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High neutrophil-lymphocyte ratio as a predictor of mortality in major burn patients

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Abstract--Major burns are a type of trauma with high mortality risk. Therefore, an accurate predictor of mortality indicators is needed in burn patients. This study used an analytical observational study design

with a retrospective case-control approach. One such indicator is the neutrophil-lymphocyte ratio which was studied further in this study. Subjects included 60 burn patients with 30 survivors and 30 mortalities. The sex characteristics of the subjects were predominantly male (70%), with a median age of 38.5 (IQR 30.5 – 52.5) years. Fire (68.3%) was the most common cause of burns. The median neutrophil-lymphocyte ratio decreased from day 1 (median 15.6, IQR 10.1–21.7) to day 3 (median 6.7, IQR 4.4 – 11.8). However, there was a different pattern in which the value of the neutrophil-lymphocyte ratio was found to increase on day 3 in the mortality group. The binomial logistic regression test found that the neutrophil-lymphocyte ratio value greater than or equal to 10 on the 3rd day was significantly associated with mortality risk with an aOR of 13.91 (95% CI 1.77 – 109.47). The conclusion is that A high neutrophil-lymphocyte ratio at day three can be used as a predictor of mortality in major burn patients.

Keywords---major burns, neutrophil-lymphocyte ratio, mortality, predictor.

Introduction

More than 95% of burns occur in low- and middle-income countries. Southeast Asia has the highest mortality rate (11.6 deaths per 100,000 population per year) (Johnson, Jordan and Shupp, 2018). The mortality rate of burn patients in Indonesia is still quite high, namely 27.6% (2012) at RSCM and 26.41% (2012) at Dr Hospital. Soetomo with an average burn area of 26% (range 1-98%) (Wardhana *et al.*, 2017). The mortality rate was 36.6% in patients with major burns with an average burn area of 44.5%, and with a burn area of > 60%, all of them died (Utami, Elfiah and Wisudanti, 2020).

Various markers of sepsis include C-reactive protein (CRP), procalcitonin (PCT), tumour necrosis factor- α (TNF- α), interleukin-6, and interleukin-1. Recent studies have reported that these indicators are difficult to apply, given the inconsistent results in determining the prognosis of burns in the early weeks after the burn event and the cost of examining these markers, which is quite expensive (Zhang *et al.*, 2021).

Neutrophils represent the nonspecific immune system that initiates the body's response to inflammation, while lymphocytes represent the protective or immune component of the immune response to the inflammatory reaction. The chronic inflammatory state induces hypersecretion of pro-inflammatory cytokines, leading to high neutrophil counts. A high neutrophil-lymphocyte ratio reflects an increased inflammatory response without adequate immune function (Wibisana *et al.*, 2019)

In Indonesia, the neutrophil-lymphocyte ratio in major burns has not been studied. The neutrophil-lymphocyte ratio, calculated by dividing the absolute number of neutrophils and lymphocytes, is very easy to obtain through the results of DL examinations routinely carried out regularly in patients with major burns. Knowing

the high neutrophil-lymphocyte ratio in patients with major burns is expected to predict mortality.

Method

This study uses an analytic observational study design with a case-control retrospective study approach study conducted at Prof. Dr IGNG Ngoerah Hospital Denpasar. The case group was patients with major burns who experienced mortality over seven days, while those who did not experience mortality were included in the control group. Research ethics permit from Udayana University with number 1147/UN14.2.2VII.14/LT/2022. Inclusion criteria: Patients with extensive burns $\geq 20\%$ TBSA and ages 18 – 65. Exclusion criteria: (1) Incomplete medical record, (2) Coming 24 hours after the burn incident, (3) Length of stay < 7 days, (4) Have comorbid diseases (heart disease, chronic kidney disease, diabetes mellitus, malignancy, autoimmune disease, HIV), The data analysis in this study consisted of descriptive statistical, bivariable, and multivariable with a significance value of $p < 0.05$.

Results and Discussion

This study uses the medical records of burn patients treated for March 2019 to February 2022 at Prof. Dr IGNG Ngoerah Hospital Denpasar. From a total of 333 medical records, 73 patients met the inclusion and exclusion criteria, which consisted of 43 cases of patients who experienced mortality and 30 patients who did not experience mortality. The purposive sampling method was used to obtain 30 cases and 30 controls. The basic characteristics of the sample are presented in Table 1.

This case-control study involved 30 cases of burn patients who experienced mortality and 30 controls of burn patients who did not experience mortality. Most burn patients in both groups (about 70%) were men with a median age of about 38 years. These demographic characteristics are by previous studies describing the characteristics of burn patients. One study in the United States found that the sex distribution of burn patients included 69.8% of men with a median age of 31 years (Vercruyse, Ingram and Feliciano, 2011). Similar findings were also found in a study in South Africa (Angelou *et al.*, 2022).

Demographics of burn patients who are predominantly male in their 30s can be related to the mechanism of trauma that occurs in burn patients. Most burns occur in work situations where young men are more likely to work in situations with a high risk of injury, especially burns. Therefore, men of reproductive age have a higher risk of burn injury than other sex and age groups. Recent developments have shown that the proportion of men is currently higher than in the previous period (Nickel, Omeis and Papp, 2020).

This study found that the clinical characteristics of burn patients were dominated by burns caused by fire (68.3%). A fairly large proportion of people with burns due to electric shock, either high or low voltage (21.7%). Meanwhile, burns due to hot water or steam were only found in 10% of the subjects. The median area of burns was found to be quite high, namely 38.5% TBSA.

Table 1
Sample basic characteristics

Variable	Total (n = 60) %	By Group		p
		Control (n = 30)	Case (n = 30)	
Gender, n (%)				
Man	42 (70.0)	20 (66.7)	22 (73.3)	0.779
Woman	18 (30,0)	10 (33.3)	8 (26.7)	
Age (years)	38.5	37.5	39.5	0.293
median (IQR)	(30.5 – 52.5)	(31.0 – 48.0)	(30.0 – 63.0)	
Burn area, n (%)	34.8	29.3	46.0	< 0.001**
median (IQR)	(26.0 – 46.0)	(23.5 – 34.5)	(36.0 – 65.0)	
BMI (kg/m ²)	24.45±3.51	23.99 ± 3.11	24.90 ± 3.88	0.157
mean ± SD				
Cause, n(%)				
Fire	41 (68.3)	16 (53.3)	25 (83.3)	0.057
Hot water	6 (10,0)	4 (13.3)	2 (6.7)	
Electricity	13 (21.7)	10 (33.3)	3 (10,0)	
Number of Neu (×10 ³ /mL) median (IQR)				
Day 1	22.0 (14.8 – 35.1)	19.0 (12.5 – 26.2)	29.0 (19.7 – 37.2)	0.028*
Day 2	12.8 (8.3 – 16.3)	12.6 (8.1 – 16.0)	13.9 (9.2 – 16.6)	0.579
Day 3	7.5 (4.7 – 9.8)	7.3 (4.2 – 8.4)	7.9 (5.1 – 12.3)	0.225
Total Lim (× 10 ³ /mL) median (IQR)				
Day 1	1.4 (1.0 – 2.0)	1.5(1.0 – 2.1)	1.4 (1.2 – 1.8)	0.712
Day 2	1.5 (1.1 – 2.0)	1.2(1.0 – 1.9)	1.6 (1.2 – 2.0)	0.119
Day 3	1.1 (0.7 – 1,4)	1.3(0.9 –1.5)	0.9 (0.5 – 1,3)	0.013*
Median Neutrophil-Lymphocyte Ratio (IQR)				
Day 1	15.6 (10.1 – 21.7)	13.2 (9.9 – 16.9)	21.4 (12.4 – 28.6)	0.003**
Day 2	8.0 (6.2 – 12.2)	7.9 (6.5 – 12.6)	8.3 (5.7 – 11.1)	0.520
Day 3	6.7 (4.4 – 11.8)	5.5 (3.6 – 7.1)	11.0 (6.8 – 15.3)	<0.001**

This characteristic is different from previous studies. One of the studies in China found that the most common cause of burns was water or steam (scalding), which was found in 41.6% of patients. Meanwhile, burns due to fire were only found in 26.9% of patients (Zheng et al., 2019). Meanwhile, another study in Turkey found that burns dominated the clinical epidemiology of burns due to fire (Güldoğan et al., 2019). The differences between the results of previous studies indicate that the characteristics of the causes of burns vary from one location to another, possibly related to the types of burn injury risk activities that are often carried out in each local community.

The burn area found in this study was higher than in other studies. Most other studies studying burns have found a median burn area in the range of 10-15% TBSA (Güldoğan et al., 2019; Nickel, Omeis and Papp, 2020; Angelou et al., 2022). This difference is most likely due to differences in inclusion criteria where the subjects of this study were limited to patients with major burns (burn area > 20% TBSA).

The characteristic differences between this study's control and case groups are comparable to those of previous studies. This is especially true in terms of differences in burn area characteristics. Burn area has been known as one of the major mortality risk factors for burn patients. This indicator has even been considered in almost all predictor indices of mortality in burn patients (Lip *et al.*, 2019). Slightly different results were found for the different characteristics of the burn mechanism. This study found a higher proportion of fire burns in the mortality group, and one study in Malawi reported similar results (Purcell *et al.*, 2021). Meanwhile, another study in Malaysia reported an equal proportion of burns caused by a fire in case and control groups (Tan Chor Lip *et al.*, 2019).

Subjects were then categorized based on the intersection points identified by Qiu *et al.* (2021) in previous research. The results of this categorization were then entered in the cross-tabulation table (Table 2) and continued with Chi-squared and Fisher's exact tests.

Table 2
Categorization and cross-tabulation of neutrophil-lymphocyte ratio values based on Qiu *et al.* (2021)

	Control (n = 30)	Case (n = 30)	p
Day 1			
< 10.00	9 (30,0)	6(20,0)	0.371 ^a
10.00	21 (70.0)	24 (80.0)	
Day 2			
< 10.00	18 (60.0)	18 (60.0)	1,000 ^a
10.00	12 (40.0)	12 (40.0)	
3rd day			
< 10.00	27 (90.0)	14 (46.7)	< 0.001 ^{**b}
10.00	3 (10,0)	16 (53.3)	

*p < 0.05; **p < 0.01; a Fisher's exact test; b Uji Chi squared

The Analysis was then continued with multiple logistic regression tests. Table 3 shows that the results found that the neutrophil-lymphocyte ratio on day three was associated with an aOR mortality risk of 13.91 (95% CI 1.77 – 109.47). The extent of burns is consistently found as a risk factor for mortality. Each 1% increase in the burn area in patients with major burns was associated with an increased mortality risk with an aOR of 1.24 (95% CI 1.07 – 1.44). The characteristics of the number of neutrophils, lymphocytes, and the value of the neutrophil-lymphocyte ratio in this study were characterized by a rapid increase on day one and a decrease on day 3. The decrease in lymphocyte count on day three was found to be more rapid in subjects with mortality outcomes, leading to a higher median neutrophil-lymphocyte ratio value at that examination point.

The movement of these three indicators is consistent with what we know about the clinical course of burn patients. The rapid increase in the number of neutrophils and the value of the neutrophil-lymphocyte ratio on day 1 indicates an acute inflammatory process in the patient. Patients with major burns experience extensive tissue damage and are exposed to infectious agents because of the

breakdown of the skin as one of the body's first line of defense. This condition causes an acute inflammatory process, especially in the first 24-48 hours after the injury (Bergquist et al., 2019).

Table 3
Multiple logistic regression results for categorizing the neutrophil-lymphocyte ratio Qiu et al., (2021).

Variable	aOR (95% CI)	p
Gender		
Man	1	0.378
Woman	3.17 (0.22 – 41.18)	
Age (every one year)	1.05 (0.98 – 1.11)	0.152
Burn area (every 1%)	1.24 (1.07 – 1.44)	0.005**
BMI (every 1 kg/m ²)	1.10 (0.82 – 1.49)	0.526
Causes of burns		
Fire	1	0.655
Water hot	0.66 (0.05 – 8.47)	
Electricity	3.11 (0.12 – 78.22)	
1st-day neutrophil-lymphocyte ratio		
< 10.00	1	0.204
10.00	3.90 (0.48 – 31.74)	
neutrophil-lymphocyte ratio day 2		
< 10.00	1	0.686
10.00	0.66 (0.09 – 4.97)	
day three neutrophil-lymphocyte ratio		
< 10.00	1	0.012**
10.00	13.91 (1.77 – 109.47)	

*p < 0.05; **p < 0.01

On day 3, the patient entered the sub-acute phase, characterized by a decrease in the number of neutrophils and lymphocytes. In this phase, humoral immunity, characterized by antibodies and pro-inflammatory cytokines, also begins to take over the inflammatory process. One study found that increased pro-inflammatory cytokines such as IL-6, IL-10, and TNF- were associated with more severe inflammation.(Bergquist et al., 2019). Hypersecretion of these pro-inflammatory cytokines also causes persistently high neutrophil levels. On the other hand, pro-inflammatory cytokines have a negative reciprocal relationship with lymphocytes, where these factors trigger lymphocyte apoptosis, triggering lymphocytopenia. Therefore, an increase in the neutrophil-lymphocyte ratio in the sub-acute phase may indicate more severe systemic inflammation in these patients.(Wibisana et al., 2019).

These findings are related to this study which found that the value of day three neutrophil-lymphocyte ratio had a discriminatory or predictive ability of mortality in patients with major burns. These results agree with the previous findings of Qiu et al., who found a relationship between the value of the neutrophil-lymphocyte

ratio and mortality in patients with major burns on day 3. (Qiu et al., 2021). The results of multivariate Analysis found that the third-day neutrophil-lymphocyte ratio value greater than or equal to 10 was an independent risk factor for mortality with an AOR of 13.91 (95% CI 1.77 – 109.47). The other independent risk factor for mortality was burn area, where every 1% increase in TBSA in major burn patients (TBSA >20%) was associated with an increased risk of mortality with an AOR of 1.24 (95% CI 1.07 – 1.44).

There was also a significant change, indicated by the p-value, between bivariate (Table 2) and multivariate (Table 3) analyses. This can be explained by controlling for the effect of confounding variables in multivariate Analysis. This means that the p-value obtained in the bivariate Analysis is still affected by the role of other variables that are not included in the Analysis. In multivariate Analysis, the role of this confounding variable is controlled, showing the magnitude of the p-value as an independent relationship between the independent and dependent variables.

More broadly, the role of the neutrophil-lymphocyte ratio as a predictor of mortality in burn patients has also been investigated with mixed results. One previous study reported that each point increase in the neutrophil-lymphocyte ratio on day 1 reduced the risk of survival with an aOR of 0.89 (95% CI 0.86 – 0.94)(Ali, 2019). Another study in China also found similar results(Hu et al., 2021). However, few studies have reported the optimal cut-off point for day one neutrophil-lymphocyte ratio predicting mortality in burn patients. The reported central tendency values of the neutrophil-lymphocyte ratio in the mortality group also varied, ranging from a mean of 10.94 ± 7.63 to a median of 12.65 (IQR 7.46–18.64)(Ali, 2019; Steinvall et al., 2021). In addition to mortality, high neutrophil-lymphocyte ratio values were also associated with acute kidney injury and sepsis in burn patients(Fuss et al., 2018; Kim et al., 2019).

Predicting prognosis and mortality is an important part of the clinical management of patients with emergency and critical conditions. This can inform the clinician about the aggressiveness of therapy to be given and the allocation of resources for intensive care. In this case, the use of laboratory indicators as predictors of mortality has advantages over the scoring system that is often used for burn patients. Although it is easier to use, predicting mortality using the score has the disadvantage that the subjectivity of the score depends on clinical proficiency in using it (Sheppard et al., 2011). Laboratory indicators do not have this weakness of subjectivity, and some laboratory indicators, such as neutrophil-lymphocyte ratio values, can be obtained easily and relatively quickly. Besides being a stand-alone predictor of mortality, laboratory indicators can also be used to increase the accuracy of predictions by using the score (Steinvall et al., 2021). Despite these advantages, there is still no consensus on the best laboratory indicators as predictors of mortality in patients with major burns. In addition to the value of the neutrophil-lymphocyte ratio, several other indicators that have been studied include platelet, albumin, and lactate levels (Güldoğan et al., 2019; Steinvall et al., 2021).

The weaknesses of this study are the use of a retrospective study with secondary data, the implementation of the study only in one center, and with a relatively small number of samples even though they have met the required sample size based on

calculations marked by the findings of a relatively wide confidence interval. Further research can be carried out to confirm the findings in this study by using a prospective, multicenter study design and involving more subjects in the Analysis.

Conclusion

Based on the results and discussion above, it can be concluded that a high neutrophil-lymphocyte ratio on day three can be used as a predictor of mortality in patients with major burns.

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