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Neutrophil-Lymphocyte Ratio (NLR) as an output-outcome predictor in moderate-severe head injury at Sanglah General Hospital, Denpasar, Indonesia

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ABSTRACT

Background: This prospective cohort study aims to determine the best cut point value and the ability to predict Neutrophil Lymphocyte Ratio (NLR), analyze the most dominant factors, and the direct influence of the NLR to output and outcome in moderate and severe trauma to the head injury at Sanglah General Hospital, Denpasar, Indonesia.

Methods: This study was an observational analytic with a prospective cohort design. The subjects of this study were head injury patients over 16 years old with Glasgow Coma Scale (GCS) ≤ 12 who visited and were treated at Sanglah General Hospital, Denpasar, Indonesia. Patients less than 16 years old, history of alcohol intoxication, stroke, metabolic disease, and multiple traumas were not included as research subjects. Data were analyzed using SPSS version 20 for Windows.

Results: The research conducted on 49 respondents found that the best cut-off point of NLR was 6.05 has the most significant predictor (OR=7.6; p=0.001) and dominant (OR=64.97; p=0.002) factors to the output-outcome predictor in moderate-severe head injury. In addition, this cut-off value (6.05) also has a direct influence (x-value=0.523) in the occurrence of output and outcome unfavorable in moderate-severe head injury.

Conclusion: the cut-off NLR values of 6.05 became the dominant predictor that directly affected the output and outcome unfavorable in moderate-severe head injury.

Keywords: Neutrophil-Lymphocyte Ratio, Unfavorable Output-Outcome, Head Trauma.

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INTRODUCTION

Head injuries are still the leading cause of disability and death worldwide.[1] This puts the prognosis as an important point for the basis of decision making for the management and evaluation of the management of head injuries that have been carried out.[1] Various factors have been known to affect the prognosis of head injuries, one of which is the inflammatory response.[2] Immediately after a trauma head injury, there is an increase in intracranial pressure and cerebral ischemia. Both of these events resulted in catecholamine and glucocorticoid surges.[3] A rise in catecholamines triggers neutrophil margins to enter the circulation, while an increase in glucocorticoid levels will increase the number of peripheral neutrophils by stimulating their release from bone marrow storage and prolonging their life span and preventing neutrophils from circulating to return to the bone marrow.[3] A few days after a head injury, neutrophils subsequently show a decrease in the formation of Reactive Oxygen Species (ROS).[4] Disruption of ROS formation may be one of the mechanisms underlying the increased susceptibility of trauma head injury patients who are hospitalized to infection and will ultimately affect the outcome of trauma head injury patients.

Head injuries cause a significant decrease in the percentage and the absolute number of circulating lymphocytes.[3] Lymphocytes are part of the adaptive immune system. This state of lymphopenia is due to an increase in circulating catecholamine levels, which results in lymphocyte retention in lymph nodes. In addition, many functional defective lymphocytes circulate after a traumatic head injury. Lymphocyte T cells in patients with severe trauma to the head injury reduce the proliferation and production of cytokines after phytohemagglutinin stimulation and increase Lymphokine-Activated Killer (LAK) cytotoxicity after incubation with IL-2.[3] Mechanically, the decrease in cell-mediated immunity is thought to be caused by serum factors with immuno-suppressive activity and the presence of suppressor lymphocytes that actively inhibit the effector lymphocyte function.

The Neutrophil-Lymphocyte Ratio (NLR) is a picture of the innate and adaptive immune system that is compared to determine the extent to which the body's immune system reacts to a stimulus both from the outside and from within, particularly in the response of inflammation.[5,6] The NLR can be easily calculated from the results of a complete blood test, and is an easily obtained marker that can indicate the status of inflammation in the body. This prospective cohort study aims to determine the best cut point value and the ability to predict the NLR, analyze the most dominant factors and the direct influence of the NLR to output and outcome in moderate and severe head trauma.

METHODS

This research was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Indonesia. This study was an observational analytic with a prospective cohort design. The subjects of this study were head injury patients over 16 years old with Glasgow Coma scale (GCS) ≤ 12 who visited and were treated at Sanglah General Hospital. Patients less than 16 years old, history of alcohol intoxication, stroke, metabolic disease, and multiple traumas were not included as research subjects.

All patients diagnosed with moderate and severe head injuries are explained the purpose of this study and the patient agrees or is willing to participate in this study. It will be followed by the signing of informed consent. All patients with moderate and severe head injury at the Emergency Ward, Sanglah General Hospital, Denpasar, Indonesia underwent the Complete Blood Count (CBC), blood glucose levels, blood gas, and electrolyte analysis after initial resuscitation. All patients diagnosed with moderate and severe head injuries were given medical treatment according to standard operating procedures at Sanglah General Hospital Denpasar, including shock treatment, respiratory distress with intubation and surgery.

Blood tests are performed less than 6 hours after a head injury diagnosis is made. The NLR value is defined as the ratio value that compares the absolute value of neutrophils and lymphocytes. The GCS value at hospital admission was recorded after initial resuscitation and the 5-point Glasgow Output Scale (GOS)

Table 1. Baseline characteristic of respondents

Variable	Total (N=49)
Age (Years), n (%)	
≥ 45	24 (49.0)
< 45	25 (51.0)
Sex, n (%)	
Male	39 (79.6)
Female	10 (20.4)
Glucose Level (mg/dl), n (%)	
High (≥ 140)	31 (63.3)
Low (<140)	18 (36.7)
Ventilation, n (%)	
Yes	27 (55.1)
No	22 (44.9)
Shock, n (%)	
Yes	9 (18.4)
No	40 (81.6)
pH, n (%)	
High	12 (24.5)
Low	18 (36.7)
Normal	19 (38.8)
Anion Gap, n (%)	
High	42 (85.7)
Low	7 (14.3)
Surgical Intervention, n (%)	
Yes	23 (46.9)
No	26 (53.1)
Level of Head Injury, n (%)	
Severe	24 (49.0)
Moderate	25 (51.0)

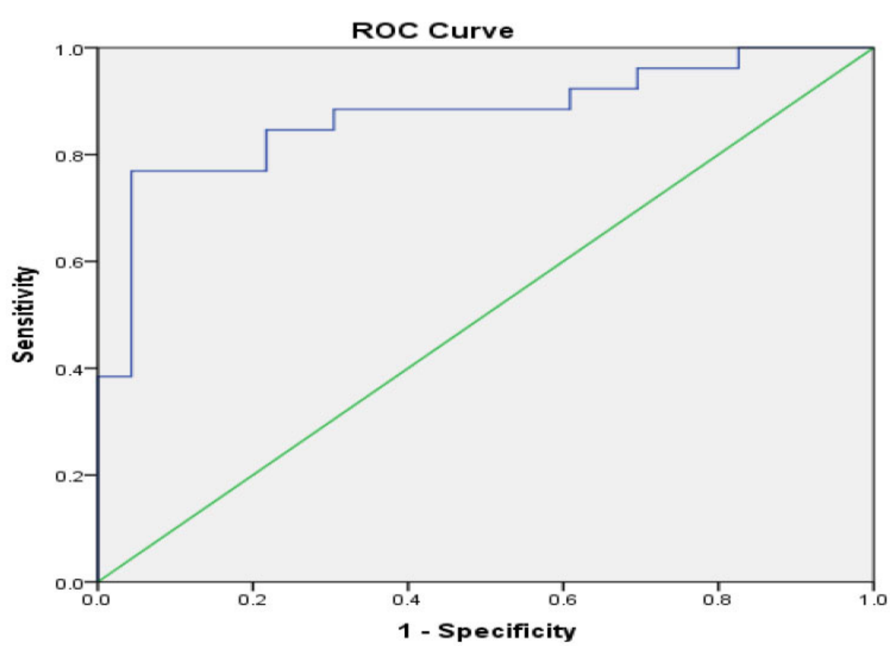

Figure 1. ROC curve for assessing the ability and the best NLR cutoff for moderate-severe head injury output and outcome.

Table 2. The relationship between NLR to the output and outcome of moderate-severe head injury

Variable	Output and Outcome of Moderate-Severe Head Injury (N=49)		OR	95% CI	p
	Unfavorable (N=26)	Favorable (N=23)			
NLR, n (%)					
≥ 6.05	20 (76.9)	7 (30.4)	7.6	2.13-27.21	0.001*
< 6.05	6 (23.1)	16 (69.6)			

NLR: Neutrophil Lymphocyte Ratio; OR: Odds Ratio; CI: Confidence Interval; *Chi-Square: statistically significant if p-value less than 0.05.

Table 3. Relationships between age, sex, blood glucose level, surgery, blood acidity, ventilation, anion gap and shock events to the output and outcome of moderate-severe head injury

Variable	Output and outcome Moderate-severe head injury (N=49)		OR	95% CI	P
	Unfavorable (N=26)	Favorable (N=23)			
Age (Years), n (%)					
≥ 45	16 (61.5)	8 (34.8)	3.0	0.93-9.63	0.062
< 45	10 (38.5)	15 (65.2)			
Sex, n (%)					
Male	20 (76.9)	19 (82.6)	0.7	0.17-2.88	0.622
Female	6 (23.1)	4 (17.4)			
Glucose Level (mg/dl), n (%)					
High (≥ 140)	21 (80.8)	10 (43.5)	5.4	1.52-19.58	0.007*
Low (<140)	5 (19.2)	13 (56.5)			
Ventilation, n (%)					
Yes	17 (65.4)	10 (43.5)	2.4	0.77-7.78	0.124
No	9 (34.6)	13 (56.5)			
Shock, n (%)					
Yes	8 (30.8)	1 (4.3)	9,7	1.11-85.65	0.017*
No	18 (69.2)	22 (95.7)			
pH, n (%)					
High	8 (30.8)	4 (17.4)	-	-	0.396
Low	10 (38.5)	8 (34.8)			
Normal	8 (30.8)	11 (47.8)			
Anion Gap, n (%)					
High	22 (84.6)	20 (87.0)	0,82	0.16-4.14	0.815
Low	4 (15.4)	3 (13.0)			
Surgical Intervention, n (%)					
Yes	13 (50.0)	10 (43.5)	1,3	0.42-4.03	0.648
No	13 (50.0)	13 (56.5)			
Level of Head Injury, n (%)					
Severe	18 (69.2)	6 (26.1)	6,3	1.82-22.22	0.003*
Moderate	8 (30.8)	17 (73.9)			

OR: Odds Ratio; CI: Confidence Interval; *Chi-Square: statistically significant if p-value less than 0.05

value was recorded at hospital discharge and 3 months after hospital discharge. The Operational Variable of GOS in this study was death (1), vegetative state (2), severe disability (3), moderate disability (4), and good recovery (1). Death and vegetative state were classified as unfavourable outcome conditions, whereas severe disability, moderate disability, and good recovery were classified as favourable outcome conditions.

Univariate analysis was performed to determine sample characteristics and the distribution of NLR values. The NLR distribution is treated with a Receiver Operating Characteristics (ROC) curve to find the best cut-off point that provides predictive results for head-to-weight head injury outcomes. Bivariate analysis to determine the relationship between NLR variables with output (life-death) and outcome (favorable-unfavorable). The test used was Chi-Square with significance level α = 0.05. This variable has a relationship with output and outcome if the value of p <0.05. The results of the bivariate analysis are presented in tabular and narrative form.

Multivariate analysis was performed to determine the factors that most influence the output and outcome in head injury patients. Factors analyzed included age, sex, blood glucose level, ventilation,

Table 4. The most dominant risk factors for the output and outcome of moderate-severe head injury.

Variable	B	Adj (OR)	95% CI	p
NLR ≥ 6.05	4.174	64.97	4.78-882.28	0.002*
Age ≥ 45 years old	2.461	11.71	1.58-86.42	0.016*
Glucose level ≥ 140 mg/dl	3.884	48.62	3.66-644.48	0.003*
Ventilation	4.395	81.01	1.14-5,749.48	0.043*
Surgical intervention	-4.413	0.01	0.00-1.00	0.050

NLR: Neutrophil Lymphocyte Ratio; Adj OR: Adjusted Odds Ratio; CI: Confidence Interval; *multiple logistic regression tests with the backward method: statistically significant if p-value less than 0.05.

Table 5. Effect of age, blood glucose level, anion gap and NLR to moderate-severe head injury output

Variable	B	R Square	Beta	t	95% CI	p
Age	-0.009	0.473	-0.170	-1.448	-0.020-0.004	0,155
Glucose Level	0.004		-0.288	-2.607	-0.008-0.001	0,012*
Anion Gap	0.001		0.008	0.074	-0.026-0.028	0,941
NLR	0.111		-0.562	-4.785	-0.158-0.064	0,000*

NLR: Neutrophil Lymphocyte Ratio; CI: Confidence Interval; *Linear Regression Test: statistically significant if p-value less than 0.05.

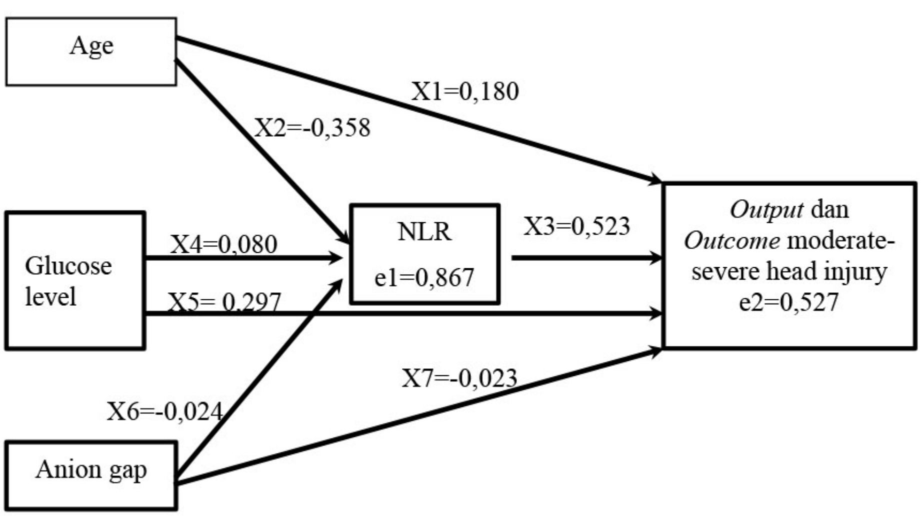

Figure 2. Pathway analysis of factors affecting the output-outcome of moderate to severe head injury.

shock condition, blood acidity, anion gap, neurosurgery. The analysis used is a multiple logistic regression test. Pathway analysis is a statistical analysis used to describe the independence of the variables that affect the output-outcome in moderate-severe head injuries. Path analysis is a further part of the regression analysis to find out the indirect effect of independent variables in the form of intervals or ratios (age, glucose levels, anion gap and NLR on output-outcome variables for a moderate-severe head injury. Strengths of each contributing variable is calculated as a coefficient. Data were analyzed using SPSS version 20 for Windows.

RESULTS

There are 49 study subjects aged 16-77 years included in the inclusion criteria of this study. Demographic data is presented in the following Table 1. Most of respondents were age < 45 years old (51.0%), male (79.6%), high glucose level (≥ 140 mg/dl) (63.3%), having ventilation (55.1%), no shock (81.6%), normal pH (38.8%), high anion gap (85.7%), no surgical intervention (53.1%), and moderate level of head injury (51.0%) (Table 1).

The NLR value in this study is based on the ROC curve with an AUC value of 87.3%. Clinically the AUC value of the NLR is satisfactory because it is greater than the minimum AUC value expected by researchers (70.0%). The best cut-off point is at 6.05 (Figure 1).

The best cut of point results of the NLR to the output and outcome of moderate and severe head injuries were subsequently analyzed using a 2x2 table (Table 3). The NLR values ≥ 6.05 provides an opportunity for an unfavorable output and outcome of 7.6 times significantly higher than the favorable output and outcome (OR=7.6; 95% CI: 2.13-27.21; p=0.001) (Table 2).

A multivariate analysis of NLR variables with other confounding variables was also performed in this study. Multivariate analysis was performed to see the effect between variables involving more than 2 variables. The scale of the data used was categorical with multiple logistic regression tests with the backward method. Data is presented in Table 3 and Table 4. There was a significant relationship between high glucose level (≥ 140 mg/dl), shock, and severe head injury to the unfavorable output and outcome of moderate-severe head injury (p<0.05) (Table 3). Table 4 shows that the NLR values ≥ 6.05 (Adj OR=64.97; 95% CI=4.78-882.28, p=0.002) are the most dominant risk factors for the output and outcome of moderate-severe head injury compared to other variables.

Stages of pathway analysis (pathway analysis) is a linear regression test variable age, glucose levels and anion gap to NLR values. Table 5 describes the effects of age, glucose anion gap levels and the NLR on the output of moderate-severe head injuries. The magnitude of the effect of the age, anion gap, glucose level, and NLR was 47.3%. This result indicates that 52.7% due to the influence of other variables not included in this model.

Furthermore, to determine the direct and indirect effects of age, glucose and anion gap variables on CKS-CKB output and outcome are depicted in Figure 2. Based on the analysis of these pathways, it can be concluded that the NLR has a direct influence on the output and outcome of moderate to severe head injury with a large effect of 0.523 while glucose has a direct effect of 0.297 (smaller than the NLR) (Figure 2).

DISCUSSION

This study shows the role of the NLR as a predictor of output and outcome of head injury. In patients with an NLR greater than or equal to 6.05, it allows an output and outcome of death or vegetative state of 7.6 times higher than the favorable outcome. Neutrophils are the most leukocytes in the human circulation and the first immune cells that arrive at the site of trauma. This direct occurrence of neutrophilia is thought to originate from an increase in catecholamines and glucocorticoids caused by trauma head injury.[7] Neutrophils from trauma head injury patients significantly result in higher ROS counts and higher gp91phox expression even at rest than neutrophils obtained from patients with general trauma without CNS injury.[8] In contrast to the increased ROS formation that has characterized the initial response to trauma head injury, neutrophils show decreased ROS formation in the days after injury.[4,8-10] In a study of trauma head injury patients who were hospitalized with moderate or severe brain trauma, Marks W et al., found that neutrophil ROS production on day 9 after injury was significantly lower than healthy controls according to age and sex.[4] Given the peak incidence of infection in trauma head injury patients hospitalized, it occurs 5-11 days after injury, and neutrophils are the first line of defense against bacteria, fungi, and yeast quickly. Hence, impaired ROS formation may be one of the mechanisms underlying the increased susceptibility of trauma head injury patients hospitalized to infections.[4] With this in mind, the comparison of ROS formation between neutrophils isolated from uninfected trauma head injury patients and infected trauma head injury patients showed a significantly greater percentage of cells that formed ROS in the uninfected group on day 6 after injury.[4]

On the other hand, B lymphocyte cells will initiate an immune response to antigens derived from brain cells after a trauma head injury. Zhang Z et al., detect autoantibodies opposite to astrocyte-residing intermediate filament proteins (GFAP) and their breakdown products in serum samples obtained from 53 patients after severe trauma to the head injury.[11] This GFAP autoantibody, which was detected as early as 4 days after injury and whose levels were positively correlated with GCS scores, was shown to induce glial cell injury in vitro, demonstrating a potential pathophysiological role for B cells during the recovery phase of trauma head injury.[11]

Severe head trauma causes a significant decrease in the percentage and an absolute number of circulating T lymphocytes.[10] This reduction, which has been observed within 24 hours after injury and also on the 4th day after the injury, is the result of a significant decrease in CD4 + helper T cells and CD8 + cytotoxic T cells.[10] At present, the mechanism underlying the decrease in the number of circulating T cells caused by trauma to the head injury remains unclear. Given that trauma head injury causes an increase in circulating catecholamine levels, lymphocyte retention in lymph nodes can be one mechanism to explain the significant decrease in T cell counts that have been observed after trauma head injury.[10]

Another study by Nunez J et al., in 2008 concluded that the NLR was an independent predictor of mortality in patients with an NLR > 4.7.[12] Another study by Kastilong M et al., in 2018 also showed that the value of the NLR > 3.62 was statistically significant as having a poor head injury outcome ($p=0.04$).[13]

In the end the output and outcome of a head injury is a multifactorial combination in which factor one is no more dominant than other factors. One of the variables that have not been controlled in this study is the condition and treatment of referrals starting from the scene until the research subjects arrived at the hospital.

CONCLUSION

The best cut-off value for the NLR to output and outcome in moderate and severe trauma to head injuries is 6.05. The NLR value ≥6.05 becomes the dominant predictor that has a direct impact on output and unfavorable outcomes in moderate-severe head injury after being controlled for age, sex, glucose level, blood acidity, ventilation, shock condition, anion gap, level severity of head injury and surgery.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ETHICS CONSIDERATION

Ethics approval has been obtained from the Ethics Committee, Medical Faculty, Universitas Udayana, Sanglah General Hospital, Denpasar, Indonesia prior to the study being conducted.

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AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the study results through publication.

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