

Neutrophil-to-Lymphocyte Ratio as an Independent Risk Factor for Mortality in Burn Patients With and Without COVID-19

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Abstract

Background: Following the initial appearance of coronavirus disease 2019 (COVID-19) in December 2019, approximately 23 million cases have been documented worldwide, illustrating its devastation. Inflammation plays a role in both COVID-19 and burn pathophysiology. Despite the necessity of understanding this impact, few research studies explore the influence of COVID-19, a novel disease, on burns. The neutrophil-to-lymphocyte ratio (NLR) is a simple and inexpensive test that can be used to detect the overall status of inflammation. The NLR has not been thoroughly examined in people with COVID-19 and burns. In this study, the value of NLR less than 72 hours since a burn accident as a risk factor for mortality in burn patients with and without COVID-19 will be evaluated.

Methods: A retrospective study was conducted between April 2020 and March 2022 at the Dr. Soetomo General Academic Hospital in East Java, Indonesia. We collected the following variable data: gender, age, cause of burn, comorbidities, percentage of the total body surface area (%TBSA), length of stay (LoS), mortality outcome, and neutrophil and lymphocyte counts. The NLR is the ratio between the absolute neutrophil and lymphocyte counts. The data were analysed using Chi-Square and Mann-Whitney tests. The difference will be considered significant if the p value is < 0.05.

Results: Based on data from 126 burn patients with and without COVID-19, the mean and standard deviation (SD) NLR for non-survivor patients were higher (12.05 and 9.7, respectively) than those for survivor patients (7.92 and 5.9, respectively). The receiver operating characteristic (ROC) curve analysis showed the area under ROC curve (AUC) for NLR value was 0.626 (95% confidence interval (CI): 0.535-0.71), which was statistically significant, namely the NLR cut-off value > 6.97 with a sensitivity value of 64.3%, a specificity of 59.5%, and a p value of 0.021. The risk of mortality with an NLR > 6.97 has an accuracy of 61.11%, a negative predictive value of 76.92%, and a positive predictive value of 44.26%.

Conclusion: Our study showed that NLR is associated with the risk of mortality in burn patients, regardless of the presence or absence of COVID-19, and that it can be used as a low-cost, readily accessible approach to identify indications of intensive care monitoring for patients.

Keywords: Neutrophil-to-Lymphocyte ratio; NLR; COVID-19; Burn; Mortality

1. Introduction

The highly contagious COVID-19 virus first appeared in China in 2019. By February 2023, the WHO had recorded 756,581,850 cases of COVID-19, including 684,267 fatalities [1]. COVID-19 is more contagious, has a longer incubation period, and is associated with greater hospitalization and fatality rates compared to severe acute respiratory syndrome coronavirus (SARS-CoV) [2, 3, 4]. Meanwhile, burns cause an estimated 180,000 deaths each year, according to WHO data from 2018; the vast majority of these deaths occur in low- and middle-income countries [5]. In 2019, a total of 8,955,228 new cases of burns were reported worldwide [6]. Due to the fact that COVID-19 can cause asymptomatic to acute respiratory failure, shock, and multiorgan system dysfunction, the latter two of which can also occur in burn injury, it is crucial to understand its clinical symptoms [2, 7]. Individuals with older ages, male gender, obesity, and chronic comorbidities including cardiovascular disease, diabetes, chronic respiratory illness, and cancer were more likely to experience adverse outcomes, both in COVID-19 and burns [2, 8, 9].

Numerous investigations have found NLR to be an independent risk factor for a variety of serious diseases, including sepsis, cardiovascular disease, and cancer. The NLR indicate changes in the inflammatory response in the body [10, 11, 12, 13]. Inflammation is a common early pathophysiologic feature of severe burn injured patients and COVID-19, including shock, and is commonly followed by sepsis and multi-organ dysfunction syndrome (MODS) [14, 15]. The NLR is calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Previous research has shown that NLR is a simple, easy-to-find predictor tool for predicting the severity of COVID-19 patients, also burn patients [7, 16, 17, 18, 19]. Nonetheless, the relationship between NLR and mortality in patients with burns and COVID-19 has received little attention. In this study, we aimed to analyse the association between NLR and mortality of burn patients with and without COVID-19.

2. Materials and Methods

This retrospective study included patients who were admitted to the Emergency Department of Dr. Soetomo General Academic Hospital in Surabaya, East Java, Indonesia, between April 2020 and March 2022. Each patient's demographic, clinical, and laboratory data were collected using electronic medical records and were approved by the Committee on Ethics of Health Research at Dr. Soetomo General Academic Hospital (1095/LOE/301.4.2/X/2022). Blood samples were analyzed in the same hospital laboratory using a fully automatic hemocyte analyzer. The inclusion criteria were cause of burn (including flame, scalding, electric, chemical, hot stream), moderate-to-severe burn injury based on the American Burn Association (2nd degree minimum %TBSA 20% on adults and 10% on pediatrics; 3rd degree minimum %TBSA 10%; burn of any area of the face, eyes, ears, hands, feet, perineum, or genitals; inhalation trauma, electric, with other traumas) [20], COVID-19 confirmed by RT-PCR (*real-time reverse-transcriptase polymerase chain reaction*) test, and acute phase burn injury (72 hours since a burn accident). The exclusion criteria were refusal to be hospitalized, discharged by self-decision, known pre-existing cardiac disease, kidney disease, malignancy, autoimmune disorder, HIV, liver disease, hemolytic anemia, bone marrow arrest, or other inflammatory disease, and a history of long-term use of corticosteroids, anti-coagulants, and anti-thrombin.

We used the Parkland Modification Formula (3 ml/kg/%TBSA) for 24-hour resuscitation of burn injuries in adults and 10% in children. Half of this volume was administered within the first eight hours, with the remaining half administered over the next sixteen hours. In pediatrics, normal saline with 5% dextrose is used for maintenance [21]. Prior to admission to the burn high-care unit, debridement in the operating room, a complete blood test, and a PCR swab test were performed in the emergency department.

Statistical analyses were carried out using SPSS 26.0 (SPSS Inc., New York, USA), with $p < 0.05$ considered significant. Continuous variables are expressed as mean $\pm$ SD, while categorical indicators are expressed as frequency (%). The Chi-Square and Mann-Whitney tests were used. In the ROC curve analysis, the NLR was used as a variable to estimate the sensitivity, specificity, and areas under the ROC curves. The maximum value of Youden's index (sensitivity + specificity - 1) was used to determine the best cut-off value.

3. Results

The clinical data of the patients included age, gender, cause of burn, %TBSA, co-morbidities, LoS, mortality, COVID-19 infection, and NLR. 126 of the 199 burn patients were analyzed, while the rest (73 patients) were excluded.

Table 1. Baseline Characteristics of Severe Burn Survivors and Non-Survivors

	Survivors	Non-Survivors	<i>p</i>
Number of patients (%)	84 (66.7)	42 (33.3)	
Age (years)	26.9 $\pm$ 18.3	43.17 $\pm$ 18.19	<0.001

Gender (%)			0.731
Male	60 (75)	28 (66.7)	
Female	24 (25)	14 (33.3)	
Co-morbidity (%)			0.022
Yes	9 (10.7)	12 (28.6)	
No	75 (89.3)	30 (71.4)	
Cause of Burns (%)			<0.001
Flame	46 (54.8)	37 (88.1)	
Scald	24 (28.6)	3 (7.1)	
Chemical	0 (0)	1 (2.4)	
Electric	13 (15.5)	1 (2.4)	
Hot stream	1 (1.2)	0 (0)	
LoS (days)	21.74 ±12.8	11.45±7.4	p < 0.001
TBSA (%)	22.78±12.89	53.11±23.11	p < 0.001

Note: data were presented as mean±SD, or number (%)

Abbreviations: LoS, length of stay; TBSA, total body surface area

Table 1 shows that there were 42 non-survivor patients, with a mortality rate of 33.3%, a mean TBSA of 53.11%, and a mean LoS of 11.45 days, while 84 patients survived. Age, co-morbidities, cause of burns, LoS, and %TBSA were all significantly higher in the non-survivor group ($p < 0.05$). There were no significant gender differences between the survivors and non-survivors.

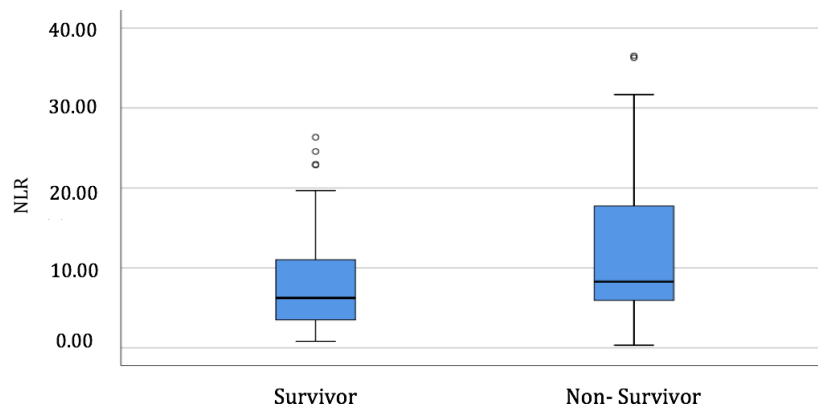


Figure 1. Bivariate Analysis of Neutrophil-to-Lymphocyte Ratio (NLR) by Mortality

There was a significant difference between survivors of moderate-to-severe burns and non-survivors in NLR < 72-hours acute phase data ($p = 0.022$). The mean ± SD NLR value of non-survivor

patients was higher, 12.05 ± 9.74 , than that of survivor patients, 7.92 ± 5.98 (showed in figure 1.). The $\text{NLR} < 72$ -hours was used as a variable in the ROC curve analysis to estimate the sensitivity, specificity, and areas under the ROC curves. The optimal cut-off value was obtained from the maximum value of Youde's index (sensitivity + specificity - 1). As shown in figure 2, the areas under the ROC curves of < 72 -hours NLR for moderate-to-severe burn-delayed mortality prediction were 0.626 (95% CI, 0.535-0.710), and the optimal cut-off value of < 72 -hours NLR was 6.97 (64.29% sensitivity, 59.52% specificity).

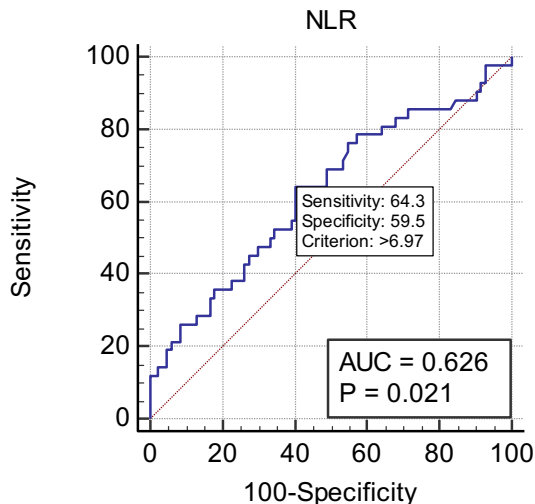


Figure 2. Receiver operating characteristic (ROC) curve analysis of neutrophil-to-lymphocyte ratio (NLR) for mortality in burn patients with and without COVID-19

In our study, 16 of the 126 patients were infected with COVID-19, while the remaining 110 were not. The Chi-Square analysis test on 107 burn patients who were not infected with COVID-19 revealed a statistically significant relationship between the NLR cut-off value of 6.97 and the mortality rate, with a p value of 0.031. The mortality rate increases if the NLR value is greater than 6.97, which is found in acute phase burn patients who are not infected with COVID-19. The Chi-Square test revealed no statistically significant relationship between NLR values > 6.97 and ≤ 6.97 and the mortality rate in acute-phase burn patients infected with COVID-19. However, an analysis of 16 COVID-19-infected burn patients revealed that 15 had a higher neutrophil value than lymphocytes (93.75%). Among the 110 burn patients who were not infected with COVID-19, 107 (97.2%) had a higher number of neutrophils than lymphocytes. Both infected and non-infected COVID-19 acute phase burn patients have a higher number of neutrophils than lymphocytes.

4. Discussion

In severe cases, COVID-19 infection disrupts the immune system by causing an excessive release of pro-inflammatory cytokines, resulting in a cytokine storm, followed by lymphopenia, activation and dysfunction of lymphocytes and neutrophils [22]. Severe COVID-19 patients presents with leucocytosis, neutrophilia, lymphopenia, and thrombocytopenia than those with non-severe ones. These patients were more likely to develop acute respiratory distress syndrome (ARDS) and require intensive care unit (ICU) level of care. As for burn, the rapid increase in the number of neutrophils and the value of the neutrophil-lymphocyte ratio during the first days indicates an acute inflammatory process in the patient. Patients with major burns experience extensive tissue damage and are exposed to infectious agents with a high risk of getting septicaemia and then shock septic. Most of the first 24-48 hours after the injury happened to be an acute inflammatory process [23]. These conditions could lead patients to a poor prognosis.

Predicting prognosis and mortality is an important part of the clinical management of patients with emergency and critical conditions, include burn and COVID-19. This can inform the clinician about the aggressiveness of therapy to be given and the allocation of resources for intensive care. Laboratory indicators, like NLR, make it simple to get results and increase the accuracy of predicting burn and COVID-19 patients' mortality. In this study, we found a significant relationship between NLR and mortality (p value = 0.022). The NLR values of non-survivor patients with and without COVID-19 were higher than those with survival outcomes (mean $\pm$ SD 12.05 $\pm$ 9.7 vs. 7.92 $\pm$ 5.9; median 8.28 vs. 6.23). That result of this study are in line with the results of several studies that generally discussed COVID-19 and stated that higher NLR values were found in COVID-19 patients with severe disease severity compared to mild-moderate ones and were found in COVID-19 patients who died compared to those who were still living [24]. Also in line with the results of Sanjaya's study, NLR in the first three days after severe burn injury affects the patient's mortality rate [16]. According to the ROC curve analysis, the NLR value's AUC was 0.626 (95% CI: 0.535–0.71), which was significant for determining an NLR value > 6.97 (sensitivity 64.3%, specificity 59.5%, $p = 0.021$). The risk of mortality with NLR > 6.97 has an accuracy of 61.11%, a negative predictive value of 76.92%, and a positive predictive value of 44.26%. Up to 64.3% of study participants with an NLR value > 6.97 were non-survivors. Specifically in burn and COVID-19 infection patients, even though there was no statistically significant relationship between NLR values > 6.97 and the mortality rate, there was a tendency to have a higher number of neutrophils than lymphocytes for both infected and non-infected COVID-19 acute phase burn patients. It was shown that 15 (93.7%) of 16 COVID-19-infected burn patients and 107 (97.2%) of 110 non-COVID-19-infected burn patients had a higher number of neutrophils than lymphocytes.

We concluded that the NLR is a straightforward, inexpensive, and independent prognostic marker. It can be calculated routinely in the early period, which aids in the planning of more effective follow-up management. The findings of this study are consistent with the findings of Qiu's study, which identified the NLR value within 90 days as a predictor of death in burn patients. It was concluded from the 577 patients that NLR was related to the mortality rate of burn patients. Many factors contribute to increased mortality, including TBSA $> 30\%$ and infection [7, 26]. The mortality rate in a cohort study of 245 COVID-19 patients was 13.47%. This value is related to the neutrophil-to-lymphocyte ratio, age, and D-Dimer value. Increased NLR increases the risk of death during hospitalization [25, 27, 28]. According to a study by Ciftci, there is a link between higher mortality and NLR in burn patients, and this method can be used to identify risk factors for death in patients with severe burns [18].

5. Conclusion

According to our findings, NLR values less than 72-hours > 6.97 can be used as a marker for patients to be closely monitored for indications of intensive care in both COVID-19-infected and non-infected burn patients. The NLR value can thus be used as an independent risk factor for a variety of serious diseases.

6. Limitation

The following are some of the study's limitations: (1) This study only collected one sample at a time, namely when the patient was first admitted to emergency department of Dr Soetomo General Academic Hospital with an acute phase burn event within 72 hours. Given that NLR values can change throughout the course of burn disease, it is suggested that future research can examine NLR values several times over longer study periods so as to describe a schematic curve of the disease course from start to finish with a larger sample size, indicating a higher confidence value. (2) The study was only conducted at one center, with limited data in a period of time.

Acknowledges

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Ethical Clearance

**PEMERINTAH PROPINSI JAWA TIMUR
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SURAT EXEMPTION
(" LETTER OF EXEMPTION ")

Ref. No. : 1095/LOE/301.4.2/X/2022

Judul Protokol Penelitian : Korelasi Rasio Neutrofil/Limfosit pada Pasien Luka Bakar Fase Akut Terinfeksi Covid-19 dan Tidak Terinfeksi Covid-19 terhadap Angka Mortalitas selama Perawatan Inap di RSUD Dr Soetomo Surabaya Periode April 2020 - Maret 2022

Dokumen yang disetujui : 1715/108/4/X/2022 (versi: 2)

Tanggal terbit : 24 Oktober 2022

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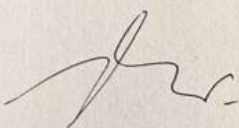
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Instalasi/Tempat Penelitian : RSUD Dr. Soetomo

Komite Etik Penelitian Kesehatan RSUD Dr Soetomo menyatakan bahwa dokumen diatas sesuai dengan The Office for Human Research Protections (OHRP) dibawah persyaratan the U.S. Department of Health and Human Services (HHS) Regulasi 45 CFR bagian 46 untuk **exempt review**.


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Sekretaris Panel 2