

Plasma Neutrophil-to-Lymphocyte Ratio on the Third Day Postburn is Associated with 90-Day Mortality Among Patients with Burns Over 30% of Total Body Surface Area in Two Chinese Burns Centers

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Introduction: Neutrophil-to-lymphocyte ratio (NLR) is a marker of inflammation. This study aimed to evaluate the potential role of NLR to predict 90-day mortality.

Methods: Data of 577 patients with burns over 30% of total body surface area were collected and retrospectively analyzed. The risk factors for 90-day mortality were evaluated using logistic regression analyses. Receiver operating characteristic (ROC) curve analysis of the 3rd day NLR was performed and the optimal cut-off value was calculated. The 90-day mortality rates were compared between high and low NLR groups using Kaplan-Meier analysis.

Results: Age, mechanical ventilation, burn index, 3rd day NLR, and 7th day red blood cell and platelet (PLT) counts were found to be independent predictive values for 90-day mortality. In contrast, percentage of total body surface area burned, inhalation injury, 1st day white blood cell and neutrophil counts, the 3rd day lymphocytes and PLT counts, and 7th day hemoglobin level were not independently associated with 90-day mortality. The area under the ROC curve of the 3rd day NLR for severe burn–delayed death prediction was 0.665 (95% confidence interval, 0.591–0.739), and the optimal cut-off value of the 3rd day NLR was 10.50. The 90-day mortality rates differed significantly between the NLR >10.5 group and the NLR ≤ 10.5 group (17.03% vs 5.92%, respectively; P < 0.01).

Conclusion: These results suggested that the 3rd day NLR was associated with an increased risk of death in severely burned patients; thus, it can provide useful information to predict 90-day mortality.

Keywords: burns, neutrophil-to-lymphocyte ratio, 90-day mortality

Introduction

According to the World Health Organization, burns remains a serious global health problem, with over 195,000 burn-related deaths each year.¹ Shock and cardiogenic injury can follow burn injury, resulting in death in the first week (“early death”).² However, subsequent infections are a significant cause of late mortality associated with burn injury.³ Infections and their complications, such as sepsis, septic shock, and multiple organ dysfunction syndrome (MODS), play an important role in the late mortality of burn patients.⁴

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The neutrophil-to-lymphocyte ratio (NLR) is calculated from the absolute neutrophil and lymphocyte counts, which are easily obtained from laboratory test data. NLR was found to be a simple and inexpensive marker of infection in clinical application.⁵ Numerous studies have documented NLR as an independent risk factor for several serious diseases, such as sepsis, cardiovascular disease and malignancies; NLR can also reflect changes in the systemic inflammatory response.^{6–9} Inflammation is a common early pathophysiologic characteristic for severe burn injured patients, including shock, and is frequently followed by sepsis and MODS.^{10,11} Nonetheless, the association between NLR and 90-day mortality in severe burn injuries has not been studied.

Therefore, we collected and retrospectively analyzed the data of patients with burns who were admitted to the First Affiliated Hospital of Anhui Medical University and Ruijin Hospital of Shanghai Jiao Tong University to investigate the predictive value of NLR for the mortality of burn patients.

Methods

Patients

This retrospective study included patients with severe burn injuries who were admitted to the First Affiliated Hospital of Anhui Medical University and Rui Jin Hospital of Shanghai Jiao Tong University between January 2008 and December 2015. All patients provided informed consent for the use of their data in research, and that this study was conducted in accordance with the Declaration of Helsinki. All procedures were approved by the Human Subjects Review Board of Anhui Medical University Hospital, Hefei, China. Patients with shock at admission were resuscitated with the Chinese formula that was adjusted according to the physiological response.^{12,13}

The inclusion criteria were burn injury (including flame, scalding, electric, contact, or spark burn) patients aged ≥ 18 years, percentage of the total body surface area (%TBSA) $\geq 30\%$, and survival time ≥ 7 days. The exclusion criteria were age < 18 years and known pre-existing cardiac disease, kidney disease, hemolytic anemia, bone marrow arrest, or other inflammatory diseases.

The China formula is as follows: 1.5 mL/kg/%TBSA + 5% dextrose solution 2000 mL, and 1.5 mL/kg/%TBSA = lactate Ringer's solution 1.0 mL/kg/%TBSA + fresh-frozen plasma 0.5 mL/kg/% TBSA.^{12,13} Half of this volume was administered in the first 8 h, and the

remaining half was administered during the next 16 h. Meanwhile, the rehydration is dynamically adjusted according to the blood pressure, central venous pressure and urine output.

A series of pathophysiological changes occur in a body after severe burn. Past studies have described early-stage postburn to range from 48 h to within 21 days of the burn.^{14–17} Early excision and autograft within one week are now considered standards of care in the treatment of severely burned patients.¹⁸ In this study, early stage was referred to 7 days postburn and late stage was referred to 7 days later. This definition is consistent with many previous studies.^{19–21}

Data Collection

Each patient's demographic, clinical, and laboratory data were obtained from the electronic medical records. The burn departments in Anhui Medical University Hospital and Ruijin Hospital are two major burn centers in east China. In these two centers, the laboratory examination was conducted at least every other day during the first week postburn for the major burn patients with burned area over 30% TBSA. Blood samples were analyzed by fully auto hemocyte analyzer in two different laboratories of the burn centers with the same national standards.

The primary outcome was 90-day mortality collected from the hospital medical records and telephone follow-up. All eligible patients were grouped as follows: (a) survivor group, which included patients who survived 90 days after severe burn injury; and (b) non-survivor group, which included patients who died between day 7 and day 90.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and values of $P < 0.05$ were considered statistically significant. Continuous variables are described as mean \pm SD, and categorical indicators were presented as frequency (%). Intergroup comparisons were performed using Student's *t*-test or Pearson's χ^2 test.

Normal analysis was performed on these 577 patients by using histograms and descriptive statistics and the results showed that the data were close to normal distribution. It was reasonable to use *t*-test for continuous variables when the samples are sufficiently large.

Logistic proportional hazard regression was performed to examine the association between NLR and 90-day

mortality, and 95% confidence intervals (CIs) were generated. The 3rd day NLR was used as a variable in the receiver operating characteristic (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 Youden's index (sensitivity + specificity - 1). The survival curves of the high and low NLR groups were calculated using the Kaplan–Meier method.

Results

Demographic and Clinical Data

There were 652 adult patients who sustained severe burns according to Chinese burn severity criteria (%TBSA burned $\geq 30\%$, or %TBSA of full-thickness burn $\geq 10\%$, or complicated with shock, moderate or severe inhalation injury, or combined injury)²² and admitted in these two centers during 2008–2015. Because 32 had a %TBSA < 30%, 8 patients' hospital stays were less than 48h, 33 patients survived less than 7 days post-burn, and 2 patients' data were incomplete, the data of 577 severe burn patients were ultimately analyzed.

The clinical data of patients included patients' demographic data, inhalation injury, mechanical ventilation, surgery during the first week, %TBSA burned and burn index. The laboratory data were only collected from the results of blood routine test and the biochemical data were not retrieved in this study. The blood routine test included white blood cell count, Neutrophils, Lymphocytes, red blood cell count, platelet count, Eosinophil count, Basophil count, Monocyte count and so on. White blood cell count, Neutrophils, Lymphocytes, red blood cell count, and platelet count were analyzed. Eosinophil count, Basophil count, and Monocyte count were missed due to non-significant changes in the early postburn period.

Table 1 shows that 55 patients died during the late postburn period, with a mortality rate of 9.53%, a mean %TBSA of 67.49%, and a mean survival time of 17.95 days, while 522 patients survived the 90-day follow-up period. Age, inhalation injury, mechanical ventilation, %TBSA burned, and burn index (BI) were significantly higher in the non-survivor group ($P < 0.05$). The burn index (BI) was referred to formula $BI = \%TBSA$ of third-degree burns + $\frac{1}{2} \%TBSA$ of second-degree burns.²³ There were no significant differences in sex or need for surgery during the first week between the survivors and non-survivors.

Table 1 Baseline Characteristics Comparing Severe Burn Survivors and Non-Survivors

	Survivor	Non-Survivor	P
Number of patients	522 (90.5%)	55 (9.5%)	
Age (years)	43.58±15.11	52.55±17.98	<0.001
Sex (%)			0.875
Male	384 (73.6)	41 (74.5)	
Female	138 (26.4)	14 (25.5)	
Inhalation injury			<0.001
Yes	131 (25.1)	34 (61.8)	
No	391 (74.9)	21 (38.2)	
Mechanical ventilation			<0.001
Yes	92 (17.6)	37 (67.3)	
No	430 (82.4)	18 (32.7)	
Surgery during the first week			0.132
Yes	302 (57.9)	26 (47.3)	
No	220 (42.1)	29 (52.7)	
%TBSA burned	49.59±17.94	67.49±25.07	<0.001
BI	33.46±17.30	52.58±25.99	<0.001

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

Abbreviations: BI, burn index; TBSA, total body surface area.

Significant differences were observed between severe burn injury survivors and non-survivors in the 1st day data (white blood cell and neutrophil counts), the 3rd day data (lymphocytes, NLR, platelets [PLT]), and the 7th day data (red blood cell and PLT counts, hemoglobin level) ($P < 0.05$; Table 2).

ROC Curves of Variables and 90-Day Mortality

The 3rd day NLR was used as a variable in the receiver operating characteristic (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 Youden's index (sensitivity + specificity - 1). As shown in Figure 1, the areas under the ROC curves of the 3rd day NLR for severe burn–delayed death prediction were 0.665 (95% CI, 0.591–0.739), and the optimal cut-off value of the 3rd day NLR was 10.50 (60.00% sensitivity, 70.10% specificity). The 3rd day NLR was converted from a continuous variable to a categorical variable for the $NLR > 10.50$ group and the $NLR \leq 10.50$ group according to the optimal cut-off value.

Table 2 Laboratory Parameters Comparing Severe Burn Survivors and Non-Survivors

	Day 1		P	Day 3		P	Day 7		P
	Survivor	Non-Survivor		Survivor	Non-Survivor		Survivor	Non-Survivor	
WBC ($\times 10^9/L$)	18.92 \pm 8.06	22.05 \pm 9.10	0.07	11.57 \pm 5.33	12.70 \pm 9.33	0.383	13.77 \pm 6.35	13.83 \pm 8.85	0.960
Neutrophils ($\times 10^9/L$)	16.33 \pm 7.39	19.11 \pm 8.12	0.009	9.58 \pm 4.83	10.93 \pm 8.50	0.252	11.49 \pm 5.86	11.78 \pm 7.93	0.725
Lymphocytes ($\times 10^9/L$)	1.43 \pm 1.04	1.66 \pm 1.36	0.226	1.10 \pm 0.56	0.91 \pm 0.40	0.017	1.27 \pm 0.82	1.19 \pm 0.75	0.448
NLR	14.45 \pm 9.46	15.30 \pm 7.99	0.517	9.58 \pm 5.22	12.21 \pm 6.11	0.001	10.55 \pm 7.45	11.62 \pm 6.61	0.305
RBC ($\times 10^{12}/L$)	5.05 \pm 0.91	5.21 \pm 1.08	0.245	4.30 \pm 0.81	4.13 \pm 0.88	0.147	3.51 \pm 0.64	3.08 \pm 0.58	<0.001
Hemoglobin (g/L)	154.53 \pm 29.04	159.92 \pm 32.88	0.197	130.62 \pm 26.25	125.95 \pm 27.90	0.213	105.97 \pm 20.48	93.56 \pm 17.22	<0.001
PLT ($\times 10^9/L$)	188.68 \pm 77.47	176.14 \pm 91.15	0.263	132.73 \pm 70.95	93.45 \pm 85.50	<0.001	207.42 \pm 93.66	137.99 \pm 75.96	<0.001

Abbreviations: WBC, white blood cell count; NLR, neutrophils/lymphocytes; RBC, red blood cell count; PLT, platelet count.

Survival Analysis for Predicting 90-Day Mortality

All variables mentioned above were gathered into the Logistic regression analysis. Age, mechanical ventilation, BI, 3rd day NLR, and 7th day red blood cell and PLT counts provided independent predictive values for 90-day mortality. However, %TBSA burned, inhalation injury, 1st day white blood cell and neutrophil counts, 3rd day lymphocytes and PLT, and 7th day hemoglobin levels were not independently associated with 90-day mortality (Table 3).

There was a significant difference in 90-day mortality between high and low NLR groups, with a 90-day overall

survival rate of 82.97% for patients with severe burn injury and NLR > 10.50 versus 94.08% for patients with an NLR \leq 10.50 ($P = 0.003$; Figure 2). The 90-day mortality rates differed significantly between the NLR >10.5 group and the NLR \leq 10.5 group (17.03% vs 5.92%, respectively; $P < 0.01$).

Discussion

Cardiac, lung, and renal dysfunction, followed by the overrelease of toxins and inflammatory mediators into the blood circulation and distributive shock, are the main causes of fatality in the early period of severe burn

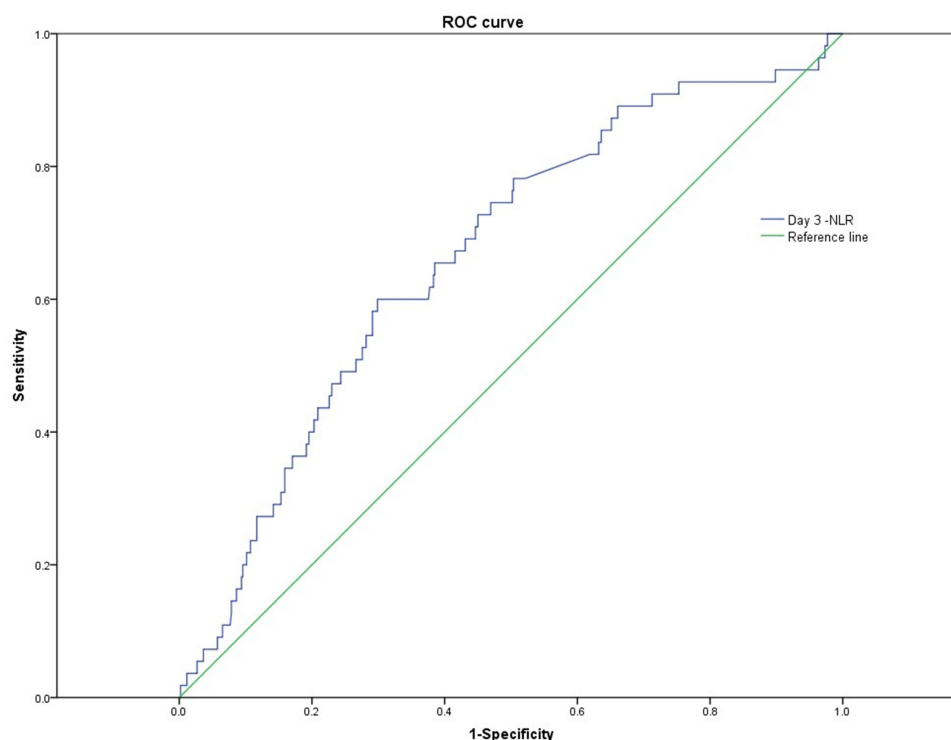


Figure 1 Receiver operating characteristic (ROC) curve analysis of preoperative neutrophil-to-lymphocyte ratio for the 90-day mortality in severely burned patients.

Table 3 Logistic Regression for the Later Postburn Period Mortality

	β	SE	Wald	P	OR	95% CI	
Age	-0.050	0.011	19.391	<0.001	0.951	0.930	0.972
Inhalation injury	-0.724	0.372	3.790	0.052	2.062	0.995	4.272
Mechanical ventilation	1.506	0.382	15.562	<0.001	4.507	2.133	9.524
%TBSA	0.006	0.019	0.091	0.764	1.006	0.970	1.043
BI	-0.032	0.009	13.700	<0.001	0.969	0.952	0.985
Day 1							
WBC ($\times 10^9/L$)	-0.022	0.130	0.029	0.864	0.978	0.758	1.262
Neutrophils ($\times 10^9/L$)	0.013	0.145	0.008	0.927	1.013	0.763	1.346
Day3							
Lymphocyte ($\times 10^9/L$)	0.442	0.456	0.943	0.332	1.557	0.637	3.802
NLR	-0.068	0.025	7.234	0.007	0.934	0.889	0.982
PLT ($\times 10^9/L$)	-0.001	0.003	0.061	0.806	0.999	0.993	1.005
Day 7							
RBC ($\times 10^{12}/L$)	0.182	0.906	0.041	0.840	1.200	0.203	7.089
Hemoglobin (g/L)	0.011	0.029	0.153	0.696	1.011	0.955	1.071
PLT ($\times 10^9/L$)	0.007	0.003	7.274	0.007	1.007	1.002	1.012

Abbreviations: TBSA, total body surface area; BI, burn index; CI, confidence interval; WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count.

injury.^{24,25} However, the mortality rate is significantly reduced in the early period, which is attributed to the timely and effective progress in the treatment of burn injuries.^{26–28} The mortality rate among severely injured patients remains high in the late postburn period, in which the main causes of fatality are generalized infection, sepsis, and MODS.^{10,29} The diagnosis of infection, sepsis, and MODS in severely burned patients represents a major challenge, and a delayed diagnosis within a few hours has been shown to lead to increased mortality.³⁰ Therefore, it is crucial to find a significant risk factor in the early period of severe burn injury that could predict the poor prognosis of fatal injuries in the late postburn period.

This study, in our opinion, was the first to investigate the value of NLR in predicting the 90-day mortality in severely burned patients. In the present study, we collected and retrospectively analyzed the data of 577 burn patients admitted to the First Affiliated Hospital of Anhui Medical University and Ruijin Hospital of Shanghai Jiao Tong University between 2008 and 2015. We found that age, mechanical ventilation, BI, and 7th day red blood cell and PLT counts were independent risk factors of mortality during the late postburn period as documented elsewhere.³¹ Furthermore, in this study, we found that the 3rd day NLR was associated with mortality during the late postburn period.

In our study, we found that the 3rd day NLR was a predictor of 90-day mortality in cases of severe burn

injury. NLR was first confirmed as an indicator of inflammation in 1967.⁵ Owing to its easy and quick calculation from clinical data and its predictive power for inflammation, NLR is used to predict the prognosis of several serious diseases, such as sepsis, cardiovascular disease and malignancies.^{6–8} In burn patients, preoperative NLR is useful for the early detection of postoperative acute kidney injury.³² The NLR, calculated from the NLR ratio, is elevated with an increase in neutrophil counts or decrease in lymphocyte counts that could reflect the immune response of the host and as the NLR value becomes above 10, the more specific and concerning it becomes.^{9,33}

A previous study documented that NLR increases rapidly following acute physiologic stress within 6 hours,³⁴ which is consistent with our study. We found that the 1st day NLR was high in the survivor and non-survivor groups, but the intergroup difference was insignificant, which could be explained by the excessive release of neutrophils followed by the intense stress of the burn.^{35–37} The NLR value remained high on the 7th day and the intergroup difference remained insignificant. Neutrophil count reflects the body's response to external stimuli. Hampson showed that the circulating number of neutrophils was elevated within 24 hours of a burn injury, returned to normal levels on day 3, and elevated again at day 7.³⁸ Studies have documented that the lymphocyte

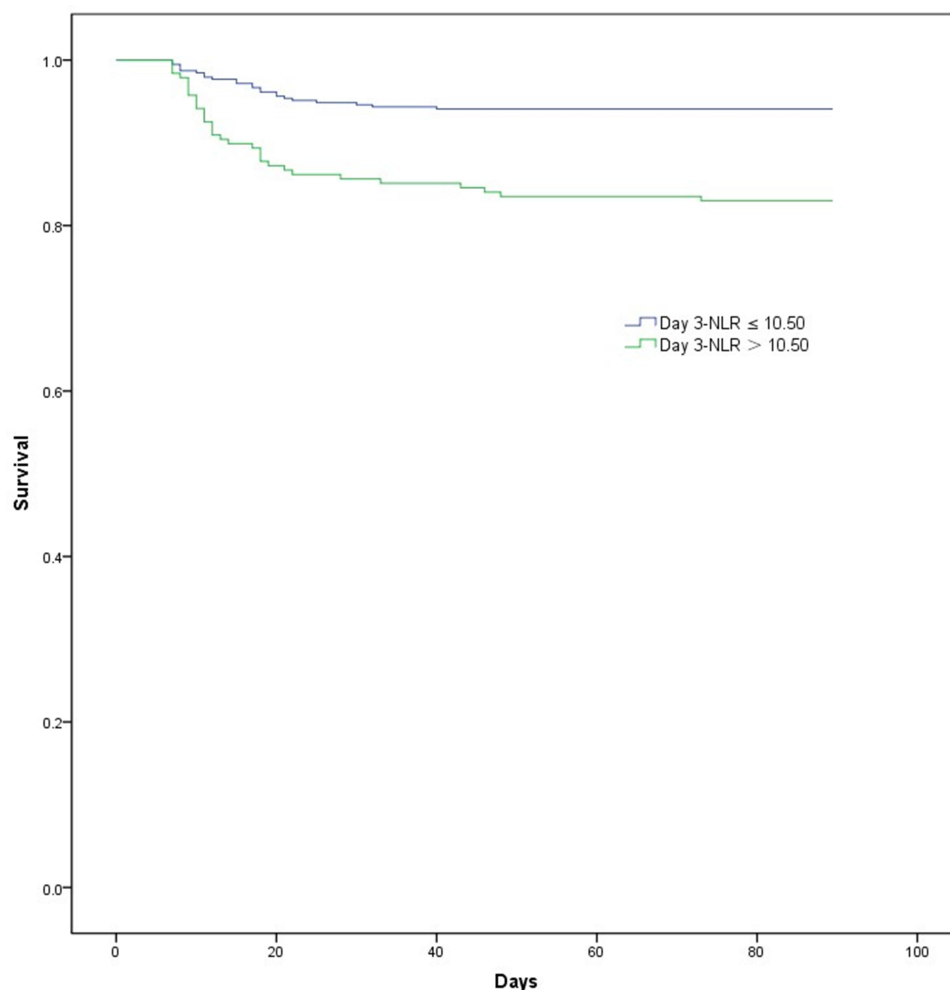


Figure 2 Kaplan–Meier curve of 90-day survival of severe burn injuries. The blue line indicates patients' survival in the 3rd NLR ≤ 10.50 group. The green line indicates patient' survival in the 3rd NLR > 10.50 group.

populations were diminished on the 3rd day postburn and the abnormal lymphocyte count at 72 hours postburn injury has been associated with adverse outcomes.^{39,40} The adverse outcomes contain infections, length of stay, intensive care unit length of stay, and ventilator days.^{39,40} As far as we know, there were few studies concerning the decline in early lymphocyte numbers with postburn 90d mortality. Since the lymphocyte count is related to the immunization activity of the body, a continuous decrease of lymphocytes may suggest a poor prognosis, which remains to be further studied.

The hemodynamics changed dramatically after severe burns for interfered by hypovolemic shock, fluid resuscitation and acute stress reaction in the first 48h after severe burn injury. With the presence of infection, inflammation and immunosuppression, the blood tests on 7th day are affected by clinical therapy. Therefore, we believe the

blood tests count on 3rd day reflect the reaction of the body to the severe burn injury. The neutrophil count and lymphocyte count have dynamic changes on 3rd day post-burn injury. Neither the association between neutrophil and acute stress reaction nor the correlation between lymphocyte and immune status can entirely explain the mortality and morbidity in severe burn injuries. Considering both parameters in the analysis can reflect the generalized health information after severe burn injury, the combination of these data may provide more meaningful results. Meanwhile, whether the 1st and 7th day NLRs are associated with burn mortality deserves further study with a larger sample size.

We found that the 3rd day NLR was 9.58 ± 5.22 in the survivor group versus 12.21 ± 6.11 in the non-survivor group, of which the difference was significant. The 3rd day NLR may reflect the immune response of the host and that

an NLR >10.50 indicates a poor prognosis in the later period of burn injury.

The predictive accuracy of NLR has been already shown in other medical conditions. In Jin-Sun Park's study, they reported that increased NLR was associated increased rate of all-cause mortality in 30-day survivors after index ST-elevation myocardial infarction (STEMI), who received a successful coronary intervention.⁴¹ In STEMI, baseline NLR can help to assess the prognosis and a more intensive treatment might be needed for patients with increased NLR. In Asuman Celikbilek's research, NLR served as a simple inexpensive, and readily available marker of prognosis in acute ischemic stroke.⁴² Simona Lattanzi and his coworkers found that the NLR was associated with 30-day mortality after intracerebral hemorrhage (ICH), and improved the accuracy of outcome prediction when added to the Modified ICH score.⁴³ That is why we described NLR as an independent risk factor for several serious diseases.

This study has several limitations. First, its retrospective nature was a disadvantage since the information was missing for many patients. Second, since only two burn centers participated in the study, patient numbers and distributions are limited. Thirdly, only severe burn injuries were analyzed in this study according to the inclusion and exclusion criteria. And finally, whether advances in therapeutic techniques and economics influenced the results and whether NLR has a prognostic role in minor burns require further investigations.

Affected by many factors, patients with burns over 30% of total body surface area will inevitably have wound infections or multiple infections throughout the treatment. Based on the results of bacterial culture of patients' wound secretions, we found that the wound of the same patient could cultivate a variety of bacteria during the whole treatment. Therefore, the relationship between NLR and different bacterial infections is difficult to define in this retrospective study. Further studies are warranted to determine the relationship between NLR and different bacterial infections in wound.

The present study demonstrated that the 3rd day NLR was an independent prognostic factor for 90-day mortality in patients with severe burn injury. Further prospective studies are needed to determine the inherent relationship between neutrophil and lymphocyte counts and 90-day mortality in severely burned patients.

Ethic Statement

This study was approved by the Ethics Committee of Anhui Medical University (20131071).

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Disclosure

The authors declare no conflicts of interest in relationship to this study.

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