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Leukocyte kinetics during the early stage acts as a prognostic marker in patients with septic shock in intensive care unit

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Abstract

The leukocytes play an important role in immune function during sepsis. We performed a retrospective study to investigate if leukocytes kinetics was associated with survival in critically ill patients with septic shock in intensive care unit (ICU).

Patients with septic shock from January 1, 2014 to June 30, 2018 in our ICU were included. We extracted the demographic, clinical and laboratory data, comorbidities from our clinical database. The number of white blood cell, neutrophil and lymphocyte on day 1 and day 3 after diagnosis were collected and neutrophil to lymphocyte ratios (NLR) were calculated. Our primary outcome was 28-day mortality. Univariate and multivariate logistic regression models and cox proportional risk model were used to analyze the association between the leukocytes kinetics during first 3 days after ICU admission and the day-28 mortality.

A total of 1245 septic shock patients with a 28-day mortality of 35.02% were included into analysis. There were no significant difference of lymphocyte number (0.83 ± 0.02 vs 0.80 ± 0.04, $P = .552$) between survival and non-survivals on day 1. However, the lymphocyte counts was significantly lower (0.95 ± 0.03 vs 0.85 ± 0.04, $P = .024$) on the third day. Both multivariate logistic and Cox regression analysis showed that lymphocyte counts on day 3 were associated with day-28 mortality. Moreover, Kaplan–Meier survival analysis revealed that increasing in lymphocyte counts and decreasing WBC, neutrophils and NLR during the first 3 days after diagnosis were associated with longer survival.

Leukocytes kinetics during the first 3 days is a valuable prognostic marker in patients with septic shock in the ICU.

Abbreviations: APACHE II = acute physiology and chronic health evaluation II, CI = confidence interval, ICU = intensive care unit, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, SOFA = sequential organ failure assessment, WBC = white blood cell.

Keywords: lymphocyte, mortality, neutrophil to lymphocyte ratios, septic shock

1. Introduction

Sepsis is defined as life-threatening organ dysfunction that caused by a dysregulated host response to infection, and septic shock is defined as circulatory failure due to sepsis.[1] It is the most common shock which results a mortality as high as 40% to 60%.[2] Moreover, septic shock is the leading causes of mortality in the intensive care unit (ICU) and critical illness worldwide which induced a significant diseases burden.[3–5]

Leukocyte is one of most important immune cells during sepsis.[6,7] Neutrophils were demonstrated that they played a crucial role in against pathogen during sepsis.[8,9] In addition, several studies showed lymphocyte apoptosis which induced immunosuppression during sepsis,[10–12] which was thought to be an important cause of death in patients with septic shock.[13,14] It was shown that the neutrophil-to-lymphocyte count ratio (NLCR) can serve as an index of systemic inflammatory response in critically ill patients and also have been a predicted marker on mortality in patients with septic shock.[15,16] The increased NLCR, which means increased neutrophils count and decreased lymphocyte counts during first 5 days was associated with death after day 5.[15] However, the lymphocyte counts was significant higher in survival patients compared to non-survivals. Considering that the lymphocyte loss occurred during early stage of sepsis, we hypothesis that the change of leukocyte counts in the first 3 days after sepsis is associated with mortality.

In this study, we investigated the relationship between leukocytes kinetics during the early stage and 28-day mortality of patients with septic shock.

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The authors confirm that all data underlying the findings are fully available. All relevant data are within the paper and its Supporting Information files.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Methods

2.1. Study design and population

This is a retrospective cohort study in a general ICU of a tertiary teaching hospital in Nanjing, China. ICU patients who diagnosed as septic shock[1] from January 2014 to June 2018 were included in this study. We exclude patients on the condition of age < 18 years old and patients readmitted in the ICU during 1 hospitalization. This study was performed in accordance with the Declaration of Helsinki and approved by Research Ethics Board of Zhongda Hospital (Southeast University, Nanjing, China, 2015ZDSYLL159-P01). Written informed consent was obtained by close relatives of the participating patients.

2.2. Data collection

Baseline demographics including age, gender, suspicious infection sites, presence of comorbidities were extracted from our medical database. Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) with 24 hours after ICU admission were calculated. We also routinely collected white blood cell (WBC) count, neutrophil count, lymphocyte count on the first and third day after ICU admission and neutrophil to lymphocyte ratios (NLR) were calculated. The primary outcome was 28-day mortality.

2.3. Definition

The sepsis and septic shock were defined according to the sepsis-3 criteria. Sepsis was defined the suspected infection plus the SOFA score increased equal or more than 2. The septic shock was defined as sepsis patients whose mean blood pressure was less than 65 mm Hg or received vasopressin and serum lactate level higher than 2 after initial fluid resuscitation.

2.4. Statistical analysis

Data were entered into STATA software version 14.0. Descriptive statistics, including the mean ± standard deviation (SD), median (interquartile range [IQR] defined as the 25th and 75th percentile), were used as appropriate according to the data distribution. Normally and non-normally distributed quantitative variables were compared using *t*-tests and rank sum test respectively. Univariate and multivariate logistic regression analysis was performed to determine the relationship between the WBC, neutrophil, lymphocyte counts and NLR and 28 day mortality. For categorical variables χ^2 test, Fisher exact test or McNemar test were applied as appropriated. The variables with a *P* value less than .05 in univariate model were included in the multivariate logistic regression model. Cox regression and the Kaplan–Meier survival curve were performed among independent variables associated with 28-day mortality. A 2-tailed *P* value of .05 was considered statistically significant.

3. Results

3.1. Population characteristics

A total of 1245 patients with septic shock from January 1, 2014 to June 30, 2018 were included in our final analysis. As showed in Taable 1, there included 840 males and 405 females with a mean age of 69.56 ± 15.48 years. The mean acute physiology and chronic health evaluation II (APACHE II) and SOFA score were 23.27 and 9.75 respectively.

The 28-day mortality was 35.02%.

Compared to the patients who survive on day 28 after diagnosis, the non-survivors had older age (71.23 ± 14.91 vs 68.66 ± 15.72, $P < .05$), higher APACHE II score (25.90 ± 8.53 vs 21.86 ± 7.26, $P < 001$) and SOFA score (10.62 ± 3.96 vs 9.29 ± 3.51, $P < .001$). There was no significant difference in gender distribution and BMI values between survivors and non-survivors. The proportion of patients had COPD, hypertension, diabetes mellitus (DM), cancer and liver cirrhosis were significant higher in non-survivors compared to survivors.

Table 1

Baseline clinical characteristics of the subjects.

Characteristics	All N = 1245	Survivors N = 809	Non-survivor N = 436	*P*
Age	69.56 ± 15.48	68.66 ± 15.72	71.23 ± 14.91	.0052
Male	840 (67.47)	545 (67.37)	295 (67.66)	.916
BMI	23.01 ± 4.52	23.13 ± 4.64	22.80 ± 4.27	.2255
APACHE II	23.27 ± 7.96	21.86 ± 7.26	25.90 ± 8.53	<.001
SOFA	9.75 ± 3.73	9.29 ± 3.51	10.62 ± 3.96	<.0001
Comorbidities, n (%)				
COPD	113 (9.10)	68 (8.41)	45 (10.32)	.262
CHD	285 (22.89)	175 (21.63)	110 (25.23)	.149
Heart failure	308 (24.74)	193 (23.86)	115 (26.38)	.326
Hypertension	675 (54.22)	442 (54.63)	233 (53.44)	.686
DM	357 (28.67)	221 (27.32)	136 (31.19)	.149
Cancer	245 (19.67)	133 (16.44)	108 (25.69)	<.001
Hematological malignancy	24 (1.92)	9 (1.11)	15 (3.44)	.004
Liver cirrhosis	33 (2.65)	23 (2.84)	10 (2.29)	.565
CKD	121 (9.72)	74 (9.15)	47 (10.78)	.354
Dialysis	29 (2.33)	(19) 2.35	10 (2.29)	.951
The length of ICU stay	10.10 (5.11–20.18)	11.78 (5.86–25.70)	8.26 (3.77–15.17)	<.001
The length of hospital stay	18.60 (9.61–30.68)	22.14 (12.73–34.96)	11.97 (5.82–21.10)	<.001

APACHE II = acute physiology and chronic health evaluation II, CAD = coronary artery disease, CHD = coronary heart disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, SOFA = sequential organ failure assessment.

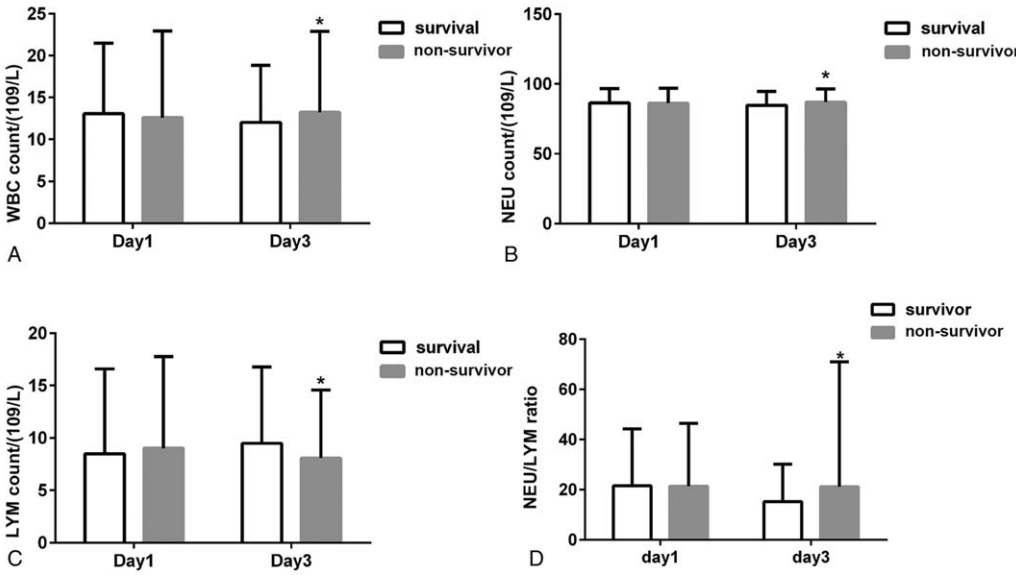

Figure 1. The circulatory number of WBC (A), neutrophils (B), lymphocytes (C) and NLCR (D) on the first and third day after ICU admission in survivor and non-survivor groups.

3.2. Circulating WBC, neutrophils, lymphocytes and NLCR in survivor and non-survivor groups

As showed in Figure 1, on the first day, there was no difference in the number of WBC, neutrophil and lymphocyte as well as NLR. By contrast, the number of WBC (12.03 ± 6.83)*10^9 vs (13.24 ± 9.67)* 10^9, $P < .05$) and neutrophils were significant lower in survivors relative survivals. In addition, lymphocyte counts was significant higher in survivals than non-survivors ((9.49 ± 7.31)* 10^9 vs (8.07 ± 6.50)*10^9, $P < .05$). Therefore, the NLR in survival was significant lower (15.25 ± 14.89 vs 21.157 ± 49.82, $P < .05$) compared with non-survivors.

We also calculated the change of WBC, neutrophil and lymphocyte counts and NLCR between the first and third day. The results showed that the delta WBC, neutrophil counts and NLCR was significant lower in survival relative non-survivals. By contrast, the delta lymphocyte counts were significant higher in survival compared with non-survivals (see Supplementary Figure S1, http://links.lww.com/MD2/A225, Supplemental Digital Content, which compared delta lymphocyte counts from third day to first day in survivors and non-survivors).

3.3. Risk factors for 28-day mortality of septic shock patients

By regression analysis, count of WBC, neutrophil and lymphocyte as well as NLR ratio on day 1 of these septic shock patients were not detected to be related to the 28-day prognosis. On day 3, the count of WBC (odds ratio [OR] 1.019, 95% confidence interval [CI], 1.003–1.035, $P = .020$) and neutrophil (OR 1.028, 95% CI, 1.012–1.044; $P < .001$) and NLR (OR 1.012, 95% CI, 1.005–1.021; $P = .002$) were found to be risk factors. Lymphocyte count on day 3 was identified to be a protective factor for 28-day survival status (OR 0.967, 95% CI, 0.946–0.988; $P = .002$) (Table 2).

The multiple logistic regression analysis revealed that older age, higher APACHE II and SOFA score, cancer and homological cancer were independent risk factors of 28-day mortality in patients with septic shock. In addition, WBC count (OR 1.014 [95% CI, 1.002–1.026], $P = .020$) and NLR (OR 1.003 [95% CI, 1.001–1.005], $P = .001$) other than neutrophil and lymphocyte counts on day 3 was significantly associated with 28-day mortality in patients with septic shock (Table 3).

3.4. Survival analysis in subgroups stratified by change of count of WBC and neutrophil and NLR

Survival analysis was conducted using Kaplan–Meier survival analysis. As Figure 2 showed, patients were divided into 2 groups according to whether the circulating blood cells count or NLR

Table 2

Univariate logistic regression analysis of the association between WBC, neutrophil, lymphocyte counts and NLR and 28-day mortality in ICU patients with septic shock.

	OR	95%CI	*P*
Day1			
WBC count (10^9/L)	0.994	0.981–1.007	.393
Neutrophil (10^9/L)	0.997	0.986–1.008	.643
Lymphocyte (10^9/L)	1.007	0.993–1.02	.303
NLR	0.999	0.994–1.005	.925
Day3			
WBC count (10^9/L)	1.019	1.003–1.035	.020
Neutrophil (10^9/L)	1.0281	1.012–1.044	<.001
Lymphocyte (10^9/L)	0.967	0.946–0.988	.002
NLR	1.012	1.005–1.021	.002
Delta (Day3-Day1)			
WBC count (10^9/L)	1.027	1.010–1.044	.001
Neutrophil (10^9/L)	1.036	1.017–1.055	<.001
Lymphocyte (10^9/L)	0.761	0.621–0.932	.008
NLR	1.011	1.005–1.017	.001

NLR = neutrophil lymphocyte ratio, WBC = white blood cell count.

Table 3

Multivariate logistic regression analysis of the association between WBC, neutrophil, lymphocyte counts and NLR and 28-day mortality in ICU patients with septic shock.

Day3	OR	95%CI	P
Day3			
WBC count (10^9/L)	1.019	1.003–1.036	.023
Neutrophil (10^9/L)	1.018	0.998–1.038	.073
Lymphocyte (10^9/L)	0.838	0.672–1.046	.118
NLR	1.012	1.003–1.020	.006
Delta (Day3-Day1)			
WBC count (10^9/L)	1.030	1.013–1.047	.001
Neutrophil (10^9/L)	1.038	1.018–1.058	<.001
Lymphocyte (10^9/L)	0.795	0.643–0.983	.034
NLR	1.011	1.005–1.018	<.001

APACHE II = acute physiology and chronic health evaluation II, SOFA = sequential organ failure Assessment, WBC = White blood cell. These results were analyzed after adjust the age, gender, patients with cancer and hematological cancer, SOFA and APACHE II score.

increases from day 1 to day 3 or not. Patients with a decrease of WBC (HR 0.605, 95% CI, 0.491–0.746, $P<.001$) and neutrophil count (HR 0.577, 95% CI, 0.466–0.714, $P<.001$) and NLR (HR 0.629, 95% CI, 0.509–0.777, $P<.001$) held a lower 28-day mortality rate than those without, respectively while patients with decrease of lymphocyte count held a higher mortality than those without (HR 1.373, 95% CI 1.109–1.700, $P=.004$). After adjust age, cancer, hematological malignancy, APACHE II and SOFA score, multivariate logistic regression analysis showed that decreased WBC, neutrophil counts and NLR and increased lymphocyte counts were associated with lower 28 day mortality (WBC, OR 1.030 [95% CI, 1.013–1.047], $P=.001$; neutrophil, OR 1.038 [95% CI, 1.01–1.058], $P<.001$; lymphocyte, OR 0.795 [95% CI, 0.643–0.983], $P=.034$; NLR, OR 1.011 [95% CI, 1.005–1.018], $P<.001$) (Table 3). Similar results were found in the cox regression model (see Supplementary Table S1, http://links.lww.com/MD2/A226, Supplemental Digital Content, which showed Cox regression analysis of the association between WBC, neutrophil, lymphocyte

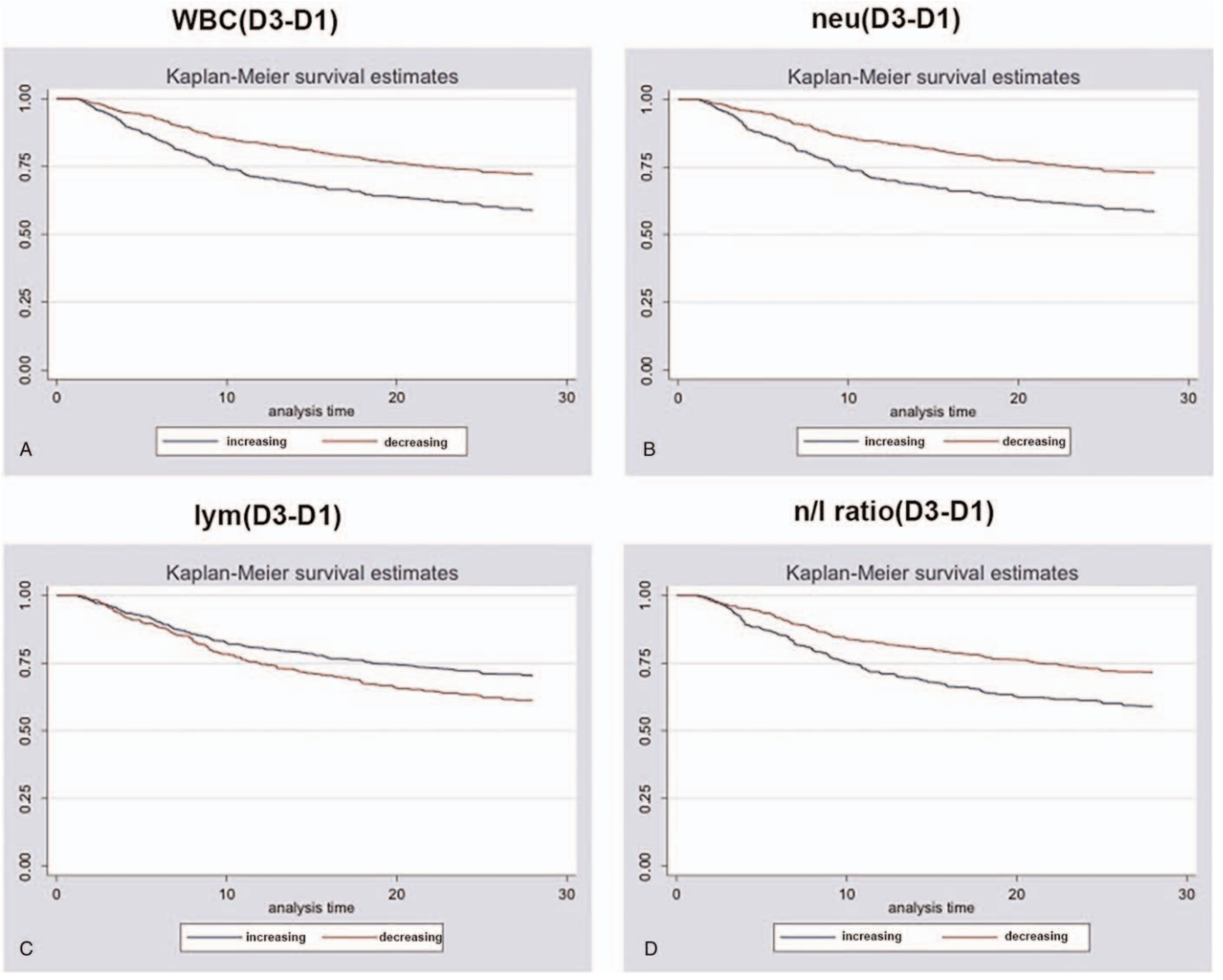

Figure 2. Kaplan–Meier survival estimates. Probabilities of survival for patients with sepsis diagnosed based on the kinetics of WBC (A), Neutrophil (B), Lymphocyte (C) and NLR (D) during the first 3 days after diagnosis in patients with septic shock.

counts and NLR and 28-day mortality in ICU patients with septic shock).

4. Discussion

Septic shock is a common critical disease creating a significant medical burden with high morbidity and mortality.[17] In this study, we found that a decreased WBC, neutrophil counts and NLR and increased lymphocyte counts were associated with lower 28 day mortality in patients with septic shock.

The white blood cells play a crucial role which helps to eliminate the invaded pathogen.[18] The number and function of neutrophils and lymphocytes may be significantly associated with outcome in patients with septic shock.[19,20] Recently, NLR was found as a valuable marker to predict mortality of septic shock patients.[21–24] Moreover, the NLR has been proven to be more accurately than routine parameters on predicting bacteremia.[25] However, different from this study,[26] there were no difference of WBC, neutrophil and lymphocyte counts and NLR on the first day at diagnosis between survival and non-survival in patients with septic shock in our study. However, we found that the circulating WBC, neutrophils, lymphocytes and NLR on the third day after ICU admission were independent risk factors of mortality in patients with septic shock in univariate logistic regression, multivariate logistic regression model and Cox's regression model. Moreover, we also found that the change of these parameters during the first 3 days were all associated with 28 day mortality after adjust potential confounders such as age and disease severity.

In this study, we found significantly difference in age, APACHE II and SOFA scores, the proportion of cancer and homological cancer between survivors and non-survivors. These results were similar to previous studies.[27–29] In Angus's report, chronic diseases, for instance, the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease and many cancers, are also risk factors for the infections that most commonly precipitate severe sepsis and septic shock.[25] Unfortunately, even if we detect these risk factors of mortality, no management strategies can be changed to improve the outcome in patients with septic shock due to these risk factors can not be treated.

The number of neutrophils increases in the early stage of most patients with septic shock.[30,31] Neutrophil excessive activation leads to destruction of organ parenchymal cells and multiple organ dysfunction during septic shock.[30] If the consistent inflammation can not be relieved during septic shock, it will induce organ dysfunction and early death. Our results showed that the decreased neutrophil counts during first 3 days after ICU admission was associated with lower mortality in patients with septic shock. Our results indicated that septic shock patients with consistent high level of neutrophils may get benefit from anti-inflammatory treatment.

Lymphocyte counts decreased due to apoptosis was very common and demonstrated to be associated with mortality in autopsy study.[32] Moreover, previous studies showed that T lymphocyte exhaustion were also a dependent risk factor of poor outcome.[33] Numerous of preclinical studies showed that revised lymphocyte function could help to improve sepsis survival.[34,35] In our study, we found that consistent decreased lymphocyte counts were associated with higher mortality, indicating revised lymphocyte number and function in the early stage of septic shock could improve survival.

In the present study, we included more than 1200 patients which was much more than previous studies. The large sample size could make the results more convince. However, several limitations should be clarify. First, this was a single center study, which may not extrapolate other centers. Second, the retrospective study also results a bias. However, in our center, the missing data was less than 5%. Therefore, our results reflect the real world phenomena in our patients with septic shock. Third, we only found the association between leukocyte and mortality in patients with septic shock. In addition, we did not include other confounders in the final analysis. Therefore, future studies should be performed to validate our results. Moreover, the causative relationship between lymphocyte and outcome also need to be determined.

5. Conclusion

Our research found that decreasing of white blood cells, neutrophil and NLR and increasing of lymphocyte counts help to control 28-day mortality in patients with septic shock. Our results indicated that revised lymphocyte number and function in the early stage of septic shock could improve survival.

Author contributions

Conceptualization: Qing Li, Yi Yang.
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Methodology: Songqiao Liu, Ling Liu.
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Supervision: Yi Yang.
Visualization: Fengmei Guo.
Writing – original draft: Qing Li, Jianfeng Xie, Yingzi Huang, Yi Yang.
Writing – review & editing: Qing Li, Yingzi Huang, Yi Yang.

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