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

Qing Li, MD, Jianfeng Xie, PhD, MD, Yingzi Huang, PhD, MD, Songqiao Liu, PhD, MD, Fengmei Guo, PhD, MD, Ling Liu, PhD, MD, Yi Yang, PhD, MD

Abstract

The leukocytes play an important role in immune function during sepsis. We performed a retrospective study to investigate if leukocyte 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=0.552) 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=0.024) 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.

It is the most common shock which results a mortality as high as 40% to 60%.[1,2] 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.
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 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 as 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 χ² 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 Table 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.

| 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         | .225  |
| 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 (8.10)   | 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.
3.2. Circulating WBC, neutrophils, lymphocytes and NLR 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) × 10⁹ vs (13.24 ± 9.67) × 10⁹, \( P < .05 \) 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) × 10⁹ vs (8.07 ± 6.50) × 10⁹, \( P < .05 \)). 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 significantly 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

| Day 1 | OR    | 95%CI            | \( P \) |
|-------|-------|------------------|-------|
| WBC count (10⁹/L) | 0.994 | 0.981–1.007 | .393 |
| Neutrophil (10⁹/L) | 0.997 | 0.986–1.008 | .643 |
| Lymphocyte (10⁹/L) | 1.007 | 0.993–1.02 | .303 |
| NLR | 0.999 | 0.994–1.005 | .925 |

| Day 3 | OR    | 95%CI            | \( P \) |
|-------|-------|------------------|-------|
| WBC count (10⁹/L) | 1.019 | 1.003–1.035 | .020 |
| Neutrophil (10⁹/L) | 1.0281 | 1.012–1.044 | .001 |
| Lymphocyte (10⁹/L) | 0.967 | 0.946–0.988 | .002 |
| NLR | 1.012 | 1.005–1.021 | .002 |

| Delta (Day 3-Day 1) | OR    | 95%CI            | \( P \) |
|---------------------|-------|------------------|-------|
| WBC count (10⁹/L) | 1.027 | 1.010–1.044 | .001 |
| Neutrophil (10⁹/L) | 1.036 | 1.017–1.055 | .001 |
| Lymphocyte (10⁹/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.
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, 1.018–1.058], \( P < .001 \); 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

| 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.

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. 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. The number and function of neutrophils and lymphocytes may be significantly associated with outcome in patients with septic shock. Recently, NLR was found as a valuable marker to predict mortality of septic shock patients. Moreover, the NLR has been proven to be more accurately than routine parameters on predicting bacteremia. However, different from this study, 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. 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. 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. Neutrophil excessive activation leads to destruction of organ parenchymal cells and multiple organ dysfunction during septic shock. 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 revised lymphocyte number and function in the early stage of septic shock could improve survival.

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.
Data curation: Qing Li, Jianfeng Xie, Yingzi Huang, Yi Yang.
Formal analysis: Jianfeng Xie, Yingzi Huang, Songqiao Liu, Ling Liu, Yi Yang.
Investigation: Songqiao Liu.
Methodology: Songqiao Liu, Ling Liu.
Project administration: Yingzi Huang.
Resources: Fengmei Guo.
Software: Fengmei Guo, Ling Liu.
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.

References

[1] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.
[2] Brun-Buisson C, Meshaka P, Pinton P, et al. EPISODES: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004;30:580–8.
[3] Vincent JL, Marshall JC, Namendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the intensive care over nations (ICON) audit. Lancet Respir Med 2014;2:380–6.
[4] Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. current estimates and limitations. Am J Respir Crit Care Med 2016;193:259–72.
[5] Seymour CW, Rea TD, Kahn JM, et al. Severe sepsis in pre-hospital emergency care: analysis of incidence, care, and outcome. Am J Respir Crit Care Med 2012;186:1264–71.
[6] Andersen MS, Lu S, Lopez GJ, et al. A novel implementation of magnetic levitation to quantify leukocyte size, morphology, and magnetic properties to identify patients with sepsis. Shock (Augusta, Ga) 2019;51:147–52.
[7] Urrechaga E, Boveda O, Aguierre U. Improvement in detecting sepsis using leukocyte cell population data (CPD). Clin Chem Lab Med 2019;57:918–26.
10. Jiang W, Zhong W, Deng Y, et al. Evaluation of a combination "lymphocyte apoptosis model" to predict survival of sepsis patients in an intensive care unit. BMC Anesthesiol 2018;18:89.

11. Liang D, Hou Y, Lou X, et al. Decoy receptor 3 improves survival in experimental sepsis by suppressing the inflammatory response and lymphocyte apoptosis. PLoS One 2015;10:e0131680.

12. Miao HJ, Wang D, Ge XH, et al. Effects of omega-3 polyunsaturated fatty acids on lymphocyte apoptosis rate in rats with sepsis. BMC Anesthesiol 2017;19:355–60.

13. Delogu G, Famularo G, Tellan G, et al. Lymphocyte apoptosis, caspase activation and inflammatory response in septic shock. Infection 2008;36:485–7.

14. Le Tulzo Y, Pangault C, Gacouin A, et al. Early circulating lymphocyte apoptosis in human septic shock is associated with poor outcome. Shock (Augusta, Ga) 2002;18:487–94.

15. Riche F, Gayet E, Barthelemy R, et al. Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock. Critical Care (London, England) 2015;19:439.

16. Hwang SY, Shin TG, Jo IJ, et al. Neutrophil-to-lymphocyte ratio as a prognostic marker in critically-ill septic patients. Am J Emerg Med 2017;35:234–9.

17. Zahorec R. Ratio of neutrophil to lymphocyte counts—rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5–14.

18. Gasteiger G, Ataide M, Kastenmuller W. Lymph node - an organ for T-cell activation and pathogen defense. Immunol Rev 2016;271:200–20.

19. Ljungstrom L, Pernestig AK, Jacobsson G, et al. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. PLoS One 2017;12:e0181704.

20. Guell E, Martin-Fernandez M, De la Torre MC, et al. Impact of lymphocyte and neutrophil counts on mortality risk in severe community-acquired pneumonia with or without septic shock. J Clin Med 2019;8.

21. Bai YL, Hu BL, Wen HC, et al. Prognostic value of plasma brain natriuretic peptide value for patients with sepsis: a meta-analysis. J Crit Care 2018;48:145–52.

22. Bu X, Zhang L, Chen P, et al. Relation of neutrophil-to-lymphocyte ratio to acute kidney injury in patients with sepsis and septic shock: a retrospective study. Int Immunopharmacol 2019;70:372–7.

23. Kim YJ, Kang J, Ryoo SM, Ahn S, Huh JW, Kim WY. Platelet-lymphocyte ratio after granulocyte colony stimulating factor administration: an early prognostic marker in septic shock patients with chemotherapy-induced febrile neutropenia. Shock (Augusta, Ga) 2018.

24. Yoon NB, Son C, Um S J. Role of the neutrophil-lymphocyte count ratio in the differential diagnosis between pulmonary tuberculosis and bacterial community-acquired pneumonia. Ann Laboratory Med 2013;33:105–10.

25. de Jager CP, van Wijk PT, Matheorda RB, et al. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Critical Care (London, England) 2010;14:R192.

26. Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.

27. Brakenridge SC, Efron PA, Storz JA, et al. The impact of age on the innate immune response and outcomes after severe sepsis/septic shock in trauma and surgical intensive care unit patients. J Trauma Acute Care Surg 2018;85:247–55.

28. Karvellas CJ, Dong Y, Abraldes JG, et al. The impact of delayed source control and antimicrobial therapy in 196 patients with cholecystitis-associated septic shock: a cohort analysis. Canadian J Sur J Canadien de Chirurgie 2019;62:189–98.

29. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the accuracy of three early warning scores with SOFA score for predicting mortality in adult sepsis and septic shock patients admitted to intensive care unit. Heart Lung 2019;48:240–4.

30. Wang B, Chen G, Li J, et al. Neutrophil gelatinase-associated lipocalin predicts myocardial dysfunction and mortality in severe sepsis and septic shock. Int J Cardiol 2017;227:589–94.

31. Stiel L, Meziani F, Helms J. Neutrophil activation during septic shock. Shock (Augusta, Ga) 2018;49:371–84.

32. Felmet KA, Hall MW, Clark RS, et al. Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia in children with nosocomial sepsis and multiple organ failure. J Immunol 2005;174:3765–72.

33. McKinney EF, Lee JC, Jayne DR, et al. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. Nature 2015;523:612–6.

34. Boomer JS, Shuherk-Shaffer J, Hotchkiss RS, et al. A prospective analysis of lymphocyte phenotype and function over the course of acute sepsis. Critical Care (London, England) 2012;16:R112.

35. Lanza-Jacoby S, Flynn JT, Miller S. Parenteral supplementation with a fish-oil emulsion prolongs survival and improves rat lymphocyte function during sepsis. Nutrition (Burbank, Los Angeles County, Calif) 2001;17:112–6.