EFFECTS OF LEVOSIMENDAN COMBINED WITH ROUTINE THERAPY ON MARKERS FOR CARDIAC FUNCTION, INFLAMMATORY FACTORS, AND APACHE II SCORE IN PATIENTS WITH SEPTIC SHOCK

Tianquan Yin, Yan Liu, Cheng Zhao, Shubin Guo*
Department of Emergency, Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, P.R.China

ABSTRACT

Objective*: The aim of this study was to investigate the effects of levosimendan combined with routine therapy on markers for cardiac function, inflammatory factors, and Acute Physiology And Chronic Health Evaluation II (APACHE II) score in patients with septic shock (SS).*

Methods*: We randomly assigned 118 patients with SS admitted to our hospital to receive levosimendan combined with routine therapy (68 cases, the research group, RG) or to receive routine therapy (50 cases, the control group, CG). The two groups were compared in the markers for cardiac function, the infection indexes, the blood flow capacity, the inflammatory factors, and the APACHE II score before and after treatment. The treatment responses in the two groups were recorded.*

Results*: After treatment, the cardiac index (CI) and left ventricular ejection fraction (LVEF) were higher in RG than in CG ($P < 0.05$), while the left ventricular end-systolic diameter (LVESd) and left ventricular end-diastolic diameter (LVEDd) were lower in RG than in CG ($P < 0.05$). Patients from RG had lower concentrations of N-type brain natriuretic peptide (BNP), troponin I (TnI), hypersensitive C-reactive protein (hs-CRP), and procalcitonin (PCT) than patients from CG after treatment ($P < 0.05$). After treatment, compared to CG, RG had lower heart rate (HR, $P < 0.05$), higher mean arterial pressure (MAP, $P < 0.05$), and lower central venous pressure (CVP, $P < 0.05$). After treatment, RG had markedly lower levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) ($P < 0.05$), and higher interleukin-10 (IL-10) level than CG ($P < 0.05$). The treatment efficacy in RG was superior over that in CG ($P < 0.05$). The APACHE II score was lower in RG than in CG ($P < 0.05$).*

Conclusion*: Levosimendan combined with routine therapy is highly effective in the treatment of SS. It can improve the expression of markers for cardiac function and inflammatory factors in patients, and reduce the APACHE II score, which is worthy of clinical popularization.*

Keywords: *Levosimendan combined with routine therapy, septic shock, markers for cardiac function, inflammatory factors, APACHE II score.*

DOI: 10.19193/0393-6384_2021_4_368

Received *October 15, 2020;* ***Accepted*** *March 20, 2021*

Introduction

Sepsis is a systemic inflammatory response syndrome induced by infections, which has the confirmed presence of bacteria or highly suspected infected focus[1]. The incidence of sepsis is already very high worldwide, what' worse, it is showing an increasing trend[2, 3]. So far, approximately 18 million cases of sepsis have been reported worldwide[4]. Deaths from sepsis are approximately 14,000 each day[5]. The pathogenesis of sepsis is not yet clear.

Studies have pointed out that the morbidity of sepsis may involve complex systemic inflammatory network effects, genetic polymorphisms, immune dysfunction, abnormal blood coagulation, tissue damage, and other multiple body function changes[6, 7]. A full understanding of the pathogenic mechanism of sepsis may be the key to the prevention and treatment of sepsis in the future.

Sepsis is divided into sepsis, severe sepsis, and septic shock (SS) according to is severity, among which SS is the most serious and special one[8].

The mortality of SS is as high as 1/4[9]. The key principles for the treatment of SS in clinical practice mainly include anti-infection, anti-shock, control of blood pressure, and maintenance of the perfusion and basic function of important tissues[10]. With the development of sepsis in recent years, many scholars noted that most SS patients are subject to a certain degree of myocardial injury during the treatment, which impairs the recovery of patients[11]. Therefore, there is an urgent need for an effective intervention in the clinic to reduce myocardial damage in patients with SS. As a novel calcium sensitizer, levosimendan is a positive inotropic drug that can strengthen myocardial contractility and improve the blood flow, showing good efficacy in the treatment of heart failure[12, 13]. The study of Bhattacharjee S et al.[14] revealed that levosimendan has a certain protective effect on cardiac function in patients with sepsis. But the effect of levosimendan in the treatment of SS has been rarely studied.

To investigate whether levosimendan can enhance the protection of myocardial function during the routine treatment of SS, here we analyzed the changes of cardiac function and inflammatory factors during the treatment, aiming to provide reliable reference and guidance for the treatment of SS.

Enrollment of research participants

A prospective analysis was performed on 118 patients with SS treated in our hospital from March 2016 to March 2018. We randomly assigned 118 patients to receive levosimendan combined with routine therapy (68 cases, the research group, RG) or to receive routine therapy (50 cases, the control group, CG). This study was carried out under the approval of the ethics committee of our hospital. We obtained the informed consent of all participants.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with SS by the results of laboratory tests in our hospital; patients with complete medical data; patients in cooperation with the study procedures; patients whose immediate family members signed the informed consent.

Exclusion criteria: Patients with multiple chronic diseases, or drug allergies, mental illness, language communication disorders; patients who transferred to another hospital; patients in pregnancy; patients who died during the treatment.

Methods

Both groups of patients were treated with routine therapy, including early fluid resuscitation, broad-spectrum antibiotics for anti-infection, norepinephrine for maintaining blood pressure, mechanical ventilation, and other supportive treatments. Patients from RG were also treated with an intravenous drip of levosimendan diluted with 5% glucose solution at a priming dose of 12μg/kg for more thanr 10 minutes and then pumping of levosimendan at 0.1μg/(kg · min). The medication lasted for 24 hours. Note: Levosimendan was manufactured by Qilu Pharmaceutical Co., Ltd. (China Food and Drug Administration Approval No. H20100043).

Outcome measures

Cardiac ultrasound at the patient bedside was employed to detect markers for cardiac function before and after treatment, including the left ventricular ejection fraction (LVEF), the left ventricular end-diastolic diameter (LVEDd), the left ventricular end-systolic diameter (LVESd), and the cardiac index (CI). A multifunctional immunoanalyzer was used to detect the troponin I (TnI), the N-type brain natriuretic peptide (BNP), the hypersensitive C-reactive protein (hs-CRP), and the procalcitonin (PCT) before and after treatment in patients. The radial artery blood pressure was monitored to record the heart rate (HR) and the mean arterial pressure (MAP) of patients before and after treatment. A central venous catheter was placed to monitor the central venous pressure (CVP) of patients before and after treatment. Enzyme-linked immunosorbent assay (ELISA) was done to detect the expression of inflammatory factors in patients before and after treatment, including the interleukin-6 (IL-6), the interleukin-10 (IL-10), and the tumor necrosis factor-α (TNF-α). The treatment efficacy was assessed based on the symptoms, vital signs, and serological indicators of patients. The APACHE II score of each patient was evaluated.

Statistical analysis

Statistical analysis was performed on SPSS22.0. Data visualization was performed on Graphpad7. The count data were represented by the percentage (%) and their intergroup comparison was analyzed by the chi-square test. The measurement data were represented by the mean ± standard deviation and their intergroup comparison was analyzed by the

t-test. The difference was statistically significant when $P < 0.05$.

Results

Comparison of basic information

The two groups were not different in age, sex ratio, BMI, living environment, smoking, drinking, ethnicity, and source of infection ($P > 0.05$). More details are shown in Table 1.

	RG (n = 68)	CG (n = 48)	t or c2	P
Age (year)			0.691	0.491
	45.3 ± 6.6	46.2 ± 7.5		
Sex			0.311	0.577
Male	50(73.53)	39 (78.00)		
Female	18 (26.47)	11 (22.00)		
BMI (KG/cm^2)			1.312	0.192
	23.52 ± 3.05	24.46 ± 4.72		
Living environment			0.035	0.851
Urban area	41 (60.29)	31 (62.00)		
Rural area	27 (39.71)	19 (38.00)		
Smoking			0.304	0.582
Yes	52 (76.47)	36 (72.00)		
No	16 (23.53)	14 (28.00)		
Drinking			0.060	0.806
Yes	45 (66.18)	32 (64.00)		
No	23 (33.82)	18 (36.00)		
Ethnicity			0.788	0.375
Han nationality	62 (91.18)	43 (86.00)		
Minority nationality	6 (8.82)	7 (14.00)		
Source of infection			0.094	0.999
Lung				
	30 (44.12)	21 (42.00)		
Abdominal cavity				
	20 (29.41)	15 (30.00)		
Limb necrosis				
	5 (7.35)	4 (8.00)		
Pancreatitis				
	7 (10.29)	5 (10.00)		
Others				
	6 (8.82)	5 (10.00)		

Tab. 1: Basic information of patients.

Comparison of markers for cardiac function

We noted no difference between the two groups in markers for cardiac function before treatment. After treatment, RG had higher LVEF and CI and lower LVEDd and LVESd than CG (all $P < 0.05$). More details are shown in Figure 1.

Comparison of markers for infection

There was no difference in TnI, BNP, hs-CRP, and PCT between the two groups before treatment ($P > 0.05$). After treatment, the concentrations of TnI, BNP, hs-CRP, and PCT declined in both groups ($P < 0.05$), with markedly lower concentrations of TnI, BNP, hs-CRP, and PCT in RG than in CG ($P < 0.05$). More details are shown in Figure 2.

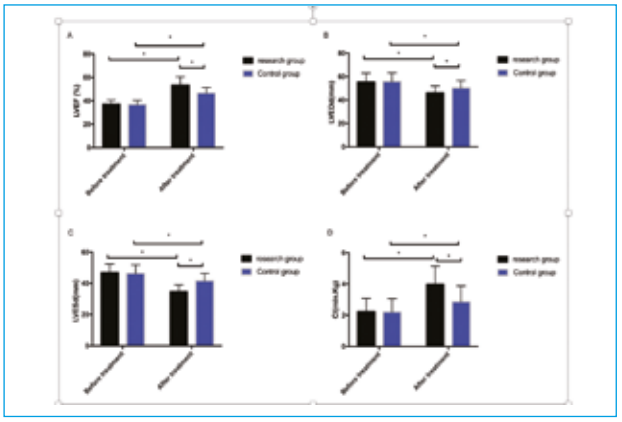

Fig. 1: Markers for cardiac function in the two groups. ***A***. *LVEF level before and after treatment*. ***B***. *LVEDd level before and after treatment*. ***C***. *LVESd level before and after treatment*. ***D***. *CI level before and after treatment*.

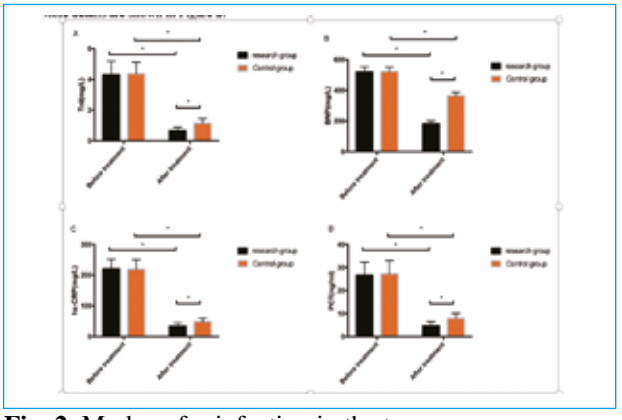

Fig. 2: Markers for infection in the two groups. ***A***. *Tnl level before and after treatment*. ***B***. *BNP level before and after treatment*. ***C***. *Hs-CRP level before and after treatment*. ***D***. *PCT level before and after treatment*.

Comparison of markers for blood flow

We noted no difference between the two groups in HR, MAP, and CVP before treatment ($P > 0.05$). After treatment, compared to CG, RG had lower HR ($P < 0.05$), higher MAP ($P < 0.05$), and lower CVP ($P < 0.05$). More details are shown in Figure 3.

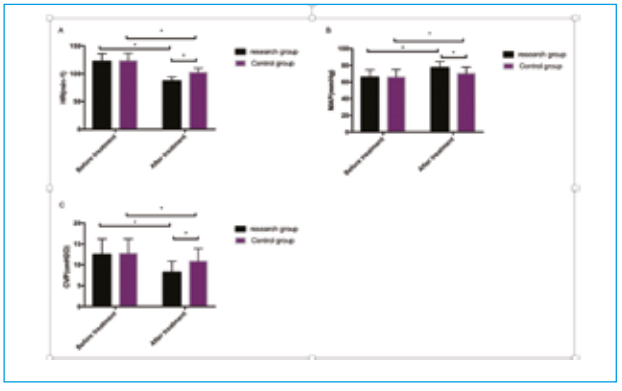

Fig. 3: Markers for blood flow in the two groups. ***A***. *HR level before and after treatment*. ***B***. *MAP level before and after treatment*. ***C***. *CVP level before and after treatment*.

Comparison of levels of inflammatary indicators in patients

We noted no difference between the two groups in levels of TNF-α, IL-6, and IL-10 before treatment (P > 0.05). After treatment, RG had remarkably lower IL-6 and TNF-α levels and higher IL-10 level than CG (all P < 0.05), More details are shown in Figure 4.

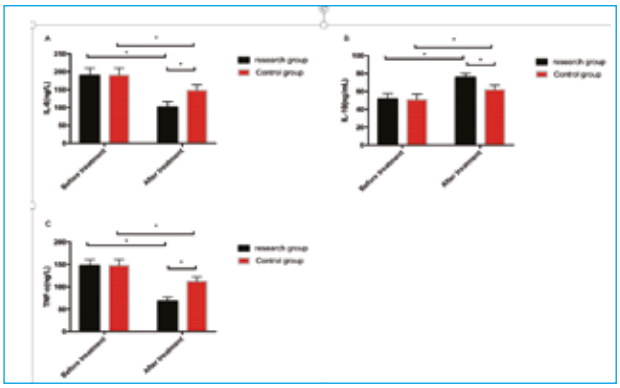

Fig. 4: Inflammatary indicators in the two groups. ***A***. *IL-6 level before and after treatment*. ***B***. *IL-10 level before and after treatment*. ***C***. *TNF-α level before and after treatment*.

Comparison of clinical efficacy

The overall response rate was markedly higher in RG than in CG (89.71% vs. 74.00%, P < 0.05). More details are shown in Table 2.

	RG (n = 68)	CG (n = 50)	X2	P
Marked response	33 (48.53)	18 (36.00)		
Moderate response	28 (41.18)	19 (38.00)		
No response	7 (10.29)	13 (26.00)		
Overall response rate (%)	61 (89.71)	37 (74.00)	5.049	0.025

Tab. 2: Treatment responses in the two groups.

Comparison of the APACHE II score

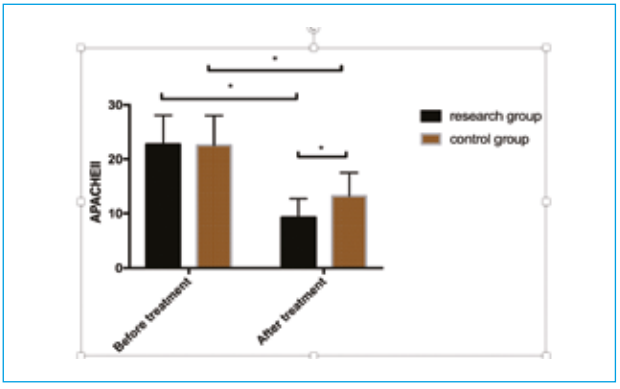

Fig. 5: The APACHE II score in the two groups.

We noted no difference between the two groups in the APACHE II score before treatment (P > 0.05). After treatment, the APACHE II score decreased in both groups, with a lower APACHE II score in RG than in CG (P < 0.05). More details are shown in Figure 5.

Discussion

The life-threatening SS is mostly secondary to serious infections, with rapid onset and severe conditions[15]. SS, if not interfered in time, can remarkably stimulate the production of inflammatory mediators that damage functions of the liver, lung, and other organs and reduce the quality of life of patients, leading to high mortality[16]. Patients with SS are prone to calcium imbalance in myocardial cells due to the loss of blood volume and then subjected to myocardial suppression and myocardial cell damage, which induce heart failure and increase the clinical mortality[17]. Levosimendan is a novel positive inotropic drug that can effectively enhance myocardial contractility and improve blood flow[18]. Here we made this study to better understand the effect of levosimendan on patients with SS.

In this study, the LVEF and CI were higher in RG than in CG after treatment, and the LVEDd and LVESd were lower in RG, suggesting that levosimendan combined with routine therapy can boost the myocardial contractility and improve the cardiac function of patients. LVEF, the percentage of stroke volume to the end-diastolic volume of the ventricle, is affected by the myocardial contractility (higher myocardial contractility leads to higher stroke volume and higher ejection fraction)[19]. CI refers to the value obtained by dividing the volume of blood pumped from the heart (liters/minute) by the body surface area square meters[20]. LVEDd and LVESd are predominant cardiac indicators detected by the color Doppler ultrasound. Levosimendan, a novel calcium sensitizer used for treating heart failure, can change the transmission of calcium-binding information and directly bind to troponin to stabilize the spatial configuration of myocardial fiber proteins necessary for calcium-induced myocardial contraction, thereby enhancing the myocardial contractility and dilating blood vessels[21].

The study by Buzzini R F[22] showed that levosimendan has satisfying efficacy in treating compensatory congestive heart failure, which is similar to our results and supports our findings. In our speculation, levosimendan is superior over conventional drugs because it can boost the sensitivity of myocardial contractile protein to Ca2+, inhibit the activity of myocardial phosphodiesterase, and exert

a positive inotropic effect. According to the detection results, the concentrations of TnI, BNP, hs-CRP, and PCT decreased in both groups after treatment, with lower concentrations of TnI, BNP, hs-CRP, and PCT in RG than in CG. BNP and TnI are commonly used clinical markers for myocardial injury. Hs-CRP is a non-specific acute-phase reaction protein synthesized by the liver, which, if reaches a certain value, may indicate the possibility of bacterial infection[23]. PCT is a protein whose concentration in plasma increases in cases of severe bacterial, fungal, and parasitic infections, as well as in cases of sepsis and multiple organ failure. The increase in PCT levels occurs in patients with severe shock, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome[24]. The detection results of markers for infection suggest that levosimendan combined with routine therapy can effectively reduce the myocardial loss and relieve left ventricular insufficiency of patients, which indicate that levosimendan can help improve the cardiac function of patients with SS and reduce myocardial damage. In this study, RG had lower HR and CVP and higher MAP than CG after treatment, suggesting that levosimendan combined with routine therapy can help to stabilize early blood flow and enhance the treatment efficacy.

The study by Ferreri C[25] which studied the role of levosimendan infusion in improving the renal function of patients with type II cardio-renal syndrome proposed that levosimendan is effective in improving the blood flow. Such results support the results of this study and confirm the safety and superior efficacy of levosimendan in the treatment of SS. Inflammatory mediators promote the progression of SS, which can cause or aggravate the failure or disorder of the lungs and other organs. IL-6 is an initial factor that can induce the synthesis and secretion of a variety of acute-phase proteins, thereby promoting the progression of inflammation[26]. TNF-α is an essential factor in initiating the inflammatory response, which can stimulate the aggregation of neutrophils and damage tissue cells[27]. IL-10 is a multi-cellular, multi-functional cytokine recognized as an inflammatory and immunosuppressive factor (28). In this study, RG had markedly lower IL-6 and TNF-α levels and higher IL-10 level than CG after treatment. Such results suggest that levosimendan combined with routine therapy can remarkably relieve the damage of myocardium and vascular endothelial tissue in patients, thereby reducing the inflammatory response and preventing excessive immune and inflammation progression. We assessed the treatment efficacy based on the symptoms, vital signs, and serological indicators of patients and evaluated the APACHE II score of each patient. The results showed that RG had markedly superior efficacy and lower APACHE II score than CG, indicating that levosimendan can enhance the efficacy of routine therapy in patients with SS and relieve disease conditions.

Here we explored the application value of levosimendan combined with routine therapy for treating SS, but there are still deficiencies due to the limited experimental conditions. For example, the study period was too short to follow up on the long-term prognosis of patients. There are many drugs against SS in the clinic. Here we assigned patients in CG to receive routine therapy only, but did not compare between levosimendan and other drugs. So we should make an in-depth analysis of this. Besides, we will expand the research sample size and extend the experimental period, and analyze the results in a more detailed and comprehensive way to refine this study.

In summary, levosimendan combined with routine therapy is highly effective in the treatment of SS. It can improve the expression of markers for cardiac function and inflammatory factors in patients, and reduce the APACHE II score, which is worthy of clinical popularization.

References

1) Rhodes A, Evans L E, Alhazzani W. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016[J]. Intensive care medicine, 2017, 43(3): 304-377.
2) Shane A L, Sánchez P J, Stoll B J. Neonatal sepsis[J]. The Lancet, 2017, 390(10104): 1770-1780.
3) Kiani M E. Sepsis monitor: U.S. Patent 10,226,576[P]. 2019-3-12.
4) Levy M M, Evans L E, Rhodes A. The surviving sepsis campaign bundle: 2018 update[J]. Intensive care medicine, 2018, 44(6): 925-928.
5) van der Poll T, van de Veerdonk F L, Scicluna B P. The immunopathology of sepsis and potential therapeutic targets[J]. Nature Reviews Immunology, 2017, 17(7): 407.
6) Meyer N, Harhay M O, Small D S. Temporal trends in incidence, sepsis-related mortality, and hospital-based acute care after sepsis[J]. Critical care medicine, 2018, 46(3): 354.
7) Levi M, van der Poll T. Coagulation and sepsis[J]. Thrombosis research, 2017, 149: 38-44.
8) Agyeman P K A, Schlapbach L J, Giannoni E. Epidemiology of blood culture-proven bacterial sepsis

in children in Switzerland: a population-based cohort study[J]. The lancet child & adolescent health, 2017, 1(2): 124-133.
9) Prescott H C, Angus D C. Enhancing recovery from sepsis: a review[J]. Jama, 2018, 319(1): 62-75.
10) Howell M D, Davis A M. Management of sepsis and septic shock[J]. Jama, 2017, 317(8): 847-848.
11) Seymour C W, Gesten F, Prescott H C. Time to treatment and mortality during mandated emergency care for sepsis[J]. New England Journal of Medicine, 2017, 376(23): 2235-2244.
12) Zhang H, Zhang G, Jie L I. The effects of levosimendan on prognosis and circulatory function of sepsis patients: a Meta-analysis[J]. Chinese Journal of Integrated Traditional and Western Medicine in Intensive and Critical Care, 2018, 25(2): 120-126.
13) Chang W, Xie J F, Xu J Y. Effect of levosimendan on mortality in severe sepsis and septic shock: a meta-analysis of randomised trials[J]. BMJ open, 2018, 8(3): e019338.
14) Bhattacharjee S, Soni K D, Maitra S. Levosimendan does not provide mortality benefit over dobutamine in adult patients with septic shock: A meta-analysis of randomized controlled trials[J]. Journal of clinical anesthesia, 2017, 39: 67-72.
15) Gómez H, Kellum J A. Sepsis-induced acute kidney injury[M]//Critical Care Nephrology. Content Repository Only!, 2019: 524-533. e3.
16) Chousterman B G, Swirski F K, Weber G F. Cytokine storm and sepsis disease pathogenesis[C]//Seminars in immunopathology. Springer Berlin Heidelberg, 2017, 39(5): 517-528.
17) Sinha M, Jupe J, Mack H. Emerging technologies for molecular diagnosis of sepsis[J]. Clinical microbiology reviews, 2018, 31(2): e00089-17.
18) Sikora J, Pstr'gowski K, Skibirka N. Impact of levosimendan on platelet function[J]. Thrombosis research, 2017, 159: 76-81.
19) Meléndez G C, Sukpraphrute B, D'Agostino Jr R B. Frequency of left ventricular end-diastolic volume–mediated declines in ejection fraction in patients receiving potentially cardiotoxic cancer treatment[J]. The American journal of cardiology, 2017, 119(10): 1637-1642.
20) Jefferson A L, Liu D, Gupta D K. Lower cardiac index levels relate to lower cerebral blood flow in older adults[J]. Neurology, 2017, 89(23): 2327-2334.
21) Wang W, Zhou X, Liao X. The efficacy and safety of prophylactic use of levosimendan on patients undergoing coronary artery bypass graft: a systematic review and meta-analysis[J]. Journal of anesthesia, 2019: 1-8.
22) Buzzini R F, Silvinato A, Floriano I. Decompensated congestive heart failure-treatment with levosimendan[J]. Revista da Associação Médica Brasileira, 2019, 65(4): 524-529.
23) Li Y, Zhong X, Cheng G. Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: a meta-analysis[J]. Atherosclerosis, 2017, 259: 75-82.
24) Huang D T, Yealy D M, Filbin M R. Procalcitonin-guided use of antibiotics for lower respiratory tract infection[J]. New England Journal of Medicine, 2018, 379(3): 236-249.
25) Ferreri C, Testa M, Feola M. The Role of Levosimendan Infusion in Improving Renal Function in Worsening Type II Cardio-Renal Syndrome[J]. International Journal of Biomedical Science, 2018, 14: 78-84.
26) Johnson D E, O'Keefe R A, Grandis J R. Targeting the IL-6/JAK/STAT3 signalling axis in cancer[J]. Nature reviews Clinical oncology, 2018, 15(4): 234.
27) Mitoma H, Horiuchi T, Tsukamoto H. Molecular mechanisms of action of anti-TNF-α agents–Comparison among therapeutic TNF-α antagonists[J]. Cytokine, 2018, 101: 56-63.
28) Ip W K E, Hoshi N, Shouval D S. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages[J]. Science, 2017, 356(6337): 513-519.

Corresponding Author:
Shubin Guo
Department of Emergency, Beijing Chao-Yang Hospital ,Capital Medical University, No.8 Gongti South Road, Chaoyang District, Beijing 100020, P.R.China
Email: 158750047@qq.com
(China)