

# The association between neutrophil to lymphocyte ratio (NLR) with mortality in patients with perforated peptic ulcer at Dr. Soetomo Hospital in Surabaya, Indonesia



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## ABSTRACT

**Background:** Perforated peptic ulcer is the most dangerous complication of peptic ulcer. Neutrophils and lymphocytes are crucial in the inflammatory process. A simple and effective biomarker to assess systemic inflammation is the neutrophil-lymphocyte ratio (NLR). This study aims to ascertain the connection between NLR and mortality in peptic ulcer patients.

**Methods:** This study was a cross-sectional observational analytic study. Data were obtained from medical records in Dr. Soetomo General Hospital from January 2018 to December 2022. The dependent variable was patient mortality, while NLR value served as the independent variable. NLR cutoff value calculated using the Receiver Operating Characteristic (ROC) curve. The collected data was tested using the Chi-square test and the Spearman rank correlation test integrated in the SPSS software.

**Results:** There were 109 patients, consisting of 74 male and 35 female patients. There were 29 patients with the Boey Score category 1, 54 patients with the Boey score category 2, and 25 patients with the Boey score 3. Using a cutoff of 15.60, the NLR values were separated into low and high NLR groups. There were 56 patients with high scores and 53 patients with low scores. A significant relationship was found between NLR values and mortality ( $p < 0.0001$ ). The results of Spearman's analysis revealed a strong correlation between the incidence of mortality and an increase in the NLR value ( $p < 0.0001$ ;  $r = 0.500$ ).

**Conclusion:** There is a significant relationship between NLR and mortality in patients with perforated peptic ulcers.

**Keywords:** perforated peptic ulcer, neutrophil to lymphocyte ratio, prognostic factors, mortality.

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## INTRODUCTION

Peptic ulcer or gastritis is one of the most common gastrointestinal diseases that occurs worldwide with around four million patients every year. Perforated peptic ulcer (PPU) is the most concerning complication as the mortality caused by PPU was 10-40%, which was ten times higher than other acute abdominal diseases such as acute appendicitis or acute cholecystitis. In emergency abdominal surgery cases, around 5% were caused by PPU. Surgery is the definitive management for PPU. Delayed in diagnosis and surgery cause higher mortality and morbidity. In Indonesia, the prevalence of PPU cases is 6-15%. In 2008, PPU was listed in the top ten causes of death in men aged 45 – 54 years old.<sup>1,2</sup>

The risk of mortality and morbidity

in PPU cases did not have significant differences on the last decade, the mortality was 6 – 30% and the morbidity was 21-43%. Some scoring systems and parameters have been made to predict the mortality of PPU, such as blood lactate level Boey Score, Peptic Ulcer Perforation Score (PULP), and American Society of Anesthesiologists (ASA), but each system has weakness in predicting the mortality of PPU.<sup>3,4</sup>

A significantly increased number of neutrophils and decreased lymphocytes have been observed in critical illnesses such as septic shock, hemorrhagic shock, multiple trauma, and acute pancreatitis. Some clinical tests have shown that neutrophils and lymphocytes reflect physiological responses from the circulated leucocyte to stress, injury, trauma, major surgery, bacteremia, systemic

inflammation, systemic inflammatory response syndrome (SIRS), and sepsis.<sup>5</sup>

The latest study explained the correlation between neutrophil to lymphocyte ratio (NLR) with mortality and severity level in some diseases such as infection, Ludwig Angina, Testicular Germ Cell Tumor (GCT), thyroid malignancy, cardiovascular disease, and general intraabdominal infection. Higher NLR can be a prognostic factor for mortality in sepsis and peritonitis cases.<sup>6-11</sup>

There has been no study on the correlation between NLR and PPU cases in Dr. Soetomo General Hospital, Surabaya. NLR examination is considered as a simple, easy to do and relatively cheap biomarker. In this study, we aimed to analyze the NLR before treatment and to analyze the association with the mortality of PPU cases.

## MATERIALS AND METHODS

### Study design and participants

This study was an observational analytic cross-sectional study aiming to associate the value of NLR ratio when the patient first came to the emergency room with the mortality of PPU patients. Data were obtained from medical records in Dr. Soetomo General Hospital (Surabaya, Indonesia) between 2018 – 2021. The sample was obtained with consecutive sampling methods in PPU adult patients who were older than 18 years old. Patients with autoimmune, immunodeficiency, and history of current corticosteroid consumption were excluded. We also excluded patients with no complete data.

### Data collection

We reviewed and collected patient data from the medical records. We collected patient data such as gender, age, outcome, comorbid diseases, treatments, onset, total Boey score, and perforation location. We also collected the laboratory test results, including neutrophil, lymphocyte, and NLR counts. All the data were obtained from paper-based medical records and electronic medical records.

### Statistical analysis

Statistical analysis was performed using the SPSS statistical software package version 23.0. The independent and dependent variables were analyzed as nominal data with the Chi-squared test. Spearman analysis and ROC curve analysis was used to obtain predictive value and correlation among the studied variable. Statistical significance was determined when the p-value was less than 0.05.

## RESULTS

### Patient characteristics

There were 109 data obtained. Seventy-four subjects were men (67.9%) and 35 subjects were women (32.1%). Based on age, there were 5 groups. Most of the patients were more than 60 years old (61.5%). Based on the outcome, most of the patients were alive (63.3%), while 40 patients passed away during the treatment (36.7%). The comorbidities commonly found in this study were related to lung disease (18.3%) and followed with heart

**Table 1. Characteristics of study participant.**

Characteristics	n	%
<b>Gender</b>		
Male	74	67.9
Female	35	32.1
<b>Age</b>		
30-39	4	3.7
40-49	10	9.2
50-59	28	25.7
≥60	67	61.5
<b>Outcome</b>		
Alive	69	63.3
Passed away	40	36.7
<b>Comorbidities</b>		
Diabetes Mellitus	15	13.8
Heart	11	10.1
Kidney	15	13.8
Obesity	4	3.7
Liver	4	3.7
Lung	20	18.3
Neurology	3	2.8
<b>Interventions</b>		
Laparotomy repair gaster	82	75.2
Laparotomy repair duodenum	6	5.5
External drainage	21	19.3

disease and diabetes mellitus (13.8%). Based on the interventions done in this study the most common intervention conducted was gastric repair through laparotomy (75.2%). The characteristics of patients are shown in [Table 1](#).

### Association between patient characteristics and outcome

This study analyzed the association between variables content patient characteristics and outcome. The data are shown in [Table 2](#). Clinical symptoms' onset showed no significant association with outcome with  $p = 0.844$ . The comorbidity variable consists of 43 patients with comorbidity and 66 patients without comorbidity. Analysis testing shown no significant association between comorbidity and outcome with  $p = 0.366$ .

The shock was found in 20 patients, where 10 passed away during treatment in the hospital. Among the patients who had not experienced shock, 59 patients were alive (66.3%) and 30 passed away (33.7%). There was no significant association between shock and mortality ( $p = 0.172$ ).

In this study, Boey score 2 was the predominant case and was observed in 54 patients. All patients with Boey score

1 survived in 29 patients (100%). Within patients with Boey score 2, thirty-two patients were alive (59.3%) and 22 were passed away (40.7%). Within patients with Boey score 3, seventy-two percent were passed away. There was a significant association between Boey score and outcome ( $p < 0.001$ ).

Based on the perforation location, we found that gastric perforation was found in 81 patients, while only 7 perforated in duodenum. Twenty-one of the sample were remained unconfirmed for the location. From the patients with perforation in gaster, we found that 72.8% of the patients were survived. A total of 57.1% of patients survived in the group where the perforation occurred in duodenum. At the same time, 66.7% patients passed away in the group where the location of perforation was unconfirmed. The analysis shown a significant association between the location of perforation and patient outcome ( $p = 0.002$ ).

### Association between laboratory findings and outcome

From the alive patients, the average neutrophil count was 11.04 (SD 6.36) and median 10. In the patients that passed away,

the neutrophil average 15.74 with median 14.85. The average lymphocyte count in alive patients was 0.97 and median 0.84 while the average was 0.68 and median 0.64. The NLR in alive patients, the average was 15.13 and median 11.79. At the same time, patients that passed away had NLR average 27.54 and median 22.9. Data showed on [Table 3](#).

### Association between laboratory findings and Boey score

From the Boey score, average neutrophil in patients with Boey score 1 was 11.95 and median 10.58. In patients with Boey score 2, the average neutrophil was 13.21 and median 11.39. In patients with Boey score 3 the average neutrophil was 12.96 and median 11.35. The average lymphocyte in

patients with Boey score 1 was 0.99 and median 0.77. In patients with Boey score 2, the average lymphocyte was 0.82 and median 0.74. In patients with Boey score 3 the average lymphocyte was 0.77 and median 0.67. The average NLR in patients with Boey score 1 was 16.54 and median 12.42. In patients with Boey score 2, the average NLR was 20.2 and median 17.33. In patients with Boey score 3 the average NLR was 22.56 and median 19.64. Data are shown in [Table 4](#).

**Table 2. Association between characteristics and outcome of the study.**

Variables	n	Outcome		P Value
		Alive	Passed away	
<b>Onset</b>				
<24 hours	64	41 (64.1%)	23 (35.9%)	0.844
≥24 hours	45	28 (62.2%)	17 (37.9%)	
<b>Comorbidities</b>				
Yes	43	25 (58.1%)	18 (41.9%)	0.366
No	66	44 (66.7%)	22 (33.3%)	
<b>Shock</b>				
Yes	20	10 (50%)	10 (50%)	0.172
No	89	59 (66.3%)	30 (33.7%)	
<b>Total Boey Score</b>				
1	29	29 (100%)	0 (0%)	<0.0001
2	54	32 (59.3%)	22 (40.7%)	
3	25	7 (28%)	18 (72%)	
<b>Perforation location</b>				
Gaster	81	59 (72.8)	22 (27.2)	0.002
Duodenum	7	3 (42.9)	4 (57.1)	
Unconfirmed	21	7 (33.3)	14 (66.7)	
<b>Gender</b>				
Male	74	47 (63.5)	27 (36.5)	0.947
Female	35	22 (62.9)	13 (37.1)	
<b>Age</b>				
30-39	4	3 (75.0)	1 (25.0)	0.739
40-49	10	5 (50.0)	5 (50.0)	
50-59	28	19 (67.9)	9 (32.1)	
≥60	67	42 (62.7)	25 (37.3)	

**Table 3. Association between laboratory findings and outcome of the study.**

Laboratory Findings	Outcome	
	Alive	Dead
<b>Neutrophil</b>		
Average	11.04	15.74
Deviation Standard	6.36	6.76
Median	10	14.85
<b>Lymphocyte</b>		
Average	0.97	0.68
Deviation Standard	0.52	0.34
Median	0.84	0.64
<b>NLR</b>		
Average	15.13	27.54
Deviation Standard	14.15	16.22
Median	11.79	22.9

### Association between NLR, Boey score, and mortality

We analyzed the association between NLR and mortality with 2 NLR cutoffs. The first cutoff was 20.72 and second cutoff was 15.6. The first one was referred to the study done before, and the second cutoff obtained with ROC analysis (AUC = 0.800; 95% CI = 0.713 – 0.886) shown in [Figure 1](#). The analysis showed that both cutoffs had significant association with patient outcome with p value less than 0.0001 for both.

The association between Boey score and patient outcome was also analyzed with two cutoffs, Boey score 1 and Boey score 2. With the cutoff, Boey scores 2, eighty patients found with high Boey scores and 29 patients with low scores. For patients with high scores, forty survived while 40 (50%) passed. In patients with low Boey scores, all patients alive. With cutoff Boey score 3, there were 25 patients with high and 84 with low scores. The high Boey score, 7 patients alive and 18 passed. In patients with low Boey scores, 62 patients alive and 22 passed.

Also, the correlation between NLR and outcome was tested with Spearman rank correlation. The result showed a significant association between increasing NLR values and mortality in PPU patients. The analysis is shown on [Table 5](#).

### Performance of NLR and Boey score as a predictive outcome factor

Performance of NLR from the first cutoff (20.72) had sensitivity 55.0%, specificity 87.0%, PPV 71.0%, NPV 76.9% and accuracy value 75.2%. The second cutoff (15.6) had sensitivity 87.5% specificity 69.6%, PPV 62.5%, NPV 90.6% and accuracy value 76.1%.

**Table 4.** Association between laboratory findings and Boey score.

Laboratory findings	Boey Score		
	Score 1	Score 2	Score 3
<b>Neutrophil</b>			
Average	11.95	13.21	12.96
Deviation Standard	6.69	6.59	7.56
Median	10.58	11.39	11.35
<b>Lymphocyte</b>			
Average	0.99	0.82	0.77
Deviation Standard	0.53	0.43	0.42
Median	0.77	0.74	0.67
<b>NLR</b>			
Average	16.54	20.2	22.56
Deviation Standard	14.82	15.42	18.1
Median	12.42	17.33	19.64

**Table 5.** Association between laboratory findings, Boey score, and mortality.

Cutoff value	n	Outcome		p-value
		Alive	Passed	
<b>NLR*</b>				
<i>Cutoff 1 (20.72)</i>	109	69 (63.3%)	40 (36.7%)	
High	31	9 (29.0%)	22 (71.0%)	<0.0001
Low	78	60 (76.9%)	18 (23.1%)	
<i>Cutoff 2 (15.60)</i>	109	69 (63.3%)	40 (36.7%)	
High	56	21 (37.5%)	35 (62.5%)	<0.0001
Low	53	48 (90.6%)	5 (9.4%)	
<b>Boey score</b>				
Boey score 2	109	69 (63.3%)	40 (36.7%)	
High	80	40 (50.0%)	40 (50.0%)	<0.0001
Low	29	29 (100%)	0 (0.0%)	
Boey score 3	109	69 (63.3%)	40 (36.7%)	
High	25	7 (28.0)	18 (72.0%)	<0.0001
Low	84	62 (73.8%)	22 (26.2%)	

Performance of Boey score from Boey scores 2 cut-offs had sensitivity 100% specificity 42.0%, PPV 50.0%, NPV 100% and accuracy value 63.3%. The second cutoff (Boey score 3) had sensitivity 45% specificity 89.9%, PPV 72.0%, NPV 73.8% and accuracy value 73.3% (Table 6) and figure 1.

## DISCUSSION

Peptic ulcer perforation is the most serious complication that mostly caused by peptic ulcer. It contributes for about 5% of all abdominal emergencies, with the mortality rate around 10-40%. In this study, we evaluate the correlation between the outcome in terms of mortality with serum NLR level. Patients' NLR serum was taken on the admission time in emergency department, then the statistical correlation with the outcome either the patient alive

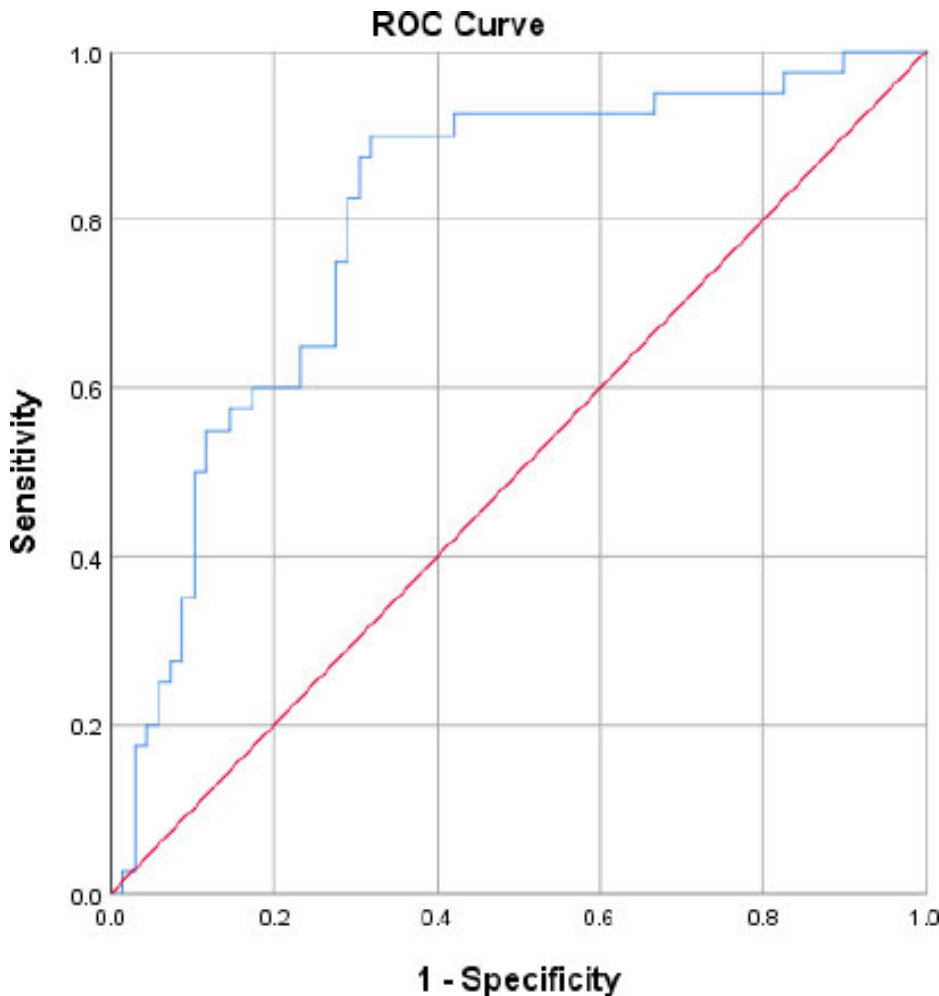
or passed away at the end of the study. Neutrophil has a significant role in host response against bacterial infection. Neutrophil has the ability to phagocytize microbes when infection occurs. NLR levels can predict bacteremia. According to a study by Iskandar, NLR level is a better bacteremia predictor compared to CRP, leucocyte count and neutrophil.<sup>12</sup>

The NLR level distribution of the patients still alive and had passed away is shown in Table 3. Table 4 shows that the NLR level distribution of the patients with high Boey scores tends to be higher in average compared to those with lower Boey scores. Furthermore, to evaluate the correlation between the NLR level and the mortality rate, The NLR was divided into 2 categories based on Receiver Operating Characteristic (ROC) curve analysis with a cutoff value 15.60. Table 5 shows that the new cutoff value based on the ROC

has greater sensitivity for predicting the mortality level than the cutoff value from Sudiarta et al.<sup>10</sup> study, with the value of 20.72 (sensitivity 87.5% vs 55%), but has lower specificity (69.6% vs 87.0%), with the cutoff accuracy based on higher ROC (76.1% vs 75.2%). The measurement of the NLR level as sepsis predictor in 86 patients with generalized peritonitis, NLR level could predict occurrence of sepsis in patients with generalized peritonitis, with the cutoff value of 20.72. The optimal cut-off was determined from the study objectives. In studies that use screening and prognostic methods, sensitivity has a more important role than specificity. On the other hand, in studies that aim to confirm a diagnosis, the specificity number has a greater role. In this study, we apply the cut-off based on the ROC curve analysis (15.6).<sup>10</sup>

In the subject characteristic table (Table 1), the highest incidence of gastric perforation was obtained in the age group  $\geq 60$  years (61.5%). This is in accordance with the previous theory which states that gastric perforation rarely occurs under the age of 40, with a peak incidence at the age of 55-65.<sup>2</sup>

Table 2 shows a significant relationship between the Boey score and mortality outcomes (p-value = 0.0001). This is consistent with a study conducted by Boey et al. which states that the mortality rate increases progressively with an increasing number of risk factors in patients with perforated peptic ulcer: Boey Score 0 has a mortality rate of 0%, Boey score 1 has a mortality rate of 10%, Boey score 2 has a mortality rate of 45.5%, and Boey score has a mortality rate of 100%. This is also in accordance with research conducted by Nuzulistinia et al.<sup>14</sup> at dr. Soetomo Hospital, Surabaya, where Boey score 1 has a mortality rate of 37%, Boey score 2 has a mortality rate of 52.94%, and Boey score has a mortality rate of 100%, although in the Nuzulistinia study (2016)<sup>14</sup> there were no statistically significant results (p>0.05).<sup>13,14</sup> Table 2 also shows that the three components of the Boey Score, such as onset (more than or less than 24 hours), the presence of comorbidities and the presence of preoperative shock, did not have a significant relationship to mortality (0.844 vs 0.366 vs 0.172) when each



**Figure 1.** ROC curve of NLR towards outcome.

**Table 6.** Boey score and NLR performance as predictor of outcome.

Cutoff values	Sensitivity	Specificity	PPV	NPV	Accuracy
<b>NLR*</b>					
Cut off 1 (20.72)	55.0%	87.0%	71.0%	76.9%	75.2%
Cut off 2 (15.60)	87.5%	69.6%	62.5%	90.6%	76.1%
<b>Boey score</b>					
Boey score 2	100.0%	42.0%	50.0%	100.0%	63.3%
Boey score 3	45.0%	89.9%	72.0%	73.8%	73.3%

component stood alone and are correlated with mortality. This is in accordance with Boey et al. where each of these components complements one another, so an increased prognostic mortality rate appears.<sup>13</sup>

Table 2 also shows the relationship between the location of the peptic ulcer perforation and mortality. It was shown that unconfirmed peptic ulcer perforation had a higher mortality rate and was statistically significant (p-value = 0.002). This is due to external drainage that is performed at the unconfirmed location of the perforation. External drainage is

performed in perforated ulcers in patients with a Boey score of 3. As in previous studies, patients with a Boey score of 3 had a high mortality rate.<sup>13-15</sup>

In the Tanrikulu et al. study, we found that NLR is a fairly sensitive and specific test in the early diagnosis of peptic ulcer perforation in patients with peptic ulcer, with a sensitivity rate of 68%, specificity of 88%, positive predictive values of 82.9% and negative predictive values of 72.9%. Whereas, in this study, we tried to obtain a correlation between preoperative NLR and mortality in patients with perforated

peptic ulcers at Dr. Soetomo Hospital, Surabaya.<sup>16</sup>

Table 2 shows this study's correlation between NLR and Boey Score is statistically significant (p-value = 0.032). The more severe of disease (the higher the Boey score), the higher the NLR rate. These results are in accordance with research conducted by Liu et al. which showed that an increase in NLR can identify patients that are in an inflammation state. This is based on the physiological relationship between neutrophilia and lymphopenia during inflammation and systemic stress. Ongoing infection or inflammation and incomplete eradication of infectious agents are responsible for increasing neutrophil production by the medulla and decreasing the number of lymphocytes by apoptotic and other mechanisms.<sup>8</sup> The intensity of neutrophilia and lymphocytopenia is related to the clinical severity and clinically beyond the patient with systemic infection or inflammation.<sup>17</sup> This suggests that NLR can be a prognostic tool in the mortality curve of patients with perforated peptic ulcer along with the high value of the Boey Score.

Table 5 shows the analysis results of the relationship between NLR and mortality in this study, which shows a statistically significant relationship (p-value <0.0001) using either the cut-off number from Sudiarta et al. study (20.72) or the cut-off from the ROC curve analysis. (15.6). The NLR is a simple index of SIRS and stress in critically ill patients, to evaluate the severity of systemic sepsis and infection, including bacteremia.<sup>17</sup> It is a biomarker that reflects the balance between two aspects of the immune system: acute or chronic inflammation as indicated by the neutrophil count and adaptive immunity as indicated by the lymphocyte count. In literatures, it is stated that NLR is widely used to evaluate the severity of outcomes in various diseases such as stroke, sepsis, infectious diseases, and malignancy.<sup>18</sup> In a study conducted by Liu et al.<sup>19</sup> which evaluated the role of NLR in predicting mortality in patients with intra-abdominal infections, it was found that on day 1 the NLR was significantly higher in the group with a high organ failure severity score (SOFA score and APACHE score).

The Boey Score is the most commonly

used prognostic score in estimating perforated peptic ulcer mortality. The Boey score is also a standard prognostic score for assessing mortality prognosis in patients with perforated peptic ulcers at Dr. Soetomo Hospital, Surabaya. The accuracy of the Boey score in predicting mortality in patients with perforated peptic ulcers is 63-85% and 91.7%.<sup>20,21</sup> In the study conducted by Meidiansyah et al. at Dr. Mohammad Hoesin Palembang of 44 patients with gastric perforation explained that the accuracy of the Boey Score in predicting mortality in patients with gastric perforation was 59.1% with a sensitivity of 57.1%, a specificity of 62.5%, 72.7% PPV, and 59.1% NPV. In this study, which is shown in table 6, the performance of the Boey score in predicting death in perforated peptic ulcer was obtained with a sensitivity of 100%, a specificity of 42% and an accuracy of 63.3% with a cutoff value of Boey Score 2 (score 2 is included in a high Boey Score, 1 is included in the low Boey score).<sup>22,23</sup>

Meanwhile, with a Boey Score cutoff of 3 (score 3 is included in the high Boey Score, and scores 1 and 2 are included in the low Boey score). Table 6 also explains NLR's sensitivity, specificity and accuracy in predicting patient death. Peptic ulcer perforation with a cutoff value of 15.6, obtained a sensitivity of 87.5%, a specificity of 69.6% and an accuracy of 76.1%. The comparison of the sensitivity, specificity and accuracy values shows that the NLR has a better prognostic value on mortality than the Boey Score.

However, there are limitations to this study, specifically this study is a cross-sectional study. Another prospective multicentric cohort study is needed to obtain more accurate data in finding the predictive value of NLR mortality in cases of perforated peptic ulcer.

## CONCLUSION

There was significant relationship between NLR with perforated peptic ulcer patient mortality. NLR can be used as a predictive factor for mortality in peptic ulcer patients with cutoff higher than 15.6.

## CONFLICTS OF INTEREST

No competing interests declared.

## AUTHOR CONTRIBUTION

Conceived the study: API. Designed the study: API, DS, and MDW. Analyzed the data: API, DS, and MDW. Wrote the manuscript: API. Review the manuscript: DS and MDW.

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## ETHICAL CONSIDERATION

This study has been approved by ethical committee Faculty of Medicine, Universitas Airlangga with ethical clearance reference number 0998/LOE/301.4.2/VII/2022.

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