Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

Mortality of severe septic patients between physician's high and low care volumes

Chun-Yao Lin [a], *Jo-Chi Tseng* [a,b], *Chih-Yu Huang* [a], *Chien-Ming Chu* [a], *Huang-Pin Wu* [a,b,*]

[a] *Division of Pulmonary, Critical Care and Sleep Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan*
[b] *Chang Gung University College of Medicine, Taoyuan, Taiwan*

ARTICLE INFO

Article history:
Received 10 April 2016
Accepted 14 June 2017
Available online 27 July 2017

Keywords:
Mortality
Severe sepsis
Intensive care unit
Physician's care volume

ABSTRACT

Background: Patients with severe sepsis frequently require intensive care unit (ICU) admission and different ICU care models may influence their outcomes. The mortality of severe septic patients between physician's high and low care volume remains unclear.
Methods: We analyzed the data from a three-year prospective observation study, which was performed in an adult medical ICU of Chung Gung Memorial Hospital, Keelung. The data included initial bundle therapies based on the Surviving Sepsis Campaign (SSC) guidelines for patients with severe sepsis.
Results: Clinical data of total 484 patients with severe sepsis were recorded. Cox regression model showed that physician's care volume was an independent factor for lowering mortality in ICU patients with severe sepsis (hazard ratio 0.708; 95% confidence interval 0.514–0.974; $p = 0.034$). Patients treated by high care volume physician had four out of nine bundle therapies that were significantly higher in percentage following the SSC guidelines. These four therapies were renal replacement therapy, administration of low-dose steroids for septic shock, prophylaxis of gastro-intestinal bleeding, and control of hyperglycemia.
Conclusion: High care volume physician may decrease mortality in ICU patients with severe sepsis through fitting bundle therapies for sepsis.

Severe sepsis or septic shock are a lethal critical illness resulting in multiple organ dysfunction and high overall hospital mortality rate of 17.9–50.0% in different populations [1,2]. The complicated physical states in patients with severe sepsis frequently require intensive and critical care, which leads to high intensive care unit (ICU) admissions [3]. Such patients remain a major challenge in modern medicine. The "Surviving Sepsis Campaign (SSC)" guidelines provide evidence-based recommendations for managing patients with sepsis and improving their outcomes [4,5]. But while better medical treatment can alter a patient's outcome, more extensive considerations should not only focus on medical treatment. An ever-increasing number of discussions about ICU care models and physician staffing has also been mentioned.

A study by Reynolds et al. concluded that critical care medicine (CCM) physicians may decrease mortality of ICU patients with septic shock [6]. A study by Brown et al. had similar results, showing that a full-time, trained critical care

* *Corresponding author*. Division of Pulmonary, Critical Care and Sleep Medicine, Chang Gung Memorial Hospital, 222 Maijin Rd., Anle Chiu, Keelung, 20401, Taiwan.
E-mail address: whanpyng@cgmh.org.tw (H.-P. Wu).
Peer review under responsibility of Chang Gung University.
http://dx.doi.org/10.1016/j.bj.2017.06.005

At a glance commentary

Scientific background on the subject

The ICU physician care volume may affect ICU pneumonia patient's mortality. The difference between physician's high and low care volume may also impact on the outcome of ICU severe septic patients.

What this study adds to the field

We proved that ICU care by high care volume physicians may be better than that by low care volume physicians in patients with severe sepsis. The benefit provided by high care volume may relate to higher complete rate of bundle therapy.

specialist may reduce ICU morbidity and mortality [7]. A systemic review demonstrated that high intensity ICU physician staffing is associated with a reduction in ICU mortality and length of stay [8]. In their study, the high intensity care group was mandatory intensivist consultation, or all-care directed by the intensivist. Now, it is generally accepted that the care model managed by a trained CCM physician leading a multi-disciplinary team improves the outcome of ICU patients [9].

Most medical ICUs in Taiwan are staffed with full-time CCM physicians to be qualified by hospital accreditation. However, these CCM physicians may not be permanently located in ICU to be an ICU physician. In Taiwan, a pulmonologist is trained to not only be a pulmonary specialist but also a CCM specialist. The pulmonologist can join the ICU team to be a full-time CCM physician, also called an intensivist, or simply manage patients with pulmonary disease in the wards. Therefore, patients may be treated by high ICU care volume physician with more experience in critical care or by low ICU care volume physician with less experience in critical care. From a analysis of Taiwan's National Health Insurance, physician's care volume significantly predicted inpatient mortality in ICU pneumonia patients [10]. Since the ICU physician care volume may affect ICU pneumonia patient's mortality, the difference between physician's high and low care volume may also impact on the outcome of ICU severe septic patients. We analyzed the data from a three-year prospective observation study to examine whether physicians with higher care volume offer ICU severe septic patients better outcomes.

Materials and methods

Subjects

From July 2007 to June 2010, we carried out an observational research program "analyzing the key treatments to increase the survival of the patients with severe sepsis". This study enrolled patients with severe sepsis who were admitted to the medical ICU of Chang Gung Memorial Hospital-Keelung (CGMH-Keelung) during the three years. Severe sepsis was defined as sepsis with organ dysfunction, hypo-perfusion, or hypotension [11]. The medical ICU at CGMH-Keelung is a 10-bed closed unit staffed with a full-time ICU physician who is a qualified pulmonary and CCM specialist. Eight physicians rotated in ICU care monthly during the three years when this full-time ICU physician was off or rotated to the general ward. If a patient was admitted to one physician and cared by another physician later, this patient was classified to the physician who cared these patients for more time during the first 3 days of admission. Repeated admission to ICU was set as a new admission and that subject had the same age, gender and medical history. High and low care volumes are defined according to Lin's study from a analysis of Taiwan's National Health Insurance [10].

This study recorded the following clinical data: age, gender, medical history, infection source, Acute Physiology and Chronic Health Evaluation (APACHE) II score, co-morbidity, and treatments in the first three days of ICU admission. The recorded treatments were the standard bundle therapies used to manage sepsis according to SSC guidelines [4]. These bundle therapies included fluid resuscitation (normal saline or hydroxyethyl starch), broad spectrum antibiotics, use of low-dose steroids in septic shock, use of activated protein C (APC), adequate blood transfusion, sedation/paralysis, blood glucose control, renal replacement therapy as needed, stress ulcer prophylaxis, and basic support. Fluid resuscitation was administered with either crystalloid or colloid infusion to maintain central venous pressure between 8 and 12 mmHg. APC was given for septic patients with an APACHE II score >25 and without contraindications. An adequate hemoglobin maintenance was red blood cell (RBC) transfusion for hemoglobin <7.0 mg/dl to target 7.0–9.0 mg/dl. All of the treatments were based on the ICU patient's condition and physician's decision without any intervention by data collectors. Survivors were defined as the patients alive after 28 days of ICU admission. The data collected from this observational study were divided into fixed and rotated groups to compare the survival of these two different ICU care strategies. Because this research program was an observational study without any intervention and

Table 1 Physician characteristics and care volume in 3 years.

	Patients	Age	Years out of training	Number of weekly outpatient service in the ICU month
Physician 1	18	47	16	3
Physician 2	31	50	16	3
Physician 3	42	46	14	3
Physician 4	38	50	9	3
Physician 5	32	41	7	3
Physician 6	298	40	6	3
Physician 7	13	35	5	3
Physician 8	12	36	4	3

Abbreviation: ICU: intensive care unit.

Table 2 Clinical characteristics (number [percentage] and mean ± standard error mean) between survivors and non-survivors with severe sepsis.

	Survivors (n = 320)	Non-survivors (n = 164)
Gender		
Male	200 (62.5)	100 (61.0)
Female	120 (37.5)	64 (39.0)
Age, year	73.93 ± 0.80	71.01 ± 1.12[a]
History		
Chronic obstructive pulmonary disease	62 (19.4)	27 (16.5)
Heart failure	37 (11.6)	12 (7.3)
Hypertension	160 (50.0)	52 (31.7)[a]
Liver cirrhosis	19 (5.9)	24 (14.6)[a]
Diabetes mellitus	113 (35.3)	43 (26.2)[a]
End stage renal disease	32 (10.0)	21 (12.8)
Old cerebral vascular accident	108 (33.8)	22 (13.4)[a]
APACHE II score	24.07 ± 0.41	29.96 ± 0.63[a]
Source of sepsis		
Pneumonia	251 (78.4)	128 (78.0)
Urinary tract infection	37 (11.6)	9 (5.5)
Others	32 (10.0)	27 (16.5)
Co-morbidity		
Shock	96 (30.0)	119 (72.6)[a]
Respiratory failure	283 (88.4)	156 (95.1)[a]
Acute renal failure	117 (36.6)	90 (54.9)[a]
Jaundice	20 (6.3)	26 (15.9)[a]
Thrombocytopenia	80 (25.0)	93 (56.7)[a]
Gastrointestinal bleeding	34 (10.6)	41 (25.0)[a]
Bacteremia	37 (11.6)	32 (19.5)[a]
Physician's care volume		
High	199 (62.2)	99 (60.4)
Low	121 (37.8)	65 (39.6)

Abbreviation: APACHE: acute physiology and chronic health evaluation.

[a] $p < 0.05$ compared with fixed strategy by T-test or Chi-square test.

patient's identification, the hospital's Institutional Review Board at Chang Gung Memorial Hospital (IRB/CGMH, No. 98-1682C) approved this study without need of informed consent from the patients or the patient's family.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) V11.0.1 for Windows (SPSS Inc., Chicago, USA). Differences in continuous variables between the two groups were analyzed by the T-test while those in categorical variables were compared using the Chi–Square test, as appropriate. Univariate and multivariate Cox proportional-hazards model was performed using methods of enter and forward stepwise to compare survival with histories, APACHE II score, co-morbidities, and physician's care volume. Survival curves after adjustment were constructed. A p value <0.05 was considered statistically significant.

Results

Information of physicians was shown in Table 1. The clinical characteristics of patients with severe sepsis were shown in Table 2. During the 3 years, physician 6 cared 298 severe septic patients and the other 186 patients were cared by other 7 physicians. Between survivors and non-survivors, there were no significant differences in gender, sources of sepsis, and physician's care volume. However, non-survivors had higher APACHE II scores and higher percentages of liver cirrhosis and co-morbidities. Non-survivors had lower age and lower percentages of hypertension, diabetes mellitus, and old cerebral vascular accident (CVA).

Results of the Cox regression analysis to determine independent factors for patient mortality were shown in Table 3. High physician's care volume and old CVA were independent factors related to decreased mortality. Shock, respiratory failure, thrombocytopenia, and gastrointestinal (GI) bleeding were independent factor increasing the risk of the mortality. Age, hypertension, liver cirrhosis, diabetes mellitus, APACHE II score, acute renal failure, jaundice and bacteremia were not independent factors affecting mortality.

Bundle therapy information on sepsis between high and low care volume groups was shown in Table 4. There was no

Table 3 Univariate and multivariate Cox regression analysis to determine independent factors of patient's mortality.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	0.997	0.986–1.008	0.599			
Hypertension	0.766	0.541–1.086	0.135			
Liver cirrhosis	0.948	0.562–1.600	0.841			
Diabetes mellitus	0.823	0.571–1.186	0.295			
Old CVA	0.539	0.336–0.864	0.010	0.478	0.302–0.756	0.002
APACHE II score	1.052	1.030–1.075	<0.001			
Shock	3.004	2.065–4.370	<0.001	3.859	2.716–5.483	<0.001
Respiratory failure	1.792	0.859–3.738	0.120	2.747	1.344–5.612	0.006
Acute renal failure	1.148	0.822–1.604	0.418			
Jaundice	1.262	0.764–2.084	0.363			
Thrombocytopenia	1.835	1.301–2.590	0.001	2.085	1.514–2.872	<0.001
Gastrointestinal bleeding	1.532	1.058–2.219	0.024	1.671	1.163–2.399	0.005
Bacteremia	0.816	0.538–1.237	0.339			
High physician's care volume	0.627	0.448–0.878	0.007	0.708	0.514–0.974	0.034

Abbreviations: HR: Hazard ratio; CI: Confidence interval; CVA: cerebral vascular accident; APACHE: Acute Physiology and Chronic Health Evaluation.

significant difference in fluid resuscitation, efficacy of antibiotics treatment, patient sedation, and use of APC. Seventy-six patients in low volume group and 138 in high volume group had septic shock. There was an 88% administration of low-dose steroid for septic shock in high care volume group, which was significantly higher than the 68.4% administration in low volume group. There was also a significantly higher percentage of adequate blood transfusion strategy in low care volume group than that in high care volume group (96.2% vs. 89.6%).

There were 181 patients and 293 patients who needed hyperglycemic control in the low and high care volume groups, respectively. Compared with low care volume group, higher percentage of patients with hyperglycemia was in less than 200 mg/dl in high care volume group. There were 73 patients cared for by low care volume physicians who developed acute renal failure within the first three days of ICU admission. Fifteen of them (20.5%) received renal replacement therapy either by hemodialysis or continuous veno-venous hemodialysis (CVVHD). In high care volume group, there was a higher percentage (38.9%) of receiving renal replacement therapy in the initial three days of ICU admission in acute renal failure patients (n = 126). Regarding GI bleeding prophylaxis, only 4% (12 in 298 patients) in high care volume group did not receive treatment, whereas 26.9% of patients in low care volume group did not receive any form of treatment.

Fig. 1 showed the 28-day survival curves of the ICU patients with severe sepsis between high and low care volume groups if other variables were not included in the model. The survival curve of low care volume group was lower than that of high care volume group (hazard ratio 0.709; 95% confidence interval 0.511–0.983; $p = 0.039$).

Table 4 Bundle therapies in patients with high and low care volume.

Variable	High	Low	p value
Fluid resuscitation on the day of ICU admission, ml[a]	1658.36	1839.05	0.18
Initial antibiotics treatment, no./total no. (%)			0.389
Culture sensitive	138/298 (46.3)	83/186 (44.6)	
Culture resistant	91/298 (30.5)	67/186 (36.0)	
Clinical improve	69/298 (23.2)	36/186 (19.4)	
Use of low dose steroid in septic shock, no./total no. (%)			<0.001
Use	122/138 (88.4)	52/76 (68.4)	
No use	16/138 (11.6)	24/76 (31.6)	
APC use in APACHE II ≥ 25, no./total no. (%)			0.06
Use	2/179 (1.1)	4/82 (4.9)	
No use	177/179 (98.9)	78/82 (95.1)	
Adequate maintenance of hematocrit/hemoglobin, no./total no. (%)			0.008
Yes	267/298 (89.6)	179/186 (96.2)	
No	31/298 (10.4)	7/186 (3.8)	
Sedation, no./total no. (%)			0.341
Use	72/298 (24.2)	38/186 (20.4)	
No use	226/298 (75.8)	148/186 (79.6)	
Glucose control in patients with available data, no./total no. (%)			0.016
<150 mg/dl	100/293 (34.1)	46/181 (25.4)	
150–200 mg/dl	130/293 (44.4)	76/181 (42.0)	
>200 mg/dl	63/293 (21.5)	59/181 (32.6)	
Renal replacement therapy in acute renal failure, no./total no. (%)			0.028
HD	16/126 (12.7)	5/73 (6.8)	
CVVHD	33/126 (26.2)	10/73 (13.7)	
No use	77/126 (61.1)	58/73 (79.5)	
Prophylactic treatment for GI bleeding, no./total no. (%)			<0.001
PPI	93/298 (31.2)	65/186 (34.9)	
H2 blocker	20/298 (6.7)	47/186 (25.3)	
Sucralfate	9/298 (3.0)	0/186 (0)	
MgO	164/298 (55.1)	24/186 (12.9)	
No use	12/298 (4.0)	50/186 (26.9)	

Abbreviations: APC: activated protein C; APACHE: acute physiology and chronic health evaluation; HD: hemodialysis; CVVHD: continuous veno-venous hemodialysis; GI bleeding: gastrointestinal bleeding; PPI: proton pump inhibitor; H2 blocker: histamine 2 blocker; MgO: magnesium oxide.

[a] Data are shown as mean.

Discussion

The present study reveals that ICU care by high care volume physicians is an independent factor lowering mortality of sepsis patients in an adult medical ICU. Although the high or low care volume physicians are all trained specialists in pulmonary and critical care medicine, a care strategy utilizing high care volume physicians seem to be better for patients with severe sepsis. Two major reasons may explain this finding.

First, high care volume physicians have a higher experience of ICU patients compared to low care volume physicians. A study reported by Durairaj et al. revealed that the risks of mortality among ICU patients with GI diagnosis or critical respiratory disease are lower in high-volume hospitals, relative to low-volume hospitals. They concluded that ICU volume was associated with mortality of patients with certain diagnoses [12]. In terms of physician's volume, Lin et al. reported that ICU physician's care volume could predict the mortality of ICU patients with pneumonia [10]. Their study brought out a "practice makes perfect" hypothesis, which suggested high-volume physicians had accumulated experience to manage different complicated diseases and perform more effectively in clinical practice. However, Lin's study has a limitation that their work is not prospective. Data in our work strongly supports this hypothesis by a prospective observational study.

Second, there are some differences in bundle therapies for sepsis between high and low care volume groups. The SSC guidelines point out that adequate initial management of sepsis and septic shock are important to improve patient outcome [5]. Most initial managements for sepsis and septic shock are based on these evidence-based guidelines. There were a total of 9 therapies with observed differences in initial managements of sepsis between high and low care volume groups. Overall, high care volume physicians performed four therapies with a higher percentage of patients managed following the SSC guidelines. These four therapies were renal replacement therapy, administration of low-dose steroids for septic shock, prophylaxis of upper GI bleeding, and control of hyperglycemia. High care volume physicians performed these therapies more actively and extensively. In contrast, low care volume physicians only had one therapy that complied more with the guidelines: adequate RBC transfusion.

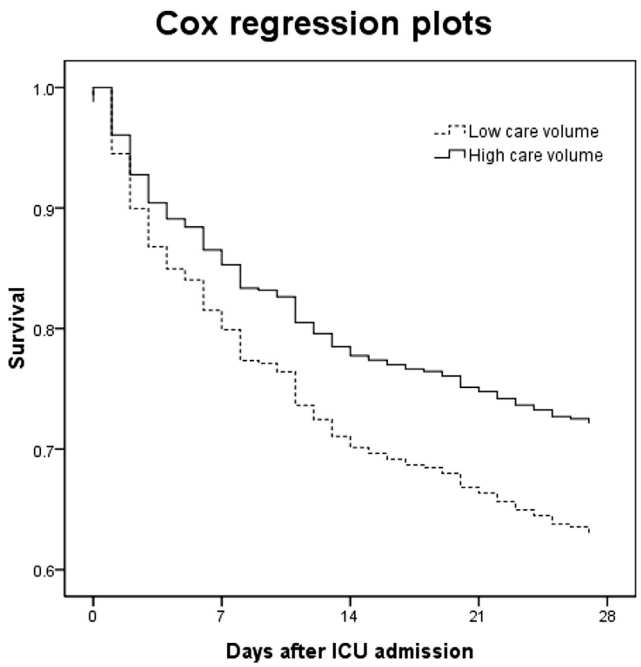

Fig. 1 The 28-day survival curves of ICU patients with sepsis between high and low care volume of physicians were drawn if other variables were not included in the model. The 28-day survival curve of the low care volume group is lower than that of the high care volume group. Solid and dotted lines represented the survival curve of high and low care volume of physicians, respectively (hazard ratio 0.709; 95% confidence interval 0.511–0.983; $p = 0.039$).

Townsend et al. reviewed several observational trials which suggested that better compliance of SSC guidelines might reduce mortality caused by sepsis and septic shock [13,14]. The SSC had reported similar results wherein a reduction of mortality in patients with severe sepsis was associated with participation and compliance of SSC guidelines [15]. This study supported that lower mortality in high care volume group may be due to better compliance to the SSC guidelines.

Regarding RBC transfusion therapy, it is noted that low care volume physicians performed more of this in the present study. Unfortunately, such better practice does not seem to lower the risk of mortality in low care volume group. Although SSC guidelines suggest adequate RBC maintenance for some specific patients with sepsis, Parsons et al. reported that RBC transfusion had no independent association with mortality in patients with sepsis and septic shock [16]. A systemic review of 45 studies by Marik et al. further reported an opposite conclusion [17]. In their review, RBC transfusion was associated with increased mortality in ICU patients. A more aggressive RBC transfusion also had no influence in patient mortality in this study. Thus, the effect of RBC transfusion in patients with sepsis still requires further evaluation.

This study was performed by analyzing the data of previously prospective observation, some limitations should be addressed. First, initial therapies for severe sepsis were not required to follow the SSC guidelines. All of the ICU physicians made clinical practices by their own decisions. Variations in managements for sepsis might result in different compliances to the guideline. If there was a strong consensus of the SCC guidelines for all physicians during the data collection, compliance between high and low care volume groups may not differ and affect the results. Second, only one physician was in high care volume group. Compliance to the guidelines might reflect this individual physician's personal compliance instead of high care volume effect. This bias in care by the single physician might also affect the results. High care volume was a concept that was opposite to low care volume. It is unclear that how many patients cared in an ICU can be considered "high enough" and how low care volume cared in physicians would affect mortality. Many issues remain uncertain and need further evaluation. Despite these limitations, the findings here still provide some suggestions of establishing an ICU care strategy of high care volume physicians.

Conclusions

Adequate staffing of ICU physicians and an appropriate care strategy improve care quality and reduce mortality. ICU care by high care volume physicians may be better than that by low care volume physicians in patients with severe sepsis. The benefit provided by high care volume may relate to higher complete rate of bundle therapy.

Funding

We confirm that no author has any financial or personal relationships with other organizations that could inappropriately influence this work.

Conflicts of interest

All authors declared that they have no competing interests.

Acknowledgements

The authors would like to thank all of the members of the medical intensive care unit for their clinical assistance and cooperation.

REFERENCES

[1] Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003;348:1546–54.
[2] Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014;5:4–11.
[3] Karlsson S, Varpula M, Ruokonen E, Pettila V, Parviainen I, Ala-Kokko TI, et al. Incidence, treatment, and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study. Intensiv Care Med 2007;33:435–43.
[4] Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis campaign guidelines for

management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
[5] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.
[6] Reynolds HN, Haupt MT, Thill-Baharozian MC, Carlson RW. Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. JAMA 1988;260:3446–50.
[7] Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. Chest 1989;96:127–9.
[8] Wilcox ME, Chong CA, Niven DJ, Rubenfeld GD, Rowan KM, Wunsch H, et al. Do intensivist staffing patterns influence hospital mortality following ICU admission? A systematic review and meta-analyses. Crit Care Med 2013;41:2253–74.
[9] Fuchs RJ, Berenholtz SM, Dorman T. Do intensivists in ICU improve outcome? Best Pract Res Clin Anaesthesiol 2005;19:125–35.
[10] Lin HC, Xirasagar S, Chen CH, Hwang YT. Physician's case volume of intensive care unit pneumonia admissions and in-hospital mortality. Am J Respir Crit Care Med 2008;177:989–94.
[11] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
[12] Durairaj L, Torner JC, Chrischilles EA, Vaughan Sarrazin MS, Yankey J, Rosenthal GE. Hospital volume-outcome relationships among medical admissions to ICUs. Chest 2005;128:1682–9.
[13] Townsend SR, Schorr C, Levy MM, Dellinger RP. Reducing mortality in severe sepsis: the surviving sepsis campaign. Clin Chest Med 2008;29:721–33.
[14] Miller III RR, Dong L, Nelson NC, Brown SM, Kuttler KG, Probst DR, et al. Multicenter implementation of a severe sepsis and septic shock treatment bundle. Am J Respir Crit Care Med 2013;188:77–82.
[15] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250–6.
[16] Parsons EC, Hough CL, Seymour CW, Cooke CR, Rubenfeld GD, Watkins TR. Red blood cell transfusion and outcomes in patients with acute lung injury, sepsis and shock. Crit Care 2011;15:R221.
[17] Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008;36:2667–74.