (25%) had a deadly outcome. Patient characteristics are shown in Table 1.

Table 1. The characteristics of patients with Ludwig's angina

Parameters	n	Percentage (%)
Total patients	96	100.0
NLR		
Low	49	51.0
High	47	49.0
Severity grade		
Severe	19	19.8
Moderate	69	71.9
Mild	8	8.3
Length of stay		
0-7 days	56	58.3
8-14 days	30	31.3
15-21 days	7	7.3
22-28 days	2	2.1
36-42 days	1	1.0
Mortality		
Death	24	25.0
Life	72	75.0

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We used ROC analysis to calculate the optimal cut-off value to predict the prognostic parameters in Ludwig's angina patients. We found that the optimal cut-off value was 16.86. The highest severity level was moderate, which amounted to 69 samples (71.8%). Then, we classified the NLR value into high-NLR (≥ 16.86) and low-NLR (< 16.86) based on the cut-off value determined by ROC curve analysis. There were 49 samples (51.0%) with low NLR and 47 (49.0%) with high NLR values. In the severe Ludwig's angina group, 73.7% with low NLR and 26.3% with high NLR were found. In the moderate group, we found 46.4% with low NLR and 53.6% with high NLR. In the mild group, we found 37.5% with low NLR and 62.5% with high NLR. We revealed that the NLR value was significantly associated with the severity of the disease (p=0.032). The ROC curve is shown in Figure 1.

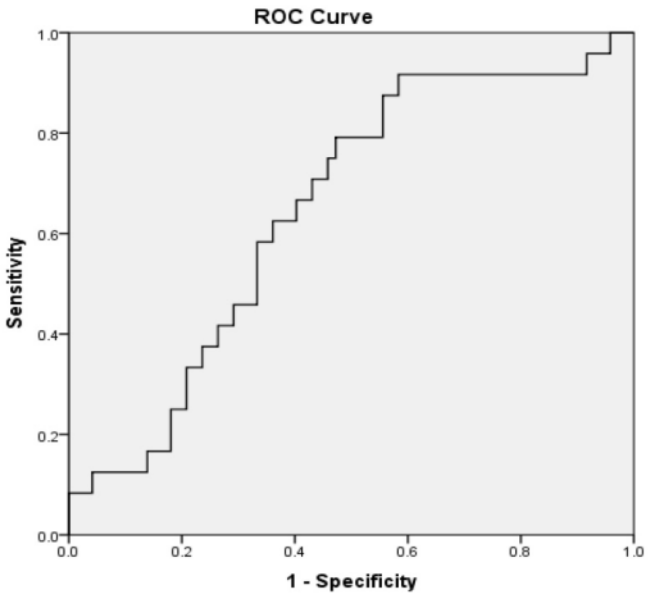

Figure 1. ROC analysis to determine NLR cut-off value

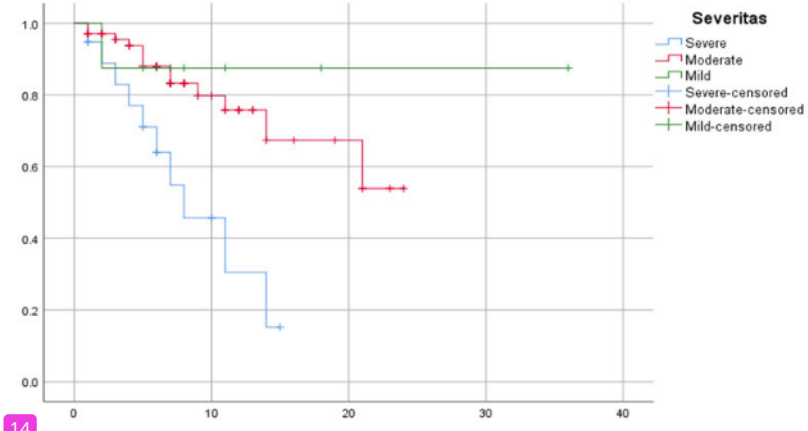

Figure 2. Kaplan Meier's survival curve based on the severity of Ludwig's Angina (the Green line represents mild Ludwig's angina, the red line represents moderate Ludwig's angina, and the blue line represents severe Ludwig's angina)

We also analyzed the survival of the patients based on the severity grade using Kaplan Meier's survival curve, as shown in Figure 2. We found differences in the survival time of Ludwig's angina patients with mild, moderate and severe degrees. The survival rate of the severe degree group was lower than the moderate degree, and the moderate degree was lower than the mild degree. Importantly, we found a significant difference in the survival of patients with different severity (P = 0.002). The association between NLR and prognostic predictor in Ludwig's angina is shown in Table 2.

We analyzed the association between length of stay and NLR values. There were 58.9% of patients with low NLR and 41.1% with high NLR value at 0-7 days of treatment. 46.7% of patients with low NLR and 53.3% with high NLR value at 8-14 days of treatment. At 15-21 days of treatment, 28.8% of patients with low NLR and 71.4% with high NLR. In the 22-28 days and 36-42 days groups, we found that all patients had high NLR (100%). These results indicate a statistically significant relationship between NLR values and length of stay (p=0.033) (Table 2).

In this study, the relationship between NLR and mortality was analyzed based on whether the patients were alive or dead at the end of treatment in the hospital. In the dead group, 70.8% of patients had low NLR, and 29.2% had high NLR. In the surviving group, there were 44.4% with low NLR and 55.6% with high NLR. There was a significant association between NLR and mortality (p=0.026). We revealed that NLR had a sensitivity of 70.8%, specificity of 55.5%, PPV of 34.6%, and NPV of 85.1% to predict the patients who could not be survived.

We also analyzed the survival of patients based on the NLR value using Kaplan Meier's analysis, as shown in Figure 3. There was a difference in the survival time of Ludwig's angina patients with high and low NLR. The survival rate of the high NLR group was significantly lower than that of the low NLR group (p=0.009). This result indicates a statistically significant relationship between high and low levels of NLR Ludwig's angina and the probability of patient survival.

Table 2. The association between NLR and prognostic predictor in Ludwig's angina

Variables	NLR Value		P value
	Low NLR	High NLR	
Severity grade, n (%)			
Severe	14 (73.7)	5 (26.3)	
Moderate	32 (46.4)	37 (53.6)	0.032*
Mild	3 (37.5)	5 (62.5)	
Length of stay, n (%)			
0-7 days	33 (58.9)	23 (41.1)	
8-14 days	14 (46.7)	16 (53.3)	
15-21 days	2 (28.6)	5 (71.4)	0.033*
22-28 days	0 (0.0)	2 (100.0)	
36-42 days	0 (0.0)	1 (100.0)	
Mortality, n (%)			
Death	17 (70.8)	7 (29.2)	0.026*
Survive	32 (44.4)	40 (55.6)	

*Chi-Square: Statistically significant if p-value less than 0.05.

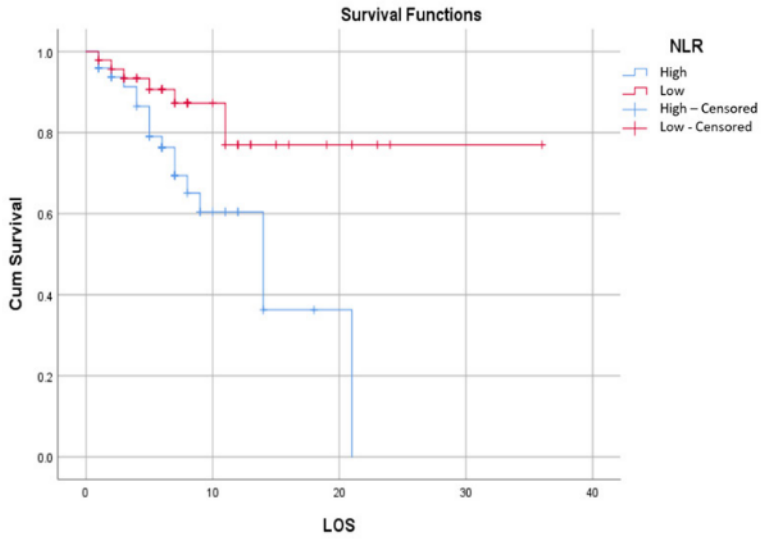

Figure 3. Kaplan Meier's survival curve by high and low NLR (the red line represents Ludwig's Angina patients with low NLR, and the blue line represents patients with high NLR)

DISCUSSION

Ludwig's angina is a cellulitis that can progress quickly and become life-threatening for the patient. Complications that can occur are mediastinitis, necrotizing fasciitis of the neck and chest, pericarditis, carotid artery rupture, jugular vein thrombosis, pleural empyema, pneumonia, and life-threatening airway obstruction. Before antibiotics were discovered, Ludwig's angina mortality was more than 50%.[10] Since the discovery of antibiotics, the mortality rate in Ludwig's angina has significantly decreased, but prompt and appropriate treatment is still required to lower patient mortality and morbidity. With proper treatment, mortality can be reduced by up to 10%.[11] In addition to surgical treatment, fluid resuscitation and broad-spectrum antibiotics are also necessary. Intubation should be performed for patients with airway obstruction for whom a CT scan has not been performed, as this can cause a critical delay that can lead to death.[12]

In Ludwig's angina, microbial infection occurs, resulting in an inflammatory reaction in an attempt to fight and destroy pathogens. This inflammatory reaction can be recognized from clinical examination by the presence of hyper or hypothermia, tachycardia, tachypnea, hypotension, and signs of inflammation locally at the site of infection, such as skin redness, warmth, pain, and edema. There are several changes in the laboratory examination, such as increased leukocytes, C-reactive Protein (CRP) and NLR. NLR is useful as a predictor and marker of inflammation. Normal NLR values in healthy adults are between 0.78 - 3.53.[13]

Neutrophils play an important role in the body's response to bacterial infections. Neutrophils can phagocytize and kill microbes in the event of infection. NLR values in patients with infection can be a predictor of bacteremia. Another study found that the NLR value was higher in patients with tonsillitis and deep neck space infection (DNSI).[14] Therefore, NLR may be used as an easy, relatively inexpensive, and simple laboratory test to see inflammation and complications in neck infections.

Lymphocytopenia was previously described as a sign of bacteremia but was not widely accepted as a sign of infection. The mechanism responsible for developing lymphocytopenia in sepsis and septic shock involves the margination and redistribution of lymphocytes in the lymphatic system and is characterized by apoptosis. Apoptosis is a feature that plays a role in sepsis. In the blood of patients in septic shock, lymphocyte apoptosis increases rapidly and leads to persistent lymphocytopenia and a complication of neck infections.[15]

In this study, NLR was divided into two categories; low NLR and high NLR. The number of samples with high and low NLR values was almost similar. This shows that the sample in this study has an even distribution of NLR values. The majority of the samples had a moderate severity rate. More than 80% of the samples were

treated for less than 14 days, and more than 50% were only treated for less than 7 days. Three-fourths of the samples had live outcomes. Our results revealed a significant association between NLR and severity and a significant association between severity and the survival rate. The more severe the severity of the disease, the lower the survival rate. These results follow a previous study that reported that an increase in NLR can identify patients in an unrelieved inflammatory state and is associated with decreased survival. The cause responsible for the increased NLR associated with poor outcomes in patients with sepsis remains unclear, although various plausible explanations exist. One of the most convincing explanations is based primarily on the physiological relationship between neutrophilia and lymphopenia during inflammation and systemic stress. Ongoing infection and incomplete eradication of the infectious nidus are responsible for the increased production of neutrophils by the medulla and decreased number of lymphocytes by apoptotic and other mechanisms.[16] The intensity of neutrophilia and lymphocytopenia is closely related to the severity of the injury, the severity of the clinical status, and the clinical outcome of patients with systemic infection or inflammation.[17] This shows that NLR can be a diagnostic tool in assessing the severity of infection and inflammation in patients suffering from Ludwig's angina.

Patients with more severe infections and sepsis tend to require longer hospital stays. As a diagnostic tool to predict the severity and prognosis, NLR is expected to be potential guidance for predicting Ludwig's angina patients who may require a longer stay in the hospital. This study showed a statistically significant relationship between NLR and the length of stay in patients suffering from Ludwig's angina. A high NLR value can predict a severe infectious and inflammatory reaction that makes the patient require a longer stay in the hospital. A study by Gurol *G et al.* revealed that the NLR has a sensitivity of 57.8% and a specificity of 83.9% in diagnosing sepsis in seriously ill patients. In addition, NLR examination is easier and cheaper than CRP examination in detecting bacterial infections in patients.[18] Another study revealed that NLR was associated with the length of hospital stay and dose of antibiotics. According to the ROC analysis, the optimal cut-off value for NLR was 16.58. The patients with high NLR needed longer hospital stays. Therefore NLR could be useful for predicting the length of hospital stay.[19]

NLR has been widely studied as a simple laboratory test that can describe the host inflammatory responses, predict chemotherapy responses, predict mortality in various critical patient populations, and be a potential diagnostic modality.[20-22] A prospective cohort study showed that a high NLR value in seriously ill patients was an independent indicator of mortality during hospitalization and 6 months after treatment.[23] Another research demonstrated that the NLR value at the time of presentation to the emergency department was an independent risk factor for predicting mortality at 28 days in patients with severe sepsis or septic shock.[24] Previous studies also reported that the NLR value at first admission was significantly lower in patients who died before day 5 of the onset of a septic shock than those who survived.[25,26] The increase in NLR from day 1 to day 5 is associated with late death. The contradictory conclusion from previous studies might be attributed to several reasons. First, the definition of the primary outcome in different research studies was different. Some of them defined 28-day death as the outcome; others defined early (before day 5 of septic shock onset) or late (on or after day 5 of septic shock onset) death as the outcome. Second, the disease severity of the enrolled patients differed in each study. However, due to the simplicity, cheap examination, and relatively high accuracy, the NLR has been widely used in critically ill patients and has proven to be a tool for assessing prognosis in septic patients.

This study has several drawbacks. This investigation was carried out in a single academic hospital. As a result, the conclusions of this study may not be sufficient to characterize the situation in Indonesia as a whole population. However, the findings in this study might be considered preliminary data in Indonesia. Second, the number of participants in this study is relatively small. Therefore, further research with a larger number of subjects or a statewide multicenter study may be required to produce better results.

CONCLUSION

We can conclude there was a significant relationship between NLR with the severity grading, survival, and length of stay in patients with Ludwig's Angina. The survival rate of the high NLR group was significantly lower than the low NLR group.

CONFLICTS OF INTEREST

No competing interests were declared in this study.

ETHICAL CLEARANCE

This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No. 0717/LOE/301.4.2/XII/2021), following the guidelines of the Declaration of Helsinki.

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AUTHORS CONTRIBUTION

Conceived the study: RS. Designed the study: RS, DAS, and MDW. Analyzed the data: RS, DAS, and MDW. Wrote the manuscript: RS and MDW. Review the manuscript: DAS and MDW.

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