Neutrophil-to-Lymphocyte Ratio (NLR) as a Prognostic Marker for Burn Patients

Bernadetta, M.D.[a], Iswinarno Doso Saputro, Dr., M.D. (Consultant of Plastic Surgery)[b], Lobredia Zarasade, Dr., M.D. (Consultant of Plastic Surgery)[c]

[a] official email address: be.berna89@gmail.com
[a] Plastic Reconstructive and Aesthetic Surgery Resident, Faculty of Medicine, Airlangga University / Dr. Soetomo General Hospital, Mayjend Prof. Dr. Moestopo Street No. 6-8, Surabaya – Indonesia, Postal code 60286
[b] Head of Plastic Reconstructive and Aesthetic Surgery Department, Faculty of Medicine, Airlangga University / Dr. Soetomo General Hospital, Mayjend Prof. Dr. Moestopo Street No. 6-8, Surabaya – Indonesia, Postal code 60286
[c] Senior staff of Plastic Reconstructive and Aesthetic Surgery Department, Faculty of Medicine, Airlangga University / Dr. Soetomo General Hospital, Mayjend Prof. Dr. Moestopo Street No. 6-8, Surabaya – Indonesia, Postal code 60286

Abstract

BACKGROUND Complications like sepsis due to infection and death can occur in the treatment of major burn trauma patients because of inflammation process. The Neutrophil-to-Lymphocyte Ratio (NLR) is believed as a prognostic marker for the incidence of mortality and sepsis in burns patient care. Various studies have stated that NLR is quite easy, inexpensive and efficient tool for clinical application.
AIMS to analyze the role of NLR as prognostic marker for mortality and sepsis in burn patients.
METHODS A cross-sectional retrospective single-center study was conducted between 2019 – 2021 using 222 medical records from 245 burn patients at our Burns Unit. Demographics and laboratory data results were recorded, including NLR levels on 1st and 3rd day of treatment. Correlation analysis of NLR levels was carried out on the incidence of mortality and sepsis using Logistic Regression and Chi Square tests.
RESULTS The subjects of this study were dominated by patients with median age of 33 years old (SD ±20), male (68.5%) and average burns area of 30.22% (SD ±23.3%). This study noted that the NLR on 1st day (cutoff of 7.97) and 3rd day (cutoff of 6.2) of treatment had a correlation with the incidence of mortality and sepsis ($p<0.05$).
CONCLUSION Neutrophil-to-Lymphocyte Ratio (NLR) can be used as a prognostic marker of mortality and sepsis in burn patients.

Keywords: Burn; Neutrophil-to-Lymphocyte Ratio; Mortality; Sepsis

1. Main text

1.1. Introduction

World Health Organisation notes that there are 180,000 deaths per year of the world's population caused by burns with the majority being in low- and middle-income countries [1]. Burns mortality rate in America has been reported at 3.1% of all cases. This mortality rate will increase to 8.6% in patient with burns areas more than 20% of Total Body Surface Area (TBSA) [2]. Indonesian mortality rate of burns was reported at 25.8% [3].

Many literature state that one of the causes of death in burns is sepsis [4,5]. Sepsis can occur due to response of inflammatory process to pathogenic bacteria infection that enter through open wound in burns, especially in burns over 20% of total body surface area [6]. Neutrophil-to-Lymphocyte Ratio (NLR) is an indicator of inflammatory process and can be prognostic index in sepsis [7-11]. Since 2008, various scientific works have stated that the NLR value is related to the degree of inflammatory process and mortality [12,13].

1.2. Material and Methods

A retrospective cohort study was conducted using data from medical records of patients who received treatment at the Burns Unit, Dr. Soetomo General Hospital - Surabaya City, Indonesia, between 2019 and 2021. We searched for association between NLR value on 1st day and 3rd day of treatment with sepsis and mortality incidence during hospitalization. This study was approved by ethics committee in our hospital and all researchers have received a certified Good Clinical Practice course. All data used in this study were anonymous and information regarding patients' personal data was kept confidential.

We collected patient medical records by consecutive total sampling according to the following inclusion criteria: an Indonesian, men/women who were diagnosed as acute burns and treated at our center. Incomplete medical record data for analysis will be excluded from this study. We recorded laboratory results for absolute neutrophil and absolute lymphocyte values from peripheral blood tests on 1st and 3rd of treatment using the Sysmec XN-1000 Hematology Analyzer machine. Calculation of NLR, based on the formula = Absolute Neutrophil Value : Absolute Lymphocyte Value. Sepsis incidence and mortality were recorded based on clinician judgement during care.

Data is processed descriptively and then calculated using correlation analysis. We use the SPSS (Statistical Program for Social Science) application/computer program version 25.0 (IBM SPSS Statistics for Windows, version 25.0 Armonk, NY: IBM Corporation) to calculate. Statistical analysis using ROC and chi-square test were performed to find associations between NLR and outcome (sepsis incidence and mortality). It has been agreed in this study that the significance value is $p < 0.05$.

This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No.: 0960/LOE/301.4.2/VII/2022) following the guidelines of the Declaration of Helsinki.

1.3. Results

Based on the results of data collection from medical records for 2019 - 2021, we obtained 222 data patients who had been processed from a total of 245 patients; where medical record data of 23 other patients had been previously excluded because the data was incomplete. Characteristics of the study subjects ranged in age from 0 – 83 years (median 33 ± 20.7 years) and the extent of burns experienced by patients was 1 – 100% TBSA (median 26 ± 23.3% TBSA) as shown in Table 1. Those variables were correlated with patient's mortality ($p<0.05$).

Absolute Neutrophil Count on 1st day had a mean value of 14.21 (±7.63 x 103cells/µL) from the range of 1.94 – 43.53 x 103cells/µL. Meanwhile, the Absolute Neutrophil Count on 3rd day was decreased to a mean value of 8.69 (±5.60 x 103cells/µL) from the range of 0.81 – 36.22 x 103cells/µL. This decreasing was also happened to Absolute Lymphocyte Count on 1st day from mean value of 2.36 (±1.90 x 103cells/µL) with a range of 0.41 – 13 x 103cells/µL to Absolute Lymphocyte Count on 3rd with a mean value of 1.53 (±1.22 x 103cell/µL) from 0.19 – 8.46 x 103cell/µL.

Calculation of the NLR value on 1st day produces a mean value of 9.70 (±8.62; with a range of 0.32 – 57.94). Meanwhile, the calculation of the NLR value on 3rd day produces mean value of 8.41 (±7.34; with a range of 0.26 – 50.61). It appears that there is a decrease in the NLR of 1st day compared to the NLR of 3rd day with a decrease difference (D NLR 1st – 3rd) of -1.29 (±9.61; with a range of -41.85 – 42.89) as shown in Table 2. Based on the dependent variable of the study, it was found that the mortality rate in the subjects of study was 27% (60 cases) and the incidence of sepsis was 34% (75 cases) as shown in Figure 1 and Figure 2.

The results of the Mann-Whitney test stated that there was an association between NLR value on 1st and 3rd day to the incidence of mortality ($p <0.05$). This result becomes the basis for us to determine the cutoff value of NLR on 1st and 3rd day using ROC curve. The optimal cutoff value for the NLR on 1st day is 7.97 and 3rd day is 6.2 based on ROC curve. Through the Chi-square test, the study proved that the cutoff values of NLR on 1st and 3rd day mentioned above were associated with the patient's prognosis ($p <0.05$) as shown in Table 3.

NLR on 1st day with the value above 7.97 had an association with mortality in burn patients ($p=0.019$) with RR of 1.68; 95% CI 1.08 – 2.60 and a sensitivity-specificity value of 58.3%-54.5%. NLR on 3rd day with the value above 6.2 also had an association with mortality in burn patients ($p=0.024$) with RR of 1.65; 95% CI 1.06 – 2.56 and a sensitivity-specificity value of 58.3%-58.6%. NLR on 1st day with the value above 7.97 had an association with the incidence of sepsis in burn

patients (p=0.011) with RR of 1.61; 95% CI 1.11 – 2.34 and a sensitivity-specificity value of 57.3%-60.5%. Whereas NLR on 3rd day had no association with the incidence of sepsis (p=0.661).

Table 1. Subjects' Parameters

Parameter	Age (years)	Burn Area (%)
Mean	33,05	30,22
Median	33	26
SD	20,71	23,3
Minimum Value	0	1
Maximum Value	83	100

Parameter		Treatment End Result n (%)		Total
		Death	Survive	
Sex	Male	40 (26,3%)	112 (73,7%)	152
	Female	20 (28,6%)	50 (71,4%)	70
Case state	Referal Case	32 (28,1%)	82 (71,9%)	114
	Primary Case	28 (25,9%)	80 (74,1%)	108
Causal of Burns Injury	Fire/Flame	49 (40,2%)	73 (59,8%)	122
	Hot Liquid	5 (9,8%)	46 (90,2%)	51
	Chemical Substance	1 (25%)	3 (75%)	4
	Electricity	2 (5,9%)	32 (94,1%)	34
	Thermal Contact	1 (16,7%)	5 (83,3%)	6
	Explosion	2 (40%)	3 (60%)	5
Degree of Burns injury	Grade I	0 (0%)	1 (100%)	1
	Grade IIA	3 (6,8%)	41 (93,2%)	44
	Grade IIB	34 (28,3%)	86 (71,7%)	120
	Grade III	23 (40,4%)	34 (59,6%)	57
Inhalation Trauma	Yes	39 (56,5%)	30 (43,5%)	69
	No	21 (13,7%)	132 (86,3%)	153
Comorbidity	Yes	33 (44,6%)	41 (55,4%)	74
	No	27 (18,2%)	121 (81,8%)	148
Acute Respiratory Distress Syndrome	Yes	26 (92,9%)	2 (7,1%)	28
	No	34 (17,5%)	160 (82,5%)	194
Acute Kidney Injury	Yes	21 (77,8%)	6 (22,2%)	27
	No	39 (20%)	156 (80%)	195
Shock	Yes	8 (47,1%)	9 (52,9%)	17
	No	52 (25,4%)	153 (74,6%)	205
Total Subject		**60 (27%)**	**162 (73%)**	**222 (100%)**

Table 2. Results

Descriptive Statistics	Neutrophil 1st day	Neutrophil 3rd day	Lymphocyte 1st day	Lymphocyte 3rd day	NLR 1st day	NLR 3rd day
Mean	14,21	8,69	2,36	1,53	9,70	8,41
Median	13,43	7,54	1,65	1,12	7,18	5,81
SD	7,63	5,60	1,90	1,22	8,62	7,34
Minimum	1,94	0,81	0,41	0,19	0,32	0,26
Maximum	43,53	36,22	13	8,46	57,94	50,61

Table 3. Chi Square test of NLR

	Cutoff NLR Value	Sensitivity (%)	Specifity (%)	Sign. (p)	RR	95% CI
On Mortality						
Cutoff value based on previous study by: Hu et al., 2020[5]						
NLR 1st day	14	31,7	79,6	0,078	-	-
NLR 3rd day	7,5	50	62,3	0,097	-	-
Cutoff value based on this study						
NLR 1st day	7,97	58,3%	54,5%	0,019	**1,68**	**1,08-2,60**
NLR 3rd day	6,2	58,3%	58,6%	0,024	**1,65**	**1,06-2,56**
On Sepsis Incident						
Cutoff value based on this study						
NLR 1st day	7,97	57,3%	60,5%	0,011	**1,61**	**1,11-2,34**
NLR 3rd day	6,2	48%	55,1%	0,661	-	-

1.4. Discussion

Burns cause severe tissue injury that can trigger hypermetabolic processes and immune response that require fast and effective treatment to reduce the risk of mortality. According to the cause, burns most often occurs due to fire and electric current [14,15]. Ibara et al. said that the most common cause of burns was due to flames in both developed and developing countries [16]. Another study, according to McInnes in 2019, flames was the most common cause of burns followed by hot liquids as the second rank [17]. We also found that our result was not much different from the study of burns at the same hospital in the previous period [18].

Our study subjects were dominated by male patients (68.47%) with an average age of 33 years. In line with previous studies at the same location, dominant patients remained male, 431 (64.8%) of a total of 665 patients [19]. According to Wardhana et al. during period 2013-2017, it recorded 465 patients burns were male out of a total of 709 patients (65.59%) with an age range of 16-35 years. In Australia & New Zealand in 2009 – 2015, experts reported that average age of burn patients was around 41-80 years with the majority was male patients, with mortality ratio of male : female was 1.7:1 [17]. Based on the data above, the characteristics of the subjects of this study also are not much different from studies of burns in other places both abroad and within the country [20].

Lymphocyte-to-Neutrophil Ratio (NLR) has been known as a marker of inflammation. NLR is relatively easy and inexpensive to apply clinically. NLR itself has been used in various medical cases such as: sepsis, cardiovascular disease, ARDS and malignancy as a marker of inflammatory processes. This inflammatory process can describe the patient's risk of falling into a state of sepsis, MODS and then death [21-25]. Various studies have recently been carried out by experts to

determine the role of NLR in predicting the incidence of sepsis and mortality, especially in cases of burns. NLR is considered more applicable, easy and simple to use in everyday life because it only requires a complete peripheral blood count. Research by Fuss et al. said that high NLR values can be found in patients with sepsis. There was a difference in NLR of approximately ±3 points between groups of burn patients with sepsis compared to those without sepsis (18.22 vs 15.75; $p<0.05$). NLR can be used as a tool to identify the risk of sepsis in the early phase [26]. Furthermore, NLR can be one of the parameters used by various models to predict mortality in burn patients, as in the study by Park J.H., et al. in 2022 [27].

Hu et al. stated that the NLR cutoff value as a predictor of mortality in burn patients on the first day was 14 (with a sensitivity of 37%, a specificity of 79.6%, and a $p=0.078$) and on the third day, it was 7.5 (with a sensitivity of 50% , specificity 62.3%, and value $p=0.097$) [5]. Those cutoff values cannot be applied to burn patients in our center because of insufficient association in mortality ($p>0.05$). We used our NLR value cutoff by statistical calculation via ROC curve. This study recorded a cut off value of the NLR on 1st day of 7.97 and NLR on 3rd day of 6.2 as a predictor of mortality. Various studies in the world state that there are still doubts in determining the exact cutoff value to be used in assessing the prognosis of critical patients. The NLR cutoff value with a range of 4.36 – 23.8 reported in various studies can still be a limit to the NLR value for assessing the prognosis of critical patients [25].

Hu argues that the first day NLR has a significant effect on mortality ($p<0.005$). A high initial NLR value is an initial inflammatory response of the body and a condition resulting from the hypermetabolism that occurs. Most of the acute-subacute mortality in burn cases is caused by infection, sepsis, and MODS; so it is necessary to establish as early as possible with clinical parameters, laboratory tests, blood culture examination and various sepsis marker scores. Infection in burns can increase the risk of death by 51% through the process of organ failure (MODS). Second and third degree burns will provide living space for bacteria to colonize and proliferate in the wound. This will trigger the septic process and increase the risk of mortality in burn patients [19]. In the study by Qiu et al. in 2021 stated that the NLR on 3rd day can also be used as a predictor of mortality in burn patients up to a period of 90 days after trauma [24]. This was also conveyed by Setiawan et al. that NLR on 3rd day was significantly related to the mortality of burn patients with an Odds Ratio of 13.91 (95% CI 1.77 – 109.47) [28].

The NLR value also can be marker for sepsis risk accurately. Okashah et al. argues that increasing NLR value is more significant for septic condition than other laboratory values such as Procalcitonin, C-Reactive Protein, Leukocytes, Serum Lactate, Neutrophilia and Lymphocytopenia [23,29,30]. It can be seen in this study, through the chi square statistical test that NLR value on 1st day can be used as a predictor of sepsis incidence with a sensitivity of 57.3% and a specificity of 60.5%. However, NLR value on 3rd day cannot be used as a prognostic marker of sepsis during hospitalization in burn patients based on the subject of this study ($p>0.05$).

Sepsis occurs due to activation of the immune response aggresively and results in disruption of the circulatory system. Escalation of pro-inflammatory cytokines level will generate complex physiological process disorders of the body and the patient will fall into a MODS condition. In addition, anti-inflammatory cytokines, that also increase, will suppress lymphocyte levels due to apoptosis. Neutrophil level will increase in response to microbial infection; and lymphocyte level will decrease due to immunosuppression as described on. Both of these will explain the increase in NLR values in septic patients. Neutrophil level usually does not decrease directly in sepsis because the apoptotic process in neutrophil occurs lately. The chaos of the body's immune system will bring the patient into a MODS condition and can eventually die. NLR was also reported by Qu et al to be used as a biomarker for the diagnosis of bloodstream infections by gram-positive, gram-negative bacteria and fungal infection (with an NLR cutoff value of 3.09, $p<0.05$; sensitivity of 75.3% and specificity of 93.6%). Infection with these pathogenic germs will trigger inflammatory process as described above [25,31-33].

A meta-analysis by Huang Z. et al. in 2019 stated that NLR could be a prognostic biomarker in sepsis patients. Patients with high NLR levels will have a poor prognosis although this study was not carried out in burns only. In some cases, such as cachectic condition, it will cause a false negative intepretation of neutrophil values to predict the incidence of sepsis. Neutrophils may not increase in these condition eventhough the patient is in a septic condition. While the value of lymphocytes can also decrease along with the inflammatory process. An assessment using both parameters simultaneously through NLR value is considered to be more reliable than using only neutrophils or lymphocytes level alone. It was also reported that in world's population, normal NLR values (1.65) tend to be stable in young and healthy adult populations; such as in extensive studies in Belgium and South Korea. The mean NLR values for the male and female sexes were also

considered not much different (1.63 for men and 1.66 for women). This concludes that the NLR value of 1.65 can be considered as a reference number in healthy adults in the world's population [25].

In addition, NLR is also reported to be used as a predictor risk of Acute Kidney Injury (AKI) during the treatment of burn patients. Inflammatory processes that occur can affect kidney function. Kidney injury, as part of MODS, can affect the final outcome of treatment. Hemodynamic changes in burn patients due to the inflammatory process that occurs in the form of rapid transfer of fluid into the interstitial space will make the patient in hypovolemic state. This hypovolemia will cause kidney injury. Providing rapid and excessive fluid resuscitation may also aggravate kidney function due to decreased of renal perfusion. By knowing the inflammatory process that occurs through the calculation of the NLR value, the clinician can predict the risk of acute kidney injury in burn patients. Kim et al. reported that NLR can be used as a predictor of kidney injury with an Odds Ratio of 1.094 (95% CI 1.064 – 1.125, $p<0.001$) [11].

1.5. Conclusion

Neutrophil-to-Lymphocyte Ratio (NLR) on 1st day of treatment with a cutoff 7.97 and NLR on 3rd day of treatment with a cutoff of 6.2 may be used as prognostic markers in burn patients (1st day NLR as mortality and sepsis predictors and 3rd day NLR as mortality predictor only). Several confounding factors still need to be noticed like patient's burn area and age because those factors may be interfere the results.

2. Author Artwork

Figure 1. Mortality Pie Chart

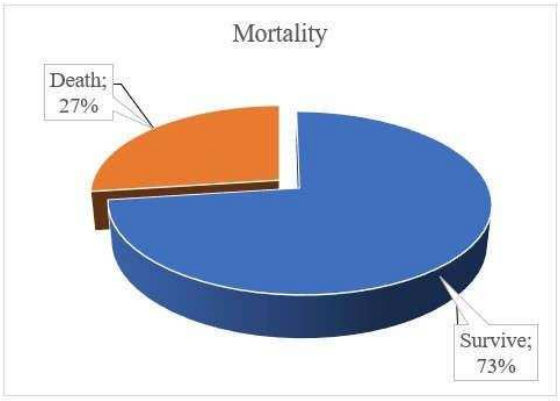
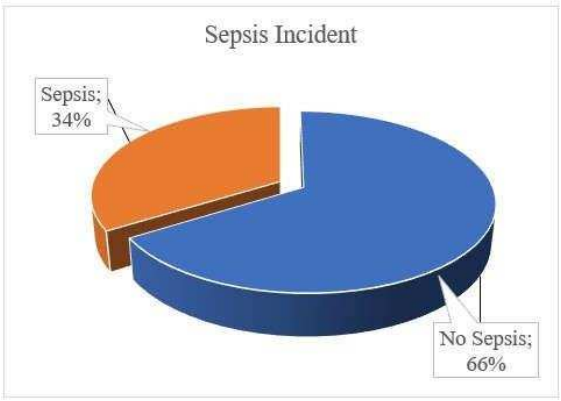


Figure 2. Sepsis Incident Pie Chart



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