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The Role of Neutrophil Lymphocyte Ratio (NLR) as a Predictor in Severity Chronic Suppurative Otitis Media (CSOM)

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Abstract:

- ***Background*:**
  Tissue damage due to microbial invasion in CSOM cases causes inflammatory mechanisms related to specific and non-specific immunity. Neutrophil Lymphocyte Ratio (NLR) is an inflammatory marker in CSOM as a prognostic indicator of the disease.

- ***Objective*:**
  To determine the role of NLR as determinant inflammatory parameters of CSOM in predicting disease prognosis.

- ***Methods*:**
  Analytical observational study with cross sectional design. Sample collection was conducted December 2022-March 2023. There were safe type dry phase CSOM, safe type active phase and dangerous type. The safe type active phase CSOM and dangerous type were given topical antibiotics for 2 weeks. Complete blood Count were repeated to assess NLR after 2 weeks in all types of CSOM. Data analysis used the Kruskal-Wallis alternative test and Spearman rank correlation.

- ***Results:***
  A total of 27 samples involved men (55.6%) and women (44.4%). Based on CSOM type, there were 40.8% of safe type dry phase CSOM, 29.6% safe type active phase and 29.6% dangerous type. The average of NLR value were found significantly different both the beginning (p-value=0.004) and the end (p-value=0.010). Comparison of three types of CSOM in the beginning and the end showed significant decrease (p-value <0.05).

- ***Conclusion:***
  NLR could not be used as a prognostic indicator in the three types of CSOM, because it is included in the very weak category.

Keywords: *Neutrophil Lymphocyte Ratio, Chronic Suppurative Otitis Media (CSOM), Inflammatory Parameters.*

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I. INTRODUCTION

Chronic Suppurative Otitis Media (CSOM) is an inflammation of the middle ear and mastoid processus more than 2 months which characterized by perforation of the tympanic membrane with or without persistent otorrhea [1],[2]. Changes in the tympanic membrane including atelectasis, perforation, tympanosclerosis, retraction, and cholesteatoma [3]. CSOM consists of two general types: atticoantral CSOM (dangerous type, closely related to cholesteatoma) and tubotympanic CSOM (safe type). Symptoms commonly associated with chronic ear disease including hearing loss, otorrhea, ear fullness, otalgia, and vertigo [4],[5],[6]. Globaly, more than 90% of the CSOM prevalence is in Southeast Asia, West Pacific, and Africa. It is very rare in America, Europe, Middle East, and Australia [7]. According to the World Health Organization (WHO), around 65-330 million people in the world suffer

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from CSOM. WHO also classifies the prevalence of CSOM in countries into 4 categories which are the highest (>4%), high (2-4%), low (1- 2%), and lowest (<1%) [6]. The high incidence of CSOM in some countries around the world requires high attention. In Indonesia, according to the Ministry of Health's Basic Health Research, the prevalence of hearing loss due to CSOM is 2.6% of the total population of Indonesia with the largest distribution over 45 years of age. Based on data at ORL-HNS Polyclinic, Undata Hospital, Palu, found that the prevalence of CSOM was 29.3% which occurred in 26-45 years and most common in the left ear [8],[9]. In 2019, ORL-HNS polyclinic at the Regional General Hospital Dr. Zainoel Abidin (RSUDZA) Banda Aceh obtained data on 484 CSOM patients who visited, of which 27 patients were patients with dangerous/malignant type of CSOM [10].

Based on some literatures, the development of CSOM is associated with inadequate antibiotic treatment, frequent upper respiratory tract infections, nasal diseases, multiple episodes of acute otitis media, genetic factors, lack of hygiene, malnutrition, and passive exposure to cigarettes. Otitis media begins as an inflammatory process following a viral infection of the upper respiratory tract involving the nasal mucosa, nasopharynx, middle ear mucosa, and eustachian tube. Inflammation in the eustachian tube could cause decreased ventilation, increased negative pressure in the middle ear, increased exudate from the inflamed mucosa, and accumulation of mucosal secretions [8],[11]. Tissue damage due to microbial invasion or injury will cause a series of inflammatory mechanisms. While the inflammatory focus expands, there are an amplification of the stimulus for endothelial cells also leukocytes to release cytokines, leukotrienes, platelet activating factors, and enzymes. As a result, neutrophils are released from the bone marrow and activated to carry out cell phagocytosis. Neutrophils play an important regulatory role in adaptive immunity and being the main effector cells during systemic inflammatory responses so that an increase in the value of neutrophils in the blood will be seen while inflammation occurs. In addition, around 10 trillion lymphocytes circulate in the blood and play a major role in the specific immune system (stimulating the proliferation, differentiation of T cells and B cells, and activating macrophages to destroy microbes) as well as chronic inflammation whose value also increases in the blood. Both non-specific and specific immune systems work very closely with each other. Having accurate inflammatory markers to determine the diagnosis or progression of CSOM is very important in the field of otology [12],[13].

Recently, Neutrophil Lymphocyte Ratio (NLR), Monocyte Lymphocyte Ratio (MLR), Platelet Lymphocyte Ratio (PLR), Neutrophil Lymphocyte Platelet Ratio (NLPR), Aggregate Index of Systemic Inflammation (AISI), and Systemic Inflammation Index (SII) are new inflammatory markers which considered in diagnosis and development of various inflammatory and infectious diseases [13]. NLR is the most widely used marker in countries including South Korea, China, Iran, even in Europe. The NLR value has been known as a reliable marker for detecting the presence of bacteremia and sepsis. Meta-analysis studies showed that a higher NLR was associated with poor prognosis for [14]. Another study on the predictive value of NLR in patients with Idiopathic Sudden Sensorineural Hearing Loss (ISSNHL) found that there was an increased NLR in recurrent ISSNHL compared to controls [15]. There is little research on hematological marker NLR which could be a prognostic parameter in the incidence of middle ear inflammation. A study regarding NLR in patients with CSOM found that the NLR in CSOM patients with cholesteatoma were higher than CSOM patients without cholesteatoma [16]. Another study that evaluated the relationship between prognosis and clinical progress of CSOM using NLR, PLR, and Platelet Count (PC), obtained the three parameters were significantly higher in dangerous type CSOM compared to safe type CSOM [3].

The role of inflammation in CSOM has been defined. However, an available and affordable markers are needed to predict the degree of inflammation in order to determine the prognosis of the disease. In several studies, NLR has been proposed as an inflammatory parameter and an indicator that is easily measured based on the results of a complete blood examination. Therefore, this is the fundamental reason for researcher to conduct research regarding the role of NLR as an inflammatory parameter to predict the prognosis of CSOM.

II. METHODS AND MATERIALS

- *Study Design and Research Location*

This research is an analytical observational study with a cross sectional design conducted at the ORL-HNS Polyclinic, Radiology Department and Clinical Pathology Laboratory RSUDZA Banda Aceh after obtaining permission from the Health Research Ethics Committee (HREC).

- *Population and Sample Research Study*

The study population were all patients who had been diagnosed with CSOM by an ORL-HNS specialist at the polyclinic with inclusion criteria including; (1) Patients who have been diagnosed with safe type dry phase CSOM, safe type active phase CSOM or dangerous type CSOM, (2) Patients who undergo laboratory blood tests and temporal CT- Scan, (3) Age >18 years. Meanwhile, exclusion criteria including; (1) Patients with a history of tumors or malignancies in the ear cavity, (2) Examination showed the conditions or diseases such as systemic inflammation, coronary heart disease, malignant neoplasms, diabetes mellitus, chronic obstructive pulmonary disease, metabolic syndrome, amyloidosis, and chronic kidney disorders, (3) Patients with a history of previous ear surgery (<6 months), and (4) Patients who are not willing. The number of samples in this study were 27 subjects.

- *Sampling Method*

The sampling technique in this research used a total sampling technique. Samples were taken from all patients in the period December 2022 to March 2023 who met the

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inclusion and exclusion criteria.

➢ *Data Collection Tools and Research Procedures*

Headlamp, otoscope, suction set, handscoon, patient examination sheet, 5 cc syringe, 70% alcohol, EDTA tube, centrifuge tube, and non-contrast mastoid CT scan results were the instrumental tools used in this research. CSOM Patients who come to the ORL-HNS di an anamnesis and physical examination of the ear (otoscope), a complete blood count laboratory examinations, and a non-contrast temporal CT scan to assess the condition of the middle ear and mastoid bone. Bacterial resistance to antibiotics is carried out only for patients with complaint of otorrhea. After the examinations data were collected (temporal CT scan, initial NLR value, and culture results), the patient received informed consent to enter the research subjects who were grouped into safe type dry phase CSOM, safe type active phase CSOM, and dangerous type CSOM. The samples with safe type active phase CSOM, and dangerous type CSOM were given antibiotic therapy namely topical ofloxacin for 2 weeks. Then, the three types of CSOM were evaluated after 2 weeks of antibiotics administration followed by complete blood count laboratory examination. All collected data will be analyzed systematically.

➢ *Data Analysis*

The unpaired T test was used, if the data was normally distributed. But the data was not normally distributed, then Kruskal-Wallis test was used. Spearman rank correlation was used to evaluate the relationship between the initial diagnosis of CSOM and the NLR value.

III. RESULTS

There were 27 samples of CSOM sufferers who agree with the research criteria. The characteristics of the research sample are presented in Table 1.

Table 1 Characteristics of the Research Sample

Characteristic	Frequency (n)	Percentage (%)
Gender		
Male	15	55.6
Female	12	44.4
Age	34 (19-72) year	
Diagnosis		
Safe type dry phase CSOM	11	40.8
Safe type active phase CSOM	8	29.6
Dangerous type CSOM	8	29.6
Duration of disease	84 (12-480) month	

Based on Table 1, it was found that this study was dominated by men (55.6%) with an average age of 34 years. Patients with safe type dry phase CSOM were the most frequently diagnosed group about 11 sufferers (40.8%). The duration of the disease was found to be an average of 84 months (7 years). However, the shortest duration being 12 months (1 year) and the longest duration being 480 months (40 years). Tables 2 and 3 presents several descriptive statistical values that describe the tendency of the NLR value for the three types of CSOM. The descriptive statistical value used was the median and its 95% confidence interval.

Table 2 Description of Initial NLR Value for the Three Types of CSOM

			95% CI		*p- value*
CSOM	**Median**	**Average**	**Lower**	**Upper limit**	
Safe type dry phase	1,45	1,52	1,23	1,81	
					0,004[b]
Safe type active phase	2,82	3,20	1,82	4,58	
Dangerous Type	1,85	1,88	1,66	2,11	

[b] *Kruskal-Wallis Test*

Table 3 Description of the Final NLR Value for the Three Types of CSOM

			95% CI		*p- value*
CSOM	**Median**	**Average**	**Lower**	**Upper limit**	
Safe type dry phase	1,65	1,59	1,39	1,78	
Safe type active phase					0,010[a]
	2,15	2,24	1,61	2,88	
Dangerous type	1,49	1,56	1,34	1,78	

[a] *Anova*

Table 2 and 3 showed generally a decreased of NLR value after 2 weeks of treatment although in safe type dry phase CSOM patients had a slight increased. Before therapy was given, the NLR value in safe type dry phase CSOM patients was 1.52. However, after therapy, the NLR value increased by 0.07 to be 1.59. Meanwhile, safe type active

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phase CSOM and dangerous type CSOM patients had a decreased NLR value respectively by 0.96 (3.20 to 2.24) and 0.32 (1.88 to 1.56). The results of the Kruskal-Wallis test and Anova showed that the NLR values for three types of CSOM were significantly different both before therapy (p- value=0.004) and after therapy (p-value=0.010).

Table 4 showed generally a decreased of NLR value after 2 weeks of treatment. This could be seen from the final average of NLR value which is lower than the initial NLR value.

Table 4 Description of the Average Initial and Final NLR Values (after 2 Weeks)

Observation Time		95% CI		
	Average	Lower	Upper limit	Median
Beginning	2,13	1,66	2,59	1,83
End	1,77	1,56	1,99	1,62

Further testing is needed to prove the significance of different NLR value using the Wilcoxon test which is an alternative method if the data does not fulfill the assumption of normality. The hypothesis in this test states that the initial and final NLR value are not significantly different. The results of the Wilcoxon test at both observation times are shown in Table 5.

Table 5 Results of Testing the Difference in Average Initial and Final NLR Values (2 Weeks)

Observation Time	Average Difference in initial and final NLR values	*p- value*
Beginning - End	-0,351	0,007

Based on the results of the Wilcoxon test in table 5, it is known that the average difference between final and initial NLR values in the research sample was -0.351. This negative value indicates that there was a decrease in the NLR value after the patient received treatment for 2 weeks. The value decreased is statistically significant as indicated by p-value test which smaller than 0.05. Thus, it can be concluded that the treatment given to the patient along 2 weeks succeeded in reducing the NLR value significantly.

Table 6 Area Under ROC Curve with the OvR Approach

Comparison	Area Under Curve (CI 95%)	*p- value*
Safe type dry phase vs others	0,176 (0,014 – 0,338)	0,005
Safe type active phase vs others	0,868 (0,711 – 1,026)	0,003
Dangerous type vs others	0,507 (0,293 – 0,720)	0,958

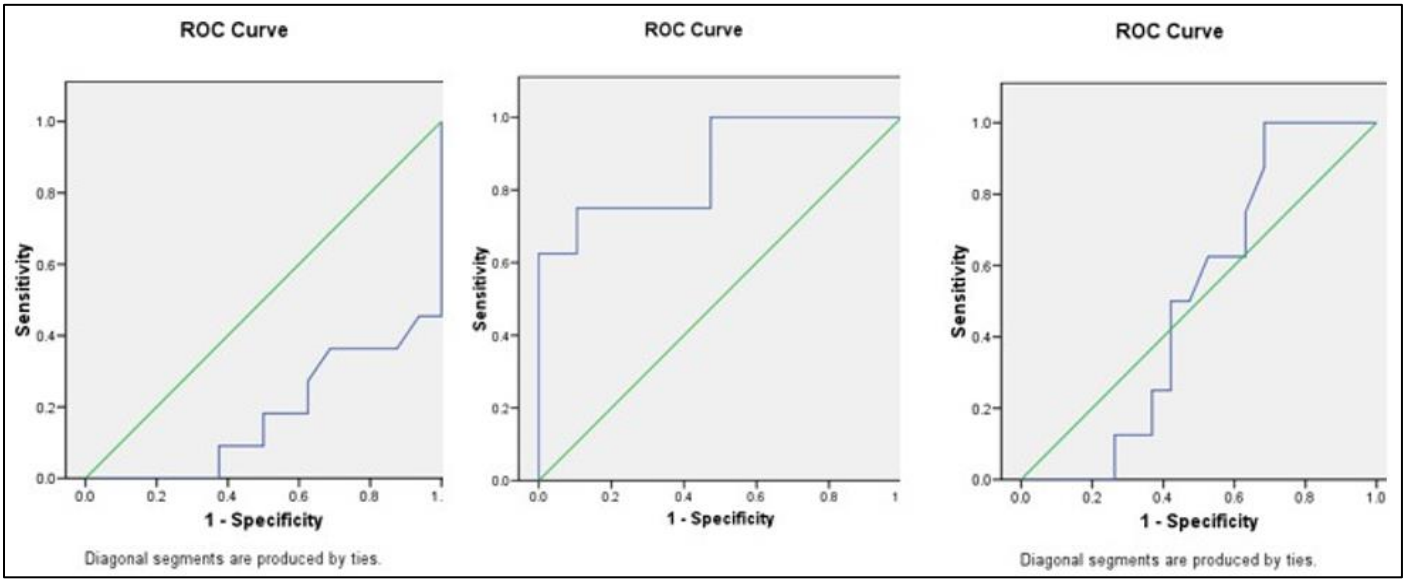

Fig 1 ROC Curve of NLR Value and CSOM Type using the OvR Approach

The average area of the ROC curve from the three OvR comparisons in table 6 and figure 1 are 0.517. It shows that the NLR value could not be used as a parameter to assess prognostic indicators, because it is included in the very weak category (interval 0.50 to 0.60). However, it is known that the comparison between safe type active phase test results vs others have a fairly large area under the curve about 0.868. The area under the ROC curve which is in the range of 0.80 to 0.90 can be categorized as good. Therefore, ROC analysis was carried out between safe type active phase and safe type dry phase as well as between the active phase safe type and the dangerous type.

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Table 7 Area under ROC Curve Between the safe Type Active Phase and the other Phase

Comparison	Are Under Curve (CI 95%)	*p- value*
Safe type active phase vs Safe type dry phase	0,898 (0,755 – 1,040)	0,004
Safe type active phase vs Dangerous type	0,828 (0,613 – 1,043)	0,027

Table 7 shows that the NLR value in the comparison between the active phase safe type and the dry phase safe type has an area under the curve of 0.898 and is significant with a p-value of 0.004. This shows that the NLR value can be used to differentiate between active phase safe type CSOM and dry phase safe type. The same thing can also be seen in the comparison between CSOM safe type active phase and dangerous type which has an area under the curve of 0.828 with a p-value of 0.027. However, the NLR value can also be used to differentiate between CSOM safe type active phase and dangerous type.

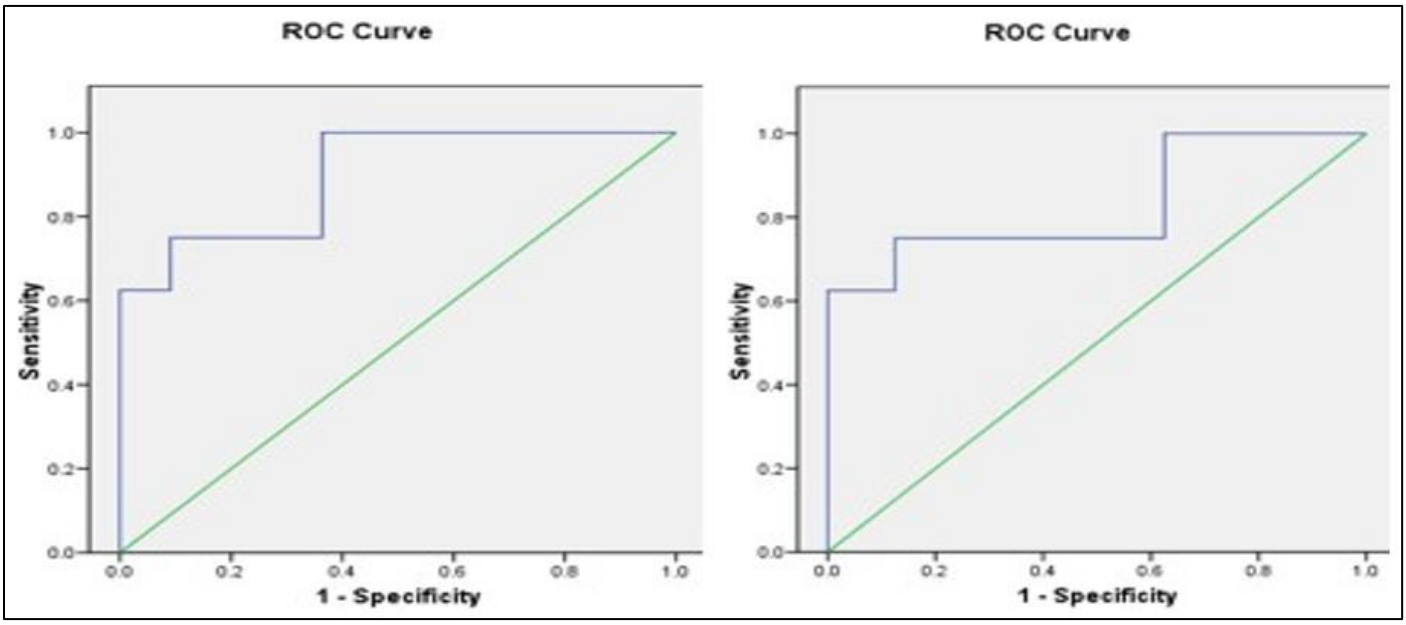

Fig 2 ROC Curve of NLR and CSOM Values for Safe Type Active Phase vs other Types

Based on the ROC curve analysis in Figure 2 found that the cut-off-point NLR value for predicting CSOM type between safe type active phase and safe type dry phase are 1.96. It is suspected safe type dry phase CSOM if the NLR value is below 1.96. However, it is suspected safe type active phase CSOM if the NLR value is above 1.96, with a sensitivity of 0.75 and a 1-specificity of 0.091. Meanwhile, the cut-off-point NLR value for predicting CSOM type between safe type active phase and dangerous type are 1.98. It is suspected dangerous type CSOM if the NLR value is below 1.98. While above 1.98, it is suspected safe type active phase CSOM with a sensitivity of 0.750 and a 1-specificity of 0.125.

IV. DISCUSSION

Based on Table 1, found that the research results were in line with several studies regarding characteristics of CSOM patients in several regions of Indonesia, including Adam Malik Hospital Medan in 2011-2012. It was found that the majority of CSOM patients were men (73.9%), and women (26.1%), also the most common age range over 18 years (56.5%) [17]. Likewise, at Sanglah General Hospital Denpasar in 2015, the highest proportion was men about 23 people (51.1%), and the largest age group was 31-40 years (28.9%) [18]. Meanwhile, research at RSUP Prof. Dr. RD Kandou Manado for the period January 2014-December 2016, it was found that there were no differences between men and women in the age group 18-40 years [19]. It was found that most CSOM patients were women (52 %) with age group >24 years (47%) at H. Abdoel Moeloek Regional Hospital in 2013-2014 [20]. In Cut Meutia North Aceh District Hospital in 2019-2020 found the most largest patients in the age range 15-25 years and female group (55.3%) [21].

Male is more dominant in experiencing CSOM due to men's work in outdoors more often so that men is more often exposed with environmental contaminant [22]. In terms of age and duration of the disease, the majority of CSOM patients are in productive age. This can be caused by a lack of awareness of maintaining ear hygiene, esutachian tube dysfunction, immune status, active or passive smoking habits and a history of chronic infections that have not been treated adequately [19],[23]. Several researchers concluded that these characteristics differences were caused by habit and geographical location of the respondents in each research area [20],[21]. In this study, it was also found that patients with safe type dry phase CSOM were the most diagnosed group about 11 patients (40.8%). Similar research results were also reported, it was found that the safe type was the most common type [17],[18],[20]. The low incidence of

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dangerous type CSOM is caused by the high level awareness of CSOM patients to seek adequate initial treatment [20].

Based on Tables 2 and 3, it is in line with several research and various research methods, such as Terzi H et al who obtained the highest average NLR value in cases of active CSOM and CSOM with cholestatoma compared to dry phase CSOM. In this study, there was a statistically significant difference in NLR between two groups (p=0.001) [3]. Sakali E et al also conducted the same research on two groups, including CSOM with cholesteatoma and CSOM without cholesteatoma. CSOM patients with cholesteatoma are higher than CSOM without cholesteatoma. However, statistically there was no significant difference in NLR values between two groups (p>0.05). This study concluded that cholesteatoma is not related to a systemic inflammatory response, although in theory it is stated that inflammation plays an important role in the pathogenesis of cholesteatoma, however this plays a greater role in the local inflammatory process than systemic inflammation [16].

Table 4 shows generally a decreased of NLR value after 2 weeks of treatment. Change in NLR values before and after therapy have been applied to assess the prognosis of malignant diseases, such as research by Yun JM et al who conducted research on change of NLR values in laryngeal carcinoma cases before and after Concurrent Chemoradiotherapy (CCRT). The NLR value after CCRT more increased than before the procedure. This result is associated with a poor prognosis. It is known that chemotherapy can cause neutropenia, thrombocytopenia and lymphopenia. Radiotherapy contributes to inducing lymphopenia and this can occur for quite a long duration in head and neck cancer [24].

Figure 1 shows that the NLR value cannot be used as a prognosis indicator parameter for the three types of CSOM, because it is included in the very weak category. However, table 7 indicates that the NLR value can be used to differentiate between safe type active phase CSOM and safe type dry phase CSOM also to differentiate between safe type active phase CSOM and the dangerous type. Based on Figure 2, it explains the cut-off-point NLR value to predict the comparison types of CSOM. A study conducted by Islek et al which found a relationship between the NLR value and CSOM based on the Middle Ear Risk Index (MERI) value. It was found that the average NLR value for the entire sample (369 samples) was 1.94 ± 0.89 with the results of ROC analysis, The AUC cut-off point is 1.95 for moderate-severe grade based on MERI score [25]. In research conducted by Sakarozi R et al, there was a significant relationship between the severity of NLR in cases of Ludwig Angina and the survival life also length of the patient's treatment. In this study, ROC curve analysis was used to obtain the cut-off- point NLR value about 16.86 [26].

V. CONCLUSION

This study shows that the NLR value could not be used as an inflammatory parameter for prognosis indicators in the three types of CSOM, because it is included in the very weak category. The limitation of this study also the samples size were too small, so that healthy and more samples are needed as a control group. Healthy and More samples are needed as a control group. However, this study used the ROC curve with OvR method, a cut-off point was obtained to differentiate between safe type dry phase CSOM and safe type active phase CSOM also the cut-off point between safe type active phase CSOM and dangerous type CSOM.

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