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Association of Lymphopenia with Outcome of Sepsis Patients

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HIGHLIGHTS

1. Lymphopenia predicts poor outcomes in sepsis.
2. Reduced lymphocyte counts signal immune dysfunction.
3. Early lymphopenia indicates higher mortality risk.
4. Immune response impairment worsens sepsis severity.
5. Monitoring lymphopenia aids patient management strategies.

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ABSTRACT

Sepsis, a life-threatening organ dysfunction caused by a dysregulated response to infection, remains a global health issue, affecting 49 million people annually. Despite advances in treatment, sepsis-induced immunosuppression often leads to secondary infections in intensive care unit patients, increasing hospital stays and mortality rates. This immunosuppression is marked by reduced lymphocyte levels, particularly CD4+ T, CD8+ T, CD19+ B and natural killer (NK) cells, which are key components of the immune system. Prolonged lymphopenia, or low lymphocyte count, has been identified as a potential marker of ongoing immunosuppression in sepsis patients. To investigate this, a cross-sectional study was conducted on 50 sepsis patients at Kempegowda Institute of Medical Sciences over a year. The study analyzed correlations between lymphopenia and factors such as patient age, ICU admission, prevalence of septic shock, mortality rates, and Sequential Organ Failure Assessment (SOFA) scores. The data was processed using descriptive statistics, and further analysis was performed using SPSS software. The mean age of participants was 58.54 years, with 84% requiring ICU admission, 56% developing septic shock, and 48% mortality. Lymphocyte counts at admission and after 48 hours were lower in patients who required ICU admission, had septic shock, or died, with these associations proving statistically significant ($P<0.005$). SOFA scores, which measure organ dysfunction, were also higher in these patients and were inversely correlated with lymphocyte counts. A significant negative correlation ($P<0.005$) was observed between SOFA scores and lymphocyte counts at both admission and 48 hours, indicating that as lymphocyte counts decreased, SOFA scores increased. The study concludes that lymphocyte counts, easily measured in routine care, may serve as valuable indicators for identifying sepsis patients at higher risk of septic shock, mortality, and ICU admission.

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INTRODUCTION

Sepsis, which affects approximately 49 million individuals globally each year, is a life-threatening condition characterized by organ dysfunction caused by a dysregulated immune response to infection. Despite advancements in sepsis management, it remains a global health priority due to its high morbidity and mortality rates. The immune system's ability to defend against infection is significantly compromised during sepsis, with a notable impact on the body's lymphocyte population. Lymphocytes, a crucial subset of white blood cells, play a vital role in the immune response by identifying and neutralizing pathogens. However, sepsis triggers a dysregulation of lymphocyte count, leading to a state known as lymphopenia, which is a hallmark of sepsis-induced immunosuppression [1,2,3].

Lymphopenia refers to an abnormally low level of lymphocytes in the blood and is commonly observed in patients with sepsis. This reduction affects nearly all subsets of lymphocytes, including T cells, B cells, and natural killer (NK) cells, although there have been some conflicting reports regarding the behavior of B cells in this context. In particular, changes in the proportion of different lymphocyte subsets, such as CD4+ T helper cells and CD8+ cytotoxic T cells, occur in conjunction with lymphopenia. A shift in the CD4+/CD8+ ratio, which is a critical indicator of immune function, is often seen in sepsis patients. The decrease in lymphocyte count is primarily driven by two mechanisms: apoptosis (programmed cell death) and the migration of activated lymphocytes out of the bloodstream towards affected tissues, particularly the lymphatic system, where they attempt to control the infection [4,5].

The association between lymphopenia and sepsis has been well-documented in the scientific literature. Multiple studies have explored how lymphopenia contributes to the poor prognosis of sepsis patients and whether it can serve as a reliable biomarker for predicting outcomes. For example, one study found that a reduced lymphocyte count early in the course of sepsis was strongly predictive of both 28-day and 1-year mortality. This finding suggests that lymphocyte levels may reflect the degree of immunosuppression in sepsis and that monitoring these levels could help clinicians identify patients at higher risk of adverse outcomes. Another study reinforced this idea by demonstrating that prolonged lymphopenia, or sustained low lymphocyte counts, could serve as a marker of persistent immunosuppression in sepsis patients. Persistent immunosuppression renders patients more vulnerable to secondary infections, which complicates their clinical course, prolongs hospital stays, and increases the likelihood of death [6,7,8].

Given the significance of lymphopenia in sepsis, it has been proposed that lymphocyte count could be used as a practical biomarker to assess the immune status of sepsis patients and predict their prognosis. This approach would provide clinicians with a valuable tool for identifying patients who are at greater risk of complications such as septic shock, multi-organ failure, and death. In septic shock, a severe form of sepsis where there is a marked reduction in blood pressure and impaired organ perfusion, the immune system's failure to control the infection is even more pronounced. As such, identifying early signs of immunosuppression through biomarkers like lymphocyte count could help guide therapeutic decisions and improve patient outcomes [9].

The present study was conducted with the aim of evaluating the role of lymphocyte count in predicting the outcome of sepsis patients. By focusing on the correlation between lymphocyte count and clinical parameters such as mortality, ICU admission, septic shock, and organ dysfunction (measured through the Sequential Organ Failure Assessment or SOFA score), the study sought to determine whether lymphocyte levels could serve as a reliable predictor of patient prognosis. Lymphocyte counts were measured at the time of hospital admission and after 48 hours, with a particular focus on their relationship with patient outcomes [10].

The findings of the study underscored the predictive value of lymphocyte count in sepsis patients. A significant association was observed between low lymphocyte counts and worse clinical outcomes, including higher mortality rates, increased need for ICU admission, and a higher prevalence of septic shock. Additionally, a negative correlation was found between lymphocyte count and SOFA score, indicating that as lymphocyte levels decreased, the severity of organ dysfunction increased. These results highlight the potential utility of lymphocyte count as a biomarker for assessing the severity of sepsis and predicting which patients are at the highest risk of adverse outcomes [11,12].

Importantly, lymphocyte count is a simple, widely available test that can be easily incorporated into routine clinical care. Its use as a prognostic tool in sepsis would not only help identify high-risk patients but could also inform treatment strategies. For example, patients with prolonged lymphopenia may

benefit from targeted immunomodulatory therapies aimed at restoring immune function. Such interventions could potentially reduce the risk of secondary infections and improve survival rates in sepsis patients [13].

Sepsis remains a major global health challenge due to its high incidence and mortality rates. The immune system's dysregulation during sepsis, particularly the depletion of lymphocytes, plays a critical role in the progression of the disease. Lymphopenia, characterized by a reduced lymphocyte count, has emerged as a key marker of immunosuppress ion in sepsis and is associated with poor patient outcomes. Studies have consistently shown that lymphocyte count can serve as a valuable biomarker for predicting mortality, septic shock, and ICU admission in sepsis patients. The present study further supports this notion, demonstrating a strong correlation between low lymphocyte counts and worse clinical outcomes. As such, monitoring lymphocyte levels in sepsis patients could provide clinicians with a practical and effective means of assessing immune function and guiding treatment decisions [14,15].

The study aimed to evaluate the lymphocyte count in patients with sepsis and explore its correlation with several clinical factors, including the patients' mean age, the need for ICU admission, the prevalence of septic shock, the incidence of mortality, and the SOFA (Sequential Organ Failure Assessment) score. By analyzing these relationships, the study sought to assess whether lymphocyte count could serve as a useful indicator for predicting patient outcomes in sepsis cases.

MATERIAL AND METHODS

This observational study was conducted at the Department of General Medicine, Kempegowda Institute of Medical Sciences, Bangalore from January 2021-June 2022 for 12 months. Ethical approval has been obtained from the Ethical Approval Committee of Kempegowda institute of medical sciences, Bangalore.

Study Population:

The study population consisted of sepsis patients admitted to the Department of General Medicine at Kempegowda Institute of Medical Sciences, Bangalore. Participants were over 18 years old, and only those without conditions affecting white blood cell (WBC) counts, such as blood dysplasia, immune deficiencies, or undergoing chemotherapy, were included. The sample size was calculated to be 50 based on a 24% SOFA score increase in sepsis patients with lymphopenia.

Data Analysis:

Data was compiled using MS Excel and analyzed with SPSS (Version 26.0). Descriptive statistics were employed to present the data, with qualitative variables expressed as frequencies and percentages, and quantitative variables as means and standard deviations. A significance level of 5% (□ = 0.05) was set for statistical testing. The student t-test was used to compare mean values between categorical variables, allowing for the identification of statistically significant differences in the data.

RESULTS

The mean age of the study participants was 58.54 ± 18.04 years, with 84% requiring admission to the ICU. The average SOFA score among participants was 10.68 ± 4.87. At admission, the mean lymphocyte count was 1342.40 ± 729.66, which decreased to 1244.82 ± 826.87 after 48 hours. The incidence of septic shock in the study was 56%, while the mortality rate was 44%.

The mean lymphocyte count at admission and after 48 hours was significantly lower in study participants requiring ICU admission compared to those who did not need ICU care. Additionally, participants requiring ICU admission had a higher mean age and SOFA score, with a statistically significant association observed between the SOFA score and the necessity for ICU admission.

The mean lymphocyte count at admission and after 48 hours was significantly lower in study participants experiencing septic shock compared to those without septic shock. Additionally, participants with septic shock exhibited higher mean age and SOFA scores, with a statistically significant association noted between the SOFA score and the incidence of septic shock among the study participants.

The mean lymphocyte count at admission and after 48 hours was significantly lower in study participants who experienced mortality compared to those who did not. Participants who succumbed to the condition also exhibited higher mean age and SOFA scores, with a statistically significant association observed between the SOFA score and the incidence of mortality. Additionally, a statistically significant negative correlation was identified between the SOFA score and lymphocyte count at both admission and 48 hours.

Table 1: Patient Characteristics

Patient Characteristics		
Age, Mean±SD		58.54±18.04
ICU Admission, N (%)	Yes	42 (84%)
	No	8 (16%)
Sofa Score, Mean±SD		10.68±4.872
Lymphocyte Count, Mean±SD	Admission	1342.40±729.660
	48 Hours	1244.82±826.872
Septic Shock, N (%)	Yes	28 (56%)
	No	22 (44%)
Mortality, N (%)	Yes	24 (48%)
	No	26 (52%)

Table 2: Correlation of Lymphocyte Count with ICU Admission

Study Variables	ICU Admission		P Value
	Yes	No	
Age	58.74±18.209	57.50±18.354	0.861
Sofa Score	11.76±4.471	5.00±2.268	0.000*
Lymphocyte Count at Admission	1150.52±584.397	2349.75±588.114	0.000*
Lymphocyte Count at 48 Hours	1070.00±703.878	2162.63±859.101	0.000*

Table 3: Correlation of Lymphocyte Count with Septic Shock

Study Variables	Septic Shock		P Value
	Yes	No	
Age	58.18±20.383	59.00±15.017	0.875
Sofa Score	14.21±2.986	6.18±2.462	0.000*
Lymphocyte Count at Admission	957.86±330.629	1831.82±808.471	0.000*
Lymphocyte Count at 48 Hours	755.64±311.454	1867.41±863.416	0.000*

Table 4: Correlation of Lymphocyte Count with Mortality

Study Variables	Mortality		P Value
	YES	NO	
Age	59.71±20.552	57.46±15.728	0.665
Sofa Score	15.00±2.359	6.69±2.635	0.000*
Lymphocyte Count at Admission	931.96±302.588	1721.27±805.151	0.000*
Lymphocyte Count at 48 Hours	718.17±288.909	1730.96±866.740	0.000*

Table 5: Correlation of Lymphocyte Count with Sofa Score

Sofa Score	Lymphocyte Count	
	At Admission	At 48 Hours
Pearson Correlation	-0.651	-0.725
P VALUE	0.000*	0.000*

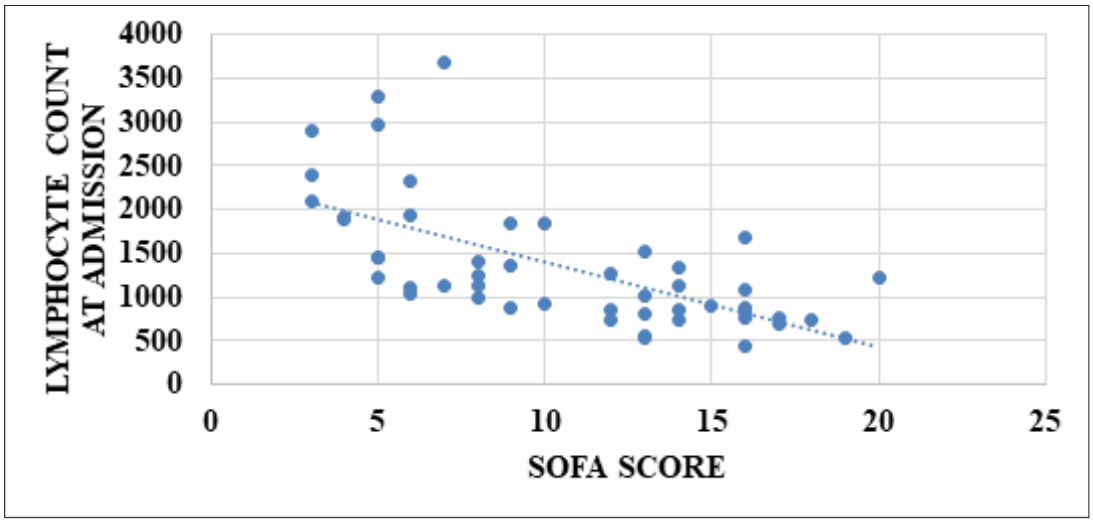

Figure 1: Correlation of Lymphocyte Count at Admission with Sofa Score

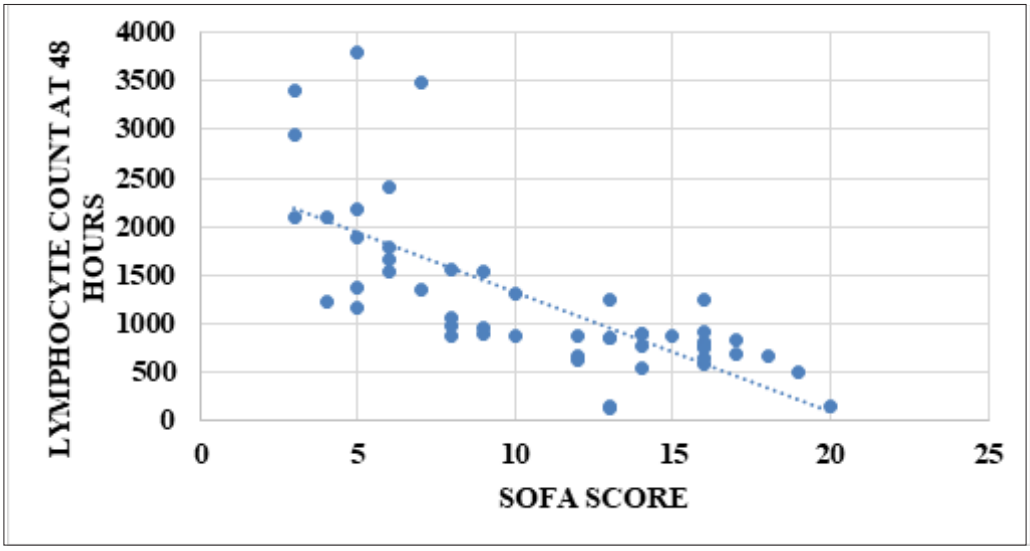

Figure 2: Correlation of Lymphocyte Count at 48 Hourds with Sofa Score

DISCUSSION

Sepsis represents a complex and multifaceted response of the immune system to invasive infections, characterized by significant disruptions in both the innate and adaptive immune systems. This pathological response involves a delicate balance between pro-inflammatory and anti-inflammatory mechanisms. When an infection occurs, the body activates a pro-inflammatory response aimed at fighting off the pathogens, while simultaneously attempting to mitigate tissue damage through anti-inflammatory processes. The magnitude and effectiveness of this immune response can vary greatly, influenced by several factors such as the site of the infection, the virulence of the infecting organism, host genetic factors, and the presence of co-morbid conditions [16].

This study focused on evaluating the relationship between lymphocyte count and several critical outcomes in sepsis patients, including the need for ICU admission, the incidence of septic shock, and mortality rates. Understanding these correlations can provide valuable insights into the immune status of patients

with sepsis and help in predicting their clinical outcomes [17].

In this study, the mean age of participants was comparable to findings in previous research, indicating that the demographic characteristics of the study group were consistent with those observed in other investigations. This consistency reinforces the validity of the findings and underscores the importance of age as a factor in sepsis outcomes. Additionally, the mean SOFA (Sequential Organ Failure Assessment) score of participants was measured at 10.68 ± 4.87. The Sofa score is a widely used tool in clinical practice to assess the degree of organ dysfunction in critically ill patients. A higher SOFA score indicates a greater level of organ failure and is often associated with worse prognoses. Previous studies have reported varying SOFA scores at admission, highlighting the variability in disease severity among different patient populations [18].

The lymphocyte count, a critical component of the immune response, was also evaluated in this study. The mean lymphocyte count at admission was found to be 1342.40 ± 729.66 cells/μL, which differs from earlier studies that reported lower median lymphocyte counts. The discrepancies in lymphocyte counts across studies can be attributed to variations in patient populations, methodologies, and the timing of the measurements. Nevertheless, the role of lymphocytes in sepsis is significant, as these cells are essential for mounting an effective immune response against infections [19].

The incidence of septic shock in the present study was observed to be 56%, while the mortality rate was 44%. These findings are notably higher than those reported in some previous studies, which indicate lower rates of mortality. Such variations may reflect differences in the patient cohorts, including the severity of illness and the healthcare settings where these studies were conducted. Septic shock is a severe manifestation of sepsis characterized by persistent hypotension despite adequate fluid resuscitation, leading to a high risk of organ failure and death [20].

In this study, it was found that participants who experienced septic shock and those who ultimately succumbed to their illness had lower mean lymphocyte counts both at admission and after 48 hours. Moreover, these patients exhibited higher SOFA scores, indicating greater organ dysfunction. The statistical significance of these associations ($P < 0.05$) suggests that low lymphocyte counts may be predictive of more severe disease outcomes.

This aligns with findings from other studies that have identified lymphopenia-defined as an abn-ormally low lymphocyte count-as a common feature in patients with sepsis. Research indicates that lymphopenic patients often require ICU admission at higher rates and have increased incidences of septic shock and mortality. The evidence suggests a strong correlation between low lymphocyte counts and adverse clinical outcomes, underscoring the importance of monitoring lymphocyte levels in critically ill patients [21].

The study also found that a lymphocyte count of less than 0.51 x 10^3 cells/μL was associated with increased 28-day mortality in severe sepsis cases. This highlights the need for careful assessment of lymphocyte counts as part of the clinical evaluation of sepsis patients. The relationship between lymphocyte count and SOFA scores was also notable, with lower lymphocyte counts correlating with higher SOFA scores, further emphasizing the potential role of lymphocyte levels in assessing the severity of sepsis [22].

Other studies have reinforced these findings, showing that lymphocyte counts are significantly lower among patients who experience mortality and septic shock. For instance, various investigations have reported similar trends, indicating that lymphopenia is a prevalent condition in patients with severe sepsis and is associated with poor prognoses. The evidence suggests that monitoring lymphocyte counts could serve as a valuable tool for healthcare providers in managing sepsis, enabling them to identify patients who are at a higher risk for severe outcomes [23].

Understanding the immune dysregulation in sepsis is critical for developing effective therapeutic strategies. Interventions aimed at restoring immune function, such as immunomodulatory therapies, may hold promise for improving outcomes in patients with low lymphocyte counts. These approaches could be particularly beneficial for patients exhibiting signs of immunosuppression, allowing for targeted treatment to mitigate the effects of sepsis.

Moreover, the implications of these findings extend beyond individual patient care; they contribute to a broader understanding of sepsis management. As research continues to unveil the complexities of the immune response in sepsis, the identification of reliable biomarkers, such as lymphocyte counts, will play a crucial role in enhancing diagnostic accuracy, prognostication, and therapeutic decision-making [24].

This study highlights the significant role of lymphocyte counts in the context of sepsis, demonstrating their association with the need for ICU admission, incidence of septic shock, and mortality. The findings underscore the importance of monitoring lymphocyte

levels as a potential prognostic indicator, helping to stratify risk among patients with sepsis. By enhancing our understanding of the immune response in sepsis, we can improve clinical outcomes and guide future research in this critical area of medicine [25].

CONCLUSION

Assessing the total lymphocyte count is straightforward and requires no specialized skills or laboratory equipment. Our study indicates that a lower lymphocyte count is linked to a higher incidence of septic shock and increased mortality, highlighting its potential as a valuable indicator in clinical practice.

REFERENCES

1. Cao M, Wang G, Xie J. Immune dysregulation in sepsis: experiences, lessons and perspectives. Cell Death Discovery. 2023 Dec 19;9(1):465.
2. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020 Jan 18;395(10219):200–11.
3. Holub M, Klucková Z, Helcl M, Príhodov J, Rokyta R, Beran O. Lymphocyte subset numbers depend on the bacterial origin of sepsis. Clin Microbiol Infect. 2003 Mar;9(3):202–11.
4. Cilloniz C, Peroni HJ, Gabarrús A, García-Vidal C, Pericàs JM, Bermejo-Martin J, Torres A. Lymphopenia is associated with poor outcomes of patients with community-acquired pneumonia and sepsis. In Open Forum Infectious Diseases 2021 Jun 1 (Vol. 8, No. 6, p. ofab169). US: Oxford University Press.
5. Guan J, Wei X, Qin S, Liu X, Jiang Y, Chen Y, Chen Y, Lu H, Qian J, Wang Z, Lin X. Continuous tracking of COVID-19 patients' immune status. International Immunopharmacology. 2020 Dec 1;89:107034.
6. Tufan ZK, Kayaaslan B, Mer M. COVID-19 and Sepsis. Turkish journal of medical sciences. 2021;51(7):3301-11.
7. Yao RQ, Ren C, Zheng LY, Xia ZF, Yao YM. Advances in immune monitoring approaches for sepsis-induced immunosuppression. Frontiers in immunology. 2022 May 10;13:891024.
8. Roth G, Moser B, Krenn C, Brunner M, Haisjackl M, Almer G, Gerlitz S, Wolner E, Boltz-Nitulescu G, Ankersmit HJ. Susceptibility to programmed cell death in T-lymphocytes from septic patients: a mechanism for lymphopenia and Th2 predominance. Biochemical and Biophysical Research Communications. 2003 Sep 5;308(4):840-6.
9. Wyllie DH, Bowler ICJW, Peto TEA. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. J Clin Pathol. 2004 Sep;57(9):950–5.
10. Spoto S, Lupoi DM, Valeriani E, Fogolari M, Locorriere L, Beretta Anguissola G, Battifoglia G, Caputo D, Coppola A, Costantino S, Ciccozzi M. Diagnostic accuracy and prognostic value of neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios in septic patients outside the intensive care unit. Medicina. 2021 Aug 7;57(8):811.
11. Tschaikowsky K, Hedwig-Geissing M, Schiele A, Bremer F, Schywalsky M, Schüttler J. Coincidence of pro- and anti-inflammatory responses in the early phase of severe sepsis: Longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. Crit Care Med. 2002 May;30(5):1015–23.
12. Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. Shock. 2014 Nov;42(5):383–91.
13. Yao RQ, Ren C, Zheng LY, Xia ZF, Yao YM. Advances in immune monitoring approaches for sepsis-induced immunosuppression. Front Immunol. 2022;13:891024.
14. Markwart R, Saito H, Harder T, Tomczyk S, Cassini A, Fleischmann-Struzek C, Reichert F, Eckmanns T, Allegranzi B. Epidemiology and burden of sepsis acquired in hospitals and intensive care units: a systematic review and meta-analysis. Intensive care medicine. 2020 Aug;46:1536-51.
15. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE open medicine. 2019Mar;7:2050312119835043.
16. Sheikh Motahar Vahedi H, Bagheri A, Jahanshir A, Seyedhosseini J, Vahidi E. Association of lymphopenia with short term outcomes of sepsis patients; a brief report. Arch Acad Emerg Med. 2019;7(1):e14.
17. Adrie C, Lugosi M, Sonneville R, Souweine B, Ruckly S, Cartier JC, Garrouste-Orgeas M, Schwebel C, Timsit JF. Persistent lymphopenia is a risk factor for ICU-acquired infections and for death in ICU patients with sustained hypotension at admission. Annals of intensive care. 2017 Dec;7:1-0.
18. Li X, Xu Z, Pang X, Huang Y, Yang B, Yang Y, Chen K, Liu X, Mao P, Li Y. Interleukin-10/lymphocyte ratio predicts mortality in severe septic patients. PLoS One. 2017 Jun 19;12(6):e0179050.
19. Chung KP, Chang HT, Lo SC, Chang LY, Lin SY, Cheng A, Huang YT, Chen CC, Lee MR, Chen YJ, Hou HH. Severe lymphopenia is associated with elevated plasma interleukin-15 levels and increased mortality during severe sepsis. Shock. 2015 Jun 1;43(6):569-75.
20. Hattori Y, Hattori K, Suzuki T, Matsuda N. Recent

advances in the pathophysiology and molecular basis of sepsis-associated organ dysfunction: Novel therapeutic implications and challenges. Pharmacology & Therapeutics. 2017 Sep 1;177:56–66.

21. Wesche DE, Lomas-Neira JL, Perl M, Chung CS, Ayala A. Leukocyte apoptosis and its significance in sepsis and shock. J Leukoc Biol. 2005 Aug;78(2):325–37.
22. Monserrat J, de Pablo R, Reyes E, Díaz D, Barcenilla H, Zapata MR, et al. Clinical relevance of the severe abnormalities of the T cell compartment in septic shock patients. Crit Care. 2009;13(1):R26.
23. Felmet KA, Hall MW, Clark RSB, Jaffe R, Carcillo JA. Prolonged lymphopenia, lymphoid depletion, and hypoprolactinemia in children with nosocomial sepsis and multiple organ failure. J Immunol. 2005 Mar 15;174(6):3765-72.
24. Venet F, Davin F, Guignant C, Larue A, Cazalis MA, Darbon R, Allombert C, Mougin B, Malcus C, Poitevin-Later F, Lepape A. Early assessment of leukocyte alterations at diagnosis of septic shock. Shock. 2010 Oct 1;34(4):358-63.
25. Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, Kurosawa S, Remick DG. The pathogenesis of sepsis. Annu Rev Pathol. 2011;6:19-48.

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