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Original Article

Serum levels of TNF-α, IL-1β, IL-9, and IL-15 in acute respiratory distress syndrome

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Abstract: Objective: This study is aimed to explore the functions of TNF-α IL-1β, IL-9, and IL-15 cytokines in the pathogenesis of acute respiratory distress syndrome (ARDS). Methods: A total of 28 patients with ARDS diagnostic criteria from the Emergency Department from June 2013 to July 2014 were selected as the ARDS group, and 22 healthy subjects were designated as the control. Clinical parameters were collected. Based on the 2012 Berlin criteria, the ARDS patients were categorised into moderate (18 cases) and severe (10 cases) groups. A total of 3 ml of peripheral venous blood was drawn from the fasted control and ARDS groups on the mornings of days one and three. ELISA was used to measure the serum concentrations of TNF-α, IL-1β, IL-9, and IL-15 in both groups. The serum concentrations of TNF-α, IL-1β, IL-9, and IL-15 were compared across all groups and time points. At the 28-day follow-up, patients were recategorised into survival (13 cases) and nonsurvival (15 cases) groups based on their prognostic situations. Results: On the first day of diagnosis, no significant differences in age, gender, APACHE II score, procalcitonin, hs-CRP, white blood cell count, lactic acid, or albumin values were observed between the survival and nonsurvival ARDS groups ($P > 0.05$). The pH values in the nonsurvival group were significantly lower than that in the survival group ($P < 0.05$). The serum levels of TNF-α, IL-1β, IL-9, and IL-15 in the ARDS group were significantly higher than those in the control group ($P < 0.05$). The serum TNF-α level in the moderate group were significantly lower than that in the severe group ($P < 0.05$). Three days after ARDS diagnosis, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 in the moderate group were significantly lower than those in the severe group ($P < 0.05$). On day three, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 in the nonsurvival group were significantly higher than those in the control group ($P < 0.05$). Conclusion: During the early stages of ARDS, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 can be used to evaluate ARDS severity and make a prognosis.

Keywords: Acute respiratory distress syndrome, cytokines, relevance

Introduction

Acute respiratory distress syndrome (ARDS) is severe acute hypoxic respiratory failure due to non-cardiogenic pathogenic factors inside and outside the lungs. The primary pathological features of ARDS include increased pulmonary microvascular permeability and the appearance of protein- rich exudate in the alveolar cavities. These symptoms can cause pulmonary edema and pulmonary hyaline membrane disease. In ARDS, pulmonary volume and pulmonary compliance are decrease, which cause severe imbalances between pulmonary ventilation and blood flow. The main clinical manifestations are acute respiratory distress and refractory hypoxemia [1].

Researchers showed that the death rate of inpatients with ARDS reaches 40% [2]. Its pathogenesis is complex. Thus, ARDS is a difficult to analyse in critical care medicine studies. Many studies indicated that inflammatory cytokines play an important role in the disease progression of ARDS, but the functions of TNF-α, IL-1β, IL-9, and IL-15 in the disease development are unclear. This study explores the effects of these cytokines in ARDS pathogenesis by examining the serum levels of the cytokines in ARDS patients.

Materials and methods

General data

A total of 28 ARDS patients who were hospitalised in the Emergency Department of the First Affiliated Hospital of Xinjiang Medical University from June 2013 to July 2014 were selected. The patients were composed of 18 males and 10 females aged 53.8±13.39 years old. A total of 23 have severe pneumonia, one has acute hydragyrism, two have severe acute pancreatitis and two have acute paraquat intoxication. A total of 22 healthy subjects from the corresponding time period were selected as the control group. The control group, included 14 males and 8 females aged 31.1±7.1 years old. The treatments were given in accordance with the Definition of Treatment Criteria from Berlin.

This study conforms to the medical ethics criteria and was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Ethical Approval No. 20140613-10). All patients or their relatives and the healthy subjects were informed and signed an informed consent form (ICF).

Inclusion criteria: (1) age ≥ 18 years old; (2) diagnosis in accordance with the 2012 Berlin Definition [3].

Exclusion criteria: (1) age ≤ 18 years old; (2) patients who died within three days of diagnosis; (3) patients or their relatives refused to participate in the study; (4) patients with chronic obstructive pulmonary disease; (5) patients with upper airway obstructive disease; (6) patients with pneumothorax or bronchopleural fistula less than two weeks after the pulmonary lobectomy operation; (7) patients with acute pulmonary embolism; (8) patients with cardiogenic pulmonary edema; (9) patients with the severe intracranial pressure; (10) patients with operations on their heart and thorax; (11) patients with no autonomous respiration; (12) patients with myasthenia gravis; (13) patients with myodystrophy.

Sample collection and indicators observation

3 mL of peripheral venous blood was drawn from the fasted control and ARDS groups on the mornings of days one and three after ARDS diagnoses. Blood tubes without anticoagulant were used to collect blood. The blood samples were centrifuged at 3,000 rpm for 10 minutes. The upper serum layer was collected, transferred to sterile anti-freezing tubes and stored at -80°C. The serum samples were thawed at room temperature prior to analyses.

ELISA assays were used to measure the serum levels of TNF-α, IL-1β, IL-9 and IL-15 cytokines. The assays were performed according to the reagent instructions. Blood pressure, respiration rate, heart rate, body temperature, procalcitonin, hypersensitive 3 C-reactive protein, routine blood panel, liver and kidney functions, vigour and chest X-ray were measured in all subjects. Lung CT examinations were performed whenever possible. The acute physiology and chronic physical conditions were scored using the marking system II (APACHE II).

Major reagent kits and instruments

TNF-α, IL-1β, and IL-15 reagent kits were purchased from Wuhan Boster Biological Technology Co., Ltd, and the IL-9 reagent kit was bought from Beijing Cheng Lin Biological Technology Co., Ltd. The major instruments include an HC-2518 high-speed centrifuge, a DNP-9082 electro-heating standing-temperature cultivator, and a Benchmarrk PLUD Multiskan Spectrum Plate Reader. A specially assigned person from the laboratory of the First Affiliated Hospital of Xinjiang Medical University uniformly and simultaneously calibrated all these instruments.

Quality control

To guarantee the accuracy and reliability of the study materials, a series of quality control measures was used during the study: (1) the subjects of the current study were diagnosed by experienced physicians in the Emergency Department of the First Affiliated Hospital of Xinjiang Medical University by closely following the 2012 Berlin ARDS criteria; (2) all TNF-α, IL-1β, IL-9 and IL-15 tests were performed in duplicate; (3) all investigators who participated in this study received strict and uniform training; (4) accurate measuring instruments were used; (5) the experimental procedures closely followed the operation specifications and instructions and were guided by the specialised technical staff. The sample addition and distribution procedures were also supervised by

Table 1. Comparison of cytokine levels between the ARDS and control groups on day one of diagnosis expressed as pg/mL [M (Q_L, Q_M)]

	Cases	TNF-α	IL-1β	IL-9	IL-15
ARDS group	28	171.42 (128.43, 263.37)	145.09 (103.54, 201.22)	3.99 (3.35, 5.20)	81.76 (66.47, 133.97)
Control group	22	17.78 (13.57, 22.90)	13.96 (13.13, 15.38)	0.57 (0.47, 0.76)	7.97 (6.95, 8.69)
Z		-6.020	-6.020	-6.020	-6.024
p		0.000	0.000	0.000	0.000

specially- assigned staff; (6) all data were independently typed into the database by two people and checked by two other individuals.

Statistical methods

SPSS17.0 software was used for data processing. Normally distributed data were presented as mean ± SD, and the independent samples t-test was used for comparisons between groups. Abnormally distributed data were presented as the median (quartile) [*M* (Q_L, Q_M)], and the independent-samples Mann-Whitney *U* test was used for comparisons between groups. The χ^2 test was conducted for enumeration data. $P < 0.05$ indicated statistical significance.

Results

Comparison of the cytokine levels between the ARDS and control groups

On day one after ARDS diagnosis, TNF-α, IL-1β, IL-9, and IL-15 serum cytokine levels were significantly higher in the ARDS group than that in the healthy control group (**Table 1**).

Comparison of cytokine levels between the moderate and severe groups

On day one after ARDS diagnosis, the serum TNF-α level in the moderate group was significantly lower than that in the severe group ($P < 0.05$). The IL-1β, IL-9, and IL-15 levels were not significantly different between the two groups ($P > 0.05$). On day three after ARDS diagnosis, the serum levels of TNF-α, IL-1β, IL-9 and IL-15 in the moderate group were significantly lower than that in the severe group ($P < 0.05$). These results are shown in **Table 2**.

Comparison of the basic indicators between the survival and nonsurvival groups

The patients were divided into groups according to their 28-day prognosis. A total of 13 survival cases and 15 death cases, were determined, which result in a 53.57% fatality rate. On day one of the ARDS diagnosis, the basic indicators of the subjects were compared for the two groups. No significant differences were observed between the survival and nonsurvival groups for age, gender, APACHE II, procalcitonin, hypersensitive 3 C-reactive protein, white blood cell count, albumin, and lactic acid levels ($P > 0.05$). However, the pH values in the nonsurvival group, were significantly lower than that in the survival group ($P < 0.05$). These results are shown in **Table 3**.

Comparison of cytokine levels between survival and nonsurvival groups

On day one after ARDS diagnosis, the serum levels of TNF-α, IL-1β, IL-9 and IL-15 in the survival group were lower than that in the nonsurvival group. However, the differences were insignificant ($P > 0.05$). On day three after ARDS diagnosis, the TNF-α, IL-1β, IL-9, and IL-15 serum cytokine levels in the survival group were significantly lower than that in the nonsurvival group ($P < 0.05$). These results are present in **Table 4**.

Discussion

In recent years, various experiments and clinical data demonstrated that ARDS is a systemic inflammatory response. This inflammatory response is caused by an imbalance of the systemic inflammatory response syndrome (SIRS) and the compensatory anti-inflammatory response syndrome [1]. SIRS occurs when the immune regulatory system of the body is out of control, and inflammatory responses increase. As a result, the body releases large amounts of inflammatory mediators and inflammatory cytokines. These substances form an inflammatory cascade, which leads to diffuse parenchymal lung disease with progressive exacerbation. These effects indicate that the inflammatory cytokines play a critical role in the pathogene-

Table 2. Comparison of cytokine levels between the moderate and severe groups, expressed as pg/mL ($\bar{x} \pm s$) or [*M* (Q_L, Q_M)]

Day 1 after ARDS diagnosis						Day 3 after ARDS diagnosis					
Group	Case	TNF-α	IL-1β	IL-9	IL-15	Group	Case	TNF-α	IL-1β	IL-9	IL-15
Moderate group	18	156.15 (110.35, 231.22)	134.90 (92.99, 161.09)	4.00±1.71	77.26 (62.47, 120.15)	Moderate group	18	102.80 (70.64, 140.99)	114.25±49.64	3.26±1.09	77.18±39.13
Severe group	10	274.20 (141.16, 446.67)	182.89 (126.60, 279.66)	4.61±0.97	115.21 (72.09, 180.05)	Severe group	10	142.84 (127.79, 357.64)	160.88±40.77	4.27±1.11	117.40±58.68
Test value		Z=-2.086	Z=-1.487	t=-1.043	Z=-1.728	Test value		Z=-2.35	t=-2.528	t=-2.337	t=-2.178
P		0.037	0.137	0.307	0.084	*p*		0.019	0.018	0.027	0.039

Table 4. Comparison of cytokine levels between the survival and the nonsurvival groups, expressed as pg/mL ($\bar{x} \pm s$) or [*M* (Q_L, Q_M)]

Day 1 after ARDS diagnosis						Day 3 after ARDS diagnosis					
Group	Case	TNF-α	IL-1β	IL-9	IL-15	Group	Case	TNF-α	IL-1β	IL-9	IL-15
Survival group	13	143.07 (119.48, 216.50)	134.60 (68.64, 162.20)	3.88±1.17	74.87 (54.06, 125.18)	Moderate group	18	102.80 (70.64, 140.99)	114.25±49.64	3.26±1.09	77.18±39.13
Non-survival group	15	224.55 (135.42, 323.85)	157.92 (122.21, 242.32)	4.51±1.72	84.21 (77.26, 134.44)	Severe group	10	142.84 (127.79, 357.64)	160.88±40.77	4.27±1.11	117.40±58.68
Test value		Z=-1.589	Z=-1.566	t=-1.099	Z=-1.406	Test value		Z=-2.35	t=-2.528	t=-2.337	t=-2.178
p		0.112	0.117	0.282	0.16	p		0.019	0.018	0.027	0.039

Table 3. Comparison of the basic indicators between the survival and nonsurvival groups on day one after ARDS diagnosis, expressed as pg/mL ($\bar{x}\pm s$) or [*M* (Q_L, Q_M)]

Indicator	Survival group (n=13)	Non-survival group (n=15)	Test value	*P*
Age	58.69±18.72	49.60±18.72	t=1.323	0.197
Gender (male/female)	8/5	10/5	χ^2=0.08	1
APACHE II	22.46±4.93	23.27±5.33	t=-0.413	0.683
Procalcitonin (ng/mL)	1.29 (0.13, 5.87)	3.41 (0.64, 8.59)	Z=-1.196	0.232
Hypersensitive 3 C-reactive protein (mg/dL)	10.88 (3.28, 17.53)	7.51 (5.60, 17.75)	Z=-0.31	0.756
White blood cell count (109)	10.10 (7.96, 11.95)	12.00 (9.90, 19.17)	Z=-1.428	0.153
pH	7.43±0.08	7.36±0.11	t=2.112	0.044
Lactic acid (mmol/L)	1.72±0.74	1.83±1.16	t=-0.259	0.798
Albumin (g/L)	26.44±7.55	23.93±5.29	t=1.028	0.313

sis of ARDS [4]. ARDS diagnoses and treatment levels improved since the AECC defined ARDS diagnosis criteria in 1994 [5]; however, the fatality rate is still around 40% [6]. Therefore, early- stage ARDS prediction is an important component in improving patient prognoses and reducing fatality rate.

Researchers showed that pro-inflammatory cytokines can promote systemic inflammatory response, which can play an important role in the pathogenesis and progression of ARDS. The most important pro-inflammatory cytokines that are involved in the disease progression and prognosis of ARDS are TNF-α [7, 8] and IL-1β [8]. Researchers also determined that IL-9 and IL-15 are related to the pathogenesis of ARDS [9]. TNF-α and IL-1β are recognised as the "early-phase reaction cytokines". TNF-α is also recognised as the initiator of the ARDS inflammatory response, which can trigger the early stage inflammatory reaction of ARDS. TNF-α is mainly produced by activated macrophages. TNF-α can directly damage blood vessels by increasing their permeability, activating natural killer cells to release substantial amounts of cytokines, magnifying inflammatory effects, reducing antioxidant generation and increasing oxygen radical generation [11]. TNF-α can also induce nitric oxide synthase and increase nitric oxide generation, resulting in significant amounts of nitric oxide, which can promote septic shock and multiple organ failure [11]. TNF-α can activate neutrophils, inhibit lung alveolar surfactant synthesis, promote the expression of adhesion molecules targeting chemokines and stimulate the generation of other inflammatory mediators to aggravate lung injuries [12].

IL-1β is a pro-inflammatory cytokine that is mainly produced in the activated T-cell nucleus, which participates in macrophage inflammatory reactions. IL-1β can promote the inflammatory cascade reactions in ARDS progression [13], induce the nitric oxide synthase generation [11] and work with cytokines TNF-α, IL-6, and IL-8 to influence biological processes [14, 15]. For example, IL-1β can stimulate the TNF-α generation and increase the expression of adhesion molecules that target chemokines to promote inflammatory cell secretion. This process can also cause neutrophils to accumulate in the pulmonary blood vessels and alveoli to further promote the inflammatory reaction.

IL-9 is mainly produced by mastocytes. It can stimulate Th2 cells, induce Th17 cell activation and act as an anti-inflammatory agent. It is also a critical antiviral immunity moderator [9]. IL-9 levels increase significantly in patients with ARDS that is caused by the flu [9].

Agouridakis P reported that IL-15 is a critical cytokine in the early stage pathogenesis and prognosis of ARDS [16]. IL-15 is mainly produced by mononuclear macrophages and is a multiple-effect cytokine [16] that participates in multiple inflammatory reactions. Its biological activity is similar to IL-2. IL-15 can induce T-cell proliferation, strengthen natural killer cell toxicity, and inhibit TH1 and TH2 [16]. IL-15 can also protect $CD8^+$ T-cells from apoptosis, activate the effector functions of memory $CD8^+$ T cells, and participate in inflammatory reactions [19]. Gómez-Nicola D. *et al.* [20] determined that IL-15 can stimulate macrophages to produce the pro-inflammatory cytokine, TNF-α.

This cytokine promotes the participation of other cytokines, such as IL-1 and IL-6, in inflammatory reactions. Kamei K determined that IL-15 is also a protective cytokine. As a result of these comprehensive cytokine studies, researchers determined that examining cytokine concentrations during patient evaluations, treatments, and prognoses has clinical significance [21].

On day one after ARDS diagnosis, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 were significantly higher than that in the healthy control group ($P < 0.05$). The findings of the current study are consistent with previous reports [9, 16]. The current study also further proved that TNF-α, IL-1β, IL-9 and IL-15 are related to ARDS pathogenesis. According to the 2012 Berlin ARDS definition and based on the basic data obtained on the first day after ARDS diagnosis, the patients were divided into moderate (18 cases) and severe groups (10 cases). A mild group was deleted because of the lowl number of patients in this group. On the first day after ARDS diagnosis, the serum TNF-α levels in the moderate group were significantly lower than that in the severe group ($P < 0.05$). However, IL-1β, IL-9, and IL-15 levels were not significantly different between groups. On day three after ARDS diagnosis, the TNF-α, IL-1β, IL-9 and IL-15 levels in the moderate group were significantly lower than that in the severe group ($P < 0.05$).

ARDS severity was categorised in 2012. No current reports discussed the expression of TNF-α, IL-1β, IL-9, and IL-15 in different severities of ARDS. Patients in the severe group exhibited severe anoxia. Early stage severe anoxia can result in rapid metabolism and reduced immunity. The immune regulatory system can be triggered to secrete significant amounts of inflammatory cytokines, which induce the inflammatory cascade reaction and waterfall effects. TNF-α is the initiator of inflammatory reactions, and IL-1β is an early- stage reaction cytokine. TNF-α can trigger an increase in IL-1β secretion and produce other cytokines. On day three after ARDS diagnosis, the TNF-α, IL-1β, IL-9, and IL-15 levels in the severe group were significantly different from that in the moderate group. The cytokines in the severe group were significantly high, whereas the cytokines in the moderate group were relatively low. These results show that the TNF-α, IL-1β, IL-9, and IL-15 levels in the early stage can reflect the severity of ARDS in patients. Thus, the severity of ARDS can be used to determine patient prognoses.

On day one after ARDS diagnosis, no significant differences were observed between the survival and nonsurvival groups in age, gender, APACHE II score, procalcitonin, hs-CRP, white blood cell count, albumin, or lactic acid. However, the pH value in the nonsurvival group was significantly lower than that in the survival group ($P < 0.05$). Patients in the nonsurvival group exhibited severe anoxia, which resulted in rapid metabolism. Thus, the pH values of these patients were significantly reduced. On day one after ARDS diagnosis, no statistically significant differences were observed in the serum levels of TNF-α, IL-1β, IL-9, and IL-15 between the survival group and the nonsurvival group, which is consistent with previous reports [9, 16, 22]. On day three after ARDS diagnosis, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 in the nonsurvival group were significantly higher than that in the survival group. The findings on TNF-α, IL-1β, and IL-9 were inconsistent with previous reports [9, 22]. However, the findings on IL-15 were consistent with the previous reports [9]. Severe patients, mainly comprise the nonsurvival group. However, some moderate patients have relatively severe anoxia. The body has compensatory responses. Thus, pro-inflammatory responses and anti-inflammatory responses occurred. On day one after ARDS diagnosis, the cytokine differences between the survival and nonsurvival groups were insignificant. When anoxia was not completely resolved, the body was compensated by releasing a large number of inflammatory cytokines and inflammatory mediators. On day three after ARDS diagnosis, the cytokine levels in the nonsurvival group were significantly higher than that in the survival group.

In conclusion, during early stage ARDS, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 were closely related to ARDS severity. Patient fatality elevated when the serum levels of TNF-α, IL-1β, IL-9, and IL-15 were high during the early- stage. Recent studies on TNF-α and IL-1β [23, 24] led to the proposed use of TNF-α and IL-1β as clinical diagnostic biomarkers of ARDS. Therefore, studies on the relationship between cytokines and ARDS are important for future research.

In summary, the serum levels of TNF-α, IL-1β, IL-9, and IL-15 in the early stage are helpful to evaluate the severity of the disease and conduct prognoses in ARDS patients. In the clinical setting, the examination of serum TNF-α, IL-1β, IL-9, and IL-15 levels during the early stage can provide a reference for first-line clinical diagnosis and treatment.

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Disclosure of conflict of interest

None.

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References

[1] Fudala R, Krupa A, Stankowska D, Allen TC, Kurdowska AK. Anti-interleukin-8 autoantibody: interleukin-8 immune complexes in acute lung injury/acute respiratory distress syndrome. Clin Sci (Lond) 2008; 114: 403-412.

[2] Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO. High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med 2013; 368: 795-805.

[3] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307: 2526-2533.

[4] Fazal F, Bijli KM, Murrill M, Leonard A, Minhajuddin M, Anwar KN, Finkelstein JN, Watterson DM, Rahman A. Critical role of non-muscle myosin light chain kinase in thrombin-induced endothelial cell inflammation and lung PMN infiltration. PLoS One 2013; 8: 1-10.

[5] Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149: 818-824.

[6] Takaoka Y, Goto S, Nakano T, Tseng HP, Yang SM, Kawamoto S, Ono K, Chen CL. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) prevents lipopolysaccharide (LPS)-induced, sepsis-related severe acute lung injury in mice. Sci Rep 2014; 4: 5204.

[7] Li H, Qian Z, Li J, Han X, Liu M. Effects of early administration of a novel anticholinergic drug on acute respiratory distress syndrome induced by sepsis. Med Sci Monit 2011; 17: 319-325.

[8] Inoue H, Nakagawa Y, Ikemura M, Usugi E, Nata M. Molecular- biological analysis of acute lung injury (ALI) induced by heat exposure and/or intravenous administration of oleic acid. Leg Med (Tokyo) 2012; 14: 304-308.

[9] Hagau N, Slavcovici A, Gonganau DN, Oltean S, Dirzu DS, Brezoszki ES, Maxim M, Ciuce C, Mlesnite M, Gavrus RL, Laslo C, Hagau R, Petrescu M, Studnicska DM. Clinical aspects and cytokine response in severe H1N1 influenza A virus infection. Crit Care 2010; 4: 203-213.

[10] Liu YD, Liu W, Liu Z. Influence of long-term drinking alcohol on the cytokines in the rats with endogenous and exogenous lung injury. Eur Rev Med Pharmacol Sci 2013; 17: 403-409.

[11] Li H, Qian Z, Li J, Han X, Liu M. Effects of early administration of a novel anticholinergic drug on acute respiratory distress syndrome induced by sepsis. Med Sci Monit 2011; 17: 319-325.

[12] Wilcox P, Milliken C, Bressler B. High-dose tumor necrodsis factor alpha produces an impairment of hamster diaphragm contractility. Attenuation with a prostaglandin inhibitor. Am J Respir Crit Care Med 1996; 153: 1611-1615.

[13] Inoue H, Nakagawa Y, Ikemura M, Usugi E, Nata M. Molecular-biological analysis of acute lung injury (ALI) induced by heat exposure and/or intravenous administration of oleic acid. Leg Med (Tokyo) 2012; 14: 304-308.

[14] Kubo K, Hanaoka M, Yamaguchi S, Hayano T, Hayasaka M, Koizumi T, Fujimoto K, Kobayashi T, Honda T. Cytokines in bronchoalveolar lavage fluid in patients with high altitude pulmonary edema at moderate altitude in Japan. Thorax 1996; 27: 860-873.

[15] Kanangat S, Meduri GU, Tolley EA, Patterson DR, Meduri CU, Pak C, Griffin JP, Bronze MS, Schaberg DR. Effects of cytokines and endotoxin on the intracellular growth of bacteria. Infect Immun 1999; 67: 2834-2840.

[16] Agouridakis P, Kyriakou D, Alexandrakis MG, Perisinakis K, Karkavitsas N, Bouros D. Association between Increased levels of IL-2 and IL-15 and outcome in patients with early acute respiratory distress syndrome. Eur J Clin Invest 2002; 32: 862-867.

[17] Berard M, Brandt K, Bulfone-Paus S, Tough DF. IL-15 promotes the survival of naive and memory phenotype CD8+ T cells. J Immunol 2003; 170: 5018-5026.
[18] Yajima T, Yoshihara K, Nakazato K, Kumabe S, Koyasu S, Sad S, Shen H, Kuwano H, Yoshikai Y. IL-15 regulates CD8+ T cell contraction during primary infection. J Immunol 2006; 176: 507-515.
[19] Liu K, Catalfamo M, Li Y, Henkart PA, Weng NP. IL-15 mimics T cell receptor crosslinking in the induction of cellular proliferation, gene expression, and cytotoxicity in CD8+ memory T cells. Proc Natl Acad Sci U S A 2002; 99: 6192-6197.
[20] Gómez-Nicola D, Valle-Argos B, Pita-Thomas DW, Nieto-Sampedro M. Interleukin 15 expression in the cns: blockade of its activity prevents glial activition after an inflammatory injury. Glia 2008; 56: 494-505.
[21] Kamei K, Yasuda T, Ueda T, Qiang F, Shiozaki H, Ohyanagi H, Takeyama Y. Significant expression of interleukin 15 in rat experimental severe acute pancreatitis. Eur Surg Res 2010; 44: 159-169.
[22] Bauer TT, Montón C, Torres A, Cabello H, Fillela X, Maldonado A, Nicolás JM, Zavala E. Comparison of systemic cytokine levels in patients with acute respiratory distress syndrome, severe pneumonia, and controls. Thorax 2000; 55: 46-52.
[23] Raghavendran K, Davidson BA, Hutson AD, Helinski JD, Nodzo SR, Notter RH, Knight PR. Predictive modeling and inflammatory biomarkers in rats with lung contusion and gastric aspiration. J Trauma 2009; 67: 1182-1190.
[24] Levitt JE, Gould MK, Ware LB, Matthay MA. The pathogenetic and prognostic value of biologic markers in acute lung injury. J Intensive Care Med 2009; 24: 151-167.