Relationship between Cellular Immunity Changes and Prognosis in Elderly Patients with Sepsis

Lei Xue¹, Qian-Mei Sun¹, Han Yu², Yang-Hong Liang¹ and Chun-Sheng Li²

Department of Geriatric Medicine¹ / Emergency Medicine², Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

ABSTRACT

Objective: To detect relationship between cellular immunity changes and prognosis in elderly patients with sepsis.

Study Design: An observational study.

Place and Duration of Study: General Department and Emergency Care Unit, Beijing Chaoyang Hospital, Beijing, China, from January to December 2016.

Methodology: Patients who had infection were included in this study, and divided into two groups; those with sepsis and no sepsis. One hundred and forty-one healthy volunteers were chosen to enroll in this study just as a control (control group). Patients were excluded if they were younger than 18 years of age; had hematological or immunological disease; had uncontrolled diabetes; and pretreated with immunosuppressive agents. Patients were further grouped according to age, their T lymphocyte subsets were compared, and their acute physiology and chronic health evaluation II (APACHE II) scores were compared. The 28-day re-hospitalisation rate was followed-up, and the effects of T lymphocyte subsets and APACHE II scores on this rate were statistical analysed.

Results: Out of the 687 patients, 350 patients had sepsis (sepsis group), and 337 patients had no sepsis (non-sepsis group). The age of these patients ranged from 19-96 years. CD3+T, CD4+T, CD8+T and natural NK cells were significantly lower in the elderly population, ($p < 0.01$). CD3+T, CD4+T, CD8+T and NK cells were significantly lower in the sepsis group, compared with patients in the non-sepsis group and control group; and the differences were statistically significant ($p < 0.05$), while APACHE II score was significantly higher ($p < 0.01$). In the sepsis group, compared with the non-elderly population, CD3+T, CD4+T and NK cells were significantly lower in the elderly population; and the differences were statistically significant ($p < 0.05$), while APACHE II score was significantly higher ($p < 0.05$). The 28-day re-hospitalisation rate was associated with CD3+T, CD4+T, CD8+T cells and APACHE II scores ($p < 0.05$).

Conclusion: CD3+T, CD4+T, CD8+T cells and APACHE II scores can be used as independent predictors of the 28-day re-hospitalisation rate.

Key Words: T Lymphocyte subsets, APACHE II, Sepsis, Elderly re-hospitalisation rate, CD, NK.

How to cite this article: Xue L, Sun QM, Yu H, Liang YH, Li CS. Relationship between cellular immunity changes and prognosis in elderly patients with sepsis. *J Coll Physicians Surg Pak* 2019; **29**(12):1144-1148.

INTRODUCTION

With the continuous development of social economy, the average life expectancy of China's population has been prolonged. The figures of the Sixth National Population Census revealed that the population with an age >60 years has reached 178 million, which account for 13.26% of the total population. Furthermore, the population with an age >65 years accounted for 8.87% of the total population. China has an ageing population.¹ Immune aging is a normal physiological phenomenon in the body, which is mainly characterised by decreased cellular and humoral immunities.² As the main component of acquired immunity, T cells play an important role in the process of immune aging. In the elderly population, the

decrease in the total number of T cells and T cell subsets affect immune functions such as adhesion functions and signal transduction; reducing the immune function of the elderly. This makes the elderly more susceptible to infections, and causes the occurrence of uncontrollable infections.³ The incidence of sepsis increases with age. Hence, age is an independent predictor of mortality in patients with sepsis.⁴

The aim of this study was to determine the changes in T lymphocyte subsets in patients with and without sepsis, in order to detect the relationship between cellular immunity changes and prognosis in elderly patients with sepsis.

METHODOLOGY

This observational study was conducted on 687 infected patients who visited at the General Department and Emergency Care Unit of Beijing Chaoyang Hospital from January to December 2016. These patients were retrospectively evaluated. Among them, 337 patients were diagnosed as sepsis according to the diagnostic criteria established in the 2001 International Sepsis

Correspondence to: Chun-Sheng Li, Department of Emergency Medicine, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China

E-mail: happychunshengli@163.com

Received: March 10, 2018; Revised: July 29, 2019;

Accepted: September 11, 2019

Definitions Conference.⁵ They were assigned to sepsis group. The remaining 350 patients, who did not meet the diagnostic criteria of sepsis, were assigned to non-sepsis group. Furthermore, 141 healthy volunteers who underwent physical examinations during the same period were chosen to enroll in the study as a control (control group). For each group, age was a stratification factor; patients aged 65 or above were assigned to the elderly group, and the rest to the non-elderly group. Patients were excluded if they were younger than 18 years of age; had hematological or immunological disease; had uncontrolled diabetes; and pretreated with immunosuppressive agents. The study was conducted after the approval of the Ethics Committee of Beijing Chaoyang Hospital, in accordance with the Declaration of Helsinki.

In the early morning of the first day of admission, under a fasting state, whole blood samples were collected from all patients and placed in EDTA tubes. Quantitative detection was conducted using the automatic cell counting method through flow cytometry (Beckman Coulter, model: FC500-MCL). The percentages of CD3 positive lymphocytes (CD3+T), CD4 positive lymphocytes (CD4+T), CD8 positive lymphocytes (CD8+T) and NK cells were detected in patients. On the first day, vital signs, routine blood indexes, blood gas, biochemistry, four coagulation indexes and urine volume were detected. APACHE II scores were drawn according to the worst data within 24 hours. Furthermore, 28-day re-hospitalisation rate was investigated by telephone.

All data were analysed using SPSS 25.0 statistical software. Measurement data were compared using test of normality (K-S method), normal data were expressed

as mean $\pm$ standard deviation ($\bar{x} \pm SD$), non-normal data were expressed as the median (percentile within 25-75%), and count data were expressed in percentage. Normally distributed measurement data were compared between two groups using independent sample t-test, while repeated measures analysis of variance was used to compare data among three groups. Non-normally distributed measurement data were compared using nonparametric tests. Count data were compared using the χ^2 -test. The $p < 0.05$ was considered statistically significant. On the basis of univariate analysis, significant variables were analysed using multivariate logistic regression analysis. The $p < 0.05$ was considered statistically significant.

RESULTS

In the sepsis group ($n=337$), the average age of patients was 70.88 ± 16.60 years, and male patients accounted for 64.98% (219/337). In the non-sepsis group ($n=350$), the average age of patients was 61.39 ± 16.49 years, and male patients accounted for 64.86% (227/350). For the control group, a total of 141 subjects were enrolled into this study; and the average age of these subjects was 65.26 ± 12.32 years, and male subjects accounted for 60.99% (86/141, Table I). In the non-elderly age group, the incidence of chronic obstructive pulmonary disease, renal insufficiency and diabetes mellitus were higher in the sepsis group than in the non-sepsis group; and the differences were statistically significant ($p=0.014$, $p=0.003$, and $p=0.042$, respectively). In the elderly age group, the incidence of chronic obstructive pulmonary disease, renal insufficiency, cerebrovascular disease, diabetes, coronary heart disease and cancers

Table I: Basic situations of patients.

No.	<65 years		p-value	≥ 65 years		p-value
	No sepsis group 165	Sepsis group 106		No sepsis group 185	Sepsis group 231	
Age (year)	49.37 $\pm$ 7.84	48.3 $\pm$ 12.92	0.444	79.03 $\pm$ 6.76	79.51 $\pm$ 7.19	0.488
Male (%)	144 (87.3)	67 (63.2)	<0.001	83 (44.9)	152 (65.8)	<0.001
Cardiac insufficiency	1 (0.6)	4 (3.8)	0.059	8 (4.3)	53 (22.9)	<0.001
Chronic obstructive pulmonary disease	10 (6.1)	16 (15.1)	0.014	13 (7.0)	55 (23.8)	<0.001
Renal insufficiency	1 (0.6)	8 (7.5)	0.003	17 (9.2)	44 (19.0)	0.005
Cerebrovascular disease	20 (12.1)	14 (13.2)	0.792	58 (31.4)	95 (41.1)	0.040
Diabetes	43 (26.1)	40 (37.7)	0.042	60 (32.4)	98 (42.4)	0.037
Hypertension	97 (58.8)	32 (30.2)	<0.001	104 (56.2)	143 (61.9)	0.240
Coronary atherosclerotic cardiopathy	26 (15.8)	19 (17.9)	0.640	59 (31.9)	100 (43.3)	0.017
Tumor	10 (6.1)	3 (2.8)	0.225	16 (8.6)	38 (16.5)	0.019

Table II: Difference in each indicators between the elderly and non-elderly age sub-groups.

No.	Control group		p-value	No sepsis group		p-value	Sepsis groups		p-value
	<65 years	≥ 65 years		<65 years	≥ 65 years		<65 years	≥ 65 years	
	75	66		165	185		106	231	
NK cell (%)	16.16 $\pm$ 0.75	15.28 $\pm$ 0.58	<0.001	15.39 $\pm$ 0.60	14.53 $\pm$ 0.64	<0.001	9.99 $\pm$ 0.38	9.76 $\pm$ 0.52	<0.001
CD3+T (individual/ul)	1389.92 $\pm$ 36.44	974.58 $\pm$ 34.45	<0.001	1363.33 $\pm$ 46.69	956.03 $\pm$ 85.81	<0.001	742.13 $\pm$ 58.42	612.25 $\pm$ 29.23	<0.001
CD4+T (individual/ul)	897.31 $\pm$ 26.02	658.16 $\pm$ 26.04	<0.001	875.81 $\pm$ 33.36	647.29 $\pm$ 59.89	<0.001	465.15 $\pm$ 41.04	364.74 $\pm$ 16.90	<0.001
CD8+T (individual/ul)	456.12 $\pm$ 15.66	302.09 $\pm$ 13.36	<0.001	451.18 $\pm$ 21.19	288.96 $\pm$ 31.12	<0.001	262.69 $\pm$ 22.90	258.50 $\pm$ 14.14	0.084
APACHEII (score)	4.78 $\pm$ 1.06	6.69 $\pm$ 1.28	0.058	14.67 $\pm$ 4.62	20.88 $\pm$ 3.75	0.038	23.62 $\pm$ 3.34	25.04 $\pm$ 3.02	0.046

Table III: Multiple logistic regression analysis of risk factors for 28d re-hospitalisation rate.

Risk factors	Regression coefficient	Standard error of regression coefficient	p-value
age	0.068	0.016	<0.001
CD3+T(individual/ul)	-0.008	0.002	<0.001
CD4+T(individual/ul)	-0.007	0.002	<0.001
CD8+T(individual/ul)	-0.011	0.001	<0.001
APACHEII(score)	0.359	0.143	0.012

were higher in the sepsis group than in the non-sepsis group; and the differences were statistically significant ($p<0.001$, $p=0.005$, $p=0.04$, $p=0.037$, $p=0.017$, and $p=0.019$, respectively).

Infection sites of sepsis: respiratory tract (273 patients, 81.01%), gastrointestinal tract (17 patients, 5.04%), hepatic and biliary system (13 patients, 3.86%), urinary system (11 patients, 3.26%), and other sites (such as at the central, skin and soft tissues; 23 patients, 6.82%).

After grouping according to age group, it was found that differences in gender composition, age and other aspects between the sepsis and control groups, as well as between the sepsis and non-sepsis groups, were not statistically significant. Compared with the non-sepsis group and control group, CD3+T, CD4+T, CD8+T and NK cells in the sepsis group revealed a decreasing trend; and the differences were statistically significant (all $p<0.001$). Furthermore, APACHE II scores also significantly increased, and the difference was statistically significant (all $p<0.001$).

As shown in Table II, in the non-sepsis and control groups, CD3+T, CD4+T, CD8+T and natural NK cells significantly decreased in the elderly population; and the differences were statistically significant (all $p<0.001$). In the sepsis group, CD3+T, CD4+T and NK cells significantly decreased in the elderly age group compared with the non-elderly age group; and the differences were statistically significant (all $P<0.001$). However, CD8+T did not significantly decrease, and the difference between these two groups was not statistically significant ($p=0.084$). In the sepsis and non-sepsis groups, APACHE II scores in the elderly population increased ($p=0.038$, and $p=0.046$, respectively).

Through the analysis of the 28-day re-hospitalisation rate, it was found that CD3+T, CD4+T and CD8+T significantly increased in patients without re-hospitalisation; and the differences were statistically significant ($p=0.002$, $p=0.005$, and $p=0.009$, respectively). The difference in NK cells between these two groups was not statistically significant ($P=0.089$). APACHE II scores were higher in patients with re-hospitalisation than in patients without re-hospitalisation, and the difference was statistically significant ($p=0.023$).

Through the univariate analysis of risk factors (age, CD3+T, CD4+T, CD8+T and NK cells, and APACHE II scores) that may affect a patient's re-hospitalisation rate,

it was found that differences in CD3+T, CD4+T, CD8+T and APACHE II scores between patients with and without re-hospitalisation were statistically significant. Furthermore, these significant variables were analysed using multivariate logistic regression analysis (Forward Waid method). The introduction level was set at 0.05, and the elimination level was set at 0.10. These variables are finally introduced into the equation included age, CD3+T, CD4+T, CD8+T and APACHE II scores. The regression coefficient and p-values were shown in Table III.

DISCUSSION

With the acceleration of the aging society in China, the incidence of sepsis has shown a continuous upward trend. Age is an independent predictor of mortality in patients with sepsis. The mortality of elderly patients with sepsis is higher than that of young patients, and the relative risk is 13.1 times as much as that of the young.⁶

The immune system of the body plays a decisive role in maintaining immune homeostasis and self tolerance. Systemic inflammatory response can lead to changes in the apoptosis process of a variety of immune cells, and further cause and aggravate the immune inflammatory response disturbance.^{7,8} T lymphocyte subsets can reflect the cellular immunity of the body to a certain extent. Once deficiency or functional defects of helper T cells or inhibitory T lymphocytes occurs, the T cell regulatory network will be unbalanced; thus, causing the occurrence of a variety of diseases.^{9,10} Therefore, through detecting the monoclonal antibodies of T lymphocytes, we can understand the changes in the T lymphocyte network under physiological and pathological conditions, and enable the accurate assessment of the immune status of the patient's body.

In this study, the same age group showed that CD3+T, CD4+T, CD8+T and NK cells were significantly lower in sepsis patients compared with patients without sepsis. In the sepsis group, CD3+T, CD4+T and NK cells were significantly lower in the elderly age group compared with the non-elderly age group ($p<0.01$). Zhou *et al.* revealed that systemic inflammatory response and immune suppression always simultaneously existed in patients with severe sepsis, manifested by significantly decreased expression levels of serum CD3+T and CD4+T.¹¹ Recently, a number of studies have revealed that sepsis patients may have an immune inhibitory state in the body, which manifest as changes in the numbers and proportions of T lymphocyte subsets at the level of cellular immunity.¹²⁻¹⁴ The results of the data evaluation in this study are consistent with previous literature reports. For patients with sepsis, the mechanism of immune impairment may be caused by regulation disorder of Fas (CD95) and its ligand, which would change apoptosis signals in immune cells after the occurrence of the disease, induce the imbalance of

changes among lymphocyte subsets, reduce the CD4+/CD8+ ratio and finally cause immune paralysis mainly in specific immune functions.¹⁵⁻¹⁷

For sepsis patients, the total 30-day re-hospitalisation rate in the adults under 65 years has been estimated to be 13.2%.¹⁸ In some specific population groups (for example, AIDS patients), there was a correlation between the decrease in CD4+ T and re-hospitalisation rate.¹⁹ T lymphocyte subsets not only reflects the immune function of patients, but also indirectly predicts the risk of mortality. In this study, our results revealed that CD3+T, CD4+T and CD8+T cells were all related to re-hospitalisation.

There are a variety of chronic diseases in elderly patients with sepsis, causing a further decrease in organ reserve function and compensatory ability. Hence, some pathogenic factors that are not so serious can lead to re-hospitalisation. Martin revealed that age was an independent risk factor for the prognosis of sepsis.²⁰ This study also revealed that age could be used as an independent risk factor for re-hospitalisation rate.

In order to accurately assess the prognosis of patients with sepsis, a number of effective scoring criteria have been put forward at present, including APACHE II scores, SOFA scores, etc.²¹ Furthermore, a number of literatures have reported that APACHE II scores could be used to effectively assess the prognosis of ICU patients and their hospitalisation days in the ICU.²²⁻²⁵ In this study, our results revealed that APACHE II scores significantly increased not only in the sepsis group ($p < 0.01$), but also in the elderly population ($p < 0.05$). In the analysis of the rate of the 28-day re-hospitalisation of patients, APACHE II score was determined as an independent risk factor. This suggests that APACHE II score has a good predictive value for the prognosis of patients with sepsis.

This study has certain limitations. First, the effect of treatment on immune status was not taken into consideration, and the indicators were not dynamically monitored. Second, APACHE II scoring system has a large number of score indices that are easily influenced by subjective factors. The prediction method for the re-hospitalisation rate needs to be confirmed through large-scale clinical trials.

CONCLUSION

The elderly have poor cellular immunity, which is likely to make them prone to infection. Detection of T lymphocyte subsets in peripheral blood has important clinical significance in assessing immune status and determining the severity of diseases.

ETHICAL APPROVAL:

This study was conducted with approval from the Ethics Committee of Beijing Chaoyang Hospital. This study was conducted in accordance with the declaration of Helsinki.

PATIENTS' CONSENT:

All patients signed a document of informed consent.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

LX, QMS, HY: Acquired data; Contributed substantially to its revision; Read and approved the final manuscript.

HY: Acquired data; Contributed substantially to its revision; read and approved the final manuscript.

LX: Drafted the manuscript.

YHL, CSL: Drafted the manuscript; Contributed substantially to its revision; Read and approved the final manuscript.

REFERENCES

1. World Health Organization. China country assessment report on ageing and health. Geneva: World Health Organization, 2015. <http://www.who.int/ageing/publications/china-country-assessment/en/>.
2. Martin S, Perez A, Aldecoa C. Sepsis and immunosenescence in the elderly patient: A review. *Front Med (Lausanne)* 2017; **4**:20.
3. Hotchkiss RS, Monneret G, Payen D. Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. *Lancet Infect Dis* 2013; **13**:260-8.
4. Biston P, Aldecoa C, Devriendt J. Outcome of elderly patients with circulatory failure. *Intensive Care Med* 2014; **40**:50-6.
5. Singer M, Deutschman CS, Seymour CW. The third international consensus definitions for sepsis and septic shock. *JAMA* 2016; **315**:801-10.
6. Finfer S, Machado FR. The global epidemiology of sepsis. Does it matter that we know so little? *Am J Respir Crit Care Med* 2016; **193**:228-30.
7. Hotchkiss RS, Opal SM. Immunotherapy for sepsis: A new approach against an ancient foe. *N Engl J Med* 2010; **363**:87-9.
8. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. *Nat Rev Immunol* 2013; **13**:862-74.
9. Monserrat J, De PR, Diazmartin D. Early alterations of B cells in patients with septic shock. *J Crit Care* 2013; **17**: R105.
10. Unsinger J, Herndon JM, Davis CG. The role of TCR engagement and activation-induced cell death in sepsis-induced T cell apoptosis. *J Immunol* 2006; **177**:7968-73.
11. LX Zhou, JJ Tan, TN Li, HT Luo, YH Shao, XH Qiang, et al. Immune and inflammation confusion in severe sepsis and effects of bi-immunomodulation therapy: A prospective, randomized, controlled clinical trial. *Chinese Med J* 2009; **89**:1028-1033.
12. Stokkeland K, Brandt L, Ekblom A, Hultcrantz R. Improved prognosis for patients hospitalized with esophageal varices in Sweden 1969-2002. *Hepatology* 2006; **43**:500-5.
13. Inoue S, Suzuki-Utsunomiya K, Okada Y, Taira T, Iida Y, Miura N, et al. Reduction of immunocompetent T cells followed by prolonged lymphopenia in severe sepsis in the elderly. *Crit Care Med* 2013; **41**:810-9.
14. Pan DF, Li FR, Liang SS, Qi KY, Ji XZ, Ke JF. Value of lympho-

- cyte subgroups jointly detected in assessing poor prognosis of patients with sepsis. *Chinese J Emerg Med* 2015; **24**:524-9.
15. Cabrera-Perez J, Condotta SA, Badovinac VP. Impact of sepsison CD4 T cell immunity. *J Leukoc Biol* 2014; **96**:767-77.
  16. Condotta SA, Cabreraperez J, Badovinac VP. T-cell-mediated immunity and the role of TRAIL in sepsis-induced immunosuppression. *Crit Rev Immunol* 2013; **33**:23-40.
  17. Rimmelé T, Payen D, Cantaluppi V. Immune cell phenotype and function in sepsis. *Shock* 2016; **45**:282-91.
  18. Wier LM, Barrett ML, Steiner C, Jiang HJ. All-cause readmissions by payer and age, 2008. HCUP Statistical Brief Agency for Healthcare Research and Quality, 2011 - 2012.
  19. Berry SA, Fleishman JA, Yehia BR. Thirty-day hospital readmission rate among adults living with HIV. *AIDS* 2013; **27**:2059-68.
  20. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; **34**:15-21.
  21. Chen K, Shan HW. Clinical application of the evaluating systems in sepsis patients. *Chinese J Critical Care Med* 2014; **34**:679-682.
  22. Li Z, Wang H, Liu J, Chen B, Li G. The utility of acute physiology and chronic health evaluation II scores for prediction of mortality among intensive care unit (ICU) and non-ICU patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol* 2012; **33**:558-64.
  23. Naved SA, Siddiqui S, Khan FH. APACHE-II score correlation with mortality and length of stay in an intensive care unit. *J Coll Physicians Surg Pak* 2011; **21**:4-8.
  24. Al Tehewy M, El Houssinie M, El Ezz NA, Abdelkhalik M, El Damaty S. Developing severity adjusted quality measures for intensive care units. *Int J Health Care Qual Assur* 2010; **23**:277-86.
  25. Friederiksen DV, Van der Merwe L, Hattingh TL, Nel DG, Moosa MR. Acute renal failure in the medical ICU still predictive of high mortality. *S Afr Med J* 2009; **99**:873-87.